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Adrenergic Agents. 1. Synthesis and Potential β-Adrenergic Agonist Activity of Some Catecholamine Analogs Bearing a Substituted Amino Functionality in the Meta Position

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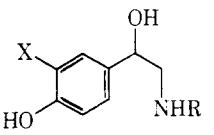
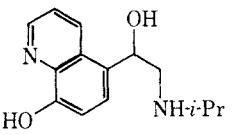
In a search for new bronchodilating agents with minimal cardiovascular side effects, a series of isoproterenol relatives was prepared. This series included compounds in which the *m*-phenolic group of the prototype was replaced with alkylamino, amido, sulfamido, ureido, and carbamate functionalities, as well as several α-ethyl derivatives, and a terbutaline analog in which the resorcinolic hydroxyls were replaced by methanesulfonamido groups. These compounds were examined for potential bronchodilator activity in an *in vitro* test for relaxation of guinea pig tracheal smooth muscle. Potential cardiac stimulant activity was evaluated *in vitro* by changes in the rate of spontaneously beating right atria of guinea pigs. Several of the compounds showed a high order of tracheal relaxant potency and selectivity; however, no conclusive structural requirement for activity could be deduced. Compounds in which the *m*-OH of catecholamines was replaced with basic or strongly or weakly acidic functionalities, or even ones without an active proton-bearing group, retained potent tracheal relaxant properties. On the basis of secondary pharmacological studies, one of the most potent and selective compounds in the *in vitro* assays, carbuterol [5-[2-(*tert*-butylamino)-1-hydroxyethyl-2-hydroxyphenyl]urea hydrochloride], was selected for clinical trial as a bronchodilator.

The classification of adrenergic receptors into α and β types[1] is well accepted. Further subclassification of the β adrenoreceptors on the basis of differences in response to selective agonists[2-4] and antagonists[5,6] has also been suggested. On the basis of these differences, Lands and his associates[2-4,7] have classified β receptors into two different groups, *i.e.*, β_1 and β_2 receptors. According to this classification β_1 receptors mediate certain heart muscle and intestinal smooth muscle responses. The β_2 adrenoreceptors predominate in other smooth muscles, including the bronchi, uterus, and vasculature, as well as in skeletal muscle. As suggested by these observations, development of a number of selective β-adrenoreceptor agonists has been reported recently. A particular objective of the present study was to develop additional selective bronchodilators with minimal cardiovascular side effects.

Isoproterenol (**1a**), the prototype of β-adrenergic agonists, is widely used clinically as a bronchodilator; however, it is not selective. It causes a high incidence of cardiovascular side effects *via* β-receptor stimulation in cardiac and vascular smooth muscle. In addition, this catechol has a short duration of effectiveness because it is rapidly metabolized by catechol *O*-methyltransferase (COMT) which catalyzes the methylation of the *m*-OH group[8] to give a comparatively ineffective *m*-OMe derivative.[9,10] Orally, in man[11] and dogs[11,12] isoproterenol is at least partially inactivated by conversion to an *O*-sulfate in the intestine. Thus, a secondary objective for a new selective bronchodilator was increased duration of action and oral efficacy. The extensive structure–activity relationships available for sympathomimetics, and particularly the β-adrenoreceptor agents,[7,13-16] suggested that our objectives for a useful bronchodilator might be achieved in this general class. Bronchial muscle selectivity is favored by *tert*-butyl substitution of the amino group. Thus, *N*-*tert*-butylnorepinephrine (**1b**) is more selective than isoproterenol (**1a**). More significantly, recent investigations have demonstrated that the *m*-phenolic function may be replaced with a variety of groups to afford compounds with improved selectivity for bronchial *vs.* cardiac musculature. The structural requirements for groups which can substitute for the *m*-phenolic moiety are not clearly defined. Thus, strongly acidic groups, *e.g.*, the methanesulfonamido group of soterenol (**1c**),[17-19] weakly acidic groupings, *e.g.*, the $HOCH_2$ group of salbutamol (**1d**),[20] homologous moieties, *e.g.*, **1e** and **1f**,[16] and even basic substituents, *e.g.*, **1g** and **1h**,[21] can substitute for isoproterenol's *m*-OH to give β-adrenoreceptor stimulants. Many of these show a degree of selectivity for bronchial muscle. Such modifications have the added advantage of being resistant to metabolic inactivation by COMT. Even the presence of a mobile proton[16] in the meta-substituted group is not an inviolate requisite for β-adrenergic activity of an analog of isoproterenol. For example, quinprenaline (**2**), which contains an 8-hydroxyquinoline metal-chelating system, demonstrates selective bronchial *vs.* cardiac activity *in vitro*, although a similar specificity is not observed *in vivo*.[22] Other structurally modified analogs of the prototype **1a** with improved bronchial selectivity include the erythro isomer of the α-ethyl derivative, isoetharine (**3**), and the resorcinol, terbutaline (**4**).[23]



1a, X = HO; R = *i*-Pr
b, X = HO; R = *t*-Bu
c, X = $MeSO_2NH$; R = *t*-Bu
d, X = $HOCH_2$; R = *t*-Bu
e, X = $HO(CH_2)_2$; R = *t*-Bu
f, X = $MeSO_2NHCH_2$; R = *t*-Bu
g, X = H_2NCH_2; R = *t*-Bu
h, X = H_2N; R = *i*-Pr



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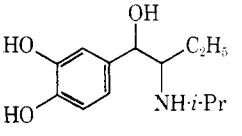

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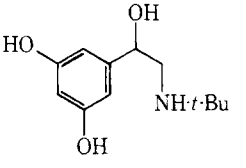

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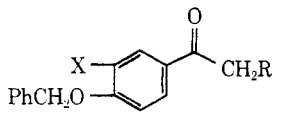
In a search for new selective bronchodilators we examined a series of catecholamine relatives in which the *m*-phenolic functionality was replaced by alkylamino, amido, sulfamido, ureido, and carbamate groups. Several *erythro*-α-ethyl relatives of isoetharine (**3**) and a 3,5-bis(methanesulfonamido) congener of terbutaline (**4**) were also included in the study. In this article are described the synthesis and results of preliminary pharmacological ex-

† This article is dedicated with appreciation to Dr. Alfred Burger, my former postdoctoral professor, long-time friend, and consultant.

Table I. 4′-Benzyloxy-3′-substituted Aceto- and Butyrophenones



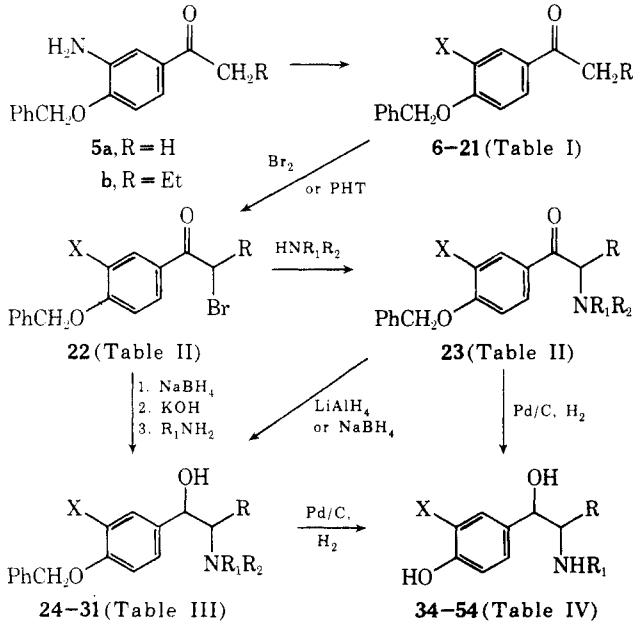
No.	X	R	Mp, °C	Recrystn solvent	Method of prepn	Yield, %	Formula[a]
6	H_2NCONH	H	182–184	Et_2O	*b*	97	$C_{16}H_{16}N_2O_3$
7	MeNHCONH	H	162–163	C_6H_6	*b*	92	$C_{17}H_{17}N_2O_3$
8	*i*-PrNHCONH	H	188–191	C_6H_6	*b*	92	$C_{19}H_{21}N_2O_3$
9	Me_2NCONH	H	146–147	C_6H_6	*b*	98	$C_{18}H_{20}N_2O_3$
10	MeOCONH	H	104–106	MeOH–Et_2O	*b*	88	$C_{17}H_{17}NO_4$
11	EtOCONH	H	82–84	EtOAc–hexane	*b*	81	$C_{18}H_{19}NO_4$
12	*i*-PrOCONH	H	99–100	EtOAc–hexane	*b*	86	$C_{19}H_{21}NO_4$
13	HCONH	H	121–123	Et_2O	*c*	90	$C_{16}H_{15}NO_3$
14	MeCONH	H	118–120	EtOAc–hexane	*d*	79	$C_{17}H_{17}NO_3$
15	Me_2NSO_2NH	H	113–115	EtOH–H_2O	*e*	77	$C_{17}H_{20}N_2O_4S$
16	HCONMe	H	85–87	Et_2O	*f*	95	$C_{17}H_{17}NO_3$
17	MeNH	H	66–67	Et_2O–hexane	*g*	98	$C_{16}H_{17}NO_2$
18	$H_2NCONMe$	H	145–147	PhMe–Et_2O	*h*	85	$C_{17}H_{18}N_2O_3$
19	H_2NCONH	Et	160–161	EtOH	*i*	87	$C_{18}H_{20}N_2O_3$
20	EtOCONH	Et	71–73	EtOAc–hexane	*b*	68	$C_{20}H_{23}NO_4$
21	Me_2NSO_2NH	Et	247–250 dec	$CHCl_3$	*j*	55	$C_{19}H_{24}N_2O_4S$

