Benzenesulfenamides as Antihypertensive Agents. Substituted Piperidine and 1-Arylpiperazine Derivatives[1]

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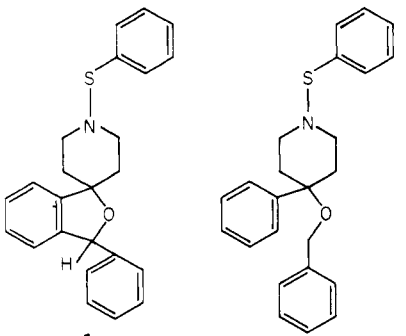
The synthesis and antihypertensive activity of several piperidinebenzenesulfenamides related to the previously reported potent hypotensive agent 1 and a series of 1-arylpiperazine-4-benzenesulfenamides **7** are described. A number of the latter compounds exhibit marked antihypertensive properties. The most interesting of these compounds, **7a** and **7k**, have been evaluated in several other animal models. In addition, benzenesulfinamides **9a** and **9b** and benzenesulfonamides **10a** and **10b** have been prepared for comparison purposes.

In a recent report from these laboratories,[2] the potent hypotensive and diuretic activities of benzenesulfenamide 1 were described. These activities, unexpected for a ring



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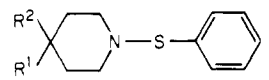
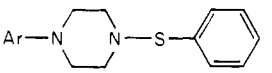


3, $R^1 = C_6H_5$; $R^2 = H$
4, $R^1 = C_6H_5CO$; $R^2 = H$
5, $R^1 = 4\text{-}CH_3C_6H_4CO$; $R^2 = H$
6, $R^1 = 4\text{-}BrC_6H_4O$; $R^2 = H$

system which was otherwise noteworthy for its CNS antidepressant and depressant properties,[3-5] led us to investigate whether or not the benzenesulfenamide linkage might impart antihypertensive and/or diuretic activity to simpler heterocyclic systems. In this regard, several piperidinebenzenesulfenamides, **2-6**, were prepared for comparison with **1**. It is interesting to note that 4-(benzyloxy)-4-phenylpiperidine-1-benzenesulfenamide (**2**) is an uncyclized analogue of **1**.[6] In addition, the arylpiperazine ring system seemed a particularly interesting choice for elaboration as a sulfenamide, since it is known that some simple arylalkylpiperazines, such as 1-methyl-4-phenylpiperazine, possess antihypertensive activity.[7] In this paper, the synthesis and hypotensive activity of several piperidinebenzenesulfenamides related to **1** and a series of 1-arylpiperazine-4-benzenesulfenamides, **7**, are described.



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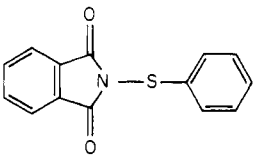
Chemistry. At first, attempts were made to prepare the desired benzenesulfenamides by reaction of the appropriately substituted secondary amine with benzenesulfenyl chloride in dichloromethane in the presence of triethylamine, the procedure used for the preparation of **1**.[2] Unfortunately, the yields obtained using this procedure were not good and the products were often quite impure.[8] We, therefore, turned to the general synthesis of sulfenamides developed by Harpp and Back, which involves refluxing the solution of an amine in benzene with *N*-(phenylthio)phthalimide (**8**), followed by cooling, removal



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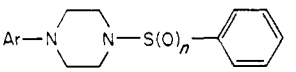
of phthalimide and unreacted **8** by filtration, and evaporation of the solvent in vacuo.[9] Thus, when the appropriate piperidines or 1-arylpiperazines were reacted with **8** as described above and the crude products recrystallized from ethanol, good to excellent yields of benzenesulfenamides were obtained.

Upon evaluation of the 1-arylpiperazine-4-benzenesulfenamides **7** for hypotensive activity, the 1-phenyl and 1-(2-pyridyl) derivatives, **7a** and **7k**, respectively, proved to be the most promising. It was, therefore, decided to prepare the corresponding sulfinamides (**9a** and **9b**) and



