58-2; **8**·HCl, 84727-59-3; **9**, 84727-62-8; **9**·HCl, 84727-63-9; **10**, 84727-70-8; **10**·2HCl, 84727-71-9; **11**, 84727-84-4; **12**, 102396-30-5; **12**·HCl, 102396-41-8; **13**, 102396-31-6; **13**·HCl, 102396-42-9; **14**, 61973-58-8; **15**, 84727-88-8; **15**·HCl, 84707-98-2; **16**, 84708-05-4; **16**·HCl, 84708-06-5; **17**, 84708-07-6; **17**·HCl, 84708-08-7; **18**, 83199-77-3; **18**·HCl, 83199-78-4; **19**, 102396-32-7; **19**·HCl, 102396-43-0; **20**, 102396-33-8; **20**·HCl, 102396-44-1; **21**, 102396-34-9; **21**·HCl, 102396-45-2; **22**, 102396-35-0; **22**·HCl, 102396-46-3; **23**, 102396-36-1; **23**·HCl, 61973-50-0; **24**, 102396-37-2; **24**·HCl, 102396-47-4; **25**, 102396-29-2; **25**·HCl, 84727-77-5; **26**, 84708-09-8; **26**·HCl, 84727-80-0; **27**, 102396-39-4; **27**·HCl, 102396-48-5; **28**, 84727-44-6; **29**, 84727-49-1; **30**, 84727-61-7; **31**, 84727-69-5; **32**, 84727-83-3; **33**, 84727-78-6; **34**, 84727-81-1; **35**, 84727-79-7; **36**, 84727-82-2; **36** (X = Br), 102396-38-3; 5-methyl-2,4,6-trichloropyrimidine, 1780-36-5; 5-methylthio-2,4,6-trichloropyrimidine, 24795-76-4; 1,4-dimethylpiperazine, 106-58-1; 4-methyl-1-piperazinecarboxaldehyde, 7556-55-0; 4,6-dihydroxy-2-(*N*-methylpiperazino)pyrimidine, 81746-24-9; 5-chloro-4,6-dihydroxy-2-(*N*-methylpiperazino)pyrimidine, 84727-48-0; 4,6-dihydroxy-5-methoxy-2-(*N*-methylpiperazino)pyrimidine, 84727-60-6; 4,6-dihydroxy-5-methyl-2-(*N*-methylpiperazino)pyrimidine, 84727-68-4; 1-methyl-4-piperazinecarboxamidine, 45798-01-4.

Synthesis and Class III Antiarrhythmic Activity of (Phenylbut-2-enyl)ammonium Salts. Effect of Conformation on Activity

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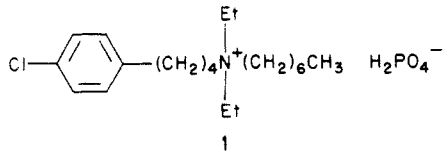
Berlex Laboratories, Inc., Cedar Knolls, New Jersey 07927. *Received September 23, 1985*

The syntheses of seven 4-(substituted phenyl)but-2-en(*or* yn)yl quaternary ammonium salts and four related tertiary amines are described. The Meerwein arylation reaction was the preferred synthetic method for the required intermediate 1-aryl-4-halo-2-butenes (**15a–c**, **18**). In the case of **18**, the trans stereochemistry of the Meerwein adduct of 2,3-dimethylbutadiene was established unambiguously by 2D NMR and X-ray studies. The title compounds represent conformationally restricted analogues of the class III antiarrhythmic agent clofilium (**1**) and exhibit comparable potency and efficacy in the in vitro evaluation using isolated canine Purkinje fibers. These results suggest that the alkylene chain in **1** is extended in the active conformation. Computer-aided conformational analysis (MM2) supports this conclusion. Selective catalytic hydrogen conditions were developed for the conversion of the unsaturated analogue **2** to clofilium (**1**) with minimal hydrogenolysis of the allylic quaternary ammonium moiety, thus completing a novel and efficient synthesis of this substance.

Sudden cardiac death is a major public health problem in the United States today.[1] Ventricular arrhythmias that progress to ventricular tachycardia and fibrillation are the most common cause of sudden cardiac death. We have been interested in the development of pure class III antiarrhythmic agents that are expected to be effective in ventricular arrhythmias caused by reentry mechanisms. According to the designation of antiarrhythmic agents defined by Vaughan Williams, a class III compound prolongs the action potential duration of the cardiac cell without depressing conduction in cardiac tissue.[2] Relatively few compounds of this type have been reported to date, and most, such as sotalol and amiodarone, possess other activities as well.[3]

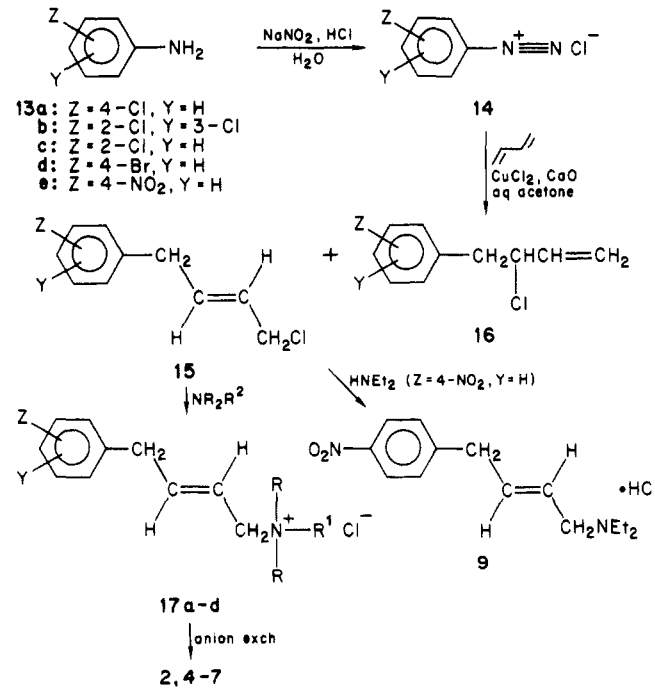
One compound that appears to exhibit pure class III activity is clofilium (**1**).[4] In this study the effect on class



1

III activity of introducing conformational restrictions between the phenyl ring and the quaternary nitrogen atom of the clofilium molecule was examined. The fully saturated four-carbon connecting chain of **1** allows the molecule to assume a variety of spatial orientations of the aromatic ring and the ammonium group including, in principle, a folded conformation in which the quaternary nitrogen interacts with the electron-rich π cloud of the aromatic

Scheme I. Synthesis of Ammonium Salts and Amines Employing the Meerwein Arylation Reaction of Butadiene



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(1) Bigger, J. T., Jr. *Am. J. Cardiol.* **1984**, *53*, 813.
(2) Vaughan Williams, E. M. In *Symposium on Cardiac Arrhythmias*; Sandoe, E., Flensted-Jansen, E., Olesen, K. H., Eds.; AB Astra: Sodertalje, Sweden, 1970; pp 449–472.
(3) Vaughan Williams, E. M. *J. Clin. Pharmacol.* **1984**, *24*, 129.

