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.

Acknowledgment. We thank L. Aberg, J. Barkus, L. Dadah, R. Heideger, L. Kofos, and B. Nylander for excellent technical assistance and Dr. B. Takman for valuable discussions.

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

Paul D. McMaster,*

College of the Holy Cross, Worcester, Massachusetts 01610

Eugene W. Byrnes,

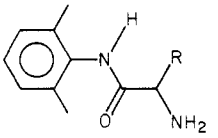
Assumption College, Worcester, Massachusetts 01609

Alan J. Block, and Paul A. Tenthorey

Astra Pharmaceutical Products, Inc., Framingham, Massachusetts 01701. *Received May 12, 1980*

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.

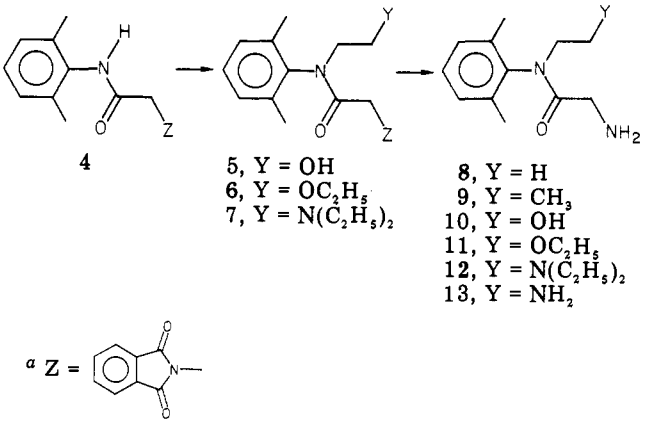
In a previous article[1] the chemical and pharmacological properties of a series of amide alkyl α-amino xylidides were reported. Although alkylation of the amide nitrogen of glycylxylidide (**1**) or tocainide (**2**) led to increased potency



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

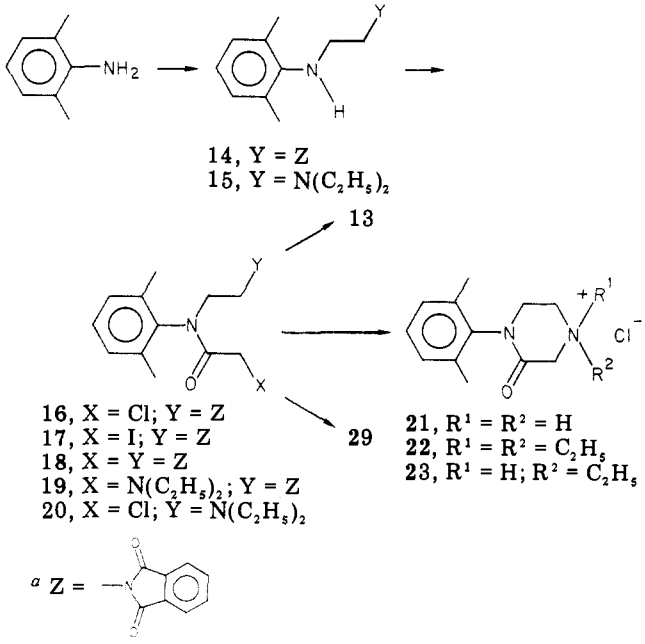
(1) Paper 2 in this series: McMaster, P. D.; Byrnes, E. W.; Feldman, H. S.; Takman, B. H.; Tenthorey, P. A. *J. Med. Chem.* **1979**, *22*, 1177.

(2) Berlin-Wahlén, A.; Barkus, J. C.; Keenaghan, J. B.; Lebeaux, M.; Tenthorey, P. A. *Acta Pharm. Suec.* **1977**, *14*, 417.

(3) Löfgren, N. "Studies on Local Anesthetics, Xylocain", Ivar Haeggstgroms, Stockholm, 1948, p 121.

0022-2623/81/1824-0053$01.00/0 © 1980 American Chemical Society

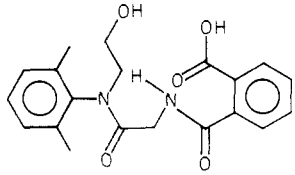
Scheme II[a]



amides, a series of primary amino acetoxylidides with functionalized amide alkyl substituents (8–13) were prepared and the antiarrhythmic and toxic properties were evaluated and compared with glycylxylidide (1) and tocainide (2). Compounds related to lidocaine (3), but with a similar set of modifications at the amide nitrogen, were made (24–29) and their pharmacological properties were compared with lidocaine. The effectiveness of several of these compounds in spinal anesthesia in sheep was also evaluated.

Chemical Methods. The primary acetoxylidides (8–12) were prepared according to Scheme I. Compounds 4, 8, and 9 have been reported previously from these laboratories.[1] Compounds 10, 11, and 12 were prepared by the hydrazinolysis[4] of the corresponding phthalimides (5, 6, and 7), which were formed by the alkylation of 4 with the appropriate halide by a modification of the procedure of Fones.[5]

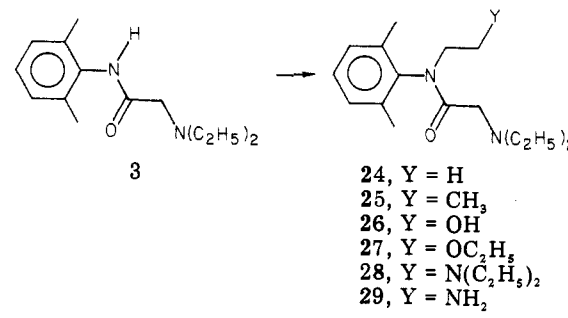
Although the synthesis of 5 by alkylation of 4 with 2-bromoethanol gave poor yields and required preparative high-pressure LC for purification, the procedure was a one-step synthesis from readily available starting materials. A byproduct, *N*-(2-hydroxyethyl)-2-(2-carboxybenzamido)-2′,6′-acetoxylidide (30), or some reactive intermediate which rapidly was hydrolyzed to 30 under aqueous conditions was present even at the early stages of the reaction. 30 was slowly hydrolyzed in our high-pressure LC solvent [acetonitrile–0.05 N sodium perchlorate, pH 4 (1:3)] to 10 and phthalic acid.



