Anal. Calcd. for $C_{10}H_{10}N_2O_3 \cdot H_2O$: C, 53.6; H, 5.40; N, 12.5. Found: C, 53.4; H, 5.27; N, 12.7.

3-Methyl-6-carboxyquinoxalone-2 hydrate. 3-Methyl-3,4-dihydro-6-carboxyquinoxalone-2 hydrate was oxidized and purified in 35.9% yield in a similar fashion to that already described for its position isomer, except that the oxidation solution of the 6-isomer required vigorous heating with a direct flame. The 3-methyl-6-carboxyquinoxalone-2 was recrystallized from ethanol (30 mg./ml.) or from water (1 mg./ml.) as a crystalline hydrate, m.p. 334–336°, dec., to give products with the same analytical values and the same ultraviolet absorption spectra.

Absorption maxima, mμ, and molar absorptivity ($\epsilon \times 10^3$), 95% ethanol: 255 (34.4); 335 (7.95); 0.1*N* sodium hydroxide: 255 (26.0); 345 (8.36); 0.1*N* hydrochloric acid: 255 (33.7); 335 (8.40).

Anal. Calcd. for $C_{10}H_8N_2O_3 \cdot H_2O$: C, 54.1; H, 4.54; N, 12.6. Found: C, 53.9; H, 4.61; N, 12.6.

Reduction of 75 mg. of 3-methyl-6-carboxyquinoxalone-2 with Raney nickel catalyst at 65° (the substance was not reduced at 25°) and 60 p.s.i. in 5 ml. of water containing 100 mg. of sodium bicarbonate gave 50 mg. of yellow, crystalline 3-methyl-3,4-dihydro-6-carboxyquinoxalone-2 hydrate, m.p. 257–259°, mixture melting point with an analytical sample of the compound, no change.

3-Methyl-6-carbethoxyquinoxalone-2. This material was prepared in 6.7% yield by direct esterification (Method B) of 3-methyl-6-carboxyquinoxalone-2; and in 40% yield from the diethyl ester of *N*-(2-nitro-5-carboxyphenyl)-*dl*-α-alanine, by the procedure (Method A) given above for the preparation of the isomeric ester. The product was purified for analysis by recrystallizing it from benzene (25 mg./ml.), colorless prisms, m.p. 229–230°.

Absorption maxima, mμ, and molar absorptivity ($\epsilon \times 10^3$), 95% ethanol: 222 (13.3); 255 (35.9); 336 (8.0).

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: N, 12.1 Found: N, 12.0.

Saponification of a sample of the ester gave 3-methyl-6-carboxyquinoxalone-2, m.p. 334–336°; there was no depression of a mixture melting point with an analytical sample of 3-methyl-6-carboxyquinoxalone-2.

3-Methyl-6- and/or 7-carboxyquinoxalone-2; equivocal procedure of Zehra.[1] A solution of 5 g. (0.0275 mole) of 3-nitro-4-aminobenzoic acid[20] in 50 ml. of 95% ethanol was catalytically reduced over palladium-charcoal catalyst; the solution was filtered without exposure to air into a water solution of 1.2 equivalents of pyruvic acid to give 1.2 g. (21.8%) of 3-methyl-7-carboxyquinoxalone, m.p. 328–330° dec. Sublimation at 180° (1 mm.) and recrystallization from ethanol of a sample of material gave m.p. 330–332° dec. Zehra[1] reported that his product did not melt below 330°. The ultraviolet absorption spectra of both crude and purified samples were identical with that of the analytical sample of 3-methyl-7-carboxyquinoxalone-2 prepared by unequivocal procedures.

