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Studies on Benzenesulfonamide Derivatives with α- and β-Adrenergic Antagonistic and Antihypertensive Activities[1]

Takashi Fujikura,* Kunihiro Niigata, Shinichi Hashimoto, Kazuo Imai, and Toichi Takenaka

Central Research Laboratories, Yamanouchi Pharmaceutical Co., Ltd., Azusawa 1-1-8, Itabashi-ku, Tokyo, 174, Japan

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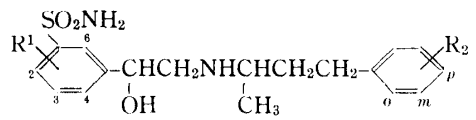
New α- and β-adrenergic blockers, benzenesulfonamide derivatives (Ia—z), were prepared from acetylbenzenesulfonamides (II) by two methods. These compounds were tested for α- and β-blocking activities and their structure–activity relationships are discussed. All the target compounds have two asymmetric centers and therefore consist of two diastereomers. 5-[1-Hydroxy-2-[3-(2-methoxyphenyl)-1-methylpropylamino]ethyl]-2-methylbenzenesulfonamide (Ir) and 5-[1-hydroxy-2-[2-(2-methoxyphenoxy)-1-methylethylamino]ethyl]-2-methylbenzenesulfonamide (Iu) showed potent α- and β-blocking activities and they were each separated into two diastereomers (Ir-A and Ir-B, and Iu-A and Iu-B). It was found that one isomer had mainly β-blocking activity and the other isomer had mainly α-blocking activity. In addition, several compounds showing relatively strong α- and β-blocking activities were also examined for antihypertensive activity in conscious spontaneously hypertensive rats. Among the compounds tested, Ir and Iu were the most active, and they were more potent than labetalol. Compounds Ir and Iu may be of practical use as potent antihypertensive agents.

Keywords——phenylethanolamine; sulfonamide; sympatholytic activity; α- and β-blocker; α-blocking activity; β-blocking activity; structure–activity relationship

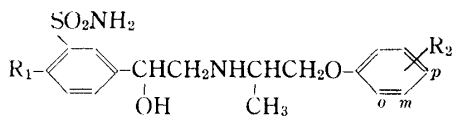
The etiology of hypertension is thought to be multifactorial, and various kinds of drugs are used in antihypertensive pharmacotherapy. For example, β-adrenergic blocking agents are now widely applied in the treatment of hypertension.[2,3] In recent years it has been reported in clinical studies that the combined administration of β-adrenergic blocking agents and α-adrenergic blocking agents results in good control of blood pressure.[4,5] Therefore, an agent that combines both α- and β-blockading activity in a single molecule, such as labetalol,[6,7] is expected to possess some advantages over pure β-blockers or pure α-blockers for the treatment of hypertension. In an attempt to find such new agents, we have synthesized a series of 3-[1-hydroxy-2-(substituted amino)ethyl]benzenesulfonamide derivatives and tested them for α- and β-blocking activities.

In this paper, we describe the synthesis of compounds of the two types shown in Fig. 1, and the determination of their α- and β-blocking activities. In addition, the antihypertensive activities of several compounds showing relatively strong α- and β-blocking activities are reported.



Ia—l, p—r

R^1=H, 2-Cl, 2-Br, 2-OH, 2-OCH_3, 3-OCH_3, 4-OCH_3, 6-OCH_3, 2-CH_3, 2-$(CH_2)_2CH_3$, 2-SCH_3, or 2-SO_2CH_3
R^2=H or *o*-OCH_3



Im—o, s—y

R^1=OH, OCH_3, or CH_3
R^2=H, *o*-OCH_3, *m*-OCH_3, *p*-OCH_3, *o*-OCH_2CH_3, or *o*-OH

Fig. 1

Synthesis

Compounds (Ia, f—z) were prepared according to the synthetic route outlined in Chart 1. Starting materials (IIa—h) were obtained from the appropriate aminoacetophenone derivatives by the procedure of Meerwein *et al.*[8] and were converted to the corresponding bromoacetyl derivatives (IIIa—h) by bromination with bromine in acetic acid. Condensation of III with

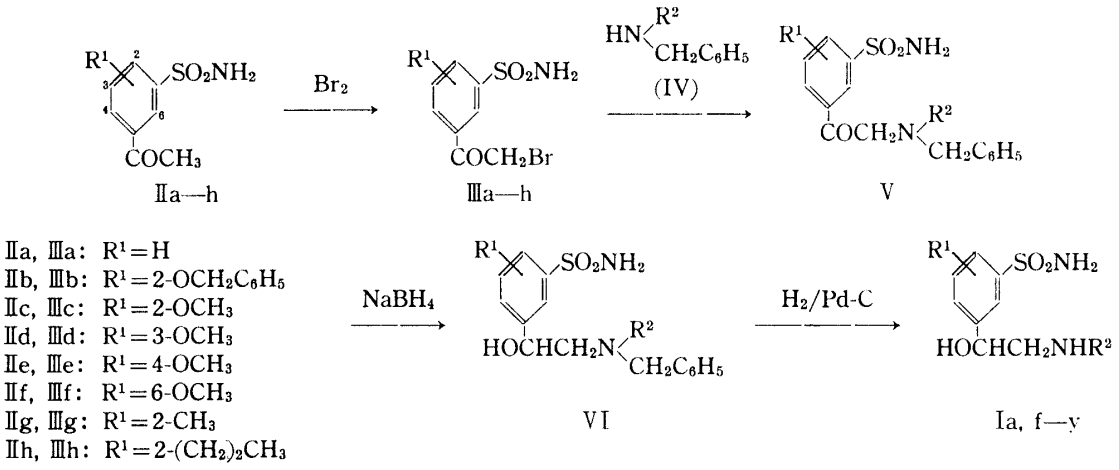


Chart 1

appropriate *N*-benzyl-*N*-substituted amines (IV) gave the amino ketones (V), which were purified by column chromatography on silica gel. Reduction of V with sodium borohydride afforded the amino alcohols (VI). Compounds VI were hydrogenated over 10% palladium on carbon to give Ia, f—z (Table I).

