Nonsteroidal Hypocholesteremic Agents. II. The Synthesis and Serum Sterol Lowering Properties of 4-(2′-Dialkylaminoalkoxy)-4′-substituted Biphenyls and Related Compounds[1]

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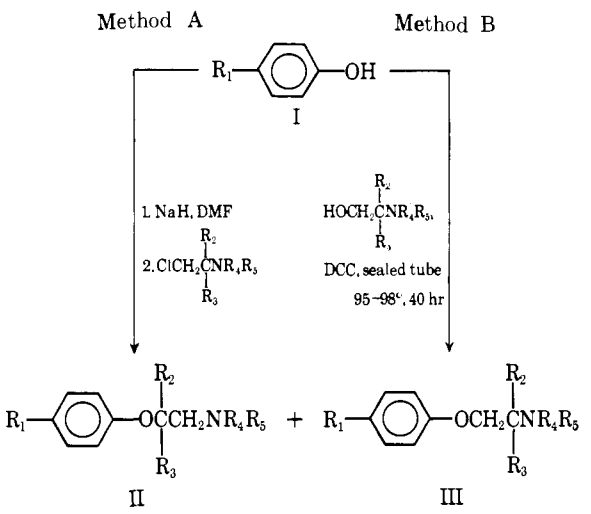
The synthesis and serum sterol lowering properties of a series of orally active 4,4′-disubstituted biphenyls and related compounds are discussed. Using 2-(4′-nitro-4-biphenylyloxy)triethylamine as a lead compound, variations in the basic ether moiety of this derivative were investigated. Maximum activity was found when the terminal tertiary amine was included in a pyrrolidine ring. Based on this study a series of 1-{2-[4′-(substituted)-4-biphenylyloxy]ethyl}pyrrolidines was synthesized leading to the discovery of 1-{2-[4′-(trifluoromethyl)-4-biphenylyloxy]ethyl}pyrrolidine (**35**), one of the most potent, nonestrogenic, nonsteroidal hypocholesteremic agents reported to date. It is capable of causing *ca.* 20% lowering of serum sterol levels (compared to control levels) when administered to rats orally at *ca.* 0.0003% of diet.

This work represents the second part[2a] of a program initiated for the purpose of synthesizing orally active, nonsteroidal hypocholesteremic agents and has led to the discovery of a series of biphenyl derivatives having marked serum sterol lowering properties.

The intermediates used in the synthesis of the nitrobiphenyl derivatives (**4**, **5**, and **16–26**) and the halobiphenyl derivatives (**10–15** and **33**) were prepared by well-known methods and the 4-(2-dialkylaminoalkoxy)-4′-substituted biphenyls reported in this paper were prepared by the alkylation methods outlined in Scheme I. The isomers (II and III) produced when branched

SCHEME I



R_1 = 2′- or 4′-substituted phenyl
R_2 and R_3 = H or CH_3
R_4 = R_5 = lower alkyl
DCC = N,N′-dicyclohexylcarbodiimide

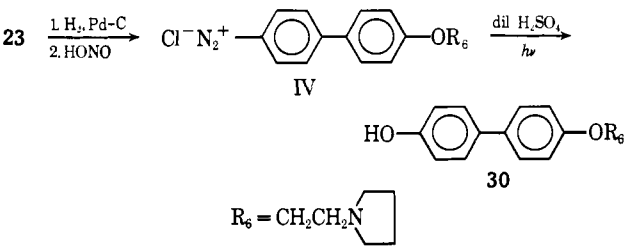
alkylating agents were used in methods A or B could be separated by liquid–liquid partition chromatographic techniques (see Experimental Section); the intermediacy of a cyclic ethylenimonium ion in method B is discussed elsewhere.[2b]

(1) Portions of this paper were presented before the Division of Medicinal Chemistry at the 151st National Meeting of the American Chemical Society, Pittsburgh, Pa., March 28–31, 1966, Abstracts of Papers, p 18P.

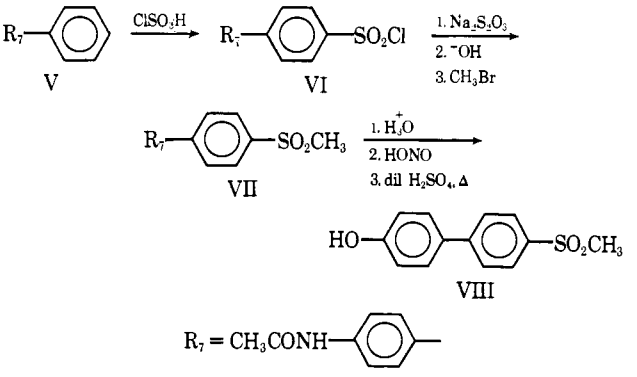
(2) (a) For part I of this series see F. L. Bach, J. C. Barclay, and E. Cohen, *J. Med. Chem.*, **10**, 802 (1967); (b) F. L. Bach and E. Cohen, *Chem. Commun.* 415 (1968).

The hydroxybiphenyl derivative (**30**) was prepared in good yield using **23** as starting material (see Scheme II), and the intermediate (VIII) required for the synthesis of **32** was prepared as outlined in Scheme III.

SCHEME II



SCHEME III



The most active biphenyl derivative, **35**, was prepared following the synthetic routes illustrated in Scheme IV. Although the Grignard route required more synthetic steps than the mixed Ullmann route, the over-all yield was much better.

Results and Discussion

One phase of the present structure–activity relationship study centered on the importance of the bridging NH group in the original lead compound (**1**) and the results are listed in Table I. As indicated, replacing the NH group in **1** by O or S (*cf.* **1–3**) resulted in a complete loss of activity; however, elimination of the bridging NH group in **1** to form the nitrobiphenyl

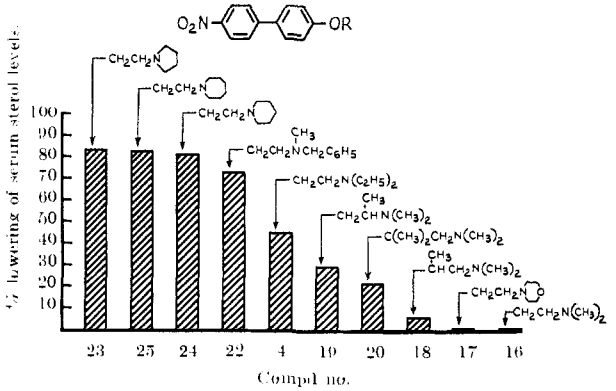
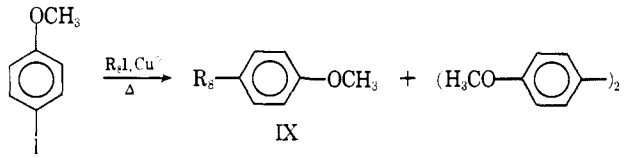