9a, Ar = C_6H_5; $n = 1$
b, Ar = 2-pyr; $n = 1$
10a, Ar = C_6H_5; $n = 2$
b, Ar = 2-pyr; $n = 2$

sulfonamides (**10a** and **10b**) for comparison with **7a** and

(1) Presented in part at the ACS/CSJ Chemical Congress: see "Abstracts of Papers", ACS/CSJ Chemical Congress, Honolulu, HI, April 2-6, 1979, American Chemical Society, Washington, D.C., 1979, Abstr. MEDI 65.
(2) S. S. Klioze and W. J. Novick, Jr., *J. Med. Chem.*, **21**, 400 (1978).
(3) V. J. Bauer, B. J. Duffy, D. Hoffman, S. S. Klioze, R. W. Kosley, Jr., A. R. McFadden, L. L. Martin, H. H. Ong, and H. M. Geyer III, *J. Med. Chem.*, **19**, 1315 (1976).
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(6) For the synthesis and pharmacological activity of the precursor, 4-(benzyloxy)-4-phenylpiperidine, see L. L. Martin, S. S. Klioze, M. Worm, C. A. Crichlow, H. M. Geyer III, and H. Kruse, *J. Med. Chem.*, **22**, 1347 (1979).
(7) L. H. Werner and W. E. Barrett, in "Antihypertensive Agents", E. Schlittler, Ed., Academic Press, New York, 1967, p 353.
(8) For example, the yield of **4**, which was prepared in this manner, was only 13%.
(9) D. N. Harpp and T. G. Back, *Tetrahedron Lett.*, 4953 (1971).

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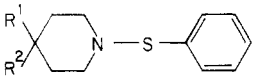
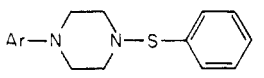
Table I[a]



no.	R^1	R^2	mp,[b] °C	yield,[c] %	formula	anal.[d]	indirect hypotensive screen[e]
2	C_6H_5	$OCH_2C_6H_5$	62-65	57.5[f]	$C_{24}H_{25}NOS$	C, H, N, S	+2 (50)
3	C_6H_5	H	47-50	81	$C_{17}H_{19}NS$	C, H, N	−9 (50)[g]
4	C_6H_5CO	H	74-76	13	$C_{18}H_{19}NOS$	C, H, N, S	−14 (25)[g]
5	$4\text{-}CH_3C_6H_4CO$	H	59-62	70	$C_{19}H_{21}NOS$	C, H, N, S	+7 (50)
6	$4\text{-}BrC_6H_4O$	H	57-59	64	$C_{17}H_{18}NOBrS$	C, H, N, S	−15 (50)
1							−66 (50), −44 (25)

[a] All structures exhibited IR and ^1H NMR spectra consistent with the assigned structures. [b] Melting points are uncorrected. [c] Yield of analytically pure material recrystallized from ethanol; yields were not optimized. [d] Analytical results within ±0.4% of theoretical values. [e] Spontaneous hypertensive rat; change in systolic pressure, mmHg, on day 3, 2 h postdrug (dose mg/kg po). [f] Recrystallized from ethanol/petroleum ether. [g] Comparisons were made using the paired Student's t test method for evaluation of statistical significance. Generally, a drop in systolic pressure greater than 15 mmHg is considered significant. These values are, therefore, probably not statistically significant.

Table II[a]



compd	Ar	mp,[b] °C	yield,[c] %	formula	anal.[d]	indirect hypotensive screen[e]
7a	C_6H_5	79.5-82	87	$C_{16}H_{18}N_2S$	C, H, N, S	90 (25), 16.5 (10)
7b	$2\text{-}CH_3C_6H_4$	68-71	83	$C_{17}H_{20}N_2S$	C, H, N, S	8[g] (50)
7c	$3\text{-}CH_3C_6H_4$	44-46	70	$C_{17}H_{20}N_2S$	C, H, N, S	16 (10)
7d	$2\text{-}CH_3OC_6H_4$	80-83	84	$C_{17}H_{20}N_2OS$	C, H, N, S	71 (50), 27 (25)
7e	$3\text{-}CH_3OC_6H_4$	70-73	88	$C_{17}H_{20}N_2OS$	C, H, N, S	35 (50)
7f	$4\text{-}CH_3OC_6H_4$	96-98	88	$C_{17}H_{20}N_2OS$	C, H, N, S	7[g] (25)
7g	$2\text{-}ClC_6H_4$	76-78	69	$C_{16}H_{17}N_2ClS$	C, H, N, S	28 (50)
7h	$3\text{-}ClC_6H_4$	65-67	85	$C_{16}H_{17}N_2ClS$	C, H, N, S	ND[h]
7i	$4\text{-}ClC_6H_4$	123-125	37[f]	$C_{16}H_{17}N_2ClS$	C, H, N, S	44 (50), 23.5 (25)
7j	$3\text{-}CF_3C_6H_4$	48-51	61.5	$C_{17}H_{17}N_2F_3S$	C, H, N, F	6[g] (50)
7k	2-pyridyl	81-84	88	$C_{15}H_{17}N_3S$	C, H, N, S	40 (50), 65 (25)
7l	$CH_2C_6H_5$	86-89	88	$C_{17}H_{20}N_2S$	C, H, N, S	17 (50), 23 (25)
guanethidine						34 (10)

[a-d] See corresponding footnotes in Table I. [e] Spontaneous hypertensive rat; drop of systolic pressure, mmHg, on day 3, 2 h postdrug (dose mg/kg po). [f] Yield of material recrystallized from ethanol, chromatographed on a silica gel dry column using $CHCl_3$ as eluent, and recrystallized again from ethanol. [g] See corresponding footnote in Table I. [h] Not determined; compound exhibited toxicity at 25 mg/kg po.

