Novel Phenoxyalkylamine Derivatives. VII.[1] Synthesis and Pharmacological Activities of 2-Alkoxy-5-[(phenoxyalkylamino)alkyl]benzenesulfonamide Derivatives

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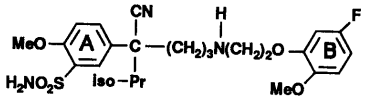
To find a novel α-blocker with high α-blocking selectivity against dopamine D_2-receptor affinity, we performed structural modification of the alkylene chains and the substituents on two benzene rings of 2-alkoxy-5-[(phenoxyalkylamino)alkyl]benzenesulfonamide derivatives. The modification of the alkylene chain between the amino moiety in the center of the molecule and the benzene ring (ring A) was found to be the most significant. 5-[2-[[2-(5-Fluoro-2-methoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide (II-4), which possesses 1-methylethyl as the alkylene chain, exhibited high α-blocking selectivity as well as potent α-blocking activity.

Keywords phenoxyalkylamine; 2-alkoxy-5-[(phenoxyalkylamino)alkyl]benzenesulfonamide; α-blocking activity; D_2-receptor affinity; structure–activity relationship; Hansch–Fujita method

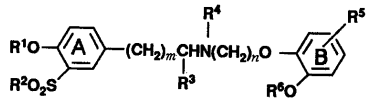
We previously[1] synthesized several α-[(phenoxyethylamino)propyl]-α-phenylacetonitrile derivatives with an aminosulfonyl group on the benzene ring (ring A) and observed the compound (I) with a fluorine atom on the benzene ring (ring B) to exhibit α-blocking activity about as potent as that of prazosin,[2] a typical α-blocker. I, however, exhibited high dopamine D_2-receptor affinity in addition to potent α-blocking activity. The high dopamine D_2-receptor affinity may occasion side effects such as nausea and emesis caused by gastrointestinal failure and hormonal failure due to disorder of prolactin secretion. Thus, I is not suitable for clinical use.

To find a more potent α-blocker having high α-blocking selectivity against dopamine D_2-receptor affinity, structural modification was made of I, as the lead compound, and 2-alkoxy-5-[(phenoxyalkylamino)alkyl]-benzenesulfonamide derivatives (II) possessing no cyano group were designed. The synthesis and pharmacological activity of II are discussed in the following.

Synthesis The desired compounds (II) were synthesized



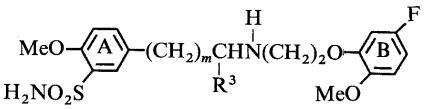
I



II

Chart 1

TABLE I. Physicochemical and Pharmacological Data for 5-[[[2-(5-Fluoro-2-methoxyphenoxy)ethyl]amino]alkyl]-2-methoxybenzenesulfonamides (I, II-1—7)



Compd. No.	*m*	R^3	Method	Yield (%)	Salt	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H	N	α (pA_2)	D_2 (pK_i)	α-Selectivity ($10^{pA_2-pK_i}$)
II-1	1	H	A	21	Free	201—205	DMF	$C_{18}H_{23}FN_2O_5S$	54.26 (53.87)	5.82 5.89	7.03 6.83)	7.28	6.18	13
II-2	2	H	A	31	Free	Oil	—	$C_{19}H_{25}FN_2O_5S$	412.1468[a] (412.1474)			6.35	6.11	1.7
II-3	3	H	A	21	Free	Oil	—	$C_{20}H_{27}FN_2O_5S$	426.1625[a] (426.1623)			7.74	7.42	2.1
II-4	1	Me	B	50	HCl	257—259	EtOH–H_2O	$C_{19}H_{25}FN_2O_5S$·HCl	50.83 (50.74	5.84 5.71	6.24 6.12)	9.50	6.88	417
II-5	2	Me	B	66	Free	Oil	—	$C_{20}H_{27}FN_2O_5S$	426.1625[a] (426.1643)			7.14	6.33	6.5
II-6	3	Me	B	41	HCl	181—183	EtOH	$C_{21}H_{29}FN_2O_5S$·HCl	52.88 (52.64	6.34 6.39	5.87 5.83)	7.81	7.69	1.3
II-7	1	Et	A	11	HCl	216—219	MeOH	$C_{20}H_{27}FN_2O_5S$·HCl	51.89 (51.63	6.10 6.12	6.05 6.04)	8.43	5.88	355
I	C(CN)	(iso-Pr)	$(CH_2)_3$									8.60	8.88	0.52

a) High resolution mass data. The upper values are calculated and the lower ones are those found.

