Naloxone hydrochloride (4 mg/kg, sc) was administered to groups of six mice, followed by sc AD_{100} doses of **4b**, **4c**, **5b**, and **5c** after a 5-min period. Analgesic activity was then measured 15 min after administration of the test compounds using the tail-flick procedure. Naloxone pretreatment completely abolished the analgesic responses of the test compounds. Groups of six mice were pretreated with morphine sulfate (5 mg/kg, AD_{100}, sc), followed 10 min later by a sc dose of 100 mg/kg of the analgesically inactive compounds or a sc dose of $2 \times AD_{50}$ of the analgesically active compounds. The mice were then evaluated for analgesia using the tail-flick procedure 20 min after administration of the test compounds.

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New Antiarrhythmic Agents. 1. Primary α-Amino Anilides

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Thirty-two α-amino anilides with various substituents in the aromatic ring and in the α position are described. Their abilities to protect mice against chloroform-induced fibrillation and to elicit toxicity were determined. Substitution of an alkyl or aryl group in the α position enhanced the antifibrillatory activity. In most cases, increased potency was accompanied by increased toxicity. Eleven compounds were tested in dogs with surgically induced myocardial infarction; most showed antiarrhythmic activity. 2-Aminopropiono-2′,6′-xylidide, tocainide, was chosen for clinical investigation.

Cardiac arrhythmias are common causes of death in man. In particular, ventricular tachycardia and ventricular fibrillation contribute to the mortality associated with myocardial infarction, digitalis intoxication, and a number of other clinical conditions.[1] Moreover, cardiac arrhythmias have been implicated in a large percentage of unexplained "sudden deaths".[2]

Antiarrhythmic agents have long been used in the treatment and prevention of life-threatening arrhythmias. While the judicious use of these drugs is of benefit, the presently available antiarrhythmic agents provide less than optimum therapy for a number of reasons.[3] In the first place, not all patients are responsive to antiarrhythmic drugs. In the second place, side effects quite commonly accompany treatment: quinidine and procainamide, the two agents most widely used chronically for oral therapy, both interfere with intracardiac conduction and both produce hypotension. Quinidine also produces a wide variety of other adverse effects, including gastrointestinal disturbances and idiosyncratic and allergic reactions. Procainamide produces, among other adverse effects, a lupus-like syndrome. Newer and less widely used agents, such as phenytoin, bretylium tosylate, and disopyramide, also produce a high incidence of adverse effects.[3]

Lidocaine is the third antiarrhythmic agent in widespread clinical use.[3] When given intravenously or in-

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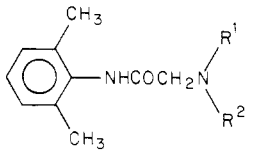
tramuscularly for short-term treatment of ventricular arrhythmias, lidocaine is a highly effective antiarrhythmic agent. Its principal side effects are manifestations of CNS toxicity. Lidocaine possesses many characteristics that are desirable in an antiarrhythmic agent for chronic administration. First, being relatively free of cardiovascular toxicity, it contrasts favorably with quinidine and procainamide. Moreover, the production of readily apparent but minor side effects, which are a forewarning of more serious CNS toxicity, serves to protect against the development of the more serious effects. Unfortunately, because of its short biological half-life, oral administration is not practical and hence lidocaine is unsuitable for chronic use.[3]

Given the need for better drugs in the chronic treatment of patients with, or susceptible to, life-threatening ventricular arrhythmias, we set as our goal the development of one or more drugs with the desirable pharmacological properties of lidocaine but lacking its pharmacokinetic disadvantages. Specifically, we sought a drug with the following properties: (a) efficacy against ventricular tachyarrhythmias; (b) minimal cardiovascular side effects at therapeutic blood levels and distinct separation of therapeutic and CNS-stimulating effects; (c) oral bioavailability at least 80%; (d) biological half-life of at least 8 h. In order to achieve these goals, we chose appropriate animal models to measure the above biological parameters and to evaluate the effects of structural modifications of the lidocaine molecule on these parameters.