[a] All compounds were analyzed for C, H, and N and analytical values were within ±0.4% of calculated values. [b] See Experimental Section, general procedure A. [c] Prepared by refluxing 0.1 mol of **5a** with 125 ml of HCO_2Et for 24 hr. [d] From 0.1 mol of **5a** and Ac_2O (50 ml), 100°, 5 hr. [e] Obtained by dropwise addition of 0.2 mol of Me_2NSO_2Cl in 40 ml of pyridine to 0.1 mol of **5a** in 200 ml of pyridine with stirring at 0°. After being stirred at 25° for 24 hr, the mixture was diluted with H_2O to give **15**. [f] Prepared by addition of 0.11 mol of CH_3I to 0.1 mol of **13** and 0.1 mol of NaH in 150 ml of DMSO at 25°, followed by heating at 60° for 30 min and dilution with H_2O. [g] From hydrolysis of 0.1 mol of **16** with 0.3 mol of KOH in 50 ml of 80% aqueous EtOH at reflux for 30 min. [h] Obtained by stirring 0.1 mol of **17** and 0.2 mol of NaOCN in 300 ml of HOAc and 200 ml of H_2O, at 40° for 1 hr, followed by dilution with H_2O. [i] From **5b** and NaOCN as described in footnote *h*. [j] From **5b** and Me_2NSO_2Cl as described in footnote *e*.

amination of these substances.

Chemistry. Synthesis of a series of isoproterenol analogs in which the *m*-phenolic group is replaced by a substituted amino functionality was achieved as outlined in Scheme I.

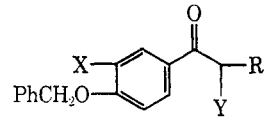
Scheme I



3′-Amino-4′-benzyloxyacetophenone (**5a**)[19] and the corresponding butyrophenone **5b**[19] were converted to 4′-benzyloxy-3′-substituted phenones **6–21** as described in the Experimental Section and Table I. Bromination of these ketones with Br_2, or with pyrrolidinone hydrotribromide (PHT) in the presence of 2-pyrrolidinone,[24] afforded phenacyl bromides **22** (Table II), many of which were characterized only by their nmr and ir spectra. 2-Bromoacetophenones (**22**, R = H) were condensed with the appropriate *N*-alkylbenzylamine to give tertiary amino ketones (**23**, R = H; R_1 = alkyl; R_2 = CH_2Ph). 2-Bromobutyrophenones (**22**, R = Et), whose reactivity was strongly influenced by the steric bulk of the amino reactant,[20] failed to condense with *N*-isopropyl- and *tert*-butylbenzylamines, but they were aminated with *tert*-butylamine, and more readily with isopropylamine, to give secondary amino ketones (**23**, R = Et; R_1 = *i*-Pr or *t*-Bu; R_2 = H). The latter compounds were reduced with $NaBH_4$ or $LiAlH_4$ to give amino alcohols **24–27** (Table III). As these products have two asymmetric centers, erythro and threo racemates are possible. The products were assigned the erythro configuration on the basis of nmr data for the H-H interaction of the two adjacent asymmetric centers. In TFA, the HCl salts of **24–27** showed a doublet (J = ~3.0 Hz) at 5.4 ppm. This is in close agreement with the structurally similar ephedrine hydrochloride [nmr (TFA) δ 5.28 (d, 1, C*H*OH, J = 3.74 Hz)] and related erythro isomers. It is in contrast with pseudoephedrine hydrochloride [nmr (TFA) δ 5.15 (d, 1, C*H*OH, J = 9.60 Hz)] and related threo compounds.[18,25,26] The configurational assignment of **24–27** is further supported by the observation[27,28] that hydride reduction of amino ketones having a H-bearing amino group produces predominantly erythro diastereomers.

The ethyl carbanilate (**23**, X = EtO_2CNH; R = H; R_1 = *t*-Bu; R_2 = CH_2Ph) and the *N*-methylformanilide (**23**, X = HCONMe; R = H; R_1 = *t*-Bu; R_2 = CH_2Ph) were reduced with $LiAlH_4$ to afford *m*-MeNH- (**28**) and Me_2N- (**29**) substituted amino alcohols (Table III). Two other tertiary amino ketones, **23** (X = MeNHCONH; R = H; R_1 = *t*-Bu; R_2 = CH_2Ph) and **23** (X = $H_2NCONMe$; R = H; R_1 = *t*-Bu; R_2 = CH_2Ph) were reduced with $NaBH_4$ to give amino alcohols **30** and **31** (Table III). Amino alcohols **32** and **33** were obtained by addition of isopropyl- or *tert*-bu-

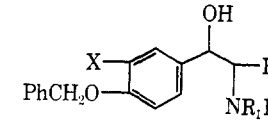
Table II. 2-Bromo- and 2-(Substituted amino)-3′-substituted 4′-Benzyloxyaceto- and butyrophenones



		Y = Br (22)[a]				Y = NR_1R_2 (23)[b]					
X	R	Mp, °C	Solvent[c]	Method[d]	Yield, %	R_1	R_2	Salt	Mp, °C	Solvent[c]	Yield, %
H_2NCONH	H	140–142[e]	EtOH	B	50	*t*-Bu	CH_2Ph	Base	149–157[f]	MeOH–Et_2O	60
MeNHCONH	H	176–180[g]	MeCN	C	70	*t*-Bu	CH_2Ph	HCl	208–210 dec	EtOH–Et_2O	73
i-PrNHCONH	H	198–200	MeCN	B	67	*t*-Bu	CH_2Ph	HCl	*h*	Et_2O	
Me_2NCONH	H	110–112[i]	EtOAc	B	45	*i*-Pr	CH_2Ph	HCl	*h*	Et_2O	
Me_2NCONH	H					*t*-Bu	CH_2Ph	HCl	*h*	Et_2O	69
MeOCONH	H	104–107	Et_2O	B	67	*t*-Bu	CH_2Ph	HCl	*h*	Et_2O	
EtOCONH	H	93–96[j]	Et_2O	B	68	*t*-Bu	CH_2Ph	HCl	138–143 dec	EtOH–Et_2O	94
i-PrOCONH	H	96–98	Et_2O	B	99	*t*-Bu	CH_2Ph	HCl	163–166 dec	MeCN–Et_2O	40
HCONH	H	124–128[k]	Et_2O	C	69	*t*-Bu	CH_2Ph	HCl	128–132 dec	Me_2CO	63
MeCONH	H	164–166	Et_2O	C	88	Me	CH_2Ph	HCl	*h*	Et_2O	86
MeCONH	H					*t*-Bu	CH_2Ph	HCl	95–100 dec	EtOH–Et_2O	67
Me_2NSO_2NH	H	87–89	Et_2O	C	71	*t*-Bu	CH_2Ph	HCl	*h*	Et_2O	77
HCONMe	H	108–113	EtOAc	C	55	*t*-Bu	CH_2Ph	Base	*l*	Et_2O	
$H_2NCONMe$	H	135–137	EtOH	B	76	*t*-Bu	CH_2Ph	HNO_3	163–164	MeCN	
NO_2	H	141–143	EtOAc	B	70						
NO_2	Et	*l*		C	100	*t*-Bu	H	HCl	214–215 dec[m]	MeOH–Et_2O	66
H_2NCONH	Et	170–171[n]	$CHCl_3$–hexane	C	71	*i*-Pr	H	HCl	222 dec[o]	MeOH–Et_2O	68
EtOCONH	Et	*l*		C	94	*i*-Pr	H	HCl	201–202 dec[p]	EtOH–Et_2O	64
Me_2NSO_2NH	Et	*l*		C	100	*t*-Bu	H	HCl	200–202 dec[q]	MeOH–Et_2O	39