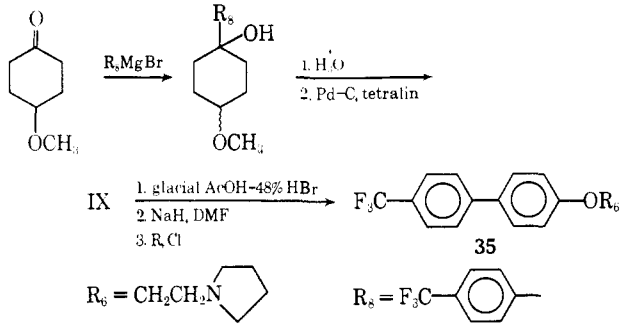
Figure 1.—The effect of variation in the basic ether portion of 4-nitro-4′-substituted biphenyls. Hypocholesteremic activity is based on per cent lowering of serum sterol levels compared to control levels when compounds were fed to rats at 0.003% of the diet for 6 days.

Scheme IV

Mixed Ullmann route



Grignard route



analog **4** led to the discovery of a very potent series of hypocholesteremic agents.

A brief inspection of the data listed in Table II encourages one to relate the high activity of **4** with the following structural features:[3] (a) a 4,4′ substitution pattern is important in the biphenyl nucleus (*cf.* **4** and **5**), and (b) maximum hypocholesteremic activity is associated with biphenyl systems having strong electron-withdrawing groups in one ring (*cf.* **4** and **6**) and a basic ether residue in the opposite ring; the O and N atoms of the basic ether group are separated by a two-carbon chain in all of the active compounds.

Having previously noted the effects of slight variations in the basic ether group of other types of nonsteroidal hypocholesteremic agents,[2a] a similar study was initiated using 4-halobiphenyl derivatives. These results are summarized in Table III and, apparently, marked differences in serum sterol activity can also be achieved by these relatively minor changes in appropriately substituted biphenyls[4] (*cf.* **11–14**).

(3) These points parallel the results obtained in the diphenylamine structure–activity relationship studies previously reported; see ref 2a.

(4) Possible changes in the inhibition of cholesterol biosynthesis due to steric effects in the basic ether residue of active biphenyls will be reported elsewhere.

Table I

Analogs of 4-(2-Diethylaminoethoxy)-4′-nitrodiphenylamine (1)

Compd	Structure	Serum sterol lowering activity,[b,c,g]
1[e]	O_2N—NH—$OCH_2CH_2N(C_2H_5)_2$	2
2[e]	O_2N—O—$OCH_2CH_2N(C_2H_5)_2$	0
3[e]	O_2N—S—$OCH_2CH_2N(C_2H_5)_2$	0
4[d]	O_2N—$OCH_2CH_2N(C_2H_5)_2$	3

[a] For a description of the animal testing procedure see ref 2a and the following paper. [b] Activity ratings were based on per cent of drug in diet necessary to bring about a 20–30% lowering of serum sterols compared to control levels: 0.05% = 0, 0.03% = 1, 0.01% = 2, 0.003% = 3, 0.001% = 4, 0.0003% = 5. Compounds eliciting a serum sterol lowering of 19% (or less) when tested at 0.05% of the diet are rated zero. [c] For the synthesis and physical properties of **1–3** see part I in this series.[2a] [d] See the Experimental Section and Table II for the synthesis and physical properties. [e] *trans*-1,4-Bis(2-chlorobenzylaminomethyl)cyclohexane (Ayerst Research Laboratories) was rated 4 on this scale. [f] The initial screening data reported in Tables I–V were determined by Dr. S. Gordon and his group in the Biochemical Research Section of this laboratory.

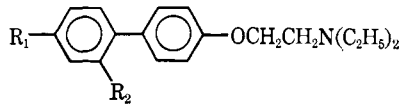
Based on the preliminary data listed in Table III, a very detailed investigation dealing with the dialkylaminoethoxy portion of **4** (the lead compound at the beginning of this study) was carried out. The initial screening results reported in Table IV clearly associate 2-polymethyleniminoethoxy residues with strong hypocholesteremic activity (*cf.* **4**, **23–25**). These results are more clearly illustrated in Figure 1 where several points are emphasized: (1) replacing a terminal dimethylamino group by a diethylamino group increases activity (*cf.* **4** and **16**); (2) joining the alkyl substituents on the N to form a polymethylene ring elicits a marked increase in activity (*cf.* **4** and **23–25**); (3) alkyl branching in 2-dimethylaminoethoxy residues did not bring about the same response in the 4-nitrobiphenyl derivatives as previously observed in the 4-nitrodiphenylamines and N-(hetero)-*p*-(2-dialkylaminoethoxy)anilines (see ref 2a, and *cf.* **16** and **18–20**); and (4) specific basicity requirements in the tertiary amine portion of the $-OCH_2CH_2N<$ group seem to be indicated by the considerable loss in activity occurring when a piperidino group is replaced by a morpholino group (*cf.* **17** and **24**). An estimate of this difference in basicity can be made by comparing the pK_a values[5] of piperidine and morpholine, *i.e.*, 11.2 and 8.7, respectively.

Our attention was next directed to functional groups which might replace the 4′-NO_2 in **23** and **24** and still impart activity to the biphenyl system. An interesting structure–activity relationship emerged from the results expressed in Table V. Reduction of the 4′-NO_2 to 4′-NH_2 caused a considerable loss in serum sterol lowering activity (*cf.* **23** and **28**) as did replacement with OH, CH_3, $C(CH_3)_3$, and $C(CH_3)$=NOH groups in the 4′ position (*cf.* **23**, **30**, and **36–38**). Based on these data and those in Table II it is apparent that strong

(5) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," John Wiley and Sons Inc., New York, N. Y., 1962, p 141.

