N-[(ω-Amino-1-hydroxyalkyl)phenyl]methanesulfonamide Derivatives with Class III Antiarrhythmic Activity

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N-[4-[4-(Ethylheptylamino)-1-hydroxybutyl]phenyl]methanesulfonamide, (*E*)-2-butenedioate (2:1) salt (ibutilide fumarate, **2E**), has been found to have Class III antiarrhythmic activity. In an in vitro rabbit heart tissue preparation designed to evaluate the cardiac electrophysiology of potential antiarrhythmic agents, it selectively prolongs the effective refractory period of papillary muscle. In vivo it increases the ventricular refractory period of the canine heart and prevents the ventricular arrhythmias induced by programmed electrical stimulation 3–9 days after a myocardial infarction. This paper describes the synthesis of **2E** and a series of related compounds. The in vitro evaluation of the cardiac electrophysiology of these compounds has allowed us to determine the structural requirements for Class III antiarrhythmic activity in this series. Evalulation of the antiarrhythmic activity of **2E** and one of the more potent analogues on the late postinfarction ventricular arrhythmias induced by programmed electrical stimulation of the canine myocardium is also described. This activity is compared with that of the Class III antiarrhythmic agent sotalol. Compound **2E** appears to be as effective and 10–30 times more potent than sotalol in this model.

Ventricular fibrillation is a primary cause of death in patients with cardiovascular disease;[1] however, generally safe and effective therapeutic interventions for the malignant ventricular arrhythmias that lead to this lethal event are not yet available. Such interventions, therefore, represent a major unmet medical need. Attempts to develop medicinal agents for treating cardiac dysrhythmias have dated from the discovery in 1914 that a cinchona alkaloid preparation alleviated the cardiac arrhythmia of a patient who was being treated for malaria. It was subsequently found that quinidine was the most potent antiarrhythmic agent in this natural product;[2] quinidine sulfate has been a mainstay for antiarrhythmic therapy since this time.[3] Quinidine sulfate is a representative of a group of antiarrhythmic agents (Vaughan Williams Class I)[4] that rely on an "interference with recovery from inactivation of sodium channels" for their activity.[5] Members of this class have been extensively evaluated for their ability to suppress ventricular premature complexes (VPCs) in the hope that such agents would also be able to prevent ventricular fibrillation and sudden cardiac death that seemed to be associated with these arrhythmias.[6] It has recently been found, however, that although the Class IC[7] agents encainide and flecainide effectively suppressed VPCs in patients who had suffered a myocardial infarction, they where associated with an *increased* incidence of death from arrhythmia in these patients.[8] While this study is definitive only for the Class IC agents investigated, it is now becoming clear that although VPCs are considered to be a risk factor for sudden death after a myocardial infarction, treating these arrhythmias with Class I antiarrhythmic agents may not be useful for preventing subsequent lethal events.

Another approach for treating arrhythmias was identified in 1970 by Singh and Vaughan Williams. From their investigations of the cardiac electrophysiology of amiodarone and sotalol it was proposed that the antiarrhythmic activity of these compounds was the result of their ability to prolong the cardiac action potential.[9,10] Such compounds that provide a uniform increase in the refractoriness of cardiac tissue, associated with a prolongation of the action potential duration (APD), but without an affect on the fast sodium current, are known as Class III antiarrhythmic agents.[4,11] Compounds with this type of activity are receiving increased attention for their ability to prevent malignant reentrant ventricular arrhythmias,[11-13] as demonstrated by recent clinical studies with clofilium,[14] sotalol,[15,16] *d*-sotalol,[17] amiodarone,[18] and bretylium tosylate.[19,20] A recent study has shown that *d*-sotatol may also be useful for treating refractory supracentricular tachyarrhythmias.[21] Several new compounds of this type are in the early stages of development.[22-24]

In this paper we will present the results of our investigation of a series of compounds with Class III antiarrhythmic activity. We began this investigation with a

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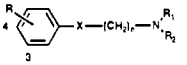
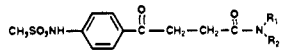
Table I. Physical and Analytical Data for the *N*-[(ω-Amino-1-hydroxyalkyl)phenyl]methanesulfonamide Derivatives



no.	R	X	n	R_1	R_2	% yield	procedure	mp, °C	recrystn solvent	formula	analyses
2	4-CH_3SO_2NH	CHOH	3	C_2H_5	n-C_7H_{15}	87	B[a]	117–119	$(CH_3)_2CO$	$C_{22}H_{38}N_2O_5S$[b]	C,H,N,S
4[r]	4-CH_3SO_2NH	CH_2	3	C_2H_5	n-C_7H_{15}	20.2	B[a]				
5	4-Cl	CHOH	3	C_2H_5	n-C_7H_{15}	65.8	B[p]	87–88	EtOAc	$C_{19}H_{33}Cl_2NO$[q]	C,H,N,Cl
8	4-CH_3SO_2NH	CO	3	C_2H_5	n-C_7H_{15}	6.8	*a*	111–112	EtOH–Et_2O	$C_{23}H_{37}N_2O_6S$[m]	C,H,N,S
9	3-CH_3SO_2NH	CHOH	3	C_2H_5	n-C_7H_{15}	78.3	B[n,d]	oil		$C_{20}H_{36}N_2O_3S$	*o*
14	4-CH_3SO_2NH	CHOH	2	C_2H_5	n-C_7H_{15}	33.7	*a*	74–75	Et_2O–pentane	$C_{19}H_{34}N_2O_3S$	C,H,N,S
17	4-CH_3SO_2NH	CHOH	1	C_2H_5	n-C_7H_{15}	84.4	*a*	71–74	Et_2O–pentane	$C_{18}H_{32}N_2O_3S$	C,H,N,S
22	4-CH_3SO_2NH	CHOH	3	C_2H_5	n-C_6H_{13}	34.8	B[e,f]	oil		$C_{19}H_{34}N_2O_3S$	*g*
23	4-CH_3SO_2NH	CHOH	3	C_2H_5	n-C_8H_{17}	72.6	B[e]	oil		$C_{21}H_{38}N_2O_3S$	*t*
24	4-CH_3SO_2NH	CHOH	3	C_2H_5	n-$C_{10}H_{21}$	72.4	B	61–62.5	pentane	$C_{23}H_{42}N_2O_3S$	C,H,N,S
25	4-CH_3SO_2NH	CHOH	3	n-C_4H_9	n-C_4H_9	50.2	B[c]	179–180	EtOH–MeOH	$C_{21}H_{36}N_2O_5S_b$	C,H,N,S
26	4-CH_3SO_2NH	CHOH	3	$-(CH_2)_7-$		26.5	B[h]	108.5–110	EtOAc–hexane	$C_{18}H_{30}N_2O_3S$	C,H,N,S
27	4-CH_3SO_2NH	CHOH	3	$(CH_2CH_2)_2CHCH_3$		48.3	B	117–178	EtOAc	$C_{17}H_{28}N_2O_3S$	C,H,N,S
28	4-CH_3SO_2NH	CHOH	3	$-(CH_2)_6-$		54.6	B	154–156	EtOAc	$C_{17}H_{28}N_2O_3S$	C,H,N,S
29	4-CH_3SO_2NH	CHOH	3	H	n-C_7H_{15}	43.7	B[i]	166–167	EtOH	$C_{20}H_{34}N_2O_5S$[b]	H,N,S;C[k]
34	4-CH_3SO_2NH	CHOH	3	CH_3	n-C_7H_{15}	67.9	B[d]	58–60	Et_2O	$C_{19}H_{34}N_2O_3S$	C,H,N,S
35	4-CH_3SO_2NH	CHOH	3	C_2H_5	n-C_5H_{11}	54	B[j]	oil		$C_{18}H_{32}N_2O_3S$	*i*