The syntheses of Ib—e were achieved according to the route shown in Chart 2. Two novel starting materials (IIk and III) were prepared as follows. 5-Acetyl-2-methylthioben-

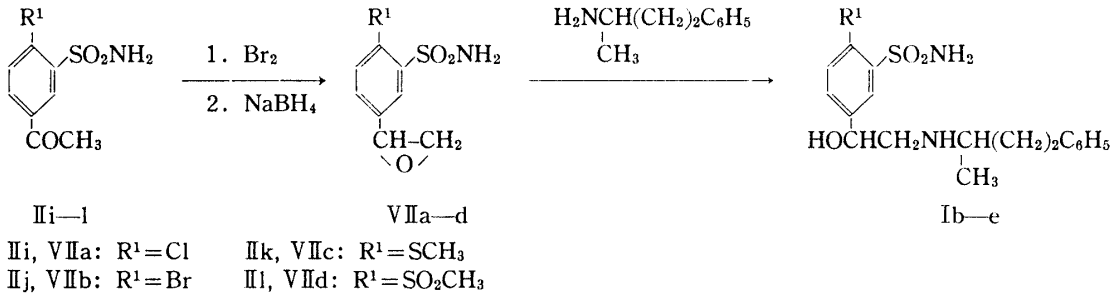


Chart 2

zenesulfonamide (IIk) was prepared by reaction of 5-acetyl-2-chlorobenzenesulfonamide (IIi)[9] with methyl mercaptan. On the other hand, 5-acetyl-2-methylsulfonylbenzenesolfonamide (III) was obtained from IIk by oxidation with chlorine in 90% aqueous acetic acid. Then, IIi—l were brominated and subsequently treated with excess sodium borohydride to afford the corresponding epoxides (VIIa—d). Reaction of VII with 1-methyl-3-phenylpropylamine[10] gave Ib—e in (Table I).

All target compounds (Ia—z) reported in this paper contain two asymmetric centers; therefore, they consist of two diastereomers. In order to examine the activities of the two diastereomers, 5-[1-hydroxy-2-[3-(2-methoxyphenyl)-1-methylpropylamino]ethyl]-2-methylbenzenesulfonamide (Ir) and 5-[1-hydroxy-2-[2-(2-methoxyphenoxy)-1-methylethylamino]-ethyl]-2-methylbenzenesulfonamide (Iu), which exhibited potent α- and β-blocking activities,

were each separated into the two possible diastereomers (Ir-A, Ir-B and Iu-A, Iu-B) as described below.

The diastereomers of Ir (Ir-A and Ir-B)were prepared from the corresponding diastereomeric amino alcohol (VIII-A and VIII-B) as shown in Chart 3. Compound VIII, the *N*-benzyl derivative of Ir, was separated into the two diastereomers of VIII (VIII-A and VIII-B) by column chromatography on silica gel. The ratio of isomer-A to isomer-B was approximately 7 : 3. They could be distinguished from the difference of nuclear magnetic resonance (NMR) signal pattern for the methylene (2H) of the *N*-benzyl group. VIII-A showed an AB-quartet at δ 3.46 and 3.88 (2H, J=13.1 Hz), and VIII-B showed a singlet at δ 3.62 (2H). VIII-A and VIII-B were led to the individual diastereomers (Ir-A and Ir-B) by catalytic hydrogenation over 10% palladium on carbon.

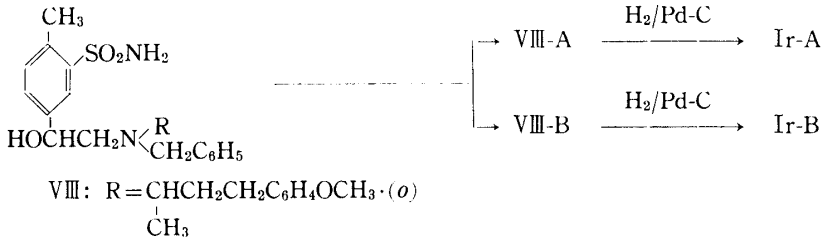
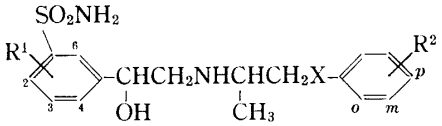


Chart 3

On the other hand, the two diastereomers of Iu (Iu-A and Iu-B) were separated by fractional crystallization of Iu from ethanol. The two diastereomers (Iu-A and Iu-B) showed a characteristic NMR signal for the methylene moiety (>CH–C<u>H</u>$_2$–NH–). The signals of Iu-A and Iu-B were observed at δ 2.89 (2H, dd, J=7.05 and 5.7 Hz) and δ 2.6—3.1 (2H, dd, J_{gem}=11.9, J_{vic}=4.2 and 6.7 Hz), respectively. Thus, the diastereomers (Iu-A and Iu-B) were distinguishable from each other by NMR spectroscopy.