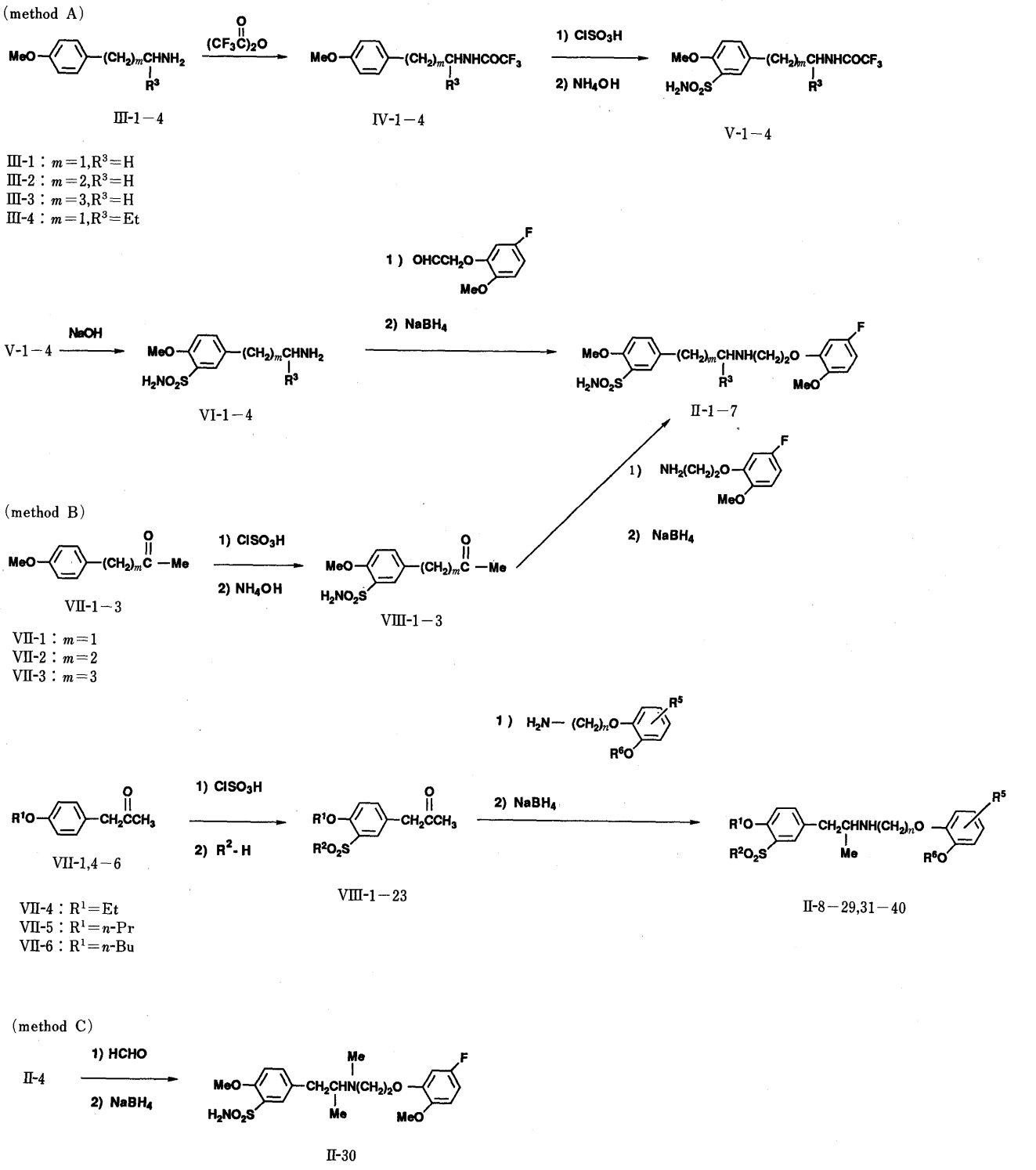


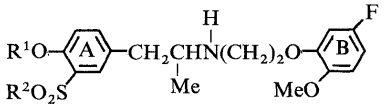
Chart 2

as shown in Chart 2.

The compounds (II-1—7) having the alkylene chain (*m*) were prepared by methods A and B. Phenylalkylamines (III-1—4) were protected by a trifluoroacetyl group, aminosulfonated, and deprotected to give the compounds (VI-1—4) which were reductively condensed with 2-(5-fluoro-2-methoxyphenoxy)acetaldehyde to give the desired compounds (II-1—3, 7) (method A). Aryl ketones (VII-1—3) were aminosulfonated to give sulfonamides which were reductively condensed with 2-(5-fluoro-2-methoxyphenoxy)ethylamine to give the desired compounds (II-4—6) (method B).

The compounds (II-8—29, 31—40) whose substituents (R^1, R^2, R^5, R^6) and alkylene chain lengths (*n*) were modified, were prepared in a manner similar to method B. The compound (II-30) with R^4=Me was obtained from II-4 by the Eschweiler–Clarke reaction (method C). The physicochemical properties of II are summarized in Tables I—IV.

TABLE II. Physicochemical and Pharmacological Data for 2-Alkoxy-5-[2-[[2-(5-fluoro-2-methoxyphenoxy)ethyl]amino]propyl]benzenesulfonamides (II-4, 8—27)



Compd. No.	R^1	R^2	Yield[a] (%)	Salt[b]	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H	N	α (pA_2)	D_2 (pK_i)	α-Selectivity ($10^{pA_2-pK_i}$)
II-8	Et	NH_2	35	HCl	240—243	MeOH	$C_{20}H_{27}FN_2O_5S \cdot HCl$	51.89 (51.60)	6.10 6.01	6.05 5.98)	9.05	6.78	186
II-9	*n*-Pr	NH_2	83	HCl	228—232	MeOH–H_2O	$C_{21}H_{29}FN_2O_5S \cdot HCl$	52.88 (52.81)	6.34 6.35	5.87 5.85)	7.97	6.77	16
II-10	*n*-Bu	NH_2	82	HCl	227—231	MeOH–H_2O	$C_{22}H_{31}FN_2O_5S \cdot HCl$	53.81 (53.56)	6.57 6.73	5.71 5.65)	8.24	6.74	32
II-11	Me	NHMe	44	o	234—235	EtOH–H_2O	$C_{20}H_{27}FN_2O_5S \cdot C_2H_2O_4$	51.16 (51.03)	5.66 5.67	5.42 5.39)	9.34	7.03	204
II-12	Me	NHEt	47	o	207—209	EtOH–H_2O	$C_{21}H_{29}FN_2O_5S \cdot C_2H_2O_4$	52.07 (51.77)	5.89 5.92	5.28 5.08)	9.14	7.03	129
II-13	Me	NH–*n*-Pr	39	f	168—170	MeOH–Et_2O	$C_{22}H_{31}FN_2O_5S \cdot 1/2C_4H_4O_4$	56.24 (55.98)	6.49 6.27	5.46 5.40)	9.10	6.89	162
II-14	Me	NH–*n*-Bu	34	o	173—175	MeOH	$C_{23}H_{33}FN_2O_5S \cdot C_2H_2O_4$	53.75 (53.66)	6.32 6.27	5.01 4.99)	9.08	7.11	93
II-15	Me	NH–*n*-hexyl	24	o	142—146	EtOH–Et_2O	$C_{25}H_{37}FN_2O_5S \cdot C_2H_2O_4$	55.28 (55.06)	6.70 6.51	4.77 4.62)	8.19	7.56	4.3
II-16	Me	NH–*n*-octyl	44	o	143—145.5	EtOH	$C_{27}H_{41}FN_2O_5S \cdot C_2H_2O_4$	56.66 (56.45)	7.05 7.10	4.56 4.37)	7.33	7.20	1.3
II-17	Me	NH–*n*-decyl	50	o	144—146	iso-PrOH	$C_{29}H_{45}FN_2O_5S \cdot C_2H_2O_4$	57.93 (57.84)	7.37 7.51	4.36 4.35)	6.26	6.77	0.31
II-18	Me	$NH(CH_2)_2OH$	31	f	180—183	MeOH	$C_{21}H_{29}FN_2O_6S \cdot 1/2C_4H_4O_4$	53.44 (53.69)	5.87 6.07	5.38 5.44)	8.96	6.79	148
II-19	Me	NHbenzyl	52	f	131—133	EtOH–H_2O	$C_{26}H_{31}FN_2O_5S \cdot C_4H_4O_4$	58.24 (57.96)	5.70 5.64	4.53 4.31)	8.64	7.04	40
II-20	Me	NMe_2	44	o	225—227	EtOH–H_2O	$C_{21}H_{29}FN_2O_5S \cdot C_2H_2O_4$	52.07 (51.93)	5.89 5.92	5.28 5.30)	9.42	6.96	288
II-21	Me	NEt_2	50	o	165.5–168	MeOH	$C_{23}H_{33}FN_2O_5S \cdot C_2H_2O_4$	53.75 (53.55)	6.32 6.04	5.01 4.94)	8.96	7.16	63
II-22	Me	N(*n*-hexyl)$_2$	27	f	121—123	iso-PrOH	$C_{31}H_{49}FN_2O_5S \cdot C_4H_4O_4$	60.32 (59.96)	7.67 7.87	4.02 4.01)	5.63	6.40	0.17
II-23	Me	1-Pyrrolidinyl	48	o	205—207	MeOH	$C_{23}H_{31}FN_2O_5S \cdot C_2H_2O_4$	53.95 (53.83)	5.98 5.96	5.03 5.01)	9.33	7.19	138
II-24	Me	1-Piperidyl	55	o	182—184	MeOH	$C_{24}H_{33}FN_2O_5S \cdot C_2H_2O_4$	54.73 (54.56)	6.18 6.05	4.91 4.89)	9.10	7.05	112
II-25	Me	4-Morpholinyl	36	o	173—174.5	MeOH	$C_{23}H_{31}FN_2O_6S \cdot C_2H_2O_4$	52.44 (52.35)	5.81 5.81	4.89 4.68)	9.21	7.02	155
II-26	Me	4-Thiomorpholinyl	48	o	181—183	MeOH	$C_{23}H_{31}FN_2O_5S_2 \cdot C_2H_2O_4$	51.01 (50.71)	5.65 5.59	4.76 4.66)	9.08	7.32	58
II-27	Me	4-Methyl-1-piperazinyl	49	Free	Oil	—	$C_{24}H_{34}FN_3O_5S$	495.2203[c] (495.2210)			8.38	7.14	17
II-4	Me	NH_2									9.50	6.88	417