With the expressed intention of obtaining a substance whose pharmacodynamics could be described as "lidocaine-like" but whose pharmacokinetics are different, it was deemed expedient to maintain certain structural similarities to lidocaine (1), viz, an aromatic ring, an amide

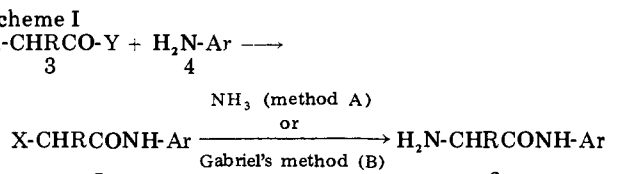


1, R^1 = Et; R^2 = Et
2a, R^1 = Et; R^2 = H
2b, R^1 = H; R^2 = H

function in the same orientation, and a basic amino group in the α position. *N*-Ethylglycinexylidide (**2a**) and glycinexylidide (**2b**), known metabolites[4] of lidocaine, both contain the desired structural features and both have antiarrhythmic activity in animal models.[5,6] Glycinexylidide (**2b**) was chosen as the starting point for a structure-modification program on the basis of its long half-life[6,7] and its metabolic stability.[6] Aiming to increase antiarrhythmic potency, we introduced alkyl and aryl substituents in the α position and alkyl and alkoxy substituents on the aromatic ring. The choice of ring substituents was influenced by the consideration that many aromatic amines induce methemoglobinemia.[8] Since metabolic hydrolysis of the amide function is an important step in the metabolism of lidocaine[4] and corresponding hydrolysis of primary amine analogues was expected to produce the parent anilines, only anilines with low propensity to induce methemoglobinemia were utilized. This paper describes the synthesis, properties, and the biological evaluation of a group of primary α-amino anilides.

Chemistry. Twenty-nine of the substances listed in Table I have not been reported previously (except in a patent[9] on these substances) and were newly synthesized for this study either by direct amination of the appropriate α-halo anilide **5** or by Sheehan's modification[10] of Gabriel's

Scheme I



X and Y = Cl or Br; R = H, alkyl or phenyl; Ar = substituted phenyl

method from the same starting material. The halo anilides were synthesized by reaction of the appropriate aromatic amine (**4**) with the appropriate haloacyl halide (**3**) by the method of Löfgren.[11] The halo anilides not previously described in the literature are listed in Table II. Seven of the aromatic amines were not commercially available and had to be synthesized. Only one, 4-propoxy-2,6-xylidine, was not previously described in the literature. All 4-alkoxyxylidines were synthesized according to a modification of the method described by Runti and Coluatti.[12] Scheme I summarizes the synthetic methods. One of these substances, **18**, was resolved by fractional crystallization of its salts with di-*p*-toluyl-*d*- and di-*p*-toluyl-*l*-tartaric acid. The (+) enantiomer was synthesized from 2,6-xylidine and (carbobenzyloxy)-L-alanine; thus, (+)-**18** has the L (or *S*) configuration.

Pharmacological Methods. The target compounds were all tested for their abilities to prevent chloroform-induced fibrillation in mice.[13] During the period between treatment and exposure to $CHCl_3$ vapor, the animals were observed for overt signs of CNS toxicity. Certain of the compounds were selected for further testing in dogs with ventricular arrhythmias produced by coronary artery ligation according to the method of Harris.[14]

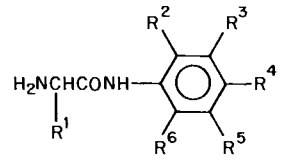
Results and Discussion

Table III presents the antifibrillatory effects of the target compounds in mice and the toxicity observed at a dose of 100 mg/kg. The 27 compounds for which ED_{50} values were determined are listed in order of decreasing potency relative to lidocaine; the five compounds for which relative potency could not be determined are placed at the end of Table III in probable order of potency, based on preliminary testing. Two of the compounds, **32** and **33**, were not sufficiently soluble, as hydrochlorides, to allow complete testing; two, **34** and **35**, did not protect half of the animals at doses of 1000 mg/kg and thus were judged to have very weak antiarrhythmic activity; for one, **31**, an acceptable dose–response relationship could not be obtained.

An examination of molecular models indicates that when both the 2 and 6 positions of the aromatic ring are substituted by alkyl, chloro, or bromo groups or when the 2 position is occupied by a *tert*-butyl group, as in **23** and **28**, the amide function and the aromatic function cannot become coplanar. Compounds **25**, **30**, and **35** are the only ones in this series that lack bulky groups in one or both ortho positions and thus allow the amide function and aromatic ring to become coplanar. This might be the reason for the low potency of these three substances as antiarrhythmic agents.

