2-Imino-3,4-dimethyl-5-phenyloxazolidine (X).[4c]—A 7.0 g. sample (0.0425 mole) of *dl*-ephedrine[30] was cyclized with cyanogen bromide using Method A. After recrystallization from ether–petroleum ether, 4.77 g. (59.5%) of pure 2-imino-3,4-dimethyl-5-phenyl-2-oxazolidine (X) was obtained, m.p. 67–71°. Literature[4c] m.p. 71–73°; λ_{max}^{KBr} 3.0, 3.35, 3.47, 5.95, 6.45, 6.65, 6.88, 7.02, 7.17, 7.27, 7.35 μ.

1-(or 3-)Acetyl-1-(β-hydroxy-α-methylphenethyl)urea (XI or XII).—To a solution of 5 g. (0.0286 mole) of 2-amino-4-methyl-5-phenyl-2-oxazoline (V) in 65 ml. of pyridine was added 8 ml. of acetic anhydride. The solution was left to stand at room temperature for 72 hr.; it was then acidified with cold 10% hydrochloric acid and washed 3 times with ether. The aqueous solution was made basic with 30% sodium hydroxide solution and extracted thoroughly with ether and methylene chloride. The extracts were dried and concentrated, affording 3.3 g. of product. The aqueous basic solution was saturated with salt and re-extracted, affording an additional gram of product. The two crops were combined and recrystallized from methanol–benzene, yielding 3.2 g. (51.5%) of the substituted urea: m.p. (198.5) 208.5–211.5° dec. The sample was recrystallized once from methanol–benzene and once from acetone affording 1.77 g. of product, m.p. 206–207.5°; λ_{max}^{KBr} 2.94, 3.02, 3.15, 3.35, 5.86, 6.10, 6.40, 6.66, 6.86, 6.96, 7.17, 7.25 μ.

Anal. Calcd. for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.83; N, 11.86. Found: C, 61.12; H, 6.90; N, 11.91.

(30) Obtained from Merck and Co., Inc.

Hypotensive 1,2,4-Benzothiadiazines

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2-Aminobenzenesulfonamides were prepared by way of (1) the chlorosulfonation of aminobenzenes, (2) the amination of 2-chlorobenzenesulfonamides and (3) the chlorine oxidation of 2-benzylmercaptonitrobenzenes. New 1,2,4-benzothiadiazine-1,1-dioxides were obtained by the cyclization of the 2-aminobenzenesulfonamides with formic acid, ortho esters, mixed anhydrides and with aldehydes. The hypotensive activities of the endocyclic sulfonamides are described.

Since the hypotensive activity of 6-chloro-7-sulfamoyl-1,2,4-benzothiadiazine-1,1-dioxide was recognized clinically,[1] there has been a search in this laboratory for sulfonamides having principally or exclusively effective hypotensive activity. This paper describes part of the investigation concerned with 1,2,4-benzothiadiazine-1,1-dioxides not containing an extranuclear 7-sulfamoyl group.

Chlorosulfonation of 3-chloro-4-methylaniline and of 4-chlorobenzoic acid yielded, respectively, 2-amino-4-chloro-5-methylbenzenesulfonyl chloride and 5-carboxy-2-chlorobenzenesulfonyl chloride. The reactive chlorine atoms of 2,3-dichloronitrobenzene and of 2-chloro-5-methylnitrobenzene were displaced by benzylthiol in alkaline solution. Chlorine oxidation of the resulting 2-benzylmercapto-3-chloronitrobenzene and 2-benzylmercapto-5-methylnitrobenzene yielded the corresponding 2-nitrobenzenesulfonyl chloride. All the above sulfonyl chlorides were converted to sulfonamides by treating them with liquid ammonia. Reactions of 5-chloro-2-nitrobenzenesulfonyl chloride with *n*-propylamine and with benzylamine yielded N-*n*-propyl- and N-benzyl-5-chloro-2-nitrobenzenesulfonamides. Catalytic reduction of the 2-nitrobenzenesulfonamides and displacement of the chlorine of 2-chloro-5-carboxybenzenesulfonamide yielded the 2-aminobenzenesulfonamides listed in Table I.

