(0.12 mole) of $NaBH_4$ in 1 l. of diglyme was added portionwise over 1 hr with good stirring. The reaction mixture was then heated at 85° for 1 hr, cooled to 25° and the complex decomposed with 600 ml of H_2O and 100 ml of concd HCl. The solvent was removed at 60–70° under reduced pressure. The viscous residue was triturated with H_2O and the crude product which solidified was filtered and washed with H_2O. After two recrystns from EtOH the product weighed 36.5 g, mp 253–259°.

Method M. 7-Chloro-3-(3-chloro-2-methylphenyl)-1,-2,3,4-tetrahydro-2-methyl-4-oxo-6-quinazolinesulfonamide.—7-Chloro-3-(3-chloro-2-methylphenyl)-3,4-dihydro-2-methyl-4-oxo-6-quinazolinesulfonamide (2.2 g, 0.006 mole) was suspended in 60 ml of EtOH and 20 ml of H_2O. $NaBH_4$ (2 g, 0.035 mole) was added under N_2 and the mixture was stirred for 10 min. It was then refluxed for 1.5 hr, poured into 500 ml of H_2O, and acidified with HCl. The crude product was filtered off and recrystd from 60 ml of absolute EtOH to yield 2.1 g of product, mp 264–267°.

Miscellaneous Procedures. Method N. 2-Allyl-7-chloro-1,2,3,4-tetrahydro-4-oxo-3-*o*-tolyl-6-quinazolinesulfonamide.—2-(3-Bromopropyl)-7-chloro-1,2,3,4-tetrahydro-4-oxo-3-*o*-tolyl-6-quinazolinesulfonamide (2.4 g, 0.005 mole) in 12 ml of DMSO was treated with 0.63 g (0.0051 mole) of 1,5-diazabicyclo[4.3.0]-nonene[6] under N_2 and the solution stirred at ambient temp for 2 hr. The solution was poured into 100 ml of H_2O, acidified, filtered, washed (H_2O), and recrystd from 5 ml of ethylene glycol, yielding 1.2 g of product, mp 281–283°.

Method P. 4-Chloro-2-dimethylamino-5-sulfamylbenzoic Acid.—2,4-Dichloro-5-sulfamylbenzoic acid (54 g, 0.20 mole) was dissolved in 250 ml of concd NH_4OH. DMF (250 ml) was added and the solution heated in a pressure vessel at 140–145° (15.46 kg/cm²) for 6 hr. Most of the solvent was removed on a rotating evaporator under reduced pressure and 400 ml of H_2O was added to the residue. The product was filtered off, washed with H_2O, and dried. It weighed 45 g, mp 227–229°. Recrystallization from 2-methoxyethanol (6 ml/g) yielded 33 g of product, mp 230–231°.

Method R. 4-Chloro-2-dimethylamino-5-sulfamyl-*N*-*o*-tolylbenzamide.—4-Chloro-2-dimethylamino-5-sulfamylbenzoic acid (20.6 g, 0.074 mole) in 300 ml of THF was treated with 7.7 g (9.55 ml, 0.076 mole) of *N*-methylmorpholine and stirred for 30 min. The thick slurry was treated with 8.3 g (6.1 ml, 0.076 mole) of $ClCO_2C_2H_5$ and stirred for 10 min. *o*-Toluidine (9.4 g, 0.09 mole) was added and the mixture stirred at room temp for 70 hr. The solvent was then removed on the Rotovap, 200 ml of H_2O was added, and the solid was filtered off. This was slurried with dil $KHCO_3$, filtered, washed with H_2O, slurried with dil HCl, filtered, and again washed with H_2O. After drying *in vacuo* over P_2O_5 it weighed 5.7 g, mp 172–178°. It could be recrystd from PrOH (1.5 ml/g) to yield a product, mp 182–184°.

Method S. 2-Amino-4-chloro-5-sulfamyl-*N*-(3-methyl-2-pyridyl)benzamide.—4-Chloro-5-sulfamylanthranilic acid cyanomethyl ester (60 g, 0.207 mole) was added to 200 ml of freshly distilled 2-amino-3-methylpyridine and the mixture heated at 110°, under N_2 and with stirring, for 4 hr. The reaction mixture was then cooled and poured into 1 l. of H_2O with vigorous stirring. The aqueous layer was discarded and the oil again treated with 1 l. of H_2O. The aq layer was discarded and the oily residue was dissolved in 400 ml of 2.5 *N* HCl. After standing overnight the hydrochloride was filtered and washed (H_2O). It was then suspended in H_2O and treated with a saturated solution of $NaHCO_3$, with stirring, until a pH of 7 to 8 was reached. The product was filtered and recrystd from 95% EtOH, yield 11.2 g, mp 188–191°.

Acknowledgment.—The authors wish to thank Mr. Michael Daily and Mr. Michael Salzman for preparing some of the intermediates, Dr. O. N. Hinsvark and his associates for many of the analytical and spectral results, and Mr. F. C. Kaiser and Mrs. B. VanDenburg for the technical assistance in the pharmacological studies.

Aminoalkenylbenzenesulfonamides with Hypotensive and Histamine-Releasing Properties

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A series of *p*- and *m*-sulfamoyl-substituted dialkylaminoalkylbenzhydrylidene derivatives were prepared and their pharmacological properties evaluated. The most active compound, *trans*-*N*,*N*-dimethyl-*p*-(3-dimethylamino-1-phenyl-1-propenyl)benzenesulfonamide (**15**), was found to cause prolonged blood pressure lowering in dogs with concomitant release of endogenous histamine on iv and oral administration.