30

Compounds 13 and 29 were prepared by an alternate procedure (Scheme II). 2-Bromoethylphthalimide was heated in 2,6-xylidine to form 14, which was heated with chloroacetyl chloride in acetone to give 16. Compound 13 was prepared by hydrazinolysis of the intermediate bisphthalimide 18, which was formed by the reaction of 16 with potassium phthalimide in dimethyl formamide.[4] 16 was converted with sodium iodide in acetone to 17, which upon heating with diethylamine gave 19. Hydrazinolysis of 19 gave 29.

Scheme III



Compound 15 was prepared by a modification of the procedure of Löfgren[6] with better results. The acetic acid–sodium acetate method of Löfgren[7] for the preparation of amides gave low yields in the preparation of 16 from 14 and chloroacetyl chloride. The reaction in acetone with sodium bicarbonate reported here is superior. The reaction of 16 with diethylamine to form 19 was very slow, and many side products were formed upon continued heating. The synthesis from the iodide 17 took 16 h but gave a good yield.

20·HCl could be prepared from 15 and chloroacetyl chloride in good yield, but the product slowly underwent cyclization to 22 on treatment with base. 20 base, on standing for 1 day, was converted to 22, which melted at 245–245.5 °C and was characterized by NMR, IR, and analysis. Anal. ($C_{16}H_{25}N_2OCl$) C, H, N, Cl. The preparation of 20 could not be followed by GC, since 20 breaks down thermally to 22, which loses ethylene to form 23 (identified by GC–MS). Attempts to prepare 28 from 20 by heating with diethylamine also resulted in the formation of 22 as well as 28. This cyclization phenomenon was evident in work with the diamines, especially 29, which gave poor recovery in the basic workup. The hydrazinolysis procedure[4] was modified so that 29·HCl, which is formed, was purified without converting it to the base. The chief contaminant in the product is hydrazine dihydrochloride, which is insoluble in cold ethanol and can be filtered off from the ethanolic solution of 29·2HCl. Hydrazinolysis of 16 resulted in formation of 21, rather than *N*-(2-aminoethyl)-2-chloroaceto-2′,6′-xylidide (31). The cyclization occurred during the hydrazinolysis, not in the subsequent workup, since the product was not made basic, and 31·HCl would not be expected to cyclize.

The syntheses of 24–28 by direct alkylation of 3 (Scheme III) proved an efficient route to the desired compounds. The synthesis of 25[8] has not been previously reported. It was prepared in these laboratories by the procedure given. Several side products were produced during the synthesis of 26 when excess hydride and 2-bromoethanol were used or when the reaction mixture of base was heated. These products could only be removed by preparative high-pressure LC. If, however, equimolar portions of hydride

(4) Sheehan, J. C.; Bolhofer, W. A. *J. Am. Chem. Soc.* **1950**, *72*, 2786.
(5) Fones, W. S. *J. Org. Chem.* **1949**, *14*, 1099.
(6) Löfgren, N.; Takman, B. H. *Acta Chem. Scand.* **1952**, *6*, 1006.
(7) Löfgren, N., ref 3, p 25.
(8) This compound was obtained from Astra Research and Development Laboratories, S-151 85 Södertälje, Sweden.

Table I. Antiarrhythmic and Toxic Effects in Mice

no.	ED_{50},[a] mmol/kg protection	ED_{50},[a] mmol/kg ataxia	therapeutic index[b]
1	0.84 (0.58-1.21)	0.62 (0.40-0.84)	0.7
8[c]	0.46 (0.26-0.80)	0.34 (0.21-0.48)	0.7
9[d]	0.12 (0.04-0.24)	0.16 (0.10-0.24)	1.3
10	1.26 (0.81-3.18)	1.08 (0.71-1.72)	0.9
11	0.19 (0.12-0.61)	0.17 (0.12-0.26)	0.9
12	0.69 (0.31-2.24)	1.13 (0.97-1.56)	1.6
13	0.39 (0.14-0.59)	1.05 (0.71-1.95)	2.7
3	0.21 (0.19-0.23)	0.18 (0.17-0.20)	0.9
24	0.14 (0.07-0.22)	0.21 (0.15-0.31)	1.5
25[e]	0.17 (0.10-0.24)	0.15 (0.04-0.24)	0.9
26	0.18 (0.09-0.27)	0.49 (0.30-1.09)	2.7
27	0.06 (0.01-0.10)	0.08 (0.05-0.14)	1.3
28	0.46 (0.30-0.77)	0.60 (0.43-0.83)	1.3
29	0.12 (0.07-0.17)	0.56 (0.32-2.03)	4.7
19	[f]	[f]	
7	0.01 (0.005-0.015)	0.01 (0.007-0.012)	1.0
2	0.55 (0.43-0.66)	0.76 (0.63-0.89)	1.4

[a] 95% Fieller limits in parentheses. [b] ED_{50} (ataxia)/ED_{50} (protection). [c] ED_{50} (protection), 0.22 (0.10-0.44).[1] [d] ED_{50} (protection), 0.24 (0.17-0.31).[1] [e] Reference 8. [f] Lethal dose very close to effective dose, no ED_{50} values could be determined. Acute sc LD_{50}, 0.6 (0.4-1.0).

and bromoethanol were used, **26**·HCl could be separated from unreacted **3**·HCl by crystallization. High-pressure LC and NMR studies of **26**·HCl and **27**·HCl indicate that these salts crystallize as one of the rotomers around the amide bond and slowly isomerize to an equilibrium mixture of the rotomers in aqueous media. This phenomenon is presently being studied and the results will be reported elsewhere.

