New Antiarrhythmic Agents. 2. Amide Alkyl α-Amino Xylidides

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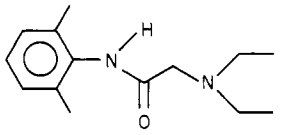
The synthesis of a series of *N*-alkyl 2-amino 2′,6′-xylidides is described. The method involved coupling of the *N*-alkyl-2′,6′-xylidine with the appropriate 2-haloacyl halide, followed by ammonolysis. Alternatively, alkylation of the 2-phthalimido 2′,6′-xylidide with NaH and the alkyl halide followed by hydrazinolysis was used. All compounds were evaluated for their ability to protect mice against chloroform-induced ventricular fibrillation. The compounds were generally more potent antifibrillatory agents than the corresponding secondary amides. All were more potent than tocainide and several showed less CNS toxicity. Five compounds were further evaluated in dogs with ventricular arrhythmias resulting from myocardial infarction. *N*-Ethyl-2-aminoaceto-4′-propoxy-2′,6′-xylidide was as potent as lidocaine and produced less CNS toxicity.

In a previous article,[1] biological and chemical procedures were described for the development of a drug pharmacologically similar to lidocaine (1) but with high oral



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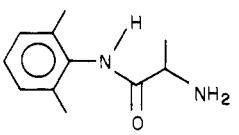

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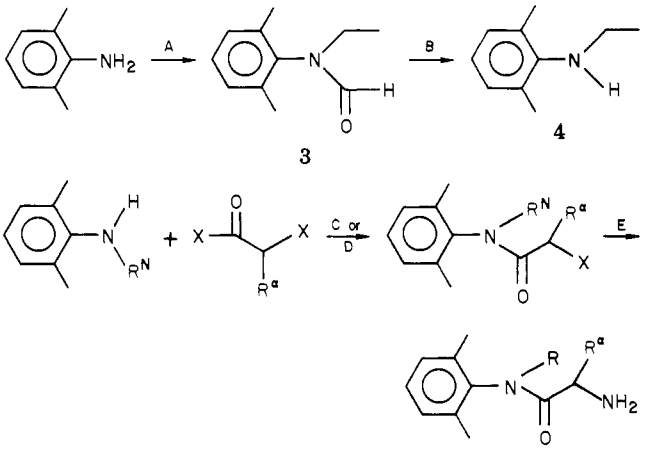
bioavailability and longer pharmacologic half-life. Tocainide (2) is an effective antiarrhythmic agent in animals[2,3] and is presently undergoing clinical trials,[4] but it has a somewhat limited therapeutic margin due to CNS toxicity. This work was undertaken to find a compound which is more potent than 2 and has an improved therapeutic index.

If the amide hydrogen of tocainide-like molecules, which have shown good therapeutic properties,[1] is replaced with various alkyl groups, their pK_a values[5,6] should be increased, their lipophilicities[7] altered, and, therefore, their distribution properties changed. Further, the increased steric crowding should decrease the metabolic amide cleavage reported for some 2,6-xylidides.[8] A series of these compounds (Table II) has been prepared, and their chemical and pharmacological properties have been evaluated and compared to tocainide.

Chemical Methods. One method of synthesis of the desired compounds is outlined in Scheme I. The preparation of the *N*-methyl-2,6-xylidine is described elsewhere.[9] *N*-Ethyl-2,6-xylidine was prepared by the reaction of 2,6-xylidine with ethyl orthoformate[10,11] (method A), followed by decarbonylation of the resulting formamide with sodium hydride[11,12] (method B). The *N*-alkyl-2,6-xylidines were treated with the appropriate 2-haloacyl halide in acetic acid and sodium acetate[13] (method C) or, alternatively, in a two-phase system, toluene–aqueous sodium hydroxide (method D).[14] The resulting *N*-alkyl 2-halo xylidides were then treated with ammonia in ethanol (method E) to yield the target compounds.