A series of sulfamoyl-substituted benzhydrylidene derivatives of general structure D was prepared (Chart I and Table I). The corresponding unsubstituted benzhydrylidene derivatives (*e.g.*, **19**, Table I) had been reported to have anticholinergic and antihistaminic properties.[2] The compounds also represent "open" analogs of sulfamoyl-substituted tricyclic derivatives such as the phenothiazine derivative thioproperazine,[3] the thioxanthene derivative thiothixene,[4] and others.[5] Julou, *et al.*, reported that the 2-dimethylsulfamoyl-substituted promethazine, dimetiotazine, possesses pronounced antiserotonin activity in addition to the antihistaminic properties of the parent compound and clinical evaluation confirmed its effectiveness in treatment of migraine and vascular chronic headache.[6] Evaluation of several of the compounds

(1) To whom inquiries should be directed.

(2) A. C. White, A. F. Green, and A. Hudson, *Brit. J. Pharmacol.*, **6**, 560 (1951).

(3) R. M. Jacob and G. L. Régnier, (Rhône-Poulenc), French Patent 1,179,968 (1959); *Chem. Abstr.*, **53**, 22025 (1959); **55**, 19964 (1961).

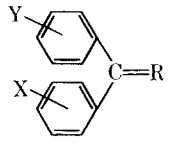
(4) (a) B. M. Bloom and J. F. Muren, (Chas. Pfizer and Co., Inc.), U. S. Patent 3,310,553 (1967); *Chem. Abstr.*, **63**, 11512 (1965); (b) J. F. Muren and B. M. Bloom, *J. Med. Chem.*, **13**, 17 (1970).

(5) For instance (a) dibenzazepine derivatives: H. Dietrich and W. Kueng (J. R. Geigy A.G.) Swiss Patents 403,770, 408,019 (1966); *Chem. Abstr.*, **65**, 13669 (1966); **66**, 18683 (1967); (b) dibenzocycloheptene derivatives: E. L. Engelhardt and M. E. Christy (Merck and Co., Inc.) U. S. Patent 3,306,934 (1967); *Chem. Abstr.*, **62**, 10394 (1965); (c) dibenzoxepine derivatives: B. M. Bloom and J. R. Tretter (Chas. Pfizer and Co., Inc.) Belgian Patent 641498 (1964); *Chem. Abstr.*, **64**, 719 (1966); (d) dibenzothiepine derivatives: SPOFA, Netherlands Application 66,08618 (1966); *Chem. Abstr.*, **67**, 43821 (1967).

(6) (a) L. Julou, R. Ducrot, M. C. Bardone, J. Y. Detaille, C. Feo, J. C. Guyonnet, G. Loiseau, and J. Pasquet *Arch. Int. Pharmacodyn. Ther.*, **159**, 70 (1966); (b) J. Geraud and L. Millet, *Therapie*, **21**, 1019 (1966).

