Pharmacological Testing. Antiinflammatory activity was examined by the method of Winter et al.[11] Ten male SLC-SD rats were used for each group. The rat hind paw volume was measured by displacement in a water bath, and the test compound, as a suspension in a 0.5% sodium carboxymethylcellulose solution (0.5% CMC), was administered orally. Thirty minutes later, 0.1 mL of 1% carrageenan was injected subcutaneously into the plantar surface of the hind paw. Three hours later, paw volume was measured again. The increase in paw volume of the drug-treated rat was compared with that of the control group for calculation of the percent inhibition.

Analgesic activity was evaluated by the AcOH writhing assay.[12] Six male STD-ddY mice were used for each group. The test compound was administered orally as a suspension in 0.5% CMC. Thirty minutes later, 0.1 mL/10 g of 0.6% AcOH was injected into the peritoneal cavity, and then the frequency of the repeated characteristic writhing movements were measured for 20 min. The response of the drug-treated mouse was compared with the response using acetic acid alone.

Acute toxicity, expressed as a LD_{50} value calculated by the method of Weil,[13] was determined 168 h after a single ip injection to groups of four male ddY mice.

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New Antiarrhythmic Agents. 4. 1′-(Aminoalkyl)-1,2,3,4-tetrahydronaphthalene-1-spiro-3′-pyrrolidine-2′,5′-dione Derivatives

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A series of 33 1′-(Aminoalkyl)-1,2,3,4-tetrahydronaphthalene-1-spiro-3′-pyrrolidine-2′,5′-dione derivatives was tested for antiarrhythmic and toxic effects in mice and dogs. In mice, 31 compounds produced some protection against chloroform-induced tachyarrhythmias at subcutaneous doses of 100 mg/kg, and 6 compounds produced no detectable toxicity at doses protecting 80% or more of the animals. Seven of the more potent and nontoxic derivatives were tested in dogs with surgically induced myocardial infarctions. All produced distinct antiarrhythmic effects at doses considerably lower than doses of lidocaine or tocainide producing comparable effects. The principal toxic effects observed in dogs were convulsion and depression of intracardiac conduction; they occurred generally at higher doses than those leading to antiarrhythmic effect. Several compounds also suppressed digitalis-induced arrhythmias in anesthetized dogs. Half-lives and total body clearance in dogs were determined for three compounds; two had half-lives comparable to that of tocainide, a long-acting, orally active antiarrhythmic agent, in clinical trials.

Antiarrhythmic agents are now widely used in the treatment and prevention of life-threatening cardiac arrhythmias. However, despite their widespread use, none of the presently available agents are ideal; each has its shortcoming.[1] The need for more effective and/or safer agents for treating arrhythmias is reflected in the growing list of new compounds undergoing clinical trial, for example, amiodarone, aprindine, ethmozin, mexiletine, tocainide, and verapamil.[2]

In considering possible approaches to the development of new agents, we were cognizant that many, if not all, direct-acting antiarrhythmic agents possess local anesthetic actions,[3] including quinidine, procainamide, bretylium, disopyramide, aprindine, and mexiletine. Conversely, many local anesthetic agents have antiarrhythmic effects,[4] including procaine, dibucaine, tetracaine, hexylcaine, piperocaine, prilocaine, mepivacaine, and bupivacaine. Lidocaine is a striking example of this interrelation, since it is used for both its local anesthetic and antiarrhythmic effects. The local anesthetic and antiarrhythmic effects

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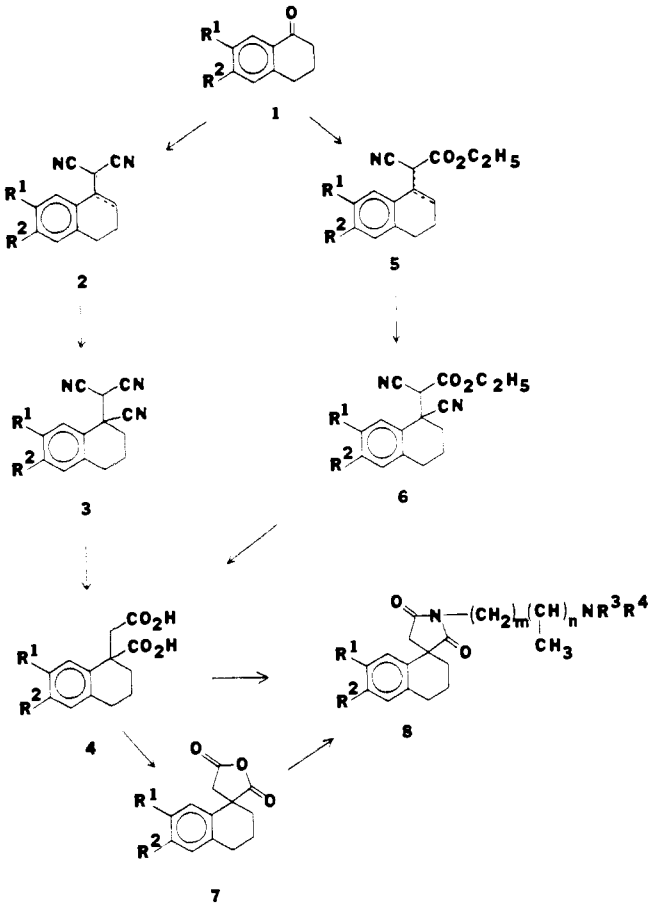
Scheme I



shared by these compounds may reflect common or similar actions on sodium and/or other channels in the excitable membranes of both neurons and cardiac cells.[5]

