1, 2, 3, 4, 5, and 6 h later. The ID_{50} value is the dose of test agent required to reduce hyperthermic response to the standard dose of fenfluramine by 50%.

Registry No. 1, 85274-64-2; **2**, 110486-57-2; **3**, 19069-84-2; **4**, 70751-26-7; **5**, 89080-92-2; **6**, 89080-93-3; **7**, 89081-03-8; **8**, 28563-01-1; **9**, 110486-58-3; **10**, 89090-29-9; **11**, 89090-96-0; **12**, 85274-46-0; **13**, 85274-48-2; **14**, 89081-06-1; **15**, 110486-59-4; **16**, 110486-60-7; **17**, 2859-30-5; **18**, 85273-99-0; **19**, 85274-81-3; **20**, 85274-82-4; **21**, 85274-80-2; **22**, 85274-79-9; **23**, 85274-01-7; **24**, 85274-83-5; **25**, 85274-86-8; **26**, 85274-00-6; **27**, 85274-88-0; **28**, 85274-84-6; **29**, 85274-85-7; **30**, 85274-87-9; **31**, 110486-61-8; **32**, 73863-47-5; **33**, 85274-57-3; **34**, 110486-62-9; **35**, 85274-89-1; **36**, 85274-90-4; **37**, 85274-91-5; **38**, 85274-92-6; **39**, 85275-18-9; **40**, 110486-63-0; **41**, 110486-64-1; **42**, 110486-65-2; **43**, 85274-56-2; **44**, 2859-50-9; **45**, 57876-69-4; **46**, 67525-28-4; **47**, 85273-92-3; **48**, 85274-50-6; **49**, 79249-33-5; **50**, 110486-66-3; **51**, 85274-12-0; **52**, 110486-67-4; **53**, 110486-68-5; **54**, 85274-51-7; **55**, 110486-69-6; **56**, 110486-70-9; **57**, 85274-52-8; **58**, 85274-53-9; **59**, 85274-54-0; **60**, 110486-71-0; **61**, 85274-02-8; **62**, 89080-84-2; **63**, 89080-83-1; **64**, 110486-72-1; **65**, 89081-01-6; **66**, 89080-98-8; **67**, 89081-04-9; **68**, 110487-07-5; **68**·HCl, 85275-04-3; **69**, 85274-03-9; **69**·HCl, 85274-04-0; **70**, 85273-95-6; **70**·HCl, 85273-96-7; **71**, 85275-10-1; **71**·oxalate, 85275-11-2; **72**, 110487-08-6; **72**·HCl, 85275-08-7; **73**, 110487-09-7; **73**·HCl, 85273-97-8; **74**, 110487-10-0; **74**·HCl, 85274-77-7; **75**, 110487-11-1; **75**·HCl, 85274-75-5; **76**, 110487-12-2; **76**·HCl, 85274-67-5; **77**, 110487-05-3; **77**·HCl, 85274-76-6; **78**, 110487-13-3; **78**·HCl, 85274-68-6; **79**, 110487-14-4; **79**·HCl, 85273-98-9; **80**, 110487-15-5; **80**·HCl, 85274-78-8; **81**, 110487-16-6; **81**·HCl, 85274-74-4; **82**, 110487-17-7; **82**·HCl, 85274-66-4; **83**, 110487-18-8; **83**·HCl, 85274-65-3; **84**, 110487-19-9; **84**·HCl, 85285-20-7; **85**, 110487-20-2; **85**·HCl, 85274-69-7; **86**, 85275-19-0; **86**·HCl, 85275-20-3; **87**, 110487-21-3; **87**·HCl, 85274-70-0; **88**, 110487-22-4; **88**·HCl, 85274-71-1; **89**, 110487-23-5; **89**·HCl, 85274-73-3; **90**, 110487-24-6; **90**·HCl, 85274-72-2; **91**, 110487-25-7; **91**·2HCl, 85274-30-2; **92**, 85274-31-3; **92**·oxalate, 85274-32-4; **93**, 85274-33-5; **93**·oxalate, 85274-34-6; **94**, 85274-35-7; **94**·oxalate, 85274-36-8; **95**, 85274-41-5; **95**·oxalate, 85274-42-6; **96**, 85274-39-1; **96**·oxalate, 85274-40-4; **97**, 89081-24-3; **97**·oxalate, 110486-73-2; **98**, 89081-07-2; **98**·oxalate, 110486-74-3; **99**, 110486-75-4; **99**·oxalate, 110486-76-5; **100**, 110486-77-6; **101**, 110486-78-7; **102**, 110487-26-8; **102**·oxalate, 110486-79-8; **103**, 110486-80-1; **104**, 85274-18-6; **104**·oxalate, 85274-17-5; **105**, 110486-82-3; **105**·oxalate, 110486-81-2; **106**, 89081-28-7; **106**·oxalate, 110486-83-4; **107**, 89081-34-5; **107**·oxalate, 110486-84-5; **108**, 110509-41-6; **108**·HCl, 110486-85-6; **109**, 110487-27-9; **109**·2HCl, 110486-86-7; **110**, 110487-28-0; **110**·2HCl, 110486-87-8; **111**, 85273-93-4; **111**·HCl, 85273-94-5; **112**, 110486-88-9; **112**·oxalate, 110486-89-0; **113**, 85274-15-3; **113**·oxalate, 85274-16-4; **114**, 110487-29-1; **114**·HCl, 85274-19-7; **115**, 85274-20-0; **115**·oxalate, 85274-21-1; **116**, 110486-90-3; **116**·oxalate, 110486-91-4; **117**, 85274-13-1; **117**·oxalate, 85274-14-2; **118**, 110486-92-5; **118**·oxalate, 110486-93-6; **119**, 110487-30-4; **119**·HCl, 110486-94-7; **120**, 110487-31-5; **120**·2HCl, 110486-95-8; **121**, 110486-96-9; **121**·oxalate, 110486-97-0; **122**, 85274-22-2; **122**·oxalate, 85274-23-3; **123**, 85274-24-4; **123**·oxalate, 85274-25-5; **124**, 85274-26-6; **124**·oxalate, 85274-27-7; **125**, 89081-32-3; **125**·oxalate, 110486-98-1; **126**, 89081-16-3; **126**·oxalate, 110486-99-2; **127**, 110487-00-8; **127**·oxalate, 110487-01-9; 2-$H_3CCOC_6H_4NHCOCH_2C_6H_5$, 41296-66-6; 2,2'-$H_3CCOC_6H_4NHCOCH_2C_6H_4OCH_3$, 70779-65-6; 2,4'-$H_3CCOC_6H_4NHCOCH_2C_6H_4F$, 89080-86-4; 3-$H_3CCOC_6H_4CH(CH_3)_2$, 7766-63-4; $H_2N(CH_2)_2SH$·HCl, 156-57-0; $(CH_3)_2N(CH_2)_2SH$·HCl, 13242-44-9; $(C_2H_5)_2N(CH_2)_2SH$·HCl, 1942-52-5; $H_3CCOCH_2CONHC_6H_5$, 102-01-2; $H_3CCHBrCH_3$, 75-26-3; $H_3CNH(CH_2)_2Cl$·HCl, 4535-90-4; 2'-acetyl-1-thienylacetanilide, 110487-02-0; 2,4-dichloro-3-phenylquinoline, 108832-15-1; 2,4-dichloro-3-(4-fluorophenyl)quinoline, 110487-03-1; 2,4-dichloro-3-(2-methylphenyl)quinoline, 89090-28-8; 2,4-dichloro-3-(3-thienyl)quinoline, 110487-04-2; 2-chloro-3-phenyl-4-carbamoylquinoline, 110487-06-4; 2-(2-(*N*-methyl-*N*-acetylamino)ethylthio)-3-phenylquinoline, 85275-09-8; thiourea, 62-56-6.

Synthesis and Cardiac Electrophysiological Activity of 2- and 3-[(Substituted phenyl)alkyl]quinuclidines. Structure-Activity Relationships

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Berlex Laboratories, Inc., Cedar Knolls, New Jersey 07927. *Received December 10, 1986*

The syntheses and cardiac electrophysiological effects of 21 2- and 3-substituted quinuclidines and some quaternary ammonium derivatives are described. The 2-substituted quinuclidines **2**–**8** were prepared by alkylation of 2-methylene-3-quinuclidinone. The Wittig reaction with 3-quinuclidinone afforded the 3-substituted derivative **9**, which was subsequently converted to **10** and **11**. The electrophysiological profiles of the compounds were determined in canine cardiac Purkinje fibers and ventricular muscle strips. The 3-[(substituted phenyl)alkyl]quinuclidines selectively increased action potential duration (Vaughan Williams class III activity). In the 2-substituted series some of the compounds both increased action potential duration and decreased conduction velocity (class I activity). For some of the 2-substituted quinuclidines, appropriate substitution of the phenyl ring was shown to be a requirement for significant class III electrophysiological activity. Selected compounds were efficacious in a programmed electrical stimulation model in the anesthetized dog.

Although there are a variety of antiarrhythmic agents in use, most of these are class I antiarrhythmic drugs (Vaughan Williams classification).[1] This type of agent slows conduction in cardiac tissue. Since arhythmias can result from a variety of etiologies, treatment of arrhythmias by class I agents is not always effective. Clearly there is a need for alternate therapeutic approaches. One approach that is beginning to receive attention is the use of class III antiarrhythmic agents. This type of agent increases the refractory period of cardiac tissue with minimal effects on conduction. There are few agents in use that exhibit selective class III activity. Amiodarone, sotalol, and bretylium are designated as class III agents but possess other actions as well.[2] Clofilium phosphate (**1**) is a clinically effective, selective class III antiarrhythmic agent;[3] however,

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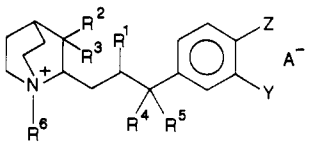
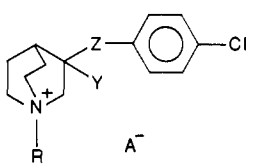
Table I. 2-[(Substituted phenyl)alkyl]quinuclidines



no.	Z	Y	R^1	R^2, R^3	R^4, R^5	R^6	A^-	mp, °C	recrystn solvent	anal.
2a	H	H	H	=O	=O	H	Cl^-	244–246 dec	EtOH	C, H, N
2b	Cl	H	H	=O	=O	H	Cl^-	257–260 dec	H_2O	C, H, N
2c	NO_2	H	H	=O	=O	H	Cl^-	255–260 dec	EtOH	C, H, N
2d	$NHSO_2CH_3$	H	H	=O	=O	H	$Cl^-·0.5H_2O$	281–282	MeOH	C, H, Cl, N, S[a]
2e	Cl	NO_2	H	=O	=O	H	Cl^-	265–267	MeOH	C, H, N
2f	Cl	$NHSO_2CH_3$	H	=O	=O	H	Cl^-	276–278 dec	MeOH	C, H, N
3a	H	H	$COCH_3$	=O	=O	H	Cl^-	215–217	EtOH	C, H, N
3b	Cl	H	$COCH_3$	=O	=O	H	Cl^-	228–233 dec	MeOH	C, H, Cl, N
3c	NO_2	H	$COCH_3$	=O	=O	H	Cl^-	227–229 dec	MeOH	C, H, N
4c	NO_2	H	CO_2Et	=O	=O	H	Cl^-	209–211 dec	acetone	C, H, N
4d	$NHSO_2CH_3$	H	CO_2Et	=O	=O	H	$Cl^-·0.25H_2O·0.25CH_3CN$	90–100	CH_3CN	C, H, Cl, N, S
4e	Cl	NO_2	CO_2Et	=O	=O	H	Cl^-	204–207 dec		C, H, N
4f	Cl	$NHSO_2CH_3$	CO_2Et	=O	=O	H	$Cl^-·0.25H_2O$	197–200 dec	EtOH	C, H, Cl, N, S
5a	H	H	H	=O	H, H	H	Cl^-	178–180	IPA	C, H, Cl, N
5b	Cl	H	H	=O	H, H	H	Cl^-	179–181	IPA	C, H, Cl, N
6	Cl	H	H	H, OH	H, H			137–138	CH_3CN	C, H, Cl, N[b]
7	Cl	H	H	H, H	H, H	H	$Cl^-·0.1H_2O$	210–212	IPA	C, H, Cl, N
8	Cl	H	H	=O	H, H	*n*-heptyl	$H_2PO_4^-·2H_2O$	145–148	H_2O	C, H, Cl, N, P

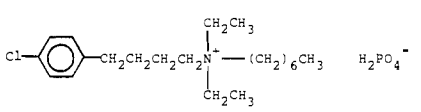
[a] Cl: calcd, 8.96; found, 9.52. [b] Cl: calcd, 12.67; found, 12.18.

