

(0.12 mole) of NaBH<sub>4</sub> 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<sub>2</sub>O and 100 ml of concd HCl. The solvent was removed at 60–70° under reduced pressure. The viscous residue was triturated with H<sub>2</sub>O and the crude product which solidified was filtered and washed with H<sub>2</sub>O. 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<sub>2</sub>O. NaBH<sub>4</sub> (2 g, 0.035 mole) was added under N<sub>2</sub> and the mixture was stirred for 10 min. It was then refluxed for 1.5 hr, poured into 500 ml of H<sub>2</sub>O, 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<sup>6</sup> under N<sub>2</sub> and the solution stirred at ambient temp for 2 hr. The solution was poured into 100 ml of H<sub>2</sub>O, acidified, filtered, washed (H<sub>2</sub>O), 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<sub>4</sub>OH. DMF (250 ml) was added and the solution heated in a pressure vessel at 140–145° (15.46 kg/cm<sup>2</sup>) for 6 hr. Most of the solvent was removed on a rotating evaporator under reduced pressure and 400 ml of H<sub>2</sub>O was added to the residue. The product was filtered off, washed with H<sub>2</sub>O, 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<sub>2</sub>C<sub>6</sub>H<sub>5</sub> 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<sub>2</sub>O was added, and the solid was filtered off. This was slurried with dil KHCO<sub>3</sub>, filtered, washed with H<sub>2</sub>O, slurried with dil HCl, filtered, and again washed with H<sub>2</sub>O. After drying *in vacuo* over P<sub>2</sub>O<sub>5</sub> 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<sub>2</sub> and with stirring, for 4 hr. The reaction mixture was then cooled and poured into 1 l. of H<sub>2</sub>O with vigorous stirring. The aqueous layer was discarded and the oil again treated with 1 l. of H<sub>2</sub>O. 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<sub>2</sub>O). It was then suspended in H<sub>2</sub>O and treated with a saturated solution of NaHCO<sub>3</sub>, 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

MARION T. DORSETT, J. MARTIN GRISAR,<sup>1</sup> KENNETH R. HICKEY, RUDOLPH L. POHL,

*Organic Chemistry Department, and*

WILLIAM J. HUDAK,<sup>1</sup> AND RICHARD E. LEWIS

*Pharmacology Department, Scientific Laboratories, The Wm. S. Merrell Company,  
Division of Richardson-Merrell Inc., Cincinnati, Ohio 45215*

*Received November 21, 1969*

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.<sup>2</sup> The compounds also represent "open" analogs of sulfamoyl-substituted tricyclic derivatives such as the phenothiazine derivative thio-properazine,<sup>3</sup> the thioxanthene derivative thiothixene,<sup>4</sup>

and others.<sup>5</sup> 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.<sup>6</sup> Evaluation of several of the compounds

(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. Ghyonnet, G. Loiseau, and J. Pasquet *Arch. Int. Pharmacodyn. Ther.*, **159**, 70 (1966); (b) J. Gerard and L. Millet, *Therapie*, **21**, 1019 (1966).

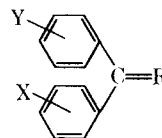
(1) To whom inquiries should be directed.

(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).