TABLE I

AMINOALKENYLBENZENESULFONAMIDES



No.	R	X	Y	Isomer	Mp, °C	λ_{max} mμ	ε	Formula	Analyses	Hypotensive activity (dogs)[d]
1	=CHCH$_2$CH$_2$N(CH$_3$)$_2$	*p*-SO$_2$N(CH$_3$)$_2$	H							
				cis	248–250	239	22,100	$C_{20}H_{26}N_2O_2S \cdot HCl$	C, H, Cl	+
				trans	213–215	265	18,700		C, H, S	++
2	=CHCH$_2$CH$_2$N(C$_2$H$_5$)$_2$	*p*-SO$_2$N(CH$_3$)$_2$	H	*cis*	174–175	239	21,700	$C_{22}H_{30}N_2O_2S \cdot HCl$	C, H, S	−
3	=CHCH(CH$_3$)CH$_2$N(CH$_3$)$_2$	*p*-SO$_2$N(CH$_3$)$_2$	H	Mixture	139–141[a]	258	17,100	$C_{21}H_{28}N_2O_2S \cdot C_4H_4O_4$	C, H, S	+
4	=CHCH$_2$CH$_2$N(CH$_2$CH$_2$)$_2$O	*p*-SO$_2$N(CH$_3$)$_2$	H							
				cis	194–195	239	22,200	$C_{22}H_{28}N_2O_3S \cdot HCl$	C, H, N	±
				trans	237–241	268	19,300		C, H, N	+
5	=CHCH$_2$CH$_2$N(CH$_2$CH$_2$)$_2$NCH$_3$	*p*-SO$_2$N(CH$_3$)$_2$	H	*trans*	189–190[b]	269	19,800	$C_{23}H_{31}N_3O_2S \cdot 2C_4H_4O_4$	C, H, N	−
6	=CHCH$_2$CH$_2$N(CH$_3$)$_2$	*p*-SO$_2$NHCH$_3$	H	*cis*	245–247	234	20,100	$C_{19}H_{24}N_2O_2S \cdot HCl$	C, H, S	+
7	CHCH$_2$CH$_2$N(CH$_3$)$_2$	*p*-SO$_2$NH$_2$	H	Mixture	185–202	257	15,600	$C_{18}H_{22}N_2O_2S \cdot HCl$	C, H, S	−
8	=CHCH$_2$CH$_2$N(CH$_3$)$_2$	*p*-SO$_2$N(C$_2$H$_5$)$_2$	H	*cis*	157–158	243	21,100	$C_{22}H_{30}N_2O_2S \cdot HCl$	C, H, S	±
9	=CHCH$_2$CH$_2$N(CH$_3$)$_2$	*p*-SO$_2$N(CH$_2$CH$_2$)$_2$O	H	*trans*	196–198[a]	266	18,500	$C_{22}H_{28}N_2O_3S \cdot C_4H_4O_4$	C, H, S	−
10	=CHCH$_2$CH$_2$N(CH$_3$)$_2$	*p*-SO$_2$N(CH$_3$)$_2$	*p*-OCH$_3$	Mixture	188–212	255	20,900	$C_{21}H_{28}N_2O_3S \cdot HCl$	C, H, S	++
11	CHCH$_2$CH$_2$N(CH$_3$)$_2$	*p*-SO$_2$N(CH$_3$)$_2$	*m*-CF$_3$	Mixture	172–175	250	17,300	$C_{21}H_{25}F_3N_2O_2S \cdot HCl$	C, H, S	+
12	=CHCH$_2$CH$_2$N(CH$_3$)$_2$	*p*-SO$_2$N(CH$_3$)$_2$	*p*-SO$_2$N(CH$_3$)$_2$		224–225	260	25,500	$C_{22}H_{31}N_3O_4S_2 \cdot HCl$	C, H, S	+
13	=CHCH$_2$CH$_2$N(CH$_3$)$_2$	*m*-SO$_2$N(CH$_3$)$_2$	H	?	159–160	250	sh	$C_{20}H_{26}N_2O_2S \cdot HCl$	C, H, S	++
14	CHCH$_2$CH$_2$N(CH$_2$CH$_2$)$_2$NCH$_3$	*m*-SO$_2$N(CH$_3$)$_2$	H	?	180–185[b]	249	sh	$C_{22}H_{31}N_3O_2S \cdot 2C_4H_4O_4$	C, H, S	−
15	CHCH$_2$N(CH$_3$)$_2$	*p*-SO$_2$N(CH$_3$)$_2$	H							
				cis	189–190	241	22,300	$C_{19}H_{24}N_2O_2S \cdot HCl$	C, H, Cl	++
				trans	226–227	263	18,000		C, H, Cl	+++
16	CHCH$_2$N(CH$_2$CH$_2$)$_2$CH$_2$	*p*-SO$_2$N(CH$_3$)$_2$	H	Mixture	195–200[a]	265	sh	$C_{22}H_{28}N_2O_2S \cdot C_4H_4O_4$	C, H, S	−
17	=CHCH$_2$CH$_2$N(CH$_3$)$_2$	H	H		95–97[a]	249	15,000	$C_{18}H_{21}N \cdot C_4H_4O_4$	C, H, N	+
18	=CHCH$_2$CH$_2$N(CH$_3$)$_2$	*p*-Cl	H	?	105–106[a]	253	17,600	$C_{18}H_{20}ClN \cdot C_4H_4O_4$	C, H, N	±
19[c]	CHCH$_2$N(CH$_3$)$_2$	H	H		168–169	252	14,900	$C_{17}H_{19}N \cdot HCl$	C, H, N	++
20	=CHCH$_2$N(CH$_3$)$_2$	*p*-OCH$_3$	H	?	140–142[a]	238	19,500	$C_{18}H_{21}NO \cdot C_4H_4O_4$	C, H, N	++
	Guanethidine sulfate									+
	Hexamethonium bromide									+++
	N,*N*-Dibenzyl-β-chloroethylamine (Dibenamine)									+

[a] Acid maleate salt. [b] Diacid maleate salt. [c] Reference 2. [d] For pharmacological methods see Experimental Section: (+) prolonged (>20 min), strong (>20 mm) hypotension at 10 mg/kg iv; (++) at 3 mg/kg iv; (+++) at 1 mg/kg iv; (±) transient depressor; (−) no effect on blood pressure.

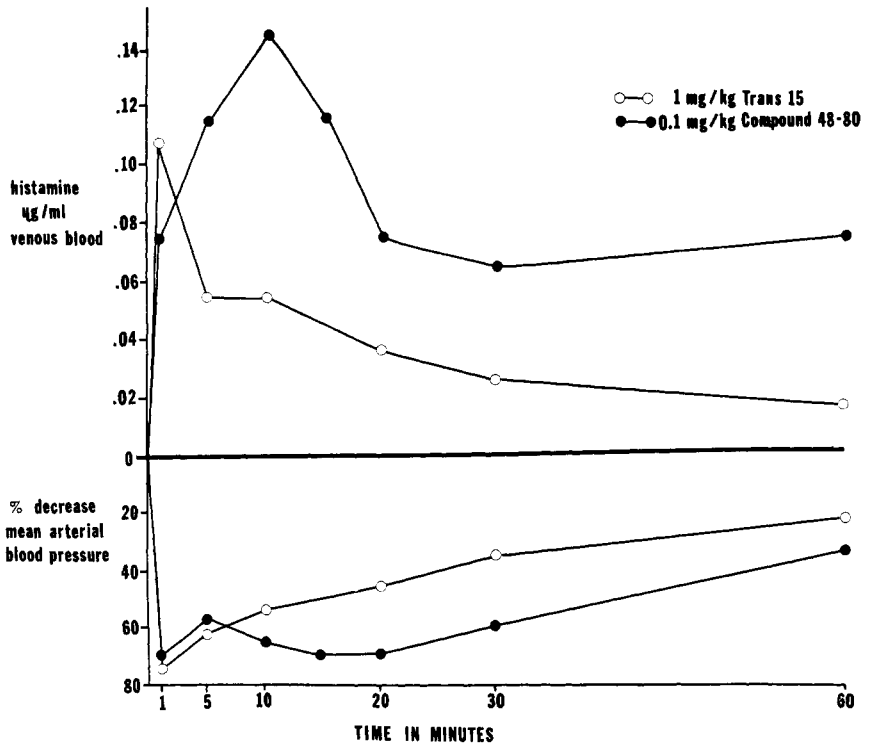


Figure 1.—The effect of 1 mg/kg iv of *trans*-*N*,*N*-dimethyl-*p*-(3-dimethylamino-1-phenyl-1-propenyl)benzenesulfonamide hydrochloride (**15**) (mean of 2 experiments) and 0.1 mg/kg of compound 48-80 on mean arterial blood pressure and the amount of histamine released in venous blood in normotensive anesthetized dogs.