TABLE II

SUBSTITUTED 4-(2-DIETHYLAMINOETHOXY)BIPHENYLS AND RELATED COMPOUNDS

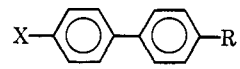


Compd	R_1	R_2	Yield, %[b]	Mp or bp (mm), °C	Formula[f]	Serum sterol lowering act.[a]
4	NO_2	H	62	49–50	$C_{18}H_{22}N_2O_3$	3
5	H	NO_2[c]	55	206–207	$C_{18}H_{22}N_2O_3 \cdot HCl$	0
6	H	H	45	176–178 (0.2)	$C_{18}H_{23}NO$	0
7	$CH_3CC{\equiv}CH$ (OH)	H	36	116–118	$C_{22}H_{27}NO_2$	0
8	COOH	H[c]	45	261–262[d]	$C_{19}H_{23}NO_3 \cdot HCl$	1
9	$COCH_3$	H	48	113–114	$C_{20}H_{25}NO_2$	2
10	Br	H[c]	45	198–199	$C_{18}H_{22}BrNO \cdot HCl$[e]	2

[a] See footnote *b* in Table I for activity ratings. [b] % yield for last step in synthesis. [c] Compound tested as a monohydrochloride. [d] Melted with decomposition. [e] C: calcd, 56.19; found, 56.78. N: calcd, 3.64; found, 3.10. [f] All compounds were analyzed for C, H, N.

TABLE III

VARIATIONS IN THE BASIC ETHER PORTION OF 4-HALO-4′-SUBSTITUTED BIPHENYLS

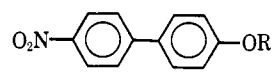


Compd	X	R	Yield, %[b]	Mp, °C	Formula[f]	Serum sterol lowering act.[a]
11	Cl	$OCH_2C(CH_3)_2N(CH_3)_2$	8[c]	115–116	$C_{18}H_{22}ClNO$[g]	1
12	Cl	$OC(CH_3)_2CH_2N(CH_3)_2$	36[c]	83–84	$C_{18}H_{22}ClNO$	2
13	Br	$OC(CH_3)_2CH_2N(CH_3)_2$[d,e]	34	77–79	$C_{18}H_{22}BrNO$	3
14	Br	$OCH_2CH_2N(CH_3)_2$	87	122–123	$C_{16}H_{18}BrNO$[h]	0
15	Br	$NHCH_2CH_2N$	20	141–142	$C_{18}H_{21}BrN_2$	1

[a] See footnote *b* in Table I for activity ratings. [b] % yield is given for last step in synthesis. [c] The distribution of isomers in the crude yield was determined by nmr analysis. The isomers were separated by partition chromatography; see the Experimental Section for details. [d] Nmr analysis indicated 89% of isomer **13** present in the reaction mixture. [e] Isomeric mixture was submitted for screening. [f] All compounds were analyzed for C, H, N. [g] C: calcd, 71.16; found, 70.51. [h] H: calcd, 5.67; found, 6.28.

TABLE IV

VARIATIONS IN THE BASIC ETHER PORTION OF 4-(2-DIALKYLAMINOETHOXY)-4′-NITROBIPHENYLS

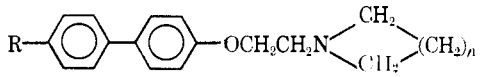


Compd	R	Yield, %[b]	Mp, °C	Formula[h]	Serum sterol lowering act.[a]
16	$CH_2CH_2N(CH_3)_2$	42	68–69	$C_{16}H_{18}N_2O_3$	2
17	CH_2CH_2NO	18	112–113	$C_{18}H_{20}N_2O_4$[i]	0
18	$CH(CH_3)CH_2N(CH_3)_2$[c,d]	40	*g*	$C_{17}H_{20}N_2O_3$	1
19	$CH_2CH(CH_3)N(CH_3)_2$[c,d]		*g*	$C_{17}H_{20}N_2O_3$	3
20	$C(CH_3)_2CH_2N(CH_3)_2$[e]	31	74–75	$C_{18}H_{22}N_2O_3$	3
21	$CH_2CH_2N(i\text{-}C_3H_7)_2$	30	50–51	$C_{20}H_{26}N_2O_3$	3
22	$CH_2CH_2N(CH_3)CH_2C_6H_5$	22	62–63	$C_{22}H_{22}N_2O_3$	4
23	CH_2CH_2N	64	69–70	$C_{18}H_{20}N_2O_3$	4
24	CH_2CH_2N[b,f]	40	227–230	$C_{19}H_{22}N_2O_3 \cdot HCl$	4
25	CH_2CH_2N[b,f]	54	225–229	$C_{20}H_{25}N_2O_3 \cdot HCl$	4
26	$CH_2CH_2CH_2N(CH_3)_2$	70	169–170	$C_{16}H_{18}N_2O_3$	0

[a] See footnote *b* in Table I for activity ratings. [b] % yield is given for last step in synthesis. [c] The isomeric distribution was determined by nmr analysis and separation of isomers was achieved by partition chromatography; see Experimental Section. [d] The racemic mixture was not resolved; structure established by nmr analysis. [e] Structure established by nmr. [f] The compound was tested as monohydrochloride. [g] Isomeric mixture melted at 48–50°. [h] All compounds were analyzed for C, H, N. [i] C: calcd, 65.84; found, 64.38.

Table V

4-(2-Polymethyleniminoethoxy)-4′-substituted Biphenyls



Compd	R	n	Yield, %[a]	Mp, °C	Formula[b]	Serum sterol lowering act.[c]
23[d]	NO_2	2				4
27		3	71	105–106	$C_{26}H_{36}N_2O_2$	0
28	NH_2	2	88	102–103	$C_{19}H_{22}N_2O$	1
29	$COCH_3$	3	42	111–113	$C_{21}H_{25}NO_2$	0
30	OH	2	57	154–155	$C_{18}H_{21}NO_2$[e]	0
31	COOH[f]	2	21	266–271	$C_{19}H_{21}NO_3 \cdot HCl$[g]	0
32	SO_2CH_3	2	41	153–154	$C_{19}H_{23}NO_3S$	2
33	Br[d]	2	28	105–107	$C_{18}H_{22}BrNO$	4
34	CN	3	23	121–123	$C_{20}H_{22}N_2O$	4
35	CF_3	2	49	109–110	$C_{19}H_{20}F_3NO$	5
36	CH_3	2	81	86–88	$C_{19}H_{23}NO$[h]	0
37	$C(CH_3)_3$	2	67	68–69	$C_{22}H_{29}NO$	0
38	$CH_3C{=}NOH$	3	97	206–208	$C_{21}H_{26}N_2O_2$	0

[a] See footnote *b* in Table I for activity ratings. [b] % yield is given for last step in synthesis. [c] Compound tested as a monohydrochloride. [d] Compound tested as a hemihydrate. [e] Physical properties reported in Table IV. [f] All compounds were analyzed for C, H, N. [g] C: calcd, 76.30; found, 77.05. N: calcd, 4.94; found, 4.30. [h] C: calcd, 62.37; found, 61.50. [i] C: calcd, 81.10; found, 81.60.

electron-withdrawing groups in the 4′ position[6] of 4-(2-polymethyleniminoethoxy)-4′-substituted biphenyls are necessary for high activity. A number of biphenyls meeting this requirement were synthesized and the results outlined in Table V seem to support this concept.[7] Placing strong electron-withdrawing groups in the 4′ position of the biphenyl systems being considered is a decisive factor in obtaining high activity; however, the exact role of these groups is not established. Although no physical measurements are available, one explanation for these changes in hypocholesteremic activity may be found in the ability of various substituents to alter lipid–water partition coefficients.[8]

Compounds **36** and **37** were synthesized to study the effect of replacing a CF_3 group by a CH_3 or $C(CH_3)_3$ group. The potency found in **35** and lost in **36** and **37** obviates any bulk requirements in the 4′ position of the compounds described in Table V; however, these results do emphasize the need for a particular type of polarity in that position.