Pharmacological Methods. The antiarrhythmic activity and acute CNS toxicity of the target compounds were determined as described under Experimental Section. The antiarrhythmic activity was determined in mice according to a modification of the method by Lawson.[9] The modifications arose in part from recent evidence from this laboratory,[10] indicating that fibrillation due to chloroform inhalation might not occur in this species. Thus, prevention of fibrillation could no longer be considered a valid criterion of efficacy. Instead, efficacy was based upon reduced incidence of ventricular tachycardia. The revised procedure had been validated with currently available standard antiarrhythmic agents, which evoked dose-dependent efficacy.[11] In prior studies from this laboratory[1,12,13] in which antiarrhythmic activity was determined for compounds **8** and **9** by the method of Lawson,[9] visual observation of the heart's activity was the only criterion for efficacy. In the present study, however, efficacy was based upon strict criteria assessed from as many as three ECG leads. Thus, any differences in antiarrhythmic activity between earlier data for those compounds and data published herein should be considered in light of the new methods. Spinal anesthesia was determined by procedures described under Experimental Section.

Pharmacological Results and Discussion

All compounds tested showed antiarrhythmic activity against ventricular tachycardia induced by chloroform in mice (Table I). In the primary amine acetoxylidide series (**8–13**), all but **10** were more potent than the secondary amide **1**. Three compounds, **8**, **9**, and **11**, were more CNS toxic than **1**, but all except **8** showed an improved therapeutic index. **9** and **11** were similar in potency to lidocaine (**3**), but neither showed any advantage in therapeutic index. **13** is more potent and less toxic than tocainide (**2**) and has a better margin of safety toward CNS activity.

In the tertiary amine acetoxylidides (**24–29**), all but **28** were of equal or greater potency than lidocaine (**3**), and all but **25** showed improved therapeutic margins. **26** and **29** show especially good properties. All of the tertiary amine acetoxylidides were more potent and had greater safety margins than **1**, but only **26** and **29** offer sufficient advantage over tocainide to merit further study.

Two of the phthalimide intermediates, **7** and **19**, were also studied, and both were very potent but very toxic compounds. **7** was the most potent compound studied but had a poor therapeutic index. **19** reduced the incidence of arrhythmias, but there was little difference between the effective and lethal doses.

Although potency data for **8** and **9** have been presented previously,[1] the testing procedure has been modified and results using the new procedure are reported here.

From this study, compounds **13**, **26**, and **29** emerge as the more interesting for further study. Preliminary studies in dogs[14] indicated that **26** was an effective antiarrhythmic agent but has a short duration. Two of these compounds, **13** and **29**, are diamines, as are **12** and **28**. The aminoethyl and (diethylamino)ethyl groups are similar to those in procainamide and should have pK_a values in the region of 9–10,[15] and these derivatives should be extensively protonated at physiological pH. We have found in other studies[16] that the therapeutic index toward CNS toxicity for aminoxylidides correlates very well with pK_a, and the present observation appears to be a further manifestation of the same effect.

It was surprising that substitution of the aminoethyl group for the hydrogen on the amide nitrogen (**13** and **29**) produced more potent compounds than the corresponding substitutions of the (diethylamino)ethyl group (**12** and **28**). The ED_{50} values for ataxia, however, showed little difference in each series. This effect is contrary to the norm of increased potency with increased lipophilicity.[16] However, it should be noted that, except for the pair **9** and **25**, the more lipophilic compounds of the lidocaine series (**24–29**) were more potent than their respective analogues in the glycylxylidide series (**8–13**).

Compounds **12**, **28**, and **29** were tested as 2% solutions in sheep for spinal anesthesia and compared to lidocaine (1.5%) and tetracaine (0.5%). Observations were made of the onset of anesthesia at the anal region and at the digits of the hind limbs. The duration of block of pain at the same sites, as well as the length of the period of loss of weight support, were also noted (Table II).

The most striking observation was that the bis(tertiary amine), **28**, did not produce any anesthesia at all, whereas the two compounds having one tertiary and one primary amine function each, **12** and **29**, showed distinct activity.

(9) Lawson, J. W. *J. Pharmacol. Exp. Ther.* **1968**, *160*, 22.
(10) Block, A. J.; Williams, J. H. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* **1979**, *38*, 588.
(11) Block, A. J., unpublished results.
(12) Paper 1 in this series: Byrnes, E. W.; McMaster, P. D.; Smith, E. R.; Blair, M. R.; Boyes, R. N.; Duce, B. R.; Feldman, H. S.; Kronberg, G. H.; Takman, B. H.; Tenthorey, P. A. *J. Med. Chem.* **1979**, *22*, 1171.
(13) Paper 3 in this series: Tenthorey, P. A.; DiRubio, R. L.; Feldman, H. S.; Takman, B. H.; Byrnes, E. W.; McMaster, P. D. *J. Med. Chem.* **1979**, *22*, 1182.
(14) Åberg, G., private communication.
(15) Hanocq, J.; Topart, J.; vanDamme, M.; Molle, L. *J. Pharm. Belg.* **1973**, *28*, 649.
(16) Paper 6 in this series: Tenthorey, P. A.; Block, A. J.; Ronfeld, R. A.; Byrnes, E. W.; McMaster, P. D., in preparation.
(17) Archer, S. U.S. Patent 3 135 794 (1964).

Table II. Spinal Anesthesia in Sheep

no.	no. of animals	dose,[a] mg	Onset of block, min		duration of block, min		
			anus	digit	anal pain	digital pain	wt support
12	4	40	19 (5-50)[b]	19 (5-50)[b]	50-300	0-140[c]	0-165[d]
28	3	40			0	0	0
29	3	40	1-5	4-15	266-270	0-132[e]	90-195
3[f]	6	30	1	1.4	61 ± 16	51 ± 9	61 ± 17
Tetracaine[f]	6	10	1.13	1.2	302 ± 66	285 ± 46	458 ± 106
5% glucose	4				0	0	0

[a] Two-milliliter solution, pH 6.1-6.5. [b] Average onset time; range for successful blocks in parentheses. [c] Frequency, 63% (five of eight limbs). [d] Frequency, 75%. [e] Frequency of obtained anesthesia, 67%. [f] Frequency for all blocks, 100%.