TABLE I  
AMINOALKENYLBENZENESULFONAMIDES



No.	R	X	Y	Isomer	Mp, °C	$\lambda_{max}$ m $\mu$	$\epsilon$	Formula	Analyses	Hypotensive activity <sup>d</sup> (logs) <sup>d</sup>
1	$=\text{CHCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	$p\text{-SO}_2\text{N}(\text{CH}_3)_2$	H	<i>cis</i>	248-250	239	22,100	$\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_2\text{S} \cdot \text{HCl}$	C, H, Cl	+
				<i>trans</i>	213-215	265	18,700		C, H, S	++
2	$=\text{CHCH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	$p\text{-SO}_2\text{N}(\text{CH}_3)_2$	H	<i>cis</i>	174-175	239	21,700	$\text{C}_{22}\text{H}_{30}\text{N}_2\text{O}_2\text{S} \cdot \text{HCl}$	C, H, S	-
3	$=\text{CHCH}(\text{CH}_3)\text{CH}_2\text{N}(\text{CH}_3)_2$	$p\text{-SO}_2\text{N}(\text{CH}_3)_2$	H	Mixture	139-141 <sup>a</sup>	258	17,100	$\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}_2\text{S} \cdot \text{C}_4\text{H}_4\text{O}_4$	C, H, S	+
4	$=\text{CHCH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)_2\text{O}$	$p\text{-SO}_2\text{N}(\text{CH}_3)_2$	H	<i>cis</i>	194-195	239	22,200	$\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_3\text{S} \cdot \text{HCl}$	C, H, N	±
				<i>trans</i>	237-241	268	19,300		C, H, N	+
5	$=\text{CHCH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)_2\text{NCH}_3$	$p\text{-SO}_2\text{N}(\text{CH}_3)_2$	H	<i>trans</i>	189-190 <sup>b</sup>	269	19,800	$\text{C}_{23}\text{H}_{31}\text{N}_3\text{O}_2\text{S} \cdot 2\text{C}_4\text{H}_4\text{O}_4$	C, H, N	-
6	$=\text{CHCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	$p\text{-SO}_2\text{NHCH}_3$	H	<i>cis</i>	245-247	234	20,100	$\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}_2\text{S} \cdot \text{HCl}$	C, H, S	+
7	$\text{CHCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	$p\text{-SO}_2\text{NH}_2$	H	Mixture	185-202	257	15,600	$\text{C}_{18}\text{H}_{22}\text{N}_2\text{O}_2\text{S} \cdot \text{HCl}$	C, H, S	-
8	$=\text{CHCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	$p\text{-SO}_2\text{N}(\text{C}_2\text{H}_5)_2$	H	<i>cis</i>	157-158	243	21,100	$\text{C}_{22}\text{H}_{30}\text{N}_2\text{O}_2\text{S} \cdot \text{HCl}$	C, H, S	±
9	$=\text{CHCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	$p\text{-SO}_2\text{N}(\text{CH}_2\text{CH}_2)_2\text{O}$	H	<i>trans</i>	196-198 <sup>a</sup>	266	18,500	$\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_3\text{S} \cdot \text{C}_4\text{H}_4\text{O}_4$	C, H, S	-
10	$=\text{CHCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	$p\text{-SO}_2\text{N}(\text{CH}_3)_2$	$p\text{-OCH}_3$	Mixture	188-212	255	20,900	$\text{C}_{21}\text{H}_{28}\text{N}_2\text{O}_3\text{S} \cdot \text{HCl}$	C, H, S	++
11	$=\text{CHCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	$p\text{-SO}_2\text{N}(\text{CH}_3)_2$	$m\text{-CF}_3$	Mixture	172-175	250	17,300	$\text{C}_{21}\text{H}_{25}\text{F}_3\text{N}_2\text{O}_2\text{S} \cdot \text{HCl}$	C, H, S	±
12	$=\text{CHCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	$p\text{-SO}_2\text{N}(\text{CH}_3)_2$	$p\text{-SO}_2\text{N}(\text{CH}_3)_2$		224-225	260	25,500	$\text{C}_{22}\text{H}_{31}\text{N}_3\text{O}_4\text{S}_2 \cdot \text{HCl}$	C, H, S	+
13	$=\text{CHCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	$m\text{-SO}_2\text{N}(\text{CH}_3)_2$	H	?	159-160	250	sh	$\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_2\text{S} \cdot \text{HCl}$	C, H, S	++
14	$=\text{CHCH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)_2\text{NCH}_3$	$m\text{-SO}_2\text{N}(\text{CH}_3)_2$	H	?	180-185 <sup>b</sup>	249	sh	$\text{C}_{23}\text{H}_{31}\text{N}_3\text{O}_2\text{S} \cdot 2\text{C}_4\text{H}_4\text{O}_4$	C, H, S	-
15	$\text{CHCH}_2\text{N}(\text{CH}_3)_2$	$p\text{-SO}_2\text{N}(\text{CH}_3)_2$	H	<i>cis</i>	189-190	241	22,300	$\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}_2\text{S} \cdot \text{HCl}$	C, H, Cl	++
				<i>trans</i>	226-227	263	18,000		C, H, Cl	+++
16	$=\text{CHCH}_2\text{N}(\text{CH}_2\text{CH}_2)_2\text{CH}_2$	$p\text{-SO}_2\text{N}(\text{CH}_3)_2$	H	Mixture	195-200 <sup>c</sup>	265	sh	$\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_2\text{S} \cdot \text{C}_4\text{H}_4\text{O}_4$	C, H, S	-
17	$=\text{CHCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	H	H		95-97 <sup>a</sup>	249	15,000	$\text{C}_{18}\text{H}_{21}\text{N} \cdot \text{C}_4\text{H}_4\text{O}_4$	C, H, N	+
18	$=\text{CHCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	$p\text{-Cl}$	H	?	105-106 <sup>c</sup>	253	17,600	$\text{C}_{18}\text{H}_{20}\text{ClN} \cdot \text{C}_4\text{H}_4\text{O}_4$	C, H, N	±
19 <sup>c</sup>	$\text{CHCH}_2\text{N}(\text{CH}_3)_2$	H	H		168-169	252	14,900	$\text{C}_{17}\text{H}_{19}\text{N} \cdot \text{HCl}$	C, H, N	++
20	$=\text{CHCH}_2\text{N}(\text{CH}_3)_2$	$p\text{-OCH}_3$	H	?	140-142 <sup>a</sup>	238	19,500	$\text{C}_{18}\text{H}_{21}\text{NO} \cdot \text{C}_4\text{H}_4\text{O}_4$	C, H, N	++
	Guanethidine sulfate									+
	Hexamethonium bromide									++
	<i>N,N</i> -Dibenzyl- $\beta$ -chloroethylamine (Dibenamine)									+

