Adrenergic Agents. 3. Synthesis and Adrenergic Activity of Some Catecholamine Analogs Bearing a Substituted Sulfonyl or Sulfonylalkyl Group in the Meta Position

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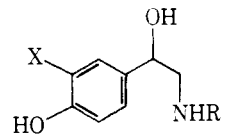
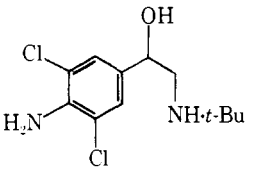
The *m*-phenolic group of catecholamine β-adrenergic agonists may be replaced by various functionalities capable of undergoing H bonding. Considerable latitude in the nature of the OH simulating group is permissible with retention of activity; however, the most extensively studied analogs are ones in which a mobile proton is attached to an O or N atom. In a search for new selective bronchodilators a series of catecholamine analogs bearing a substituted sulfonyl or sulfonylalkyl group in the meta position (i.e., groups in which the mobile H is attached to a C atom) was examined. These compounds were studied for β-adrenergic agonist activity in vitro by measuring their ability to relax tracheal smooth muscle and to increase the rate of spontaneously beating right atria of guinea pigs. Adrenergic activity was influenced by the nature of the alkylene bridge between the sulfonyl and aromatic groups, branching of the ethanolamine side chain, stereochemistry, and substitution of the sulfonyl and amino groups. β-Adrenergic blockade was noted for some compounds having the sulfonyl attached directly to the ring. Greatest β-adrenergic agonist potency and tissue selectivity was observed with a *m*-$MeSO_2CH_2$ substituent. One of these compounds, α-[[(1,1-dimethylethyl)amino]methyl]-4-hydroxy-3-[(methylsulfonyl)methyl]benzenemethanol hydrochloride (sulfonterol hydrochloride, USAN), was studied more extensively in animals and is presently being examined for bronchodilator activity in man.

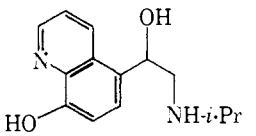
Isoproterenol (**1a**), the prototype of β-adrenergic receptor agonists, is a powerful bronchodilator; however, it also interacts with related cardiovascular sites to produce positive inotropic and chronotropic cardiac responses and a decrease in blood pressure. That these actions, classed as β_2- and β_1-adrenoreceptor responses,[1-4] can be separated by replacement of the prototype's *m*-phenolic group has been clearly established. For example, replacement of this group by a methanesulfonamido moiety (**1b**, soterenol[5]), a hydroxymethyl functionality (**1c**, salbutamol[6-8]), or various amino and substituted amino groups, notably a ureido substituent (**1d**, carbuterol[9,10]), affords derivatives with varying degrees of potency and bronchodilator vs. cardiovascular selectivity. Considerable latitude in the nature of the



1a, X = HO; R = *i*-Pr
b, X = $MeSO_2NH$; R = *i*-Pr
c, X = $HOCH_2$; R = *t*-Bu
d, X = H_2NCONH; R = *t*-Bu
e, X = $HO(CH_2)_2$; R = *t*-Bu
f, X = $H_2N(CH_2)_2$; R = *t*-Bu
g, X = Me_2N; R = *t*-Bu



2a



2b

m-phenolic substitute is possible. Thus, compounds in which an OH or NH_2 is separated from the aromatic ring by a two methylene bridge (**1e**, **1f**[11]) retain a high degree of β-adrenoreceptor agonist activity. Generally a labile proton in the vicinity of the meta position seems to be a requirement for activity; however, several compounds lacking a proton in this area, such as **1g**,[9] **2a**,[12] and even the 8-hydroxyquinoline, quinprenaline (2b),[13] are potent β-adrenergic agonists in vitro.

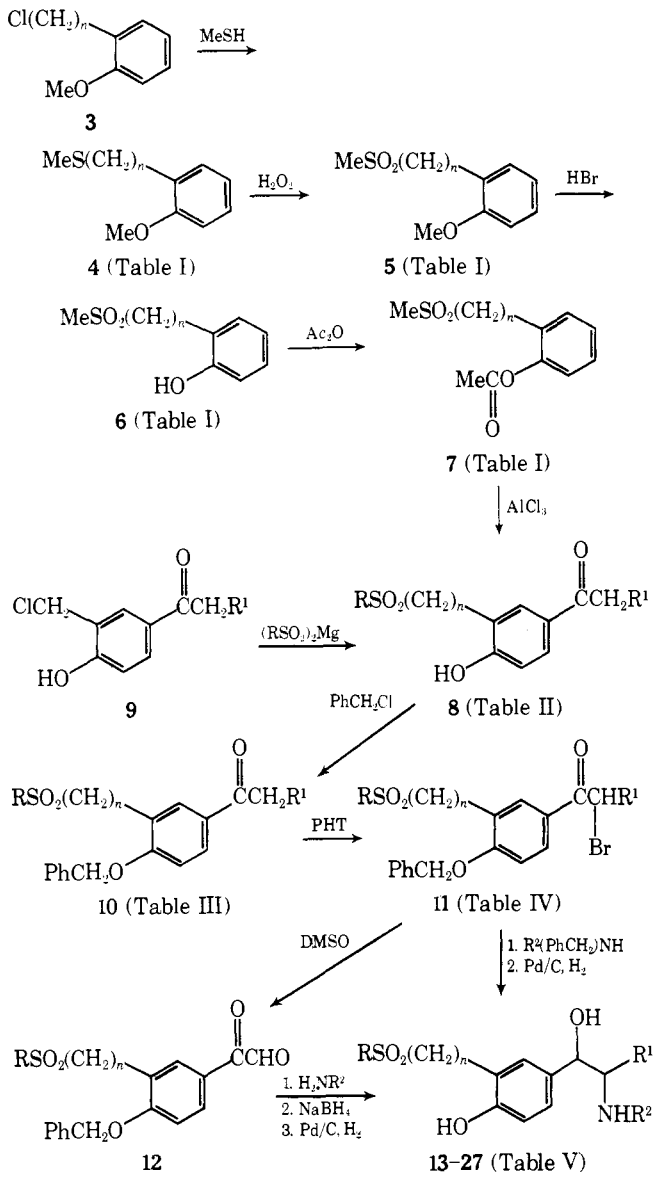
A group's ability to simulate the *m*-phenolic OH of catecholamine β-adrenoreceptor agonists has been attributed to "bioisosterism",[5] "water-ordering effects",[7,8] and chelating properties.[13] Among the many suggestions advanced[5,11,14-16] to rationalize the activity of these substances, a currently favored concept[11,14-16] is that the β-adrenergic agonists associate with a lipoprotein surface (likely associated with adenylate cyclase) where specific interactions induce a highly favorable and specific conformational perturbation of the enzyme. The potency enhancement produced by catechol OH groups and the various alternative meta substituents is attributed to steric fit into the lattice of a localized water cluster, thus increasing a favorable proton mobility or hydrogen bonding condition.

Although not an inviolate structural requirement, in most potent β-adrenoreceptor agonists the aromatic ring bears a substituted O or N group capable of hydrogen bonding. In our continuing[9,17] search for new bronchodilators with minimal cardiovascular side effects, it seemed pertinent to examine some catecholamine analogs in which the mobile proton (hydrogen donor) was one attached to a C rather than the more usual O or N atoms. Such a mobile proton is provided by an alkyl or substituted alkyl group adjacent to a sulfonyl moiety. For example, the pK_a of dibenzylsulfone is 22.[18] For this reason we prepared and studied the adrenergic activity of a series of catecholamine analogs bearing a substituted sulfonyl or sulfonylalkylene group in the meta position. In this article are described the synthesis and results of preliminary pharmacological study of some of these compounds.

Chemistry. A series of catecholamine analogs related to isoproterenol, but bearing an alkylsulfonylalkylene or methylsulfonyl group in place of the prototype's *m*-OH, was prepared as illustrated in Scheme I.