When ethyl 3,4-diaminobenzoate was prepared from ethyl 3-nitro-4-aminobenzoate[12] and condensed with pyruvic acid in the same general fashion described above, 55.5% yield of 3-methyl-7-carbethoxyquinoxalone-2, m.p. 194–197°, was obtained. One recrystallization of the crude product from benzene gave m.p. 200–201°. A mixture melting point of this substance with an analytical sample of 3-methyl-7-carbethoxyquinoxalone-2, gave no depression of the melting point; ultraviolet absorption spectra of both crude (m.p. 194–197°) and purified (m.p. 200–201°) esters were identical with that of the analytical sample prepared by unequivocal procedures.

But when ethyl 3,4-diaminobenzoate was condensed with ethyl pyruvate in absolute ethanol solution by procedures similar to those described above, a 100% yield of mixed esters melting at 173–185° was obtained. Examination of the ultraviolet absorption spectrum of this product indicated approximately equal portions of the two isomers were present in the crude reaction mixture.

By recrystallizing (with frequent treatment with charcoal) the crude product repeatedly from toluene, 17% of pure 3-methyl-7-carbethoxyquinoxalone-2 was obtained. The residue gave a like amount of pure 3-methyl-6-carbethoxyquinoxalone-2 when recrystallized repeatedly (again with frequent charcoal treatment) from benzene. Melting point, mixture melting point with analytical sample, and ultraviolet absorption spectrum of each ambiguous product proved the identity of the material.

CORAL GABLES 34, FLA.

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[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Diuretics. IV. 6-Chloro-3-substituted 7-Sulfamoyl-1,2,4-benzothiadiazine 1,1-Dioxides

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Trifluoroacetic acid anhydrides of carboxylic acids were allowed to react with 6-amino-4-chlorobenzene-1,3-disulfonamide to yield 6-carbamyl-4-chlorobenzene-1,3-disulfonamides. These latter compounds were cyclized in base to 6-chloro-3-substituted 7-sulfamoyl-1,2,4-benzothiadiazine 1,1-dioxides. Titrations of the 3-substituted 1,2,4-benzothiadiazine 1,1-dioxides indicated the influence of the 3-substituent on the ionization potential of the proton in the 2-position. Definite correlations are observed between diuretic activity and the nature of the 3-substituent.

Since the discovery of the diuretic activity of 6-chloro-7-sulfamoyl-1,2,4-benzothiadiazine-1,1-dioxide (I. R = H)[1] more active compounds have been prepared by modifying this interesting structure.[2–6] Ameliorable changes have been 1, saturation of the 3,4-double bond and 2, introduction of appropriate substituents in the 3-position. Derivatives of the 3,4-dihydro compound II are gen-

(1) F. C. Novello and J. M. Sprague, *J. Am. Chem. Soc.*, **79**, 2028 (1957).

(2) W. J. Close, L. R. Swett, L. E. Brady, J. H. Short, and M. Vernsten, *J. Am. Chem. Soc.*, **82**, 1132 (1960).

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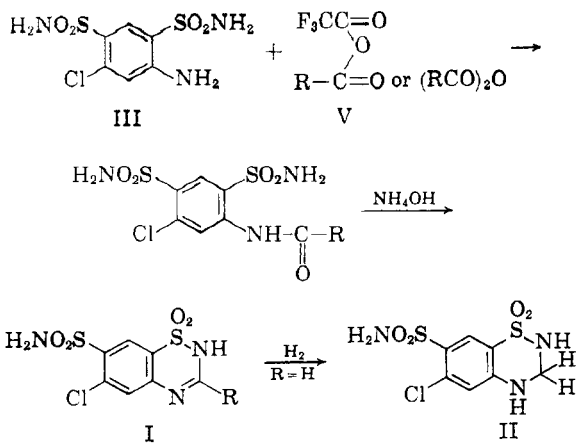
(4) L. H. Werner, A. Halmandaris, S. Ricca, Jr., L. Dorfman, and G. DeStevens, *J. Am. Chem. Soc.*, **82**, 1161 (1960).

