105139-94-4; **5**, 105139-95-5; **6**, 105139-96-6; **7**, 56981-68-1; **8**, 105139-97-7; **9**, 105139-98-8; **10**, 105162-44-5; **11**, 105139-99-9; **12**, 105162-45-6; **13**, 105140-00-9; **14**, 105140-01-0; **15**, 105140-02-1; **16**, 105140-03-2; **17**, 105140-04-3; **18**, 105140-05-4; **19**, 105140-06-5; **20**, 105140-07-6; **21**, 105140-08-7; **22**, 105140-09-8; **23**, 105140-10-1; **24**, 105140-11-2; **25**, 105140-12-3; **26**, 103864-79-5; **27**, 105140-13-4; N_2CH_2, 334-88-3; N_2CHMe, 1117-96-0; N_2CHPh, 766-91-6; $HO(CH_2)_2OH$, 107-21-1; *i*-PrOH, 67-63-0; $CH_2{=}CHCH_2OH$, 107-18-6; $CH{\equiv}CCH_2OH$, 107-19-7; $PhCH_2OH$, 100-51-6; $Cl(CH_2)_3OH$, 627-30-5; $HO(CH_2)_3OH$, 504-63-2; $HO(CH_2)_2O(CH_2)_2OH$, 111-46-6; $HO(CH_2)_2S(CH_2)_2OH$, 111-48-8; $HO(CH_2)_2SS(CH_2)_2OH$, 1892-29-1; MeO, 111-77-3; $EtO(CH_2)_2O(CH_2)_2OH$, 111-90-0; $Me_2N(CH_2)_2OH$, 108-01-0; $PhN{=}NNH(CH_2)_2OH$, 105140-14-5; $PhN{=}NNH(CH_2)_3OH$, 105140-15-6; $NH_2(CH_2)_3OH$, 156-87-6; $PhN{=}NNHCH_2CH(OH)CH_2OH$, 105140-16-7; $NH_2CH_2CH(OH)CH_2OH$, 616-30-8; $PhN{=}NNHCH_iCH(OMe)_2$, 105140-18-9; $PhN{=}NNH(CH_2)_2CN$, 105140-19-0; $NH_2CH_2CH(OMe)_2$, 22483-09-6; $NH_2(CH_2)_2CN$, 151-18-8; $NH_2(CH_2)_2OH$, 141-43-5; mitomycin C, 50-07-7; 7-hydroxymitosane, 7041-61-4; *N*-methylmitomycin A, 18209-14-8; cyclobutylmethanol, 4415-82-1; tetrahydrofurfurol, 97-99-4; 3-tetrahydrofuranol, 453-20-3; tetrahydropyranmethanol, 100-72-1; 2,2-dimethyl-4-(hydroxymethyl)dioxolane, 98-00-0; 4-morpholineethanol, 622-40-2; dicyclohexylcarbodiimide, 538-75-0; benzenediazonium hexafluorophosphate, 369-58-4; 3-furfuryl-1-phenyltriazene, 105140-17-8; furfurylamine, 617-89-0.

Substituted (Aryloxy)alkanoic Acids as Antagonists of Slow-Reacting Substance of Anaphylaxis

Ronald A. LeMahieu,*† Mathew Carson,† Ru-Jen Han,† William C. Nason,† Margaret O'Donnell,*‡ Deborah L. Brown,‡ Herman J. Crowley,‡ and Ann F. Welton‡

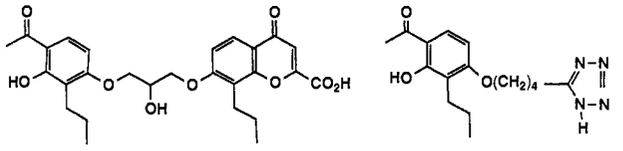
Chemistry Research Department and Pharmacology Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110.
Received June 2, 1986

A series of compounds in which the 4-acetyl-3-hydroxy-2-propylphenoxy moiety of the standard SRS-A antagonist, FPL-55712, is linked by a polymethylene or a polyether chain to substituted (aryloxy)alkanoic acids was prepared. The compounds were evaluated for their ability to antagonize SRS-A-induced contractions of guinea pig ilea and LTE-induced bronchoconstriction in the guinea pig. The results showed that the compounds were all less potent than FPL-55712 in vitro, yet surprisingly, most were more potent by the inhalation route of administration. Some of the most potent analogues were selected for further pharmacological evaluation and, by inhalation, exhibited selective antagonism of leukotrienes as compared with PAF or histamine. In comparison to FPL-55712, compounds **28** and **37** were more potent against LTE (40- and 80-fold, respectively), LTD (4- and 3-fold, respectively), and LTC (27- and 20-fold, respectively) induced bronchoconstriction when tested by inhalation.

In recent years, evidence has accumulated to support the concept that the bronchoactive peptidoleukotrienes, leukotriene C_4, D_4, and E_4 (LTC, LTD, and LTE), which constitute slow-reacting substance of anaphylaxis (SRS-A) are the predominant mediators of immediate hypersensitivity reactions.[1,2] For this reason, there has been considerable interest in the pharmaceutical industry in the development of leukotriene receptor antagonists as potential therapeutics for the treatment of allergic asthma and other diseases whose pathophysiology may be mediated by leukotrienes.

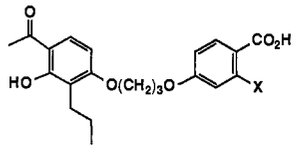
FPL-55712 (**1**)[3] has long been used as a pharmacological tool because it is a potent SRS-A antagonist, yet it is considered to have limited clinical potential because it is poorly absorbed when given orally and displays a short biological half-life after intravenous administration.[4] Many analogues of **1** have been described.[2] However, there was no evidence that a drug of this structural type was under development until recently when a tetrazole, LY171883 (**2**),[5] was reported to be an orally active LTD antagonist.

