The intercepts differed significantly ($p < 0.005$) but the slopes differ only at the 50% level. Our results using silylated columns more closely resemble those of Haggerty[6] than those of McCall.[7]

Further there is good correlation when comparing V_R (silylated) with V_R (nonsilylated) at pH 4.0 for sulfonamides

$$\log V_R \text{ (silylated)} = 0.975\ (0.05) \log V_R \text{ (nonsilylated)} - 0.44\ (0.04) \quad (95)$$
$$n = 11;\ r = 0.994;\ s = 0.09$$

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Adrenergic Sulfonanilides. 4. Centrally Active β-Adrenergic Agonists

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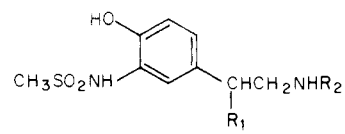
The central nervous system (CNS) activities of a number of soterenol analogs have been investigated, and several of these compounds possessed potent morphine antagonistic and anorexiant properties. The CNS activity of these compounds was enhanced by certain lipophilic [e.g., 1,1-dimethyl-2-phenethyl (**43**) or cyclopropyl (**40** and **44**)] nitrogen substituents; however, minor structural changes on either the aromatic or side-chain moieties drastically reduced central activity. Toxicity in this series was related to the inherent α-adrenergic stimulating component (direct or indirect).

While screening for potential narcotic antagonists, we observed that phenethylamine **40**, a weak β-adrenergic agonist, possessed potent morphine antagonism properties (ED_{50} = 0.21 mg/kg). Compound **40** as well as other appropriately substituted analogs of soterenol[1] was observed to have a multiplicity of CNS activities. The presence or absence of central activity seems to depend upon the nature of the nitrogen substituent; certain nitrogen substituents, especially cyclopropyl, allow pseudo-catechol derivatives which are normally peripheral agents devoid of central properties to elicit a variety of central activities.

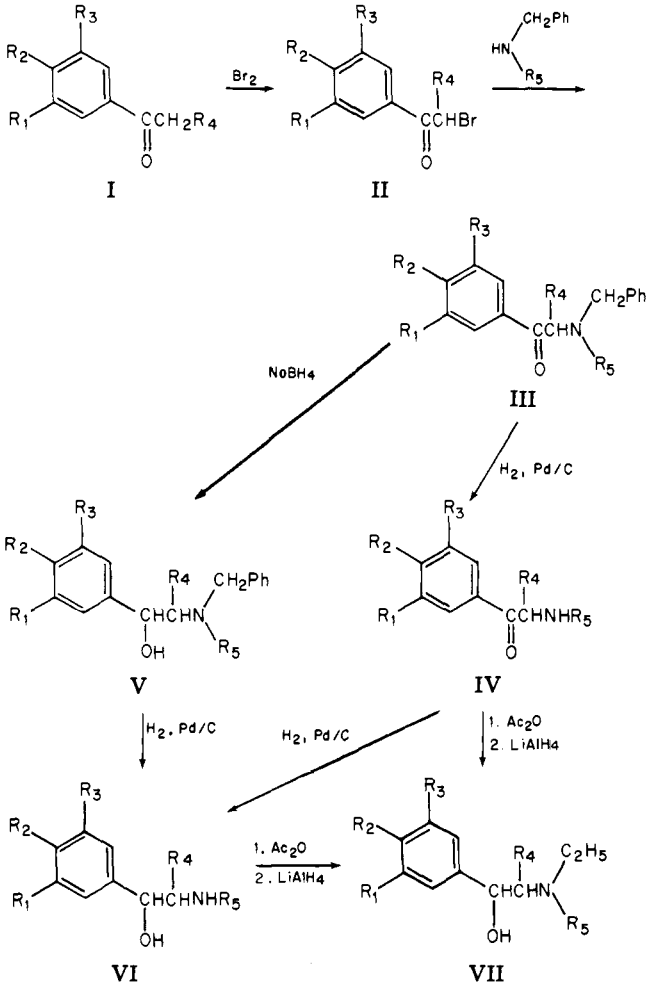


soterenol, R_1 = OH; R_2 = $CH(CH_3)_2$
40, R_1 = H; R_2 = c-C_3H_5
43, R_1 = OH; R_2 = $C(CH_3)_2CH_2C_6H_5$
44, R_1 = OH; R_2 = c-C_3H_5

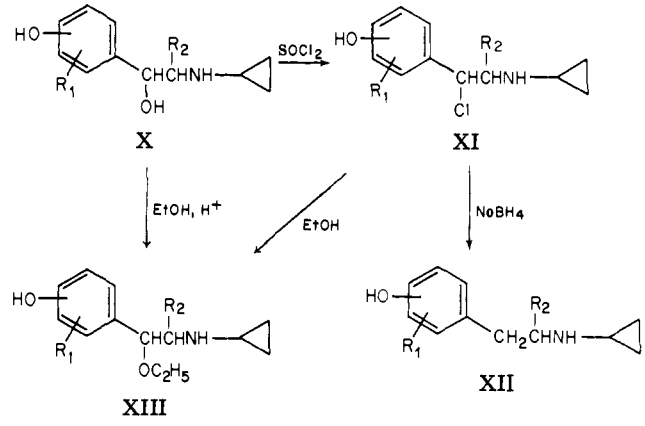
Compounds **40**, **43**, and **44** (all β agonists) are potent anorexiants ("free-feeding" method,[2] 5.5, 11, and 22 times *d*-amphetamine, respectively), and phenylethanolamines **43** and **44** are also active as narcotic antagonists (ED_{50} = 18.8 and 0.275 mg/kg, respectively), thus indicating CNS involvement. The concept of central β-adrenergic involvement is suggested by the work of Leibowitz[3] who has shown that β-"satiety" receptors may exist in the hypothalamus and play a role in regulating food intake. Furthermore, the existence of β-adrenergic receptors has been demonstrated in the rat hypothalamus[4] and cerebral cortex.[5] These receptors were sensitive to both norepinephrine and isoproterenol, causing significant increases in cyclic adenosine 3',5'-monophosphate (cAMP). As **43** is not a CNS stimulant, but is a potent anorexiant, and as **40** and **44** do not conform to normal amphetamine structure–activity relationships (SAR),[6] these compounds are not amphetamine-like. Instead, their anorexiant activity may be mediated via β-adrenergic receptors.