7k. These compounds were prepared by reacting the appropriate 1-arylpiperazine with benzenesulfinyl or benzenesulfonyl chloride in dichloromethane in the presence of triethylamine.

Pharmacology. Antihypertensive activity was evaluated using spontaneous hypertensive rats (SHR). The data summarized in Table I indicate that among the piperidinebenzenesulfenamides **2–6** only the 4-bromophenoxypiperidine derivative **6** possessed even marginal antihypertensive activity. It is very interesting that **2**, which is an uncyclized version of **1**, exhibits none of the potent hypotensive properties of **1**.

A number of the 1-arylpiperazine-4-benzenesulfenamides **7** exhibited potent SHR activity. The data summarized in Table II indicate that both the unsubstituted derivative **7a** as well as compounds containing electron-donating substituents (**7d** and **7e**) and electron-withdrawing substituents (**7g** and **7i**) elicited marked hypotensive responses. The 2-pyridyl derivative **7k** also possessed excellent antihypertensive activity. While there is no easily discernible pattern for the effect of aromatic substitution on hypotensive response, it is interesting that three of the four meta-substituted compounds prepared (**7c**, **7h**, and **7j**) are poorly active in this assay. The introduction of a methylene between the phenyl ring and the piperazine nitrogen leads to a compound (**7l**) with considerably diminished antihypertensive activity.

The extremely interesting hypotensive properties of a number of the 1-arylpiperazine-4-benzenesulfenamides **7**, in particular **7a** and **7k**, stimulated us to prepare the corresponding benzenesulfinamides (**9a** and **9b**) and benzenesulfonamides (**10a** and **10b**) for comparison purposes. The data for these compounds, which are summarized in Table III, indicate that the sulfinamides **9a** and **9b** retain the potent antihypertensive effect of the corresponding sulfenamides **7a** and **7k**, respectively. However, while sulfonamide **10a** still possesses some SHR activity, sulfonamide **10b** is devoid of hypotensive properties.

Although several compounds prepared during this work (e.g., **2–4**, **6**, **7f**, **7i**, **9b**, and **10b**) possessed some diuretic activity[10] at higher doses (50 or 25 mg/kg po), none exhibited a diuretic potency of the order of magnitude of **1**.

In view of the extremely potent activity exhibited by **7a** and **7k** in the SHR, follow-up investigations in other models and species were performed. Both compounds produced a marked hypotensive response in the DOCA rat at 25 mg/kg po.[11] Compound **7k**, but not **7a**, showed activity in the acute anesthetized dog (5 mg/kg iv). The 2-pyridyl derivative **7k** also possessed an antihypertensive

(10) This assay was conducted and the data were analyzed as described in ref 2.

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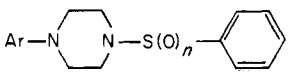
Table III[a]



no.	Ar	n	mp,[b] °C	yield,[c] %	formula	anal.[d]	indirect hypotensive screen[e]
9a	C_6H_5	1	101–104	74	$C_{16}H_{18}N_2OS$	C, H, N	83 (50), 42 (25), 22 (10)
9b	2-pyridyl	1	83–86	62	$C_{15}H_{17}N_3OS$	C, H, N	80 (50), 59 (25), 36 (10)
10a	C_6H_5	2	138–141	90	$C_{16}H_{18}N_2O_2S$	C, H, N	26 (50), 33 (25)
10b	2-pyridyl	2	154–157	89	$C_{15}H_{17}N_3O_2S$	C, H, N	5[f] (50)

[a-d] See corresponding footnotes in Table I. [e] Spontaneous hypertensive rat; drop of systolic pressure, mmHg, on day 3, 2 h postdrug (dose mg/kg po). [f] See footnote *g* in Table I.

effect in the unanesthetized dog at 20 mg/kg po.

