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



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^{5,8} should be increased, their lipophilicities⁷ 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 acetate¹³ (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 dimethylformamide¹⁵ (method F) and subsequently were alkylated by a modification of the method of Fones¹⁶ (method G). The alkylated phthalimides were generally of sufficient purity to give the



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

Scheme II



X = Cl, Br; methods: F, DMF/potassium phthalimide; G, NaH/xylene; H, N₂H₄/EtOH

desired xylidides in good yield on hydrazinolysis in $e thanol^{15}$ (method H).





				0	0				
	ъP	лN	Dα	37	0.0		yield,		
no.	R*	R*	Ru	X	mp, °C	solv	%	method	formula
5	Н	CH_3	Н	Cl	51-54	а	40	С	C ₁₁ H ₁₄ NOCl
6	H	CH ₃	CH_3	Br	78.5-80	а	27	С	C ₁ ,H ₁₆ NOBr
7	H	CH ₃	C ₂ H,	Br	b	b	93	D	C ₁ ,H ₁ ,NOBr
8	н	C_2H_5	H	Cl	ь	b	96	D	C ₁₂ H ₁₆ NOCl
9	H	C ₂ H ₅	CH_3	\mathbf{Br}	64-66	а	98	D	C ₁₃ H ₁₈ NOBr
10	H	C_2H_5	C_2H_s	\mathbf{Br}	b	b	84	D	C ₁₄ H ₂₀ NOBr
11	H	H	H	Y	288-291	а	87	F	$C_{18}H_{16}N_{2}O_{3}$
12	H	CH_3	Н	Y	ь	b	82	G	$C_{19}H_{18}N_{2}O_{3}$
13	Н	$n - C_3 H_7$	н	Y	170-176	с	77	G	$C_{21}H_{22}N_{2}O_{3}$
14	H	<i>i</i> -C ₃ H ₇	н	Y	187-192	с	55	G	$C_{21}H_{22}N_{2}O_{3}$
15	Н	$C_6H_5CH_2$	Н	Y	155-160	с	87	G	$C_{25}H_{22}N_{2}O_{3}$
16	H	Н	CH_3	Y	202 - 203.5	а	90	\mathbf{F}	$C_{19}H_{18}N_2O_3$
17	<i>n</i> -C ₃ H ₇ O-	H	Н	Y	> 270	а	94	F	$C_{21}H_{22}N_{2}O_{4}$
18	<i>n</i> -C ₃ H ₇ O-	H	CH_3	Y	208 - 209.5	а	79	\mathbf{F}	$C_{22}H_{24}N_{2}O_{4}$
19	n-C₃H ₇ O-	CH_3	Н	Y	d	d	66	G	$C_{22}H_{24}N_{2}O_{4}$
20	<i>n</i> -C ₃ H ₇ O-	CH_3	CH_3	Y	d	d	е	G	$C_{23}H_{26}N_{2}O_{4}$
21	<i>n</i> -C ₃ H ₇ O-	C ₂ H ₅	Н	Y	126 - 128	с	70	G	$C_{23}H_{26}N_{2}O_{4}$
22	n-C₄H ₉ O	Н	Н	Y	264-266	а	86	F	$C_{22}H_{24}N_{2}O_{4}$
23	$n-C_4H_9O$	H	CH_3	Y	195-197	а	80	\mathbf{F}	$C_{23}H_{26}N_{2}O_{4}$
24	n-C₄H ₉ O	CH_3	н	Y	d	d	е	G	$C_{23}H_{26}N_{2}O_{4}$
25	$n-C_4H_9O$	CH_3	CH_3	Y	d	d	е	G	$C_{24}H_{28}N_{2}O_{4}$
26	$n-C_4H_9O$	C_2H_5	Н	Y	d	d	е	G	$C_{24}H_{28}N_{2}O_{4}$
27	n-C ₄ H ₉ O	C_2H_5	CH ₃	Y	d	d	е	G	$C_{25}H_{30}N_{2}O_{4}$

^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 Harris¹⁸ 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 paper¹ 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 Decarbonylation¹² 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 Löfgren¹³ (method C) was used. A two-phase system¹⁴ (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