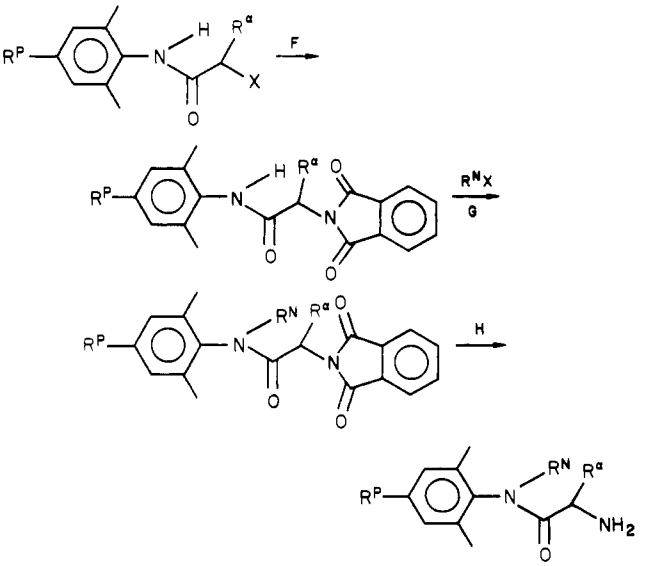
Alternatively, the target compounds were prepared according to Scheme II. The necessary 2-halo xylidides have been described elsewhere.[1] The phthalimides were prepared by refluxing the halide with potassium phthalimide in dimethylformamide[15] (method F) and subsequently were alkylated by a modification of the method of Fones[16] (method G). The alkylated phthalimides were generally of sufficient purity to give the desired xylidides in good yield on hydrazinolysis in ethanol[15] (method H).

Scheme I



X = Cl, Br; methods: A, $(C_2H_5O)_3CH$, H_2SO_4; B, NaH then H_2O; C, CH_3COOH, CH_3COONa; D, HOH/NaOH, toluene; E, NH_3/EtOH

Scheme II



X = Cl, Br; methods: F, DMF/potassium phthalimide; G, NaH/xylene; H, N_2H_4/EtOH

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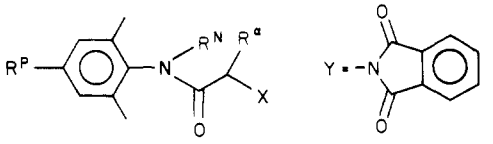
Table I. Structures and Physical Properties of Intermediate Anilides



no.	R^P	R^N	R^α	X	mp, °C	solv	yield, %	method	formula
5	H	CH_3	H	Cl	51-54	*a*	40	C	$C_{11}H_{14}NOCl$
6	H	CH_3	CH_3	Br	78.5-80	*a*	27	C	$C_{12}H_{16}NOBr$
7	H	CH_3	C_2H_5	Br	*b*	*b*	93	D	$C_{13}H_{18}NOBr$
8	H	C_2H_5	H	Cl	*b*	*b*	96	D	$C_{12}H_{16}NOCl$
9	H	C_2H_5	CH_3	Br	64-66	*a*	98	D	$C_{13}H_{18}NOBr$
10	H	C_2H_5	C_2H_5	Br	*b*	*b*	84	D	$C_{14}H_{20}NOBr$
11	H	H	H	Y	288-291	*a*	87	F	$C_{18}H_{16}N_2O_3$
12	H	CH_3	H	Y	*b*	*b*	82	G	$C_{19}H_{18}N_2O_3$
13	H	*n*-C_3H_7	H	Y	170-176	*c*	77	G	$C_{21}H_{22}N_2O_3$
14	H	*i*-C_3H_7	H	Y	187-192	*c*	55	G	$C_{21}H_{22}N_2O_3$
15	H	$C_6H_5CH_2$	H	Y	155-160	*c*	87	G	$C_{25}H_{22}N_2O_3$
16	H	H	CH_3	Y	202-203.5	*a*	90	F	$C_{19}H_{18}N_2O_3$
17	*n*-C_3H_7O-	H	H	Y	>270	*a*	94	F	$C_{21}H_{22}N_2O_4$
18	*n*-C_3H_7O-	H	CH_3	Y	208-209.5	*a*	79	F	$C_{22}H_{24}N_2O_4$
19	*n*-C_3H_7O-	CH_3	H	Y	*d*	*d*	66	G	$C_{22}H_{24}N_2O_4$
20	*n*-C_3H_7O-	CH_3	CH_3	Y	*d*	*d*	*e*	G	$C_{23}H_{26}N_2O_4$
21	*n*-C_3H_7O-	C_2H_5	H	Y	126-128	*c*	70	G	$C_{23}H_{26}N_2O_4$
22	*n*-C_4H_9O	H	H	Y	264-266	*a*	86	F	$C_{22}H_{24}N_2O_4$
23	*n*-C_4H_9O	H	CH_3	Y	195-197	*a*	80	F	$C_{23}H_{26}N_2O_4$
24	*n*-C_4H_9O	CH_3	H	Y	*d*	*d*	*e*	G	$C_{23}H_{26}N_2O_4$
25	*n*-C_4H_9O	CH_3	CH_3	Y	*d*	*d*	*e*	G	$C_{24}H_{28}N_2O_4$
26	*n*-C_4H_9O	C_2H_5	H	Y	*d*	*d*	*e*	G	$C_{24}H_{28}N_2O_4$
27	*n*-C_4H_9O	C_2H_5	CH_3	Y	*d*	*d*	*e*	G	$C_{25}H_{30}N_2O_4$

[a] Material used without recrystallization. [b] Crude oil, greater than 95% by GC. [c] 95% ethanol. [d] Contains some mineral oil. [e] Theory, hydrazinolysis yields base which is greater than 95% pure by GC.

