The **methiodide** was recrystallized once from benzene-ether and twice from methanol-ether, affording 5.57 g. of pure XLVII, m.p. 261.5–262.5° dec.; λ_{max}^{Nujol} 4.27 (w), 5.97 (w), 6.24 (w), shl. 6.68 μ.

Synthesis and Diuretic Activity of 3,3-Spiro-Substituted Hydrothiazides[1]

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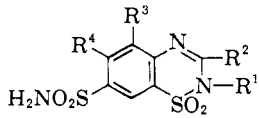
Forty-one 3,3-spiro-substituted hydrothiazides were synthesized by the condensation of substituted 4-amino-1,3-benzenedisulfonamides with cyclic ketones or the corresponding ethylene ketals. Five different synthetic procedures were employed and a comparison of these and other methods was made using the reaction of 4-amino-6-chloro-1,3-benzenedisulfonamide with cyclohexanone as a prototype.

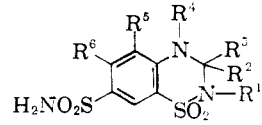
The relative naturetic activity, as determined in rats and dogs, is presented and the structure-activity relationships are discussed. The two most active compounds, 4′-methyl-6-chloro[2H-1,2,4-benzothiadiazine-3(4H)-1′-cyclohexane]-7-sulfonamide-1,1-dioxide and the 6-trifluoromethyl analog, were found to be about ten times as potent as hydrochlorothiazide in dogs and in man.

The advent of 6-chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1- dioxide[2–4] (III) as a diuretic and saluretic agent with outstanding

(1) The term "thiazide" is restricted to 2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide derivatives of the general structure I. The term "hydrothiazide" refers to the corresponding 3,4-dihydro derivatives (II). These terms have received wide usage in the biological and medi-

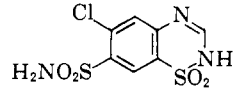


I



II

cal literature for compounds of this type which potentially possess electrolyte excreting or diuretic properties. Adherence to the terminology defined here would serve to differentiate these compounds from the closely related non-diuretic antihypertensive drugs which lack the 7-sulfamoyl group.

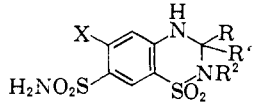


III

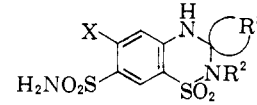
clinical utility stimulated an intensive study of the structure–activity relationships in this class of agents. Early in this investigation[5–7] several generalizations emerged which served to guide subsequent study. Optimal activity was achieved when the sulfamoyl group was located in the 7-position. Furthermore, substitution of the hydrogen atoms on the sulfamoyl group was contraindicated. The introduction of a halogen atom or one of several other groups (including trifluoromethyl, methyl and nitro) in the 6-position markedly enhanced the activity over that of the unsubstituted parent compound. Substitution of certain groups (usually methyl) for the hydrogen atom in the 2-position is reported often to produce compounds with increased potency.[8–10] Saturation of the 3,4-bond nearly always led to more active compounds.[5,7]

In the 3,4-dihydro series, the introduction of certain substituents in the 3-position resulted in compounds with greater potency. The preparation of a wide variety of 3-substituted derivatives presented no synthetic problems and offered a challenging opportunity to observe the effect of structural variation upon biological activity. Since the carbon atom in the 3-position bears two hydrogen atoms, the possibilities for structural variation at this point are greatly multiplied.

The synthesis of 3-*mono*-substituted derivatives (IV, where either R or R′ = H) has been the subject of intensive investigation in these



IV



V

(2) Chlorothiazide, DIURIL®.

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

(4) F. C. Novello and J. M. Sprague, 132nd Meeting of the American Chemical Society, New York, New York, September 8–13, 1957; Abstracts, pp. 32–40.

(5) J. M. Sprague, *Ann. N. Y. Acad. Sci.*, **71**, 328 (1958).

(6) F. C. Novello, S. C. Bell, E. L. A. Abrams, C. Ziegler, and J. M. Sprague, *J. Org. Chem.*, **25**, 965 (1960).

(7) F. C. Novello, S. C. Bell, E. L. A. Abrams, C. Ziegler, and J. M. Sprague, *J. Org. Chem.*, **25**, 970 (1960).

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

(9) W. J. Close, L. R. Swett, and C. W. Nordeen, *J. Org. Chem.*, **26**, 3423 (1961).

(10) J. H. Short and L. R. Swett, *J. Org. Chem.*, **26**, 3428 (1961).

and a number of other laboratories. Several useful diuretic agents belong to this class. On the other hand, the 3,3-disubstituted derivatives (IV, where neither R nor R′ = H) have received very little attention.

The 3,3-disubstituted derivatives can be divided into two types: (1) those in which R and R′ of structure IV are separate substituents and (2) the spiro compounds (V) where R and R′ are part of a ring (R^3). It became clear in the initial phase of this study that, with the synthetic methods available, the number of compounds of the first type which could be prepared readily was very limited. In fact, it appeared that one of the two substituents (IV, R or R′) must be methyl or ethyl and that the other must conform to very narrow steric limitations, *i.e.*, methyl, ethyl or ethoxycarbonyl. Data published[11–13] subsequent to this investigation appear to conform to this generalization, although the nature of the second substituent was extended to include chloromethyl, acetyl and ethoxycarbonylmethyl groups.