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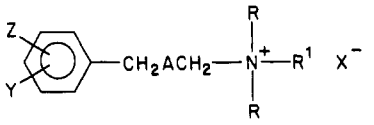
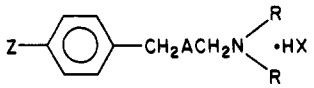
Table I. Unsaturated Quaternary Ammonium Salts



	Z	Y	A	R	R^1	X	mp, °C	recryst solvent	elemental anal.
2a	4-Cl	H	(*E*)-CH=CH	CH_2CH_3	$(CH_2)_6CH_3$	$H_2PO_4^-·0.2H_3PO_4·0.6H_2O$	55		C, H, N, Cl, P
2b	4-Cl	H	(*E*)-CH=CH	CH_2CH_3	$(CH_2)_6CH_3$	TsO^-	132–132.5	2-butanone	C, H, N, Cl, S
3	4-Cl	H	(*Z*)-CH=CH	CH_2CH_3	$(CH_2)_6CH_3$	TsO^-	79–80	ethyl acetate	C, H, N
4	2-Cl	3-Cl	(*E*)-CH=CH	CH_2CH_3	$(CH_2)_6CH_3$	TsO^-	105–106		C, H, N, Cl, S
5	2-Cl	H	(*E*)-CH=CH	CH_2CH_3	$(CH_2)_6CH_3$	$Cl^-·H_2O$	63–63.5		C, H, N
6	4-Br	H	(*E*)-CH=CH	CH_2CH_3	$(CH_2)_6CH_3$	$H_2PO_4^-$	82–83	acetone/ether	C, H, N, Br, P
7	4-Cl	H	(*E*)-CH=CH	CH_3	CH_3	Cl^-	178–180	acetonitrile	C, H, N
8	4-Cl	H	C≡C	CH_2CH_3	CH_2CH_3	I^-	157–158	acetonitrile/ether	C, H, N

Table II. Unsaturated Tertiary Amines



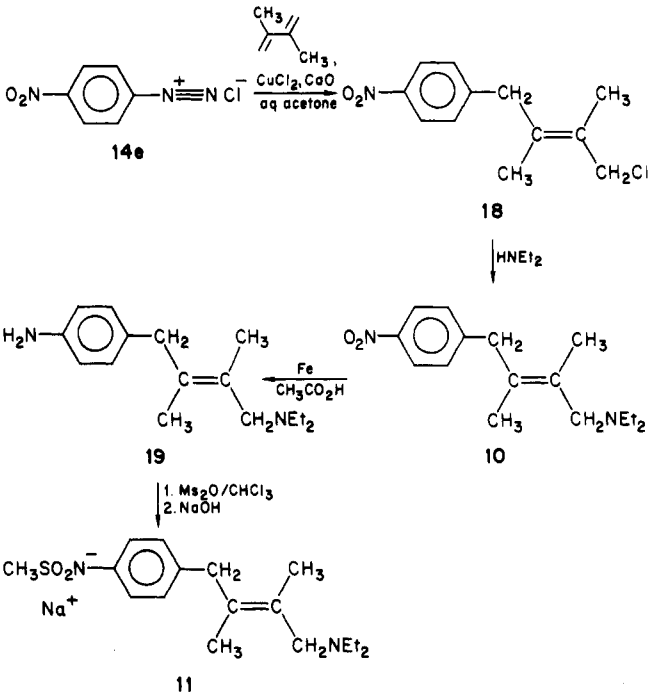
	Z	A	R	HX	mp, °C	recryst solvent	elemental anal.
9	4-NO_2	(*E*)-CH=CH	CH_2CH_3	HCl·0.7H_2O	134–135	acetone	C, H, N
10	4-NO_2	(*E*)-C(CH_3)=C(CH_3)	CH_2CH_3	HCl	193–195	ethanol	C, H, Cl, N
11	4-CH_3SO_2NH-	(*E*)-C(CH_3)=C(CH_3)	CH_2CH_3	Na^+ salt·2.5H_2O	205–207		C, H, N, Na, S
12	4-Cl	C≡C	CH_2CH_3	HCl	106–108	ethyl acetate	C, H, N

ring. A folded conformation would partially mask the positive charge on the quaternary nitrogen, rendering the molecule more lipophilic and could affect bioavailability and transport across the cell membrane. Modifications of the connecting chain to limit the degrees of conformational freedom would provide information about the folded conformation and also about the orientation and steric requirements at the "class III site of action".[5] To this end we have prepared a series of analogues of clofilium (**1**) with unsaturation between the 2,3-positions of the four-carbon connecting chain. Reported here are the syntheses and cardiac electrophysiological activities of these unsaturated quaternary ammonium salts and related unsaturated tertiary amines.

Chemistry. The unsaturated quaternary ammonium salts **2–8** synthesized for this study are listed in Table I.[6] The tertiary amines **9–12** are shown in Table II. The nitro compounds **9** and **10** were prepared in analogy to reported saturated 4-(nitrophenyl)butanamines.[7]

The key step in the synthesis of compounds **2**, **4–7**, and **9–11** was the Meerwein arylation reaction[8] (See Scheme I). This method provides a convenient way of attaching an end-functionalized four-carbon atom chain to an aromatic ring. Diazotization of the appropriately substituted aniline **13** with sodium nitrite in hydrochloric acid gave the corresponding diazonium salt **14**. The aqueous solution of **14** was added to a solution of butadiene, copper(II) chloride, and calcium oxide in aqueous acetone to afford the mixture of allylic chlorides **15** and **16**, resulting from 1,4-addition and 1,2-addition, respectively. The predominant isomer in all cases was the desired 1,4-addition product **15**. Stereochemistry at the double bond of **15** was established by NMR (Coupling constants for the vinyl protons in **15** were ca. 15 Hz). For the subsequent reaction

Scheme II. Synthesis of Amines Employing the Meerwein Arylation Reaction of 2,3-Dimethylbutadiene



step it was not necessary to separate **15** and **16** since both compounds afforded ammonium salt **17** when reacted with tertiary amines.[9] When necessary the ammonium chloride **17** was treated with basic anion-exchange resin and titrated with an appropriate acid to provide a crystalline salt.

All attempts to react **15e** (4-NO_2 substituent) with tertiary amines to give the corresponding quaternary ammonium salts proved unsuccessful. The major product isolated from the reaction was 1-(4-nitrophenyl)butadiene.

(4) (a) Steinberg, M. I.; Molloy, B. B. *Life Sci* **1979**, *25*, 1397. (b) Molloy, B. B.; Steinberg, M. I. U.S. Patent 4 289 787, 1981.
(5) Clofilium has been shown to decrease the outward potassium current: Snyders, D. J.; Katzung, B. G. *Circulation, Suppl. III*, **1985**, *72*, 233.
(6) Lumma, W. C., Jr.; Wohl, R. A. EP 134424, 1984.
(7) Molloy, B. B.; Steinberg, M. I. U.S. Patent 4 336 269, 1982.
(8) Rondestvedt, C. S., Jr. *Org. React.* **1976**, *24*, 225.
(9) Compound **15** affords **17** by an S_N2 pathway, whereas compound **16** provides **17** by an S_N2' mechanism. Isomer **15** could be reacted selectively in the presence of **16** by using milder reaction conditions; the unreacted **16** was removed on aqueous workup.

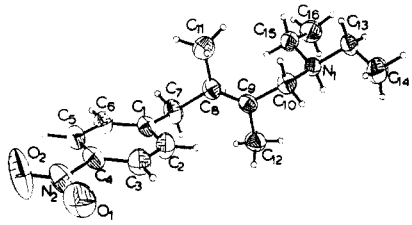


Figure 1. Perspective drawing of the cation portion of the hemioxalate complex of **10** determined by X-ray analysis showing the trans stereochemistry C_8–C_9 double bond.

However, **15e** reacted with diethylamine to provide the tertiary amine **9**.

An analogous Meerwein reaction was used to prepare amines **10** and **11** (Scheme II). Reaction of diazonium salt **14e** with 2,3-dimethylbutadiene afforded a mixture of allylic chlorides with **18** as the major product. The mixture was not separated but was reacted directly with diethylamine to provide tertiary amine **10** in 49% yield.

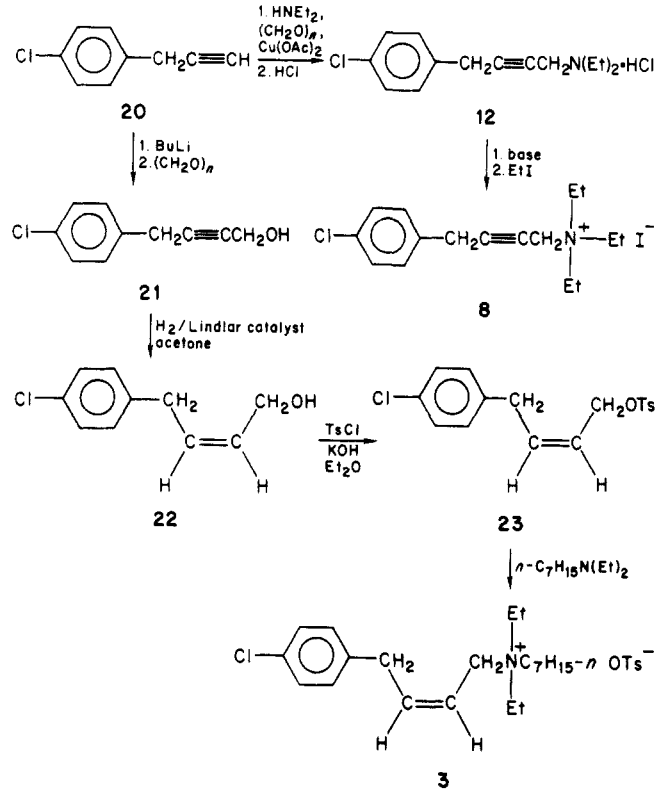
Although the Meerwein reaction of 2,3-dimethylbutadiene is inferred in the literature to give the trans adduct,[10] no physical data were given to support this assignment. The trans stereochemistry of **10** was established by 2D NOE (nuclear Overhauser enhancement) studies. The 2D NOE spectrum showed an enhancement between the methyl groups and the adjacent vicinal methylene groups. No enhancement was seen between the two methyl groups. Similar results were obtained from a 1 D NOE analysis. Therefore, the methyl groups are on opposite sides of the double bond in **10**. The trans stereochemistry was further confirmed by an X-ray analysis of the hydrochloride hemioxalate complex of **10** (Figure 1).