Table II. 3-Substituted Quinuclidines



no.	Y, Z	R	A^-	mp, °C	recrystn solvent	anal.
9	(*E*) $=CHCH_2-$	H	Cl^-	285 dec	MeOH	C, H, N
10	(*E*) $=CHCH_2-$	$(CH_2)_6CH_3$	Br^-	176–180 dec	IPA	C, H, Cl, N
11	H, $-CH_2CH_2-$	$(CH_2)_6CH_3$	Br^-	145–147.5	acetone + H_2O (99 + 1)	C, H, Cl, N

the oral bioavailability of this compound is low. In a previous paper[4] we reported on the effect on class III activity and bioavailability associated with conformational restrictions in the connecting chain between the phenyl moiety and the ammonium group in a series of clofilium-like compounds. In pursuit of an orally active selective class III agent, we have examined the electrophysiological profile and bioavailability of compounds that constrain the quaternary ammonium moiety of **1** to the rigid cage skeleton of 2- and 3-substituted 1-azoniabicyclo[2.2.2]octanes (quinuclidinium salts) (Figure 1). We also report on the electrophysiological activity of some related non-quaternary quinuclidines. The results of the studies are described below.



1

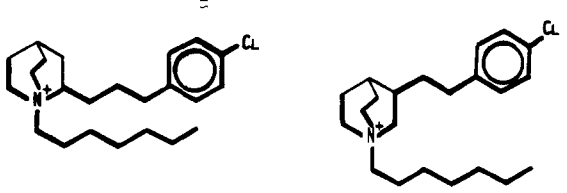


Figure 1. Clofilium framework in boldface.

Chemistry

The 2-substituted quinuclidines (**2–8**) synthesized for this work are shown in Table I; the 3-substituted quinuclidines (**9–11**) are listed in Table II.[5]

For the synthesis of the 2-substituted quinuclidines, 2-methylene-3-quinuclidinone (**12**), prepared by reaction of 2-(hydroxymethyl)-1-azabicyclo[2.2.2]octane-3,3-diol hydrochloride (**13**) with aqueous potassium carbonate,[6] was employed (Scheme I). Treatment of **12** with the appropriate benzoylacetone in a procedure modified from Bondarenko et al.[7] afforded the acetyl compounds **3a–c**. Hydrolysis of **3a** and **3b** in aqueous hydrochloric acid readily proceeded to give diketones **2a** and **2b**, respectively. The synthesis of **2a** and **3a** has been described previously by Bondarenko and co-workers. Wolff–Kishner reduction of **2b** provided amine **7**. Hydrolysis of **3c** under the above conditions produced **2c** contaminated with 4-nitrobenzoic acid due to debenzoylation of **3c**, which was competitive with deacetylation for this compound. Extraction of the

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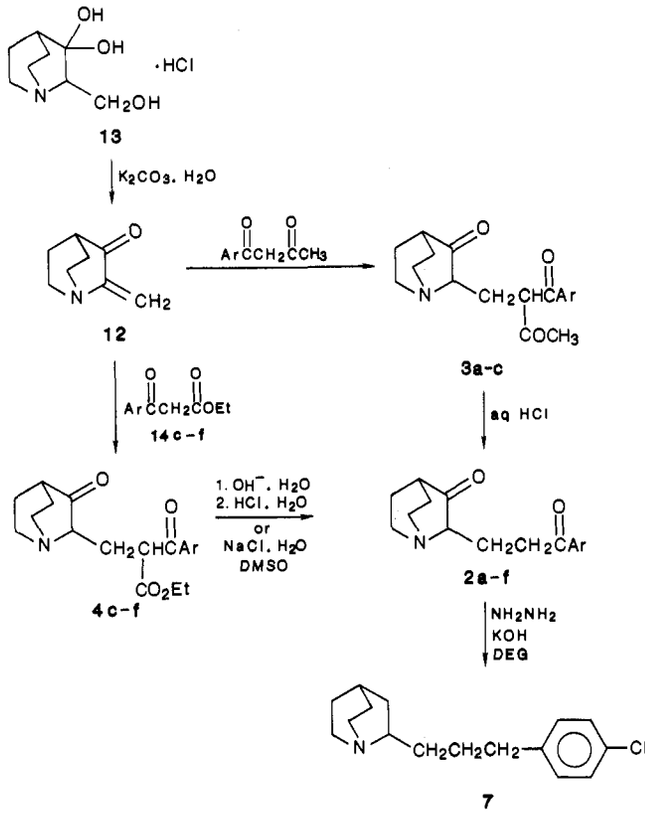
(5) Morgan, T. K., Jr. U.S. Patent 4 599 344, 1986.
(6) Hansen, A. R.; Bader, H. *J. Heterocycl. Chem.* **1966**, *3*, 109.
(7) Bondarenko, V. A.; Mikhlina, E. E.; Filipenko, T. Ya.; Turchin, K. F.; Sheinker, Yu. N.; Yakhontov, L. N. *Khim. Geterotsikl. Soedin.* **1981**, 1397; *Chem. Abstr.* **1982**, *96*, 52153*d*.

Scheme I

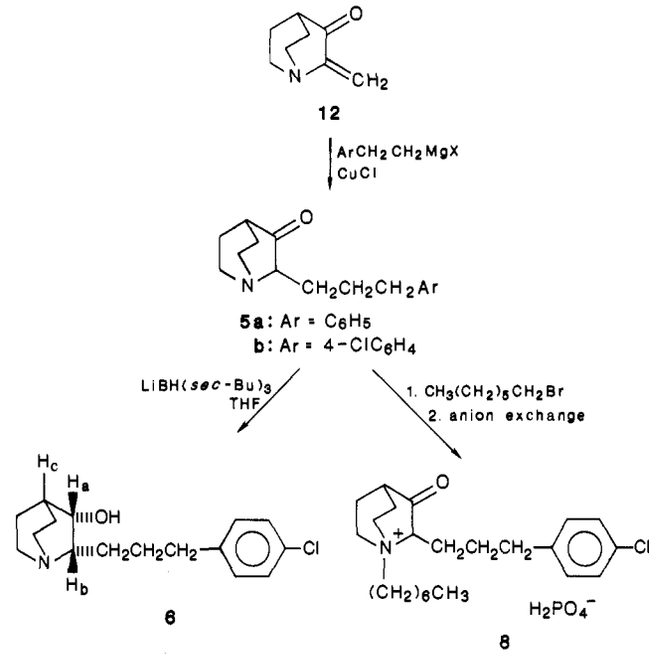


a, Ar = C_6H_5; b, Ar = 4-ClC_6H_4; c, Ar = 4-$NO_2C_6H_4$; d, Ar = 4-$CH_3SO_2NHC_6H_4$; e, Ar = 4-Cl-3-$NO_2C_6H_3$; f, Ar = 4-Cl-3-$CH_3SO_2NHC_6H_3$

mixture with aqueous sodium hydroxide removed the 4-nitrobenzoic acid. The free base of **2c** was converted to the hydrochloric acid salt and recrystallized to provide pure material. The debenzoylation problem was avoided by an alternate synthetic route that was employed for diketones **2d–f**. Unsaturated ketone **12** was reacted with the required β-keto esters **14c–f**, under similar conditions to those used for the above Michael addition to β-diketones, to provide diketo esters **4c–f**. Compounds **4d–f** were converted to diketones **2d–f** either in a two-step process of ester hydrolysis with potassium hydroxide followed by decarboxylation in aqueous hydrochloric acid (**3d** and **3f**) or in a one-step process in dimethyl sulfoxide with a catalytic amount of water and sodium chloride (**3e**).[8] The NMR spectra of triketones **3** and diketo esters **4** indicate that these compounds exist in solution as mixtures of diastereomers and are predominantly in the keto form.

The β-keto esters **14d–f** used above have not been described previously but were prepared by standard methods. Reaction of 4-amino-β-oxobenzenepropanoic acid ethyl ester[9] with methanesulfonyl chloride in methylene chloride with 1.5 equiv of pyridine afforded **14d**. Benzoylation of the sodium salt of ethyl acetoacetate with 4-chloro-3-nitrobenzoyl chloride in ethanol followed by deacetylation in aqueous ammonia/ammonium chloride gave **14e**.[10] Reduction of the nitro group in **14e** with tin(II) chloride dihydrate in ethyl acetate[11] afforded amine **15**, which was mesylated as described above to provide **14f**.

Scheme II



The syntheses of the remaining 2-substituted quinuclidines are outlined in Scheme II. Copper(I) chloride catalyzed 1,4-addition of the Grignard reagents derived from 2-phenethyl bromide and 2-(4-chlorophenyl)ethyl bromide to **12** afforded **5a** and **5b**, respectively.[12] Reduction of the ketone **5b** with the hindered reducing agent lithium tri-*sec*-butylborohydride (L-Selectride, Aldrich) in tetrahydrofuran gave as expected the cis amino alcohol **6**.

The assignment of cis stereochemistry for amino alcohol **6** is based on the coupling constants (J_{ab} = 7.6 Hz and J_{ac} = 4.3 Hz) for the proton on the carbon bearing the hydroxyl group when the hydroxyl proton is decoupled. Local minima were calculated for **6** and its trans isomer by using the variation of Allinger's molecular mechanics program (MMFF) employed in CHEMLAB-II.[13] From these models appropriate dihedral angles were measured. The dihedral angles for H_a to H_b were 13.6° and 129.2° for the cis and trans isomers, respectively. The dihedral angles for H_a to H_c were 54.1° and 61.8° for the cis and trans isomers, respectively. Using these values in the Karplus equation,[14] the predicted J_{ab}'s for cis and trans isomers are 7.7 and 3.5 Hz, respectively. The calculated bridgehead couplings, J_{ac}, are 2.6 and 1.6 Hz for the cis and trans isomers, respectively. The experimental value for J_{ab} better fits the predicted value for the cis isomer.

