ences in milligram per cent between zero-time samples and samples taken at 1, 2, and 4 hr in the control groups (ΔC) and in the treated groups (ΔT). $\Delta T - \Delta C$/control blood glucose value at that hour equals per cent changes (Tables I–IV). Normally the zero-time values are in the 55–65 mg per cent range.

Acknowledgments. We are indebted to Messrs. A. Villani and T. Resnick of our Organic Chemistry Section for implementing the alternative synthesis of 1 shown in Scheme I. We are also thankful to Mr. Resnick for providing supplies of 3-aminopicolinic acid and to Mr. D. Kirkpatrick for supplies of 5-chloroquinolinic acid. We gratefully acknowledge the expert assistance of Mrs. Y. Li, Mrs. L. Cieslinski, and Mr. J. Foley in performing the biological assays and of Miss J. M. Pang for contributions in the preparation of **15**. We are obliged to the Analytical and Physical Chemistry Section for thiol determinations (Mr. A. Post and staff) and elemental analyses (Miss E. Reich and Mrs. S. S. Ward).

References

(1) C. M. Veneziale, P. Walter, N, Kneer, and H. A. Lardy, *Biochemistry*, 6, 2129 (1967); H. A. Lardy in "Inhibitors Tools in Cell Research," Th. Bucher and H. Sies, Ed., Springer-Verlag, New York–Heidelberg–Berlin, 1969, p 374; H. G. McDaniel, W. J. Reddy, and B. R. Boshell, *Biochim. Biophys. Acta*, **276**, 543 (1972).
(2) N. W. DiTullio, C. E. Berkoff, B. Blank, V. Kostos, E. J. Stack, and H. L. Saunders, *Biochem. J.*, **138**, 387 (1974).
(3) E. Sucharda and C. Z. Troszkiewiczowna, *Rocz. Chem.*, **12**, 493 (1932); *Chem. Abstr.*, **27**, 5076c (1933).
(4) J. Delarge, *J. Pharm. Belg.*, **22**, 257 (1967).
(5) J. Delarge, D. Fernandez, and C. L. Lapiére, *J. Pharm. Belg.*, **22**, 213 (1967).
(6) J. Delarge, *Farmaco, Ed. Sci.*, **22**, 1069 (1967).
(7) J. Delarge, *Pharm. Acta Helv.*, **44**, 637 (1969).
(8) A. Binz and C. Rath, *Justus Liebigs Ann. Chem.*, **487**, 105 (1931).
(9) L. Katz, W. Schroeder, and M. Cohen, *J. Org. Chem.*, **19**, 711 (1954).
(10) V. A. Portnyagina and V. K. Karp, *Ukr. Khim. Zh.*, **32**, 1306 (1966); *Chem. Abstr.*, **67**, 3058u (1967).
(11) G. H. Cooper and R. L. Rickard, *J. Chem. Soc. C*, 772 (1971).
(12) J. Schmidt-Thome and H. Goebel, *Z. Physiol. Chem.*, **288**, 237 (1951).
(13) L. W. Deady, R. A. Shanks, A. D. Campbell, and S. Y. Chooi, *Aust. J. Chem.*, **24**, 385 (1971).
(14) S. Kruger and F. G. Mann, *J. Chem. Soc.*, 3905 (1954).
(15) M. B. Newman and H. A. Karnes, *J. Org. Chem.*, **31**, 3980 (1966).
(16) H. Kwart and E. R. Evans, *J. Org. Chem.*, **31**, 410 (1966).
(17) G. F. Holland and J. N. Pereira, *J. Med. Chem.*, **12**, 1001 (1969).
(18) P. F. Juby, T. W. Hudyma, and M. Brown, *J. Med. Chem.*, **11**, 111 (1968).
(19) F. R. Benson in "Heterocyclic Compounds," Vol. 8, R. C. Elderfield, Ed., Wiley, New York–London–Sydney, 1967, pp 78–85.
(20) S. Akabori, S. Sakakibara, Y. Shimonishi, and Y. Nobuhara, *Bull. Chem. Soc. Jap.*, **37**, 433 (1964); S. Sakakibara, Y. Nabuhara, Y. Shimonishi, and R. Kiyo, *ibid.*, **38**, 120 (1965).
(21) H. Tanaka and A. Yokoyama, *Chem. Pharm. Bull.*, **8**, 280 (1960).
(22) V. Oakes and H. N. Rydon, *J. Chem. Soc.*, 4433 (1956).
(23) J. P. Phillips and R. L. Elbinger, *J. Amer. Chem. Soc.*, **71**, 3986 (1949).
(24) A. Edinger and H. Lubberger, *J. Prakt. Chem.*, **162**, 340 (1896).
(25) E. Sucharda, *Chem. Ber.*, **58**, 1727 (1925).
(26) J. R. McDermott and N. L. Benoiton, *Chem. Ind. (London)*, 169 (1972).
(27) J. G. Murray and C. R. Hauser, *J. Org. Chem.*, **19**, 2008 (1954).
(28) H. B. Dahlig and T. Urbanski, *Chem. Abstr.*, **48**, 1338c (1954).
(29) R. B. Arnold, A. W. Johnson, and A. B. Mauger, *J. Chem. Soc.*, 4466 (1958).