[a] See the Experimental Section. [b] (*E*)-2-Butenedioate (2:1 salt). [c] The base was purified by silica gel chromatography with 5% Et_3N–45% EtOAc–50% hexane. [d] Purified by silica gel chromatography with 0.75% NH_4OH–7.5% MeOH–CH_2Cl_2. [e] The intermediate keto amide was obtained in 44% yield by procedure E and purified by silica gel chromatography with 5% MeOH–$CHCl_3$. [f] Purified by silica gel chromatography with 0.5% NH_4OH–7% MeOH-$CHCl_3$. [g] FABMS calcd for $C_{19}H_{35}N_2O_3S$ m/z 371.2368 ($M + H^+$), found 371.2361. [h] Purified by silica gel chromatography with 0.5% NH_4OH–5% MeOH–$CHCl_3$. [i] FABMS calcd for $C_{18}H_{33}N_2O_3S$ m/z 357.2212 ($M + H^+$), found 357.2221. [j] Purified by silica gel chromatography with 0.5–1% NH_4OH–5 to 10% MeOH–$CHCl_3$. [k] C: calcd, 57.94; found, 57.38. [l] Purified by silica gel chromatography with 12.5% MeOH–$CHCl_3$. [m] (*E*)-2-Butenedioate (4:3 salt). [n] See the Experimental Section for the preparation of intermediate 13. [o] FABMS calcd for $C_{20}H_{37}N_2O_3S$ m/z 385.2525 ($M + H^+$), found 385.2529. [p] See the Experimental Section for the preparation of intermediate 7. [q] Hydrochloride salt. [r] This compound has been reported in ref 28. [s] Purified by silica gel chromatography with 0.5% NH_4OH–7 to 10% MeOH–$CHCl_3$. [t] MS calcd for $C_{21}H_{38}N_2O_3S$ m/z 398.2603 (M^+), found 398.2604.

Table II. γ-Oxo-4-[(methylsulfonyl)amino]benzenebutanamide Intermediates



	R_1	R_2	% yield	procedure	mp, °C	recrystn solvent	formula	analyses	ref[a]
3	C_2H_5	n-C_7H_{15}	75.0	A[b]	102–103	EtOAc–hexane	$C_{20}H_{32}N_2O_4S$	C,H,N,S	45
30	n-C_4H_9	n-C_4H_9	99.3	C[b]	118.5–120	EtOAc–hexane	$C_{19}H_{30}N_2O_4S$	C,H,N,S	
31	$(CH_2CH_2)_2CHCH_3$		81.9	D[b]	179–180.5	EtOAc	$C_{17}H_{24}N_2O_4S$	C,H,N,S	
32	$-(CH_2)_7-$		74.6	E[b]	151–152	EtOAc–hexane	$C_{18}H_{26}N_2O_4S$	C,H,N,S	
36	CH_3	n-C_7H_{15}	68.2	E	154–155	EtOAc	$C_{19}H_{30}N_2O_4S$	C,H,N	46
37	C_2H_5	n-$C_{10}H_{21}$	59.1	E[c]	92.5–93.5	EtOAc–hexane	$C_{23}H_{38}N_2O_4S$	C,H,N	47
38	C_2H_5	n-C_5H_{11}	60.5	E	98.5–99.5	EtOAc–hexane	$C_{18}H_{28}N_2O_4S$	C,H,N	48
39	$-(CH_2)_6-$		58.9	E	146.5–148	EtOAc–hexane	$C_{17}H_{24}N_2O_4S$	C,H,N	
40	H	n-C_7H_{15}		*d*	183–184	EtOAc	$C_{18}H_{28}N_2O_4S$	C,H,N,S	
41	C_2H_5	n-C_8H_{17}	4.44	C	95–96	EtOAc	$C_{21}H_{34}N_2O_4S$	C,H,N,S	49

[a] Literature reference for the amine. [b] See the Experimental Section. [c] Purified by silica gel chromatography with 30% EtOAc–CH_2Cl_2. [d] Isolated from a preparation of 3 in which the ethylheptylamine was contaminated with heptyl amine; purified by silica gel chromatography with 3.5% MeOH–$CHCl_3$.

consideration of the structures of known compounds with Class III activity. We were particularly intrigued by the fact that the β-adrenergic blocking agent sotalol was unique among a large series of β-blockers in having Class III antiarrhythmic activity. Its distinguishing feature appeared to be the methanesulfonamide moiety. Since sotalol has structural similarities to the Class III antiarrhythmic agent clofilium phosphate,[25] it was of interest to determine if a combination of certain structural features of these two agents might give compounds with improved antiarrhythmic activity.[26] A series of methanesulfonanilides was thus prepared and evaluated for Class III antiarrhythmic activity.[27] Data for selected members of this series are presented in Table I. Several methods were used to synthesize these compounds; the synthesis of one representative example of each type will be discussed.

The key intermediate (1, Chart I) for the preparation of 2 was prepared by an aluminum chloride catalyzed Friedel–Crafts condensation of methanesulfonanilide with succinic anhydride. This acid (1) was then condensed with ethylheptylamine to give amide 3, which was reduced with lithium aluminum hydride to give 2. Several condensing agents were used to prepare 3 and its analogues which are presented in Table II; the experimental conditions for these condensations are described in procedures A and C–E in the Experimental Section. Mild conditions were required for the lithium aluminum hydride reduction of 3 to 2. When the reduction was carried out at 0 °C, 2 was obtained in 87% yield; however, when refluxing tetrahydrofuran was used for the reduction, a mixture composed of 4 (20%) and 2 (47%) resulted. Another method for the preparation of 4 has been reported.[28] The chloro analogue (5) of 2 was similarly prepared by condensing 6

(25) Steinberg, M. I.; Molloy, B. B. *Life Sci.* **1979**, *25*, 1397.
(26) Similar reasoning apparently led to the discovery of LY190, 147 (4) which we also prepared early in our investigation, see ref 27.
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(28) Molloy, B. B.; Steinberg, M. I. U.S. Patent 4,569,801, 1986.

Table III. Effects of Selected Compounds on in Vitro Cardiac Electrophysiology and Contractility[i]

no.	ERP1[a]	ERP3[b]	CT1[c]	CT3[d]	FOC[e]	rate[f]
2[k]	18.0 ± 4.1[j] (7)	15.8 ± 2.0[j] (7)	14.6 ± 5.7 (7)	31.2 ± 7.6[j] (7)	1.9 ± 4.0 (7)	−22 ± 1 (4)
4	28.3 ± 14.1[j] (4)	19.2 ± 2.9[j] (4)	67.2 ± 16.8 (4)	140.2 ± 28.0[j] (4)	−24.2 ± 5.0 (4)	−27 ± 2[j] (3)
5[m]	10.5 ± 4.0 (4)	14.0 ± 5 (4)	4.0 ± 6.0 (4)	NT	−21 ± 2[j] (6)	−12 (1)
8[l]	6.6 ± 3.7 (6)	9.4 ± 1.6[j] (6)	−2.7 ± 12.7 (5)	0.6 ± 0.6 (5)	−6.7 ± 3.7 (6)	−21 ± 5 (3)
9	25.2 ± 5.2 (2)	19.0 ± 0.5 (2)	21.3 ± 19.3 (2)	54.0 ± 26.0 (2)	−15.0 ± 7.0 (2)	−16 ± 1 (2)
14	37.5 ± 1.6 (2)	39.3 ± 10.7 (2)	15.7 ± 9.3 (2)	40.3 ± 19.7 (2)	−23.0 ± 13.0 (2)	−35 ± 1[j] (2)
17	22.9 ± 3.6[j] (4)	26.2 ± 3.2[j] (4)	10.2 ± 6.0[j] (3)	NT	−7.0 ± 10.0 (4)	−38 ± 7 (2)
20[g]	7.3 ± 3.6 (9)	4.9 ± 3.1 (9)	−11.7 ± 4.2 (4)	NT	6.0 ± 11.0 (9)	−10 ± 1[j] (5)
21[h]	3.0 ± 3.9 (4)	3.4 ± 2.9 (4)	0 ± 0 (4)	−1.4 ± 1.7 (4)	−10.0 ± 2.3 (4)	−22 ± 10 (2)
22	12.1 ± 1.0[j] (4)	7.8 ± 6.0 (4)	−6.5 ± 3.3 (4)	0 ± 7.6 (4)	−10.9 ± 5.7 (4)	−16 ± 4 (2)
23[k]	5.3 ± 2.5 (4)	4.3 ± 2.0 (4)	17.3 ± 9.7[j] (4)	29.8 ± 16.0[j] (4)	0.7 ± 19.6 (2)	−28 ± 3 (2)
24	11.8 ± 1.8 (2)	16.1 ± 5.0 (2)	63.2 ± 3.3 (2)	74.3 ± 0.7 (2)	−23.1 ± 6.0 (2)	−11 ± 0 (2)
25[k]	9.5 ± 2.9[j] (5)	10.4 ± 4.6 (5)	−8.5 ± 4.5 (5)	5.2 ± 1.3 (5)	0 ± 4.2 (5)	−20.3 ± 0.5 (5)
26	21.4 ± 9.2[j] (3)	23.5 ± 11.8 (3)	−4.5 ± 1.7 (4)	−4.7 ± 3.0 (4)	−5.6 ± 1.4 (3)	−10 ± 2
27	4.5 ± 4.5 (2)	10.5 ± 1.0 (2)	−2.0 ± 7.5 (2)	−6.5 ± 1.5 (2)	−1.0 ± 2.0 (2)	NT
28	17.1 ± 15.0 (3)	18.3 ± 15.9 (3)	1.0 ± 12.4 (4)	0.2 ± 15.4 (4)	3.4 ± 0 (3)	−11 ± 2 (4)
29[k]	0.4 ± 4.8 (5)	6.8 ± 2.6 (5)	−7.4 ± 3.2 (5)	8.3 ± 3.8 (5)	−12.1 ± 4.9 (5)	−25 ± 9 (3)
34	16.5 ± 1.5 (2)	17.2 ± 0.0 (2)	13.0 ± 8.0 (2)	70.0 ± 22.4 (2)	8.5 ± 10.5 (2)	−34 ± 16 (2)
35	20.8 ± 7.2 (2)	11.6 ± 2.1 (2)	8.6 ± 16.0 (2)	11.9 ± 15.4 (2)	17.1 ± 8.7 (2)	−20 ± 12 (2)

