Table I. Anticonvulsant Activity of BW A78U[a]

compound	MES in rats: ED_{50}, mg/kg			MES in mice: ED_{50}, mg/kg		
	po	ip	iv	po	ip	iv
BW A78U (1)[b]	2.5 ± 0.4	1.7 ± 0.4	0.2 ± 0.06	14 ± 2	5 ± 1	4 ± 0.2
phenytoin	20 ± 3	10 ± 2	4 ± 0.6	22 ± 3	9 ± 2	1.8 ± 0.4

[a] The compounds were tested for their ability to protect animals against maximal electroshock-induced seizures (MES) as described in ref 4. The ED_{50} was the dose needed to protect 50% of the animals against the hind-limb extensor component. For each ED_{50} value the number of animals was greater than 18. [b] Tested as the hydrochloride salt.

useful in the treatment of seizure disorders for which phenytoin is presently indicated. It is more potent than phenytoin, has appreciable water solubility and does not induce tolerance upon repeated administration. Amongst commonly used anticonvulsants, BW A78U has a unique structure that provides a novel lead for the development of agents that may be useful in the treatment of seizure disorders.

Acknowledgment. The excellent technical assistance of R. E. Bache and B. T. Kenney is acknowledged. The LD_{50} values were provided by A. Mackars. We also thank T. Cozart, S. Paris, J. Appleton, and D. Alston for assistance in preparation of the manuscript.

Registry No. 1, 101155-02-6; 1·HCl, 101190-60-7; 2, 5413-85-4; 3, 101155-07-1; 4, 101155-08-2; 2-fluorobenzylamine, 89-99-6; triethyl orthoformate, 122-51-0.

(9) Miller, L. C.; Tainter, M. L. *Proc. Soc. Exp. Biol. Med.* **1944**, *57*, 261.

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Articles

Novel 1,3-Bis(aryloxy)propanes as Leukotriene D_4 Antagonists[1]

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The synthesis and structure–activity relationships of a number of 1,3-bis(aryloxy)propanes, which are in vivo antagonists of LTD_4 in the guinea pig, are described. One of these compounds, 4 (Wy-44,329), was not only approximately equipotent with the standard 1 (FPL 55712) in the LTC_4 (ID_{50} = 0.17 and 0.23 mg/kg iv, respectively) and LTD_4 (ID_{50} = 0.11 and 0.15 mg/kg iv, respectively) challenge models but also possessed greater potency in the ovalbumin challenge model (ID_{50} = 0.47 mg/kg and 4.1 mg/kg iv, respectively) and a longer duration of action. This compound was a competitive LTD_4 antagonist on guinea pig ileum (pA_2 = 9.4) and possessed mediator release (rat PCA, ID_{50} = 0.26 mg/kg iv) and 5-lipoxygenase (IC_{50} = 32 μM vs. 5-HETE) inhibitory activities.

The identification of SRS-A as a mixture of LTC_4, LTD_4, and LTE_4 and the mounting evidence that these substances are mediators in human allergic asthma has stimulated considerable interest in the development of both inhibitors of the synthesis of leukotrienes and antagonists acting at leukotriene receptors.[2] The development of the prototype drug in this latter category 1 (FPL-55712) has been hampered by both its short biological half-life and its lack of oral activity.[3,4] Numerous chemical efforts to improve upon 1 have met with mixed results.[5]

We have previously reported on the orally active mediator release inhibitors 2 (Wy-16,922) and 3 (Wy-41,195), the latter of which is undergoing clinical trials.[6,7] The stereoelectronic similarity of the chromonecarboxylate portion of 1 to these compounds prompted us to synthesize hybrid structures 4–12 with the goal of obtaining a compound that was not only a mediator release inhibitor but also a leukotriene antagonist.[8] In this paper, we describe

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(1) Presented in part at the 189th National Meeting of the American Chemical Society, Miami Beach, FL, April 1985; MEDI 84.
(2) For a recent review, see: Musser, J. H.; Kreft, A. F.; Lewis, A. J. In *Annual Reports in Medicinal Chemistry*; Bailey, D. M., Ed.; Academic: New York, 1985; Vol. 20, Chapter 8.
(3) Chand, N. *Agents Actions* **1979**, *9*, 133.
(4) For a recent report on the improved half life of 1 via the aerosol route, see: O'Donnell, M.; Welton, A. F. *Agents Actions* **1984**, *14*, 43.
(5) For a recent review, see: Musser, J. H.; Kreft, A. F.; Lewis, A. J. *Agents Actions*, in press.
(6) Sellstedt, J. H.; Guinosso, C. J.; Begany, A. J.; Bell, S. C.; Rosenthale, M. *J. Med. Chem.* **1975**, *18*, 926.
(7) Klaubert, D. H.; Sellstedt, J. H.; Guinosso, C. J.; Capetola, R. J.; Bell, S. C. *J. Med. Chem.* **1981**, *24*, 742.