Pharmacological Methods. The target compounds were evaluated first in mice. Antiarrhythmic activity was measured as the ability to protect the animals against chloroform-induced ventricular fibrillation, according to a modification of the method of Lawson.[17] On the same animals, CNS toxicity was observed and compared to antiarrhythmic effects. The ED_{50} for each compound was determined with a minimum of three doses. Promising compounds were also studied in dogs with myocardial infarction. Two-step ligation of the left anterior descending coronary artery according to the method of Harris[18] produced an anterior myocardial infarction, with ventricular arrhythmias that demonstrated a high percentage of ectopic beats 20–24 h after ligation. Drug solutions were infused intravenously at a rate of 0.5 mg kg^{-1} min^{-1}, and the antiarrhythmic effect was observed as a reduction in the percentage of beats of abnormal origin. Clearing was defined as a reduction of ventricular ectopic activity to 5% or less for 5 consecutive min. Details of both methods are described in a previous paper[1] of this series.

Results and Discussion

The physical properties of intermediates and target compounds are summarized in Tables I and II, respectively.

In the 2,6-xylidine series, the synthesis of the secondary amines is complicated by the *o*-methyl groups. In these laboratories, direct alkylation of 2,6-xylidine, or reductive amination with the appropriate aldehyde by the method of Borch,[19] resulted in difficult to separate mixtures of mono- and disubstitution products. Preparation of the pure secondary amine by cleavage of the appropriate amide or sulfonamide required very harsh conditions and long reaction times due to the steric hindrance of the *o*-methyl groups. Similarly, lithium aluminum hydride reduction of the 2,6-acetoxylidide required long reaction times and gave low yields.[9] The reaction of 2,6-xylidine with sodium borohydride in acetic acid[20] gave mono- and disubstituted mixtures even at early stages of the reaction.[11] Decarbonylation[12] of *N*-ethylformo-2,6-xylidide (**3**, Scheme I) gave pure *N*-ethyl-2,6-xylidine (**4**) in 58% yield, but the same sequence was less satisfactory with the *N*-methyl analogue.[11]

The coupling of the *N*-alkyl-2,6-xylidines with acyl halides resulted in much poorer yields than with N-unsubstituted 2,6-xylidines when the method of Löfgren[13] (method C) was used. A two-phase system[14] (method D) was more successful.

The alkylation of the phthalimide (method G) with alkyl halide and sodium hydride dispersion in xylene provided an efficient route for preparation of these compounds. The formation of the amide salt was complete in about 2 h. Several more hours of reflux with the alkyl halide were sufficient to alkylate the salt. Excess NaH must be avoided in this reaction. In the preparation of **39**, an excess of NaH was used to ensure the complete conversion of **17** to the sodium salt. After alkylation and hydrazinolysis of the crude phthalimide, the resulting amine was examined by GC–MS. Besides the desired amine, an impurity, 2-(ethylamino)-*N*-ethyl-4′-propoxy-2′,6′-acetoxylidide, amounting to about 5% of the total product, was identified. This product most likely resulted from a hydride-induced opening of the phthalimide ring, followed by alkylation of the amide formed. Attempts to isolate the ring-opening intermediate have not been successful. In the early experiments in this series, the alkylated phthalimides were not purified prior to hydrazinolysis. Purification of the alkylated phthalimides by crystallization removes the ring-opened intermediate from the phthalimide and results in pure primary amines upon hydrazinolysis.

