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Linked Aryl Aryloxypropanolamines as a New Class of Lipid Catabolic Agents

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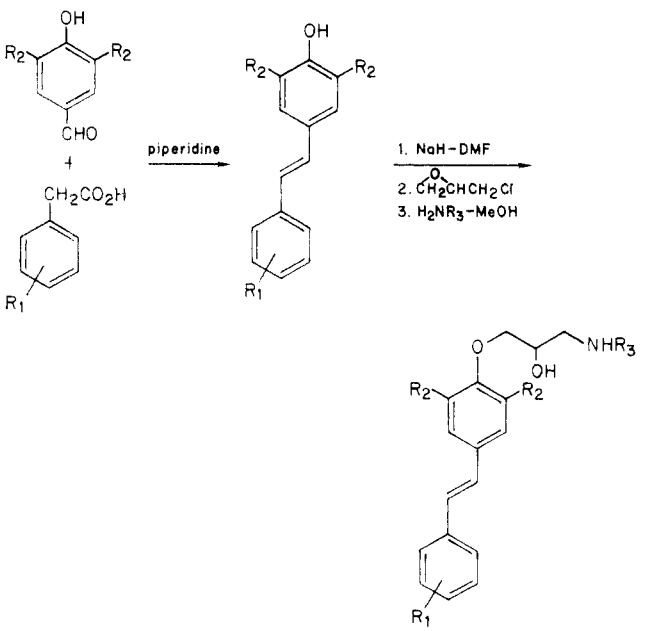
The synthesis of a series of stilbene, biaryl, tolane, diaryl ether, sulfide, sulfoxide, and sulfone oxypropanolamines as potential antiobesity agents is described. These compounds were evaluated in a mouse lipid catabolism screen, and the more active members of the series, **4**, **57**, and **58**, were further investigated in rats and dogs. 1-(2,6-Di-*tert*-butyl-4-*trans*-styrylphenoxy)-3-isopropylamino-2-propanol (**4**) possessed considerable lipid catabolic activity in mice and caused a significant reduction in the body weight of rats after 5 weeks and of dogs after 6 weeks. Only hematological irregularities in a chronic toxicity study precluded further development of this compound as an alternative antiobesity treatment.

The existing methods for the treatment of obesity rely heavily on the use of anorectic drugs, particularly the phenethylamine group[1,2] and more recently mazindol.[3] An alternative approach to this treatment would be by the use of calorigenic or lipid-catabolic drugs which would lower the carcass fat content of individuals.

We have been evaluating compounds for their lipid-catabolizing effects in rodents. The term "lipid catabolizing" is used to describe the ability to cause a net lipid loss, initially demonstrated by a reduction in uterofat and subsequently confirmed by carcass analysis. This effect is achieved other than by a simple reduction in food intake. Weak lipid-catabolizing activity of 2,4,6-tri-*tert*-butylphenol was observed in these laboratories and this encouraged the systematic and progressive modification of this structure leading to the preparation and evaluation of a series of linked diaryl oxypropanolamines, which is the subject of this report. The goal for this research effort was a compound which reduced body fat and consequently body weight without drastically affecting food intake.

Chemistry. The stilbene propanolamines were prepared by the route outlined in Scheme I. Condensation of the appropriately substituted arylacetic acid with a substituted *p*-hydroxybenzaldehyde was carried out in xylene with piperidine as a basic catalyst.[4] The crude phenolic *trans*-stilbene was usually purified by chromatography on a short column of Florisil. Sodium hydride in dimethylformamide was used to generate the sodium salts of the hydroxystilbenes and reaction with epichlorohydrin in refluxing dimethylformamide gave the glycidyl ethers in moderate to good yield. These epoxides reacted with the appropriate amine in methanol giving the desired propanolamines. Compounds **1**–**4**, **7**–**32**, and **34**–**51**

Scheme I



were prepared using this procedure and are listed in Table I. The 4-hydroxystilbene **33** was prepared by pyridine hydrochloride demethylation of **32**.

Compound **4** was initially selected for further biological evaluation and several derivatives of it were prepared. The stilbene double bond in **4** was readily hydrogenated over palladium on carbon giving the dihydro derivative **52**. Compound **4** was resolved using both *d*- and *l*-*p*-toluoyltartaric acids. Solutions of **4** in various solvents were

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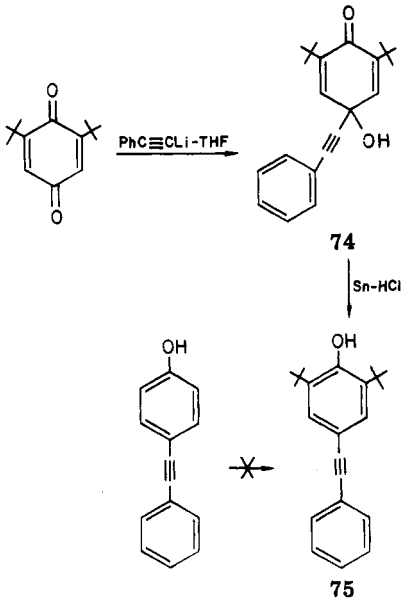
Scheme II



irradiated under nitrogen in an attempt to prepare the cis isomer. There was no evidence of dihydrophenanthrene formation but small amounts of cyclobutanes, derived by dimerization, were observed in acidic solvents. At the photostationary state in neutral solvents, a 4:1 cis–trans mixture was obtained, which proved impossible to separate into the individual isomers, partly on account of the lability of the cis isomer.

As the study progressed, the 4-chloro analogue **25** became of interest pharmacologically as well as compound **4**. This governed the choice of substituent for the nonstilbene analogues **53–73**.