TABLE I. [1-Hydroxy-2-(substituted amino)ethyl]benzenesulfonamide Derivatives



Compd. No.	R^1	X	R^2	mp (°C) Recrystn. solvent	Yield[a] (%)	Formula	Analysis (%) Calcd (Found) C	H	N	Sympatholytic act. ED_{50} mg/kg *i.v.* α[b]	β[c]
Ia	H	CH_2	H	243—247 iso-PrOH	71	$C_{18}H_{24}N_2O_3S\cdot HCl$	56.17 (56.25	6.55 6.50	7.28 7.21)	8.7	0.072
Ib	2-Cl	CH_2	H	108—113[d] iso-PrOH	57[e]	$C_{18}H_{23}ClN_2O_3S\cdot HCl\cdot 0.5H_2O$	52.43 (52.36	6.11 6.07	6.79 6.97)	2.1	0.14
Ic	2-Br	CH_2	H	103—105 EtOH	56[e]	$C_{18}H_{23}BrN_2O_3S\cdot HCl$	46.61 (46.89	5.22 5.62	6.04 5.82)	4.7	0.27
Id	2-SCH_3	CH_2	H	109—110 iso-PrOH	66[e]	$C_{19}H_{26}N_2O_3S$	57.84 (57.54	6.64 6.77	7.10 6.93)	1.6	0.19
Ie	2-SO_2CH_3	CH_2	H	136—145 iso-PrOH	72[e]	$C_{19}H_{26}N_2O_5S_2$	53.50 (53.61	6.14 5.94	6.54 6.63)	3.0<	3.0<
If	2-OH	CH_2	H	190—194 MeOH	39	$C_{18}H_{24}N_2O_4S\cdot HCl$	53.93 (54.08	6.28 6.21	6.99 7.15)	0.039	0.067
Ig	2-OCH_3	CH_2	H	185—188 EtOH	27	$C_{19}H_{26}N_2O_4S\cdot HCl$	55.00 (54.15	6.56 6.56	6.75 6.58)	1.3	0.035
Ih	2-CH_3	CH_2	H	169—172 iso-PrOH	68	$C_{19}H_{26}N_2O_3S\cdot HCl$	57.30 (57.11	6.82 6.82	7.02 6.70)	3.5	0.057

Compd. No.	R^1	X	R^2	mp (°C) Recrystn. solvent	Yield[a] (%)	Formula	Analysis (%) Calcd (Found) C	H	N	Sympatholytic act. ED_{50} mg/kg *i.v.* α[b]	β[c]
Ii	2-$(CH_2)_2CH_3$	CH_2	H	172—174 MeOH	16	$C_{21}H_{30}N_2O_3S\cdot HCl$	59.07 (58.96	7.32 7.28	6.56 6.50)	4.3	1.3
Ij	3-OCH_3	CH_2	H	160—162 EtOH	66	$C_{19}H_{26}N_2O_4S\cdot HCl$	55.00 (54.94	6.56 6.52	6.75 6.67)	1.8	0.052
Ik	4-OCH_3	CH_2	H	127—129 EtOH	13	$C_{19}H_{26}N_2O_4S\cdot HCl$	55.00 (54.89	6.56 6.53	6.75 6.74)	5.6	11
Il	6-OCH_3	CH_2	H	133—135 iso-PrOH	23	$C_{19}H_{26}N_2O_4S\cdot HCl$	55.00 (55.01	6.56 6.55	6.75 6.73)	27	33
Im	2-OH	O	H	96— 98 iso-PrOH	49	$C_{17}H_{22}N_2O_5S$	55.71 (55.38	6.05 5.99	7.65 7.39)	0.0084	3.1
In	2-OCH_3	O	H	90— 96 EtOH	54	$C_{18}H_{24}N_2O_5S\cdot HCl$	51.85 (51.52	6.04 5.80	6.72 6.33)	0.22	2.0
Io	2-CH_3	O	H	90— 94 EtOH	41	$C_{18}H_{24}N_2O_4S\cdot HCl\cdot H_2O$	51.61 (51.48	6.50 6.43	6.69 6.72)	1.7	0.32
Ip	2-OH	CH_2	*o*-OCH_3	220—225 EtOH	63	$C_{19}H_{26}N_2O_5S\cdot HCl$	52.96 (52.73	6.31 6.52	6.50 6.31)	0.034	0.55
Iq	2-OCH_3	CH_2	*o*-OCH_3	180—185 iso-PrOH	26	$C_{20}H_{28}N_2O_5S\cdot HCl$	53.98 (54.02	6.57 6.62	6.30 6.27)	0.15	0.070
Ir	2-CH_3	CH_2	*o*-OCH_3	164—165 iso-PrOH	39	$C_{20}H_{28}N_2O_4S\cdot HCl$	56.00 (55.83	6.81 6.90	6.53 6.66)	0.43	0.095
Ir-A	2-CH_3	CH_2	*o*-OCH_3	176—177 iso-PrOH	*f*	$C_{20}H_{28}N_2O_4S\cdot HCl$	56.00 (55.96	6.81 6.87	6.53 6.62)	1.3	0.073
Ir-B	2-CH_3	CH_2	*o*-OCH_3	151—153 iso-PrOH	*f*	$C_{20}H_{28}N_2O_4S\cdot HCl$	56.00 (55.99	6.81 7.10	6.53 6.51)	0.086	0.48
Is	2-OH	O	*o*-OCH_3	194—196 iso-PrOH	42	$C_{18}H_{24}N_2O_4S\cdot HCl$	49.92 (49.94	5.82 5.91	6.47 6.27)	0.0091	0.53
It	2-OCH_3	O	*o*-OCH_3	156—159 iso-PrOH	36	$C_{19}H_{26}N_2O_6S\cdot HCl$	51.06 (51.12	6.09 5.99	6.27 6.24)	0.068	0.28
Iu	2-CH_3	O	*o*-OCH_3	141—144 iso-PrOH	56	$C_{19}H_{26}N_2O_5S$	57.85 (57.61	6.64 6.74	7.10 7.05)	0.27	0.083
Iu-A	2-CH_3	O	*o*-OCH_3	145—147 EtOH	*f*	$C_{19}H_{26}N_2O_5S$	57.85 (57.76	6.64 6.68	7.10 7.08)	0.23	0.053
Iu-B	2-CH_3	O	*o*-OCH_3	153—154 EtOH	*f*	$C_{19}H_{26}N_2O_5S$	57.85 (57.78	6.64 6.60	7.10 6.98)	0.044	0.43
Iv	2-CH_3	O	*m*-OCH_3	92— 94 iso-PrOH	43	$C_{19}H_{26}N_2O_5S\cdot HCl\cdot H_2O$	50.83 (50.90	6.51 6.42	6.24 6.37)	5.2	0.28
Iw	2-CH_3	O	*p*-OCH_3	132—134 iso-PrOH	43	$C_{19}H_{26}N_2O_5S\cdot HCl$	52.95 (52.59	6.32 6.48	6.50 6.18)	7.1	0.29
Ix	2-CH_3	O	*o*-OCH_2CH_3	156—159 EtOH	28	$C_{20}H_{28}N_2O_5S\cdot HCl$	53.99 (53.76	6.57 6.47	6.30 6.39)	0.066	0.27
Iy	2-CH_3	O	*o*-OH	124—126 EtOH	41	$C_{18}H_{24}N_2O_5S\cdot HCl$	51.86 (51.98	6.04 6.11	6.72 6.59)	0.66	0.044
Iz	*N*-Methyl derivative of 7[g]			162—164 iso-PrOH	46	$C_{20}H_{28}N_2O_4S\cdot HCl$	56.00 (56.65	6.81 6.87	6.53 6.38)	6.5	0.16
	Propranolol									10<	0.063
	Phentolamine									0.054	10<
	Labetalol									0.70	0.11