All compounds tested showed some antifibrillatory activity when tested in the chloroformed mouse (Table III). In those cases where death resulted, protection is reported

Table II. Structures, Physical Properties, and Yields of Primary Amines

no.	R^P	R^N	R^α	yield,[a] %	method	formula	mp, °C	solv	anal.
28	H	CH_3	H	90	E	$C_{11}H_{16}N_2O{\cdot}C_4H_6O_6$[b]	173-176[l]	c	C, H, N
29	H	CH_3CH_2	H	86	E	$C_{12}H_{18}N_2O{\cdot}HCl$	173-176	d	C, H, N
30	H	$CH_3CH_2CH_2$	H	76	H	$C_{13}H_{20}N_2O{\cdot}C_4H_6O_6$[b]	151-151.5	e	C, H, N
31	H	$(CH_3)_2CH$	H	86	H	$C_{13}H_{20}N_2O{\cdot}C_4H_6O_6$[b]	168-168.5[l]	f	C, H, N
32	H	$C_6H_5CH_2$	H	71	H	$C_{17}H_{20}N_2O{\cdot}HCl$	232-234	g	C, H, N, Cl
33	H	CH_3	CH_3	96	E	$C_{12}H_{18}N_2O{\cdot}HCl$	212-214	h	C, H, N, Cl
34	H	CH_3	CH_3CH_2	51	E	$C_{13}H_{20}N_2O{\cdot}HCl{\cdot}H_2O$	173.5-175.5	e	C, H, N, Cl
35	H	CH_3CH_2	CH_3	81	E	$C_{13}H_{20}N_2O{\cdot}HCl$	195-196	d	C, H, N, Cl
36	H	CH_3CH_2	CH_3CH_2	61	E	$C_{14}H_{22}N_2O{\cdot}HCl$	207.5-209.5	e	C, H, N, Cl[i]
37	n-C_3H_7O	CH_3	H	66	H	$C_{14}H_{22}N_2O_2{\cdot}C_2H_2O_4$[j]	125-127	c	C, H, N
38	n-C_3H_7O	CH_3	CH_3	80	H	$C_{15}H_{24}N_2O_2{\cdot}HCl$	206-207	e	C, H, N, Cl
39	n-C_3H_7O	CH_3CH_2	H	80	H	$C_{15}H_{24}N_2O_2{\cdot}C_2H_2O_4{\cdot}H_2O$[j]	96-98	g	C, H, N[k]
40	n-C_4H_9O	CH_3	H	79	H	$C_{15}H_{24}N_2O_2{\cdot}C_2H_2O_4$[j]	143-147	g	C, H, N
41	n-C_4H_9O	CH_3	CH_3	87	H	$C_{16}H_{26}N_2O_2{\cdot}HCl$	204-205	e	C, H, N
42	n-C_4H_9O	CH_3CH_2	CH_3	68	H	$C_{17}H_{28}N_2O_2{\cdot}HCl$	190-191	e	C, H, N, Cl

[a] Crude base greater than 95% pure by GC. [b] d-Tartrate salt. [c] Acetonitrile. [d] Ethanol–ethyl acetate. [e] Ethanol–ether. [f] Ethanol. [g] 95% ethanol. [h] CH_2Cl_2–ether. [i] N: calcd, 10.35; found, 10.82. Cl; calcd, 13.09; found, 13.69. [j] Oxalate salt. [k] Analysis on anhydrous salt. [l] Decomposition.

as a percentage of those animals which survived to be challenged with chloroform.

Data for the unalkylated compounds **43-48** were previously reported[1] and are included for comparison (Table V). Compounds **28**, **30–32**, **34–36**, **38**, and **41** show increased CNS toxicity over tocainide (**2**) but only **30** and **36** were more CNS toxic than lidocaine, which causes ataxia, loss of righting reflex, and convulsion at doses of 100 mg/kg. In the glycylxylidide series, **28–32**, alkylation of the amide nitrogen increases potency over the secondary amide **43**, but little change in potency is evident after the alkyl group becomes larger than ethyl.

The effects of lidocaine were evaluated in five coronary artery ligated dogs (Table IV). In three dogs the arrhythmia was cleared by doses of 0.045, 0.085, and 0.096 mmol/kg without accompanying toxicity. However, in two dogs, clearing of the arrhythmia required doses of 0.39 and 0.44 mmol/kg, and convulsions occurred in both animals at doses only slightly lower than those which abolished the arrhythmia. While the reasons for the resistance to lidocaine of the arrhythmias of the last two dogs are not readily apparent, it is significant that one of these animals possessed the most severe arrhythmia in the group and that among dogs with arrhythmias due to coronary artery ligation, those with the most severe arrhythmias are less responsive to treatment with procainamide or with lidocaine.[21]

The responses to tocainide were more consistent than those for lidocaine. However, tocainide required higher doses to clear these arrhythmias, and in 7 of 14 dogs convulsions were produced at or slightly below the doses which abolished the arrhythmias.

