Biological Activity. Antiinflammatory tests were performed on compounds 2, 3, 8, and 9 using the uv erythema screen[2] (guinea pigs) and anticarrageenin (rat paw edema) screen.[3]

Compounds 2 and 3 were inactive in these screens. Compounds 8 and 9 showed marginal activity in the anticarrageenin screen, 14 and 12%, respectively, at 100 mg/kg po, and 9 exhibited 44% inhibition in the uv erythema test at 100 mg/kg po.

By comparison 1 caused 39 and 48% inhibition in the anticarrageenin screen at doses of 2 and 4 mg/kg po, respectively. In the uv test 1 exhibited 58% inhibition at a dose of 4 mg/kg po.

Experimental Section†

3-Nitro-4-(2-nitropropenyl)anisole (5). This was prepared from 2-nitroanisaldehyde[5] (10 g) and nitroethane (7 ml) by the method of Beer, *et al.*[6] The product crystallized from ethanol as long yellow needles (5.5 g, 38.3%), mp 109–110°.

6-Methoxy-2-methylindole (4a). To 3-nitro-4-(2-nitropropenyl)-anisole (5 g, 0.02 mole) in glacial AcOH (125 ml) and EtOH (125 ml) was added 5% Pd/C (1 g), and the mixt was hydrogenated at atm pressure and room temp until 6 mole equiv of H_2 was absorbed. The catalyst was filtered, and the filtrate neutralized with $NaHCO_3$ in the presence of Et_2O. The neutralized soln was further extracted with Et_2O (3 × 500 ml), dried (Na_2CO_3), and evapd to yield a pale green solid. This was purified by Soxhlet extraction with petr ether (bp 60–80°), yielding colorless prisms (2.5 g, 75%), mp 102–103° (lit.[7] 102–103°).

3-*p*-Chlorobenzimidoyl-6-methoxy-2-methylindole (6a). Crude 6-methoxy-2-methylindole (7.5 g, 0.046 mole) and *p*-chlorobenzonitrile (18.8 g, 0.14 mole) were dissolved in 50 ml of Et_2O. Anhydrous HCl was bubbled through the soln for 8 hr. A solid pptd initially, then redissolved after about 2 hr. After 5 hr, a solid again began to separate. The reaction flask was stoppered and stored at 5° for 5 days. The Et_2O was decanted, fresh Et_2O (100 ml) was added, and the mixt was stirred for 1 hr. The imine HCl was removed by filtration, dried *in vacuo*, dissolved in hot EtOH, and basified (pH 9) with 10% NH_4OH. The product crystd from $CHCl_3$–petr ether as off-white prisms (2.5 g, 17%), mp 204–205°. *Anal.* ($C_{17}H_{15}ClN_2O$) N.

3-*p*-Chlorobenzoyl-6-methoxy-2-methylindole-1-acetic Acid (2). A mixt of 3-*p*-chlorobenzimidoyl-6-methoxy-2-methylindole (5.25 g, 0.017 mole), ethyl bromoacetate (3.3 g, 0.02 mole), reagent grade Me_2CO (30 ml), and anhyd K_2CO_3 (16 g) was heated under reflux for 18 hr. After cooling, the solid was filtered and washed well with Me_2CO (250 ml). The filtrates were evapd yielding a brown oily residue (≃5 g), which was heated under reflux with 3 *N* NaOH (75 ml) for 2 hr. The Na salt of 2 was crystd from the mixt, collected by filtration, and dissolved in hot H_2O (1 l.), and the soln filtered to remove the insol by-product 7a. Acidification of the filtrate with 10% H_2SO_4 yielded a pale yellow ppt which was collected, dried *in vacuo*, and then crystd from EtOH as pale yellow needles (1.5 g, 25%), mp 237–238°. *Anal.* ($C_{19}H_{16}ClNO_4$) C, H, N, Cl.

3-*p*-Chlorobenzimidoyl-5-methoxy-2-methylindole (6b). This was prepared in a manner analogous to 3-*p*-chlorobenzimidoyl-6-methoxy-2-methylindole (6a). The product crystd from aqueous EtOH as colorless needles (43%), mp 190–192°. *Anal.* ($C_{17}H_{15}ClN_2O$) C, H, N, Cl.

3-*p*-Chlorobenzoyl-5-methoxy-2-methylindole-1-acetic Acid (3). This was prepared in a manner analogous to 3-*p*-chlorobenzoyl-6-methoxy-2-methylindole-1-acetic acid (2). The product crystd from EtOH as colorless needles (33%), mp 248–249°. *Anal.* ($C_{19}H_{16}ClNO_4$) C, H, N, Cl.

