(1 H, s, Ar OH).

***N*-(Trifluoroacetyl)-7,9-*epi*-4-demethoxy-10,10-dimethyldaunomycin (19a)** (6 mg, 8%); ^{1}H NMR δ 1.28 (3 H, d, J = 6 Hz, CCH_3), 1.35 (3 H, s, CCH_3), 1.85 (3 H, s, CCH_3), 1.45–1.70 (2 H, m, C-2′ CH_2), 1.85–2.40 (2 H, m, C-8 CH_2), 2.37 (3 H, s, $COCH_3$), 3.40 (1 H, s, C-4′ OH), 3.60 (1 H, m, C-4′ H), 4.05–4.45 (2 H, m, C-3′ and C-5′ H), 4.57 (1 H, s, C-9 OH), 5.30 (1 H, dd, W_H = 6 Hz, C-7 H), 5.43 (1 H, dd, J = 2, 3 Hz, C-1′ H), 6.60 (1 H, d, J = 9 Hz, NH), 7.70–7.85 (2 H, m, C-2 and C-3 H), 8.20–8.40 (2 H, m, C-1 and C-4 H), 13.65 (1 H, s, Ar OH), 14.25 (1 H, s, Ar OH).

***N*-(Trifluoroacetyl)-1′-*epi*-4-demethoxy-10,10-dimethyldaunomycin (18a)** (1 mg, 2%). This substance was characterized as its cleavage product due to its small quantity.

Isomeric 4-Demethoxy-10,10-dimethyldaunomycins. The individual *N*-(trifluoroacetyl) glycosides were deblocked by cooling their THF solutions to 0–5 °C and bringing the pH to 13–14 through slow addition of 0.1 N NaOH. After the solutions were stirred for 16 h at 0 °C, the pH was adjusted to 8.0–8.5 by careful addition of 0.1 N HCl, and the solutions were extracted with CH_2Cl_2. The glycosides were purified by individual evaporation and passage over silica gel columns impregnated with 4% KH_2PO_4 using $CHCl_3$–MeOH–HOH (8:2:0.3) for elution. Yields were approximately 80%. Each glycoside was converted to its HCl salt by adding a stoichiometric quantity of MeOH–HCl in MeOH at 0 °C. After stirring 20 min, the salts were precipitated in 90% yield by addition of dry Et_2O.

4-Demethoxy-10,10-dimethyldaunomycin (3): mp 174–6 °C; HCl salt mp, 165–166 °C; UV λ_{max} (MeOH) 254 nm (ε 33 280), 286 (7600), 463 (7910), 492 (9340), 525 (6050); IR (KBr) 3500 cm^{-1}, 1700, 1625; ^{1}H NMR δ 1.25 (3 H, d, J = 6 Hz, CCH_3), 1.30 (3 H, s, CCH_3), 1.70 (3 H, s, CCH_3), 1.50–1.70 (2 H, m, C-2′ CH_2), 1.80–2.60 (2 H, m, C-8 CH_2), 2.40 (3 H, s, $COCH_3$), 3.30–4.70 (5 H, m, C-3′, C-4′, and C-5′ H and C-4′ and C-9 OH), 5.20–5.45 (2 H, m, C-7 and C-1′ H), 7.40–8.20 (2 H, m, C-2 and C-3 H), 8.30–8.65 (2 H, m, C-1 and C-4 H); CD (MeOH) $[\theta]_{287}$ −1.22 × 10^4.

7,9-*epi*-4-Demethoxy-10,10-dimethyldaunomycin (19b): mp 173–176 °C; HCl salt mp 138–140 °C; UV λ_{max} (MeOH) 253 nm (ε 23 790), 285 (6250), 462 (5530), 493 (6630), 527 (4720); IR (KBr) 3500 cm^{-1}, 1710, 1630; ^{1}H NMR δ 1.23 (3 H, s, CCH_3), 1.27 (3 H, s, CCH_3), 1.70 (3 H, s, CCH_3), 1.20–2.30 (4 H, m, C-2′ and C-8 CH_2), 2.30 (3 H, s, $COCH_3$), 3.30–4.40 (5 H, m, C-3′, C-4′, C-5′ H and C-4′ and C-9 OH), 5.10–5.30 (2 H, m, C-7 and C-1′ H), 7.50–7.80 (2 H, m, C-2 and C-3 H), 7.90 and 8.30 (2 H, m, C-1 and C-4 H); CD (MeOH) $[\theta]_{287}$ 0.86 × 10^4.

