been reported in the literature. With certain of the tri- and tetrahydroxyphenethylamines the corresponding tri- or tetramethoxyphenethylamine[19] was suspended in H_2CCl_2 and cooled to −60° and 6 equiv of BBr_3 in H_2CCl_2 was added. The mixture was allowed to warm to room temperature. After another 2 hr, excess water was added and the products were absorbed on a Dowex 50-X8 column and eluted with 1 *N* HCl. After evaporation, the amine hydrochlorides were recrystallized from methanol–ether (yields 20–60%). This method proved more satisfactory than the demethylation with HBr.[19]

All other compounds were from commercial sources or as previously acknowledged.[9,15,19,20]

[^{3}H]-DL-Norepinephrine (sp act. 5–10 Ci/mmol) was purchased from the New England Nuclear Corp. and from Sigma Chemical Co. It was prepared in normal saline at a final concentration of 50 μCi/ml and stored at −20° until use.

Methods. All animal experiments were with National Institutes of Health, general-purpose, male albino mice of 17–20 g. Inhibition of uptake of radioactive norepinephrine was assayed by measurement of tritium content of cardiac tissue 20 min after intraveneous administration of 2.5 μCi of [^{3}H]-DL-norepinephrine in 0.1 ml of saline either alone or in the presence of the test substance. Details of the methodology have been reported.[19,20] Release of radioactive norepinephrine was assessed by measurement of tritium content of cardiac tissue 3 hr after intravenous administration of 5 μCi of [^{3}H]-DL-norepinephrine in 0.1 ml of saline. Compounds tested for releasing activity were administered 1 hr after the norepinephrine. Details of the methodology have been reported.[9,20] Long-term effects of compounds on uptake of radioactive active norepinephrine were measured after subcutaneous administration of the test compound. Five days later, the tritium content of cardiac tissue was measured 20 min after intravenous administration of 5.0 μCi of [^{3}H]-DL-norepinephrine in 0.1 ml of saline.[19,20]

References

(1) G. Hertting, J. Axelrod, and R. W. Patrick, *Biochem. Pharmacol.*, 8, 246 (1961).
(2) L. T. Potter, J. Axelrod, and I. J. Kopin, *Biochem. Pharmacol.*, 11, 254 (1962).
(3) J. Axelrod, G. Hertting, and L. Potter, *Nature (London)*, 194, 297 (1962).
(4) J. Axelrod, L. G. Whitby, and G. Hertting, *Science*, 133, 383 (1961).
(5) G. Hertting, J. Axelrod, and R. W. Patrick, *Brit. J. Pharmacol. Chemother.*, 18, 161 (1962).
(6) L. T. Potter and J. Axelrod, *J. Pharmacol. Exp. Ther.*, 140, 199 (1963).
(7) J. Axelrod, G. Hertting, and R. W. Patrick, *J. Pharmacol. Exp. Ther.*, 134, 325 (1961).
(8) J. Axelrod and R. Tomchick, *Nature (London)*, 184, 2027 (1959).
(9) J. W. Daly, C. R. Creveling, and B. Witkop, *J. Med. Chem.*, 9, 273 (1966).
(10) J. W. Daly, C. R. Creveling, and B. Witkop, *J. Med. Chem.*, 9, 280 (1966).
(11) C. R. Creveling, J. W. Daly, and B. Witkop, *J. Med. Chem.*, 9, 284 (1966).
(12) A. Carlsson and B. Waldeck, *J. Pharm. Pharmacol.*, 18, 252 (1966).
(13) L. Volicer and W. R. Reid, *Int. J. Neuropharmacol.*, 8, 1 (1969).
(14) F. Benington and R. D. Morin, *J. Med. Chem.*, 11, 896 (1968).
(15) C. R. Creveling, J. W. Daly, and B. Witkop, *J. Med. Chem.*, 11, 595 (1968).
(16) C. R. Creveling, J. W. Daly, R. T. Parfitt, and B. Witkop, *J. Med. Chem.*, 11, 596 (1968).
(17) C. R. Creveling, J. W. Daly, and B. Witkop, *J. Pharmacol. Exp. Ther.*, 158, 46 (1967).
(18) H. H. Ong, C. R. Creveling, and J. W. Daly, *J. Med. Chem.*, 12, 458 (1969).
(19) J. Lundstrom, H. Ong, J. Daly, and C. R. Creveling, *Mol. Pharmacol.*, 9, 505 (1973).
(20) C. R. Creveling, J. Lundstrom, E. T. McNeal, L. Tice, and J. W. Daly, *Mol. Pharmacol.*, in press.
(21) C. Sachs, *Eur. J. Pharmacol.*, 20, 149 (1972).
(22) R. Katz and A. E. Jacobson, *Mol. Pharmacol.*, 9, 495 (1973).
(23) R. Katz, S. R. Heller, A. E. Jacobson, A. Rotman, and C. R. Creveling, Proceedings of the VIIth Jerusalem Symposium on Molecular and Quantum Pharmacology, Jerusalem, Israel, March 31–April 4, 1974, in press.
(24) R. Katz, S. R. Heller, and A. E. Jacobson, *Mol. Pharmacol.*, 9, 486 (1973).
(25) R. R. Ison, P. Partington, and G. C. K. Roberts, *Mol. Pharmacol.*, 9, 756 (1973).
(26) T. Kappe and M. D. Armstrong, *J. Med. Chem.*, 8, 368 (1965).
(27) R. Baltzly, J. S. Buck, and W. S. Ide, *J. Amer. Chem. Soc.*, 72, 382 (1950).
(28) K. H. Slotta and H. Heller, *Chem. Ber.*, 63, 3029 (1930).
(29) J. Daly, L. Horner, and B. Witkop, *J. Amer. Chem. Soc.*, 83, 4787 (1961).
(30) R. A. Heacock and O. Hutzinger, *Can. J. Chem.*, 41, 543 (1963).
(31) F. G. H. Lee, D. E. Dickson, and A. A. Manian, *J. Med. Chem.*, 14, 266 (1971).

Antiarrhythmic Agents. 2-, 3-, and 4-Substituted Benzylamines

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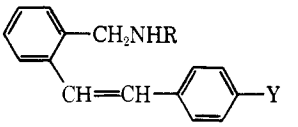
The synthesis of a series of 2-, 3-, and 4-substituted benzylamine derivatives is described. These compounds were studied for their effect on experimental cardiac arrhythmias. Many of the derivatives, but in particular 2-(*p*-methoxyphenylethynyl)benzylamine (**3d**), α,α-dimethyl-4-(phenylethynyl)benzylamine (**7a**), and α,α-dimethyl-4-phenethylbenzylamine (**12g**), showed good antiarrhythmic activity.