erally more active than derivatives of the unsaturated compound I; however, only a few direct comparisons have been made of similarly substituted examples of each type:[7] Our premise is: the introduction of an R group in the 3-position of II has an effect upon the biological activity relatively similar to that produced by the same R group in the 3-position of I, *i.e.*, a substituent R that enhances the activity of I would be expected to enhance the activity of II. Methods for the preparation of the saturated compounds II are more laborious than those for the unsaturated derivatives I; therefore, it appeared the effect of variations in the R group upon diuretic activity could be most easily determined by a study of 6-chloro-3-substituted 7-sulfamoyl-1,2,4-benzothiadiazine-1,1-dioxides. Results of this investigation are described in the present paper.

Cyclohexylacetic acid anhydride was allowed to react with 6-amino-4-chlorobenzene-1,3-disulfonamide (III) to yield 4-chloro-6-cyclohexylacetylaminobenzene-1,3-disulfonamide (IV. R = cyclohexylmethyl). The mixed anhydride of trifluoroacetic acid and cyclopentylacetic acid (V. R = cyclopentylmethyl) was prepared by mixing trifluoroacetic anhydride with cyclopentylacetic acid. The crude mixed anhydride reacted with III to yield 4-chloro-6-cyclopentylacetylaminobenzene-1,3-disulfonamide. There was no evidence of the other possible product, 4-chloro-6-trifluoroacetylaminobenzene - 1,3 - disulfonamide having been formed in the reaction. This is in contrast to the results previously observed[8] with aniline and trifluoroacetic acetic anhydride whereby a mixture of acetanilide and trifluoroacetanilide was obtained. Diminution of the base strength of the amine, *i.e.*, effect of *o*, *p*-sulfamoyl substituents apparently



favors the formation of acetamides rather than trifluoroacetamides.

The mixed anhydride method had two definite advantages over the symmetrical anhydride method. First, the mixed anhydride is very conveniently prepared *in situ* while the symmetrical anhydride is not so prepared and must be purified. Second, the mixed anhydride required a smaller amount of cycloalkylacetic acid to obtain a given amount of the 4-chloro-6-cycloalkylacetylamino-1,3-disulfonamide. The mixed anhydride method was used to convert other carboxylic acids (Table I) to the desired 4-chloro-6-carbamylbenzene-1,3-disulfonamides IV. Two acids, 4-chlorocyclohexylacetic acid and 3-cyclohexenylacetic acid have not been previously reported and were prepared in the following manner. The action of a mixture of concentrated hydrochloric acid and calcium chloride on 4-hydroxycyclohexylacetic acid yielded a mixture of 4-chlorocyclohexylacetic acid and unchanged starting hydroxy acid. This mixture was then treated with thionyl chloride to yield 4-chlorocyclohexylacetyl chloride which was in turn hydrolyzed with dilute hydrochloric acid to give 4-chlorocyclohexylacetic acid. Ethyl 4-hydroxycyclohexylacetate was converted to methyl 4-carbethoxymethylcyclohexyl sulfite by the method of Berti.[9] Pyrolysis of this sulfite ester yielded ethyl 3-cyclohexenylacetate. Hydrolysis of the ester gave 3-cyclohexenylacetic acid.

The 6-carbamyl-4-chlorobenzene-1,3-disulfonamides (V) were cyclized with ammonium hydroxide to obtain 6-chloro-3-substituted 7-sulfamoyl-1,2,4-benzothiadiazine-1,1-dioxides (I), Table I. Hydrogenation of 6-chloro-7-sulfamoyl-1,2,4-benzothiadiazine-1,1-dioxide over platinum catalyst readily converted it to 6-chloro-3,4-dihydro-7-sulfamoyl-1,2,4-benzothiadiazine-1,1-dioxide. Attempts to hydrogenate the 3-substituted 1,2,4-benzothiadiazine-1,1-dioxides (IV) over platinum and also over palladium failed to yield 3,4-dihydro derivatives. Hydrogenation of 6-chloro-3-benzyl-7-sulfamoyl-1,2,4-benzothiadiazine-1,1-dioxide yielded 6-chloro-3-cyclohexylmethyl-7-sulfamoyl-1,2,4-benzothiadiazine-1,1-dioxide.