[a] Effective refractory period measured at a pacing rate of 1 Hz. [b] Effective refractory period measured at a pacing rate of 3 Hz. [c] Conduction time measured at a pacing rate of 1 Hz. [d] Conduction time measured at a pacing rate of 3 Hz. [e] Force of contraction measured at a pacing rate of 2 Hz. [f] Rate of automaticity measured from unpaced right atria. [g] Sotalol hydrochloride, ref 41. [h] Clofilium phosphate, ref 50. [i] Determined from in vitro rabbit cardiac tissue at 10^{-5} M concentration. All data are expressed as percent change from baseline. The number in parentheses represents the number of tissues tested with each agent. See the Experimental Section for further details. [j] Statistically different from control ($P < 0.05$). [k] Data obtained on the (*E*)-2-butenedioate (2:1 salt). [l] Data obtained on the (*E*)-2-butenedioate (4:3 salt). [m] Data obtained on the hydrochloride salt.

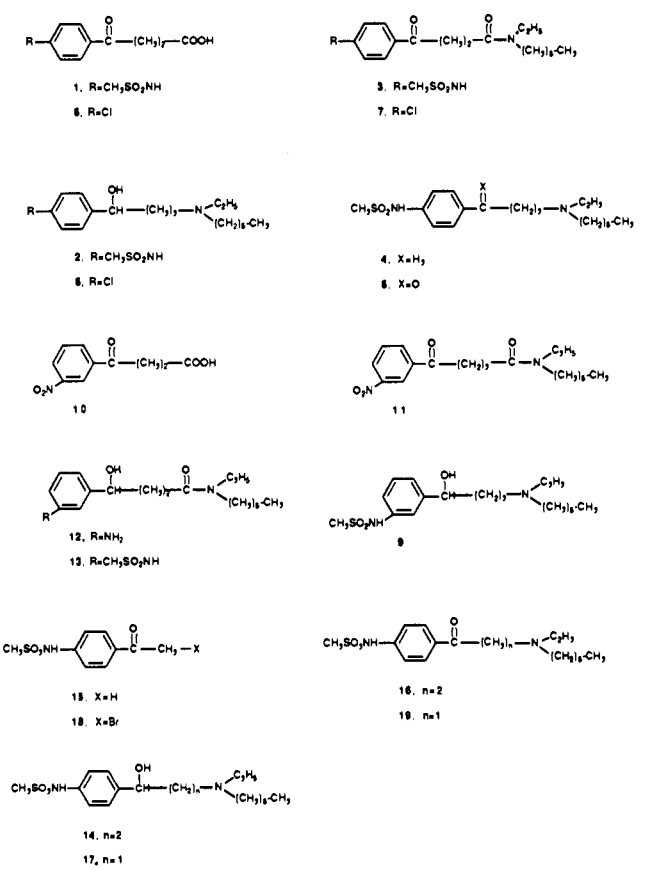
with ethylheptylamine and reducing the resulting amide **7** with lithium aluminum hydride. Oxidation of **2** with Jones reagent[29] in acetone gave ketone **8**. The meta-substituted isomer (**9**) of **2** was prepared in four steps from **10**. A dicyclohexylcarbodiimide-mediated condensation of **10** with ethylheptylamine gave amide **11**, which was hydrogenated over a palladium catalyst to give **12**. Methanesulfonamide **13** was formed by the reaction of **12** with methanesulfonyl chloride in pyridine; it was reduced with lithium aluminum hydride to give **9**. Compound **14**, with three carbons separating the aromatic ring from the side-chain amine, was prepared in two steps. Acetophenone **15** was allowed to react with the Mannich reagent prepared in situ by the reaction of bis(ethylheptylamino)methane with acetyl chloride in tetrahydrofuran; the resulting crude ketone (**16**) as its hydrochloride salt was reduced with sodium borohydride to give **14** in 34% yield. The two-carbon analogue (**17**) was prepared by the reaction of bromo ketone **18** with ethylheptylamine to give **19**, which as its hydrochloride salt was reduced by hydrogenation with a palladium catalyst.

Results and Discussion

Our initial evaluation of the cardiac electrophysiology of compounds with potential antiarrhythmic activity is carried out in vitro with rabbit heart tissue preparations. As discussed in the Experimental Section, this methodology allows us to evaluate the effects of several concentrations of a compound on the refractoriness, contractility, automaticity, and conduction velocity of tissue from a single heart. In addition, by employing two pacing rates, it allows us to determine if the observed effects on refractoriness or conduction are rate dependent. Recent studies have demonstrated that the magnitude of the effects of several Class I antiarrhythmic agents on conduction velocity is dependent on the stimulation rate.[30] Compounds such as lidocaine and tocainide, for example, have an inhibitory effect on cardiac conduction velocity that increases with stimulation rate; it is believed that this may be important for their ability to suppress tachyarrhythmias. Compounds with a rate-dependent effect on refractoriness could be similarly useful. The results for this series of compounds at a concentration of 10^{-5} M are presented in Table III.

As discussed above, our primary interest was to identify compounds that increased the refractoriness of cardiac tissue without having a negative effect on contractility, automaticity, or conduction velocity. Compound **2** was one

Chart I



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(30) Courtney, K. R. *J. Mol. Cell. Cardiol.* **1980**, *12*, 1273.