<sup>a</sup> Acid maleate salt. <sup>b</sup> Diacid maleate salt. <sup>c</sup> Reference 2. <sup>d</sup> 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.

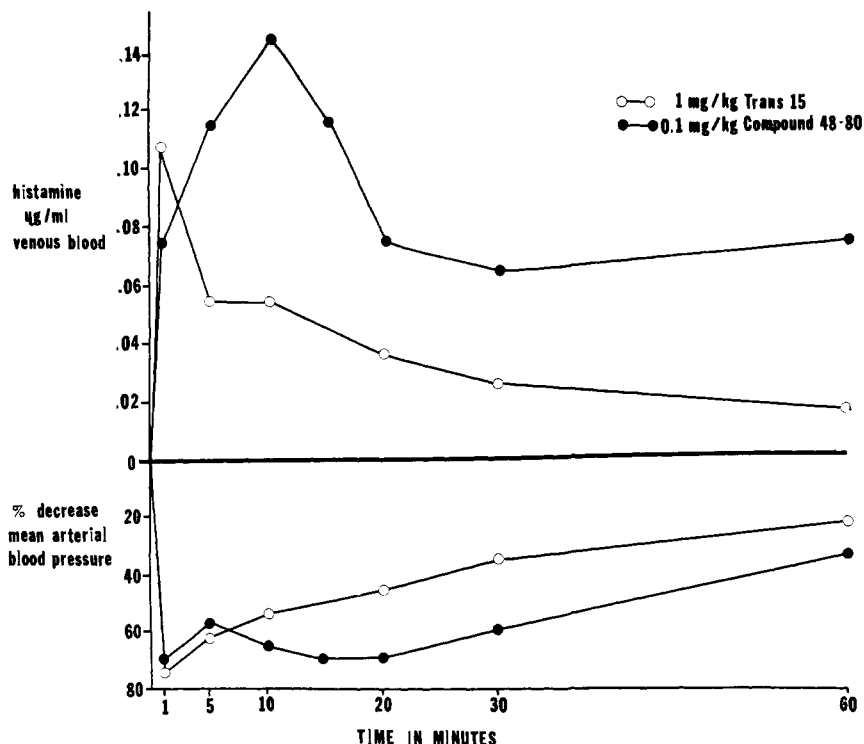


Figure 1.—The effect of 1 mg/kg iv of *trans-N,N*-dimethyl-*p*-(3-dimethylamino-1-phenyl-1-propenyl)benzenesulfonamide hydrochloride (**15**) (mean of 2 experiments) and 0.1 mg/kg of compound 48-80 on mean arterial blood pressure and the amount of histamine released in venous blood in normotensive anesthetized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