We previously observed that aerosol administration of **1** effectively protected guinea pigs against leukotriene-induced bronchoconstriction with a reasonably long biological half-life.[6] Other investigators showed that aerosolized **1** abolished the cough response and bronchoconstriction due to inhalation of LTC and LTD in two normal volunteers[7] and significantly improved forced expiratory volume in two of four chronic asthmatic patients.[8] Taken together, these results with inhaled **1** prompted us to investigate the development of an aerosolized SRS-A antagonist. Inhalation may be the preferred route of ad-

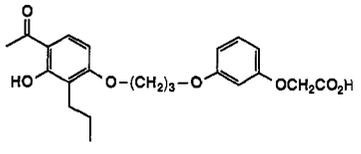


FPL-55712 (1)

LY 171883 (2)



3, (X = H)
4, (X = OH)



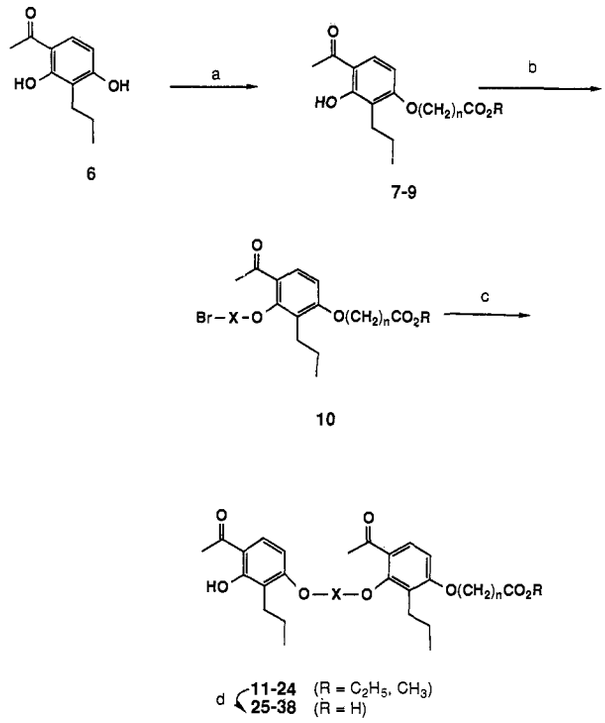
5

† Chemistry Research Department.
‡ Pharmacology Department.

(1) Dahlen, S-E.; Hansson, G.; Hedqvist, P.; Björck, T.; Granström, E.; Dahlen, B. *Acta Physiol. Scand., Suppl.* **1983**, *512*, 1.
(2) Krell, R. D.; Brown, F. J.; Willard, A. K.; Giles, R. E. *The Leukotrienes Chemistry and Biology*; Chakrin, L. W.; Bailey, D. M., Ed.; Academic: Orlando, FL, 1984; Chapter 11.
(3) Appleton, R. A.; Bantick, J. R.; Chamberlain, T. R.; Hardern, D. N.; Lee, T. B.; Pratt, A. D. *J. Med. Chem.* **1977**, *20*, 371.

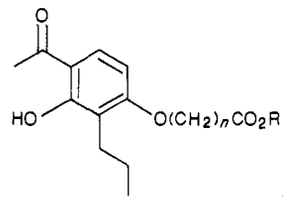
0022-2623/87/1830-0173$01.50/0

Scheme I



(a) $Br(CH_2)_nCOOR$, K_2CO_3. (b) Br-X-Br, K_2CO_3. (c) **6**, K_2CO_3 (d) NaOH

Table I. (4-Acetyl-3-hydroxy-2-propylphenoxy)alkanoic Acid Esters



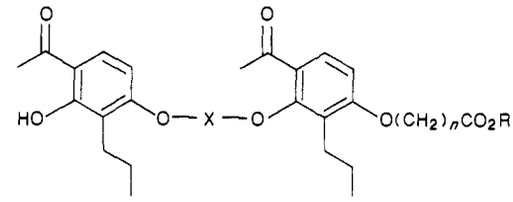
compd	n	R	yield, %	mp, °C	formula[a]
7	1	C_2H_5	73	63–65	$C_{15}H_{20}O_5$
8	3	C_2H_5	54	oil	$C_{17}H_{24}O_5$
9	5	CH_3	62	oil	$C_{18}H_{26}O_5$

[a] C, H analyses were within ±0.4% of the calculated values, unless otherwise noted.

ministration for a bronchopulmonary therapeutic because the highest concentration of drug can be delivered to the target organ (lung) with minimal side effects.

We decided to replace the chromone carboxylic acid portion of **1** with aromatic carboxylic acids that were readily available. Aerosolized compounds **3** and **4**, prepared in our early work, were approximately equipotent to **1** as inhibitors of LTE-induced bronchoconstriction in the guinea pig but exhibited short durations of action (<20 min). We then prepared the phenoxyacetic acid **5**, which was 11-fold more potent than **1** but also had a short duration of action (15 min). Compounds **3–5** were described in the patent literature during the course of our work.[9] Further modification of **5** led to the compounds that are described in this paper.