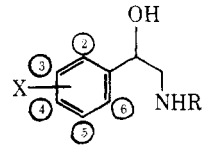
Adrenergic Agents. 2. Synthesis and Potential β-Adrenergic Agonist Activity of Some Ring-Chlorinated Relatives of Isoproterenol

Carl Kaiser,* Donald F. Colella, Alex M. Pavloff, and Joe R. Wardell, Jr.

Research and Development Division, Smith Kline & French Laboratories, Philadelphia, Pennsylvania 19101. *Received April 12, 1974*

A series of 2-, 5-, and 6-chloro-substituted analogs of isoproterenol was prepared in an attempt to find potent and tissue selective bronchodilators with a prolonged duration of action. Compounds were examined for potential bronchodilator activity in an *in vitro* test for relaxation of the spontaneous tone of a guinea pig tracheal chain preparation. Potential cardiac stimulant activity was evaluated in a similar *in vitro* test which monitors changes in the rate of spontaneously beating guinea pig right atria. Substitution of the 2 position of isoproterenol and several derivatives bearing different N substituents generally resulted in compounds with greater tracheal muscle relaxant potency than their nonchlorinated counterparts; however, a high degree of tracheobronchial *vs.* cardiac tissue specificity was not observed. None of the 2-chloro derivatives demonstrated the *in vitro* specificity of clorprenaline, although all were more potent. Chlorination of the 2 position of isoproterenol did not alter the duration of bronchodilator activity. Thus, both this compound and the prototype had the same duration of effectiveness after subcutaneous administration of equiactive doses in a test for inhibition of acetylcholine-induced bronchospasm in guinea pigs. In all instances chlorination of position 5 or 6 of isoproterenol and several derivatives decreased β-adrenergic agonist potency as determined in the *in vitro* tests. A marked decrease in potency was also observed for some 5-chlorocatecholamines in which the meta OH was methylated and for similar para-methoxylated 6-chloro-substituted analogs.

The influence of additional aromatic substitution upon the biological activity of adrenergic catecholamines has been the subject of only limited study. A 6-OH analog **1a** of epinephrine induces release of norepinephrine in isolated mouse heart.[1] Sympathomimetic activity is claimed[2,3] for 5-hydroxynorepinephrine (**1b**) and several 5-acyloxy derivatives. Various 2-alkyl-, cycloalkyl-, and alkoxy-substituted catecholamines, *e.g.*, **1c** and **1d**, have been patented for their sympathomimetic and broncholytic actions.[4-6] The 2-, 5-, and 6-methyl and methoxyl derivatives of isoproterenol were only weakly active in a test for norepinephrine-releasing ability in mouse heart.[7]

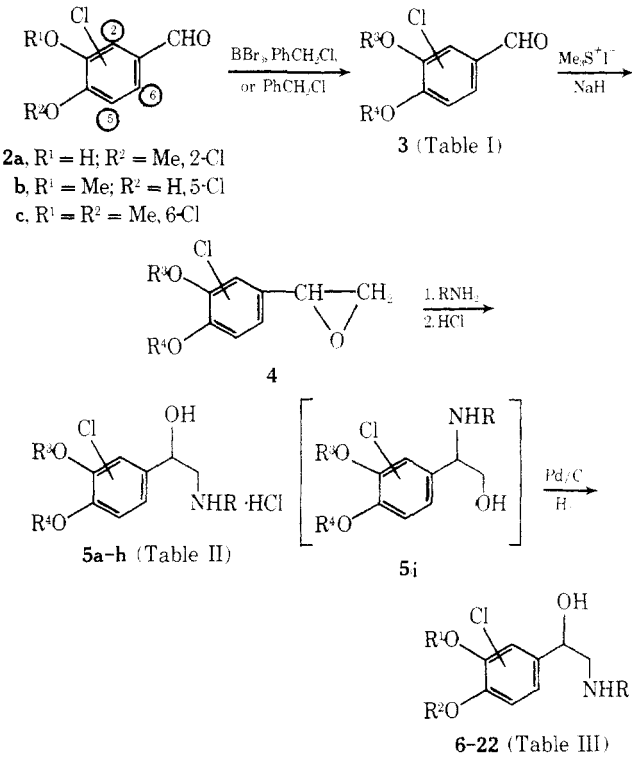


1a, X = 3,4,6-$(OH)_3$; R = Me
b, X = 3,4,5-$(OH)_3$; R = H
c, X = 2-OMe, 3,4-$(OH)_2$; R = *i*-Pr
d, X = 2-Me, 3,4-$(OH)_2$; R = *i*-Pr
e, X = 5-Me, 3,4-$(OH)_2$; R = *i*-Pr
f, X = 2-Cl; R = *i*-Pr
g, X = 3,4-Cl_2; R = *i*-Pr
h, X = 4-NH_2, 3,5-Cl_2; R = *t*-Bu