Table IV. In Vivo Electrohphysiologic Actions of Selected Compounds[a]

no.		baseline	dose, mg/kg, iv 0.1	0.3	1.0	3.0	10.0
2	AH[b]	73 ± 3	73 ± 5	75 ± 4	77 ± 6	NT[c]	NT
	HV[d]	17 ± 1	16 ± 1	17 ± 1	17 ± 2	NT	NT
	QTc[e]	352 ± 7	372 ± 9[i]	387 ± 9[i]	364 ± 9[i]	NT	NT
	S2VERP[f]	137 ± 4	151 ± 5[i]	154 ± 7[i]	146 ± 7[i]	NT	NT
	S3VERP[g]	123 ± 4	137 ± 5[i]	139 ± 5[i]	128 ± 8	NT	NT
20	AH	69 ± 6	NT	NT	77 ± 7	90 ± 6[i]	107 ± 9[i]
	HV	40 ± 4	NT	NT	40 ± 4	39 ± 4	42 ± 4
	QT[h]	196 ± 6	NT	NT	197 ± 6	197 ± 7	181 ± 7
	S2VERP	133 ± 6	NT	NT	145 ± 6	152 ± 6[i]	157 ± 4[i]
	S3VERP	116 ± 5	NT	NT	126 ± 5	138 ± 5[i]	141 ± 4[i]
25	AH	70 ± 6	71 ± 5	66 ± 4	64 ± 4[i]	64 ± 9	NT
	HV	15 ± 3	13 ± 3	15 ± 3	15 ± 3	13 ± 1	NT
	QTc	347 ± 8	370 ± 13	358 ± 7	361 ± 6	367 ± 13	NT
	S2VERP	138 ± 6	145 ± 9	147 ± 7	145 ± 7	145 ± 20	NT
	S3VERP	122 ± 6	128 ± 7	127 ± 7	120 ± 8	115 ± 15	NT

[a] All values are in milliseconds ± SEM; see the Experimental Section for details. [b] Conduction time from the atrium to the His bundle, see ref 51. [c] Not tested [d] Conduction time from the His bundle to the onset of ventricular depolarization. [e] Interval from the Q wave to the T wave of lead II electrocardiogram corrected for heart rate. [f] Ventricular refractory period of the first premature stimulus. [g] Ventricular refractory period of the second premature stimulus. [h] Interval from the Q wave to the T wave of the lead II electrocardiogram. [i] Statistically different from baseline ($p < 0.05$).

of the first compounds in this series found to have this desired type of activity. It produced a significant, concentration-dependent increase in both ERP1 and ERP3 (see Figure 1) and had no significant effect on FOC, RATE, or CT1. It did, however cause a modest but significant increase in conduction time at the 10^{-5} M concentration and the faster pacing rate (CT3). We believe that this rate-dependent effect on conduction velocity may be a useful property for an antiarrhythmic agent of this type; it should complement the Class III activity for treating tachyarrhythmias. At the concentration of 10^{-5} M, compound **2** had a considerably greater effect on papillary muscle refractoriness than either sotalol hydrochloride or clofilium phosphate (compare **2** with **20** and **21**, Table III).[31,32]

In an attempt to optimize this activity we studied the structural modifications of **2** shown in Table I. Analogous to the results reported for clofilium analogues[13] the *n*-heptyl substituent on the side chain nitrogen appears to confer optimum activity to this series. Compounds with both the *n*-hexyl and *n*-octyl substituents had less effect on papillary muscle refractoriness (compare **22** and **23** with **2**). Increasing the length of this substituent also appeared to increase the negative effect on conduction velocity (compare **24** with **2**). In addition to **2** the *N,N*-dibutyl and heptamethyleneimino analogues (**25** and **26**) selectively enhance papillary muscle refractoriness. Cyclic derivatives with ring sizes smaller than seven were, however, less effective (compare **27** with **26**). A tertiary amine appears to be required for activity in this series; the desethyl derivative **29** had little effect on cardiac electrophysiology in this preparation. Both the methanesulfonamide moiety and its position on the aromatic ring were important for the selective effect of these compounds on ERP. When the methanesulfonamide was replaced by a chloro substituent to give **5**, the primary electrophysiological effect was a decreased contractility. The meta-substituted isomer (**9**) of **2** had a negative effect on both contractility and

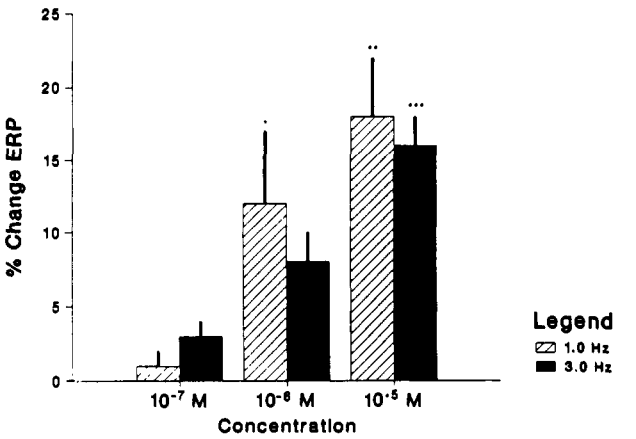

Figure 1. Effects of the (*E*)-2-butenedioate (2:1 salt) of **2** on the effective refractory period (ERP) of isolated rabbit papillary muscle stimulated at 1.0 Hz (ERP1) and 3.0 Hz (ERP3). The data represents the percent change in ERP of the drug treated tissue from that of the vehicle control; $*p = 0.0111$, $**p = 0.0001$, and $***p = 0.0008$.

conduction velocity at concentrations that increased papillary muscle refractoriness. The alcohol moiety was also important: the ketone had a greatly diminished effect on papillary muscle refractoriness (compare **8** with **2**) while deshydroxy derivative **4** caused a decrease in contractility and a marked rate-dependent decrease in conduction velocity at concentrations that increased ERP.[33] Modification of the side-chain length had surprisingly little effect on the activity of these compounds. Thus, the analogues of **2** where the amine was separated from the aromatic ring by two (**17**) or three (**14**) carbons caused a marked and relatively selective increase in papillary muscle ERP.

Compounds with interesting electrophysiology in the in vitro rabbit heart preparations were further evaluated in in vivo models of ventricular tachycardia and fibrillation. One such model which has many characteristics of the pathophysiology of postinfarction arrhythmias in humans has been described by Gibson and Lucchesi.[34] In this model, postinfarction ventricular arrhythmias were in-

(31) The enantiomers of **2** have been prepared and evaluated. This data will be published separately.

(32) Compound **2** has been screened for binding to a variety of central nervous system receptors. Specifically at concentrations of 10^{-6} and 10^{-5} M it did not displace the tritiated ligands dihydroalprenolol, prazosin, or clonidine from the β_1-adrenergic, α_1-adrenergic, or α_2-adrenergic receptors, respectively: R. A. Lahti, unpublished results.

(33) For a more detailed discussion of the pharmacology of this compound, see: Steinberg, M. I. and Smallwood, J. K. *Hand. Exp. Pharmacol.* **1989**, *89*, 389.

(34) Gibson, J. K.; Lucchesi, B. R. *J. Pharmacol. Exp. Ther.* **1980**, *214*, 347.

Table V. In Vivo Antiarrhythmic Actions of the Compounds Presented in Table IV

no.		baseline[f]	dose, mg/kg, iv 0.1	0.3	1.0	3.0	10.0
2	NI[a]	1	3	5	4	NT[c]	NT
	NSVT[b]	1	5	2	2	NT	NT
	VT[c]	3	2	0	0	NT	NT
	VF[d]	6	1	2	1	NT	NT
20	NI	5	NT	NT	8	7	5
	NSVT	0	NT	NT	0	2	1
	VT	2	NT	NT	2	1	0
	VF	3	NT	NT	0	0	0
	AV block[e]	0	0	0	0	0	4
25	NI	2	1	2	2	0	NT
	NSVT	2	2	4	3	1	NT
	VT	1	1	0	0	2	NT
	VF	1	0	0	1	0	NT

[a] Ventricular arrhythmias were not inducible. [b] Nonsustained ventricular arrhythmias were induced. [c] Sustained ventricular arrhythmias were induced. [d] Ventricular fibrillation was induced. [e] Conduction block at the atrioventricular node prevented atrial pacing. [f] Numbers represent animals in each arrhythmia category.

duced in dogs by programmed electrical stimulation 3–9 days after a myocardial infarction. The ability of test compounds to modify or prevent these arrhythmias could then be determined and correlated with their effects on cardiac electrophysiology. Details of the experimental procedure are discussed in the Experimental Section. The electrophysiologic activity of compounds **2** and **25** is compared with that of sotalol hydrochloride (**20**) in Table IV; the resulting antiarrhythmic activity is presented in Table V. Compound **2** produced a significant increase in QTc and ventricular refractoriness (S2VERP and S3VERP) at the 0.1 mg/kg dose level. This effect appeared to increase slightly at the 0.3 mg/kg dose; it then decreased at the 1 mg/kg dose level.[35] Compound **2** was about 30 times more potent than sotalol hydrochloride (**20**) for increasing ventricular refractoriness. In addition, at the effective doses, **20** depressed AH conduction velocity, an undesirable activity that has been reported previously.[36] The effect of **2** on ventricular refractoriness was reflected in its antiarrhythmic activity (Table V). Thus 0.1 mg/kg of **2** prevented the induction of VF or VT in six of nine animals that without drug were inducible to VF or VT; these animals now could only be induced to NSVT or were not inducible to a dysrhythmic state (NI). This effect was maintained throughout the dose range tested. Similarly sotalol (**20**) made three of five animals NI at 1 mg/kg and four of five animals could only be induced to NSVT or NI at 3 mg/kg. Although antiarrhythmic, the 10 mg/kg dose of **20** also produced an AV nodal conduction block which prevented atrial pacing in four of 10 animals. Compound **25**, although very potent in vitro, appeared to be somewhat less effective than **2** for increasing ventricular refractoriness in dogs. It did, however, prevent induction of VT or VF in two of two animals at a dose of 0.3 mg/kg.