In some instances 2-(chloroalkyl)anisole derivatives 3 (n = 2, 3) were converted in sequence to **4**, **5**, and **6** (Table I). 2-Methylsulfonylphenol (**6**, n = 0) was derived from 2-bromoanisole[19-21] according to the general procedure of Bordwell and Boutan.[22] Acetylation of phenols **6** afforded the acetates **7** (Table I). Several routes were employed to derive appropriately substituted aceto- and butyrophenones **8** (Table II). Fries rearrangement of the phenyl acetates **7** gave the acetophenones **8a**, **8c**, and **8d**. In other instances 3′-chloromethyl-4′-hydroxyacetophenone[23] or 3′-chloromethyl-4′-hydroxybutyrophenone (**9**), prepared by chloromethylation of the corresponding 4′-hydroxyphenone, were condensed with the requisite magnesium alkylsulfinate[24] to produce the ring-substituted aryl alkyl ketone **8b** and **8e–i**. Benzylation of the 4′-hydroxy-3′-substituted aceto- and butyrophenones **8** yielded corresponding 4′-benzyloxy derivatives **10** (Table III). One of these (**10b**) was methylated to give the alkylene branched homolog, 4′-benzyloxy-3′-[1-(methylsulfonyl)ethyl]acetophenone (**10j**). Bromination of the benzyloxy-substituted phenones **10** with pyrrolidinone hydrotribromide (PHT) in the presence of 2-pyrrolidinone[25] afforded the phenacyl bromides **11** listed in Table IV. Two different routes were employed for conversion of

Scheme I



the 4′-benzyloxy-2-bromo-3′-substituted aceto- and butyrophenones **11** to the catecholamine relatives **13–27** (Table V). One of these sequences involved DMSO oxidation of **11** to a glyoxal derivative **12** which was transformed to the catecholamine analog by amination with the appropriate primary amine followed by subsequent reduction and hydrogenolysis of the resulting imino ketone. The second, more conventional procedure, entailed amination of the α-bromo ketone **11** with an *N*-alkylbenzylamine followed by catalytic reduction. As a consequence of steric hindrance, as noted previously,[6,9] the α-bromobutyrophenone **11i** was condensed with *tert*-butylamine to give a secondary amino ketone which on reduction with sodium borohydride gave a single diastereomer (TLC) whose hydrogenolysis product was assigned the anticipated[26–28] erythro configuration on the basis of NMR data. Compounds **18** and **19,** which bear two asymmetric centers, probably exist as diastereoisomers; no attempt was made to separate them.

A primary amine related to the catecholamine adrenergic agents, but having a methylsulfonylmethyl group instead of a hydroxyl in the meta position, was obtained by a different synthetic sequence as outlined in Scheme II.

The chloromethyl derivative, obtained by conventional chloromethylation of 4-hydroxybenzaldehyde, was condensed with magnesium methylsulfinate.[24] Benzylation of the resulting phenol afforded **28** which was condensed with nitromethane in the presence of sodium ethoxide to give **29.** Catalytic hydrogenation of **29** proceeded with difficulty. The primary amine **30** was obtained in low yield only after prolonged hydrogenation in the presence of platinum oxide.

Two isoproterenol congeners bearing a sulfamyl group in the meta position were prepared as shown in Scheme III.

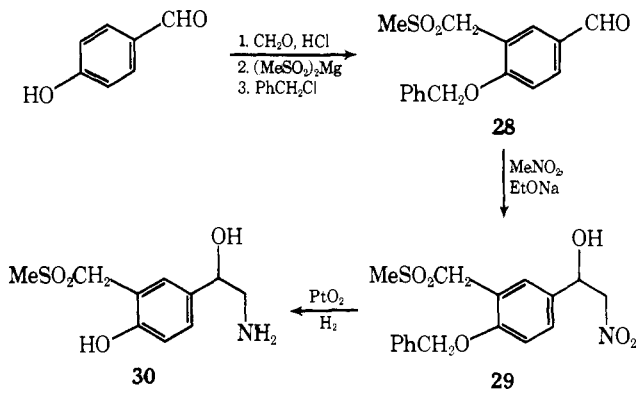
Treatment of the diazonium salt derived for 3′-amino-4′-benzyloxyacetophenone[5] with cupric chloride and sulfur dioxide, according to the general procedure of Meerwein et al.,[29] gave the 3′-chloro-sulfonated acetophenone **31.** Amination of **31** with ammonia or methylamine afforded the corresponding sulfamyl derivatives **32a** and **32b,** which were converted to the meta-sulfamylated isoproterenol congeners **33** and **34** via the conventional bromination–amination–reduction sequence.

One of the most promising potential bronchodilators arising from this study, **14** (sulfonterol[30]), was resolved into its (−) and (+) enantiomers as described in the Experimental Section.

Results and Discussion

As a measure of β_2-adrenoreceptor activity, catecholamine analogs **13–27, 30, 33,** and **34** bearing a substituted sulfonyl or sulfonylalkyl group in the meta position were examined in vitro for their ability to relax a spontaneously contracted guinea pig tracheal chain preparation.[31]

Scheme II



Scheme III

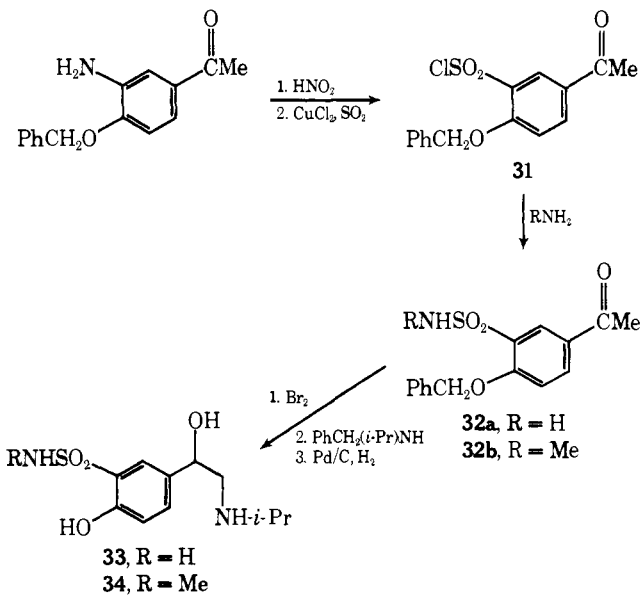
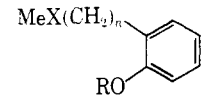


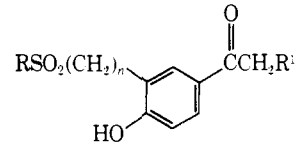
Table I. 2-Substituted Anisole, Phenol, and Phenyl Acetate Derivatives 4-7



No.	X	n	R	Mp or bp (Torr), °C	Recrystn solvent	Method[a]	Yield, %	Formula[b]
4a	S	2	Me	107 (0.5)		A	77	$C_{10}H_{14}OS$[c]
4b	S	3	Me	116 (0.5)		A	92	$C_{11}H_{16}OS$[d]
5a	SO_2	2	Me	51–53	*i*-PrOH	B	70	$C_{10}H_{14}O_3S$
5b	SO_2	3	Me	68–69	EtOAc–hexane	B	72	$C_{11}H_{16}O_3S$
6a	SO_2	2	H	84–86	EtOAc–hexane	C	82	$C_9H_{12}O_3S$
6b	SO_2	3	H	78–80	EtOAc–hexane	C	99	$C_{10}H_{14}O_3S$
7a	SO_2	2	MeCO	80–82	EtOAc–hexane	D	77	$C_{11}H_{14}O_4S$
7b	SO_2	3	MeCO	243 (0.25)		D	99	$C_{12}H_{16}O_4S$[e]
7c	SO_2	0	MeCO	104–106	EtOAc–hexane	D[f]	82	$C_8H_{10}O_4S$

[a] See Experimental Section, Chemistry, General Procedures. [b] Compounds for which formulas are given were analyzed for C and H; analytical values were within ±0.4% of the calculated values unless noted otherwise. [c] C: calcd, 65.89; found, 66.60. [d] C: calcd, 67.30; found, 66.24. [e] C: calcd, 56.23; found, 55.77. [f] Prepared from 6 (n = 0), ref 21, which was obtained from 2-bromoanisole by the general method of ref 22.

Table II. 4′-Hydroxy-3′-substituted Aceto- and Butyrophenones 8



No.	R	n	R^1	Mp, °C	Recrystn solvent	Method[a]	Yield, %	Formula[b]
8a	Me	0	H	168–169	EtOH–hexane	E	75	$C_9H_{10}O_4S$
8b	Me	1	H	207–209	$CHCl_3$	F	52	$C_{10}H_{12}O_4S$
8c	Me	2	H	176–178	EtOH–hexane	E	53	$C_{11}H_{14}O_4S$
8d	Me	3	H	140–141	EtOH–hexane	E	48	$C_{12}H_{16}O_4S$
8e	Et	1	H	137–141	$CHCl_3$	F	30	$C_{11}H_{14}O_4S$
8f	*n*-Pr	1	H	73.5–76	EtOH–hexane	F	36	$C_{12}H_{16}O_4S$[c]
8g	*i*-Pr	1	H	96.5–100	EtOH–hexane	F	83	$C_{12}H_{16}O_4S$
8h	4-MePh	1	H	173–175	EtOAc	F	42	$C_{16}H_{16}O_4S$[d]
8i	Me	1	Et	130–132	$CHCl_3$–hexane	F	50	$C_{12}H_{16}O_4S$

[a] See footnote *a*, Table I. [b] See footnote *b*, Table I. [c] C: calcd, 56.23; found, 56.76. [d] C: calcd, 63.14; found, 62.56.