In contrast, halogen-substituted phenylethanolamines have been examined extensively and several demonstrate significant adrenergic agonist and antagonist activity. For example, clorprenaline (**1f**) is a relatively potent β-adrenergic agonist at bronchial and cardiovascular sites,[8] has some β-antagonist activity,[9] and is a clinically effective bronchodilator.[10] Dichlorisoproterenol (**1g**), the prototype of β-adrenergic antagonists, also possesses some agonist activity.[11] Several 4-amino-3,5-dichlorophenylethanolamines, *e.g.*, **1h**, are potent β-adrenergic agents. Interestingly, (−)-**1h** is a potent β_2-adrenoreceptor agonist whereas the (+) isomer selectively inhibits β_1 adrenoreceptors.[12]

Adrenergic catecholamines bearing a nuclear chlorine substituent, however, do not appear to have been studied. Although halogen substitution of the 4 position of metaproterenol-like structures is claimed,[3] biological data are not recorded. As nuclear alteration, particularly that involving the meta substituent of catecholamines with β-adrenergic agonist activity, sometimes results in products with tissue selectivity,[13] examination of 2-, 5-, and 6-chloro-substituted analogs of isoproterenol was of interest in our attempts to develop new selective bronchodilators with minimal cardiovascular side effects.[14] A second objective involved exploration of the possibility that such nuclear substitution, particularly in position 2, might sterically retard the primary route of metabolic inactivation of such catecholamines, *i.e.*, reaction with catechol *O*-methyltransferase (COMT), to provide bronchodilators having an enhanced duration of activity. In this report we present the synthesis of a series of α-[(substituted amino)methyl]-2-, -5-, and -6-chloro-3,4-dihydroxybenzyl alcohols and the results of preliminary pharmacological examination of these substances.

Scheme I



Chemistry. Ring-chlorinated relatives of isoproterenol were prepared from 2-chloroisovanillin (**2a**),[15] 5-chlorovanillin (**2b**),[16] and 6-chloroveratraldehyde (**2c**)[17] by the general route outlined in Scheme I.

Table I. Ring-Chlorinated Benzaldehyde Derivatives **3**

No.	Cl position	R^3	R^4	Mp, °C	Recrystn solvent	Method[a]	Yield, %	Formula[b]
3a	2	H	H	193–195	EtOH–H_2O	A	90	$C_7H_5ClO_3$
3b	5	H	H	232–233	EtOH–H_2O	A	90	$C_7H_5ClO_3$
3c[c]	6	H	H	218–219	EtOH–H_2O	A	83	$C_7H_5ClO_3$
3d	2	$PhCH_2$	Me	91–93	EtOH	B	64	$C_{15}H_{13}ClO_3$
3e	2	$PhCH_2$	$PhCH_2$	128–129	EtOH	B	47	$C_{21}H_{17}ClO_3$
3f	5	Me	$PhCH_2$	43–45[d]	PhH–hexane	B	48	$C_{15}H_{13}ClO_3$
3g	5	$PhCH_2$	$PhCH_2$	94–95	Et_2O–hexane	B	63	$C_{21}H_{17}ClO_3$
3h	6	$PhCH_2$	$PhCH_2$	108–109	Et_2O–hexane	B	71	$C_{21}H_{17}ClO_3$

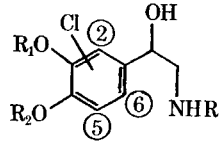
[a]See Experimental Section: Chemistry. General Procedures. [b]All compounds were analyzed for C and H and analytical values were within ±0.4% of calculated values. [c]Reported mp 211° [K. Weise, *Ber.*, **43**, 2605 (1910)]. [d]Bp 165–167° (2.7 mm).

Table II. Chlorinated Benzyloxy-Substituted Phenylethanolamine Hydrochlorides **5**

No.	Cl position	R^3	R^4	R	Mp, °C	Recrystn solvent	Yield, %	Formula[a]
5a	2	$PhCH_2$	Me	*i*-Pr	172–173	EtOH–Et_2O	81	$C_{19}H_{25}Cl_2NO_3$
5b	2	$PhCH_2$	$PhCH_2$	*i*-Pr	171–172	MeCN	45	$C_{25}H_{29}Cl_2NO_3$
5c	2	$PhCH_2$	$PhCH_2$	c-C_5H_{11}	181–182	EtOH–Et_2O	40	$C_{27}H_{31}Cl_2NO_3$
5d	2	$PhCH_2$	$PhCH_2$	*t*-Bu	191–192	MeOH–MeCN	42	$C_{26}H_{31}Cl_2NO_3$
5e	2	$PhCH_2$	$PhCH_2$	*b*	176–178	EtOH–Et_2O	23	$C_{33}H_{37}Cl_2NO_5$
5f	2	$PhCH_2$	$PhCH_2$	*c*	141–143	MeCN	22	$C_{38}H_{39}Cl_2NO_4$
5g	5	Me	$PhCH_2$	*b*	157–160	MeCN–Et_2O	18	$C_{27}H_{33}Cl_2NO_5$
5h	5	$PhCH_2$	$PhCH_2$	*i*-Pr	162–164	MeCN	36	$C_{25}H_{29}Cl_2NO_3$

[a]All compounds were analyzed for C, H, and N and analytical values were within ±0.4% of calculated values unless otherwise noted. [b]$CH(Me)CH_2C_6H_3$-3,4-$(OMe)_2$. [c]$CH(Me)CH_2C_6H_4$-4-OCH_2Ph.