7,9,1′-*epi*-4-Demethoxy-10,10-dimethyldaunomycin (20b): mp 187–193 °C; HCl salt mp 152–153 °C; UV_{max} (MeOH) 253 nm (ε 30 700), 287 (7690), 463 (7270), 490 (8500), 525 (6000); IR (KBr) 3500 cm^{-1}, 1700, 1625; ^{1}H NMR δ 1.23 (3 H, s, CCH_3), 1.30 (3 H, s, CCH_3), 1.75 (3 H, s, CCH_3), 1.20–2.20 (4 H, m, C-2′ and C-8 CH_2), 2.40 (3 H, s, $COCH_3$), 3.25–4.00 (5 H, m, C-3′, C-4′, and C-5′ H and C-4′ and C-9-OH), 4.80–5.10 (2 H, m, C-1′ and C-7 H), 7.50–7.80 (2 H, m, C-2 and C-3 H), 7.90–8.40 (2 H, m, C-1 and C-4 H); CD $[\theta]_{287}$ 0.78 × 10^4.

1′-*epi*-4-Demethoxy-10,10-dimethyldaunomycin (18b): amorphous; HCl salt mp 142–144 °C.

Testing in Mice against the P388 Lymphocytic Leukemia Model. Doxorubicin and the glycoside hydrochloride **3** were dissolved in saline (Cremophor:saline for the analogue) to final concentrations of 0.01, 0.033, 0.1, 0.33, and 1.0 mg/mL. Female CDF_1 and DBA_2 mice (Laboratory Animal Supply Co., Indianapolis, IN) were fed Purina Laboratory Chow and water ad lib. and adapted to their cages for at least 1 week before use. The tumor was maintained by continuous passage in DBA_2 mice. On day 0, ascitic fluid was removed, diluted with Hawk's balanced salt solution, and counted, and 10^6 cells were implanted ip in a total volume of 0.2 mL. Twenty-four hours later, drug was given ip to groups of five mice for each dilution. The mice were observed for 30 days and T/C (percent) values were determined from the survival rate as compared to the controls. In this test, the lowest dose of doxorubicin (0.1 mg/kg) had a T/C value of 135 and 10 mg/kg of doxorubicin had a T/C value grater than 316. The analogue **3** ranged from 85 to 93 with doses from 0.1 mg/kg to 10 mg/kg. Insufficient drug was available for titrations, but this T/C values is considered to be insignificant.

Acknowledgment. The authors at Kansas University are grateful to Adria Laboratories for generous financial support of this work and all authors are grateful to Dr. H. J. Eichel for support and encouragement.

Registry No. **3**, 91003-74-6; **3**·HCl, 91108-53-1; **6**, 37464-90-7; **7**, 91003-61-1; **8**, 91003-64-4; **9a** (isomer 1), 91003-66-6; **9a** (isomer 2), 91003-67-7; **9b** (isomer 1), 91003-68-8; **9b** (isomer 2), 91003-69-9; **10**, 91003-65-5; **11**, 91003-70-2; **12**, 91003-72-4; **13**, 91003-71-3; **14**, 52471-40-6; **15**, 91108-50-8; **16**, 90146-27-3; **17**, 91003-73-5; **18a**, 91108-52-0; **18b**, 91108-56-4; **18b**·HCl, 91176-63-5; **19a**, 91108-51-9; **19b**, 91108-54-2; **19b**·HCl, 91176-61-3; **20a**, 91109-35-2; **20b**, 91108-55-3; **20b**·HCl, 91176-62-4; 5,8-dimethoxy-1,1,3-trimethyl-2-tetralone, 91003-62-2; 5,8-dimethoxy-1-methyl-2-tetralone, 91003-63-3; methyl vinyl ether, 107-25-5.