Quaternization of **5b** with heptyl bromide at 90 °C followed by anion exchange of the crude bromide salt on AG-1-X8 resin (hydroxide form) and titration with phosphoric acid gave **8** as the dihydrogen phosphate. The anion exchange was performed in order to provide a crystalline solid.

The 3-substituted quinuclidines were prepared from 1-azabicyclo[2.2.2]octan-3-one (**16**) as shown in Scheme III. The Wadsworth–Emmons modification[15] of the Wittig

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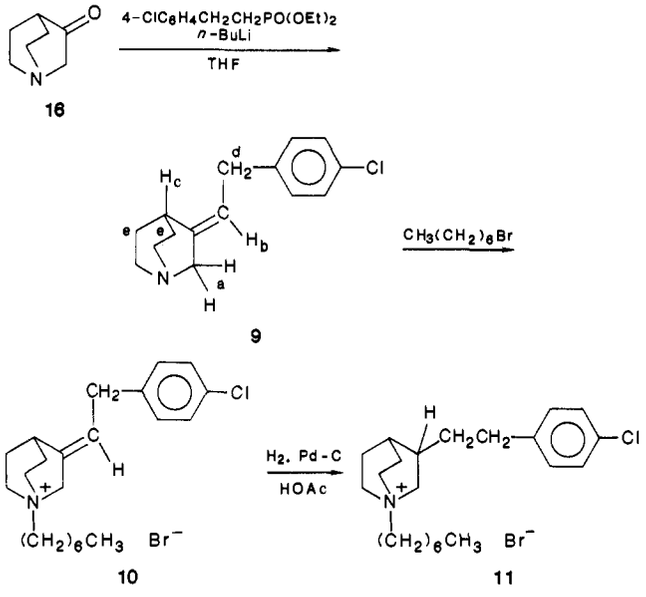
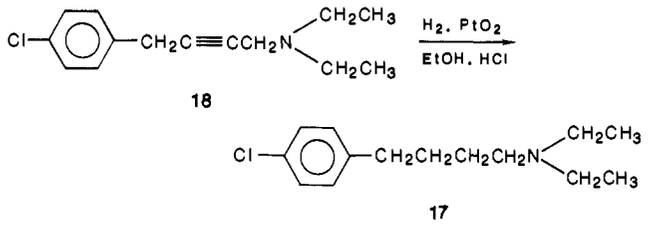
(12) Posner, G. *Org. React.* **1972**, *19*, 1.
(13) CHEMLAB-II is a product of Molecular Design, Ltd., San Leandro, CA 94577.
(14) Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*; 2nd ed.; Pergamon: New York, 1969; pp 280–304.
(15) Wadsworth, W. S.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733.

Scheme III



Scheme IV



reaction employing the anion derived from 2-(4-chlorophenyl)phosphonic acid diethyl ester[16] with **16** yielded unsaturated amine **9**.

The *E* stereochemistry of the double bond in **9** was established by difference nuclear Overhauser enhancement[17] studies in trifluoroacetic acid. Irradiation of H_a (4.14 ppm) produced a 6.7% enhancement in the vinylic proton H_b. Irradiation of bridgehead proton H_c (3.32 ppm) produced a 10.5% enhancement in ring methylene protons H_e and a 6.1% enhancement of the benzylic protons H_d. No enhancements were observed between H_a and H_d or H_c and H_b. These results are consistent with *E* stereochemistry for olefin **9**.

Reaction of unsaturated amine **9** with excess heptyl bromide gave the quaternary ammonium salt **10**. Hydrogenation of **10** over palladium on charcoal in acetic acid afforded the saturated ammonium salt **11**.

In order to compare the cage amines with an unrestricted analogue, we prepared 4-chloro-*N*,*N*-diethylbenzenebutanamine hydrochloride (**17**).[18] Catalytic hydrogenation of acetylene **18**[4] over platinum oxide in ethanol containing a small amount of hydrochloric acid afforded **17** (Scheme IV).

Pharmacology

The primary electrophysiological evaluation of the new compounds was carried out in canine cardiac Purkinje fibers (PF) by using standard microelectrode techniques.[19] The effects of the compounds on action potential duration (APD) and the rate of rise of phase 0 ($\dot{V}_{max}$) of the action potential were determined simultaneously at a basic cycle length of 1 s. In Table III we report the percent change in APD_{95} ($\Delta\%APD_{95}$) at a concentration of 10 μM, the maximum percent change observed in APD_{95} ($max\Delta\%APD_{95}$) with the concentration where the maximum occurred, the percent change in $\dot{V}_{max}$ ($\Delta\%\dot{V}_{max}$) at 10 μM, and the maximum percent change in $\dot{V}_{max}$ ($max\Delta\%\dot{V}_{max}$) with the associated concentration. Decreases in $\dot{V}_{max}$ of <10% or increases in $\dot{V}_{max}$ were not considered significant and were classified as minimal (M).

Compound activity was divided into three groups based on increases in APD_{95} as follows: good activity (≥20% increase in APD_{95} at ≤10 μM), moderate activity (10–19% increase in APD_{95} at ≤10 μM), and inactive (<10% increase in APD_{95} at ≤10 μM). We have observed that compounds that increase APD_{95} by ≥20% at or below 10 μM usually have in vivo efficacy at reasonable doses (ca. 10 mg/kg iv or lower). Selective class III activity was defined as an increase in APD_{95} with minimal effects on $\dot{V}_{max}$. Significant decreases in $\dot{V}_{max}$ (≥10%) indicated class I electrophysiological activity.

Some compounds (**2–8, 10**) were further evaluated in a preparation employing canine ventricular muscle strips to determine electrophysiological effects in this tissue. This model is an adaptation of the in vivo extra-stimulus conduction interval method of Carson and Dresel.[20] Canine muscle strips from the right ventricle and papillary muscle near the base of the heart were immersed in oxygenated Tyrode's solution and recording and stimulating electrodes were attached. The tissue was stimulated at a basic frequency (S_1) of 1 Hz. After a stabilization period an extra stimulus (S_2) was introduced after a train of 10 basic stimulations (S_1) and conduction time (CT) was determined. The S_1–S_2 interval was decreased until the S_2 failed to produce a propagated action potential (functional refractory period, FRP). The FRP and CT were graphically represented on a conduction–interval curve. The procedure was then repeated in the presence of various concentrations of test compound. In Table III we report the percent change in FRP ($\Delta\%$FRP) at 10 μM, the maximum percent change in FRP ($max\Delta\%$FRP) with the concentration at which the maximum was observed, percent change in CT ($\Delta\%$CT) at 10 μM, and the maximum effect on CT ($max\Delta\%$CT) with the associated concentration. Increases in CT of <10% or decreases in CT were not considered significant and were classified as minimal (M). In vitro data are given in Table III for the new compounds and selective class III agent **1** as well as for the class IA agents quinidine (Q) and procainamide (P) and the class IB agent lidocaine (L). For all in vitro experiments the test compounds were dissolved in deionized water (10 mM concentration) and diluted into Tyrode's solution. Each fiber or muscle strip was used only once and served as its own control.

The ventricular muscle assay (VM) was used to augment the information gained from the Purkinje fiber studies. Good activity in this model is defined as a ≥20% increase in FRP at a concentration of 10 μM or below and moderate activity as a 10–19% increase in FRP at 10 μM or below. Compounds that produced <10% increase in FRP were classified as inactive in this model. Both class IA and class III agents can increase FRP; however, only the class I agents increase CT.

Selected compounds were assessed for activity after intraduodenal administration as a suspension in 0.5% tra-

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gacanth to anesthetized dogs by the method of Carson and Dresel[20] to get an indication of potential oral activity. FRP and CT were determined at 15, 30, and 45 min after dosing; heart rate (HR) and blood pressure (BP) were measured during nonpacing intervals. A compound was considered active in this model if FRP or CT were prolonged by ≥12%. Changes in HR or BP, while possibly indicative of drug action, were not considered indicative of direct cardiac electrophysiological activity. The stability of this preparation was demonstrated in a separate set of experiments [vehicle (5% dextrose in water/tragacanth), n = 8]. Minimal effects were observed on the measured parameters [FRP (−3 ± 2%), CT (−0.8 ± 1.3%), HR (2.6 ± 2.1%), and BP (8.9 ± 3.5%)]. The results for the new compounds in this study are listed in Table IV.

Three compounds (**2b**, **9**, and **10**) were chosen for antiarrhythmic efficacy evaluation in a programmed electrical stimulation (PES) model in the pentobarbital-anesthetized dog.[21] This model is analogous to techniques used to determine antiarrhythmic efficacy in the clinical setting for arrhythmic patients.[22] In the efficacy model, dogs that had undergone a coronary ligation according to the method of Harris[23] were studied after 24 h. The animals were anesthetized, the chests were reopened, and stimulating and recording electrodes were attached to the myocardium. Before the test compound was administered, the animals were shown to have a reproducible PES-induced sustained ventricular tachycardia (SVT) or ventricular fibrillation (VF). SVT was terminated by burst pacing; VF was terminated by DC electrocountershock. The test compound, dissolved in 0.9% saline solution, 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. Placebo administration (0.9% saline) was effective in only one out of seven animals. The results of the PES efficacy studies are listed in Table V.

Discussion

In the Purkinje fiber assay (Table III) compounds **2c**, **3c**, **4c**, **6–11**, and **17** showed good class III activity (≥20% prolongation of APD_{95}); compounds **2b**, **2d**, **3b**, **4d**, and **5b** exhibited moderate activity as class III agents. The remaining new compounds were classified as inactive. As expected, the standard **1** prolonged APD_{95} significantly at 10 μM; the class I agents shortened APD_{95} with lidocaine, causing the largest decrease in APD_{95} at 10 μM, followed by quinidine and procainamide (essentially no effect on APD_{95}). The conduction slowing of the class I standards was not significant at 10 μM but became manifest at higher concentrations.

The three quaternized quinuclidines **8**, **10**, and **11** all exhibited significant class III electrophysiological activity at 10 μM in PF. At this concentration the effect of **10** on APD_{95} was comparable to that of **1** while **8** and **11** were somewhat less potent. The two compounds **8** and **11** as well as the standard **1**, which were tested at a 100 μM concentration, exhibited significant conduction slowing (decrease in $\dot{V}_{max}$). This is probably due to general membrane stabilization effects. However, compound **8** at this concentration caused a significant attenuation of the increase in APD_{95} relative to the 10 μM concentration. Incorporation of the ammonium moiety of **1** into the rigid cage of a quinuclidine resulted in maintenance of class III activity; however, when the point of attachment is at the 2-position of the quinuclidine (as in **8**), there appear to be additional electrophysiological effects (attenuation of the increase in of APD_{95}) at the highest concentration that are not evident in the 3-substituted compounds **10** and **11**. Since the class I agents lidocaine and quinidine shorten APD_{95} in Purkinje fiber as well as decreasing $\dot{V}_{max}$, we interpret this decrease in APD_{95} relative to the maximum prolongation and the decrease in $\dot{V}_{max}$ to be due to specific class I activity at the higher concentration.