Cyclization of 2-aminobenzenesulfonamides with formic acid, triethyl orthoformate, triethyl orthoacetate and with triethyl orthopropionate yielded 3-H-, 3-methyl- and 3-ethyl-1,2,4-benzothiadazine-1,1-dioxides (Table II). Mixed anhydrides of trifluoroacetic acid with alkane, aralkane and cycloalkanecarboxylic acids reacted with the 2-aminobenzenesulfonamides to give 2-carboxamidobenzenesulfonamides. One of these, 5-chloro-2-phenacetylaminobenzenesulfonamide, was isolated and characterized. The other crude 2-carboxamidobenzenesulfonamides were cyclized in concentrated ammonium hydroxide to yield 3-alkyl (4 or more carbons), 3-aralkyl- and 3-cycloalkyl-1,2,4-benzothiadiazine-1,1-dioxides (Table II). The mixed anhydride method was not successful with benzoic acid, and 6-methyl-3-trifluoromethyl-1,2,4-benzothiadiazine-1,1-dioxide was obtained from the reaction with the anhydride of trifluoroacetic acid and 3,4,5-trimethoxybenzoic acid. Condensations of aldehydes with the 2-aminobenzenesulfonamides in acid gave the 2,3-dihydro-3-alkyl-, aralkyl- and cycloalkyl-1,2,4-benzothiadiazine-1,1-dioxides (Table III). The unusual and new adamantane-1-carboxaldehyde was prepared by the lithium aluminum hydride reduction of N-methyl-N-phenyl-adamantane-1-carboxamide. This amide was obtained from adamantane-1-carboxylic acid through the acid chloride.

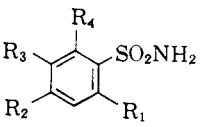
Experimental

Chlorosulfonations (Table I).—To 1 kg. of chlorosulfonic acid was added carefully 100 g. of 3-chloro-4-methylaniline or 100 g. of *p*-chlorobenzoic acid. The mixture was stirred mechanically, and 150–200 g. of NaCl was added in small portions. The escaping hydrogen chloride was conducted to a water-wash column. The reaction mixture was heated in an oil-bath at 160° for 5 hr., then cooled and added to ice water. The separated sulfonyl chloride was extracted with ether or collected on a filter, washed with water and dried. The product was added cautiously to excess liquid ammonia in an open beaker. After the excess ammonia had evaporated, the solid sulfonamide was recrystallized from alcohol.

2-Benzylmercaptonitrobenzenes and their Chlorine Oxidation (Table I).—To a cold solution of KOH (54–108 g.) in 2 l. of alcohol was added 100 g. of benzylmercaptan and either 154.5 g. of 2,3-dichloronitrobenzene or 128 g. of 2-chloro-5-methylnitro-

(1) W. Hollander and R. W. Wilkins, *Boston Med. Quart.*, **8**, 69 (1957); R. W. Wilkins, *New England J. Med.*, **257**, 1026 (1957); A. A. Rubin, F. E. Roth, R. M. Taylor, and H. Rosenkilde, *J. Pharmacol. Exptl. Therap.*, **136**, 344 (1962).