These observations prompted us to study a variety of related compounds in order to determine what structural parameters are necessary for central nervous system (CNS)

Scheme I



Scheme II



activity and the relationship of β-adrenergic agonism and CNS activity, with particular emphasis placed on morphine antagonism.

Chemistry. The phenylethanolamines shown in Table III were prepared according to the procedures outlined in Scheme I. Aminoacylmethanesulfonanilides (III, R_1 or R_2 = $NHSO_2CH_3$,Table II) were prepared by methods described earlier.[1,7] Compounds **54** and **55** which contain 1-methylcyclopropylamino and 1-benzylcyclopropylamino moieties, respectively, were prepared in a similar manner using 1-benzylcyclopropylamine[8] and *N*-benzyl-1-methylcyclopropylamine (prepared from 1-methylcyclopropylamine[9] via reduction of the Schiff's base formed with benzaldehyde). The related aminoacylphenol intermediates (III, R_1 or R_2 = OH) were also prepared by this route. The amino ketones (III) were catalytically hydrogenated to either IV or VI. In those cases where the aromatic nucleus of III contained a hydrogen-labile function (e.g., **36**, R_3 = Cl), the slow catalytic hydrogenation of the carbonyl was replaced by a sodium borohydride reduction followed by a rapid catalytic debenzylation to VI. For those phenylethanolamines which have two adjacent asymmetric carbon atoms (VI, R_4 = alkyl), the erythro racemic modifications were obtained as determined by NMR ($J \approx 3$ Hz).[1] Tertiary amines (VII) were prepared via $LiAlH_4$ reduction of intermediate acetamides of VI. The low yield (17%) of **51** is indicative of the difficulties encountered during $LiAlH_4$ reduction of compounds containing this 3,4-"pseudo-catechol" system.

The single sulfamide derivative **66** was prepared by a similar procedure to that used for the methanesulfonanilides, using *N*,*N*-dimethylsulfamoyl chloride rather than methanesulfonyl chloride.

Compound **44** was resolved by treatment of the racemic base in acetone with (+)-mandelic acid to form a crystalline, although hygroscopic salt. After several recrystallizations of the salt from acetone followed by acidification of an acetone suspension, pure (-) enantiomer **45** was obtained. The (+) enantiomer (**46**) was obtained in a similar manner using (-)-mandelic acid as the resolving agent. Either racemic base or base from the mother liquors of the separation of **45** was used.

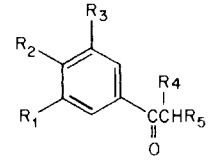
Phenethylamines were prepared according to Scheme II. Phenylethanolamines (X) were treated with $SOCl_2$[10] to give the corresponding β-chloro intermediates XI. On reaction with $SOCl_2$, the erythro alcohol **50** gave a 50:50 mixture of erythro (J_{H_1,H_2} = 2.6 Hz) and threo (J_{H_1,H_2} = 10 Hz) racemates (XI). Hydrogenolysis of XI by $NaBH_4$[11] gave the corresponding phenethylamimes (XII) in reasonable yield. β-Ethoxy analogs (XIII) were obtained by treating XI with ethanol or, in the case of the labile alcohol **65**, by simply heating with ethanolic HCl.

Biological Results and Discussion. Several of the arylethylamines possessed significant analgetic or morphine antagonistic activity (Table IV). The most active analgetic compounds in the phenylquinone writhing test were the phenylethylamine **40**, the phenylethanolamine **44**, and its (-) isomer **45**. No compound was more potent than either **40** or **44** as a narcotic antagonist. Both compounds were also active in the rat tail flick test, verifying analgetic activity. The very strict SAR of this series was seen in the loss of activity following even limited chemical modification. For instance, addition of a 3'-CH_3 (**52**) or a 3'-Cl (**53**) to the aromatic ring of **44** virtually eliminated CNS activity, as did changing the aromatic nucleus from "pseudo-catechol" (e.g., **40**) to catechol (**61**), possibly due to the lack of metabolic methylation by COMT for the "pseudo-catechols"[14] or to different tissue distributions. Compound **56** in which the hydroxyl group is meta to the sulfonanilide moiety was inactive, as was compound **58** which has no hydroxyl group. An additional "pseudo-catechol" derivative (sulfamide **66**) was a potent narcotic antagonist.

Converting the nitrogen substituent from cyclopropyl to cyclobutyl (**57**) or isopropyl (soterenol) eliminated CNS activity; however, the cyclopropyl group may be substituted in the 1 position with retention of narcotic antagonism activity. The 1-methylcyclopropyl and 1-benzylcyclopropyl analogs (**54**) and **55**, respectively) were active β-adrenergic agonists and narcotic antagonists; however, compound **55** was extremely toxic.

Substitution in the α position of either the phenethylamine or phenylethanolamine series produced inactive