here reported soon revealed that they did not antagonize acetylcholine, histamine, or serotonin 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,  $\alpha$ -adrenergic blockade, stimulation of the Bezold-Jarish reflex, or by ACh-like activity (see Experimental Section). Spectrophotofluorometric determination<sup>7</sup> of blood levels of histamine revealed that *trans-15* causes histamine release.<sup>8</sup> Figure 1 shows the

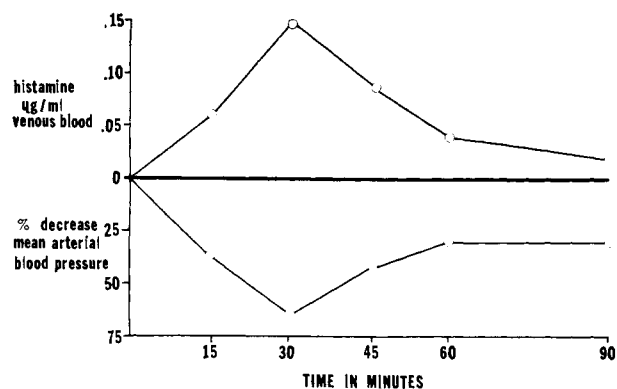


Figure 2.—The effect of 30 mg/kg po of *trans-N,N*-dimethyl-*p*-(3-dimethylamino-1-phenyl-1-propenyl)benzenesulfonamide hydrochloride (**15**) on mean arterial blood pressure and the amount of histamine released in venous blood in an unanesthetized neurogenic hypertensive dog.

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.<sup>9</sup> Figure 2 shows these effects after oral administration 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.<sup>8</sup> 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-

(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).

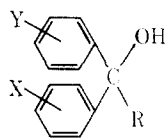
(9) Compound 48-80 is a reaction product of *p*-methoxy-*N*-methylphenethylamine with formaldehyde: R. Baltzly, J. S. Buck, E. J. deBeer, and F. J. Webb, *J. Amer. Chem. Soc.*, **71**, 1301 (1949). See ref 8 for pharmacological properties.

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

Intication	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 <sup>a</sup>	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
Benal hypertensive, unanesthetized <sup>b</sup>	10 po	1	185	44	24	240
	30 po	2	182	60	38	210
Neural hypertensive, unanesthetized <sup>c</sup>	10 po	1	224	78	35	180
	30 po	2	216	119	55	240