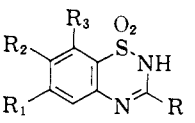
TABLE I



R_1	R_2	R_3	R_4	Empirical formula	M.p., °C.	Yield, %	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
NH_2	Cl	CH_3	H	$C_7H_9ClN_2O_2S$	185	45	38.09	4.11	12.69	38.16	4.28	12.49
Cl	H	CO_2H	H	$C_7H_6ClNO_4S$	260	70	35.67	2.56	5.84	35.85	2.77	5.73
NO_2	H	H	Cl	$C_6H_5ClN_2O_4S$	144	70	30.40	2.13	11.83	30.37	2.16	11.77
NH_2	H	CH_3	H	$C_7H_{10}N_2O_2S$	125	15	45.14	5.41	15.04	45.23	5.68	15.00
NH_2	H	H	Cl	$C_6H_7ClN_2O_2S$	135	91	34.90	3.41	13.56	35.09	3.39	13.42
NH_2	H	CO_2H	H	$C_7H_8N_2O_4S$	263 d.	42	38.88	3.72	12.96	38.96	3.70	12.98
C_8H_8NO[a]	H	Cl	H	$C_{14}H_{13}ClN_2O_3S$	148	60	51.75	4.03	8.63	51.92	4.06	8.47

[a] Phenylacetamido.