Recently, we synthesized a series of new tetralinespirosuccinimides and evaluated them as potential new local anesthetic agents.[6,7] Because of the clinical need for new, orally effective, long-acting antiarrhythmic drugs, and in view of the commonality of local anesthetic and antiarrhythmic effects, we also investigated the potential of these compounds as antiarrhythmic agents. We report here the results of the pharmacological testing of these compounds for antiarrhythmic and toxic effects in mice and dogs and present data on half-lives and total body clearances in dogs for three compounds.

Chemistry. The synthetic route to the target compounds is outlined in Scheme I. α-Tetralone derivatives, 1, were condensed with malononitrile according to Mowry.[8] The tetrahydronaphthylidenemalononitriles, 2, obtained were converted to the tricyano compounds, 3, by treatment with sodium cyanide, followed by hydrochloric acid. Hydrolysis and decarboxylation yielded the diacid derivatives, 4. Alternatively, condensation of α-tetralone derivatives with ethyl cyanoacetate, addition of hydrogen cyanide, and acidic hydrolysis (1 → 5 → 6 → 4) also yielded the diacids 4. These were cyclized to the anhydrides 7, which were aminated with the appropriate aminoalkylamines to give the target compounds 8. Alternatively, amination of the diacid derivatives, 4, also yielded the target compounds.

Details of the synthetic work are published elsewhere.[6,7] The Experimental Section describes the synthesis of several new compounds, as well as an improvement in methodology.

Pharmacology. All compounds were evaluated for their ability to prevent chloroform-induced tachyarrhythmia in unanesthetized mice according to the method described by Lawson.[9] Drugs, dissolved in 0.9% saline, were injected subcutaneously into groups of 10 mice. For 20 min the mice were observed for overt signs of toxicity and were then placed individually in an atmosphere saturated with chloroform vapor. When respiration ceased, the thorax was opened and the presence or absence of fibrillation was determined visually. If coordinated ventricular contractions were observed, the mouse was considered to be "protected" from the arrhythmogenic effects of chloroform. This procedure was used for two types of tests. In a preliminary test, each drug was administered at a dose of 100 mg/kg. For more complete testing, at least three doses of drug were chosen to give low, intermediate, and high degrees of protection against fibrillation. From these data, the ED_{50} and the 95% Fieller limits were calculated according to the logit chi-square method of Berkson.[10]

Certain of the compounds were further tested against ventricular arrhythmias. These were induced in adult female dogs (6.7–14.5 kg) by two-stage ligation of the left anterior descending coronary artery[11,12] on the day before testing. Control data were gathered and the drug, as the hydrochloride in isotonic solution, was infused intravenously (without anesthesia or sedation) at a rate of 0.1, 0.5, or 1.0 (mg/kg)/min until the arrhythmia was abolished or, in some cases, cardiovascular or central nervous system toxicity developed.

The antiarrhythmic activity of four compounds was evaluated in pentobarbital-anesthetized dogs with ventricular arrhythmias induced by ouabain. After three control electrocardiograms were taken, serial doses of ouabain were injected intravenously until a persistent ventricular arrhythmia developed. An initial dose of 40 μg/kg of ouabain was followed by 20 μg/kg 30 min later, and additional doses of 10 μg/kg were given at successive 30-min intervals if required. All doses were given over a period of 2 min.

After the arrhythmia had persisted for 10 min, the compound being evaluated was administered intravenously at an infusion rate of 2 (mg/kg)/min until 60 s after reversion to normal sinus rhythm. Thus, each dog received 2 mg/kg of the drug in excess of that required to abolish the arrhythmia.

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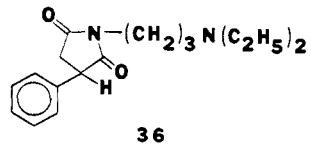
Pharmacokinetics. The pharmacokinetics of three compounds were estimated using blood-level data from dogs in which antiarrhythmic effects were being studied. Half-lives were calculated from the log linear terminal concentrations following discontinuation of the infusion. Total body clearances were calculated by dividing the total dose by the area under the blood level curve (zero to infinity). Volumes of distribution were calculated by dividing clearance by the elimination rate constant.