These compounds were better anesthetics with regard to the anal region than the digital, as evidenced by the onset time, duration, and frequency of block. This indicates, perhaps, that the agents do not distribute well from the site of injection, which is close to the nerves supplying the anal region and distant from those innervating the digits. It should be added that all three compounds caused irritation (pain) on injection (gross observation of animal behavior).

Conclusions

Compounds **13** and **29** represent a new class of diamines which show promise as antiarrhythmic agents. Substitution of an aminoethyl group on the amide nitrogen of glycylxylidide and lidocaine increased the potency and improved the therapeutic index over the corresponding secondary amides when tested in mice. Further studies are being conducted in other animal models to determine if these compounds meet our goals as defined previously.[12]

Experimental Section

Melting points (uncorrected) were determined on a Thomas-Hoover Mel-Temp apparatus. The microanalyses were performed by Atlantic Microlab, Inc., Atlanta, Ga., or Alfred Bernhardt Microanalytical Laboratories, Elbach über Engelskirchen, West Germany. 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 quadrupole 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%) or by high-pressure liquid chromatography (LC; Waters μ-Bondapak C_{18} column, LDC spectromonitor III UV detector, 205 nm). Mixtures of acetonitrile–0.05 N aqueous $NaClO_4$, pH 4.0, were used as solvents and are reported with acetonitrile portions given first, i.e., 1:3 acetonitrile–perchlorate. No efforts have been made to maximize yields.

***N*-(2-Hydroxyethyl)-2-phthalimidoaceto-2′,6′-xylidide (5).** 4 (15.4 g, 0.05 mol) was suspended in 100 mL of dry xylene (CaH_2) under an argon atmosphere. Sodium hydride (52% dispersion; 2.3 g, 0.05 mol) was added, and the mixture was heated under reflux for 2 h. Hydrogen evolution was rapid just prior to reflux. The mixture was cooled and the water condenser was exchanged for a Dewar condenser. Sodium hydride (52%; 2.3 g, 0.05 mol) was added, followed by 2-bromethanol (6.2 g, 0.05 mol). Hydrogen evolution occurred immediately. The mixture was heated under reflux for 1.5 h, cooled, and filtered. The precipitate was washed with xylene, and the combined xylene phases were evaporated, yielding **5**: 10.3 g of a yellow solid. The solid was suspended in hot CH_2Cl_2, filtered free of unreacted **4**, and evaporated, yielding **5**: 7.9 g of a tan solid which high-pressure LC (1:2) indicated was contaminated by **4**. **5**, 7.1 g, was purified on a Waters Prep 500 (silica gel; 3:2 ethyl acetate–hexane), giving **5**: 3.5 g (20% overall) mp 190.5–191.5 °C. Anal. ($C_{20}H_{20}N_2O_4$) C, H, N.

***N*-(2-Ethoxyethyl)-2-phthalimidoaceto-2′,6′-xylidide (6).** **4** (15.4 g, 0.05 mol) was suspended in 100 mL of dry xylene (CaH_2) under an argon atmosphere. Sodium hydride (52% dispersion; 2.3 g, 0.05 mol) was added, and the mixture was heated under reflux for 2 h. Hydrogen evolution was rapid just prior to reflux. The solution was cooled slightly and 2-chloroethyl ethyl ether (11.0 g, 0.10 mol) was added. The mixture was heated under reflux for 5 h and allowed to cool. The solid was filtered and washed with xylene, and the xylene phases were concentrated to a yellow oil. The oil was extracted with 3 × 500 mL of hot petroleum ether (35–60 °C), and the petroleum ether phase was decanted from a residual yellow oil in each case. The petroleum ether extract was chilled, producing crystals which were filtered, washed, and dried, giving **6**: 9.4 g (50%); mp 114–115 °C. A further 1.7 g (9%), mp 114–115 °C, was obtained from the mother liquor. An analytical sample, mp 114–115 °C, was prepared by recrystallization from hexane. Anal. ($C_{22}H_{24}N_2O_4$) C, H, N.

***N*-[2-(Diethylamino)ethyl]-2-phthalimidoaceto-2′,6′-xylidide (7).** **4** (30.8 g, 0.10 mol), 2-(diethylamino)ethyl chloride hydrochloride (17.2 g, 0.10 mol), and sodium hydride (52% dispersion; 9.2 g, 0.2 mol) were added to 500 mL of anhydrous xylene (CaH_2), and the mixture was heated under reflux for 2 h. Sodium hydride (52% dispersion; 4.6 g, 0.10 mol) and 2-(diethylamino)ethyl chloride hydrochloride (8.6 g, 0.05 mol) were added and reflux was continued for 3 h. Methanol, 50 mL, was added, and the solvent was evaporated. The brown oil was dissolved in 500 mL of acetone, and the sodium chloride was removed by filtration. The acetone was evaporated, and the product was taken into ether (250 mL) and extracted with water (2 × 250 mL). The ether phase was dried (Na_2SO_4) and the solvent was evaporated, giving 41.9 g (>100%) of a brown oil. The oil was dissolved in 150 mL of 1 N HCl (hot), filtered, decolorized, and allowed to cool with stirring. The crystals were filtered, washed in water, and dried, giving **7**·HCl: 21.3 g (48%); mp 254.5–257 °C dec. On concentration the mother liquor gave **7**·HCl: 1.7 g (4%); mp 248–249 °C dec. An analytical sample was prepared by recrystallization from acetonitrile–water (3:1), giving **7**·HCl·0.5H_2O, mp 256–257 °C dec. Anal. ($C_{24}H_{30}N_3O_3Cl$·0.5H_2O) C, H, N, Cl.