Synthesis and Antiarrhythmic and Parasympatholytic Properties of Substituted Phenols. 2.[1] Amides

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Thirty amides patterned after the antiarrhythmic drug changrolin were synthesized and their antiarrhythmic and parasympatholytic activities were assessed. There was no correlation between antiarrhythmic and parasympatholytic activities. Several of the amides were found to be potent antiarrhythmic agents that possessed low parasympatholytic activity. All of the compounds appear to act by a class I mechanism.

The term "arrhythmia" encompasses a variety of cardiac disorders including rhythm irregularities, increased or decreased frequency of beats, and abnormalities in the propagation of beats. It is therefore not surprising that the drugs available for treating arrhythmias cover a broad spectrum, both structurally and in their mechanisms of action. Unfortunately, all antiarrhythmic drugs also have unwanted side effects, most notably cardiotoxicity, gastrointestinal complications, and adverse CNS effects. Because of the complex nature of arrhythmias and the deleterious side effects of known antiarrhythmic agents, the search for drugs that work by novel mechanisms

[†] Section of Medicinal/Organic Chemistry.
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(1) For part 1, see: Stout, D. M.; Matier, W. L.; Barcelon-Yang, C.; Reynolds, R. D.; Brown, B. S. *J. Med. Chem.* **1983**, *26*, 808.

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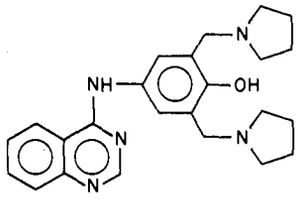
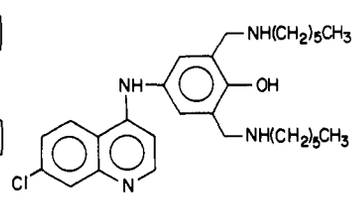
and/or possess new chemical structures continues.

One new structure is the bis(pyrrolidinylmethyl)phenol changrolin 1. Bis(aminomethyl)phenols have been the basic segment of many compounds possessing biological activity, ranging from antimalarial action, such as haloquin (**2**),[2] to antiinflammatory action, as in **3**,[3] diuretic activity, such as **4**,[4] and antiarrhythmic action, typified by rhythmol (**5**).[5] Changrolin (1) was recently reported by researchers in the People's Republic of China as having potent antiarrhythmic activity.[6] Since that initial publication, the Chinese scientists have reported the synthesis of several derivatives based on changrolin that also possess significant antiarrhythmic activity.[7,8]



1



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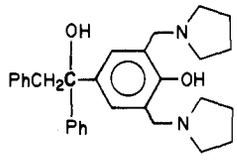
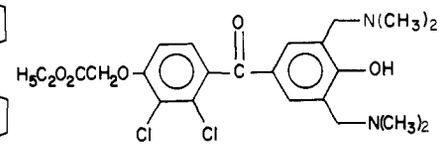
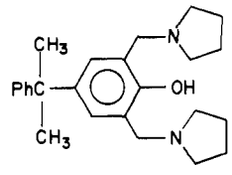


3



4



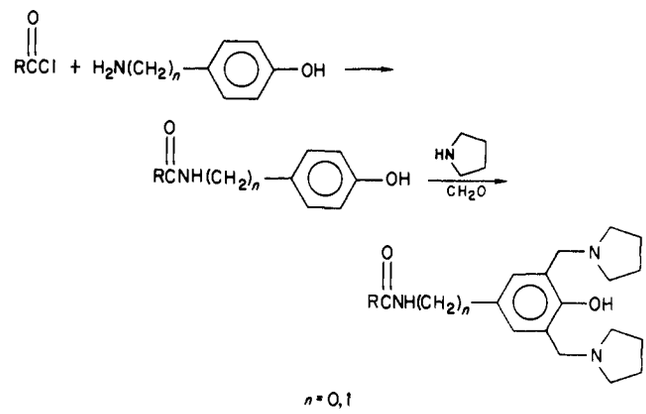
5

The goal of our research has been to use the changrolin structure as a starting point in the hope that modifications to the molecule will result in a potent antiarrhythmic agent possessing few undesirable side effects. Our initial report described several heteroarylamine derivatives that had varying degrees of antiarrhythmic and parasympatholytic activities.[1] We found that the bis(pyrrolidinylmethyl)-phenol moiety in changrolin was optimal for antiarrhythmic activity but that the aminoquinazoline could be replaced by a variety of heterocycles. We report herein our results whereby the heterocycle is replaced by aryl amides.

