residue was diluted with water (50 mL), and the resulting slurry was filtered to remove small amounts of solid. The aqueous was concentrated to a thick oil and crystallized from ethanol/water to yield 4.55 g of slightly impure urea. Another 1.30 g of impure urea was isolated from the mother liquor. Both crops of the urea were combined and recrystallized from ethanol/water (cooled to 4 °C) to afford 2.42 g (29%) of the urea as a white powder: mp 259–265 °C; ^{1}H NMR (DMSO-d_6) δ 9.44 (s, 1 H), 7.8–7.5 (m, 4 H), 6.67 (t, 1 H, J = 5.3 Hz), 3.5–3.3 (m, 2 H, overlapping water peak), 2.65 (t, 2 H, J = 6.2 Hz); ^{13}C NMR (DMSO-d_6) δ 154.5, 145.3, 133.1, 119.6, 117.4, 102.1, 50.8, 36.0; IR (KBr) cm^{-1} 3500, 3360, 3180, 3100, 2240, 1700, 1600, 1540, 1520, 1420, 1320, 1240, 1200, 1180. Anal. Calcd for $C_{10}H_{10}N_3O_4NaS\cdot0.67H_2O$: C, 39.57; H, 3.73; N, 13.84. Found: C, 39.56; H, 3.53; N, 13.70.

***N*-(4-Cyanophenyl)-*N'*-[(sodiosulfo)methyl]urea (7).** To a stirred solution of 4-cyanophenyl isocyanate (42.3 g, 293 mmol) in 500 mL of acetonitrile was added a solution aminomethanesulfonic acid (33.3 g, 300 mmol) and NaOH (12.0 g, 300 mmol) in 100 mL of H_2O. The reaction slurry was stirred for 24 h and then filtered to yield 52 g of crude product. The crude product was slurried in 200 mL of hot H_2O (90 °C) and filtered to remove symmetrical urea impurities. The filtrate was concentrated to 100 mL, heated to reflux, filtered through cotton, and then allowed to cool. The resulting white crystals were isolated by filtration and dried in vacuo to afford 37.6 g (46%) of the desired urea: mp 270–280 °C dec; ^{1}H NMR (DMSO-d_6) δ 9.37 (s, 1 H, NH), 7.57 (d, 2 H, J = 9.0 Hz, Ar), 7.52 (d, 2 H, J = 9.0 Hz, Ar), 7.23 (t, 1 H, J = 6.0 Hz, NH), 3.99 (d, 2 H, J = 6.0 Hz, CH_2); ^{13}C NMR (DMSO-d_6) δ 154.1, 145.0, 132.9, 119.5, 117.5, 102.3, 55.9; IR (KBr) cm^{-1} 3600 (br), 3580, 2240, 1720, 1600, 1560, 1520, 1420, 1180, 1060. Anal. Calcd for $C_9H_8N_3O_4NaS\cdot0.98H_2O$: C, 36.66; H, 3.40; N, 14.27. Found: C, 36.65; H, 3.02; N, 14.27.

Registry No. 1, 140-46-5; 4, 139583-43-0; 5, 139583-44-1; 6, 139583-45-2; 7, 134555-22-9; 4-cyanophenyl isocyanate, 40465-45-0; 2-aminoethanephosphonic acid, 2041-14-7; aminomethanephosphonic acid, 1066-51-9; taurine, 107-35-7; aminomethanesulfonic acid, 13881-91-9.

Selective β_3-Adrenergic Agonists of Brown Adipose Tissue and Thermogenesis. 1. [4-[2-[(2-Hydroxy-3-phenoxypropyl)amino]ethoxy]phenoxy]acetates

Ralph Howe,* Balbir S. Rao, Brian R. Holloway, and Donald Stribling

ICI Pharmaceuticals, Alderley Park, Macclesfield, Cheshire, SK10 4TG, England. *Received September 12, 1991*

The ester methyl [4-[2-[(2-hydroxy-3-phenoxypropyl)amino]ethoxy]phenoxy]acetate (8) has been identified as the most interesting member of a series of selective β_3-adrenergic agonists of brown adipose tissue and thermogenesis in the rat. In vivo it acts mainly via the related acid 10. Potency was generally markedly reduced by placing substituents on the phenyl ring of the phenoxypropanolamine unit of 8; only the 2-fluoro analogue 16 had comparable potency to 8. Other structure–activity relationships are discussed. Further testing of 8 (ICI 198157) has shown that in the rat it stimulates the β_3-adrenergic receptor in brown adipose tissue at doses lower than those at which it affects β_1 and β_2 adrenergic receptors in other tissues. It increases metabolic rate, as judged by an increase in oxygen consumption, and in the genetically obese Zucker rat it causes a reduced rate of weight gain. This class of compound may be useful in the treatment of obesity in man.

There is considerable evidence to suggest that the sympathetic nervous system (SNS) is important in the control of energy balance and weight regulation.[1] Agents which directly or indirectly enhance the SNS have been shown to be thermogenic and to cause weight reduction in obese animals[2] and man.[3] Although such compounds are useful pharmacological tools, their value as therapies for the treatment of obesity may be limited by lack of selectivity (at adrenergic receptors or in enhancing local concentrations of noradrenaline) and by lack of tissue specificity. The discovery that brown adipose tissue (BAT) is an important site of thermogenesis in the rat[4] indicated a tissue-specific means of modulating energy expenditure. The physiological effector of BAT is noradrenaline acting through β-adrenoceptors.[5] Work which suggested that β-receptors on BAT were different from conventional β_1 or β_2 subtypes on other tissues[6] pointed to a way of selectively stimulating BAT and thermogenesis without producing unwanted side effects on atria and trachea and other β_1- and β_2-receptor-mediated tissues. A human gene encoding for a third (β_3) β-adrenoceptor has been isolated recently and evidence presented for its presence in adipose tissue.[7]

We have synthesized various novel β_3-adrenergic agonists which show appropriate selectivity for BAT. Three tests were used in a screen to identify compounds of interest. The first was designed to determine whether compounds increased the core temperature of post-cold-adapted rats (see Pharmacology section). Core temperature can be increased by a variety of mechanisms and it was necessary to identify and eliminate those compounds which do not act by stimulting thermogenesis in BAT, i.e. which act by a nonspecific or toxic mechanism. This was achieved in the second test by measuring any increase in GDP binding

(1) Landsberg, L.; Young, J. B. Fasting, Feeding and Regulation of the Sympathetic Nervous System. *N. Eng. J. Med.* **1978**, *298*, 1295–1301.
(2) Dulloo, A. G.; Miller, D. S. Thermogenic Drugs for the Treatment of Obesity: Sympathetic Stimulants in Animal Models. *Br. J. Nutr.* **1984**, *52*, 179–196.
(3) Astrup, A.; Lundsgaard, C.; Madsen, J.; Christensen, N. J. Enhanced Thermogenic Responsiveness During Chronic Ephedrine Treatment in Man. *Am. J. Clin. Nutr.* **1985**, *42*, 83–93.
(4) Foster, D. O.; Frydman, M. L. Non-Shivering Thermogenesis in the Rat. II. Measurements of Blood Flow with Microspheres Point to Brown Adipose Tissue as the Dominant Site of the Calorigenesis Induced by Noradrenaline. *Can. J. Physiol. Pharmacol.* **1979**, *56*, 110–122.
(5) Himms-Hagen, J. Brown Adipose Tissue Thermogenesis and Obesity. *Prog. Lipid Res.* **1989**, *28*, 67–115.
(6) Arch, J. R. S.; Ainsworth, A. T.; Cawthorne, M. A.; Piercy, V.; Sennitt, M. V.; Thody, V. E.; Wilson, C.; Wilson, S. Atypical β-Adrenoceptor on Brown Adipocytes as Target for Anti-Obesity Drugs. *Nature (London)* **1984**, *309*, 163–165.
(7) Emorine, L. J.; Marullo, S.; Briend-Sutren, M. M.; Patey, G.; Tate, K.; Delavier-Klutchko, C.; Strosberg, D. Molecular Characterization of the Human β_3-Adrenergic Receptor. *Science* **1989**, *245*, 1118–1121.

0022-2623/92/1835-1751$03.00/0

Table I

no.	R^1	R^2	test A,[a] Δ °C	sc: GDP ED_{50}, mg kg^{-1}	sc: SI (bpm)	po: GDP ED_{50}, mg kg^{-1}	po: SI (bpm)
			$R^1C_6H_4CHOHCH_2NHCH(CH_3)CH_2C_6H_4R^2$				
1	H	4-CO_2Me	1.6	0.68	34	0.94	>10 (474)[b]
2	3-Cl	4-OCH_2CO_2Me	1.9	0.003	>100 (497)	0.007	>100 (437)
			$C_6H_5OCH_2CHOHCH_2NHCH(R^1)CH_2C_6H_4R^2$				
3[c]	Me	4-CO_2Me	1.2	0.34	<1		
4A[d]	Me	4-OCH_2CO_2Me	2.2	0.007	15.7		
4B[d]	Me	4-OCH_2CO_2Me	not tested	0.003	43		
5	H	4-OCH_2CO_2Me	2.0	0.024	100	0.078	>100 (490)
	X	R	$C_6H_5OCH_2CHOHCH_2NHCH_2CH_2XC_6H_4R$				
6	O	H	1.2	0.6	8		
7	NHCO	H	0.6	5.0	>10 (466)		
8	O	4-OCH_2CO_2Me	1.4	0.43	>100 (497)	0.12	>100 (462)
9	NHCO	4-OCH_2CO_2Me	not active				

[a] See Pharmacology section. [b] Heart rate reached 474 beats per minute at 10 times the GDP ED_{50}. This information is recorded when it is known. [c] 1:1 mixture of racemates by NMR. [d] The letters A and B distinguish a pure racemate 4B and a mixture of racemates 4A containing 37% of racemate 4B.