Table III. Ring-Chlorinated Relatives of Isoproterenol **6–22**[a]



No.	Cl position	R_1	R_2	R	Salt	Mp, °C	Recrystn solvent	Yield, %	Formula[b]	Guinea pig tracheal test,[c,d] ED_{50} (molar concn) (95% confidence limits)	Guinea pig atrial rate,[c] ED_{25} (molar concn) (95% confidence limits)	Intrinsic activity (α) in atrial test[e]	Separation ratio[f]
6	2	H	H	*i*-Pr	HCl	162–163	MeOH–MeCN–Et_2O	91	$C_{11}H_{17}Cl_2NO_3$[g]	1.5×10^{-9} ($0.73–2.9 \times 10^{-9}$)	4.1×10^{-9} ($2.3–7.3 \times 10^{-9}$)	1	2.7
7	2	H	H	*t*-Bu	HCl	*h*		84	$C_{12}H_{19}Cl_2NO_3$[i]	4.6×10^{-10} ($3.7–5.8 \times 10^{-10}$)	8.9×10^{-11} ($1.0–73.0 \times 10^{-11}$)	0.9	0.2
8	2	H	H	c-C_5H_{11}	HCl	165–167	*i*-PrOH	74	$C_{13}H_{19}Cl_2NO_3$	4.0×10^{-9}	1.3×10^{-8}	1	3.3
9	2	H	H	*j*, *k*	HCl	118	EtOH–Et_2O	94	$C_{19}H_{25}Cl_2NO_5$[l]	3.8×10^{-8} ($0.92–13.0 \times 10^{-10}$)	1.3×10^{-7} ($0.94–1.6 \times 10^{-7}$)	0.9	3.4
10	2	H	H	*k*, *m*	HCl	90[k]		98	$C_{17}H_{21}Cl_2NO_4$	8.0×10^{-10} ($5.0–13.0 \times 10^{-10}$)	1.9×10^{-9} ($1.2–3.0 \times 10^{-9}$)	1	2.4
11	2	H	Me	*i*-Pr	HCl	220 dec	EtOH–Et_2O	72	$C_{12}H_{19}Cl_2NO_3$	9.6×10^{-7}, 35%	*n*		
12	2	H	Me	c-C_5H_{11}	HCl	187–189	EtOH–Et_2O	71	$C_{14}H_{21}Cl_2NO_3$	3.3×10^{-7} [o]	9.4×10^{-7}, 24%		
13	2	H	Me	*j*, *k*	HCl	185–187	EtOH–Et_2O	45	$C_{20}H_{27}Cl_2NO_5$	1.3×10^{-5}, 26%	*n*		
14	5	H	H	*i*-Pr	HCl	*h*		88	$C_{11}H_{17}Cl_2NO_3$[p]	1.3×10^{-7} ($0.73–2.4 \times 10^{-7}$)	2.4×10^{-8} ($0.65–8.8 \times 10^{-8}$)	1	0.2
15	5	H	H	c-C_5H_{11}	Base	159 dec	MeOH–EtOAc–Et_2O	72	$C_{13}H_{18}ClNO_3$	$\sim 2.1 \times 10^{-7}$	$\sim 2.6 \times 10^{-7}$	0.8	1.2
16	5	H	H	*j*, *k*	HCl	182 dec	MeOH–Et_2O	90	$C_{19}H_{25}Cl_2NO_5$	3.4×10^{-7} ($0.52–18.0 \times 10^{-7}$)	9.2×10^{-7} ($6.8–12.0 \times 10^{-7}$)	0.5	2.7
17	5	Me	H	*i*-Pr	HCl	171–173	MeCN	96	$C_{12}H_{19}Cl_2NO_3$	$\sim 2.4 \times 10^{-6}$[q]	$\sim 5.7 \times 10^{-6}$	0.4	~2
18	5	Me	H	c-C_5H_{11}	Base	164 dec	MeCN	48	$C_{14}H_{19}ClNO_3$	$\sim 1.1 \times 10^{-5}$[q]	8.7×10^{-7}, 11%		
19	5	Me	H	*j*, *k*	HCl	159–161	EtOH–Et_2O	86	$C_{20}H_{27}Cl_2NO_3$[r]	3.8×10^{-5}, 43%	*n*		
20	6	H	H	*i*-Pr	HCl	171–172	EtOH–Et_2O	52	$C_{11}H_{17}Cl_2NO_3$	$\sim 2.3 \times 10^{-7}$	$\sim 1.1 \times 10^{-7}$	1	0.5
21	6	H	H	c-C_5H_{11}	Maleate	185 dec	MeOH–MeCN	80	$C_{17}H_{22}ClNO_7$	3.8×10^{-7}	5.2×10^{-7}	1	1.4
22	6	H	H	*j*, *k*	HCl	196 dec	EtOAc–Et_2O	55	$C_{19}H_{25}Cl_2NO_5$[s]	$\sim 8.6 \times 10^{-8}$	$\sim 6.1 \times 10^{-7}$	0.5	~7
Isoproterenol										7.1×10^{-9} ($5.2–9.9 \times 10^{-9}$)	3.4×10^{-9} ($2.6–4.6 \times 10^{-9}$)	1	0.48
N-tert-Butylnorepinephrine										1.3×10^{-9} ($0.93–1.8 \times 10^{-9}$)	7.1×10^{-9} ($5.3–10.0 \times 10^{-9}$)	1	5.5
N-Cyclopentylnorepinephrine										1.1×10^{-8} ($0.63–2.0 \times 10^{-8}$)	4.0×10^{-9} ($1.5–11.0 \times 10^{-9}$)	1	0.4
Clorprenaline (**1f**)										1.1×10^{-7} ($0.88–1.6 \times 10^{-7}$)	2.0×10^{-6} ($0.28–14 \times 10^{-6}$)	0.3	18.1