Chemistry. The amides (Table I) were prepared by reacting *p*-aminophenol or *p*-hydroxybenzylamine with the appropriate acid chloride and then aminomethylating (Scheme I).

Pharmacology. Antiarrhythmic activity was determined in ouabain-intoxicated dogs[9] in place of the Harris dog model used previously.[1] This allowed a more rapid screening of antiarrhythmic activity. Parasympatholytic activity was assessed in the electrically stimulated isolated guinea pig ileum. Anticholinergic activity was determined in the methacholine-treated isolated guinea pig ileum. All doses were calculated as the free base.

Scheme I



Results and Discussion

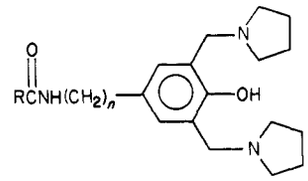
The amide derivatives of changrolin are, for the most part, potent antiarrhythmic agents in comparison to the standard class I agents disopyramide, quinidine, or procainamide (Table I). There was no obvious trend in antiarrhythmic potency with position or type of substituent on the aromatic ring. A thiophene moiety readily substituted for a phenyl ring and insertion of a methylene unit between the phenol and the amide group failed to cause any dramatic changes in activity (**1–4** and **8–10** vs **24–30**). A methylene unit on the carbonyl side of the amide (**19** vs. **23**) resulted in the loss of antiarrhythmic activity.

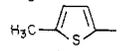
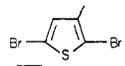
A significant undesirable action of many class I agents is parasympatholytic activity. This property is most evident with disopyramide and, to a lesser extent, with quinidine, though procainamide has little of this activity. Similarly, changrolin and the heteroaryl analogues that we reported previously tended to be potent parasympatholytic agents.[1] These parallel activities did not occur with the amide derivatives. While compounds that had electron-donating substituents (negative Hammett σ values, e.g., **1, 5, 6, 11, 14**) had lower parasympatholytic activity (0 ± 2 to 32 ± 6% inhibition of guinea pig ileum) than those having electron-withdrawing substituents (positive Hammett σ values, e.g., **2, 8, 9**) (42 ± 3 to 62 ± 3%), no such correlation was observed for antiarrhythmic activity. Indeed, six compounds, **4, 7, 10, 14, 16,** and **30**, were very potent as antiarrhythmics while having low parasympatholytic activity. However, the three compounds that lacked antiarrhythmic activity (**15, 18, 23**) also had weak parasympatholytic activity. The only trend in activities resided with the ortho-substituted compounds, which tended to be potent antiarrhythmic agents that had relatively low parasympatholytic activity (**4, 7, 10, 16, 30**).

We selected a few of the compounds in order to examine the parasympatholytic activity more specifically as anticholinergic activity. This was carried out in the guinea pig ileum by challenging the response of the cholinergic agonist methacholine with test compounds. The results are shown in Table II. In all cases the amides had significantly less anticholinergic activity than disopyramide and quinidine. A preliminary investigation of the electrophysiology of **1**

(2) Rabinovich, S. A.; Moshkorskii, Sh. D. *Med. Parazitol. Parazit. Bolezni* **1964**, *33*, 472; *Chem. Abstr.* **1967**, *66*, 453040g.
(3) British Patent 1 033 920; *Chem. Abstr.* **1966**, *65*, 8826C.
(4) German Patent 3 038 011; *Chem. Abstr.* **1981**, *95*, 42695X.
(5) Moe, R. A. *Arch. Int. Pharmacodyn.* **1961**, *132*, 295.
(6) Liangquan, L.; Zhixiang, Q.; Zhimin, W.; Yanlin, Z.; Guangsheng, D.; Guojun, H.; Xueyi, Y. *Sci. Sin. (Engl. Ed.)* **1979**, *22*, 1220.
(7) Sun, C.; Zhang, X.; Yang, X.; Wang, P.; Shen, J.; Shu, Y.; Ji, R.; Kyi, Z. *Yao Hsueh Hsueh Pao* **1981**, *16*, 564; *Chem. Abstr.* **1982**, *96*, 1227227V.
(8) Lin, M.; Liu, Y.; Lu, Y.; Zhang, H.; Zheng, W. *Yao Hsueh Hsueh Pao* **1981**, *16*, 757; *Chem. Abstr.* **1982**, *96*, 122728W.
(9) Lucchesi, B. R.; Hardman, H. F. *J. Pharmacol. Exp. Ther.* **1961**, *132*, 372.