Table II

compd	form	crystn solvent	mp, °C	formula	analyses	methods[a]
1[b]	base	MeOH–H_2O	87–89[c]			ref 17
2[d]	HBr	MeOH–EtOAc–Et_2O	137–138[e]			ref 18
3[f]	hydrogen oxalate	EtOH–Et_2O	128–131	$C_{22}H_{27}NO_8$	C, H, N	exptl sectn
4A[g]	HCl	MeOH–Et_2O	112–114	$C_{21}H_{28}ClNO_5 \cdot {}^1/_2H_2O$	C, H, Cl, N, H_2O	C
4B[g]	HCl	MeOH–Et_2O	120–122	$C_{21}H_{28}ClNO_5 \cdot {}^3/_4H_2O$	C, H, Cl, N, H_2O	C
5	hydrogen oxalate	MeOH	146–148	$C_{22}H_{27}NO_9$	C, H, N	A[h]
8	HCl	MeOH	170	$C_{20}H_{26}ClNO_6$	C, H, Cl, N	A; exptl sectn[i]
	base[j]	MeOH	116–117	$C_{20}H_{25}NO_6$	C, H, N	
9	HCl	MeOH–MeOAc	185–188	$C_{21}H_{27}ClN_2O_6$	C, H, Cl, N	A[k] (50)

[a] Methods refer to the Experimental Section. [b] Single racemate (*RR,SS*). [c] Lit.[17] mp 89–91 °C. [d] Single racemate (*RR,SS*). [e] Lit.[18] mp 137–138 °C. [f] Mixture of racemates. [g] See footnote *d* of Table I. [h] Amine component 45 analogous to 49 described in Experimental Section. [i] Intermediates 46–49 described in the Experimental Section. [j] Treatment of 8·HCl with 5% aqueous $NaHCO_3$ and extraction with CH_2Cl_2. [k] Intermediate 50 described in the Experimental Section.

to BAT mitochondria from suitably prepared rats. A dose (GDP ED_{50}) necessary to produce 50% of the maximal isoprenaline effect was determined. It was important to have an early measure of whether a compound selectively stimulated BAT rather than heart rate. This was determined in the third test in which selectivity is expressed as the ratio of the dose of compound (D_{500}) which elevates rat heart rate to 500 beats per minute (bpm) to the GDP ED_{50}. The normal rat heart rate is around 380–400 bpm and it can be stimulated to around 560 bpm by isoprenaline without ill effect. 500 bpm was chosen as an appropriate level of submaximal stimulation. The ratio, which we have called the selectivity index (SI) has proved useful for identifying compounds worthy of more detailed study.

In order to identify lead compounds, selected compounds available from our previous studies on β-adrenergic agents[8] (*J. Med. Chem.*, 1968 to present) were screened. Selection was on the basis of variety of chemical structure and no account was taken of known pharmacological properties so as not to introduce bias. This revealed that compounds of the phenoxypropanolamine class had agonist effects on BAT. This observation was new at the time. Arch et al.[6] had reported that the phenylethanolamines BRL 26830A (1) and BRL 35135A (2), tested in vitro as their related acids, stimulated lipolysis in brown adipocytes and moreover had selectivity for brown adipocyte lipolysis over effects on atria (β_1) and trachea (β_2). The selectivity was much more marked for β_3 versus β_1 than versus β_2-receptors. Accordingly we synthesized the phenoxypropanolamine compounds **3**, **4A**, **4B**, and **5** related to compounds **1** and **2**. Smith[9] had drawn attention to the surprising cardioselectivity (β_1 vs β_2) of (aryloxy)propanolamines such as **6**[10] and **7**,[11] which are partial agonists of β-adrenergic receptors and which express antagonist activity. It was of interest to find that these compounds were active as agonists of BAT and moreover had a measure of selectivity, albeit low, for BAT versus heart rate in our screening test (Table I). It was important therefore to incorporate the salient structural features of these molecules into the design of further compounds such as **8** and **9** with the hope that β_1 and more importantly β_2 effects would be more attenuated than in compounds such as BRL 26830A and BRL 35135A. Tremor, which is a β_2 effect, had been observed in patients treated with BRL 26830A.[12,13] It was pleasing to note the activity and se-

(8) Howe, R.; Crowther, A. F.; Stephenson, J. S.; Rao, B. S.; Smith, L. H. β-Adrenergic Blocking Agents. 1. Pronethalol and Related N-Alkyl and N-Aralkyl Derivatives of 2-Amino-1-(2-naphthyl)ethanol. *J. Med. Chem.* **1968**, *11*, 1000–1008.

(9) Smith, L. H. Cardio-selective β-Adrenergic Blocking Agents. *J. Appl. Chem. Biotechnol.* **1978**, *28*, 201–212.

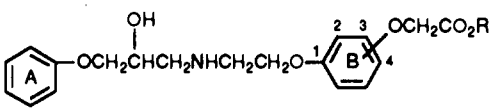
(10) Smith, L. H.; Tucker, H. β-Adrenergic Blocking Agents. 17. 1-Phenoxy-3-phenoxyalkylamino-2-propanols and 1-Alkoxyalkylamino-3-phenoxy-2-propanols. *J. Med. Chem.* **1977**, *20*, 1653–1656.

(11) Large, M. S.; Smith, L. H. β-Adrenergic Blocking Agents. 22. 1-Phenoxy-3-[[(substituted-amido)alkyl]amino]-2-propanols. *J. Med. Chem.* **1982**, *25*, 1286–1292.

(12) Chapman, B. J.; Farquahar, D. L.; Galloway, S. McL.; Simpson, G. K.; Munro, J. F. The Effects of a New β-Adrenoceptor Agonist BRL 26830A in Refractory Obesity. *Int. J. Obes.* **1988**, *12*, 119–123.

(13) Connacher, A. A.; Lakie, M.; Powers, N.; Elton, R. A.; Walsh, E. G.; Jung, R. T. Tremor and the Anti-Obesity Drug BRL 26830A. *Br. J. Clin. Pharmacol.* **1990**, *30*, 613–615.

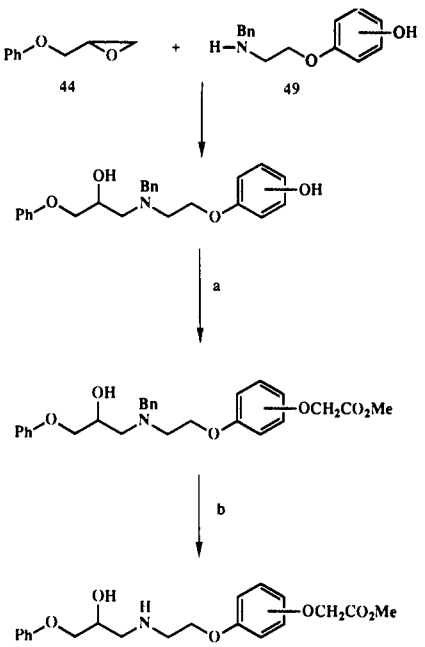
Table III



compd	ring B subst	R	form	crystn solvent	mp, °C	formula	analyses	methods
S-8	4	Me	(−)-HDTT[a]	MeOH–MeOAc	146–148	$C_{40}H_{43}NO_{14}\cdot{}^1/_4H_2O$	C, H, N, H_2O	Exptl Sectn
			HCl[b]	MeOH–MeOAc	156–157	$C_{20}H_{26}ClNO_6$	C, H, N	Exptl Sectn[c]
R-8	4	Me	(+)-HDTT[d]	MeOH–MeOAc	148–150	$C_{40}H_{43}NO_{14}$		Exptl Sectn
			HCl[e]	MeOH–MeOAc	155–157	$C_{20}H_{26}ClNO_6$	C, H, Cl, N	Exptl Sectn
10	4	H	amino acid	H_2O	186–188	$C_{19}H_{23}NO_6\cdot{}^1/_4H_2O$	C, H, N, H_2O	Exptl Sectn
			HCl	2 M HCl	182–183	$C_{19}H_{24}ClNO_6$	C, H, Cl, N	Explt Sectn
S-10	4	H	HCl[f]	2 M HCl	184	$C_{19}H_{24}ClNO_6$	C, H, Cl, N	As for 10 (b)
R-10	4	H	HCl[g]	2 M HCl	184	$C_{19}H_{24}ClNO_6$	C, H, Cl, N	As for 10 (b)
11	4	Et	HCl	EtOH–EtOAc	170–172	$C_{21}H_{28}ClNO_6$	C, H, Cl, N	Exptl Sectn
12	4	Pr^i	HCl	Pr^{i}OH	178	$C_{22}H_{30}ClNO_6$	C, H, Cl, N	As for 11
13	4	Bu^t	base	Et_2O–pet. ether[h]	74–76	$C_{23}H_{31}NO_6$	C, H, N	A[i]
14	3	Me	HCl	MeOH	164–167	$C_{20}H_{26}ClNO_6$	C, H, Cl, N	A[j]
15	3	H	HCl	H_2O	153–155	$C_{19}H_{24}ClNO_6$	C, H, Cl, N	As for 10 (b)