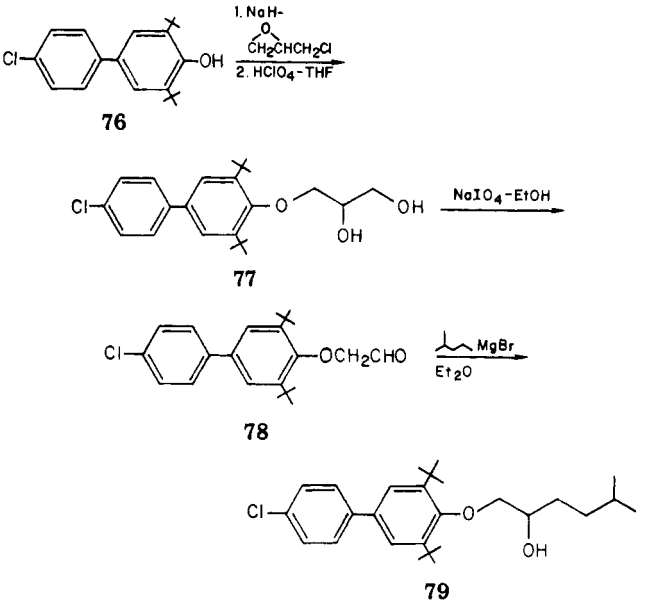
The biaryl analogues **53–57**, **72**, and **73**, the diaryl ethers **58–60**, the sulfides **63–65**, and sulfones **69–71** were all prepared by alkylation of the appropriate phenol as described for the stilbenes above. The phenols themselves were obtained by standard procedures. The sulfoxides **66–68** were prepared by sodium periodate in methanol oxidation of the sulfides **63–65**, respectively.

The phenol **75** required for the synthesis of **62** could not be obtained by conventional alkylation of 4-phenethynylphenol,[5] the precursor of **61**. The preparation of **75** is shown in Scheme II. Lithium phenylacetylide and 2,6-di-*tert*-butylquinone in THF gave the alcohol **74** which proved difficult to reduce in a reproducible manner. Tin and hydrochloric acid finally proved to be the method of choice. It was then found that the sodium salt of **75** was unreactive toward epichlorohydrin. It did, however, react slowly with epibromohydrin and the resultant glycidyl ether reacted with isopropylamine to give **62**.

When the biphenyl analogue **55** became of some pharmacological interest, the synthesis of the carbon for nitrogen isostere **79** was undertaken (Scheme III). The glycidyl ether of **76** was cleaved to the diol **77** with perchloric acid in THF. The diol was oxidatively cleaved with periodate in ethanol and the resulting aldehyde **78** was converted to alcohol **79**. This compound was inactive in the mouse lipid catabolism test.

Biological Results. New compounds were initially tested in a mouse lipid catabolism screen. The test compound was dosed by admixture with the diet during 10 days. A dose of 0.04% is approximately equal to 40 mg/kg depending on the amount of food eaten. The percentage lipid reduction was determined for all candidate drugs and is reported in Table I, as is comparative data

Scheme III



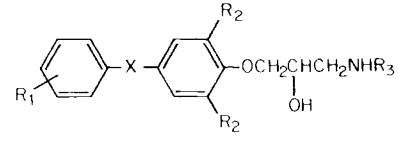
for reference anorexiant compounds *d*-amphetamine and fenfluramine. Food intake was monitored for all compound treatments but data for this are not included in Table I, because in practice it was demonstrated that only when several replicate groups of control and treated mice were considered could valid statistical significance be achieved. However, experiments with controls, standard drugs (e.g., *d*-amphetamine), and active compounds such as **4** were performed which demonstrated that the concept of lipid catabolism in small rodents was indeed valid for compound **4** and like structures.

Dose–response curves and ED_{25} values (the effective dose needed to produce a 25% reduction in uterofat weight) were determined for the more active members of the series. The majority of analogues exhibited normal dose–response relationships but compound **4** had a dose–response curve which leveled off at lower doses. The reason for the persistence of biological effect at lower doses for this compound is not known.

Although the thiophene-containing compounds **43**, **72**, and **73** showed high activity in the mouse lipid catabolism screen, they were too toxic to merit further investigation. An intriguing result was obtained from the individual isomers **5** and **6** of the racemic compound **4**. The (+) isomer was inactive at the routine test dose (0.04% in the diet) and the (–) isomer was inactive at a dose of 0.02% in the diet, whereas the racemate gave good activity at a dose of 0.01% in the diet.

After evaluation of the mouse screen data for the compounds listed in Table I, several analogues (see Table II) were selected for more detailed study in mice. These analogues were representative of a range of activities and structures. None of the compounds selected for further study resulted in death following a single dose of 1000 mg/kg po in mice. The determination of a single figure summarizing the chronic (3 week) toxicity of these derivatives was more problematic. The highest nontoxic dose in mice receiving the drug po for 21 days was selected as an approximate measure of their chronic toxicities. From these data, an estimation of the chronic therapeutic ratio can be calculated and, thence, a ranking of the compounds of interest. It can be seen from Table II that the 4-methoxystilbene **32** and the 4-chlorobiphenyl **54** are relatively more toxic, whereas the 4-chlorostilbene derivative **28** is less toxic than the majority of the series. Liver hypertrophy was observed with one biphenyl derivative