[a]The 2-bromoacetophenones **22** (R = H) were characterized by their nmr ($CDCl_3$) δ ~4.5 (s, 2, $COCH_2Br$). 2-Bromobutyrophenones **22** (R = Et) had nmr ($CDCl_3$) δ ~5.1 (t, 1, COCHBr). These contrasted with the starting acetophenones [nmr ($CDCl_3$) δ ~2.5 (s, 3, $COCH_3$)] and butyrophenones [nmr ($CDCl_3$) δ ~3.0 (t, 2, $COCH_2$–)]. Generally, acetophenones had ir (Nujol mull) 1670–1700 cm^{-1} (C=O); 2-bromo derivatives had ir (Nujol mull) 1640–1670 cm^{-1}. [b]See Experimental Section, general procedure D. [c]In some instances the indicated solvent was only employed for trituration; in others it was used for recrystallization. [d]See Experimental Section, general procedures B and C. [e]*Anal.* ($C_{16}H_{15}BrN_2O_3$) C, H, N, Br. [f]*Anal.* ($C_{27}H_{31}N_3O_3$) C, H, N. [g]*Anal.* ($C_{17}H_{17}BrN_2O_3$) C, H, N. [h]Obtained as a noncrystalline amorphous solid by trituration with Et_2O. [i]*Anal.* ($C_{18}H_{19}BrN_2O_3$) C, H, N. [j]*Anal.* ($C_{18}H_{19}BrN_2O_4$) C, H, N. [k]Nmr analysis indicated ~20% of **13**. [l]Used for further reaction without purification. [m]*Anal.* ($C_{21}H_{27}ClN_2O_4$) C, H, N. [n]*Anal.* ($C_{18}H_{19}BrN_2O_3$) C, H, N. [o]*Anal.* ($C_{21}H_{28}ClN_3O_3 \cdot 0.25H_2O$) C, H, N. [p]*Anal.* ($C_{23}H_{31}ClN_3O_4$) C, H, N. [q]*Anal.* ($C_{23}H_{34}ClN_3O_4S$) C, H, N.

Table III. 4-Benzyloxy-3-substituted Phenylethanolamines



No.	X	R	R_1	R_2	Salt	Mp, °C	Recrystn solvent	Method[a]	Yield, %	Formula[b]
24[c]	NO_2	Et	*t*-Bu	H	HCl	244–245 dec	MeOH–Et_2O	E	77	$C_{21}H_{29}ClN_2O_4$
25[c]	H_2NCONH	Et	*i*-Pr	H	HCl	216–218 dec	MeOH–Et_2O	E	78	$C_{21}H_{30}ClN_3O_3$[d]
26[c]	EtOCONH	Et	*i*-Pr	H	HCl	205–206 dec	MeOH–Et_2O	E	67	$C_{23}H_{33}ClN_2O_4$
27[c]	Me_2NSO_2NH	Et	*t*-Bu	H	HCl	221–222 dec	MeOH–Et_2O	F	56	$C_{23}H_{36}ClN_3O_4S$
28	MeNH	H	*t*-Bu	$PhCH_2$	Base	111–113	Cyclohexane	F	52	$C_{17}H_{34}N_2O_2$
29	Me_2N	H	*t*-Bu	$PhCH_2$	Base	*e*		F		
30	MeNHCONH	H	*t*-Bu	$PhCH_2$	HCl	155–157	EtOH–Et_2O	E	74	
31	$H_2NCONMe$	H	*t*-Bu	$PhCH_2$	Base	119–121	EtOAc–hexane	E	67	$C_{28}H_{35}N_3O_3$
32	O_2N	H	*i*-Pr	H	HCl	194–196	EtOH–Et_2O	G	64	$C_{18}H_{23}ClN_2O_4$
33	O_2N	H	*t*-Bu	H	HCl	189–191	EtOAc–Et_2O	G	26	

[a]See Experimental Section, general procedures E, F, and G. [b]Compounds for which the formula is given were analyzed for C, H, and N, and analytical values were within ±0.4% of the calculated values. [c]Nmr (TFA) δ 5.40 (d, 1, benzylic H, J = ~3.0 Hz). [d]*Anal.* Calcd for 0.25 mol of H_2O. [e]The noncrystalline product was employed for further reaction without purification.

tylamine to 4-benzyloxy-1-(epoxyethyl)-3-nitrobenzene, prepared as described in the Experimental Section.

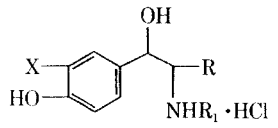
In most instances, crude tertiary amino ketones (**23**, R = H; R_1 = alkyl; R_2 = CH_2Ph) and the benzyloxy-substituted amino alcohols (**24–33**, Table III) were hydrogenated in the presence of Pd/C in aqueous MeOH or EtOH[29] to give the *m*-amino- and substituted aminocatecholamine analogs **34–54** (Table IV). In the course of reduction the nitro derivatives **24**, **32**, and **33** were converted to amines **51**, **34**, and **35**, respectively. The *erythro* stereochemistry of **51–54** follows from the configuration of their precursors **24–27** and is supported by their nmr spectra (TFA) which like that of their precursors **24–27** show a doublet (J = ~3.0 Hz) at 5.4 ppm.

One of the most promising β-adrenoreceptor stimulants arising from this study, **41** (carbuterol),‡ was resolved into its (−) and (+) enantiomers.

An analog **57** of terbutaline (**4**), in which the resorcinol's two phenolic groups are replaced by the bioisosteric methanesulfonamido functionalities,[17,19] was prepared

‡ The USAN generic name for **41**, [5-[2-(*tert*-butylamino)-1-hydroxyethyl]-2-hydroxyphenyl]urea hydrochloride, is carbuterol.

Table IV. Catecholamine Analogs with an Amino or Substituted Amino Group in the Meta Position[a]