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

TABLE III  
AMINOALKANOLBENZENESULFONAMIDES

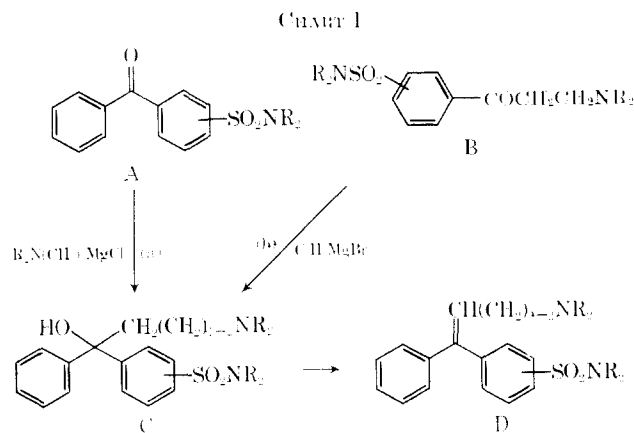


No.	R	X	Y	Mp, °C	Formula	Analyses
21	(CH <sub>2</sub> ) <sub>3</sub> N(CH <sub>3</sub> ) <sub>2</sub>	<i>p</i> -SO <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	H	125-128 <sup>a</sup>	C <sub>20</sub> H <sub>28</sub> N <sub>2</sub> O <sub>3</sub> S · C <sub>4</sub> H <sub>4</sub> O <sub>4</sub>	C, H, S
22	CH <sub>2</sub> CH(CH <sub>3</sub> )CH <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	<i>p</i> -SO <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	H	149-151 <sup>a</sup>	C <sub>21</sub> H <sub>30</sub> N <sub>2</sub> O <sub>3</sub> S · C <sub>4</sub> H <sub>4</sub> O <sub>4</sub>	C, H, S
23	(CH <sub>2</sub> ) <sub>3</sub> N(CH <sub>2</sub> CH <sub>2</sub> ) <sub>2</sub> O	<i>p</i> -SO <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	H	149-153 <sup>a</sup>	C <sub>22</sub> H <sub>30</sub> N <sub>2</sub> O <sub>4</sub> S · C <sub>4</sub> H <sub>4</sub> O <sub>4</sub>	C, H, N
24	(CH <sub>2</sub> ) <sub>3</sub> N(CH <sub>2</sub> CH <sub>2</sub> ) <sub>2</sub> NCH <sub>3</sub>	<i>p</i> -SO <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	H	176-178 <sup>b</sup>	C <sub>23</sub> H <sub>33</sub> N <sub>3</sub> O <sub>3</sub> S · 2C <sub>4</sub> H <sub>4</sub> O <sub>4</sub>	C, H, N
25	(CH <sub>2</sub> ) <sub>3</sub> N(CH <sub>2</sub> CH <sub>2</sub> ) <sub>2</sub> NCH <sub>3</sub>	<i>m</i> -SO <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	H	174-175 <sup>b</sup>	C <sub>23</sub> H <sub>33</sub> N <sub>3</sub> O <sub>3</sub> S · 2C <sub>4</sub> H <sub>4</sub> O <sub>4</sub>	C, H, S
26	(CH <sub>2</sub> ) <sub>3</sub> N(CH <sub>3</sub> ) <sub>2</sub>	<i>p</i> -SO <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	<i>m</i> -CF <sub>3</sub>	230-231	C <sub>21</sub> H <sub>27</sub> F <sub>3</sub> N <sub>2</sub> O <sub>3</sub> S · HCl	C, H, S
27	(CH <sub>2</sub> ) <sub>3</sub> N(CH <sub>3</sub> ) <sub>2</sub>	<i>p</i> -SO <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	<i>p</i> -OCH <sub>3</sub>	122-124	C <sub>21</sub> H <sub>30</sub> N <sub>2</sub> O <sub>4</sub> S	C, H, S
28	(CH <sub>2</sub> ) <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	<i>p</i> -SO <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	H	155-158 <sup>a</sup>	C <sub>19</sub> H <sub>26</sub> N <sub>2</sub> O <sub>3</sub> S · C <sub>4</sub> H <sub>4</sub> O <sub>4</sub>	C, H, S
29	(CH <sub>2</sub> ) <sub>2</sub> N(CH <sub>2</sub> CH <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub>	<i>p</i> -SO <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	H	246-247	C <sub>22</sub> H <sub>30</sub> N <sub>2</sub> O <sub>3</sub> S · HCl	C, H, Cl
30 <sup>c</sup>	(CH <sub>2</sub> ) <sub>2</sub> N(CH <sub>2</sub> ) <sub>2</sub>	H	H	204-205	C <sub>17</sub> H <sub>21</sub> NO · HCl	C, H, Cl

<sup>a-c</sup> 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.<sup>8</sup> 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.<sup>10</sup> 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

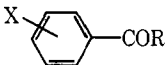


the Mannich bases B. The sulfamoylbenzophenones A as well as sulfamoylacetophenones required for preparation of B (Table IV) were conveniently obtained by a procedure first described by Meerwein and coworkers<sup>11</sup> that involves diazotization of the corresponding amines and reaction of the diazonium salts with SO<sub>2</sub> 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. Delacouris, L. Dautrebande, and C. Heymans, *Arch. Int. Pharmacodyn. Ther.*, **108**, 238 (1956).