Table I. Linked Aryl Aryloxypropanolamines



No.	R_1	R_2	R_3	X	Yield, %	Crystn solvent[m]	Mp, °C	Formula	Dose[g,r]	% redn,[h,r] utero fat	Phenol prepn[m,n] (lit. ref)
1	H	*t*-Bu	Me	-CH=CH-	31[a]	A-B-C	174 dec[c]	$C_{26}H_{37}NO_2 \cdot C_2H_2O_4 \cdot H_2O$	0.04	44	90-91 (6)
2	H	*t*-Bu	Et	-CH=CH-	28[a]	C	97-98[d]	$C_{27}H_{39}NO_2$	0.04	24	90-91 (6)
3	H	*t*-Bu	*n*-Pr	-CH=CH-	39[a]	C	99-100[d]	$C_{28}H_{41}NO_2$	0.04	NA	90-91 (6)
(±)-**4**	H	*t*-Bu	*i*-Pr	-CH=CH-	70[a]	D	109-110.5[d]	$C_{28}H_{41}NO_2$	0.01	26	90-91 (6)
(+)-**5**	H	*t*-Bu	*i*-Pr	-CH=CH-		E	87-88[d]	$C_{28}H_{41}NO_2$	0.04	NA	90-91 (6)
(−)-**6**	H	*t*-Bu	*i*-Pr	-CH=CH-		E	87-88[d]	$C_{28}H_{41}NO_2$	0.04	39	90-91 (6)
7	H	*t*-Bu	Cyclopropyl	-CH=CH-	56[a]	F	77-80[d]	$C_{28}H_{39}NO_2$	0.04	NA	90-91 (6)
8	H	*t*-Bu	*n*-Bu	-CH=CH-	19[b]	G	104-105[d]	$C_{29}H_{43}NO_2$	0.04	25	90-91 (6)
9	H	*t*-Bu	$-CH(CH_3)CH_2CH_3$	-CH=CH-	69[a]	C	98-99[d]	$C_{29}H_{43}NO_2$	0.04	23	90-91 (6)
10	H	*t*-Bu	*t*-Bu	-CH=CH-	43[a]	F	136-138[d]	$C_{29}H_{43}NO_2$	0.04	20	90-91 (6)
11	H	*t*-Bu	$CH_2CH(CH_3)_2$	-CH=CH-	63[a]	C	99-100[d]	$C_{29}H_{43}NO_2$	0.04	NA	90-91 (6)
12	H	*t*-Bu	Cyclohexyl	-CH=CH-	55[a]	F	119-120[d]	$C_{31}H_{45}NO_2$	0.04	24	90-91 (6)
13	H	*t*-Bu	*n*-Hexyl	-CH=CH-	14[a]	D	62-64[d]	$C_{31}H_{47}NO_2$	0.04	NA	90-91 (6)
14	H	*t*-Bu	$-CH_2Ph$	-CH=CH-	25[a]	H-C	100-101[d]	$C_{32}H_{41}NO_2$	0.04	NA	90-91 (6)
15	H	*t*-Bu	$-CH_2CH_2NMe_2$	-CH=CH-	29[a]	D	195-196[e]	$C_{29}H_{44}N_2O_2 \cdot 2C_4H_4O_4$	0.04	NA	90-91 (6)
16	H	*t*-Bu	$-(CH_2)_3NEt_2$	-CH=CH-	26[a]	D-H	234-235[f]	$C_{32}H_{50}N_2O_2 \cdot 2HCl$[o]	0.04	NA	90-91 (6)
17	H	*t*-Bu	$-(CH_2)_2NHCONHPh$	-CH=CH-	9[a]	D-H	150-153[e]	$C_{34}H_{45}N_3O_3 \cdot C_4H_4O_4$	0.04	NA	90-91 (6)
18	H	*t*-Bu	$-CH_2CH_2OH$	-CH=CH-	28[a]	A-B-C	187-190[c]	$C_{27}H_{39}NO_3 \cdot C_2H_2O_4$	0.04	NA	90-91 (6)
19	H	*t*-Bu	$-(CH_2)_3NMe_2$	-CH=CH-	37[a]	D-H	265-267[f]	$C_{30}H_{46}N_2O_2 \cdot 2HCl$	0.04	45	90-91 (6)
20	H	*t*-Bu	$-(CH_2)_3N$-*n*-Bu_2	-CH=CH-	26[a]	D-H	173-174[e]	$C_{36}H_{58}N_2O_2 \cdot 2C_4H_4O_4$	0.04	25	90-91 (6)
21	4-Me	*t*-Bu	*i*-Pr	-CH=CH-	46[a]	A-B-C	190-193[c]	$C_{29}H_{43}NO_2 \cdot C_4H_4O_4$	0.04	NA	98-98.5, B
22	2-Me	*t*-Bu	*i*-Pr	-CH=CH-	20[a]	B-C	89-92[d]	$C_{29}H_{43}NO_2$[p]	0.04	42	110-111, B
23	4-*t*-Bu	*t*-Bu	*i*-Pr	-CH=CH-	26[b]	C	131-132[d]	$C_{32}H_{49}NO_2$	0.04	NA	118-120, B
24	4-F	*t*-Bu	*i*-Pr	-CH=CH-	16[b]	C	120-122[d]	$C_{28}H_{40}FNO_2$	0.04	NA	80-81, F
25	4-Cl	*t*-Bu	*i*-Pr	-CH=CH-	26[a]	C	117-118[d]	$C_{28}H_{40}ClNO_2$	0.04	22	120-122, F
26	H	*t*-Bu	Cyclopropyl	-CH=CH-	53[b]	C	111-114[d]	$C_{28}H_{38}ClNO_2$	0.02	30	120-122, F
27	H	*t*-Bu	*n*-Bu	-CH=CH-	49[b]	C	110-111[d]	$C_{29}H_{42}ClNO_2$	0.04	NA	120-122, F
28	H	*t*-Bu	*t*-Bu	-CH=CH-	30[a]	C	154-155[d]	$C_{29}H_{42}ClNO_2$	0.02	28	120-122, F
29	3-Cl	*t*-Bu	*i*-Pr	-CH=CH-	21[b]	F	123-125[d]	$C_{28}H_{40}ClNO_2$	0.04	21	102-104, B
30	2-Cl	*t*-Bu	*i*-Pr	-CH=CH-	11[b]	C	104-107[d]	$C_{28}H_{40}ClNO_2$	0.04	NA	116-117, B
31	4-Br	*t*-Bu	*i*-Pr	-CH=CH-	28[a]	C	110-112	$C_{28}H_{40}BrNO_2$	0.02	31	128-130, B
32	4-MeO	*t*-Bu	*i*-Pr	-CH=CH-	15[b]	C	107-109[d]	$C_{29}H_{43}NO_3$	0.02	26	118-120, F
33	4-OH	*t*-Bu	*i*-Pr	-CH=CH-	20[b]	D-J	177-178[e]	$C_{28}H_{41}NO_3 \cdot C_4H_4O_4$	0.02	20	
34	4-NO_2	*t*-Bu	*i*-Pr	-CH=CH-	32[b]	C	129-130[d]	$C_{28}H_{40}N_2O_4$[q]	0.04	45	209-211, B