Results and Discussion

The structures of the target compounds as well as their antiarrhythmic and toxic effects in mice are listed in Table I. Test results obtained with four related compounds (**36**–**39**) and with the reference compounds lidocaine and



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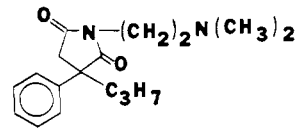

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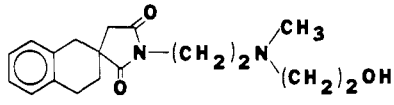

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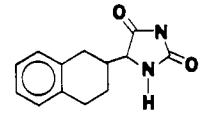

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tocainide are also given. All compounds exhibited some antiarrhythmic effect except **25** and **27**, and several showed good separation between antiarrhythmic effect and toxicity: **11**, **21**, **30**–**32**, and (±)-**35** produced no apparent toxicity at doses which protected 80% or more of the animals. Approximately one-half of the compounds were subjected to further testing, employing three or four doses, and ED_{50} values for protection were calculated for 17 of them. The range of ED_{50} values obtained was rather small, since the weaker or more toxic compounds were not tested at multiple doses. Where toxicity in the form of ataxia was observed at the doses selected to quantitate antiarrhythmic effects, ED_{50} values for ataxia also were calculated. No effort was made to quantitate toxic effects of the less toxic compounds, e.g., **11**, **21**, **30**–**32**, and (±)-**35**.

Based on the limited biological information, only tentative conclusions regarding structure–activity relationships could be drawn. Comparisons of the series **11**, **21**, **31**; **10**, **17**, **29**, (±)-**35**; and **9**, **14**, **28** demonstrated that increasing the length of the intermediate chain between the two nitrogen atoms did not influence potency and had no effect on toxicity, except possibly a slight reduction in one case [(±)-**35** vs. **29**]. Comparisons of the series **9**, **10**; **14**, **17**; and **28**, **29** established that the modification of the amine substituents from R^3, R^4 = CH_3, CH_2CH_2OH to R^3 = R^4 = C_2H_5 led to an increase of both potency and toxicity. Tentative conclusions regarding the effect of ring substitution (R^1, R^2) could be drawn from the following comparisons. In the series **29**, **31**, **33**, introduction of a hydroxy group in the 7 position (R^1) led to a reduction in toxicity without affecting potency, as compared to R^1 = H, and to a better potency than a hydroxy group in the 6 position (R^2). In the series **17**, **19**, **20**, **21**, **24**, potency again was not changed by substitution in the 7 position, but derivatives with R^1 = CH_3 or OH were less toxic than derivatives with R^1 = H, Cl, and $(CH_3)_2CHO$. Finally, a general comparison of the results in Table I indicated that four of the six compounds with high selectivity have a substituent R^1 = OH, one has R^1 = CH_3O, and one has R^1 = H and that compounds with a substituent in the 6 position (**13**, **25**–**27**) were of little interest except **33**. Derivatives with other structural modifications, e.g., opening of the saturated tetraline ring (**36**, **37**), shifting the spiral carbon to the 2 position (**38**), or modifying the succinimide to a hydantoin ring (**39**), did not give any promising leads.

Seven compounds were evaluated for their effects in dogs with ventricular arrhythmias produced by coronary artery ligation. Six of them were given by continuous intravenous infusion until either antiarrhythmic and/or toxic effects were seen. These results are summarized in Table II. All six compounds, **11**, **21**, **23**, **30**, **31**, and **32**, exhibited distinct antiarrhythmic effects, each being capable of essentially abolishing these arrhythmias. They were 4–14 times more potent than lidocaine. The principal toxic effects produced by these compounds were depression of intracardiac conduction (increased P-R interval of the electrocardiogram of normal sinus beats) (**21** and **31**), convulsion (**23**), or the combination of both effects (**11**, **30**, and **32**). For compounds **21**, **31**, and **32** there was a consistent separation of antiarrhythmic and toxic effects.

Compound (±)-**35** was tested for effects upon oral administration. It was administered as two or more oral doses of 25, 50, or 100 mg/kg to each of four dogs, with doses separated by at least 1 h. Distinct antiarrhythmic effects were seen in all dogs, but in each case the suppression of the arrhythmias was accompanied by an increase in the rate of the sinoatrial node. In each animal convulsions were produced when dosing was continued and were either preceded by or accompanied by a distinct mydriasis.

Blood levels were determined in the majority of experiments assessing antiarrhythmic and toxic effects in dogs. If toxicity occurred at a higher dose than antiarrhythmic effects, therapeutic margins based on blood levels were consistently smaller than those based on cumulative doses. This relationship applied for cardiotoxity (e.g., P-R prolongation with **21** or A-V block with **30**), as well as for CNS toxicity (e.g., convulsions with **30**).

Because pharmacokinetic properties are relevant to the selection of antiarrhythmic agents for clinical use, pharmacokinetic parameters were calculated for three compounds. Sufficient blood-level data for an analysis was available for **21**, **30**, and **32** (Table III).