An examination of the substituents in Table I, which is arranged in the same order as Table III, shows that the compounds for which R^1 = H are clustered near the bottom of the table and, conversely, those for which R^1 is greater than methyl cluster at the top of the table. The set of compounds **26**, **13**, and **8** and the similar set **27**, **17**, and **9** have the same aromatic ring, with R^1 varying from H to methyl to ethyl. Both sets show a decrease in ED_{50} as R^1 increases from H to methyl to ethyl. Other sets that

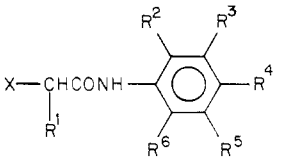
Table I. Structures, Physical Properties, and Yields of Compounds Tested



compd	R^1	R^2	R^3	R^4	R^5	R^6	method[a]	yield from halo compd, %	formula	crystn solv[b]	mp, °C	anal.
7	C_6H_5	CH_3	H	H	H	CH_3	A	10	$C_{16}H_{18}N_2O\cdot HCl\cdot 0.5H_2O$	C	255-256.5	C, H, N, Cl
8	C_2H_5	C_2H_5	H	H	H	C_2H_5	A	44	$C_{14}H_{22}N_2O\cdot HCl\cdot 0.5H_2O$	F	221-223.5	C, H, N, Cl
9	C_2H_5	CH_3	H	H	H	C_2H_5	A	59	$C_{13}H_{20}N_2O\cdot HCl\cdot 0.5H_2O$	C	177-179	C, H, N, Cl
10	CH_3	CH_3	H	H	H	Cl	A	71	$C_{10}H_{13}ClN_2O\cdot HCl$	C	253-255	C, H, N, Cl
11	CH_3	Br	H	H	H	Br	A	82	$C_9H_{10}Br_2N_2O\cdot HCl$	I	228-229	C, H, N, Br, Cl
12	CH_3	CH_3	CH_3	H	H	CH_3	A	89	$C_{12}H_{18}N_2O\cdot HCl$	C	245	C, H, N, Cl
13	CH_3	C_2H_5	H	H	H	C_2H_5	A	84	$C_{13}H_{20}N_2O\cdot HCl\cdot H_2O$	C	220-221	C, H, N, Cl
14	CH_3	CH_3	H	C_4H_9O	H	CH_3	A	77	$C_{15}H_{24}N_2O_2\cdot HCl\cdot H_2O$	C	225	C, H, N, Cl
15	CH_3	CH_3	H	C_3H_7O	H	CH_3	A	40	$C_{14}H_{22}N_2O_2\cdot HCl\cdot 0.25H_2O$	C	226-227[g]	C, H, N, O, Cl
16	H	CH_3	H	CH_3	H	CH_3	B	50	$C_{11}H_{16}N_2O\cdot HCl$	E	305	C, H, N, Cl
17	CH_3	CH_3	H	H	H	C_2H_5	A	70	$C_{12}H_{18}N_2O$	H	68.5-70[d]	C, H, N
D-18	CH_3	CH_3	H	H	H	CH_3			$C_{11}H_{16}N_2O\cdot HCl$	C	264.5[d]	
2b	H	CH_3	H	H	H	CH_3	B	50	$C_{10}H_{14}N_2O\cdot HCl$	E	296[c]	C, H, N, Cl
19	C_2H_5	CH_3	H	H	H	CH_3	A	48	$C_{12}H_{18}N_2O\cdot HCl$	I	213.5-214.5	C, H, N, Cl
20	CH_3	CH_3	H	CH_3O	H	CH_3	B	69	$C_{12}H_{18}N_2O_2HCl\cdot 0.5H_2O$	C	248-248.5	C, H, N, Cl
21	CH_3	CH_3	H	C_6H_5O	H	CH_3	B	43	$C_{17}H_{20}N_2O_2\cdot HCl$	C	266-268	C, H, N, Cl
22	CH_3	CH_3	H	C_2H_5O	H	CH_3	B	68	$C_{13}H_{20}N_2O_2\cdot HCl\cdot 0.5H_2O$	C	227-228.5	C, H, N, Cl
23	CH_3	$(CH_3)_3C$	H	H	H	H	A	82	$C_{13}H_{20}N_2O$	G	80-81	C, H, N
24	CH_3	CH_3	H	CH_3	H	CH_3	A	76	$C_{12}H_{18}N_2O\cdot HCl$	C	247.5-249	C, H, N, Cl
25	CH_3	CF_3	H	H	H	H	A	74	$C_{10}H_{11}F_3N_2O\cdot HCl$	I	226-228	C, H, N, Cl
26	H	C_2H_5	H	H	H	C_2H_5	B	82	$C_{12}H_{18}N_2O\cdot HCl$	C	266.5-268	C, H, N, Cl
27	H	CH_3	H	H	H	C_2H_5	A	68	$C_{11}H_{16}N_2O\cdot HCl$	C	248-250.5	C, H, N, Cl
DL-18	CH_3	CH_3	H	H	H	CH_3	A	28	$C_{11}H_{16}N_2O\cdot HCl$	K	246-247[d]	C, H, N, Cl
28	H	$(CH_3)_3C$	H	H	H	H	A	51	$C_{12}H_{18}N_2O$	G	112.5-114	C, H, N
29	H	CH_3	CH_3	H	H	CH_3	B	63	$C_{11}H_{16}N_2O\cdot HCl$	E	283.5-284.5[d,g]	C, H, N, Cl
30	CH_3	CH_3O	H	H	H	H	A	54	$C_{10}H_{14}N_2O_2\cdot HCl$	C	173-174.5	C, H, N, Cl
L-18	CH_3	CH_3	H	H	H	CH_3			$C_{11}H_{16}N_2O\cdot HCl$	C	264.5[d]	
31	H	CH_3	H	C_4H_9O	H	CH_3	B	26	$C_{14}H_{22}N_2O_2\cdot HCl$	D	293-294[e]	C, H, N, Cl
32	H	CH_3	H	C_3H_7O	H	CH_3	B	76	$C_{13}H_{20}N_2O_2\cdot HCl$	E	295[g]	C, H, N, Cl
33	H	CH_3	H	H	H	Cl	A	58	$C_9H_{11}ClN_2O\cdot HCl$		296-301[f,g]	C, H, N, Cl
34	H	CH_3	H	CH_3O	H	CH_3	B	39	$C_{11}H_{16}N_2O_2\cdot HCl$	E	292.5-295	C, H, N, Cl
35	CH_3	F	F	F	F	F	A	64	$C_9H_7F_5N_2O\cdot HCl$	J	193-195	C, H, N, Cl, F