here reported soon revealed that they did not antagonize acetylcholine, histamine, or sertonin as determined *in vitro* on smooth muscle preparations. To confirm the latter result in an *in vivo* preparation, **1** was administered iv to anesthetized dogs to observe effects on blood pressure after administration of serotonin. These experiments confirmed the lack of antiserotonin activity, but revealed prolonged hypotensive activity at 10 mg/kg iv. Additional structural modification and an investigation of stereochemistry were then undertaken to uncover a more potent agent of this type. As can be seen from the screening data listed in the last column of Table I, variation of the amine function (**1**–**5**), the sulfamoyl group (**6**–**9**) and its position (**13** and **14**), and the introduction of additional aromatic substituents (**10**–**12**) did not enhance, and in most cases decreased activity. Compound **15**, on the other hand, in which the side chain is shortened by one C, was 3–10 times more potent. The parent, nonsulfamoyl compounds **19** and **20** have less activity and **17** and **18** were inactive under the conditions of the test system.

trans-*N*,*N*-Dimethyl-*p*-(3-dimethylamino-1-phenyl-1-propenyl)benzenesulfonamide hydrochloride (**15**), showed strong and prolonged hypotensive activity at 1 mg/kg iv in anesthetized and unanesthetized dogs and was orally active in renal and neural hypertensive dogs (Table II). During evaluation of the mechanism of action, *trans*-**15** was found not to act *via* ganglionic blockage, α-adrenergic blockade, stimulation of the Bezold–Jarish reflex, or by ACh-like activity (see Experimental Section). Spectrophotofluorometric determination[7] of blood levels of histamine revealed that *trans*-**15** causes hitamine release.[8] Figure 1 shows the correlation of histamine concentration in venous blood and concurrent decrease in blood pressure in anesthetized dogs after 1 mg/kg iv of *trans*-**15** and 0.1 mg/kg iv of the known histamine releaser 48–80.[9] Figure 2 shows these effects after oral admistration in an unanesthetized hypertensive dog. It can be seen that the degree of blood pressure lowering is directly related to the concentration of histamine in the venous blood. Also, in these unanesthetized dogs intense scratching and reddening of the skin occurred.[8] Tachyphylaxis, *i.e.*, decreasing responses after several injections at short intervals due to depletion of histamine stores, could not be obtained consistently; however, cross-tachyphyl-

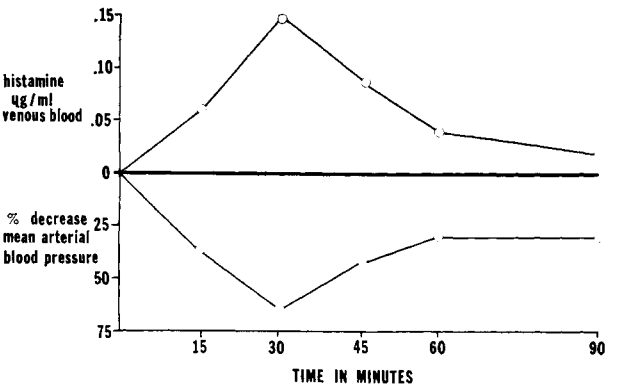


Figure 2.—The effect of 30 mg/kg po of *trans*-*N*,*N*-dimethyl-*p*-(3-dimethylamino-1-phenyl-1-propenyl)benzenesulfonamide hydrochloride (**15**) on mean arterial blood pressure and the amount of histamine released in venous blood in an unanesthetized neurogenic hypertensive dog.

(7) P. A. Shore, A. Burkhalter, and V. H. Cohn, Jr., *J. Pharmacol. Exp. Ther.*, **127**, 182 (1959).

(8) For a general review see W. D. M. Paton, *Pharmacol. Rev.*, **9**, 269 (1957).

(9) Compound 48–80 is a reaction product of *p*-methoxy-*N*-methylphenethylamine with formaldehyde: R. Baltzly, J. S. Buck, E. J. deBeer, and F. J. Webb, *J. Amer. Chem. Soc.*, **71**, 1301 (1949). See ref 8 for pharmacological properties.

TABLE II

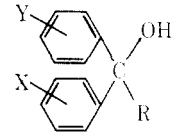
HYPOTENSIVE ACTIVITY OF *trans*-*N*,*N*-DIMETHYL-*p*-(3-DIMETHYLAMINO-1-PHENYL-1-PROPENYL)BENZENESULFONAMIDE HYDROCHLORIDE (**15**) IN DOGS

Preparation	Dose-route (mg/kg)	Number of animals	Initial blood pressure (mm Hg)	Max decrease of blood pressure (mm Hg)	% decrease of blood pressure	Duration (min)
Normotensive, anesthetized[a]	1 iv	26	137 ± 4.5	94 ± 13	68 ± 7.6	79 ± 16
	3 iv	20	121 ± 5.5	75 ± 5.7	62 ± 12	72 ± 9
	10 iv	4	125 ± 7.5	40 ± 12	33 ± 9.8	25 ± 6
Normotensive, unanesthetized	1 iv	1	85	37	44	30
	3 iv	1	117	42	36	>60
	10 iv	1	200	136	68	60
Renal hypertensive, unanesthetized[b]	10 po	1	185	44	24	240
	30 po	2	182	69	38	210
Neural hypertensive, unanesthetized[c]	10 po	1	224	78	35	180
	30 po	2	216	119	55	240

[a] Pentobarbital sodium, 35 mg/kg iv. [b] Prepared by the method of A. Grollman, *Proc. Soc. Exp. Biol. Med.*, **57**, 102 (1944). [c] Prepared by the method of K. S. Grimson, *Arch. Surg.*, **43**, 284 (1941).