Conclusions

We have systematically evaluated a series of Class III antiarrhythmic agents. The activity was initially evaluated in an in vitro rabbit heart preparation designed to determine the effect of test compounds on cardiac electrophysiology. Compounds which selectively increased papillary muscle refractoriness were further evaluated in dogs for their effect on the late, postinfarction ventricular arrhythmias induced by programmed electrical stimulation. It was found that in vitro compound **2** produced a selective, concentration-dependent increase in the refractoriness of rabbit papillary muscle. In the dog this activity was reflected in an increased ventricular ERP which was associated with an excellent antiarrhythmic activity.

The evaluation of the cellular electrophysiology and animal pharmacology of compound **2E** will be reported separately.[37] Compound **2E** is currently being evaluated in humans for its ability to prevent atrial and ventricular tachyarrhythmias.

Experimental Section

Chemistry. Melting points, taken in a capillary tube, are uncorrected. The structures of the compounds were supported by IR, UV, NMR, and mass spectra. IR spectra were determined in Nujol with a Digilab Model FTS15E spectrophotometer. UV spectra were determined in 95% EtOH with a Perkin-Elmer λ 7UV/Vis spectrophotometer. NMR spectra were recorded on a Varian Model FT80A or a Bruker AM300 spectrometer; chemical shifts were recorded in parts per million downfield from Me_4Si. Mass spectra were obtained on a Varian CH5 or CH7 or a Finnegan MAT 8230B spectrometer. The analytical results obtained were within ±0.4% of the theoretical values if not otherwise stated. The silica gel used for chromatography was obtained from E. Merck A.G., Darmstadt, Germany. Silica gel GF 250-μm slides obtained from Analtech, Inc., Newark, DE, were used for TLC. Celite is a filter aid manufactured by Johns-Manville, New York.

4-[(Methylsulfonyl)amino]-γ-oxobenzenebutanoic Acid (1). A mechanically stirred suspension of aluminum chloride (88.0 g, 0.66 mol) in 130 mL of carbon disulfide under N_2 was cooled in an ice bath. Methanesulfonanilide[38] (30.0 g, 0.175 mol) and succinic anhydride (17.5 g, 0.175 mol) were combined and added rapidly to the cooled reaction mixture. The ice bath was removed and the mixture was stirred at ambient temperature for 6 h and at 55 °C for 18 h. The reaction mixture had separated into two layers, the bottom of which had solidified. The upper layer was decanted and the remaining solid layer was decomposed with ice. The resulting suspension was filtered and the solid was washed several times with CH_2Cl_2 and dissolved in a mixture of saturated aqueous $NaHCO_3$ (500 mL) and water (500 mL). This solution was acidified (pH 2) with HCl and the resulting precipitate was collected by filtration, redissolved in $NaHCO_3$ and reprecipated with HCl. The solid was collected by filtration and dried to give 19.1 g of **1**, mp 198–200 °C. The analytical sample was recrystallized from EtOH: mp 200 °C; UV max (EtOH) 217 nm (ε 9950), 272 (17 200); IR (Nujol) 3235.5 (NH), 1692.5 and 1667.4 (CO) cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$–DMSO-d_6) δ 2.64 (t, 2 H, J = 6.4 Hz, CH_2), 3.22 (t, 2 H, J = 6.4 Hz, CH_2), 3.02 (s, 3 H, CH_3), 7.33 (d, 2 H, J = 8.8 Hz, ArH), 7.82 (d, 2 H, J = 8.0 Hz, ArH); MS, m/z (relative intensity) 271 (29), 198 (100), 119 (17), 91 (8), 64 (3). Anal. ($C_{11}H_{13}NO_5S$) C, H, N, S.

***N*-Ethyl-*N*-heptyl-γ-oxo-4-[(methylsulfonyl)amino]-benzenebutanamide (3). Procedure A.** A stirred solution of **1** (12.0 g, 0.044 mol) in DMF (100 mL) under N_2, was cooled in an ice bath and treated with 1-hydroxybenzotriazole (5.94 g, 0.044 mol) and *N*,*N*′-dicyclohexylcarbodiimide (9.08 g, 0.044 mol). After 1 h ethylheptylamine (6.3 g, 0.044 mol) was added and after an additional 30 min the ice bath was removed and the mixture was kept at ambient temperature for 18 h. The reaction mixture was filtered over Celite and the filtrate was concentrated under reduced pressure. The resulting material was dissolved in CH_2Cl_2, washed successively with dilute HCl, (aqueous) $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed over silica gel (1.25 kg) with 5% MeOH–1% NH_4OH–CH_2Cl_2. The product thus obtained was crystallized from EtOAc–hexane to yield 10.77 g (mp 100–102 °C) and 2.32 g (mp

(35) Higher dose levels were not investigated since the maximum effect had apparently been reached at the 0.3 mg/kg dose level.

(36) See, for example: Gomoll, A. W.; Bartek, M. J. *Eur. J. Pharmacol.* **1986**, *132*, 123.

(37) For preliminary reports, see: Lee, K. S. *J. Mol. Cell. Cardiol.* **1990**, *22* (Suppl. I), S15. McKay, M. C.; Sykes, J. S.; Lee, K. S. *J. Mol. Cell. Cardiol.* **1990**, *22* (Suppl. I), S15. Lee, E. W.; McKay, M. C.; Lee, K. S. *J. Mol. Cell. Cardiol.* **1990**, *22* (Suppl. I), S15.

(38) Marvel, C. S.; Melfrick, M. D.; Belsley, J. P. *J. Am. Chem. Soc.* **1929**, *51*, 1272.

99–101 °C) of **3**. The analytical sample had the following data: mp 102–103 °C; UV max 272 nm (ε 16500), 323 (2300), sh 215 (13400); IR (Nujol) 3142 (NH), 1680.9 and 1615.3 (CO) cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 0.7–1.6 (m, 16 H, $(CH_2)_5CH_3$, CH_2CH_3), 2.65–3.5 (m, 8 H, $C(O)CH_2CH_2C(O)$, NCH_2, 2.99 (s, 3 H, CH_3S), 7.21 (d, 2 H, J = 8.8 Hz, ArH), 7.79 (d, 2 H, J = 8.8 Hz, ArH), 8.8 (s, 1 H, NH); MS m/z (relative intensity) 396 (12), 254 (100), 226 (6), 198 (65), 175 (13), 142 (66).

***N*-[4-[4-(Ethylheptylamino)-1-hydroxybutyl]phenyl]methanesulfonamide (2), (*E*)-2-Butenedioate (2:1) Salt. Procedure B.** A stirred, ice-cold slurry of $LiAlH_4$ (41.99 g, 1.1 mol) in THF (700 mL), under N_2, was treated during 3.5 h with a solution of **3** (146.94 g, 0.371 mol) in THF (2099 mL). The mixture was kept in the ice bath for an additional hour and then, with the temperature below 20 °C, treated cautiously with 2050 mL of 0.5 M potassium sodium tartrate. It was stirred for 1 h, allowed to stand at ambient temperature for 18 h, and stirred for one additional hour. The mixture was extracted with EtOAc (3.3 L) and the extract was washed with 0.5 M potassium sodium tartrate (1.35 L) and twice with brine (2.7 L). The aqueous layers were back-extracted three times with EtOAc (2 L). The EtOAc solution was concentrated and the residue was chromatographed on silica gel (2 kg). Elution of the column with 0.5 % NH_4OH–5% MeOH–CH_2Cl_2 (20 L) and 1% NH_4OH–10% MeOH–CH_2Cl_2 (15 L) gave 93 g of pure **2** (free base) and 52 g of a mixture. The latter was rechromatographed on silica gel (1.3 kg) to give 30.6 g of additional product (87% yield).