a) All compounds were prepared by method B. b) o, oxalate; f, fumarate. c) High resolution mass data. The upper values are calculated and the lower ones are those found.

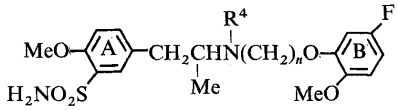
Results and Discussion

α-Blocking activity was assessed in isolated rabbit thoracic aorta and expressed as pA_2 by the method of Furchgott.[3] Dopamine D_2-receptor affinity was tested in isolated rat brain striata and shown as pK_i by the method of Cheng and Prusoff.[4] The data obtained are listed in Tables I—IV.

Effects of the Alkylene Chain between Ring A and the Amino Moiety at the Molecular Center (Table I) We have heretofore mainly performed structural modification of the alkylene chain having a cyano group for the chain between ring A and the amino moiety at the molecular center,[1,5,6] because this series of structural modifications was started from verapamil.[7] Here, we investigate the effect of changing the alkylene chain with the cyano group to a straight or branched one on the α-blocking activity and dopamine D_2-receptor affinity. Other structures were kept the same as in the lead compound (I).

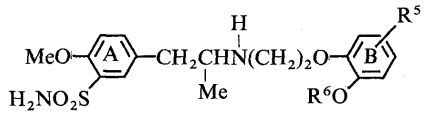
First, α-blocking activity was studied. Among the compounds (II-1—3) with straight alkylene chains, II-3 with butylene exhibited the most potent activity. The introduction of a methyl group to these alkylene chains increased the activity. The activity of II-4 was shown to be nearly 170 times as potent as that of II-1 bearing no methyl group. This indicates that the introduction of a methyl group to the ethylene chain greatly increases the potency. Replacement of the methyl group by an ethyl group (II-7) led to remarkable decrease in the activity.

TABLE III. Physicochemical and Pharmacological Data for 5-[2-[[2-(5-Fluoro-2-methoxyphenoxy)alkyl]amino]propyl]-2-methoxybenzenesulfonamides (II-4, 28—30)



Compd. No.	n	R^4	Method	Yield (%)	Salt	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H	N	α (pA_2)	D_2 (pK_i)	α-Selectivity ($10^{pA_2-pK_i}$)
II-28	3	H	B	57	HCl	214—216	EtOH	$C_{20}H_{27}FN_2O_5S \cdot HCl$	51.89 (51.52	6.10 6.14	6.05 5.98)	7.19	5.52	47
II-29	4	H	B	19	HCl	192—193	EtOH	$C_{21}H_{29}FN_2O_5S \cdot HCl$	52.88 (52.67	6.34 6.10	5.87 5.75)	6.55	5.54	10
II-30	2	Me	C	21	Free	119—121	EtOH	$C_{20}H_{27}FN_2O_5S$	56.32 (56.08	6.38 6.37	6.57 6.55)	7.80	5.10	501
II-4	2	H										9.50	6.88	417

TABLE IV. Physicochemical and Pharmacological Data for 5-[2-[[2-(2-Alkoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamides (II-4, 31—40)



Compd. No.	R^5	R^6	Yield[a] (%)	Salt	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H	N	α (pA_2)	D_2 (pK_i)	α-Selectivity ($10^{pA_2-pK_i}$)
II-31	5-F	Et	48	HCl	236—241	EtOH–H_2O	$C_{20}H_{27}FN_2O_5S \cdot HCl$	51.89 (51.85	6.10 6.02	6.05 5.97)	9.69	7.63	115
II-32	5-F	*n*-Pr	13	HCl	199—202	MeOH	$C_{21}H_{29}FN_2O_5S \cdot HCl$	52.88 (52.91	6.34 6.37	5.87 5.65)	9.18	7.60	38
II-33	5-F	*n*-Bu	17	HCl	207—209	MeOH	$C_{22}H_{31}FN_2O_5S \cdot HCl$	53.81 (53.57	6.57 6.57	5.71 5.54)	8.98	7.62	23
II-34	5-F	*n*-Hexyl	16	HCl	206—209	EtOH	$C_{24}H_{35}FN_2O_5S \cdot HCl$	55.53 (55.53	6.99 7.01	5.40 5.40)	8.38	6.57	65
II-35	5-F	*n*-Octyl	20	HCl	198—201	EtOH	$C_{26}H_{39}FN_2O_5S \cdot HCl$	57.08 (56.71	7.37 7.45	5.12 5.18)	7.35	6.21	14
II-36	5-F	*n*-Decyl	17	HCl	197—200	EtOH	$C_{28}H_{43}FN_2O_5S \cdot HCl$	58.47 (58.37	7.71 7.38	4.87 4.68)	6.31	5.94	2.3
II-37	3-F	Me	39	HCl	211—212	MeOH	$C_{19}H_{25}FN_2O_5S \cdot HCl \cdot 1/2H_2O$	49.83 (50.03	5.94 5.81	6.12 6.12)	8.10	6.44	46
II-38	4-F	Me	28	HCl	257—259	EtOH–H_2O	$C_{19}H_{25}FN_2O_5S \cdot HCl$	50.83 (50.78	5.84 5.65	6.24 6.22)	8.48	6.18	200
II-39	5-Cl	Me	45	HCl	260—264	EtOH–H_2O	$C_{19}H_{25}ClN_2O_5S \cdot HCl$	49.04 (48.76	5.63 5.64	6.02 6.12)	8.88	6.46	263
II-40	H	Me	21	HCl	265—268	EtOH–H_2O	$C_{19}H_{26}N_2O_5S \cdot HCl$	52.95 (52.68	6.31 6.39	6.50 6.43)	9.05	6.56	309
II-4	5-F	Me									9.50	6.88	417

a) All compounds were prepared by method B.

