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

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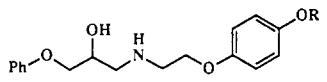
The ester methyl [4-[2-[(2-hydroxy-3-phenoxypropyl)amino]ethoxy]phenoxy]acetate (1) (R^1 = OMe) had previously been identified as the most interesting member of a series of selective β_3-adrenergic agonists of brown adipose tissue and thermogenesis in the rat. In vivo it acts mainly via the related acid 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

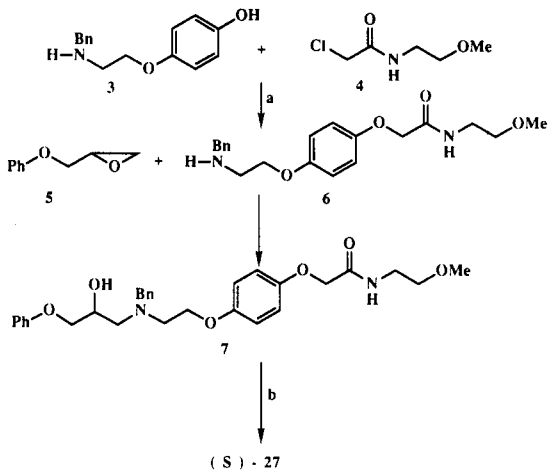
2 R = H

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.

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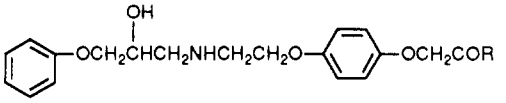
Table I