It should also be noted that activity was lost when the 2-pyrrolidinylethoxy portion of **33** was replaced by a 2-pyrrolidinylethylamino residue (*cf.* **15** and **33**).[9]

The 4-trifluoromethylbiphenyl derivative (**35**)[10] has been selected as the most promising compound developed in this program. The ability of **35** to lower serum sterol levels significantly (*ca.* 20%) in rats at doses between 0.0001 and 0.0003% of the diet established it as the most effective, nonsteroidal, nonestrogenic hypocholesteremic agent reported to date. Its activity has been demonstrated in mice, rats, dogs, and monkeys.[11]

Experimental Section

The melting points were determined in open, capillary tubes using a Hershberg apparatus; both melting points and boiling points are uncorrected. Infrared spectra were measured in mineral oil mulls or KBr disks using a Perkin-Elmer spectrophotometer (Model 21); nmr spectra were obtained at 60 Mc using a Varian Associates A-60 instrument with TMS as an internal standard, and glpc analyses were made using an F & M (Model 720) glpc apparatus. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

General synthetic procedures for the preparation and isolation of the compounds included in this paper are given in the following section. Where necessary, specific preparations are described and the analyses, yields, and physical data are recorded in the tables.

The following substituted biphenyls were either commercially available or were prepared according to methods previously reported: 4-hydroxy-4′-nitrobiphenyl,[12] 4-acetyl-4′-methoxybiphenyl,[13] 4-bromo-4′-hydroxybiphenyl,[14] 4-chloro-4′-hydroxybiphenyl,[15] *p*-phenylphenol,[16] *p*-phenylanisole,[17] and 4-aminobiphenyl.[18]

Alkylation of 4-Hydroxybiphenyl Derivatives. Method A.—The preparation of 2-(4′-nitro-4-biphenylyloxy)triethylamine (**4**) may be considered a general method. A solution consisting of 21.5 g (0.1 mole) of 4-hydroxy-4′-nitrobiphenyl in dry DMF (200 ml) was treated with 4.3 g (0.1 mole) of NaH (54.7%) added portionwise. After warming the reaction mixture at 95–98° for 20 min (or until a clear solution resulted), 13.5 g (0.1 mole) of 2-diethylaminoethyl chloride dissolved in DMF (75 ml) was added at once and the suspension was refluxed for 20 hr. The reaction mixture was cooled and filtered, and the clear filtrate was concentrated *in vacuo* to a semisolid residue. Two 100-ml portions of H_2O were used to triturate the crude product which was then dissolved (C_6H_6); the solution was decolorized

(6) This assumption also requires that the functional groups substituted in the 4 position of the parent compound, 4-(2-pyrrolidinyl- or 4-(2-piperidinoethoxy)biphenyl, do not undergo metabolic modifications before reaching the site of action.

(7) At a dose level of 0.003% of the diet there is a rough correlation between the Hammett σ constants of the substituents in the 4′ position of 4-(2-polymethyleniminoethoxy)-4′-substituted biphenyls and the activity imparted to the biphenyl derivatives by these groups.

(8) For a more complete discussion relating physical properties to biological activities see N. J. Doorenbos in "Medicinal Chemistry," A. Burger, Ed., 2nd ed, Interscience Publishers, Inc., New York, N. Y., 1960, p 46.

(9) Similar isosteric effects are discussed in part 1 of this series; see ref 2.

(10) The generic name boxidine has been adopted for **35** (U. S. Adopted Names Council).

(11) For a comparison of the potency of **35** with other effective serum sterol lowering agents see S. Gordon and W. P. Cekleniak, *J. Med. Chem.*, **11**, 993 (1968).

(12) B. Jones and F. Chapman, *J. Chem. Soc.*, 1829 (1952).

(13) G. W. Gray, J. B. Hartley, and B. Jones, *ibid.*, 1412 (1955).

(14) S. E. Hazlet, G. Alliger, and R. Tiede, *J. Amer. Chem. Soc.*, **61**, 1447 (1939).

(15) C. M. S. Savoy and J. L. Abernethy, *ibid.*, **64**, 2719 (1942).

(16) Matheson Coleman and Bell.

(17) Eastman Organic Chemicals.

(18) Aldrich Chemical Co., Inc.

(charcoal) and dried (Na_2SO_4), and the C_6H_6 was removed. Compound **4** was isolated as a yellow, crystalline solid, yield 19.5 g (62%), mp 49–50°.

Compounds **4–10**, **14**, and **16–38** were prepared by this procedure.

N,N-Dimethyl-2-(4′-nitro-4-biphenylyloxy)propylamine (18) and N,N,1-Trimethyl-2-(4′-nitro-4-biphenylyloxy)ethylamine (19).—Following the procedure described in method A 25.3 g (0.1 mole) of the potassium salt of 4-hydroxy-4′-nitrobiphenyl and 12.2 g (0.1 mole) of 2-dimethylaminopropyl chloride were added to a toluene–*n*-AmOH (100:100 ml) solution, and the resulting suspension was refluxed 40 hr. A crude, heavy oil containing racemic isomers **18** and **19** was isolated following the work-up described above. The ratio of **18**:**19** was estimated to be 52:48 based on nmr spectral analyses; proton integration of the peaks ($CDCl_3$) at 227 (singlet CH_2O) and 147 cps (singlet CH_2N) were used in this determination.

Separation of **18** and **19** was achieved by liquid–liquid partition chromatography using an *n*-heptane–1,2-dimethoxyethane solvent system. A column was packed (600 g; acid-washed Celite 545, Johns-Manville, coated with 330 ml of stationary phase) and 1.0 g of the isomeric mixture (**18** and **19**) was added to the top of the packing before development. The first peak (**18**) was eluted at 3.0–3.5 hold-back volumes and the second peak (**19**) was collected at 3.5–4.0 hold-back volumes; the eluate was scanned at 233 mμ. Concentration of the eluates afforded 75 mg (**18**), a yellow oil, and 60 mg (**19**), a yellow, crystalline material, mp 62–64°.