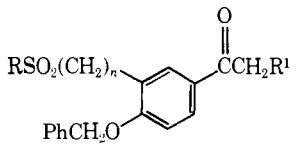
Changes in the contraction rate of spontaneously beating guinea pig right atria in vitro[32] were used to evaluate β_1-adrenoreceptor activity. Selectivity of the compound for tracheobronchial vs. cardiac muscle was estimated by comparison of the ED_{50} for tracheal relaxation with the ED_{25} for atrial rate increase. Results of these in vitro studies for the present series and for the standards isoproterenol and *N-tert*-butylnorepinephrine are presented in Table V.

Structural variations involving length and branching of the alkylene bridge between the substituted sulfonyl group and the aromatic ring, the nature of the sulfonyl substituent, the amino substituent, and introduction of an ethyl branch on the methylene adjacent to the basic amino functionality were studied.

Both length and branching of the alkylene bridge joining the substituted sulfonyl group to the aromatic ring had a profound influence on adrenergic activity. The order of β-adrenergic agonist potency as measured in the guinea pig tracheal test was CH_2 (**14**) > $(CH_2)_2$ (**20**) ≫ $(CH_2)_3$ (**21**) ≈ CH(Me) (**26**) ≫ no alkylene bridge (**13**). In fact, several derivatives lacking an alkylene bridge exhibited β-adrenergic antagonist activity in preliminary experiments. For example, in the guinea pig right atrial test **13** attenuated the rate increase induced by isoproterenol in a manner suggestive of competitive inhibition. Likewise, the sulfamyl analog **33** produced effects characteristic of competitive β-adrenergic blockade in the isolated rabbit heart and the dog cardiovascular tests. In the latter preparation it caused a dose-related antagonism of isoproterenol-induced decrease of blood pressure and increase of heart rate. In the guinea pig tracheal test it produced contraction at a concentration of 9.1×10^{-7} *M*. These effects coincide with those observed with several other compounds having an electron-withdrawing moiety in place of the *m*-phenolic group of a catecholamine β-adrenergic agonist. As an example, the *m*-H_2NCO congener (AH 3474) related to **33** is a β-adrenoreceptor blocker,[33] as is also the corresponding *N*-phenylisopropyl derivative (AH 5158).[34,35] The salicylic acid precursor of the saligenin derivative salbutamol (**1b**) likewise is devoid of β-adrenergic agonist activity, although antagonistic properties have not been reported.[6] Methylation of the *m*-sulfamyl group of **33** resulted in compound **34** which somewhat unexpectedly was moderately effective in causing relaxation of guinea pig tracheal tissue in vitro.

As indicated, a methylene bridge between the aromatic ring and the sulfonyl moiety results in greatest β-adrenoreceptor agonist potency. For example, in the guinea pig tracheal test **14** (sulfonterol[30]) was approximately 40 times

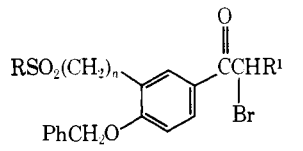
Table III. 4′-Benzyloxy-3′-substituted Aceto- and Butyrophenones 10[a,b]



No.	R	n	R^1	Mp, °C	Recrystn solvent	Yield, %	Formula[c]
10a	Me	0	H	147–148	EtOAc–hexane	96	$C_{16}H_{16}O_4S$
10b	Me	1	H	118–119	EtOAc–hexane	61	$C_{17}H_{18}O_4S$
10c	Me	2	H	176–178	EtOH–hexane	93	$C_{18}H_{20}O_4S$
10d	Me	3	H	79–81	EtOAc–hexane	89	$C_{19}H_{22}O_4S$
10e	Et	1	H	79–82	EtOH–hexane	95	$C_{18}H_{20}O_4S$
10f	n-Pr	1	H	112–115	MeCN	94	$C_{19}H_{22}O_4S$
10g	i-Pr	1	H	104–106	MeCN	74	$C_{19}H_{22}O_4S$
10h	4-MePh	1	H	148–149	MeOH	60	$C_{23}H_{22}O_4S$
10i	Me	1	Et	120–122	PhH–hexane	61	$C_{19}H_{22}O_4S$
10j	Me	*d*	H	126–130	EtOAc–hexane	25[e]	$C_{18}H_{20}O_4S$

[a]Prepared according to Experimental Section, Chemistry, General Procedure G, unless noted otherwise. [b]The acetophenones had NMR ($CDCl_3$) δ ~2.5 ppm (s, 3, $COCH_3$). The butyrophenone **10i** had NMR ($CDCl_3$) δ ~3.0 ppm (t, 2, $COCH_2Et$). [c]See footnote *b*, Table I. [d]$(CH_2)_n$ = CH(Me). [e]Prepared by methylation of **10b** as described in the Experimental Section.

Table IV. 4′-Benzyloxy-2-bromo-3′-substituted Aceto- and Butyrophenones 11[a,b]



No.	R	n	R^1	Mp, °C	Solvent[c]	Yield, %	Formula[d]
11a	Me	0	H	148–149	EtOAc–hexane	69	$C_{16}H_{15}BrO_4S$
11b	Me	1	H	144–146	EtOAc	47	$C_{17}H_{17}BrO_4S$[e]
11c	Me	2	H	135–137	EtOH	82	$C_{18}H_{19}BrO_4S$
11d	Me	3	H	110–113	EtOAc–hexane	49	$C_{19}H_{21}BrO_4S$
11e	Et	1	H	137–139	MeCN	70	$C_{18}H_{19}BrO_4S$
11f	n-Pr	1	H	149–151	MeCN	70	$C_{19}H_{21}BrO_4S$
11g	i-Pr	1	H	136–138	EtOH	52	$C_{19}H_{21}BrO_4S$
11h	4-MePh	1	H	161–163	MeCN	63	$C_{23}H_{21}BrO_4S$
11i	Me	1	Et	93–96	$CHCl_3$	83	*f*
11j	Me	*g*	H	122–126	EtOAc–hexane	68	$C_{18}H_{19}BrO_4S$[h]

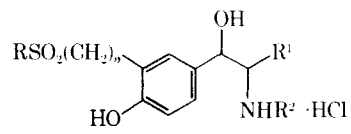
[a]Prepared according to Experimental Section, Chemistry, General Procedure H. [b]The 2-bromoacetophenones 11, R^1 = H, were characterized by their NMR ($CDCl_3$) δ ~4.5 ppm (s, 2, $COCH_2Br$). The 2-bromobutyrophenone 11i had NMR ($CDCl_3$) δ ~5.1 ppm [t, 1, COCH(Et)Br]. [c]In some instances the solvent was employed for recrystallization; in others, the solvent was used only for trituration. [d]See footnote *b*, Table I. [e]C: calcd, 51.40; found, 50.55. [f]Used for further reaction without additional purification. [g]$(CH_2)_n$ = CH(Me). [h]C: calcd, 52.56; found, 53.23.

more potent than its ethylene-bridged counterpart **20**, a result that contrasts somewhat with the relationship between salbutamol (**1c**) and its bridged homolog **1e** which are almost equally active as relaxants of bronchial smooth muscle.[11] The propylene-bridged **21** and branched **26** analogs of sulfonterol (**14**) exerted tracheal relaxant activity only at concentrations about 10^{-5} *M*. Another feature noted with sulfonterol (**14**) was its marked tissue selectivity. In contrast to its highly potent activity in the guinea pig tracheal test, **14** was comparatively ineffective in the atrial assay; it had a separation ratio (see Table V) of 1650. Additionally, in the atrial test the intrinsic activity,[36,37] i.e., the portion of maximal isoproterenol-induced response that can be produced by the test compound, was only 0.3 for **14**.

Substitution of the sulfonyl group also affected adrenergic activity in a profound fashion. In general, β-adrenergic agonist potency decreased as the bulk of the substituent increased. Thus, in the guinea pig tracheal test the methyl derivative sulfonterol (**14**), which is about one-half as potent as isoproterenol (**1a**), is three to four times more potent than the ethyl derivative **22** and about 300 times more potent than the n-propyl homolog **23**. It is noteworthy that **22** decreased the rate of contraction in the guinea pig atrial test. The bulkier isopropyl derivative **24** was less effective in the guinea pig tracheal test than its n-propyl isomer **23**, and the still larger p-toluene congener **25** was even less potent. In addition, **25** produced pharmacological actions suggestive of β-adrenergic antagonism in the guinea pig heart test.