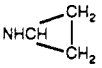
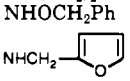
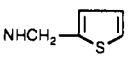
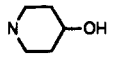
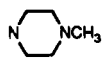
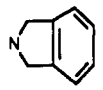
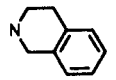
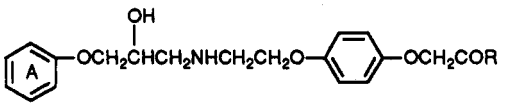
compd	R	form	crystn solvent	mp, °C	formula	analyses	methods[a]	po: test B; GDP ED_{50}, mg kg^{-1}	po: test C; SI (bpm)
9[b]	NH_2	base	MeOH	142–144	$C_{19}H_{24}N_2O_5$	C, H, N	A	0.3	>100 (455)
		HCl	MeOH	223–225	$C_{19}H_{25}ClN_2O_5$	C, H, Cl, N			
10	NHMe	base	EtOAc	114–115	$C_{20}H_{26}N_2O_5$	C, H, N	A	1.2	>50 (493)
S-10	NHMe	base[c]	EtOAc	114–116	$C_{20}H_{26}N_2O_5$	C, H, N	A	0.57	>100 (418)
11	NHEt	base	EtOAc	104–105	$C_{21}H_{28}N_2O_5$	C, H, N	A[d]	0.5	>100 (459)
12	$NHPr^n$	base	EtOAc	105–107	$C_{22}H_{30}N_2O_5$	C, H, N	A	0.2	>100 (438)
		HCl	MeOH/EtOAc	192	$C_{22}H_{31}ClN_2O_5$	C, H, Cl, N			
13	$NHPr^i$	base	MeOAc/hex.	110	$C_{22}H_{30}N_2O_5$	C, H, N	A[d]	0.4	>100 (464)
		HCl	MeOH/EtOAc	196–198	$C_{22}H_{31}ClN_2O_5$	C, H, Cl, N			
14	$NHBu^n$	base	EtOAc	106	$C_{23}H_{32}N_2O_5$	C, H, N	A	1.5	>100 (426)
15	$NHBu^i$	base	EtOAc	104	$C_{23}H_{32}N_2O_5$	C, H, N	A	3.2	not tested
		HCl	MeOH/EtOAc	197–198	$C_{23}H_{33}ClN_2O_5$	C, H, Cl, N			
16	$NHBu^s$	HCl	MeOH/EtOAc	167–168	$C_{23}H_{33}ClN_2O_5 \cdot {}^1/_4H_2O$	C, H, Cl, N, H_2O	A[e]	1.7	not tested
17	$NHBu^t$	base	EtOAc/hex.	77	$C_{23}H_{32}N_2O_5$	C, H, N	B[f]	not tested[g]	
18	$NHCH_2Bu^t$	base	EtOAc	96	$C_{24}H_{34}N_2O_5$	C, H, N	A	not tested[h]	
19	$NH(CH_2)_5CH_3$	base	EtOAc	106–107	$C_{25}H_{36}N_2O_5$	C, H, N	A	not tested[i]	
20	$NHCH_2CH{=}CH_2$	base	EtOAc	98	$C_{22}H_{28}N_2O_5$	C, H, N	A	0.64	>100 (459)
		HCl	MeOH/EtOAc	180	$C_{22}H_{29}ClN_2O_5$	C, H, Cl, N			
21		base	EtOAc	107	$C_{22}H_{28}N_2O_5$	C, H, N	A	0.79	>50 (439)
22		base	EtOAc	103	$C_{24}H_{32}N_2O_5$	C, H, N	A[j]	3.1	>10 (451)
23	$NH(CH_2)_2OH$	base	MeOAc	120–121.5	$C_{21}H_{28}N_2O_6$	C, H, N	A	0.67	>100 (483)
		HCl	MeOH/EtOAc	182–183	$C_{21}H_{29}ClN_2O_6$	C, H, Cl, N			
S-23	$NH(CH_2)_2OH$	base[k]	EtOAc	111–112.5	$C_{21}H_{28}N_2O_6$	C, H, N	A	0.77	>50 (462)
24	$NH(CH_2)_3OH$	base	MeOH/EtOAc	103–104	$C_{22}H_{30}N_2O_6$	C, H, N	A[l]	0.47	>100 (497)
25	$NHCH(CH_3)CH_2OH$	base	EtOAc	114–115	$C_{22}H_{30}N_2O_6 \cdot {}^1/_3H_2O$	C, H, N, H_2O	A	0.85	>50 (452)
26	$NHC(CH_3)_2CH_2OH$	base	EtOAc	113–115	$C_{23}H_{32}N_2O_6$	C, H, N	A[l]	not tested[m]	
		HCl	MeOH/EtOAc	138–140	$C_{23}H_{33}ClN_2O_6$	C, H, Cl; N[n]			
27	$NH(CH_2)_2OCH_3$	base	EtOAc	96–97	$C_{22}H_{30}N_2O_6$	C, H, N	A[j]	0.24	>100 (443)
		HCl	MeOH/EtOAc	168	$C_{22}H_{31}ClN_2O_6 \cdot {}^1/_2H_2O$	C, H, Cl, N, H_2O			
S-27	$NH(CH_2)_2OCH_3$	HCl[o]	MeOH/EtOAc	169–70	$C_{22}H_{31}ClN_2O_6$	C, H, Cl, N	A[l,p]	0.34	>100 (430)
R-27	$NH(CH_2)_2OCH_3$	HCl[q]	MeOH/EtOAc	169–170	$C_{22}H_{31}ClN_2O_6$	C, H, Cl, N	A	69.9	
28	$NH(CH_2)_3OCH_3$	base	EtOAc	88	$C_{23}H_{32}N_2O_6$	C, H, N	A	0.83	>100 (451)
29	$NHCH(CH_3)CH_2OCH_3$	HCl	MeOH/EtOAc	153	$C_{23}H_{33}ClN_2O_6$	C, H, Cl, N	A[r]	3.88	
30	$NH(CH_2)_2NH_2$	2HCl	MeOH	240	$C_{21}H_{31}Cl_2N_3O_5 \cdot {}^2/_5H_2O$	C, H, Cl, N, H_2O	A[r]	not tested[s]	
31	$NHCH_2CONH_2$	HCl	MeOH	208.5	$C_{21}H_{28}ClN_3O_6$	C, H, Cl, N	A[e]	1.18	>50 (442)
32	NHOH	HCl	MeOH	190–191	$C_{19}H_{25}ClN_2O_6$	C, H, Cl, N	A[d]	0.5	>100 (424)
33	$NHNH_2$	base	MeOH	125–127	$C_{19}H_{25}N_3O_5$	C, H, N	A[d]	1.15	
34	NHPh	base	EtOAc	119–121	$C_{25}H_{28}N_2O_5$	C, H, N	B[t]	1.38	
35	NHPh-2,6-$(CH_3)_2$	base	EtOAc	123–125	$C_{27}H_{32}N_2O_5$	C, H, N	B[u]	not tested[v]	
36	$NHCH_2Ph$	base	MeOAc	112–113	$C_{26}H_{30}N_2O_5$	C, H, N	A	0.25	>100 (452)
		HCl	MeOH/MeOAc	190–192	$C_{26}H_{31}ClN_2O_5$	C, H, Cl, N			
37	$NHCH_2Ph$-4-CH_3	base	EtOAc	119	$C_{27}H_{32}N_2O_5$	C, H, N	A[l]	not tested[v]	
38	$NHCH_2Ph$-4-OCH_3	base	EtOAc	124	$C_{27}H_{32}N_2O_6$	C, H, N	A[l]	not tested[v]	
39	$NHCH_2Ph$-2-Cl	HCl	MeOH	192–194	$C_{26}H_{30}Cl_2N_2O_5$	C, H, Cl, N	A[r]	not tested[w]	
40	$NHCH_2Ph$-4-Cl	base	MeOH	126	$C_{26}H_{29}ClN_2O_5$	C, H, Cl, N	A[r]	0.92	>50 (470)
		HCl	MeOH/EtOAc	192	$C_{26}H_{30}Cl_2N_2O_5$	C, H, Cl, N			
41	$NHCH_2Ph$-2,4-Cl_2	base	EtOAc	105	$C_{26}H_{28}Cl_2N_2O_5$	C, H, Cl, N	B[f]	2.77	
		HCl	EtOAc/Et_2O[x]	193	$C_{26}H_{29}Cl_3N_2O_5$	C, H, Cl, N			
42	$NH(CH_2)_2Ph$	base	MeOH	133–134	$C_{27}H_{32}N_2O_5$	C, H, N	A[l]	1.23	>50 (447)
S,S-43	$NHCH(CH_3)Ph$	HCl[y]	EtOAc	172–174	$C_{27}H_{33}ClN_2O_5$	C, H, Cl, N	A[r]	0.96	>10 (431)
44	$NH(CH_2)_2OPh$	base	EtOAc/hex.	105	$C_{27}H_{32}N_2O_6$	C, H, N	A[d]	0.72	>100 (435)
45	$NHOCH_2Ph$	base	EtOAc	113–115	$C_{26}H_{30}N_2O_6$	C, H, N	C	0.48	
46		base	MeOH/EtOAc	176	$C_{24}H_{29}ClN_2O_6 \cdot {}^1/_2H_2O$	C, H, Cl, N, H_2O	A[e]	1.53	
47		HCl	MeOH/EtOAc	181	$C_{24}H_{29}ClN_2O_5S$	C, H, Cl, N, S	C	0.69	
48	$N(CH_3)_2$	base	EtOAc	84	$C_{21}H_{28}N_2O_5 \cdot {}^4/_5H_2O$	C, H, N, H_2O	A	1.4	>50 (481)
		HCl	MeOH/EtOAc	144–146	$C_{21}H_{29}ClN_2O_5$	C, H, Cl, N			
49	$N(CH_3)(CH_2)_2OH$	base	EtOAc	82	$C_{22}H_{30}N_2O_6 \cdot {}^1/_4EtOAc$	C, H, N	A[r]	not tested[z]	
50	$N(CH_3)(CH_2)_2OCH_3$	base	EtOAc/hex.	73–75	$C_{23}H_{32}N_2O_6$	C, H, N	B	not tested[z]	
51	$N(CH_3)CH_2Ph$	base	EtOAc/hex.	105	$C_{27}H_{32}N_2O_5$	C, H, N	B[aa]	8.6	
52	$N(CH_2CH_3)_2$	base	EtOAc/hex.	60–62	$C_{23}H_{32}N_2O_5 \cdot {}^1/_2H_2O \cdot {}^1/_6C_6H_{14}$	C, H, N, H_2O	B[bb]	1.16	33