The plasma half-lives of **21** and **32** were relatively long compared to that of lidocaine (45 min)[13] and similar to that of tocainide (282 min)[14] in the dog. Tocainide has a half-life of 11 h or longer in man.[15] Based on this fact and on the similar pharmacokinetics of **21**, **32**, and tocainide in the dog, we might expect these compounds to have suitable pharmacokinetic properties for an oral agent in man. With data available for three compounds only, it is difficult to generalize on the influence of structural effects on pharmacokinetic parameters. Conceivable pathways of metabolism for this group of drugs might be the conjugation of the aromatic hydroxyl group and N-dealkylation. The results indicated that the presence or absence of a free hydroxyl group did not have a major influence on half-life: **21** and **32**, both diethylamines, had half-lives in the range of 3–4 h. On the other hand, the dimethyl-

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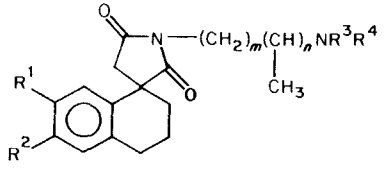
Table I. Structures of Spirosuccinimides Derivatives and Their Antiarrhythmic and Toxic Effects in Mice



							preliminary test						complete test	
									toxicity, %					
compd	R^1	R^2	R^3	R^4	m	n	dose,[a] mg/kg	protection,[b] %	at.[c]	c[d]	lrr[e]	d[f]	ED_{50}[a,b,g] for protection, mmol/kg	ED_{50}[a,g] for ataxia, mmol/kg
9	H	H	CH_3	$(CH_2)_2OH$	2	0	100	30	0	0	0	0	*h*	*h*
10	H	H	C_2H_5	C_2H_5	1	1	100	50	100	100	0	0	*h*	*h*
11	HO	H	C_2H_5	C_2H_5	2	0	79	90	0	0	0	0	0.15 (0.12-0.20)	*h*
12	HO	H	C_2H_5	C_2H_5	1	1	100	60	50	0	0	0	*h*	*h*
13	H	CH_3O	CH_3	CH_3	2	0	100	20	100	0	0	0	*h*	*h*
14	H	H	CH_3	$(CH_2)_2OH$	3	0	100	30	0	0	0	0	0.56 (0.36-1.22)	0.76 (0.44-4.64)[i]
15	H	H	CH_3	$(CH_2)_2OCH_3$	3	0	100	30	100	100	100	0	*k*	*h*
16	H	H	$-(CH_2)_2O(CH_2)_2-$		3	0	100	20	100	0	0	0	*h*	*h*
17	H	H	C_2H_5	C_2H_5	3	0	100	80	100	0	0	0	0.20 (0.14-0.32)	0.19 (0.13-0.43)
18	H	H	C_2H_5	C_2H_5	2	1	100	40	100	0	0	0	*h*	*h*
19	Cl	H	C_2H_5	C_2H_5	3	0	100	90	100	0	0	0	0.16 (0.12-0.25)	0.11 (0.05-0.16)
20	CH_3	H	C_2H_5	C_2H_5	3	0	100	70	0	0	0	0	0.21 (0.14-0.43)	*h*
21	HO	H	C_2H_5	C_2H_5	3	0	100	80	0	0	0	0	0.09 (0.04-0.20)	*h*
22	HO	H	C_2H_5	C_2H_5	2	1	100	80	100	100	100	20	0.08 (0.05-0.11)	0.08 (0.01-0.11)
23	$(CH_3)_2CHO$	H	CH_3	CH_3	3	0	100	50	100	0	10	0	*h*	*h*
24	$(CH_3)_2CHO$	H	C_2H_5	C_2H_5	3	0	100	90	100	100	0	0	0.14 (0.10-0.17)	0.11 (0.05-0.15)
25	H	CH_3O	CH_3	CH_3	3	0	100	0	100	0	0	0	*h*	*h*
26	H	CH_3O	C_2H_5	C_2H_5	3	0	100	40	100	20	0	0	*h*	*h*
27	H	CH_3O	C_2H_5	C_2H_5	2	1	100	0	60	0	0	0	*h*	*h*
28	H	H	CH_3	$(CH_2)_2OH$	4	0	100	10	0	0	0	0	*h*	*h*
29	H	H	C_2H_5	C_2H_5	4	0	100	90	100	0	0	0	0.18 (0.11-0.28)	0.18 (0.12-0.41)
30	HO	H	CH_3	CH_3	4	0	100	100	0	0	0	0	0.16 (0.12-0.28)	*h*
31	HO	H	C_2H_5	C_2H_5	4	0	79	100	0	0	0	0	0.13 (0.10-0.20)	*h*
32	CH_3O	H	C_2H_5	C_2H_5	4	0	100	80	0	0	0	0	0.13 (0.07-0.25)[l]	*h*
33	H	HO	C_2H_5	C_2H_5	4	0	100	70	0	0	0	0	0.26 (0.20-0.39)	*h*
34	H	H	H	H	5	0	100[m]	20	0	0	0	0	*h*	*h*
(±)-35	H	H	C_2H_5	C_2H_5	5	0	100	80	0	0	0	0	0.24 (0.19-0.36)	*h*
(+)-35	H	H	C_2H_5	C_2H_5	5	0	100	50	100	0	0	0	0.21 (0.15-0.30)	*h*
(−)-35	H	H	C_2H_5	C_2H_5	5	0	100	90	100	30	0	0	0.16 (0.13-0.20)	*h*
36[q]			see text				100	30	0	0	0	0	*n*	*h*
37[q]			see text				100	40	100	0	0	0	0.39 (0.27-0.57)	0.27 (0.12-0.41)
38[q]			see text				100	30	100	40	0	0	*k*	*h*
39			see text				100	20	0	0	0	0	*h*	*h*
lidocaine[r]							100	100	100	100	100	0	0.26 ± 0.09[o]	0.18 (0.17-0.20)
tocainide[r]							100	20	10	0	0	0	1.3 ± 0.6[p]	0.76 (0.63-0.89)