Method B. 2-(4′-Bromo-4-biphenylyloxy)-N,N,2-trimethylpropylamine (13).—The following preparation may be considered a general method. A mixture consisting of 4-bromo-4′-hydroxybiphenyl (12.8 g, 0.05 mole), 7.9 g (0.07 mole) of 2-dimethyl-2-methyl-1-propanol, and 12.8 g (0.06 mole) of N,N′-dicyclohexylcarbodiimide was placed in a Pyrex tube (2.9 × 28 cm, 0.2-cm wall thickness) which was flushed with Ar before sealing the open end. The reaction mixture, initially a clear solution at 50–55°, was converted to a semicrystalline mass after heating (95–98°) for 40 hr. The reaction mass in the tube was triturated with two 100-ml portions of Et_2O[19] which was concentrated to a heavy, oily residue; the insoluble N,N′-dicyclohexylurea (DCU) was air dried and yielded 6.9 g (61%).[20] Concentration of the Et_2O extracts afforded 3.2 g (47%) of an isomeric mixture.[21] A pure sample of **13** (mp 77–79°) was deposited from a concentrated solution (petroleum ether, bp 30–60°) of the isomeric mixture.

N,N,2-Trimethyl-2-(4′-nitro-4-biphenylyloxy)propylamine (20).—A solution consisting of 12.7 g (0.05 mole) of the potassio derivative of 4-hydroxy-4′-nitrobiphenyl and 6.8 g (0.05 mole) of 2-dimethylamino-2-methylpropyl chloride in CH_3OH (200 ml) and H_2O (200 ml) was refluxed for 40 hr. After cooling, the reaction mixture was filtered and the clear filtrate was concentrated to a semisolid isomeric mixture. The ratio of **20** to its isomer, 2-(4′-nitro-4-biphenylyloxy)-N,N,1,1-tetramethylethylamine, was *ca.* 9:1 (nmr spectral analysis). A solution of the crude mixture was taken up in Et_2O, decolorized (charcoal), dried (Na_2SO_4), and treated with an excess of dry HCl. Precipitation of the HCl salt was immediate and the yellow, crystalline solid was collected and dissolved in H_2O (50 ml). The free base, released from the acidic solution using an excess of 1 *N* NaOH, was collected by filtration and recrystallized (Et_2O–petroleum ether); 2.4 g (14%), mp 74–75° (the structure of **20** was confirmed by its nmr). None of the isomers of **20** could be obtained pure from the mother liquor.

1,1′-[4,4′-Biphenylylenebis(oxyethylene)]dipiperidine (27).—Following the procedure outlined in method A 23.2 g of the disodio derivative of *p*-(*p*-hydroxyphenyl)phenol[17] and 15.0 g (0.1 mole) of 2-piperidinoethyl chloride were refluxed in DMF (80 ml) for 60 hr. After cooling, the reaction mixture was filtered and worked up as previously described. The desired product (**27**) was recrystallized (heptane) and air dried; 8.2 g (40%), mp 105–106°.

Demethylation of 4-Methoxy-4′-substituted Biphenyls. Method C.—This procedure is exemplified in the preparation of 4-acetyl-4′-hydroxybiphenyl. A solution consisting of 15.9 g (0.07 mole) of 4-acetyl-4′-methoxybiphenyl[13] in glacial AcOH (627 ml) and 48% HBr (127 ml) was refluxed under N_2 for *ca.* 17 hr. After cooling, the acidic reaction mixture was poured into H_2O (1.5 l.) and the pink solid which separated was collected and air dried; 14.0 g (94%). Recrystallization (*i*-PrOH) afforded the desired intermediate, mp 211–212°.

Biphenyl Synthesis. Mixed Ullmann. 1-{2-[4′-(Trifluoromethyl)-4-biphenylyloxy]ethyl}pyrrolidine (35).—A suspension consisting of 89.8 g (0.33 mole) of *p*-iodobenzotrifluoride,[22] 152.5 g (0.65 mole) of *p*-iodoanisole, and 322.7 g of Cu powder[23] in DMF (175 ml) was heated (225–230°) with stirring in a resin pot for *ca.* 5 days. After cooling, the solid reaction mass was pulverized and continuously extracted (heptane) for 2 days. Evaporation of the solvent left a dark brown residue (*ca.* 50 g) which was dissolved (heptane, 200 ml), decolorized (charcoal), and concentrated to 100 ml. On standing *ca.* 20 g of impure 4,4′-dimethoxybiphenyl was deposited as colorless crystals. Fractional crystallization was continued until the crops of crystalline material were free of impurities by tlc (80:20 heptane–EtOAc). Pure 4-methoxy-4′-trifluoromethylbiphenyl was isolated as colorless granules, 21.6 g (26%), mp 124–126°. *Anal.* ($C_{14}H_{11}F_3O$) C, H, F.

A solution consisting of 21.6 g (0.09 mole) of 4-methoxy-4′-trifluoromethylbiphenyl dissolved in glacial AcOH and HBr (48%) was refluxed for approximately 24 hr. The procedure and work-up described in method C was used to isolate 18.0 g (83%) of the crude product which was taken up in Et_2O (100 ml), decolorized (charcoal), filtered, and concentrated to one-third the original volume. The material which separated from the Et_2O solution (mp 147–148°) was pure enough for the next synthetic step (structure verified by nmr).

Following alkylation method A, 15.6 g (0.06 mole) of the sodio derivative of 4-hydroxy-4′-trifluoromethylbiphenyl was allowed to react with 8.0 g (0.06 mole) of 2-pyrrolidinylethyl chloride in refluxing DMF (100 ml) for 18 hr. The resulting suspension was cooled, filtered, and worked up as described in method A. Several fractional crystallizations from acetone afforded 9.8 g (49%) of pure **35**, mp 109–110°.

Grignard Route.—*p*-Bromobenzotrifluoride[22] (157 g, 0.7 mole) and *ca.* 1.0 g of MeI dissolved in dry Et_2O (200 ml) was added to 19 g (0.8 g-atom) of Mg suspended in Et_2O (20 ml) under the usual conditions.[24] Addition of the aromatic halide was regulated to maintain a gentle reflux and refluxing was continued an additional 1 hr after addition was complete. 4-Methoxycyclohexanone[25] (64 g, 0.5 mole) dissolved in 75 ml of dry Et_2O was added to the freshly formed Grignard reagent with vigorous stirring and, after addition of the ketone was complete, the reaction mixture was refluxed with stirring for approximately 1 hr. Decomposition of the Grignard reagent–ketone addition product was achieved by adding excess cold, aqueous NH_4Cl (53 g in 1 l. of H_2O), and the crude product was removed using two 100-ml portions of Et_2O. The combined extracts were decolorized (charcoal), filtered, and dried (Na_2SO_4). Removal of the Et_2O left a brown, oily residue which was distilled *in vacuo* affording 51.3 g (38%) of 1-(*p*-trifluoromethylphenyl)-4-methoxycyclohexanol, bp 121–122° (0.4–0.5 mm), mp 53–54°. *Anal.* ($C_{14}H_{17}F_3O_3$) C, H, F.