[a] Described under the Experimental Section. [b] Recrystallization solvents: C, $C_2H_5OH/(C_2H_5)_2O$; D, CH_3OH/C_2H_5OH; E, C_2H_5OH/H_2O; F, CH_3OH; G, $CH_3COOC_2H_5$/pet. ether; H, $(C_2H_5)_2O$/pet. ether; I, $C_2H_5OH/CH_3CO_2C_2H_5$; J, $CH_3COCH_3/CH_3COOC_2H_5$; K, $CH_3CH_2COCH_3/C_2H_5OH$. [c] U. Lindberg and B. Akerman, German Patent 2 305 870 (Aug. 23, 1973). [d] See ref 9. [e] AB Astra, British Patent 705 460 (Mar. 10, 1954). [f] P. P. Koelzer and K. H. Wehr, *Arzneim.-Forsch.*, 8, 406 (1958). [g] Decomposition.

Table II. Structures, Melting Points, and Yields of α-Halo Anilides



X	R'	R^2	R^3	R^4	R^5	R^6	mp, °C	yield, %
Br	C_6H_5	CH_3	H	H	H	CH_3	160-162	82
Br	CH_3	CH_3	CH_3	H	H	CH_3	165-167	85
Br	CH_3	CH_3	H	CH_3O	H	CH_3	170-171	77
Br	CH_3	CH_3	H	C_2H_5O	H	CH_3	186.5-187.5	85
Cl	H	CH_3	H	C_3H_7O	H	CH_3	137-138	62
Br	C_2H_5	CH_3	H	H	H	C_2H_5	207-210	72
Br	C_2H_5	C_2H_5	H	H	H	C_2H_5	205-209 (dec)	57
Br	CH_3	$(CH_3)_3C$	H	H	H	H	134-134.5	73
Br	CH_3	Br	H	H	H	Br	173.5-175	82
Br	CH_3	CH_3	H	C_6H_5O	H	CH_3	177.5-178.5	93
Br	CH_3	F	F	F	F	F	136.5-137.5	80