α,α-Dimethyl-4-(α,α,β,β-tetrafluorophenethyl)benzylamine (1), a new orally effective antiarrhythmic compound, has been selected for clinical evaluation in man. The synthesis,[1] pharmacological properties,[2] and metabolic disposition[3] of 1 have been described. Concurrent with this work, ancillary explorations of the structure–activity relationships of a series of similar compounds were undertaken. Of particular interest was the extent to which the tetrafluoroethyl bridge of 1 and related structures contributed to its potent antiarrhythmic activity. In order to delineate this structure–activity relationship, a series of 2-, 3-, and 4-substituted benzylamine derivatives, having substituents other than the tetrafluroethyl moiety, were prepared and examined for antiarrhythmic activity.

Chemistry. Several possibilities exist for modifying the tetrafluoroethyl bridge of 1. Changes that have been made

Table I. Stilbene Derivatives

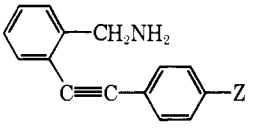


2

Compd	R	Y	Stereochemistry	Formula (analyses)	Mp, °C	Recrystn solvent	Procedure
2a	H	H	Cis	$C_{15}H_{15}N \cdot HCl$ (C, H, Cl)	192–193	6 *N* HCl	3
2b	H	H	Trans	$C_{15}H_{15}N \cdot HCl \cdot 0.25H_2O$[a] (C, H, Cl, H_2O)	213–214	H_2O	3
2c	CH_3	H	Trans	$C_{16}H_{17}N \cdot HCl$ (C, H, N)	189–191	*i*-PrOH	
2d	H	CH_3O	Trans	$C_{16}H_{17}NO \cdot HCl \cdot 0.15H_2O$[b] (C, H, Cl, H_2O)	204–205	H_2O	3

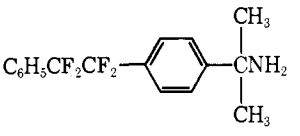
[a] H_2O: found, 0.22 mol. Sublimation of **2b** at 138° (0.5 mm) did not change C and H values significantly. [b] H_2O: found, 0.12 mol.

Table II. Ortho-Substituted Benzylamines



3

Compd	Z	Formula (analyses)	Mp, °C	Recrystn solvent	Procedure
3a	H	$C_{15}H_{13}N \cdot HCl$ (C, H, Cl)	187–188	*i*-PrOH–Et_2O	1, 2, 3
3b	F	$C_{15}H_{12}FN \cdot HCl$ (C, H, Cl, F)	172–174	*i*-PrOH	1, 2, 3
3c	CH_3	$C_{16}H_{15}N \cdot HCl$ (C, H, Cl)	205–207	*i*-PrOH	1, 2, 3
3d	CH_3O	$C_{16}H_{15}NO \cdot HCl$ (C, H, Cl)	206.5–208	*i*-PrOH–Et_2O	1, 2, 3

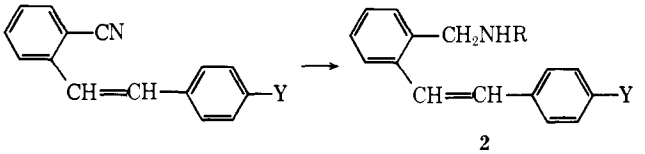


1

include replacement of this bridge by ethane, ethene, and ethyne groups and also replacement by a heteroatom.

The *cis*- and *trans*-ethene-bridged derivatives **2a,b,d** (Table I) were prepared by $LiAlH_4$ reduction of the corresponding cyanostilbene derivatives as shown in Scheme I. The latter were prepared by the general method of DeTar and Carpino.[4] The secondary amine **2c** was obtained by treating **2b** with ethyl formate to give an *N*-formyl derivative which then was reduced.

Scheme I

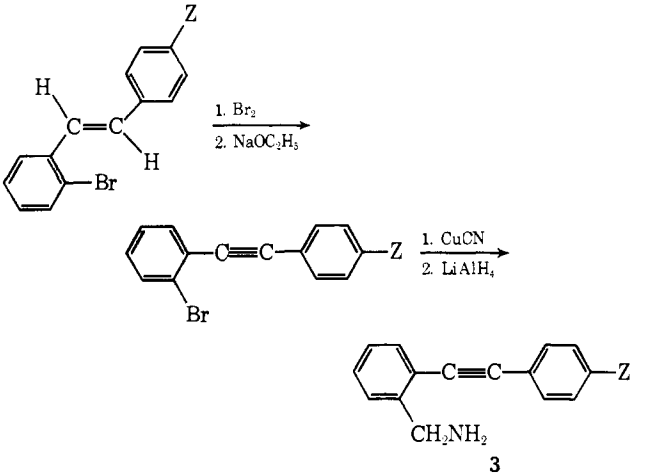


2

DeTar's method was also used to prepare the *trans*-stilbene derivatives shown in Scheme II (Z = H, F, CH_3, CH_3O). The addition of bromine to each of these compounds gave the respective stilbene dibromide that was dehydrohalogenated to the acetylene derivative. Cyanide replacement of the nuclear bromine atom in each of these acetylenes followed by $LiAlH_4$ reduction of the nitrile moiety gave the ethyne-bridged compounds 3 (Table II).

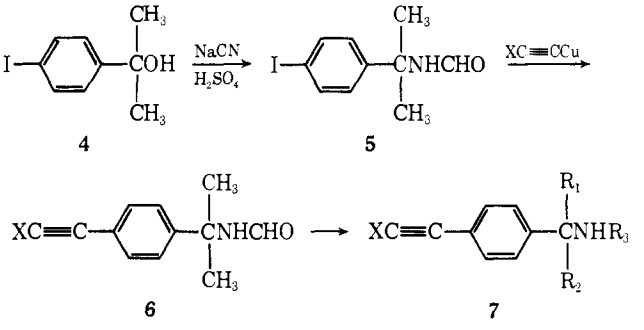
A general procedure for the preparation of the benzylamine derivatives **7a–g** (Table III) is given in Scheme III. The common intermediate **5** was prepared by means of

Scheme II



3

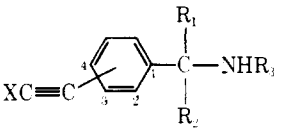
Scheme III



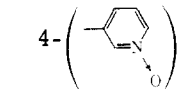
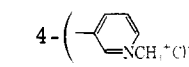
4 5 6 7

the Ritter reaction[5] on **4**. Freshly prepared copper(I) acetylide salts then were condensed with **5** in refluxing pyri-