Reduction of the nitro group in **10** was accomplished with iron in acetic acid to afford aniline **19**. Further reaction of aniline **19** with methanesulfonic anhydride in chloroform, followed by precipitation with aqueous sodium hydroxide, provided the sodium salt **11**.

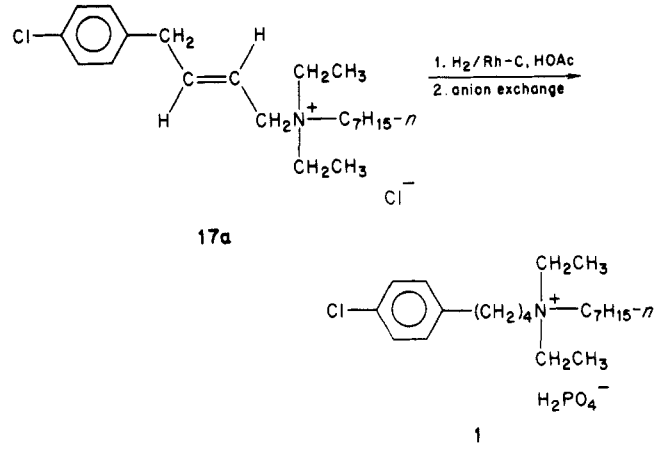
The preparation of the cis olefinic quaternary ammonium salt **3** and the acetylenic compounds **8** and **12** proceeded from the common intermediate, 3-(4-chlorophenyl)propyne (**20**)[11] (Scheme III). Nef synthesis of **20** with paraformaldehyde afforded the acetylenic alcohol **21**.[12] Catalytic reaction of the triple bond in **21** employing Lindlar catalyst[13] provided the cis olefinic alcohol **22**. Conversion of **22** to the corresponding crystalline tosylate ester **23** was accomplished using tosyl chloride and powdered potassium hydroxide in diethyl ether. Attempted preparation of **23** by reaction of **22** with tosyl chloride in pyridine was not successful. Reaction of **23** with 4 equiv of *N,N*-diethylheptanamine[14] in acetonitrile afforded ammonium salt **3**. The (*Z*) configuration of the double bond in **3** was confirmed by NMR (the vinyl proton coupling constant in compound **3** is 11 Hz).

Mannich reaction of **20** with diethylamine and paraformaldehyde in the presence of copper(II) acetate yielded the acetylenic amine **12**. Quaternization of **12** with iodoethane afforded the acetylenic target **8**.

Scheme III. Preparation of (*Z*) Quaternary Ammonium Salt **3** and Acetylenic Compounds **8** and **12**



Scheme IV. Preparation of Clofilium Phosphate (**1**) from **17a**



Reduction of compound **17a** would constitute a novel and practical synthesis of clofilium. We investigated the reduction of **17a** by several methods. Hydrogenation of **17a** over palladium on carbon or platinum on carbon in a variety of solvents (ethanol, dimethylformamide, methylene chloride) all led to partial or complete hydrogenolysis of the quaternary ammonium group. Diimide and diborane reductions were also unsuccessful. Finally, we found that **17a** could be converted in good yield to clofilium (**1**) (chloride) by catalytic hydrogenation over rhodium on carbon in acetic acid. Anion exchange provided the phosphate salt in 57% overall yield (Scheme IV).[6]

Pharmacology. The class III antiarrhythmic activity of all new compounds was evaluated via standard microelectrode electrophysiological techniques in isolated canine Purkinje fibers.[15] The effects of the compounds on action potential duration (APD) and the rate of rise of

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Table III. Intracellular Electrophysiology in Canine Purkinje Fiber of Unsaturated Quaternary Ammonium Salts and Amines

	n^a	dose range, μM	C_{20} APD_{95},[b] μM	max APD_{95} % (concn, μM)[c]	max $\dot{V}_{max}$, % (concn, μM)[d]
2a	3	0.01–10.0	0.1	28 (10)	minimal
		0.01–10.0	1.9	29 (10)	minimal
		0.01–10.0	3.4	23 (10)	minimal
2b	3	0.01–10.0	3.5	23 (10)	minimal
		0.01–10.0	0.01	42 (10)	minimal
		0.01–10.0	0.21	47 (10)	minimal
3	3	0.1–10.0	<0.1	84 (10)	minimal
		0.01–10.0	1.9	24 (10)	−7 (10)
		0.01–10.0	1.4	32 (10)	minimal
4	1	0.1–10.0	2.0	35 (10)	minimal
5	2	0.1–1.0	<0.1	72 (1)	minimal
		0.1–10.0	NR[e]	16 (10)	minimal
6	1	0.1–10.0	5.7	23 (10)	minimal
7	1	0.1–10.0	0.3	43 (10)	minimal
8	1	0.1–10.0	0.3	53 (10)	−6 (10)
9	1	0.1–10.0	0.9	25 (10)	−13 (10)
10	3	0.1–10.0	0.4	27 (1)	minimal
		0.1–100.0	<0.1	66 (10)	−28 (100)
		0.01–100.0	0.05	55 (10)	−52 (100)
11	1	0.1–100.0	2.2	78 (100)	−13 (100.0)
12	1	0.1–100.0	NR[e]	−6 (100)	−34 (100μM)
1	6	0.01–1.0	0.2	29 (1.0)	minimal
		0.01–1.0	0.13	46 (1.0)	minimal
		0.01–1.0	0.3	78 (1.0)	minimal
		0.01–10.0	2.0	27 (10.0)	minimal
		0.01–1.0	0.6	25 (1.0)	minimal
		0.01–1.0	0.3	29 (1.0)	−21 (1.0)

[a] Number of studies done. Data for each experiment shown. [b] Concentration of compound that caused a 20% prolongation of APD_{95}. [c] Maximum prolongation of APD_{95} observed and the concentration at which this occurred. [d] Maximum observed effect on $\dot{V}_{max}$ and the concentration at which this occurred. Minimal, ≤5% change. [e] NR = not reached.

phase 0 of the action potential ($\dot{V}_{max}$) were simultaneously determined. Our criterion for selective in vitro class III electrophysiological activity is a greater than 20% prolongation of the action potential duration at 95% repolarization (APD_{95}) with minimal (<20%) decrease of $\dot{V}_{max}$. A decrease in $\dot{V}_{max}$ generally is correlated with a slowing of electrical conduction in the tissue and is defined as class I antiarrhythmic activity.[2] The results of the in vitro experiments for the new compounds and the standard, clofilium (1), are summarized in Table III.

After our criterion for in vitro class III activity was met, compounds were assessed for bioavailability in anesthetized dogs by determining the change in cardiac functional refractory period (FRP) after intraduodenal (i.d.) administration. The FRP was measured using the method of Carson and Dresel.[16] A compound was considered bioavailable in this model if it prolonged the FRP by at least 12–15% in two of three animals studied. The effects of the compound on heart rate and blood pressure were measured during nonpacing intervals. The results of the bioavailability study are listed in Table IV.