35	3,4-Me_2	*t*-Bu	*i*-Pr	-CH=CH-	51[b]	D-H	203-204[d]	$C_{30}H_{45}NO_2 \cdot C_4H_4O_4$	0.04	NA	112-114, B
36	3,4-Cl_2	*t*-Bu	*i*-Pr	-CH=CH-	25[b]	D-H	217-218[d]	$C_{28}H_{39}Cl_2NO_2 \cdot C_4H_4O_4$	0.04	NA	135-137, B
37	3,4-OCH_2O-	*t*-Bu	*i*-Pr	-CH=CH-	75[b]	C	118-120[d]	$C_{29}H_{41}NO_4$	0.04	NA	125-127, B
38	3-Br-4-MeO	*t*-Bu	*i*-Pr	-CH=CH-	30[a]	C	119-121[d]	$C_{29}H_{42}BrNO_3$	0.04	NA	148-148.5, B
39	3-Br-4-MeO	*t*-Bu	*t*-Bu	-CH=CH-	42[b]	C	144-147[d]	$C_{30}H_{44}BrNO_3$	0.04	NA	148-148.5, B
40	*i*	*t*-Bu	*i*-Pr	-CH=CH-	19[b]	D-H	172-174[e]	$C_{32}H_{43}NO_2 \cdot C_4H_4O_4$	0.04	NA	148-150, C
41	*j*	*t*-Bu	*i*-Pr	-CH=CH-	31[b]	D-H	212-214[e]	$C_{32}H_{43}NO_2 \cdot C_4H_4O_4$	0.04	NA	144-146, C
42	*k*	H	*i*-Pr	-CH=CH-	11[b]	H-C	105-107[d]	$C_{19}H_{24}N_2O_2$	0.04	24	278-280, B
43	*l*	*t*-Bu	*i*-Pr	-CH=CH-	28[b]	C	132-134[d]	$C_{26}H_{39}NO_2S$	0.02	30	80-82, B
44	H	Me	*i*-Pr	-CH=CH-	91[a]	F	125-127[d]	$C_{22}H_{29}NO_2$	0.04	31	138-140, F
45	H	Et	*i*-Pr	-CH=CH-	57[b]	E	117-118[d]	$C_{24}H_{33}NO_2$	0.02	20	137-139, B
46	2-F	Et	*i*-Pr	-CH=CH-	43[a]	A	112-114[d]	$C_{24}H_{32}FNO_2$	0.04	37	99.5-100.5, C
47	2-CF_3	Et	*i*-Pr	-CH=CH-	15[a]	C	75-77[d]	$C_{25}H_{32}F_3NO_2$	0.04	20	41-42, K
48	H	*i*-Pr	*i*-Pr	-CH=CH-	60[a]	C	114-116[d]	$C_{26}H_{37}NO_2$	0.04	20	48-49, K
49	H	*s*-Bu	*i*-Pr	-CH=CH-	61[a]	C	121-124[d]	$C_{28}H_{41}NO_2$	0.04	NA	Oil
50	H	Cyclohexyl	*i*-Pr	-CH=CH-	32[b]	D-H	167-168[e]	$C_{32}H_{45}NO_2 \cdot C_4H_4O_4$	0.04	27	124-125, C
51	H	Me, *t*-Bu	*i*-Pr	-CH=CH-	55[a]	C	89-91[d]	$C_{25}H_{35}NO_2$	0.04	NA	88-91, F
52	H	*t*-Bu	*i*-Pr	-CH_2CH_2-		A-B-C	214[f] dec	$C_{28}H_{43}NO_2$	0.04	NA	
53	H	H	*i*-Pr	Direct	26[b]	H-C	115-116[d]	$C_{18}H_{23}NO_2$	0.04	24	Aldrich
54	4-Cl	H	*i*-Pr	Direct	33[b]	H	215-217[f]	$C_{18}H_{22}NO_2 \cdot HCl$	0.04	23	(7)
55	4-Cl	*t*-Bu	*i*-Pr	Direct	26[b]	H-C	136-137[d]	$C_{26}H_{38}ClNO_2$	0.04	36	(8)
56	4-MeO	*t*-Bu	*i*-Pr	Direct	40[b]	C	115-117[d]	$C_{27}H_{41}NO_3$	0.04	NA	(9)
57	H	*t*-Bu	*i*-Pr	Direct	17[b]	H	215-216[f]	$C_{26}H_{39}NO_2 \cdot HCl$	0.04	28	(10)
58	4-Cl	H	*i*-Pr	O	37[b]	H-C	75-76[d]	$C_{18}H_{22}ClNO_3$	0.02	25	(11)
59	H	*t*-Bu	*i*-Pr	O	25[b]	D-H	175-176[e]	$C_{26}H_{39}NO_3 \cdot C_4H_4O_4$	0.04	20	(12)
60	4-Cl	*t*-Bu	*i*-Pr	O	19[b]	H-C	110-112[d]	$C_{26}H_{38}ClNO_3$	0.04	NA	137-139, C
61	H	H	*i*-Pr	C≡C	16[b]	H-C	138-139[d]	$C_{20}H_{23}NO_2$	0.04	28	(5)
62	H	*t*-Bu	*i*-Pr	C≡C	27[b]	H	193-194[e]	$C_{28}H_{39}NO_2 \cdot C_4H_4O_4$	0.04	25	114-115, P
63	H	*t*-Bu	*i*-Pr	S	31[b]	D-H	158-159[e]	$C_{26}H_{39}NO_2S \cdot C_4H_4O_4$	0.04	NA	(13)
64	4-Cl	*t*-Bu	*i*-Pr	S	20[b]	C	114-115[d]	$C_{26}H_{38}ClNO_2S$	0.04	NA	(13)
65	4-Cl	H	*i*-Pr	S	36[b]	L	88-90[d]	$C_{18}H_{22}ClNO_2S$	0.04	22	(14)
66	H	*t*-Bu	*i*-Pr	SO	58	D-H	85-89[d]	$C_{26}H_{39}NO_3S$	0.04	NA	
67	4-Cl	*t*-Bu	*i*-Pr	SO	58	D-H	100-104[e]	$C_{26}H_{38}ClNO_3S \cdot C_4H_4O_4$	0.04	23	
68	4-Cl	H	*i*-Pr	SO	38	M	156-158[e]	$C_{18}H_{22}ClNO_3S \cdot C_4H_4O_4$	0.04	NA	
69	H	*t*-Bu	*i*-Pr	SO_2	13[b]	D-H	208-210[e]	$C_{26}H_{39}NO_4S \cdot C_4H_4O_4$	0.04	NA	(15)
70	4-Cl	*t*-Bu	*i*-Pr	SO_2	17[b]	D-H	110[e]	$C_{26}H_{38}ClNO_4S \cdot C_4H_4O_4$	0.04	NA	187-189, H-C
71	4-Cl	H	*i*-Pr	SO_2	18[b]	H-C	107-109[d]	$C_{18}H_{22}ClNO_4S$	0.04	NA	(16)
72	*l*	*t*-Bu	*i*-Pr	Direct	22[b]	D-H	193-195[e]	$C_{24}H_{37}NO_2S \cdot C_4H_4O_4$	0.005	33	Oil
73	*l*	H	*i*-Pr	Direct	24[b]	N	119-120[d]	$C_{16}H_{21}NO_2S$	0.01	34	(17)