Methylation of 6-chloro-3-cyclopentylmethyl-7 - sulfamoyl - 1,2,4 - benzothiadiazine - 1,1-dioxide was expected to yield the 4-methyl derivative. This did not occur and the product obtained with dimethylsulfate was 6-chloro-3-cyclopentylmethyl-7-(*N*-methylsulfamoyl)- 1,2,4 - benzothiadiazine-1,1-dioxide. The position of the methyl group was established by showing the presence of two titratable groups pK'_a, 7.8 and 13.6. Only one value, 13.6, could be obtained if either the 4- or 2-position was alkylated.

Titration characteristics. The parent 6-chloro-7-sulfamoyl-1,2,4-benzothiadiazine-1,1-dioxide is a dibasic acid with pK'_a values of 6.8 and 9.4 in

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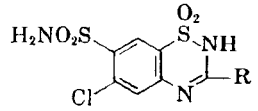
TABLE I

6-CHLORO-3-SUBSTITUTED 7-SULFAMOYL-1,2,4-BENZOTHIADIAZINE-1,1-DIOXIDES



No.	R	Formula	M.P.	Yield, %	pK'_a	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	Cyclopentyl	$C_{12}H_{14}ClN_3O_4S_2$	>340	30	8.0; 12.2	39.61	3.88	11.55	39.98	3.83	11.29
2	2-Cyclopentenylmethyl	$C_{13}H_{14}ClN_3O_4S_2$	260	30	7.6; 12.1	41.54	3.75	11.18	41.91	4.10	10.98
3	Cyclopentylmethyl	$C_{13}H_{16}ClN_3O_4S_2$	292–293	39	7.9; 12.0	41.31	4.81	11.12	41.40	4.02	11.50
4	Phenoxymethyl	$C_{14}H_{12}ClN_3O_5S_2$	315 dec.	57	6.3; 12.1	41.84	3.01	10.46	42.06	3.37	10.19
5	Phenylsulfonylmethyl	$C_{14}H_{12}ClN_3O_6S_3$	265–270 dec.	20	5.4; 12.1	37.37	2.69	9.34	37.27	3.21	9.12
6	1-Cyclohexenylmethyl	$C_{14}H_{16}ClN_3O_4S_2$	265–266	30	7.6; 12.1	43.13	4.14	10.78	43.14	4.27	10.55
7	2-Cyclohexenylmethyl	$C_{14}H_{16}ClN_3O_4S_2$	277–279	27	7.9; 12.3	43.13	4.14	10.78	43.50	4.26	10.65
8	3-Cyclohexenylmethyl	$C_{14}H_{16}ClN_3O_4S_2$	267–268	32	7.9; 12.2	43.13	4.14	10.78	42.88	4.12	10.64
9	Cyclohexylmethyl	$C_{14}H_{18}ClN_3O_4S_2$	277–278[a]	40	7.9; 12.2	42.90	4.63	10.72	42.97	4.34	10.68
10	Cyclohexylmercaptomethyl	$C_{14}H_{18}ClN_3O_4S_3$	279–280	25	7.0; 12.2	39.66	4.28	9.91	39.48	4.08	9.93
11	Cyclohexyloxymethyl	$C_{14}H_{18}ClN_3O_5S_2$	244–245	22	7.1; 12.2	41.22	4.45	10.30	41.10	4.32	10.15
12	4-Methylcyclohexylmethyl	$C_{15}H_{20}ClN_3O_4S_2$	245–246	30	8.0; 12.3	44.40	4.96	10.37	44.27	5.40	10.00
13	2-Cyclohexylethyl	$C_{15}H_{20}ClN_3O_4S_2$	273–275	42	7.8; 12.0	44.40	4.96	10.37	43.91	5.35	9.94
14	4-Methoxycyclohexylmethyl	$C_{15}H_{20}ClN_3O_5S_2$	274–275	22	7.9; 12.2	42.70	4.78	9.96	42.96	5.21	9.89
15	α-1-Cyclohexenylpropyl	$C_{15}H_{20}ClN_3O_4S_2$	265	25	8.2; 12.5	45.98	4.82	10.05	46.45	4.90	9.96
16	4-Acetylaminocyclohexylmethyl	$C_{15}H_{21}ClN_4O_5S_2$	278–280	18		41.87	4.61	12.21	42.12	4.58	12.00
17	1-Cyclohexylpropyl	$C_{15}H_{22}ClN_3O_4S_2$	252–254	25	8.2; 12.4	45.76	5.28	10.01	46.04	5.25	9.72
18	3-Cyclohexylpropyl	$C_{15}H_{22}ClN_3O_4S_2$	237–239	36	7.9; 12.2	45.76	5.28	10.01	45.69	5.18	9.95