TABLE III

AMINOALKANOLBENZENESULFONAMIDES



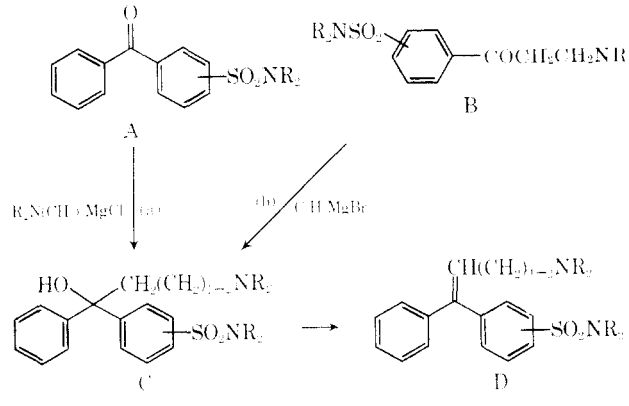
No.	R	X	Y	Mp, °C	Formula	Analyses
21	$(CH_2)_3N(CH_3)_2$	*p*-$SO_2N(CH_3)_2$	H	125–128[a]	$C_{20}H_{28}N_2O_3S \cdot C_4H_4O_4$	C, H, S
22	$CH_2CH(CH_3)CH_2N(CH_3)_2$	*p*-$SO_2N(CH_3)_2$	H	149–151[a]	$C_{21}H_{30}N_2O_3S \cdot C_4H_4O_4$	C, H, S
23	$(CH_2)_3N(CH_2CH_2)_2O$	*p*-$SO_2N(CH_3)_2$	H	149–153[a]	$C_{22}H_{30}N_2O_4S \cdot C_4H_4O_4$	C, H, N
24	$(CH_2)_3N(CH_2CH_2)_2NCH_3$	*p*-$SO_2N(CH_3)_2$	H	176–178[b]	$C_{23}H_{33}N_3O_3S \cdot 2C_4H_4O_4$	C, H, N
25	$(CH_2)_3N(CH_2CH_2)_2NCH_3$	*m*-$SO_2N(CH_3)_2$	H	174–175[b]	$C_{23}H_{33}N_3O_3S \cdot 2C_4H_4O_4$	C, H, S
26	$(CH_2)_3N(CH_3)_2$	*p*-$SO_2N(CH_3)_2$	*m*-CF_3	230–231	$C_{21}H_{27}F_3N_2O_3S \cdot HCl$	C, H, S
27	$(CH_2)_3N(CH_3)_2$	*p*-$SO_2N(CH_3)_2$	*p*-OCH_3	122–124	$C_{21}H_{30}N_2O_4S$	C, H, S
28	$(CH_2)_2N(CH_3)_2$	*p*-$SO_2N(CH_3)_2$	H	155–158[a]	$C_{19}H_{26}N_2O_3S \cdot C_4H_4O_4$	C, H, S
29	$(CH_2)_2N(CH_2CH_2)_2CH_2$	*p*-$SO_2N(CH_3)_2$	H	246–247	$C_{22}H_{30}N_2O_3S \cdot HCl$	C, H, Cl
30[c]	$(CH_2)_2N(CH_3)_2$	H	H	204–205	$C_{17}H_{21}NO \cdot HCl$	C, H, Cl

[a–c] See footnotes, Table I.

axis with compound 48–80 could be demonstrated clearly: 1 and 3 mg/kg iv of *trans*-**15** did not affect blood pressure (dog) after 4 consecutive doses of compound 48–80 (0.1 mg/kg iv at 30-min intervals). The antihistaminic agent diphenhydramine (5 mg/kg iv) did not block the depressor response of *trans*-**15**. The rabbit was shown to have a low sensitivity to compounds that cause histamine release.[8] In this species only transient depressor responses were obtained after *trans*-**15** or compound 48–80. On the other hand, 5 mg of *trans*-**15** produced approximately 80% bronchial constriction in the isolated guinea pig lung preparation.[10] This response was almost completely blocked by the antihistaminic agent chlorpheniramine. It was concluded from these experiments, that the hypotensive activity of *trans*-**15** is due to histamine release. Similarly, the hypotensive effect of *cis*-**1** (10 mg/kg iv) and **19** (5.5 mg/kg iv) was shown to be due to histamine release.

Chemistry.—The compounds listed in Table I were prepared by the procedures outlined in Chart I. The benzhydrylidenes D were obtained by dehydration of benzhydrols C by standard methods. The benzhydrols C (Table III) were obtained by either (a) reaction of sulfamoylbenzophenones A with dialkylaminopropyl magnesium chlorides or (b) reaction of PhMgBr with

CHART I

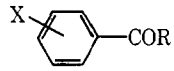


the Mannich bases B. The sulfamoylbenzophenones A as well as sulfamoylacetophenones required for preparation of B (Table IV) were conveniently obtained by a procedure first described by Meerwein and coworkers[11] that involves diazotization of the corresponding amines and reaction of the diazonium salts with SO_2 in the presence of a Cu salt. An example of each of these steps is given in the Experimental Section and physical properties of the compounds obtained are listed in

(10) A. L. Delaunois, L. Dautrebande, and C. Heymans, *Arch. Int. Pharmacodyn. Ther.*, **108**, 238 (1956).

(11) H. Meerwein, G. Dittmar, R. Göllner, K. Hafner, F. Mensch, and O. Steinfort, *Chem. Ber.*, **90**, 841 (1952).