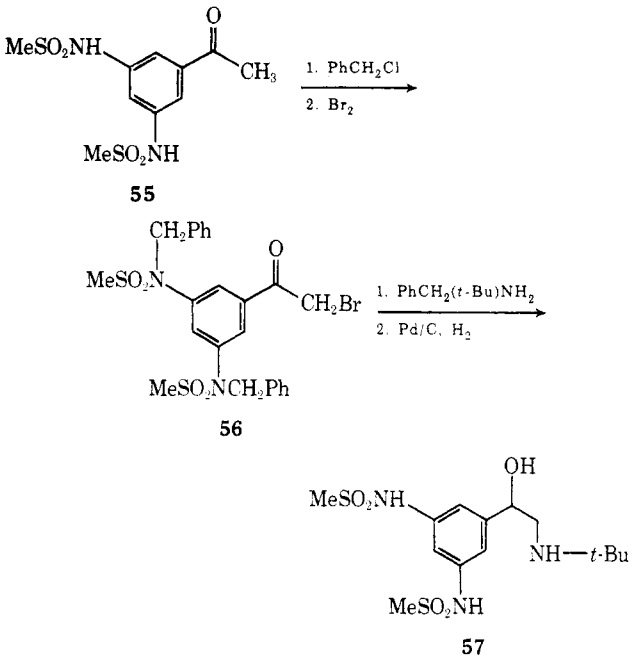
No.	X	R	R_1	Mp, °C	Recrystn solvent	Yield, %	Formula[b]	Guinea pig tracheal test,[c,d] ED_{50} (molar concn) (95% confidence limits)	Guinea pig atrial rate,[e] ED_{25} (molar concn) (95% confidence limits)	Intrinsic activity (α) in atrial test[e]	Separation ratio[f]
34[g]	H_2N	H	*i*-Pr	175–176	MeOH–Et_2O	52	$C_{11}H_{19}ClN_2O_2$	4.8×10^{-8} ($2.4–10.0 \times 10^{-8}$)	1.0×10^{-7} ($0.8–1.3 \times 10^{-7}$)	1	2.1
35[g]	H_2N	H	*t*-Bu	209–210 dec	EtOAc–Et_2O	65	$C_{12}H_{21}ClN_2O_2$	2.1×10^{-8} ($1.2–4.0 \times 10^{-8}$)	1.1×10^{-7} ($0.58–2.4 \times 10^{-7}$)	1	5.2
36	MeNH	H	*t*-Bu	160–161	MeCN	50	$C_{13}H_{22}N_2O_2$[h]	1.0×10^{-10} ($0.5–2.1 \times 10^{-10}$)	9.2×10^{-9} ($6.3–15.0 \times 10^{-9}$)	1	92
37	Me_2N	H	*t*-Bu	108–110	Et_2O	48	$C_{14}H_{24}N_2O_2$[h]	1.2×10^{-7} ($0.23–5.7 \times 10^{-7}$)	2.9×10^{-5} ($0.32–2.7 \times 10^{-5}$)	0.3	242
38	HCONH	H	*t*-Bu	192–193 dec	EtOH–Et_2O	31	$C_{13}H_{21}ClN_2O_3$[i]	1.1×10^{-9} ($0.67–1.9 \times 10^{-9}$)	1.7×10^{-8} ($1.1–2.4 \times 10^{-8}$)	0.9	15
39[j]	MeCONH	H	Me	174–175	MeOH–Et_2O	40	$C_{11}H_{17}ClN_2O_3$[i]	4.0×10^{-5}[k,l]	1.3×10^{-5}[k]	0.3	0.33
40	MeCONH	H	*t*-Bu	215–216 dec	EtOH–Et_2O	85	$C_{14}H_{23}ClN_2O_3$	2.8×10^{-8} ($1.8–4.1 \times 10^{-8}$)	1.4×10^{-6} ($0.38–5.4 \times 10^{-6}$)	0.5	50
41	H_2NCONH	H	*t*-Bu	205–207 dec	MeOH–Et_2O	80	$C_{13}H_{22}ClN_3O_3$	1.9×10^{-8} ($0.8–5.0 \times 10^{-8}$)	6.4×10^{-7} ($3.4–12.3 \times 10^{-7}$)	0.5	34
(−)-**41**	H_2NCONH	H	*t*-Bu	211–212 dec	MeOH–Et_2O			6.7×10^{-9} ($3.6–13.1 \times 10^{-9}$)	12.7×10^{-8} ($2.1–77.1 \times 10^{-8}$)	0.4	18
(+)-**41**	H_2NCONH	H	*t*-Bu	211–212 dec	MeOH–Et_2O			2.7×10^{-6} ($2.1–3.5 \times 10^{-6}$)	9.4×10^{-5} ($0.7–152 \times 10^{-5}$)	0.3	35
42	MeNHCONH	H	*t*-Bu	185–187 dec	MeCN	86	$C_{14}H_{24}ClN_3O_3$	1.8×10^{-7} ($0.5–6.5 \times 10^{-7}$)	6.5×10^{-6} ($1.8–24.0 \times 10^{-6}$)	0.4	36
43	*i*-PrNHCONH	H	*t*-Bu	154–156	MeCN	39[m]	$C_{16}H_{27}N_3O_3$[h]	4.8×10^{-5}, 19%	*n*		
44	Me_2NCONH	H	*i*-Pr	184–186 dec	EtOH–Et_2O	40[m]	$C_{14}H_{24}ClN_3O_3$	1.8×10^{-5}, 23%	*n*		
45	Me_2NCONH	H	*t*-Bu	196–197 dec	MeOH–Et_2O	18[m]	$C_{15}H_{26}ClN_3O_3$	1.7×10^{-5}, 24%			
46	$H_2NCONMe$	H	*t*-Bu	145–148 dec	EtOH–Me_2CO	55	$C_{17}H_{30}BrN_3O_4$[o]	$\sim 1.6 \times 10^{-4}$[k,l]	5.3×10^{-5}, 11%		
47	MeOCONH	H	*t*-Bu	215–217 dec	EtOH–Et_2O	8[m]	$C_{14}H_{23}ClN_2O_4$	9.6×10^{-9} ($5.7–16.0 \times 10^{-9}$)	1.2×10^{-7} ($0.64–2.4 \times 10^{-7}$)	0.7	12.5
48	EtOCONH	H	*t*-Bu	218–219 dec	EtOH–Et_2O	88	$C_{15}H_{25}ClN_2O_4$	6.7×10^{-8} ($4.7–9.8 \times 10^{-8}$)	3.4×10^{-7} ($2.0–5.7 \times 10^{-7}$)	0.8	5.0
49	*i*-PrOCONH	H	*t*-Bu	197–198 dec	MeOH–Et_2O	41	$C_{16}H_{27}ClN_2O_4$	2.5×10^{-7} ($1.9–3.2 \times 10^{-7}$)	1.4×10^{-6} ($0.26–7.7 \times 10^{-6}$)	0.7	4.8
50	Me_2NSO_2NH	H	*t*-Bu	189–191 dec	MeOH–Et_2O	31	$C_{14}H_{26}ClN_3O_4S$[i]	1.1×10^{-7} ($0.66–1.7 \times 10^{-7}$)[p]	9.7×10^{-7} ($3.6–26.0 \times 10^{-7}$)	0.6	8.8
								5.9×10^{-7}	$\sim 1.1 \times 10^{-4}$		

51	H_2N	Et	*t*-Bu	233.5 dec	*i*-PrOH–*i*-Pr_2O	82	$C_{14}H_{25}ClN_2O_2$[i]	(3.3–11.0 × 10^{-7}) 7.1 × 10^{-7}		0.3	~186
52	H_2NCONH	Et	*i*-Pr	224 dec	MeOH–Et_2O	94	$C_{14}H_{24}ClN_3O_3$[i]	4.1 × 10^{-6} (3.2–16.0 × 10^{-7}) ~9.7 × 10^{-6} [k]		0.3	5.8
53	EtOCONH	Et	*i*-Pr	199–200 dec	MeOH–Et_2O	82	$C_{16}H_{27}ClN_2O_4$	4.9 × 10^{-5}, 8%			
54	Me_2NSO_2NH	Et	*t*-Bu	212–214 dec	MeOH–Et_2O	77	$C_{16}H_{30}ClN_3O_4S$[q]	4.2 × 10^{-5}, 16% 4.0 × 10^{-5}, 14%	*n*		
57[r]									*n*		
								7.1 × 10^{-9}	3.4 × 10^{-9}		
1a	Isoproterenol							(5.2–9.9 × 10^{-9}) 1.3 × 10^{-9}	(2.6–4.6 × 10^{-9}) 7.1 × 10^{-9}	1	0.48
1b	*N-tert*-Butylnorepinephrine							(0.93–1.8 × 10^{-9}) 2.6 × 10^{-8}	(5.3–10.0 × 10^{-9}) 7.6 × 10^{-8}	1	5.5
1c	Soterenol							(0.97–6.9 × 10^{-8}) 1.2 × 10^{-7}	(1.0–59.0 × 10^{-8}) 3.4 × 10^{-7}	0.7	3.0
4	Terbutaline							(0.44–2.8 × 10^{-7})	(0.8–15.0 × 10^{-7})	0.8	2.8

[a] All compounds were obtained by hydrogenation of appropriate ketones (**23**, Table II) or amino alcohols (**24–33**, Table III) according to general procedure H or as otherwise described in the Experimental Section. [b] Compounds were analyzed for C, H, and N and analytical values were within ±0.4% of the calculated values. [c] See Experimental Section. Where ED's were not determined results are given as per cent response at indicated concentration. [d] The intrinsic activity, α, *i.e.*, maximum effect of test compounds divided by the maximum effect of papaverine, is equal to 1 for all compounds for which ED_{50}'s were obtained, unless indicated otherwise. [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] Reference 21 reports mp 230–240° for the sulfate salt. [h] Base. [i] *Anal.* for 0.25 mol of H_2O. [j] Reference 37 reports mp 187–188° for HBr salt. [k] ED estimated since compound is a partial agonist. [l] α = 0.5. [m] Yield based on bromo ketone; the amino ketone was not isolated. [n] Not tested. [o] HBr salt. *Anal.* for 1 mol of Me_2CO. [p] α = 0.7. [q] *Anal.* for 0.75 mol of H_2O. [r] See Scheme II for structure of **57**.

from 3′,5′-diaminoacetophenone[30] *via* **55** as outlined in Scheme II.

Scheme II



Initial attempts to condense the bromo ketone derived from **55** with *N-tert*-butylbenzylamine gave polymeric self-condensation products. For this reason the sulfonamide functionalities were benzylated to give, after bromination, the bromo ketone **56**. Condensation of **56** with *N-tert*-butylbenzylamine gave the expected amino ketone which upon hydrogenolysis afforded the terbutaline relative **57**. Thus, catalytic hydrogenolysis of benzyl-protected sulfonamide groups, which fails in the case of related *N*-benzylcarboxamides,[31] offers a mild method of sulfonamide group protection.[32]

Results and Discussion

As a measure of potential bronchodilating activity, catecholamine analogs **34–54** and **57** bearing an amino or substituted amino functionality in the meta position were examined *in vitro* for their ability to relax a spontaneously contracted guinea pig tracheal chain preparation.[33] Cardiac stimulant potential was evaluated *in vitro* by changes induced in the contraction rate of spontaneously beating guinea pig right atria.[34] Comparison of the ED_{50} for tracheal relaxation with the ED_{25} for atrial stimulation offers an index of the selectivity of the compound for tracheobronchial *vs.* cardiac muscle. The results of such studies for the present series and for several standard β-adrenoreceptor agents are tabulated in Table IV. Intrinsic activity,[35,36] *i.e.*, the portion of the maximal tissue response which can be induced by the test compound, offers another measure of the agent's β-agonist activity. These values are also recorded in Table IV.