***N*-(2-Hydroxyethyl)-2-aminoaceto-2′,6′-xylidide (10).** **5** (3.0 g, 0.009 mol) was dissolved in 50 mL of hot ethanol. Hydrazine hydrate (85%; 1 mL) was added, the mixture was heated at reflux for 2 h and cooled slightly, and 3 mL of concentrated HCl was added. Heating was continued for 0.5 h. The mixture was cooled and filtered, and the filter cake was washed with H_2O until neutral and dried giving 1.2 g of phthalhydrazide (86%). The aqueous phase was evaporated, giving **10**·HCl, 3.4 g (>100%). The solid was suspended in cold ethanol, and the solid (hydrazine dihydrochloride) was filtered. The ethanol was evaporated, giving **10**·HCl, 2.4 g (~100%). Recrystallization from ethanol–ether (1:3) gave **10**·HCl: 2.0 g (87%); mp 163–165 °C. Anal. ($C_{12}H_{19}N_2O_2Cl$) C, H, N, Cl.

***N*-(2-Ethoxyethyl)-2-aminoaceto-2′,6′-xylidide (11).** **6** (9.4 g, 0.025 mol) was suspended in 100 mL of 95% ethanol and heated until solution resulted. Hydrazine hydrate (85%; 4 mL) was added, and the solution was heated at reflux for 2 h. The mixture was cooled slightly, concentrated HCl (12 mL) was added, and heating was continued for 0.5 h. The mixture was cooled, and the precipitate was filtered and washed with water (2 × 25 mL). The aqueous phase was evaporated, and excess water was removed as an azeotrope with ethanol. The white solid was dissolved in 50 mL of water, extracted with ether (2 × 25 mL), and made basic to pH ~11 with 7 M sodium hydroxide. The base was extracted into ether (3 × 50 mL), the ethereal phase was dried (K_2CO_3), and the solvent was evaporated, giving **11**: 5.6 g (90%) of an oil. **11** (4.8 g, 0.019 mol) was dissolved in 25 mL of anhydrous ethyl ether, and the solution was added to a solution of L-tartaric acid

(2.9 g, 0.019 mol) in 25 mL of anhydrous ethanol. Crystals soon formed, which were filtered, washed with ethanol–ether (1:2), and dried, giving 11·L-tartrate: 7.1 g (92%); mp 133.5–134.5 °C dec. Anal. ($C_{18}H_{28}N_2O_8$) C, H, N.

N-[2-(Diethylamino)ethyl]-2-aminoaceto-2′,6′-xylidide (12). 7 (15.0 g, 0.035 mol) was suspended in 150 mL of hot ethanol and 3 mL of hydrazine hydrate (85%) was added. The mixture was heated at reflux, cooled, and 30 mL concentrated HCl was added. After heating was continued for 1 h, the mixture was cooled and filtered, and the precipitate was washed with water (2 × 50 mL). The solvent was evaporated, and the solid was taken into 200 mL of water, filtered, extracted with ether (2 × 50 mL), and made basic (pH ~11) with 7 M NaOH. The base was extracted into ether (4 × 75 mL), the ethereal phases were dried (K_2CO_3), and the solvent was evaporated, giving 12: 7.4 g (76%) of a colorless oil. Extraction of the aqueous phase with methylene chloride (3 × 25 mL) gave an additional 0.7 g (8%). The combined oils were dissolved in 70 mL of 1 M HCl and filtered through Celite, and the solvent was evaporated, giving 12·2HCl. Recrystallization from 95% ethanol–ether (2:3) gave 12·2HCl: 10.5 g (85%); mp 247.5–248.5 °C dec. Anal. ($C_{16}H_{29}N_3OCl_2$) C, H, N, Cl.

N-(2-Aminoethyl)-2-aminoaceto-2′,6′-xylidide (13). 18 (13.0 g, 0.027 mol) was dissolved in 200 mL of 95% ethanol at reflux, cooled slightly, and 5.8 mL of hydrazine (64% in water) was added. After 2 h of reflux, the mixture was cooled and 18 mL of concentrated HCl was added. The mixture was heated under reflux for 0.5 h, cooled, and filtered. The precipitate was washed with water, and the combined filtrates were concentrated by distillation. The product was taken up in 100 mL of H_2O, extracted with ether (2 × 50 mL), made basic with 7 M NaOH, and extracted into methylene chloride. The organic phase was dried and the solvent was distilled, yielding 6.3 g of an oil. The oil was dissolved in 50 mL of methylene chloride and acidified with HCl (gas), and the precipitate was filtered, washed, and dried, giving 13·2HCl, 7.5 g (95%). Recrystallization from ethanol (95%) gave 13·2HCl·0.25H_2O (73%), mp 270–271 °C. Anal. ($C_{12}H_{21}N_3OCl_2$·0.25H_2O) C, H, N, Cl.

N-(2-Phthalimidoethyl)-2′,6′-xylidine (14). N-(2-bromoethyl)phthalimide (40.8 g, 0.16 mol) and 2,6-xylidine (48.4 g, 0.40 mol) were heated at 160 °C for 1 h. The purple solution was cooled, acidified with 4 N HCl, and diluted with H_2O to a total volume of 1 L. The precipitate was filtered, and the purple solution was extracted with ether. The 14·HCl was extracted with methylene chloride (9 × 100 mL). The combined methylene chloride phases were dried (Na_2SO_4) and the solvent was evaporated, yielding 14·HCl: 40.8 g (77%) of a purple amorphous solid. 14·HCl was taken into water, made basic with 7 N NaOH, and extracted with methylene chloride (3 × 100 mL). The CH_2Cl_2 phases were combined and dried (K_2CO_3), and the solvent was distilled, yielding 35.6 g of a brown oil. Crystallization from 100 mL of ethanol gave 14: 34.1 g (72%); mp 69–70 °C; IR (KBr) ν_{max} 3362 (NH), 1722 and 1779 (imide), 786 (3 adj H's), 725 cm^{-1} (4 adj H's); NMR ($CDCl_3$; Me_4Si) δ 2.24 (s, 6, CH_3), 3.28 (t, J = 6 Hz, 2, CH_2NHAr), 3.80 (t, J = 6 Hz, 2, CH_2N phth), 6.87 (m, 3, aromatic), 7.74 (m, 4, aromatic).