[a] Prepared by method B. All others in the table were prepared by method A.

TABLE II

RELATIVE EFFECT[a] OF THE 6-CHLORO-3-SUBSTITUTED 7-SULFAMOYL-1,2,4-BENZOTHIADIAZINE-1,1-DIOXIDES UPON URINE VOLUME AND URINE ELECTROLYTES

No.	Vol.	Na	K	Cl
1	1.1	2.2	8.9	1.6
2	12.5	19.8	8.4	13.9
3	11.4	13.2	>20.0	11.8
4	<0.1	<0.1	<0.1	<0.1
5	0.9	0.9	1.7	1.1
6	11.0	13.6	18.0	15.1
7	17.3	9.8	4.1	10.6
8	17.0	18.0	17.0	18.0
9	4.8	10.1	1.7	6.7
10	1.2	1.46	0.3	0.6
11	0.2	0.3	0.6	0.2
12	2.0	7.4	2.1	3.9
13		No activity		
14	0.3	0.4	0.2	0.2
15	0.2	0.1	0.2	0.1
16	<0.1	<0.1	<0.1	<0.1
17	0.3	0.2	0.2	0.1
18	0.8	0.3	0.4	0.4

[a] The values given in this table are estimates of relative potency referred to 6-chloro-7-sulfamoyl-1,2,4-benzothiadiazine-1,1-dioxide as 1 and based on an equal and optimal diuretic or saluretic effect.

water. The lower value, 6.8, is attributed to the ionization of the cyclic sulfonamide and the higher value to the exocyclic sulfonamide.[10] When 66% *N,N*-dimethylformamide is used as the solvent, the pK'_a values are 6.9 and 12.1.[11] Solvation of the exocyclic sulfonamide group is probably the reason for the increased value of 12.1 in dimethylformamide. Acid strengths of the 3-substituted benzothiadiazines determined in 66% dimethylformamide are listed in Table I. These values show the ionization of the cyclic sulfonamide is effected by the 3-substituent. Cycloalkylmethyl groups decrease the ionization. A double bond in the ring of the cycloalkylmethyl group appears to lessen this effect if the double bond is in a position nearest the methyl carbon attached to the ring. Introduction of an electronegative element, *i.e.*, oxygen or sulfur, between the methyl carbon and the cycloalkyl ring practically nullifies the effect of the cycloalkyl group. The cyclic sulfonamide is a much stronger acid, pK'_a 5.4 and 6.3 when the 3-substituent is arylsulfonylmethyl and aryloxymethyl. Introduction of one methyl group on the 7-sulfamoyl nitrogen increased the pK'_a of that group 1.3 units to *ca.* 13.6.

Diuretic activity. The relative diuretic and saluretic activities of the 6-chloro-3-substituted 7-sulfamoyl-1,2,4-benzothiadiazine-1,1-dioxides were determined in rats by a modified method of Lipschitz *et al.*[12] The results are briefly summarized in Table II.