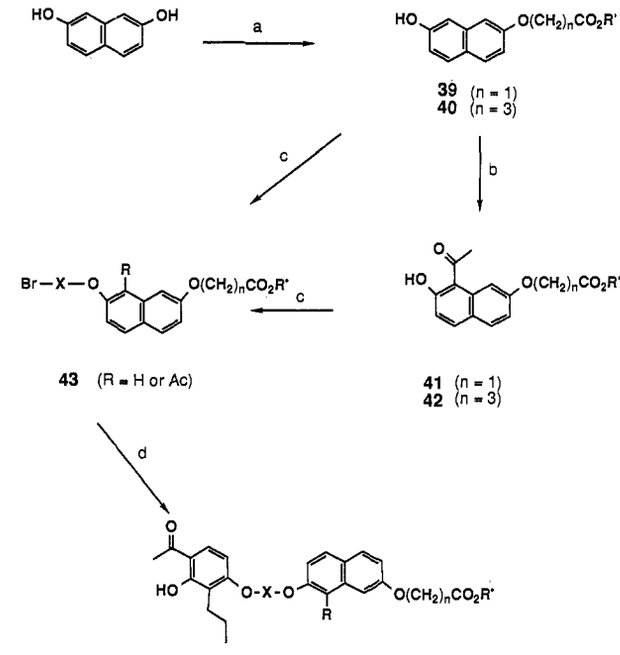
Table II. Phenoxyalkanoic Esters



compd	X	n	R	yield, %	formula[b]
11	$(CH_2)_3$	1	C_2H_5	68[a]	$C_{29}H_{38}O_8$
12	$(CH_2)_3$	3	C_2H_5	76	$C_{31}H_{42}O_8$
13	$(CH_2)_3$	5	CH_3	68	$C_{32}H_{44}O_8$
14	$(CH_2)_5$	1	C_2H_5	59	$C_{31}H_{42}O_8$
15	$(CH_2)_5$	3	C_2H_5	84	$C_{33}H_{46}O_8$
16	$(CH_2)_2O(CH_2)_2$	1	C_2H_5	70	$C_{30}H_{40}O_9$
17	$(CH_2)_2O(CH_2)_2$	3	C_2H_5	18	$C_{32}H_{44}O_9$[c]
18	$(CH_2)_2O(CH_2)_2$	5	CH_3	77	$C_{33}H_{46}O_9$
19	$(CH_2)_2[O(CH_2)_2]_2$	1	C_2H_5	70	$C_{32}H_{44}O_{10}$
20	$(CH_2)_2[O(CH_2)_2]_2$	3	C_2H_5	69	$C_{34}H_{48}O_{10}$
21	$(CH_2)_2[O(CH_2)_2]_3$	1	C_2H_5	40	$C_{34}H_{48}O_{11}$
22	$(CH_2)_3O(CH_2)_3$	1	C_2H_5	72	$C_{32}H_{44}O_9$
23	$(CH_2)_3O(CH_2)_3$	3	C_2H_5	82	$C_{34}H_{48}O_9$
24	$(CH_2)_4O(CH_2)_4$	1	C_2H_5	87	$C_{34}H_{48}O_9$

[a] Melting point 45–46 °C; all other compounds in this table are oils. [b] C, H analyses were within ±0.4% of the calculated values. [c] This compound was not submitted for microanalyses; however, satisfactory NMR and mass spectra were obtained.

Scheme II

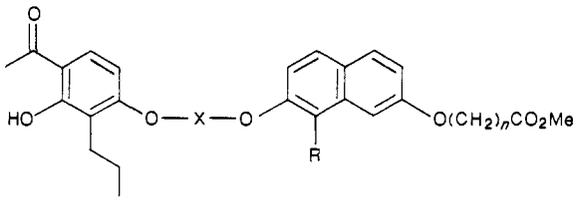


(a) $Br(CH_2)_nCOOR'$, K_2CO_3. (b) $AlCl_3$, CH_3COCl. (c) Br-X-Br, K_2CO_3 (d) **6**, K_2CO_3. (e) NaOH.

Chemistry. Alkylation of the dihydroxyacetophenone **6**[10] (Scheme I) with a bromo alkanoic ester gave the esters

(4) Sheard, P.; Lee, T. B.; Tattersal, M. L. *Monogr. Allergy* **1977**, *12*, 245.
(5) Fleisch, J. H.; Rinkema, L. E.; Haisch, K. D.; Swanson-Bean, D.; Goodson, T.; Ho, P. P. K.; Marshall, W. S. *J. Pharm. Exp. Ther.* **1985**, *233*, 148.
(6) O'Donnell, M.; Welton, A. F. *Agents Actions* **1984**, *14*, 43.
(7) Holroyde, M. C.; Altounyan, R. E. C.; Cole, M.; Dixon, M.; Elliot, E. V. *Lancet* **1981**, *2*, 17.
(8) Lee, T. H.; Walport, M. J.; Wilkinson, A. H.; Turner-Warwick, M.; Kay, A. B. *Lancet* **1981**, *2*, 304.
(9) Oxford, A. W.; Ellis, F. U.K. Patent Application, 1981, GB2058785; *Chem. Abstr.* **1982**, *96*, 51977*p*.
(10) Baker, W.; Lothian, O. M. *J. Chem. Soc.* **1935**, 628.

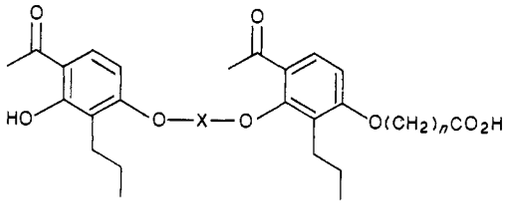
Table III. (Naphthalenyloxy)alkanoic Esters



compd	X	R	n	yield,[a] %	mp, °C	formula[b]
44	$(CH_2)_3$	H	1	70	88–90	$C_{27}H_{30}O_7$
45	$(CH_2)_3$	$COCH_3$	1	78	107–108	$C_{29}H_{32}O_8$
46	$(CH_2)_5$	$COCH_3$	1	69	87–89	$C_{31}H_{36}O_8$
47	$(CH_2)_3$	H	3	79	75–77	$C_{29}H_{34}O_7$
48	$(CH_2)_3$	$COCH_3$	3	63	oil	$C_{31}H_{36}O_8$

[a] Compounds were purified by recrystallization from ether–hexane or chromatography on silica gel. [b] C, H analyses were within ±0.4% of the calculated values.