Compound **29** was studied in two coronary artery ligated dogs (Table IV). Although some clearing was evident in each experiment, the doses necessary to completely clear the severe arrhythmias (93–100% ectopic beats) produced respiratory arrest in both animals. One dog exhibited convulsions at a dose of 0.08 mmol/kg which continued until death at 0.47 mmol/kg. The second animal showed no CNS toxicity but exhibited a marked drop in mean arterial blood pressure (MABP) at 0.11 mmol/kg, followed by death at 0.21 mmol/kg. The *N*-benzyl derivative **32** was also tested in coronary artery ligated dogs. In the first pair of experiments, infusion was stopped when either clearing or convulsion was observed. In the third experiment, infusion was continued until clearing resulted. Although **32** is as potent as lidocaine and more potent than tocainide, the therapeutic index toward CNS toxicity is lower due to enhanced CNS effects.

In the alanylxylidides **33** and **35**, a marked increase in potency and CNS toxicity, compared to the secondary amide **2**, is observed when R^N is ethyl (**35**). In the α-amino butyroxylidides **34** and **36**, amide alkylation increases potency over the secondary amide **44**. The R^N = ethyl compound, **36**, exhibits marked potency and toxicity. Compound **35** was tested in two coronary artery ligated dogs. While both animals tested exhibited some reduction in ectopics, no complete clearing resulted. Both animals died from respiratory arrest after exhibiting symptoms of CNS toxicity, i.e., either convulsions or ophistotonus and clonic spasms.

Since the data of Byrnes et al.[1] suggests that propoxy or butoxy groups at the 4 position of the aromatic ring had improved the potency and decreased the CNS toxicity in the alanyl and glycyl series (Table V), several amide alkyl analogues (**37–42**) were made to test the combined effects of *p*-alkoxy and amide alkyl substitutions.

Table III. Antifibrillatory and Toxic Effects in Mice

no.	no. treated[a]	protection[b]	toxicity at[c]	toxicity c[d]	toxicity lrr[e]	toxicity d[f]	ED_{50} for protection, mmol/kg (95% Fieller limits)	potency[g]
1	10	100	100	100	100	0	0.26 ± 0.09[h]	1.0
2	10	20	10	0	0	0	1.30 ± 0.60[i]	0.2
28	10	60	100	0	0	0	0.49 (0.05-1.05)	0.5
29	10	70	0	0	0	0	0.22 (0.10-0.44)	1.2
30	10	100	100	100	100	70	0.24 (0.17-0.31)	1.1
31	10	90	100	100	0	0	0.24 (0.16-0.37)	1.1
32	10	100	100	10	0	0	0.18 (0.13-1.27)	1.4
33	10	20	0	0	0	0	0.85 (0.63-1.23)	0.3
34	10	30	100	0	0	0	0.49 (0.39-0.65)	0.5
35	10	90	100	10	40	0	0.42 (0.33-1.09)	0.6
36	10	100	100	100	0	30		[j]
37	10	70	20	0	0	0	0.34 (0.27-0.47)	0.8
38	20	95	100	40	0	0	0.20 (0.14-0.28)	1.3
39	10	100	0	0	0	0	0.16 (0.06-0.54)	1.6
40	10	100	0	0	0	0	0.27 (0.17-0.55)	1.0
41	10	30	100	30	0	0	0.46 (0.33-0.75)	0.6
42	10	10	0	0	0	0	0.86 (0.58-1.57)	0.3

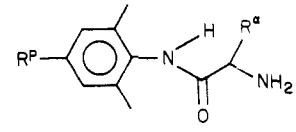
[a] Subcutaneous administration of 100 mg/kg in preliminary experiments. [b] Percent of animals challenged which were protected against ventricular fibrillation induced by chloroform. [c-f] Percent of animals treated which showed ataxia, convulsions, loss of righting reflex, and death. [g] Calculated relative to 1 on a molar basis. [h] Mean and standard deviation of 72 determinations. [i] Mean and standard deviation of 14 determinations. [j] Lethal dose very close to maximum effective dose; ED_{50} and potency could not be determined.

Table IV. Antiarrhythmic and Toxic Effects in Coronary Artery Ligated Dogs

	predrug control values			clearing values			dose, mmol/kg, to cause:		
no.	vent. ect, %	vent. rate, beats/min	MABP, mmHg	vent. ect, %	vent. rate, beats/min	MABP, mmHg	clearing	toxicity	death
1	96 ± 5	174 ± 34	81 ± 11	4 ± 3	133 ± 16	101 ± 21	0.21 ± 0.19[a]	0.27 ± 0.15[b]	
2[c]	94 ± 5	207 ± 25	91 ± 19	2 ± 2	148 ± 16	108 ± 21	0.32 ± 0.11	0.30 ± 0.06[b,d]	
29	93	240	100					0.08[b]	0.47[e]
	100	258	80					0.11[f]	0.21[e,g]
32	100	213	80					0.07[b,h]	
	99	168	120	0	138	155	0.08[h]		
	100	225	80	0	171	80	0.17	0.07[b]	
35	100	171	90					0.05[b]	0.27[e]
	89	168	90					0.06[i,j]	0.27[e]
38	99	219	105	5	150	100	0.16[h]	0.16[j]	
	86	237	125	0	141	75	0.17[h]	0.14[b]	
39	79	201	115	1	192	90	0.09	0.16[b,h]	
	99	185	120	2	168	90	0.13	0.13[b,k]	