a) Yields were calculated on the basis of the bromides (III). *b*) The mean dose producing 50% of the phenylephrine (10 μg/kg *i.v.*)-induced vassopressor response in 3—8 anesthetized rats treated with pentolium. *c*) The mean dose producing a 50% blockade of isoproterenol (0.1 μg/kg *i.v.*)-induced tachycardia in 3—8 anesthetized rats treated with reserpine. *d*) Ref. 9, mp 88—94°C. *e*) Yield was calculated on the basis of the epoxide (VII). *f*) See "Experimental." *g*) 5-[1-Hydroxy-2-(1-methyl-3-phenylpropylamino)ethyl]-2-methoxy-*N*-methylbenzenesulfonamide.

Pharmacology and Structure-Activity Relationships

All compounds (Ia—z) in Table I were tested for α- and β-adrenergic blocking activities in anesthetized rats. Compounds bearing a hydroxy, methoxy, or methyl group at the 2-position (If—h) showed more potent α- and β-blocking activities than the unsubstituted compound (Ia). In a series of methoxy derivatives, the α- and β-blocking activities of the 3-

methoxy isomer (Ij) were nearly equal to that of 2-methoxy isomer (Ig), and the *N*-methyl analogue (Iz) had lower potencies than Ig. Modification for the side chain N substituents of If—h gave the following results. Analogues (Im—o) which contained an *N*-phenoxyalkyl side chain showed an increase in α-blocking and a decrease in β-blocking activity as compared with the corresponding *N*-phenylalkyl ones (If—h). Similar relationships were observed for *o*-methoxy analogues of *N*-phenylalkyl and *N*-phenoxyalkyl compounds (Ip—r or Is—u *vs.* If—h). Among the analogues of Iu, the α-blocking potency of the *o*-ethoxy analogue (Ix) and the β-blocking potency of the *o*-hydroxy analogue (Iy) were superior to those of Iu, respectively. Structure–activity relationships between the two diastereomers of Ir or Iu revealed that Ir-A and Iu-A had mainly β-blocking activity whereas Ir-B and Iu-B had mainly α-blocking activity (Ir-A *vs.* Ir-B and Iu-A *vs.* Iu-B).

Table II. Hypotensive Activity in SHR

Compd. No.	Fall in systolic blood pressure (mmHg)[a] dose (mg/kg *p.o.*)	
	10	30
If		12±6.8
Ig		31±8.1
Ih	27±6.1	38±4.5
Io		29±5.0
Ir	40±6.5	
Is	33±6.9	
It	20±4.3	43±4.6
Iu	43±5.8	
Ix	17±3.9	58±5.2
Labetalol	25±3.4	38±5.6

a) See "Experimental." *b*) Mean ± S.E.M. of 5 to 10 experiments.

Several compounds showing relatively strong α- and β-blocking activities were selected and tested orally for antihypertensive activity in conscious spontaneously hypertensive rats (SHR). Most of the compounds tested possessed potent antihypertensive activity, as shown in Table II. Among them, Ir and Iu were most active, and they were more potent than labetalol.

In summary, these pharmacological studies show that compounds Ir and Iu possess marked α- and β-blocking activities and show potent antihypertensive activity in SHR. Compounds Ir and Iu may therefore be of practical use as potent antihypertensive agents.

Experimental

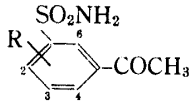
All melting points and boiling points are uncorrected. ^{1}H-NMR spectra were recorded either on a JEOL FX90Q or a JEOL FX100 instrument using tetramethylsilane as an internal standard. Infrared (IR) spectra were determined on a Hitachi 215 infrared spectrophotometer. Mass spectra (MS) were obtained using a Hitachi RMU-6MG double-focusing mass spectrometer. Silica gel 60 F_{254} (Merck) was used for thin layer chromatography (TLC). For column chromatography, silica gel (Wakogel C-200) was used. Solutions were concentrated in rotary evaporators under reduced pressure.

General Procedure for the Synthesis of II——a) The general literature procedure[8] was modified as follows. A solution of 10.3 g of $NaNO_2$ in 25 ml of H_2O was added dropwise to a suspension of 0.1 mol of the appropriate aminoacetophenone in a mixture of 50 ml of AcOH and 50 ml of conc. HCl at 0—5°C. The reaction mixture was stirred at 5°C for 30 min followed by rapid addition of a cold mixture of 5 g of $CuCl_2 \cdot 2H_2O$ and 30 g of SO_2 in 75 ml of AcOH at −15°C. After being stirred at 0—5°C for 16—48 h, the reaction mixture was diluted with 250 ml of H_2O. The resulting oily precipitates were extracted twice with 400 ml of benzene. The extracts were washed with water and dried over $MgSO_4$. After removal of the solvent, the oily residue was used for the subsequent step without further purification. Three chlorosulfonylaceto-

phenones were isolated. 4′-Chloro-3′-chlorosulfonylacetophenone: Yield, 71%. mp 111—112°C (from iso-PrOH–ether). 4′-Benzyloxy-3′-chlorosulfonylacetophenone: Yield, 69%. mp 181—183°C (from AcOEt). 3′-Chlorosulfonyl-4′-methylacetophenone: Yield, 78%. mp 142—145°C (from iso-PrOH–ether). The spectral data for 3′-chlorosulfonyl-4′-methylacetophenone are given as an example of this class of compounds. IR ν_{max}^{KBr} cm^{-1}: 1680, 1590, 1350, 1250, 1165. MS *m/e*: 234, 232 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.65 (3H, s), 2.85 (3H, s), 7.55 (1H, d, J=7.9 Hz), 8.18 (1H, dd, J=1.7 and 7.9 Hz), 8.59 (1H, d, J=1.7 Hz).