Table IV. Phenoxyalkanoic Acids



compd	X	n	yield,[a] %	mp, °C	formula[b]	inhibn of SRS-A-induced contraction: IC_{50}, μM	inhibn of LTE-induced bronchoconstriction: % at 10 mg/kg iv	inhibn of LTE-induced bronchoconstriction: aerosol IC_{50}, %	inhibn of LTE-induced bronchoconstriction: aerosol duration, min
25	$(CH_2)_3$	1	71	124–125	$C_{27}H_{34}O_8$	2.0	95 ± 1	0.07	90
26	$(CH_2)_3$	3	87	96–99	$C_{29}H_{38}O_8$	0.2	97 ± 1	0.18	22
27	$(CH_2)_3$	5	89	105–108	$C_{31}H_{42}O_8$	1.0	91 ± 3	0.02	55
28	$(CH_2)_5$	1	88	86–89	$C_{29}H_{38}O_8$	0.1	73 ± 7	0.02	55
29	$(CH_2)_5$	3	87	66–69	$C_{31}H_{42}O_8$	1.0	92 ± 2	0.01	46
30	$(CH_2)_2O(CH_2)_2$	1	80	96–99	$C_{28}H_{36}O_9$	0.2	86 ± 3	0.02	14
31	$(CH_2)_2O(CH_2)_2$	3	80	52–58	$C_{30}H_{40}O_9$	0.1	91 ± 1	0.22	17
32	$(CH_2)_2O(CH_2)_2$	5	86	55–57	$C_{32}H_{44}O_9$	0.2	91 ± 2	1.0	
33	$(CH_2)_2[O(CH_2)_2]_2$	1	92	74–77	$C_{30}H_{40}O_{11}$	1.0	85 ± 1	0.04	42
34	$(CH_2)_2[O(CH_2)_2]_2$	3	93	oil	$C_{32}H_{44}O_{10}$	0.5	57 ± 1	1.0	
35	$(CH_2)_2[O(CH_2)_2]_3$	1	66	oil	$C_{32}H_{44}O_{11}$	0.3	90 ± 1	0.04	73
36	$(CH_2)_3O(CH_2)_3$	1	81	86–90	$C_{30}H_{40}O_9$	0.4	91 ± 2	0.1	30
37	$(CH_2)_3O(CH_2)_3$	3	92	36–40	$C_{32}H_{44}O_9$	0.2	93 ± 1	0.01	37
38	$(CH_2)_4O(CH_2)_4$	1	82	68–71	$C_{32}H_{44}O_9$	0.5	54 ± 4	0.1	45
5						0.5	64 ± 6	0.07	15
1	(FPL-55712)					0.035	98 ± 1	0.79	77

[a] The solids were purified by recrystallization from ether–hexane, and the oils were purified by column chromatography on silica gel. [b] C, H analyses were within ±0.4% of the calculated values.

7–9 (Table I), which were alkylated with use of an excess of dibromo compound to give the intermediates **10**. These bromides were in most cases used without purification but could be purified by column or high-pressure liquid chromatography. Since they are all thermally unstable viscous oils, no attempt was made to obtain microanalyses. Their structures were confirmed by mass and NMR spectra, which usually showed minor olefinic impurities. Finally, alkylation of **6** with the bromides **10** yielded the esters **11–24** (Table II), which were hydrolyzed to the desired acids **25–38** (Table IV).[11]

Alkylation of 2,7-dihydroxynaphthalene (Scheme II) gave esters **39** and **40** in low yield. Friedel–Crafts acylation provided the ketones **41** and **42**. Alkylation of the phenols with excess dibromo compound gave the intermediate bromides **43**. Finally, alkylation of **6** with **43** yielded the esters **44–48** (Table III), which were hydrolyzed to the desired acids **49–53** (Table V.)[12]

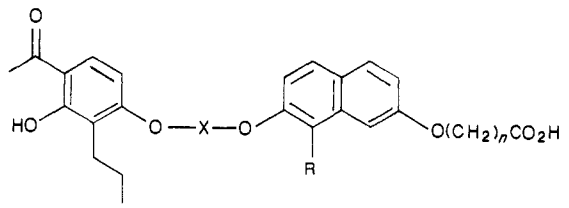
Results and Discussion

Table IV summarizes the in vitro activity of the phenoxyalkanoic acids as antagonists of SRS-A-induced contractions of guinea pig ileum and the in vivo activity as inhibitors of LTE-induced bronchoconstriction in guinea pigs when administered intravenously and by aerosol. The earlier work on FPL-55712[3] had established the optimal substitution pattern on the 2-hydroxyacetophenone moiety. We chose to maintain this pattern and also to fix the substituents on the phenoxyalkanoic acid so that the same intermediate **6** could be used for both aromatic portions of the acids **25–38**. In comparison with **25**, the unsubstituted phenoxyacetic acid **5** exhibited lower intravenous activity (95% vs. 64% inhibition) and a substantially reduced aerosol duration of action (90 vs. 15

(11) Carson, M.; LeMahieu, R. A.; Nason, W. C. U.S. Patent 4507498, 1985; *Chem. Abstr.* 1984, *100*, 51267*h*.

(12) LeMahieu, R. A. U.S. Patent 4550190, 1985; *Chem. Abstr.* 1986, *104*, 148569*d*.

Table V. (Naphthalenyloxy)alkanoic Acids



compd	X	R	n	yield, %	mp, °C	formula[a]	inhibn of SRS-A-induced contraction: IC_{50}, μM	inhibn of LTE-induced bronchoconstriction: % at 10 mg/kg iv	aerosol: IC_{50}, %	aerosol: duration, min
49	$(CH_2)_3$	H	1	84	156–158	$C_{26}H_{28}O_7$	0.3	bc[b]	0.46	49
50	$(CH_2)_3$	$COCH_3$	1	69	132–135	$C_{28}H_{30}O_8$	0.2	90 ± 3	0.01	25
51	$(CH_2)_5$	$COCH_3$	1	78	103–106	$C_{30}H_{34}O_8$	0.2	60 ± 3	0.14	7
52	$(CH_2)_3$	H	3	88	143–146	$C_{28}H_{32}O_7$	5.0	75 ± 10	1.0	
53	$(CH_2)_3$	$COCH_3$	3	64	121–124	$C_{30}H_{34}O_8$	0.08	93 ± 3	0.61	9

[a] C, H analyses were within ±0.4% of the calculated values. [b] This compound caused bronchoconstriction.