This unpromising synthetic picture along with the disappointing biological results obtained with the few compounds of the first type (IV) diverted our attention to compounds of the second type, *i.e.*, the spiro derivatives (IIB). This series proved to be more rewarding both from the standpoint of the ease of syntheses and from saluretic potency.

In general, the 3-*mono*-substituted derivatives are prepared either by the interaction of an aldehyde or aldehyde derivative with the appropriate substituted-4-amino-1,3-benzenedisulfonamide or by reduction of the corresponding thiazide. For the 3,3-disubstituted derivatives, the second method, obviously, is not applicable. However, using cyclic ketones, or their derivatives, the first method proved adequate for the synthesis of the large variety of 3,3-spiro derivatives that are presented in this report.

The details of the synthesis of forty-one 3,3-spiro-substituted hydrothiazides are summarized in Table III. Each of eight different 4-amino-1,3-benzenedisulfonamide derivatives was condensed with one or more of twenty-three different cyclic ketones or their ethylene ketal derivatives.

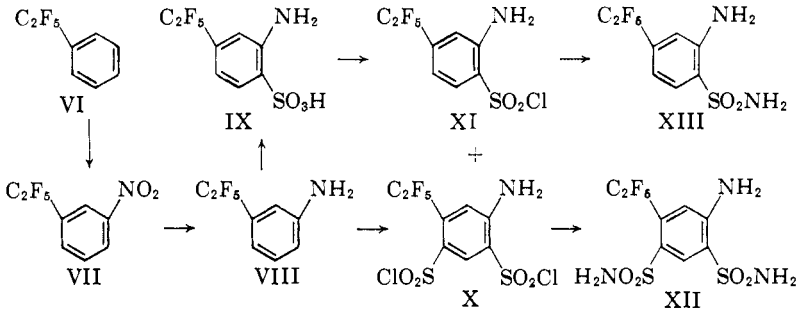
The eight 4-amino-1,3-benzenedisulfonamide derivatives which were employed were the 6-chloro-, 6-trifluoromethyl-, 6-pentafluoro-

(11) C. T. Holdrege, R. B. Babel, and L. C. Cheney, *J. Am. Chem. Soc.*, **81**, 4807 (1959).

(12) F. J. Lund and W. Kobinger, *Acta pharmacol. et toxicol.*, **16**, 297 (1960).

(13) F. J. Lund and W. Kobinger, British Patent Application 26,063 (8/13/58); 30,897 (9/26/58); 36,437 (11/12/58); and 37,997 (11/25/58); Belgian Patent 581,589 (9/3/59); Australian Patent 51,470 (9/10/59).

ethyl-, 6-methyl-, 6-nitro-, 5,6-dichloro-, 5-aza-6-methyl- and 3-N-methyl-6-chloro-substituted derivatives. Among these the only new compound is 4-amino-6-pentafluoroethyl-1,3-benzenedisulfonamide (XII). This compound was synthesized via two routes as illustrated in Scheme I.



(Pentafluoroethyl)benzene (VI), prepared by the method of Hasek, *et al.*,[14] was nitrated to produce the *m*-nitro derivative VII in 87% yield. Catalytic hydrogenation gave the corresponding amine (VIII) in 95% yield. Heating VIII with chlorosulfonic acid and sodium chloride gave a mixture of the monosulfonyl chloride (XI) and disulfonyl chloride (X). Treatment of this mixture with ammonia produced the corresponding sulfonamides (XII) and (XIII) which were separated readily due to their differential solubility in benzene. The yield of XII was 56%; the yield of XIII was small.

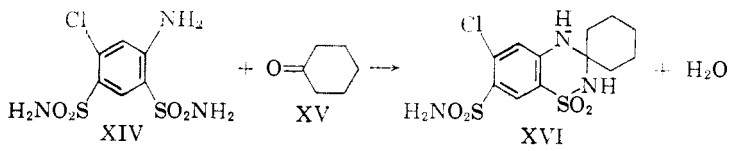
When a procedure comparable to that employed for the synthesis of the 6-trifluoromethyl analog[6] of XII was used, it was found to be longer and the overall yield poorer. Compound VIII was first converted to the sulfonic acid derivative (IX) by heating with 1 ***M*** equivalent of chlorosulfonic acid in *s*-tetrachloroethane. The sulfonic acid (IX), obtained in 98% yield, was then heated with chlorosulfonic acid and sodium chloride. The resulting mixture (X and XI) was treated with ammonia to give a mixture of the corresponding sulfonamides, which were readily separated into the pure components, XII (16%) and XIII (26%).

The ketones (or the corresponding ethylene ketals) that were successfully converted to the spiro-hydrothiazides (V) are the following: cyclobutanone, cyclopentanone, 3-methylcyclopentanone, cyclohexanone, 3-methyl-, 4-methyl-, 4-ethyl-, 4-propyl-, 4-isopropyl-, 4-butyl-, 4-*sec*-butyl-, 4-*tert*-butyl-, 4-isopentyl-, 4-*tert*-pentyl-, 4-cyclopentyl-, 4-cyclohexyl-, and 4-methoxycyclohexanones, tetrahy-

(14) W. R. Hasek, W. C. Smith, and V. A. Engelhardt, *J. Am. Chem. Soc.*, **82**, 543 (1960).