The 4-methoxycyclohexanol derivative (27 g, 0.1 mole), purified as described above, was added to a vigorously stirred concentrated H_2SO_4–glacial AcOH (10:40 ml) solution. When a clear solution resulted (*ca.* 2 min), the reaction mixture was poured all at once into a previously cooled (5–10°) mixture of H_2O (300 ml) covered with Et_2O (300 ml). The Et_2O layer was separated, dried (Na_2SO_4), and concentrated to a brown, oily residue. Fractionation of the crude oil yielded 18.3 g (71%) of 1-(*p*-trifluoromethylphenyl)-4-methoxycyclohexene, bp 104–105° (0.3–0.4 mm), $n^{25}D$ 1.5045 (av). *Anal.* ($C_{14}H_{15}F_3O_2$) C, H, F.

Dehydrogenation of the purified 4-methoxycyclohexene derivative, obtained as described above, was accomplished using a modification of the method described by Ainsworth.[26] A suspen-

(19) DCU is insoluble in the common organic solvents; mp 230–231°.

(20) Recovered DCU may be considered a measure of the extent of reaction. When reaction is incomplete, the unreacted carbodiimide can be converted to the urea derivative by adding a calculated amount of oxalic acid to the ethereal extract; see F. L. Bach, *J. Org. Chem.*, **30**, 1300 (1965).

(21) Nmr spectral analysis indicated a 93:7 distribution of isomers. A detailed discussion of the mechanism involved in this reaction has been published.[2b]

(22) Columbia Organic Chemicals Co., Inc.

(23) Natural copper fine (44-F), United States Bronze Powders, Inc.

(24) See, for example, M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, p 28.

(25) D. Papa, F. J. Villani, and H. F. Ginsberg, *J. Am. Chem. Soc.*, **76**, 4446 (1954).

(26) C. Ainsworth, *ibid.*, **79**, 5242 (1957).

sion consisting of 1-(*p*-trifluoromethylphenyl)-4-methoxycyclohexene (500 g, 1.95 moles), 166 g of Pd–C (10%), and nitrobenzene was refluxed for 22 hr. Aliquots of the reaction mixture taken periodically and analyzed by tlc (heptane–EtOAc (4:1) solvent system) indicated that aromatization was complete after this period of time. Removal of the nitrobenzene under reduced pressure left 442 g (89.9%) of the crude biphenyl derivative. Two recrystallizations (petroleum ether) produced material identical with that obtained from the "mixed Ullmann" procedure described above.

1-[2-(4′-*t*-Butyl-4-biphenylyloxy)ethyl]pyrrolidine (37).—This 4,4′-disubstituted biphenyl synthesis is a modification of the Grignard route described previously. A solution of 4-*t*-butylcyclohexanone[18] (46.3 g, 0.3 mole) in anhydrous Et_2O (150 ml) was added dropwise (30 min) to a stirred, ethereal solution of the Grignard reagent formed by addition of *p*-bromoanisole (61.7 g, 0.33 mole) to a suspension of Mg turnings (8.0 g, 0.33 g-atom) in Et_2O (200 ml). Next, the reaction mixture was added to a stirred, cooled (0–5°) slurry consisting of NH_4Cl (50 g), H_2O (125 ml), and ice (125 g). After 30 min, stirring was discontinued and the Et_2O layer was separated and filtered. The clear filtrate was decolorized (charcoal), dried (Na_2SO_4), and concentrated to a semisolid residue; the residual material was taken up in Et_2O and fractionally crystallized. The first four crops were combined after tlc (heptane–EtOAc, 4:1) showed the absence of starting material; 74.5 (93%). The crude 4-*t*-butyl-1-(*p*-methoxyphenyl)cyclohexanol obtained in this manner was used in the next step without further purification.

Dehydration of the 1,4-disubstituted cyclohexanol was carried out as described previously in the synthesis of **35**. A yield of 15 g (60%) of 4-*t*-butyl-1-(*p*-methoxyphenyl)cyclohexene was obtained from 26.2 g (0.1 mole) of the tertiary alcohol. The crude dehydration product melted at 77–78° and was used in the next step without further purification. Ir absorption bands were as expected.

A solution consisting of 17.1 g (0.07 mole) of 4-*t*-butyl-1-(*p*-methoxyphenyl)cyclohexene and 34.4 g (0.14 mole) of chloranil in 150 ml of xylene was refluxed for *ca.* 100 hr. After cooling, petroleum ether (150 ml) was added to the reaction mixture and precipitated tetrachlorohydroquinone was removed by filtration. The clear filtrate was washed successively with aqueous KOH (4 g in 96 ml of H_2O) and two 150-ml portions of H_2O, dried ($MgSO_4$), decolorized (charcoal), and concentrated to a solid residue, 16 g (96%). Recrystallization from a MeOH–Et_2O solution afforded pure 4-*t*-butyl-4′-methoxybiphenyl, 15 g (84%), mp 140–142°. *Anal.* ($C_{17}H_{20}O$) C, H.

Demethylation (method C) of the 4-methoxybiphenyl derivative (14.9 g, 0.06 mole) furnished an excellent yield of 4-*t*-butyl-4-hydroxybiphenyl, 13.3 g (98%), mp 152–153°. *Anal.* ($C_{16}H_{18}O$) C, H.

Following alkylation method A, 10 g (0.04 mole) of the sodio derivative of 4-*t*-butyl-4′-hydroxybiphenyl was allowed to react with 5.4 g (0.4 mole) of 2-pyrrolidinylethyl chloride in refluxing DMF (150 ml). The general work-up described previously afforded 8.7 g (68%) of crude material. A pure sample of **37** was isolated from an Et_2O–petroleum ether solution; mp 69–70°.