EXPERIMENTAL

6-Amino-4-chlorobenzene-1,3-disulfonamide. Methods previously described for the preparation of 6-amino-4-chlorobenzene-1,3-disulfonamide could not be used for 1–2 mole quantities. The following procedure was found readily adaptable to quantities of this size and could be conveniently carried out in the laboratory fume hood.

In a 12-l. three-necked, round-bottomed flask, fitted with a long reflux condenser and efficient mechanical stirrer, was placed 3000 ml. of redistilled tetrachloroethane (b.p. 145°). The flask was cooled in an ice bath and 2000 g. (17.18 moles) of chlorosulfonic acid was carefully added. The cooled solution of chlorosulfonic acid was stirred continuously and 200 g. (1.57 moles) of *m*-chloroaniline was added dropwise through a dropping funnel. Sodium chloride, 1100 g. (18.8 moles) was added in portions from a 500-ml. Erlenmeyer flask attached to the neck of the large flask by means of Gooch tubing. The cooling bath was replaced with a heating mantle and the temperature raised to 110°. Copious evolution of hydrogen chloride started, and vigorous stirring was necessary to prevent excess foaming. After 0.5 hr. the temperature was increased to 140–145° and maintained for 4.5 hr. The reaction mixture was cooled and poured onto 10 kg. of crushed ice. The tetrachloroethane layer was separated and washed four times with cold water then dried over anhydrous magnesium sulfate. Evaporation of the tetrachloroethane under reduced pressure yielded 6-amino-4-chlorobenzene-1,3-disulfonylchloride. The disulfonyl chloride was added to a large excess of liquid ammonia and allowed to stand until the ammonia had evaporated. The solid 6-amino-4-chlorobenzene-1,3-disulfonamide was crystallized from hot water after treatment with carbon, yield 250 g., 57.5%, m.p. 262° (reported 259–260°).[1]

Carbocyclic acid. Cyclopentylcarboxylic acid, 2-cyclopentenylacetic acid, cyclopentylacetic acid, cyclohexylacetic acid, β-cyclohexylpropionic acid, α-1-cyclohexylbutyric acid, γ-cyclohexylbutric acid and α-cyclohexylbutyric acid were obtained from Aldrich Chemical Company, Milwaukee, Wis. Phenylsulfonylacetic acid,[13] 2-cyclohexenylacetic acid,[14] cyclohexylmercaptoacetic acid,[15] 3-methyl-2-cyclohexenylacetic acid,[16] and 4-acetamidocyclohexylacetic acid[17] were prepared by the methods described in the literature. Catalytic reduction[18] of phenoxyacetic acid, *p*-methylphenylacetic acid and *p*-methoxyphenylacetic acid yielded, respectively, cyclohexyloxyacetic acid,[19] 4-methylcyclohexylacetic acid,[19] and 4-methoxycyclohexylacetic acid.[20]

Ethyl 4-hydroxycyclohexylacetate. Ethyl *p*-hydroxyphenylacetate in ethanol under hydrogen at 3000 lbs. per sq. in. and 40° with 5% rhodium on alumina gave an 83% yield of ethyl 4-hydroxycyclohexylacetate[21] boiling at 106–109° at 0.8 mm.

(10) J. M. Sprague, *Ann. N. Y. Acad. Sci.*, 71 (4), 340 (1958).

(11) Titrations in 66% *N,N*-dimethylformamide were carried out according to the procedure of T. V. Parke and W. W. Davis, *Anal. Chem.*, 26, 642 (1954).

(12) W. L. Lipschitz, Z. Hadidian, and A. Kerpcsar, *J. Pharmacol. Exptl. Therap.*, 79, 97 (1943).

(13) R. Otto, *Ber.*, 19, 3138 (1886).