Table VI. Inhibitory Potency of Aerosolized Compounds against Various Bronchoconstrictive Agents in Guinea Pigs

compd	IC_{50} (%) against bronchoconstrictive agent: LTC	LTD	LTE	PAF	histamine
1[a]	>3.0	0.5	0.79	>1.0	>1.0
28	0.11	0.13	0.02	1.0	>1.0
29	0.16	0.57	0.01	>1.0	0.9
33	0.36	0.19	0.04	>1.0	0.8
35	1.3	0.18	0.04	>1.0	0.8
37	0.15	0.19	0.01	1.0	>1.0
50	0.22	0.32	0.02	>1.0	>1.0

[a] FPL-55712.

min), indicating the importance of the acetyl and/or propyl substituents. All of the compounds in Table IV were active as antagonists of SRS-A in the guinea pig ileum assay and as antagonists of LTE-induced bronchoconstriction in vivo. Although the compounds were significantly less potent than FPL-55712 in vitro, most were more potent by the inhalation route. Compounds **25** and **27–29**, with a polymethylene link between the two aromatic rings, showed only small differences in aerosol potency while **26** was less active. Compounds **30–38** with ether links in the X chain were prepared to alter the hydrophilic character in an attempt to improve the in vivo profile. Although the most potent compound by aerosol, **37**, emerged from this series, no improvement in duration of action was found. An increase in the length of the *n* chain (**30–32** and **33–34**) caused a loss of aerosol potency.

In the naphthalenyloxy series (Table V) all compounds were leukotriene antagonists in vitro and by inhalation. Clearer structure–activity relationships were apparent in this series. Introduction of the acetyl substituent into the naphthalene moiety resulted in increased potency in vitro as well as in vivo by the intravenous and aerosol routes of administration. Lenthening the X chain from three to five carbons or the *n* chain from one to three carbons resulted in loss of potency.

The compounds that exhibited aerosol IC_{50} values of 0.04% or better and durations of greater than 20 min against LTE-induced bronchoconstriction were selected for more extensive pharmacological evaluation. These compounds were tested by inhalation for their ability to inhibit bronchoconstriction induced by LTC, LTD, platelet activating factor (PAF), and histamine (Table VI). They were all less potent against LTC- or LTD-induced bronchoconstriction and were inactive or weakly active against PAF- or histamine-induced bronchoconstriction. Most of the compounds were substantially more potent against LTC- and LTD-induced bronchoconstriction than FPL-55712.

In conclusion, we have described SRS-A antagonists that exhibit much greater aerosol potency than the standard, FPL-55712. Compounds **28** and **37** showed the best spectrum of activity against the three leukotrienes while **27** and **28** showed the best combination of high potency and long duration against LTE. Further development of these compounds was not carried out since a more potent LTD antagonist (Ro 23-3544, 6-acetyl-7-[[5-(4-acetyl-3-hydroxy-2-propylphenoxy)pentyl]oxy]-3,4-dihydro-2*H*-1-benzopyran-2-carboxylic acid) was discovered during later work in these laboratories.[13]

Experimental Section

Melting points were taken in a Thomas-Hoover capillary apparatus and are uncorrected. Microanalyses were performed by the Roche microanalytical department. The IR, NMR, UV, and mass spectral data for all compounds were consistent with the assigned structures.

4-(4-Acetyl-3-hydroxy-2-propylphenoxy)butanoic Acid Ethyl Ester (8). A mixture of 2.91 g (0.015 mol) of **6**,[10] 2.92 g (0.015 mol) of ethyl 4-bromobutyrate, and 3.1 g (0.0225 mol) of anhydrous K_2CO_3 in 35 mL of anhydrous DMF was stirred at 75 °C for 12 h. The solvent was removed on an oil pump, water was added to the residue, and the product was extracted with ethyl acetate. The dried ($MgSO_4$) extract was concentrated at reduced pressure and the residual oil was purified by chromatography on 200 g of silica gel. Elution with 5% ethyl acetate–toluene gave 2.55 g (54%) of **8** as an oil. Anal. ($C_{17}H_{24}O_5$) C, H.

4-[4-Acetyl-3-[(5-bromopentyl)oxy]-2-propylphenoxy]butanoic Acid Ethyl Ester (10, X = $(CH_2)_5$, *n* = 3, R = C_2H_5). A mixture of 3.50 g (0.011 mol) of **8**, 15.4 mL (0.11 mol) of 1,5-dibromopentane, and 1.2 g (0.009 mol) of anhydrous K_2CO_3 in 60 mL of anhydrous acetone was stirred at reflux for 77 h. Additional 1.2-g portions of K_2CO_3 were added at 4, 21, 28, and 45 h. The reaction mixture was filtered and the filtrate was concentrated at reduced pressure. The residual oil was purified by high-pressure liquid chromatography using 17% ethyl acetate–hexane to give 4.35 g (84%) of the above bromo compound as an oil, which gave spectral data consistent with the assigned structure.

4-[4-Acetyl-3-[[5-(4-acetyl-3-hydroxy-2-propylphenoxy)-pentyl]oxy]-2-propylphenoxy]butanoic Acid Ethyl Ester (15). A mixture of 0.96 g (0.005 mol) of **6**, 2.26 g (0.005 mol) of **10** [X = $(CH_2)_5$, *n* = 3, R = C_2H_5], and 1.38 g (0.010 mol) of anhydrous K_2CO_3 in 40 mL of anhydrous acetone and 20 mL of anhydrous DMF was stirred at reflux for 17 h. The reaction mixture was filtered and the filtrate was concentrated at reduced pressure. The resultant oil was purified by high-pressure liquid

(13) O'Donnell, M.; Brown, D.; Cohen, N.; Weber, G. F.; Welton, A. F. *Ann. Allergy* **1985**, *55*, 278.

chromatography using 25% ethyl acetate–hexane to yield 2.36 g (84%) of **15** as an oil. Anal. ($C_{33}H_{46}O_8$) C, H.

4-[4-Acetyl-3-[[5-(4-acetyl-3-hydroxy-2-propylphenoxy)-pentyl]oxy]-2-propylphenoxy]butanoic Acid (29). A solution of 2.26 g (0.004 mol) of **15** and 20 mL (0.02 mol) of 1.0 N NaOH in 50 mL of methanol was stirred at reflux for 3 h. The solvent was removed at reduced pressure and the aqueous residue was acidified. The product was extracted with methylene chloride and the dried ($MgSO_4$) extract was concentrated at reduced pressure to a solid. Recrystallization from ether–hexane gave 1.87 g (87%) of **29**, mp 66–69 °C. Anal. ($C_{31}H_{42}O_8$) C, H.