The alteration of adrenergic activity induced by replacement of the *tert*-butyl substituent on the basic nitrogen of sulfonterol (**14**) was similar to that noted with similar relatives of soterenol (**1b**)[5] and salbutamol (**1c**).[6] The unsubstituted primary amine **30** contracted guinea pig tracheal tis-

Table V. Catecholamine Analogs with a Substituted Sulfonyl or Sulfonylalkyl Group in the Meta Position



No.	R	n	R^1	R^2	Mp, °C, dec	Recrystn solvent	Method[a]	Yield,[b] %	Formula[c]	Guinea pig tracheal test,[d,e] ED_{50} (molar concn) (95% confidence limits)	Guinea pig atrial rate,[d,f] ED_{25} (molar concn) (95% confidence limits)	Separation ratio[g]
13	Me	0	H	*t*-Bu	214.5	MeOH–Et_2O	J, M	54	$C_{13}H_{22}ClNO_4S$	5.2×10^{-5}, 24% 1.7×10^{-8}	5.2×10^{-5}, 9% 2.8×10^{-5}	
14	Me	1	H	*t*-Bu	227–228	MeOH–Et_2O	K, L	59	$C_{14}H_{24}ClNO_4S$	$(0.8–3.6\times10^{-8})$ 8.0×10^{-9}	$(0.3–23.4\times10^{-5})^h$ 4.7×10^{-6}	1,650
(−)-14	Me	1	H	*t*-Bu	232	MeOH–Et_2O	*i*			$(3.4–19.0\times10^{-9})$	$(0.4–54.0\times10^{-6})^j$	588
(+)-14	Me	1	H	*t*-Bu	232	MeOH–Et_2O	*i*			9.0×10^{-7}[k] $(3.8–21.5\times10^{-7})$ 6.9×10^{-8}	3.0×10^{-5}, 4%	>33[l]
15	Me	1	H	*c*-Bu	193–194	MeOH–Et_2O	J, M	47	$C_{14}H_{22}ClNO_4S$	$(2.6–18.0\times10^{-8})$	1.5×10^{-4}, 16%	>2,170[l]
16	Me	1	H	1-Adamantyl	221.5	MeOH–Et_2O	J, M	84	$C_{20}H_{30}ClNO_4S$	4.0×10^{-6}, 46% 7.8×10^{-9}	*m* 2.0×10^{-7}[j]	
17	Me	1	H	4-$MeOPhCH_2C(Me)_2$	180–182	MeOH–Et_2O	J, M	81	$C_{21}H_{30}ClNO_5S$	$(4.7–13.0\times10^{-9})$ 8.2×10^{-9}	$(0.1–35.0\times10^{-7})$ 2.0×10^{-6}[j]	26
18	Me	1	H	4-$HOPhCH_2CH(Me)$			K, L	20	*n*	$(3.4–19.0\times10^{-9})$ 1.7×10^{-8}	$(0.8–5.1\times10^{-6})$	244
19	Me	1	H	3,4-OCH_2OPhCH_2-CH(Me)	182–184	MeOH–Et_2O	K, L	30	$C_{20}H_{28}ClNO_6S$	$(0.4–6.2\times10^{-8})$ 7.0×10^{-7}[p]	2.2×10^{-4}, 10%	>13,000[l]
20	Me	2	H	*t*-Bu	176–177	MeOH–EtOAc	K, L	38	$C_{15}H_{26}ClNO_4S$[o]	$(0.4–110.0\times10^{-7})$	5.1×10^{-6}, 8%	>7[l]
21	Me	3	H	*t*-Bu	187–188	MeOH–EtOAc	K, L	52	$C_{16}H_{28}ClNO_4S$	4.6×10^{-5}, 9% 6.1×10^{-8}[k]	4.6×10^{-5}, 2%	
22	Et	1	H	*t*-Bu	191–192	MeOH–Et_2O	J, M	24	$C_{15}H_{26}ClNO_4S$	$(3.1–12.0\times10^{-8})$	3.8×10^{-4}, −25%[q]	
23	*n*-Pr	1	H	*t*-Bu	183–184	MeOH–Et_2O	J, M	43	$C_{16}H_{28}ClNO_4S$[r]	$\sim5.1\times10^{-5}$	4.6×10^{-5}, 9%	>1[l]
24	*i*-Pr	1	H	*t*-Bu	201–202	MeOH–Et_2O	J, M	42	$C_{20}H_{28}ClNO_4S$	1.5×10^{-5}, 30%	1.5×10^{-5}, 8%	
25	4-MePh	1	H	*t*-Bu	156–158	MeOH–Et_2O	K, L	21	$C_{20}H_{28}ClNO_6S$[s]	4.0×10^{-5}, 14%	*m*, *l*	
26	Me	*u*	H	*t*-Bu	215–216	MeOH–EtOAc	K, L	31	$C_{15}H_{26}ClNO_4S$	1.6×10^{-5}, 29%	4.8×10^{-5}, 0%	
27[v]	Me	1	Et	*t*-Bu	135–137	*i*-PrOH–Et_2O	K		$C_{16}H_{28}ClNO_4S$[w]	6.6×10^{-5}, 33%	3.0×10^{-4}, 4%	

30	Me	1	H	H	183–184	$MeOH–Et_2O$	*i*		$C_{10}H_{16}ClNO_4S$	*x*	*m*	
33	H_2N	0	H	*i*-Pr	183–184	$MeOH–Et_2O$	J, M	91	$C_{11}H_{19}ClNO_4S$	*y*	*m*	
34	MeNH	0	H	*i*-Pr	197–198	$EtOH–Et_2O$	J, M	71	$C_{12}H_{21}ClNO_4S$	1.7×10^{-5}, 48% 7.1×10^{-9}	*m*, *z* 3.4×10^{-9aa}	
Isoproterenol										$(5.2–9.9\times10^{-9})$	$(2.6–4.6\times10^{-9})$	0.48
										1.3×10^{-9} $(0.9–1.8\times10^{-9})$	7.1×10^{-9aa} $(5.3–10.0\times10^{-9})$	5.5
N-*tert*-Butylnorepinephrine												

[a]See Experimental Section, Chemistry, General Procedure for description of the method or combination of methods employed for synthesis of the indicated compound. [b]Overall yield for indicated method or combination of methods used. [c]See footnote *b*, Table I. [d]See Experimental Section, Pharmacology, Methods, for description of the test procedure. Where ED_{50}'s were not determined results are given as percent response at the indicated concentration. [e]Intrinsic activity α, i.e., maximum effect of the test compound divided by the maximum response to papaverine, is equal to 1.0 in all cases where ED_{50}'s were determined, unless noted otherwise. [f]See Experimental Section, Pharmacology, Method B. [g]Guinea pig atrial test ED_{25} divided by tracheal test ED_{50}. [h]Intrinsic activity α in the atrial test was determined as described in footnote *e*, except the maximum effect of the test compound was divided by the maximum response to isoproterenol. For **14** atrial α = 0.3. [i]Prepared as described in the Experimental Section. [j]α (see footnote *h*) = 0.4. [k]α = 0.9. [l]An absolute separation ratio could not be calculated as the highest concentration tested produced an increase in atrial rate which was less than 25%. [m]Not tested. [n]Product obtained as an amorphous solid with satisfactory ir and NMR. Tlc (Analtech silica gel GF, 250-μ plates) using 90:20:3 $CHCl_3$–MeOH–HCOOH gave a single spot, R_f = 0.27. Mass spectrum of the $(Me_3Si)_3$ derivative had M^+ 580. [o]Analysis for 0.75 mol of H_2O. [p]α = 0.6. [q]Rate of contraction was decreased. [r]Analysis for 0.125 mol of H_2O. [s]Analysis for 1.0 mol of H_2O. [t]At a concentration of 1×10^{-5} *M* of **25**, isoproterenol-induced increases of guinea pig heart rate were attenuated by 26%. Base line heart rate was also decreased. [u]$(CH_2)_n$ = CH(Me). [v]Erythro isomer: NMR (D_2O) δ 5.05 ppm (d, J = ~3.0 Hz). See ref 26–28. [w]Analysis for 0.5 mol of H_2O. [x]Contraction of the guinea pig tracheal chain preparation was noted at 2.0×10^{-5} *M*. [y]A concentration of 9.1×10^{-7} *M* of **33** caused contraction of the guinea pig tracheal chain preparation. In an isolated rabbit heart preparation (Experimental Section, Pharmacology, Method C) isoproterenol-induced rate increases were attenuated 24% by a concentration of 1×10^{-6} *M*; however, base line rate was unaffected. In the dog cardiovascular test (Experimental Section, Pharmacology, Method D) **33** caused a dose-related competitive antagonism of isoproterenol-induced decrease in blood pressure (17% at 5 mg/kg; 44% at 10 mg/kg) and increase in heart rate (10% at 5 mg/kg; 22% at 10 mg/kg). [z]Concentrations as high as 1×10^{-4} *M* failed to attenuate isoproterenol-induced rate increases in an isolated rabbit heart preparation (Experimental Section, Pharmacology, Method C). [aa]α (see footnote *h*) = 1.0.