N-[2-(Diethylamino)ethyl]-2′,6′-xylidine (15). 2-Chloroethyldiethylamine (25 g, 0.18 mol) was dissolved in 120 mL of ethanol, and the solution was added to 2,6-xylidine (63.0 g, 0.52 mol). The mixture was heated to 80 °C on an oil bath for 0.5 h, cooled, and was concentrated by distillation. The residue was taken up in 300 mL of 1 N HCl, extracted with ether, and the pH was adjusted to 4–5 with 2 N NaOH. The xylidine was exhaustively extracted, the pH was raised in 11, and the oil was extracted into ether. The ethereal solution was dried (K_2CO_3), and the solvent was distilled, yielding 15, 23.0 g (57%), which was greater than 98% pure by GC (JXR-3). Fractional distillation gave 15: 16.2 g (40%); bp (0.02 mmHg) 73–75 °C, lit.[6] bp (0.6 mmHg) 105 °C.

N-(2-Phthalimidoethyl)-2-chloroaceto-2′,6′-xylidide (16). 14 (20.0 g, 0.07 mol) and sodium bicarbonate (8.4 g, 0.1 mol) were added to 200 mL of acetone. Chloroacetyl chloride (9.0 g, 0.09 mol) was added slowly. The mixture was refluxed for 1.5 h and filtered, and the solvent was distilled, yielding 16, 25.2 g (100%). Recrystallization from 150 mL of 95% ethanol gave 16: 24.4 g (96%); mp 133.5–134 °C; IR (KBr) ν_{max} 1780 and 1720 (imide), 1680 (amide I), 800 (aromatic, 3 H), 730 cm^{-1} (aromatic 4 H); NMR ($CDCl_3$; Me_4Si) δ 2.29 (s, 6, CH_3), 3.61 (s, 2, CH_2), 3.90 (m, 4-CH_2CH_2), 7.11 (s, 3, aromatic), 7.72 (m, 4, aromatic).

N-(2-Phthalimidoethyl)-2-iodoaceto-2′,6′-xylidide (17). 16 (11.1 g, 0.03 mol) and NaI (5.1 g, 0.034 mol) were refluxed in 150 mL of acetone. The hot solution was filtered and concentrated by distillation. The product was suspended in 200 mL of water, filtered, washed with water, and dried, giving 17: 13.8 g (99%); mp 125–126 °C. Recrystallization from 25 mL of ethanol gave 17: 10.3 g (75%); mp 127.5–128.5 °C.

N-(2-Phthalimidoethyl)-2-phthalimidoaceto-2′,6′-xylidide (18). 16 (11.2 g, 0.03 mol) and potassium phthalimide (6.0 g, 0.032 mol) were refluxed in 27 mL of dimethylformamide for 3 h. A solution of 11 mL of acetic acid in 26 mL of water was added to the cooled solution, and the precipitate was filtered, washed until neutral, and dried, giving 18: 14.1 g (98%); mp 241.5–243 °C; IR (KBr) ν_{max} 1780 and 1720 (imide), 1680 (amide I), 791 (aromatic, 3 H), 720 cm^{-1} (aromatic 4 H); NMR ($CDCl_3$; Me_4Si) δ 2.44 (s, 6, CH_3), 3.91 (m, 6, CH_2), 7.7 (s, 3, aromatic), 7.68 (m, 8, aromatic).

N-(2-Phthalimidoethyl)-2-(diethylamino)aceto-2′,6′-xylidide (19). 17 (15.4 g, 0.03 mol) and diethylamine (52.0 g, 0.71 mol) were refluxed in 330 mL of ethanol for 16 h. The solvent was distilled, and the oil was shaken with 300 mL of water and extracted into ether (3 × 50 mL). The ether was distilled, and the product was dissolved in 60 mL of 1 N HCl (pH ~1). The aqueous phase was extracted with methylene chloride (5 × 100 mL), and the organic phase was dried (Na_2SO_4). The solvent was evaporated, giving 19·HCl, 12.4 g (85%) of a tan solid. Recrystallization from ethanol–ether (1:2) gave 9.2 g (74%), mp 222–224 °C. Anal. ($C_{24}H_{30}N_3O_3Cl$) C, H, N, Cl.

N-[2-(Diethylamino)ethyl]-2-chloroaceto-2′,6′-xylidide (20). 15 (11.0 g, 0.05 mol) was dissolved in 100 mL of acetone with stirring. Chloroacetyl chloride (6.75 g, 0.06 mol) was added slowly, and the mixture was stirred for 1 h. The acetone was evaporated and the solid was dissolved in 100 mL of methylene chloride. The solution was extracted with water (2 × 20 mL) and dried (Na_2SO_4), and the solvent was evaporated, giving 20·HCl, 14.6 g (87%). High-pressure LC (1:3) indicated >98% purity. 20·HCl (1.4 g, 0.004 mol) was dissolved in 5 mL of water, made basic with 7 M sodium hydroxide, and extracted into ether. The ether phase was dried (K_2CO_3) and added to a stirred solution of D-tartaric acid (0.63 g, 0.004 mol) in 5 mL of ethanol. An oil formed which dissolved upon heating. Crystals formed upon cooling with stirring. The crystals were filtered, washed with ether, and dried, giving 20·D-tartrate: 1.3 g (72%); mp 101 °C dec. Recrystallization from ethanol–ether gave 20·D-tartrate: 1.0 g (77%); mp 104–105 °C dec.