0022-2623/86/1829-1134$01.50/0

Scheme I

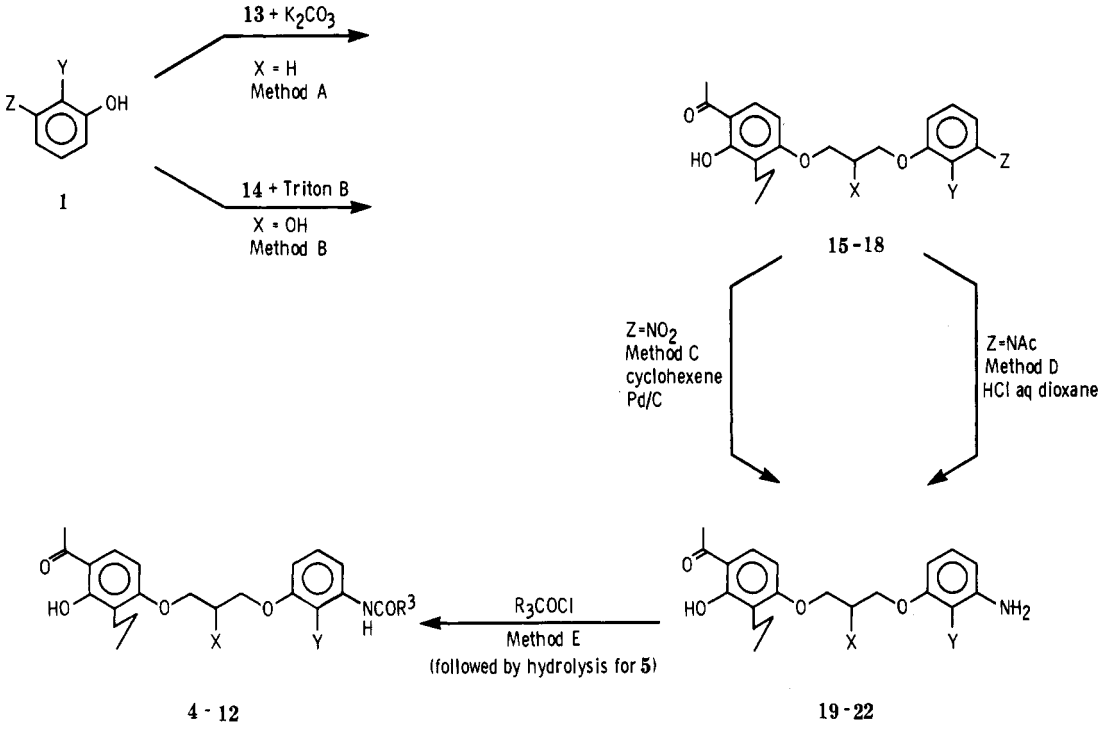
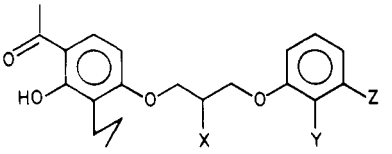


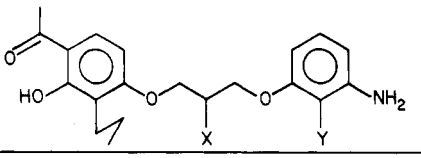
Table I. Physical Data of 3-Alkoxyacetamido- or Nitrobenzenes



no.	X	Y	Z	mp, °C	purification method[a] (solvent[b])	formula[c]	yield, %
15	OH	CN	NO_2	117–119	A(I) + B(II)	$C_{21}H_{22}N_2O_7$	34[d]
16	H	CN	NO_2	99–101	A(III) + B(IV)	$C_{21}H_{22}N_2O_6$	40[d]
17	H	H	NO_2	72–74	A(III) + B(V)	$C_{20}H_{23}NO_6$	41
18	OH	*n*-Pr	NHAc	116–118	A(I) + B(VI)	$C_{25}H_{33}NO_6$	33