Table I (Continued)

compd	R	form	crystn solvent	mp, °C	formula	analyses	methods[a]	po: test B; GDP ED_{50}, mg kg^{-1}	po: test C; SI (bpm)
53		base	EtOAc/hex.	66	$C_{23}H_{30}N_2O_5 \cdot {}^3/_4H_2O$	C, H, N, H_2O	A[d]	1.8	>50 (455)
		HCl	MeOH/EtOAc	167.5	$C_{23}H_{31}ClN_2O_5$	C, H, Cl, N			
54		base	EtOAc	68	$C_{24}H_{32}N_2O_5$	C, H, N	A[d]	0.4	>100 (445)
		HCl	MeOH/EtOAc	184–186	$C_{24}H_{33}ClN_2O_5$	C, H, Cl, N			
55		HCl	MeOH/EtOAc	147	$C_{24}H_{33}ClN_2O_6$	C, H, Cl, N	A[r]	not tested[z]	
56		HCl	MeOH/EtOAc	155–157	$C_{23}H_{31}ClN_2O_6$	C, H, Cl, N	A[j]	0.54	>100 (448)
		oxalate	MeOH	168–169	$C_{24}H_{31}N_2O_8 \cdot {}^1/_4H_2O$	C, H, N, H_2O			
57		base	EtOAc/hex.	50–52	$C_{24}H_{33}N_3O_5 \cdot {}^1/_2H_2O \cdot {}^1/_3C_6H_{14}$	C, H, N, H_2O	A[d]	not tested[cc]	
58		base	EtOAc	113	$C_{27}H_{30}N_2O_5$	C, H, N	B[dd]	1.3	
59		HCl	MeOH/EtOAc	154–156	$C_{28}H_{33}ClN_2O_5 \cdot {}^1/_4H_2O$	C, H, Cl, N, H_2O	A[d]	0.44	>100 (485)
60		HCl	MeOH/EtOAc	139	$C_{22}H_{29}ClN_2O_6$	C, H, Cl, N	B	0.49	
61[ee]	NH_2	HCl	MeOH	206–208	$C_{19}H_{25}ClN_2O_5$	C, H, Cl, N	A	not tested[ff]	
62[ee]	$NHCH_3$	HCl	MeOH/EtOAc	184–186	$C_{20}H_{27}ClN_2O_5$	C, H, Cl, N	A[d]	0.31	74
63[gg]	$NHCH_3$	base	EtOAc	98.5	$C_{21}H_{28}N_2O_5$	C, H, N	A	0.25	>10 (470)
64[gg]	$NHCH_2CH{=}CH_2$	base	EtOAc/hex.	97–99	$C_{23}H_{30}N_2O_5$	C, H, N	A	1.03	>20 (473)

[a] Methods refer to Experimental Section. [b] Compounds are racemates unless specified otherwise. When the compound has two asymmetric centers the two racemates were not separated unless specified otherwise. [c] $[\alpha]^{23}_D$ −8.9° (*c* 0.99, EtOH). [d] Heated under reflux. [e] Heated under reflux, solvent EtOH. [f] Intermediate chloroacetamide.[18] [g] Test D; 10 mg kg^{-1}, 2.1 ± 1.2 mL of O_2 min^{-1} $(kg^{0.75})^{-1}$. [h] Test D; 10 mg kg^{-1}, 3.2 ± 0.6 mL of O_2 min^{-1} $(kg^{0.75})^{-1}$. [i] Test B; 10 mg kg^{-1}, sc, not active. [j] Heated at 100 °C, solvent toluene. [k] $[\alpha]^{23}_D$ −7.1° (*c* 0.99, EtOH). [l] Ambient temperature, excess amine, no solvent. [m] Test D; 10 mg kg^{-1}, 2.8 ± 0.8 mL of O_2 min^{-1} $(kg^{0.75})^{-1}$. [n] N: calcd, 5.4; found, 6.0. [o] $[\alpha]^{23}_D$ −10.1° (*c* 0.9, MeOH), made by method A. [p] Also prepared starting from **5** and **6**, see Experimental Section. [q] $[\alpha]^{23}_D$ +10.6° (*c* 1.0, MeOH). [r] Heated at 100 °C, excess amine, no solvent. [s] Test D; 1 mg kg^{-1}, not active. [t] Intermediate chloroacetamide.[19] [u] Intermediate chloroacetamide.[20] [v] Test A; 10 mg kg^{-1}, sc, not active. [w] Test D; 10 mg kg^{-1}, 4.1 ± 0.9 mL of O_2 min^{-1} $(kg^{0.75})^{-1}$. [x] Solid by trituration, not crystallized. [y] $[\alpha]^{23}_D$ −26.1° (*c* 1.0, MeOH). [z] Test D; 1 mg kg^{-1}, not active. [aa] Intermediate chloroacetamide.[21] [bb] Intermediate chloroacetamide.[22] [cc] Test D; 1.9 ± 0.8 mL of O_2 min^{-1} $(kg^{0.75})^{-1}$. [dd] Intermediate chloroacetamide.[23] [ee] Oxyacetamide side chain in the 3 rather than the 4 position. Ester intermediate described in ref 1. [ff] Test B; tested sc, ED_{50} ≥ 0.39 mg kg^{-1}, SI > 100 (475). [gg] Compounds of type **8**, with a methyl substituent in the linking group. Ester intermediate was compound **36** in ref 1.