Table III. Para- and Meta-Substituted Benzylamines

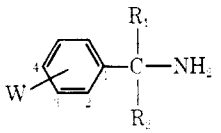


7 (para) and 8 (meta)

Compd	R_1	R_2	R_3	Position (X)	Formula (analyses)	Mp, °C	Recrystn solvent	Procedure
7a	CH_3	CH_3	H	4-C_6H_5	$C_{17}H_{17}N \cdot HCl$ (C, H, N, Cl)	278–280	*i*-PrOH–Et_2O	4, 5
7b	CH_3	CH_3	H	4-*p*-FC_6H_4	$C_{17}H_{16}FN \cdot HCl$ (C, H, N)	262–266	*i*-PrOH–Et_2O	4, 5
7c	CH_3	CH_3	H	4-*p*-$CH_3C_6H_4$	$C_{18}H_{19}N \cdot C_2H_4O_3$[a] (C, H, N)	188–192	EtOH–Et_2O	4, 5
7d	CH_3	CH_3	H	4-*p*-$CH_3OC_6H_4$	$C_{18}H_{19}NO \cdot C_2H_4O_3$[a] (C, H, N)	202–208	*i*-PrOH–Et_2O	4, 5
7e	CH_3	CH_3	H	4-(3-Pyridyl)	$C_{16}H_{16}N_2 \cdot 2HCl$ (C, H, N, Cl)	278–280	EtOH–Et_2O	4, 5
7f	CH_3	CH_3	H	4-*n*-C_4H_9	$C_{15}H_{21}N \cdot C_4H_4O_4$[b] (C, H, N)	133–135	H_2O	4, 5
7g	CH_3	CH_3	CH_3	4-C_6H_5	$C_{18}H_{19}N \cdot HCl$ (C, H, N)	266–268	EtOH	4, 5, 6
7h	CH_3	CH_3	H	4- 	$C_{16}H_{16}N_2O \cdot 2HCl$ (C, H, Cl, N)	228–230	MeOH–Et_2O	*c*
7i	CH_3	CH_3	H	4- 	$C_{17}H_{19}ClN_2 \cdot HCl$ (C, H, Cl, N)	297–300	MeOH–Et_2O	*c*
7j	Cyclopropyl		H	4-C_6H_5	$C_{17}H_{15}N$ (C, H, N)	117–118	Hexane	*c*
8a	CH_3	CH_3	H	3-C_6H_5	$C_{17}H_{17}N \cdot HCl$ (C, H, Cl, N)	212–213	EtOH–Et_2O	4, 5
8b	CH_3	CH_3	H	3-(3-Pyridyl)	$C_{16}H_{16}N_2 \cdot 2HCl$ (C, H, Cl, N)	260–262	EtOH	4, 5

[a] Glycolate salt. [b] Maleate salt. [c] See Experimental Section.

Table IV. Miscellaneous Benzylamines



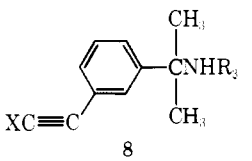
12

Compd	R_1	R_2	W	Formula (analyses)	Mp, °C	Recrystn solvent
12a	H	H	2-C_6H_5O–	$C_{13}H_{13}NO \cdot HCl$ (C, H, N)	221–223	*i*-PrOH
12b	CH_3	CH_3	4-C_6H_5O–	$C_{15}H_{17}NO \cdot C_2H_4O_3$[a] (C, H, N)	166–171	EtOH–Et_2O
12c	CH_3	CH_3	4-C_6H_5S–	$C_{15}H_{17}NS \cdot HCl$ (C, H, N)	205.5–209.5	EtOH–Et_2O
12d	H	H	2-$C_6H_5SO_2$–	$C_{13}H_{13}NO_2S \cdot HCl$ (C, H, Cl, S)	224–228	95% EtOH
12e	CH_3	CH_3	4-$C_6H_5SO_2$–	$C_{15}H_{17}NO_2S \cdot HCl$ (C, H, N)	272–274	EtOH–Et_2O
12f	CH_3	CH_3	4-C_6H_5COCO–	$C_{17}H_{17}NO_2 \cdot C_2H_4O_3$[a] (C, H, N)	164–166	EtOH
12g	CH_3	CH_3	4-$C_6H_5CH_2CH_2$–	$C_{17}H_{21}N \cdot HCl$ (C, H, N)	225–228	*i*-PrOH–Et_2O
12h[b]	CH_3	CH_3	3-I	$C_9H_{12}IN \cdot HCl$ (C, H, N)	239–241	*i*-PrOH
12i	CH_3	CH_3	4-I	$C_9H_{12}IN \cdot HCl$ (C, H, I, N, Cl)	269–270	*i*-PrOH–Et_2O

[a] $C_2H_4O_3$ = glycolate salt. [b] Prepared by acid hydrolysis of *N*-formyl-α,α-dimethyl-3-iodobenzylamine according to the procedure used to hydrolyze 5 to 12i.

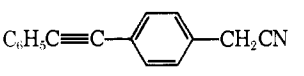
dine to give generally good yields of the formamides 6. Acid hydrolysis or $LiAlH_4$ reduction of the *N*-formyl moieties of 6 gave the desired final products **7a–g**.

The meta-substituted benzylamines **8a–b** (Table III) were prepared by an analogous reaction sequence.

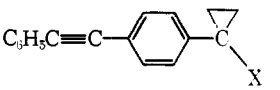


8

The synthesis of **7j** started with alkylation of nitrile 9 by 1-bromo-2-chloroethane to give the cyclopropane derivative **10a**. Hydrolysis of **10a** directly to **10c** proved unsuccessful in that hydration of the acetylene moiety occurred during acid hydrolysis, and incomplete reactions occurred during basic hydrolysis. This transformation was accomplished in a stepwise manner *via* the amide **10b**. The desired amine **7j** then was prepared from acid **10c** *via* a Curtius rearrangement.



9



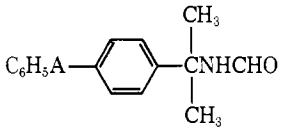
10a, X = CN
b, X = $CONH_2$
c, X = COOH

Five benzylamine derivatives, **12a–e** (Table IV), having a heteroatom bridge were prepared. The oxygen and sulfur compounds **11a** and **11b** were synthesized by phenoxide

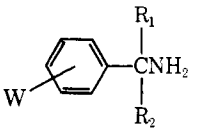
and thiophenoxide displacement of the iodine of **5**. Hydrogen peroxide oxidation of **11b** gave sulfone **11c**. Acid hydrolysis of these formamide intermediates gave **12b**, **12c**, and **12e**. The iodo compound **12i** also was prepared by an acid hydrolysis of the intermediate **5**.