Table VI. Approximate Relative Potencies[a] of Sulfonterol (**14**) in Cats[b]

Test[b]	Rel potency[a]
Pulmonary resistance, decrease	1/5
Heart rate, increase	1/34
Diastolic blood pressure, decrease	1/2290
Soleus muscle tension, decrease	1/31

[a]Potencies are related to isoproterenol which has been arbitrarily assigned a value of 1; i.e., it represents the ED value for isoproterenol divided by the corresponding ED value for sulfonterol (**14**) in the same test. [b]See Experimental Section, Pharmacology, Method E.

sue at a concentration of 2×10^{-5} *M*. Although it was not tested for this activity, **30** might be anticipated to behave as an α-adrenergic agonist.[4,11] A 1-adamantyl derivative **16** was much less potent than sulfonterol (**14**) in the tracheal chain test. Substituted phenyl-branched alkyl groups, e.g., **17**, **18**, and **19**, retained, or slightly enhanced, potency relative to sulfonterol (**14**) as guinea pig tracheal relaxants and also exhibited a significant degree of tissue selectivity. The cyclobutyl derivative **15** was only one-fourth as potent as sulfonterol and also was quite selective.

Introduction of an ethyl branch on the side-chain carbon adjacent to the basic nitrogen afforded an erythro isomer **27** that in contrast to the soterenol analog, but similar to the comparable salbutamol derivative, resulted in a markedly less potent β-adrenoreceptor agonist than its parent sulfonterol (**14**).

As in other racemic β-adrenergic agonists, the activity of **14** apparently resides primarily in only one of its enantiomers. Thus (−)-**14** was about twice as potent as the racemate in the guinea pig tracheal test, whereas the (+) enantiomer was less than 1/10th as potent.

As a consequence of its high order of potency and tissue selectivity in the in vitro tests, sulfonterol (**14**) was selected for further evaluation in the cat, according to pharmacological method E described in the Experimental Section. The results of this study are presented in Table VI.

These preliminary in vivo data substantiated the in vitro results. Thus, sulfonterol (**14**) was approximately one-fifth as potent as isoproterenol in decreasing pulmonary resistance in the cat. Selectivity for tracheobronchial vs. cardiac muscle noted in vitro was also confirmed in vivo; sulfonterol (**14**) was only about 1/34th as potent as isoproterenol in causing an increase in the cat heart rate. These results are in good agreement with the proposal originally advanced by Lands and his associates,[1-3] by Furchgott,[38] and since supported by numerous other studies[5-7,10] that the β-receptors mediating bronchodilation and cardiac stimulation are of two subtypes. In contrast, β-receptors causing bronchodilation, vasodilation, and reduction of incomplete tetanic contractions in skeletal (soleus) muscle are reported to be of the same subtype; i.e., β_2.[39-41] Our data for the effect of sulfonterol (**14**) on pulmonary resistance, diastolic blood pressure, and soleus muscle tension in the cat test, however, do not support this conclusion but rather indicate that these actions may also be separable. This is especially striking in comparing the pulmonary resistance decrease (bronchodilator) and diastolic blood pressure lowering effects of sulfonterol (**14**) in the cat test. Here, sulfonterol (**14**) was only about 1/2300th as potent as isoproterenol in reducing diastolic blood pressure and consequently showed a separation of bronchodilation vs. diastolic blood pressure

decrease greater than three orders of magnitude. Similarly, sulfonterol (**14**) was considerably more potent in decreasing pulmonary resistance than in decreasing soleus muscle tension in the cat; it was only about 1/30th as potent as isoproterenol in the latter test.

These data strongly suggest that more than one β-receptor type may be involved in causing these effects which have previously been classed together as resulting from β_2-adrenoreceptor agonism.[39-41] This is of particular interest since potency in the soleus muscle tension test has been related to the disturbing side effect of physiological tremor produced by β-adrenergic bronchodilators in man.[42] Evidence has been presented to suggest that carbuterol (**1d**) also discriminates between β-receptors in tracheobronchial and vascular smooth muscle.[9,10] Other workers[43,44] have also suggested that the β-receptors mediating these responses may differ.

The studies reported herein demonstrate convincingly that the mobile proton of an activated methylene group may replace the *m*-phenolic group of a catecholamine β-adrenergic agonist with retention of a high degree of activity. Further, such modification appears to afford compounds with marked selectivity for β-adrenoreceptors. On the basis of these preliminary studies, sulfonterol (**14**) appears to be a β-adrenoreceptor agonist which is more selective for airway smooth muscle than for cardiovascular β-receptors. These observations, coupled with sulfonterol's apparent lessened propensity to decrease soleus muscle tension, have led to its selection for clinical trial. Sulfonterol (**14**) is presently being examined for bronchodilator activity in man.

Experimental Section[45]

Chemistry. General Procedures. A. 2-(Methylmercaptoalkyl)anisoles. To a stirred and refluxing solution prepared by addition of 0.5 mol of MeSH to 0.5 mol of NaOH and 250 ml of EtOH, 0.5 mol of 2-(2-chloroethyl)-[46] or 2-(3-chloropropyl)anisole[47] was added at a rate which enabled maintenance of reflux without external heating. After being stirred and refluxed for 1 hr following completion of the addition, the reaction mixture was concentrated in vacuo. The residue was suspended in H_2O and the mixture was extracted with Et_2O. The Et_2O extracts were dried and concentrated. Distillation of the residual liquids afforded **4a** and **4b** (Table I).

B. Oxidation of 2-(Methylmercaptoalkyl)anisoles. A solution of 0.1 mol of the mercapto derivative and 0.3 mol of 30% H_2O_2 in 100 ml of HOAc was stirred and refluxed for 2 hr. After being diluted with H_2O, the mixture was extracted with Et_2O or $CHCl_3$; the extracts were dried, treated with decolorizing C, and concentrated. Recrystallization of the residual solid afforded **5a** and **5b** (Table I); **5** ($n = 0$)[20] was prepared in a similar manner.

C. Demethylation of 2-Substituted Anisole Derivatives. A mixture of 0.1 mol of the 2-(methylsulfonylalkyl)anisole in 200 ml of 48% HBr was stirred and refluxed for 3 hr. The mixture was cooled to ambient temperature; then it was extracted with PhMe or $CHCl_3$. Recrystallization of the residue obtained by concentration of the dried extracts which were treated with decolorizing C gave **6a** and **6b** (Table I). Compound **6** ($n = 0$)[21] was prepared in a similar fashion.

D. Acetylation of Phenolic Derivatives. The appropriate phenol (0.1 mol) and 200 ml of Ac_2O were stirred and refluxed for 3 hr. The residue remaining after concentration of the solution was distilled or recrystallized to give **7a–c** (Table I).

E. 4′-Hydroxy-3′-methylsulfonylalkylacetophenones 8a, 8c, and 8d. To a solution of 0.1 mol of the phenyl acetate **7a–c** in 125 ml of $PhNO_2$ was added, in portions, 0.3 mol of $AlCl_3$. The mixture was stirred at ambient temperature for 1 hr and at 50–60° for 1.5 hr and then it was poured into ice–H_2O. Products were isolated either by filtration, by diluting the dried $PhNO_2$ layer with Et_2O, or by $CHCl_3$ extraction. In the $CHCl_3$ isolation method the organic layer was extracted with 0.5 *N* NaOH; then the alkaline extracts were acidified and the mixture was extracted with $CHCl_3$. After being dried, the $CHCl_3$ solution was concentrated in vacuo to give a crystalline residue. Recrystallization of solid products, thus obtained, afforded **8a**, **8c**, and **8d** (Table II).