Table III. Antiarrhythmic Activity and Toxicity of Compounds in the Chloroform Mouse Test[a]

	preliminary test[b]					
compd	protected, %	ataxic, %	convulsive, %	LRR, %	ED_{50}, mmol/kg (95% Fieller limits)	rel potency (lidocaine = 1)
1	100	100	100	100	0.26 ± 0.09[c]	1.0
7	80	100	100	100	0.22 (0.13-0.39)	1.2
8	100	100	100	0	0.23 (0.17-0.35)	1.2
9	100	100	100	0	0.25 (0.19-0.36)	1.1
10	90	20	20	0	0.31 (0.17-0.68)	0.8
11	0	100	100	0	0.47 (0.32-0.80)	0.6
12	40	0	0	0	0.52 (0.36-0.83)	0.5
13	20	100	10	0	0.53 (0.41-0.79)	0.5
14	20	0	0	0	0.57 (0.22-1.2)	0.5
15	25	0	0	0	0.77 (0.52-1.1)	0.3
16	10	100	80	0	0.79 (0.57-0.99)	0.3
17	10	0	0	0	0.82 (0.47-1.4)	0.3
D-18	10	70	0	0	0.93 (0.63-1.3)	0.3
2b	10	0	0	0	0.90 (0.6-2.3)	0.3
19	50	50	50	5	1.0 (0.65-2.5)	0.3
20	10	0	0	0	1.0 (0.57-1.7)	0.3
21	40	0	0	0	1.0 (0.79-1.3)	0.3
22	10	50	50	0	1.0 (0.71-1.8)	0.2
23	30	90	0	0	1.1 (0.88-1.5)	0.2
24	80	0	0	0	1.2 (0.40-2.7)	0.2
25	15	100	20	0	1.2 (0.73-2.1)	0.2
26	10	100	0	0	1.2 (0.78-1.9)	0.2
27	20	100	0	0	1.3 (0.90-8.1)	0.2
DL-18	20	10	0	0	1.3 ± 0.6[c]	0.2
28	20	70	0	0	1.5 (1.2-4.4)	0.2
29	20	60	0	0	1.7 (0.95-3.2)	0.2
30	15	0	0	0	2.7 (2.2-3.8)	0.1
L-18	0	0	0	0	3.1 (1.4-5.2)	0.1
31	60	0	0	0	*d*	
32	40	100	0	0	*e*	
33	10	0	0	0	*e*	
34	0	0	0	0	*f*	
35	0	0	0	0	*f*	

[a] Details of the test method are described under the Experimental Section. [b] Preliminary test was run at a dose of 100 mg/kg in order to estimate appropriate doses for full screen. LRR = loss of righting reflex. [c] Mean plus or minus standard deviation. [d] ED_{50} was not determined because data could not be evaluated statistically. [e] ED_{50} could not be determined because of solubility limitations. [f] ED_{50} was not determined because of very large doses that would be needed to give high fractional protection.

show the same relationship are **29** and **12**, and **28** and **23**.

Increasing lipophilicity of the molecules might be offered as an explanation for the increasing potencies of these substances. As the number of CH_2 groups in the molecule increases, so does its potency. This is seen among the group of 4'-alkoxypropionoxylidides (**20**, **22**, **15**, and **14**). As the size of the alkoxy group increases, the ED_{50} values decrease. On the other hand, a comparison of the sets **2b** and **29**, **2b** and **16**, DL-**18** and **12**, and DL-**18** and **24**, the second member of each set having one more methyl group attached to the aromatic ring, shows that the correlation of increased lipophilicity and increased potency fails in two of the four sets.

The L enantiomer of **18** is considerably weaker than the D enantiomer, as judged by their ED_{50} values. This difference may result from differences in absorption, distribution, or metabolism or from an inherent difference resulting from interaction at a specific site.

The preliminary screen did not provide a quantitative measure of toxicity, but overt signs of CNS toxicity were