Wolfe[6] has shown that reaction of acetylenes with NBS in DMSO gives good yields of 1,2-diketones. Application of this reaction to **6** (X = C_6H_5) gave, after hydrolysis, **12f**.

Hydrogenation of **7a** proceeded smoothly over PtO_2 to give **12g**, the hydrocarbon analog of **1**.



11a, A = O
b, A = S
c, A = SO_2



12f, $R_1 = R_2 = CH_3$; W = 4-C_6H_5COCO-
g, $R_1 = R_2 = CH_3$; W = 4-$C_6H_5CH_2CH_2$-
i, $R_2 = R_2 = CH_3$; W = 4-I

Biological Activity. Antiarrhythmic activity was assessed in a ventricular arrhythmia (VA) model in anesthetized dogs. Small volumes of a sclerosing agent, tetrafluorohexachlorobutane (TFHCB), were injected into the anterior descending coronary artery which resulted in myocardial damage in the area supplied by the artery and led to a multifocal VA within 2 min[7,8] In control animals 33% died following ventricular fibrillation shortly after the onset of the VA. Due to the high incidence of fibrillation, compounds were evaluated according to their ability to prevent or modify the development of the VA. Under the experimental conditions in control animals less than 20% of all ECG patterns recorded during a 60-min post-infarction period were of sinus origin (normal). A description of the testing method is given in the Experimental Section.

Data relating to the effects of **1** and the standard antiarrhythmic agents and β-adrenergic blocking agents in this experimental infarction arrhythmia model have been published.[1,9,10]

Structure–Activity Relationships. Comparison of the ED_{75} values in Table V shows that many of the compounds are more active as antiarrhythmic agents than quinidine when tested under similar conditions. The most active compounds ($ED_{75} \leq 0.8$ mg/kg) are **3d**, **7a**, and **12g**. Replacing the tetrafluoroethyl bridge of **1** with a heteroatom significantly reduces activity (*cf.* **1** with **12b**, **12c**, and **12e**). This conclusion appears valid whether the substituents are located ortho (**12a** and **12d**) or para (**12b**, **12c**, and **12e**). The benzylamines **12h** and **12i**, lacking the whole tetrafluorophenethyl moiety of **1** but having a large iodine atom in the meta or para positions, respectively, are inactive at the highest dose tested.

When the tetrafluoroethyl bridge of **1** is replaced by an ethyne bridge, a compound (**7a**) of comparable antiarrhythmic activity is obtained. The addition of nuclear substituents in the terminal aromatic ring of the ethyne bridged compound **7** to give **7b**, **7c**, and **7d** has an adverse effect on activity. Also, when the phenylethynyl group is moved from the para (**7a**) to the meta (**8a**) position, reduced activity is observed.

Good antiarrhythmic activity is maintained when the tetrafluoroethyl bridge of **1** is replaced by an ethane unit thus showing that antiarrhythmic activity is not contingent on the presence of fluorine atoms in **1**. However, under other experimental conditions, the oral duration of

Table V. Compounds Prepared for Testing as Antiarrhythmic Agents

Compd	Iv dose, mg/kg	N^a	ECG pattern,[b] % normal	ED_{75},[b] mg/kg
	Stilbene Derivatives (**2**, from Table I)			
2a	5.0	2	24	
2b	2.5	2	94	1.7
	0.6	2	24	
2c	2.5	2	88	2.4
	1.25	3	38	
2d	2.5	2	55	
	Ortho-Substituted Benzylamines (**3**, from Table II)			
3a	2.5	4	87	2.5
	1.25	4	36	
3b	2.5	2	58	5.4
	1.25	3	13	
3c	1.25	4	86	1.7
	0.6	3	21	
3d	1.25	2	97	0.65
	0.3	3	60	
	Para- and Meta-Substituted Benzylamines (**7** and **8**, from Table III)			
7a	1.25	5	93	0.8
	0.3	5	47	
7b	2.5	2	71	2.9
	1.25	2	43	
7c	2.5	2	56	5.0
	1.25	1	6	
7d	5.0	2	18	
7e	1.25	3	76	1.2
	0.6	3	53	
7f	2.5	2	96	1.0
	1.25	3	88	
7g	2.5	2	61	3.5
	1.25	2	31	
7h	2.5	2	63	
7i	2.5	2	36	
7j	1.25	2	37	
8a	5.0	1	88	5.4
	2.5	1	38	
8b	5.0	2	92	5.4
	2.5	2	23	
	Miscellaneous Benzylamines (**12**, from Table IV)			
12a	2.5	2	60	
12b	2.5	3	59	3.8
	1.25	3	27	
12c	2.5	2	58	
12d	2.5	2	72	6.3
	1.25	2	32	
12e	2.5	2	12	
12f	2.5	2	39	
12g	2.5	2	99	0.32
	0.04	4	30	
12h	5.0	2	0	
12i	5.0	2	0	
1	2.5	3	98	0.6
	1.25	3	89	
	0.5	10	75	
	0.25	4	50	
	0.06	9	35	
Quinidine	10.0	4	89	7.6
	5.0	12	46	
	2.5	4	25	
Control	NaCl	50	13	

N = number of animals. [b] See Experimental Section.

action of **12g** was short when compared to **1** (unpublished observation).

Whereas nuclear substituents in the terminal benzene ring of **7** (*e.g.*, **7b**, **7c**, and **7d**) have an adverse effect on the antiarrhythmic activity, nuclear substituents (Z) in the acetylene derivatives **3** can have a beneficial or adverse effect. Thus, the methoxy-substituted compound **3d** shows activity comparable to **1**, while the fluoro compound **3b** is less active than the parent compound **3a**.

Experimental Section

Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values. The ir (Perkin-Elmer Model 21 spectrophotometer) and nmr spectra (Varian A-60A) were consistent with all assigned structures. All boiling points are uncorrected; melting points were taken on a Thomas-Hoover Uni-Melt capillary melting point apparatus and are uncorrected. Where several compounds of similar structure have been prepared by a particular method, only one example has been given.