[a] A = silica gel chromatography; B = recrystallization. [b] Solvents: I, CH_2Cl_2–EtOAc; II, EtOAc–hexane; III, CH_2Cl_2–hexane; IV, EtOH, V, cyclohexane; VI, toluene. [c] The analysis for C, H, and N for all compounds was within ±0.4% of the calculated values. [d] Yield before recrystallization.

Table II. Physical Data of 3-Alkoxyanilines



no.	X	Y	mp, °C	purification method[a] (solvent[b])	formula[c]	yield, %
19	OH	CN	124–127	A(I)	$C_{21}H_{24}N_2O_5$	66
20	H	CN	120–122	B(II)	$C_{21}H_{24}N_2O_4$	48
21	H	H	73–75	C(III)	$C_{20}H_{25}NO_4$	14
22	OH	*n*-Pr	101–104	B(IV)	$C_{23}H_{31}NO_5$	49

[a] A = trituration; B = silica gel chromatography; C = recrystallization. [b] Solvents: I, Et_2O; II, Et_2O–hexane; III, cyclohexane; IV, CH_2Cl_2–EtOAc. [c] The analysis for C, H, and N for all compounds was within ±0.4% of calculated values.

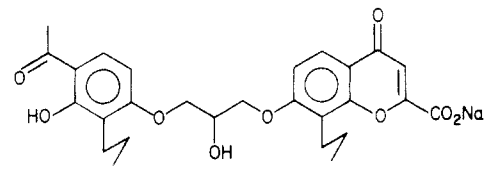
the successful accomplishment of this goal.

Chemistry. The modification of **1** to obtain the desired hybrids **4–12** largely involved chemistry first described by Appleton et al.[9] Reaction of the appropriate phenol (I) with either the known bromide **13** or the known epoxide **14** (Scheme I, method A and B) afforded the intermediate adducts **15–18** (Table I). Subsequent reduction using cyclohexene–palladium on charcoal (Scheme I, method C) or hydrolysis (Scheme I, method D) afforded the corresponding amino compounds **19–22** (Table II), which were then acylated with the appropriate acid chloride (and subsequently hydrolyzed when desired) to afford the target compounds **4–12** (Scheme I, method E and Table III).

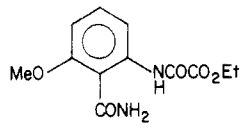
The appropriate phenols when not commercially available were synthesized by utilizing standard methodology. Thus, the novel phenol **23** was obtained from the

(8) For a previous example of this approach, see: Buckle, D. R.; Outred, D. J.; Ross, J. W.; Smith, H.; Smith, R. J.; Spicer, B. A.; Gasson, B. C. *J. Med. Chem.* **1979**, *22*, 158.

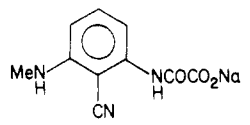
(9) Appleton, R. A.; Bantick, J. R.; Chamberlain, T. R.; Hardern, D. N.; Lee, T. B.; Pratt, A. D. *J. Med. Chem.* **1977**, *20*, 371.



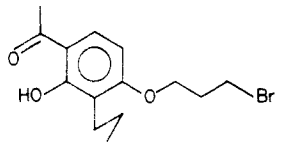
1 (FPL 55712)



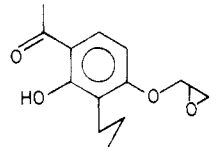
2 (Wy-16,922)



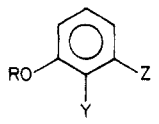
3 (Wy-41,195)



13



14



23: R = H, Y = CN, Z = NO_2
24: R = CH_3, Y = CN, Z = NO_2
25: R = H, Y = propyl, Z = NHAc
26: R = H, Y = allyl, Z = NHAc

known[10] anisole **24** by demethylation with pyridine hydrochloride. The novel phenol **25** was prepared by catalytic hydrogenation of the known[11] allyl compound **26**.