Selected compounds were further evaluated for antiarrhythmic efficacy in the dog in a programmed electrical stimulation (PES) model.[17] This model is analogous to those used to determine antiarrhythmic efficacy in the clinical setting for arrhythmia patients.[18] In the efficacy model, dogs that had undergone a coronary ligation according to the method of Harris[19] were studied after 24 h. The animals were anesthetized, the chest was reopened, and stimulating and recording electrodes were attached to the myocardium. Before the test compound was administered, the animals were subjected to a programmed electrical stimulation protocol to induce sustained ventricular tachycardia (SVT) or ventricular fibrillation (VF). SVT was terminated by burst pacing; VF was terminated by electrocountershock. The test compound was then administered and the inducibility redetermined. The compound was considered effective if SVT or VF could not be reinduced in two of three test animals. The results of the PES efficacy studies are listed in Table V.

Table IV. Intraduodenal Bioavailability in Anesthesized Dogs of Unsaturated Quaternary Ammonium Salts and Amines

	n^a	dose range[b] low/high, mg/kg	LV-FRP[c,d] low/high, %	HR[c] low/high, %	mean PB[c] low/high, %
2a	3	10/30	9/14	−25/−33	6/−7
		1/3	7/14	−5/−12	−4/−4
		1/3	6/16	−4/−14	4/7
3	2	10/30	12/23	13/−25	11/−11
		10/30	6/7	−21/−5	19/25
4	1	10/60	5/10	−3/−4	13/23
5	2	10/30	5/12	−2/−19	6/2
		10/30	9/16	−1/−9	8/8
6	2	10/30	26/32	−21/−29	−13/+19
		3/10	4/12	3/−1	30/47
7	2	10/30	5/1	−13/−30	7/26
		10/30	7/6	−8/−38	8/49
8	2	10/30	8/27	−19/−50	27/−15
		10/30	15/28	−24/−56	11/−19
9	2	30/10	10/14	−16/−18	−6/0
		30/10	14/28	−11/−28	10/31
10	2	10/30	11/44	−5/−47	19/3
		3	19	−10	9
11	3	10/30	11/15	−16/−35	2/16
		10/30	2/3	−3/−13	9/−18
		10/30	8/12	−13/−29	14/6
12					
1		3/10	10/22	−9/−24	−7/−11
		1/3	−1/2	−2/6	−2/−14
		1/3/10	4/4/23	−1/−7/−11	−3/0/4

[a] Number of animals studied. Data for each experiment shown. [b] Animals generally given two doses of test compound, the second value being a cummulative dose. [c] Values reported as percent changes from control for the low dose/high dose. [d] LV-FRP = left ventricular functional refractory period.

Table V. In Vivo Antiarrhythmic Efficacy in Anesthetized Dogs for Selected Compounds

	no. effective/no. tested	eff doses (iv), mg/kg		no. effective/no. tested	eff doses (iv), mg/kg
2a	2/2	0.3	**10**	2/2	0.1, 0.3
5	2/2	0.3, 1.0	**1**	2/3	0.1, 0.5[a]
6	2/2	1.0, 3.0			

[a] Ineffective at 3 mg/kg.

Discussion

An examination of the in vitro data (Table III) for ammonium salts of **2** (*trans*-2-butenyl connecting chain), **3** (*cis*-2-butenyl connecting chain), **8** (2-butynyl connecting chain), and clofilium (1) show that all four compounds exhibit comparable class III potency and efficacy in the Purkinje fiber screen. This indicates that conformational restrictions imposed by unsaturation at the 2,3-position of the connecting chain do not adversely affect the activity of the compounds. The activity of **8** in the in vitro tests

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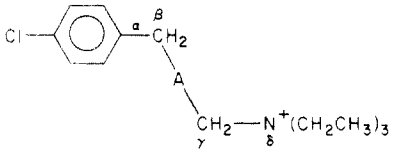
Table VI. Calculated Steric Energies and Distances for $ClC_6H_4CH_2ACH_2N^+(CH_2CH_3)_3$[a,b]



A	conformn	steric energy, kcal	ring center–N^+ dist, Å
CH_2CH_2	CA[c]	32.0	4.4[e]
	ext[d]	27.0	7.7[f]
(*E*)-CH=CH	CA	21.6	5.6[e]
	ext	16.9	7.1[g]
(*Z*)-CH=CH	CA	22.3	4.9[e]
	ext	23.2	6.7[g]
C≡C	CA	16.3	5.9[h]
	ext	17.1	7.1[i]

[a] MDL-CHEMLAB II version of Allinger's MM2 program employed for calculations. [b] Conformations restricted for initial calculations and then restrictions removed for final calculation. [c] CA = close approach. [d] ext = extended conformation. [e] Folded conformation—quaternary nitrogen over plane or ring. [f] Dihedral angles from α through connecting chain to δ 180 ± 1.50°. [g] Ring and quaternary nitrogen on opposite sides of the double-bond plane. [h] α, β, γ, δ dihedral angle 17.8°. [i] α, β, γ, δ dihedral angle 176.6°.

also rules out the requirement of a close interaction between the π cloud of the aromatic ring and the ammonium center of the drug molecule in the active conformation since this is an impossible conformation for the acetylene **8**.

In order to further assess the conformations for these compounds, molecular mechanics calculations were performed on a series of model triethylammonium cations related to **1**, **2**, **3**, and **8**. Local minima were calculated for both a "close-approach" and an extended conformation, and the distance from the center of the benzene ring to the quaternary nitrogen for these conformations was determined. Table VI summarizes the results of these calculations. The steric energy differences between the extended and close-approach conformations are not large enough to rule out any of the conformations on energetic grounds alone. The acetylenic compound **8** possesses the largest close-approach distance, calculated at 5.8 Å (see Table VI). Clearly, the other active compounds are not required to assume folded conformations, with close-approach distances of less than 5.8 Å. Similarly, the maximum distance separating the two moieties is estimated at 6.7 Å from the cis compound.[20]

Changing the substituent pattern on the aryl moiety (compare compounds **2**, **4**, and **6**) in the trans compounds does not affect the overall activity of the compounds in the dose range studied. A long alkyl moiety on the quaternary nitrogen may not be required for efficacy since compound **7**, which contains a trimethylammonium moiety, is comparable to other active compounds. The long chain may be necessary to make the compound bioavailable (See Table IV).

While no direct comparisons are available among the tertiary amines, it is notable that compound **12** with a 4-chloro substituent was not effective as a class III agent in vitro but the tertiary amines with a 4-nitro or a 4-(methylsulfonyl)amino moiety had activity comparable to **1**. It is tempting to speculate from the above results that the hydrophilicity of the molecule is important for class III activity. That is, a decrease in hydrophilic character (i.e., ammonium group → tertiary amine) in one part of the molecule must be offset by an increase in hydrophilic character (4-Cl → 4-O_2N or 4-CH_3SO_2NH) in the aromatic moiety in order to maintain class III activity.

None of the active compounds showed significant conduction slowing (decrease in $\dot{V}_{max}$) at their C_{20} APD_{95} (see Table III). Only the tertiary amines **10** and **12** exhibited a strong decrease in $\dot{V}_{max}$ and this only at high concentrations.

The in vivo data indicate that the trans ammonium salt **2** and trans tertiary amine **9** have bioavailability comparable to that of clofilium (**1**). Compound **7**, which contains a trimethylammonium moiety, is not bioavailable while compound **8**, which possesses a triethylammonium group, and **2**–**6**, which contain the diethylheptylammonium moiety, are bioavailable. This suggests that a certain degree of lipophilicity is needed for large ammonium species to cross intestinal membranes. The percent bioavailability for compounds **1**, **2a**, **5** and **6** can be estimated from a comparison of intravenous dose in the in vivo efficacy model with the intraduodenal dose from the bioavailability studies. In the bioavailability studies the effective doses were approximately 10 times higher than the doses needed for efficacy. This suggests that the bioavailability for these compounds, including **1**, is ca. 10%. Such a low bioavailability has been observed previously for other quaternary ammonium salts.[21]

The effect of the compounds on heart rate after intraduodenal administration was consistent; when significant class III activity was observed (increase in LV-FRP), there was a corresponding decrease in heart rate. Blood pressure effects of the test compounds were variable and in most cases moderate. The variability of this parameter is probably due to the anesthesia used in this model (sodium pentobarbital).

The four compounds **2**, **5**, **6**, and **10** studied in the efficacy model were equieffective with clofilium (**1**).

