500 ml. of water, extracted with toluene, and made basic with excess 50% sodium hydroxide. The amine was taken up in toluene, dried, and distilled to give 38 g. (82%) of 4-amino-2-phenyl-2-butanol (II), b.p. 105–115° (1.7 mm.). This crystallized and after recrystallization from heptane melted at 75–77°.

Anal. Calc'd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.84; H, 9.02; N, 8.43.

A *hydrochloride* was prepared and this melted at 142–143° after recrystallization from a 20:1 mixture of acetone and isopropyl alcohol.

Anal. Calc'd for $C_{10}H_{16}ClNO$: C, 59.54; H, 7.99; N, 6.94; Cl, 17.6. Found: C, 59.85; H, 8.17; N, 7.05; Cl, 17.5.

(*Method B*). *Directly from α-methylstyrene, formaldehyde, and ammonium chloride.* A stirred mixture of 108 g. (2.02 moles) of ammonium chloride, 334 g. (4.13 moles) of 37% aqueous formaldehyde, and 118 g. (1.00 mole) of α-methylstyrene was warmed to 60° and held at 60–61° by external cooling until the exothermic reaction subsided. Stirring was continued another ½ hour while the temperature fell to 40°. There was added 300 ml. of methanol, the mixture was stirred for ½ hour, and then was heated to 90° while the methanol distilled off. The methanol treatment was repeated twice and the mixture was poured into 1 l. of water, extracted with toluene, and made basic with excess 50% sodium hydroxide. The amine was taken up in toluene, dried, and distilled to give 102 g. (62%) of 4-amino-2-phenyl-2-butanol (II), b.p. 95–105° (0.65 mm.). This solidified and was recrystallized from heptane, m.p. 75–77°. The melting point of a mixture with the material from *Method A* was 75–77°.

3-Phenyl-2-butenylamine (III). *A. Using hydrochloric acid.* A mixture of 50 g. (0.30 mole) of 4-amino-2-phenyl-2-butanol (II) and 200 g. (1.0 mole) of 18.5% hydrochloric acid was stirred on a steam-bath for 4 hours, cooled, diluted with 300 ml. of water, and made basic with excess 50% sodium hydroxide solution. The amine was taken up in toluene, dried, and distilled to give 15 g. (34%) of 3-phenyl-2-butenylamine (III), b.p. 80–90° (1.0 mm.). There was also recovered 12 g. of unreacted II, b.p. 100–105° (1.0 mm.) which solidified and melted at 75–77° after recrystallization from heptane.

Anal. Calc'd for $C_{10}H_{13}N$: C, 81.58; H, 8.90; N, 9.52. Found: C, 81.76; H, 9.05; N, 9.34.

B. Using polyphosphoric acid (115% ortho-equivalent). To 50 g. (0.30 mole) of stirred 4-amino-2-phenyl-2-butanol was slowly added 100 g. of polyphosphoric acid, the exotherm being controlled by external cooling so that the temperature did not rise above 150°. The mixture was stirred 15–20 minutes at 125–150° and then for one hour while cooling took place. There was added 500 ml. of water and excess 50% sodium hydroxide solution. The amine was taken up in toluene, dried, and distilled to give 10 g. (23%) of 3-phenyl-2-butenylamine (III), b.p. 83–93° (1.6 mm.).

Anal. Calc'd for $C_{10}H_{13}N$: C, 81.58; H, 8.90; N, 9.52. Found: C, 81.70; H, 8.97; N, 9.59.

A *hydrochloride* was prepared which melted at 204–206° after recrystallization from a 20:1 mixture of acetone and isopropyl alcohol.

Anal. Calc'd for $C_{10}H_{14}ClN$: C, 65.39; H, 7.68; N, 7.63; Cl, 19.3. Found: C, 64.94; H, 7.69; N, 7.71; Cl, 19.4.

3-Phenylbutylamine. Quantitative hydrogenation of 3-phenyl-2-butenylamine (III) using a 5% palladium on alumina catalyst in 95% ethanol at atmospheric pressure required 0.99 *molar*-equivalent of hydrogen. A *picrate* prepared from the resulting solution of 3-phenylbutylamine melted at 137–139°. Tsukervanik and Grebenyuk[7] reported m.p. 138–139°.

Anal. Calc'd for $C_{16}H_{18}N_4O_7$: C, 50.79; H, 4.79; N, 14.81. Found: C, 50.41; H, 4.90; N, 14.59.

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Heterocyclic Sulfonamides as Carbonic Anhydrase Inhibitors. 2-Acylamido- and 2-Sulfonamido-1,3,4-thiadiazole-5-Sulfonamides

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The observation reported here that the 2-propionamido analog of 2-acetamido-1,3,4-thiadiazole-5-sulfonamide,[2,3,4] has appreciable *in vitro* carbonic anhydrase inhibitory activity led to the synthesis of other compounds of this type. A series of analogs was prepared, therefore, in which the 2-acetamido group in the parent compound was replaced by other 2-acylamido and by 2-sulfonamido groups. The compounds prepared and their relative *in vitro* activities are listed in Table I.

Ordinary, well-known reaction conditions for the acylation of amines were used throughout in the preparation of this series of 2-N-substituted aminothiadiazoles. The efficiency of the various techniques varied markedly over the series, however. Thus, the low-molecular-weight aliphatic acyl groups, formyl through propionyl, were introduced by heating 2-amino-1,3,4-thiadiazole-5-sulfonamide[3] with the corresponding acid anhydrides. The higher acyl analogs, butyryl through valeryl, could not be obtained by this procedure but were prepared by causing the corresponding acid chlorides to react with the aminothiadiazole in pyridine. Schotten-Baumann conditions were unsuccessful with these acid chlorides.