Table II



compd	ring A subst	R	form	crystn solvent	mp, °C	formula	analyses	methods[a]	po: test B; GDP ED_{50}, mg kg^{-1}	po: test C; SI (bpm)
65[b]	2-F	NH_2	base	EtOAc	123	$C_{19}H_{23}FN_2O_5$	C, H, F, N	A	2.24	>10 (448)
66	2-F	$NHCH_3$	HCl	MeOH/EtOAc	168–169	$C_{20}H_{26}ClFN_2O_5$	C, H, Cl, N	A[c]	1.1	>50 (453)
67	2-F		HCl	MeOH/Et_2O	144–146	$C_{24}H_{32}ClFN_2O_5$	C, H, Cl, N	A[c]	7.9	
68	2,6-F_2	$NHCH_3$	HCl	MeOH/Et_2O	171–172	$C_{20}H_{25}ClF_2N_2O_5$	C, H, Cl, N	A[d]	not active[e]	
69	4-OH	NHMe	base	MeOH/EtOAc	125–127	$C_{20}H_{26}N_2O_6$	C, H, N	A	not tested[f]	
70	4-OH	$NH(CH_2)_2OCH_3$	HCl	MeOH/EtOAc	166–168	$C_{22}H_{31}ClN_2O_7$	C, H, Cl, N	A[g]	not active[e]	
S-70	4-OH	$NH(CH_2)_2OCH_3$	HCl[h]	MeOH/EtOAc	166–168	$C_{22}H_{31}ClN_2O_7$	C, H, Cl, N	A[g]	4.16	

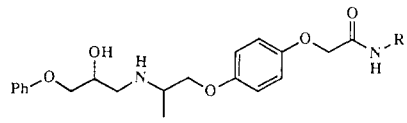
[a] Methods refer to Experimental Section. [b] Compounds are racemates unless specified otherwise. [c] Heated under reflux. [d] Heated under reflux, solvent EtOH. [e] Test B, at 100 mg kg^{-1}. [f] Test D, 10 mg kg^{-1}, not active. [g] Heated at 100 °C, excess amine, no solvent. [h] $[\alpha]^{23}_D$ −9.6° (*c* 1.0, MeOH).

S-**27** was also prepared by debenzylation of the tertiary amine **7** formed from (*S*)-1,2-epoxy-3-phenoxypropane (**5**) and amine **6** (Scheme I). Similarly enantiomer *S*-**70** was made from (*S*)-1-[4-(benzyloxy)phenoxy]-2,3-epoxypropane[4] and amine **6**, followed by bis-debenzylation using 10% Pd–C and ammonium formate.[5]

Two compounds of general formula **8** (i.e., **63**, R = Me, and **64**, R = $CH_2CH{=}CH_2$) having a methyl substituent on the carbon atom of the linking group to the nitrogen atom were made for comparison with their unsubstituted analogues **10** and **20**.

(4) Jones, G.; Taylor, D. C. Xamoterol Esters as Prodrugs and Their Preparation. Eur. Patent 307115, 1989.

(5) Ram, S.; Ehrenkaufer, R. E. Ammonium Formate in Organic Synthesis: A Versatile Agent in Catalytic Hydrogen Transfer Reactions. *Synthesis* **1988**, 91–95.



8

Literature references are given in Table I for most of the chloroacetamide intermediates used in method B; the new ones used for compounds **50** and **60** were made as described for compound **4**.

Pharmacology

The screening tests A, B, and C used to identify compounds of interest were described in the previous paper.[1] Test A, which detects increases in core temperature of post-cold-adapted rats, was rarely used in this study because an active series was being pursued. A further test, D, which measures the increase in oxygen consumption in post-cold-adapted rats, was occasionally used as a screening test. In this test rats were cold adapted at 4 °C for 4 days to increase their capacity for thermogenesis. They were then transferred to a warm environment at 23 °C for 2 days. On the following day, the basal metabolic rate of groups of six animals was determined using a close-circuit oxygen-consumption apparatus of the type described by Arundel et al.[6] The rats were then dosed (orally or subcutaneously) with test compound as a solution or suspension in 0.45% w/v aqueous sodium chloride, 0.25% w/v Polysorbate 80. Metabolic rate was then determined for at least 1 h after dosing and expressed[7] as mL of O_2 min^{-1} $(kg^{0.75})^{-1}$. Compounds were considered active in this test if they caused a significant increase in metabolic rate as compared to control animals (Student's t-test: $p < 0.05$) dosed only the solution or suspension vehicle.