b) To a solution of 0.1 mol of chlorosulfonylacetophenone in 100 ml of THF was dropwise added 250 ml of conc. NH_4OH at 5—10°C. The mixture was allowed to stand overnight at room temperature. The precipitated solid was obtained by filtration and purified by recrystallization. The ^{1}H-NMR data for IIg are given as an example of this class of compounds. ^{1}H-NMR (DMSO-d_6) δ: 2.60 (3H, s), 2.68 (3H, s), 7.52 (1H, d, J=7.5 Hz), 7.57 (2H, s), 8.05 (1H, dd, J=1.8 and 7.5 Hz), 8.40 (1H, d, J=1.8 Hz). The physical data and total yields of IIa—j prepared by the above method are shown in Table III.

Table III. Acetylbenzenesulfonamide Derivatives



Compd. No.	R	mp (°C) Recrystn. solvent	Yield[a] (%)	Formula	Analysis (%) Calcd (Found) C	H	N
IIa	H	144—146[b] iso-PrOH	76	$C_8H_9NO_3S$	.....		
IIb	2-$OCH_2C_6H_5$	185—186[c] MeOH	63	$C_{15}H_{15}NO_4S$	.....		
IIc	2-OCH_3	205—206 EtOH	24	$C_9H_{11}NO_4S$	47.15 (47.14	4.84 4.93	6.11 6.21)
IId	3-OCH_3	145—146 $CHCl_3$	53	$C_9H_{11}NO_4S$	47.15 (47.33	4.84 4.61	6.11 6.16)
IIe	4-OCH_3	129—131 $CHCl_3$	15	$C_9H_{11}NO_4S$	47.15 (47.11	4.84 4.65	6.11 6.13)
IIf	6-OCH_3	131—133 Benzene	27	$C_9H_{11}NO_4S$	47.15 (47.24	4.84 4.64	6.11 6.35)
IIg	2-CH_3	141—146 iso-PrOH	71	$C_9H_{11}NO_3S$	50.69 (50.56	5.20 5.12	6.57 6.16)
IIh	2-$(CH_2)_2CH_3$	128—129 $CHCl_3$	17	$C_{11}H_{15}NO_3S$	54.75 (54.64	6.27 6.34	5.80 5.51)
IIi	2-Cl	157—158[d] iso-PrOH	65	$C_8H_8ClNO_3S$	.....		
IIj	2-Br	158—160[e] iso-PrOH	48	$C_8H_8BrNO_3S$	.....		

a) Yields were calculated on the basis of the aminoacetophenones.
b) Ref. 10, mp 147—148°C.
c) Ref. 11, mp 183—185°C.
d) Ref. 7, mp 154—155°C.
e) Ref. 7, mp 155—156°C.

5-Acetyl-2-methoxy-*N*-methylbenzenesulfonamide (IIm)——Aqueous $MeNH_2$ (40% soln., 50 ml) was added dropwise to a solution of 12.5 g of 3′-chlorosulfonyl-4′-methoxyacetophenone in 70 ml of THF at 5°C. The mixture was worked up in the same manner as described above, followed by recrystallization of the product from iso-PrOH to give IIm (11.4 g, 94%), mp 163—164°C. *Anal.* Calcd for $C_{10}H_{13}NO_4S$: C, 49.37; H, 5.39; N, 5.76. Found: C, 49.52; H, 5.56; N, 5.61.

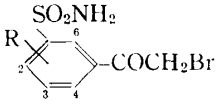
5-Acetyl-2-methylthiobenzenesulfonamide (IIk)——A mixture of 2.3 g of IIi[9] and 8.1 g of methylmercaptan sodium salt (*ca.* 20% in water) was refluxed for 15 min. The reaction mixture was acidified with conc. HCl. The precipitated crystals were collected by filtration and washed with water. Recrystallization from iso-PrOH afforded IIk (1.5 g, 64%), mp 180—182°C. *Anal.* Calcd for $C_9H_{11}NO_3S_2$: C, 44.07; H, 4.52; N, 5.71. Found: C, 43.92; H, 4.63; N, 5.54.

5-Acetyl-2-methylsulfonylbenzenesulfonamide (III)——Chlorine was passed into a solution of 4.2 g of IIk in 70 ml of 90% aqueous AcOH at 5°C until no further crystals were precipitated. The crystals were collected by filtration and recrystallized from EtOH to give III (3.3 g, 80%), mp 218—222°C. *Anal.* Calcd

for $C_9H_{11}NO_5S_2$: C, 38.98; H, 4.00; N, 5.05. Found: C, 38.65; H, 3.82; N, 5.13.

General Procedure for the Synthesis of III——Bromine (1 eq) was added dropwise to a solution of 0.1 mol of II in 200 ml of AcOH at 35—40°C. The reaction mixture was stirred at room temperature for 30 min, then the solvent was evaporated off, and the solid was purified by recrystallization. The ^{1}H-NMR data for IIIg, as an example of this class of compounds, were as follows. ^{1}H-NMR (DMSO-d_6) δ: 2.68 (3H, s), 4.90 (3H, s), 7.56 (2H, s), 7.56 (1H, d, J=7.6 Hz), 8.11 (1H, dd, J=1.7 and 7.6 Hz), 8.41 (1H, d, J=1.7 Hz). The physical data and yields of IIIa—l prepared by the above method are shown in Table IV.