Results and Discussion

The compounds listed in Table III were evaluated for their ability to antagonize the effects of LTD_4 in vivo by utilizing a modified version of the guinea pig lung overflow model described by Lewis et al.[12] Anesthesized guinea pigs were pretreated with succinylcholine (2 mg/kg iv) and indomethacin (10 mg/kg iv) 9 min before leukotriene challenge. Test drugs were administered intravenously 10 min before LTD_4 (400 ng/kg) challenge. ID_{50} values were computed for each drug to its own control with use of the common slope estimates, the response being measured at 5 min after challenge.

Among the series of 1,3-bis(aryloxy)propanes tested, the most potent compound was found to be the ethyl ester **4** (Wy-44,329). Its activity was comparable to that of the prototype **1**. The corresponding carboxylic acid **5** was more than 1 order of magnitude less potent than **4**. This could reflect problems of absorption, distribution, and/or metabolism; however, Tilley et al. have reported a similar result in in vitro studies on SRS-A antagonists.[13]

The neopentyl ester **6** related to **4** had a similar though reduced potency. Increasing the spacer between the two side-chain carbonyls afforded the less potent malonate derivative **7**. Substituting an *n*-propyl group for the cyano group in **4** afforded the drastically less potent derivative **8**. This result is of particular interest, since in the FPL 55712 series the *n*-propyl substituent led to optimal activity.[9]

Removal of the central hydroxyl in **4** resulted in compound **9**, which had approximately one-third the original activity. This result may be contrasted with the FPL 55712 series where this substitution leads to a more potent compound. However, it is difficult to compare in vitro and in vivo results.[14]

Multiple changes in **4** afforded less potent compounds. Removal of the central hydroxyl and lengthening of the spacer between the two side-chain carbonyls afforded **10**, which had only 5.5% of the potency of **4**. Removal of central hydroxyl and substitution of the cyano with hydrogen afforded **11**, which had 8.7% of the potency of **4**. Finally, removal of the central hydroxyl, substitution of the cyano with hydrogen, and lengthening of the spacer between the two carbonyls in the side chain afforded **12**, which had 7.7% of the potency of **4**.

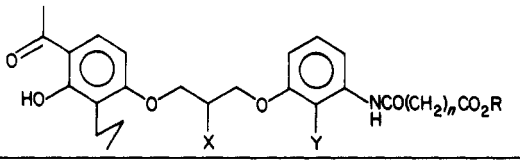
To summarize, the structural requirements for potent LTD_4 antagonism in the hybrids of **1–3** are an oxanilate ester in the right-hand position of the molecule with an adjacent aromatic nitrile substituent.

Detailed comparative pharmacology of **1** and **4** has been undertaken.[15,16] Unlike **1**, the lead compound **4** inhibited 5-lipoxygenase in the rat neutrophil system (IC_{50} = 32 μM vs. 5-HETE).[17,18] In the isolated guinea pig ileum, **4** competitively antagonized LTD_4 and was of comparable potency to **1** (pA_2 = 9.4 and 8.7, respectively). Although in the guinea pig lung overflow model vs. LTC_4 **4** and **1** had comparable potencies (0.17 and 0.23 mg/kg iv, respectively), **4** possessed a much greater potency vs. ovalbumin challenge (0.47 and 4.1 mg/kg iv, respectively). The superior potency of **4** in the ovalbumin model may be due to the additional component of mediator release inhibition, and this is corroborated by its activity in the rat PCA model (ID_{50} = 0.26 mg/kg iv, **1** showed 21% inhibition at 4 mg/kg).[19]

In addition to superior potency, **4** possessed a much longer duration of activity than **1**. Thus, **1** administered iv 10 min before LTC_4 challenge showed essentially no antagonist activity (note that **1** completely blocked the LTC_4 response when administered 1 min before challenge) whereas **4** administered iv 40 min before LTC_4 challenge showed greater than 50% inhibition of bronchoconstriction in the guinea pig lung overflow model. Although the bioconversion[20] of LTC_4 to LTD_4 and subsequently to LTE_4 and the involvement of TXA_2 as a secondary mediator[21] make a direct interpretation of these results difficult, the longer duration of action of **4** is of considerable interest. Unfortunately, **4** was not orally effective (nor was the carboxylic acid **5** or its salts) at doses as high as 100 mg/kg.