[a] Means and standard deviations of five experiments. [b] Convulsions. [c] Means and standard deviations of 14 experiments. [d] Mean of eight experiments. [e] Respiratory arrest. [f] Drop in MABP. [g] Infusion rate 0.375 mg kg^{-1} min^{-1}. [h] Infusion off. [i] Ophistotonus. [j] Clonic spasms. [k] Infusion rate 0.66 mg kg^{-1} min^{-1}.

Table V. Structure and Antifibrillatory and Toxic Effects of Reference Compounds in Mice[a]



no.	R^P	R^α	no. treated[b]	protection[b]	toxicity[b] at	c	lrr	d	ED_{50}[b]	potency[b]
43	H	H	10	10	0	0	0	0	0.90 (0.67-2.3)	0.3
44	H	CH_3CH_2	20	50	50	50	5	0	1.01 (0.65-2.5)	0.3
45	n-C_3H_7O	H	10	40	100	0	0	0	[c]	
46	n-C_4H_9O	H	10	60	0	0	0	0	[d]	
47	n-C_3H_7O	CH_3	20	25	0	0	0	0	0.77 (0.52-1.1)	0.3
48	n-C_4H_9O	CH_3	10	20	0	0	0	0	0.57 (0.22-1.2)	0.5

[a] Data taken from ref 1 and included for reference. [b] As defined in Table III. [c] Not statistically evaluated (slope too small). [d] ED_{50} not evaluated due to solubility limitations.

The changes introduced into the molecules by the addition of p-propoxy or p-butoxy groups were evaluated. In the glycyl series, **28**, **37**, and **40** (R^N = methyl), the potency increased and CNS toxicity decreased slightly as the size of the para substituent increased. Compounds **29** and **39** (R^N = ethyl) exhibited a similar effect. In the alanyl series, **33**, **38**, and **41** (R^N = methyl), the potency increased markedly when the para group was propoxy. The change to a butoxy group decreased the potency when compared to the propoxy compound **38** but improved

potency over the unsubstituted compound **33**. Both **38** and **41** were more CNS toxic than **33**. When R^N = ethyl (**35** and **42**), the addition of a butoxy group to the para position decreased both the potency and CNS toxicity.

Compounds **38** and **39** were evaluated in the coronary artery ligated dog (Table IV). The substitution of the propoxy group for a hydrogen at the para position had a very beneficial effect in these experiments. The propoxy derivative **39** abolished severe ventricular arrhythmias at nonlethal doses, while **29** did not. CNS toxicity seemed to be slightly diminished compared to **29**.

Both **38** and **39** abolished severe ventricular arrhythmias at lower doses than either **1** or **2** and were slightly less CNS toxic than tocainide. Compound **39** is of comparable potency and may have a better margin of safety than lidocaine.

The pharmacokinetics of **2**, **28**, **29**, **33**, **35**, **39**, **43**, **44**, and **47** have been studied in these laboratories.[22] Although amide alkylation has resulted in increased potency and, in some cases, more favorable therapeutic margins when compared to the secondary amide, this structural modification results in greatly shortened plasma half-lives. None of these compounds had as favorable pharmacokinetic properties as tocainide (**2**). Due to the short plasma half-lives of the amide alkyl compounds, no oral bioavailability studies were done. However, in view of its favorable margin of safety and short biological half-life, further studies are underway to investigate the potential of **39** as an antiarrhythmic drug for administration by intravenous infusion.

Experimental Section

All chemicals were reagent grade or purer. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Microanalyses were performed by Alfred Bernhardt Microanalytical Laboratories, Elbach über Engelskirchen, West Germany, or Chemalytics, Inc., Tempe, Ariz. Compounds were characterized by elemental analysis and by NMR (Hitachi Perkin-Elmer Model R-20), IR (Perkin-Elmer Model 257 spectrophotometer), and, in many cases, by mass spectra (Finnigan 1015D quadrapole GC–MS). All spectra and experimental analyses, except where noted, were in accord with the assigned structures. The progress of reactions and product purity were determined by gas chromatography (Varian 1200, OV-101, 1.5%; Varian 200, OV-17 3% or JXR 3%).