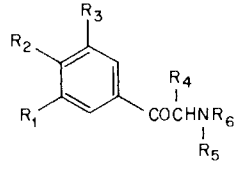
Table I. Aryl Ketones



Compd no.	R_1	R_2	R_3	R_4	R_5	Yield, % (pure)	Recrystn solvent[a]	Mp, °C	Formula	Analyses
1[c]	$MeSO_2NH$	HO	H	H	H	80	A	205-207[b]	$C_9H_{11}NO_4$	C, H, N, S
2[c]	$MeSO_2NH$	HO	H	H	Br	96	B	200-201[b]	$C_9H_{10}BrNO_4S$	C, H, N, S
3[c]	$MeSO_2NH$	HO	Cl	H	H	26	C	208-210[b]	$C_9H_{10}ClNO_4S$	C, H, N, Cl
4[c]	$MeSO_2NH$	HO	Cl	H	Br	26	D	192-193[b]	$C_9H_9BrClNO_3S$	C, H, N, Br, Cl
5[c]	$MeSO_2NH$	$PhCH_2O$	CH_3	H	H	75	D	104.5-105.5	$C_{17}H_{19}NO_4S$	C, H, S
6[d]	$MeSO_2NH$	$PhCH_2O$	CH_3	H	Br	72	A	94-96.5	$C_{17}H_{18}BrNO_4S$	C, H, N
7[e]	$MeSO_2NH$	$PhCH_2O$	H	CH_2CH_3	H	86	A	113.5-116.5[b]	$C_{18}H_{21}NO_4S$	C, H, N
8[e]	$MeSO_2NH$	$PhCH_2O$	H	CH_2CH_3	Br	94	A	95.5-97.5[b]	$C_{18}H_{20}BrNO_4S$	C, H, N
9[c]	$MeSO_2NH$	H	$PhCH_2O$	H	H	91	C	110-113.5[b]	$C_{16}H_{17}NO_4S$	C, H, N, S
10[c]	$MeSO_2NH$	H	HO	H	Br	76[h]	A	190-190.5	$C_9H_{10}BrNO_4S$	C, H, N, S
11[f]	$MeSO_2NH$	H	H	H	H	49	A	96-97.5[b]	$C_9H_{11}NO_3S$	C, H, N, S
12[f]	$MeSO_2NH$	H	H	H	H	79	A	124.5-126[b]	$C_9H_{10}BrNO_3S$	C, H, N, S
13[f]	$MeSO_2NH$	H	H	CH_3	H	57	E	105.5-107[b]	$C_{10}H_{23}NO_3S$	C, H, N, S
14[f]	$MeSO_2NH$	H	H	CH_3	Br	74	A	116.5-118[b]	$C_{10}H_{12}BrNO_3S$	C, H, N, S
15[f]	H	$MeSO_2NH$	H	H	H	75	A	156.5-158.5[b]	$C_9H_{11}NO_3S$	C, H, N, S
16[f]	H	$MeSO_2NH$	H	H	Br	44	E	190-191.5[b]	$C_9H_{10}BrNO_3S$	C, H, N
17[g]	H	$PhCH_2O$	H	H	H	89	E	90-92[b]	$C_{15}H_{14}O_2$	C, H, N
18[g]	H	$PhCH_2O$	H	H	Br	96	F	59-62[b]	$C_{15}H_{13}BrO_2$	C, H, N
19	Me_2NSO_2NH	HO	H	H	H	54	F	153.0-154.0	$C_{10}H_{14}N_2O_4S$	C, H, N, S
20	Me_2NSO_2NH	HO	H	H	Br	58	F	151.0-152.5	$C_{10}H_{13}BrN_2O_4S$	C, H, N, S

[a] A, *i*-PrOH; B, DMF-H_2O; C, dissolved in dilute NaOH and precipitated with HCl; D, EtOAc-petroleum ether (bp 30-60°); E, EtOH; F, *i*-Pr_2O-petroleum ether (bp 30-60°). [b] Uncorrected. [c] Prepared according to the procedures described in ref 7. [d] Prepared by bromination of 5 with phenyltrimethylammonium tribromide in THF. All other phenacyl bromides were prepared by bromination of the corresponding phenones in $CHCl_3$ with Br_2. [e] Reference 7. [f] Reference 1. [g] Reference 12. [h] Crude yield.

Table II. Arylamino Ketones



Compd no.	R_1	R_2	R_3	R_4	R_5	R_6	Yield, % (pure)	Procedure	Recrystn solvent[a]	Mp, °C	Formula	Analyses
21	$MeSO_2NH$	HO	H	H	CH_2Ph	c-C_3H_5	88	1	A	187.0-187.5	$C_{19}H_{22}N_2O_4S\cdot HCl$	
22	$MeSO_2NH$	HO	H	H	H	c-C_3H_5	96	2	B	214.5-216.5	$C_{12}H_{16}N_2O_4S\cdot HCl$	C, H, N, Cl
23[d]	$MeSO_2NH$	HO	H	H	CH_2Ph	c-C_4H_7	90[b]	1		Oil	$C_{27}H_{30}N_2O_4S\cdot HCl$	

24	$MeSO_2NH$	$PhCH_2O$	H	Me	CH_2Ph	c-C_3H_5	40	1	C	136–138[c]	$C_{27}H_{30}N_2O_4$	C, H, N
25	$MeSO_2NH$	$PhCH_2O$	H	Et	CH_2Ph	c-C_3H_5	62	1	D	193–195[c]	$C_{28}H_{32}N_2O_4S$·HCl	C, H, N, Cl
26	$MeSO_2NH$	HO	H	Et	H	c-C_3H_5	88	2	E	227–229[c]	$C_{14}H_{20}N_2O_4S$·HCl	C, H, N, Cl
27	$MeSO_2NH$	HO	Me	H	H	c-C_3H_5	66	2	F	230 dec[c]	$C_{13}H_{18}N_2O_4S$·HCl	C, H, N, Cl
28	$MeSO_2NH$	HO	Cl	H	CH_2Ph	c-C_3H_5	62	1	B	191–192[c]	$C_{19}H_{21}ClN_2O_4S$·HCl	C, H, N, Cl
29	$MeSO_2NH$	HO	H	H	CH_2Ph	1-Me-c-C_3H_4	93	1		Oil	$C_{20}H_{24}N_2O_4S$·HCl	
30	$MeSO_2NH$	HO	H	H	H	1-Me-c-C_3H_4	40	2	B	210–212	$C_{18}H_{18}N_2O_4S$·HCl	C, H, N, Cl
31	$MeSO_2NH$	HO	H	H	H	1-CH_2Ph-c-C_3H_4	35	1	B	185–186	$C_{19}H_{22}N_2O_4S$·HCl	C, H, N, Cl
32	$MeSO_2NH$	H	OCH_2Ph	H	CH_2Ph	c-C_3H_5	78	1	G	185–186	$C_{26}H_{28}N_2O_4S$·HCl	C, H, N
33	$MeSO_2NH$	H	H	Me	CH_2Ph	c-C_3H_5	54	1	H	181–183	$C_{20}H_{24}N_2O_3S$·HCl	C, H, N
34[d]	$MeSO_2NH$	H	H	Me	H	c-C_3H_5	62	2	I	180–183[c]	$C_{13}H_{18}N_2O_3S$·HCl	C, H, N
35[d]	H	HO	Cl	H	CH_2Ph	c-C_3H_5	82[b]	1	J	200 dec[c]	$C_{18}H_{18}NO_2$·HCl	
36	H	HO	Cl	H	H	c-C_3H_5	77	2	F	223–225[c]	$C_{11}H_{12}NO_2$·HCl	C, H, N, Cl
37	H	$PhCH_2O$	H	H	CH_2Ph	c-C_3H_5	74	1	H	69–71	$C_{25}H_{25}NO_2$	C, H, N
38	H	$MeSO_2NH$	H	H	CH_2Ph	c-C_3H_5	41	1	D	198–199	$C_{19}H_{22}N_2O_3S$·HCl	C, H, N
39	Me_2NSO_2NH	HO	H	H	CH_2Ph	c-C_3H_5	80	1	B	188–190[c]	$C_{20}H_{25}N_3O_4S$·HCl	C, H, N, Cl