[a] Subcutaneous administration. [b] Protection against chloroform-induced arrhythmias. [c] Ataxia. [d] Convulsions. [e] Loss of righting reflex. [f] Death. [g] 95% Fieller limits in parentheses. [h] ED_{50} not determined. [i] At 398 mg/kg, 90% of the animals had bloody urine. [k] ED_{50} not determined due to deaths at high doses. [l] 95% Fieller limits approximate due to limited biological responses. [m] At 100 mg/kg, 20% of the mice had bloody urine. [n] ED_{50} not determined due to poor dose-response curve. [o] Mean and standard deviation of 72 determinations. [p] Mean and standard deviation of 14 determinations. [q] See ref 7. [r] See ref 16.

Table II. Antiarrhythmic and Toxic Effects of Spirosuccinimides in Dogs with Myocardial Infarction

		control values[a]			values at max antiarrhythmic effect[b]					toxicity		
compd	exp no.	vent rate, bpm	ectopic beats, %	MABP, mmHg	cum dose, mmol/kg	blood level, μmol/mL	vent rate, bpm	ectopic beats, %	MABP, mmHg	nature	cum dose	blood level, μmol/mL
11	1	162	97	110	0.026		132	3	130	convulsion; prolonged P-R[c]	0.042;[d] 0.042	
	2	156	100	80	0.053		102	7	135	convulsion; prolonged P-R[c]	0.026;[d] 0.026	
21	3	210	86	100	0.004	0.019	168	3	85	prolonged P-R[c]	0.007	0.022
	4	228	100	115	0.014[e]	0.010	150	0		prolonged P-R[c]	0.029[d]	0.015
	5	195	98	115	0.028[e]		153	6	125	prolonged P-R[c]	0.035[d]	
23	6	141	100	65	0.038[f]		120	2	75		ND[g]	
	7	222	99	95	0.084	0.021	138	15	125	convulsion	0.077[d]	0.021
	8	171	96	90	0.042		150	4	90	convulsion	0.133[d]	
	9	174	90	80	0.056		171	5	110		ND[g]	
	10	180	97	100	0.042	0.013	165	17	100	convulsion	0.066	0.019
30	11	231	96	90	0.058	0.017	171	4	95	prolonged P-R[c]	0.015	0.012
	12	204	100	95	0.038	0.023	171	0	105		>0.083	
	13	180	93	105	0.018	0.022	150	1	120	A-V block; convulsion	0.048; 0.245	0.028; 0.062
	14	171	95	95	0.023	0.020	138	93	110	A-V block; convulsion	0.053; 0.109	0.013; 0.038
	15	228	94	95	0.015	0.024	165	0	85	A-V block; convulsion	0.023; 0.045	0.030; 0.043
	16	186	96	105	0.053	0.028	183	3	135	A-V block; convulsion	0.065; 0.182	0.030; 0.056
31	17	222	94	95	0.005[e]		162	2	80		ND[g]	
	18	219	97	105	0.026[e]		132	0	90		ND[g]	
	19	258	98	55	0.021[e]		168	0	70		ND[g]	
	20	231	100	75	0.042[e]		147	0	100		>0.058	
	21	180	94	110	0.017[e]	0.016	153	2	95		>0.126	>0.028
	22	204	92	70	0.029[e]	0.007	141	0	90	prolonged P-R[c]	0.063	0.010
32	23	222	100	80	0.047	0.020	165	0	100	convulsion; prolonged P-R[c]	0.081[d]	0.029
	24	171	88	80	0.016	0.011	147	1	95	prolonged P-R[c]	0.020[d]	0.018
lidocaine[h]		174 ± 34	96 ± 5	81 ± 11	0.21 ± 0.19		133 ± 16	4 ± 3	101 ± 21	convulsion	0.27 ± 0.15	
tocainide[i]		207 ± 25	94 ± 5	91 ± 19	0.32 ± 0.11		148 ± 16	2 ± 2	108 ± 21	convulsion	0.30 ± 0.06	