(11) H. Meerwein, G. Dittmar, R. Göllner, K. Hafner, F. Meusch, and O. Stöfner, *Chem. Ber.*, **90**, 841 (1957).

TABLE IV  
 BENZOYL- AND AMINOPROPIONYL-BENZENESULFONAMIDES



No.	X	R	Mp, °C	Formula	Analyses
31	<i>p</i> -SO <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	C <sub>6</sub> H <sub>5</sub>	119–120	C <sub>15</sub> H <sub>15</sub> NO <sub>2</sub> S	C, H, N
32	<i>m</i> -SO <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	C <sub>6</sub> H <sub>5</sub>	96–98	C <sub>15</sub> H <sub>15</sub> NO <sub>2</sub> S	C, H, S
33	<i>p</i> -SO <sub>2</sub> NH <sub>2</sub>	C <sub>6</sub> H <sub>5</sub>	174–175	C <sub>13</sub> N <sub>11</sub> NO <sub>3</sub> S	C, H, S
34	<i>p</i> -SO <sub>2</sub> NHCH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	136–137	C <sub>14</sub> H <sub>13</sub> NO <sub>3</sub> S	C, H, S
35	<i>p</i> -SO <sub>2</sub> N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	C <sub>6</sub> H <sub>5</sub>	90–91	C <sub>17</sub> H <sub>19</sub> NO <sub>2</sub> S	C, H, S
36	<i>p</i> -SO <sub>2</sub> N(CH <sub>2</sub> CH <sub>2</sub> ) <sub>2</sub> O	C <sub>6</sub> H <sub>5</sub>	214–216	C <sub>17</sub> H <sub>17</sub> NO <sub>4</sub> S	C, H, S
37	<i>p</i> -SO <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	C <sub>6</sub> H <sub>4</sub> OCH <sub>2</sub> - <i>p</i>	166–167	C <sub>16</sub> H <sub>17</sub> NO <sub>4</sub> S	C, H
38	<i>p</i> -SO <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	C <sub>6</sub> H <sub>4</sub> CF <sub>3</sub> - <i>m</i>	130–131	C <sub>16</sub> H <sub>14</sub> F <sub>3</sub> NO <sub>3</sub> S	C, H, S
39	<i>p</i> -SO <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	C <sub>6</sub> H <sub>4</sub> SO <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub> - <i>p</i>	233–234	C <sub>17</sub> H <sub>20</sub> N <sub>2</sub> O <sub>5</sub> S <sub>2</sub>	C, H, S
40	<i>p</i> -SO <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>2</sub> CH <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	183–184	C <sub>13</sub> H <sub>20</sub> N <sub>2</sub> O <sub>3</sub> S · HCl	C, H, Cl
41	<i>p</i> -SO <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	CH <sub>2</sub> CH <sub>2</sub> N(CH <sub>2</sub> CH <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub>	217–218	C <sub>16</sub> H <sub>24</sub> N <sub>2</sub> O <sub>3</sub> S · HCl	C, H, N

Tables I, III, and IV. The *cis*, *trans* isomers<sup>12</sup> 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 <sup>a</sup>	$\tau$ (vinyl H) <sup>b</sup>	$\lambda_{\max}$ <sup>c</sup>	$\epsilon$
<b>1</b> , <i>cis</i>	3.82 ( <i>J</i> = 7.0)	238	22,100
<i>trans</i>	3.73 ( <i>J</i> = 7.0)	265	18,700
<b>17</b>	3.92 ( <i>J</i> = 7.0)	249	15,000
<b>12</b>	3.63 ( <i>J</i> = 7.0)	260	25,500
<b>15</b> , <i>cis</i>	3.66 ( <i>J</i> = 7.0)	241	22,300
<i>trans</i>	3.52 ( <i>J</i> = 7.0)	263	18,000
<b>19</b>	3.70 ( <i>J</i> = 7.0)	252	14,900

<sup>a</sup> See Table I. <sup>b</sup> Nmr spectra in CDCl<sub>3</sub> after addition of NaOD on a Varian 60 instrument. <sup>c</sup> 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 structure 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<sup>13</sup>

*N,N*-Dimethyl-*p*-benzoylbenzenesulfonamide (**31**).—A soln of 39.4 g of *p*-aminobenzophenone in 400 ml of AcOH containing 44

(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. F. Petrarca, and J. E. Rugh, *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  $\pm 0.4\%$ . Melting points were determined on a Hoover capillary melting point apparatus and are corrected.