Table IV. Antiarrhythmic and Toxic Effects of Compounds in Coronary Ligated Dogs

	control values[a]			clearing values[b]			iv dose, mmol/kg, to cause:		
compd	% vent. ect	vent. rate	MABP	% vent. ect	vent. rate	MABP	clearing	convulsion	death
1[c]	96 ± 5	174 ± 34	81 ± 11	4 ± 3	133 ± 16	101 ± 21	0.21 ± 0.19	0.27 ± 0.15	
2b	80	135	105	0	123	155	0.56	0.48	0.56[d]
	73	141	85	0	141	85	0.48	e	
	94	189	110	0	126	125	0.67	e	
9	100	222	75	15[f]	162[f]	90[f]	0.14[d,f]	0.14[g]	
	93	225	90	32[f]	165[f]	120[f]	0.12[d,f]	0.12[g]	
10	99	186	110	2	136	125	0.40	0.31	0.63
	100	210	110	0	126	115	0.28	0.28	0.84
13	95	213	105	5	159	145	0.26	0.30	0.51
	92	225	150	2	124	140	0.33	0.23	0.45
15	72	189	100	1	114	110	0.21	0.16	0.38
	88	237	105	16[f]	162[f]	110[f]	0.18[f]	0.16	0.33
17	100	183	105	2	129	105	0.15	0.25	0.81
	100	218	110	2	153	160	0.33	0.24	0.50
D-18	100	237	115	0	123	105	0.31	0.21	
	97	225	90	0	138	135	0.37	0.26	
	93	234	90	0	141	130	0.31	0.29	
DL-18	94 ± 5[h]	207 ± 25[h]	91 ± 19[h]	2 ± 2[h]	148 ± 16[h]	108 ± 21[h]	0.32 ± 0.11[h]	0.30 ± 0.06[i]	
L-18	98	192	90	0	99	90	0.44	e	
	90	186	105	1	105	110	0.11	e	
	99	177	80	0	144	85	0.35	e	
	82	219	105	0	129	110	0.53	e	
24	96	165	80	0	38	85	0.32	0.31	
	94	192	65	0	135	75	0.38	e	
	79	174	65	5	135	60	0.12	0.37	
33	95	225	70	23[f]	144[f]	75[f]	0.58[f]	0.58[g]	
	98	189	85	52[f]	138[f]	75[f]	0.52[f]	0.52[g]	
	84	162	90	0	138	90	0.76	0.79	

[a] Values of percent ventricular ectopic beats, ventricular rate (beats/min), and mean arterial blood pressure (Torr) before start of drug infusion. [b] Clearing = less than 5% ectopic for 5 min. [c] Means and standard deviations of five experiments. [d] Dog died 87 min after end of infusion. [e] Infusion shut off at clearing. [f] Values and dose at the time of the lowest incidence of ectopic beats. [g] Infusion shut off when toxicity was observed. [h] Mean and standard deviation of 14 experiments. [i] Eight experiments.

observed and reported during the 20-min period between treatment and exposure to $CHCl_3$ vapor. The results are given in Table III, wherein it is obvious that most of the more potent substances are also the more toxic ones, especially when the occurrence of convulsions is considered. The most notable exception to this generalization is **10**, for which a dose that protected nine of ten animals from fibrillation caused convulsions in only two of the animals. By way of contrast, **7–9** and **11**, compounds which have ED_{50} values similar to **10**, caused convulsions in all animals at doses that protected all or almost all from fibrillation.

Another anomaly is **22**, which is considerably less potent but which caused convulsions in half of the animals at a dose that protected 10%, although its close congeners **20**, **15**, **14**, and **21** elicited no overt toxicity at doses that manifested antiarrhythmic properties. The reason for this anomaly is not apparent.

Of the 32 compounds tested in the primary screen, 11 were selected for a study of their effects against ventricular arrhythmias in the coronary dog. These results are given in Table IV.

Most of the compounds tested in dogs cleared the arrhythmias (reduced the percentage of ectopic beats from ~90 to <5 for 5 min) at doses of 0.2–0.4 mmol/kg. In the cases of **9** and **33**, the infusion was stopped when toxicity was observed. Both substances showed significant reduction in the percentage of ectopic beats, although they did not meet our criteria for clearing. The enantiomers of **18**, in contrast to their different potencies in mice, cleared arrhythmias in dogs at about the same dose. Compounds **9**, **15**, and **33** did not clear the arrhythmias in all dogs. Of the remaining substances, all except **2b** cleared arrhythmias at about the same doses; **2b** required about twice as much drug to bring about clearing. With the exception of L-**18**, all of the compounds showed CNS toxicity at doses at or below the clearing dose.

The biological half-lives in dogs of three of these compounds, **2b**, DL-**18**, and **19**, have been reported.[7] The half-life of **19** was deemed too short (1.5 h) to justify further studies on this compound; **2b** and DL-**18** had longer half-lives (3.7 and 4.7 h, respectively). The oral bioavailability in dogs of DL-**18** has been determined to be 80%.[15] Based upon these pharmacodynamic and pharmacokinetic data, clinical studies on DL-**18** have begun.[16] The half-life of DL-**18** in man (11 h)[17] satisfies criterion d.