A mixture of this product (40.3 g) and saturated $NaHCO_3$ was extracted twice with Et_2O. The extracts were washed with saturated $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated to give 31.9 g (0.0829 mol) of the base. This was dissolved in absolute EtOH (134 mL) and mixed with a solution of fumaric acid (4.3 g, 0.037 mol) in absolute EtOH (203 mL). The solution was concentrated under reduced pressure and the residue was dissolved in hot acetone and allowed to crystallize. A recrystallization from acetone gave a solid that was dried under reduced pressure for 4 days at 50 °C to give 31.4 g of the (*E*)-2-butenedioate (2:1) salt of **2**: mp 117–119 °C; UV max 228 nm (ε 16670), 267 (894), sh 283 (575); IR (Nujol) 3382.1 (NH, OH); ^1H NMR (300 MHz, DMSO-d_6) δ 0.858 (t, 3 H, J = 6.8 Hz, $(CH_2)_6CH_3$), 1.00 (t, 3 H, J = 7.1 Hz, CH_2CH_3), 1.25–1.57 (m, 14 H, CCH_2C), 2.50–2.66 (m, 6 H, NCH_2), 2.94 (s, 3 H, CH_3S), 4.49 (t, 1 H, CHOH), 6.45 (s, 1 H, C=CH), 7.15 (d, 2 H, J = 8.4 Hz, ArH), 7.27 (d, 2 H, J = 8.5 Hz, ArH); MS m/z (relative intensity) 384 (6.5), 305 (19.1), 299 (30.6), 240 (7.3), 200 (10.0), 156 (100).

***N*-[4-[4-(Dibutylamino)-1,4-dioxobutyl]phenyl]methanesulfonamide (30). Procedure C.** A solution of **1** (3.53 g, 0.01 mol) in 60 mL of THF, under N_2, was treated with 2.1 mL (1.52 g, 0.015 mol) of Et_3N. The mixture was stirred for 0.5 h, cooled to −15 °C (a suspension formed) and treated, dropwise during 15 min, with 1.95 mL (2.05 g, 0.015 mol) of isobutyl chloroformate. This mixture was stirred at −15 °C for 2 h and treated with 2.1 mL (1.52 g, 0.015 mol) of Et_3N and then with 2.36 mL (1.81 g, 0.014 mol) of di-*n*-butylamine in 5 mL of THF, dropwise at a rate such that the temperature was maintained at −15 ± 5 °C. After 1 h this mixture was poured into a mixture of 140 mL of 1 N HCl and 160 mL of EtOAc. The layers were separated and the organic layer was washed with saturated $NaHCO_3$, dried ($MgSO_4$), and concentrated. One crystallization from EtOAc gave 3.80 g of **30**.

***N*-[4-[4-(4-Methyl-1-piperidinyl)-1,4-dioxobutyl]phenyl]methanesulfonamide (31). Procedure D.** A suspension of **1** (15.05 g, 0.0555 mol) in 350 mL of THF, under N_2, was treated with 10 g (0.0617 mol) of 1,1-carbonyldiimidazole in portions over 5 min. The mixture was stirred at ambient temperature; after 15 min a solution formed which gave way to a thick suspension (50 mL more of THF was added). After 1 h a solution of 4-methylpiperidine (5.51 g, 0.0555 mol) in 10 mL of THF was added and the suspension was stirred for 18 h at ambient temperature and 2 h at 50 °C. The mixture which still contained a suspended solid was cooled in an ice bath and filtered. The filtrate was concentrated and the residue was mixed with 700 mL of EtOAc, washed with 8% $NaHCO_3$, 1 N $KHSO_4$ and brine, and concentrated. The residue was crystallized from EtOAc to give 16.02 g of **31**.

***N*-[4-[4-(Heptamethylenimino)-1,4-dioxobutyl]phenyl]methanesulfonamide (32). Procedure E.** A stirred mixture of **1** (1.37 g, 5.0 mmol), 0.565 g (5.0 mmol) of heptamethylenimine, and 0.81 g (6.0 mmol) of 1-hydroxybenzotriazole in 4 mL of DMF, under N_2, was cooled in an ice bath, treated in portions over 2 min with 0.96 g (5.0 mmol) of 1-ethyl-3-[3-(dimethylamino)-propyl]carbodiimide hydrochloride, and kept in the ice bath for 1 h and at ambient temperature for 18 h. The solvent was removed by distillation under reduced pressure at less than 35 °C, and the residue was mixed with EtOAc, washed successively with 8% $NaHCO_3$, 1 N $KHSO_4$, water, and brine, dried (Na_2SO_4), and concentrated. The residue was crystallized from EtOAc–hexane to give 1.36 g of **32**, mp 151–152 °C.

***N*-[4-[4-(Ethylheptylamino)butyl]phenyl]methanesulfonamide (4) and *N*-[4-[4-(Ethylheptylamino)-1-hydroxybutyl]phenyl]methanesulfonamide (2).** A solution of **3** (0.903 g, 2.28 mmol) in THF (10 mL) was added dropwise, under N_2, to a stirred, ice-cold suspension of $LiAlH_4$ (0.29 g, 7.57 mmol) in THF (10 mL). The mixture was refluxed for 27 h, kept at ambient temperature for 2 days, cooled in an ice bath, and treated, dropwise, with a saturated aqueous solution of potassium sodium tartrate (10 mL). This mixture was extracted with EtOAc; the extract was washed with water and brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed over silica gel with 0.5% NH_4OH–6% MeOH–CH_2Cl_2. The first product eluted from the column was mixed with aqueous $NaHCO_3$ and extracted with Et_2O. The extract was dried ($MgSO_4$) and concentrated to give 0.17 g (20.3%) of **4**: FABMS calcd for $C_{20}H_{37}N_2O_2S$ m/z 369.2576 (M + H^+), found 369.2585. The second product eluted from the column amounted to 0.41 g (46.8%) of **2** (free base): FABMS calcd for $C_{20}H_{37}N_2O_3S$ m/z 385.2525 (M + H^+), found 385.2505.

***N*-Ethyl-*N*-heptyl-3-[(methylsulfonyl)amino]-γ-hydroxybenzenebutanamide (13).** A mixture of 11.15 g (0.05 mol) of 3-nitro-γ-oxobenzenebutanoic acid (**10**),[39] 7.15 g (0.05 mol) of ethylheptylamine, and 8.0 g (0.06 mol) of the 1-hydroxybenzotriazole in 350 mL of CH_2Cl_2 was cooled in an ice bath and treated with 11.0 g (0.053 mol) of dicyclohexylcarbodiimide in 50 mL of CH_2Cl_2 dropwise over 15 min. The mixture was stirred at ambient temperature for 2 h, cooled in an ice bath, and filtered. The solid was washed with CH_2Cl_2 and the filtrate was concentrated. A solution of the residue in EtOAc was washed successively with cold 1 N NaOH, cold water, 1 N $KHSO_4$, water, and brine. The organic solution was dried (Na_2SO_4) and concentrated; the residue was chromatographed over silica gel with 10% EtOAc–CH_2Cl_2 to give 9.5 g (54.6%) of amide **11**. A solution of this material in MeOH (550 mL) was mixed with 10% palladium-on-carbon catalyst (0.95 g) and hydrogenated at an initial pressure of 400 kPa for 80 min. The mixture was filtered through Celite, and the filtrate was concentrated to give 8.5 g of **12**.