[a]See Scheme I for general structure. [b]See footnote *a*, Table II. [c]See ref 14 and 24 for experimental procedure. Where ED's were not determined results are given as per cent response at the indicated concentration. [d]The intrinsic activity, α, *i.e.*, maximum effect of test compounds divided by the maximum effect induced by papaverine, is equal to 1 for all compounds for which ED_{50}'s were obtained, unless otherwise indicated. [e]Determined as defined in footnote *d* but related to maximum isoproterenol-induced response. [f]Guinea pig atrial test ED_{25} divided by tracheal test ED_{50}. [g]C: calcd, 46.82; found, 47.26. [h]Amorphous solid with indefinite melting point. [i]H: calcd, 6.47; found, 7.34. Nmr (D_2O) δ 1.8 [s, 9, $C(CH_3)_3$], 3.6 (m, 2, CH_2), 5.6 (m, 1, C*H*OH), 7.1 ppm (m, 2, Ar H); tlc, silica GF, 70:30:3 $CHCl_3$–MeOH–90% HCO_2H, R_f 0.5). [j]See footnote *b*, Table II. [k]This compound may be a mixture of diastereomers. [l]*Anal.* for 0.5 mol of H_2O. [m]$CH(Me)CH_2C_6H_4$-4-OH. [n]Not tested. [o]α = 0.9. [p]Mass spectrum *m/e* 227 (M − H_2O); nmr (D_2O) δ 1.5 (s, 3, CH_3), 1.6 (s, 3, CH_3), 3.4 (m, 3, CH_2NCH), 5.5 (m, 1, C*H*OH), 7.05 ppm (m, 2, Ar H). [q]α = 0.8. [r]*Anal.* for 0.25 mol of H_2O. [s]*Anal.* for 1.0 mol of H_2O.

Chloro-substituted protocatechualdehydes **3a–c** (Table I), derived by BBr_3 cleavage of the methyl ethers **2a–c,** as well as the monophenols **2a** and **2b,** were benzylated. Resulting benzyloxybenzaldehydes **3d–h** (Table I) upon treatment with dimethylsulfonium methylide[18] in DMSO gave the styrene oxides **4.** From amination of these epoxides with *i*-$PrNH_2$, *t*-$BuNH_2$, c-$C_5H_{11}NH_2$, 3,4-$(MeO)_2C_6H_3CH_2CH(Me)NH_2$, or 4-$PhCH_2OC_6H_4CH_2CH(Me)NH_2$, a reaction which can produce β-phenylethanolamines, *e.g.,* **5a–h** and the kinetically less favored isomers **5i,** were isolated the benzyloxy-substituted phenylethanolamines listed in Table II. Hydrogenolysis of these compounds, as well as several crude amination products, following purification, gave the phenolic amino alcohols **6–22** (Table III). Homogeneity of the products listed in Table III was based on chromatographic data. Isomeric composition of the purified compounds listed in Tables II and III was established by nmr methods and mass spectral fragmentation patterns as described in the Experimental Section.

Results and Discussion

Ring-chlorinated relatives **6–22** of isoproterenol were examined for their ability to relax spontaneously contracted guinea pig tracheal smooth muscle in an *in vitro* test.[14] This provides a measure of potential bronchodilating activity. Cardiac stimulant potential was evaluated in an *in vitro* assay[14] utilizing guinea pig right atria. This test measures changes in the rate of spontaneously beating right atria induced by the test compounds. As an index of selectivity of the compounds for tracheobronchial *vs.* cardiac muscle, a separation ratio was calculated by dividing the ED_{25}, *i.e.,* the dose causing a rate increase equal to 25% of the maximum isoproterenol-induced response, in the guinea pig right atria test by the ED_{50}, *i.e.,* the dose producing 50% of the maximum papaverine-induced relaxation, in the tracheal chain assay.