Generally, a change in the activity by modification of the alkylene chain may contribute to the hydrophobicity or bulkiness of the molecule. In this case, the steric size of the alkylene chain appeared to affect the activity, since any compound with a straight chain having an even number of carbon atoms showed relatively higher activity and the compound with a straight chain showed a potency of activity differing from that of the corresponding compound with a branched chain consisting of the same number of carbon atoms.

Next, the activity of dopamine D_2-receptor affinity was studied. Among the compounds (II-1—3) with a straight alkylene chain, II-3 with a butylene chain exhibited the most potent activity. The length of the alkylene chain was not correlated to the activity and great increase in the activity was observed in II-3 with butylene. This result indicates that steric size affects activity, as was also observed for α-blocking activity. The introduction of a methyl group to these alkylene chains increased the activity, but the degree of increase was less than that noted for α-blocking activity. Replacement of the methyl group by an ethyl group (II-7) led to remarkable decrease in the activity.

The steric size of the alkylene chain was found to affect

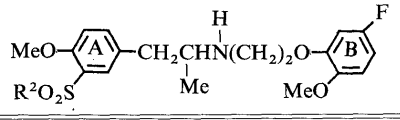
both α-blocking activity and D_2-receptor affinity. However, since the degree of contribution differed, the ratio of α-blocking activity to D_2-receptor affinity was calculated. The compound with a methyl (II-4) or ethyl group (II-7) on the ethylene chain was found to have high selectivity. II-4 exhibited potent α-blocking activity and also high α-blocking selectivity. Thus, the ethylene chain with a methyl group is the most favorable.

Effects of the Substituent OR^1 on Ring A (Table II) Changing of the carbon chain from a methoxy group (II-4) to ethoxy (II-8), propoxy (II-9), and butoxy groups (II-10) led to decrease in α-blocking activity, but no change in dopamine D_2-receptor affinity. No substituent superior to the methoxy group was found in α-blocking activity or α-blocking selectivity.

This result indicates that α-blocking activity is influenced by hydrophobicity or steric size of the substituent OR^1 but that dopamine D_2-receptor affinity is not.

Effects of the Sulfonamide Substituent R^2 on Ring A (Table II) First, α-blocking activity was examined. Though a number of monosubstituted, disubstituted, and cyclic sulfonamide compounds were synthesized, no compound was superior to the unsubstituted sulfonamide compound (II-4). On closer examination, the following was found. In monoalkylsulfonamide compounds (II-11—17), the longer the alkyl group, the lower was the activity, and the activity of the compound (II-17) with *n*-decylamino group was about 1000 times less potent than that of II-4. Replacement of the alkyl group by a 2-hydroxyethyl (II-18) or a benzyl group (II-19) gave no satisfactory result. The activity of dialkylsulfonamide compounds (II-20—22) also

Table V. α-Blocking Activity and Physicochemical Parameters of R^2-Substituted Compounds (II)



Compd. No.	R^2	π[a]	pA_2 Obsd.	pA_2 Eq. 1 Calcd.	pA_2 Eq. 1 (Δ)[b]
II-4	NH_2	−1.82[c]	9.50	9.18	(0.32)
II-11	NHMe	−1.39	9.34	9.20	(0.14)
II-12	NHEt	−0.97	9.14	9.18	(−0.04)
II-13	NH-*n*-Pr	−0.52	9.10	9.09	(0.01)
II-14	NH-*n*-Bu	0.00	9.08	8.93	(0.15)
II-15	NH-*n*-hexyl	0.95	8.19	8.42	(−0.23)
II-16	NH-*n*-octyl	1.90	7.33	7.67	(−0.34)
II-17	NH-*n*-decyl	2.85	6.26	6.67	(−0.41)
II-18	$NH(CH_2)_2OH$	−2.77	8.96	8.95	(0.01)
II-19	NHbenzyl	0.19	8.64	8.85	(−0.21)
II-20	NMe_2	−0.78[c]	9.42	9.15	(0.27)
II-21	NEt_2	0.08	8.96	8.89	(0.07)
II-22	$N(n\text{-hexyl})_2$	3.92	5.63	5.24	(0.39)
II-23	1-Pyrrolidinyl	−0.22	9.33	9.01	(0.32)
II-24	1-Piperidyl	0.25	9.10	8.82	(0.28)
II-25	4-Morpholinyl	−1.37	9.21	9.20	(0.01)
II-26	4-Thiomorpholinyl	−0.35	9.08	9.05	(0.03)
II-27	4-Methyl-1-piperazinyl	−1.92	8.38	9.17	(−0.79)

a) Each value was that of the substituent SO_2R^2 calculated according to the equations in the Experimental section, unless otherwise noted. *b*) Δ, the difference between observed and calculated values. *c*) Taken from ref. 9.

became less with lengthening of the alkyl chains. Cyclic sulfonamide compounds (II-23—26), except for 4-methyl-1-piperazinyl analog (II-27), exhibited relatively high potency, but less than that of unsubstituted sulfonamide compound.

To clarify the physicochemical background of the effects of substituent R^2 on α-blocking activity, we performed quantitative structure–activity analyses by the Hansch–Fujita method.[8] Activity was found to be parabolically related to the hydrophobic parameter π, as shown in Eq. 1. In Eq. 1, the number in parenthesis is the 95% confidence interval, n is the number of data points, r is the correlation coefficient, s is the standard deviation and $F_{2,15}$ is the F-ratio between the variances of calculated and observed activities. The π value of each substituent SO_2R^2 was calculated by equation in the Experimental section and is listed in Table V.

$$pA_2 = -0.14\pi^2 - 0.40\pi + 8.93 \quad (1)$$
$$(0.05)\quad (0.11)\quad (0.21)$$
$$(n=18,\ r=0.96,\ s=0.32,\ F_{2,15}=90.89)$$

Equation 1 shows that optimum π value is −1.43. The π value of the most potent compound (II-4) is −1.82, which is slightly lower than the optimum value but not inconsistent with the present analysis.