Conclusion

We have shown that conformational restrictions induced by unsaturation in the connecting chain between the aromatic ring and the quaternary ammonium moiety have little or no effect on the class III activity of a series of clofilium analogues either in vitro or in vivo. The present studies indicate that a folded conformation of **1** is not required for class III activity since this is not possible in compounds **2** and **8**. We suggest, therefore, that the most likely conformation at the active site is one in which the distance between the center of the benzene ring and the quaternary nitrogen lies between 5.8 and 6.7 Å. The new compounds exhibit comparably low gastrointestinal bioavailability as observed for clofilium (**1**) in our models.

Experimental Section

Melting points were taken on a Fisher-Johns or a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by the Berlex Analytical Section, Cedar Knolls, NJ, Galbraith Laboratories, Knoxville, TN, or Microlit Laboratories, Caldwell, NJ, and results were within ±0.4% of the calculated values. NMR spectra were recorded on either a Varian EM-360 (60-MHz) or a Varian XL-300 (300-MHz) spectrometer. Tetramethylsilane was used as the internal standard in all solvents except D_2O, where 2,2,3,3-tetradeuterio-3-(trimethylsilyl)propanoic acid sodium salt was employed. Coupling constants are accurate to ±0.6 Hz. IR spectra were obtained on either a Beckman Acculab 2 or a Beckman 4230 spectrometer. All NMR and IR spectra were consistent with the assigned structures. X-ray

(20) The center of the ring to nitrogen distance in the oxalate complex of **10** is 7.1 Å, determined from the X-ray data.

(21) Levine, R. *Arzneim. Forsch.* **1966**, *16*, 1373.

structural analysis was performed by Crystalytics Co., Lincoln, NB.

General Procedure for the Meerwein Reaction. Preparation of Substituted (4-Chloro-2-butenyl)benzenes (15). To a suspension of (0.89 mol) of aniline **13** in 300 mL of water was added 200 mL of concentrated hydrochloric acid. The mixture was heated to reflux for 20 min and then cooled to 0 °C. To this suspension was added dropwise a solution of (0.89 mol) of sodium nitrite in 90 mL of water. The temperature was not allowed to exceed 0 °C. The resulting solution of diazonium salt **14** was added dropwise to a cold (−15 °C) mixture of 1,3-butadiene (120 mL), copper(II) chloride (27.6 g, 0.2 mol), and calcium oxide (32.9 g, 0.59 mol) in 1500 mL of acetone and 90 mL of water. After the addition was complete, the reaction mixture was allowed to warm gradually to room temperature and stand overnight. The two phases were separated, and the aqueous layer was extracted with three 600-mL portions of diethyl ether. The combined organic phases were washed with three 400-mL portions of saturated sodium chloride solution. The organic extracts were treated with 3 g of charcoal and 500 g of silica gel, filtered, and evaporated in vacuo to provide crude **15** and **16**. When necessary, the crude product mixture was further purified by vacuum distillation.

(*E*)-1-Chloro-4-(4-chloro-2-butenyl)benzene (15a)[22] and 1-Chloro-4-(2-chloro-3-butenyl)benzene (16a). 4-Chloroaniline gave ca. 6:1 mixture of **15a** and **16a**: bp 72 °C (0.15 mmHg); NMR ($CDCl_3$) (**15a**) δ 3.36 (d, 2 H, J = 6.7 Hz, $ArCH_2$), 4.05 (d, 2 H, J = 6.5 Hz, CH_2Cl), 5.66 (m, 1 H, $=CHCH_2Cl$), 5.89 (m, 1 H, $ArCH_2CH=$), 7.10 (d, 2 H, Ar), 7.27 (d, 2 H, Ar); (**16a**) 3.08 (d 2 H, J = 7 Hz, $Ar\ CH_2$), 4.49 (m, 1 H, CHCl), 5.12–5.25 (m, 2 H, $=CH_2$), 5.87 (m, 1 H, $CH=CH_2$), 7.14 (d, 2 H, Ar), 7.28 (d, 2 H, Ar); ratio of $ArCH_2$ protons for **15a**:**16a**, ca. 6:1.

(*E*)-1-(4-Chloro-2-butenyl)-2,3-dichlorobenzene (15b) and 1-(2-Chloro-3-butenyl)-2,3-dichlorobenzene (16b). 2,3-dichloroaniline gave ca. 9:1 mixture of **15b** and **16b**, bp 109–113 °C (0.25 mmHg). Anal. ($C_{10}H_9Cl_3$) C, H, Cl.

(*E*)-1-Chloro-2-(4-chloro-2-butenyl)benzene (15c) and 1-Chloro-2-(2-chloro-3-butenyl)benzene (15b). 2-Chloroaniline gave ca. 7:1 mixture of **15c** and **16c**, undistilled.

(*E*)-1-Bromo-4-(4-chloro-2-butenyl)benzene (15d) and 1-Bromo-4-(2-chloro-3-butenyl)benzene (16d). 4-Bromoaniline gave ca. 4:3 mixture of **15d** and **16d**, bp 91–94 °C (0.04–0.07 mmHg) [lit.[23] bp of **15d** 118–122 °C (0.5 mmHg)].

(*E*)-1-(4-Chloro-2-butenyl)-4-nitrobenzene (15e) and 1-(2-Chloro-3-butenyl)-4-nitrobenzene (16c). 4-Nitroaniline gave ca. 3:1 mixture of **15e** and **16e**, undistilled.

(*E*)-1-(4-Chloro-2,3-dimethyl-2-butenyl)-4-nitrobenzene (18). 4-Nitroaniline and 2,3-dimethylbutadiene afforded **18** as the major component of a mixture of halides, as judged by NMR, which was used without further purification.

General Procedure for the Preparation of Quaternary Ammonium Chlorides (17). The mixture of halides **15** and **16** was heated with the tertiary amine either neat at 80–140 °C or in refluxing acetonitrile or propionitrile. When the reaction was complete, as judged by thin-layer chromatography, the solvent was removed in vacuo (if necessary) and the reaction residue dissolved in water. The aqueous solutions were extracted with diethyl ether (discarded) and then with several portions of methylene chloride. The combined methylene chloride extracts were washed with 5% hydrochloric acid and then with water and dried over anhydrous magnesium sulfate. Removal of the drying agent and evaporation of the solvent gave the crude ammonium salt **17**.

General Procedure for Anion-Exchange Chromatography of Quaternary Ammonium Chloride (17). Biorad AG-1-X8, hydroxide form, anion-exchange resin was pretreated with 2 N sodium hydroxide (low chloride) solution and then washed with distilled water until the eluate was pH 7. A 2-equiv portion of resin was used for each 1 equiv of salt to be exchanged. The crude ammonium chlorides **17a,b,d** were applied to the column as a solution either in water or in aqueous methanol and were eluted with deionized water. The eluates with pH ≥8 were combined, washed with diethyl ether, and then titrated with the appropriate acid. For monobasic acids (e.g., TsOH) the solutions were titrated to pH 6.5; for phosphoric acid the solutions were titrated to pH 4.5 to obtain the 1:1 salt. Removal of the water was accomplished by freeze-drying or by rotary evaporation. The crude salts were then further purified by trituration or recrystallization.

(*E*)-4-(4-Chlorophenyl)-*N*,*N*-diethyl-*N*-heptyl-2-butenaminium 4-Methylbenzenesulfonate (2b). A solution of 35.6 g (0.18 mol) of **15a** and **16a** and 27.7 g (0.16 mol) of *N*,*N*-diethyl-1-heptanamine[14] in 220 mL of acetonitrile was heated at reflux for 6 h. Workup follwed by anion-exchange chromatography, titration with 4-methylbenzenesulfonic acid solution, and evaporation of solvent provided the crude salt. Recrystallization from 2-butanone afforded 46.3 g (52%) of **2b** as a white solid: ^1H NMR (Me_2SO-d_6) δ 0.86 (t, 3 H, $(CH_2)_6CH_3$), 1.15–1.35 (m, 14 H), 1.57 (m, 2 H), 2.29 (s, 3 H, TsO^-), 3.05 (m, 2 H), 3.20 (quar, 4 H, NCH_2CH_3), 3.45 (d, 2 H, J = 7.8 Hz, $ArCH_2$), 3.84 (d, 2 H, J = 2.5 Hz, CH_2N), 5.75 (dt, 1 H, J = 14.9 Hz, J = 7.5 Hz, $=CHCH_2N$), 6.19 (dt, 1 H, J = 14.9 Hz, J = 7.2 Hz, $ArCH_2CH=$), 7.11 (d, 2 H, TsO^-), 7.27 (d, 2 H, Ar), 7.37 (d, 2 H, Ar), 7.47 (d, 2 H, TsO^-).