Table IV. Bromoacetylbenzenesulfonamide Derivatives



Compd. No.	R	mp (°C) Recrystn. solvent	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N
IIIa	H	130—132[a] iso-PrOH	81	$C_8H_8BrNO_3S$	.....		
IIIb	2-$OCH_2C_6H_5$	160—162[b] MeOH	85	$C_{15}H_{14}BrNO_4S$	.....		
IIIc	2-OCH_3	190—191 EtOH	73	$C_9H_{10}BrNO_4S$	35.08 (35.12	3.27 3.24	4.55 4.53)
IIId	3-OCH_3	140—142 EtOH	74	$C_9H_{10}BrNO_4S$	35.08 (34.95	3.27 3.26	4.55 4.65)
IIIe	4-OCH_3	136—137 EtOH	89	$C_9H_{10}BrNO_4S$	35.08 (35.23	3.26 3.44	4.55 4.66)
IIIf	6-OCH_3	105—106 iso-PrOH	60	$C_9H_{10}BrNO_4S$	35.08 (35.22	3.27 3.36	4.55 4.55)
IIIg	2-CH_3	146—147 EtOH	71	$C_9H_{10}BrNO_3S$	37.00 (37.14	3.45 3.43	4.79 4.63)
IIIh	2-$(CH_2)_2CH_3$	113—114 iso-PrOH	92	$C_{11}H_{14}BrNO_3S$	41.26 (41.21	4.41 4.33	4.37 4.45)
IIIi	2-Cl	167—170[c] MeOH	73	$C_8H_7BrClNO_3S$	.....		
IIIj	2-Br	179—180 MeOH	67	$C_8H_7Br_2NO_3S$	26.91 (26.95	1.98 2.02	3.92 3.94)
IIIk	2-SCH_3	179—180 EtOH	82	$C_9H_{10}BrNO_3S_2$	33.34 (33.44	3.11 3.15	4.32 4.51)
IIIl	2-SO_2CH_3	167—171 MeOH	34	$C_9H_{10}BrNO_5S_2$	30.35 (30.38	2.83 2.94	3.93 3.83)

a) Ref. 9, mp 129—131°C. *b*) Ref. 11, mp 153—156°C. *c*) Ref. 12, mp 169°C.

5-(2-Bromoacetyl)-3-methoxy-*N*-methylbenzenesulfonamide (IIIm)——This compound was prepared from IIm (2.5 g) in the same manner as described for IIIa—l. Recrystallization from EtOH afforded IIIm (2.9 g, 87%), mp 133—134°C. *Anal.* Calcd for $C_{10}H_{12}BrNO_4S$: C, 37.28; H, 3.75; N, 4.35. Found: C, 37.28; H, 3.52; N, 4.41.

General Procedure for the Synthesis of I (Compounds Ia, If—z)——a) A solution of 0.023 mol of the appropriate III and 0.05 mol of the requisite IV in 50 ml of methyl ethyl ketone was refluxed for 1—4 h. The reaction mixture was cooled to 0°C, and the precipitated *N*-substituted amine hydrobromide was filtered off. The filtrate was evaporated to dryness. The residue was purified by column chromatography (silica gel, 100 g; eluent, either benzene–AcOEt=10: 1 or $CHCl_3$–MeOH=95: 5) to give an amorphous solid which was employed for the subsequent reaction. The precursor amino ketone (V) for Iu was crystallized. Yield, 72%. mp 138—139°C (from EtOH). *Anal.* Calcd for $C_{26}H_{30}N_2O_5S$: C, 64.71; H, 6.27; N, 5.80. Found: C, 64.51; H, 6.41; N, 5.86. IR ν_{max}^{KBr} cm^{-1}: 3280, 3170, 1680, 1590. ^{1}H-NMR (DMSO-d_6) δ: 1.17 (3H, d, J=6.6 Hz), 2.65 (3H, s), 2.8—3.5 (3H, m), 3.69 (3H, s), 3.80 (2H, br s), 3.8—4.5 (4H, m), 6.88 (4H, br s), 7.1—7.5 (6H, m), 7.48 (2H, br s), 8.38 (1H, d, J=1.5 Hz), 8.45 (1H, dd, J=1.5 and 7.7 Hz).

b) A solution of 0.02 mol of V in 50 ml of MeOH was treated portionwise with 0.76 g of $NaBH_4$ at 0—5°C. After being stirred at room temperature for 2 h, the mixture was concentrated and the residue was

extracted with AcOEt. The AcOEt extract was washed with water and dried over Na_2SO_4. After removal of the solvent, the oily residue was used without further purification for the subsequent step. The desired product (VI) showed a single spot on TLC (solvent system, AcOEt–benzene=2: 1). Characterization was based on the absence of the IR absorption band (1680—1695 cm^{-1}) of the amino ketone (V).

c) A mixture of 0.1 mol of VI, 100 ml of MeOH and 1 g of 10% Pd-C was hydrogenated at room temperature until H_2 uptake ceased. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was either recrystallized or converted into the HCl salt. The physical data and total yields of I (Ia, f—z) prepared by the above method are shown in Table I.

General Procedure for the Synthesis of VII——A solution of 0.03 mol of the appropriate III in 200 ml of MeOH was treated portionwise with 6.5 g of $NaBH_4$ at 5°C. The mixture was stirred at room temperature for 2.5 h, then concentrated, and the residue was dissolved in a mixture of AcOEt and H_2O. The AcOEt layer was separated, washed with water and dried over Na_2SO_4. After removal of the solvent, the residue was purified by recrystallization. The physical data and yields of VIIa—d are given below.

2-Chloro-5-(1,2-epoxyethyl)benzenesulfonamide (VIIa): Yield, 56%. mp 145—146°C (from MeOH). *Anal.* Calcd for $C_8H_8ClNO_3S$: C, 41.12; H, 3.45; N, 5.99. Found: C, 41.06; H, 3.56; N, 6.06.

2-Bromo-5-(1,2-epoxyethyl)benzenesulfonamide (VIIb): Yield, 69%. mp 139—141°C (from MeOH). *Anal.* Calcd for $C_8H_8BrNO_3S$: C, 34.55; H, 2.90; N, 5.04. Found: C, 34.46; H, 2.84; N, 5.11.

5-(1,2-Epoxyethyl)-2-methylthiobenzenesulfonamide (VIIc): Yield, 60%. mp 143—146°C (from iso-PrOH). *Anal.* Calcd for $C_9H_{11}NO_3S_2$: C, 44.07; H, 4.52; N, 5.71. Found: C, 44.12; H, 4.42; N, 5.64.