Next, our attention was focused on the D_2-receptor affinity. The *n*-hexylsulfonamide compound (II-15) was the most potent. Because variation in activity among these compounds (II-4, II-8—27) was small, quantitative structure–activity analysis gave no satisfactory correlation equation. However, the activity appeared to be influenced by hydrophobicity or steric size of the substituent R^2.

Though monosubstituted, disubstituted, and cyclic sulfonamide compounds in addition to the unsubstituted analog were synthesized, no compound superior to the unsubstituted one in α-blocking activity or α-blocking selectivity could be found.

Effects of the Alkylene Chain between Ring B and the Amino Moiety at the Molecular Center and Substituent R^4 (Table III) Lengthening of the alkylene chain from ethylene (II-4) to propylene (II-28) and butylene (II-29) led to remarkable decrease in α-blocking activity. Decrease was also observed in D_2-receptor affinity, but no compound having more α-blocking selectivity than that with ethylene could be found.

N-Methylation of the amino group at the molecular center did not influence α-blocking selectivity but decreased α-blocking activity. This indicates that the tertiary amino group is not favorable for both α-blocking selectivity and α-blocking activity.

Effects of Substituents R^5 and OR^6 on Ring B (Table IV) As the substituent OR^6 group at the 2-position on ring B, alkoxy (II-31—36) from ethoxy to *n*-decyloxy in addition to the methoxy (II-4) were examined. The ethoxy compound (II-31) was the most potent in α-blocking activity, while the ethoxy, propoxy (II-32) or butoxy group (II-33) was the most potent in D_2-receptor affinity. However, no compound superior to II-4 could be found in α-blocking selectivity.

As the second substituent R^5 on the ring B, 3-fluoro (II-37), 4-fluoro (II-38), 5-chloro (II-39) and hydrogen

(II-40) in addition to 5-fluoro (II-4) were included. However, no compound superior to II-4 in α-blocking activity or α-blocking selectivity could be detected.

In summary, removal of the cyano group from the lead compound (I) decreased not only D_2-receptor affinity but also α-blocking activity. However, as a result of successive structural modifications, 5-[2-[[2-(5-fluoro-2-methoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide hydrochloride (II-4) with both potent α-blocking activity and high α-blocking selectivity was found. Since II-4 has one asymmetric carbon atom, two optical isomers exist. The synthesis and pharmacological activity of the two isomers will be reported in future.

Experimental

α-Blocking Activity The rabbit thoracic aorta was cut helically and mounted vertically in an organ bath. The pA_2 values were calculated from dose ratios estimated graphically from the parallel shifts of concentration–response curves to noradrenaline.[5]

Dopamine D_2 Receptor Binding Assay Dopamine D_2 receptor binding assays were performed according to the method of Urwyler and Coward.[9] Brain striata were isolated from male Wistar rats to obtain D_2 receptor preparations. ^{3}H-Spiperone was used as a ligand. Non-specific binding of ^{3}H-spiperone was determined in the presence of 10 μM sulpiride. The dissociation constants (K_i) of the test compounds were calculated by the equation of Cheng and Prusoff.[4]

Calculation of Hydrophobic Parameter π The π values of substituents other than those presented in ref. 10 were estimated from the following equations.

SO_2NHMe, SO_2NHEt, SO_2NH–*n*-Pr, SO_2NH–*n*-Bu, SO_2NH–*n*-hexyl, SO_2NHbenzyl, SO_2NMe_2, SO_2NEt_2, SO_2N(*n*-hexyl)$_2$, SO_2(1-pyrrolidinyl) and SO_2(1-piperidyl) Groups: As described in ref. 11, the logarithm of the partition coefficient (log *P*) of amines ($NR_1R_2R_3$) can be estimated from Eq. 2.

$$\log P = 0.962\pi + 4.034\sigma_i + 0.270[E_s'^c(R_1) + E_s'^c(R_2)] - 1.251 \quad (2)$$
$$[E_s'^c(R_1) \geqq E_s'^c(R_2) \geqq E_s'^c(R_3)]$$

Where π and σ_i are the sum of the hydrophobic π values for aliphatic groups and the inductive electronic σ_i values, respectively, and $E_s'^c(R_i)$ is a modified steric constant derived from the Dubois E_s' value considering the branching effect of *N*-substituents. On the basis of the assumption that the most bulky substituent R_3 is benzenesulfonyl in Eq. 2, the log *P* of $Ph-SO_2NR_1R_2$ is given by the following Eq. 3.

$$\log P(Ph-SO_2NR_1R_2) = 0.962[\pi(R_1) + \pi(R_2) + \pi(Ph-SO_2)] + 4.034[\sigma_i(R_1) + \sigma_i(R_2) + \sigma_i(Ph-SO_2)] + 0.270[E_s'^c(R_1) + E_s'^c(R_2)] - 1.251 \quad (3)$$

If the π value of a substituent ($SO_2NR_1'R_2'$) has been observed, the unknown π value of the substituent ($SO_2NR_1R_2$) can be estimated from Eq. 4.

$$\pi(SO_2NR_1R_2) = \pi(SO_2NR_1'R_2') + [\log P(Ph-SO_2NR_1R_2) - \log P(Ph-SO_2NR_1'R_2')] = \pi(SO_2NR_1'R_2') + 0.962[\pi(R_1) + \pi(R_2) - \pi(R_1') - \pi(R_2')] + 4.034[\sigma_i(R_1) + \sigma_i(R_2) - \sigma_i(R_1') - \sigma_i(R_2')] + 0.270[E_s'^c(R_1) + E_s'^c(R_2) - E_s'^c(R_1') - E_s'^c(R_2')] \quad (4)$$

The known π values of SO_2NH_2 and SO_2NMe_2 groups[10] were used as the standard $SO_2NR_1'R_2'$ to give the calculated π value from Eq. 4.

SO_2NH–*n*-octyl and SO_2NH–*n*-decyl Groups: The values were estimated from Eq. 5, where *m* is the number of carbon atoms.

$$\pi(SO_2NH\text{–}n\text{-octyl or } SO_2NH\text{–}n\text{-decyl}) = \pi(SO_2NH\text{–}n\text{-hexyl}) + (m-6)/2 \times [\pi(SO_2NH\text{–}n\text{-hexyl}) - \pi(SO_2NH\text{–}n\text{-butyl})] \quad (5)$$

$SO_2NH(CH_2)_2OH$ Group: Equation 6 was used.

$$\pi[SO_2NH(CH_2)_2OH] = \pi(SO_2NHEt) + \pi(OH/\text{aliphatic})^{12} \quad (6)$$

SO_2(4-morpholinyl) and SO_2(4-thiomorpholinyl) Groups: From Eqs. 7 and 8, respectively.