Table I. Antiarrhythmic and Parasympatholytic Activities of Substituted Phenols



compd	R	n	mp, °C	formula	active dose of base in ouabain dog,[a] mg/kg	N[b]	% inhibn of guinea pig ileum contractile force at 4 mg/L[a] of base	N[b]
	changrolin				5.5 ± 2.3	5	43 ± 6	7
1	C_6H_5	0	160–161	$C_{23}H_{29}N_3O_2$	3.4 ± 0.7	6	30 ± 4	10
2	4-Cl-C_6H_4	0	133–135	$C_{23}H_{28}N_3O_2Cl$	1.5	1	49 ± 9	5
3	3-Cl-C_6H_4	0	79–83	$C_{23}H_{28}N_3O_2Cl\cdot 2HCl\cdot H_2O$	3.8 (3.5, 4.0)	2	37 ± 9	3
4	2-Cl-C_6H_4	0	139–149	$C_{23}H_{28}N_3O_2Cl$	5.0 (1.5, 8.5)	2	0 ± 2	3
5	4-CH_3-C_6H_4	0	50–55	$C_{24}H_{31}N_3O_2\cdot 0.5H_2O$	3.0 (3.0, 3.0)	2	22 ± 2	5
6	3-CH_3-C_6H_4	0	68–69	$C_{24}H_{31}N_3O_2\cdot 2HCl\cdot 1.25H_2O$	5.2 (7.5, 3.0)	2	32 ± 6	5
7	2-CH_3-C_6H_4	0	204–205	$C_{24}H_{31}N_3O_2\cdot 2HCl\cdot 1.5H_2O$	2.7 ± 0.5	8	9 ± 0.7	3
8	4-CF_3-C_6H_4	0	165–166	$C_{24}H_{28}N_3O_2F_3$	5.3 (5.5, 5.0)	2	42 ± 3	3
9	3-CF_3-C_6H_4	0	90–93	$C_{24}H_{28}N_3O_2F_3\cdot HCl\cdot H_2O$	2.3 (2.5, 2.0)	2	62 ± 3	3
10	2-CF_3-C_6H_4	0	113–115	$C_{24}H_{28}N_3O_2F_3\cdot 2HCl\cdot 1.5H_2O$	6.5 ± 2.1	4	0 ± 3	6
11	4-CH_3O-C_6H_4	0	55–57	$C_{24}H_{31}N_3O_3$	7.3 ± 2.2	4	24 ± 9	3
12	2-CH_3O-C_6H_4	0	233–235	$C_{24}H_{31}N_3O_3\cdot 2HCl$	3.0 (2.5, 3.5)	2	31 ± 10	3
13	4-NO_2-C_6H_4	0	158–159	$C_{23}H_{28}N_4O_4$	11.0 (18, 4.0)	2	24 ± 5	3
14	4-NH_2-C_6H_4	0	88–90	$C_{23}H_{30}N_4O_2\cdot 0.25H_2O$	4.5 (4.5, 4.5)	2	0 ± 2	3
15	2,4-Cl_2-C_6H_3	0	118–120	$C_{23}H_{27}N_3O_2Cl_2\cdot 2HCl\cdot 2H_2O$	not effective[c]	3	11 ± 3	6
16	2,6-Cl_2-C_6H_3	0	185–187	$C_{23}H_{27}N_3O_2Cl_2\cdot 2HCl\cdot H_2O$	4.6 ± 1.7	4	14 ± 0.4	3
17	2,6-$(CH_3)_2$-C_6H_3	0	74–76	$C_{25}H_{33}N_3O_2\cdot 2HCl\cdot 3H_2O$	3.2 ± 0.6	8	15 ± 2	3
18	3,4,5-$(CH_3O)_3$-C_6H_2	0	69–70	$C_{26}H_{35}N_3O_5\cdot 2HCl\cdot 2H_2O$	inactive[d]	1	6 ± 2	3
19		0	148–150	$C_{21}H_{27}N_3O_2S$	2.0 ± 0.2	7	44 ± 1	5
20		0	151–153	$C_{22}H_{29}N_3O_2S\cdot H_2O$	4.3 ± 1.1	4	g	
21		0	41–44	$C_{22}H_{29}N_3O_2S\cdot 0.5H_2O$	1.6 ± 0.4[e]	5	g	
22		0	55–65	$C_{21}H_{25}N_3O_2Br_2S$	4.3 ± 0.7	5	g	
23		0	181–182	$C_{22}H_{29}N_3O_2S$	not effective[f]	2	13 ± 1	3
24	C_6H_5	1	94–95	$C_{24}H_{31}N_3O_2$	3.0 (2.5, 3.5)	2	34 ± 8	5
25	4-Cl-C_6H_4	1	88–90	$C_{24}H_{30}N_3O_2Cl\cdot 2HCl\cdot H_2O$	3.7 (2.0, 5.5)	2	56 ± 10	3
26	3-Cl-C_6H_4	1	205–207	$C_{24}H_{30}N_3O_2Cl\cdot 2HCl$	9.0 (13, 5)	2	78 ± 3	3
27	2-Cl-C_6H_4	1	89–90	$C_{24}H_{30}N_3O_2Cl\cdot 2HCl\cdot 2H_2O$	2.5 ± 0.5	4	19 ± 3	5
28	4-CF_3-C_6H_4	1	85–87	$C_{25}H_{30}N_3O_2F_3\cdot 2HCl\cdot H_2O$	4.5 (7.5, 1.5)	2	50 ± 13	3
29	3-CF_3-C_6H_4	1	187–188	$C_{25}H_{30}N_3O_2F_3\cdot 2HCl$	5.5 (6.5, 4.5)	2	72 ± 9	3
30	2-CF_3-C_6H_4	1	67–68	$C_{25}H_{30}N_3O_2F_3\cdot 2HCl\cdot H_2O$	1.9 ± 0.3	4	8 ± 0.6	3
quinidine					10.5 (8, 13)	2	62 ± 6	8
disopyramide					4.4 ± 0.9	5	81 ± 7	5
procainamide					29.0 ± 6.2	5	0 ± 2	5