F. 3′-Alkylsulfonylmethyl-4′-hydroxyaceto- and -butyrophenones 8b, 8e, and 8i. A mixture of 0.1 mol of 3′-chloromethyl-4′-hydroxyaceto-[23] or -butyrophenone in 100 ml of MeOH and 0.06–0.075 mol of the appropriate magnesium alkylsulfinate[24] in 50 ml of H_2O was heated under reflux for 18 hr. The hot mixture was filtered, allowing the filtrate to drop into a vigorously stirred excess of H_2O. In some instances crystalline solids precipitated. In other cases the products precipitated as viscous liquids. The liquids were extracted into $CHCl_3$. The $CHCl_3$ solutions were extracted with aqueous Na_2CO_3 which afforded the products upon acidification. In some cases, chromatography on a silica gel column using EtOAc as an eluent was required to obtain a crystalline material. Recrystallization of the solid products gave **8b** and **8e–i** (Table II).

G. Benzylation of 4′-Hydroxy-3′-Substituted Aceto- and Butyrophenones. A stirred mixture of 0.1 mol of the appropriate 4′-hydroxy-3′-substituted aceto- or butyrophenone **8**, 0.11 mol of $PhCH_2Cl$, 0.12 mol of K_2CO_3, and 2 g of NaI in 150 ml of Me_2CO and 110 ml of H_2O was heated under reflux for 18 hr. Upon dilution of the mixture with excess ice–H_2O, crystalline products were formed. Recrystallization afforded the benzyloxy derivatives **10a–i** (Table III).

H. Bromination of Aceto- and Butyrophenone Derivatives with Pyrrolidinone Hydrotribromide (PHT).[25] A mixture of 0.1 mol of 4′-benzyloxy-3′-substituted aceto- or butyrophenone **10**, 0.11 mol of PHT, 0.11 mol of 2-pyrrolidinone, and 400 ml of THF was refluxed for 2 hr. The mixture was cooled to 10° and filtered to remove precipitated 2-pyrrolidinone hemihydrobromide, and the filtrate was poured into H_2O. The resulting precipitate was filtered and purified by trituration or recrystallization, using the appropriate solvent (Table IV).

I. Bromination of 4′-benzyloxy-3′-sulfamylacetophenones (32a and 32b) with Br_2 was performed according to the general method for Br_2 bromination described previously.[9] 4′-Benzyloxy-2-bromo-3′-sulfamylacetophenone (**32a**) was obtained in 71% yield, mp 153–156°, after recrystallization from EtOH. 4′-Benzyloxy-2-bromo-3′-(*N*-methylsulfamyl)acetophenone (**32b**) was obtained in 62% yield: mp 142–146° (from EtOH). Both products were characterized by NMR methods: δ ($CDCl_3$) 4.5 ppm (s, 2, $COCH_2Br$).

J. Preparation of Amino Ketone Derivatives. The appropriate 2-bromoacetophenone **11** (0.01 mol) was stirred and refluxed with 0.02 mol of the requisite N-substituted benzylamine [$PhCH_2$(*t*-Bu)NH, $PhCH_2$(c-Bu)NH, $PhCH_2$(1-adamantyl)NH,[48] $PhCH_2$(4-$MeOC_6H_4CH_2CMe_2$)NH, $PhCH_2$(*i*-Pr)NH] in 50 ml of MeCN for 4 hr. The bromobutyrophenone **11i** (0.01 mol in 30 ml of MeCN) was refluxed with 0.2 mol of *t*-$BuNH_2$ for 3 hr. The resulting mixtures were cooled to 0°, diluted with about 500 ml of Et_2O, and filtered. The filtrate was washed with H_2O, dried, treated with decolorizing C, filtered, and concentrated. The amino ketone precursor to **13** crystallized: mp 110–112° (from EtOAc–hexane); 86% yield. This and the other residual liquids were dissolved or suspended in MeOH and acidified with HCl. Upon addition of ether the amino ketone precursors of **15** (mp 95–98°, 92% yield), **16** (mp 177–179°, from MeOH–Et_2O, 70% yield), **17** (mp 178–179°, from EtOAc layer in suspension with H_2O, 20% yield), and **33** (mp 181–183°, from MeOH–Et_2O, 70% yield) crystallized and were used for further reaction in this form. In all other instances, the acidified MeOH solution was treated with a large excess of Et_2O; the precipitated viscous liquid was separated by decantation and washed several times with Et_2O to give an amorphous solid which was employed for subsequent reaction.

K. Preparation of Glyoxals.[49] A solution of 0.01 mol of the appropriate 2-bromoacetophenone **11** in 30 ml of DMSO was allowed to stand at about 25° for 2–5 days; then it was added dropwise to vigorously stirred ice–H_2O. Resulting solid precipitates were filtered. Viscous liquid precipitates were isolated by decantation and dissolved in Me_2CO and the resulting solution was dried and concentrated to leave residual glyoxals which were used as such for further reaction. Three of the solid glyoxals **[4-benzyloxy-3-(methylsulfonylmethyl)phenylglyoxal hydrate** [88% yield, mp 108–111° (from EtOH)]; **4-benzyloxy-3-(methylsulfonylpropyl)-phenylglyoxal hemihydrate** [90% yield, mp 143–144° (from Me_2CO). Anal. ($C_{19}H_{20}O_5S$·EtOH) C, H]; and **4-benzyloxy-3-(*p*-toluenesulfonylmethyl)phenylglyoxal ethanolate** [75% yield, mp 130–131° (from EtOH). Anal. ($C_{23}H_{20}O_5S$·EtOH) C, H] were isolated and recrystallized prior to further reaction.

L. Amino Alcohols (Table IV) via Glyoxals. To a solution of 0.01 mol of the glyoxal in 100 ml of MeOH was added 0.1 mol of *t*-$BuNH_2$ or, for synthesis of the amino alcohols **18** and **19**, 0.01 mol

of 4-$PhCH_2OPhCH_2CH(Me)NH_2$[50] or 3,4-$OCH_2OPhCH_2CH(Me)NH_2$,[51] respectively. The solution was stirred at ambient temperature for 1 hr and refluxed for 18 hr and then it was concentrated in vacuo. The resulting solid imino ketone precursors to 14 (mp 156–158°), 18 (mp 116–118°), 19 (mp 110–116°), 20 (mp 124–126°), and 25 (mp 135–136°) were recrystallized from EtOH. These crystalline imino ketones, as well as others that were not recrystallized, were redissolved in EtOH, 0.05 mol of $NaBH_4$ was added, and the solution was stirred at about 25° for 18 hr. After diluting the solution with H_2O, the consequent mixture was extracted with Et_2O or $CHCl_3$. The organic extracts were dried and concentrated. Residual benzyloxy-substituted amino alcohols were taken into MeOH and the resulting solutions were made acidic with HCl. Two of these benzyloxy-substituted phenylethanolamine hydrochlorides were recrystallized from MeOH–Et_2O: i.e., the precursor to 14 (mp 180–182°) and the precursor to **15** [**4-benzyloxy-3-(*p*-toluenesulfonylmethyl)-α-(*tert*-butylaminomethyl)benzyl alcohol hydrochloride hemihydrate**, mp 178–179°. Anal. ($C_{27}H_{34}ClNO_4S \cdot 0.5H_2O$) C, H, N]. In all other experiments, the acidified MeOH solution was diluted with a large excess of Et_2O to precipitate a viscous liquid which was isolated by decantation and washed several times with Et_2O to give an amorphous solid. Benzyloxy-substituted phenylethanolamine hydrochloride derivatives thus obtained were employed for catalytic hydrogenation according to general procedure M.

M. Catalytic Hydrogenation of Amino Ketones and Amino Alcohols. A mixture of 0.02 mol of the requisite amino ketone derivative obtained by general procedure J or amino alcohol from general procedure L, 2.0 g of 10% Pd/C, and 100 ml of 70% aqueous EtOH was hydrogenated on a Parr apparatus at 25° and an initial H_2 pressure of 3.5 kg/cm^2. After H_2 uptake was completed (10–15 min was required for the amino alcohols; 2–4 hr for the amino ketones), the mixture was filtered. The filtrate was concentrated and azeotroped twice with PhMe and the residue recrystallized to afford the catecholamine analogs listed in Table V; i.e., **13–27, 30, 33,** and **34.**

3′-Chloromethyl-4′-hydroxybutyrophenone (**9**, R = Et). To 28 ml (11.2 g, 0.37 mol) of a 37% CH_2O solution and 215 ml of 11 *N* HCl at 50–60° was added 49.2 g (0.3 mol) of 4′-hydroxyacetophenone in 150 ml of dioxane. After being heated at 50–60° for 1 hr the reaction mixture was poured into H_2O. The precipitated solid was filtered and recrystallized from PhH–hexane to give 35.2 g (55%) of light tan crystals: mp 121–123°; NMR ($CDCl_3$) δ 4.8 ppm (s, 2, $ArCH_2Cl$).