[a] A, MeOH-*i*-Pr_2O; B, Me_2CO; C, EtOH-*i*-PrOH; D, MeOH; E, EtOH, F, EtOH-Me_2CO; G, EtOH–MeOH; H, *i*-PrOH; I, MeOH-*i*-PrOH-Et_2O; J, MeCN-Et_2O. [b] Crude. [c] Uncorrected. [d] Reduced without further purification.

compounds (41, 49, 50) as did conversion to a tertiary amine (51). Changing β-OH to β-OC_2H_5 (48) in the "pseudo-catechol" series also eliminated activity.

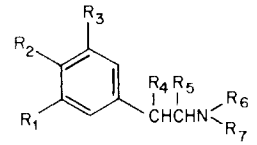
As seen from Table IV, the active narcotic antagonists 43, 44, 45, and 54 were more potent β-adrenergic agonists in vitro than were 40, 55, and 66. It is further apparent that sulfonanilide 43 [*N*-(1,1-dimethyl-2-phenethyl)] was a more potent β-adrenergic agonist than the cyclopropyl compound 44 or the corresponding cyclopropyl sulfamide analog 66 (ratio of β-adrenergic activity on the isolated tracheal spiral is 282:25:1, respectively), whereas 44 was approximately 70 times more potent than 43 as a morphine antagonist and approximately three times more potent than sulfamide 66. Thus, there is no quantitative correlation between β-adrenergic agonist potencies in vitro and morphine antagonism in vivo. Yet none of the potent morphine antagonists are without some degree of β-adrenergic agonism, so the adrenergic component may be necessary but not sufficient. If there is indeed a correlation between the β-adrenergic activity of these compounds and their central effects, one has to consider the probability of metabolic β-hydroxylation of 40 to 44. If β-hydroxylation is indeed a determining factor, lack of morphine antagonism by 42 suggests that this compound is β-hydroxylated to 43 at a lesser rate than 40 is to 44. It is puzzling that among the amine moieties, only the cyclopropylamines appear to be advantageous for *potent* morphine antagonism activity.

The toxicity of these compounds appears to parallel their inherent α-adrenergic component; e.g., 44 is an α agonist and quite toxic, while 43 is a weak α-blocker and nontoxic. Amphetamine or α-adrenergic activity is further indicated by the ability of several of these compounds to antagonize reserpine (Table V). "Pseudo-catechols" 52 and 53 both possess an additional meta substituent and are extremely weak β agonists; however, both compounds are potent in both prevention and reversal of reserpine-induced ptosis, suggesting an amphetamine-like mechanism of action. Comparison of the (−) enantiomer (45) and the (+) enantiomer (46) of 44 reveals that the preponderance of the biological activity (morphine antagonism, β agonism, and reserpine antagonism) and toxicity resides in the (−) isomer 45.

The chloroform–water (buffered pH 7.4) partition coefficients of representative compounds (Table VI) were determined but do not explain why some of these compounds exhibit potent central effects while other closely related analogs do not. For instance, the partition coefficient of 44 is not greater than that of the isopropyl analog (soterenol) or the cyclobutyl analog (57) which are inactive in CNS tests. The more lipophilic *N*-(1,1-dimethyl-2-phenethyl) analog 43 is somewhat less potent as an anorexiant and narcotic antagonist even with its greater β-adrenergic potency. This may be ascribed to central adrenergic receptors having different structural requirements than peripheral β-adrenergic receptors or to an inadequacy in partition coefficients representing central distribution.

In a further effort to determine if these compounds are distributed to the CNS in significant concentrations, the relative tissue distributions of radiolabeled soterenol-7-^3H hydrochloride and 44-7-^3H hydrochloride (for preparative procedures, see ref 18) were studied in rats. Adult Sprague–Dawley rats were given a single intraperitoneal dose of 0.2 mg/kg of 44-7-^3H or soterenol-7-^3H and three rats were sacrificed at various time periods. Radioactivity (nonvolatile) in the hypothalamus, whole brain, heart, lung, and plasma was measured at different time intervals.