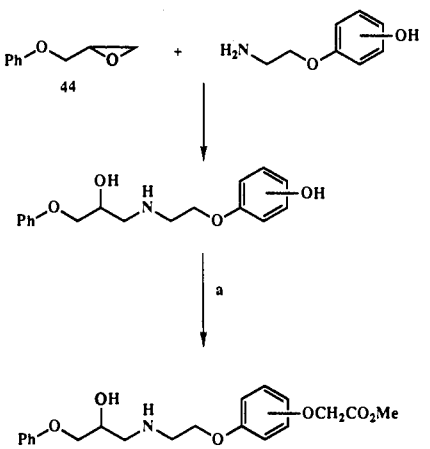
[a] Hydrogen di-*p*-toluoyltartrate, $[\alpha]^{25}_D$ −80.3° (*c* 0.97, MeOH). [b] $[\alpha]^{23}_D$ −12.1° (*c* 1.0, MeOH). [c] Also prepared by method A from the *S*-enantiomer of **44** (1.77 g) in 72% yield, mp and mixed mp 156–157 °C, $[\alpha]^{23}_D$ −12.2° (*c* 1.01 in MeOH). [d] Hydrogen di-*p*-toluoyltartrate, $[\alpha]^{23}_D$ +81.6° (c 1.04, MeOH). [e] $[\alpha]^{23}_D$ +12.2° (c 0.96, MeOH). [f] $[\alpha]^{23}_D$ −12.7° (*c* 1.02, MeOH). [g] $[\alpha]^{23}_D$ +12.1° (c 1.01, MeOH). [h] Petroleum ether (bp 60–80 °C). [i] *tert*-Butyl bromoacetate used in place of methyl bromoacetate. [j] Intermediate *N*-benzyl-2-(3-hydroxyphenoxy)-ethylamine hydrochloride (**58**) prepared as for **49**, method A, mp 148–149 °C (from MeOH–EtOAc). Anal. ($C_{15}H_{18}ClNO_2$) C, H, Cl, N.

Scheme I.[a] Method A



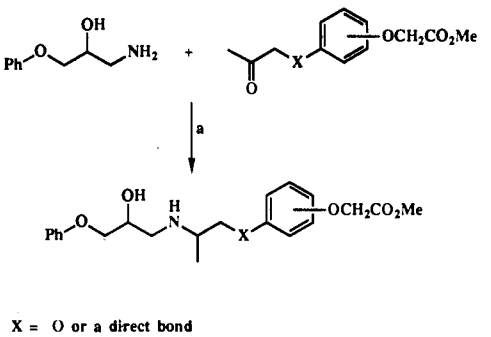
[a] (a) $BrCH_2CO_2Me$; (b) H_2, Pd–C.

Scheme II.[a] Method B



[a] (a) $BrCH_2CO_2Me$.

Scheme III.[a] Method C



X = O or a direct bond

[a] (a) H_2, Pt_2O.

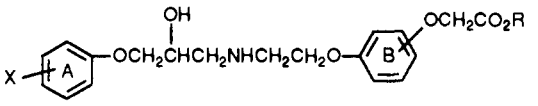
lectivity of compound 8, which has the same ethoxy linking group between the amine and the phenyl ring as **6**. The lack of activity of compound **9** was a disappointment. On the basis of the results given in Table I, compounds **4A/4B**, **5**, and **8** were deemed worthy of further study. Chemical details of compounds **1–9** are given in Table II. Although compound **8** was not the most potent of the leads, the result from oral dosing led to the view that it and its analogues may prove to have selectivity advantages on more detailed testing. Thus, the remainder of this paper deals with work on compound **8**[14] and its analogues listed in Tables III–V. Patent applications have been published which include the use of compound **4**[15] and the acid related to the ester **5**[16] for the treatment of obesity and diabetes.

Chemistry

Most of the compounds were made by method A shown in Scheme I. Use of the benzyl-protected amine **49** avoided the formation of tertiary amines either from two

(14) Holloway, B. R.; Howe, R.; Rao, B. S.; Stribling, D. 2-Hydroxy-3-phenoxypropylamines. Eur. Patent 210849, 1987.
(15) Alig, L.; Muller, M. Phenoxypropanolamines. Eur. Patent 140243, 1985, p 35.
(16) Alig, L.; Muller, M. Preparation of [p-[2[[(S)-2-Hydroxy-3-phenoxypropyl]amino]ethyl]phenoxy]acetic Acid and Salts as Antiobesity and Antidiabetic Agents. Eur. Patent 300290, 1989.

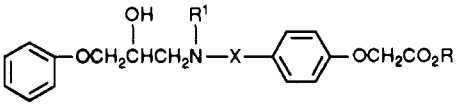
Table IV



compd	X	ring B subst	R	form	crystn solvent	mp, °C	formula	analyses	methods
16	2-F	4	Me	HCl	MeOH–Et_2O	120–122	$C_{20}H_{25}ClFNO_6$	C, H, Cl, N	A
17	2-F	4	H	HCl	H_2O	159–160	$C_{19}H_{23}ClFNO_6$	C, H, Cl, N	as for 10 (b)
18	2-CN	4	Me	HCl	MeOH–MeOAc	134–135	$C_{21}H_{25}ClN_2O_6$	C, H, N	B
19	2-Cl	4	Me	HCl	MeOH–Et_2O	112–114	$C_{20}H_{25}Cl_2NO_6$	C, H, Cl, N	B
20	2-Me	4	Me	HCl	MeOH–MeOAc	143–145	$C_{21}H_{28}ClNO_6$	C, H, N	A
21	3-F	4	Me	HCl	MeOH–Et_2O	147–148	$C_{20}H_{25}ClFNO_6 \cdot {}^1/_4H_2O$	C, H, N, H_2O	A
22	3-Me	4	Me	HCl	MeOH–Et_2O	147–149	$C_{21}H_{28}ClNO_6 \cdot {}^1/_4H_2O$	C, H, N, H_2O	A
23	3-OMe	4	Me	HCl	MeOH–Et_2O	151–153	$C_{21}H_{28}ClNO_7$	C, H, N	A
24	3-CF_3	4	Me	HCl	MeOH–Et_2O	133–135	$C_{21}H_{25}ClF_3NO_6$	C, H, N	A
25	4-F	4	Me	HCl	MeOH–Et_2O	151–152	$C_{20}H_{25}ClFNO_6$	C, H, N	A
26	4-Cl	4	Me	HCl	MeOH–Et_2O	172–174	$C_{20}H_{25}Cl_2NO_6$	C, H, N	A
27	4-Me	4	Me	HCl	MeOH–Et_2O	192–194	$C_{21}H_{28}ClNO_6$	C, H, N	A
28	4-OCH_2Ph	4	Me	HCl	MeOH	200	$C_{27}H_{32}ClNO_7$	C, H, Cl, N	A[a]
29	4-OH	4	Me	HCl	MeOH–MeOAc	185	$C_{20}H_{26}ClNO_7$	C, H, Cl, N	A[a]
30	4-OMe	4	Me	HCl	MeOH–MeOAc	177–179	$C_{21}H_{28}ClNO_7$	C, H, N	A
31	4-OPh	4	Me	HCl	MeOH–MeOAc	169	$C_{26}H_{30}ClNO_7$	C, H, Cl, N	A
32	4-CH_2CONH_2	4	Me	HCl	MeOH	235–237	$C_{22}H_{29}ClNO_7$	C, H, Cl, N	A
33	2,4-F_2	4	Me	HCl	MeOH–Et_2O	121–122	$C_{20}H_{24}ClF_2NO_6$	C, H, Cl, N	A
34	2,6-F_2	4	Me	HCl	MeOH–Et_2O	125–126	$C_{20}H_{24}ClF_2NO_6$	C, H, Cl, N	A
35	2-F	3	Me	HCl	MeOH–Et_2O	117–118	$C_{20}H_{25}ClFNO_6$	C, H, Cl, N	A[b]

[a] Starting from 4-(benzyloxy)phenol and proceeding via the *N*-benzyl analogue of compound 28. Under the standard hydrogenation conditions of method A, compound 29 was normally obtained. The occasional formation of 28 is attributed to deactivation of the catalyst. [b] See footnote *j* in Table III for intermediate.