[a] Ventricular rate (beats/min); ectopic beats (% of ventricular rate); mean arterial blood pressure (mmHg) before start of drug infusion. [b] Drugs infused at 0.5 (mg/kg)/min. [c] Prolongation of the P-R interval of normal sinus beats by 25% or more. [d] Emesis at lower doses. [e] Infusion rate = 0.1 (mg/kg)/min. [f] Infusion rate = 1.0 (mg/kg)/min. [g] ND = not determined. Infusion terminated before toxicity was observed. [h] Means and standard deviations of five experiments. [i] Means and standard deviations of 14 experiments (antiarrhythmic effects) and eight experiments (toxicity).

Table III. Pharmacokinetics

compd	exp no.	total dose, μmol/kg	max concn, μmol	$T_{1/2}$,[a] min	Cl_B,[b] (mL/min)/kg	V_D,[c] L/kg
21	3	25	31	290	3.81	1.58
	4	29	15	185	6.06	1.60
	$\bar{X}$			226	4.94	1.59
30	11	227	37	80	31.6	3.35
	12	83	30	120	17.5	3.02
	$\bar{X}$			96	24.6	3.33
32	23	81	29	230	10.4	3.41
	24	43	20	210	8.22	2.47
	25	34	12	144	12.8	2.64
	$\bar{X}$			187	10.5	2.84

[a] Harmonic mean. [b] Total body clearance. [c] Volume of distribution.

amine **30** had a short half-life, indicating that N-dealkylation may be the predominant pathway and that N-demethylation may occur more readily than N-deethylation.

Four compounds, **21** and **30–32**, were studied further for their ability to suppress ouabain-induced arrhythmias in pentobarbital-anesthetized dogs. All of these substances except **31** produced antiarrhythmic effects at cumulative doses of 3.0–13.5 mg/kg. **31** suppressed the arrhythmia in one dog, but in three other animals even lethal doses were ineffective. In three normal, unanesthetized dogs intravenous infusions of **31** were arrhythmogenic, actually provoking arrhythmias at doses of 17.4–19.6 mg/kg, the lethal doses being 47.2–58.6 mg/kg.

Each of the seven substances evaluated in the dog possessed one or more undesirable features. **11**, **23**, and **30** all had rather low margins of safety in unanesthetized dogs with coronary occlusion-induced arrhythmias, especially when blood levels were considered. **31** also had a rather low margin of safety, failed to suppress ouabain-induced arrhythmias, and at high doses was arrhythmogenic. Relatively low doses of (±)-**35**, which was tested orally, produced both an increase in sinus rate and mydriasis, suggesting either that it possessed rather pronounced anticholinergic activity or that in some other manner it interfered with cholinergic neuroeffector transmission and/or function.

21 and **32**, the two remaining compounds, exhibited distinct antiarrhythmic effects in the dogs and, in addition, **21** had a rather long plasma half-life. Unfortunately, while both compounds exhibited at least some margin of safety in the dog, the margin was low and, furthermore, the toxicity observed represented depression of intracardiac conduction. Compounds which have strong depressant effects on intracardiac conduction probably are not acceptable for use in most patients with cardiac arrhythmias and underlying heart disease.

Conclusion

With the objective of finding new, long-acting and orally active antiarrhythmic agents, we investigated the antiarrhythmic and toxic effects of 33 tetralinespirosuccinimides, a new class of local anesthetic compounds. The rationale for this approach to the design of new antiarrhythmic agents was the recognition that many antiarrhythmic drugs have local anesthetic properties and, conversely, many local anesthetic drugs have antiarrhythmic properties. Most of the 33 compounds provided some protection against chloroform-induced tachyarrhythmias in mice; among these, several of the more potent and nontoxic compounds were also effective against ventricular arrhythmias induced in dogs either by coronary artery ligation or by administration of ouabain. Two compounds were found to have a long half-life in dogs, indicating the possibility of finding compounds with a long half-life and low metabolic clearance in man. These results, viz., effectiveness against arrhythmias in three different animal models and desirable pharmacokinetic parameters, indicate the viability of our approach. However, the cardiovascular toxicity associated with several of these compounds exclude them from further consideration as potential new antiarrhythmic agents.

Experimental Section

Blood Level Analysis. A similar analytical procedure was used in the dog experiments to analyze five of the compounds in blood. Samples of 1 mL of blood, 1 mL of internal standard, and 1 mL of buffer were extracted with 5 mL of methylene chloride. The extraction mixture was mixed gently for 20 min and centrifuged to separate the phases, the aqueous layer was discarded, and the methylene chloride was evaporated to dryness at 50 °C. The dry residue was dissolved in 20 μL of methylene chloride and reacted with 20 μL of heptafluorobutyrylimidazole. After the solution was mixed, 1 μL was injected on a gas chromatograph equipped with a flame-ionization detector. The buffer used in the extraction was pH 10.3 and consisted of equal parts of 2 M ammonium citrate and 28% ammonia. Compound **31** was the internal standard for the analysis of **23**, **30**, and **32**, and compound **30** was the internal standard for **21** and **31**. The gas chromatograph conditions were as follows: 2 m × 2 mm glass column packed with 3% JXR (Varian, Walnut Creek, CA); injector, column, and detector temperatures of 250, 220, and 250 °C, respectively. Concentrations were calculated from the peak height ratio of drug to internal standard and established standard curves.