In the tertiary amine series a comparison of **6**, **7**, and **9** with **17** illustrates the effect on electrophysiological activity (APD_{95} and $\dot{V}_{max}$) in Purkinje fiber of cage versus open-chain compounds. The 3-substituted compound **9** exhibited comparable activity to the open-chain amine **17**. The 2-substituted quinuclidines **6** and **7** displayed a different profile. The class III electrophysiological activity of these compounds reached a maximum below 10 μM (generally at 1 μM). Indications of additional electrophysiological activity (decreased $\dot{V}_{max}$ and attenuation of the initial increase in APD_{95}) were seen in the majority of experiments at concentrations of 10 μM and above. Thus the tertiary amines paralleled the quaternary salts in that the 3-substituted quinuclidines appeared to be more selective as class III agents than the 2-substituted quinuclidines, which showed some class I activity as well. It is of interest to note that the class IA drug quinidine contains a 2-substituted quinuclidine moiety. The predominant effect of quinidine is to inhibit the fast sodium current; however, the drug also inhibits an outward potassium current and a slow inward calcium current.[24]

Initially, diketone **2b** was prepared as an intermediate. However, the electrophysiological activity of this compound led us to prepare additional compounds in the series. In Purkinje fibers the most potent diketone was **2c** with a *p*-nitro group on the phenyl ring. Compound **2c** was as active as clofilium (**1**) at 10 μM. Compounds **2b** and **2d** exhibited equivalent effects on APD_{95} at 10 μM; however, **2b** had its peak effect on APD_{95} at 1 μM while **2d** showed a maximum effect at 100 μM. Furthermore, **2b** showed a dose-dependent decrease in $\dot{V}_{max}$. In this respect **2b** might be considered to be like quinidine but with greater class III activity in the lower (1–10 μM) dose range. We were surprised that the methanesulfonamide **2d** showed only weak/moderate class III activity since we had used the methanesulfonamide moiety successfully in several other series.[4,25] Compounds **2a**, **2e**, and **2f** were essentially devoid of class III activity in the PF.

In general, the activity of the triketones **3a–c** and diketo esters **4c–f** were parallel to that of the corresponding diketones. Compounds **3c** and **4c** (*p*-nitro) were the most potent of these groups. The inclusion of the acetyl or ethoxycarbonyl substituents on the connecting chain does not enhance the electrophysiological activity of the compounds relative to the diketone series **2a–f**.

For some of the 2-substituted quinuclidines, appropriate substitution of the phenyl ring was shown to be a requirement for significant class III electrophysiological activity. Compounds **2a**, **3a**, and **5a**, which contain an unsubstituted moiety, shorten APD_{95}, while **2b**, **3b**, and

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Table III. In Vitro Electrophysiology in Canine Purkinje Fibers and Canine Ventricular Muscle Strips

	Purkinje fiber[a]						ventricular muscle[b]					
no.	n[c]	concn range, μM	Δ%-APD_{95} at 10 μM[d]	maxΔ%APD^{95} (concn)[e]	Δ%$\dot{V}_{max}$ at 10 μM[f]	maxΔ%-$\dot{V}_{max}$ (concn)[g]	n[c]	concn range (μM)	Δ%FRP at 10 μM[h]	maxΔ%FRP (concn)[i]	Δ%CT at 10 μM[j]	maxΔ%-CT (concn)[k]
2a	2	0.1–100	−3	−16 (100)	M	M	1	0.1–100	12	12 (10)	M	17(100)
		1–100	−1	−14 (100)	−36	−52 (100)						
2b	2	0.1–30	13	14 (1)	−10	−26 (30)	2	0.1–10	17	22 (1)	M	M
		0.1–30	5	12 (1)	M	−18 (30)		0.1–30	10	15 (1), −9 (30)	M	M
2c	3	1–100	36	36 (10)	M	M	2	0.1–100	15	25 (100)	M	M
		1–100	53	53 (10), 13 (100)	−17	−23 (100)		0.1–100	17	22 (100)	M	M
		1–100	25	25 (10), −10 (100)	M	M						
2d	5	1–100	16	36 (100)	M	M	3	0.1–100	18	32 (100)	M	M
		1–100	5	18 (100)	M	M		0.1–100	12	21 (100)	M	M
		0.1–100	−1	4 (100)	M	M		0.1–100	13	24 (100)	M	M
		0.1–100	10	28 (100)	M	−24 (100)						
		0.1–100	24	43 (100)	M	M						
2e	3	0.1–100	4	11 (100)	M	−13 (100)	3	0.1–100	21	21 (10)	M	M
		1–100	3	4 (100)	M	−37 (100)		0.1–100	14	14 (1)	M	14 (100)
		1–100	1	−11 (100)	M	−42 (100)		0.1–100	26	44 (100)	M	21 (100)
2f	2	1–100	−4	17 (100)	M	M	3	0.1–100	9	21 (100)	M	M
		1–100	−3	21 (100)	M	−28 (100)		0.1–100	27	32 (100)	M	M
								0.1–100	8	15 (100)	M	M
3a	2	0.1–100	−6	−6 (10)	M		1	0.1–100	14	20 (100)	M	M
		1–100	−5	−19 (100)	M	M						
3b	4	0.1–10	23	23 (10)	M	M	1	0.1–10	24	24 (10)	M	M
		1–100	16	16 (10)	M	−27 (100)						
		1–100	6	−16 (100)	M	−71 (100)						
		1–100	4	4 (10)	−10	CB						
3c	2	1–100	28	28 (10)	−18	−24 (100)	2	0.1–100	21	23 (100)	M	M
		0.1–100	29	29 (10)	M	M		0.1–100	28	30 (100)	M	M
4c	3	0.1–100	2	−12 (100)	M	−26 (100)	2	0.1–100	22	22 (10)	M	M
		0.1–100	23	23 (10), 0 (100)	M	−13 (100)		0.1–100	35	38 (100)	M	M
		0.1–100	22	22 (10), −5 (100)	−12	−18 (100)						
4d	2	1–100	11	39 (100)	−24	−36 (100)	2	0.1–100	5	7 (100)	M	M
		1–100	12	40 (100)	M	M		0.1–100	9	16 (100)	M	M
4e	2	1–100	0	−2 (100)	M	M	1	0.1–100	17	20 (100)	M	M
		1–100	−2	−7 (100)	M	−12 (100)						
4f	2	1–100	9	9 (10)	−11	−19 (100)	4	0.1–100	5	12 (100)	M	12 (100)
		1–100	−4	−16 (100)	−10	−21 (100)		0.1–100	−7	5 (100)	M	M
								1–100	10	15 (100)	M	14 (100)
								0.1–100	6	14 (100)	M	M
5a	2	0.1–100	−6	−38 (100)	M	M	1		5	5 (10)	M	M
		0.1–100	1	−35 (100)	M	M						
5b	4	0.1–10	6	6 (10)	M	M	2	0.1–10	39	39 (10)	M	M
		0.1–100	17	17 (10), −11 (100)	M	−12 (100)		0.1–10	23	23 (10)	M	M
		0.1–100	64	64 (10)	−41	CB						
		0.1–100	19	19 (10), −18 (100)	M	−12 (100)						
6	6	0.1–10	12	30 (1)	M	M	1	0.1–10	21	21 (10)	M	11 (0.1)
		0.1–100	14	14 (10), −24 (100)	M	−48 (100)						
		0.1–100	40	40 (10)	−24	CB (100)						
		1–100	13	41 (1), 13 (10)	−13	CB (100)						
		0.1–100	15	25 (1)	M	CB (100)						
		0.1–100	11	15 (1), −7 (100)	−20	−48 (100)						
7	5	0.1–100	2	13 (1)	−13	−65 (100)	1	0.1–100	25	25 (10)	M	M
		1–100	−20	12 (1), −20 (10)	M	CB (100)						
		0.1–100	21	68 (1), 21 (10)	M	CB (100)						
		0.1–30	30	53 (1), 30 (10)	−23	CB (30)						
		0.1–100	12	40 (1), 12 (10)	−10	CB (100)						
8	4	0.1–100	9	9 (10), −23 (100)	M	−74 (100)	3	0.1–30	26	29 (30)	M	17 (30)
		0.1–100	38	38 (10), 13 (100)	M	−33 (100)		0.1–30	22	27 (30)	M	M
		0.1–100	69	69 (10), 12 (100)	−18	−78 (100)		0.1–100	5	10 (100)	M	31 (100)
		0.1–100	35	35 (10), 9 (100)	−15	−79 (100)						
9	3	0.1–10	29	29 (10)	M	M	NT					
		0.1–100	16	35 (100)	M	−59 (100)						
		0.1–100	50	50 (10)	−12	CB (100)						
10	2	0.1–10	40	50 (1)	M	M	1	0.1–30	21	30 (30)	M	M
		0.1–30	64	64 (10)	M	M						
11	2	0.1–10	23	26 (1)	M	M	NT					
		0.1–100	22	23 (100)	M	−58 (100)						

Table III (Continued)

	Purkinje fiber[a]						ventricular muscle[b]					
no.	n^c	concn range, μM	Δ%-APD_{95} at 10 μM[d]	maxΔ%APD^{95} (concn)[e]	Δ%$\dot{V}_{max}$ at 10 μM[f]	max Δ%-$\dot{V}_{max}$ (concn)[g]	n^c	concn range (μM)	Δ%FRP at 10 μM[h]	maxΔ%-FRP (concn)[i]	Δ%CT at 10 μM[j]	maxΔ%-CT (concn)[k]
17	3	1–100	21	25 (1), −15 (100)	M	−57(100)	NT					
		0.1–100	38	38 (10)	M	−49 (100)						
		0.1–100	27	27 (10)	M	M						
Q[l]	3	0.1–100	−9	−24 (100)	−10	−53 (100)	4	0.1–100	14	27 (100)	17	72 (100)
		5–50	−9	−19 (50)	−11	−40 (100)		0.1–100	9	24 (100)	11	79 (100)
		0.1–30	−21	−39 (30)	M	−19 (30)		0.1–100	21	46 (100)	M	15 (100)
								0.1–100	22	22 (10)	M	38 (100)
P[l]	3	1–100	−4	−7 (1)	M	−14 (100)	3	0.1–100	17	27 (100)	M	M
		1–100	−1	−8 (100)	M	−10 (100)		0.1–100	8	10 (100)	M	M
		1–100	0	3 (100)	M	−10 (100)		0.1–100	2	7 (100)	M	M
L[l]	4	5–100	−23	−33 (100)	M	−11 (100)	3	0.1–100	6	23 (100)	M	M
		0.1–100	−23	−48 (100)	M	M		0.1–100	4	8 (100)	M	M
		0.1–100	−23	−43 (100)	M	−10 (100)		0.1–100	2	18 (100)	M	M
		1–30	−30	−43 (30)	M	−42 (30)						
1	7	1–100	49	67 (100)	−50	−69 (100)	4	0.1–100	−3	−3 (0.1)	M	M
		1–100	18	22 (1)	−49	−65 (100)		0.1–10	38	38 (10)	M	M
		0.1–100	48	52 (100)	M	−80 (100)		0.1–100	11	14 (100)	11	19 (100)
		0.1–100	46	46 (10)	M	−22 (100)		0.1–100	5	7 (100)	M	M
		0.01–10	27	27 (10)	M	M						
		0.01–10	55	55 (10)	M	M						
		0.1–10	52	52 (10)	−11	−11 (10)						

[a] Intracellular electrophysiology. [b] Extracellular electrophysiology. [c] Number of experiments. Results from individual experiments shown. NT = not tested. [d] Percent change from control value for the action potential duration at 95% repolarization (APD_{95}) at a 10 μM concentration of the test compound. [e] Maximum percent change from control value for APD_{95} observed for the test compound and the concentration at which it occurred. When a significant biphasic response (>20% change in the opposite direction from the previous response) was noted, both values are given. [f] Percent change from control value for $\dot{V}_{max}$ at a 10 μM concentration of the test compound. M = minimal (<10% decrease or an increase in $\dot{V}_{max}$). [g] Maximum percent change in $\dot{V}_{max}$ observed for the test compound and the concentration at which it occurred. CB = conduction block. [h] Percent change from control for functional refractory period (FRP) at a 10 μM concentration of the test compound. [i] Maximum percent change from control for FRP observed for the test compound and the concentration at which it occurred. [j] Percent change from control for conduction time (CT) at a 10 μM concentration of the test compound. M = minimal (<10% increase or a decrease in CT). [k] Maximum percent change from control for CT observed for the test compound and the concentration at which it occurred. [l] Q = quinidine, P = procainamide, L = lidocaine.