[a] Yield from epoxide. [b] Yield from phenol. [c] Oxalate. [d] Free base. [e] Maleate. [f] Hydrochloride. [g] Percentage by weight of compound administered in the diet. [h] Only compounds producing ≥ 20% reduction were considered active. [i] 1-Naphthyl replaces R_1-phenyl. [j] 2-Naphthyl replaces R_1-phenyl. [k] 4-Pyridyl replaces R_1-phenyl. [l] 2-Thienyl replaces R_1-phenyl. [m] A, toluene; B, absolute EtOH; C, petroleum ether (bp 60–80 °C); D, MeOH; E, aqueous MeOH; F, aqueous EtOH; G, petroleum ether (bp 40–60 °C); H, EtOAc; J, ether; K, distilled in Kugelrohr; L, cyclohexane; M, CH_3CN; N, *i*-PrOH; P, hexane. [n] Melting point (°C) and crystallization solvent; compounds designated "oil" were used without purification. [o] C: calcd, 67.7; found, 67.2. [p] C: calcd, 79.6; found, 79.1. [q] C: calcd, 71.8; found, 72.3. [r] Results for standard drugs: *d*-amphetamine 0.01% diet, 34% reduction in uterofat, 0.04% diet, 59% reduction in uterofat; fenfluramine 0.04% diet, NA, 0.08% diet, 20% reduction in uterofat.

Table II. Comparison of Effective and Toxic Doses of Selected Compounds in Mice

No.	ED_{25},[a] mice	Highest nontoxic dose[b]	Estd therapeutic ratio[c]
4	10, 45	50	5.0
25	100	100	1.0
28	25	200	8.0
29	72	100	1.4
31	34	150	4.3
32	20	25	1.25
43	6	<25	<4.1
45	45	75	1.7
50	38	100	2.6
54	50	25	0.5
55	30	100	3.6
57	20	100	5.0
58	18	100	5.5
59	20	100	5.0
67	45	75	1.7

[a] Effective dose for a 25% reduction in uterofat (mg/kg/10 days). [b] Estimated highest nontoxic dose (mg/kg/21 days). [c] Ratio of ED_{25} (mg/kg/10 days) to nontoxic dose (mg/kg/21 days).

57 but was not observed in any of the stilbene analogues. Compound **4** was found to be nonestrogenic in rodents and monkeys and none of the series possessed any significant β-blocking activity.

As a result of the studies carried out in mice, the following three derivatives were investigated further in rats: the stilbene **4**, the diphenyl derivative **57**, and the diphenyl ether **58**. The results of these investigations are reported in Table III. The compounds were administered in the diet for the periods indicated, and the integrated food intake and body composition were analyzed at the end of the period under investigation. Statistically significant body weight and uterofat losses were observed for the stilbene **4** after 5 weeks, while only marginal or nonsignificant changes in these parameters were observed for all three compounds after 5 days. A short-term anorexiant effect with rapid tolerance is indicated by the data for food intake for compound **4**. Enlarged adrenal glands were observed with the high doses of **4** used in this study and some liver hypertrophy was seen in the animals treated with the diphenyl ether derivative **57**.

A comparison of placebo, fenfluramine, and the stilbene **4** in a latin square design, dog emesis test, in which dogs received standard doses of all three treatments at weekly intervals, confirmed that fenfluramine was not emetic at doses up to 10 mg/kg and further showed that **4** produced no emesis at doses up to 150 mg/kg. A chronic 6-week study in dogs was carried out monitoring food intake and body weight, in which each dog received a single daily dose of the stilbene **4** of 10 mg/kg. Analysis of the food intake and body weight change and composition at the end of the experiment revealed a 40% decrease in food intake and a 13% drop in body weight. Food intake returned to normal 9 days after drug withdrawal. Chronic anorexia in the dog, slight anorexia and tolerance in the rat, and chronic lipid-catabolic activity in the mouse suggest species differences in response to compound **4**. The net result in each case is a reduction in body weight.