4′-(2′-Diethylaminoethoxy)-α-ethynyl-α-methyl-4-biphenylmethanol (7).—Li (0.3 g, 0.04 g-atom) was dissolved in liquid NH_3 (50 ml) at −70° and then treated with an excess of anhydrous acetylene. The ammoniacal suspension of lithium acetylide was placed in a steel bomb cooled to −70° and treated with **9** (4.94 g, 0.02 mole). The sealed bomb was then warmed to 25–30° and shaken for 18 hr. After recooling the bomb to −70°, the system was opened and the excess NH_3 was evaporated in a stream of dry N_2. The residue was then converted to an aqueous suspension by adding NH_4Cl (2.4 g) dissolved in H_2O (50 ml) and the suspension was extracted using two 50-ml portions of Et_2O. A crude product was isolated by washing the combined Et_2O extracts with two 100-ml portions of 0.1 *N* H_2SO_4 and neutralizing the acidic washes with an excess of 1 *N* NaOH to yield 3.1 g. A pure sample of (**7**) was obtained from an Et_2O solution; 1.9 g (36%), mp 116–117°.

4′-(*p*-2-Piperidinoethoxyphenyl)acetophenone Oxime (38).—A mixture of 3.2 g (0.01 mole) of **29** and 1.0 g (0.01 mole) of hydroxylamine HCl was dissolved in EtOH (150 ml) and treated with an aqueous solution of KOH (1.0 g in 10 ml of H_2O). After a 5-hr reflux period, the suspension was filtered and cooled, and the precipitate which formed on standing was collected and triturated with two 50-ml portions of H_2O. Compound **38** was air dried, 3.0-g yield (97%), mp 206–208°.

1-[2-(4′-Amino-4-biphenylyloxy)ethyl]pyrrolidine (28).—A solution of 6.8 g (0.03 mole) of $SnCl_2 \cdot 2H_2O$ and 6.7 g (0.02 mole) of **23** in EtOH (700 ml) was saturated with dry HCl gas and stirred at room temperature for *ca.* 2 hr. The crystalline material deposited after this time was collected, dissolved in a minimum volume of H_2O, and made basic with an excess of 1.0 *N* NaOH. The crude product collected by filtration and dried (P_2O_5) for 15 hr weighed 5.2 g (88%). A pure sample of **28** was isolated from C_6H_6; mp 102–103°.

***p*-[2-(1-Pyrrolidinyl)ethoxy]phenyl]phenol (30).** The diazonium salt of **28** (prepared from 5.8 g (0.02 mole) of **28** and 2.1 g (0.03 mole) of $NaNO_2$) was dissolved in 200 ml of 0.1 *N* H_2SO_4 and irradiated in a 400-ml Vycor vessel with an Hanovia Utility Model Lamp No. 30620 for 4 days at 25–30°. The yellow, granular material which separated from the dark brown acidic solution was collected, dissolved in excess 10 *N* NaOH, filtered, decolorized (charcoal), and released from solution using an excess of solid CO_2. A pure sample of **30** was isolated from a C_6H_6 solution; 2.1 g (57%), mp 154–155°.

4′-(2′-Piperidinoethoxy)-4-biphenylcarbonitrile (34).—Following the procedure of Friedman and Shechter[27] a suspension consisting of 7.49 g (0.03 mole) of 4-bromo-4′-hydroxybiphenyl and 3.23 g (0.04 mole) of $Cu_2(CN)_2$ in DMF (25 ml) was refluxed 6 hr and then treated with an aqueous solution of ethylenediamine (2.7 g in 20 ml of H_2O). The suspension was filtered and the clear, dark blue filtrate was extracted with three 50-ml portions of C_6H_6. The combined extracts were washed with two 30-ml portions of aqueous NaCN (10 wt %) and the C_6H_6 layer was separated, dried (Na_2SO_4), and concentrated to the crude product, 3.7 g (64%). Recrystallization (Me_2CO–petroleum ether) of the crude material afforded a pure sample of 4-cyano-4′-hydroxybiphenyl, mp 196–199°. *Anal.* ($C_{13}H_9NO$) C, H, N.

Compound **34** was obtained by alkylating 4-cyano-4′-hydroxybiphenyl using method A described above.

Carbonation of Biphenyl Grignards. Method D.—The preparation of 4′-(2-diethylaminoethoxy)-4-biphenylcarboxylic acid (**8**) may be considered a general method. Mg turnings (0.5 g, 0.02 g-atom) were added to a solution consisting of 7.6 g (0.02 mole) of **10**, a trace of I_2, anhydrous Et_2O (20 ml), and THF (10 ml) and refluxed for *ca.* 22 hr; the resulting dark brown suspension was poured on crushed, solid CO_2. After hydrolyzing the reaction mixture with 1.0 *N* HCl (100 ml), the acidic, aqueous solution was extracted with two 100-ml portions of Et_2O. Concentration of the acidic solution to one-third the original volume and neutralizing with 1.0 *N* NaOH solution afforded a fine, crystalline product which was collected by filtration and dissolved in MeOH (75 ml). The methanolic solution was saturated with dry HCl and cooled to 0–10° whereupon 3.5 g (45%) of **8** precipitated, mp 261–262°.

Following the procedure outlined in method D the Grignard reagent prepared from 0.4 g (0.02 g-atom) of Mg turnings and 5.9 g (0.017 mole) of **33** was poured on crushed, solid CO_2. Following the work-up described in method D 3.9 g (37%) of the monohydrochloride of 4′-[2-(1-pyrrolidinyl)ethoxy]-4-biphenylcarboxylic acid (**31**) was isolated as a crystalline solid, mp 266–271°.

1-[2-[4′-(Methylsulfonyl)-4-biphenylyloxy]ethyl]pyrrolidine (32).—4-Acetamido-4′-chlorosulfonylbiphenyl[28] (6.9 g, 0.02 mole) was added to an aqueous solution of Na_2SO_3 (10 g in 200 ml of H_2O) and the suspension was stirred at room temperature for 20 hr; the pH of the suspension was maintained above 7 by adding portions of 50% aqueous NaOH as required. Dissolution of sodium 4-(*p*-acetamidophenyl)phenyl sulfinate was accomplished by adding an additional amount of H_2O (800 ml) and the clear solution resulting was acidified with excess concentrated H_2SO_4. The intermediate biphenylyl sulfinic acid derivative was collected by filtration, air dried, and used without further purification. Absorption bands of ir spectra were as expected.

A suspension consisting of 5.5 g (0.02 mole) of 4-(*p*-acetamidophenyl)phenylsulfinic acid in 100 ml of H_2O was adjusted to pH 8–9 by adding a sufficient amount of K_2CO_3 and then refluxed with 4.3 g (0.03 mole) of CH_3I for 64 hr. The suspension was filtered and the insoluble material was combined with the residue obtained by concentrating the aqueous filtrate. Trituration of the crude product using two 50-ml portions of hot H_2O afforded 4.5 g of the desired 4-methylsulfonylbiphenyl derivative. A

(27) L. Friedman and H. Shechter, *J. Org. Chem.*, **26**, 2522 (1961).