3-(*p*-Chlorobenzoyl)-5-methoxy-2-methylindole-1-propionic Acid (8). 3-*p*-Chlorobenzimidoyl-5-methoxy-2-methylindole (5.0 g, 0.017 mole), methyl acrylate (1.7 g, 0.017 mole), Me_2CO (150 ml), and anhyd K_2CO_3 (1.0 g) were combined and heated under reflux for 72 hr. On cooling, the solid was filtered and washed well with Me_2CO (100 ml). The combined filtrates were evapd to yield a brown oily residue, which was heated under reflux with 3 *N* NaOH (50 ml) until a homogenous soln was obtained (~2 hr). On cooling, a white ppt formed (Na salt), which was collected by filtration, dissolved in hot H_2O (750 ml), and acidified (pH 2) with 10% H_2SO_4. The product was collected, dried *in vacuo*, and crystd from EtOH as colorless needles (3.6 g, 58%). *Anal.* ($C_{20}H_{18}ClNO_4$) C, H, N, Cl.

3-(*p*-Chlorobenzoyl)-5-methoxy-α,2-dimethylindole-1-propionic Acid (9). 3-*p*-Chlorobenzimidoyl-5-methoxy-2-methylindole (5.0 g, 0.017 mole) and methyl methacrylate (10 g, 0.1 mole) reacted under conditions similar to those for 8. The product was recrystd from EtOH as pale yellow needles (400 mg, 6.2%), mp 178–179°. *Anal.* ($C_{21}H_{20}ClNO_4$) C, H, N, Cl.

Acknowledgments. We wish to express our appreciation to Mrs. M. L. Graeme and coworkers for the antiinflammatory testing and to Mr. S. Lopoukhine for technical assistance. We are indebted to Mrs. M. Myers and associates for the microanalyses.

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†Melting points were determined with a Thomas-Hoover apparatus equipped with a corrected thermometer. Microanalyses were performed by the Analytical Research Department of Geigy Chemical Corp. Where analyses are indicated only by symbols of the elements, analytical results for those elements were within ±0.4% of the theoretical values. pK_{mcs} were determined by the method of Simon and Heilbronner.[4] Distribution coefficients were detd spectrophotometrically on aqueous buffer solns of the compds equilibrated with $CHCl_3$.

Some Hypotensive Thiadiazoles†

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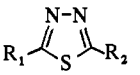
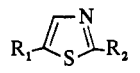
In two structurally unrelated series of diuretics it has been observed that removal of the sulfamoyl group results in a loss of diuretic activity and the enhancement of hypotensive activity. Firstly, the diuretic benzothiadiazines[2] led to the development of diazoxide[3] and studies of its analogs.[4,5] Secondly, various hypotensive phthalimidines[6,7] related to chlorthalidone[8] were described. We now report a third series structurally unrelated to the other two, derived from acetazolamide.[9] The compounds discussed here, except for some analogous thiazoles, are all related to 2-amino-1,3,4-thiadiazole by substitution in the amino group and, in a few cases, in the 5 position. Derivatives of acetazolamide, a powerful carbonic anhydrase inhibitor, have not previously been described as having hypotensive properties. However, it was observed by Rubin, *et al.*,[10] that "removal of the sulfamoyl group from substances having diuretic properties usually yields compounds lacking diuretic effect but showing antihypertensive activity."

†This project was performed in the George Hyman Memorial Research Building at the Washington Hospital Center and was supported by the Research Foundation of the Washington Hospital Center and by N.I.H. Grant 5RO1 HE12963. A preliminary report of part of this work was given at the National Meeting of the American Federation for Clinical Research, Atlantic City, N. J., May 1970.[1]