[(7-Hydroxy-2-naphthalenyl)oxy]acetic Acid Methyl Ester (39). A mixture of 32 g (0.02 mol) of 2,7-dihydroxynaphthalene and 36 g (0.26 mol) of anhydrous K_2CO_3 in 250 mL of anhydrous acetone was stirred at 22 °C for 3 h. Methyl bromoacetate (20.8 mL, 0.22 mol) was added and the reaction mixture was stirred at 22 °C for 19 h. The reaction mixture was filtered and the solid was washed with acetone. The filtrate was concentrated under reduced pressure, the residue was acidified, and the product was extracted with methylene chloride. The extract was washed with 1 N NaOH (3 × 200 mL), and the combined aqueous layer was left at 22 °C for 16 h and then acidified and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated $NaHCO_3$ solution. The insoluble sodium salt that formed was removed by filtration, combined with the aqueous layer, and acidified. The product was extracted with ethyl acetate and the dried ($MgSO_4$) extract was concentrated under reduced pressure to a solid (17 g). This carboxylic acid was esterified by refluxing in 300 mL of methanol with 4 mL of concentrated H_2SO_4 for 6 h. The solvent was removed under reduced pressure and the residue was taken up in methylene chloride and washed with $NaHCO_3$ solution. After removal of the solvent, the residue was recrystallized from methylene chloride–hexane to give 15.1 g (33%), mp 122–123 °C of **39**. Anal. ($C_{13}H_{12}O_4$) C, H.

4-[(7-Hydroxy-2-naphthalenyl)oxy]butanoic Acid Methyl Ester (40). A mixture of 32 g (0.2 mol) of 2,7-dihydroxynaphthalene and 36 g (0.26 mol) of anhydrous K_2CO_3 in 250 mL of anhydrous acetone was stirred at 23 °C for 1 h. Ethyl 4-bromobutyrate (31.5 g, 0.22 mol) was added and stirring was continued at reflux for 29 h. The reaction mixture was worked up as in the preceding example and the product was recrystallized from methylene chloride–hexane to give 11.7 g (23%), mp 122–125 °C, of **40**.

[(8-Acetyl-7-hydroxy-2-naphthalenyl)oxy]acetic Acid Methyl Ester (41). To 5.8 g (0.044 mol) of aluminum chloride suspended in 100 mL of dichloroethane stirred at 23 °C under argon was added 3.1 mL (0.044 mol) of acetyl chloride followed by 8.09 g (0.035 mol) of **39**. After stirring at 22 °C for 2 h, the reaction mixture was stirred at reflux for 19 h. The reaction mixture was cooled, treated with 100 mL of 6 N HCl and stirred vigorously for 10 min. Methylene chloride was added and the organic layer was separated, washed with $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated under reduced pressure to a solid. Recrystallization from methylene chloride–ether gave 6.03 g (63%), mp 113–114 °C, of **41**. Anal. ($C_{15}H_{14}O_5$) C, H.

4-[(8-Acetyl-7-hydroxy-2-naphthalenyl)oxy]butanoic Acid Methyl Ester (42). To 5.15 g (0.039 mol) of aluminum chloride suspended in 120 mL of dichloroethane stirred at 22 °C under argon was added 2.8 mL (0.039 mol) of acetyl chloride followed by 8.00 g (0.031 mol) of **40**. After stirring at 23 °C for 30 min and at reflux for 16 h, the reaction mixture was worked up as in the preceding example, and the product was purified by high-pressure liquid chromatography using 2% ethyl acetate–toluene to give 2.72 g (29%) of **42** as an oil. Anal. ($C_{17}H_{18}O_5$) C, H.

[[8-Acetyl-7-(3-bromopropoxy)-2-naphthalenyl]oxy]acetic Acid Methyl Ester (43, X = $(CH_2)_3$, R = Ac, n = 1). A mixture of 4.99 g (0.018 mol) of **41**, 18 mL (0.18 mol) of 1,3-dibromopropane, and 3.7 g (0.027 mol) of anhydrous K_2CO_3 in 150 mL of anhydrous acetone was stirred at reflux for 17 h. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was purified by chromatography on silica gel. Elution with 10% ethyl acetate–toluene gave 6.73 g (95%) of **43**. The NMR and mass spectra were consistent with the structure.

[[8-Acetyl-7-[3-(4-acetyl-3-hydroxy-2-propylphenoxy)-propoxy]-2-naphthalenyl]oxy]acetic Acid Methyl Ester (45). A mixture of 0.665 g (1.7 mmol) of **43** (X = $(CH_2)_3$, R = Ac, n = 1), 0.333 g (1.7 mmol) of **6**, and 0.35 g (2.5 mmol) of anhydrous K_2CO_3 in 15 mL of anhydrous acetone was stirred at reflux for 20 h. The solvent was removed under reduced pressure and the residue was acidified. The solid product was filtered and recrystallized from ether–hexane to give 0.66 g (78%), mp 107–108 °C, of **45**. Anal. ($C_{29}H_{32}O_8$) C, H.

[[8-Acetyl-7-[3-(4-acetyl-3-hydroxy-2-propylphenoxy)-propoxy]-2-naphthalenyl]oxy]acetic Acid (50). A solution of 0.66 g (1.3 mmol) of **45** and 6.5 mL (6.5 mmol) of 1.0 N NaOH in 20 mL of methanol was stirred at reflux for 5 h. The solvent was removed under reduced pressure and the residue was acidified. The product was extracted with ethyl acetate and the dried ($MgSO_4$) extract was concentrated. Crystallization of the residue from methylene chloride–hexane gave 0.44 g (69%), mp 132–135 °C, of **50**. Anal. ($C_{28}H_{30}O_8$) C, H.

Pharmacological Techniques. Effects on SRS-A-induced contraction of guinea pig ileum were evaluated by a modification of the technique originally described by Orange and Austin.[14] Isotonic contractions of ileum segments suspended in an oxygenated buffer solution containing 1 μM atropine sulfate and 1 μM pyrilamine maleate were elicited with SRS-A biologically generated by antigen challenge of actively sensitized chopped guinea pig lung fragments. A concentration of SRS-A (5.0 units/mL) that gave 50% of the maximal contraction of the ileum was used. The compounds were tested in duplicate at three concentrations that caused inhibitory effects between 10% and 90% and the IC_{50} values given in the tables were determined from linear regression calculated by log concentration–response curves. The correlation coefficient for the regression line of each antagonist was always greater than 0.95.