Phenylacetylene[11] and 1-hexyne[12] are commercially available. *p*-Fluorophenylacetylene,[13] *p*-tolylacetylene,[14] *p*-anisylacetylene,[15] 3-pyridylacetylene,[16] and copper(I) iodide[17] were prepared by literature procedures. Each of the acetylenes was purified thru its solid silver salt. The copper(I) salts of the above acetylenes were prepared by a method based on that described by Gensler[18] for hexynyl-1-copper.

cis- and *trans*-2-bromostilbenes and *cis*- and *trans*-2-cyanostilbenes were prepared by the method of DeTar and Carpino.[4] Starting with 4-fluoro-, 4-methyl-, and 4-methoxyphenylacetic acids, and using the above method, *trans*-2-bromo-4′-fluorostilbene, *trans*-2-bromo-4′-methylstilbene, and *trans*-2-bromo-4′-methoxystilbene, respectively, were prepared.

The preparation of the compounds in Table II is exemplified by the preparation of **2-(phenylethynyl)benzylamine hydrochloride (3a)**.

Procedure 1. To a solution of 27.39 g (0.106 mol) of *trans*-2-bromostilbene in 100 ml of CCl_4 was added dropwise a solution of 16.9 g of Br_2 in 50 ml of CCl_4. After the addition, the solution was stirred for 1 hr at room temperature. Removal of the solvent gave, after recrystallization from heptane, 2-bromostilbene dibromide, mp 181–183° (lit.[4] 182–183°). To a solution of 9.2 g (0.4 mol) of Na in 150 ml of EtOH was added 15.0 g (0.036 mol) of 2-bromostilbene dibromide. The mixture was refluxed for 1 hr. The bulk of the EtOH was removed by evaporation and H_2O was added. The oil that precipitated was extracted into Et_2O. Evaporation of the Et_2O gave 8.3 g of 2-(phenylethynyl)bromobenzene that was 95% pure by glc and showed the characteristic acetylene absorption at 2250 cm^{-1} in the ir.

Procedure 2. A mixture of 8.3 g (0.032 mol) of 2-(phenylethynyl)bromobenzene, 3.18 g (0.036 mol) of CuCN, and 2.81 g (0.036 mol) of pyridine was refluxed for 3 hr. The residue was partitioned between Et_2O and 3 *N* HCl and filtered. The Et_2O phase was removed and washed with 3 *N* HCl and H_2O and dried ($MgSO_4$). The residue was distilled to give 2.16 g (33%) of 2-(phenylethynyl)benzonitrile, bp 127–129° (0.1 mm).

Procedure 3. To a cooled solution of 0.69 g (0.018 mol) of $LiAlH_4$ in 15 ml of Et_2O was added dropwise over 0.5 hr a solution of 2.16 g (0.0165 mol) of 2-(phenylethynyl)benzonitrile in 25 ml of Et_2O. After stirring for 1 hr, 4 *N* NaOH was added slowly until a clear Et_2O phase was obtained. The Et_2O was decanted and the gelatinous residue was reextracted five times with Et_2O. After drying ($MgSO_4$), the combined ether phase was treated with HCl(g) and the product was recrystallized to give **3a**.

***trans*-*N*-Methyl-2-styrylbenzylamine Hydrochloride (2c).** A solution of 1.54 g (0.00736 mol) of the free base of **2b** in 50 ml of ethyl formate was refluxed for 24 hr. Evaporation of the solvent gave a crystalline *N*-formyl derivative. This material, dissolved in 50 ml of C_6H_6, was treated with 5 ml of "Red-Al."[11] After standing overnight, 3 ml of H_2O was added, the C_6H_6 was decanted, and the gummy residue was extracted with C_6H_6. Evaporation of the combined extracts gave an oil that was treated with HCl(g) to give **2c**.

The synthesis of compounds **7a–g** and **8a,b** (Table III) is exemplified by the preparation of α,α-dimethyl-4-(phenylethynyl)benzylamine hydrochloride (**7a**). α,α-Dimethyl-4-iodobenzyl alcohol (**4**) was prepared by action of excess CH_3MgBr on ethyl-4-iodobenzoate. Using the procedure described by Ritter and Kalish,[5] alcohol **4** was converted to the *N*-formyl derivative **5** in 23% yield. [The major by-product from this reaction was shown to be 2-(*p*-iodophenyl)prop-1-ene.]

Procedure 4. *N*-Formyl-α,α-dimethyl-4-(phenylethynyl)benzylamine (6, X = C_6H_5). A mixture of 21.2 g (0.073 mol) of **5**, 11.7 g (0.071 mol) of freshly prepared copper(I) phenylacetylide, and 300 ml of pyridine was refluxed under N_2 for 10 hr. The homogeneous reaction mixture was poured over 2 l. of ice and then was extracted with three 400-ml portions of C_6H_6–Et_2O (1:1). The combined extracts were washed with 3 *N* HCl and H_2O, dried ($MgSO_4$), and filtered.

Evaporation of solvent gave 15.77 g (85%) of crystalline **6** (X = C_6H_5) that was recrystallized from *i*-PrOH, mp 135–141°.

Procedure 5. α,α-Dimethyl-4-(phenylethynyl)benzylamine Hydrochloride (7a). A mixture of 0.5 g of **6** (X = C_6H_5), 10.7 ml of glacial HOAc, 7 ml of H_2O, and 1 ml of concentrated HCl was refluxed for 2.5 hr. Evaporation of solvent gave 0.45 g (87%) of **7a**.

Procedure 6. *N*,α,α-Trimethyl-4-(phenylethynyl)benzylamine Hydrochloride (7g). A solution of 1.0 g (0.0038 mol) of **6** (X = C_6H_5) in 10 ml of C_6H_6 was reduced by addition of 2.7 g of "Red-Al."[11] After standing overnight, 2 ml of H_2O was added, the C_6H_6 was decanted, and the gelatinous residue was extracted with Et_2O. Evaporation of the combined extracts gave 0.80 g (85%) of oil that was treated with HCl(g) to give **7g**.

3-[4-(α,α-Dimethylaminomethyl)phenylethynyl]pyridine 1-Oxide Dihydrochloride (7h). A solution of **6** (X = 3-pyridyl) (2.0 g, 0.0076 mol) in 20 ml of glacial HOAc was treated with 2 ml of 30% H_2O_2. The solution was heated to 85–90° for 5 days, and each day a fresh 3–5-ml aliquot of 30% H_2O_2 was added. The cooled solution was made basic with 20% NaOH. The solution was extracted with three 100-ml portions of $CHCl_3$, and the combined $CHCl_3$ extracts then were extracted with three 75-ml portions of 6 *N* HCl. The combined acid extracts were concentrated to dryness on a rotary evaporator at 70° to give 0.55 g (22%) of **7h**.