(*E*)-4-(4-Chlorophenyl)-*N*,*N*-diethyl-*N*-heptyl-2-butenaminium Phosphate (1:1) 0.75 Hydrate (2a). Anion-exchange chromatography of 1.0 g of **2b** followed by titration with 1 M H_3PO_4 provided 0.75 g (85%) of **2a**.

(*E*)-4-(2,3-Dichlorophenyl)-*N*,*N*-diethyl-*N*-heptyl-2-butenaminium 4-Methylbenzenesulfonate (4). A mixture of 5.0 g (21 mmol) of **15b** and **16b** and 3.61 g (21 mmol) of *N*,*N*-diethyl-1-heptanamine was heated at 140 °C for ca. 6 h. Workup followed by anion-exchange chromatography, titration with 4-methylbenzenesulfonic acid solution, and evaporation of solvent afforded the product as a yellow oil. Trituration of the oil with diethyl ether provided 2.0 g (18%) of **4** as a tan solid: NMR (Me_2SO-d_6) δ 3.63 (d, 2 H, J = 6.4 Hz, $ArCH_2$), 3.86 (d, 2 H, J = 7.3 Hz, CH_2N), 5.73 (dt, 1 H, J = 15.2 Hz, J = 7.5 Hz, $=CHCH_2N$), 6.17 (dt, 1 H, J = 15.2 Hz, J = 6.3 Hz, $ArCH_2CH=$).

(*E*)-4-(2-Chlorophenyl)-*N*,*N*-diethyl-*N*-heptyl-2-butenaminium Chloride Hydrate (5). A mixture of 11.01 g (52 mmol) of **15c** and **16c** and 9.15 (53 mmol) of *N*,*N*-diethyl-1-heptanamine was heated at 115 °C for 2.5 h. Trituration of the crude product with ethyl acetate yielded 5.0 g (24%) of **5** as a white solid: NMR (Me_2SO-d_6) δ 3.57 (d, 2 H, J = 6.7 Hz, $ArCH_2$), 3.86 (d, 2 H, J = 6.9 Hz, CH_2N), 5.70 (dt, 1 H, J = 15.3 Hz, J = 7.1, $=CHCH_2N$), 6.19 (dt, 1 H, J = 15.3 Hz, J = 6.4 Hz, $ArCH_2CH=$).

(*E*)-1-(4-Bromophenyl)-*N*,*N*-diethyl-*N*-heptyl-2-butenaminium Phosphate (1:1) 1.2 Hydrate (6). A solution of 16.9 g (69 mmol) of **15d** and **16d** and 10.3 g (60 mmol) of *N*,*N*-diethyl-1-heptanamine in 50 mL of propionitrile was heated at reflux for 8 h. Workup followed by anion-exchange chromatography, titration with 1 M H_3PO_4, and freeze-drying gave the crude phosphate salt. Two recrystallizations from acetone/diethyl ether provided 1.95 g (6.5%) of **6** as a yellow solid: NMR (Me_2SO-d_6) δ 3.43 (d, 2 H, J = 6.7 Hz, $ArCH_2$), 3.85 (d, 2 H, J = 6.92 Hz, $=CHCH_2N$), 5.74 (dt, 1 H, J = 15.0 Hz, J = 7.3 Hz, $=CHCH_2N$), 6.17 (dt, 1 H, J = 15.0 Hz, J = 7.0 Hz, $ArCH_2CH=$).

(*E*)-4-(4-Chlorophenyl)-*N*,*N*,*N*-trimethyl-2-butenaminium Chloride (7). A mixture of 4.4 g (22 mmol) of **15a** and **16a** and 4.7 g (80 mmol) of trimethylamine was heated at 80 °C for 2 h in a pressure tube. The mixture was cooled and the excess trimethylamine evaporated to give 5.41 g of crude material, which was triturated with two portions of diethyl ether and three portions of ethyl acetate and then recrystallized from ethyl acetate to yield **7** as a white solid: NMR (300 MHz, Me_2SO-d_6) δ 3.47 (d, 2 H, J = 6.7 Hz, $ArCH_2$), 3.93 (d, 2 H, J = 7.5 Hz, $=CHCH_2N$), 5.78 (dt, 1 H, J = 14.9 Hz, J = 7.3 Hz, $=CHCH_2N$), 6.13 (dt, 1 H, J = 14.9 Hz, J = 6.7 Hz, $ArCH_2CH=$).

(*E*)-*N*,*N*-Diethyl-4-(4-nitrophenyl)-2-buten-1-amine Hydrochloride 0.7 Hydrate (9). A mixture of 30 g (0.14 mol) of **15e** and **16e** was added dropwise to 250 mL of diethylamine at 0–10 °C. The reaction mixture was stirred overnight and warmed to room temperature. At this time the excess diethylamine was evaporated and the residue dissolved in 250 mL of ethyl acetate. The organic solution was extracted with two 100-mL portions of 10% hydrochloric acid solution. The combined acidic extracts were made basic with solid potassium carbonate and extracted with three 100-mL portions of diethyl ether. The combined ether extracts were treated with charcoal and anhydrous magnesium sulfate. Removal of the drying agent and evaporation of the

(22) Muller, E. *Angew. Chem.* **1949**, *61*, 179.
(23) Ropp, G. A.; Coyner, E. C. *J. Am. Chem. Soc.* **1950**, *72*, 3960.

solvent provided the crude free base as an oil. The oil was dissolved in 100 mL of ethanol, and 1.5 equiv of concentrated hydrochloric acid was added. The solution was evaporated to dryness and the residue crystallized from tetrahydrofuran. Recrystallization from acetone afforded **9** as a tan solid: NMR (Me_2SO-d_6) δ 1.21 (t, 6 H, NCH_2CH_3), 3.04 (m, 4 H, NCH_2CH_3), 3.60 (d, 2 H, J = 7.2 Hz, $ArCH_2$), 3.69 (dd, 2 H, J = 6.7 Hz, J = 4.8 Hz, $=CHCH_2N$) 5.73 (dt, 1 H, J = 15.3 Hz, J = 7.2 Hz, $=CHCH_2N$), 6.15 (dt, 1 H, J = 15.3 Hz, J = 6.7 Hz, $ArCH_2CH$), 7.52 (d, 2 H, Ar), 8.20 (d, 2 H, Ar).

(*E*)-*N*,*N*-Diethyl-2,3-dimethyl-4-(4-nitrophenyl)-2-buten-1-amine Hydrochloride (10). In a similar manner as that for **9**, 70 g of **18** was added to diethylamine to yield **10** as a white solid: NMR ($CDCl_3$) δ 1.47 (t, 6 H, CH_2CH_3), 1.77 (s, 3 H, CH_3), 2.24 (s, 3 H, CH_3), 3.04 (m, 2 H, CH_2CH_3), 3.23 (m, 2 H, CH_2CH_3), 3.62 (s, 2 H, $ArCH_2$), 3.70 (d, 2 H, $=CHCH_2N$), 7.33 (d, 2 H, Ar), 8.19 (d, 2 H, Ar).

(*E*)-4-(4-Aminophenyl)-*N*,*N*-diethyl-2,3-dimethyl-2-buten-1-amine (19). To a solution of 10.0 g (34 mmol) of **10** in 200 mL of acetic acid and 50 mL of water was added 30.0 g (0.54 mol) of iron powder. The mixture was stirred vigorously, and the temperature rose gradually to 50 °C. After ca. 30 min the residual solids were removed by filtration. The filtrate was made basic with saturated sodium carbonate solution and extracted with two 400-mL portions of ethyl acetate. The combined ethyl acetate extracts were treated with charcoal and dried over anhydrous magnesium sulfate. Removal of the drying agent and evaporation of solvent gave 7.5 g (85%) of **19** as a red oil that was used without further purification.