Table I



Compd	R_1	R_2	Formula	Ref or anal.[a]	Hypotensive activity[b]	Urine output[c]	Blood sugar[c]
1	H	NH_2	$C_2H_3N_3S$	17	–	–	–
2	H	NHCHO	$C_3H_3N_3OS$	18	–	–	–
3	H	$NHCOCH_3$	$C_4H_5N_3OS$	17	50	–74	+10
4	H	$NHCOC_2H_5$	$C_5H_7N_3OS$	19	–	–	–
5	H	$NHCOCH(CH_3)_2$	$C_6H_9N_3OS$	C, H, N, S	–	–	–
6	H	$NHCO(CH_2)_{16}CH_3$	$C_{20}H_{37}N_3OS$	19	–	–	NT
7	H	$NHCOCH{=}CHCO_2H$	$C_6H_5N_3O_3S$	C, H, N, S	–	–	NT
8	H	$NHCOCH_2CH_2CO_2H$	$C_6H_7N_3O_3S$	C, H, N, S	–	–	NT
9	H	$NHCOC_6H_4OCH_3$-*p*	$C_{10}H_9N_3O_2S$	C, H, N, S	–	–	–9
10	H	$NHCOCH_2Cl$	$C_4H_4ClN_3OS$	20	–	–54	–
11	H	$NHCOCH_2NHCO_2C(CH_3)_3$	$C_9H_{14}N_4O_3S$	C, H, N, S	–	–	–
12	H	$NHCOCH_2NHCO_2CH_2C_6H_5$	$C_{12}H_{12}N_4O_3S$	C, H, N, S	–	–40	–
13	H	$NHCO_2CH_3$	$C_4H_5N_3O_2S$	C, H, N, S	50	–	+18
14	H	$NHCO_2CH(CH_3)_2$	$C_7H_{11}N_3O_2S$	C, H, N, S	50	–	–
15	H	$NHCONH_2$	$C_3H_4N_4OS$	21	–	–	–
16	H	$NHCONHC_6H_5$	$C_9H_8N_4OS$	C, H, N, S	50	–	–13
17	H	$NHCONHC_6H_4Cl$-*m*	$C_9H_7ClN_4OS$	C, H, N, S	–	–	–
18	H	$NHCONHSO_2C_6H_4CH_3$-*p*	$C_{10}H_{10}N_4O_3S_2$	22	–	–	–
19	H	$NHCSNHC_2H_5$	$C_5H_8N_4S_2$	C, H, N	–	–	–
20	H	$NHNO_2$	$C_2H_2N_4O_2S$	17	100	–	–
21	H	$NHNH_2$	$C_2H_4N_2S$	C, H, N	–	NT	NT
22	H	$NHCH_3 \cdot HCl$	$C_3H_6ClN_3S$	23	–	–	–
23	H	$N(CH_3)COCH_3$	$C_5H_7N_3OS$	24	100	–	–
24	H	$N(CH_3)CONHC_6H_5$	$C_{10}H_{10}N_4OS$	C, H, N, S	–	–	–
25	H	$N(CH_3)NO$	$C_3H_4N_4OS$	21	–	NT	NT
26	CH_3	$NHCOCH_3$	$C_5H_7N_3OS$	25	–	–	–
27	CH_3	$NHCONHC_6H_5$	$C_{10}H_{10}N_4OS$	26	100	+111	–
28	CH_3	$NHNO_2$	$C_3H_4N_4O_2S$	27	–	NT	NT
29	C_2H_5	$NHCOC_2H_5$	$C_7H_{11}N_3OS$	28	200	+77	–
30	C_6H_5	$NHCOCH_3$	$C_{10}H_9N_3OS$	29	–	–	–
31	C_6H_5	$NHNO_2$	$C_{10}N_9N_3OS$	27	–	NT	NT
32	$NHCOCH_3$	$NHCOCH_3$	$C_6H_8N_4O_2S$	30	–	NT	NT
33	SH	NH_2	$C_2H_3N_3S_2$	31	–	NT	NT
							
34	H	$NHCOCH_3$	$C_5H_6N_2OS$	32	100	+62	–
35	H	$NHCO_2CH_3$	$C_5H_6N_2O_2S$	33	–	NT	NT
36	H	$NHCONHC_6H_5$	$C_{10}H_9N_3OS$	C, H, N, S	100	NT	NT

[a] Elementary analyses are indicated by symbols of the elements; analytical results obtained for those elements were within ±0.4% of the theoretical values. [b] Hypotensive activity is expressed as minimum effective (see text) dose in mg/kg. The "dash" symbol (–) denotes inactivity by this criterion. [c] Urine output and blood sugar (at 4 hr) are expressed as percentage increase or decrease compared with controls, where statistically significant. "NT" denotes compounds not tested.

The structures and hypotensive activities of these compounds are given in Table I. Ten compounds caused a significant reduction in blood pressure, and in one case **(34)** the effect continued for 24 hr. When some compounds **(16, 34)** were tested on DOCA hypertensive rats[11] and some **(3, 16, 21, 34)** on spontaneously hypertensive rats,[12] only one **(34)** showed hypotensive activity. Further investigation of the action of this compound revealed that tolerance developed within 48 hr during daily administration.