dro-4H-pyran-4-one, tetrahydro-4H-thiopyran-4-one, 5-oxo-*m*-dithiane and 1-methyl-4-piperidone. Five sets of conditions or procedures, that are described in detail in the experimental section, were used to carry out the condensations. These processes[15] consist of treating the selected 4-amino-1,3-benzenedisulfonamide derivative with (A) the cyclic ketone in dimethylformamide, (B) the cyclic ketone in dimethylformamide with potassium fluoride[7] as a catalyst, (C) the ketone ethylene ketal in 1-butanol with sulfuric acid as a catalyst,[11] (D) an excess of ketone with *p*-toluenesulfonic acid as a catalyst[12,13] and (E) the ketone in dioxane with *p*-toluenesulfonic acid as a catalyst.[12,13]

A somewhat detailed study relating the method of condensation to the yield of product was made involving the reaction of 4-amino-6-chloro-1,3-benzenedisulfonamide (XIV) with cyclohexanone (XV) to give 6-chlorospiro-[2H-1,2,4-benzothiadiazine-3(4H),1′-cyclohexane] 7-sulfonamide-1,1-dioxide (XVI). The results are summarized in Table I. No condensation occurred in polyphosphoric acid, toluene



and calcium hydride nor xylene and zinc chloride (experiments 1–3). When dimethylformamide was used as a solvent, the concentration of the reactants appeared to be an important factor. In this medium, potassium fluoride served as a good catalyst (experiments 4–9) but zinc chloride had no effect on the reaction (experiment 10). The maximum yields using dimethylformamide as a solvent were about 67%, even when measures were taken to remove the water formed in the reaction (experiment 11). Maximal yields were obtained using cyclohexane ethylene ketal in 1-butanol and a few drops of sulfuric acid (experiment 12). Using an excess of cyclohexanone under reflux with *p*-toluenesulfonic acid as a catalyst, a very rapid reaction occurred giving an excellent yield of XVI (experiment 13). Dioxane served as an excellent reaction solvent, but like dimethylformamide, the reaction was more rapid with a catalyst (*p*-toluenesulfonic acid, in this instance) and the maximum yield was 70% (experiments 14–15).

Since all of the results recorded in Table I were not available at the

(15) The references indicate methods that now have been published which are similar to those described here.

TABLE I

XIV (1 mole) + XV (3 moles) → XVI

Expt.	Method	Solvent: Name	Solvent: Ml./Mole XIV	Catalyst: Name	Catalyst: Mole/Mole XIV	Temp., °C.	Time, hr.	XVI Yield %
1		Polyphosphoric acid	3700 (g.)	None		100	5	0
2		Toluene	2500	CaH_2[a]	1.2	Reflux	5	50
3		Xylene	2500	$ZnCl_2$	0.1	Reflux	5	0
4		Dimethylformamide	500	None		100	18	Small
5	A	Dimethylformamide	1500	None		100	2	Small
6	A	Dimethylformamide	1500	None		100	18	67
7	A	Dimethylformamide	1500	None		Reflux	1.25	58
8	B	Dimethylformamide	1500	KF	2	100	2	57
9	B	Dimethylformamide	1500	KF	2	100	18	60
10		Dimethylformamide	1500	$ZnCl_2$	0.2	100	2	Small
11		Dimethylformamide	1500	CaH_2[b]	2	Reflux	1.25	45
12	C[c]	1-Butanol	3000	H_2SO_4	0.1	Reflux	1.25	95
13	D	Cyclohexanone	3000	*p*-Toluenesulfonic acid	0.03	Reflux	0.25	85
14		Dioxane	2500	None		Reflux	18	36
15	E	Dioxane	2500	*p*-toluenesulfonic acid	0.03	Reflux	18	70

[a] This agent was added to combine with the water formed in the reaction. [b] The CaH_2 was placed in a soxhlet cup placed above the reaction mixture and the condensate directed into the cup. [c] One mole each of XIV and cyclohexane ethylene ketal were used.

time when many of the 3,3-spirohydrothiazides were prepared, it can be said that many of the reactions recorded in Table III probably were not carried out under optimal conditions.

One of the most serious problems in many cases was the tendency of some of the spirohydrothiazides (V) to hydrolyze during the isolation and purification process. Whenever possible, isolation and crystallization were carried out using anhydrous conditions. When aqueous media were employed, care was taken to prevent or minimize hydrolysis by operating at low temperatures and keeping the operation times at a minimum.

Some comparison of the reactivity of the eight 4-amino-1,3-benzenedisulfonamide derivatives can be made, since an attempt was made to condense each one with 4-methylcyclohexanone. Unfortunately the same method was not used in each case. However, it does appear that the 5,6-dichloro derivatives react slower than the other

benzenoid derivatives. The aza analog, 2-amino-6-methyl-3,5-pyridinedisulfonamide, reacts with considerably less facility than its benzenoid counterpart. Although a number of attempts were made to react 2-chloro-4-amino-5-methylsulfamoylbenzenesulfonamide (XVII) (which bears a methyl group on the sulfamoyl group *ortho* to the amino) with this ketone, no condensation product was isolated.

Of the ketones that were studied, cyclobutanone appears to be the most reactive. In fact, this was the only ketone that condensed with the N-methylsulfamoyl compound (XVII), even though attempts with several other ketones were made. Although cyclopentanone readily reacted with three different 4-amino-1,3-benzenedisulfonamide derivatives by method C, 3-methylcyclopentanone gave much better results when method E was used. Similarly, cyclohexanone reacted readily with XIV by method A but with 3-methylcyclohexanone it was necessary to resort to method B.