As in other series of β-adrenergic stimulants, selectivity of action and potency of ring-chlorinated catecholamines **6–22** was significantly influenced by the nature of the amine substituent group.[14,19] In this series most potent β-adrenergic agonist activity was observed with the isoproterenol congeners bearing a chloro substituent in the 2 position. In general, 2-chlorinated derivatives were more potent than their catecholamine counterparts in the guinea pig tracheal chain test, but relative selectivity varied. Thus **6,** the 2-chlorinated derivative of isoproterenol, was about five times as potent as the prototype of β-adrenergic agonists as a relaxant of tracheal muscle and it gave a somewhat higher separation ratio (2.7 *vs.* 0.48). As in the catecholamine series, the 2-chlorinated *tert*-butyl derivative **7** was even more potent than its nonchlorinated analog in the tracheal chain test; however, in this case it was less selective. The separation ratio for **7** was 0.2, as compared to 5.5 for *N-tert*-butylnorepinephrine. Likewise, the 2-chlorinated *N*-cyclopentyl compound **8** was about three times as potent as its unsubstituted counterpart in the tracheal chain assay. In this case, however, a slightly higher separation ratio was noted for **8,** *i.e.,* 3.3 *vs.* 0.4 for *N*-cyclopentylnorepinephrine. Although replacement of the *N*-isopropyl group of isoproterenol with a 4-$MeOC_6H_4CH_2CH(Me)$[19] or 3,4-$OCH_2OC_6H_3CH_2CH(Me)$[19,20] (*i.e.,* protokylol) is associated with a high order of bronchodilating activity, the 3,4-$(MeO)_2C_6H_3CH_2CH(Me)$ derivative **9** was only about 0.2 as potent as isoproterenol. A 4-$HOC_6H_4CH_2CH(Me)$-substituted congener **10,** as similarly noted in the ring unsubstituted parent series,[21] was very potent in both the tracheal and atrial tests and it had a separation ratio of 2.4. All of the 2-chlorinated relatives **6–10** of isoproterenol were more potent but less selective for tracheobronchial *vs.* cardiac muscle than their noncatecholic analog, clorprenaline.

As ring-chlorinated phenylethanolamine derivatives, such as clorprenaline (**1f**),[8,9] dichlorisoproterenol (**1g**),[11] and **1h,**[12] cause both β-adrenergic antagonist and agonist activity depending on the tissue site, it is conceivable that compounds in the present series may exert a similar dual profile. Although β-antagonist activity was not measured in the current study some compounds had low intrinsic activity in atrial tissue. This may suggest the possibility of partial β-adrenoreceptor antagonistic activity for these substances as clorprenaline (**1f**) also has only limited intrinsic activity at this site (Table III). In contrast, nearly all of the compounds had an intrinsic activity of one in the tracheal chain preparation.

In general, 5- (**14–16**) and 6- (**20–22**) chloro-substituted isoproterenol relatives were less effective β-adrenergic agonists, as measured in both the guinea pig tracheal chain and right atria tests, than their nonchlorinated parents. Methylation of either the para (**11–13**) or meta (**17–19**) hydroxy of chlorinated isoproterenol analogs resulted in a pronounced diminution in potency in the *in vitro* guinea pig tissue tests.

To examine the influence of chlorination on the duration of action of these compounds, **6** (selected because 2-substitution might be expected to have a greater steric influence on reaction of the catechol with COMT) and isoproterenol were studied in an inhibition of acetylcholine-induced bronchospasm test in guinea pigs.[14] Time–action curves for equiactive doses of **6** and isoproterenol were virtually identical. Both compounds exhibited a significant protective action against the acetylcholine aerosol challenge for only about 15 min following subcutaneous administration.

In conclusion, substitution of position 2 of isoproterenol and several N-substituted derivatives generally afforded compounds with greater potency than their nonchlorinated counterparts, whereas substitution of either the 5 or 6 position with chlorine decreased β-adrenergic potency as determined in *in vitro* assays measuring relaxation of guinea pig tracheal tissue and increased rate of right atrial contraction. No significant trend relative to tissue selectivity was noted. Chlorination of the 2 position of isoproterenol had no measurable effect on the duration of bronchodilator activity following subcutaneous administration.

Experimental Section†

Chemistry. General Procedures. A. 2-, 5-, and 6-Chloroprotocatechualdehydes (3a–c). To a stirred mixture of 12.0 g (0.064 mol) of 2-chloroisovanillin,[15] 5-chlorovanillin,[16] or 6-chloroveratraldehyde[17] in 36 ml of CH_2Cl_2 at 0° was added dropwise 25 g (0.1 mol) [50 g (0.2 mol) was used for 6-chloroveratraldehyde] of BBr_3. After being stirred at ambient temperature for 4 hr, the mixture was concentrated *in vacuo.* The residue was dissolved in MeOH; the resulting solution was heated at reflux for 0.5 hr and concentrated. After the residual solid was extracted with Et_2O, the Et_2O solution was washed with H_2O, dried ($MgSO_4$), and concentrated. Recrystallization of the remaining solid from aqueous EtOH afforded **3a–c** (Table I).