***N*-Ethylformo-2,6-xylidide (3). Method A.** Triethyl orthoformate (222.3 g, 1.5 mol) and 2,6-xylidine (121.1 g, 1.0 mol) were refluxed with 5 g of *p*-toluenesulfonic acid with continuous removal of ethanol. After 2 h, 6 mL of H_2SO_4 was added and the remainder of the ethanol was distilled. The reaction mixture was distilled, yielding **3**: 150 g (85%), oil; bp 94–100 °C (0.5 mm). The product was homogeneous by GC.

***N*-Ethyl-2,6-xylidine (4). Method B.** **3** (150 g, 0.85 mol) and NaH (60 g, 1.25 mol as a 52% oil dispersion) were suspended in 400 mL of dimethoxyethane and refluxed for 3 days. The reaction mixture was poured into 500 mL of H_2O, and 100 mL of ethyl ether was added. The ethereal phase was removed and the aqueous phase was extracted twice with ether. The ether extracts were combined, dried (Na_2SO_4), and evaporated. Fractional distillation of the residual oil gave **4**: yield 73 g (58%); bp 51–54 °C (0.1 mm), lit.[9] 93–95 (15 mm).

***N*-Alkyl 2-Halo 2′,6′-Xylidides. Method C.** The *N*-alkyl-2,6-xylidine (0.1 mol) was dissolved in 70 mL of glacial acetic acid, and the solution was cooled to 10 °C. The acid halide (0.102 mol) was added and followed immediately by a cooled solution of 31 g of sodium acetate trihydrate in 135 mL of water. The solution was shaken mechanically for 0.5 h, 400 mL of water was added, and the oil which formed was allowed to solidify. The product was filtered, washed with water, and dried. The product was of sufficient purity for further use.

Method D. A two-phase system consisting of 96 mL of 9% aqueous sodium hydroxide and 0.1 mol of *N*-alkyl-2,6-xylidine in 45 mL of toluene was cooled to 10 °C. To the rapidly stirred mixture was slowly added 0.13 mol of the α-haloacyl halide in 12 mL of toluene. The mixture was allowed to warm to 20 °C and stirred for 1 h. Diethyl ether, 100 mL, was added, and the phases were separated. The aqueous phase was extracted with diethyl ether, and the combined organic phases were washed with water and dried (Na_2SO_4). The solvent was evaporated, leaving the halide of sufficient purity for use as an intermediate.

***N*-Alkyl 2-Amino 2′,6′-Xylidides. Method E.** The 2-halo xylidide (0.1 mol) was dissolved in 42 mL of 95% ethanol, 63 mL (0.96 mol) of concentrated aqueous ammonia was added, and the solution was placed in a steel autoclave at 75 °C for 6 h. The autoclave was cooled and the solvent evaporated. The residue was dissolved in water, made basic with 7 M NaOH, and extracted with methylene chloride. The extract was washed with water and dried (K_2CO_3). Evaporation of the solvent gave the crude base. The compound was purified as the salt (see Table II).

2-Phthalimido 2′,6′-Xylidides. Method F. To a solution of 0.1 mol of the 2-halo 2′,6′-xylidide in 90 mL of dimethylformamide (DMF) was added 0.11 mol of potassium phthalimide. The solution was refluxed for 2 h, cooled, and 125 mL of 28% acetic acid was added. The solid was filtered, washed with water, and dried, yielding product of sufficient purity.

***N*-Alkyl 2-Phthalimido 2′,6′-Xylidides. Method G.** The 2-phthalimido 2′,6′-xylidide (0.1 mol) was suspended in 320 mL of xylene (CaH_2 dried) under an argon atmosphere. Xylene, 50 mL, was distilled to remove any remaining water and 5.2 g of a 52% dispersion of NaH (0.11 mol of NaH) was added in several portions. The mixture was refluxed for 2 h, cooled slightly, and 0.15 mol of the alkyl halide was added slowly. After 3 h at reflux, the sodium halide was filtered free and the xylene evaporated. The crude product was generally of sufficient purity but was preferably purified by recrystallization.