TABLE IV
BENZOYL- AND AMINOPROPIONYLBENZENESULFONAMIDES



No.	X	R	Mp, °C	Formula	Analyses
31	p-$SO_2N(CH_3)_2$	C_6H_5	119–120	$C_{15}H_{15}NO_3S$	C, H, N
32	m-$SO_2N(CH_3)_2$	C_6H_5	96–98	$C_{15}H_{15}NO_3S$	C, H, S
33	p-SO_2NH_2	C_6H_5	174–175	$C_{13}N_{11}NO_3S$	C, H, S
34	p-SO_2NHCH_3	C_6H_5	136–137	$C_{14}H_{13}NO_3S$	C, H, S
35	p-$SO_2N(C_2H_5)_2$	C_6H_5	90–91	$C_{17}H_{19}NO_3S$	C, H, S
36	p-$SO_2N(CH_2CH_2)_2O$	C_6H_5	214–216	$C_{17}H_{17}NO_4S$	C, H, S
37	p-$SO_2N(CH_3)_2$	$C_6H_4OCH_3$-p	166–167	$C_{16}H_{17}NO_4S$	C, H
38	p-$SO_2N(CH_3)_2$	$C_6H_4CF_3$-m	130–131	$C_{16}H_{14}F_3NO_3S$	C, H, S
39	p-$SO_2N(CH_3)_2$	$C_6H_4SO_2N(CH_3)_2$-p	233–234	$C_{17}H_{20}N_2O_5S_2$	C, H, S
40	p-$SO_2N(CH_3)_2$	$CH_2CH_2N(CH_3)_2$	183–184	$C_{13}H_{20}N_2O_3S\cdot HCl$	C, H, Cl
41	p-$SO_2N(CH_3)_2$	$CH_2CH_2N(CH_2CH_2)_2CH_2$	217–218	$C_{16}H_{24}N_2O_3S\cdot HCl$	C, H, N

Tables I, III, and IV. The *cis, trans* isomers[12] of **1**, **4**, and **15** were separated by fractional crystallization as described in the Experimental Section. The uv spectra of the isomers showed a striking difference and allowed assignment of *trans* structure to the isomer with absorption at the longer wavelength. To confirm this assignment, the nmr spectra of the isomers of **1** were compared with those of the unsubstituted **17** and the symmetrically disubstituted **12** (see Table V). The environment of the

TABLE V
ASSIGNMENT OF *cis, trans* ISOMERIC STRUCTURE TO ISOMERS OF **1** AND **15**

Compd[a]	τ (vinyl H)[b]	λ_{max}[c]	ϵ
1, *cis*	3.82 (J = 7.0)	238	22,100
trans	3.73 (J = 7.0)	265	18,700
17	3.92 (J = 7.0)	249	15,000
12	3.63 (J = 7.0)	260	25,500
15, *cis*	3.66 (J = 7.0)	241	22,300
trans	3.52 (J = 7.0)	263	18,000
19	3.70 (J = 7.0)	252	14,900

[a] See Table I. [b] Nmr spectra in $CDCl_3$ after addition of NaOD on a Varian 60 instrument. [c] In MeOH.

vinyl proton of the *trans* isomer corresponds to that of the disubstituted compound, and that of the *cis* isomer corresponds to that of the unsubstituted compound. Similarly, the *cis* isomer of **15** corresponds to the unsubstituted analog **19**. Nmr data thus confirms the assignment based on uv spectra. One isomer each of **2**, **5**, **6**, **8**, and **9** was obtained during the process of purification and their isomeric strucure and purity could be assigned on the basis of uv wavelength and intensity. That the isomers are indeed *cis, trans* isomers and not due to a rearrangement (however unlikely) is shown by the nmr spectra of the isomers of **15** and the isomerization studies on **1** (see Experimental Section).

Experimental Section[13]

***N,N*-Dimethyl-*p*-benzoylbenzenesulfonamide (31).**—A soln of 39.4 g of *p*-aminobenzophenone in 400 ml of AcOH containing 44 ml of concd HCl and 80 g of ice was diazotized at 5–10° by dropwise addition of a soln of 13.8 g of $NaNO_2$ in 20 ml of H_2O over 30 min. The cold soln was added slowly to a cold soln of approx 100 g of SO_2 gas in 400 ml of AcOH containing 4 g of $CuCl_2$ in 20 ml of H_2O. After a period of 1 to 3 hr, evolution of N_2 ceased and, on addition of 400 ml of H_2O, a ppt resulted that was collected on a filter and washed with H_2O. The resulting *p*-benzoylbenzenesulfonyl chloride was dissolved in 150 ml of Me_2CO, 150 ml of a 25% aq $(CH_3)_2NH$ was added, and the mixture was acidified with 2 N HCl. The resulting ppt was collected on a filter, washed with H_2O, and recryst from *i*-PrOH to give 41.25 g (71%) of **31** (Table IV). Compounds **32–36** (Table IV) were obtained in comparable yield by this same procedure, first described by Meerwein and coworkers.[11]

***N,N*-Dimethyl-*p*-(*m*-trifluoromethylbenzoyl)benzenesulfonamide (38).**—A solution of 26.25 g of *N,N*-dimethyl-*p*-cyanobenzenesulfonamide[14] in 200 ml of dry THF was added to *m*-$CF_3C_6H_4MgBr$ (prepared from 6.7 g of Mg turnings and 61.8 g of *m*-$CF_3C_6H_4Br$ in 200 ml of dry THF) and the mixture was refluxed for 24 hr. The mixture was allowed to cool and 250 ml of 2 N HCl was added dropwise. Solvent and excess reactants were removed by steam distillation that was prolonged sufficiently (30 min at 100°) to assure complete hydrolysis of the ketimine salt, that is formed initially in this reaction, to the corresponding ketone. The product was extracted into $CHCl_3$ and the extract was washed with H_2O and $NaHCO_3$ soln and dried (Na_2SO_4). The oil obtained after evapn of solvent cryst from MeCN (61%) was recryst from *i*-PrOH, to give **38** (Table IV). Compound **37** was obtained in comparable yield by the same procedure. 4,4′-Bis(dimethylsulfamoyl)benzophenone (**39**) was obtained in poor yield. Bis(*p*-dimethylsulfamoylphenyl)methane was obtained by reaction of crude bis(*p*-chlorosulfonylphenyl)methane[15] in Me_2CO with aq Me_2NH and recryst of the resulting ppt from Me_2CO, mp 182–183°. *Anal.* ($C_{17}H_{22}N_2O_4S_2$), C, H, S.