[a] Average of experimental valves, which are given in parentheses, or means plus or minus the standard of the mean. [b] Number of experiments. [c] Cumulative doses of 3, 3, and 13 mg/kg killed each of three dogs without producing normal sinus rhythm. [d] Inactive to 30 mg/kg. [e] Killed one dog at 1.0 mg/kg. Data not included. [f] Drug exacerbated arrhythmia. [g] Experiment not run.

indicates the amides are class I agents.[10]

Thus, in comparison to the antiarrhythmic drugs disopyramide, quinidine, procainamide, and changrolin, these amides are potent antiarrhythmic agents, some of which exhibit low parasympatholytic and anticholinergic activity.

Experimental Section

Pharmacological Evaluation. Ouabain-Induced Arrhythmia. Adult male mongrel dogs (10–17 kg) were anesthetized with pentobarbital (30 mg/kg iv) and intubated for spontaneous respiration. Lead II of the ECG was recorded. Ouabain was administered intravenously in bolus doses: 40 μg/kg, followed in 30 min by 20 μg/kg and then in 15-min intervals 10 μg/kg until a stable ventricular arrhythmia (>95% ectopic ventricular complexes) was present for 15 min.[9] The test compound was administered at a rate of 0.5 (mg/kg) min intravenously until ar-

Table II. Anticholinergic Activity

antagonist	[antagonist], μM	pA_2 (x + SE)	N
disopyramide	3	6.44 ± 0.11	4
quinidine	10	6.00 ± 0.22[a]	4
1	30	5.00 ± 0.12[b]	4
4	50	5.12 ± 0.10[b]	4
7	30	4.71 ± 0.31[b]	4
10	50	4.76 ± 0.20[b]	4
16	50	5.33 ± 0.05[b]	3
17	50	5.26 ± 0.26[b]	4
19	30	4.80 ± 0.34[b]	4
27	50	4.92 ± 0.12[b]	4

[a] Not significantly less than disopyramide. [b] Significantly less than quinidine and disopyramide ($P < 0.05$).