In general, *tert*-butyl substitution of the side-chain amino group, as noted in related series,[16,37] provides advantages of potency and selectivity for the tracheal muscle. In our tests, the *tert*-butyl (**1b**) homolog of isoproterenol (**1a**) was 5.5 times more potent than the prototype in causing tracheal relaxation, whereas it was only 0.5 as potent as an atrial rate stimulant. This selectivity is indicated numerically by the separation ratio, *i.e.*, the ED_{25} in the atrial test divided by the ED_{50} in the tracheal relaxation assay: 0.48 for **1a** and 5.5 for **1b**. A similar selectivity was noted for *m*-NH_2 congeners.[21] Thus, **35** is more

than twice as potent as a relaxant of the guinea pig tracheal muscle preparation as its isopropyl counterpart **34** and it is more selective; the separation ratio is 2.1 for **34** and 5.2 for **35**. For this reason, in our systematic study of substituted amino modification of the *m*-OH of β-adrenergic agents, the alkyl substituent generally introduced on the side-chain N was *tert*-butyl.

Although the *m*-NH_2 derivative **35** was only 0.34 as potent as isoproterenol in the tracheal test, monomethylation significantly increased potency. In fact, the NHMe congener **36** was the most potent member of the entire series. It was 71 times more effective than the prototype. It was also selective, having a separation ratio of 92. By contrast, the *tert*-NMe_2 analog **37** was only 0.06 as potent as **1a**, although it too showed pronounced selectivity, with a ratio of 242.

Modification of the *m*-amino functionality to produce a variety of substituents, including amides, ureas, and carbanilates, generally resulted in retention of a high order of potency in the tracheal chain test and significantly increased the separation ratio relative to the catecholic prototype. Although very few generalizations can be made, potency usually increased with decreasing size of the acyl substituent. Thus, the formanilide **38**, a very potent relaxant of the tracheal chain preparation (about 6.5 times more potent than isoproterenol), was considerably more effective than the corresponding acetanilide **40**, which was 0.25 as potent as **1a**. Nonetheless, the acetanilide is noteworthy because of its high separation ratio of 50. Potential selectivity of **40** for bronchial smooth muscle is also suggested by its lowered intrinsic activity ($\alpha = 0.5$) in the atrial preparation. This value is close to that of the side-chain NHMe analog **39**. This epinephrine congener,[38] which was relatively ineffective and has a lowered intrinsic activity in both the tracheal and atrial tests, has a separation ratio of only 0.33.

The urea derivative **41** (carbuterol‡),[39,40] although only 0.37 as potent as isoproterenol in the tracheal test, was highly specific. It had an intrinsic activity value of 0.5 in the atrial system and afforded a separation ratio of 34. In common with other β-adrenoreceptor agonists, the activity of **41** resided almost exclusively in one of its enantiomers; (−)-**41** was 2.8 times more potent than the racemate in the tracheal test whereas (+)-**41** was only marginally effective. Substitution of the terminal urea N with a Me group (**42**) decreased potency (about 0.1 as potent as **41**), although the product retained a high degree of specificity for tracheal muscle (separation ratio = 36). Substitution with the bulkier isopropyl group (**43**), dimethylation (**44**, **45**) of the terminal N of the ureido substituent, as well as methylation of the anilino N (**46**) of **41** markedly diminished activity in this test. A similar relationship between the size of the substituent and tracheal relaxant activity was noted among a series of alkyl carbanilates. The Me (**47**), Et (**48**), and *i*-Pr (**49**) carbanilates had potencies, relative to isoproterenol, of 0.74, 0.11, and 0.028, respectively. Nevertheless, as can be seen from their lowered intrinsic activities in the atrial test and their separation ratios (Table IV), these compounds are potential bronchodilators with limited cardiovascular activity. One sulfamide, a *m*-Me_2NSO_2NH derivative **50**, although only 0.07 as potent as isoproterenol, was selective (separation ratio = 8.8) and its intrinsic activity was less than 1.0 in both tracheal ($\alpha = 0.7$) and atrial ($\alpha = 0.6$) tissues.

As erythro isomers of α-ethyl-substituted catecholamine β-adrenergic agents, *e.g.*, isoetharine (**3**), often have enhanced selectivity for bronchial *vs.* atrial and vascular smooth muscle,[16] similar modification was examined in the present series of *m*-amino and substituted amino analogs of catecholamines. In all instances the *erythro*-α-ethyl derivatives **51–54** were less potent tracheal muscle relaxants than their ethanolamine counterparts. For example, **51** was 0.04 as potent as its unbranched congener **35**. Similarly, the α-ethyl congener **52** (which bears an isopropylamino group on the side chain) related to carbuterol (**41**) was only 0.3 as potent as the parent. Even greater potency decreases were noted for **53** and **54** as compared to their α-unsubstituted relatives. Further, perhaps as a consequence of their weak activities, no significant conclusion relative to selectivity could be ascertained for these α-ethyl derivatives.

Table V. Relative Pharmacological Potencies[a] of Some Catecholamine Analogs

No.	Bronchospasm inhibition, guinea pigs, po[b]	Pulmonary resistance decrease, cats, iv[b]	Heart rate increase, dogs, iv[b]	Diastolic blood pressure decrease, dogs, iv[b]
36	13.9	1.0	1.0	1.0
37		~0.007		
40	~0.1	~0.1	0.014	0.007
41[c]	0.5	0.3	~0.03	~0.05
1a	1.0	1.0	1.0	1.0

[a] Relative potencies are expressed as multiples of the equiactive (ED_{50}) dose of isoproterenol (**1a**). In the dog heart rate and blood pressure tests relative potency was derived as described in the Experimental Section, pharmacology method E. [b] See Experimental Section, pharmacology methods C–E. [c] Data taken from ref 39.

The 3,5-bis(methanesulfonamide) hybrid **57** of soterenol (**1c**) and terbutaline (**4**) was only weakly effective as a relaxant of the tracheal chain preparation.

In summary, our structure–activity studies with *m*-amino and substituted amino analogs of β-adrenoreceptor agonists of the isoproterenol type indicate that such modification may lead to potent agents with a greater selectivity for tracheobronchial smooth muscle rather than for cardiac muscle. The physicochemical factors required for such reactivity are not apparent. Compounds with basic or strongly acidic or very weakly acidic functionalities, as well as ones with or without a mobile proton in the vicinity of the meta position, may induce a high order of activity.

On the basis of the potency and selectivity data derived from the *in vitro* screening of these compounds, many were examined in a variety of secondary pharmacological tests aimed toward verification of bronchodilating activity, routes of efficacy, and duration of action *in vivo*. A summary of potencies relative to isoproterenol in several of these secondary procedures is presented in Table V for compounds **36**, **37**, **40**, and **41** which afforded promising *in vitro* results. On the basis of the data outlined in Table V, the most promising *in vivo* selective bronchodilator was considered to be **41** (carbuterol). Further, in the test for inhibition of acetylcholine-induced bronchospasm in guinea pigs, upon aerosol administration carbuterol caused an effect lasting more than 45 min, whereas the duration of isoproterenol was less than 5 min.[39] Extensive pharmacological studies[40] indicate carbuterol is a β-adrenoreceptor agonist which is more selective for airway smooth muscle than for cardiovascular β receptors. These studies describe the pharmacological comparison of carbuterol with isoproterenol (**1a**) and salbutamol (**1d**), a selective new bronchodilator.[20] Carbuterol is presently being examined for bronchodilator activity in man.

Experimental Section§

Chemistry. General Procedures. A. 4′-Benzyloxy-3′-substituted Aceto- and Butyrophenones (9–14 and 20). To a stirred

solution of 1 mol of $COCl_2$ in 500 ml of PhMe at 25° was added, in portions, 0.3 mol of 3′-amino-4′-benzyloxyacetophenone (**5a**)[19] or the corresponding butyrophenone **5b**.[19] The mixture was stirred and refluxed for 1.5 hr; then it was flushed with N_2 and concentrated *in vacuo*. Trituration of the residual solid with Et_2O gave crude isocyanates in nearly quantitative yield. The isocyanate derived from **5a** melted at 101–103°; the one from **5b** was not isolated. For both compounds, the ir (Nujol mull) showed intense absorption at 2250 (NCO) and 1680 cm^{-1} (CO). The isocyanate (0.1 mol) derived from **5a** was treated with an excess of the appropriate amine (NH_3, $MeNH_2$, Me_2NH, or *i*-$PrNH_2$) in 50 ml of PhMe at ambient temperature for 1 hr to give urea derivatives **6–9**. For the carbanilates **10–12**, 0.1 mol of this isocyanate was refluxed with 50 ml of the appropriate alcohol (MeOH, EtOH, or *i*-PrOH) for 1 hr. The isocyanate (0.1 mol) derived from **5b** was refluxed and stirred with 50 ml of EtOH to give **20**. Products were isolated by concentration of resulting solutions and recrystallization of the residue from solvents indicated in Table I.

B. Bromination of Acetophenone Derivatives with Br_2. To a solution of 0.1 mol of the acetophenone (in some instances 0.1–0.2 g of dibenzoyl peroxide was added) in 250 ml of $CHCl_3$ was added, dropwise, 1 equiv of Br_2. The reaction mixture was stirred at room temperature until the Br_2 color had disappeared, N_2 was bubbled through the solution for 15–30 min, and the solvent was evaporated *in vacuo*. The residue was triturated with Et_2O or recrystallized from the indicated solvent (see Table II).