(*E*)-*N*-[4-[4-(Diethylamino)-2,3-dimethyl-2-buten-1-yl]-phenyl]methanesulfonamide Sodium Salt 2.5 Hydrate (11). To a solution of 4.0 g (16 mmol) of **19** in 100 mL of chloroform was added 2.8 g (16 mmol) of methanesulfonic anhydride. The reaction mixture was refluxed for 18 h and then evaporated to dryness. The residue was dissolved in water and made basic (pH 14) with 50% sodium hydroxide solution. The resulting precipitate was collected, triturated in ethanol, and dried to give 2.9 g (46%) of **11** as a white solid: NMR (Me_2SO-d_6) δ 0.93 (t, 3 H, CH_2CH_3), 1.56 (s, 3 H, CH_3), 1.74 (s, 3 H, CH_3), 2.38 (quar, 4 H, CH_2CH_3), 2.49 (s, 3 H, CH_3SO_2N), 2.91 (s, 2 H), 3.16 (s, 2 H), 6.68 (d, 2 H, Ar), 6.71 (d, 2 H, Ar).

4-(4-Chlorophenyl)-2-butyn-1-ol (21).[12] To a solution of 150.6 g (1.0 mol) of 1-chloro-4-(2-propynyl)benzene (**20**)[11] in 600 mL of anhydrous diethyl ether cooled to −78 °C under a nitrogen atmosphere was added dropwise 400 mL of 2.5 M *n*-butyllithium in hexane. The solution was stirred for 30 min after the addition was complete. To this solution of the propargyl anion was added 31 g of paraformaldehyde (1 mol equiv of formaldehyde). The reaction mixture was stirred at −78 °C for 1 h and then allowed to warm to room temperature over an additional 1 h. Then, 400 mL of saturated sodium chloride solution was added. The biphasic system was separated, and the aqueous layer was extracted with two 100-mL portions of diethyl ether. The combined ether extracts were washed with water and dried over anhydrous magnesium sulfate. Removal of the drying agent and evaporation of solvent gave an oil that crystallized on cooling. The solid was triturated with cyclohexane and filtered to give 102.5 g (57%) of **21**: mp 30–32 °C; NMR agrees with that reported previously.[12]

(*Z*)-4-(4-Chlorophenyl)-2-buten-1-ol (22). A solution of 10.0 g (0.055 mol) of **21** in 100 mL of acetone was hydrogenated at atmospheric pressure over 0.6 g of freshly prepared Lindlar catalyst.[13] The reaction was complete after 2 days as monitored by NMR. The catalyst was removed by filtration through Celite, and the Celite was washed with four 30-mL portions of methylene chloride. Evaporation of solvent afforded 8.1 g (81%) **22** as an oil: NMR ($CDCl_3$) δ 2.03 (br s, 1 H, OH) 3.37 (d, 2 H, $ArCH_2$), 4.27 (d, 2 H, CH_2OH), 5.33–5.97 (m, 2 H, vinylic), 6.92–7.37 (m, 4 H, Ar).

(*Z*)-4-(4-Chlorophenyl)-2-buten-1-ol 4-Methylbenzenesulfonate (23). To a suspension of 6.7 g (0.036 mol) of **22** and 3.2 g (0.049 mol) of 85% potassium hydroxide in 100 mL of anhydrous diethyl ether, cooled to 0–5 °C, was added a solution of 7.0 g (0.037 mol) of tosyl chloride in 30 mL of anhydrous diethyl ether. The mixture was stirred at 0–5 °C for 30 min and then overnight at room temperature. After filtration of the solids, the ether solution was washed with saturated sodium bicarbonate solution and water and then dried over anhydrous magnesium sulfate. Removal of the drying agent and evaporation of solvent provided the crude product that was triturated with three portions of cyclohexane and then recrystallized from cyclohexane to give **23** as a white solid: mp 55–56 °C; NMR δ 2.42 (s, 3 H, TsO), 3.32 (d, 2 H, $ArCH_2C=$), 4.72 (d, 2 H, CH_2OTs), 5.35–6.15 (m, 2 H, vinylic), 7.08 (d, 2 H, Ar), 7.35 (d, 2 H, Ar), 7.48 (d, 2 H, TsO), 7.87 (d, 2 H, TsO).

(*Z*)-4-(4-Chlorophenyl)-*N*,*N*-diethyl-*N*-heptyl-2-butenaminium 4-Methylbenzenesulfonate (3). A solution of 5.40 g (0.016 mol) of **23** and 10.9 g (0.064 mol) of *N*,*N*-diethyl-1-heptanamine in 200 mL of acetonitrile was stirred for 2 h at room temperature. The solvent was then evaporated; the residue was triturated with petroleum ether and recrystallized from ethyl acetate to obtain 7.4 g (91%) of **3** as a white solid: NMR (Me_2SO-d_6) δ 0.86 (t, 3 H, $(CH_2)_6CH_3$), 1.10–1.30 (m, 14 H), 1.50 (m, 2 H), 2.29 (s, 3 H, TsO^-), 3.15 (m, 2 H), 3.28 (quar, 4 H, NCH_2CH_3), 3.54 (d, 2 H, J = 7.5 Hz, $ArCH_2$), 4.05 (d, 2 H, J = 7.8 Hz, $=CHCH_2N$), 5.76 (dt, 1 H, J = 11 Hz, J = 7.5 Hz), 6.10 (dt, 1 H, J = 11 Hz, J = 7.8 Hz), 7.11 (d, 2 H, TsO^-), 7.26 (d, 2 H, Ar), 7.38 (d, 2 H, Ar), 7.46 (d, 2 H, TsO^-).

4-(4-Chlorophenyl)-*N*,*N*-diethyl-2-butyn-1-amine Hydrochloride (12). A mixture of 30.1 g (0.20 mol) of **20**, 15.4 g (0.21 mol) of diethylamine, 6.3 g of paraformaldehyde (0.21 mol equiv of formaldehyde), and 4.2 g (0.021 mol) of copper(II) acetate monohydrate in 80 mL of dioxane was heated at 90 °C for 16 h. The solvent was then evaporated in vacuo and the residue dissolved in 200 mL of methylene chloride. The methylene chloride solution was washed several times with water and then extracted with two 100-mL portions of 2 N hydrochloric acid. The acid extracts were made basic (pH 14) with 4 N sodium hydroxide. The basic solution was then extracted with three 100-mL portions of methylene chloride. The combined organic extracts were washed with water and dried over anhydrous magnesium sulfate. Removal of the drying agent and evaporation of the solvent gave 45 g of the free base as a brown oil. The free base was converted to the hydrochloride and recrystallized four times from ethyl acetate to give 21 g (39%) of **12** as a light tan solid: IR (KBr) 2240 (C≡C) cm^{-1}; NMR ($CDCl_3$) δ 1.50 (t, 6 H), 3.22 (quin, 4 H), 3.67 (m, 2 H, $ArCH_2$), 4.01 (m, 2 H, CH_2N), 7.33 (S, 4 H, Ar).

4-(4-Chlorophenyl)-*N*,*N*,*N*-triethyl-2-butyn-1-aminium Iodide (8). A 10.9 g (0.04 mol) portion of **12** was dissolved in a minimal amount of water and made basic (pH 14) with ca. 20 mL of 4 N sodium hydroxide solution. The basic solution was extracted with methylene chloride. The organic extract was washed with four portions of water and then dried over anhydrous magnesium sulfate. Removal of the drying agent and evaporation of solvent provided 9 g of free base. The amine was heated at 90 °C for 15 min with 6 mL (0.075 mol) of ethyl iodide. The reaction mixture was allowed to cool to room temperature overnight. The resulting solid was triturated with diethyl ether to give 11 g of crude product. Recrystallization from acetonitrile/diethyl ether afforded 9.6 g (61%) of **8** as an off-white solid: IR (KBr) 2190 (C≡C) cm^{-1}; NMR ($CDCl_3$) δ 1.43 (t, 9 H, CH_3), 3.62 (quar, 6 H, NCH_2CH_3), 3.73 (t, 2 H), 4.43 (t, 2 H), 7.32 (s, 4 H, Ar).