(14) M. Mousseron and F. Winternitz, *Bull. Soc. Chim. France*, 604 (1946).

(15) M. Mousseron, *Compt. rend.*, 220, 462 (1945).

(16) M. Mousseron, R. Granger, and F. Winternitz, *Compt. rend.*, 217, 246 (1943).

(17) E. Ferber and H. Bendix, *Ber.*, 72B, 839 (1939).

(18) The catalytic reductions were carried out by Mr. W. B. Scanlon of this laboratory and the procedure will be reported in another paper.

(19) B. V. Bhide and J. J. Sudborough, *J. Indian Inst. Sci.*, 8A, 89–127 (1925) [*Chem. Abstr.*, 19, 3251 (1925)].

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(21) H. E. Ungnade and F. V. Morriss, *J. Am. Chem. Soc.*, 70, 1898 (1948).

Ethyl 3-cyclohexenylacetate. The methyl sulfite ester of ethyl 4-hydroxycyclohexylacetic acid was prepared by the general method reported by Berti.[9] The sulfite ester was pyrolyzed[22] in a bath at 200–210° for 6 hr. Nitrogen was passed through the liquid during this time. The end of the pyrolysis was determined by testing for sulfur dioxide evolution by passing the escaping gas into dilute permanganate solution. The ester was distilled at 72–73° at 2.8 mm., yield 23.5 g. (61%), n_D^{25} 1.4557.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.58. Found: C, 71.37; H, 9.78.

3-Cyclohexenylacetic acid. To 6 g. (0.15 mole) of sodium hydroxide in 50 ml. of water was added 18.5 g. (0.11 mole) of ethyl 3-cyclohexenylacetate. The mixture was heated at 85°, with stirring, for 5 hr., cooled, and acidified to *p*H 3 with hydrochloric acid. About 15 g. of sodium chloride was added and the product was extracted with ether. The extracts were washed once with water and dried over magnesium sulfate. Distillation gave 13.4 g. (87%) of the acid boiling at 93–95° at 0.5 mm., n_D^{25} 1.4768.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 67.93; H, 8.60.

4-Chlorocyclohexylacetic acid. A mixture of 25.2 g. (0.016 mole) of 4-hydroxycyclohexylacetic acid, 37 ml. of concd. hydrochloric acid and 15 g. of calcium chloride was refluxed overnight. After cooling, the insoluble oil was isolated by chloroform extraction. After drying over magnesium sulfate, the material was distilled but analysis was low for chlorine.

The distillate and residue, a total of 14 g., in 50 ml. of benzene and 50 g. of thionyl chloride was refluxed for 3 hr. The benzene and thionyl chloride were removed by distillation and the residue was stirred with 100 ml. of 6*N* hydrochloric acid for 2 hr. The product was extracted with chloroform and the extracts were washed with water and dried over magnesium sulfate. Distillation gave 7.4 g. (27%) boiling at 112–113° at 0.25 mm., n_D^{25} 1.4860.

Anal. Calcd. for $C_8H_{13}ClO_2$: C, 54.40; H, 7.42; Cl, 20.07. Found: C, 54.97; H, 7.52; Cl, 19.34.

6-Chloro-3-substituted 7-sulfamoyl-1,2,4-benzothiadiazine-1,1-dioxides, Table I. Method A. A mixed anhydride was prepared by adding 0.053 mole of the appropriate carboxylic acid to 11 g. (0.053 mole) of trifluoroacetic anhydride and allowing the mixture to stand for a few minutes. This was then added to 14 g. (0.05 mole) of 4-amino-6-chlorobenzene-1,3-disulfonamide in 175 ml. of purified dioxane. The mixture was refluxed overnight and the clear solution was taken to dryness under reduced pressure. The residue was dissolved in 250 ml. of concd. ammonium hydroxide and heated for 5 hr. on a steam bath. It was cooled and acidified with 10% hydrochloric acid. The crude product was dissolved in 1*N* sodium hydroxide, filtered and precipitated with 1*N* hydrochloric acid. Recrystallization several times from dilute ethanol afforded the pure product. The product was dried in the presence of phosphorus pentoxide and sodium hydroxide under reduced pressure before the melting point was determined.