C. Bromination of Aceto- and Butyrophenones with Pyrrolidinone Hydrotribromide (PHT).[24] A mixture of 0.1 mol of the acetophenone, 0.1 mol of PHT, and 0.1 mol of 2-pyrrolidinone in 200 ml of THF was stirred at ambient temperature from 18–42 hr (until deep red orange color indicative of pyrrolidinone hydrotribromide was gone). The mixture was filtered to remove 2-pyrrolidinone hemihydrobromide. The filtrate was evaporated *in vacuo*, redissolved in $CHCl_3$, washed with H_2O, and dried over $MgSO_4$–decolorizing C, and the solvent was evaporated *in vacuo*. The residue was triturated in Et_2O or recrystallized from the appropriate solvent to give the corresponding bromo ketone **22** (Table II).

D. Preparation of Amino Ketone Derivatives 23. A solution of 0.1 mol of the 2-bromoacetophenone **22** (R = H) in 300 ml of MeCN was stirred with 0.2 mol of $PhCH_2$(*i*-Pr)NH (1 hr at 25°) or $PhCH_2$(*t*-Bu)NH (for 3 hr at reflux). 2-Bromobutyrophenones (0.1 mol in 300 ml of MeCN) were refluxed with an excess of *i*-$PrNH_2$ or *t*-$BuNH_2$ for 3 hr. The reaction mixture was cooled to 0°, diluted with an equal volume of Et_2O, and filtered. The filtrate was diluted with an additional 500 ml of Et_2O and extracted with H_2O. The Et_2O solution was dried ($MgSO_4$–decolorizing C). Following acidification with dry HCl, the precipitated gum was triturated or recrystallized from the solvent indicated in Table II to give HCl salts **23**. Bases were isolated by neutralization of an aqueous solution of **23**·HCl with NH_3 and extraction of the precipitated base with Et_2O, followed by drying ($MgSO_4$–decolorizing C), and concentration of the Et_2O solution. In some instances the base was reconverted to an acid salt.

E. Reduction of Amino Ketones with $NaBH_4$. To a solution of 0.01 mol of the appropriate amino ketone base **23** in 50 ml of EtOH at 0° was added, in portions, 0.012 mol of $NaBH_4$. After being stirred at 25° for 2 hr, 10 ml of 2 *N* H_2SO_4 was added; the mixture was concentrated *in vacuo* to remove EtOH, diluted with H_2O, and made alkaline (K_2CO_3). The mixture was extracted with Et_2O or EtOAc. After being dried ($MgSO_4$), the extracts were concentrated. The residual base was either recrystallized or converted into a HCl salt in the indicated solvent (Table III) to give **24–26, 30,** and **31**.

F. Reduction of Amino Ketones with $LiAlH_4$. To a stirred suspension of 5.0 g (0.13 mol) of $LiAlH_4$ in 200 ml of Et_2O was added dropwise 0.1 mol of the appropriate amino ketone base **23** in 50 ml of Et_2O. After being refluxed for 6 hr, 5 ml of 2.5 *N* NaOH and 20 ml of H_2O were added dropwise with *caution*. The mixture was filtered and the filtrate was concentrated to give the amino alcohols **27–29** (Table III).

G. Addition of Amines to 4-Benzyloxy-1-(epoxyethyl)-3-nitrobenzene. A mixture of 7.2 g (0.027 mol) of 4-benzyloxy-1-(epoxyethyl)-3-nitrobenzene and 35 ml of *i*-$PrNH_2$ or *t*-$BuNH_2$ in 100 ml of MeOH was stirred and refluxed for 5 hr. The solution was concentrated *in vacuo*, the residual base was taken into Et_2O, and the solution was extracted with 1 *N* HCl. The acidic extracts were made alkaline (NaOH) and precipitated base was extracted with Et_2O. The extracts were dried ($MgSO_4$) and concentrated. The residual amines were treated with HCl in the solvent indicated in Table III to give **32** and **33**.

H. Catalytic Hydrogenation of Amino Ketones 23 and Amino Alcohols (Table III). A mixture of 0.02 mol of the intermediate amino ketone hydrochloride **23** (bases and other salts were converted to HCl salts prior to reduction), or 0.02 mol of the amino alcohols **24–33**, 100 ml of 70% aqueous EtOH, and 2.0 g of 10% Pd/C was hydrogenated at 25° at an initial H_2 pressure of 3.5 kg/cm^2. After H_2 uptake was completed (2–4 hr was required for the amino ketones; 10–15 min for the amino alcohols) the mixture was filtered, the filtrate was concentrated and azeotroped twice with PhMe, and the residue was recrystallized from the solvent indicated in Table IV to give **34–54**. Compound **31**, reduced as a base, gave **46**, which was converted to a HBr salt.

4-Benzyloxy-1-(epoxyethyl)-3-nitrobenzene. To a solution of 28.9 g (0.083 mol) of 4′-benzyloxy-2-bromo-3′-nitroacetophenone (Table II, X = NO_2, R = H) in 250 ml of dioxane was added dropwise a solution of 3.3 g (0.09 mol) of $NaBH_4$ in 60 ml of H_2O. After being stirred at 25° for 4 hr, 20 ml of 2 *N* H_2SO_4 was added dropwise; the mixture was diluted with ice–H_2O and extracted with 150 ml of Et_2O. The Et_2O solution was stirred vigorously with a solution of 9.7 g (0.17 mol) of KOH in 180 ml of H_2O. The Et_2O layer was separated, dried, and concentrated to give 20.7 g (67%) of yellow crystals: mp 71–73°; nmr ($CDCl_3$) δ 2.73 (m, 1, epoxy CH_2, cis to aryl group), 3.13 (m, 1, epoxy CH_2, trans to aryl group), 3.82 (m, 1, benzylic CH). The identical compound (ir and nmr) was obtained in 61% yield from 4-benzyloxy-3-nitrobenzaldehyde[41] and 1 equiv of dimethylsulfonium methylide in the usual fashion.[42]

Resolution of [5-[2-(*tert*-Butylamino)-1-hydroxyethyl]-2-hydroxyphenyl]urea (41). To a suspension of 10.0 g (0.033 mol) of **41**·HCl in 75 ml of EtOH was added a solution of 1.85 g (0.033 mol) of KOH in 15 ml of MeOH. The resulting mixture was filtered through Celite and the filtrate was concentrated to leave the amorphous base which crystallized on standing, mp 174–176° dec. To a solution of 6.6 g (0.022 mol) of **41** base in 50 ml of MeOH was added a solution of 3.3 g (0.22 mol) of (+)-tartaric acid in 20 ml of MeOH to give 8.7 g of crystalline salt, mp 163–169°. Three recrystallizations from MeOH gave 1.5 g of crystals, mp 184–185° dec. A solution of this (+)-tartrate salt in MeOH was passed through a column of an excess of Amberlite IRA-401.‡ The eluate was concentrated *in vacuo* and the residue was recrystallized from MeOH–Et_2O to give 0.45 g of (−)-**41**·HCl: $[\alpha]^{25}D$ −43.0 (*c* 1, MeOH).

All mother liquors from the recrystallization of the (+)-tartrate were converted into a HCl salt by passage of a MeOH solution through a column of Amberlite IRA-401.‡ The eluates were concentrated and the residual **41**·HCl was converted to base (4.5 g) as described for the racemate. The base (4.5 g) was treated with (−)-tartaric acid in the same fashion as described for the enantiomer. Two recrystallizations from MeOH gave 2.3 g of the (−)-tartrate of **41**, mp 184–185 dec. The salt was converted to (+)-**41**·HCl, 0.8 g, $[\alpha]^{25}D$ +43.4 (*c* 1, MeOH), as described for the (−) isomer.

***N,N′*-(5-Acetyl-*m*-phenylene)bis(methanesulfonamide) (55).** To a stirred solution of 15.0 g (0.1 mol) of 3′,5′-diaminoacetophenone[30] in 150 ml of pyridine, at 5°, was added dropwise a solution of 22.9 g (0.2 mol) of $MeSO_2Cl$. The solution was stirred at 25° for 2 hr and at 60–70° for 10 min. The mixture was poured into 1.5 l. of H_2O. The precipitate was filtered and redissolved in 2.5 *N* NaOH, and the solution was extracted with Et_2O. Acidification of the alkaline solution with 2 *N* HCl gave a crystalline precipitate, 20.4 g (78%), mp 221–223°, after recrystallization from MeOH. *Anal.* ($C_{10}H_{14}N_2O_5S_2$) C, H, N.