(10) Russell, A.; Tebbens, W. G.; *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, p 293.
(11) Budesinsky, Z.; Rockova, E. *Chem. Listy* **1954**, *48*, 427.
(12) Lewis, A. J.; Blumenthal, A.; Dervinis, A. *Agents Actions* **1983**, *13*, 269.
(13) Tilley, J. W.; Levitan, P.; Welton, A. F.; Crowley, H. J. *J. Med. Chem.* **1983**, *26*, 1638.
(14) For a recent discussion of this problem, see: Huttenrauch, R.; Speiser, P. *Pharm. Res.* **1985**, 97.
(15) Lewis, A. J.; Kreft, A. F.; Blumenthal, A.; Schwalm, S.; Dervinis, A.; Chang, J.; Hand, J. M.; Klaubert, D. H. 1984 *IV Int. George Washngton University Spring Symp. Health Sci.* **1984**, May; Abstr. 276.
(16) Lewis, A. J.; Chang, J.; Hand, J.; Carlson, R. P.; Kreft, A. *Int. J. Immunopharmacol.* **1985**, *7*, 384.
(17) For experimental details, see: Chang, J.; Skowronek, M. D.; Cherney, M. L.; Lewis, A. J. *Inflammation* **1984**, *8*, 143.
(18) For a report of the 5-lipoxygenase activity of **1** in a cell-free system, see: Casey, F. B.; Appleby, B. J.; Buck, D. C. *Prostaglandins* **1983**, *25*, 1.
(19) For experimental details, see: Carlson, R. P.; Dervinis, A.; DiLuigi, J. M.; Capetola, R. J.; Rosenthale, M. E.; Lewis, A. J.; *Arzneim.-Forsch.* **1982**, *32*, 1546.
(20) Fleisch, J. H.; Rinkema, L. E.; Haisch, K. D.; Swanson-Bean, D.; Goodson, T.; Ho, P. P. K.; Marshall, W. S. *J. Pharmacol. Exp. Ther.* **1985**, *233*, 148.
(21) Muccitelli, R. M.; Osborn, R. R.; Weichman, B. N. *Prostaglandins* **1983**, *26*, 197.

Table III. Physical Data of 3-Alkoxy-acylamidobenzenes and in Vivo LTD_4 Antagonism



no.	X	Y	n	R	mp, °C	purification method[a] (solvent[b])	formula[c]	yield, %	ID_{50}[d]	(95% limits)
4	OH	CN	0	Et	168–172	A(I)	$C_{25}H_{28}N_2O_8$	48	0.113	(0.051–0.251)
5[e]	OH	CN	0	H	95 dec	B(II)	$C_{23}H_{24}N_2O_8 \cdot H_2O$	66	1.800	(0.704–5.145)
6	OH	CN	0	NeoPent	51–55	C(III)	$C_{28}H_{34}N_2O_8$	66	0.461	(0.260–0.875)
7	OH	CN	1	Et	124–126	D(IV) + A(I)	$C_{26}H_{30}N_2O_8$	14	0.640	(0.368–1.200)
8	OH	n-Pr	0	Et	112–114	A(I)	$C_{27}H_{35}NO_8$	46	2.600	(0.954–7.366)
9	H	CN	0	Et	157–160	D(V) + A(I)	$C_{25}H_{28}N_2O_7$	13	0.342	(0.185–0.652)
10	H	CN	2	Et	120–122	D(IV) + A(VI)	$C_{27}H_{32}N_2O_7$	15	1.773	(0.986–3.195)
11	H	H	0	Et	118–121	C(II)	$C_{24}H_{29}NO_7$	95	1.095	(0.556–2.277)
12	H	H	2	Et	130–131	A(VII)	$C_{26}H_{33}NO_7$	50	1.277	(0.692–2.557)
1 (FPL 55712)									0.153	(0.088–0.281)

[a] A = recrystallization; B = precipitation; C = trituration; D = silica gel chromatography. [b] Solvents: I, toluene; II, H_2O; III, hexane; IV, CH_2Cl_2–EtOAc; V, Et_2O–hexane; VI, cyclohexene; VII, acetone. [c] The analysis for C, H, and N for all compounds was within ±0.4% of the calculated values. [d] Milligrams/kilogram iv; compounds were administered 10 min before LTD_4 (except 1, given 2 min before LTD_4). [e] Obtained by hydrolysis of 4 with sodium bicarbonate in aqueous methanol.