The twelve 4-substituted cyclohexanones were sufficiently reactive to give satisfactory condensations with XIV (and in most cases with the corresponding 6-trifluoromethyl analog) using method A. Only in the case of 4-cyclohexylcyclohexanone was it necessary to resort to other procedures. Cycloheptanone gave only a 16% yield of product with XIV using method B and cycloöctanone gave no product using methods A, C, or E. The results obtained with cycloheptanone and cycloöctanone are not unexpected on the basis of theoretical considerations regarding the steric arrangement of the carbonyl group.[16]

The condensations of the selected heterocyclic ketones with XIV proceeded without difficulty. Tetrahydro-4H-pyran-4-one gave satisfactory results using method A. Method B was employed for tetrahydro-4H-thiopyran-4-one, and method C gave excellent results with both tetrahydro-2H-thiopyran-3(4H)-one and 5-oxo-*m*-dithiane.

With five other ketones, 9-fluorenone, α-tetralone, 2-cyclohexenone, 3,4-dimethylcyclohexanone, and tropanone, little or none of the desired product was obtained from the reaction with XIV using method A or B.

Pharmacology[17]

Each of the forty-one compounds was assayed for its saluretic-diuretic potency in both rats and dogs. In the rat test, animals weighing about 150 g. were maintained overnight on a sodium and potassium free diet and then they were hydrated with 5 ml. of tap water.

(16) V. Prelog, *J. Chem. Soc.*, 420 (1950).

(17) We are indebted to Dr. E. Alpert and his staff for the information concerning studies in man which is presented here and for their assistance in its interpretation.

One and one-half hours later, 5 ml. of drug in aqueous suspension was injected intraperitoneally. The urine volume and total sodium, potassium and chloride output for the following 5 hr. was measured.

Groups of 16 rats received hydrochlorothiazide at 0.16 mg./kg. and 0.64 mg./kg. Groups of 8 rats received the test compounds at each of the two dose levels. Compounds whose potency did not fall well within this dose range were repeated at the appropriate dose levels. The potency relative to hydrochlorothiazide was based on a simplified 4-point assay equation. Because analyses were performed on pooled samples, no fiducial limits were established; therefore, the relative potency values must be regarded as rough approximations. The data for comparing structure with naturetic potency in rats are presented in Table II; the chloruretic activity was very nearly the same. In regard to the potassium and water excretion, the flatness of the dose-response curves does not permit a reliable quantitative distinction between many of the compounds with respect to these parameters.

Each compound also was tested in dogs using intravenous administration. The relative potencies of the compounds as compared with one another in dogs were found to parallel the rat data quite closely. However, in dogs, the spiro compounds, as a group, appeared relatively more potent (by at least a factor of about two). A few of the more active compounds were found to be active in both rats and dogs upon oral administration.

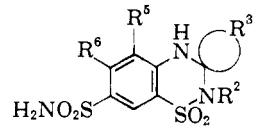
With the data available in Table II, it is not possible to make a detailed structure-activity analysis. However, some generalizations are obvious and appear to be reliable.

In comparing the 6-chlorospiro-[2H-1,2,4-benzothiadiazine-3(4H),-1′ - cycloalkane] - 7 - sulfonamide - 1,1 - dioxides, as the cycloalkane ring size is increased from 4 to 7 atoms (no. 1, 3, 7 and 41), optimum activity is found with the 6-membered ring (no. 7). Substitution of a methyl group in the 3-position of either the 5- or 6-membered ring (no. 6 and 12) has little effect upon activity.

With a 6-membered ring, substitution of a methyl group in the 4-position (no. 13) produces one of the most active compounds in the series. This compound is over 5 times as potent as hydrochlorothiazide in rats and over 10 times as potent in dogs. However, as increasingly larger alkyl or cycloalkyl groups are introduced into the 4-position (no. 20, 22, 24, 25, 26, 28, 30, 31, 32 and 33), the potency gradually diminishes. When a methoxy group occupies the 4-position (no. 35), the molecular size and biological potency is about the same as the 4-ethyl derivative (no. 20).

TABLE II

COMPARISON OF STRUCTURE WITH NATURETIC POTENCY IN RATS



No.	R^2	Spiro ring (C, R^3)	R^5	R^6	Relative (i.p.) potency in rats
	H	None (Hydrochlorothiazide)	H	Cl	1
1	H	Cyclobutane	H	Cl	0.6
2	CH_3		H	Cl	0.8
3	H	Cyclopentane	H	Cl	0.6
4	H		H	CF_3	0.5
5	H		Cl	Cl	<0.1
6	H	3-Methylcyclopentane	H	Cl	0.5
7	H	Cyclohexane	H	Cl	1
8	H		H	CH_3	0.5
9	H		H	CF_3	0.8
10	H		H	NO_2	0.9
11	H		Cl	Cl	0.1
12	H	3-Methylcyclohexane	H	Cl	1.6
13	H	4-Methylcyclohexane	H	Cl	5.6
14	H		H	CF_3	5.9
15	H		H	C_2F_5	<0.1
16	H		Cl	Cl	0.4
17	H		H	NO_2	3.1
18	H		H	CH_3	1.9
19	H		aza[a]	CH_3	0.2
20	H	4-Ethylcyclohexane	H	Cl	3.6
21	H		H	CF_3	2.1
22	H	4-Propylcyclohexane	H	Cl	1.3
23	H		H	CF_3	1.6
24	H	4-Isopropylcyclohexane	H	Cl	1
25	H	4-Butylcyclohexane	H	Cl	1.1
26	H	4-*sec*-Butylcyclohexane	H	Cl	2.6
27	H		H	CF_3	<0.2
28	H	4-*tert*-Butylcyclohexane	H	Cl	0.5
29	H		H	CF_3	1
30	H	4-Isopentylcyclohexane	H	Cl	1.1
31	H	4-*tert*-Pentylcyclohexane	H	Cl	0.5
32	H	4-Cyclopentylcyclohexane	H	Cl	0.5
33	H	4-Cyclohexylcyclohexane	H	Cl	0.2
34	H		H	CF_3	0.7