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<sub>2</sub> in 20 ml of H<sub>2</sub>O over 30 min. The cold soln was added slowly to a cold soln of approx 100 g of SO<sub>2</sub> gas in 400 ml of AcOH containing 4 g of CuCl<sub>2</sub> in 20 ml of H<sub>2</sub>O. After a period of 1 to 3 hr, evolution of N<sub>2</sub> ceased and, on addition of 400 ml of H<sub>2</sub>O, a ppt resulted that was collected on a filter and washed with H<sub>2</sub>O. The resulting *p*-benzoylbenzenesulfonyl chloride was dissolved in 150 ml of Me<sub>2</sub>CO, 150 ml of a 25% aq (CH<sub>3</sub>)<sub>2</sub>NH was added, and the mixture was acidified with 2 *N* HCl. The resulting ppt was collected on a filter, washed with H<sub>2</sub>O, 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.<sup>11</sup>

*N,N*-Dimethyl-*p*-(*m*-trifluoromethylbenzoyl)benzenesulfonamide (**38**).—A solution of 26.25 g of *N,N*-dimethyl-*p*-cyanobenzenesulfonamide<sup>14</sup> in 200 ml of dry THF was added to *m*-CF<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>MgBr (prepared from 6.7 g of Mg turnings and 61.8 g of *m*-CF<sub>3</sub>C<sub>6</sub>H<sub>4</sub>Br 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 ketimide salt, that is formed initially in this reaction, to the corresponding ketone. The product was extracted into CHCl<sub>3</sub> and the extract was washed with H<sub>2</sub>O and NaHCO<sub>3</sub> soln and dried (Na<sub>2</sub>SO<sub>4</sub>). 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<sup>15</sup> in Me<sub>2</sub>CO with aq Me<sub>2</sub>NH and recryst of the resulting ppt from Me<sub>2</sub>CO, mp 182–183°. *Anal.* (C<sub>17</sub>H<sub>22</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub>), C, H, S.

*N,N*-Dimethyl-*p*-( $\beta$ -dimethylaminopropionyl)benzenesulfonamide · HCl (**40**).<sup>16</sup>—*p*-Acetyl-*N,N*-dimethylbenzenesulfonamide<sup>17</sup> 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<sub>2</sub>O)<sub>3</sub>, and 36.9 g (0.45 mole) of Me<sub>2</sub>NH · 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<sub>2</sub>O)<sub>3</sub> was added and refluxing was continued overnight. The hot reaction mixture was poured on 500 ml of CCl<sub>4</sub>, 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

(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. Tierman 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**, 2914b, 5467f (1958).