In order to gain some insight into the biochemical mechanisms important in realizing the decrease in carcass fat observed for the more active members of this series of lipid-catabolic agents, some blood parameters were measured. Mice were treated with stilbene **4** at 0.04% in the diet and compound **43** at 0.01% in the diet for 10 days, and the plasma glucose and insulin levels were determined and compared to control animals. Blood glucose was unchanged but insulin levels were depressed. The insulin level of animals treated with compound **43** was profoundly depressed (−46%, $p = 0.02$) and that of the animals treated with the stilbene **4** was nonsignificantly depressed (−27%).

The effect of a number of the stilbene derivatives on in vitro fatty acid synthesis and glucose production from [^{14}C]lactate provided another indication of their mode of action. A significant proportion of the stilbene analogues inhibited fatty acid synthesis from lactate; those compounds that showed no effect on fatty acid synthesis were of low activity in the mouse lipid catabolism screen. Thus an interesting relationship between some of the observed lipid-catabolic activities and the inhibition of fatty acid synthesis has been uncovered. A plausible hypothesis emerges that these compounds are active antiobesity agents because of their ability to inhibit the incorporation of lactate into fatty acids.

Thus the stilbene **4** has been shown to possess desirable lipid-catabolic properties and a satisfactory therapeutic ratio in rodents. This compound compared favorably in laboratory tests with the known anorexiant agents *d*-amphetamine and fenfluramine as an alternative method for treating obesity. However, the detailed results of the chronic toxicity study in rats revealed hematological irregularities. Even though it was found that a restriction of food intake in rats led to a small decrease in the numbers of circulating lymphocytes and the administration of *d*-amphetamine or fenfluramine caused a similar nonsignificant decrease in lymphocyte count, the prolonged administration of compound **4** resulted in an unacceptable lymphopenia and precluded further development of these potentially interesting antiobesity agents.

Experimental Section

Melting points were determined on a Büchi-Tottoli apparatus and are uncorrected. Where analyses are indicated by symbols of the elements, the analytical results obtained were within ±0.4% of the theoretical values. Petroleum ether is of bp 60–80 °C unless otherwise indicated. THF was distilled from $LiAlH_4$ and DMF was dried over molecular sieves 4A.

2,6-Di-*tert*-butyl-4-(4′-chlorophenoxy)phenol (Cf. Ref 10). 4-(4-Chlorophenoxy)phenol (86.8 g) was dissolved in xylene (500 mL) containing concentrated H_2SO_4 (1.0 mL). The solution was heated to 100 °C with stirring and 2-methylpropene was slowly passed through the solution for 18 h. The cooled solution was washed with water (3 × 50 mL), the organic layer was evaporated, and the resultant solid was recrystallized twice from petroleum ether giving a white solid: yield 67 g; mp 137–139 °C. Anal. ($C_{20}H_{25}ClO_2$) C, H.

2,6-Di-*tert*-butyl-4-(4′-chlorophenylsulfonyl)phenol. 2,6-Di-*tert*-butyl-4-(4′-chlorophenylthio)phenol (3.49 g, 0.01 mol) in glacial acetic acid (50 mL) and 30% H_2O_2 (2.2 mL, 0.02 mol) was refluxed for 4 h. After cooling the mixture was diluted with water (400 mL) and the solid extracted with EtOAc. The organic layer was washed with 5% aqueous $NaHCO_3$ until neutral and

Table III. Effect of Selected Compounds on Food Intake and Body and Selected Organ Weights in Female Rats

No.	Dose (mg/kg), duration	Food intake, %	Body wt, %	Uterofat, %	Adrenals, %	Liver, %
4	80, 5 weeks	−10 (NS)	−9 ($p = 0.001$)	−35 ($p = 0.001$)	+16 ($p = 0.01$)	−3.4 (NS)
4	80, 5 days	−79 ($p = 0.02$)	−10 (NS)	Not measured	+21 ($p = 0.05$)	−9 (NS)
57	100, 5 days	−51 ($p = 0.02$)	−4 (NS)	−28 ($p = 0.05$)	+16 ($p = 0.01$)	+21 ($p = 0.01$)
58	100, 5 days	−22 (NS)	−1 (NS)	−18 (NS)	+8 (NS)	+11 (NS)

then with brine. Evaporation gave an off-white solid which was recrystallized from EtOAc–petroleum ether: yield 2.8 g; mp 187–189 °C. Anal. ($C_{20}H_{25}ClO_3S$) C, H.

2,6-Di-*tert*-butyl-4-(2-thienyl)phenol. To a stirred solution of thiophene (2.63 g, 0.03 mol) in dry THF (100 mL) at 0 °C under an argon atmosphere was added a 1.6 M solution of BuLi in hexane (18.7 mL, 0.03 mol) during 30 min. After a further 30 min at 0 °C, a solution of 2,6-di-*tert*-butylbenzoquinone (7.0 g, 0.03 mol) in dry THF (50 mL) was added at 0 °C and then the mixture was stirred at room temperature for 3 h.

This solution was then added to a suspension of $LiAlH_4$ (0.80 g, 0.02 mol) in dry THF (100 mL) at 18 °C during 30 min. After stirring overnight, 1 N H_2SO_4 (200 mL) was cautiously added with cooling in an ice bath. The aqueous layer was separated and extracted with ether. The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated to an oil which was chromatographed on silica gel (125 g) eluting with petroleum ether. The required eluates furnished 2.5 g of an oil whose IR and NMR spectra were consistent with those expected for the title compound. The compound was used without further purification in the alkylation stage.

Preparation of Oxypropanolamines. The stilbene oxypropanolamines were all prepared by the same general method and the procedure is exemplified by the preparation of compound **31**.