$$\pi[SO_2(4\text{-morpholinyl})] = \pi[SO_2(1\text{-piperidyl})] + [[\log P(4\text{-phenylmorpholine})^{13} - \log P(\text{benzene})^{13}] - \pi(1\text{-piperidyl/benzene})]^{10} \quad (7)$$

$$\pi[SO_2(4\text{-thiomorpholinyl})] = \pi[SO_2(4\text{-morpholinyl})] + [f(\text{–S–})^{14} - f(\text{–O–})^{14}] \quad (8)$$

SO_2(4-methyl-1-piperazinyl) Group: Through a process similar to that used to derive Eq. 4, Eq. 9 for SO_2(4-methyl-1-piperazinyl) group was formulated, where R_1 is methyl. Here, the π value of SO_2(1-piperazinyl) was given by Eq. 10.

$$\pi[SO_2(4\text{-methyl-1-piperazinyl})] = \pi[SO_2(1\text{-piperazinyl})] + 0.962\pi(Me) + 4.034\sigma_i(Me) + 0.270[E_s'^c(Me) - E_s'^c(H)] \quad (9)$$

$$\pi[SO_2(1\text{-piperazinyl})] = \pi[SO_2(1\text{-piperidyl})] + [\log P(\text{piperidine})^{13} - \log P(\text{cyclohexane})^{13}] \quad (10)$$

Compounds Melting points were measured with a Yanaco MT-3 melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded using a Hitachi 270-30 spectrophotometer. High-resolution mass spectra were obtained on a JMS-DX300 mass spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured with a JNM FX-90Q spectrometer using tetramethylsilane as an internal standard. Merck Aluminiumoxide 90 (70—230 mesh) was used for column chromatography.

5-[2-[[2-(5-Fluoro-2-methoxyphenoxy)ethyl]amino]ethyl]-2-methoxybenzenesulfonamide (II-1) A mixture of 5-(2-aminoethyl)-2-methoxybenzenesulfonamide hydrochloride (VI-1, 1.0 g, 3.7 mmol) and Et_3N (0.5 ml, 3.6 mmol) in MeOH (35 ml) was refluxed for 1 h, then 2-(5-fluoro-2-methoxyphenoxy)acetaldehyde (0.67 g, 3.6 mmol) was added to the above solution, and the mixture was refluxed for 10 min. After the mixture was chilled in an ice bath, $NaBH_4$ (0.3 g, 7.9 mmol) was added. The mixture was stirred at room temperature for 30 min, and then concentrated. The residue was acidified with aq. HCl and washed with Et_2O. The aqueous layer was made alkaline with K_2CO_3 and extracted with AcOEt. The AcOEt layer was washed with water and dried over Na_2SO_4. After removal of the solvent, the residue was recrystallized from dimethylformamide (DMF) to give II-1 (0.3 g, 21%) as pale yellow crystals, mp 201—205 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.56—3.36 (5H, m, CH_2CH_2NH), 2.92 (2H, t, J=5.5 Hz, $NHCH_2CH_2O$), 3.71, 3.87 (each 3H, s, OCH_3), 4.02 (2H, t, J=5.5 Hz, $NHCH_2CH_2O$), 6.46—7.04 (5H, m, Ar–H, SO_2NH_2), 7.09 (1H, d, J=8.5 Hz, Ar–H^3), 7.41 (1H, dd, J=8.5, 2 Hz, Ar–H^4), 7.59 (1H, d, J=2 Hz, Ar–H^6).

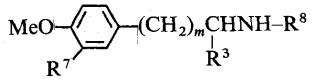
Compounds II-2, 3, 7 were also prepared in a similar manner to that described above. The physicochemical properties of the products are listed in Table I.

(±)-5-[2-[[2-(5-Fluoro-2-methoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzenesulfonamide Hydrochloride (II-4) A solution of 2-methoxy-5-(2-oxopropyl)benzenesulfonamide (VIII-1, 12.0 g, 49 mmol) and 2-(5-fluoro-2-methoxyphenoxy)ethylamine (9.6 g, 52 mmol) in MeOH (360 ml) was refluxed for 1 h and the solvent was removed under reduced pressure. To the residue was added benzene (50 ml) and the solvent was evaporated to dryness under reduced pressure to remove water azeotropically. To a solution of the residue in MeOH (360 ml) was added $NaBH_4$ (3.0 g, 79 mmol) under ice-cooling and the mixture was stirred at room temperature for 3 h. The precipitates were collected by filtration and dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with water, dried over Na_2SO_4, and acidified with alcoholic HCl. The precipitates were collected by filtration and recrystallized from a mixture of EtOH and water (7:3) to give II-4 (11.0 g, 50%) as colorless needles, mp 257—259 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.17 (3H, d, J=6.5 Hz, CH_3), 2.50—3.68 (5H, m, CH_2CHNCH_2), 3.75, 3.90 (each 3H, s, OCH_3), 4.37 (2H, t, J=5.5 Hz, $NHCH_2CH_2O$), 6.60—7.10 (5H, m, Ar–H, SO_2NH_2), 7.16 (1H, d, J=8.5 Hz, Ar–H^3), 7.45 (1H, dd, J=8.5, 2 Hz, Ar–H^4), 7.64 (1H, d, J=2 Hz, Ar–H^6), 9.39 (2H, br s, NH_2^+).

Compounds II-5, 6, 8—29, 31—40 were prepared in a similar manner to that described above. The physicochemical properties of the products are listed in Tables I—IV.

(±)-5-[2-[*N*-[2-(5-Fluoro-2-methoxyphenoxy)ethyl]-*N*-methylamino]propyl]-2-methoxybenzenesulfonamide (II-30) A formaldehyde solution (37%, 2.9 ml) was added to a solution of II-4 (2.4 g, 5.8 mmol) in MeOH (72 ml) and the mixture was refluxed for 1 h. After the mixture was chilled in an ice bath, $NaBH_4$ (0.55 g, 15 mmol) was added. The mixture was

TABLE VI. Physicochemical Properties of (4-Methoxyphenyl)alkylamines (IV-1—4, V-1—4, VI-1—4)