																	, Z
	anal.	C, H, N	C, H, N	C, H, N	C, H, N	C, H, N, CI	C, H, N, CI	C, H, N, CI	C, H, N, CI	C, H, N, Cl ⁱ	C, H, N	C, H, N, CI	C, H, N^k	C, H, N	C, H, N	C, H, N, CI	^h CH ₁ Cl ₁ -ether.
	solv	v	p	ø	f	. D.C	ų	e	q	ø	c	ø	æ	oo'	e	ø	% ethanol.
	mp, °C	173-176 ¹	173-176	151 - 151.5	$168 - 168.5^{l}$	232-234	212-214	173.5 - 175.5	195 - 196	207.5-209.5	125 - 127	206-207	96-98	143-147	204-205	190-191	Ethanol. ^g 95
R ^N R ^d NH ₂	formula	C.,H.,N,O·C,H,O, ^b	C, H, N, O.HCI	ĊţĨĦĴŇĴO·ĊĨĦĸOĸ	C, H, N, O.C, H, O,	Ċ, H, N, O·HĊI	C, H, N, O.HCI	C, H, N, O·HCI·H, O	C, H, N, O.HCI	C, H, N, O·HCI	Ci H, N, O, C, H, O,	C, H, N, O, HCI	C, H, N, O, C, H, O, H, O	C, H, N,O, C,H,O,	Ċ, H, N, O, HĊI	C ₁ ,H ₂ ,N ₂ O ₂ ,HCl	-ethyl acetate. e Ethanol-ether. f inhydrous salt. l Decomposition.
	method	ы	E	Н	Η	Н	ы	ы	E	ы	H	Η	Н	Н	Н	Н	^d Ethanol- Analysis on a
2 2 2	yield, ^a %	06	86	76	86	71	96	51	81	61	66	80	80	79	87	68	Acetonitrile. late salt. k_{I}
	\mathbf{R}^{lpha}	H	Н	Н	Η	Η	CH,	CH,CH,	CH,	CH, CH,	, H	ĊH,	н	Н	CH,	CH,	<i>l</i> -Tartrate salt. ^c nd, 13.69. ^j Oxa
	$\mathbf{R}^{\mathbf{N}}$	CH,	CH,CH,	CH, CH, CH, CH,	(CH,),ĊH	Ċ, H, ĆH,	ĊĤ,	ĊH,	CHICH	CH, CH,	CH,	CH,	CH, CH,	CH,	CH,	CH ₃ CH ₂	5% pure by GC. ^b , 31; calcd, 13.09; fou
	RP	H	Н	Н	Н	Н	Н	Н	Н	Н	n-C,H,O	<i>n</i> -C,H,O	<i>n</i> -C,H,O	$n-C_{A}H_{O}$	$n-C_{a}H_{a}O$	$n-C_4H_0O$	greater than 95 und, 10.82. C
	.ou	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	^{<i>a</i>} Crude base { calcd, 10.35; fo

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

Data for the unalkylated compounds 43-48 were previously reported¹ 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 \mathbb{R}^N is ethyl (35). In the α -amino butyroxylidides 34 and 36, amide alkylation increases potency over the secondary amide 44. The \mathbb{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 II. Structures, Physical Properties, and Yields of Primary Amines

Table III. Antifibrillatory and Toxic Effects in Mice

no					toxi	city	ED_{50} for protection,			
no.		treated ^a	$protection^b$	at ^c	c ^d	lrr ^e	d ^f	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		i	
	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	Ó	0	0	0	0.16(0.06-0.54)	1.6	
	40	10	100	Ó	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	Ō	0	Ō	Õ	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; ED₅₀ and potency could not be determined.

Table IV.	Antiarrhythmic and	Toxic Effects i	n Coronary .	Artery	Ligated	Dogs
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	predrug control values		clearing values				_				
	vent. ect. vent. rat		MABP.	vent. ect. vent. rate.		MABP.	dose, mmol/kg, to cause:				
no.	%	beats/min	mmHg	%	beats/min	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	$0.30 \pm 0.06^{b,d}$			
29	93	240	100					0.08	0.47^{e}		
	100	258	80					0.11^{t}	$0.21^{e,g}$		
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			
35	100	171	90					0.05	0.27^{e}		
	89	168	90					0.06 ¹³	0.27^{e}		
38	99	219	105	5	150	100	0.16^{h}	0.16			
	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

H Rª
NH ₂

				no	pro- tec-	$\operatorname{toxicity}^b$						
no.	$\mathbf{R}^{\mathbf{p}}$	\mathbf{R}^{lpha}	treated ^b	tion ^b	at	с	lrr	d	ED ₅₀ ^b	$potency^b$		
	43	Н	H	10	10	0	0	0	0	0.90 (0.67-2.3)	0.3	
	44	Н	$CH_{3}CH_{2}$	20	50	50	50	5	0	1.01(0.65 - 2.5)	0.3	
	45	$n-C_3H_2O$	н	10	40	100	0	0	0	С		
	46	n-C₄H₀O	н	10	60	0	0	0	0	d		
	47	$n-C_{3}H_{2}O$	CH_3	20	25	0	0	0	0	0.77(0.52 - 1.1)	0.3	
	48	n-C₄H O	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*} ED₅₀ 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 (\mathbb{R}^N = methyl), the potency increased and CNS toxicity decreased slightly as the size of the para substituent increased. Compounds 29 and 39 (\mathbb{R}^{N} = ethyl) exhibited a similar effect. In the alanyl series, 33, 38, and 41 (\mathbb{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

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potency over the unsubstituted compound 33. Both 38 and 41 were more CNS toxic than 33. When \mathbb{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 bioavilability 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 (Na₂SO₄), 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 (Na₂SO₄). 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 (CaH₂ 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 article¹ we have described biological and chemical procedures to obtain an antiarrhythmic drug pharmacologically similar to lidocaine (1), with pharma-



cokinetic properties allowing oral administration. Tocainide (2) was found to be an effective antiarrhythmic agent in animals¹⁻³ with suitable pharmacokinetic parameters in man⁴ 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