Table III. Arylethylamines and Arylethanolamines



Compd no.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Yield, %	Method	Recrystn solvent[a]	Mp, °C[b]	Formula	Analyses
40	$MeSO_2NH$	HO	H	H	H	H	c-C_3H_5	53	3	A	204.5-205.5	$C_{12}H_{18}N_2O_3S\cdot HCl$	C, H, N, Cl
41	$MeSO_2NH$	HO	H	H	Et	H	c-C_3H_5	68	3	B	176.0-179.0	$C_{14}H_{22}N_2O_3S\cdot HCl$	C, H, N, Cl
42	$MeSO_2NH$	HO	H	H	H	H	CMe_2-CH_2Ph	50	3	N	205.5-207.0	$C_{19}H_{26}N_2O_3S\cdot HCl$	C, H, N, Cl
43[c]	$MeSO_2NH$	HO	H	HO	H	H	CMe_2-CH_2Ph	89	4	C	215-216	$C_{19}H_{26}N_2O_4S\cdot HCl$	C, H, N, S
44	$MeSO_2NH$	HO	H	HO	H	H	c-C_3H_5	68	4	B	174.5-177	$C_{12}H_{18}N_2O_4S\cdot HCl$	C, H, N, Cl
45[d]	$MeSO_2NH$	HO	H	HO	H	H	c-C_3H_5	18	5	B	174.5-175.5 dec	$C_{12}H_{18}N_2O_4S\cdot HCl\cdot 0.25CH_3COCH_3$	C, H, N, Cl
46[e]	$MeSO_2NH$	HO	H	HO	H	H	c-C_3H_5	21	5	B	173.5-174.5 dec	$C_{12}H_{18}N_2O_4S\cdot HCl\cdot 0.25CH_3COCH_3$	C, H, N, Cl
47[d]	$MeSO_2NH$	HO	H	HO	H	H	c-C_3H_5	16	5	D	187.0 dec	$C_{12}H_{18}N_2O_4S\cdot HCl$	C, H, N, Cl
48	$MeSO_2NH$	HO	H	EtO	H	H	c-C_3H_5	97	6	E	177.5-178.0 dec	$C_{14}H_{22}N_2O_4S\cdot HCl$	C, H, N, Cl
49[f]	$MeSO_2NH$	HO	H	HO	Me	H	c-C_3H_5	81	4	E	190-192 dec	$C_{13}H_{20}N_2O_4S\cdot HCl$	C, H, N
50[f]	$MeSO_2NH$	HO	H	HO	Et	H	c-C_3H_5	79	4	B	173.5-176.0 dec	$C_{14}H_{22}N_2O_4S\cdot HCl\cdot H_2O$	C, H, N, Cl
51	$MeSO_2NH$	HO	H	HO	H	Et	c-C_3H_5	17	7	B	145.0-150.0	$C_{14}H_{22}N_2O_4S\cdot HCl$	C, H, N, Cl
52	$MeSO_2NH$	HO	Me	HO	H	H	c-C_3H_5	66	4	B	153.0-155.0 dec	$C_{13}H_{20}N_2O_4S\cdot HCl$	C, H, N, Cl
53	$MeSO_2NH$	HO	Cl	HO	H	H	c-C_3H_5	59	8	B	177.5-179.5 dec	$C_{12}H_{17}N_2O_4SCl\cdot HCl$	C, H, N, Cl
54	$MeSO_2NH$	HO	H	HO	H	H	1-Me-c-C_3H_4	84	4	M	200.0-203.0	$C_{13}H_{20}N_2O_4S\cdot HCl$	C, H, N, Cl
55	$MeSO_2NH$	HO	H	HO	H	H	1-CH_2Ph-c-C_3H_4	46	4	B	161.5-162.5 dec	$C_{19}H_{24}N_2O_4S\cdot HCl\cdot 0.5H_2O$	C, H, N, Cl
56	$MeSO_2NH$	H	HO	HO	H	H	c-C_3H_5	59	4	F	200.5-203	$C_{12}H_{18}N_2O_4S\cdot HCl$	C, H, N
57	$MeSO_2NH$	HO	H	HO	H	H	c-C_4H_7	70	4	G	187.0-189.5	$C_{13}H_{20}N_2O_4S\cdot HCl$	C, H, N, S
58	$MeSO_2NH$	H	H	HO	H	H	c-C_3H_5	45	4	L	144.5-145.5	$C_{12}H_{18}N_2O_3S$	C, H, N
59[f]	$MeSO_2NH$	H	H	HO	CH_3	H	c-C_3H_5	78	4	E	179.0-181.0 dec	$C_{13}H_{20}N_2O_3S\cdot HCl$	C, H, N
60	H	$MeSO_2NH$	H	HO	H	H	c-C_3H_5	69	4	N	166-167.5	$C_{12}H_{18}N_2O_3S\cdot HCl$	C, H, N
61	HO	HO	H	H	H	H	c-C_3H_5	53	9	H	200.5-202.5	$C_{11}H_{15}NO_2\cdot HCl$	C, H, N, Cl
62	H	HO	Cl	HO	H	CH_2-Ph	c-C_3H_5	64	8	B	173.5-174.5 dec	$C_{18}H_{20}ClNO_2\cdot HCl$	C, H, N, Cl
63	H	HO	Cl	HO	H	H	c-C_3H_5	40	8	I	133.5-135.5	$C_{11}H_{14}ClNO_2$	C, H, N, Cl
64	H	$PhCH_2O$	H	HO	H	CH_2-Ph	c-C_3H_5	84	8	J	71-73	$C_{25}H_{21}NO_2$	C, H, N
65	H	HO	H	HO	H	H	c-C_3H_5	86	8	K	159-161	$C_{11}H_{15}NO_2$	C, H, N
66	Me_2NSO_2-NH	HO	H	HO	H	H	c-C_3H_5	76	4	N	165.0-168.0	$C_{13}H_{21}N_3O_4S\cdot HCl$	C, H, N, Cl

[a] A, MeOH-*i*-PrOH; B, acetone; C, MeOH; D, MeOH-Et_2O; E, EtOH-Et_2O; F, EtOH-*i*-Pr_2O; G, MeOH-*i*-Pr_2O; H, EtOH; I, Et_2O; J, *n*-C_6H_{14}; K, MeCN; L, *i*-PrOH; M, Me_2CO-MeOH; N, MeOH-EtOAc. [b] Corrected. [c] Reference 13. [d] (−) enantiomer. [e] (+) enantiomer. [f] Erythro.