Table V



compd	X	R	R^1	form	crystn solvent	mp, °C	formula	analyses	methods
36	$-CH(CH_3)CH_2O-$	Me	H	base	MeOAc	103–105	$C_{21}H_{27}NO_6 \cdot {}^1/_4H_2O$	C, H, N, H_2O	C[a]
37	$-CH(CH_3)CH_2O-$	Me	H	base	MeOH–MeOAc	116–117	$C_{21}H_{27}NO_6$	C, H, N	C[a]
38	$-CH_2C(CH_3)_2O-$	Me	H	HCl	MeOH–MeOAc	138–140.5	$C_{22}H_{30}ClNO_6$	C, H, Cl, N	Exptl Sectn[b]
39	$-CH_2C(CH_3)_2O-$	H	H	HCl	MeOAc	119–121	$C_{21}H_{28}ClNO_6$	C, H, Cl, N	as for 10 (b)
40	$-(CH_2)_3O-$	Me	H	HCl	MeOH–Et_2O	166–168	$C_{21}H_{28}NO_6$	C, H, Cl, N	A[c]
41	$-(CH_2)_4O-$	Me	H	HCl	MeOH–Et_2O	155–157	$C_{22}H_{30}ClNO_6$	C, H, N	A[d]
42	$-CH_2CH_2CONH-$	Me	H	HCl	MeOH–Et_2O	amorphous	$C_{21}H_{21}ClN_2O_6 \cdot {}^1/_2H_2O$	C, H, Cl, N, H_2O	A[e]
43	$-CH_2CH_2O-$	Me	Me	HCl	MeOH–Et_2O	112	$C_{21}H_{28}ClNO_6$	C, H, Cl, N	Exptl Sectn

[a] The mixture of diastereoisomeric racemates was separated by fractional crystallization of the hydrogen oxalate salts from MeOH to give first the hydrogen oxalate of 36, mp 191–192 °C, and then from MeOAc to give the hydrogen oxalate of 37, mp 125–127 °C. Compound 36 was of >95% isomeric purity based on the presence of only one doublet of doublets in the 400-MHz NMR spectrum at δ 3.11. Compound 37 contained approximately 25% of compound 36 and 75% of the other racemate, based on 400-MHz NMR measurement of the two doublets of doublets of δ 3.11. [b] Intermediates 52, 53, and 55 described in the Experimental Section. [c] Intermediate *N*-benzyl-3-(4-hydroxyphenoxy)propylamine prepared as for compound 49 but starting from 4-(3-bromopropoxy)phenol.[35] [d] Intermediate *N*-benzyl-4-(4-hydroxyphenoxy)butylamine prepared as for compound 49 but starting from 4-(4-bromobutoxy)phenol.[36] [e] Intermediates 56 and 57 described in the Experimental Section.

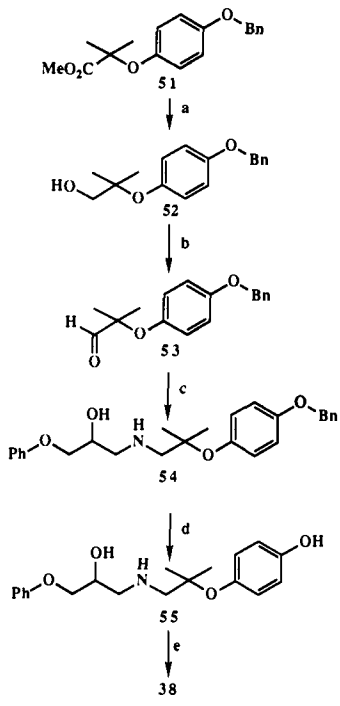
molecules of epoxide 44 and one molecule of a primary amine or from alkylation of nitrogen when alkylation of the phenolic hydroxyl group was desired. The benzyl group was removed by hydrogenolysis at the final stage. Occasionally, removal of such protection was not compatible with the other substituents in the molecule and method B (Scheme II) was used. Method C (Scheme III) is a standard reaction.[8] Intermediate epoxides such as 44 were made by reaction of epichlorohydrin with the appropriate phenol in the presence of a base such as sodium hydroxide. Generally intermediates were not isolated and characterized; those that were and are new or were made by a new route are described in the Experimental Section. Compounds made by the standard routes are not mentioned further. Compounds 1[17] and 2[18] (Table II) were made by published methods. Compound 3 was made from epoxide 44 and the appropriate amine. Preparative details are given for intermediates 45, 46–49, and 50 required for the syntheses of compounds 5, 8, and 9 respectively.

The *S*- and *R*-enantiomers of compound 8 were obtained by resolution of racemic 8. The *S*-enantiomer of 8 was also prepared from the *S*-enantiomer of epoxide 44 by route A, which served to prove the absolute configuration of this biologically active enantiomer. These enantiomers and analogues of 8 unsubstituted at the phenyl ring of the phenoxypropanolamine unit are listed in Table III. Amino acid 10 related to methyl ester 8 was obtained as the hydrochloride by acid hydrolysis and as the zwitterion by base hydrolysis. It was used to prepare the ethyl (11) and isopropyl (12) esters. *tert*-Butyl ester 13 was made in the

(17) Ainsworth, A. T.; Smith, D. G. Secondary Amines and Their Use in Pharmaceutical Compositions. Eur. Patent 21636, 1981, p 34.

(18) Hindley, R. M. Secondary Phenylethanolamines and Their Pharmaceutical Application. Eur. Patent 70133, 1983, p 80.

Scheme IV[a]



[a] (a) Red Al; (b) pyridinium chlorochromate; (c) $PhOCH_2CHOHCH_2NH_2$, $NaBH_4$; (d) H_2, Pd–C; (e) NaH, $BrCH_2CO_2Me$.

same way as 8 but using *tert*-butyl bromoacetate in place of methyl bromoacetate.

Analogues with substituents on the phenyl ring of the phenoxypropanolamine unit are listed in Table IV.

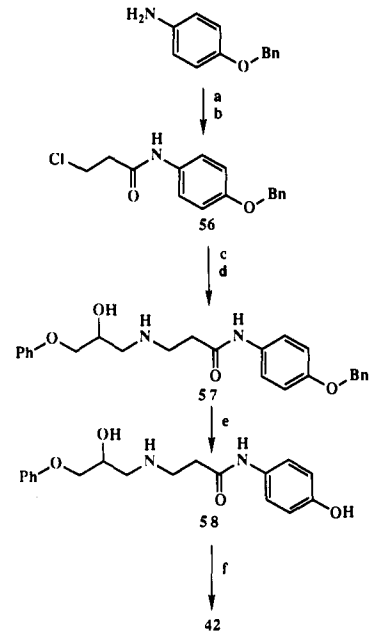
In Table V are listed compounds in which the group linking the phenyl ring B to the amino group is varied and also analogue 43 of compound 8 in which the nitrogen atom bears a methyl group, introduced by the action of formic acid and formaldehyde on compound 8. Two compounds (38 and 42) were made by the routes shown in Schemes IV and V, respectively. Intermediates **52**, **53**, and **55** for compound **38**, and **56** and **57** for compound **42** were characterized (see Experimental Section).

Pharmacology

To demonstrate the thermogenic effect of compounds (test A), rats were cold adapted by being placed in a cold environment at 4 °C for 10 days in order to increase their capacity for thermogenesis. They were then transferred to a thermoneutral environment at 29 °C. Three hours later the baseline core temperature was measured in a group of six rats using a thermocouple (Hale instruments) inserted 4 cm into the rectum until a steady reading was obtained and then the thermocouple was withdrawn. Compound was then administered subcutaneously or orally as a solution or suspension in 0.45% aqueous sodium chloride and 0.25% w/v Polysorbate 80. After 1 h the core temperature was again measured. Measurements were also carried out on a group of six rats dosed with the dosing vehicle alone. Compounds causing an increase in core temperature of >0.3 °C, which was statistically significant ($p < 0.05$; Student's *t*-test), at a dose of 15 mg kg^{-1} or less were considered to be active.

To demonstrate that the thermogenic effects observed in the above test were mediated by an effect on BAT (test B), rats were cold adapted at 4 °C for 4 days and then transferred to a warm environment at 23 °C for 2 days. On the following day, compounds were administered subcutaneously or orally as described above. One hour later, animals were sacrificed and the interscapular BAT pad was removed. BAT mitochondria were prepared by differential centrifugation and GDP binding was determined[19] as a measure of thermogenic activation. Each test included a control group of six rats which was dosed with the solution/suspension vehicle only and a positive control group of six rats which was dosed with isoprenaline (as its sulfate) at 1 mg kg^{-1}. Test compounds were routinely dosed in groups of six rats at 0.1, 0.3, 1.0, 3.0, and 10 mg kg^{-1} and results expressed in terms of the effect on GDP binding produced by isoprenaline. The dose necessary to produce 50% of the isoprenaline effect (GDP ED_{50}) was calculated by linear regression analysis. Compounds were considered active in this test if they caused a significant elevation ($p < 0.05$; Student's *t*-test) in GDP binding as compared to controls. To obtain a measure of whether a compound selectively stimulated BAT rather than heart rate (test C), rats were adapted to a thermoneutral environment at 29 °C for 2 weeks in order to decrease their capacity for BAT-mediated thermogenesis. This adaptation was so that any indirect effects of a compound on heart rate via stimulation of thermogenesis would be minimal, enabling direct effects on heart rate to be assessed. During the final 3 days of the 2 weeks, the animals were trained to use an apparatus for measuring heart rate noninvasively via foot-pad electrodes connected to an ECG integrator giving a continuous readout of heart rate. Compounds were administered subcutaneously or orally to groups of six rats at the ED_{50} determined in test B, and heart rate was determined 15–30 min after dosing. The procedure was then repeated in subsequent tests using increasing multiples of the ED_{50} determined in test B until the heart rate reached or exceeded 500 beats per minute, allowing the dose necessary to produce a heart rate of 500 beats per minute (D_{500}) to be calculated. A control group of six rats received dosing vehicle alone. We have defined the ratio of D_{500} to ED_{50} in test B as the selectivity index

Scheme V[a]



[a] (a) $ClCH_2CH_2COCl$; (b) Et_3N; (c) $PhOCH_2CHOHCH_2NH_2$; (d) Et_3N; (e) H_2, Pd–C; (f) NaH, $BrCH_2CO_2Me$.