(10) Reynolds, R. D.; Brown, B. S. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1983**, *42*, 2007.

rhythmia reverted to normal sinus rhythm for at least 10 min.

Isolated Guinea Pig Ileum, Electrically Stimulated. Fasted, male Hartley guinea pigs (300–400 g) were killed by a blow to the head. A 1-cm segment of ileum was removed and placed in a bath containing physiological saline solution (in mmol/L: NaCl, 120; $NaHCO_3$, 25; KCl, 4.7; $MgSO_4$, 0.57; KH_2PO_4, 1.2; $CaCl_2$, 1.96; dextrose, 11.1) at 37 °C and gassed with 95% O_2/5% CO_2. One end of the ileal strip was impaled onto a platinum wire electrode. The other end was tied with a silk suture attached to a Gould Statham Model UC3 force-displacement transducer. Basal tension was set at 0.1–0.3 g, and plastic contractions were elicited by field stimulation pulses (100–150 V, 2.5-ms duration) delivered at a frequency of 0.2 Hz. After an equilibration period of approximately 60 min, tension development was assessed just before and during the steady-state response to the test drug at a concentration of 4 mg/L. Contractile tension in this preparation is due to the electrically stimulated release of acetylcholine from postganglionic parasympathetic nerve terminals and interaction of acetylcholine with postsynaptic receptors. Drug-induced reduction of contractile force, regardless of mechanism, was thus termed parasympatholytic activity.

Isolated Guinea Pig Ileum, Methacholine. Fasted, male Hartley guinea pigs (300–400 g) were killed by a blow to the head. A 1-cm segment of ileum was removed and placed in a muscle bath containing physiological saline solution (in mmol/L: NaCl, 120; $NaHCO_3$, 25; KCl, 4.7; $MgSO_4$, 0.57; KH_2PO_4, 1.2; $CaCl_2$, 1.96; dextrose, 11.1) at 37 °C and gassed with 95% O_2/5% CO_2. Mechanical activity was monitored by using a Gould Statham Model UC3 force-displacement transduced and a Gould Model 2800 strip chart recorder. Basal tension was set at 0.1–0.3 g. Each ileum was initially exposed to incremental concentrations of methacholine chloride (3×10^{-8} to 9×10^{-6} M), and peak contractile responses were recorded. All muscles were washed with fresh physiological saline solution before the next higher methacholine concentration was administered. The methacholine/wash sequence was repeated in each tissue except that a single dose of an antagonist was given 15 min prior to the administration of each incremental methacholine concentration. The methacholine EC_{50} (concentration of methacholine required to produce 50% of maximal response) in the presence and absence of antagonist was determined for each muscle. An antagonist pA_2 value was then calculated by using the following formula: $pA_2 = -\log KB$; K_B = [antagonist]/((EC_{50} with antagonist/EC_{50} without antagonist) − 1).

A linear regression analysis revealed no significant relationship between antiarrhythmic potency and parasympatholytic activity. A two-factor nested analysis of variance model was used to determine that a significant difference in parasympatholytic activity existed between compounds having low activity and those having high activity ($P = 0.0198$). The anticholinergic activity was analyzed statistically by using a one-tailed t test for unpaired data.

Chemistry. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 283 spectrophotometer as KBr pellets. NMR spectra were determined on a Varian T-60A spectrometer in $CDCL_3$, Me_2SO-d_6, or CD_3OD with tetramethylsilane as internal standard or in D_2O with 4,4-dimethyl-4-silapentane-4-sulfonate as a standard. Elemental analyses were performed by Martine Bunting and Mark Eliason of our laboratories. All compounds were analyzed for C, H, and N and were within ±0.4% of theoretical values.

***N*-Benzoyl-3,5-bis(*N*-pyrrolidinylmethyl)-4-hydroxyaniline.** (1). The procedure describe is typical for the amides. A mixture of 11.6 g (106 mmol) of *p*-aminophenol and 10.7 g (106 mmol) of triethylamine in 50 mL of dioxane was treated by dropwise addition with 15.0 g (106 mmol) of benzoyl chloride. The mixture was stirred for 3 h and was then treated with 100 mL of water. The product was collected by filtration, washed with water, and dried, yielding the amide as an off-white solid in quantitative yield. The amide was used without further purification: mp 196–200 °C; NMR (Me_2SO-d_6) δ 6.6–6.9 (m, 2 H), 7.3–8.2 (m, 8 H), 10.01 (s, 1 H).