Compd. No.	R^3	R^7	R^8	m	Yield (%)	mp (°C) (Recrystn. solvent)	IR ν_{max}^{KBr} cm^{-1} C=O	IR S=O	Formula	Analysis (%) Calcd (Found) C	H	N
IV-1	H	H	$COCF_3$	1	73	80.5—81 (iso-Pr_2O)	1704	—	$C_{11}H_{12}F_3NO_2$	53.44 (53.17)	4.89 4.98	5.67 5.65)
IV-2	H	H	$COCF_3$	2	90	Oil	1712[a]	—	$C_{12}H_{14}F_3NO_2$	261.0977[b] (261.0983)		
IV-3	H	H	$COCF_3$	3	83	67—68 (iso-Pr_2O)	1702	—	$C_{13}H_{16}F_3NO_2$	56.72 (56.72	5.86 5.97	5.09 5.12)
IV-4	Et	H	$COCF_3$	1	87	82—83 (iso-Pr_2O)	1702	—	$C_{13}H_{16}F_3NO_2$	56.72 (56.55	5.86 5.96	5.09 4.91)
V-1	H	SO_2NH_2	$COCF_3$	1	47	165—166 (EtOH)	1710	1328	$C_{11}H_{13}F_3N_2O_4S$	40.49 (40.55	4.02 4.26	8.59 8.68)
V-2	H	SO_2NH_2	$COCF_3$	2	49	139—143 (EtOH–Et_2O)	1706	1318	$C_{12}H_{15}F_3N_2O_4S$	340.0705[b] (340.0694)		
V-3	H	SO_2NH_2	$COCF_3$	3	32	145—147 (EtOH)	1704	1308	$C_{13}H_{17}F_3N_2O_4S$	44.06 (43.77	4.84 4.99	7.91 7.88)
V-4	Et	SO_2NH_2	$COCF_3$	1	35	189—192 (EtOH)	1700	1340	$C_{13}H_{17}F_3N_2O_4S$	44.06 (43.85	4.84 5.09	7.91 7.91)
VI-1	H	SO_2NH_2	H	1	52	263—266 (H_2O)	—	1328	$C_9H_{14}N_2O_3S\cdot HCl$	40.52 (40.46	5.67 5.50	10.50 10.60)
VI-2	H	SO_2NH_2	H	2	79	255—257 (EtOH–H_2O)	—	1336	$C_{10}H_{16}N_2O_3S\cdot HCl$	42.78 (42.83	6.10 6.15	9.98 9.97)
VI-3	H	SO_2NH_2	H	3	26	178—181 (H_2O)	—	1332	$C_{11}H_{18}N_2O_3S\cdot HCl$	258.1038[b] (258.1035)		
VI-4	Et	SO_2NH_2	H	1	33	246—250 (MeOH)	—	1322	$C_{11}H_{18}N_2O_3S\cdot HCl$	44.82 (44.56	6.50 6.29	9.50 9.42)

a) Film. *b*) High resolution mass data. The upper values are calculated and the lower ones are those found.

stirred at room temperature for 1 h and then concentrated. The solution of the residue in AcOEt was washed with water and dried over Na_2SO_4. After removal of the solvent, the residue was purified by column chromatography on alumina using $CHCl_3$–MeOH (99 : 1) as an eluent to give II-30 (0.52 g, 21%) as colorless crystals. The crystals were recrystallized from EtOH to give colorless prisms, mp 119—121 °C. ^{1}H-NMR (DMSO-d_6) δ: 0.90 (3H, d, J=6 Hz, CH_3), 2.30 (3H, s, NCH_3), 2.36—3.08 (5H, m, CH_2CHNCH_2), 3.73, 3.87 (each 3H, s, OCH_3), 3.99 (2H, t, J=6 Hz, $NHCH_2C\underline{H}_2O$), 6.52—7.00 (5H, m, Ar–H, SO_2NH_2), 7.06 (1H, d, J=8.5 Hz, Ar–H^3), 7.40 (1H, dd, J=8.5, 2 Hz, Ar–H^4), 7.57 (1H, d, J=2 Hz, Ar–H^6).

***N*-[2-(4-Methoxyphenyl)ethyl]trifluoroacetamide (IV-1)** Trifluoroacetic anhydride (35 ml, 0.25 mol) was added dropwise to a solution of *p*-methoxyphenethylamine (12.5 g, 83 mmol) in CH_2Cl_2 (120 ml) at room temperature. The mixture was stirred at the same temperature for 30 min and then concentrated. The residue was dissolved in Et_2O, washed twice with water and dried over Na_2SO_4. After removal of the solvent, the residue was recrystallized from iso-Pr_2O to give IV-1 (14.9 g, 73%) as colorless crystals, mp 80.5—81 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.82 (2H, t, J=7 Hz, $C\underline{H}_2CH_2N$), 3.52 (2H, q, J=7 Hz, $CH_2C\underline{H}_2N$), 3.79 (3H, s, OCH_3), 6.14—6.48 (1H, br s, NH), 6.86, 7.11 (each 2H, d, J=9 Hz, Ar–H).

Compounds IV-2—4 were prepared in a similar manner to that described above. The physicochemical properties of the products are listed in Table VI.

5-[2-(Trifluoroacetylamino)ethyl]-2-methoxybenzenesulfonamide (V-1) Chlorosulfonic acid (12 ml, 0.18 mol) was added dropwise to a solution of IV-1 (14.9 g, 60 mmol) in CH_2Cl_2 (45 ml) at below 0 °C and the mixture was refluxed for 2 h. After cooling, the mixture was poured into ice water and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with water and dried over Na_2SO_4. After removal of the solvent, 5-[2-(trifluoroacetylamino)ethyl]-2-methoxybenzenesulfonyl chloride (13.5 g) was given as a pale yellow oil. This oil was dissolved in tetrahydrofuran (THF) (20 ml) and added dropwise to conc. NH_4OH (30 ml). The mixture was stirred at room temperature for 30 min and the solvent was removed under reduced pressure. The residue was recrystallized from EtOH to give V-1 (9.2 g, 47%) as colorless needles, mp 165—166 °C. ^{1}H-NMR (CD_3OD) δ: 2.84 (2H, t, J=7.5 Hz, $C\underline{H}_2CH_2N$), 3.49 (2H, t, J=7.5 Hz, $CH_2C\underline{H}_2N$), 3.96 (3H, s, OCH_3), 7.12 (1H, d, J=8.5 Hz, Ar–H^3), 7.43 (1H, dd, J=8.5, 2 Hz, Ar–H^4), 7.71 (1H, d, J=2 Hz, Ar–H^6).

Compounds V-2—4 were prepared in a similar manner to that described above. The physicochemical properties of the products are listed in Table VI.

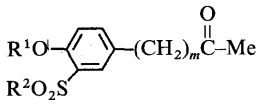
5-(2-Aminoethyl)-2-methoxybenzenesulfonamide hydrochloride (VI-1) Aqueous NaOH solution (10%, 60 ml) was added to a suspension of V-1 (10.0 g, 31 mmol) in MeOH (100 ml) and the mixture was stirred at room temperature for 30 min. To the mixture was added conc. HCl under ice-cooling. The precipitates were collected by filtration and recrystallized from water to give VI-1 (4.2 g, 52%) as colorless crystals, mp 263—266 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.95 (4H, br s, CH_2CH_2N), 3.89 (3H, s, OCH_3), 6.90 (2H, br s, SO_2NH_2), 7.15 (1H, d, J=8.5 Hz, Ar–H^3), 7.46 (1H, dd, J=8.5, 2 Hz, Ar–H^4), 7.62 (1H, d, J=2 Hz, Ar–H^6), 8.15 (3H, br s, NH_3^+).