(19) Holloway, B. R.; Davidson, R. G.; Freeman, S.; Wheeler, H.; Stribling, D. Post-Natal Development of Interscapular (Brown) Adipose Tissue in the Guinea Pig: Effect of Environmental Temperature. *Int. J. Obes.* 1984, *8*, 295–303.

Table VI

		sc		po	
no.	test A; Δ °C	test B; GDP ED_{50}, mg kg^{-1}	test C; SI (bpm)	test B; GDP ED_{50}, mg kg^{-1}	test C; SI (bpm)
8	1.4	0.43	>100 (497)	0.12	>100 (462)
S-8	not tested	0.11	>100 (479)		
10	2.3	0.31	>100 (454)	3.5	>62 (437)
S-10	not tested	0.13	>77 (437)	0.45	>22 (375)
11	1.5			0.62	>100 (429)
12	1.9			1.09	>10 (434)
13	2.4	0.29	>50 (458)	0.25	>100 (495)
14	1.8	0.67	>100 (462)	5.28	>10 (477)
15	2.4	0.55	>10 (462)		
16	1.8	0.15	>100 (452)	0.54	>100 (472)
17	1.5	0.3	>100 (448)		
19	not tested	4.8			
21	1.1	16.3			
26	1.6	4.1	>10 (442)		
29	1.6	30.9			
35	1.6			4.8	>10 (491)
36	2.2	0.34	>100 (491)	0.43	>10 (492)
37	2.2	0.5	>10 (430)	2.57	

(SI) and used it as a measure of the selectivity of the compound for BAT as opposed to the cardiovascular system. Nonselective compounds for the β_3-receptor have an SI of <1; for example, isoprenaline, a nonselective β_1- and β_2-agonist (GDP ED_{50} = 0.16 mg kg^{-1}, sc), has an SI of 0.06; prenalterol, a selective β_1-agonist (GDP ED_{50} = 0.27 mg kg^{-1}, sc), has an SI of <1; and clenbuterol, a selective β_2-agonist (GDP ED_{50} = 0.09 mg kg^{-1}, sc), has an SI of <1. Several compounds of the present study could be dosed at 100 times the ED_{50} without causing the heart rate to rise to 500 beats per minute.

Discussion

Table VI contains the test results of those compounds which proved active in both test A and test B. Compounds excluded were either inactive in test A and therefore not tested in test B or, if active in test A, proved to be inactive in test B when dosed subcutaneously at up to 25 mg kg^{-1}. The aim was to obtain sufficient information to judge whether a compound merited further investigation.

Although methyl ester 8 is itself active in stimulating brown adipocyte lipolysis in vitro, the effect observed in vivo is largely mediated by the corresponding acid 10. Pharmacokinetic experiments in the rat and dog demonstrated that after dosing ester 8 only acid 10 was detectable in plasma.[20] Acid 10, when dosed orally, is much less potent than the ester (Table VI) because of poorer absorption.[21] In agreement with this, other esters (11–13) were also active, but they offered no advantage over the methyl ester when dosed orally.

Analogue 14 with the oxyacetic ester unit in the 3-position of ring B was much less potent than 8 when dosed orally, and there was a similar fall in oral potency when the positional isomer 35 was compared to compound 16. Of those analogues (16–34) substituted on the phenyl ring A, only 2-fluoro analogue 16 (and its related acid 17) was of similar potency to compound 8. Potency was reduced when larger ortho substituents such as 2-cyano 18, 2-chloro 19, and 2-methyl 20 were introduced. Two small ortho substituents as in 2,6-difluoro analogue 34 were not tolerated. Potency was markedly decreased by 3-fluoro substitution (21) and was lost with 4-fluoro substitution (25), although low potency was noted for the 4-chloro (26) and 4-hydroxy (29) analogues. In view of the inactivity of the 4-fluoro analogue it was perhaps not surprising that 2,4-difluoro analogue 33 was inactive. In short, substitution of phenyl ring A with other than a single o-fluorine produced a fall in potency. In this respect it is of interest that in their compounds related to 4 and 5 Alig and Miller limit substitution on the phenyl ring A to o-fluoro and o-chloro.[15] Compound 36, one of a pair of racemates related to 8 which have a methyl group on the carbon atom of the ethoxy linking group adjacent to the nitrogen atom, had about the same potency as 8 but appeared less selective on oral dosing. The second racemate of the pair was not obtained pure, but a mixture, 37, containing 75% of the second racemate and 25% of 36, obtained with some difficulty, proved less potent than 8 on oral dosing, which did not provide encouragement to persevere to obtain pure material. Compound 38 and related acid 39, which have two methyl groups on the carbon atom of the ethoxy linking group adjacent to the oxygen atom, were inactive. Analogues in which the ethoxy linking group had been extended to propoxy (40) and butoxy (41) were inactive.

In another variant of the linking group the oxygen atom of the ethoxy linkage of 8 was replaced by –CONH– to give compound 42; like its analogue 9 (–NHCO–) it was inactive.

Tertiary amine 43, the N-methyl analogue of 8, was inactive.

Activity was shown to reside in the S-enantiomer of 8, the R-enantiomer having a GDP ED_{50} of 35 mg kg^{-1} when dosed subcutaneously.

The end result of this screening program was that no compound superior to compound 8 and the related acid 10 (or their S-isomers) was identified, and so compound 8 (ICI 198157) and 10 (ICI 201651) were subjected to more detailed testing. These tests showed that compounds 8 (in vivo) and 10 (in vitro) stimulated brown adipose tissue at doses lower than those at which they affected β_1- and β_2-adrenergic receptors in other tissues.[22] In particular, a comparison of compounds in a cat model of tremor and on changes in blood potassium in the conscious dog indicated that, unlike BRL 26830A and BRL 35135A, ICI 198157 appears virtually free from effects on these β_2-mediated parameters. Further, it increases metabolic rate, as judged by an increase in oxygen consumption, and genetically obese Zucker rats dosed twice daily with ICI 198157 (5 mg kg^{-1}, po) had a reduced rate of weight gain compared to controls. Over the course of the 56-day experiment the compound had no effect on food intake, indicating that the reduced rate of weight gain was due to increased thermogenesis.[22] Studies with other β_3-adrenoceptor agonists have demonstrated similar effects on body weight in obese Zucker rats.[23,24] Studies in man with other thermogenic agents[3,25,26] indicate that this class

(20) Law, B.; Lynch, J.; Warrander, A. Unpublished results.
(21) Lynch, J. Unpublished results.

(22) Holloway, B. R.; Howe, R.; Rao, B. S.; Stribling, D. ICI 198157: A Novel Selective Agonist of Brown Fat and Thermogenesis. *Obesity in Europe 88, Proceedings of the 1st European Congress on Obesity*; Bjorntorp, P., Rossner, S., Eds.; John Libbey: London, 1989; pp 323–328.
(23) Meier, M. K.; Blum-Kaelin, D.; Gerold, M.; Isler, D.; Mueller, M. Ro40-2148: A Novel Thermogenic β-Agonist with Anti-Obesity Activity. *Obesity in Europe 88, Proceedings of the 1st European Congress on Obesity*; Bjorntorp, P., Rossner, S., Eds.; John Libbey: London, 1989; pp 329–338.
(24) Arch, J. R. S.; Ainsworth, A. T.; Ellis, R. D. M.; Piercy, V.; Thody, V. E.; Thurlby, P. L.; Wilson, C.; Wilson, S.; Young, P. Treatment of Obesity with Thermogenic β-Adrenoceptor Agonists: Studies on BRL 26830A in Rodents. *Int. J. Obes.* 1984, *8*, Suppl. 1, 1–11.
(25) Connacher, A. A.; Jung, R. T.; Mitchell, P. E. G. Weight Loss in Obese Subjects on a Restricted Diet Given BRL 26380A, a New Atypical β-Adrenoceptor Agonist. *Br. Med. J.* 1988, *296*, 1217–1220.

of compound may be useful in the treatment of obesity if therapeutic effects are separated from unwanted β-adrenoceptor side effects.

Experimental Section

Organic extracts were dried with anhydrous $MgSO_4$. Melting points were obtained with a Büchi capillary melting point apparatus and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. ^1H NMR spectra were determined at 200 MHz in Me_2SO-d_6 using tetramethylsilane as the internal standard and are expressed as δ values (parts per million) for protons relative to TMS, using conventional abbreviations to describe signal types; all compounds examined gave the expected spectra.

Methyl 4-[2-[(2-Hydroxy-3-phenoxypropyl)amino]-2-methylethyl]benzoate (3). Methyl 4-(2-amino-2-methylethyl)benzoate[27] (0.6 g, 3.1 mmol) and 1,2-epoxy-3-phenoxypropane (**44**; 0.47 g, 3.1 mmol) in EtOH (50 mL) were heated under reflux for 36 h and then the solvent was evaporated. The residual gum was chromatographed on SiO_2 and the product, eluted with CH_2Cl_2 and CH_2Cl_2–MeOH 19:1 (R_f 0.25, CH_2Cl_2–MeOH 9:1), was converted to the hydrogen oxalate salt to yield 0.51 g (37%).