***N,N′*-(5-Acetyl-*m*-phenylene)bis(*N*-benzylmethanesulfonamide).** A stirred solution of 20.4 g (0.067 mol) of **55**, 25 ml (27.5 g, 0.219 mol) of $PhCH_2Cl$, and 250 ml of 2.5 *N* NaOH in 750 ml of EtOH was refluxed for 18 hr; then an additional 10 ml of $PhCH_2Cl$ in 50 ml of EtOH was added and the mixture was refluxed for 5 hr more. Addition of 10 ml of $PhCH_2Cl$ and 25 ml of 2.5 *N* NaOH was repeated and the mixture was refluxed for a further 18 hr. After concentration of the solution to remove EtOH,

§ All melting points were obtained by the capillary method; they are uncorrected. Microanalyses were obtained 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. Infrared spectra were obtained with a Perkin-Elmer spectrophotometer. The nmr spectra were recorded with a Varian T-60 spectrometer using Me_4Si as an internal reference and the indicated solvent at ambient temperatures.

‡ A synthetic porous base anion exchange resin, quaternary amine type, chloride form, was obtained from the Fisher Scientific Co., Fair Lawn, N. J.

the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with 2.5 *N* NaOH and water, dried, and concentrated. Trituration of the residue gave 15.6 g (59%) of crystals, mp 136–138° (from EtOAc). *Anal.* ($C_{24}H_{26}N_2O_5S_2$) H, N; C: calcd, 59.24; found, 59.93.

***N,N'*-[5-(Bromoacetyl)-*m*-phenylene]bis(*N*-benzylmethanesulfonamide) (56)** was prepared by bromination of *N,N'*-(5-acetyl-*m*-phenylene)bis(*N*-benzylmethanesulfonamide) as described in general procedure B. The yield was 86%, mp 137–139° (from EtOAc). *Anal.* ($C_{24}H_{25}BrN_2O_5S_2$) H, N; C: calcd, 50.97; found, 51.78.

***N,N'*-[5-[(Benzyl-*tert*-butylamino)acetyl]-*m*-phenylene]bis(*N*-benzylmethanesulfonamide)** was prepared from **56** and $PhCH_2(t\text{-}Bu)NH$ as described in general procedure D. The amino ketone, mp 139–141° (from EtOH), was obtained in 29% yield. *Anal.* ($C_{35}H_{41}N_3O_5S_2$) C, H, N. The base was converted to a HCl salt, mp 182–185° (from MeCN–Et_2O). *Anal.* ($C_{35}H_{42}ClN_3O_5S_2 \cdot 0.75H_2O$) C, H, N.

***N,N'*-[5-[2-(*tert*-Butylamino)-1-hydroxyethyl]-*m*-phenylene]bis(methanesulfonamide) (57) hydrochloride** was prepared by reduction of *N,N'*-[5-[(benzyl-*tert*-butylamino)acetyl]-*m*-phenylene]bis(*N*-benzylmethanesulfonamide) hydrochloride in the presence of an equal weight of 10% Pd/C according to general procedure H. The colorless crystals (78%) melted at 172–181° after recrystallization from MeOH–Et_2O. *Anal.* ($C_{14}H_{26}ClN_3O_5S_2$) C, H; N: calcd, 10.10; found, 9.34; M^+ 379.

Pharmacology. Methods. A. Guinea Pig Tracheal Chain Test. A guinea pig tracheal chain prepared by a modification[43] of the method of Castillo and deBeer[44] was suspended in a bath of pH 7.3 Kreb's HCO_3^- solution[45] aerated with a mixture of 95% O_2 and 5% CO_2 at 37.5°. After an equilibration period, during which time spontaneous tone developed, isotonic relaxations of the tracheal chains (under a tension of 250 mg) produced by cumulative dosing with the test compound were recorded *via* a linear motion transducer. Responses were expressed as the per cent of the maximum relaxation induced by 10 μg/ml of papaverine hydrochloride which we have shown to produce the same maximal relaxation as isoproterenol. Usually one compound was tested per tissue over the entire cumulative dose–response range. The best fitting log dose–response line was drawn for each chain and the ED_{50}, *i.e.*, the dose producing 50% of the maximum papaverine-induced relaxation, was estimated from the plot. Mean ED_{50}'s (usually from five tissues), with 95% confidence limits, were obtained by the direct assay method.[46] Intrinsic activity (α)[35,36] was derived by dividing the maximum response to the compound by the maximum papaverine-induced response.

B. Guinea Pig Right Atria Test. Isolated guinea pig right atria were suspended in an aerated (95% O_2–5% CO_2) bath of pH 7.3 Kreb's HCO_3^- solution.[45] Atrial contraction rate was recorded *via* a force transducer with a diastolic tension maintained constant at 0.5 g. After an equilibration period, increases in atrial rate in response to cumulative dosing were measured. They were expressed as per cent of the previously determined maximum isoproterenol-induced rate increase (324 ± 10 beats per minute—the average of 22 control experiments). Usually one compound was tested per atrium over the entire cumulative dose–response range. The ED_{25}'s, mean ED_{25}, and intrinsic activity were determined in the same manner as outlined for the guinea pig tracheal chain test, except that comparisons were made with maximum isoproterenol-induced rate increases.

C. Inhibition of Acetylcholine-Induced Bronchospasm in Guinea Pigs. Groups of eight control and drug-treated (at the predetermined time of peak effect) guinea pigs were placed in individual Plexiglass chambers and exposed to a 1% acetylcholine aerosol (produced by a No. 40 DeVilbiss nebulizer at a pressure of 200 mm). The average time (seconds) between initiation of the aerosol exposure and prostration was measured for drug-treated (A) and control (B) animals. Maximum aerosol exposure time (C) was 420 sec. Drug activity was expressed as per cent inhibition using the following formula: $[(\log A - \log B)/(\log C - \log B)]100$. ED_{50}'s, *i.e.*, the dose causing 50% inhibition, and 95% confidence limits were calculated according to the method of Finney.[40]

D. Cat Pulmonary Resistance Test. Following a period of physiological stabilization, the decreases in spontaneously increased resting pulmonary resistance (indicative of bronchodilation) were measured after increasing iv doses of the test compound in a minimum of three anesthetized cats as described previously.[47] The best fitting line for the average log dose–response regression curve was employed to determine the ED_{50}, *i.e.*, the dose producing a 50% decrease in resting pulmonary resistance.

E. Dog Cardiovascular Tests. Blood pressure and heart rate were measured *via* a catheterized femoral artery and vein in a minimum of four pentobarbital-anesthetized dogs. Doses of isoproterenol and test compound (calculated as base) were injected iv in a randomized block design in each animal. Parallel lines were fitted for average dose–response curves and relative potencies were calculated.[46]