(22) C. C. Price and G. Berti, *J. Am. Chem. Soc.*, **76**, 1207 (1954).

Method B. Fourteen grams (0.05 mole) of 4-amino-6-chlorobenzene-1,3-disulfonamide and 0.05 mole of cyclohexylacetic acid anhydride were dissolved in 250 ml. of hot dioxane. The solution was boiled under reflux for 8 hr. and then filtered. The filtrate was concentrated under reduced pressure. The resulting 6-chloro-4-cyclohexylacetylaminobenzene-1,3-disulfonamide was cyclized to 6-chloro-3-cyclohexylmethyl-7-sulfamoyl-1,2,4-benzothiadiazine-1,1-dioxide in concentrated ammonium hydroxide and purified as described in the preceding paragraph.

Catalytic reduction experiments. 6-chloro-3,4-dihydro-7-sulfamoyl-1,2,4-benzothiadiazine-1,1-dioxide. Five grams of 6-chloro-7-sulfamoyl-1,2,4-benzothiadiazine-1,1-dioxide was dissolved in 150 ml. of ethanol at 80°. The hot solution was shaken with platinum oxide catalyst in a hydrogen atmosphere of 30 lb. per sq. in. After several hours the catalyst was separated by filtration and the alcohol filtrate concentrated to yield 4.5 g. (88%) of product melting at 262°, (reported[6] m.p. 262°).

6-Chloro-3-cyclohexylmethyl-7-sulfamoyl-1,2,4-benzothiadiazine-1,1-dioxide. Fourteen grams of 3-benzyl-6-chloro-7-sulfamoyl-1,2,4-benzothiadiazine-1,1-dioxide was dissolved in 500 ml. of ethanol and shaken with 1.5 g. of platinium oxide catalyst at 100° in a hydrogen atmosphere of 1000 lb. per sq. in. for 10 hr. The catalyst was separated and the filtrate concentrated to yield 7 g., (50%) of 6-chloro-3-cyclohexylmethyl-7-sulfamoyl-1,2,4-benzothiadiazine-1,1-dioxide, Table I.

6-Chloro-3-cyclopentylmethyl-7-(N-methylsulfamoyl)-1,2,4-benzothiadiazine-1,1-dioxide. A suspension of 29.5 g. (0.078 mole) of 6-chloro-3-cyclopentylmethyl-7-sulfamoyl-1,2,4-benzothiadiazine-1,1-dioxide in 250 ml. of water containing 5.2 g. (0.13 mole) of sodium hydroxide was stirred until solution was complete. The solution was cooled in ice and 9.8 g. (0.078 mole) of dimethyl sulfate was added dropwise. After the addition was complete the solution was stirred at room temperature for 0.5 hr. The product was precipitated by the addition of dilute hydrochloric acid. It was dried in air and dissolved in 800 ml. of 1:1 ethyl acetate–ethanol mixture. Two grams of insoluble 6-amino-4-chlorobenzene-1,3-disulfonamide was collected by filtration. The filtrate was concentrated and petroleum ether (b.p. 40–60°) added to give 25 g. of product melting at 250–252°. After recrystallization from dilute ethanol, it melted at 255–257°. Titration in 66% *N,N*-dimethylformamide indicated that the methyl group is on the 7-sulfamoyl nitrogen rather than in the expected 2-position. If the latter were true only one group would titrate, but there were still two pK'_a's, 7.8 and 13.6.

Anal. Calcd. for $C_{14}H_{18}ClN_3O_4S_2$: C, 42.89; H, 4.63; N, 10.72. Found: C, 43.16; H, 4.54; N, 10.88.

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