Chemistry. Melting points were determined on a Buchi melting point apparatus and are uncorrected. Analyses were performed by Professor K. J. Karrman, Lund, Sweden, (N, Cl), or at the Astra Control Laboratories, Sodertalje, Sweden (N, neutralization equivalent). Where analyses are indicated by symbols of elements, the analytical results are within ±0.4% of the theoretical values.

1′-[2-(Diethylamino)ethyl]-7-hydroxy-1,2,3,4-tetrahydronaphthalene-1-spiro-3′-pyrrolidine-2′,5′-dione (11). 1-Carboxy-7-hydroxy-1,2,3,4-tetrahydronaphthaleneacetic acid[6] (5.00 g, 20 mmol) and 2-(diethylamino)ethylamine (2.33 g, 20 mmol) were mixed and heated at 180 °C for 1.5 h. The product was distilled (bp 215–220 °C at 0.4 mm) to yield 5.0 g (76%) of **11**, and the distilled base was converted to the hydrochloride salt. Recrystallization from ethyl acetate–methanol gave 4.1 g of **11**·HCl, mp 223–228 °C. Anal. ($C_{19}H_{26}N_2O_3$·HCl) N, Cl.

1′-[4-(Diethylamino)butyl]-6-hydroxy-1,2,3,4-tetrahydronaphthalene-1-spiro-3′-pyrrolidine-2′,5′-dione (33). 1-Carboxy-6-hydroxy-1,2,3,4-tetrahydronaphthaleneacetic acid[6] (4.50 g, 18 mmol) and 4-(diethylamino)butylamine (2.59 g, 18 mmol) were mixed and heated at 180 °C for 1.5 h. The product was converted to the hydrochloride and recrystallized from 2-propanol, yielding 5.6 g (79%) of **33**·HCl, mp 178.5–181 °C. Anal. ($C_{21}H_{30}N_2O_3$·HCl) N, Cl.

1′-(5-Aminopentyl)-1,2,3,4-tetrahydronaphthalene-1-spiro-3′-pyrrolidine-2′,5′-dione (34). A solution of 1-carboxy-1,2,3,4-tetrahydronaphthaleneacetic acid anhydride[6] (4.3 g, 200 mmol) in benzene (40 mL) was added dropwise to a solution of 1,5-diaminopentane (20.4 g, 200 mmol) in benzene (100 mL). The solvent and excess amine were distilled off, and the residue was heated at 170 °C for 2 h. The product was distilled, yielding 3.6 g (60%) of **34**, bp 205 °C (0.9 mm). Anal. ($C_{18}H_{24}N_2O_2$) N; neutralization equivalent: calcd, 300.41; found, 297.6.

1-Carboxy-7-hydroxy-1,2,3,4-tetrahydronaphthaleneacetic Acid (4, R^1 = HO; R^2 = H). A mixture of **3**[6] (R^1 = CH_3O, R^2 = H; 25.1 g, 0.1 mol), acetic acid (35 mL), and concentrated HCl (92 mL) was heated under reflux for 24 h, at which time GC analysis (OV 17, 200–250 °C at 20 °C/min) showed that the starting material was completely converted to a mixture of the 7-hydroxy and 7-methoxy derivatives of **4**. The mixture was cooled and saturated with gaseous HCl. Sodium iodide (7.5 g, 0.05 mol) was added and the heating was continued for 48 h. More HCl (to saturation) and NaI (1.0 g, 0.007 mol) was added, and after

24 h of further heating the reaction was found complete (>98%) by GC. The mixture was cooled, the solvent was removed by distillation, and ammonium hydroxide (60 mL) was added. After the solution was filtered, the pH of the filtrate was adjusted to 1 with concentrated HCl. The precipitate was filtered and dried, yielding 22.8 g (91%) of 4 (R^1 = HO; R^2 = H), mp 205–206 °C. Recrystallization from methanol–water (1:10) gave 19.8 g (79%), mp 208–211 °C, 99% pure by GC.