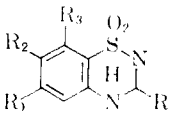
TABLE II



R	R_1	R_2	R_3	Empirical formula	M.p., °C.	Yield, %	Analyses % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Average % blood pressure change
H	H	$NHCOCH_3$	H	$C_9H_9N_3O_3S$	301	50	45.18	3.79	17.65	45.10	3.85	18.09	0.0
H	H	NH_2	H	$C_7H_7N_3O_2S$	325	70	42.60	3.58	21.30	42.56	3.94	21.60	0.0
H	H	NO_2	H	$C_7H_5N_3O_4S$	262	85	37.00	2.22	14.11[a]	36.50	2.18	13.74[a]	−8.0
CH_3	Cl	H	H	$C_8H_7ClN_2O_2S$	280	48			12.25			12.45	−2.9
CH_3	Cl	CH_3	H	$C_9H_9ClN_2O_2S$	304	72	44.20	3.71	11.45	44.14	3.87	11.21	−2.3
C_2H_5	Cl	CH_3	H	$C_{10}H_{11}ClN_2O_2S$	290	70	46.42	4.26	10.82	46.65	4.51	10.65	0.0
$CH(C_6H_5)_2$	Cl	CH_3	H	$C_{21}H_{17}ClN_2O_2S$	285	11	63.55	4.31	7.06	63.74	4.51	7.01	+3.3
$CH_2SO_2C_6H_5$	Cl	CH_3	H	$C_{15}H_{13}ClN_2O_4S_2$	307	13	46.81	3.40	7.28	47.08	3.58	7.02	+1.2
CH_3	H	H	Cl	$C_8H_7ClN_2O_2S$	261	81	41.20	3.06	12.25	41.09	2.91	12.02	+3.1
C_2H_5	H	H	Cl	$C_9H_9ClN_2O_2S$	229	70	44.20	3.71	11.45	44.81	4.15	11.15	−3.9
H	Cl	Cl	H	$C_7H_4Cl_2N_2O_2S$	303	52	33.47	1.59	11.15	33.66	1.41	11.37	−3.2
CH_3	Cl	Cl	H	$C_8H_6Cl_2N_2O_2S$	322	48	36.26	2.28	10.57	36.34	2.49	10.33	−14.9
C_2H_5	Cl	Cl	H	$C_9H_8Cl_2N_2O_2S$	311	70	38.38	2.89	10.04	39.04	3.10	10.04	−13.1
C_3H_7	Cl	Cl	H	$C_{10}H_{10}Cl_2N_2O_2S$	310	43	40.96	3.43	9.56	40.84	3.24	9.39	−7.6
$C_{10}H_{16}$[b]	Cl	Cl	H	$C_{17}H_{18}Cl_2N_2O_2S$	>400	21	53.00	4.71	7.27	52.85	5.10	6.97	−3.1
1-$CH_2C_{10}H_7$	Cl	Cl	H	$C_{18}H_{12}Cl_2N_2O_2S$	314	20	55.25	3.09	7.16	55.37	3.07	6.87	0.0
$CH_2SC_6H_5$	Cl	Cl	H	$C_{14}H_{10}Cl_2N_2O_2S_2$	241	34	45.04	2.70	7.50	45.24	2.92	7.27	+1.2
CH_3	CF_3	H	H	$C_9H_7F_3N_2O_2S$	326	36	40.90	2.67	10.61	41.36	2.92	10.42	−13.7
C_2H_5	CF_3	H	H	$C_{10}H_9F_3N_2O_2S$	312	39	43.17	3.26	10.07	43.26	3.04	10.05	−15.9
$CH_2SC_6H_{11}$	CF_3	H	H	$C_{15}H_{17}F_3N_2O_2S_2$	196	32	47.60	4.53	7.40	48.06	4.51	7.14	0.0
CH_3	CH_3	H	H	$C_9H_{10}N_2O_2S$	250	56	51.47	4.79	13.34	51.38	5.01	13.09	+3.1
C_2H_5	CH_3	H	H	$C_{10}H_{12}N_2O_2S$	218	83	53.57	5.37	12.49	53.71	5.21	12.34	−4.9
$(CH_2)_2C_6H_5$	CH_3	H	H	$C_{16}H_{16}N_2O_2S$	244	46	63.97	5.37	9.33	64.07	5.48	9.12	0.0
$CH_2SCH_2C_6H_5$	CH_3	H	H	$C_{16}H_{16}N_2O_2S_2$	191	54	57.80	4.85		58.12	4.78		−5.8
CH_3	Cl	H	Cl	$C_8H_6Cl_2N_2O_2S$	370	61	36.26	2.29	10.57	36.44	2.46	10.46	−3.6
C_2H_5	Cl	H	Cl	$C_9H_8Cl_2N_2O_2S$	337	80	38.74	2.89	10.04	38.74	2.99	9.83	−2.0
$CH_2OC_6H_5$	Cl	H	Cl	$C_{14}H_{10}Cl_2N_2O_3S$	265	57	47.15	2.83	7.85	47.02	2.88	7.60	0.0
$CH_2C_6H_5$	Cl	H	Cl	$C_{14}H_{10}Cl_2N_2O_2S$	230	28	47.90	2.87	7.98	47.84	2.89	7.97	−1.9
C_6H_{11}	Cl	H	Cl	$C_{13}H_{14}Cl_2N_2O_2S$	326	29	46.80	4.24	8.42	46.94	4.39	8.22	0.0
$C_{10}H_{16}$[b]	Cl	H	Cl	$C_{17}H_{18}Cl_2N_2O_2S$	400	18	52.85	4.93	7.25	52.95	4.89	7.00	+2.4
CH_3	H	Cl	H	$C_8H_7ClN_2O_2S$	327	60	41.60	3.06	12.13	42.01	3.31	11.90	−3.9
C_2H_5	H	Cl	H	$C_9H_9ClN_2O_2S$	272	83	44.17	3.71	11.45	44.37	3.96	11.44	−4.6
C_7H_9[c]	H	Cl	H	$C_{14}H_{13}ClN_2O_2S$	268	19	54.40	4.24	9.07	53.81	4.30	8.67	−3.0
$CH_2OC_6H_5$	H	Cl	H	$C_{14}H_{11}ClN_2O_3S$	240	31	52.10	3.44	8.67	52.23	3.51	8.57	0.0
$CH_2C_6H_5$	H	Cl	H	$C_{14}H_{11}ClN_2O_2S$	262	32	54.75	3.61	9.13	54.68	3.70	9.07	+2.1
C_6H_9[d]	H	Cl	H	$C_{13}H_{14}ClN_2O_2S$	246	27	52.55	4.74	9.42	52.69	4.62	9.23	−1.3
C_6H_{11}	H	Cl	H	$C_{13}H_{15}ClN_2O_2S$	312	28	52.20	5.06	9.37	52.19	5.19	9.23	0.0
C_5H_5S[e]	H	Cl	H	$C_{12}H_9ClN_2O_2S_2$	298	50	45.90	2.87	8.93	46.57	3.17	9.00	
CF_3	CH_3	H	H	$C_9H_7F_3N_2O_2S$	298	40	40.90	2.67		41.48	2.77		−3.8
CH_3	H	CO_2H	H	$C_9H_8N_2O_4S$	390 d.	6	44.99	3.35	11.66	44.76	3.35	11.45	+1.9