With the aromatic acyl and sulfonyl chlorides, exactly the opposite was true. The products could not be obtained in pyridine, but were obtained, usually in low yield, under conditions of the Schotten-Baumann reaction.

We are indebted to Dr. T. H. Maren and staff of the Pharmacological Research Department for the *in vitro* activities reported in Table I.

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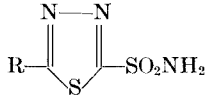
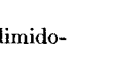
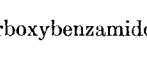
(3) Roblin and Clapp, *J. Am. Chem. Soc.*, **72**, 4890 (1950).

(4) Miller, Dessert, and Roblin, *J. Am. Chem. Soc.*, **72**, 4893 (1950).

TABLE I

ACETAZOLAMIDE ANALOGS PREPARED



Name	R	M.p.,[a] °C. (dec.)	Empirical Formula	Analysis[b] Calc'd C	Calc'd H	Calc'd N	Found C	Found H	Found N	*In Vitro*[c] Carbonic Anhydrase Activity
Formamido-	HCONH—	>285	$C_3H_4N_4O_3S_2$	17.3	1.94	26.9	17.5	1.96	26.6	0.62
Propionamido-	CH_3CH_2CONH—	147–148	$C_5H_8N_4O_3S_2$	25.4	3.41	23.7	25.6	3.48	22.7[d]	1.2
n-Butyramido-	$CH_3CH_2CH_2CONH$—	260–262	$C_6H_{10}N_4O_3S_2$	28.8	4.03	22.4	28.8	4.14	22.6	1.2
Isobutyramido-	$(CH_3)_2CHCONH$—	280–283	$C_6H_{10}N_4O_3S_2$	28.8	4.03	22.4	28.9	4.09	21.9	0.55
Isovaleramido-	$(CH_3)_2CHCH_2CONH$—	246–248	$C_7H_{12}N_4O_3S_2$	31.8	4.58	21.2	32.0	4.71	21.0	1.6
Chloroacetamido-	$ClCH_2CONH$—	236–240	$C_4H_5ClN_4O_3S_2$	18.7	1.96	21.8	18.9	2.24	21.6	0.6
Trifluoroacetamido-	F_3C—CONH—	221–222	$C_4H_3F_3N_4O_3S_2$	17.4	1.09	20.3	17.5	1.26	20.2	0.31
Benzamido-	C_6H_5CONH—	277–279	$C_9H_8N_4O_3S_2$	38.0	2.84	19.7	38.4	2.88	19.4	2.1
Phthalimido-		282–283	$C_{10}H_6N_4O_4S_2$	38.7	1.95	18.1	38.7	2.17	17.8	3.1
2-Carboxybenzamido		242–246	$C_{10}H_8N_4O_5S_2$	36.6	2.46	17.1	36.6	2.63	17.1	1.9
Carbobenzoxamido-	$C_6H_5CH_2OCONH$—	230–234	$C_{10}C_{10}N_4O_4S_2$	38.2	3.21	17.8	38.3	3.38	16.9[d]	2.6
Carbobenzoxyaminoacetamido-	$C_6H_5CH_2OCONHCH_2CONH$—	215–216	$C_{12}H_{13}N_5O_5S_2$	38.8	3.53	18.9	39.0	3.61	18 4	0.48
Aminoacetamido-•HBr	H_2NCH_2CONH—	>215	$C_4H_7N_5O_3S_2$•HBr	15.1	2.53	22.0	15.1	2.92	22.1	0.03
Benzenesulfonamido-	$C_6H_5SO_2NH$—	238–241	$C_8H_8N_4O_4S_3$	30.0	2.52	17.5	30.1	2.60	17.3	5.1
4-Methylbenzenesulfonamido-	4-$CH_3C_6H_4SO_2NH$—	267–268	$C_9H_{10}N_4O_4S_3$	32.3	3.01	16.8	32.3	2.98	17.0	4.4
4-Chlorobenzenesulfonamido-	4-$ClC_6H_4SO_2NH$—	270–271	$C_8H_7ClN_4O_4S_3$	27.1	1.99	15.8	27.2	2.15	16.0	3.7
3,4-Dichlorobenzenesulfonamido-	3,4-$Cl_2C_6H_3SO_2NH$—	274–276	$C_8H_6Cl_2N_4O_4S_3$	24.7	1.55	14.4	24.6	1.70	14.5	2.6
4-Bromobenzenesulfonamido-	4-Br—$C_6H_4SO_2NH$—	271–272	$C_8H_7BrN_4O_4S_3$	24.1	1.77	14.0	24.4	1.96	14.3	2.3
4-Acetamidobenzenesulfonamido-	4-$CH_3CONHC_6H_4SO_2NH$—	285–290	$C_{10}H_{11}N_5O_5S_3$	31.8	2.94	18.6	31.8	2.98	18.2	2.6
4-Aminobenzenesulfonamido-	4-$H_2NC_6H_4SO_2NH$—	259–261	$C_8H_9N_5O_4S_3$	28.7	2.70	20.9	28.7	2.86	21.0	1.7

[a] Melting points were determined on a Fisher-Johns block and are uncorrected. [b] We are indebted to Dr. J. A. Kuck and his staff of these laboratories for the microanalyses. [c] Carbonic anhydrase inhibition compared to Acetazolamide as 1.0, on a weight basis. Determined by the method of Maren, Ash, and Bailey, *Bull. Johns Hopkins Hosp.*, **95**, 244 (1954). [d] A satisfactory analysis was not obtained.