Enantiomers of 1′-[5-(diethylamino)pentyl]-1,2,3,4-tetrahydronaphthalene-1-spiro-3′-pyrrolidine-2′,5′-dione (35). Equimolar amounts of 5-(diethylamino)-1-pentylamine and the respective enantiomer of 1-carboxy-1,2,3,4-tetrahydronaphthalene-1-acetic acid were heated together at 160 °C for 1.5 h. The product was dissolved in dilute hydrochloric acid, and the aqueous solution was washed with diethyl ether and then made alkaline with dilute sodium hydroxide solution. The precipitated base was taken up in diethyl ether, and the ether solution was washed with water and then dried over potassium carbonate. The hydrochloride was precipitated from the ether solution by means of hydrogen chloride in diethyl ether. Recrystallization from 2-pentanone yielded the enantiomers of **35**·HCl, mp 172.5–174.5 °C (71%). (−)-Imide from the (+)-acid: $[\alpha]^{20}_D$ −0.22° (95% ethanol, 5% solution). Anal. ($C_{22}H_{32}N_2O_2$·HCl) Cl. (+)-Imide from the (−)-acid, $[\alpha]^{20}_D$ +0.36° (95% ethanol, 5% solution).

1-[2-(Dimethylamino)ethyl]-3-phenyl-3-propylpyrrolidine-2,5-dione (37). Equimolar amounts of 2-phenyl-2-propylsuccinic acid and (dimethylamino)ethylamine were heated together at 160 °C for 1.5 h. The product was distilled [bp 112–116 °C (0.01 mm Hg)] and converted to the hydrochloride, which was recrystallized from ethanol–diethyl ether, yielding **37**·HCl, mp 175.5–177.5 °C (54%). Anal. ($C_{17}H_{24}N_2O_2$·HCl) Cl.

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New Antiarrhythmic Agents. 5. α-Aminoaceto-2,6-xylidides with Functionalized Amide Alkyl Substituents

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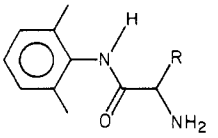
The synthesis of aminoaceto-2′,6′-xylidides substituted on the amide nitrogen with 2-(diethylamino)ethyl, 2-aminoethyl, 2-hydroxyethyl, and 2-ethoxyethyl groups is described. The 2-aminoethyl derivatives were prepared by treatment of *N*-(2-phthalimidoethyl)-2′,6′-xylidine with chloroacetyl chloride, followed by treatment with either potassium phthalimide or diethylamine. Hydrazinolysis of the phthalimides liberated the free amines. The remaining target compounds were produced by alkylation of lidocaine or of 2-phthalimidoaceto-2′,6′-xylidide with the appropriate halide and sodium hydride, followed by hydrazinolysis where necessary. All target compounds were evaluated for antiarrhythmic efficacy against chloroform-induced ventricular tachycardia, as well as for acute CNS toxicity in mice. Most of the target compounds were more potent than the corresponding secondary amides and had improved therapeutic margins toward CNS toxicity. The diamines *N*-(2-aminoethyl)-2-aminoaceto-2′,6′-xylidide (**13**) and *N*-(2-aminoethyl)-2-(diethylamino)aceto-2′,6′-xylidide (**29**) are especially promising in this respect. Several compounds were tested as spinal anesthetics.

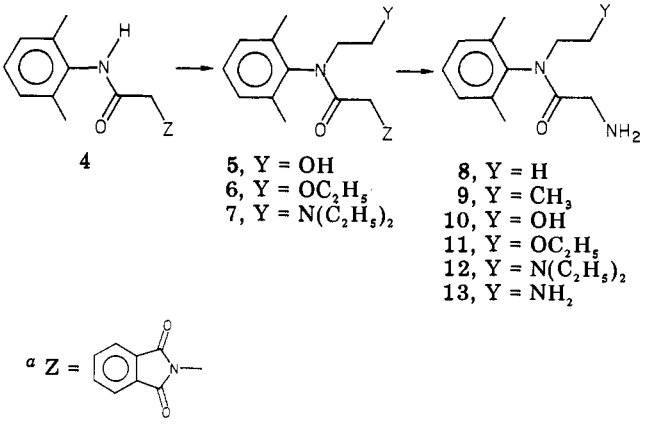
In a previous article[1] the chemical and pharmacological properties of a series of amide alkyl α-amino xylidides were reported. Although alkylation of the amide nitrogen of glycylxylidide (**1**) or tocainide (**2**) led to increased potency



1, R = H
2, R = CH_3

and, in some cases, more favorable therapeutic margins when compared to the secondary amides, this structural modification resulted in greatly shortened plasma half-lives.[2] The plasma half-life decreased as the amide substituent was changed from hydrogen to methyl to ethyl. Since alkylation of the amide nitrogen had been shown to increase the lipophilicity compared to the secondary amide,[3] it seemed possible that this increased lipophilicity is directly related to the decreased plasma half-life.

Scheme I[a]



4

5, Y = OH
6, Y = OC_2H_5
7, Y = $N(C_2H_5)_2$

8, Y = H
9, Y = CH_3
10, Y = OH
11, Y = OC_2H_5
12, Y = $N(C_2H_5)_2$
13, Y = NH_2

[a] Z =

In order to maintain the improvement gained by amide alkylation but yet decrease the lipophilicity of the tertiary

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