[a] Values for S. [b] 1-Adamantyl. [c] 5-Norbornen-2-yl. [d] Cyclopent-2-enylmethyl. [e] Thiophene-2-methyl.

TABLE III



R	R_1	R_2	R_3	Empirical formula	M.p., °C.	Yield, %	Analyses %, Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Average % blood pressure change
C_7H_9[a]	Cl	Cl	H	$C_{14}H_{14}Cl_2N_2O_2S$	239	17	48.70	4.07	8.12	48.86	4.15	8.26	+1.4
$(CH_2)_2C_6H_5$	H	H	Cl	$C_{15}H_{15}ClN_2O_2S$	229	48	55.77	4.68	8.68	56.18	4.84	8.14	+2.6
$CH_2CH(CH_3)_2$	H	H	Cl	$C_{11}H_{15}ClN_2O_2S$	213	83	48.10	5.50	10.20	48.04	5.67	10.06	+1.3
C_2H_5	CF_3	H	H	$C_9H_{11}F_3N_2O_2S$	198	26	42.85	3.95	10.00	42.89	4.03	9.95	−4.7
$CH_2C_5H_9$	CF_3	H	H	$C_{14}H_{17}F_3N_2O_2S$	242	35	50.29	5.12	8.38	50.38	5.10	8.51	−3.9
C_7H_9[a]	CF_3	H	H	$C_{15}H_{15}F_3N_2O_2S$	239	40	52.35	4.38	8.13	52.88	4.49	8.11	+1.6
$CH_2C_6H_{11}$	CF_3	H	H	$C_{15}H_{19}F_3N_2O_2S$	237	6	51.71	5.50	8.04	51.82	5.74	7.92	0.0
3,4-$(OC_2H_5)_2C_6H_3$	CF_3	H	H	$C_{19}H_{19}F_3N_2O_4S$	178	10	51.92	4.60	6.74	51.75	4.80	6.71	−4.6
$(CH_2)_2C_6H_5$	CH_3	H	H	$C_{16}H_{18}N_2O_2S$	166	41	63.54	6.00	9.27	64.05	6.35	9.00	+4.5
$CH_2CH(CH_3)_2$	Cl	H	Cl	$C_{11}H_{14}Cl_2N_2O_2S$	266	88	42.75	4.57	9.07	42.65	4.55	8.92	0.0
$CH(C_2H_5)_2$	Cl	H	Cl	$C_{12}H_{16}Cl_2N_2O_2S$	241	43	44.60	4.99	8.67	44.44	5.17	8.51	−3.3
C_4H_3O[b]	Cl	H	Cl	$C_{11}H_8Cl_2N_2O_3S$	260	45	41.38	2.52	8.78	41.66	2.35	8.84	0.0
$CH_2C_5H_9$	Cl	H	Cl	$C_{13}H_{16}Cl_2N_2O_2S$	283	55			8.36			8.27	
C_7H_9[a]	Cl	H	Cl	$C_{14}H_{14}Cl_2N_2O_2S$	255	30	48.74	4.09	8.12	48.67	4.27	7.92	0.0
1-$C_{10}H_7$	Cl	H	Cl	$C_{17}H_{12}Cl_2N_2O_2S$	279	78	53.85	3.19	7.38	54.49	3.29	7.33	+2.1
$C_{10}H_{15}$[c]	Cl	H	Cl	$C_{17}H_{20}Cl_2N_2O_2S$	341	46	52.71	5.20	7.23	52.81	5.23	7.08	0.0
$CH_2C_6H_{11}$	Cl	H	Cl	$C_{14}H_{18}Cl_2N_2O_2S$	270	57	48.18	5.20	8.03	48.14	5.30	7.86	0.0
$(CH_2)_2C_6H_5$	Cl	H	Cl	$C_{15}H_{14}Cl_2N_2O_2S$	249	42	50.46	3.92	7.84	50.53	4.05	7.85	0.0
3,4-$(OC_2H_5)_2C_6H_3$	H	Cl	H	$C_{17}H_{19}ClN_2O_4S$	232	6	53.34	5.00	7.32	53.56	5.06	7.23	+1.8
C_5H_7O[d]	H	Cl	H	$C_{12}H_{13}ClN_2O_3S$	274	21	47.88	4.35	9.31	47.99	4.46	9.18	−2.3
C_7H_9[a]	H	Cl	H	$C_{14}H_{15}ClN_2O_2S$	205	4	54.07	4.86	9.01	54.21	4.93	9.21	+2.4
$CH_2C_5H_9$	H	Cl	H	$C_{13}H_{17}ClN_2O_2S$	209	28	51.90	5.71	9.33	51.85	5.66	9.55	
C_7H_{13}[e]	H	Cl	H	$C_{14}H_{17}ClN_2O_2S$	200	60	53.72	6.48	8.95	53.78	5.65	8.84	−1.1
$(CH_2)_2C_6H_5$	H	Cl	H	$C_{15}H_{15}ClN_2O_2S$	179	16	55.77	4.68	8.68	55.70	4.73	8.86	+2.6
C_6H_9[f]	H	Cl	H	$C_{13}H_{15}ClN_2O_2S$	191	14	52.25	5.06	9.38	52.46	5.13	9.20	+1.5
C_7H_{15}[g]	H	Cl	H	$C_{14}H_{19}ClN_2O_2S$	197	28	53.41	6.08	8.90	53.21	6.03	8.86	0.0
H	H	Cl	H	$C_{16}H_{13}ClN_2O_2S$[h]	140	86	46.06	5.02	10.74	45.87	4.98	10.57	+2.1
H	H	Cl	H	$C_{14}H_{13}ClN_2O_2S$[i]	160	70	54.59	3.93	9.10	54.34	4.17	9.21	−7.9