Not all the tests were carried out on each compound; the aim was to obtain sufficient information to judge whether a compound merited further investigation.

Screening Results. Methyl ester **1** (R^1 = OMe) and acid **1** (R^1 = OH) refer to compounds described in the previous paper.[1] Some of the data related to them are from that paper with new information (test D) added where pertinent. Methyl ester **1** showed an oral GDP ED_{50} (test B) of 0.12 mg kg^{-1} and a selectivity index (test C) of >100 (the maximal heart rate being 462 bpm). In test D at 0.8 mg kg^{-1} it caused an increase in oxygen consumption of 4.8 ± 0.8 mL min^{-1} $(kg^{0.75})^{-1}$. It is clear from Table I that amides of comparable potency and selectivity to methyl ester **1** (R^1 = OMe) could be obtained; over 20 compounds had an ED_{50} of <1 mg kg^{-1} in test B. There are no consistent structure–activity relationships within the data. In those compounds containing a single alkyl group on the amide nitrogen atom, potency was generally lower when the number of carbon atoms was greater than three (e.g. compounds **14–19** and **22**). That this lowering was not a feature of chain length was suggested by the beneficial effect of having an ether oxygen atom in a chain of four or five atoms (e.g. compounds **27** and **28**). The high potency of benzyl compound **36** was surprising.

The observed result in test B is of course a composite of the potency of the parent amide and acid **1** (R^1 = OH) formed from it by hydrolysis in vivo. Thus, inter alia, the rates of absorption and of hydrolysis of the amide will be contributing factors and these in turn will have been influenced by such factors as solubility and partitioning.

A key question was how to select the best compound to study in more detail.

Table III

compd	GDP ED_{50}, mg kg^{-1}	log P^a	solubility[b], mg mL^{-1}
12	0.2	2.4	0.6
27	0.24	1.7	11
36	0.25	3.2	0.04
9	0.3	1.1	0.4
13	0.4	2.4	0.9
54	0.4	2.6	2.0
59	0.44	3.6	0.06
24	0.47	0.5	36[c]

[a] Octanol–water. [b] Measured on hydrochloride salts in aqueous buffer (0.15 M sodium chloride, 0.01 M sodium dihydrogen phosphate) at pH 7. [c] Estimated using the Yalkowsky approach.[24]

Further Considerations. One feature of methyl ester **1** (R^1 = OMe) was that it had a relatively short half-life in both the rat ($t_{1/2} \sim 1$ h) and the dog ($t_{1/2} \sim 1.3$ h),[8] which would predict a short half-life in man. On the basis of the greater stability to chemical hydrolysis of amides relative to esters, it was considered that amides may have somewhat longer half-lives. For a few compounds of appropriate potency in the GDP-binding test which were examined in the rat and the dog this proved not to be so. Amides which exhibited relative resistance to hydrolysis when incubated with dog liver microsomes appeared also to show resistance to hydrolysis in vivo, although there were exceptions.[8]

Accordingly, the possibility of a sustained-release-formulation approach was considered as a means of achieving an appropriate duration of action in man. This approach led to the inclusion of additional selection criteria which were based on optimal properties compatible with sustained-release formulation in a microspheroid preparation including (1) log P (octanol)[9] > 1 and preferably ~1.5, to assure good absorption throughout the GI tract; (2) solubility around 10 mg mL^{-1}, based on experience with another sustained-release formulation; and (3) resistance to hydrolysis in the gut lumen. As well as satisfying these criteria, the compound had to be as potent as possible.

Oral potency (GDP ED_{50} = 3.5 mg kg^{-1})[1] as well as the first two criteria excluded parent acid **1** (R′ = OH) from consideration (log D, i.e. log P corrected for the ionized species,[10] −3.0; solubility, 0.42 mg kg^{-1}, measured as for compounds in Table III).[11] Methyl ester **1** (R^1 = OMe) is broken down by gut juices[8] to yield acid **1** (R^1 = OH), and so it too was unsuitable for sustained release. The amide analogues examined were stable in the gut[8] and so satisfied criterion 3; they also had a range of log P values and solubilities.

In Table III, compounds are listed in order of potency in test B, and log P and solubility data are given.[11] Clearly, among the potent compounds **27** is closest to satisfying the criteria set. Thus, the enantiomers were made and the active enantiomer *S*-**27** was checked for potency and solubility. Its aqueous solubility is pH dependent, illustrating a classical weak-base profile and is

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(11) Leahy, D. E.; Wait, A. R. Unpublished results.

around 15 mg mL^{-1} over the normal intestinal pH range of 6.5–7.4. The properties of *S*-27 are shown in Table I; in test D at 1 mg kg^{-1} it caused an increase in oxygen consumption of 4.6 ± 0.7 mL min^{-1} $(kg^{0.75})^{-1}$. The *R*-enantiomer was essentially inactive in test B.

S-27, given the number ICI D7114, was examined in further efficacy and selectivity tests in rats, cats, and dogs which are reported in detail elsewhere.[12] In particular, it is a selective agonist of brown fat and oxygen consumption. Treatment of rats with ICI D7114 caused potent stimulation of oxygen consumption and brown adipose tissue mitochondrial GDP binding with little effect on heart rate (a β_1-mediated parameter). Furthermore, ICI D7114 was without effect on a cat soleus model of tremor or on blood potassium levels in the dog (β_2-mediated parameters).[12] Conventional β-agonists exhibited no such selectivity. Administration of ICI D7114 to cats and dogs led to an increase in oxygen consumption;[12] slimming effects were observed in the dog.[13] Studies in man with other thermogenic agents[14-17] indicate that this class of compound may be useful in the treatment of obesity and diabetes if therapeutic effects are separated from unwanted β-adrenoceptor side effects. ICI D7114 may be a selective thermogenic agent in man and may be useful in the treatment of obesity and diabetes.