3-[4-(α,α-Dimethylaminomethyl)phenylethynyl]-1-methylpyridinium Chloride Hydrochloride (7i). A solution of 2.90 g of **6** (X = 3-pyridyl) in 100 ml of CH_3I and 50 ml of CH_3OH was refluxed for 12 hr. Evaporation of the solvents gave a foam that was dissolved in a mixture of 100 ml of glacial HOAc, 10 ml of concentrated HCl, and 57 ml of H_2O. After refluxing for 4 hr, the solvents were removed by evaporation and the residue was dissolved in water and passed over a column of Dowex-1 (Cl^-). Evaporation of the water and crystallization of the residue from MeOH–Et_2O gave **7i**.

4-(Phenylethynyl)phenylacetonitrile (9). To a solution of 6.0 g (0.0288 mol) of 4-(phenylethynyl)benzyl alcohol[19] in 100 ml of $CHCl_3$ was added dropwise 7 ml of $SOCl_2$. The solution was stirred at room temperature for 6 hr. Evaporation of the solvents left a solid that was sublimed at 65° (0.05 mm) to give 6.0 g (92%) of 4-(phenylethynyl)benzyl chloride, mp 61.5–63.5°. *Anal.* ($C_{15}H_{15}Cl$) C, H.

A mixture of 3.72 g (0.076 mol) of NaCN and 30 ml of dry DMSO was heated to 90–95°. On cooling to 35°, the mixture formed a gelatinous mass that was stirred manually while 8.0 g (0.0354 mol) of the chloride was added. The mixture was stirred overnight and poured into 400 ml of H_2O. The precipitate was collected, dissolved in C_6H_6, washed with H_2O, and dried ($MgSO_4$), and the solvent was removed. The residue was recrystallized from cyclohexane to yield 13.25 g (88%) of **9**, mp 76–79°. An analytical sample was prepared by sublimation at 80° (0.05 mm), mp 78–80°. *Anal.* ($C_{16}H_{11}N$) C, H, N.

1-[4-(Phenylethynyl)phenyl]cyclopropanecarbonitrile (10a). Sodamide, prepared from 0.46 g (0.02 g-atom) of Na and suspended in 10 ml of Et_2O, was stirred at room temperature while a solution of 2.17 g (0.01 mol) of **9** in 15 ml of Et_2O was added dropwise. The mixture was refluxed for 4 hr and then cooled in an ice-salt bath while a solution of 1.43 g (0.01 mol) of 1-bromo-2-chloroethane in 2 ml of Et_2O was added dropwise. The mixture was stirred overnight at room temperature, refluxed for 4 hr, cooled, and diluted with 20 ml of H_2O. The aqueous phase was separated and reextracted with Et_2O, and the combined organic phases were washed (H_2O) and dried ($MgSO_4$). The oily solid residue was freed from oil by trituration with a minimum of Et_2O and sublimed at 80° (0.05 mm) to yield 1.28 g (53%) of **10a**, mp 86–92°. Two recrystallizations from MeOH gave pure **10a**, mp 93–95°. *Anal.* ($C_{18}H_{13}N$) C, H, N.

1-[4-(Phenylethynyl)phenyl]cyclopropanecarboxamide (10b). A mixture of 3.49 g (0.014 mol) of **10a**, 20 drops of 25% KOH, 18 ml of 30% H_2O_2, and 140 ml of MeOH was heated at 55–60° for 8 hr, with additions of 10 ml of 30% H_2O_2 and 10 drops of 25% KOH after 4.5 hr and 5 ml of 30% H_2O_2 after 6 hr. The product

crystallized on cooling to give 3.03 g (81%), mp 174–176°. The product was recrystallized from C_6H_6–hexane: mp 174–175.5°. *Anal.* ($C_{18}H_{15}NO$) C, H, N.

1-[4-(**Phenylethynyl**)**phenyl**]**cyclopropanecarboxylic Acid** (**10c**). A mixture of 2.92 g (0.0112 mol) of **10b**, 90 ml of MeOH, 90 ml of THF, and 60 ml of 10% NaOH was refluxed for 66 hr. After removing solvents, the sodium salt was collected and washed with H_2O and CH_2Cl_2. The precipitate was stirred in a mixture of 6 *N* HCl and CH_2Cl_2 until all of the solid had dissolved. The organic phase was removed, washed, dried, and evaporated to yield 1.95 g (66%) of **10c**, mp 214–218°. The product was recrystallized from C_6H_6–hexane, mp 215–218°. *Anal.* ($C_{18}H_{14}O_2$) C, H.

1-[4-(**Phenylethynyl**)**phenyl**]**cyclopropylamine** (**7j**). To a stirred suspension of 2.52 g (0.0096 mol) of **10c** in 12 ml of Me_2CO–2 ml of H_2O cooled in an ice–salt bath was added dropwise a solution of 1.13 g (0.0112 mol) of Et_3N in 9.5 ml of Me_2CO followed by a solution of 1.31 g (0.012 mol) of $ClCOOC_2H_5$ in 5.5 ml of Me_2CO. After stirring for 0.5 hr, a solution of 0.94 g (0.0145 mol) of NaN_3 in 3 ml of H_2O was added. After stirring for 1 hr, the mixture was poured into 80 ml of H_2O and the azide was extracted into toluene. The H_2O-washed and dried ($MgSO_4$) extract was heated for 0.5 hr on the steam bath and evaporated to about 15 ml and benzyl alcohol (2 ml) was added. The mixture was heated for 6 hr on the steam bath and filtered hot. *N*-Benzyloxycarbonyl-1-[4-(phenylethynyl)phenyl]cyclopropylamine precipitated from the cooled filtrate: 2.9 g (82%); mp 169–170°. The material was recrystallized from C_6H_6–hexane and from *i*-PrOH: mp 171–173°. *Anal.* ($C_{25}H_{21}NO_2$) C, H, N.

A solution of the benzylurethane (1.0 g, 0.0027 mol) and 8 g of KOH in 40 ml of *n*-BuOH was heated at 115–120° for 7 hr, cooled, and poured into 250 ml of H_2O. The aqueous layer was separated and extracted with C_6H_6. The combined organic phases were washed with H_2O and extracted with 0.5 *M* citric acid. Neutralization of the acid extract with 40% NaOH precipitated 0.51 g (80%) of **7j** as white crystals, mp 112–116°. The product was recrystallized from hexane: mp 117–118°. *Anal.* ($C_{17}H_{15}N$) C, H, N.

2-Phenoxybenzylamine Hydrochloride (**12a**). 2-Cyanodiphenyl ether was prepared from 2-bromobenzonitrile by the method of Tomita and Sato:[20] bp 125–127° (0.3 mm) [lit. bp 150–154° (1 mm)]. The compound was reduced by procedure 3 in 81% yield to give **12a**.