1-[2,6-Di-*tert*-butyl-4-(4′-bromo-*trans*-styryl)phenoxy]-3-isopropylamino-2-propanol (31). Piperidine (8.43 g, 0.119 mol) was added to a solution of *p*-bromophenylacetic acid (11.25 g, 0.0523 mol) in xylene (100 mL) whereupon a dense white solid precipitated. 3,5-Di-*tert*-butyl-4-hydroxybenzaldehyde (11.7 g, 0.05 mol) was added and the resulting mixture was stirred and refluxed for 7 h under N_2 in a Dean and Stark apparatus suitable for the continuous removal of the water formed in the reaction. The resulting dark solution was cooled and filtered, and the filtrate was evaporated in vacuo at 70 °C. The residual red oil was chromatographed on a column (ca. 4 × 50 cm) of Florisil using petroleum ether (bp 40–60 °C) as eluent. The required eluates were evaporated in vacuo at 60 °C, and the residue was crystallized from EtOH to give the desired phenol derivative: yield 4.9 g; mp 128–130 °C.

Attachment of the Basic Side Chain. A solution of the foregoing phenol (3.87 g, 0.01 mol) in DMF (20 mL) was added to a stirred suspension of oil-free sodium hydride (0.35 g, 0.015 mol) in DMF (20 mL). When the resulting effervescence had ceased (after 20 min) epichlorohydrin (1.4 mL, 0.018 mol) was added. The mixture was refluxed for 3 h, cooled, added to water (200 mL), and extracted with ether (2 × 150 mL). The ethereal extract was washed successively with water (100 mL) and saturated brine (100 mL) and then dried (Na_2SO_4), and the solvent was evaporated at 40 °C in vacuo. The residual oil was dissolved in MeOH (150 mL) and isopropylamine was added. The mixture was refluxed for ca. 18 h and then cooled. The solid which formed was filtered off and crystallized from petroleum ether to give the title compound: yield 1.3 g; mp 110–112 °C.

1-[2,6-Di-*tert*-butyl-4-(4′-hydroxy-*trans*-styryl)phenoxy]-3-isopropylamino-2-propanol (33). Compound **32** (3 g, 6.6 mmol) was added to freshly precipitated pyridine hydrochloride (4.6 g, 40 mmol) and heated at 190 °C under N_2 in the dark for 105 min. After cooling, the residue was partitioned between 1 N NaOH and Et_2O. The ether layer was washed with brine and dried (Na_2SO_4), and the maleate salt precipitated by addition of ethereal maleic acid. It was recrystallized from MeOH and Et_2O: yield 850 mg; mp 177–178 °C.

2,6-Di-*tert*-butyl-4-phenethynylphenol (75). To a solution of phenylacetylene (10.2 g, 0.1 mol) in dry THF (200 mL) at 0 °C under an argon atmosphere was slowly added a 1.6 M solution of BuLi in hexane (62.5 mL, 0.1 mol). After the black solution had been stirred at 0 °C for 30 min, a solution of 2,6-di-*tert*-butylbenzoquinone (22.0 g, 0.1 mol) in dry THF (100 mL) was slowly added so that the temperature did not exceed 5 °C. The mixture was allowed to come to room temperature and stirred thus for 3 h. The reaction mixture was then cooled to 0 °C and a saturated aqueous solution of ammonium chloride (200 mL) added. The organic layer was separated, combined with an ethereal extract of the aqueous layer, washed with brine, dried (Na_2SO_4), and evaporated to a dark gum.

The gum was dissolved in a minimum of ether and added to a vigorously stirred suspension of coarse tin powder (30 g) in concentrated HCl (250 mL) and water (250 mL). The mixture was stirred overnight and extracted with ether and the combined ether extracts were washed with brine, dried (Na_2SO_4), and evaporated to a dark gum. This gum was chromatographed on silica gel (600 g) in hexane, yielding 15.8 g of yellow crystals. An analytical sample was obtained from hexane, mp 114–115 °C. Anal. ($C_{22}H_{26}O$) C, H.

3-[2,6-Di-*tert*-butyl-4-(4′-chlorophenyl)phenoxy]-1,2-propanediol (77). An 80% dispersion of NaH in mineral oil (0.9 g, 0.03 mol) was freed of oil and suspended in dry DMF (20 mL) under an argon atmosphere. A solution of phenol **76** (6.2 g, 0.02 mol) in dry DMF (25 mL) was added slowly and when effervescence ceased, epichlorohydrin (4.6 mL, 0.06 mol) was added and the mixture heated at 150 °C for 4 h. After cooling, the mixture was diluted with water (500 mL) and extracted with ether (2 × 200 mL). The organic extract was washed with brine and evaporated to an oil. The oil was dissolved in dioxane (50 mL) and 2 N NaOH (20 mL) added. The mixture was stirred for 1 h at room temperature and then the separated aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated to an oil. This oil was dissolved in THF (100 mL) and 30% $HClO_4$ (20 mL) and stirred overnight at room temperature. The mixture was extracted with ether and the ether extracts were washed with water and brine. After drying (Na_2SO_4), removal of the solvent gave an oil which crystallized on trituration with petroleum ether. The solid was recrystallized from EtOAc–petroleum ether: yield 3.5 g; mp 174–176 °C. An analytical sample was obtained after a second recrystallization: mp 179–181 °C. Anal. ($C_{23}H_{31}ClO_3$) C, H.

2-[2,6-Di-*tert*-butyl-4-(4′-chlorophenyl)phenoxy]acetaldehyde (78). The foregoing diol (3.6 g, 9.2 mmol) was stirred in EtOH (140 mL) at 45 °C. A solution of sodium metaperiodate (2.07 g, 9.7 mmol) in 1 N H_2SO_4 (100 mL) was quickly added and the mixture stirred at 45 °C for 1 h. The mixture was added to water (1 L) and then extracted with ether. The organic extracts were washed with brine, dried (Na_2SO_4), and evaporated to an oil that was filtered through silica gel (50 g) in toluene. The required eluates furnished a white solid which was recrystallized from petroleum ether: yield 2.8 g; mp 89–91 °C. Anal. ($C_{22}H_{27}ClO_2$) C, H.