In summary, of a series of hybrids of **1–3** synthesized, one of these compounds, **4**, was a potent leukotriene antagonist in vivo and in vitro with a relatively long duration of action following iv administration. It also exhibited mediator release inhibitory activity that may contribute to its superior profile in the ovalbumin challenge model relative to **1**.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Spectral data (IR, NMR) were recorded for all new compounds and were consistent with the assigned structures. Microanalytical data were determined for C, H, and N on all new compounds and agree to within ±0.4% of the calculated values, except as indicated.

Method A. 2-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)-propoxy]-6-nitrobenzonitrile (16). A mixture of the [(bromopropyl)oxy]acetophenone[9] **13** (3.43 g, 0.01 mol), 2-hydroxy-6-nitrobenzonitrile (**23**; 1.52 g, 0.01 mol), anhydrous K_2CO_3 (1.38 g, 0.01 mol), KI (0.5 g), and Me_2CO (200 mL) was refluxed for 19 h and then filtered while hot. After removal of the solvent, the residue was taken up in EtOAc, washed with 40 mL of 0.5 N NaOH, dried over $MgSO_4$, and evaporated to 3.83 g of an oil. Chromatography on silica gel and elution with 3:1 CH_2Cl_2–hexane afforded **16** (1.6 g, 40%) as a white solid, mp 88–93 °C. Recrystallization from EtOH afforded white crystals, mp 99–101 °C (Table I).

Method B. 2-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)-2-hydroxypropoxy]-6-nitrobenzonitrile (15). To a solution of 2-hydroxy-6-nitrobenzonitrile (**23**; 34.0 g, 0.23 mol) and the epoxide[9] **14** (60.0 g, 0.24 mol) in 450 mL of dry DMF was added 30 drops of Triton B. The solution was refluxed under nitrogen for 1.5 h. The solvent was then evaporated, and the residue was taken up in EtOAc and washed sequentially with 0.5 N NaOH and H_2O and dried (Na_2SO_4). The organic extract was evaporated to 83.0 g of a semisolid, which was chromatographed on silica gel (95:5 CH_2Cl_2–EtOAc), affording **15** (31.4 g, 34%), which was recrystallized from EtOAc–hexane to afford white crystals, mp 117–119 °C (Table I).

Method C. 2-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)-2-hydroxypropoxy]-6- aminobenzonitrile (19). A solution of the nitrobenzonitrile **15** (10.0 g, 0.024 mol), 10% Pd on carbon (2.5 g), and cyclohexene (10.0 g, 0.12 mol) in 500 mL of EtOH was refluxed for 30 min. The reaction mixture was cooled to 25 °C, filtered through Celite, and freed of solvent. Trituration with Et_2O and drying of the insolubles gave **19** (6.1 g, 66%) as a white solid, mp 124–127 °C (Table II).

Method D. 1-[4-[3-(3-Amino-2-propylphenoxy)-2-hydroxypropoxy]-2-hydroxy-3-propylphenyl]ethanone (22). A solution of the acetamide **18** (2.0 g, 0.0045 mol) in a mixture of 2:1 dioxane–concentrated HCl (15 mL) was refluxed for 2.25 h under N_2. After cooling, the reaction mixture was diluted with CH_2Cl_2 (40 mL), washed with saturated $NaHCO_3$ (75 mL), dried over $MgSO_4$, and evaporated to 2.1 g of a semisolid. Chromatography of the residue on silica gel and elution with 9:1 CH_2Cl_2–EtOAc afforded **22** (0.88 g, 49%) as white crystals, mp 101–104 °C (Table II).

Method E. [[3-[3-(4-Acetyl-3-hydroxy-2-propylphenoxy)-2-hydroxypropoxy]-2-cyanophenyl]amino]oxoacetic Acid Ethyl Ester (4). To a solution of the aminobenzonitrile **19** (1.0 g, 0.0026 mol) in CH_2Cl_2 (20 mL) at 0 °C under N_2 was added ethyl oxalyl chloride (0.27 mL, 0.0024 mol). After 40 min at 0 °C the reaction mixture was allowed to warm to 25 °C and stirring was continued for 3 h. The reaction mixture was then added to saturated $NaHCO_3$ solution. The organic layer was separated and dried over $MgSO_4$. Evaporation of the solvent and crystallization of the residue from toluene afforded **4** (0.56 g, 48%) as white crystals, mp 168–172 °C (Table III).