1-(2′,6′-Xylyl)-2-piperazinone (21). 16 (3.7 g, 0.01 mol) was dissolved in 50 mL of hot 95% ethanol, hydrazine (1 mL of 64% aqueous solution) was added, and the solution was heated under reflux for 2 h. The mixture was cooled slightly, 3 mL of concentrated HCl was added, and heating was continued for 0.5 h. The mixture was cooled, the solid was filtered, and the filtrate was concentrated by distillation. The solid was dissolved in water and extracted with ether, and the aqueous phase was brought to pH 11 with 7 N NaOH. Extraction with methylene chloride, drying, and evaporation of the solvent gave 21: 1.5 g (63%) of an oil. The oil was dissolved in 50 mL of CH_2Cl_2, and the hydrochloride was precipitated with gaseous HCl. The solid was filtered and dried, yielding 21·HCl: 1.7 g (100%) of a white solid. Three recrystallizations from acetonitrile gave 21·HCl·0.5H_2O: 1.0 g (59%); mp 145–147 °C dec, lit.[17] mp 224.8–226 °C on anhydrous salt. Anal. ($C_{12}H_{17}N_2OCl$·0.5H_2O) C, H, N, Cl.

N-Ethyl-2-(diethylamino)aceto-2′,6′-xylidide (24). 3 (23.4 g, 0.1 mol) was dissolved in 200 mL of anhydrous xylene (CaH_2) under argon, and sodium hydride (52% dispersion; 5.4 g, 0.116 mol) was added. The mixture was heated under reflux for 2 h. Ethyl idodide (18.7 g, 0.12 mol) was added, and heating was continued for 2 h. The hot solution was filtered, the precipitate was washed with xylene, and the combined xylene phases were evaporated. The oil was dissolved in 200 mL of ether and 100 mL of water. The ether phase was separated and dried (Na_2SO_4), and the solvent was evaporated. The milky aqueous phase was extracted with 100 mL of CH_2Cl_2, and the CH_2Cl_2 phase was filtered through Celite, dried, and distilled. The combined organic phases gave 24: 28.2 g (>100%), which was >95% pure by GC

(OV-17, 200 °C). The base was dissolved in 50 mL of ether and made acidic with ethereal HCl, and the yellow oil which formed was allowed to crystallize. The crystals were filtered and washed with ether. The crystals were very hygroscopic, so they were dissolved in water, made basic with 7 M NaOH, extracted into ether, and dried, and the solvent was evaporated, giving **24**: 24.0 g (92%). The base was dissolved in 90 mL ether, and the solution was added to a solution of D-tartaric acid (13.5 g, 0.09 mol) in 90 mL of ethanol. The addition of 90 mL of ether produced an oil which crystallized. The crystals were filtered, washed, and dried, giving the D-tartrate salt: 28.7 g (77%); mp 114–117 °C dec. Several recrystallizations from ethanol–ether gave **24**·1.5D-tartrate, mp 116–118 °C dec. Anal. ($C_{22}H_{35}N_2O_{10}$) C, H, N.

***N*-Propyl-2-(diethylamino)aceto-2′,6′-xylidide (25).** **3** (5.9 g, 0.025 mol) was dissolved in 100 mL of anhydrous xylene (CaH_2) under nitrogen. Sodium hydride (52% dispersion; 1.2 g, 0.025 mol) was added, and the mixture was heated for 2 h. The mixture was cooled, and 1-bromopropane (3.4 g, 0.03 mol) was added. The mixture was heated under reflux for 3 h and filtered, and the xylene was removed by distillation. The white oil was dissolved into 1 N HCl to pH 1, extracted with ether (2 × 50 mL), and made basic with 7 N NaOH, and the base was taken up in ether (3 × 25 mL). The ethereal solution was dried (Na_2CO_3), and the solvent was distilled, giving **25**: 5.5 g (80%) of a white oil. Fractional distillation gave **25**, 4.9 g (71%), bp (0.02 mmHg) 105–110 °C which was identical by high-pressure LC (3:4) and NMR with an analytical sample.[8]

***N*-(2-Hydroxyethyl)-2-(diethylamino)aceto-2′,6′-xylidide (26).** **3** (5.9 g, 0.025 mol) was dissolved in 100 mL of anhydrous xylene (CaH_2) under argon. Sodium hydride (52% dispersion; 1.2 g, 0.025 mol) was added, and the mixture was heated for 2 h. The mixture was cooled to room temperature, and the water condenser was exchanged for a Dewar condenser. Sodium hydride (52%; 1.2 g, 0.025 mol) was added, followed slowly by 2-bromoethanol (3.1 g, 0.025 mol) in 20 mL of dry xylene. The mixture was stirred for 5 h and filtered, and the xylene was removed by distillation. The brown oil was dissolved in 1 N HCl to pH 1, extracted with ether (2 × 50 mL), and made basic with 7 N NaOH, and the base was taken up in ether (3 × 25 mL). The ethereal solution was dried (Na_2CO_3) and the solvent was distilled, giving **26**: 5.8 g (83%) of a brown oil. The oil was dissolved in 1 N HCl to pH 1 and the solvent was distilled, giving **26**·HCl, 6.4 g (82%), which was 70% pure by high-pressure LC (1:3). Recrystallization from ethanol–ether gave 4.0 g (51%) which was contaminated by **3**. Several more recrystallizations gave an analytical sample of **26**·HCl, mp 148.5–150 °C. Anal. ($C_{16}H_{27}N_2O_2Cl$) C, H, N, Cl. **3** was removed more efficiently by preparative chromatography (silica gel; 3:7 hexane–CH_2Cl_2).