5-(1,2-Epoxyethyl)-2-methylsulfonylbenzenesulfonamide (VIId): Yield, 51%. mp 83—85°C (from EtOH). *Anal.* Calcd for $C_9H_{11}NO_5S_2$: C, 38.98; H, 4.00; N, 5.05. Found: C, 38.82; H, 3.96; N, 5.15.

General Procedure for the Synthesis of I (Compounds Ib—e)——A solution of 0.01 mol of VII and 1.5 g of 1-methyl-3-phenylpropylamine[10] in 50 ml of MeOH was refluxed for 8—16 h. The reaction mixture was evaporated to dryness, and the residue was purified by column chromatography (silica gel, 100 g; eluent, $CHCl_3$–MeOH=95: 5) to give I as an amorphous solid. The solid was either crystallized or converted into the HCl salt. The physical data and yields of I (Ib—e) prepared by the above method are given in Table I.

Separation of a Diastereomeric Mixture of 5-[1-Hydroxy-2-[*N*-benzyl-3-(2-methoxyphenyl)-1-methylpropylamino]ethyl]-2-methylbenzenesulfonamide (VIII) into VIII-A and VIII-B——VIII (10 g), obtained as a gum by the general procedure was separated by column chromatography (silica gel, 500 g; eluent, benzene–AcOEt=5: 1) to give 4.3 g of VIII-A as the first fraction, 3.5 g of a mixture of VIII-A and VIII-B as the second fraction and 1.1 g of VIII-B as the third fraction. VIII-A: mp 98—100°C (from iso-PrOH). *Anal.* Calcd for $C_{27}H_{34}N_2O_4S$: C, 67.19; H, 7.10; N, 5.80. Found: C, 67.12; H, 7.14; N, 5.92. ^{1}H-NMR ($CDCl_3$) δ: 1.02 (3H, d, J=6.6 Hz), 1.4—2.1 (2H, m), 2.2—3.1 (6H, m), 2.63 (3H, s), 3.46, 3.88 (2H, q, J=13.1 Hz), 3.80 (3H, s), 4.60 (1H, dd, J=9.7 and 4.4 Hz), 4.8 (2H, m), 6.7—7.6 (11H, m), 7.88 (1H, d, J=2.0 Hz). VIII-B: oil. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (3H, d, J=6.8 Hz), 1.3—2.2 (2H, m), 2.2—3.0 (6H, m), 2.56 (3H, s), 3.62 (2H, br s), 3.77 (3H, s), 4.30 (1H, dd, J=9.5 and 4.5 Hz), 4.6 (2H, m), 6.6—7.5 (1H, m), 7.79 (1H, br s).

5-[1-Hydroxy-2-[3-(2-methoxyphenyl)-1-methylpropylamino]ethyl]-2-methylbenzenesulfonamide (Ir-A and Ir-B)——Hydrogenation of VIII-A (4.3 g) was carried out according to the general procedure for the preparation of I. The resulting free base was converted into the HCl salt. Recrystallization from iso-PrOH gave 2.9 g of Ir-A, mp 176—177°C. *Anal.* Calcd for $C_{20}H_{29}ClN_2O_4S$: C, 56.00; H, 6.81; N, 6.53. Found: C, 55.96; H, 6.87; N, 6.62. ^{1}H-NMR (CD_3OD) δ: 1.40 (3H, d, J=6.4 Hz), 1.7—2.4 (2H, m), 2.6—3.0 (2H, m), 2.65 (3H, s), 3.1—3.4 (3H, m), 3.81 (3H, s), 4.8—5.2 (1H, m). 6.8—7.3 (4H, m), 7.37 (1H, d, J=7.7 Hz), 7.55 (1H, dd, J=7.7 and 1.6 Hz), 8.04 (1H, d, J=1.6 Hz). Ir-B was prepared from VIII-B (1.1 g) in the same manner as Ir-A. Recrystallization from iso-PrOH afforded 0.7 g of Ir-B, mp 151—153°C. *Anal.* Calcd for $C_{20}H_{29}ClN_2O_4S$: C, 56.00; H, 6.81; N, 6.53. Found: C, 55.99; H, 7.10; N, 6.51. ^{1}H-NMR (CD_3OD) δ: 1.42 (3H, d, J=6.6 Hz), 1.7—2.4 (2H, m), 2.6—3.0 (2H, m), 2.65 (3H, s), 3.1—3.4 (3H, m), 3.81 (3H, s), 4.8—5.2 (1H, m), 6.8—7.3 (4H, m), 7.37 (1H, d, J=8.9 Hz), 7.55 (1H, dd, J=8.9 and 1.6 Hz), 8.03 (1H, d, J=1.6 Hz).

Separation of a Diastereomeric Mixture of 5-[1-Hydroxy-2-[2-(2-methoxyphenoxy)-1-methylamino]ethyl]-2-methylbenzenesulfonamide (Iu) into Iu-A and Iu-B——A suspension of 100 g of Iu in 200 ml of EtOH was stirred for 1 h at room temperature. The undissolved crystalline mass was filtered off. The collected crystals were recrystallized four times from EtOH to give 7.5 g of Iu-B, mp 153—154°C. *Anal.* Calcd for $C_{19}H_{26}N_2O_2S$: C, 57.85; H, 6.64; N, 7.10. Found: C, 57.72; H, 6.60; N, 6.98. ^{1}H-NMR (CD_3OD) δ: 1.22 (3H, d, J=6.6 Hz), 2.64 (3H, s), 2.6—3.1 (2H, dd, J_{gem}=11.9 Hz, J_{vic}=4.2 and 6.7 Hz), 3.0—3.3 (1H, m), 3.7—4.1 (2H, m), 3.81 (3H, s), 4.7—4.8 (1H, m), 7.30 (1H, d, J=7.7 Hz), 7.49 (1H, dd, J=7.7 and 1.5 Hz), 8.00 (1H, d, J=1.5 Hz). The mother liquor obtained above after filtration of the first crystals of Iu-B was allowed to stand overnight at room temperature. The precipitated crystals were collected by filtration. Repeated recrystallizations from EtOH afforded 20.6 g of Iu-A, mp 145—147°C. *Anal.* Calcd for $C_{19}H_{26}N_2O_2S$: C, 57.85; H, 6.64; N, 7.10. Found: C, 57.75; H, 6.68; N, 7.06. ^{1}H-NMR (CD_3OD) δ: 1.15 (3H, d, J=6.3 Hz), 2.63 (3H, s), 2.89 (2H, dd, J=7.0 and 5.7 Hz), 3.0—3.2 (1H, m), 3.7—4.1 (2H, m), 3.75 (3H, s), 4.7—4.8 (1H, m), 6.89 (4H, br s), 7.30 (1H, d, J=7.9 Hz), 7.47 (1H, dd, J=7.9 and 1.5 Hz), 8.00 (1H, d, J=1.5 Hz).