3-Chloromethyl-4-hydroxybenzaldehyde was prepared in 45% yield by the same method described for the synthesis of **9** (R = Et): mp 126–129° (from PhH); NMR ($CDCl_3$) δ 4.83 ppm (s, 2, $ArCH_2Cl$).

4-Hydroxy-3-(methylsulfonylmethyl)benzaldehyde was prepared by general procedure H. It was obtained in 52% yield as a crystalline solid, mp 161–163.5°. Anal. ($C_9H_{10}O_4S$) C, H.

4-Benzyloxy-3-(methylsulfonylmethyl)benzaldehyde (**28**) was prepared by a modification (250 ml of 50% aqueous dioxane was used as solvent; the reflux time was 3 hr) of general procedure G. The product (59% yield) was obtained as light tan crystals, mp 118.5–120°. It gave a single spot (R_f 0.63) on Analtech silica gel GF (250-μ plates) (Analtech, Inc., Newark, Del.) upon development with 50:50 PhH–EtOAc: NMR ($CDCl_3$) δ 2.77 (s, 3, CH_3SO_2), 4.6 (s, 2, SO_2CH_2Ar), 5.4 ($PhCH_2O$), 7.2–8.4 (m, 8, ArH), 10.0 ppm (s, 1, ArCHO).

α-Aminomethyl-4-hydroxy-3-(methylsulfonylmethyl)benzyl Alcohol Hydrochloride (30). To a solution of 3.0 g (0.01 mol) of **28** in 25 ml of dioxane and 25 ml of H_2O was added 0.7 g (0.01 mol) of $MeNO_2$. The solution was cooled to 0°, a solution prepared by addition of 0.25 g of Na to 25 ml of EtOH was added, and the mixture was stirred at 0–5° for 1 hr. The solid precipitate produced by dilution with excess Et_2O was filtered and dissolved in H_2O. Acidification (HOAc) of the resulting solution produced a yellow liquid precipitate. The mixture was extracted with $CHCl_3$; the extracts were dried and concentrated to give 3.4 g of a yellow liquid **29.** A mixture of this liquid, 0.1 g of PtO_2, and 100 ml of MeOH was hydrogenated at 25° on a Parr apparatus using an initial H_2 pressure of 3.5 kg/cm^2. After H_2 uptake was completed (40 hr), the mixture the filtered; the filtrate was acidified with HCl and concentrated in vacuo. The residue was triturated with *i*-PrOH to give 0.45 g (16%) of **30** (Table V).

4′-Benzyloxy-3′-[1-(methylsulfonyl)ethyl]acetophenone (**10j**). To a solution of 15.9 g (0.05 mol) of 4′-benzyloxy-3′-(methylsulfonylmethyl)acetophenone in 100 ml of DMF at −30° was added 2.15 g (0.051 mol) of a 57% dispersion of NaH in mineral oil. After being stirred at −30 to −10° for 30 min, 7.1 g (0.05 mol) of MeI was added dropwise. The solution was allowed to come to 25°; then it was concentrated in vacuo. A $CHCl_3$ solution of the residue was washed with H_2O, dried, treated with decolorizing C, and concentrated. Recrystallization of the residue gave **10j** (Table IV): NMR ($CHCl_3$) δ 1.75 [d, 3, $SO_2CH(CH_3)Ar$], 5.0 ppm [q, 1, $SO_2CH(CH_3)Ar$].

4′-Benzyloxy-3′-chlorosulfonylacetophenone (**31**). A solution of 10.5 g (0.15 mol) of $NaNO_2$ in 25 ml of H_2O was added dropwise to a stirred solution of 3′-amino-4′-benzyloxyacetophenone[5] in 50 ml of HOAc and 50 ml of 11 *N* HCl at 0–5°. After being stirred at 0–5° for 15 min a mixture of 5.0 g of $CuCl_2 \cdot 2H_2O$ and 30 g of SO_2 in 75 ml of HOAc was added to the solution. The mixture was stirred at 25° for 2.5 hr; then it was filtered. The solid was washed with H_2O and dried to give 15.6 g (48%) of **31**, mp 146–148°. Anal. ($C_{15}H_{13}ClO_4S$) C, H.

4′-Benzyloxy-3′-sulfamylacetophenone (**32a**). Concentrated aqueous ammonia (25 ml) was added dropwise to a stirred solution of 3.2 g (0.01 mol) of 4′-benzyloxy-3′-chlorosulfonylacetophenone (**31**) in 15 ml of dioxane. The mixture was stirred at 25° for 20 min, 100 ml of H_2O was added, and the solid precipitate was filtered. Recrystallization from EtOAc gave 2.4 g (78%) of colorless crystals, mp 183–185°. Anal. ($C_{15}H_{15}NO_4S$) C, H, N.

4′-Benzyloxy-3′-(*N*-methylsulfamyl)acetophenone (**32b**) was prepared in the same manner as described for the synthesis of **32a** except that 40% aqueous $MeNH_2$ was used instead of aqueous NH_3. The colorless crystalline product, mp 149–151° (from EtOH), was obtained in 82% yield. Anal. ($C_{16}H_{17}NO_4S$) C, H, N.

4-Methoxyphenyl-*tert*-butylamine Hydrochloride. A suspension of 20.7 g (0.1 mol) of 4-methoxyphenyl-*tert*-butylformamide[52] in 225 ml of 11 *N* HCl and 65 ml of H_2O was stirred and refluxed for 2 hr; then it was cooled to 20° and extracted with Et_2O. The acidic solution was made alkaline by addition of 10 *N* NaOH and the resulting mixture was extracted with Et_2O. The Et_2O extracts were dried and concentrated and the residual liquid was distilled, bp 98–105° (1.8 Torr). A solution of the distillate in EtOH was made acidic with HCl. Addition of Et_2O gave 17.2 g (80%) of colorless crystals, mp 173–174° (from EtOH–Et_2O). Anal. ($C_{11}H_{18}ClNO \cdot 0.5H_2O$) C, H, N, Cl.

***N*-Benzyl-4-methoxyphenyl-*tert*-butylamine Hydrochloride.** A solution of 35.8 g (0.2 mol) of 4-methoxyphenyl-*tert*-butylamine and 23.3 g (0.22 mol) of PhCHO in 130 ml of PhMe was refluxed azeotropically for 2 hr; then it was concentrated in vacuo. To the resulting liquid in 300 ml of MeOH was added, in portions, 7.0 g (0.2 mol) of $NaBH_4$. The resulting solution was stirred at ambient temperature for 1 hr and then it was refluxed for 2 hr, concentrated in vacuo, and diluted with H_2O. The mixture was extracted with Et_2O. After being dried and treated with decolorizing C, the Et_2O solution was concentrated. A solution of the residual base in EtOH was made acidic with HCl and Et_2O was added to precipitate the crystalline salt: 35.2 g (58%); mp 173–174° (from MeCN). Anal. ($C_{18}H_{24}ClNO$) C, H, N.

Resolution of α-[[(1,1-Dimethylethyl)amino]methyl]-4-hydroxy-3-[(methylsulfonyl)methyl]benzenemethanol Hydrochloride (**14**). To a solution of 5.0 g (0.015 mol) of 14 in 25 ml of H_2O was added an excess of K_2CO_3. Liberated base was extracted with EtOAc. The extracts were dried and concentrated to give 4.1 g of a viscous liquid. To a solution of this liquid in 25 ml of EtOH was added 2.1 g of (+)-tartaric acid in 25 ml of EtOH. On standing 5.5 g of crystals, mp 173.5–176.5°, was deposited. Five recrystallizations from EtOH–H_2O afforded 1.3 g of colorless crystals, mp 170.5–172.5° dec. A solution of this product in MeOH was passed through a column of excess Amberlite IRA-401,[53] eluting with MeOH. The eluate was concentrated to give 0.85 g of (+)-14 (Table V): $[\alpha]^{25}D$ +40.4° (c 1, MeOH).

All filtrates from recrystallizations of the (+)-tartrate were reconverted to the HCl salt by passage through the Cl anion exchange column as described above. The HCl salt thus derived was converted to the base as described for the racemate. This base (2.0 g) was treated with an equimolar amount of (−)-tartaric acid to give the (−)-tartrate, which was processed as described for the (+) enantiomer to give 0.035 g of (−)-14 (Table V): $[\alpha]^{25}D$ −38.7° (c 1, MeOH).