of *N,N*-dimethyl-*p*-benzoylbenzenesulfonamide, (**31**), in 250 ml of dry THF was added to  $\text{Me}_2\text{N}(\text{CH}_2)_3\text{MgCl}$  (prepared from 7.6 g of Mg powder and 37.9 g of  $\text{Me}_2\text{N}(\text{CH}_2)_3\text{Cl}$  in 300 ml of dry THF) and the mixture was stirred at room temp overnight under  $\text{N}_2$ . The reaction mixture was decomposed by addition of 200 ml of 3 *N*  $\text{NH}_4\text{Cl}$ , the THF phase was separated and evaporated to dryness, and the product was extracted into  $\text{Et}_2\text{O}$  and washed. The product was purified by extraction into 2 *N* HCl, washing with  $\text{Et}_2\text{O}$ , reconversion into the free base by addition of  $\text{Na}_2\text{CO}_3$  soln, and extraction into  $\text{Et}_2\text{O}$ . The crude product obtained after evaporation of solvent was recrystallized from EtOH to give 27.9 g (71%) of **21**, 98–99°. Addition of 1 equiv of maleic acid and recrystallization 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  $\text{PhMgBr}$  (prepared from 18.5 g of Mg turnings and 119.0 g of  $\text{PhBr}$  in 1 l of  $\text{Et}_2\text{O}$ ). The resulting suspension was stirred vigorously for 18 hr at room temperature. The resulting Mg complex was decomposed by addition of 3 *N*  $\text{NH}_4\text{Cl}$ . Part of the product precipitated and was collected. Additional product was obtained from  $\text{Et}_2\text{O}$  on evaporation. The two portions were combined and 1 equiv of maleic acid in *i*-PrOH was added. After two recrystallizations from  $\text{Me}_2\text{CO}-\text{C}_6\text{H}_{14}$ , the title compound 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)  $\text{H}_2\text{SO}_4$  was refluxed for 2 hr. The soln was made alkaline by addition of 10%  $\text{Na}_2\text{CO}_3$  soln and the resulting ppt was extracted into  $\text{Et}_2\text{O}$ . The  $\text{Et}_2\text{O}$  extract was dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent was evaporated 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 crystallization from that solvent resulted in separation of the *cis* isomer, mp 248–250°, uv max (MeOH) 239  $\text{m}\mu$  ( $\epsilon$  22,200). From the mother liquor separated the *trans* isomer, mp 213–215° uv max (MeOH) 265  $\text{m}\mu$  ( $\epsilon$  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 evaporated under reduced pressure, the product was dissolved in  $\text{H}_2\text{O}$ , concd  $\text{NH}_4\text{OH}$  was added to make the soln basic, and the product was extracted into  $\text{Et}_2\text{O}$ . The  $\text{Et}_2\text{O}$  extract was dried ( $\text{MgSO}_4$ ).

The HCl salt was precipitated by addition of 1 equiv of HCl in *i*-PrOH to the  $\text{Et}_2\text{O}$  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 recrystallization from *i*-PrOH- $\text{C}_6\text{H}_{14}$  gave pure *cis* isomer, mp 189–190°, uv max (MeOH) 241  $\text{m}\mu$  ( $\epsilon$  22,200). From the mother liquor separated the *trans* isomer, mp 225–226° uv max (MeOH) 263  $\text{m}\mu$  ( $\epsilon$  18,300). The nmr spectra of the isomers of **15** (as free base in  $\text{CDCl}_3$ ) were *cis*-**15**:  $\tau$  7.66 [s, 6,  $(\text{CH}_3)_2\text{NSO}_2$ ], 7.22 (s, 6,  $(\text{CH}_3)_2\text{NCH}_2$ ], 6.90 (d, 2,  $J = 7$  Hz,  $\text{NCH}_2\text{CH}=\text{C}$ ), 2.6–2.8 (m, 7, aromatic), 2.21 (d, 2,  $J = 8$  Hz, aromatic protons adjacent to sulfamoyl group); *trans*-**15**:  $\tau$  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 inspirimeter (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;  $\alpha$ -adrenergic blockage by 15 mg/kg iv of *N,N*-dibenzyl- $\beta$ -chloroethylaniline (Dibenamine). Test compounds were injected into a femoral vein. The isolated guinea pig lung preparation was obtained by the method described by Delannois, *et al.*<sup>10</sup> Test compound was injected into the pulmonary artery; chlorpheniramine was added to the perfusate at concentrations of 1–5  $\mu\text{g}/\text{ml}$ . The isolated guinea pig ileum preparation was used to determine anticholinergic and antihistaminic activity. The isolated rat fundus was used to determine antiserotonergic activity.

**Acknowledgments**.—We are indebted to R. W. Lucas and R. L. Stacey for technical assistance in the pharmacological evaluations; to Drs. H. J. Keily, D. H. Gustafson, M. J. Gordon, and associates for microanalyses, spectra, and acid equilibration studies; to Dr. E. C. Schreiber and J. F. Lang for metabolism studies. We acknowledge with appreciation the interest and advice of Drs. R. W. Fleming and W. L. Kuhn.