The in vivo ability of compounds to inhibit LTE-induced bronchoconstriction in guinea pigs was assessed by the intravenous and aerosol routes of administration. The intravenous technique[15] utilized male guinea pigs (Hartley strain, Charles River) weighing 400–600 g. Animals were anesthetized with urethane (2 g/kg) intraperitoneally and a polyethylene cannula was inserted into the jugular vein for intravenous drug administration. Tracheal pressure (cm of H_2O) was recorded from a Statham pressure transducer (P 32 AA). Since previous work[15] had demonstrated a potentiating effect of intravenous propranolol (0.1 mg/kg) on bronchoconstriction induced with synthetic leukotrienes, propranolol was administered 5 min prior to challenge with leukotriene. Two minutes later spontaneous breathing was arrested with succinylcholine chloride (1.2 mg/kg) administered intravenously, and the animals were ventilated with a Harvard (Model 680) small animal respirator set at 40 breaths/min and 4.0-cm^3 stroke volume. Control vehicle or test drug (10 mg/kg) was administered through the cannula into the jugular vein at 30 s before the animals were challenged with a maximum constrictory dose of LTE (25 μg/kg) given intravenously. The change in tracheal pressure was averaged for three control and five drug-treated animals and percent inhibition was calculated.

The aerosol technique[6] utilized male guinea pigs anesthetized and surgically prepared as described above. Propranolol (0.1 mg/kg) was administered intravenously 5 min prior to aerosol exposure. Spontaneously breathing animals were exposed for a 5-min period to an aerosol prepared from an aqueous solution of test drug neutralized with sodium hydroxide or to distilled water. A Monaghan (Model 670) ultrasonic nebulizer was used to administer varying concentrations (% w/v) of all compounds by inhalation. Aqueous solutions were freshly prepared and introduced into the chamber of the nebulizer. The output of the nebulizer was made available to the animal by directing a bias flow of aerosol through a "Y" tube connected to the tracheal cannula. At the end of the exposure period, spontaneous breathing was arrested with succinylcholine (1.2 mg/kg, i.v), and the animals were ventilated with a Harvard (Model 680) small animal respirator set at 40 breaths/min and 4.0-cm^3 stroke volume. The animals were challenged with a maximum constrictory dose of LTE (50 μg/kg) administered intravenously 30 s after the end

(14) Orange, R. P.; Austen, K. F. *Adv. Immunol.* **1969**, *10*, 105.
(15) Welton, A. F.; Crowley, H. J.; Miller, D. A.; Yaremko, B. *Prostaglandins* **1981**, *21*, 287.

of exposure to aerosolized drug. The effects on LTC-, LTD-, PAF-, and histamine-induced bronchoconstriction were also evaluated by using techniques similar to those described for LTE except that maximally constrictory doses of LTC (50 μg/kg), LTD (50 μg/kg), PAF (10 μg/kg), and histamine (50 μg/kg) were employed.

For determination of the relative potency (IC_{50} values) of drugs delivered by this route, varied percentage concentrations of test drug were administered via the nebulizer. For determination of the time course of inhibition for various drugs, the animals were exposed for 5 min to a 1% concentration of drug, and the time to challenge with LTE was varied from 30 s to 5, 10, 30, 60, or 90 min. The change in tracheal pressure was averaged for three control and five drug-treated animals and the percent inhibition at each aerosol concentration was calculated. The median inhibitory concentrations (IC_{50} values) were determined from linear regression calculated by log concentration–response curves generated by at least three concentrations that caused inhibitory effects between 10% and 90%. The correlation coefficient for the regression line of each antagonist was always greater than 0.95. The duration of activity was calculated as the time when inhibition decreased to 40%.

Acknowledgment. We thank the staff of the Physical Chemistry Department of Hoffmann-La Roche Inc. for determination of the spectral and analytical data and Marilyn Satchwell for her able assistance in preparation of the manuscript. We appreciate the guidance and encouragement of Dr. R. W. Kierstead during the course of this work.