TABLE II (*Continued*)

No.	R^2	Spiro ring C R^3	R^5	R^8	Relative (i.p.) potency in rats
35	H	4-Methoxycyclohexane	H	Cl	3
36	H	4-Oxacyclohexane[b]	H	Cl	0.8
37	H	4-Thiacyclohexane[b]	H	Cl	1.8
38	H	3-Thiacyclohexane[b]	H	Cl	<0.2
39	H	3,5-Dithiacyclohexane[b]	H	Cl	1.8
40	H	4-(N-Methyl-aza)-cyclohexane[b]	H	Cl	<0.2
41	H	Cycloheptane	H	Cl	0.4

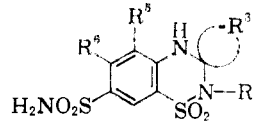
[a] The carbon and hydrogen atoms located in the 5-position are replaced by a nitrogen atom. [b] For convenience, the ring is named as a derivative of a cycloalkane.

The replacement of the methylene group in the 4-position of the 6-membered spiro ring (no. 7) with a hetero atom, such as oxygen (no. 36), produced little change in activity. It might be anticipated that compounds with a sulfur atom in the 3-position or in the 3- and 5-positions would show the enhanced potency reported by Scriabine and co-workers[18-21] for 3-alkylmercaptomethyl-6-chloro-2H-1,2,4-benzothiadiazone-7-sulfonamide-1,1-dioxides. Indeed, the 3,5-dithia derivative (no. 39) had about double the potency of the parent carbocyclic compound (no. 7). However, the 4-thia derivative (no. 37) was as active as the 3,5-dithia compound. Issekutz and co-workers,[22] who recently reported a study of the diuretic properties of the 4-thia derivative (and several other spirohydrothiazides), indicated it to be more potent than hydrochlorothiazide. On the other hand, the 3-thia derivative (no. 38) exhibited a drastically reduced potency. The 4-methyl-aza compound (no. 40) had only a fraction of the activity of its carbocyclic analog (no. 13).

The introduction of a methyl group in the 2-position (no. 2) of the 3-spirocyclobutane derivative (no. 1) produced an insignificant change in activity, although in a single experiment in dogs there is an indication of increased potency.

The influence of substituents in the 5- and 6-positions of the 1,2,4-benzothiadiazine ring was about the same as that which has been

(18) A. Scriabine, S. Y. P'An, D. Rowland, and C. Bertrand, *Federation Proc.*, **19**, 363 (1960).
(19) J. M. McManus, A. Scriabine, and W. M. McLamore, *Federation Proc.*, **20**, 411 (1961).
(20) A. Scriabine, J. M. McManus, B. Kontradas, M. Yu, S. Y. P'An, and W. M. McLamore, *Federation Proc.*, **20**, 411 (1961).
(21) S. Y. P'An, A. Scriabine, D. E. McKersie, and W. M. McLamore, *J. Pharmacol. Exptl. Therap.*, **128**, 122 (1960).
(22) B. Issekutz, N. Jobbagyi, E. Oszvald, and M. Szekely, *Arch. intern. pharmacodynamie*, **132**, 237 (1961).