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.

Method A. [4-[2-[(2-Hydroxy-3-phenoxypropyl)amino]ethoxy]phenoxy]-*N*-methylacetamide (10). A mixture of ester 1 (R^1 = OMe; 0.38 g, 1.0 mmol) in MeOH (20 mL) and a 33% w/v solution of methylamine in EtOH (10 mL, 100 mmol) was allowed to stand at ambient temperature for 3 h. The solvent was evaporated and the residue was crystallized from EtOAc to give **10**, mp 115 °C, yield 0.24 g (66%).

Unless otherwise stated in a footnote to Table I, other amides prepared by method A were made in a similar way using an excess of amine and carrying out the reaction essentially to completion as judged by TLC on silica, the yields being in the region of 60–90%. Occasionally the mixture was heated under reflux or a different solvent was used; these variations are noted in Table I.

Method B. [4-[2-[(2-Hydroxy-3-phenoxypropyl)amino]ethoxy]phenoxy]-*N*-phenylacetamide (34). NaH (60% dispersion in mineral oil, 132 mg, 3.3 mmol) was added to a solution of phenol **2**[1] (1.0 g, 3.3 mmol) in dry DMF (50 mL) and the resulting suspension was stirred for approximately 30 min until a clear solution was obtained. A solution of *N*-phenyl-2-chloroacetamide (0.55 g, 3.3 mmol) in dry DMF (20 mL) was added and the mixture was stirred for 18 h. The mixture was then poured into water (150 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The extract was washed with water (6 × 100 mL) and dried, and the solvent evaporated to give **34**, mp 119–121 °C, yield 0.37 g (25%).

Method C. *N*-(Benzyloxy)[4-[2-[(2-hydroxy-3-phenoxypropyl)amino]ethoxy]phenoxy]acetamide (45). The hydrochloride of acid 1 (R^1 = OH) (1.32 g, 3.4 mmol), *O*-benzylhydroxylamine hydrochloride (0.89 g, 5.1 mmol), and 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (1.28 g, 6.5 mmol) were stirred in a mixture of THF (20 mL) and water (20 mL), and 2 N NaOH was added to adjust and maintain the pH at 4.5 for 30 min. The THF was removed by evaporation under reduced pressure and then the aqueous mixture was basified with solid sodium hydrogen carbonate. The mixture was extracted with EtOAc (2 × 75 mL), and then the extracts were washed with saturated brine (30 mL), dried, and evaporated. The residue was crystallized from EtOAc to give **45**, mp 113–115 °C, yield 0.68 g (44%).

***N*-(2-Methoxyethyl)chloroacetamide (4).** A solution of 2-methoxyethylamine (10 g, 133 mmol) and triethylamine (13.5 g, 133 mmol) in CH_2Cl_2 (20 mL) was added during 2 h to a stirred solution of chloroacetyl chloride (15.04 g, 133 mmol) in CH_2Cl_2 (80 mL) at 0 °C. The mixture was stirred for a further 16 h and then water (100 mL) was added. The CH_2Cl_2 layer was separated and dried, and then the solvent was evaporated to give **4** as an oil, yield 16.4 g (81%), which after NMR characterization was used without further purification in the next preparation.

***N*-(2-Methoxyethyl)[4-[2-(benzylamino)ethoxy]phenoxy]acetamide (6).** NaH (60% dispersion in mineral oil, 328 mg, 8.3 mmol) was added to a stirred solution of *N*-benzyl-2-(4-hydroxyphenoxy)ethylamine (**3**)[1] (2.0 g, 8.3 mmol) in dry DMF (15 mL) and after approximately 2 h a clear solution was obtained. To this was added a solution of **4** (1.25 g, 8.3 mmol) in dry DMF (5 mL) and the mixture was stirred for 72 h. It was then poured into water (100 mL) and extracted with CH_2Cl_2 (100 mL). The extract was washed with water (2 × 50 mL) and dried, and the solvent evaporated. The residual oil was dissolved in EtOAc and treated with a slight excess of ether saturated with hydrogen chloride to precipitate **6**·HCl mp 196–197 °C, yield 1.3 g (40%). Anal. ($C_{20}H_{27}ClN_2O_4$) C, H, Cl, N.

(*S*)-[4-[2-[(2-Hydroxy-3-phenoxypropyl)amino]ethoxy]phenoxy]-*N*-(2-methoxyethyl)acetamide (*S*-27). A mixture of **6** (1.11 g, 3.1 mmol; from 1.3 g of **6**·HCl and (*S*)-1,2-epoxy-3-phenoxypropane (**5**, 0.465 g, 3.1 mmol) in propan-2-ol (25 mL) was heated under reflux for 16 h and then the solvent was

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(23) Richter, S. B.; Levin, A. A. Thiocyanoacetamides. U.S. Patent 3,723,439, 1973.