The hypotensive benzothiadiazines and phthalimidines are known to possess antidiuretic and hyperglycemic activity.[5,7] It was therefore pertinent to investigate the effects of the present series of compounds upon urine output and blood sugar. Some compounds increased urine output and some decreased it, but in only a few cases was the observed change statistically significant ($p < 0.05$). Effects on blood sugar level were likewise confined to a few compounds and were minimal. In comparison with diazoxide, this series of compounds generally lacked the hyperglycemic and antidiuretic side effects, but were also less potent as hypotensive agents.

Experimental Section

2-Isobutyramido-1,3,4-thiadiazole (5). Isobutyryl chloride (4.5 g, 0.042 *M*) was added dropwise to a stirred slurry of 2-amino-1,3,4-thiadiazole (4.04 g, 0.04 *M*) in dry pyridine (50 ml) at 0°. After 3 hr at room temperature, water (150 ml) was added, and the resulting solution concentrated to 50 ml. The precipitated product was collected, washed with water, and recrystallized from MeOH: mp 180–182°; yield, 5.6 g (82%).

2-Maleamido-1,3,4-thiadiazole (7). Maleic anhydride (4.90 g, 0.05 *M*) in MeCN (50 ml) was added to 2-amino-1,3,4-thiadiazole (5.05 g, 0.05 *M*), dissolved in warm MeCN (150 ml). The solution was heated for 15 min under reflux. After cooling, the precipitated product was collected and recrystallized from water: mp 159–160° dec; yield, 3.8 g (38%).

2-Succinamido-1,3,4-thiadiazole (8). Succinic anhydride (2.00 g, 0.02 *M*) was added to a solution of 2-amino-1,3,4-thiadiazole (2.02 g, 0.02 *M*) in hot MeCN, and the solution was heated for 1 hr under reflux. After cooling, the precipitated product was collected and recrystallized from water: mp 325°; yield 2 g (49%).

2-(4'-Methoxybenzamido)-1,3,4-thiadiazole (9). Anisoyl chloride (5.63 g, 0.033 *M*) was added dropwise to the stirred slurry of 2-amino-1,3,4-thiadiazole (3.03 g, 0.03 *M*) in dry pyridine (50 ml) at 0°. After 3 hr at room temperature, water (150 ml) was added, and the precipitated product was collected and recrystallized from EtOH: mp 234–235°; yield, 6.5 g (92%).

2-*tert*-Butoxycarbonylaminoacetamido-1,3,4-thiadiazole (11).

tert-Butoxycarbonylglycine (1.75 g, 0.01 *M*) and NEt_3 (1.45 ml) in MeCN (30 ml) was cooled to −10°, and isobutyl chloroformate (1.4 ml, 0.011 *M*) was added with stirring. After 20 min at −10°, a shaken suspension of 2-amino-1,3,4-thiadiazole hydrochloride (1.37 g) in MeCN (25 ml) containing NEt_3 (1.4 ml) was added. The mixture was stirred at room temperature overnight and then evaporated, and EtOAc (35 ml) added. A white solid was filtered off, washed with water, and recrystallized from EtOH as needles: mp 217–218°; yield, 1.26 g (49%).

2-Benzyloxycarbonylaminoacetamido-1,3,4-thiadiazole (12). Carbobenzoxyglycine (7.25 g, 0.036 *M*) and NEt_3 (7.25 ml) in MeCN (120 ml) was cooled to −10°, and isobutyl chloroformate (7 ml, 0.054 *M*) added with stirring. After 20 min at −10°, a shaken suspension of 2-amino-1,3,4-thiadiazole hydrochloride (6.85 g, 0.05 *M*) in MeCN (100 ml) containing NEt_3 (7 ml) was added. The mixture was stirred at room temperature overnight and then evaporated, and the residue agitated with water (100 ml). The solid was filtered off and recrystallized from DMF–water, then from AcOH to afford the product as needles: mp 218–220°; yield, 7.34 g (71%).

2-Methoxycarbonylamino-1,3,4-thiadiazole (13). Methyl chloroformate (0.9 ml, 0.012 *M*) was added to a briskly stirred mixture of 2-amino-1,3,4-thiadiazole hydrochloride (1.37 g, 0.01 *M*), $NaHCO_3$ (2 g), water (20 ml), and EtOAc (20 ml). After 24 hr, the solid was separated, and the EtOAc layer washed with water, dried (Na_2SO_4), and evaporated. Combined residue and solid recrystallized from EtOH as needles: mp 212–215° dec; yield, 1.45 g (91%).