TABLE

No.	R^2		R^5	R^6	Prep. Method	% Yield	M.p.,[12] °C.
1	H	Cyclobutane	H	Cl	E	94	272
2	CH_3	Cyclobutane	H	Cl	E	67	273–275
3	H	Cyclopentane	H	Cl	A, 11; C, 74		250–252[b]
4	H	Cyclopentane	H	CF_3	C	77	235–236[c]
5	H	Cyclopentane	Cl	Cl	C	79	260–262
6	H	3-Methylcyclopentane	H	Cl	C, 0; E, 79		231–232
7[d]	H	Cyclohexane	H	Cl	A, 67; C, 95		285.5–286.5[e]
8[f]	H	Cyclohexane	H	CH_3	A	50	279–280[g]
9	H	Cyclohexane	H	CF_3	C	85	259.5–260.5[h]
10[i]	H	Cyclohexane	H	NO_2	A	53	257–258[j]
11[f]	H	Cyclohexane	Cl	Cl	B	83	272.5–274
12	H	3-Methylcyclohexane	H	Cl	A, 0; B, 18		234.5–237
13	H	4-Methylcyclohexane	H	Cl	A, 59; D, 91		272–273
14	H	4-Methylcyclohexane	H	CF_3	A	61	247–249
15	H	4-Methylcyclohexane	H	C_2F_5	D	56	222–223.5
16	H	4-Methylcyclohexane	Cl	Cl	A	79	273–274
17[i]	H	4-Methylcyclohexane	H	NO_2	A	35	255–256
18[f]	H	4-Methylcyclohexane	H	CH_3	A	43	250.5
19	H	4-Methylcyclohexane	aza[k]	CH_3	D, 11; E, 0		250–251.5
20	H	4-Ethylcyclohexane	H	Cl	A	56	248–249
21	H	4-Ethylcyclohexane	H	CF_3	A	29	261–262
22	H	4-Propylcyclohexane	H	Cl	A	36	245–246
23	H	4-Propylcyclohexane	H	CF_3	A	82	225–227
24	H	4-Isopropylcyclohexane	H	Cl	A	53	259–260
25	H	4-Butylcyclohexane	H	Cl	A	40	216.5–217.5
26	H	4-*sec*-Butylcyclohexane	H	Cl	A	25	248–249
27	H	4-*sec*-Butylcyclohexane	H	CF_3	A	71	231.5–232.5
28	H	4-*tert*-Butylcyclohexane	H	Cl	A	30	276–277
29	H	4-*tert*-Butylcyclohexane	H	CF_3	A	69	252.5–254
30	H	4-Isopentylcyclohexane	H	Cl	A	39	240–242
31	H	4-*tert*-Pentylcyclohexane	H	Cl	A	34	262–263
32	H	4-Cyclopentylcyclohexane	H	Cl	A	44	239–242
33[l]	H	4-Cyclohexylcyclohexane	H	Cl	B	24	252.5–253.5
34	H	4-Cyclohexylcyclohexane	H	CF_3	C	21	256–257
35	H	4-Methoxycyclohexane	H	Cl	A, 50; C, 0		227–229
36	H	4-Oxacyclohexane	H	Cl	A	46	256–258
37[l,m]	H	4-Thiacyclohexane	H	Cl	B	37	271–272
38	H	3-Thiacyclohexane	H	Cl	A	0	
					C	85	261-262.5
39	H	3,5-Dithiacyclohexane	H	Cl	C	86	269
40	H	4-(N-Methylaza)cyclohexane	H	Cl	A	24	234-235
41[l]	H	Cycloheptane	H	Cl	B	16	230

[a] Code: M-W, methanol-water; BA, the product crystallized from the 1-butanol reaction solvent; DMF-W, dimethylformamide–water; Et, ethanol; A–W, acetone–water; A–P acetone–petroleum ether; Ac-W, acetic acid-water; Et–W, ethanol-water; Ac-DMF, acetic acid-dimethylformamide; Me–W, 2-methoxyethanol-water. [b] Lund and Kobinger[12,13] report m.p. 234°. [c] Holdrege *et al.*[11] report a yield of 19%, m.p. 225–226°; Lund and Kobinger[12,13] report m.p. 234.5–236°. [d] Novello *et al.*[1] report m.p. 259–260° (uncorr.). [e] Lund and Kobinger[12,13] report m.p. 283.5–285°. [f] We are indebted to Dr. F. C. Novello and Mr. A. A.