Table IV. Intraduodenal Bioavailability in the Anesthetized Dog

no.	n	dose,[a] mg/kg	LV-FRP,[b] %	CT,[b] %	HR,[b] %	mean BP,[b] %
2b	2	10/30	15/15	5/14	−13/−18	−5/0
		10/30	12/6	4/13	−15/−21	18/23
2c	2	10/30	14/15	−1/2	−23/−31	−11/−21
		10/24	16/19	6/11	−35/−40	−10/−1
3b	3	10/30	4/1	3/9	1/2	−5/−6
		10/30	11/18	0/7	−14/−28	−4/−16
		10/30	11/15	8/13	−15/−22	7/7
3c	2	10/30	9/13	−3/−3	−11/−14	10/12
		10/30	16/22	9/11	−36/−32	−39/−30
5b	2	10/30	15/19	0/2	−17/−31	−4/5
		3/10	5/9	3/13	−2/−14	20/24
6[c]	2	10/30	4/3	5/7	−6/−14	14/14
		10/30	7/9	4/8	−7/−9	0/−3
9[d]	2	3/10	5/3	0/3	−2/4	19/25
		10/20	3/2	0/−4	−1/1	12/12
10	2	3/10	2/15	0/−5	5/−9	5/15
		10	16	5	−13	42
1	3	3/10	10/22	−4/−7	−9/−24	−7/−11
		1/3	−1/2	−5/−7	−2/−6	−2/−14
		1/3/10	4/4/23	0/−7/−11	−2/−7/−11	−3/0/4
Q[e]	2	10/30	13/20	7/51	−22/−42	2/−4
		10/30	16/28	10/38	−18/−39	−7/15

[a] Animals were generally given two doses of test compound; the second value being a cummulative dose (low dose/high dose). [b] LV-FRP = left ventricular functional refractory period, CT = conduction time, HR = heart rate, mean BP = mean blood pressure; values reported as percent change from control for low dose/high dose. [c] Not considered active (id). When administered intravenously (3 mg/kg) to two additional animals, **6** increased FRP by 12% and 8%. [d] Not considered active (id). When administered intravenously (3 mg/kg) to two additional animals, **9** increased FRP by 17% and 15%. [e] Q = quinidine.

5b, which have a 4-chlorophenyl group, increase APD_{95} in PF.

In general, the results from the extracellular muscle assay paralleled the results from the intracellular Purkinje fiber screen, with the observation that borderline cases in Purkinje fiber tended to move to the next higher classification in ventricular muscle (e.g. moderate → good). The notable exceptions were **2c** (PF-good/VM-moderate), **2e** (PF-inactive/VM-good), and **4d** (PF-moderate/VM-inactive). We are examining these compounds further to determine the nature of these differences.

Eight compounds (**2b,c**, **3b,c**, **5b**, **6**, **9**, and **10**) were studied in vivo for electrophysiological effects after intraduodenal administration and compared to **1** and quin-

Table V. Antiarrhythmic Efficacy in the 24-h Infarcted Anesthetized Dog

no.	n	no. effective	effective doses (iv)[a]
2b[b]	4	3	1 mg/kg (1), 3 mg/kg (1), and 10 mg/kg (1)
9[c]	3	2	0.1 mg/kg (1) and 0.3 mg/kg (1)
10	2	2	0.3 mg/kg (2)
1[d]	10	7	0.1 mg/kg (3), 0.3 mg/kg (2), 0.5 mg/kg (1), 3 mg/kg (1)
Q[e]	10	8	1 mg/kg (1), 3 mg/kg (2), 5 mg/kg (2), 10 mg/kg (2), 15 mg/kg (1)
L[f]	4	1	3 mg/kg (1)
P[g]	3	0	

[a] Number of animals in which the compound was effective at the indicated dose is given in parentheses. [b] Not effective in one animal at 10 mg/kg. [c] Not effective in one animal at 3 mg/kg. [d] Not effective in one animal at 3 mg/kg and in two animals at 10 mg/kg. [e] Not effective in one animal at 20 mg/kg and in one animal at 30 mg/kg (Q = quinidine). [f] Not effective in three animals at 30 mg/kg (L = lidocaine). [g] Not effective in three animals at 60 mg/kg (P = procainamide).

idine as standards (Table IV). Compounds **2c**, **3c**, **6**, **9**, and **10** were chosen due to good class III activity in the Purkinje fiber screen; **3b** and **5b** had shown moderate class III activity in Purkinje fibers but good activity in ventricular muscle. Although **2b** exhibited moderate class III activity in both in vitro screens, it was chosen for in vivo studies because it showed "quinidine-like" conduction effects in the in vitro assays. Compounds **2b,c**, **3b,c**, and **5b** were considered to be active in this assay, whereas **6** and **9** were not. Compounds **6** and **9** may undergo rapid N-oxidation after absorption, while **2b,c**, **3b,c**, and **5b** may not. A possible explanation may be that the inductive effect of the carbonyl group at the 3-position in the active compounds decreases the reactivity of the quinuclidine nitrogen toward oxidation. Oxidation of the quinuclidine nitrogen in quinidine affords the essentially inactive quinidine N_{al}-oxide, which is one of the main metabolites of quinidine detected in plasma.[26] The quaternary compound **10** had similar effects to clofilium (**1**). All of the compounds that had class III activity decreased heart rate. The blood pressure effects were variable and not excessive.

Three compounds (**2b**, **9**, and **10**) were examined in the PES efficacy model in the anesthetized dog (Table V). Compounds **9** and **10** were chosen for a comparison of a tertiary amine with a quaternized compound. Although **2b** was not the most potent of the introduodenally active 2-substituted quinuclidines, it was selected because of its combined class III and class I effects. The nitro compounds **2c** and **3c** were not studied since nitroaromatic compounds generally have increased potential for mutagenic toxicity and would not be of interest for development. Amine **9** and its quaternary analogue **10** were approximately equivalent to **1** in potency and efficacy. The diketone **2b** was less potent than **1** but comparable to quinidine in potency. A decrease in spontaneous ectopy was noted when **2b** was given in this model. This may be due to the class I activity of this compound. Compounds **9**, **10**, and **1**, which are selective class III, agents had no significant effect on spontaneous ectopy. Quinidine, as would be expected, decreased spontaneous ectopic activity. A comparison of the effective intravenous dose in the PES model with the effective dose after intraduodenal administration in the FRP model for **1** and **10** suggests that both compounds would possess low oral bioavailability.

(26) (a) Bonora, M. R.; Guentert, T. W.; Upton, R. A.; Riegelman, S. *Clin. Chim. Acta* **1979**, *91*, 277. (b) Bizzard, G.; Vanlerenberghe, J.; Cuingnet, E.; Robelet, A.; Milbled, G. *J. Physiol. (Paris)* **1954**, *46*, 254.

Conclusions

The electrophysiological activity of clofilium analogues in which the quaternary ammonium moiety has been incorporated into a rigid quinuclidinium skeleton appears to depend on the point of attachment to the quinuclidine. Attachment at the 3-position, as in **10** and **11**, produces compounds that are electrophysiologically similar to clofilium (**1**). Compound **8** (substituted at the 2-position), however, appears to show some activity similar to the class I agents quinidine and lidocaine (significant attenuation of the initial increase in APD_{95}) at high concentrations in addition to class III electrophysiological activity. Similarly, in the tertiary amines the 3-substituted quinuclidine **9** shows selective class III activity while the 2-substituted compounds **2–7** exhibit a range of activities from predominant class III effects, e.g., **2d**, to compounds with significant class I effects as well as class III activity, e.g., **2b**, **6**, and **7**. We suggest that the more flexible 2-substituted quinuclidines can accommodate the sites responsible for class I and class III activity whereas the more rigid 3-substituted compounds react selectively with class III sites.

At least for some of the 2-substituted quinuclidines (e.g., **2**, **3**, and **5**), appropriate substitution of the phenyl ring is a requirement for significant class III electrophysiological activity.

Of the compounds selected for intraduodenal bioavailability studies, amines **6** and **9** were conspicuous for their lack of activity. We suggest that this is due to rapid first pass oxidation of the quinuclidine nitrogen. Oxidation is deterred in **2b**, **3b**, and **5b** by the electron-withdrawing carbonyl group that is β to the nitrogen.

Of the three compounds tested in the PES model, **9** and **10** were dropped from further study due to low intraduodenal activity, which indicates poor oral bioavailability. Diketone **2b**, although efficacious in the PES model and active after intraduodenal administration, was not pursued after tests in conscious animals showed undesirable CNS activity.[27]

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 except where indicated. NMR spectra were recorded with either a Varian EM-360 (60 MHz) spectrometer 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 Beckmann Acculab 2 spectrometer or a Sargent Welch 3-300 spectrometer. All NMR and IR spectra were consistent with the assigned structures.

2-Methylene-1-azabicyclo[2.2.2]octan-3-one (12).[6] To a solution of 255 g (1.85 mol) of potassium carbonate in 350 mL of water was added 95.4 g (0.455 mol) of 2-methylene-3-quinuclidinone dihydrate monohydrochloride (**13**). When all of the solid had dissolved, 500 mL of methylene chloride was added and the two-phase system was stirred overnight. After the layers were separated, the aqueous phase was further extracted with three 500-mL portions of methylene chloride. The methylene chloride extracts were dried over anhydrous potassium carbonate. Filtration of the drying agent and evaporation of the solvent in vacuo provided 60 g (96%) of **12** as an oil, which was used without further purification. A small amount of the oil was further purified by Kugelrohr distillation at 80 °C (0.5 mmHg) [lit.[6] bp 91–92 °C (7 mmHg)]: NMR ($CDCl_3$) δ 1.99 (td, 4 H, J = 7.9 Hz, J = 3.0 Hz, $HC(CH_2CH_2)_2$), 2.60 (quin, 1 H, J = 3.0 Hz, bridgehead), 2.99

(27) Sullivan, M., unpublished results.

(m, 2 H, $(CH_2CH_2)_2N$), 3.14 (m, 2 H, $(CH_2CH_2)_2N$), 5.23 (s, 1 H, olefinic), 5.83 (s, 1 H, olefinic).

2-[(1-Azabicyclo[2.2.2]oct-2-yl)methyl]-1-phenyl-1,3-butanedione Hydrochloride[7] (3a). Reaction of 10.7 g (66 mmol) of 1-phenyl-1,3-butanedione with 9.2 g (67 mmol) of **12** under conditions used to prepare **3b** below gave **3a** in 63% yield. The crude product was recrystallized from ethanol: NMR (DMSO-d_6) δ 2.22 and 2.30 (s, total 3 H, CH_3CO).