A mixture of the crude product, 15.0 g (212 mmol) of pyrrolidine, and 20.0 mL (246 mmol) of a 37% aqueous solution of formaldehyde in 100 mL of ethanol was heated to reflux for 6 h. The solvent was removed on a rotary evaporator, leaving a dark solid product. Three recrystallizations from 2-propanol yielded 5.5 g (14% overall) of white crystals: NMR (CD_3OD) δ 1.5–2.2 (m, 8 H), 2.2–2.9 (m, 8 H), 3.77 (s, 4 H), 7.3–7.7 (m, 5 H), 7.8–8.1 (m, 2 H).

Alternatively, crude products were chromatographed on silica gel (EtOAc/MeOH/NH_4OH, 9:1:0.05) and recrystallized from EtOAc/EtOH.

Benzyl amides **24–30** were prepared by converting *p*-methoxybenzylamine to *p*-hydroxybenzylamine as previously reported.[1] Amine **14** was prepared from the nitro compound **13** by catalytic hydrogenation according to the procedure of Mendenhall and Smith.[11] Thus, a mixture of 1.1 g (2.6 mmol) of **13** and 0.13 g of Pd/C in 150 mL of methanol saturated with hydrogen chloride under an atmosphere of hydrogen at 40 psi was shaken in a Parr hydrogenator for 3 h. The mixture was filtered, the solvent was removed, and the resulting solid was neutralized with aqueous K_2CO_3. Extraction with CH_2Cl_2, drying ($MgSO_4$), and evaporation of the solvent afforded 0.71 g (70% yield) of off-white crystals: NMR ($CDCl_3$) δ 1.6–2.0 (m, 8 H), 2.4–2.8 (m, 8 H), 3.70 (s, 4 H), 6.5–6.8 (m, 2 H), 7.33 (s, 2 H), 7.5–7.7 (m, 4 H).

Registry No. **1**, 81079-97-2; **2**, 90446-38-1; **3**, 90446-45-0; **3**·2HCl, 91111-99-8; **4**, 90446-44-9; **5**, 90446-39-2; **6**, 90446-49-4; **6**·2HCl, 91112-00-4; **7**, 90446-50-7; **7**·2HCl, 91112-01-5; **8**, 90446-47-2; **9**, 91112-02-6; **9**·2HCl, 91112-03-7; **10**, 90446-46-1; **10**·2HCl, 91112-04-8; **11**, 90446-42-7; **12**, 90446-48-3; **12**·2HCl, 91112-05-9; **13**, 90446-41-6; **14**, 90446-62-1; **15**, 90446-40-5; **15**·2HCl, 91112-06-0; **16**, 90446-51-8; **16**·2HCl, 91112-07-1; **17**, 90446-53-0; **17**·2HCl, 91129-68-9; **18**, 91112-08-2; **18**·2HCl, 90446-52-9; **19**, 90446-54-1; **20**, 91112-09-3; **21**, 91112-10-6; **22**, 91112-11-7; **23**, 90446-55-2; **24**, 90446-56-3; **25**, 90446-57-4; **25**·2HCl, 91112-12-8; **26**, 90446-61-0; **26**·2HCl, 91112-13-9; **27**, 90446-60-9; **27**·2HCl, 91112-14-0; **28**, 90446-74-5; **28**·2HCl, 91112-15-1; **29**, 90446-59-6; **29**·2HCl, 91112-16-2; **30**, 90446-58-5; **30**·2HCl, 91112-17-3; *p*-aminophenol, 123-30-8; benzoyl chloride, 98-88-4; *N*-(4-hydroxyphenyl)benzamide, 15457-50-8; pyrrolidine, 123-75-1; *p*-hydroxybenzylamine, 696-60-6.

(11) Mendenhall, G. C.; Smith, P. A. S. "Organic Syntheses"; Wiley: New York, 1973; Collect. Vol. V, p 829.