Table IV. Pharmacological Activities of Arylethylamines and Arylethanolamines

Compd no.	Phenylquinone writhing,[a] AED_{50}, mg/kg sc	Tail flick,[b] AED_{50}, mg/kg sc	Morphine antagonism,[c] AED_{50}, mg/kg sc or deviation from control	β stimulation[d,e] (isolated tracheal spiral)	α stimulation[d,f] (rat seminal vesicle)	Acute toxicity, ALD_{50}, mg/kg po
22	>6		11% at 20 mg/kg			>2000
40	0.62	2.77	0.21 [9.5 mg/kg po (60 min)]	2.0×10^{-3}		50
41	>6		17.7% at 20 mg/kg	1.30×10^{-3}		2000
42			Inactive at 20 mg/kg	0.31		>2000
43	39.0	Inactive	18.8	7.9	0[g]	1000
44	0.56	5.0	0.275	0.70	68.8	50
45	0.66		0.50	1.9	108	22.5
46	>50		Inactive at 1.2 mg/kg	3.5×10^{-3}	0[h]	>2000
48	>6		Inactive at 20 mg/kg			1000–2000
49			Inactive at 20 mg/kg	0.11		330
50	>6		Inactive at 20 mg/kg	0.23	0[i]	>2000
51	>6		Inactive at 20 mg/kg			
52			20.8% at 20 mg/kg	5.8×10^{-6}	8.7	31.3–62.5
53	>6		20.8% at 20 mg/kg	4.8×10^{-2}	4.9	>125
54			1.0	2.33		62.5–125
55			4.7	0.14		7.9
56			Inactive at 20 mg/kg	Inactive	Inactive	>2000
57	>6		Inactive at 20 mg/kg	0.36		>2000
58	>6		Inactive at 20 mg/kg	$<1 \times 10^{-2}$[j]		>2000
59	>6		Inactive at 20 mg/kg	0[k]		2000
60			Inactive at 20 mg/kg			>2000
61	>6		32.8% at 20 mg/kg			
63	>6		14.5% at 20 mg/kg			1000–2000
65	5.6	Inactive	Inactive at 20 mg/kg	1.36×10^{-2}		1000–2000
66	1.7	50	0.72	2.8×10^{-2}		90
Soterenol	>40	Inactive	Inactive at 20 mg/kg	1	1	>2000
Nalorphine hydrochloride	2.5	Inactive	0.37			1300
Morphine sulfate	0.62	1.9	Inactive			2000

[a] Reference 15. [b] Reference 16. [c] Reference 17. [d] For a description of test methods, see ref 23. [e] Relative potency for relaxing by 75% the spontaneous contractions of guinea pig tracheal spiral (0.0070 μg/ml of soterenol = 1). [f] Relative potency for producing contractions of the rat seminal vesicle 50% as intense as those produced by 2.0 μg/ml of *l*-epinephrine (63 μg of soterenol = 1). [g] α block 0.1 × phentolamine. [h] α block 3×10^{-4} × phentolamine. [i] α block 4×10^{-5} × phentolamine. [j] β block ca. 5×10^{-2} sotalol. [k] β block 0.1 × sotalol.

Table V. Prevention and Reversal of Reserpine-Induced Ptosis in Mice[a] (Reserpine, 2 mg/kg iv)

Compd no.	Prevention, ED_{50}, mg/kg po	Reversal, ED_{50}, mg/kg po
40	3.6	1.5
43	Inactive at 25	
44	0.265	0.255
45	0.175	0.23
46	31.3	
48	35	9.6
49	0.51	0.76
50	20	8.9
52	0.15	0.67
53	0.072	0.082
54	0.52	1.1
55	0.15	0.32
57	20	24.0
58	1.0	0.8
66	0.94	1.30
Soterenol	7.6	16.5
dl-Amphetamine sulfate	0.67	1.94
Imipramine hydrochloride	4.97	>320

[a] For a description of test methods, see ref 33.

Representative data (30 min) are expressed as μg of drug/g of tissue in Figure 1.

Neither 44-7-^3H nor soterenol-7-^3H *concentrated* in whole brain or hypothalamus; however, the levels of drug observed in each tissue may be sufficient for biological activity. The relative hypothalamic concentrations are

Table VI. Chloroform–Water Partition Coefficients[a]

Compd no.	$K_{CHCl_3-H_2O}$
40	0.12
43	0.56, 0.42[b]
44	0.04
55	4.00
57	0.00
Isoproterenol	0.00
Soterenol	0.03

[a] For a procedural description, see the Experimental Section. [b] Initial concentration of 4 μg/ml.

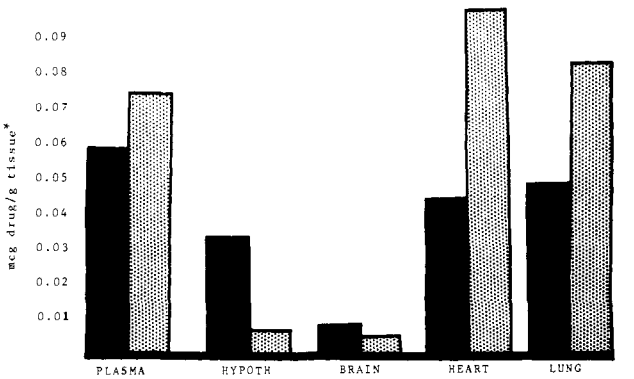


Figure 1. Relative distributions of 44-7-^3H (shaded area) and soterenol-7-^3H (dotted area) following 0.20 mg/kg ip (30 min). *, each value is a mean from three adult Sprague–Dawley rats.

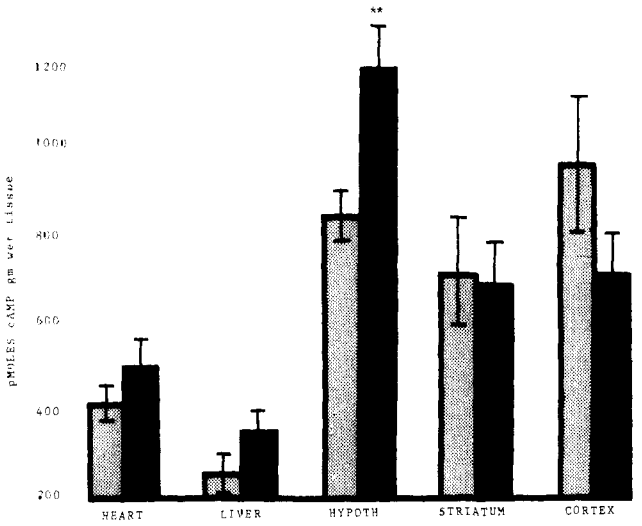


Figure 2. Changes in cAMP levels 30 min post-saline (dotted area) and 0.30 mg/kg of 44 (shaded area) sc. Six rats per group. **, $p < 0.05$.

different for the two drugs, but at a higher subcutaneous dose (0.3 mg/kg), more soterenol-7-^3H than 44-7-^3H was found in the hypothalamus. However, at the low levels of radioactivity that were measured, these differences may not be significant. This suggests that the observed differences in biological activity are not primarily determined by distribution.