***N*-(2-Ethoxyethyl)-2-(diethylamino)aceto-2′,6′-xylidide (27).** **3** (11.7 g, 0.05 mol) was dissolved in 200 mL of anhydrous xylene (CaH_2) under argon. Sodium hydride (52% dispersion; 2.3 g, 0.05 mol) was added, and the mixture was heated at reflux for 2 h. The mixture was cooled slightly, 2-chloroethyl ethyl ether (5.5 g, 0.05 mol) in 10 mL of dry xylene was added, and heating was continued for 4 h. The mixture was cooled, and the salts were removed by filtration. The xylene was evaporated. The oil was taken into 50 mL of 1 M HCl, extracted with ether (2 × 50 mL), and made basic with 7 M NaOH. The base was extracted with ether (2 × 50 mL) and the ether was distilled, giving **27**: 12.6 g (82%) of a yellow oil. **27** was dissolved in 50 mL of 1 N HCl and the solvent was distilled, giving **27**·HCl: 14.0 g (100%) of a white glass which crystallized very slowly on standing. Recrystallization from acetonitrile gave an analytical sample, mp 143.5–145.5 °C. Anal. ($C_{18}H_{31}N_2O_2Cl$) C, H, N, Cl.

***N*-[2-(Diethylamino)ethyl]-2-(diethylamino)aceto-2′,6′-xylidide (28).** **3** (11.7 g, 0.05 mol) was dissolved in 150 mL of anhydrous xylene (CaH_2) under argon. Sodium hydride (52% dispersion; 2.3 g, 0.05 mol) was added, and the mixture was heated under reflux for 2 h. The mixture was cooled slightly, and to it was added a mixture of 2-chloroethyldiethylamine hydrochloride (8.6 g, 0.05 mol) and sodium hydride (52% dispersion; 2.3 g, 0.05 mol) in 100 mL of dry xylene. The mixture was heated under reflux, and after 2 h GC (JXR-3, 150–270 °C at 20 °C/min) showed the reaction to be 80% complete. Little change was noted on further heating. Sodium hydride (0.50 g, 0.01 mol) and 2-chloroethyldiethylamine hydrochloride (1.7 g, 0.01 mol) were added, and heating was continued for 2 h. The xylene was distilled, and the oil was taken up 100 mL of ether. The base was extracted into 100 mL of 1 M HCl, and the aqueous phase was extracted with ether (2 × 50 mL). The aqueous phase was made basic (pH ~11) with NaOH and extracted with ether (3 × 100 mL). The ethereal phase was dried (K_2CO_3) and the solvent was evaporated, giving **28**: 14.6 g (87%) of a yellow oil. **28** (10.2 g, 0.03 mol) was dissolved in 50 mL of ether and added with stirring to a solution of D-tartaric acid (9.2 g, 0.06 mol) in 100 mL of ethanol. The oil which formed dissolved upon heating, the volume was reduced to 70 mL, and the solution was allowed to cool with stirring. The crystals which formed were filtered, washed with ethanol, and dried, giving **28**·2D-tartrate: 17.3 g (89%); mp 139–141 °C. Recrystallization from ethanol gave 16.4 g (85%), mp 140–141.5 °C. Anal. ($C_{29}H_{47}N_3O_{13}$) C, H, N.

***N*-(2-Aminoethyl)-2-(diethylamino)aceto-2′,6′-xylidide (29).** **19** (9.2 g, 0.021 mol) was dissolved in 200 mL of 95% ethanol at reflux temperature. The solution was cooled slightly, and hydrazine (2.8 mL of 64% aqueous solution) was added. The solution was heated under reflux for 3 h cooled slightly, and 18 mL of concentrated HCl was added. After heating for 1 h under reflux, the mixture was cooled to room temperature, and the solid (phthalhydrazide) was removed by filtration. The filtrate was concentrated, and residual water was removed azeotropically with ethanol, giving **29**·2HCl: 7.7 g (>100%) of a white solid. Three recrystallizations from 95% ethanol–ether (1:1) gave **29**·2HCl: 2.0 g (27%); mp 254.4–255 °C dec. Anal. ($C_{16}H_{29}N_3OCl_2·H_2O$) C, H, N, Cl.

Antiarrhythmic Activity and Acute CNS Toxicity. Drug, as the hydrochloride in isotonic solution, or saline was administered subcutaneously to groups of ten female mice (Charles River CD1; 18–24 g), which were then observed for signs of toxicity. Twenty minutes following administration of target compounds, mice were placed in an atmosphere of chloroform until respiratory arrest occurred. Following a thoracotomy, leads I and II and an epicardial electrocardiogram were recorded for 30–40 s on a Grass Model 7 polygraph and a Tektronix 5100 series oscilloscope. A mouse was assumed to have a tachycardia if the 30- to 40-s ECG recording contained at least 5 s in which the ventricular rate exceeded 520 beats/min. Conversely, a mouse was "protected" from the arrhythmogenic effects of chloroform if these criteria were not fulfilled. The ED_{50} for protection was calculated according to the Logit Chi square method of Berkson[18] and was based upon the percentage of mice protected at each of at least three equally log-spaced doses.

Acute CNS toxicity was assessed during the 20-min period prior to chloroform exposure. Any mouse which displayed either staggered gait, splayed limbs, or hypertonia was assumed to have acute CNS toxicity in the form of ataxia. In general, doses were increased until at least eight animals displayed these symptoms. The ED_{50} for ataxia was calculated also according to the method of Berkson.[18]

Spinal Anesthesia. Sterile solutions containing 20 mg/mL base (2%) and 50 mg/mL glucose were prepared from the salts and adjusted to pH 6.1–6.5 by addition of the necessary amount of dilute NaOH. Two milliliters of the test solution were injected intrathecally in sheep as described by Lebeaux.[19] Control experiments were performed using aqueous solutions of 5% glucose, 0.5% tetracaine–5% glucose, and 1.5% lidocaine–5% glucose.

Acknowledgment. We thank K. Landry and D. Charron for technical assistance and H. S. Feldman for the spinal anesthesia data. We also thank J. B. Keenaghan for mass spectral data.

(18) Berkson, J. *J. Am. Stat. Assoc.* **1953**, *48*, 565.
(19) Lebeaux, M. *Lab. Anim. Sci.* **1975**, *25*, 629.