III

Recryst. Solvent[a]	Formula	Analyses %: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
M-W	$C_{10}H_{12}ClN_3O_4S_2$	35.55	35.83	3.58	3.73	12.44	12.35
M-W	$C_{11}H_{14}ClN_3O_4S_2$	37.55	37.65	4.01	4.33	11.94	11.85
BA	$C_{11}H_{14}ClN_3O_4S_2$	37.55	37.44	4.01	4.11	11.94	11.83
M-W	$C_{12}H_{14}F_3N_3O_4S_2$	37.39	37.84	3.66	4.09	10.90	10.70
DMF-W	$C_{11}H_{13}Cl_2N_3O_4S_2$	35.30	34.89	3.50	3.51	11.23	10.94
M-W	$C_{12}H_{16}ClN_3O_4S_2$	39.39	39.76	4.41	4.68	11.41	11.39
DMF-W	$C_{12}H_{16}ClN_3O_4S_2$	39.39	39.64	4.41	4.52	11.50	11.60
Et	$C_{13}H_{19}N_3O_4S_2$	45.20	45.19	5.54	5.40	12.16	11.92
M-W	$C_{13}H_{16}F_3N_3O_4S_2$	39.09	39.19	4.04	4.04	10.52	10.50
A-W	$C_{12}H_{16}N_4O_6S_2$	38.29	38.29	4.29	4.39	14.89	15.15
DMF-W	$C_{12}H_{16}Cl_2N_3O_4S_2$	36.01	36.60	3.78	4.09	10.50	10.35
M-W	$C_{13}H_{18}ClN_3O_4S_2$	41.10	41.52	4.78	4.87	11.06	10.97
Me-W	$C_{13}H_{18}ClN_3O_4S_2$	41.10	40.99	4.78	4.93	11.06	10.96
M-W	$C_{14}H_{18}F_3N_3O_4S_2$	40.67	40.78	4.39	4.49	10.16	10.09
Ac-W	$C_{15}H_{18}F_6N_3O_4S_2$	38.87	39.05	3.91	4.18	9.07	8.90
A-P	$C_{13}H_{17}Cl_2N_3O_4S_2$	37.68	38.17	4.19	4.06	10.14	10.09
A-W	$C_{13}H_{18}N_4O_6S_2$	40.61	40.27	4.72	4.64	14.57	14.32
A-P	$C_{14}H_{21}N_3O_4S_2$	46.78	46.84	5.89	5.80	11.69	11.62
Ae-W	$C_{13}H_{20}N_4O_4S_2$	43.31	43.80	5.59	5.65	15.54	15.24
A-P	$C_{14}H_{20}ClN_3O_4S_2$	42.68	43.16	5.12	5.20	10.67	10.58
M-W	$C_{15}H_{20}F_3N_3O_4S_2$	42.14	42.45	4.72	4.89	9.83	9.76
A-P	$C_{15}H_{22}ClN_3O_4S_2$	44.16	44.08	5.44	5.33	10.30	10.21
M-W	$C_{16}H_{22}F_3N_3O_4S_2$	43.52	43.93	5.02	5.34	9.52	9.39
A-P	$C_{15}H_{22}ClN_3O_4S_2$	44.16	44.56	5.44	5.30	10.30	10.19
A-P	$C_{16}H_{24}ClN_3O_4S_2$	45.54	45.26	5.73	5.93	9.96	9.87
A-P	$C_{16}H_{24}ClN_3O_4S_2$	45.54	45.83	5.73	5.73	9.96	9.89
M-W	$C_{17}H_{24}F_3N_3O_4S_2$	44.82	45.04	5.31	5.28	9.23	9.16
Ac-DMF	$C_{16}H_{24}ClN_3O_4S_2$	45.54	45.48	5.73	5.50	9.96	9.80
A-P	$C_{17}H_{24}F_3N_3O_4S_2$	44.82	45.01	5.31	5.56	9.23	9.15
Et-W	$C_{17}H_{26}ClN_3O_4S_2$	46.83	46.69	6.01	6.41	9.64	9.54
A-P	$C_{17}H_{26}ClN_3O_4S_2$	46.83	46.66	6.01	5.80	9.64	9.55
A-P	$C_{17}H_{24}ClN_3O_4S_2$	47.04	47.60	5.57	5.54	9.68	9.54
Et-W	$C_{18}H_{26}ClN_3O_4S_2$	48.25	48.14	5.85	5.64	9.38	9.26
M-W A-P	$C_{19}H_{26}F_3N_3O_4S_2$	47.38	47.22	5.44	5.67	8.73	8.62
A-P	$C_{13}H_{18}ClN_3O_4S_2$	39.44	39.15	4.58	4.58	10.61	10.58
DMF-W	$C_{11}H_{14}ClN_3O_5S_2$	35.91	36.21	3.84	3.74	11.42	11.47
A-W	$C_{11}H_{14}ClN_3O_4S_3$	34.42	34.89	3.68	3.57	———	———[n]
BA	$C_{11}H_{14}ClN_3O_4S_3$	34.42	34.83	3.68	3.71	10.95	10.91
BA	$C_{10}H_{12}ClN_3O_4S_4$	29.88	30.26	3.01	3.06	10.46	10.37
DMF-W	$C_{12}H_{17}ClN_4O_4S_2$	37.84	38.14	4.50	4.76	14.71	14.62
Et-W	$C_{13}H_{18}ClN_3O_4S_2$	41.11	41.22	4.76	5.02	11.06	10.78

Deana for this synthesis. [g] Lund and Kobinger[12,13] report m.p. 261.5–263°. [h] Holdrege *et al.*[11] report m.p. 260–262°. Lund and Kobinger[12,13] report m.p. 261–262°. [i] We are indebted to Mr. C. Ziegler for this synthesis. [j] Lund and Kobinger[12,13] report m.p. 261.5°. [k] The CH group located in the 5-position is replaced by a nitrogen atom. [l] We are indebted to Mr. J. A. Nicholson for this synthesis. [m] Issekutz *et al.*[22] present the pharmacology on this compound but give no chemical data. [n] Calcd.: S, 25.05. Found: S, 24.85.

observed in other series. Optimal activity was achieved when a chlorine atom was located in the 6-position. Placing chlorine atoms in both the 5- and 6-positions markedly reduced activity (no. 5, 11 and 16). Generally, the activity of the 6-trifluoromethyl compounds was in the same range as the 6-chloro derivatives (no. 3 and 4, 7 and 9, 13 and 14, 20 and 21, 22 and 23, 28 and 29). There were two exceptions, one where the 6-chloro derivative is more active (no. 26 and 27) and one where the reverse is true (no. 33 and 34). The data obtained in dogs with these two pairs of compounds were comparable to those obtained in rats.

In comparing the other 6-substituents, the methyl derivatives (no. 8 and 18) were no more than half as active as the corresponding chloro compounds (no. 7 and 13), while the activity of the nitro compounds (no. 10 and 17) lay between that of the methyl and chloro derivatives. The activity of the 6-pentafluoroethyl derivative (no. 15) was markedly less than the corresponding 6-trifluoromethyl compound (no. 14).

The replacement of the CH group in the 5-position of compound no. 13 by a nitrogen atom to give the aza analog, 4′,6-dimethylspiro-[2H-1,2,4-pyrido[2.3-e]-1,2,4-thiadiazine-3(4H),1′-cyclohexane]-7-sulfonamide-1,1-dioxide (no. 19) caused about a ten-fold reduction in activity.