2-[(1-Azabicyclo[2.2.2]oct-2-yl)methyl]-1-(4-chlorophenyl)-1,3-butanedione Hydrochloride (3b). To a solution of 93.1 g (0.47 mol) of 1-(4-chlorophenyl)-1,3-butanedione[28] in 500 mL of acetone was added 60.0 g (0.39 mol) of **12** and the solution was refluxed for 24 h. The reaction mixture was cooled in an ice/water bath and acidified by dropwise addition of 35 mL (0.42 mol) of concentrated hydrochloric acid. Filtration of the resulting solid provided 131 g (90%) of **3b**, which was further recrystallized from methanol: IR (KBr) 1730, 1710, 1660 cm^{-1} (carbonyls); NMR (DMSO-d_6) δ 1.96–2.34 (m, 6 H), 2.22 and 2.30 (s, total 3 H, CH_3CO), 2.56–2.70 (m, 1 H), 3.24–3.68 (m, 4 H), 4.02–4.22 (br s, 1 H), 5.58–5.80 (br s, 1 H), 7.68 and 7.71 (d, total 2 H), and 8.08 and 8.21 (d, total 2 H).

2-[(1-Azabicyclo[2.2.2]oct-2-yl)methyl]-1-(4-nitrophenyl)-1,3-butanedione Hydrochloride (3c). Reaction of 14.0 g (68 mmol) of 1-(4-nitrophenyl)-1,3-butanedione[29] with 9.28 g (68 mmol) of **12** under conditions used to prepare **3b** above gave 18.6 g (72%) of **3c**: NMR (DMSO-d_6) δ 2.22 and 2.32 (s, total 3 H, CH_3CO).

4-[(Methylsulfonyl)amino]-β-oxobenzenepropanoic Acid Ethyl Ester (14d). Reaction of 4-amino-β-oxobenzenepropanoic acid ethyl ester[9] with methanesulfonyl chloride as described for **14f** afforded crude **14d** in 70% yield. Recrystallization from ethanol provided **14d**: mp 117–118 °C; NMR ($CDCl_3$) δ 1.28 (t, 2.5 H), 1.32 (t, 0.5 H), 3.08 (s, 0.5 H), 3.12 (s, 2.5 H), 3.98 (s, 1.67 H), 4.23 (m, 2 H), 5.62 (s, 0.16 H), 7.10 (br s, 1 H), 7.39 (m, 2 H), 7.80 (d, 0.33 H), 7.98 (d, 1.67 H), 12.63 (s, 0.16 H) (ca. 5:1 mixture of keto:enol tautomers). Anal. ($C_{12}H_{15}N_5OS$) C, H, N.

4-Chloro-3-nitro-β-oxobenzenepropanoic Acid Ethyl Ester (14e). To a cold solution of sodium ethoxide, prepared from 5.92 g (0.26 mol) of sodium metal and 125 mL of ethanol, was added dropwise 32.8 g (0.25 mol) of ethyl acetoacetate.[10] To the chilled (–10 °C) solution of anion was added a solution of 28.25 g (0.13 mol) of 4-chloro-3-nitrobenzoyl chloride in 250 mL of tetrahydrofuran. The reaction mixture was stirred overnight with the temperature maintained below 20 °C. The reaction mixture was recooled to –10 °C and 160 mL of 1.6 M sodium ethoxide solution was added dropwise. After the addition was complete, a second portion of 28.25 g of 4-chloro-3-nitrobenzoyl chloride in 250 mL of tetrahydrofuran was added to the cold mixture. After the mixture was stirred for 2 h, the solvent was removed in vacuo. The resulting oil was triturated with anhydrous diethyl ether. The solid, which had formed, was filtered and dissolved in 750 mL of water. To the aqueous solution was added 10 mL of concentrated ammonium hydroxide and 10 g (0.19 mol) of ammonium chloride. The reaction mixture was stirred overnight at room temperature. The crude product was filtered and recrystallized from ethanol to give 27.9 g (40%) of **14e**: mp 89–90 °C; NMR ($CDCl_3$) δ 1.26 (t, 1.5 H), 1.35 (t, 1.5 H), 4.02 (s, 1 H), 4.23 (quar, 1 H), 4.29 (quar, 1 H), 5.76 (s, 0.5 H), 7.61 (d, 0.5 H), 7.70 (d, 0.5 H), 7.90 (dd, 0.5 H), 8.09 (dd, 0.5 H), 8.27 (d, 0.5 H), 8.43 (d, 0.5 H), 12.62 (s, 0.5 H) (ca. 1:1 mixture of tautomers). Anal. ($C_{11}H_{10}ClNO_5$) C, H. N.

3-Amino-4-chloro-β-oxobenzenepropanoic Acid Ethyl Ester (15). To a solution of 1.0 g (3.68 mmol) of **14e** in 10 mL of ethyl acetate was added 4.14 g (18.5 mmol) of tin(II) chloride dihydrate.[11] The reaction mixture was heated at 70 °C for 30 min and then poured on to ice/water. The pH of the aqueous mixture was adjusted to 7–8 with solid sodium bicarbonate and the mixture was extracted with two 25-mL portions of methylene chloride. The combined extracts were dried over anhydrous sodium sulfate. Removal of the drying agent and evaporation of the solvent provided 0.7 g (78%) of crude product. Recrystallization from ethanol afforded **15**: mp 86–88 °C; NMR ($CDCl_3$) δ 1.25 (t, 3 H), 3.95 (s, 2 H), 4.0–4.4 (br s, 2 H, NH_2), 4.25 (quar, 2 H), 7.1–7.5 (m, 3 H). Anal. ($C_{11}H_{12}ClNO_3$) C, H, N.

4-Chloro-3-[(methylsulfonyl)amino]-β-oxobenzenepropanoic Acid Ethyl Ester (14f). To a solution of 9.09 g (38 mmol) of **15** and 4.6 mL (57 mmol) of pyridine in 60 mL of methylene chloride cooled to –10 °C was added a solution of 3.2 mL (41 mmol) of methanesulfonyl chloride in 10 mL of methylene chloride. The temperature of the reaction mixture was held below 0 °C during the addition and then gradually warmed to room temperature and stirred for 4 h. The reaction mixture was washed with three 50-mL portions of 5% aqueous hydrochloric acid and then dried over anhydrous sodium sulfate. Removal of the drying agent and evaporation of the solvent provided an oil, which was crystallized from ethanol to yield 6.8 g (56%) of product. Recrystallization from ethanol gave analytically pure **14f**: mp 105–107 °C; NMR ($CDCl_3$) δ 1.28 (t, 2.4 H), 1.34 (t, 0.6 H), 3.05 (s, 0.6 H), 3.08 (s, 2.4 H), 3.98 (s, 1.6 H), 4.22 (quar, 1.6 H), 4.27 (quar, 0.4 H), 5.68 (s, 0.2 H), 6.80–7.00 (br s, 1 H), 7.50–7.80 (m, 2 H), 8.06 (s, 0.2 H), 8.70 (s, 0.8 H), 12.62 (s, 0.2 H) (ca. 4:1 mixture of keto:enol tautomers). Anal. ($C_{12}H_{14}ClNO_5S$) C, H, N.

α-(4-Nitrobenzoyl)-3-oxo-1-azabicyclo[2.2.2]octane-2-propanoic Acid Ethyl Ester Hydrochloride (4c). Reaction of 1.52 g (11 mmol) of **12** with 2.52 g (11 mmol) of 4-nitro-β-oxobenzenepropanoic acid ethyl ester[10] in acetone following the procedure for **3b** afforded 3.3 g (73%) of **4c**: IR (Nujol) 1730, 1670 cm^{-1}; NMR (DMSO-d_6) δ 0.90–1.14 (2 t, 3 H, OCH_2CH_3), 1.90–2.24 (m, 4 H), 2.34–2.82 (m, 3 H), 3.20–3.68 (m, 4 H), 3.94–4.14 (2 quar, 2 H, OCH_2CH_3), 4.16–4.36 (m, 1 H), 5.60 (m, 1 H), 8.52–8.24 (m, 4 H), 12.02 (br s, 1 H) (mixture of diastereomers in solution).

α-[4-[(Methylsulfonyl)amino]benzoyl]-3-oxo-1-azabicyclo[2.2.2]octane-2-propanoic Acid Ethyl Ester Hydrochloride (4d). A solution of 2.12 g (15.4 mmol) of **12** and 4.54 g (15.9 mmol) of **14d** was refluxed overnight in 25 mL of acetone. The crude product was chromatographed on silica gel with acetonitrile eluent. The product fractions were dissolved in methanol and acidified (pH 1) with methanolic hydrochloric acid. The acid salt was recrystallized from ethanol and then acetonitrile to give 2.3 g (30%) or **4d**: IR (Nujol) 1730, 1670 cm^{-1}; NMR (DMSO-d_6) δ 1.16 (2 t, 3 H, OCH_2CH_3), 1.92–2.80 (br m, 7 H), 3.15 (s, 3 H, SO_2CH_3), 3.24–3.70 (m, 4 H), 4.00–4.20 (2 quar, 2 H, OCH_2CH_3), 4.25 (m, 1 H), 5.32–5.52 (m, 1 H), 7.35 (d, 2 H), 8.07 (d, 1 H), 8.15 (d, 1 H), 10.56 (s, ca. 0.5 H, $NHSO_2CH_3$), 10.58 (s, ca. 0.5 H, $NHSO_2CH_3$), 11.80–12.15 (br, 1 H) (ca. 1:1 mixture of diastereomers in solution).

α-(4-Chloro-3-nitrobenzoyl)-3-oxo-1-azabicyclo[2.2.2]octane-2-propanoic Acid Ethyl Ester Hydrochloride (4e). Reaction of 1.24 g (9 mmol) of **12** and 2.45 g (9 mmol) of **14e** in 10 mL of acetone as described for **3b** gave 2.5 g (62%) of **4e**: IR (Nujol) 1725, 1715, 1690 cm^{-1}; NMR (DMSO-d_6) δ 1.05 (2 t, 3 H, OCH_2CH_3), 1.90–2.24 (m, 4 H), 2.30–2.80 (m, 3 H), 3.16–3.64 (m, 4 H), 4.06 (2 quar, 2 H, OCH_2CH_3), 4.18 (br ca. 0.5 H), 4.28 (br ca. 0.5 H), 5.48–5.64 (m, 1 H), 8.03 (d, 1 H), 8.36 (dd, ca. 0.5 H), 8.43 (dd, ca. 0.5 H), 8.73 (dd, 1 H), 11.7–11.90 (br, 1 H) (ca. 1:1 mixture of diastereomers in solution).

α-[4-Chloro-3-[(methylsulfonyl)amino]benzoyl]-3-oxo-1-azabicyclo[2.2.2]octane-2-propanoic Acid Ethyl Ester Hydrochloride (4f). A solution of 1.55 g (11 mmol) of **12** and 3.6 g (11 mmol) of **14f** was refluxed in 10 mL of acetone overnight. After this time the solvent was evaporated and the residue was chromatographed on silica gel with acetonitrile. The product fractions were combined, and the solvent was removed in vacuo. The residue was dissolved in 25 mL of ethanol and was saturated with hydrogen chloride gas. The solvent was evaporated and the residue was triturated with diethyl ether to give a solid. The crude solid was recrystallized from ethanol to provide 1.0 g (18%) of **4f**: IR (KBr) 1730, 1690 cm^{-1}; NMR (DMSO-d_6) δ 1.06 (2 t, 3 H, OCH_2CH_3), 1.92–2.22 (m, 4 H), 2.22–2.74 (m, 3 H), 3.12 (s, 3 H, CH_3SO_2NH), 3.20–3.72 (m, 4 H), 4.00–4.30 (br m, 1 H), 4.06 (2 quar, 2 H, OCH_2CH_3), 5.32 (br s, 1 H), 7.76 (d, 1 H), 7.98 (dd, 0.5 H), 8.06 (dd, 0.5 H), 8.11 (d, 1 H), 9.78 (s, 1 H), 11.5 (br, 1 H) (ca. 1:1 mixture of diastereomers in solution).