[a] 5-Norbornen-2-yl. [b] 2-Furyl. [c] 1-Adamantyl. [d] 2,3-Dihydro-4H-pyranyl-2. [e] Cyclohex-2-enylmethyl. [f] Cyclopent-2-enylmethyl. [g] 3-Methylcyclopentylmethyl. [h] Contains a 2-*n*-propyl substituent. [i] Contains a 2-benzyl substituent.

benzene. The ensuing reaction was exothermic, and the yellow product separated after 2 hr. The product was collected and recrystallized from dilute alcohol or water.

The substituted phenyl benzyl sulfide, prepared above, was added to 1–2 l. of 30–50% acetic acid and stirred while chlorine gas was bubbled into the mixture. The reaction became warm, and the solid disappeared after 4–8 hr. Water was added, and the aqueous mixture was extracted with ether. The ether solution was washed with water, dried over $MgSO_4$, filtered and evaporated. The resulting sulfonyl chloride was added to excess liquid ammonia, and the ammonia was allowed to evaporate. The resulting sulfonamide was recrystallized from dilute alcohol.

2-Aminobenzenesulfonamides. Method A. Reduction of 2-Nitrobenzenesulfonamides (Table I).—An alcoholic solution containing 25 g. of 4-chloro-5-methyl-2-nitrobenzenesulfonamide or 6-chloro-2-nitrobenzenesulfonamide was hydrogenated at 2.8 kg./cm.^{2} with Raney nickel. The catalyst was separated by filtration, and the filtrate was concentrated. The crystalline products were recrystallized from dilute alcohol while the *n*-propyl and benzyl amides of 2-amino-5-chlorobenzenesulfonic acid were intractable gums and were used in the subsequent reactions without further purification.