***N*-Benzyltyramine (45).** Tyramine (11.3 g, 82 mmol) and benzaldehyde (8.76 g, 82 mmol) in EtOH (400 mL) were stirred for 1.5 h at room temperature, and then $NaBH_4$ (4 g, 110 mmol) was added in 4 portions during 10 min. Stirring was continued for 3 h and then the solvent was evaporated. The residue was dissolved in water, the pH adjusted to 7, and the mixture extracted with EtOAc. The extract was dried and the solvent evaporated to give **45**, mp 141–143 °C (lit.[28] mp 143 °C), yield 15.2 g (81%). Anal. ($C_{15}H_{17}NO$) C, H, N.

***N*-[2-[4-(Benzyloxy)phenoxy]ethyl]acetamide (46).** 2-[4-(Benzyloxy)phenoxy]ethylamine[29] (16.2 g, 67 mmol) was dissolved in Ac_2O (100 mL) with warming and the solution was kept at room temperature for 18 h during which time **46** separated out. Compound **46** was isolated by filtration and then crystallized from MeOH, mp 132–134 °C, yield 9.6 g (50%). Anal. ($C_{17}H_{19}NO_3$) C, H, N.

***N*-[2-(4-Hydroxyphenoxy)ethyl]acetamide (47).** Compound **46** (9 g, 32 mmol) in 50% aqueous AcOH (180 mL) was hydrogenated at 60 °C and 60 psi in the presence of 5% Pd–charcoal (90 mg) until hydrogen uptake ceased. The mixture was filtered and the solvent was evaporated from the filtrate. The residue of **47** was crystallized from EtOAc–petroleum ether (bp 60–80 °C), mp 102–104 °C, yield 4.8 g (78%). Anal. ($C_{10}H_{13}NO_3$) C, H; N: calcd, 7.2; found, 6.7.

2-(4-Hydroxyphenoxy)ethylamine (48). Compound **47** (4.1 g, 21 mmol) and 5 N HCl (50 mL) were heated under reflux for 2 h, and then the acid was removed by evaporation under a vacuum. The residual solid hydrochloride of **48** was crystallized from a mixture of MeOH and EtOAc, mp 175 °C (lit.[30] mp 175 °C), yield 3.3 g (83%). Anal. ($C_8H_{12}ClNO_2$) C, H, Cl, N.

***N*-Benzyl-2-(4-hydroxyphenoxy)ethylamine (49).** (a) A mixture of 4-(2-bromoethoxy)phenol[31] (100 g, 0.46 mol), benzylamine (49.1 g, 0.46 mol), and triethylamine (46.8 g, 0.46 mol) in ethanol (600 mL) was heated under reflux for 60 h and then the solvent was evaporated. The residue was partitioned between 5% aqueous $NaHCO_3$ (300 mL) and EtOAc (300 mL). The organic layer was dried and then treated with ethereal HCl to precipitate the hydrochloride of **49**, which was crystallized from a mixture of MeOH and EtOAc, mp 179 °C, yield 37.0 g (29%). Anal. ($C_{15}H_{18}ClNO_2$) C, H, Cl, N.

(b) A stirred mixture of **48** (4.1 g, 22 mmol) and benzaldehyde (5.0 g, 47 mmol) in MeOH (50 mL) was cooled with ice, and $NaBH_4$ (2.0 g, 53 mmol) was added in portions over 1 h. After a further 18 h the solvent was evaporated and the residue was partitioned between 2 M HCl (200 mL) and EtOAc (100 mL). The acid layer was separated, made alkaline with potassium carbonate, and then extracted with EtOAc (3 × 50 mL). The extracts were dried, and the solvent was evaporated. The residual oil was dissolved in EtOAc and dry HCl gas was passed through the solution to precipitate the hydrochloride of **49**, yield 2.3 g (38%).,

***N*-[2-(Benzylamino)ethyl]-4-hydroxybenzamide (50).** A stirred mixture of *N*-(2-aminoethyl)-4-hydroxybenzamide[32] (12.0 g, 67 mmol) and benzaldehyde (10.44 g, 98 mmol) in MeOH (150 mL) was cooled with ice, and $NaBH_4$ (3.0 g, 79 mmol) was added in portions during 0.5 h. After a further 18 h the solvent was evaporated. Work up was as for **49** (method a) except that the free base **50** was isolated and crystallized from a mixture of MeOH and EtOAc, mp 131–133 °C, yield 10.4 g (58%). Anal. ($C_{16}H_{18}N_2O_2$) H, N; C: calcd, 71.1; found, 70.6.

Method A. Methyl [4-[2-[(2-Hydroxy-3-phenoxypropyl)amino]ethoxy]phenoxy]acetate (8). A mixture of **49** (2.5 g, 10 mmol; from 2.9 g **49**·HCl) and 1,2-epoxy-3-phenoxypropane (1.54 g, 10 mmol) in propan-2-ol (50 mL) was heated under reflux for 72 h. The solvent was removed by evaporation to give *N*-benzyl-*N*-[2-(4-hydroxyphenoxy)ethyl]-2-hydroxy-3-phenoxypropylamine (A) as an oil which was essentially pure by TLC (R_f 0.85; eluant 5% MeOH in CH_2Cl_2) and which was used without purification.

A mixture of A (4.0 g, 10 mmol), methyl bromoacetate (1.56 g, 10 mmol), anhydrous K_2CO_3 (1.7 g, 10 mmol), and KI (0.05 g, 3 mmol) was stirred under reflux in dry acetone (50 mL) for 24 h. The mixture was cooled and filtered to remove unwanted solid, and the solvent evaporated from the filtrate. The residue of crude methyl *N*-benzyl-[4-[2-[(2-hydroxy-3-phenoxypropyl)amino]ethoxy]phenoxy]acetate (3.4 g) was dissolved in MeOH (90 mL) and AcOH (30 mL) and hydrogenated in the presence of Pd–C (10%, 0.4 g) at about 20 bar and 60 °C for 48 h. The mixture was cooled and filtered, and the solvent evaporated from the filtrate. The residual oil was dissolved in MeOH and a solution of ether saturated with hydrogen chloride was added. The solid precipitate was crystallized from MeOH to give the hydrochloride of **8**, mp 170 °C, yield 0.22 g (5%). NMR: δ 3.08 (dd, 1 H, $CHCH_2NH$), 3.26 (dd, 1 H, $CHCH_2NH$), 3.36 (t, 2 H, $NHCH_2CH_2$), 3.7 (s, 3 H, CO_2CH_3), 4.0 (d, 2 H, OCH_2CH), 4.25 (m, 3 H, OCH_2CHOH), 4.74 (s, 2 H, OCH_2CO), 6.8–7.05 (m, 7 aromatic H), 7.31 (m, 2 aromatic H).

Method B. Methyl [4-[2-[[3-(2-Cyanophenoxy)-2-hydroxypropyl]amino]ethoxy]phenoxy]acetate (18). A mixture of **49**·HCl (5.5 g, 29.1 mmol) and Et_3N (3.0 g, 29.7 mmol) in 1-butanol (100 mL) was heated under reflux for 20 min and then a warm solution of 3-(2-cyanophenoxy)-1,2-epoxypropane (2.78 g, 15.9 mmol) in 1-butanol (50 mL) was added during 20 min. Heating under reflux was continued for 2 h and then the mixture was cooled and filtered. The solvent was evaporated from the filtrate and the residue was partitioned between CH_2Cl_2 (200 mL) and a saturated solution of $NaHCO_3$ (200 mL). The CH_2Cl_2 layer was washed with H_2O (2 × 60 mL), dried, and evaporated. The residual oil (3.8 g) was chromatographed on SiO_2 (100 g). Elution with MeOH–CH_2Cl_2 (1:19) gave 4-[2-[[3-(2-cyanophenoxy)-2-hydroxypropyl]amino]ethoxy]phenol as an oil (R_f 0.3, MeOH–CH_2Cl_2 1:9) with satisfactory NMR which was used

(26) Henny, C.; Schutz, Y.; Buckert, A.; Maylar, M.; Jéquier, E.; Felber, J. P. Thermogenic Effect of the New β-adrenoceptor Agonist RO 16-8714 in Healthy Male Volunteers. *Int. J. Obes.* **1987**, *11*, 473–483.

(27) Ainsworth, A. T.; Smith, D. G. Secondary Amines and Their Use in Pharmaceutical Preparations. *Eur.* Patent 6735, 1980, p 70.

(28) F. Hoffman-La Roche and Co., Manufacture of N-Alkaryl Compounds of p-Hydroxyphenylethylamine. German Patent 259874, 1912; *Chem. Abstr.* **1913**, *7*, 3197.

(29) Goldenberg, C.; Wandestrick, R.; Binon, F.; Charlier, R. Benzofuran Series. XLIX. Synthesis of Aralkyl- and Aryloxyalkyl(2,3-dihydro-2-benzofuryl)methylamines and Related Structures. *Chim. Ther.* **1973**, *8*, 259–270.

(30) Aktiebolaget Hassle, 3-[4-(2-Alkoxycarbonylaminoethyl)phenoxy]-1-isopropylaminopropan-2-ols, Methods for Their Preparation and Compositions Containing Them. U.K. Patent 1495422, 1977, p 7.