References

(1) R. P. Ahlquist, *Amer. J. Physiol.*, **153**, 586 (1948).
(2) A. M. Lands and T. G. Brown, Jr., *Proc. Soc. Exp. Biol. Med.*, **116**, 331 (1964).
(3) A. M. Lands, A. Arnold, J. P. McAuliff, F. P. Luduena, and T. G. Brown, Jr., *Nature (London)*, **214**, 597 (1967).
(4) A. M. Lands, F. P. Luduena, and H. J. Buzzo, *Life Sci.*, **6**, 2241 (1967).
(5) R. F. Furchgott, *Ann. N. Y. Acad. Sci.*, **139**, 553 (1967).
(6) D. Dunlop and R. G. Shanks, *Brit. J. Pharmacol.*, **32**, 201 (1968).
(7) A. M. Lands and T. G. Brown, Jr., in "Drugs Affecting the Peripheral Nervous System," Vol. 1, A. Burger, Ed., Marcel Dekker, New York, N. Y., 1967, p 399.
(8) S. B. Ross, *Acta Pharmacol. Toxicol.*, **20**, 267 (1963).
(9) J. W. Paterson, M. E. Conolly, D. S. Davies, and C. T. Dollery, *Lancet*, **2**, 426 (1968).
(10) J. Champagne, A. D'Iorio, and A. Beaulnes, *Science*, **132**, 419 (1960).
(11) M. E. Conolly, D. S. Davies, C. T. Dollery, C. D. Morgan, J. W. Paterson, and M. Sandler, *Brit. J. Pharmacol.*, **46**, 458 (1972).
(12) W. D. Conway, H. Minatoya, A. M. Lands, and J. M. Shekosky, *J. Pharm. Sci.*, **57**, 1135 (1968).
(13) R. B. Barlow in "Introduction to Chemical Pharmacology," Methuen, London, 1964, p 282.
(14) P. Pratesi and E. Grana, *Advan. Drug Res.*, **2**, 127 (1965).
(15) B. M. Bloom and I. M. Goldman, *ibid.*, **3**, 121, (1966).
(16) R. T. Brittain, D. Jack, and A. C. Ritchie, *ibid.*, **5**, 197 (1970).
(17) A. A. Larsen and P. M. Lish, *Nature (London)*, **203**, 1283 (1964).
(18) R. H. Uloth, J. R. Kirk, W. A. Gould, and A. A. Larsen, *J. Med. Chem.*, **9**, 88 (1966).
(19) A. A. Larsen, W. A. Gould, H. R. Roth, W. T. Comer, R. H. Uloth, K. W. Dungan, and P. M. Lish, *ibid.*, **10**, 462 (1967).
(20) D. T. Collin, D. Hartley, D. Jack, L. H. C. Lunts, J. C. Press, A. C. Ritchie, and P. Toon, *ibid.*, **13**, 674 (1970).
(21) N. V. Philips' Gloeilampenfabrieken, Dutch Patent 85,197 (May 15, 1957); *Chem. Abstr.*, **52**, 11121*d* (1958).
(22) A. Scriabine, P. F. Moore, L. C. Iorio, I. M. Goldman, W. K. McShane, and K. D. Booher, *J. Pharmacol. Exp. Ther.*, **162**, 60 (1968).
(23) R. G. Shanks, I. Brick, K. Hutchison, and I. C. Roddie, *Brit. Med. J.*, **1**, 610 (1967).
(24) W. E. Daniels, M. E. Chiddix, and S. A. Glickman, *J. Org. Chem.*, **28**, 573 (1963).
(25) P. S. Portoghese, *J. Med. Chem.*, **10**, 1057 (1967).
(26) J. D. Hyne, *Can. J. Chem.*, **39**, 2563 (1961).
(27) J. Van Dijk and H. D. Moed, *Recl. Trav. Chim. Pays-Bas*, **78**, 22 (1959).
(28) J. Van Dijk and H. D. Moed, *ibid.*, **80**, 573 (1961).
(29) J. R. Vaughan, Jr., and J. Blodinger, *J. Amer. Chem. Soc.*, **77**, 5757 (1955).
(30) L. Berend and F. Heymann, *J. Prakt. Chem.*, **173**, 290 (1902).
(31) S. Sugasawa and T. Fujii, *Chem. Pharm. Bull.*, **6**, 587 (1958).
(32) B. Loev, M. A. Haas, and F. Dowalo, *Chem. Ind. (London)*, 973 (1968).
(33) R. W. Foster, *J. Pharm. Pharmacol.*, **18**, 1 (1966).
(34) J. R. Blinks, *Ann. N. Y. Acad. Sci.*, **139**, 673 (1967).
(35) J. M. Van Rossum, *Arch. Int. Pharmacodyn. Ther.*, **143**, 299 (1963).
(36) E. J. Ariëns, A. M. Simonis, and J. M. Van Rossum in "Molecular Pharmacology," Vol. 1, E. J. Ariëns, Ed., Academic Press, New York, N. Y., 1964, p 171.
(37) E. J. Ariëns, *Ann. N. Y. Acad. Sci.*, **139**, 606 (1967).
(38) O. Schnider (to Hoffman-LaRoche, Inc.) U. S. Patent 2,393,820 (Jan 29, 1946); *Chem Abstr.*, **40**, 3475 (1946).
(39) J. R. Wardell, Jr., D. Colella, C. Kaiser, and S. Ross, Abstracts of Volunteer Papers, 5th International Congress on Pharmacology, San Francisco, Calif., July 23–28, 1972, p 246.
(40) J. R. Wardell, Jr., D. F. Colella, A. Shetzline, and P. J. Fowler, *J. Pharmacol. Exp. Ther.*, in press.
(41) A. A. Larsen and W. A. Gould, French Patent 5963 (June 17,

1968); *Chem. Abstr.*, 71, 30232 (1969).
(42) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, 87, 1353 (1965).
(43) A. Akcasu, *Arch. Int. Pharmacodyn. Ther.*, 122, 201 (1959).
(44) J. C. Castillo and E. J. deBeer, *J. Pharmacol. Exp. Ther.*, 90, 104 (1947).
(45) L. A. Chahl and S. R. O'Donnell, *Eur. J. Pharmacol.*, 2, 77 (1967).
(46) D. J. Finney, "Statistical Methods in Biological Assay," Hafner Publishing Co., New York, N. Y., 1952.
(47) R. G. Familiar, J. R. Wardell, Jr., and L. C. Greene, *J. Pharm. Sci.*, 56, 768 (1967).

Analogs of Phenothiazines. 5. Synthesis and Neuropharmacological Activity of Some Piperidylidene Derivatives of Thioxanthenes, Xanthenes, Dibenzoxepins, and Acridans

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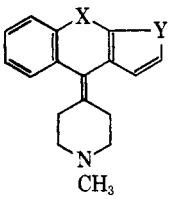
A series of piperidylidene derivatives of thioxanthenes, xanthenes, dibenzoxepins, and acridans was prepared and examined for neuropharmacological activity. Several of these compounds having an appropriate substituent, *e.g.*, CF_3, Cl, SMe, in the 2 position of the tricyclic nucleus were potent neuroleptic agents. For example, in a ptosis production test in rats 1-methyl-4-(2-trifluoromethylthioxanthen-9-ylidene)piperidine (11) and its 10-methylacridan congener 17 were seven to eight times more potent than chlorpromazine. In the same test the *N*-cyclobutylmethyl analog (26) of 11 was the most effective member of the series; it was about 18 times more potent than chlorpromazine. In the piperidylidene derivatives of tricyclic compounds, for which neuroleptic activity has not been reported previously, the spatial relationship between the basic nitrogen and the tricyclic nucleus is more restricted than in their antipsychotic aminopropyl- and aminopropylidene-substituted relatives. Some consequences of this observation on the conformational requirements for potent neuroleptic activity of tricyclic compounds are considered.

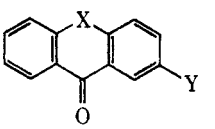
Cyproheptadine (**1a**), a clinically useful antipruritic drug, has potent antihistamine and antiserotonin properties, but it is without notable action on the central nervous system.[1] Antihistamine and antiserotonin activities also have been reported[2] for a series of piperidylidene-substituted tricyclic compounds, including the thioxanthene **1b**,[2] the xanthene **1c**,[2] and the dibenzo[*b,e*]thiepin, perithiadene **1d**.[3] Central depressant, as well as imipramine-like (antidepressive), actions were likewise noted for the latter compound,[3] whereas several benzothieno relatives, **1e**[4] and **1f**,[5,6] caused significant antidepressive effects. Sedative, narcosis-potentiating, adrenolytic, and antipyretic properties are claimed for **1b**,[7] and related piperidines, *i.e.*, side chain reduced congeners of **1**, are claimed as antispasmodics.[8] Although a more distantly related dibenzo[*b,f*]thiepin, bearing a 4-methylpiperidinyl substituent, produces neuroleptic actions in animals,[9] this kind of activity has not previously been recorded for piperidylidene derivatives of compounds with a typical psychotropic tricyclic nucleus.

In the course of an extensive study of structure–activity relationships in the phenothiazine series,[10] we prepared a piperidylidene-substituted trifluoromethylthioxanthene (**11**, Table II) and found it to be remarkably potent in several animal tests for neuroleptic activity. To examine the influence of chemical structure on neuroleptic activity a series of related piperidylidene, and a few piperidine, derivatives of thioxanthenes, xanthenes, dibenzoxepins, and acridans was prepared and tested pharmacologically. The results of this investigation are described in this paper.

Synthesis. Tricyclic carbinols (**3–10**, Table I, and **35**), prepared by addition of Grignard reagents derived from



1a, X = Y = CH=CH
b, X = S; Y = CH=CH
c, X = O; Y = CH=CH
d, X = CH_2S; Y = CH=CH
e, X = CH_2S; Y = S
f, X = $(CH_2)_2$; Y = S



2
X = S, O, CH_2O, NMe, NEt
Y = H, Cl, CF_3, SMe

4-chloro-1-methylpiperidine or α-3-chlorotropane[11] (the β-isomer[12] failed to react with Mg under similar conditions) to ketones **2**, were dehydrated to olefins (**11–31**, Table II, and **36**) under acidic or thermal conditions. The requisite 9-acridanones (**2**, X = NH) were obtained by cyclization of appropriate 2-carboxydiphenylamines, produced by Ullman condensation of a halogen-substituted benzoic acid with an aniline or of an anthranilic acid with a halobenzene, as described in the Experimental Section. Cyclization with $POCl_3$ afforded 9-chloroacridines which were converted to acridines by alkaline decomposition of intermediate 9-(*p*-toluenesulfonylhydrazides).[13] 10-Substituted derivatives (**2**, X = NMe, NEt) were prepared by alkylation of 9-acridanones.

The secondary amine **23**, obtained by HCl hydrolysis of the cyanamide **22** derived from **11** by the von Braun reaction, was converted to N-substituted piperidylidenes **24–31** by conventional methods.

Reduction of the ylidenes **11** and **36** using P–HI gave the saturated piperidine (**32**) and tropane (**37**) derivatives, respectively. A piperidyl-substituted acridan **33** was ob-

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