Pharmacology. Methods. A. Guinea Pig Tracheal Chain Test. This test was performed as described previously.[9]

B. Guinea Pig Right Atria Test. This test was carried out in the manner described previously.[9] This preparation was also employed to evaluate **13** and **22** for their ability to attenuate isoproterenol-induced increases in atrial contraction rate. In these experiments, after adding 3.5×10^{-6} *M* **13** or 1.6×10^{-4} *M* **22**, the tissue

was allowed to equilibrate. Responses to a predetermined ED_{25} and ED_{75} concentration of isoproterenol were then redetermined. Both compounds shifted the isoproterenol dose–response curve to the right in a manner suggestive of competitive inhibition (at the indicated concentrations, **13** and **22** produced approximately 22 and 36% inhibition, respectively, of atrial rate increases induced by the doses of isoproterenol).

C. Guinea Pig and Rabbit Heart Test. Freshly isolated guinea pig or rabbit hearts suspended from an aortic cannula of an Anderson heart perfusion apparatus[54] were perfused with Chenoweth's solution[55] at 37.5° and a perfusion pressure of 50 cm of H_2O according to the general method of Anderson and Craver.[56] The heart rate was measured by recording ventricular contractions with a force transducer attached to the ventricular apex by a thin thread. After a period of equilibration, control increases in contraction rate were obtained by addition of 3×10^{-7} *M* isoproterenol. The rate was allowed to return to normal and **25**, **33**, and **34** were then tested for their effects on heart rate (see Table V). After 15–30 min the control dose of isoproterenol was added again. Inhibition of the isoproterenol-induced heart rate increase (indicative of β-adrenergic blockade) was determined by comparing the second response (beats per minute) to the initially determined control value.

D. Dog Cardiovascular Test. Blood pressure was measured via a catheterized femoral artery in three pentobarbital-anesthetized dogs. The heart rate was determined from an EKG tracing. Infusions of **33** (5 and 10 mg/kg) were administered over a 5-min period by means of a catheter inserted into the femoral vein. Doses (0.3 and 2.7 μg/kg) of isoproterenol were administered iv to each animal before and 30–45 min after administration of **33**. The compound **33** antagonized the blood pressure decrease and heart rate increase produced by these doses of isoproterenol (Table V).

E. Cat Pulmonary Resistance, Cardiovascular, and Soleus Muscle Tension Test. Following a period of physiological stabilization, the decrease in spontaneously increased pulmonary resistance (indicative of bronchodilation) was measured after administration of increasing iv doses of **14** in five anesthetized cats according to the method described previously.[10,57] 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* (0.065 μg/kg for isoproterenol).

Cardiovascular activity (blood pressure measured via a catheter inserted into the femoral artery and heart rate monitored by means of an EKG tracing) and *soleus muscle tension*[58] were measured in a separate group of eight α-chloralose-anesthetized cats. In these experiments soleus muscle tension, measured as described previously,[58] and cardiovascular responses were determined for a series of increasing iv doses of isoproterenol. Following an equilibration period, **14** was administered in a similar manner. As a consequence of the variability in responsiveness between cats, isoproterenol and **14** were compared in each animal. The best fitting line for the average log dose–response regression curve was utilized to determine the ED_{25} for increase of heart rate (0.38 μg/kg for isoproterenol), the ED_{30} for decrease of diastolic blood pressure (0.002 μg/kg for isoproterenol), and the ED_{50} for decrease in soleus muscle tension (0.034 μg/kg for isoproterenol), i.e., the dose causing a 25% increase in heart rate, a 30% decrease in diastolic blood pressure, and a 50% decrease in the area under the soleus muscle tension curve, respectively. Changes in heart rate and diastolic blood pressure were determined relative to base line values. Soleus muscle response was expressed as a percent of the maximum response to a supramaximal iv dose of isoproterenol administered at the conclusion of each dose range study. Potency of **14** relative to isoproterenol was estimated by comparing corresponding ED values (see Table VI).

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using Me_4Si as a reference and the indicated solvent at ambient temperatures. Although ir and NMR data are reported only where considered significant, these spectra were determined for all reported compounds and were considered consistent with the assigned structures. Mass spectral data were obtained on a Hitachi Perkin-Elmer RMU-6E mass spectrometer.
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N-Hydroxylation of 1-(2,5-Dimethoxy-4-methylphenyl)-2-aminopropane by Rabbit Liver Microsomes

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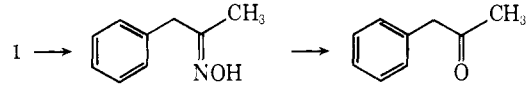
Metabolic N-hydroxylation of the potent psychotomimetic amine 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (**5**) by rabbit liver microsomal preparations has been investigated. Synthetic hydroxylamine **8** was obtained by sequential reduction of the corresponding nitropropene **10** with sodium borohydride followed by zinc reduction of the resulting nitropropane **11**. Compound **8** in water (pH 7.4) was rapidly air oxidized to oxime **12**; this oxidation was completely blocked by rabbit liver microsomes. Microsomal incubations of amine **5** or its bis(methoxy-d_3)hexadeuterio analog **5**-d_6 resulted in the formation of **8** and **8**-d_6, respectively, identified as their bis(trifluoroacetyl) derivatives by GLC–MS. Quantitative estimations of metabolite formation employing selected ion monitoring with the aid of an accelerating voltage alternator were accomplished by stable isotope dilution analyses with **5**-d_6 as substrate and **8**-d_0 as internal standard. Similar analyses starting with "pseudoracemates" (*R*)-**5**-d_0:(*S*)-**5**-d_6 or (*R*)-**5**-d_6:(*S*)-**5**-d_0 as substrates established metabolite **8** to be enriched with its *R* enantiomer.

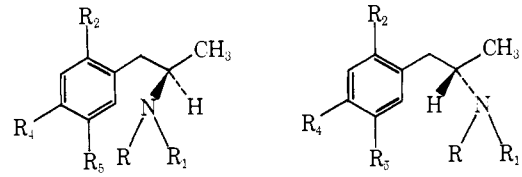
The metabolic N-hydroxylation of aromatic amines, a reaction thought to be involved in the carcinogenic and other toxic effects of some aromatic amines, has been investigated extensively.[1] Recently, interest in metabolic N-hydroxylation has been extended to aliphatic amines.[2] The in vitro[2a,b,g] and in vivo[2f] N-hydroxylation of amphetamine (**1**) has been studied by several groups.[2b,c,g] It has been suggested[3] that phenyl-2-propanone (**3**), a major urinary metabolite[4] of amphetamine in man and several other species, may arise, in part, via the oxime **2** (eq 1). However, the



2 3 (1)

mode of formation of oxime **2** is a matter of controversy. Beckett and his coworkers have suggested that **2** arises from hydroxylamine **4** (a metabolite of **1**) via nonenzymatic oxidation, while Hucker and his group have proposed[2g,3b] other pathways to oxime **2**. Indeed, it has been claimed that[2g,3b] no *N*-hydroxyamphetamine (**4**) is formed in incubations of **1** with rabbit liver microsomes under conditions where others[2b,c] report N-hydroxylation.

These inconsistencies may be partly due to the instability of aliphatic *N*-hydroxy compounds, especially when subjected to basic conditions in the presence of oxygen[2a,5] (see below). Metabolic studies[2b] by Beckett and Al-Sarraj on the influence of the chiral center of amphetamines on N-hydroxylation have shown that (*R*)-(−)-amphetamine [(*R*)-**1**] is about eight times better as a substrate for N-hydroxylation than the *S* enantiomer (*S*)-**1**. This metabolic stereoselectivity, although described without detailed evidence, is interesting in view of the greater CNS stimulant activity of (*S*)-(+)-amphetamine.[6] Benington and his coworkers found[7] that replacement of the amino group in a series of 1-phenyl-2-aminopropanes by the hydroxylamino group decreases but does not abolish the central stimulant



R *S*

	R	R_1	R_2	R_4	R_5
1	H	H	H	H	H
4	H	OH	H	H	H
5	H	H	OCH_3	CH_3	OCH_3
5-d_3	H	H	OCH_3	CD_3	OCH_3
5-d_6	H	H	OCD_3	CH_3	OCD_3
5-TFA	H	$COCF_3$	OCH_3	CH_3	OCH_3
5-d_6-TFA	H	$COCF_3$	OCD_3	CH_3	OCD_3
6	H	H	OH	CH_3	OCH_3
7	H	H	OCH_3	CH_3	OH
8	H	OH	OCH_3	CH_3	OCH_3
8-TFA	$COCF_3$	$OCOCF_3$	OCH_3	CH_3	OCH_3
8-d_6	H	OH	OCD_3	CH_3	OCD_3
8-d_6-TFA	$COCF_3$	$OCOCF_3$	OCD_3	CH_3	OCD_3