Compounds VI-2—4 were prepared in a similar manner to that described above. The physicochemical properties of the products are listed in Table VI.

2-Methoxy-5-(2-oxopropyl)benzenesulfonamide (VIII-1) *p*-Methoxyphenylacetone (10.0 g, 61 mmol) was added dropwise to chlorosulfonic acid (28.5 ml, 0.43 mol) at below 0 °C and the mixture was stirred at room temperature for 2 h. The mixture was poured into ice water and extracted with AcOEt. The AcOEt layer was washed with water and dried over Na_2SO_4. After removal of the solvent, 2-methoxy-5-(2-oxopropyl)benzenesulfonyl chloride (11.4 g) was given as a yellow solid. Conc. NH_4OH (10 ml) was added dropwise to a solution of the above solid in THF (114 ml). The mixture was stirred at room temperature for 2 h and concentrated. To the residue was added water, the precipitates were collected by filtration and recrystallized from MeOH to give VIII-1 (7.9 g, 53%) as pale brown prisms, mp 194—196 °C. ^{1}H-NMR (CD_3OD) δ: 2.18 (3H, s, CH_3), 3.79 (2H, s, CH_2), 3.97 (3H, s, OCH_3), 7.14 (1H, d, J=8.5 Hz, Ar–H^3), 7.40 (1H, dd, J=8.5, 2.5 Hz, Ar–H^4), 7.67 (1H, d, J=2.5 Hz, Ar–H^6).

Compounds VIII-2—23 were prepared in a similar manner to that

TABLE VII. Physicochemical Properties of 2-Alkoxy-5-(oxoalkyl)benzenesulfonamides (VIII-1—23)



Compd. No.	R^1	R^2	m	Yield (%)	mp (°C) (Recrystn. solvent)	IR ν_{max}^{KBr} cm^{-1} C=O	IR ν_{max}^{KBr} cm^{-1} S=O	Formula	Analysis (%) Calcd (Found) C	H	N
VIII-1	Me	NH_2	1	52	194—196 (MeOH)	1706	1338	$C_{10}H_{13}NO_4S$	49.37 (49.32	5.39 5.44	5.76 5.63)
VIII-2	Et	NH_2	1	51	158—159 (MeOH)	1706	1336	$C_{11}H_{15}NO_4S$	51.35 (51.41	5.88 5.97	5.44 5.54)
VIII-3	*n*-Pr	NH_2	1	26	105.5—107 (EtOH)	1712	1332	$C_{12}H_{17}NO_4S$	53.12 (53.01	6.32 6.51	5.16 5.15)
VIII-4	*n*-Bu	NH_2	1	24	107—109 (AcOEt–iso-Pr_2O)	1712	1336	$C_{13}H_{19}NO_4S$	54.72 (54.58	6.71 6.52	4.91 4.84)
VIII-5	Me	NHMe	1	39	103.5—104.5 (AcOEt)	1722	1314	$C_{11}H_{15}NO_4S$	51.28 (51.35	5.78 5.88	5.72 5.44)
VIII-6	Me	NHEt	1	69	Oil	1716	1326[a]	$C_{12}H_{17}NO_4S$	271.0878[b] (271.0879)		
VIII-7	Me	NH–*n*-Pr	1	65	Oil	1716	1324[a]	$C_{13}H_{19}NO_4S$	285.1035[b] (285.1038)		
VIII-8	Me	NH–*n*-Bu	1	45	Oil	1714	1328[a]	$C_{14}H_{21}NO_4S$	299.1191[b] (299.1180)		
VIII-9	Me	NH–*n*-hexyl	1	24	Oil	1716	1328[a]	$C_{16}H_{25}NO_4S$	327.1504[b] (327.1495)		
VIII-10	Me	NH–*n*-octyl	1	66	Oil	1714	1328[a]	$C_{18}H_{29}NO_4S$	355.1817[b] (355.1813)		
VIII-11	Me	NH–*n*-decyl	1	71	Oil	1716	1328[a]	$C_{20}H_{33}NO_4S$	383.2130[b] (383.2146)		
VIII-12	Me	$NH(CH_2)_2OH$	1	68	Oil	1714	1324[a]	$C_{12}H_{17}NO_5S$	287.0827[b] (287.0799)		
VIII-13	Me	NHbenzyl	1	45	86—87 (EtOH)	1718	1316	$C_{17}H_{19}NO_4S$	61.24 (61.02	5.74 5.92	4.20 4.14)
VIII-14	Me	NMe_2	1	53	Oil	1720	1330[a]	$C_{12}H_{17}NO_4S$	271.0879[b] (271.0883)		
VIII-15	Me	NEt_2	1	67	Oil	1720	1326[a]	$C_{14}H_{21}NO_4S$	299.1191[b] (299.1179)		
VIII-16	Me	N(*n*-hexyl)$_2$	1	65	Oil	1720	1332[a]	$C_{22}H_{37}NO_4S$	411.2443[b] (411.2435)		
VIII-17	Me	1-Pyrrolidinyl	1	44	104—105 (iso-PrOH)	1722	1324	$C_{14}H_{19}NO_4S$	56.55 (56.29	6.44 6.48	4.71 4.59)
VIII-18	Me	1-Piperidyl	1	41	103—105 (iso-PrOH)	1716	1322	$C_{15}H_{21}NO_4S$	57.86 (57.74	6.80 6.51	4.50 4.36)
VIII-19	Me	4-Morpholinyl	1	44	Oil	1718	1342[a]	$C_{14}H_{19}NO_5S$	313.0984[b] (313.0987)		
VIII-20	Me	4-Thiomorpholinyl	1	35	118—122 (EtOH)	1710	1338	$C_{14}H_{19}NO_4S_2$	51.04 (50.70	5.81 6.07	4.25 4.15)
VIII-21	Me	4-Methyl-1-piperazinyl	1	19	108—109 (iso-PrOH)	1726	1340	$C_{15}H_{22}N_2O_4S$	55.19 (55.13	6.79 6.86	8.58 8.48)
VIII-22	Me	NH_2	2	77	176—179 (EtOH)	1690	1336	$C_{11}H_{15}NO_4S$	51.35 (51.20	5.88 5.80	5.44 5.51)
VIII-23	Me	NH_2	3	19	115—116 (EtOH)	1720	1310	$C_{12}H_{17}NO_4S$	53.12 (52.96	6.32 6.18	5.16 5.01)

a) Film. *b*) High resolution mass data. The upper values are calculated and the lower ones are those found.

described above. The physicochemical properties of the products are listed in Table VII.

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