A solution of **12** (8.0 g, 0.025 mol) in 20 mL of pyridine, under N_2, was cooled in an ice bath and treated with 2.06 g (0.0266 mol) of methanesulfonyl chloride, dropwise over 10 min. The mixture was stirred in the cold for 1 h and at ambient temperature for 90 min; it was concentrated in vacuo. A solution of the residue in EtOAc was washed successively with 0.5 N HCl, water, and brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed over silica gel with 4% MeOH–CH_2Cl_2 to give 8.1 g (81.7%) of **13**: FABMS m/z (relative intensity) 399 (M + H^+, 100), 381 (87), 321 (5), 303 (8), 198 (13), 170 (18), 142 (21).

Bis(ethylheptylamino)methane (33). According to the method of Harradence and Lions,[40] ethylheptylamine (11.4 g, 0.08 mol) was stirred and cooled in an ice bath under N_2 and treated dropwise over 2 min with 3.25 g of 37% aqueous formaldehyde. Enough solid K_2CO_3 (about 4.1 g) to saturate the mixture was added, the ice bath was removed, and the mixture was stirred at ambient temperature for 26 h. It was then extracted with Et_2O; the extract was dried ($MgSO_4$) and concentrated. The residue was distilled to give 7.15 g (60%) of **33**: bp 126–130 °C (0.15 kPa). Anal. ($C_{19}H_{42}N_2$) C, H, N.

***N*-[4-[3-(Ethylheptylamino)-1-hydroxypropyl]phenyl]methanesulfonamide (14).** A stirred solution of **33** (6.1 g, 0.0204 mol) in 25 mL of THF, under N_2, was cooled in an ice bath and

(39) Martin, E. L. *J. Am. Chem. Soc.* **1936**, *58*, 1441.
(40) Harradence, R. H.; Lions, F. J. *Proc. R. Soc. N.S. Wales* **1939**, *73*, 22.

treated dropwise over 5 min with a solution of 1.47 mL (0.0206 mol) of acetyl chloride in THF (12 mL). The mixture was stirred in the ice bath for 15 min and at ambient temperature for 45 min; it was recooled in an ice bath and treated, dropwise during 10 min with a solution of 4'-acetylmethanesulfonanilide[41] (15, 4.35 g, 0.0204 mol) in THF (50 mL). This mixture was kept in the ice bath for 20 min and at ambient temperature for 3 days; it was concentrated in vacuo and the residue was mixed with cold, dilute HCl and thoroughly extracted with Et_2O. The aqueous solution was neutralized to pH 8.5 with saturated $NaHCO_3$ and extracted with EtOAc. The extracts were washed with water and brine, dried (Na_2SO_4), treated with a slight excess of anhydrous HCl in Et_2O to form the salt, and concentrated. A stirred solution of the residue in EtOH (100 mL) was cooled in an ice bath, under N_2, and treated portionwise with powdered $NaBH_4$ (1.56 g, 0.041 mol) during 15 min. The mixture was kept in the ice bath for 45 min and at ambient temperature for 2 h; it was then cooled in an ice bath and treated with cold water (120 mL) during 10 min. This mixture was extracted with $CHCl_3$; the extracts were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was crystallized from Et_2O–pentane to give 2.55 g (33.7%) of 14, mp 73–75 °C.

***N*-[4-[(Ethylheptylamino)acetyl]phenyl]methanesulfonamide (19), Monohydrochloride.** 4'-(2-Bromoacetyl)-methanesulfonanilide[41,42] (18, 10.8 g, 0.037 mol) was added in portions to a mechanically stirred ice-cold solution of ethylheptylamine (12.3 g, 0.0858 mol) in 250 mL of MeOH under N_2. The reaction was then allowed to continue at ambient temperature for 18 h, at which time the mixture was concentrated in vacuo. The residue was combined with 15% aqueous NaOH and extracted well with ether. The resulting aqueous layer was acidified with dilute HCl (pH 4–5) and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue in EtOH was acidified with ethanolic HCl and the product was crystallized from EtOH–EtOAc to yield 8.8 g (66.3%) of the monohydrochloride salt of 19, mp 168–169 °C. The analytical sample had mp 169–170 °C. Anal. ($C_{18}H_{31}N_2ClO_3S$) C, H, Cl, N, S.

***N*-[4-[2-(Ethylheptylamino)-1-hydroxyethyl]phenyl]-methanesulfonamide (17).** A solution of 19 (4.0 g, 0.0103 mol) in 150 mL of MeOH was hydrogenated with 10% palladium-on-carbon catalyst (0.3 g) at an initial pressure of 345 kPa. After 18 h the reaction mixture was filtered over Celite and the filtrate was concentrated in vacuo. The residue was mixed with aqueous $NaHCO_3$ and extracted well with CH_2Cl_2. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was dissolved in Et_2O, decolorized with activated carbon, and crystallized from Et_2O–pentane to yield 3.1 g of 17, mp 65–67 °C. The analytical sample had mp 71–72 °C.

***N*-[4-[4-(Ethylheptylamino)-1-oxobutyl]phenyl]-methanesulfonamide (8), (*E*)-2-Butenedioate (4:3) Salt.** To an ice-cold solution of 3.16 g (8.2 mmol) of 2 (free base) in 25 mL of acetone was added, dropwise over 5 min, 2.3 mL of Jones reagent (26.72 g of CrO_3 and 23 mL of concentrated H_2SO_4 diluted to 1000 mL with water). The mixture was stirred in the cold for 15 min and at room temperature for 90 min, diluted with 100 mL of CH_2Cl_2, and treated with cold dilute $NaHCO_3$ until the aqueous layer had a pH of 10–11. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The organic layers were washed with dilute $NaHCO_3$, water, and brine, dried ($MgSO_4$), and filtered. The filtrate was treated with 0.5 mL of acetic acid and concentrated, and the residue was chromatographed over silica gel with 1% HOAc–15% MeOH–$CHCl_3$. The product was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$ and the organic extract was dried ($MgSO_4$) and concentrated to give 1.66 g of the free base. A salt was formed with fumaric acid and crystallized from EtOH–Et_2O to give 0.26 g of the (*E*)-2-butenedioate (4:3) salt of 8: FABMS calcd for $C_{20}H_{35}N_2O_3S$ m/z 383.2368 ($M + H^+$), found 383.2350; m/z (relative intensity) 383 (100), 305 (5), 240 (13), 198 (5).

4-Chloro-*N*-ethyl-*N*-heptyl-γ-oxobenzenebutanamide (7). A solution of 4-chloro-γ-oxobenzenebutanoic acid (6,[43] 2.0 g, 0.0094 mol) in 30 mL of DMF, under N_2, was cooled in an ice bath and treated with *N,N'*-dicyclohexylcarbodiimide (1.94 g, 0.0094 mol) and 1-hydroxybenzotriazole (1.27 g, 0.0094 mol). One hour later ethylheptylamine (1.35 g, 0.0094 mol) was added. After 20 min the ice bath was removed and the reaction was allowed to proceed at ambient temperature for 18 h. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was dissolved in CH_2Cl_2, washed with dilute HCl, dilute $NaHCO_3$, and brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed over silica gel with 2.5% MeOH–CH_2Cl_2 to yield 2.1 g (66.1%) of the liquid product (7): MS calcd for $C_{19}H_{28}ClNO_2$ m/z 337.1808 (M^+), found 337.1812.