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evaporated to give 7 as an oil (1.61 g) which was essentially pure by TLC (silica plate, eluant 10% MeOH in CH_2Cl_2, R_f 0.8) and which was used without further purification. It was dissolved in a mixture of MeOH (70 mL) and acetic acid (30 mL) and hydrogenated in the presence of 10% Pd-C (0.4 g) at about 20 bar and 60 °C for 48 h. The mixture was cooled and filtered, and the solvent evaporated to give *S*-**27** as an oil. This was converted to *S*-**27**·HCl which was crystallized from a mixture of MeOH and EtOAc, mp 171-173 °C, yield 1.34 g (95%), $[\alpha]^{23}_D$ -10.7° (*c* 1.0, MeOH).

(*S*)-[4-[2-[[2-Hydroxy-3-(4-hydroxyphenoxy)propyl]amino]ethoxy]phenoxy]-*N*-(2-methoxyethyl)acetamide (*S*-70). A mixture of **6** (5.58 g, 15.6 mmol) and (*S*)-1-[4-(benzyloxy)phenoxy]-2,3-epoxypropane (4.0 g, 15.6 mmol; $[\alpha]^{23}_D$ +8.1° (*c* 1.03 in MeOH) [lit.[4] $[\alpha]^{20}_D$ +8.6° (*c* 1.02 in MeOH)]) in propan-2-ol (50 mL) was heated under reflux for 16 h and then the solvent was evaporated to give an oil A (8.8 g) which was essentially pure by TLC (silica plate, eluant 10% MeOH in CH_2Cl_2, R_f 0.85) and which was used without further purification. The oil A (4.7 g, 7.7 mmol), 10% Pd-C (800 mg) and ammonium formate (0.98 g, 15.5 mmol) in EtOH (200 mL) was heated at 50 °C for 2.5 h. A TLC check showed the presence of some starting material. A further amount of ammonium formate (0.5 g, 7.9 mmol) was added and heating continued for 2 h. The mixture was filtered and the solvent evaporated. The residual oil was converted to *S*-**70**·HCl, which was crystallized from a mixture of MeOH and EtOAc, mp 166-167 °C, yield 1.75 g from oil A (49%), $[\alpha]^{23}_D$ -10.5° (*c* 1.02 in MeOH).