B. Benzylation of Phenolic Benzaldehyde Derivatives 3d–h. A mixture of 30.0 g (0.16 mol) of 2-chloroisovanillin[15] or 5-chlorovanillin,[16] 23.4 g (0.17 mol) of K_2CO_3, 1.0 g of NaI, 23.4 g (0.18 mol) of $PhCH_2Cl$, and 500 ml of EtOH was stirred and refluxed

† All melting points were obtained by the capillary method and are uncorrected. Microanalyses were determined by the Analytical and Physical Chemistry Section of Smith Kline & French Laboratories. Where analyses are reported by the symbols of elements, results were within ±0.4% of calculated value. The nmr spectra were recorded with a Varian T-60 spectrometer using Me_4Si and the indicated solvent at ambient temperatures. Mass spectra data were obtained on a Hitachi Perkin-Elmer RMU-6E mass spectrometer.

for 6 hr. After the mixture was concentrated, it was diluted with H_2O and extracted with Et_2O. The Et_2O extracts were washed with H_2O, dried, and concentrated. Recrystallization of the residual product gave **3d** and **3f** (Table I). 2-, 5-, and 6-chloroprotocatechualdehydes (**3a-c**) were benzylated in a similar fashion, however, employing twice the above indicated quantities of K_2CO_3, $PhCH_2Cl$, and NaI and a 16-hr reflux period to give dibenzyloxy derivatives **3e, 3g,** and **3h** (Table I).

C. Preparation of Chlorobenzyloxy-1-(epoxyethyl)benzene Derivatives 4. A mixture of 4.2 g (0.1 mol) of a 57% dispersion of NaH in mineral oil and 70 ml of DMSO was heated at 70–75°, under N_2, until evolution of H_2 was completed (30–45 min). The solution was diluted with 70 ml of THF and cooled to 0–5°, 20.0 g (0.1 mol) of trimethylsulfonium iodide was added in portions during 5 min, and 0.025 mol of the appropriate aldehyde **3** in 30 ml of THF was added rapidly. After being stirred at 25° for 1 hr the mixture was diluted with 500 ml of H_2O and extracted with Et_2O. The Et_2O solution was washed (H_2O), dried ($MgSO_4$), and concentrated to give crude epoxide derivatives **4** which were used for subsequent reaction without purification. Identification was based on absence of ir absorption in the region of the precursor aldehyde CHO group (1715–1695 cm^{-1}) and observation of a single spot on silica gel GF tlc plates using 4:1 cyclohexane–EtOAc as the solvent system. Nmr spectra were consistent with the epoxide structure: nmr ($CDCl_3$) δ ~2.77 (q, 1, epoxide CH cis to aromatic ring), 3.12 (m, 1, epoxide CH trans to aromatic ring), and 3.18 ppm (q, 1, benzylic CH).

D. Addition of Amines to Ring-Chlorinated 1-(Epoxyethyl)benzene Derivatives. A mixture of 0.01 mol of the appropriate ring-chlorinated 1-(epoxyethyl)benzene **4**, 20 ml of *i*-$PrNH_2$ or *t*-$BuNH_2$, and 0.015 mol of c-$C_5H_{11}NH_2$ or 4-$PhCH_2OC_6H_4CH_2CH(Me)NH_2$[22] or 0.011 mol of 3,4-$(CH_3O)_2C_6H_3CH_2CH(Me)NH_2$[23] in 40 ml of MeOH was stirred and refluxed for 3–5 hr. The solution was concentrated *in vacuo*, the residual base was dissolved in Et_2O, and the solution was extracted with 1 *N* HCl. The acidic solution was made alkaline (NaOH) and the resulting mixture was extracted with Et_2O. After being dried, the Et_2O solution was concentrated and the residual liquid converted into a HCl salt. In several instances (**5a-h,** Table II), HCl salts were prepared by addition of a solution of HCl in Et_2O to the base in the indicated solvent; they were purified by recrystallization. Assignment of β-phenylethanolamine structures listed in Table II was based on nmr (DMSO-d_6) δ ~2.5–3.0 ppm attributed to the CH_2NHR methylene protons (part of the ABX system). Isomeric **5i**, bearing a CH_2OH group, would be expected to have δ ~3.5–4.0 ppm for these methylene protons. Other benzyloxychlorophenylethanolamines **5** (R^3, R^4 = $PhCH_2$ or Me) not listed in Table II were converted into HCl salts by addition of a solution of HCl in Et_2O to a solution of the base in a minimum volume of EtOH, followed by addition of an excess of Et_2O. Resulting amorphous solids were isolated by filtration or decantation and exhaustive washing with Et_2O. They were employed for hydrogenolysis without further purification.

E. Hydrogenolysis of Chloro-α-[(substituted amino)methyl]-benzyloxybenzyl Alcohols. A mixture of 0.02 mol of the appropriate chlorinated benzyloxy-substituted phenylethanolamine hydrochloride **5,** 100 ml of MeOH, and 1.0 g of 10% Pd/C (wetted with H_2O) was hydrogenated at an initial H_2 pressure of 3.5 kg/cm^2. After H_2 uptake was completed (about 15 min) the mixture was filtered. The filtrate was concentrated and azeotroped twice by stripping with PhMe, and the residue was recrystallized and converted to base (by treatment of a concentrated aqueous solution with K_2CO_3 followed by extraction into EtOAc) or converted to another acid salt (**21** base was treated with maleic acid in MeOH–MeCN) to give **6-22** (Table III). Homogeneity of the products was based on observation of a single spot on Analtech silica gel GF (250μ, tlc plates) (Analtech, Inc., Newark, Del.) upon development with 70:30:3 or 90:10:3 $CHCl_3$–MeOH–90% HCOOH. Assignment of isomeric composition was based on their mass spectral fragmentation patterns. Major fragments were as expected for these compounds. Most significantly, in all cases major fragments were observed for $CH_2{=}NHR^+$ and $ArCH{=}OH^+$ which are characteristic for the β-arylethanolamines.[24]