(28) Prepared by the method C. T. van Meter, J. A. Bianculli, and A. Lowy, *J. Am. Chem. Soc.*, **62**, 3143 (1940).

pure sample of 4-acetamido-4′-methylsulfonylbiphenyl, recrystallized from glacial AcOH, melted at 267–268°. *Anal.* ($C_{15}H_{15}NO_3S$) C, H, N, S.

The 4-acetamido group of the biphenyl derivative described above was hydrolyzed by refluxing 1.89 g (0.01 mole) of 4-acetamido-4′-methylsulfonylbiphenyl in 20% HCl (100 ml) for *ca.* 20 hr. The reaction mixture was then filtered hot and the clear filtrate was made strongly basic with 10 *N* NaOH solution. The crude, hydrolysis product was collected by filtration and recrystallized (MeOH); 1.4 g (82%), mp 203–205°. *Anal.* ($C_{13}H_{13}NO_2S$) C, H, N, S.

Diazotization of the hydrolysis product was accomplished by adding an aqueous solution of $NaNO_2$ (1.6 g in 4 ml of H_2O) dropwise (20 min) to a vigorously stirred, cooled (0–5°) suspension of 4-amino-4′-methylsulfonylbiphenyl (2.3 g, 0.01 mole) in glacial AcOH (15 ml) and concentrated H_2SO_4 (15 ml). When diazotization was complete, the excess HNO_2 was decomposed by the cautious addition (30 min) of urea at 0–5°. The cold solution of the diazonium sulfate was then added slowly (20 min) to a refluxing H_2SO_4 solution (40 wt %) and, after addition was complete, the reation mixture was allowed to reflux an additional 15 min. Dilution of the acidic solution with H_2O afforded a crude solid which was collected by filtration, dissolved in 1 *N* NaOH (20 ml) and refiltered. Acidification of the clear filtrate using an excess of 1 *N* H_2SO_4 furnished a precipitate which was washed with two 75-ml portions of H_2O and then air dried. The yield of crude 4-hydroxy-4′-methylsulfonylbiphenyl obtained following the procedures outlined above melted at 189–190°; 1.7 g (75%). The ir absorption bands were as expected and the intermediate was used in the final step without further purification.

Following method A, 1.9 g (0.01 mole) of the sodio derivative of 4-hydroxy-4′-methylsulfonylbiphenyl was allowed to react with 1.3 g (0.01 mole) of 2-pyrrolidinylethyl chloride in refluxing DMF. After a 60-hr reflux period, the reaction mixture was cooled, filtered, and concentrated to a semisolid residue. Trituration of the crude yield with two 50-ml portions of H_2O yielded an insoluble product which was taken up in C_6H_6 (75 ml). The C_6H_6 solution was decolorized (charcoal), dried (Na_2SO_4), and then treated with excess HCl gas. The HCl salt which precipitated was dissolved in H_2O (100 ml), decolorized (charcoal), and filtered, and the clear, acidic filtrate was made basic (excess 1.0 *N* NaOH). The desired product (**32**) which separated from the basic solution was collected and recrystallized (C_6H_6), 1.0 g (41%), mp 153–154°.

1-{2-[*p*-(*p*-Bromophenyl)anilino]ethyl}pyrrolidine (**15**).—To a suspension consisting of 6.2 g (0.025 mole) of the lithio derivative of 4-amino-4′-bromobiphenyl in dry toluene (100 ml) was added 3.4 g (0.025 mole) of 2-pyrrolidinylethyl chloride and the reaction mixture was refluxed 22 hr. The LiCl was removed by filtration and the clear filtrate was concentrated to a semisolid residue which was dissolved in an Et_2O (50 ml) and C_6H_6 (50 ml) solution. The solution was then treated with an excess of dry HCl gas and the crude precipitated HCl salt was collected and dissolved in a minimum amount of H_2O. A gray-white solid separated from the acid solution after addition of an excess of aqueous KOH solution (10 *N*). The solid isolated in this manner was recrystallized once (heptane); 3.8 g (44%), mp 141–142°.

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1-{2-[4′-(Trifluoromethyl)-4-biphenylyloxy]ethyl}pyrrolidine. A Potent Hyposterolemic Agent

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The oral hypocholesteremic compound, 1-{2-[4′-(trifluoromethyl)-4-biphenylyloxy]ethyl}pyrrolidine (boxidine),[1] was studied in rats, mice, monkeys, and dogs and found to be active in all species. In the rat, the species studied most intensively, it was active at a dose of 0.0003% in the diet, equivalent to the ingestion of approximately 0.3 mg/kg of body weight. Triglycerides and phospholipids were reduced as well. Boxidine was ten times as active as *trans*-1,4-bis(2-chlorobenzylaminomethyl)cyclohexane dihydrochloride,[2] 1000 times as active as clofibrate,[3] and 50 times as active as triparanol.[4] It inhibited the biosynthesis of cholesterol at the 7-dehydrocholesterol stage but its primary mechanism of action may be the inhibition of sterol absorption.

Sustained interest in hypocholesteremic agents has resulted in a plethora of reports on compounds which lower blood cholesterol level by inhibiting its synthesis at various stages in the biosynthetic pathway. Most of these compounds exert their inhibitory action at the desmosterol stage,[4-6] whereas *trans*-1,4-bis(2-chlorobenzylaminomethyl)cyclohexane dihydrochloride inhibits at 7-dehydrocholesterol.[7] In the course of our search for means of lowering serum and tissue cholesterol, a class of compounds was discovered whose hyposterolemic activity may be due indirectly to the formation of 7-dehydrocholesterol and directly to the inhibition of sterol absorption. A preliminary study of these compounds has been reported[8] and the details of synthesis have been described.[9]

We wish to report on some biological studies done on a representative member of this class, 1-{2-[4′-(trifluoromethyl)-4-biphenylyloxy]ethyl}pyrrolidine (boxidine, **35**) in the series described by Bach, *et al.*[9]

(1) The name of this compound was approved by the U. S. Adopted Names Council; *J. Am. Med. Assoc.*, **203**, 143 (1968).

(2) AY9944, Ayerst Research Laboratories, Montreal, Canada.

(3) Atromid-S®, ethyl α-(*p*-chlorophenoxy)isobutyrate, Ayerst Research Laboratories, Montreal, Canada.

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(9) F. L. Bach, J. C. Barclay, F. Kende, and E. Cohen, *J. Med. Chem.*, **11**, 987 (1968).