Registry No. **5**, 79558-07-9; **6**, 40786-69-4; **7**, 88420-24-0; **8**, 88420-31-9; **9**, 88420-36-4; **10** (X = $(CH_2)_5$, n = 3, R = Et), 88420-45-5; **10** (X = $(CH_2)_3$, n = 1, R = Et), 88420-25-1; **10** (X = $(CH_2)_3$, n = 3, R = Et), 88420-32-0; **10** (X = $(CH_2)_3$, n = 5, R = Me), 88420-37-5; **10** (X = $(CH_2)_5$, n = 1, R = Et), 88420-28-4; **10** (X = $(CH_2)_2O(CH_2)_2$, n = 1, R = Et), 104835-61-2; **10** (X = $(CH_2)_2O(CH_2)_2$, n = 3, R = Et), 104835-62-3; **10** (X = $(CH_2)_2O(CH_2)_2$, n = 5, R = Me), 104835-63-4; **10** (X = $(CH_2)_2[O(CH_2)_2]_2$, n = 1, R = Et), 88420-44-4; **10** (X = $(CH_2)_2[O(CH_2)_2]_2$, n = 3, R = Et), 104835-64-5; **10** (X = $(CH_2)_2[O(CH_2)_2]_3$, n = 1, R = Et), 104835-65-6; **10** (X = $CH_2)_3O(CH_2)_3$, n = 1, R = Et), 88420-46-6; **10** (X = $(CH_2)_3O(CH_2)_3$, n = 3, R = Et), 88420-47-7; **10** (X = $(CH_2)_4O(CH_2)_4$, n = 1, R = Et), 104835-66-7; **11**, 88420-23-9; **12**, 88420-04-6; **13**, 88420-07-9; **14**, 88420-01-3; **15**, 88420-14-8; **16**, 88420-06-8; **17**, 88420-10-4; **18**, 88420-12-6; **19**, 88420-11-5; **20**, 88420-20-6; **21**, 88420-13-7; **22**, 88420-15-9; **23**, 88420-16-0; **24**, 88420-17-1; **25**, 88419-74-3; **26**, 88419-79-8; **27**, 88419-82-3; **28**, 88419-76-5; **29**, 88419-89-0; **30**, 88419-81-2; **31**, 88419-85-6; **32**, 88419-86-7; **34**, 88419-95-8; **35**, 88419-88-9; **36**, 88419-90-3; **37**, 88419-91-4; **38**, 88419-92-5; **39**, 95265-23-9; **39** (R′ = OH), 72836-76-1; **40**, 95265-24-0; **41**, 95265-27-3; **42**, 95265-25-1; **43** (X = $(CH_2)_3$, R = Ac, n = 1), 101463-93-8; **43** (X = $(CH_2)_3$, R = H, n = 1), 104835-67-8; **43** (X = $(CH_2)_5$, R = Ac, n = 1), 101463-96-1; **43** (X = $(CH_2)_3$, R = H, n = 3), 104835-68-9; **43** (X = $(CH_2)_3$, R = Ac, n = 3), 101464-01-1; **44**, 104835-58-7; **45**, 101463-94-9; **46**, 101463-97-2; **47**, 104835-59-8; **48**, 101464-02-2; **49**, 84701-83-7; **50**, 101463-95-0; **51**, 101463-98-3; **52**, 104835-60-1; **53**, 101464-03-3; $Br(CH_2)_2O(CH_2)_2Br$, 5414-19-7; $Br(CH_2)_2O(CH_2)_2O(CH_2)_2Br$, 31255-10-4; $Br(CH_2)_2O(CH_2)_2O(CH_2)_2O(CH_2)_2Br$, 31255-26-2; $Br(CH_2)_3O(CH_2)_3Br$, 58929-72-9; $Br(CH_2)_4O(CH_2)_4Br$, 7239-41-0; ethyl 4-bromobutyrate, 2969-81-5; 1,5-dibromopentane, 111-24-0; 2,7-dihydroxynaphthalene, 582-17-2; methyl bromoacetate, 96-32-2; acetyl chloride, 75-36-5; 1,3-dibromopropane, 109-64-8; ethyl bromoacetate, 105-36-2; methyl 6-bromohexanoate, 14273-90-6.

Conformationally Defined Adrenergic Agents. 4. 1-(Aminomethyl)phthalans: Synthesis and Pharmacological Consequences of the Phthalan Ring Oxygen Atom

John F. DeBernardis,* David L. Arendsen, John J. Kyncl, and Daniel J. Kerkman

Division of Cardiovascular Research, Abbott Laboratories, Abbott Park, Illinois 60064. *Received January 13, 1986*

The synthesis of a series of 1-(aminomethyl)phthalans **1b** is reported. The radioligand binding to α_1- and α_2-receptors and the in vitro pharmacology in α_1 (rabbit aorta) and α_2 (phenoxybenzamine-pretreated dog saphenous vein) tissues were determined and were compared to the activity of the corresponding 1-(aminomethyl)indans. The activity of this series of phthalans was found to be consistent with the electrostatic repulsion hypothesis that was used to design the parent indan (ERBCOP) compounds.[1] The effect of the phthalan ring oxygenation was to somewhat improve α_1-receptor potency relative to the 6-ERBCOP indans without having a general effect on the α_2-receptor potency. We conclude from the overall pattern of activity that while the norepinephrine type β-hydroxyl group may be beneficial for binding to the α_1-adrenoceptor, it is not required for strong binding to or full stimulation of the α_2-adrenergic receptor, provided that the conformational mobility associated with the phenylethylamine is restricted and maintained in a favorable conformation for receptor interaction.

We have previously[1] reported the synthesis and the α-adrenergic activity associated with a series of (aminomethyl)tetralin and (aminomethyl)indan derivatives (Figure 1, **1a**). These compounds were designed around a hypothesis we formulated that accounts for the adrenergic selectivity associated with 2- and 6-fluoronorepinephrines (FNEs)[2] on the basis of a conformational preference induced by an electrostatic repulsion between the aromatic fluorine atom and the side-chain hydroxyl group. These (aminomethyl)tetralins and (aminomethyl)indans (designated: electrostatic repulsion based conformational prototypes, ERBCOPs) were shown to exhibit α-adrenergic selectivity. In particular, the 6-ERBCOPs were highly α_2 selective with the greatest α_2 selectivity being seen for the 6-ERBCOP (aminomethyl)indan derivatives having nitrogen substituents no larger than methyl.

Having found these 6-ERBCOP compounds to have strong affinity and good selectivity for the α_2-adrenoceptor in radioligand binding assays, we decided to investigate the effects of reintroduction of the oxygen atom of the norepinephrine (NE) side-chain β-hydroxyl group. A number of reports have appeared that have indicated the importance of the benzylic hydroxyl group of phenethylamines interacting at α_1[3] and α_2-adrenergic receptors.[4-6]

(1) DeBernardis, J. F.; Kerkman, D. J.; Winn, M.; Bush, E. N.; Arendsen, D. L.; McClellan, W. J.; Kyncl, J. J.; Basha, F. Z. *J. Med. Chem.* **1985**, *28*, 1398.
(2) Kirk, K. L.; Cantacuzene, D.; Nimitkitpaisan, Y.; McCulloh, D.; Padgett, W. L.; Daly, J. W.; Creveling, C. R. *J. Med. Chem.* **1979**, *22*, 1493.
(3) Patil, P. N.; Miller, D. D.; Trendelenburg, U. *Pharmacol. Rev.* **1974**, *26*, 323.
(4) Stjärne, L. *Acta Physiol. Scand.* **1974**, *90*, 286.
(5) Ruffolo, R. R., Jr.; Yaden, E. L.; Waddell, J. E. *J. Pharmacol. Exp. Ther.* **1982**, *222*, 645.
(6) Goldberg, M. R.; Tung, C.-S.; Ring, M.; Oates, J. A.; Gerkens, J. F.; Robertson, D. *J. Pharmacol. Exp. Ther.* **1982**, *220*, 552.

0022-2623/87/1830-0178$01.50/0