2-(3-Oxo-3-phenylpropyl)-1-azabicyclo[2.2.2]octan-3-one Hydrochloride (2a).[7] Acid hydrolysis of 10.0 g (29 mmol) of **3a** under conditions used for hydrolysis of **2b** and recrystallization

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(29) Walker, H. G.; Hauser, C. R. *J. Am. Chem. Soc.* **1946**, *68*, 2742.

from ethanol afforded 2.0 g (23%) of **2a**: IR (Nujol) 1740, 1685 cm^{-1}.

2-[3-(4-Chlorophenyl)-3-oxopropyl]-1-azabicyclo[2.2.2]octan-3-one Hydrochloride (2b). A solution of 105.28 g (0.28 mol) of **3b** was refluxed for 5 h in 500 mL of concentrated hydrochloric acid. After this time the reaction mixture was cooled in an ice/water bath and the resulting solid was filtered to give 89.3 g (97%) of crude product. Recrystallization of the crude material from water afforded **3b**: IR (Nujol) 1720, 1670 cm^{-1}; NMR (CF_3COOD) δ 2.20–2.64 (m, 5 H), 2.64–2.84 (m, 1 H), 3.54–3.72 (m, 1 H), 3.72–4.10 (m, 5 H), 4.44 (t, 1 H), 7.58 (d, 2), 8.04 (d, 2).

2-[3-(4-Nitrophenyl)-3-oxopropyl]-1-azabicyclo[2.2.2]octan-3-one Hydrochloride (2c). Acid hydrolysis of 13.0 g (34 mmol) of **3c** in 50 mL of concentrated hydrochloric acid provided after filtration a mixture of product and 4-nitrobenzoic acid. The mixture was suspended in 10% sodium hydroxide solution and extracted with methylene chloride. The solvent was evaporated and the residue was dissolved in methanol. Acidification of the methanol solution with methanolic hydrochloric acid afforded a solid, which was recrystallized from 2-propanol to give 1.73 g (15%) of **2c**: IR (KBr) 1730, 1685 cm^{-1}; NMR (DMSO-d_6) δ 2.00–2.24 (m, 4 H), 2.30–2.44 (m, 1 H), 2.63 (m, 1 H), 3.24–3.70 (m, 7 H), 4.22 (m, 1 H), 8.21 (d, 2 H), 8.38 (d, 2 H), 13.00 (br s, 1 H).

***N*-[4-[1-Oxo-3-(3-oxo-1-azabicyclo[2.2.2]oct-2-yl)propyl]phenyl]methanesulfonamide Hydrochloride (2d).** A solution of 4.22 g (9 mmol) of **4d** in 10 mL of 3.9 M potassium hydroxide solution was stirred for 2 h. The mixture was acidified with 5.5 mL of concentrated hydrochloric acid, causing immediate gas evolution and formation of a solid, which was collected by filtration. Analysis by NMR indicated a mixture of salt and free base. The material was slurried in methanolic hydrochloric acid and filtered to provide 2.3 g (65%) of **2d**: IR (Nujol) 1715, 1660 cm^{-1}; NMR (DMSO-d_6) δ 2.00–2.26 (m, 5 H), 2.34 (m, 1 H), 2.63 (m, 1 H), 3.12 (s, 3 H, CH_3SO_2NH), 3.30–3.68 (m, 6 H), 4.23 (t, 1 H), 7.32 (d, 2 H), 7.99 (d, 2 H), 10.50 (br s, 1 H), 11.78 (br s, 1 H). Anal. ($C_{17}H_{22}N_2O_4S \cdot HCl \cdot 0.5H_2O$) C, H, N, S; Cl: calcd, 8.96; found, 9.52.

2-[3-(4-Chloro-3-nitrophenyl)-3-oxopropyl]azabicyclo-[2.2.2]octan-3-one Hydrochloride (2e). To a solution of 35 mL of dimethyl sulfoxide and 0.28 mL of water were added 3.47 g (7.8 mmol) of **4e** and 0.56 g (9.6 mmol) of sodium chloride.[8] The mixture as heated at 135 °C for 8 h during which time gas evolution was observed. On cooling the solid that formed was collected by filtration. The dimethyl sulfoxide solution was poured on to 200 mL of water and made basic (pH 9) with 5% aqueous sodium hydroxide solution. The aqueous mixture was extracted with four 25-mL portions of methylene chloride. The combined methylene chloride extracts were washed with two 50-mL portions of water and then dried over anhydrous sodium sulfate. The drying agent was removed and the solvent was evaporated. The residue was dissolved in methanol and acidified with methanolic hydrochloric acid. The resulting solid was collected by filtration. Thin-layer chromatography on silica gel (methanol/1 N sodium chloride solution, 95:5) indicated that the initial precipitate and workup material were identical. The two solids were combined and recrystallized from methanol to give 2.4 g (82%) of **2e**: IR (Nujol) 1720, 1680 cm^{-1}; NMR (DMSO-d_6) δ 1.98–2.26 (m, 5 H), 2.35 (m, 1 H), 2.64 (t, 1 H), 3.20–3.72 (m, 6 H), 4.23 (m, 1 H, $NCHCH_2CH_2$), 8.00 (d, 1 H), 8.24 (dd, 1 H), 8.56 (d, 1 H), 11.58 (br s, 1 H).

***N*-[2-Chloro-5-[1-oxo-3-(3-oxo-1-azabicyclo[2.2.2]oct-2-yl)propyl]phenyl]methanesulfonamide Hydrochloride (2f).** To 30 mL of 5% aqueous sodium hydroxide solution was added 2.19 g (4.8 mmol) of **4f**. The reaction mixture was stirred overnight at room temperature and then 15 mL of 6 N hydrochloric acid was added. After gas evolution had ceased, the mixture was made basic (pH 8) with concentrated ammonium hydroxide solution and extracted with two 50-mL portions of methylene chloride. Evaporation of solvent from the combined extracts afforded 700 mg (38%) of crude free base as an oil. The oil was dissolved in methanol and acidified with methanolic hydrochloric acid. Collection of the resulting solid gave **2f**: IR (KBr) 1740, 1690 cm^{-1}; NMR (DMSO-d_6) δ 2.0–2.6 (m, 5 H), 2.35 (m, 1 H), 2.65 (m, 1 H), 3.09 (s, 3 H, $NHSO_2CH_3$), 3.24–2.72 (m, 6 H), 4.22 (br s, 1 H), 7.73 (d, 1 H), 7.84 (dd, 1 H), 7.98 (d, 1 H), 9.80 (br s, 1 H), 10.8 (br s, 1 H).

2-(3-Phenylpropyl)-1-azabicyclo[2.2.2]octan-3-one Hydrochloride (5a). The title compound was prepared from 6.02 g (33 mmol) of (2-bromoethyl)benzene and 2.05 g (15 mmol) of **12** by the procedure for **5b** in 40% yield. Recrystallization from 2-propanol gave **5a**: IR (Nujol) 1740 cm^{-1}; NMR (DMSO-d_6) δ 1.90 (m, 4 H), 1.96–2.23 (m, 4 H), 2.64 (m, 3 H), 3.24–3.58 (m, 4), 4.20 (m, 1 H), 7.18–7.38 (m, 5 H), 11.30 (br s, 1 H).

2-[3-(4-Chlorophenyl)propyl]-1-azabicyclo[2.2.2]octan-3-one Hydrochloride (5b). To 3.30 g (0.136 mol) of magnesium turnings in 50 mL of anhydrous diethyl ether under a nitrogen atmosphere was added slowly 28.6 g (0.13 mol) of 2-(4-chlorophenyl)ethyl bromide.[30] The reaction mixture was refluxed gently with stirring for 1.5 h. After this time the reaction mixture was cooled in an ice/methanol bath and 1.29 g (0.013 mol) of copper(I) chloride was added. To the chilled mixture was added slowly a suspension of 10.3 g (0.075 mol) of **12** in 30 mL of anhydrous diethyl ether. When the addition was complete, the reaction mixture was refluxed for 2 h. After this time the reaction mixture was cooled and then quenched with 25 mL of saturated ammonium chloride solution. The two-phase mixture was filtered, and the layers were separated. The aqueous layer was extracted with 50 mL of diethyl ether. The combined ether extracts were dried over anhydrous potassium carbonate. Removal of the drying agent by filtration and evaporation of the ether solvent afforded the crude free base as a green oil. The oil was redissolved in 25 mL of diethyl ether and hydrogen chloride gas was bubbled through the solution. Filtration of the resulting precipitate gave 13.2 g (56%) of crude hydrochloride salt. Recrystallization from 2-propanol provided **5b**: IR (KBr) 1740 cm^{-1}; NMR (DMSO-d_6) δ 1.88 (m, 4 H), 1.94–2.24 (m, 4 H), 2.62 (m, 3 H), 3.18–3.56 (m, 4 H), 4.18 (br s, 1 H), 7.30 (d, 2 H), 7.38 (d, 2 H), 11.42 (br s, 1 H).

***cis*-2-[3-(4-Chlorophenyl)propyl]-1-azabicyclo[2.2.2]octan-3-ol (6).** A suspension of 2.4 g (7.6 mmol) of **5b** in 10 mL of methylene chloride was treated with excess concentrated ammonium hydroxide. When the solid had dissolved, the layers were separated, and the methylene chloride layer was dried over anhydrous sodium sulfate. Removal of the drying agent by filtration and evaporation of the solvent in vacuo afforded the ketone free base, which was then dissolved in 25 mL of dry tetrahydrofuran. The solution was cooled to −78 °C under a nitrogen atmosphere and 16 mL of a 1 M solution of lithium tri-*sec*-butylborohydride (L-Selectride) in tetrahydrofuran was added dropwise. The progress of the reaction was followed by thin-layer chromatography on silica gel (acetonitrile/ammonium hydroxide, 9:1). At the completion of the reaction, the mixture was quenched with 25 mL of water. The aqueous mixture was acidified (pH 1) with concentrated hydrochloric acid and extracted with two 25-mL portions of diethyl ether (discarded). The aqueous phase was then made basic (pH 11) with concentrated ammonium hydroxide and extracted with three 25-mL portions of methylene chloride. The combined extracts were dried over anhydrous sodium sulfate. Removal of the drying agent by filtration and evaporation of the solvent gave the crude amino alcohol. Recrystallization from acetonitrile provided 1.4 g (65%) of **6**: NMR (DMSO-d_6) δ 1.12 (m, 1 H), 1.32–1.80 (m, 7 H), 2.40 (t, 1 H), 2.50–2.72 (m, 6 H), 2.78 (m, 1 H), 3.65 (m, 1 H, CHOH), 4.42 (d, 1 H CHO*H*), 7.20 (d, 2 H), 7.31 (d, 2 H). Anal. C, H, N; Cl: calcd, 12.67; found, 12.18.