***N*-Alkyl 2-Amino 2′,6′-Xylidides. Method H.** *N*-Alkyl 2-phthalimido xylidide, 0.1 mol, was dissolved in 600 mL of 95% ethanol by heating, the solution was cooled slightly, and 8.3 mL of 85% hydrazine hydrate was added. After 1 h under reflux, the mixture was cooled slightly and acidified with 20 mL of 12 M HCl. The mixture was refluxed for 2 h, cooled, filtered, and washed with water. The combined filtrates were evaporated. The solid was taken up in 300 mL of water, made basic, and extracted with ether. The extract was dried (K_2CO_3) and the solvent was distilled, giving crude base. The compound was purified as a salt (Table II).

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New Antiarrhythmic Agents. 3. Primary β-Amino Anilides

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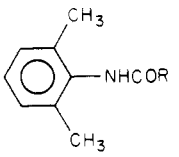
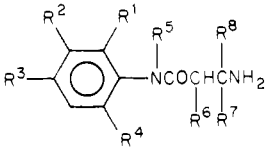
The synthesis and pharmacologic evaluation of primary β-amino anilides, as well as comparisons with tocainide, lidocaine, and its β homologue, are described. Substituted anilines were acylated with 3-bromoacyl chlorides and converted to the title compounds by direct amination or via 3-phthalimido anilides and subsequent hydrazinolysis. Alternatively, anilines were acylated with substituted acryloyl chlorides and the amines prepared by addition of ammonia to the double bond. The target compounds were evaluated for their ability to protect against chloroform-induced fibrillation in mice. All were found to have some antifibrillatory activity; several were more potent than tocainide, a compound in clinical trials as an oral antiarrhythmic drug. Four compounds were tested for their effects against ventricular arrhythmias in dogs with myocardial infarction. 3-Amino-2′,6′-butyroxylidide (**38**) was found to be more potent and less CNS toxic than tocainide.

In a previous article[1] we have described biological and chemical procedures to obtain an antiarrhythmic drug pharmacologically similar to lidocaine (**1**), with pharma-



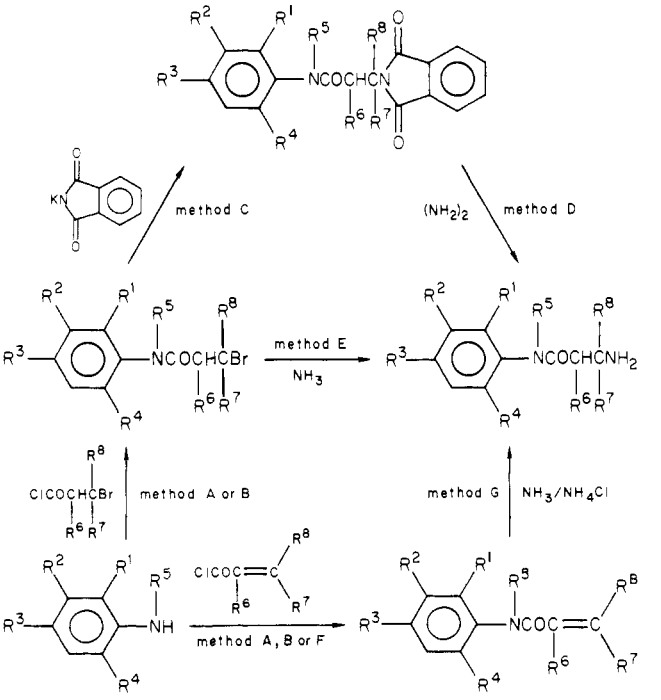


A

1, R = $-CH_2N(Et)_2$
2, R = $-CH(CH_3)NH_2$
3, R = $-CH_2CH_2N(Et)_2$

cokinetic properties allowing oral administration. Tocainide (**2**) was found to be an effective antiarrhythmic agent in animals[1-3] with suitable pharmacokinetic parameters in man[4] and is presently undergoing clinical trials.[5] Animal experiments demonstrated early that the limiting toxicity of tocainide represented effects upon the central nervous system (CNS). We therefore decided to search for a drug with improved properties, particularly lower CNS toxicity. One of the approaches utilized was an attempt to alter drug distribution in the body by increasing the basicity and, consequently, the degree of protonation at physiological pH. Primary β-amino anilides (formula A) are considerably stronger bases than the corresponding primary α-amines but remain chemically and pharmacologically closely related to this class, of which many members had shown antiarrhythmic effects.[1] A structure-modification program (formula A) encompassing variation of substitution on the aromatic ring (R^1–R^4), the amide nitrogen (R^5), and the intermediate chain (R^6–R^8)

Scheme I



was devised according to principles previously described.[1,6] We report here the syntheses and pharmacological test results of primary β-amino anilides, as well as comparisons with tocainide (**2**), lidocaine (**1**), and its β homologue **3**.[7]

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