F. The guinea pig right atria test was carried out as described previously.[14]

G. Inhibition of Acetylcholine-Induced Bronchospasm in Guinea Pigs. ED_{50}'s, *i.e.*, the dose causing 50% inhibition in the test, were determined as described previously[14,25] with 95% confidence limits being calculated according to the method of Finney.[26] Each compound was tested at its ED_{50} sc, *i.e.*, 7.9 (4.8–11.4) μg/kg[25] for isoproterenol and 1.8 (1.4–2.3) μg/kg for **6.** Comparative time-action curves were determined by challenging groups of eight guinea pigs with the acetylcholine aerosol at varying times (0, 2.5, 5, 10, 15, 30, 45, 60, and 90 min) following sc administration of the test compound. Each animal was exposed only once to the acetylcholine challenge.

References

(1) J. W. Daly, C. R. Creveling, and B. Witkop, *J. Med. Chem.*, **9,** 273 (1966).
(2) K. Wismayr, O. Schmid, and G. Zoelss, Austrian Patent 225,700 (1963); *Chem. Abstr.*, **59,** 2716*g* (1963).
(3) Lentia GmbH, German Patent 1,443,291 (1961).
(4) C. H. Boehringer Sohn, Netherlands Appl. 6,607,489 (1966); *Chem. Abstr.*, **67,** 11339*b* (1967).
(5) C. H. Boehringer Sohn, French Patent 1,541,394 (1968); *Chem. Abstr.*, **72,** 31420*c* (1970).
(6) A. Mentrup, K. Schromm, K. Zeile, and O. Thoma, U. S. Patent 3,657,244 (1972).
(7) C. R. Creveling, J. W. Daly, and B. Witkop, *J. Med. Chem.*, **11,** 595 (1968).
(8) T. Igarashi, T. Wakabayashi, T. Shoji, and T. Tomiuga, *Arzneim.-Forsch.*, **20,** 1738 (1970).
(9) M. Watanabe, A. Ohwaki, N. Nemoto, and Y. Kasuya, *Arch. Int. Pharmacodyn. Ther.*, **184,** 343 (1970).
(10) R. E. Johnston and R. E. Shipley, *Amer. J. Med. Sci.*, **233,** 303 (1957).
(11) C. E. Powell and I. H. Slater, *J. Pharmacol. Exp. Ther.*, **122,** 480 (1958).
(12) (a) G. Engelhardt, *Arzneim.-Forsch.*, **22,** 869 (1972); (b) Thomae Gesellschaft GmbH K., Netherlands Patent 7,303,612 (March 16, 1972).
(13) R. T. Brittain, D. Jack, and A. C Ritchie, *Advan. Drug Res.*, **5,** 197 (1970).
(14) C. Kaiser, D. F. Colella, M. S. Schwartz, E. Garvey, and J. R. Wardell, Jr., *J. Med. Chem.*, **17,** 49 (1974).
(15) J. K. Faulkner and D. Woodcock, *J. Chem. Soc.*, 4737 (1962).
(16) L. C. Raiford and J. G. Lichty, *J. Amer. Chem. Soc.*, **52,** 4576 (1930).
(17) L. C. Raiford and D. E. Floyd, *J. Org. Chem.*, **8,** 358 (1943).
(18) W. G. Duncan, W. T. Colwell, C. R. Scott, and D. W. Henry, *J. Med. Chem.*, **11,** 1221 (1968).
(19) A. M. Lands and T. G. Brown, Jr., in "Drugs Affecting the Peripheral Nervous System," Vol. I, A. Burger, Ed., Marcel Dekker, New York, N. Y., 1967, pp 399–472.
(20) C. G. Arman, L. M. Miller, and M. P. O'Malley, *J. Pharmacol. Exp. Ther.*, **133,** 90 (1961).
(21) H. D. Moed, J. van Dijk, and H. Niewind, *Recl. Trav. Chim. Pays-Bas*, **74,** 919 (1955).
(22) J. van Dijk, U. S. Patent 3,250,803 (1966); *Chem. Abstr.*, **65,** 12138*d* (1966).
(23) C. Mannich and W. Jacobsohn, *Chem. Ber.*, **43,** 189 (1910).
(24) A. Makriyannis, J. S. Frazee, and J. W. Wilson, *J. Med. Chem.*, **16,** 118 (1973).
(25) J. R. Wardell, Jr., D. F. Colella, A. Shetzline, and P. J. Fowler, *J. Pharmacol. Exp. Ther.*, **189,** 167 (1974).
(26) D. J. Finney, "Statistical Methods in Biological Assay," Hafner Publishing Co., New York, N. Y., 1952.