***N,N*-Dimethyl-*p*-(β-dimethylaminopropionyl)benzenesulfonamide·HCl (40).**[16]—*p*-Acetyl-*N,N*-dimethylbenzenesulfonamide[17] was obtained in 70% yield from *p*-aminoacetophenone by the procedure described above for *N,N*-dimethyl-*p*-benzoylbenzenesulfonamide (**31**). A soln of 71.0 g (0.31 mole) of *p*-acetyl-*N,N*-dimethylbenzenesulfonamide, 12.1 g of $(CH_2O)_3$, and 36.9 g (0.45 mole) of $Me_2NH\cdot HCl$ in 200 ml of EtOH containing 1 ml of concd HCl was refluxed 6 hr. An additional 4.6 g (total 0.56 mole) of $(CH_2O)_3$ was added and refluxing was continued overnight. The hot reaction mixture was poured on 500 ml of CCl_4, the resulting ppt was collected and washed twice by slurrying in 500 ml of EtOAc to give 82.0 g (82%) of the title compd **40**, mp 179–181° (See Table IV). Compound **41** (Table IV) was prepared similarly.

***N,N*-Dimethyl-*p*-(4-dimethylamino-1-hydroxy-1-phenylbutyl)benzenesulfonamide Acid Maleate (21).**—A soln of 30.0 g

(12) We designated as *trans* the isomer in which the larger groups are on opposing sides, thus the *cis* isomer is *Z*, the *trans* isomer *E* by Cahn–Ingold–Prelog rules; (a) R. S. Cahn, C. Ingold, and V. Prelog, *Angew. Chem. Int. Ed. Engl.*, **5**, 385 (1966); (b) J. E. Blackwood, C. L. Gladys, K. L. Loening, A. E. Petrarca, and J. E. Rush, *J. Amer. Chem. Soc.*, **90**, 509 (1968).

(13) Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for these elements or functions were within ±0.4%. Melting points were determined on a Hoover capillary melting point apparatus and are corrected.

(14) C. H. Andrews, H. King, and J. Walker, *Proc. Roy. Soc. London*, **B133**, 20 (1946).

(15) (a) A. Lapworth, *J. Chem. Soc.*, **73**, 402 (1898); (b) C. S. Marvel and P. D. Caesar, *J. Amer. Chem. Soc.*, **73**, 1097 (1951).

(16) We are indebted to Mr. Paul L. Tiernan for perfecting this procedure that had previously given poor yields.

(17) W. A. Gregory (E. I. du Pont de Nemours and Co.) U. S. Patent 2,680,135 (1954); 2,726,264 (1955); and 2,726,265 (1955); *Chem. Abstr.*, **49**, 7596c (1955); **52**, 2914*b*, 5467*f* (1958).

of *N,N*-dimethyl-*p*-benzoylbenzenesulfonamide, (**31**), in 250 ml of dry THF was added to $Me_2N(CH_2)_3MgCl$ (prepared from 7.6 g of Mg powder and 37.9 g of $Me_2N(CH_2)_3Cl$ in 300 ml of dry THF) and the mixture was stirred at room temp overnight under N_2. The reaction mixture was decomp by addition of 200 ml of 3 *N* NH_4Cl, the THF phase was separated and evapd to dryness, and the product was extracted into Et_2O and washed. The product was purified by extraction into 2 *N* HCl, washing with Et_2O, reconversion into the free base by addition of Na_2CO_3 soln, and extraction into Et_2O. The crude product obtained after evap of solvent was recryst from EtOH to give 27.9 g (71%) of **21**, 98–99°. Addition of 1 equiv of maleic acid and recryst from *i*-PrOH gave the acid maleate salt of **21** (Table III). Compounds **22–27** (Table III) as well as other aminoalkanolbenzenesulfonamides that were not purified but converted directly into aminoalkenylbenzenesulfonamides (Table I) were also prepared by this procedure.

***N,N*-Dimethyl-*p*-(3-dimethylamino-1-hydroxy-1-phenylpropyl)benzenesulfonamide Acid Maleate (28).**—*N,N*-Dimethyl-*p*-(β-dimethylaminopropionyl)benzenesulfonamide·HCl (**40**) (50.0 g) was finely powdered and was added in portions to a cooled soln of PhMgBr (prepared from 18.5 g of Mg turnings and 119.0 g of PhBr in 1 l of Et_2O). The resulting suspension was stirred vigorously for 18 hr at room temperature. The resulting Mg complex was decompd by addition of 3 *N* NH_4Cl. Part of the product pptd and was collected. Additional product was obtained from Et_2O on evapn. The two portions were combined and 1 equiv of maleic acid in *i*-PrOH was added. After two recrystn from Me_2CO–C_6H_{14}, the title compd was obtained in 80% yield (Table III). Compound **29** was similarly prepared from **41**.