General Procedure for the Synthesis of IV——A mixture of 0.1 mol of either the appropriate substituted

benzylacetone or phenoxyacetone, 100 ml of MeOH and 0.5 g of PtO_2 was stirred at room temperature until H_2 uptake ceased. The catalyst was removed by filtration, and the filtrate was concentrated. The residual oil was purified by distillation. The physical data and yields of IV prepared by the above method are given below.

N-Benzyl-1-methyl-3-(2-methoxyphenyl)propylamine: Yield, 66%. bp 153—155°C (0.4 mmHg).
N-Benzyl-1-methyl-2-(2-methoxyphenoxy)ethylamine: Yield, 56%. bp 140—145°C (0.1 mmHg).
N-Benzyl-1-methyl-2-(3-methoxyphenoxy)ethylamine: Yield, 42%. bp 150—154°C (0.3 mmHg).
N-Benzyl-1-methyl-2-(4-methoxyphenoxy)ethylamine: Yield, 76%. bp 175—178°C (0.4 mmHg).
N-Benzyl-1-methyl-2-(2-ethoxyphenoxy)ethylamine: Yield, 49%. bp 152—155°C (0.1 mmHg).

The following amines, required for preparation of V, were prepared by the literature procedures: 1-methyl-3-phenylpropylamine,[10] *N*-benzyl-1-methyl-3-phenylpropylamine,[15] *N*-benzyl-1-methyl-2-phenoxyethylamine,[16] and *N*-benzyl-1-methyl-2-(2-hydroxyphenoxy)ethylamine.[17]

3′-Methoxy-5′-nitroacetophenone——To a solution of 21.5 g of 3-hydroxy-5-nitrobenzoic acid[18] and 9.2 g of NaOH in 60 ml of H_2O was added dropwise 76 g of $(CH_3)_2SO_4$ at 95°C. During the addition, it was necessary to keep the reaction mixture basic by further addition of 50% aqueous NaOH. The resulting mixture was refluxed for 1 h. After cooling, the reaction mixture was acidified with conc. HCl, and the precipitates were collected. Recrystallization from iso-PrOH afforded 3-methoxy-5-nitrobenzoic acid (15 g, 65%), mp 167—169°C. *Anal.* Calcd for $C_8H_7NO_5$: C, 48.74; H, 3.58; N, 7.10. Found: C, 48.58; H, 3.61; N, 7.00.

A mixture of 46 g of the above acid and 28 ml of $SOCl_2$ was heated until HCl evolution ceased. The excess of $SOCl_2$ was distilled off, and the resulting chloride was used immediately in the next reaction.

Conversion of the acid chloride to the desired acetophenone was carried out according to the procedure of Mathieson.[19] Recrystallization from iso-PrOH afforded 3′-methoxy-5′-nitroacetophenone (31 g, 69%), mp 66—67°C. *Anal.* Calcd for $C_9H_9NO_4$: C, 55.39; H, 4.65; N, 7.18. Found: C, 55.23; H, 4.61; N, 7.13.

Substituted 3′-Aminoacetophenones——3′-Aminoacetophenones substituted with benzyloxy,[20a] bromo,[20b] chloro,[20b] methoxy,[20c] methyl,[20d] and propyl[20e] groups at the 4′-position and 2′-methoxy-5′-aminoacetophenone[19] were prepared by the cited procedures. 3′-Amino-2′-methoxyacetophenone was prepared from 2′-methoxy-3′-nitroacetophenone[21] according to the reduction procedure of Oelschläger.[20b] A similar reduction of 3′-methoxy-5′-nitroacetophenone gave 3′-amino-5′-methoxyacetophenone.

3′-Amino-2′-methoxyacetophenone (Hydrochloride): Yield, 67%. mp 130—132°C (from EtOH). *Anal.* Calcd for $C_9H_{12}ClNO_2$: C, 53.61; H, 6.00; N, 6.95. Found: C, 53.67; H, 5.96; N, 7.13.

3′-Amino-5′-methoxyacetophenone (Hydrochloride): Yield, 64%. mp 148—151°C (from EtOH). *Anal.* Calcd for $C_9H_{12}ClNO_2$: C, 53.61; H, 6.00; N, 6.95. Found: C, 53.69; H, 6.02; N, 7.18.

α- and β-Adrenoceptor Blocking Activities in Anesthetized Rats——Male Wistar rats were used. α-Blocking activity was estimated from the antagonism of the increase in mean blood pressure induced by *l*-phenylephrine (10 μg/kg *i.v.*) in pentolinium (5 mg/kg *i.v.*)-treated rats anesthetized with urethane. β-Blocking activity[22] was estimated from the antagonism of the increase in heart rate induced by *l*-isoproterenol (0.1 μg/kg *i.v.*) in vagotomized (reserpine-pretreated) rats anesthetized with pentobarbital.

Antihypertensive Activity in Conscious SHR——Male spontaneously hypertensive rats of the Okamoto-Aoki strain (SHR; 25 to 35 weeks of age) were used. Systolic blood pressure was measured indirectly by the tail-cuff method using a programed electrosphygmomanometer (Narco Biosystems, Inc.). Test compounds were dissolved or suspended in 0.5% methylcellulose solution.

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References and Notes

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