Preparation of 4-Chloro-*N*,*N*-diethyl-*N*-heptylbenzenebutanaminium Phosphate (1:1) (1) from 17a. A solution of 2.1 g (5.6 mmol) of **17a** in 100 mL of glacial acetic acid was hydrogenated over 0.11 g of 5% rhodium on charcoal at atmospheric pressure. After 19 h the reaction was complete and the catalyst was removed by filtration. The filtrate was diluted with 100 mL of water and extracted with four 100-mL portions of methylene chloride. The combined extracts were washed with 100 mL of 1 N hydrochloric acid, two 250-mL portions of saturated sodium bicarbonate solution, and 200 mL of saturated sodium chloride solution and then dried over anhydrous sodium sulfate. Removal of the drying agent and evaporation of the solvent gave 2.8 g of oil. This oil was dissolved in 75 mL of 50% aqueous methanol and applied to an anion-exchange resin (Biorad-AG-1-X8, hydroxide form) column. The column was eluted with water. Fractions with a pH ≥9 were collected and combined. The basic solution was titrated with 10% phosphoric acid to pH 4.5. The water was removed in vacuo, and the residual oil was triturated with diethyl ether and then dried [25 °C (0.1 mmHg)] to afford 1.25 g (51%) of **1** as a solid. NMR, TLC, R_f value, and HPLC

retention time were identical with that of a sample of authentic clofilium phosphate (1:1) (1) obtained from Eli Lilly.

Pharmacology. Intracellular Electrophysiological Profile. Canine cardiac Purkinje fibers were anchored in a tissue bath and perfused at a rate of 6 mL/min with modified Tyrode's solution (concentration (mmol/L): Na^+, 156.7; K^+, 4.0; Mg^{2+}, 0.5; Ca^{2+}, 2.5; Cl^-, 145.9; $H_2PO_4^-$, 1.8; HCO_3^-, 18.0; glucose, 5.0). The solution was gassed with a 95:5 O_2/CO_2 mixture (pH 7.35–7.40) and maintained at 37 ± 0.5 °C. The tissues were stimulated at a control rate of 1.0 Hz through bipolar Teflon-coated platinum electrodes with square wave pulses of 2-ms duration and 2 times the diastolic threshold current. Intracellular potentials were recorded with glass microelectrodes (3 M KCl) using standard electrophysiological techniques.[15] Parameters measured were resting membrane potential, threshold current, action potential amplitude, maximum upstroke velocity, and action potential duration at 50% and 95% repolarizations. Fibers were stabilized for up to 1 h before control measurements were taken. Test compounds were screened in the range of 10^{-8}–10^{-4} M concentrations. Data were collected for each compound after 30 min of exposure to a given concentration.

Intraduodenal Bioavailability. Normal healthy dogs (8–20 kg) of either sex were anesthetized with sodium pentobarbital (30 mg/kg, i.v.). Following induction of anesthesia, the dogs were mechanically respired. Respiratory parameters were adjusted to maintain blood gases within acceptable limits. Lead II ECG and esophageal temperature were monitored throughout the experiment. The right femoral artery and vein were cannulated to monitor blood pressure (BP) and for the administration of fluids, respectively. A longitudinal incision (2 in.) was made at the umbilicus along the linea alba and the duodenum isolated. A small incision was made into the duodenum and a catheter (PE 240) inserted for compound administration. The heart was exposed through a lateral thoracotomy, and sliver bipolar plaque electrodes were sutured onto the surface of the right atrium and the left ventricle (LV). Unipolar Teflon-coated stainless-steel plunge electrodes were positioned close to the endocardial surface under the left ventricular recording plaque. A towel clamp served as the stimulus anode for unipolar cathodal stimulation of the LV. The animal was then allowed to equilibrate 15–30 min before any experimental determinations were made.

Heart rate (HR) and blood pressure (BP) were determined prior to any stimulation. The LV functional refractory period (FRP) was obtained by sequential pacing of the atria and ventricles at a basic cycle length of 300–450 ms using 2-ms pulses at a stimulus intensity 4 times the diastolic threshold (4DT). A single premature stimulus (S2) was delivered at the same ventricular site following 15 driving stimuli (S1) at decreasing intervals (S1–S2) until ventricular refractoriness occurred. Transmural conduction time was determined for each S1–S2 interval that produced a propagated ventricular response. Transmural conduction time was measured as the time interval from the stimulus introduction to the peak of the local LV electrogram.

Prior to compound administration, HR and BP were again measured. The test compound was administered via the intraduodenal catheter as a homogeneous suspension using 0.5% tragacanth as the vehicle. After administration of the test compound, HR, BP, right atrial DT, left ventricular DT, FRP, and CI curves were determined at 15-, 30-, and 45-min postdose. If there was a greater than 12–15% change in FRP and/or conduction time after 45-min postdose, no second dose was administered. Additional measurements at 15–30-min intervals were made to determine the time course of the observed effects on FRP and/or conduction time. If the test compound failed to produce an effect on FRP and/or conduction time (i.e., 12–15% change from control), a second intraduodenal dose was administered and the above procedure repeated. If the second intraduodenal dose failed to change the FRP and/or conduction time (less than 5%), then an intravenous dose of 3 mg/kg (as base) was given as a positive control.

Antiarrhythmic Efficacy. Evaluation of antiarrhythmic efficacy was determined by the procedure of Scherlag et al.[17]

X-Ray Crystallography. Hydrochloride **10** and 0.5 mol equiv of oxalic acid dihydrate were heated in methanol until complete solution occurred. The solvent was removed in vacuo and the residue recrystallized from acetonitrile/ethyl acetate to provide crystals for the X-ray studies: mp 135–142 °C. The crystals were triclinic of the space group P_1–C_1^1. The cell parameters found from preliminary X-ray experiments were a = 7.442 (2) Å, b = 11.920 (3) Å, c = 12.791 (3) Å, α = 110.04 (2)°, β = 113.24 (2)°, and γ = 96.13 (3)° for Z = 2. A computer-controlled four-circle Nicolet autodiffractometer equipped with Mo K$\bar{\alpha}$ radiation (λ = 0.710 73 Å) was used to measure 4325 unique reflections with $2\theta \leq 55°$. Of these 3053 were observed ($I \geq 3\sigma I$) and corrected for Lorentz and polarization effects. The structure was solved by using the Nicolet SHELXTL interactive crystallogrpahic program and refined by using a cascade block-diagonal matrix least squares. The function minimized was $\sum w(|F_o| - |F_c|)^2$ with $w = 1/(\sigma F)^2$ to give an unweighted residual value of 0.046 and a weighted value of 0.051. Tables VII–XI in the supplementary material contain the final fractional coordinates, temperature parameters, bond distances, and bond angles. Figure 1 is a perspective drawing of the cation protion of the hemioxalate complex of **10** generated from X-ray coordinates.

Acknowledgment. We thank the Berlex Analytical Section for analytical support of this project, in particular we thank Dr. C. A. Evans for acquisition and interpretation of 2D NMR spectra. We are grateful to Ellen Ambelas, Michael Doroshuk, Roy Winters, and Ronald Barbati, who carried out the pharmacological experiments. Finally, we thank Drs. Jay Wiggins and Jeffrey Hill for helpful discussions during the course of the study.

Registry No. 1, 68379-02-2; **2a**, 98011-75-7; **2b**, 102285-40-5; **3**, 98011-78-0; **4**, 102285-42-7; **5**, 102285-43-8; **6**, 102285-45-0; **7**, 102285-46-1; **8**, 102285-47-2; **9**, 102285-48-3; **10**, 102285-49-4; **11**, 102285-50-7; **12**, 102285-51-8; **13a**, 106-47-8; **13b**, 608-27-5; **13c**, 95-51-2; **13d**, 106-40-1; **13e**, 100-01-6; **14a**, 2028-74-2; **14b**, 73260-77-2; **14c**, 89-90-7; **14d**, 2028-85-5; **14e**, 100-05-0; **15a**, 97163-33-2; **15b**, 102285-52-9; **15c**, 102285-53-0; **15d**, 102285-54-1; **15e**, 102285-55-2; **16a**, 98011-63-3; **16b**, 102285-56-3; **16c**, 102285-57-4; **16d**, 102285-58-5; **16e**, 102285-59-6; **17a**, 98011-73-5; **17b**, 102285-60-9; **17d**, 102285-61-0; **18**, 102285-62-1; **19**, 102285-63-2; **20**, 70090-69-6; **21**, 34905-12-9; **22**, 98011-68-8; **23**, 98011-69-9; $C_7H_{15}NEt_2$, 26981-81-7.

Supplementary Material Available: Fractional coordinates and isotropic thermal parameters, anisotropic thermal parameters, hydrogen atom coordinates, bond lengths, and bond angles in the hemioxalate complex of **10** (Tables VII–IX) and a summary of the syntheses (6 pages). Ordering information is given on any current masthead page.