2-[3-(4-Chlorophenyl)propyl]-1-azabicyclo[2.2.2]octane Hydrochloride (7). To 15.06 g (46 mmol) of **2b** in 75 mL of diethylene glycol were added 45 mL (0.93 mol) of hydrazine hydrate and 50.6 g (0.9 mol) of potassium hydroxide, and the mixture was heated at 100 °C for 3 h. The reaction flask was fitted with a distillation head and the mixture heated to 190 °C while the excess hydrazine and water were removed by distillation. The reaction temperature was maintained at 190 °C for 5 h and the reaction cooled to room temperature and then quenched with 500 mL of H_2O. The aqueous solution was taken to pH 1 with concentrated hydrochloric acid and extracted with 250 mL of diethyl ether. The aqueous solution was then taken to pH 11 with concentrated ammonium hydroxide and extracted with three

(30) Saunders, W. H., Jr.; Williams, R. A. *J. Am. Chem. Soc.* **1957**, *79*, 3712.

250-mL portions of methylene chloride. The combined methylene chloride extracts were dried over anhydrous potassium carbonate. The drying agent was removed and the solvent evaporated in vacuo to give the crude free base as an orange oil. The oil was dissolved in 50 mL of ethanol and this solution was acidified with hydrogen chloride gas. The ethanol was removed in vacuo and the residue triturated with diethyl ether to give 7.5 g (54%) of crude hydrochloride salt. Several recrystallizations from 2-propanol afforded **7**: NMR (DMSO-d_6) δ 1.37 (m, 1 H), 1.52–1.90 (m, 7 H), 2.00 (m, 2 H), 2.62 (t, 2 H), 2.98–3.46 (m, 5 H), 7.29 (d, 2 H), 7.38 (d, 2 H), 10.12 (br s, 1 H).

2-[3-(4-Chlorophenyl)propyl]-1-heptyl-3-oxo-1-azoniabicyclo[2.2.2]octane Phosphate (1:1) Dihydrate (8). A mixture of 2.2 g (7.9 mmol) of **5b** as free base and 10 mL (63 mmol) of heptyl bromide was heated at 90 °C under a nitrogen atmosphere for 24 h. After this time the reaction mixture was cooled to room temperature and triturated with anhydrous diethyl ether. The resulting solid was filtered and dissolved in 10 mL of water. The aqueous solution was passed through 6 g of Bio-Rad AG-1-X8 (hydroxide form) anion exchange resin. The basic fraction was titrated to pH 4.5 with phosphoric acid. The resulting solid was filtered to give 1.1 g (27%) of **8**: IR (KBr) 1730 cm^{-1}; NMR (DMSO-d_6) δ 0.87 (t, 3 H), 1.1–1.50 (m, 8 H), 1.58–2.16 (m, 8 H), 2.20–2.40 (m, 2 H), 2.64 (br s, 3 H), 3.24–3.70 (m, 4 H), 3.74–3.94 (m, 2 H), 4.16 (m, 1 H, NC*H*C=O), 6.00 (br s, 6 H, $H_2PO_4^-$ and H_2O), 7.27 (d, 2 H), 7.35 (d, 2 H).

(*E*)-3-[2-(4-Chlorophenyl)ethylidene]-1-azabicyclo[2.2.2]octane Hydrochloride (9). To 136.8 g (0.49 mol) of [2-(4-chlorophenyl)ethyl]phosphonic acid diethyl ester[16] in 1.4 L of dry 1,2-dimethoxyethane, which was cooled to −10 °C under a nitrogen atmosphere, was added 210 mL (ca. 0.56 mol) of 2.9 M *n*-butyllithium in hexane. The red solution was stirred for 1 h and then a solution of 59.0 g (0.47 mol) of 3-quinuclidinone (**16**) in 940 mL of 1,2-dimethoxyethane was added dropwise over 2 h. At the completion of the addition, the mixture was warmed to room temperature and then refluxed for 4 h. The reaction mixture was cooled to room temperature and 30 mL of methanol was added. The solvent was removed in vacuo. The residue was suspended in 300 mL of water and 90 mL of concentrated hydrochloric acid was added. The resulting precipitate was filtered, washed sparingly with water, and air-dried to give 32.3 g (24%) of crude **9**. The crude product was recrystallized from 2-propanol and then methanol to provide pure **9**: NMR (CD_3OD) δ 1.96 (m, 2 H), 2.12 (m, 2 H), 3.22 (m, 1 H, bridgehead), 3.25–3.50 (m, 6 H), 4.00 (s, 2 H, NCH_2C=), 5.60 (t, 1 H, olefinic), 7.20 (d, 2 H), 7.30 (d, 2 H).

(*E*)-3-[2-(4-Chlorophenyl)ethylidene]-1-heptyl-1-azoniabicyclo[2.2.2]octane Bromide (10). To 4.22 g (15 mmol) of **9** suspended in 100 mL of methylene chloride was added 20 mL of 1 N sodium hydroxide solution. The mixture was shaken thoroughly, and the layers were separated. The aqueous layer was further extracted with two 25-mL portions of methylene chloride. The combined methylene chloride extracts were dried over anhydrous sodium sulfate. The drying agent was removed and the filtrate evaporated in vacuo to give **9** as the free base. To the amine was added 16.0 g (89 mmol) of heptyl bromide. The mixture was heated at 115 °C for 10–15 min under a nitrogen atmosphere. The reaction mixture was cooled to room temperature and triturated with 25 mL of diethyl ether. The resulting solid was collected by filtration and then recrystallized two times from 2-propanol to give 3.14 g (49%) of **10**: NMR (DMSO-d_6) δ 0.87 (t, 3 H), 1.28 (br s, 8 H), 1.67 (m, 2 H), 1.84 (m, 2 H), 2.04 (m, 2 H), 3.18 (m, 4 H), 3.28–3.59 (m, 5 H), 4.09 (s, 2 H, NCH_2C=), 5.47 (t, 1 H, olefinic), 7.26 (d, 2 H), and 7.38 (d, 2 H).

3-[2-(4-Chlorophenyl)ethyl]-1-heptyl-1-azoniabicyclo[2.2.2]octane Bromide (11). A solution of 2.47 g (5.8 mmol) of **10** in 50 mL of acetic acid and 5 mL of water was hydrogenated at 40 psi over 0.2 g of 10% palladium-on-carbon catalyst. After 2 days the theoretical amount of hydrogen was taken up. The catalyst was filtered and the filtrate evaporated in vacuo. The residue was triturated with several portions of diethyl ether to give a hygroscopic solid. The solid was suspended in 100 mL of water and the pH of the mixture was adjusted to 10 with 20% aqueous sodium hydroxide solution. The aqueous mixture was extracted with three 50-mL portions of diethyl ether (discarded). The aqueous mixture was then taken to pH 2 with 48% aqueous hydrobromic acid and extracted with four 75-mL portions of methylene chloride. The combined organic extracts were dried over anhydrous sodium sulfate. Removal of the drying agent and evaporation of the solvent afforded 1.89 g (76%) of a waxy solid. Two recrystallizations from 99% aqueous acetone afforded analytically pure **11**: NMR (CF_3CO_2D) δ 0.67–2.37 (m, 21 H), 2.71 (t, 2 H, benzylic), 2.97–3.80 (m, 8 H, $(CH_2)_4N$), 7.00–7.47 (m, 4 H, aromatic).

4-Chloro-*N*,*N*-diethylbenzenebutanamine (17).[18] A solution of 1.5 g (5.5 mmol) of **18**[4] in 100 mL of ethanol and 0.5 mL of concentrated hydrochloric acid was hydrogenated over 0.17 g of platinum(IV) oxide in a Parr apparatus. When the reaction was complete, the catalyst was removed by filtration and the solvent removed in vacuo. The oily hydrochloride was converted to the free base by addition of 10% aqueous sodium hydroxide and extraction with methylene chloride. After evaporation of the solvent, the crude free base was chromatographed on silica gel with methylene chloride/methanol. The hydrochloride salt was reformed by addition of 10% hydrochloric acid to an ethanolic solution of the free base. After evaporation of the solvent the residue was recrystallized from ethyl acetate to provide 0.38 g (25%) of **17**: mp 72–74 °C; NMR (DMSO-d_6) δ 1.18 (t, 6 H), 1.54–1.72 (m, 4 H), 2.58–2.74 (m, 2 H), 2.96–3.16 (m, 6 H), 7.25 (d, 2 H), 7.35 (d, 2 H), 7.88 (br s, 1 H). Anal. ($C_{14}H_{22}ClN$·HCl) C, H, N.

Pharmacology. The experimental protocols describing the intracellular electrophysiological studies in canine Purkinje fibers,[4] the extracellular studies in ventricular muscle,[25a] the intraduodenal activity studies in anesthetized dogs,[4] and the PES efficacy model[25a] have been reported previously.

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Registry No. **2a**·HCl, 80473-34-3; **2b**·HCl, 104536-20-1; **2c**·HCl, 104536-26-7; **2d**, 110473-43-3; **2e**, 110473-44-4; **2f**, 104536-44-9; **2f**·HCl, 104536-24-5; **3a**·HCl (isomer 1), 80473-29-6; **3a**·HCl (isomer 2), 80473-37-6; **3b**·HCl (isomer 1), 110473-45-5; **3b**·HCl (isomer 2), 110473-63-7; **3c**·HCl (isomer 1), 110473-46-6; **3c**·HCl (isomer 2), 110473-64-8; **4c**·HCl (isomer 1), 110473-47-7; **4c**·HCl (isomer 2), 110473-65-9; **4d**·HCl (isomer 1), 110473-48-8; **4d**·HCl (isomer 2), 110473-66-0; **4e**·HCl (isomer 1), 110473-49-9; **4e**·HCl (isomer 2), 110486-13-0; **4f**·HCl, 110473-50-2; **5a**·HCl, 110473-51-3; **5b**, 104536-33-6; **5b**·HCl, 104536-07-4; **6**, 110473-52-4; **7**·HCl, 104536-21-2; **8**, 104536-17-6; **9**·HCl, 110473-53-5; **10**, 110473-54-6; **11**, 104535-98-0; **12**, 5291-26-9; **13**, 5832-55-3; **14c**, 838-57-3; **14d** (keto), 110473-55-7; **14d** (enol), 110473-58-0; **14e** (keto), 110473-56-8; **14e** (enol), 110473-59-1; **14f** (keto), 110473-57-9; **14f** (enol), 110473-61-5; **15**, 110473-60-4; **16**, 3731-38-2; **17**·HCl, 110473-62-6; **18**·HCl, 102285-51-8; $PhC(O)CH_2C(O)CH_3$, 93-91-4; *p*-$ClC_6H_4C(O)CH_2C(O)CH_3$, 6302-55-2; *p*-$NO_2C_6H_4C(O)CH_2C(O)CH_3$, 4023-82-9; $Br(CH_2)_2Ph$, 103-63-9; *p*-$ClC_6H_4(CH_2)_2Br$, 6529-53-9; ethyl 4-amino-β-oxobenzenepropanoate, 61252-00-4; ethyl acetoacetate, 141-97-9; 4-chloro-3-nitrobenzoyl chloride, 38818-50-7; heptyl bromide, 629-04-9; diethyl [2-(4-chlorophenyl)ethyl]-phosphonate, 85093-30-7.