α,α-**Dimethyl-4-phenoxybenzylamine Glycolate** (**12b**). A mixture of 1.45 g (0.0266 mol) of $NaOCH_3$, 2.5 g (0.0266 mol) of phenol, 7.67 g of **5**, 20 mg of Cu dust, and 35 ml of CH_3OH was stirred for 2 hr. The CH_3OH was distilled off until a viscous residue remained, and this residue was heated at 200–210° for 3 hr. After cooling, the mixture was poured into H_2O and extracted with two 50-ml portions of Et_2O–C_6H_6 (1:1). These combined extracts were washed with 10% NaOH and H_2O and dried ($MgSO_4$). Evaporation of the solvent gave 5.61 g (93%) of a clear oil that was converted to a hydrogen glycolate salt and was purified by recrystallization from EtOH–Et_2O to give **12b**.

α,α-**Dimethyl-4-thiophenoxybenzylamine Hydrochloride** (**12c**). The above procedure was repeated except that thiophenol was substituted for phenol. Work-up as above and recrystallization gave **12c**.

α,α-**Dimethyl-4-(phenylsulfonyl)benzylamine Hydrochloride** (**12e**). A stirred solution of 0.50 g (0.0018 mol) of **11b** in 6 ml of glacial HOAc and 1 ml of 30% H_2O_2 was heated at 80° for 3 hr. After cooling, H_2O was added until no further precipitation occurred. The product was removed by filtration and dried to give 0.35 g of crystalline **11c**. Hydrolysis of **11c** by procedure 5 gave 0.48 g (84%) of **12e**.

2-(Benzenesulfonyl)benzylamine Hydrochloride (**12d**). o-Bromophenyl phenyl sulfone was prepared in 47% yield by a Friedel–Crafts reaction between C_6H_6 and o-bromobenzenesulfonyl chloride: mp 114–117° (lit.[21] 118–119°). A mixture of 5.60 g (0.0188 mol) of o-bromophenyl phenyl sulfone, 1.85 g (0.0206 mol) of CuCN, 56 ml of quinoline, and 5.6 ml of DMF was refluxed for 3 hr. After filtration, the black solution was diluted with 6 *N* HCl and extracted with three 100-ml portions of Et_2O. The combined extracts were washed with 3 *N* HCl and H_2O, and dried ($MgSO_4$). Evaporation of solvent gave a tan crystalline solid that was triturated and washed with hexane to give 3.40 g (75%) of o-cyanophenyl phenyl sulfone, mp 99–102°.

A solution of 1.0 g (0.0042 mol) of o-cyanophenyl phenyl sulfone in 25 ml of EtOH that was saturated with NH_3 (g) was hydrogenated over 0.25 tsp of W-2 Raney nickel for 12 hr at 1500 psi and 75°. The catalyst was removed by filtration and the ammoniacal EtOH was removed by evaporation. The hydrochloride salt was prepared and recrystallized from 95% EtOH to give **12d**.

α,α-**Dimethyl-4-(phenyloxalyl)benzylamine Glycolate** (**12f**). To a solution of 4.81 g (0.02 mol) of **6** (X = C_6H_5) in 85 ml of dry, distilled DMSO was added 5.65 g of NBS. After stirring at room temperature for 4 days, an additional 0.5 g of NBS was added, and the solution was stirred one additional day. The solution was poured into 800 ml of H_2O and extracted with three 100-ml portions of C_6H_6. The combined C_6H_6 extracts were washed with H_2O, dried ($MgSO_4$), and filtered, and the C_6H_6 was removed on a rotary evaporator. The residue was dissolved in a mixture of 100 ml of glacial HOAc, 84 ml of H_2O, and 6 ml of concentrated HCl and refluxed for 3 hr. The solvents were removed under reduced pressure and 5% NaOH was added to the residue. The resulting oil was dissolved in C_6H_6, washed with water, and dried ($MgSO_4$) to give 5.0 g (91%) of a clear oil that was converted to the glycolate salt **12f**.

α,α-**Dimethyl-4-phenethylbenzylamine Hydrochloride** (**12g**). A solution of 1.0 g (0.0037 mol) of **7a** in 200 ml of MeOH was hydrogenated over 0.36 g of PtO_2 for 1 hr at 40 psi. The catalyst was removed by filtration and the solvent was evaporated to give 0.75 g (74%) of crystalline **12g**.

α,α-**Dimethyl-4-iodobenzylamine Hydrochloride** (**12i**). A mixture of 1.0 g (0.00346 mol) of **5**, 22 ml of glacial HOAc, 14 ml of H_2O, and 2.2 ml of concentrated HCl was stirred and refluxed for 15 hr. The solvents were removed on a rotary evaporator and the residue was recrystallized from *i*-PrOH–Et_2O to give 0.37 g of **12i**.

Pharmacological Method. Beagle dogs of 5–6 months of age and 6–10 kg of weight were used in all experiments. The animals were anesthetized with vinbarbital (50 mg/kg iv) and heart rate and blood pressure were recorded. Under artificial respiration and direct visualization the anterior descending coronary artery was identified and a small segment approximately 20 mm from the ostia was freed from the surrounding myocardium. Mecamylamine (1.0 mg/kg iv), a ganglionic blocking agent, was given 20 min prior to infarction to provide a more uniform preinfarction heart rate. Test compounds were given 10 min prior to infarction. The ECG was recorded prior to the test compound and immediately before infarction to measure effects on conduction (PR and QT). The infarcting agent TFHCB was given into the anterior descending coronary artery and the ECG was recorded every 2 min for 1 hr to determine the average electrical rate and the number of normal complexes (defined as those of sinus origin). From these data the per cent normal ECG patterns were calculated. For active compounds an ED_{75} was calculated, *i.e.*, the dose that would be expected to protect from the arrhythmia to such a degree that 75% of all recorded ECG patterns were normal.