Experimental Section

Melting points were determined on a Thomas-Hoover Meltemp and are uncorrected. Elemental analyses, performed by Alfred Bernhardt, Elsbach u. Engelskirchen, West Germany, and IR and NMR spectra, determined on Perkin-Elmer Model 257 and Hitachi Perkin-Elmer Model R-20, respectively, were consistent with the structures.

4-Propoxy-2,6-xylidine. A solution of 0.66 mol of sulfanilic acid and 0.34 mol of Na_2CO_3 in 660 mL of water was cooled to <15 °C and a solution of 0.72 mol of $NaNO_2$ in 140 mL of H_2O was added. This was immediately poured into a mixture of 142 mL of 12 M HCl and 800 g of ice. After stirring for 0.5 h, the diazonium solution was added to a chilled (5 °C) solution of 0.66 mol of 3,5-dimethylphenol in 500 mL of 7 M NaOH. The filtered solution was evaporated to a paste of sodium 2,6-dimethyl-4-hydroxyazobenzene-4′-sulfonate. The paste was suspended in 1.15 L of ethanol, 1.36 mol of 1-bromopropane was added, and the mixture was heated under reflux for 48 h. The solvent was evaporated and the pasty residue was dissolved in 1.3 L of water. At 70 °C, 315 g of $Na_2S_2O_4$ was added in small portions. A solid was filtered off and washed. The filtrate and washes were extracted with 3 × 200 mL of ether. The ether extracts were washed with 7 M NaOH, dried (Na_2SO_4), and evaporated. Distillation gave 26.1 g (22%) of oil: bp 79–80 °C (0.02 mm); n_D 1.5398.

α-Halo Anilides 5.[11] To a chilled solution of 1.0 mol of aromatic amine in 0.85 L of glacial acetic acid was added 1.1 mol

of acyl halide. After adding 1.5 L of chilled 1.6 M sodium acetate, the mixture was shaken for 30 min to 1 h. Filtration, washing with water, and drying gave 60–80% yields of the compounds **5**. The products were used without further purification, unless gas chromatographic analysis (Varian 200, 3% OV 17 column, 200 °C) showed them to be contaminated. When recrystallization was indicated, either toluene or aqueous methanol was used.

α-Amino Anilides 6. Method A. A suspension of 0.16 mol of **5** in a mixture of 500 mL of 95% ethanol and 400 mL of 27% NH_3 was saturated with gaseous NH_3 and left to stir at 25 °C until all of **5** dissolved (usually 3 to 5 days). At this point, gas chromatographic analysis (OV 17, 200 °C) usually showed >80% conversion of **5** to **6**. The solvent was evaporated and the residue was taken up in 1.5 equiv of 1 M HCl. The solution of **6**·HCl was extracted with one-fifth its volume of CH_2Cl_2 to remove nonbasic impurities, made basic with 7 M NaOH, and extracted three times with one-tenth its volume of CH_2Cl_2; then the extracts were dried and evaporated. In the cases of the more hydrophilic examples of **6**, extraction of the base was facilitated by salting out with K_2CO_3. The base **6** was dissolved in $CHCl_3$ or preferably CH_2Cl_2 (about 1 M), and an excess of anhydrous HCl was introduced. The **6**·HCl thus obtained was recrystallized from an appropriate solvent (see Table I).

Method B.[10] To a 1.0 M solution of **5** in dimethylformamide was added a 10% excess of potassium phthalimide. After 2 h at reflux temperature, the mixture was cooled to <100 °C and 1.26 volumes of 28% acetic acid were added. After thorough cooling, the substituted phthalimide was recovered in >90% yield. The intermediate was immediately suspended in 1.0 L of 95% ethanol, was heated to reflux, and 0.25 mol of N_2H_4 (64% aqueous) was added. If the suspension was not brought up to reflux temperature before the addition of N_2H_4, there resulted a thick and difficult to stir suspension, which hindered the hydrazinolysis. The suspended intermediate, after the addition of N_2H_4, dissolved almost immediately and, after 10 to 30 min, solid began to appear. Reflux was continued for 2 h. The mixture was allowed to cool to <50 °C, 0.4 mol of 12 M HCl was added, and reflux was continued for 1 h. After thorough cooling, the solid which formed (phthalhydrazide) was filtered off and the filtrate was concentrated, leaving crude **6**·HCl as a residue, which was recrystallized from the solvent listed in Table I. When the hydrochloride would not crystallize, its aqueous solution was made basic with 7 M NaOH and extracted with CH_2Cl_2. The base was isolated by evaporation of the solvent and recrystallized.