2-Hydroxy-6-nitrobenzonitrile (23). A solution of 2-methoxy-6-nitrobenzonitrile[10] (**24**; 55.5 g, 0.31 mol) and pyridine hydrochloride (83.6 g, 0.72 mol) was heated for 20 min at 200 °C under nitrogen. The reaction mixture was allowed to come to 25 °C and then added to H_2O and $CHCl_3$. The insoluble solid and the aqueous layer were heated to reflux whereupon a homogeneous solution was obtained. Upon cooling to 5 °C, brown crystals of **23** separated (45.0 g, 88%), mp 205–209 °C.

2-Propyl-3-acetamidophenol (25). A solution of 2-allyl-3-acetamidophenol[9] (1.91 g, 0.01 mol) and 80 mg of 10% Pd/C in 20 mL of EtOH was hydrogenated at atmospheric pressure until 1 equiv of hydrogen was taken up (~30 min). The reaction mixture was filtered through Celite and evaporated to afford **25** (1.8 g, 93%) as a colorless liquid. NMR revealed no vinyl hydrogens left.

In Vivo Antagonism of LTD_4 and LTC_4-Induced Bronchoconstriction in Guinea Pigs. A modified version of the guinea pig lung overflow model described by Lewis et al.[12] was employed. Guinea pigs were anesthesized with sodium pentobarbital (50 mg/kg ip), bilateral vagotomy was performed, and the jugular vein, carotid artery and trachea were cannulated for drug administration, blood pressure monitoring, and ventilation, respectively. Animals were then pretreated with succinylcholine (2 mg/kg iv) and indomethacin (10 mg/kg iv in Trizma–8.3 buffer) 9 min prior to leukotriene challenge. Test drugs (dissolved in propylene glycol) were administered intravenously 10 min before leukotriene challenge (LTD_4, 400 ng/kg; LTC_4, 500 ng/kg). Control animals received solvent.

Respiratory volume changes were determined according to the methods described by Lewis et al.[12] and recorded on a Beckman Dynograph. Overflow volumes at 5 min were determined from the chart recordings. Maximal overflow volume (V_{max}) was obtained by clamping off the trachea at the end of the experiment.

ID_{50} values were determined by inverse prediction from a parallel line assay of regression lines through points between 10% and 90% inhibition. Doses were increased in approximately 1/2 log intervals (3-fold) with two to six animals tested at each dose. ID_{50} values were computed for each drug to its own control with use of both the common and separate slopes. Since there were no significant departures from parallelism at the 5% level, only the common slope estimates are shown in Table III. All of the drugs reported in Table III produced essentially complete blockage of the LTD_4-induced bronchoconstriction at 10 mg/kg iv.

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New Antiarrhythmic Agents. 2,2,5,5-Tetramethyl-3-pyrroline-3-carboxamides and 2,2,5,5-Tetramethylpyrrolidine-3-carboxamides

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N-(ω-Aminoalkyl)-2,2,5,5-tetramethyl-3-pyrroline- or -pyrrolidine-3-carboxamides were acylated on the primary amino group of the side chain by means of reactive acid derivatives (acid chlorides, activated esters, phthalic anhydrides, phthalimide, 2-alkyl-4*H*-3,1-benzoxazin-4-ones) or they were alkylated by forming the Schiff bases and subsequent sodium borohydride reduction. Other tetramethyl-3-pyrrolinecarboxamide compounds were synthesized by acylating the aminoalkyl compounds with 2,2,6,6-tetramethyl-3,5-dibromo-4-piperidinone in a reaction involving Favorskii rearrangement. Saturation of the double bond of some pyrroline derivatives furnished the pyrrolidinecarboxamides. The new compounds of each type were active against aconitine-induced arrhythmia and several of them had higher activity and better chemotherapeutic index than quinidine. A few selected examples from each type of the active new compounds showed strong activity against ouabain-induced arrhythmia; for comparison known drugs such as lidocaine, mexiletine, and tocainide were selected. The most potent compounds were oxidized to the paramagnetic nitroxides and the latter were reduced to the *N*-hydroxy derivatives; these products had no or only decreased antiarrhythmic effect.