Registry No. 1 (R^1 = OMe), 139733-51-0; 1 (R^1 = OH), 139733-52-1; **2**, 139733-53-2; **3**, 108856-98-0; **4**, 10263-66-8; **5**, 71031-03-3; **6**, 133025-88-4; **7**, 139733-54-3; **9**, 139733-55-4; **9**·HCl, 139733-56-5; **10**, 139733-57-6; (*S*)-**10**, 115656-35-4; (*S*)-**10** ester, 107332-64-9; **11**, 139733-58-7; **12**, 139733-59-8; **12**·HCl, 139733-60-1; **13**, 139733-61-2; **13**·HCl, 139733-62-3; **14**, 139733-63-4; **15**, 139733-64-5; **15**·HCl, 139733-65-6; **16**, 139733-66-7; **16**·HCl, 139733-67-8; **17**, 139733-68-9; **18**, 139733-69-0; **19**, 139733-70-3; **20**, 139733-71-4; **20**·HCl, 139733-72-5; **21**, 139733-73-6; **22**, 139733-74-7; **23**, 139733-75-8; **23**·HCl, 139733-76-9; (*S*)-**23**, 115656-45-6; **24**, 139733-77-0; **25**, 139733-78-1; **26**, 139733-79-2; **26**·HCl, 139733-80-5; **27**, 139892-81-2; **27**·HCl, 139892-82-3; (*S*)-**27**, 129689-30-1; (*S*)-**27**·HCl, 129689-28-7; (*R*)-**27**, 139733-81-6; (*R*)-**27**·HCl, 139733-82-7; (*R*)-**27** ester, 139733-51-0; **28**, 139733-83-8; **29**, 139733-84-9; **29**·HCl, 139733-85-0; **30**, 139733-86-1; **30**·2HCl, 139733-87-2; **31**, 139733-88-3; **31**·HCl, 139733-89-4; **32**, 139733-90-7; **32**·HCl, 139733-91-8; **33**, 139733-92-9; **34**, 139733-93-0; **35**, 139733-94-1; **36**, 139733-95-2; **36**·HCl, 139733-96-3; **37**, 139733-97-4; **38**, 139733-98-5; **39**, 139733-99-6; **39**·HCl, 139734-00-2; **40**, 139734-01-3; **40**·HCl, 139734-02-4; **41**, 139734-03-5; **41**·HCl, 139734-04-6; **42**, 139734-05-7; (*S,S*)-**43**, 139734-06-8; (*S,S*)-**43**·HCl, 139734-04-6; **44**, 139734-08-0; **45**, 139734-09-1; **46**, 139734-10-4; **47**, 139734-11-5; **47**·HCl, 139734-12-6; **48**, 139734-13-7; **48**·HCl, 139734-14-8; **49**, 139734-15-9; **50**, 139734-16-0; **51**, 139734-17-1; **52**, 139734-18-2; **53**, 139734-19-3; **53**·HCl, 139734-20-6; **54**, 139734-21-7; **54**·HCl, 139734-22-8; **55**, 139734-23-9; **55**·HCl, 139734-24-0; **56**, 139734-25-1; **56**·HCl, 139734-26-2; **56**·oxalate, 139734-27-3; **57**, 139734-28-4; **58**, 139734-29-5; **59**, 139734-30-8; **59**·HCl, 139734-31-9; **60**, 139734-32-0; **60**·HCl, 139734-33-1; **61**, 139734-34-2; **61**·HCl, 139734-35-3; **61** ester, 139734-36-4; **62**, 139734-37-5; **62**·HCl, 139734-38-6; **63**, 139734-39-7; **63** ester, 139734-40-0; **64**, 139734-41-1; **65**, 139734-42-2; **65** ester, 139734-43-3; **66**, 139734-44-4; **66**·HCl, 139734-45-5; **67**, 139734-46-6; **67**·HCl, 139734-47-7; **68**, 139734-48-8; **68**·HCl, 139734-49-9; **68** ester, 139734-50-2; **69**, 139734-51-3; **69** ester, 139734-52-4; **70**, 139734-53-5; **70**·HCl, 139734-54-6; (*S*)-**70**, 139892-83-4; (*S*)-**70**·HCl, 139892-84-5; $ClCH_2CON(CH_3)CH_2Ph$, 73685-56-0; $ClCH_2CON(CH_3)(CH_2)_2OCH_3$, 139734-55-7; $ClCH_2CONHC_6H_3$-2,6-$(CH_3)_2$, 1131-01-7; $ClCH_2CONHCH_2C_6H_3$-2,4-Cl_2, 56978-45-1; $ClCH_2CONHBu$-*t*, 15678-99-6; $ClCH_2CONHPh$, 587-65-5; $ClCH_2CON(CH_2CH_3)_2$, 2315-36-8; NH_2CH_3, 74-89-5; NH_2Et, 75-04-7; NH_2Pr-*n*, 107-10-8; NH_2Pr-*i*, 75-31-0; NH_2Bu-*n*, 109-73-9; NH_2Bu-*i*, 78-81-9; NH_2Bu-*s*, 13952-84-6; NH_2CH_2Bu-*t*, 5813-64-9; $NH_2(CH_2)_5CH_3$, 111-26-2; $NH_2CH_2CH{=}CH_2$, 107-11-9; NH_2Pr-*c*, 765-30-0; NH_2 C_5H_9-*c*, 1003-03-8; $NH_2(CH_2)_2OH$, 141-43-5; $NH_2(CH_2)_3OH$, 156-87-6; $NH_2CH(CH_3)CH_2OH$, 78-91-1; $NH_2C(CH_3)_2CH_2OH$, 124-68-5; $NH_2(CH_2)_2OCH_3$, 109-85-3; $NH_2(CH_2)_3OCH_3$, 5332-73-0; $NH_2CH(CH_3)CH_2OCH_3$, 37143-54-7; $NH_2(CH_2)_2NH_2$, 107-15-3; $NH_2CH_2CONH_2$, 598-41-4; NH_2CH_2Ph, 100-46-9; $NH_2CH_2C_6H_4$-*p*-CH_3, 104-84-7; $NH_2CH_2C_6H_4$-*p*-OCH_3, 2393-23-9; $NH_2CH_2C_6H_4$-*o*-Cl, 89-97-4; $NH_2CH_2C_6H_4$-*p*-Cl, 104-86-9; $NH_2(CH_2)_2Ph$, 64-04-0; (*S*)-$NH_2CH(CH_3)Ph$, 2627-86-3; $NH_2(CH_2)_2OPh$, 1758-46-9; NH_2OCH_2Ph·HCl, 2687-43-6; $NH(CH_3)_2$, 124-40-3; $NH(CH_3)(CH_2)_2OH$, 109-83-1; (*S*)-1-[4-(benzyloxy)phenoxy]-2,3-epoxypropane, 122797-04-0; 2-(aminomethyl)thiophene, 27757-85-3; *N*-chloroacetyl-2,3,4,5-tetrahydroisoxazole, 139734-56-8; *N*-chloroacetyl-1,3-dihydroisoindole, 41910-53-6; 2-(aminomethyl)furan, 617-89-0; pyrrolidine, 123-75-1; piperidine, 110-89-4; 4-hydroxypiperidine, 5382-16-1; morpholine, 110-91-8; 1-methylpiperazine, 109-01-3; 1,2,3,4-tetrahydroisoquinoline, 91-21-4; chloroacetyl chloride, 79-04-9.

Quinolone Antibacterial Agents. Synthesis and Structure-Activity Relationships of a Series of Amino Acid Prodrugs of Racemic and Chiral 7-(3-Amino-1-pyrrolidinyl)quinolones. Highly Soluble Quinolone Prodrugs with in Vivo Pseudomonas Activity

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A series of amino acid prodrugs of racemic and chiral 7-(3-amino-1-pyrrolidinyl)-6-fluoro-1,8-naphthyridine-3-carboxylic acids, 1-cyclopropyl-6,8-difluoro-3-quinolinecarboxylic acids, 1-cyclopropyl-6-fluoro-3-quinolinecarboxylic acids, and 5-amino-1-cyclopropyl-6,8-difluoro-3-quinolinecarboxylic acids have been prepared and evaluated for comparative antibacterial activity. Compounds were prepared by acylation of the 3-amino group of the pyrrolidine with common amino acids using standard peptide chemistry. This series has been compared with the parent compounds for antibacterial activity in vitro and in vivo as well as for comparative solubility. The amino acid analogues were less active in vitro, but had equal or increased efficacy in vivo. Indeed, it was proven that these compounds, which were stable to acid and base under the reaction conditions for their preparation, were rapidly cleaved in serum to give the parent quinolones. The amino acid derivatives showed a 3-70 times improved solubility when compared to the parent compounds. The most active compound of the series was [*S*-(*R**,*R**)]-7-[3-[(2-amino-1-oxopropyl)amino]-1-pyrrolidinyl]-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid (PD 131112).

The search for the ideal quinolone antibacterial agent continues in many laboratories.[1] Such an agent will have potent activity against a broad spectrum of Gram-positive and Gram-negative aerobic and anaerobic organisms as

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