***cis*- and *trans*-*N,N*-Dimethyl-*p*-(4-dimethylamino-1-phenyl-1-butenyl)benzenesulfonamide Hydrochloride (1).**—A soln of 32.44 g of *N,N*-dimethyl-*p*-(4-dimethylamino-1-hydroxy-1-phenylbutyl)-benzenesulfonamide (**21**) in 100 ml of 25% (by vol) H_2SO_4 was refluxed for 2 hr. The soln was made alkaline by addition of 10% Na_2CO_3 soln and the resulting ppt was extracted into Et_2O. The Et_2O extract was dried (Na_2SO_4) and the solvent was evap leaving 30.40 g of crude *N,N*-dimethyl-*p*-(4-dimethylamino-1-phenyl-1-butenyl)benzenesulfonamide. It was converted into the HCl salt by addition of 1 equiv of HCl in *i*-PrOH. Repeated slow crystn from that solvent resulted in separation of the *cis* isomer, mp 248–250°, uv max (MeOH) 239 mμ (ε 22,200). From the mother liquor separated the *trans* isomer, mp 213–215° uv max (MeOH) 265 mμ (ε 18,700). Compounds **2–20** (Table I) were prepared by this procedure or that described below for **15**. Separation of isomers was carried out only for **1**, **4**, and **15**; in some cases, however, isomerically pure material was obtained during the process of purification. After the assignment of *cis* and *trans* isomers of **1** and **15** was confirmed by nmr (see below and text) uv was used to assign isomeric structure and purity to those compounds of which only one isomer was obtained. No assignment of isomeric structure was possible for the *meta*-substituted analogs **13** and **14** and the Cl- and MeO-substituted analogs of **18** and **20**.

***cis*- and *trans*-*N,N*-Dimethyl-*p*-(3-dimethylamino-1-phenyl-1-propenyl)benzenesulfonamide·HCl (15).**—A soln of 33.0 g of *N,N*-dimethyl-*p*-(3-dimethylamino-1-hydroxy-1-phenylpropyl)-benzenesulfonamide (**28**) in a mixture of 220 ml of AcOH and 35 ml of concd HCl was refluxed for 1 hr. The acids were evapd under reduced pressure, the product was dissolved in H_2O, concd NH_4OH was added to make the soln basic, and the product was extracted into Et_2O. The Et_2O extract was dried ($MgSO_4$). The HCl salt was pptd by addition of 1 equiv of HCl in *i*-PrOH to the Et_2O soln of the product yielding 20.5 g (60%) of material, mp 75–95° consisting of a mixture of *cis* and *trans* isomers. Repeated fractional recrystn from *i*-PrOH–C_6H_{14} gave pure *cis* isomer, mp 189–190°, uv max (MeOH) 241 mμ (ε 22,200). From the mother liquor separated the *trans* isomer, mp 225–226° uv max (MeOH) 263 mμ (ε 18,300). The nmr spectra of the isomers of **15** (as free base in $CDCl_3$) were *cis*-**15**: τ 7.66 [s, 6, $(CH_3)_2NSO_2$–], 7.22 (s, 6, $(CH_3)_2NCH_2$], 6.90 (d, 2, J = 7 Hz, NCH_2CH=), 2.6–2.8 (m, 7, aromatic), 2.21 (d, 2, J = 8 Hz, aromatic protons adjacent to sulfamoyl group); *trans*-**15**: τ 7.55 (s, 6), 7.32 (s, 6), 6.66 (d, 2, J = 7 Hz), 2.5–2.9 (m, 7), 2.30 (d, 2, J = 9 Hz).

Equilibration Studies.—Both isomers of **1** were found to be stable to 0.1 *N* HCl at 37° for 24 hr. In refluxing 2 *N* HCl either isomer equilibrated reaching equilibrium (approximately 1:1 mixture of isomers) in 9–12 hr. Uv absorption was used to follow equilibration.

Metabolic Demethylation.—A brief study of metabolic demethylation, using a rat liver microsomal *in vitro* preparation, showed that only one of the 4 Me groups of **1** is metabolized to formaldehyde. That this was an amino *N*-Me group is indicated by the fact that the morpholino analog **4** that possesses only sulfamoyl *N*-Me groups is not demethylated under the same conditions. The monomethylsulfamoyl analog **6** also lost only one of its 3 *N*-Me groups, presumably an amino *N*-Me.

Pharmacological Tests. Methods.—Adult mongrel dogs of either sex were anesthetized with pentobarbital sodium (35 mg/kg iv). Blood pressure was obtained directly from the right femoral artery by standard manometric techniques. Respiration was recorded kymographically *via* a tracheal cannula and an inspirometer (Metro Industries). Lead II electrocardiograms were continuously monitored on a Grass oscillograph. The preparations were also used to examine possible mechanism of hypotensive action through the utilization of the following test methods: bilateral carotid occlusion; stimulation of the distal and proximal stump of the cut vagus nerve (15 V, 1 msec duration, 15/sec for 15 sec); bilateral vagotomy; tachyphylaxis; and iv injections of epinephrine, ACh, and dimethylphenylpiperazinium bromide (DMPP). Ganglionic blockade was achieved by 3 consecutive doses of 3 mg/kg iv of hexamethonium bromide at 15-min intervals; α-adrenergic blockage by 15 mg/kg iv of *N,N*-dibenzyl-β-chloroethylamine (Dibenamine). Test compounds were injected into a femoral vein. The isolated guinea pig lung preparation was obtained by the method described by Delaunois, *et al.*[10] Test compound was injected into the pulmonary artery; chlorpheniramine was added to the perfusate at concentrations of 1–5 μg/ml. The isolated guinea pig ileum preparation was used to determine anticholinergic and antihistamic activity. The isolated rat fundus was used to determine antiserotonin activity.

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