Method B. Amination of 2-Chloro-5-carboxybenzenesulfonamide (Table I).—A mixture of 2-chloro-5-carboxybenzenesulfonamide (100 g.), $(NH_4)_2CO_3$ (100 g.), $CuSO_4$ (5 g.) and of concd. NH_4OH (250 ml.) was sealed in a bomb and heated at 130° for 18 hr. It was concentrated on the steam bath, neutralized with acetic acid and the residue extracted into alcohol. The alcohol solution was clarified with carbon, concentrated and diluted with water. The product crystallized and was recrystallized several times from dilute alcohol.

Method C.—These 2-aminobenzenesulfonamides were prepared by methods described in the literature: 2-amino-5-chlorobenzenesulfonamide,[2] 2-amino-4,6-dichlorobenzenesulfonamide,[3] 2-amino-4-chlorobenzenesulfonamide,[3] 2-amino-4,5-dichlorobenzenesulfonamide,[3] 2-amino-5-nitrobenzenesulfonamide,[4] and 2-amino-4-trifluoromethylbenzenesulfonamide.[5]

N-Methyl-N-phenyl-adamantane-1-carboxamide.—To prepare adamantane-1-carbonyl chloride a mixture of 30 g. of adamantane-1-carboxylic acid[6] and 42 g. of PCl_5 was heated under reflux for 4 hr. The solution then was distilled under reduced pressure to remove $POCl_3$. The residue, which solidified upon cooling, was dissolved in dry ether. The ether solution was filtered, and the ether was removed by distillation under reduced pressure. The product was purified by sublimation. The yield of acid chloride was 21.3 g. (64.5%), and 9.6 g. of the starting acid was recovered. The acid chloride hydrolyzes rapidly at room temperature and was placed in an evacuated desiccator until it was used. A solution of 20.3 g. of adamantane-1-carbonyl chloride in 70 ml. of dry benzene was added dropwise to a stirred mixture of 13.5 g. of N-methylaniline, 9.5 g. of triethylamine and 70 ml. of dry benzene which was cooled in ice. The stirring was continued for 15 min. after the addition of the acid chloride solution. The benzene was removed under reduced pressure, and the residue was dissolved in petroleum ether. The solution was dried overnight with $MgSO_4$. The petroleum ether was removed under reduced pressure, and water was added to the residue. The product then was recrystallized from an acetone–water mixture, m.p. 99°, yield, 23.3 g. (86%).

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Anal. Calcd. for $C_{18}H_{23}NO$: C, 80.25; H, 8.60. Found: C, 80.04; H, 8.58.

Adamantane-1-carboxaldehyde.—N-Methyl-N-phenyladamantane-1-carboxamide (32 g., 0.082 mole) was dissolved in 100 ml. of dry, redistilled tetrahydrofuran. The stirred solution was maintained at 0–5° with an ice bath. A slurry of 1.03 g. (0.027 mole) of $LiAlH_4$ in 50 ml. of dry redistilled tetrahydrofuran was added portionwise to the cooled, stirred solution through a cotton-stoppered dropping funnel with a large bore. The mixture was allowed to come to room temperature overnight with stirring. It was cooled in ice and decomposed by the dropwise addition of cold 6 *N* HCl. The strongly acidic aqueous mixture was extracted with three 300 ml. portions of ether. The combined ether extract was washed with water to remove acid and then dried over $MgSO_4$. An oil was obtained when the ether was removed under reduced pressure. Unreduced anilide (4 g.) was recovered from the oil when it was cooled in ice. The remaining oil was shown to be approximately a 50% mixture of anilide and aldehyde by comparing the relative infrared absorption intensities of the aldehyde and of the amide bands observed in the oil. Further attempts to separate the aldehyde from the anilide, including distillation, were fruitless. The oily mixture was used as such, yield 7 g. (presumably 3.5 g. of aldehyde, 26%). The aldehyde portion was characterized by converting it to 3-(adamantane-1)-6,7-dichloro-1,2,4-benzothiadiazine-1,1-dioxide (Table II).