2-Isobutyloxycarbonylamino-1,3,4-thiadiazole (14). Isobutyl chloroformate (1.3 ml, 0.01 *M*) was added to a briskly stirred mixture of 2-amino-1,3,4-thiadiazole hydrochloride (1.37 g, 0.01 *M*), $NaHCO_3$ (2 g), water (20 ml), and EtOAc (20 ml). After 2 hr, the EtOAc layer was separated and washed with aqueous NaCl. The aqueous phase was extracted with EtOAc, and the combined extracts were dried (Na_2SO_4) and evaporated. The residual solid crystallized from EtOAc–petroleum ether as prisms: mp 149–151°; yield, 0.79 g (39%).

1'-(1,3,4-Thiadiazol-2-yl)-3'-phenylurea (16). A mixture of 2-amino-1,3,4-thiadiazole (5.05 g, 0.05 *M*) and phenyl isocyanate (11.9 g, 0.1 *M*) was stirred for 1 hr at 80–100°. After cooling, the crude product was washed with ether and recrystallized from EtOH as needles: mp 237–239° dec; yield, 5.0 g (45%).

1'-(1,3,4-Thiadiazol-2-yl)-3'-*m*-chlorophenylurea (17). *m*-Chlorophenyl isocyanate (3.07 g, 0.02 *M*) was added to a well-stirred slurry of 2-amino-1,3,4-thiadiazole (2.02 g, 0.02 *M*) in dry benzene (50 ml). After 30 min at room temperature, the mixture was heated under reflux for 30 min. After cooling, the precipitated product was separated and recrystallized from DMF–water (with charcoal) to give the product: mp 235–237° dec; yield, 4.9 g (96%).

1'-(1,3,4-Thiadiazol-2-yl)-3'-ethylthiourea (19). Ethyl isothiocyanate (8.7 g, 0.1 *M*) and 2-amino-1,3,4-thiadiazole (5.05 g, 0.05 *M*) in DMF (25 ml) were heated for 16 hr at 130°. After cooling, the solution was added to water (150 ml), and the precipitated product washed with ether and recrystallized from EtOH: mp 205–206°; yield, 3.1 g (33%).

2-Hydrazino-1,3,4-thiadiazole (21). 2-Bromo-1,3,4-thiadiazole[13] (13.0 g, 0.08 *M*) was added to a stirred mixture of hydrazine hydrate (50 ml) and EtOH (50 ml) at 0°, and stirring was continued at room temperature for 24 hr. After evaporation *in vacuo*, the residue was three times recrystallized from MeOH to afford a product, $C_2H_4N_4S \cdot N_2H_4$: mp 156–157°; yield, 7.1 g (60%). After 15 hr at 80° (1 mm), an elementary analysis for $C_2H_4N_4S$ was obtained.

1'-Methyl-1'-(1,3,4-thiadiazol-2-yl)-3'-phenylurea (24). Phenyl isocyanate (0.75 ml, 0.007 *M*) and 2-methylamino-1,3,4-thiadiazole (0.50 g, 0.0043 *M*) in dry benzene (9 ml) were heated under reflux for 3.5 hr, then evaporated. The residue recrystallized from EtOH as needles: mp 137–138.5°; yield, 0.81 g (80%).

Hypotensive Activity. Compounds were administered orally as a suspension in 2% gelatin to conscious, male Sprague–Dawley rats. Doses of 50, 100, and 200 mg/kg were given to 6 rats at each dose level. The blood pressure was measured at 0, 4, and 24 hr after drug administration by means of an indwelling catheter in the carotid artery.[14] In the spontaneously hypertensive rats blood pressure was measured by the tail-cuff method.[15] Statistical analysis entailed use of the paired *t* test to compare 4-hr and initial blood pressure. Minimum doses required to produce a statistically significant reduction in blood pressure are given in Table I.

Urine Output Studies. Each compound was administered orally in 2% gelatin to 6 male Sprague–Dawley rats at a dose of 200 mg/kg. Water (5 ml) was administered orally 30 min before the test compound. Urine output was measured in metabolic cages, and comparison was made with output from rats which received gelatin as control.

Hyperglycemic Activity. Each compound was administered orally in gelatin to 6 male Sprague–Dawley rats at a dose of 200 mg/kg. The animals received standard cube diet prior to administration of the test compound, and only water thereafter. Blood sugar was measured at 0, 4, and 24 hr by the method of Hoffman.[16]

Acknowledgments. We thank Dr. W. Alford (National Institutes of Health) for the microanalyses, and C. Allen, E. Cooper, E. McNeal, W. Picciotta, M. Terry, and K. Weinhardt for technical assistance.

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