Antiarrhythmic drugs in current use can reduce the occurrence of cardiac arrhythmias; however, the search for better agents preventing death in man due to myocardial infarction has remained an important task of drug research.[1-4] Although no universally effective antiarrhythmic agent exists,[5] certain criteria would characterize an ideal antiarrhythmic drug.[6] Such characteristics would be, for example: (a) efficacy against resistant ventricular arrhythmias, (b) minimal toxicity to the central nervous system, (c) high oral and intravenous absorption (better than 80% bioavailability), (d) long biologial half-life, lasting at least 8 h.

With these targets in mind we synthesized new compounds that are chemically close to those antiarrhythmic agents belonging to class I according to Vaughan Williams' classification,[7] e.g., quinidine, procainamide, mexiletine, and tocainide. This group is characterized by the presence of three structural units:[4] (a) an aromatic ring capable of intercalating between the alkyl chains of phospholipids, (b) an amino group undergoing ionization in the biological system at pH 8–9, (c) an interconnecting chain (between the aromatic ring and the amino group) bearing substituents capable of hydrogen bonding.

Chemistry. In the present work we describe the syntheses of compounds containing a strongly basic amino group, connected through chains of different length (–V–, –Y–, –W–) to functional aryl or heteroaryl groups. The amino compounds selected were the sterically hindered 2,2,5,5-tetramethyl-3-pyrroline-3-carboxamides (**1**) and 2,2,5,5-tetramethylpyrrolidine-3-carboxamides (**2**) containing an aminoalkyl side chain. 3,5-Dibromo-2,2,6,6-tetramethyl-4-piperidinone hydrobromide (**3**) was prepared in the known way[8] by the bromination of triacetonamide (2,2,6,6-tetramethyl-4-piperidinone). The reaction of **3** with diaminoalkanes gave, by Favorskii rearrangement, the *N*-(ω-aminoalkyl)-2,2,5,5-tetramethyl-3-pyrroline-3-carboxamides (**1a–g**) (method A). Catalytic hydrogenation (method B) of **1b** furnished *N*-(3-aminopropyl)-2,2,5,5-tetramethylpyrrolidine-3-carboxamide (**2**) (Scheme I).

The primary amino group of compounds **1a–g** were acylated with reactive acid derivatives, such as activated esters (**4**, **5**) or acid chlorides (**6**) (methods C, D) to obtain the diacyl derivatives **7a–o** and **8a–z**.

The alkylated derivatives **9a–s**, **10a–k**, and **11a–l** were synthesized by the reduction of the Schiff bases prepared from the amines **1a–g** with oxo compounds (**12**) (method E).

The dibromo ketone **3** was allowed to react with amino compounds (**13**) [commercially available aralkylamines, *N*-(α-aminoacyl)-2,6-xylidines[9] and 1-(2,6-dimethylphenoxy)-2-propanamine[10]] to yield products **14a–l** (method F).

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(1) Koch-Weser, J. *Postgrad. Med. J.* **1976**, *59*, 168.
(2) Jewitt, D. E. *Postgrad. Med. J.* **1977**, 53(Suppl. 1), 12.
(3) Anderson, J. L.; Harrisson, D. C.; Mettin, P. J.; Winkle, R. A. *Drugs* **1978**, *15*, 271.
(4) Thomas, R. E. In *Burger's Medicinal Chemistry*, 4th ed.; Wolf, M. E., Ed.; Wiley-Interscience: New York, 1981; Chapter 38, pp 47–102.
(5) Zipes, D. P. *Am. J. Cardiol.* **1978**, *41*, 975.
(6) Dreifus, L. S.; Ogawa, S. *Am. J. Cardiol.* **1977**, *39*, 466.
(7) Singh, B. N.; Vaughan Williams, E. M. *Cardiovasc. Res.* **1972**, *6*, 109.
(8) Pauly, H. *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 670.
(9) Byrnes, E. W.; McMaster, P. D.; Smith, E. R.; Blair, M. R.; Boyes, N. R.; Duce, B. R.; Feldman, H. S.; Kronberg, G. H.; Takman, B. H.; Tenthorey, P. A. *J. Med. Chem.* **1979**, *22*, 1171.

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