1-[2,6-Di-*tert*-butyl-4-(4′-chlorophenyl)phenoxy]-5-methyl-2-hexanol (79). A Grignard reagent was prepared from magnesium (0.17 g, 7.1 mmol) and 1-bromo-3-methylbutane (1.1 g, 7.2 mmol) in dry ether (30 mL) at reflux. After cooling to room temperature, a solution of the foregoing aldehyde (1.7 g, 4.7 mmol) in ether (10 mL) was added and the mixture refluxed for 2 h. The reaction mixture was then treated cautiously with 2 N H_2SO_4 (100 mL) at ice temperature. The separated organic layer was washed with brine, dried (Na_2SO_4), and evaporated to an oil which slowly crystallized. The solid was recrystallized from petroleum ether: yield 1.2 g; mp 107–110 °C. Anal. ($C_{27}H_{39}ClO_2$) C, H.

Resolution of Racemic Amine 4. A solution of di-*p*-toluoyl-*d*-tartaric acid (9.1 g, 0.024 mol) in EtOH (200 mL) was added to a solution of **4** (20 g, 0.047 mol) in EtOH (250 mL). After 4 h at room temperature 11.6 g of salt was precipitated: mp 204–205 °C. Three recrystallizations from aqueous EtOH raised the mp to 208.5–209 °C. Neutralization and recrystallization of the free base from aqueous MeOH afforded the (+)-amine: yield 3.3 g; mp 87–88 °C; $[\alpha]^{25}_D$ +5.4° (EtOH).

The ethanolic filtrate from the first crystallization above was evaporated to dryness and the residue partitioned between 2 N NaOH and Et_2O. The ether layers were washed with brine, dried (Na_2SO_4), and evaporated to a solid (12.8 g). This solid was dissolved in EtOH (250 mL) with warming and treated with a solution of di-*p*-toluoyl-*l*-tartaric acid (5.76 g, 0.015 mol) in EtOH (100 mL). After cooling slowly to room temperature during 2 h, 11.1 g of salt was deposited, mp 205–206 °C. Three recrystallizations from aqueous EtOH raised the mp to 209.5–210 °C. Neutralization and recrystallization from aqueous MeOH afforded the (−)-amine: yield 3.2 g; mp 87–88 °C; $[\alpha]^{25}_D$ −5.2° (EtOH). An equal weight of the two isomers had a mmp of 110–112 °C.

Attempted Isomerization of 4. Solutions (1.5×10^{-3} M) of **4** were prepared in several solvents (4:1 MeOH–H_2O, 55:45 EtOH–H_2O, 2-propanol, hexane, cyclohexane) and irradiated

under N_2 with light from an immersed 100-W high-pressure mercury lamp fitted with a filter to exclude light below about 300 nm. The reaction was followed by taking samples and diluting 1:50 for UV spectroscopy. Calculations showed that, at the photostationary state, a 4:1 cis–trans mixture was produced. It did not prove possible to separate a sample of the pure cis isomer.

Bioassay. (a) Mice. For the lipid catabolism screening test, the test compound was administered in the diet to groups of ten female mice for a period of 10 days. Groups of mice were carefully organized to have the same mean group body weight and distribution about the mean at the start of the test period. Food consumption was measured by weighing powdered diet at the beginning and end of the treatment period. Food was provided to groups of ten mice in a specially designed, individually partitioned metal hopper which minimized spillage. The mice were killed by anesthetic and the mean group body weight was determined. Mice were then individually dissected to provide tissues. The parametrial fat organ which is simply termed "uterofat", because of its proximity to and attachment to the uterine horns of the mouse, was weighed for each group of mice. Comprehensive studies showed that the simple "wet" weight of this fat depot bears a useful predictive correlation (correlation coefficient of 0.77 in one major study) with total carcass fat of mice as determined by petroleum ether extraction techniques and further that both parameters responded similarly to administered compounds. Changes in uterofat weight, therefore, reflect changes in carcass lipid of the mice. The maximum dietary dose used was 0.04% diet, approximately equivalent to 40 mg/kg of body weight of the mouse per day, dependent upon the amount of food consumed. At these dose levels, nonacceptability of compound (palatability) was not encountered with these compounds. Changes in uterofat weights in treated groups were determined by comparison with five untreated control groups each of ten mice and four positive control groups each of ten mice using standards, e.g., *d*-amphetamine.

For the purposes of the glucose and insulin assays, on the morning of the tenth day of the lipid catabolism test the animals were killed without prior starvation by ether anesthesia. Blood samples were withdrawn from the left ventricle during the anesthesia into heparinized tubes and the plasma was separated. Plasma glucose was determined by a glucose oxidase method (Boehringer). Plasma insulin levels were determined by the double antibody method of Hales and Randle[18] using a rat insulin standard.

(b) Rats. In the 5-day rat experiments the compounds were administered as an aqueous suspension po for five consecutive days to groups of six 180–200-g female rats. Controls were dosed with vehicle, the food intake was measured daily, and the rats were killed on the sixth day and body and organ weights determined.

For the 5-week studies compounds were administered in the diet to 150–200-g female rats fed ad libitum. The rats were arranged five to a cage with total group sizes of 20–30 rats per control or treatment level. Animals were weighed before, during, and at the end of the study, and food intake was measured weekly. At the end of the test the animals were killed by ether anesthesia. Organ weights were determined and the carcass was stored at −20 °C. Carcass analyses were performed by standard procedures.[19]

(c) Dogs. Compounds were administered daily to female beagles in gelatin capsules (empty gelatin capsules for controls) 30 min before access to weighed quantities of dog food. The daily food intake was assessed by weighing the food remaining after a 2-h access period. Body weight was determined at the beginning of the experiment and weekly thereafter.

(d) Biochemical Studies. Hepatocyte suspensions were prepared essentially according to Zahlten and Stratman[20] and incubated with [^{14}C]lactate and the drug in question for 2 h. The incubation was terminated with perchloric acid and the mixture centrifuged. The pellet was extracted overnight with $CHCl_3$–MeOH (2:1) and the extract washed three times with 4 mM $MgCl_2$ solution. The solution was then transferred to a scintillation vial, the solvent was evaporated, and the residue was counted in the usual manner.

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