In order to determine whether these relatively low central concentrations of 44 were sufficient to affect biological activity, the influence of 44 on cAMP levels was measured according to the method of Gilman[19] in several rat tissues. When injected subcutaneously (0.3 mg/kg), compound 44 elevated the cAMP content in the hypothalamus (Figure 2), consonant with its possible central β-adrenergic stimulant activity. This effect was specific for the hypothalamus since no significant change in the cAMP levels was observed in the other tissues examined. The elevation of cAMP levels induced by 44 was not antagonized by the subcutaneous administration of morphine sulfate (15 mg/kg) 30 min prior to sacrifice.

Narcotics, Narcotic Antagonists, and Adrenergics. The Relationship. The mechanism of action of these compounds is unclear, since their structural relationship to any known narcotic antagonist or analgetic is not apparent, although the previously discussed SAR and influence on cAMP levels do suggest an adrenergic mechanism.

The mechanism of action of morphine is currently an area of intense study. The reported facts are quite conflicting and a variety of adrenergic and cholinergic explanations has been advanced. For instance, Gardella and co-workers[20] have shown by stereotaxic intraventricular administration of a variety of catecholamines in the rabbit that their order of effectiveness in lowering the nociceptive threshold suggests that their actions are mediated by β receptors. Conversely, propranolol, a β-adrenergic blocking agent, is useful in the treatment of heroin addiction.[21] It prevents the euphoric effects of heroin and eliminates, or reduces, the residual craving in addicts from whom the drug is withdrawn. Propranolol, however, was not active in our acute tests for morphine antagonism and may be affecting the dependence component rather than the acute analgesia, especially since morphine dependence is multipartite,[22] and in our studies only 10 min separate the subcutaneous administration of test drug and morphine. Another β blocker, pronethalol, has been claimed to antagonize morphine analgesia.[23] More in agreement with our data is the observation that three structurally diverse β blockers (USVC-6524,[24] bunolol, and H 64/52[25]) all potentiate morphine analgesia.

Probably the best evidence for a β-adrenergic mechanism of action for the morphine antagonism by these compounds is found in the work of Ho et al.,[26-28] who have antagonized the effects of morphine with cAMP, dibutyryl-cAMP, and the phosphodiesterase inhibitor, theophylline. They further showed that β-adrenergic receptor blockade reverses cAMP effects on morphine analgesia, tolerence, and physical dependence. These results are in agreement with our cAMP data which indicate that certain β-adrenergic agonist-type molecules may elicit CNS effects by increasing central cAMP.

Another possible mechanism for morphine antagonism by soterenol analogs is depletion of brain catecholamines.[29-33] Direct or indirect (norepinephrine release) α-adrenergic agonism does not appear to be involved in the morphine antagonism by these compounds since 43 is not an α agonist, while on the other hand 44 is a potent α agonist (and much more toxic) and β agonist.

At this time, these facts do not adequately explain the complex pattern of narcotic–narcotic antagonist–adrenergic relationships. However, we have shown that CNS activity can be conferred on the basic β-adrenergic stimulant molecule by certain specific structural changes.

Experimental Section

Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements are within ±0.4% of the theoretical values. Corrected melting points were obtained according to USP XVII, Class I, which requires immersion at 30° below the expected melting point. NMR spectra were obtained on either a Varian T-60 or XL-100 and coupling constants are expressed in hertz.

Measurement of Partition Coefficients. Aliquots of 1 mg/ml of aqueous drug solution were diluted with pH 7.4 buffer to obtain a 40 μg/ml concentration. The buffered drug solution was equilibrated with 5 ml of $CHCl_3$ using a Vortex mixer; then the two phases were separated by centrifugation. Ultraviolet absorption curves were recorded on a Beckman ACT A III uv–visible spectrophotometer. Partitioned drug concentrations were determined by utilizing direct optical density readings of the aqueous solutions at 280–287 nm before and after equilibration. Duplicate analyses showed the data in Table VI to be reproducible. Compound 43 was also run at a concentration of 4 μg/ml.

Procedure 1. 5'-[2-(*N*-Benzylcyclopropylamino)-butyryl]-2'-benzyloxymethanesulfonanilide Hydrochloride (25). A solution of 21.70 g (0.051 mol) of 8 and 14.98 g (0.10 mol) of *N*-benzylcyclopropylamine[8] in 100 ml of dry MeCN was refluxed for 3 h. The mixture was cooled and poured into 500 ml of Et_2O and 8.0 g (86%) of *N*-benzylcyclopropylamine hydrobromide was filtered. The filtrate was acidified with 5 N ethanolic HCl and a white solid was filtered. Recrystallization from MeOH gave 16.60 g (62%) of **25**: mp 193–195°.

Procedure 2. 5'-[(Cyclopropylamino)acetyl]-2'-hydroxymethanesulfonanilide Hydrochloride (22). A solution of 10.00 g (0.024 mol) of **21** in 50 ml of EtOH and 50 ml of H_2O was hydrogenated in the presence of 10% Pd/C until an equivalent of hydrogen uptake was observed. The mixture was filtered and concentrated in vacuo to give an oil. The oil was dissolved in hot Me_2CO and crystallization was induced by scratching. The mixture was filtered to yield 7.32 g (96%) of **22**: mp 214.5–216.5°. An additional recrystallization from Me_2CO did not alter the melting point.