(31) Renshaw, R. R.; Hopkins, C. Y. Basis for the Physiological Activity of Onium Compounds. XII. Aryl Ethers of Choline. *J. Am. Chem. Soc.* **1933**, *55*, 1524–1528.

(32) Gutkowska, B.; Biniecki, S. Preparation of β-Aminoethylamides and Guanylhydrazides of Aromatic Acids. *Acta Pol. Pharm.* **1962**, *19*, 243–249; *Chem. Abstr.* **1963**, *59*, 7425e.

without further purification. This material (1.13 g, 3.5 mmol) and NaH (60%, 0.13 g, 3.3 mmol) in dry DMF (20 mL) were stirred at 0 °C for 10 min, and then methyl bromoacetate (0.52 g, 3.4 mmol) was added. After 2 h the reaction mixture was poured into water (200 mL) and saturated aqueous $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The extract was washed with 2 N NaOH (5 mL) and water (2 × 60 mL) and dried. The solvent was evaporated to give an oil (1.12 g) which was chromatographed on SiO_2 (100 g) and eluted with MeOH–CH_2Cl_2 (1:9). The main component, compound 18 (R_f 0.3, MeOH–CH_2Cl_2 1:9) was isolated and converted to the hydrochloride, yield 0.35 g (5%).

Method C. Methyl [4-[2-[(2-Hydroxy-3-phenoxypropyl)-amino]-2-methylethyl]phenoxy]acetate (4A and 4B). A mixture of 2-hydroxy-3-phenoxypropylamine (6.54 g, 3.9 mmol) and 1-[4-(carbomethoxymethoxy)phenyl]propan-2-one[33] (8.7 g, 3.9 mmol in toluene (130 mL) was heated under reflux for 4 h under azeotropic conditions to drive off H_2O and then the toluene was evaporated. The residue was dissolved in MeOH (130 mL) and hydrogenated at room temperature and pressure in the presence of prereduced Adam's catalyst (0.2 g). The mixture was filtered and the solvent evaporated from the filtrate. The residue (15.2 g) was converted to the hydrochloride with ethereal hydrogen chloride and repeatedly crystallized from MeOH–Et_2O (20 times) to give **4B** as a single racemate, yield 0.16 g (1%) containing 1% of the other racemate. Less rigorous purification gave **4A** as a mixture of racemates containing 37% of racemate **4B** by NMR, yield 2.4 g (15%).

(*S*)-(−)-Methyl [4-[2-[(2-Hydroxy-3-phenoxypropyl)-amino]ethoxy]phenoxy]acetate (*S*-8). A mixture of 8 (0.92 g, 2.4 mmol) and (−)-di-*p*-toluoyltartaric acid monohydrate (0.991 g, 2.4 mmol) in MeOH (15 mL) was evaporated to give a final volume of 5 mL. MeOAc (10 mL) was added and the mixture was again concentrated to a 5-mL volume. This treatment was repeated once more and then the mixture was left at ambient temperature for 18 h. The solid which separated was collected and the mother liquors were retained for the preparation of *R*-8. The solid was crystallized three times from MeOH–MeOAc to give *S*-8 hydrogen (−)-di-*p*-toluoyltartrate, mp 146–148 °C, $[\alpha]^{25}_D$ −80.3° (*c* 0.97 in MeOH). *S*-8 Hydrogen (−)-di-*p*-toluoyltartrate (0.33 g, 0.43 mmol) was partitioned between 5% w/v aqueous $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL). The organic layer was separated and dried, and the solvent evaporated. The residual solid (0.148 g, 32%) mp 114–116 °C, $[\alpha]^{23}_D$ −7.8° (*c* 0.97 in CH_2Cl_2) was dissolved in MeOAc and dry HCl gas passed through the solution to precipitate *S*-8·HCl, mp 156–157 °C, $[\alpha]^{23}_D$ −12.1° (*c* 1.0 in MeOH).

(*R*)-(+)-Methyl [4-[2-[(2-Hydroxy-3-phenoxypropyl)-amino]ethoxy]phenoxy]acetate (*R*-8). The mother liquors retained from the preparation of *S*-8 were evaporated and the residual solid was converted to free base with aqueous $NaHCO_3$ in the conventional way. This free base (0.53 g, 1.4 mmol) and (+)-di-*p*-toluoyltartaric acid monohydrate (0.57 g, 1.4 mmol) in MeOH (15 mL) were processed as in the preparation of *S*-8 to give *R*-8 hydrogen (+)-di-*p*-toluoyltartrate [mp 148–150 °C, $[\alpha]^{25}_D$ +81.6° (*c* 1.04 in MeOH)] and then *R*-8·HCl [mp 155–157 °C, $[\alpha]^{25}_D$ +12.2° (*c* 0.96 in MeOH)], total yield 75 mg (28%).

[4-[2-[(2-Hydroxy-3-phenoxypropyl)amino]ethoxy]phenoxy]acetic Acid (10). (a) A mixture of 8·HCl (507 mg, 1.23 mmol) and NaOH (100 mg, 2.5 mmol) in MeOH (5 mL) and H_2O (15 mL) was heated at 95–100 °C for 18 h. The MeOH was removed by distillation and then the pH of the residual solution was adjusted to 6 with 2 M HCl. 10 separated as an oil which solidified and was then crystallized from H_2O, yield 220 mg (45%).

(b) A suspension of 8·HCl (1.5 g, 3.65 mmol) in 2 M HCl (100 mL) was heated at 95–100 °C for 30 min. The clear solution was allowed to cool to ambient temperature and 10·HCl crystallized out, yield 1.20 g (83%).

Ethyl [4-[2-[(2-Hydroxy-3-phenoxypropyl)amino]ethoxy]phenoxy]acetate (11). Thionyl chloride (0.5 mL, 7.0 mmol) was added to a solution of 10·HCl (0.5 g, 1.22 mmol) in EtOH (20 mL) and the mixture was heated under reflux for 65 h. The solvent was evaporated and the residual solid crystallized to give 11, yield 0.36 g (68%).

Methyl *N*-Methyl-[4-[2-[(2-hydroxy-3-phenoxypropyl)-amino]ethoxy]phenoxy]acetate (43). Compound 8 (0.86 g, 2.3 mmol), 37% aqueous formaldehyde (6 mL, 74 mmol), and 98% formic acid (0.5 mL, 13 mmol) were heated at 100 °C for 3 h and then cooled. Aqueous $NaHCO_3$ (5%, 20 mL) was added and the mixture was extracted with CH_2Cl_2 (twice with 25 mL each time). The dried organic extract yielded **43**, which was converted to the hydrochloride, mp 112 °C, yield 0.45 g (46%).

2-[4-(Benzyloxy)phenoxy]-2-methylpropanol (52). A solution of compound **51** (12.6 g, 0.042 mol)[34] in toluene (50 mL) was added during 30 min to a 3.4 M solution of sodium bis(2-methoxyethoxy)aluminum hydride in toluene (Red-Al, 14 mL) in added toluene (150 mL) stirred under argon at −5 °C to 0 °C. The mixture was stirred for 30 min more at 0 °C, cooled to −10 °C, and the excess reagent decomposed by the dropwise addition of a solution of MeOH (10 mL) in toluene (45 mL). The reaction mixture was poured into ice–water (500 mL) and then stirred for 1 h. The mixture was filtered through a Celite pad and the pad was washed with Et_2O (3 × 100 mL). The aqueous layer was extracted with Et_2O (2 × 50 mL). The combined Et_2O extracts were washed with brine (2 × 50 mL) and dried, and the solvent evaporated. The residue was crystallized from a mixture of EtOAc and hexane to give **52**, mp 75–77 °C, yield 10.8 g (94%). Anal. ($C_{17}H_{20}O_3$) C, H.

2-[4-(Benzyloxy)phenoxy]-2-methylpropionaldehyde (53). A solution of **52** (10.0 g, 36.7 mmol) in CH_2Cl_2 (80 mL) was added with stirring to a suspension of pyridinium chlorochromate (12.0 g, 55.6 mmol) in CH_2Cl_2 (180 mL) at 0 °C. The mixture was stirred at room temperature for 16 h and then the organic layer was decanted. The product was isolated by dry column flash chromatography on silica gel (Merck silica gel 60H, Art. 7736, eluant CH_2Cl_2) and crystallized from hexane to give **53**, mp 54–56 °C, yield 7.8 g (78.6%). Anal. ($C_{17}H_{18}O_3$) C, H.

4-[1,1-Dimethyl-2-[(2-hydroxy-3-phenoxypropyl)amino]-ethoxy]phenol (55). Aldehyde **53** (6.62 g, 24.5 mmol) and 2-hydroxy-3-phenoxypropylamine (4.1 g, 24.5 mmol) in toluene (200 mL) were heated for 3 h under azeotropic conditions to drive off water and then the solvent was evaporated. The residue was dissolved in MeOH (300 mL), and $NaBH_4$ (2.0 g, 52.9 mmol) was added with stirring. After 16 h the solvent was evaporated and 2 N HCl (300 mL) was added to the residue. The mixture was extracted with CH_2Cl_2 (3 × 100 mL). The combined extracts were washed, dried, and evaporated. The residue was triturated with EtOAc to give solid crude **54** (1.9 g). The crude material (1.56 g) in EtOH (100 mL) and AcOH (30 mL) was hydrogenated in the presence of 10% Pd–charcoal (200 mg) until hydrogen uptake ceased. The mixture was filtered and the solvent evaporated from the filtrate. The residue was dissolved in EtOAc (10 mL) and a slight excess of ethereal HCl added. The hydrochloride of **55** which separated out was crystallized from MeOH–EtOAc, mp 165–167 °C, yield 1.0 g (11.1%). Anal. ($C_{19}H_{26}ClNO_4$) C, H, Cl, N.