Resolution of DL-**18.** A solution of 51.9 g (0.270 mol) of DL-**18** in 184 mL of alcohol was added to a hot solution of 104.3 g (0.270 mol) di-*p*-toluyl-*d*-tartaric acid (Aldrich Chemical Co.) in 300 mL of alcohol. After thorough chilling of the solution, the diastereomeric salts were filtered, washed, and dried. Recrystallization from alcohol (20 mL/g) gave 55.2 g (35%) of pure diastereomeric salt: $[\alpha]_D$ −112° (*c* 0.50, methanol). The salt was dissolved in 442 mL of H_2O, made alkaline with 7 M NaOH, extracted into CH_2Cl_2, and dried (K_2CO_3). Evaporation of the solvent gave 17.0 g (93%) of (−)-D-**18**: $[\alpha]_D$ −24.6° (*c* 3.45, methanol). The hydrochloride was formed by passing anhydrous HCl into a chloroform solution of the base: $[\alpha]_D$ −44.1° (*c* 2.63, methanol). From the filtrates, 30.5 g of **18** was recovered, dissolved in 108 mL of alcohol, and added to a warm solution of 61.4 g (0.159 mol) of di-*p*-toluyl-*l*-tartaric acid in 177 mL of alcohol. After thorough chilling, filtration, and recrystallization, there was obtained 34.9 g (38%) of the pure diastereomeric salt: $[\alpha]_D$ +155° (*c* 0.50, methanol). By a procedure similar to that above, (+)-L-**18**, $[\alpha]_D$ +24.9° (*c* 1.69, methanol), and (+)-L-**18**·HCl, $[\alpha]_D$ +43.7° (*c* 2.63, methanol), mp 264.5 °C, were obtained.

(*S*)-(+)-2-Amino-2′,6′-propionoxylidide (L-**18**). To a solution of 4.50 g (0.020 mol) of (carbobenzyloxy)-L-alanine (Aldrich Chemical Co.) and 2.72 g (0.022 mol) of 2,6-xylidine in 50 mL of CH_2Cl_2 was added a solution of 4.6 g (0.022 mol) of dicyclohexylcarbodiimide in 20 mL of CH_2Cl_2. After the solution was left standing at 25 °C for 1 h, dicyclohexylurea (97%) was filtered off. The solvent was evaporated from the filtrate, leaving 6.7 g of white solid, mp 167–169.5 °C, whose IR spectrum was consistent with that expected for the carbobenzyloxy derivative.

The carbobenzyloxy derivative (3.25 g, 0.010 mol) was catalytically hydrogenated (5% Pd/C) in 1:1 C_2H_5OH–CH_2Cl_2 at 4.25 atm and 25 °C. Isolation and purification of L-**18**·HCl followed the procedure for the resolution: yield 1.50 g (66%); $[\alpha]_D$ +41.7° (*c* 2.64, methanol); mp 264.5–265.5 °C.

Chloroform Mouse Test. Drug, as the hydrochloride in isotonic solution, or saline was administered subcutaneously to groups of ten female Swiss albino mice (Ham/ICR; 18–25 g), which were then observed for signs of toxicity. Twenty minutes after administation, the mice were exposed to $CHCl_3$ vapor until respiration ceased, and the presence or absence of ventricular fibrillation was ascertained by observation of the opened thorax. At least three doses of each drug were given, with doses chosen to give low, intermediate, and high fractions of animals protected against the development of fibrillation. The results were treated statistically according to the Berkson[18] minimum logit chi square analysis.

Coronary Dog Test. Ventricular arrhythmias were induced in adult female dogs (8.6–13.4 kg) by two-stage ligation of the left anterior descending coronary artery.[14,15] On the following day, control data were gathered, and drug, as the hydrochloride in isotonic solution, was infused intravenously (without anesthesia or sedation) at a rate of 0.5 mg kg^{-1} min^{-1} until the arrhythmia was "cleared" or, in some cases, when CNS toxicity developed. Clearance was defined as a reduction in ectopic beats to less than 5% of the total ventricular beats for 5 min.

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