Experimental Section

The structures of all compounds are supported by their IR (Perkin-Elmer 457 or 727) and ^1H NMR (JEOL C6OHL; in $CDCl_3$ relative to an internal Me_4Si standard). Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Micro-Tech Labs, Skokie, Ill. Results are within ±0.4% of theoretical values.

4-Benzoylpiperidine-1-benzenesulfenamide (4). To a mixture of 4.51 g (0.02 mol) of 4-benzoylpiperidine hydrochloride and 4.55 g (0.045 mol) of triethylamine in 100 mL of dichloromethane was added dropwise with stirring under nitrogen a solution of 3.18 g (0.022 mol) of benzenesulfenyl chloride in 40 mL of dichloromethane. The reaction mixture was stirred for 2.5 h at room temperature, diluted with 150 mL of dichloromethane, and washed with 150 mL of water and 150 mL of 1 N NaOH solution. The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo to a brown oil. This oil was chromatographed on 100 g of silica gel using 5% MeOH/$CHCl_3$ as eluent. Evaporation of the solvent in vacuo afforded 3.23 g of a yellow oil, which partially crystallized on standing. Trituration with 4:1 petroleum ether/ether and cooling gave 2.06 g (35%) of a slightly yellow crystalline solid. Recrystallization from ethanol afforded 0.79 g (13.2%) of 4 as fine white crystalline solid, mp 74–76 °C.

1-Phenylpiperazine-4-benzenesulfenamide (7a). A mixture of 12.98 g (0.08 mol) of *N*-phenylpiperazine and 20.42 g (0.08 mol) of *N*-(phenylthio)phthalimide (8) in 400 mL of benzene was heated at reflux under nitrogen for 17 h, cooled to room temperature, and filtered to remove precipitated solid. The solid was washed with a small quantity of benzene, and the combined filtrate and washing were evaporated in vacuo to a yellow solid. Recrystallization from ethanol afforded 18.74 g (87%) of **7a** as fine colorless leaflets, mp 79.5–82 °C. The properties of compounds **2**, **3**, **5**, **6**, and **7b–l**, prepared in an analogous manner, are included in Tables I and II.

1-Phenylpiperazine-4-benzenesulfinamide (9a). To a solution of 4.87 g (0.03 mol) of *N*-phenylpiperazine in 150 mL of dichloromethane containing 4.59 mL (0.033 mol) of triethylamine was added dropwise with stirring under nitrogen a solution of 4.82 g (0.03 mol) of benzenesulfinyl chloride in 50 mL of dichloromethane. The reaction mixture was stirred for 3 h at room temperature, diluted with 100 mL of dichloromethane, and washed with 150 mL of water and 100 mL of 5% aqueous K_2CO_3 solution. The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo to a nearly colorless crystalline solid. Recrystallization from ethanol afforded 6.37 g (74%) of **9a** as a nearly colorless crystalline solid, mp 101–104 °C. The properties of compounds **9b**, **10a**, and **10b**, prepared in an analogous manner, are included in Table III.

SHR Test for Antihypertensive Activity. The assay was conducted and the data were analyzed as described in ref 2.

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Synthesis and Analgesic Properties of Some Conformationally Restricted Analogues of Profadol

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N-Methylspiro[5-hydroxytetralin-1,3'-pyrrolidine] (**2j**) and *N*-methylspiro[7-hydroxytetralin-1,3'-pyrrolidine] (**2n**), conformationally restricted analogues of profadol, were synthesized via initial reaction of the appropriately substituted 1-tetralone with ethyl cyanoacetate to give the ethyl 1-tetralylidenecyanoacetate derivative (**3**), which was then reacted with KCN to give the corresponding 1-cyano-1-(cyanomethyl)tetralin (**4**). Treatment of **4** with either HBr in dry ether–dichloromethane or acetic acid–sulfuric acid afforded the spiro[tetralin-1,3'-pyrrolidine-2',5'-dione] derivative (**5**), which was then reduced with $LiAlH_4$–THF and N-methylated with HCHO–HCO_2H to give the appropriately substituted spiro[tetralin-1,3'-pyrrolidine] (**2**). Both **2j** and **2n** and the isomeric 6-hydroxy derivative **21** all showed no significant analgesic activity in hot-plate and writhing tests. However, spiro[tetralin-1,3'-pyrrolidine] (**2a**) and its *N*-methyl derivative (**2b**) both possessed codeine-level analgesic activity.

The 3-alkyl-3-arylpyrrolidine derivative profadol (**1**) is the most potent analgesic in its structural class[1,2] and its enantiomers have been studied extensively both in animals and in man.[3-7] Numerous structure–activity studies of profadol derivatives have concentrated mainly on varying

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