Methyl [4-[1,1-Dimethyl-2-[(2-hydroxy-3-phenoxypropyl)amino]ethoxy]phenoxy]acetate (38). NaH (60% dispersion in mineral oil, 0.108 g, 45 mmol) was added to a stirred solution of compound **55** (0.9 g, 27.2 mmol) in DMF (30 mL). After 30 min, methyl bromoacetate (0.414 g, 27.1 mmol) was added and 4 h later the mixture was added to water (200 mL) and extracted with Et_2O (2 × 100 mL). The combined extracts were washed with water (8 × 30 mL) and dried, and the Et_2O was evaporated. The residual oil was converted to **38**·HCl with ethereal HCl.

4-(Benzyloxy)-3-chloropropionanilide (56). Triethylamine (0.51 g, 0.05 mol) was added to a stirred suspension of 4-(ben-

(33) Ainsworth, A. T.; Smith, D. G. Ethanamine Derivatives and Their Use in Pharmaceutical Compositions. Eur. Patent 23385, 1981, p 25.

(34) Fukami, H.; Nakase, Y.; Sako, Y.; Miyoshi, F.; Onishi, K. Anticholesteremic 2-Methyl-2-phenoxypropionic Acid Derivatives. German Patent 2356655, 1974; *Chem. Abstr.* 1974, *81*, 49435*g*.

(35) Diana, G. D.; Carabateas, P. M. Phenylene Bis(diketones). German Patent 2802281, 1978; *Chem. Abstr.* 1978, *89*, 179696*u*.

(36) Diana, G. D.; Carabateas, P. M.; Salvador, J.; Williams, G. L.; Zalay, E. S.; Pancic, F.; Steinberg, B. A.; Collins, J. C. Antiviral Activity of Some β-Diketones. 3. Aryl Bis(β-Diketones). *J. Med. Chem.* 1978, *21*, 689–692.

zyloxy)aniline hydrochloride (11.75 g, 0.05 mol) in toluene (200 mL) and to the resulting solution was added 3-chloropropionyl chloride (6.35 g, 0.05 mol) in toluene (200 mL) during 30 min. After a further 30 min the toluene layer was washed with water (3 × 100 mL) and dried and the solvent evaporated. The residual solid **56** was crystallized from a mixture of EtOAc and hexane, mp 139–140 °C, yield 4.6 g (32%). Anal. ($C_{16}H_{16}ClNO_2$) C, H, Cl, N.

4-(Benzyloxy)-3-[(2-hydroxy-3-phenoxypropyl)amino]propionanilide (57). A mixture of **56** (1.96 g, 6.8 mmol), 2-hydroxy-3-phenoxypropylamine (1.13 g, 6.8 mmol), and triethylamine (0.68 g, 6.8 mmol) in EtOH (100 mL) was refluxed for 60 h and then the solvent was evaporated. CH_2Cl_2 (100 mL) was added and the organic layer was washed successively with aqueous saturated K_2CO_3 solution (2 × 20 mL) and water (3 × 20 mL). The organic layer was dried and the solvent evaporated to give a solid which was crystallized from MeOH to give **57**, mp 143–145 °C, yield 1.35 g (47.5%). Anal. ($C_{25}H_{28}N_2O_4$) C, H, N.

Methyl [4-[[3-[(2-Hydroxy-3-phenoxypropyl)amino]propionyl]amino]phenoxy]acetate (42). Compound **57** (1.17 g, 2.8 mmol) in EtOH (50 mL) was hydrogenated in the presence of 10% Pd–charcoal (100 mg) until hydrogen uptake ceased. The mixture was filtered and the solvent was evaporated from the filtrate. The residue of crude **58** (0.52 g, 1.6 mmol) was dissolved in DMF (20 mL) and stirred while NaH (60% dispersion in mineral oil, 63 mg, 1.6 mmol) was added, followed by methyl bromoacetate (0.24 g, 1.6 mmol). The mixture was stirred for 16 h, poured into H_2O (200 mL), and extracted with CH_2Cl_2 (2 × 50 mL). The extract was washed with water (6 × 50 mL) and dried, and the solvent evaporated. The residual **42** was converted to the hydrochloride which formed an amorphous powder from MeOH–Et_2O, yield 0.18 g (15%).

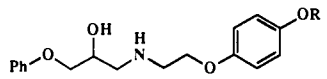
Selective β_3-Adrenergic Agonists of Brown Adipose Tissue and Thermogenesis. 2. [4-[2-[(2-Hydroxy-3-phenoxypropyl)amino]ethoxy]phenoxy]acetamides

Ralph Howe,* Balbir S. Rao, Brian R. Holloway, and Donald Stribling

ICI Pharmaceuticals, Alderley Park, Macclesfield, Cheshire SK10 4TG, England. *Received September 12, 1991*

The ester methyl [4-[2-[(2-hydroxy-3-phenoxypropyl)amino]ethoxy]phenoxy]acetate (1) (R^1 = OMe) had previously been identified as the most interesting member of a series of selective β_3-adrenergic agonists of brown adipose tissue and thermogenesis in the rat. In vivo it acts mainly via the related acid 1 (R^1 = OH). Amides have been examined to determine whether they have advantages over the ester. In particular, in the rat and dog the half-lives of amides of appropriate potency were no longer than those of the ester. The amide (*S*)-4-[2-[(2-hydroxy-3-phenoxypropyl)amino]ethoxy]-*N*-(2-methoxyethyl)phenoxyacetamide [*S*-27, ICI D7114] was selected as having properties consistent with a sustained-release formulation should that prove necessary. Unlike the ester it is resistant to hydrolysis in the gut lumen. Further testing of ICI D7114 has shown that in the rat, cat, and dog it stimulates the β_3-adrenergic receptor in brown adipose tissue at doses lower than those at which it affects β_1- and β_2-adrenergic receptors in other tissues. Slimming effects were observed in the dog. ICI D7114 may be a selective thermogenic agent in man and may be useful in the treatment of obesity and diabetes.

In the previous paper[1] ester 1 (R^1 = OMe) was identified as the most interesting member of a series of selective β_3-adrenergic agonists of brown adipose tissue (BAT) and thermogenesis in the rat. In vivo it acts mainly via the related acid 1 (R^1 = OH). It was of interest to determine whether amides 1 ($R^1 = NR^1R^2$)[2] related to the acid had thermogenic activity and if so, whether they had advantages over the ester.



1 R = CH_2COR^1

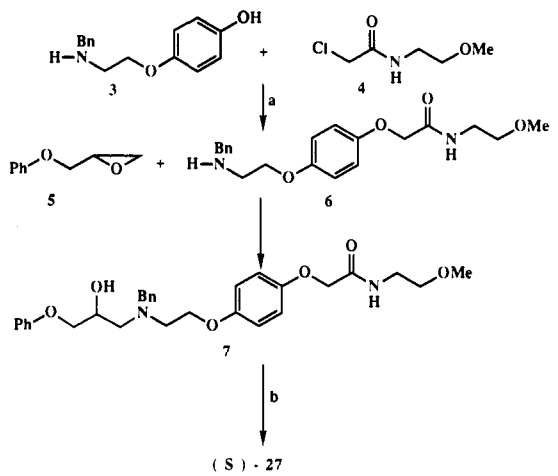
2 R = H

Chemistry

The amides listed in Tables I and II were generally made by the action of a large excess of the appropriate amine on an ester (method A). The esters are described in Part 1.[1] Various reaction conditions were encompassed within method A (see Experimental Section). Some amides were made by alkylating phenol **2**[1] with a chloroacetamide (method B). For two compounds a water-soluble carbodiimide was used to form the amide from an acid and an amine (method C).[3]

Amide enantiomers were generally prepared from the corresponding ester enantiomer and the appropriate amine, which in the case of *S,S*-**43** was the *S*-amine. Compound

Scheme I[a]



[a] (a) NaH; (b) H_2, Pd–C.

(1) Holloway, B. R.; Howe, R.; Rao, B. S.; Stribling, D. Selective β_3-Adrenergic Agonists of Brown Adipose Tissue and Thermogenesis. [4-[2-[(2-Hydroxy-3-phenoxypropylamino]ethoxy]phenoxy]acetates. *J. Med. Chem.*, previous paper in this issue.

(2) Holloway, B. R.; Howe, R.; Rao, B. S.; Stribling, D. Amide Derivatives. Eur. Patent 254532, 1988.

(3) Miller, M. J.; Bajwa, J. S.; Mattingly, P. G.; Peterson, K. Enantioselective Syntheses of 3-Substituted 4-(Alkoxycarbonyl)-2-azetidinones from Malic Acid. *J. Org. Chem.* **1982**, *47*, 4928–4933.

0022-2623/92/1835-1759$03.00/0