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References and Notes

(1) M. E. Christy, C. D. Colton, M. Mackay, W. H. Staas, J. B. Wong, E. L. Engelhardt, M. L. Torchiana, and C. A. Stone, 167th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1–5, 1974, MEDI 40.
(2) M. L. Torchiana and C. A. Stone, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **33** (3), 475 (1974).
(3) A. Zacchei, L. Weidner, and C. A. Stone, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **33** (3), 475 (1974).
(4) D. F. De Tar and L. Carpino, *J. Amer. Chem. Soc.*, 78, 475 (1956).
(5) J. J. Ritter and J. Kalish, *Org. Syn.*, 44, 44 (1964).
(6) S. Wolfe, W. R. Pilgrim, T. F. Garrard, and P. Chamberlain, *Can. J. Chem.*, **49**, 1099 (1971).
(7) G. Ascanio, F. Barrera, E. V. Lautsch, and M. J. Oppenheimer, *Amer. J. Physiol.*, **209**, 1081 (1965).
(8) F. Barrera, G. Ascanio, J. H. Baitwell, M. P. Panis, and M. J. Oppenheimer, *Amer. J. Med. Sci.*, **252**, 177 (1966).
(9) M. L. Torchiana and C. A. Stone, *Pharmacologist*, 12, 304 (1970).
(10) E. T. Angelakos and M. L. Torchiana in "Cardiac Arrhythmias," L. S. Drifus and W. Likoff, Ed., Grune and Stratton, New York, N.Y., 1973, p 505.
(11) Aldrich Chemical Co.

(12) Columbia Organic Chemical Co.
(13) M. R. Tirpak, C. A. Hollingsworth, and J. H. Wotiz, *J. Org. Chem.*, **25**, 687 (1960).
(14) L. I. Smith and H. H. Hoehm, *J. Amer. Chem. Soc.*, 63, 1175 (1941).
(15) J. R. Johnson and W. L. McEwen, *J. Amer. Chem. Soc.*, 48, 469 (1926).
(16) A. A. Alberts and G. B. Bachman, *J. Amer. Chem. Soc.*, 57, 1284 (1935).
(17) G. B. Kauffman and R. P. Pinnell, *Inorg. Syn.*, 6, 3 (1960).
(18) W. J. Gensler and A. P. Mahadevan, *J. Org. Chem.*, **21**, 180 (1956).
(19) J. K. Kochi and G. S. Hammond, *J. Amer. Chem. Soc.*, 75, 3452 (1953).
(20) M. Tomita and T. Sato, *Yakugaku Zasshi*, **77**, 1024 (1957); *Chem. Abstr.*, **52**, 3719 (1958).
(21) W. E. Truce and M. F. Amos, *J. Amer. Chem. Soc.*, **73**, 3013 (1951).

Cardioselective β-Adrenergic Blocking Agents. 1. 1-[(3,4-Dimethoxyphenethyl)amino]-3-aryloxy-2-propanols

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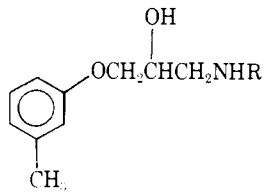
A series of 1-amino-3-aryloxy-2-propanols has been synthesized and examined for cardioselective β-blockade. The introduction of the (3,4-dimethoxyphenethyl)amino group lead to the most cardioselective agents. Structure–activity relationships are discussed. Of the compounds tested 1-[(3,4-dimethoxyphenethyl)amino]-3-(*m*-tolyloxy)-2-propanol was selected for clinical trial because of optimal potency and selectivity.

The first class of compounds which were shown to possess a significant degree of specificity for β-adrenergic receptors in the myocardium was the 3-amino-2-hydroxypropoxy-substituted anilides[1] of which practolol is the best known example. It appears that the *p*-acylamino substituent is responsible for the cardioselectivity in this series and this has been substantiated by other workers.[2]

Recently it has been shown that it is possible to increase the cardioselectivity in a series of 1-aryloxy-3-[(aryloxyalkyl)amino]-2-propanols[3] by the proper choice of the amino substituent. The present report is concerned with the effect of various amino substituents on the β-blocking activity and the cardioselectivity in a series of 1-amino-3-(*m*-tolyloxy)-2-propanols (I). Previous investigators[4] had

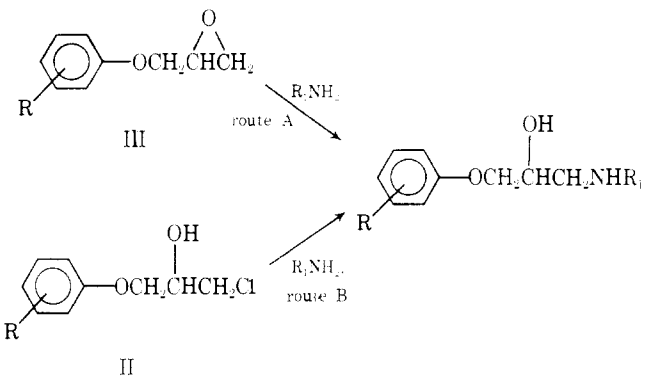


I

shown that compound I (where R = isopropyl or *tert*-butyl) possessed potent β-blocking activity, but no selectivity of action was demonstrated. However, early in our investigations it became apparent that certain amino substituents did have an effect on cardioselectivity in this series and that this selectivity was optimum for the (3,4-dimethoxyphenethyl)amino group. In addition, it was shown that the incorporation of this amino substituent into a series of 1-amino-3-(substituted phenoxy)-2-propanols enhanced cardioselectivity in all cases. Furthermore, incorporation of this same amino substituent into several known β-blocking agents produced the same effect.

Chemistry. The compounds were prepared by methods previously described[4] where the 1-chloro-3-(substituted phenoxy)-2-propanol (II) or 1,2-epoxy-3-(substituted phenoxy)propane (III) was treated with the appropriate amine.

The various substituted phenethylamines were prepared by lithium aluminum hydride reduction of the corresponding substituted phenylacetonitrile, or when this intermediate was not commercially available, the β-nitrostyrenes were prepared as described by Gairaud and Loppin[5] and then reduced with lithium aluminum hydride.[6]



Pharmacology. An *in vitro* guinea pig model was developed to identify β-blocking agents with cardioselective action.[7] Isoproterenol dose–response curves were determined on isolated atria and tracheal chains. Atrial response was represented by an increase in heart rate, while the tracheal response was represented by a decrease in resting tone. Values were calculated and plotted as the per cent of maximum response *vs.* concentration of isoproterenol in the incubation media. The antagonist concentration generally worked with was 10^{-6} *M*. The dose–response curves following β-blockade were shifted to the right of control values proportional to the degree of isoproterenol inhibition. Thus, cardioselective agents demonstrated a greater shift of the atrial *vs.* tracheal curves.

The K_B values, or apparent dissociation constants of the antagonists, were calculated as described by Furchgott.[8] Thus

$$K_B = [B]/(\text{dose ratio} - 1)$$

where [B] is the concentration of the antagonist, and the dose ratio is the ratio of equipotent concentrations of the agonist with/without test compound. The accuracy of the K_B values so determined was contingent upon the presence of competitive inhibition, which was shown to be the case with compound I because of the parallel nature of the