Biology. In Vitro Cardiac Electrophysiology. New Zealand White rabbits of either sex (1.5–2.0 kg) were anesthetized and their hearts were removed. The heart was immersed in ice cold perfusate while the right atria (RA), papillary muscles (PAP), and right ventricular strips (RV) were isolated. The perfusate (pH 7.4) was continuously oxygenated with 95% O_2 and 5% CO_2; it contained (millimolar concentrations) the following: NaCl (118.0), KCl (5.4), $NaHCO_3$ (25.0), $MgCl_2$ (1.2), KH_2PO_4 (1.0), $CaCl_2$ (2.4), glucose (10.0), and pyruvic acid (2.0). The tissues were individually mounted on a Plexiglas holder containing platinum stimulating electrodes and suspended in a 100-mL bath maintained at 30 °C by a circulating heat pump (Haake Type F). All tissues were attached by silk suture to a force-displacement transducer (Grass FT03) and a tissue-dependent preload of 500–1000 mg was applied. Right atria were allowed to contract spontaneously. Right ventricular strips and papillary muscles were stimulated (Grass Model S88 stimulator, 2X threshold, 4-ms pulses) at a basal rate of 2 Hz. Effective refractory period (ERP) and conduction time (CT) measurements were made at 1 and 3 Hz and are ERP1, ERP3, CT1, and CT3, respectively. Between measurements these tissues were stimulated at a basal rate of 2 Hz. Each tissue served as its own baseline control and was allowed an equilibration period of 2 h prior to experiments. During this period the perfusate was changed every 15 min. Working solutions of the drugs were prepared daily in glass-distilled water. Measurements were made on each set of tissues after exposure to 10^{-7}, 10^{-6}, and 10^{-5} M concentrations of drug for 15 min, at which time the maximum effect was observed. Data obtained for the 10^{-5} M concentration are presented in Table III. Automaticity (RATE) measured in beats per minute and force of contraction (FOC) measured in milligrams are recorded directly on a polygraph (Grass Model 7D). The effective refractory period of cardiac tissues by definition is the longest coupling interval between the basic drive impulse (S1) and the premature impulse (S2) that fails to propagate through the tissue.[44] The premature stimulus was introduced in decreasing millisecond intervals after every eighth S1 impulse to allow time for recovery of cardiac refractoriness. Refractory period measurements were made with a digital timing circuit; the limit of resolution for these refractory period measurements was 6 ms. Conduction time measurements were recorded directly in milliseconds by gently placing a Teflon-coated silver bipolar electrode against the endocardial surface of the right ventricular strip with the resulting electrocardiogram displayed on an oscilloscope (Textronix 7603 with 7D20 digitizer). An increase in conduction time is equivalent to a decrease in cardiac conduction velocity. Data are reported as percent baseline mean ± SEM (standard error of the mean). Data were analyzed by an RS1

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integrated One-Way ANOVA data-analysis program. Those values achieving a $p < 0.05$ vs the control were deemed significant.

In Vivo Cardiac Arrhythmias.[34] Adult male mongrel dogs weighing 11-20 kg were anesthetized (sodium pentobarbital, 30 mg/kg iv) and a thoracotomy was performed under aspetic conditions at the left fourth interspace. A two-stage occlusion (90 min) of the left anterior descending coronary artery (LAD) and subsequent reperfusion through a critical stenosis produced a myocardial infarction. The animals were then closely monitored during recovery from anesthesia and returned to their kennel for complete surgical recovery.

The animals where then studied 3-9 days after the myocardial infarction. On the day of study, the animals were reanesthetized with pentobarbital and placed on a respirator, and a thoracotomy was performed to insert electrodes for cardiac stimulation and recording of cardiac conduction. Arterial blood gases were monitored during the experiment and respiration adjusted to maintain physiologic conditions. Isolation of the right carotid artery allowed for placement of a quadripolar HIS-bundle catheter. The heart was exposed and suspended in a pericardial cradle. An electromagnetic flow probe (Carolina Medical Electronics, Inc.) measured coronary artery blood flow through the LAD to establish patency of the vessel.

A quadripolar electrode was sewn onto the left atrial appendage to control the heart rate by atrial pacing and to record an atrial electrogram. A plunge bipolar electrode was sewn on the anterior ventricular wall at the junction of the left and right ventricle, i.e., interventricular septum, for introducing premature ventricular stimuli (4-ms duration; 2 × diastolic threshold square-wave pulses).

A preset control module (W-P Instruments, Inc., Model 842) triggered the ventricular stimulus from the R wave of the lead II EKG or from the normal zone electrogram. A Grass S8 stimulator and SIU-478 stimulus isolation unit were used for pacing during PES. The lead II EKG, arterial blood pressure, composite electrograms, atrial electrogram, and HIS-bundle electrogram were displayed on a multichannel oscillographic recorder (Model VR-12, Electronics for Medicine) and recorded on photographic paper.

Programmed electrical stimulation involved the introduction of one (S_2), two (S_2S_3), and three ($S_2S_3S_4$) premature ventricular stimuli to the right outflow tract during normal sinus rhythm or atrial pacing (180-220 bpm, 4-ms duration, 2 × threshold). In this manner, the effective refractory period (ERP) of normal myocardium was obtained and ventricular arrhythmias were induced. In this study, nonsustained tachycardia (NSVT) involved the production of at least three spontaneous ventricular beats in response to premature ventricular stimuli. Ventricular tachycardia lasting for at least 30 s was considered sustained (VT) and usually required an intervention to convert the animal to normal sinus rhythm. Animals that failed to display at least 2 "runs" of ventricular tachycardia at baseline were considered noninducible (NI).

Baseline electrophysiologic values (at a paced rate of 180-220 bpm), atrial and ventricular ERPs, and reproducible inducibility were determined as control data. Then, the dogs received cumulative intravenous doses of drug. Compounds **2** and **25** were tested as the (*E*)-2-butenedionate (2:1) salts which were dissolved in glass-distilled water (pH 6.7 and 6.1, respectively). Compound **20** (sotalol hydrochloride) was dissolved in saline and neutralized with NaOH (pH 6.7-7.0). Control experiments showed that these vehicles had no electrophysiologic activity (data not shown).

Statistical Analysis. A general linear models procedure was used to determine a two-way analysis of variance for data comparison. In this study, significance is defined as $p < 0.05$. All data are expressed as mean ± standard error of the mean.

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Registry No. 1, 100632-57-3; 2, 100632-81-3; 2·$^1/_2$fumarate, 130350-52-6; 3, 100632-58-4; 4, 100632-59-5; 5·HCl, 130350-53-7; 6, 3984-34-7; 7, 130350-54-8; 8, 130350-55-9; 8·$^3/_4$fumarate, 130350-56-0; 9, 100633-01-0; 10, 6328-00-3; 11, 130350-57-1; 12, 130350-58-2; 13, 130377-67-2; 14, 100632-78-8; 15, 5317-89-5; 17, 100632-63-1; 18, 5577-42-4; 19·HCl, 130350-59-3; 20, 959-24-0; 21, 68379-03-3; 22, 130350-60-6; 23·$^1/_2$fumarate, 130350-62-8; 24, 100632-86-8; 25·$^1/_2$fumarate, 130377-68-3; 26, 100632-84-6; 27, 130350-63-9; 28, 100632-82-4; 29·$^1/_2$fumarate, 130350-65-1; 30, 130350-66-2; 31, 130350-67-3; 32, 130350-68-4; 33, 130350-69-5; 34, 130350-70-8; 35, 100632-83-5; 39, 130350-71-9; 40, 130350-72-0; isobutyl chloroformate, 543-27-1; 4-methylpiperidine, 626-58-4; heptamethyleneimine, 1121-92-2; 1-ethyl-3-[3-(dimethylamino)-propyl]carbodiimide hydrochloride, 7084-11-9; potassium sodium tartrate, 304-59-6; ethylheptylamine, 66793-76-8; methanesulfonyl chloride, 124-63-0; methanesulfonanilide, 1197-22-4; succinic anhydride, 108-30-5.

Boron-Containing Thiouracil Derivatives for Neutron-Capture Therapy of Melanoma

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Boron-containing derivatives of 2-thiouracil and 2,4-dithiouracil and the corresponding 6-propyl compounds, containing a dihydroxyboryl group in the 5-position, have been prepared. These compounds accumulate in B16 melanoma in mice in concentrations up to 30 μg of boron per gram tissue. The uptake persists. The toxicity of both 2-thiouracil derivatives is low. These compounds are therefore good candidates for boron neutron-capture therapy of malignant melanoma.

Melanomas are tumors that derive from melanin-forming cells. They therefore are different in their metabolism from almost all other cells of the body due to their greatly enhanced synthesis of melanin. This metabolic difference can be used to selectively deliver substances to the tumor cells.

Cyclic thioureas, and especially 2-thiouracils, are known as specific melanoma seekers.[1,2] They are bound covalently to the newly formed melanin polymer via the sulfur. Their accumulation in melanomas therefore is both selective and persistent.

Neutron-capture therapy utilizes the property of the boron-10 nucleus to capture thermal (i.e. slow) neutrons and then undergo nuclear disintegration. The nuclear fragments (a ^{4}He and a ^{7}Li nucleus) are able to selectively

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