1,2,4-Benzothiadiazine-1,1-dioxides (Table II). Method A. R = H, CH_3, C_2H_5.—The 2-aminobenzenesulfonamide (5 g.) was heated on the steam bath with excess formic acid according to the procedure of Park and Williams,[7] or with excess triethyl orthoformate, orthoacetate or orthopropionate according to Freeman and Wagner.[8] The reaction mixture was added to water or the excess reagent was distilled, and the resulting solid was recrystallized from dilute alcohol.

Method B. R is Other than H, CH_3, C_2H_5.—The 2-aminobenzenesulfonamide (5 g.) was treated with an equal molar amount of the mixed anhydride of the appropriate carboxylic acid and trifluoroacetic acid, and the resulting 2-*N*-acylaminobenzenesulfonamides were cyclized in NH_4OH according to the previously reported procedure.[9]

2,4-Dihydro-1,2,4-benzothiadiazine-1,1-dioxides (Table III).—The 2-aminobenzenesulfonamide (5 g.) was treated with an equal molar amount of the appropriate aldehyde in alcoholic-aqueous HCl according to previously reported procedures.[10] The products were recrystallized from dilute alcohol.

Pharmacology.—The compounds were tested in renal hypertensive rats prepared by the procedure described by Kempf and Page.[11] Systolic blood pressure was determined by the microphonic manometric method of Friedman and Freed.[12] Following the control blood pressure determination the compounds were administered by mouth to groups of three rats. Blood pressure readings were recorded hourly for 7 hr.

The results are reported in Tables II and III as the average percentage change in blood pressure from control over the 7 hr. observation period. Each figure represents the mean change in blood pressure for three animals resulting from an oral dose of 20 mg./kg. From past experience in this laboratory with known hypotensive agents a 5% blood pressure lowering is considered to be significant. Eight representative compounds from Tables II and III produced electrolyte retention in saline-loaded female rats. There did not seem to be a relationship between the intensity of electrolyte retention and this hypotensive activity.

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Sympathetic Nervous System Blocking Agents. Derivatives of Guanidine and Related Compounds[1]

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A series of 84 derivatives of guanidine, including 2-amino-2-imidazolines, 2-amino-1,4,5,6-tetrahydropyrimidines, nitroguanidines, and aminoguanidines, has been prepared by standard methods. These compounds have been investigated for their ability to block the sympathetic nervous system, but without blocking the parasympathetic nervous system. Pharmacology and structure–activity relationships are discussed.

In our Laboratories for a number of years we have been interested in derivatives of guanidine both as chemotherapeutic agents and for their effects on the cardiovascular system. In this paper we wish to report our efforts to find an effective antihypertensive agent in this series of compounds.

With the discovery of the potent antihypertensive agent, guanethidine[2,3] [2-(octahydro-1-azocinyl)-ethyl]-guanidine sulfate, we were prompted to reinvestigate our series of compounds in comparison with guanethidine, and to synthesize others which might show this type of activity. Guanethidine differs from older antihypertensive agents in that it blocks the effects of stimulation of the sympathetic nervous system, as do the ganglionic blocking agents, but does not at the same time block the parasympathetic nervous system. Since parasympathetic blockade causes undesirable side effects such as constipation, dry mouth, urinary retention, and impaired visual accommodation, guanethidine maintains the advantages of the ganglionic blocking agents without many of their disadvantages.

Chemistry.—The guanidines described in Tables III–VII were prepared by standard methods. Method A is that of Rathke[4] and involves the reaction of a

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