Procedure 3. 5'-[2-(Cyclopropylamino)butyl]-2'-hydroxymethanesulfonanilide Hydrochloride (41). To a suspension of 4.78 g (0.137 mol) of **50** in 20 ml of dry MeCN was added 5.24 g (0.044 mol) of $SOCl_2$. The mixture was refluxed 8 min and poured into Et_2O. The Et_2O was decanted and the residual oil was dissolved in Me_2CO. Upon cooling a precipitate formed and was filtered to provide 4.34 g (86%) of 5'-[2-(cy-

clopropylamino)-1-chlorobutyl]-2'-hydroxymethanesulfonanilide hydrochloride [50:50 mixture of erythro (J_{H_1,H_2} = 2.6 Hz) and threo (J_{H_1,H_2} = 10 Hz) racemates]: mp 165–167° dec. To a solution of 1.06 g (0.028 mol) of $NaBH_4$ in 30 ml of EtOH was added 2.00 g (0.0054 mol) of the above chloro compound at 10–15°. The mixture was stirred at 25° for 1 h and then acidified with 6 N HCl and refluxed for 1.5 h. Solids were filtered (Celite) and the filtrate was concentrated in vacuo to provide an oil which crystallized upon standing. Recrystallization from MeCO provided 2.16 g (68%) of 41: mp 176.0–179.0°.

Procedure 4. ***erythro*-5'-[2-(Cyclopropylamino)-1-hydroxybutyl]-2'-hydroxymethanesulfonanilide Hydrochloride Hydrate (50).** A solution of 20.0 g (0.038 mol) of **25** in 200 ml of MeOH was hydrogenated in the presence of 10% Pd/C until a theoretical uptake of hydrogen was observed (24 h). The mixture was filtered and the filtrate was concentrated in vacuo to provide an oil which crystallized. Recrystallization from Me_2CO provided 10.4 g (79%) of **50** (erythro alcohol, J_{H_1,H_2} = 2.5 Hz): mp 173.5–176.0° dec.

Procedure 5. Resolution of 44. (+)- and (−)-5'-[2-(Cyclopropylamino)-1-hydroxyethyl]-2-hydroxymethanesulfonanilide Hydrochlorides (45, 46, 57). An Me_2CO suspension of 21.50 g (0.067 mol) of **44** was made distinctly basic with NH_4OH. The NH_4Cl was filtered and the filtrate concentrated to an orange oil which was dissolved in 150 ml of dry acetone. To this solution was added 10.20 g (0.067 mol) of (+)-mandelic acid. After standing (5°) for 2 h, a hygroscopic, white solid was filtered which was recrystallized three times from Me_2CO. Acidification of the Me_2CO suspension provided 3.80 g (18%) of the (−) enantiomer **45**: mp 174.5–175.5 dec; $[\alpha]^{25}D$ −29.0°. When this material was taken through the same resolution process, a material was obtained which showed a similar $[\alpha]^{25}D$. The stable Me_2CO solvate could not be dissociated by heat; however, recrystallization from MeOH provided a MeOH solvate which was decomposed by heating in vacuo to give unsolvated (−) enantiomer **47**: mp 187.0° dec; $[\alpha]^{25}D$ −30.0°. In a similar manner, **44** was resolved using (−)-mandelic acid as the resolving agent to provide the (+) enantiomer **46** in 21% yield: mp 173.5–174.0° dec; $[\alpha]^{25}D$ +29.4°. Either racemic base or base from the mother liquors of the separation of **45** was used to obtain **46**.

Procedure 6. 5'-[2-(Cyclopropylamino)-1-ethoxyethyl]-2'-hydroxymethanesulfonanilide Hydrochloride (48). Compound **44** reacted with $SOCl_2$ (see procedure 3) to provide 5'-[2-(cyclopropylamino)-1-chloroethyl]-2'-hydroxymethanesulfonanilide hydrochloride, mp 162° dec, in 90% yield. A solution of 3.00 g (0.0088 mol) of the above chloro compound in 10 ml of absolute EtOH was refluxed for 45 min. Et_2O was added to the cooled solution and a tan solid was filtered. Recrystallization from EtOH–Et_2O provided 3.00 g (97%) **48**: mp 177.5–178.0° dec.

Procedure 7. 5'-[2-(*N*-Cyclopropyl-*N*-ethylamino)-1-hydroxyethyl]-2'-hydroxymethanesulfonanilide Hydrochloride (51). To 18 ml of stirred Ac_2O, 4.73 g (0.017 mol) of **22** was added in portions. The solution warmed and a white solid precipitated. The solid was filtered and washed with Et_2O to give 3.26 g (60%) of the desired acetamide: mp 190–193°. The amide was refluxed with 1.00 g (0.026 mol) of $LiAlH_4$ in 30 ml of dry THF for 2 h; NH_4OH was added to decompose the complex. The gelatinous precipitate was filtered and washed repeatedly with boiling MeOH. The washings were combined and concentrated in vacuo to provide an oil which was converted to the HCl salt and recrystallized from Me_2CO to provide 0.58 g (17%) of **51** as tan crystals: mp 145.0–150.0°.

Procedure 8. 3-Chloro-α-[(cyclopropylamino)methyl]-4-hydroxybenzyl Alcohol (63). To a solution of 9.45 g (0.25 mol) of $NaBH_4$ in 100 ml of absolute EtOH at 0° was added 9.45 g (0.027 mol) of **35** in portions. Additional EtOH was added as needed. The mixture was stirred for 4 h at 25° and then was acidified with 5 N ethanolic HCl. Solids were filtered and the filtrate was concentrated in vacuo to provide a brown oil. The oil was dissolved in Me_2CO, and upon standing (5°) white crystals were deposited and filtered to provide 6.15 g (64%) of **62**: mp 173.5–174.5° dec. Hydrogenation of 6.00 g (0.017 mol) of **62** as described in procedure 4 provided an oil which was dissolved in H_2O and neutralized with NH_4OH. Filtration provided a solid which was dissolved in 1 N HCl and then precipitated with NH_4OH to yield 1.55 g (40%) of **63**: mp 133.5–135.5°.

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