Two compounds, 4′-methyl-6-chlorospiro-[2H-1,2,4-benzothiadiazine - 3(4H),1′ - cyclohexane] - 7 - sulfonamide - 1,1 - dioxide (no. 13) and the corresponding 6-trifluoromethyl derivative (no. 14) have had a limited study in man. Both compounds were found to be effective saluretic agents at about one-tenth the dose required for hydrochlorothiazide. This is about the potency that was predicted from the data obtained in dogs and about twice that indicated from the studies in rats.

Experimental[23,24]

I. Intermediates. A. Cyclic Ketones.—Cyclobutanone, cyclopentanone, cyclohexanone, 3-methylcyclohexanone, 4-methylcyclohexanone, 3,4-dimethylcyclohexanone, 4-cyclohexylcyclohexanone, 2-cyclohexenone, cycloheptanone, cyclooctanone, α-tetralone, 9-fluorenone, 1-methyl-4-piperidone and tropanone were commercially available materials. Tetrahydro-4H-pyran-4-one,[25] tetrahydro-4H-thiopyranone,[26] tetrahydro-2H-thiopyran-3(4H)-one[27] and 5-oxo-*m*-dithiane[28] were prepared by published methods.

(23) All melting and boiling points are corrected.
(24) We are indebted to Mr. K. B. Streeter and his staff for the analytical data.
(25) E. Hanschke, *Chem. Ber.*, **88**, 1053 (1955).
(26) C. Barkenbus, V. C. Midkiff, and R. M. Newman, *J. Org. Chem.*, **16**, 232 (1951).
(27) N. J. Leonard and J. Figueras, Jr., *J. Am. Chem. Soc.*, **74**, 917 (1952).
(28) E. G. Howard and R. V. Lindsey, Jr., *J. Am. Chem. Soc.*, **82**, 158 (1960).

4-Ethyl-, 4-propyl-, 4-isopropyl-, 4-butyl-, 4-*sec*-butyl, 4-*tert*-butyl, 4-isopentyl-, 4-*tert*-pentyl-, 4-methoxy- and 4-cyclopentylcyclohexanone each has been described in the literature. Regardless of the literature method, each was prepared by the sodium dichromate oxidation of the corresponding cyclohexanol according to the procedure of Sandborn.[29] The required cyclohexanols which were not available commercially were prepared by the hydrogenation[30] of the corresponding phenol using Raney nickel catalyst and 129 kg. of hydrogen/cm.^{2} at 190° as described by Frank, *et al.*[31] 4-Cyclopentylcyclohexanol was prepared from 4-(1-cyclopentenyl)-phenol.

B. Ethylene Ketals. General Method.—The required ketone (1 mole), ethylene glycol (1.05 moles), benzene (200 ml.) and *p*-toluenesulfonic acid (200 mg.) were placed in a flask fitted with a modified Dean-Stark constant water separator attached to a reflux condenser. The reaction mixture was vigorously refluxed until an aqueous layer no longer formed in the distillate. The desired ethylene ketal was isolated by careful fractional distillation of the reaction mixture.

1,4-Dioxaspiro[4.4]nonane[32] (from cyclopentanone), 1,4-dioxaspiro[4.5]decane[33] (from cyclohexanone), and 1,4-dioxa-7,9-dithiaspiro[4.5]decane[34] (from 5-oxo-*m*-dithiane) have been described in the literature. The following two new compounds were prepared.

8-Cyclohexyl-1,4-dioxaspiro[4.5]decane was synthesized in 43% yield from 4-cyclohexylcyclohexanone; b.p. 117° (0.4 mm.); m.p. 42.5–43.5°.

Anal. Calcd. for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 75.16; H, 10.68.

1,4-Dioxa-7-thiaspiro[4.5]decane was prepared in 73% yield from tetrahydro-2H-thiopyran-3-one; b.p. 108–110° (8 mm.); $n^{25}D$ 1.5162.

Anal. Calcd. for $C_7H_{12}O_2S$: C, 52.47; H, 7.55. Found: C, 51.95; H, 7.60.

C. 4-Amino-1,3-benzenedisulfonamides.—The 6-chloro-, 6-trifluoromethyl-, 6-methyl-, 6-nitro- and 5,6-dichloro derivatives of 4-amino-1,3-benzenedisulfonamide[6] as well as 2-chloro-4-amino-5-methylsulfamoylbenzenesulfonamide[7] and 2-amino-6-methyl-3,5-pyridinedisulfonamide[35] have been reported in the literature.

4-Amino-6-pentafluoroethyl-1,3-benzenedisulfonamide.—**(Pentafluoroethyl)-benzene** (VI) was prepared[30] in 83% yield by the method of Hasek, Smith and Engelhardt,[14] $n^{26}D$ 1.3925.

2. *m*-Nitro-pentafluoroethylbenzene (VII).—Compound VI (74 g., 0.4 mole) was stirred and cooled to 5° and treated dropwise with a mixture of nitric acid (sp. gr. 1.5) (22 g., 0.33 mole) and concd. sulfuric acid (33 g., 0.32 mole). The temperature was maintained at 5–15° during the 1 hr. addition period and then raised to 45° for 1 hr. The reaction mixture was cooled and poured onto ice. The oil that separated was extracted with ether, washed with water, dried over sodium sulfate and fractionally distilled. The yield of material, b.p. 74–75° (0.35 mm.), was 84 g. (87%); $n^{25}D$ 1.4382.

(29) L. T. Sandborn, *Org. Synth.*, Coll. Vol. I, John Wiley and Sons, Inc., New York, 1941, p. 340.

(30) We are indebted to Dr. W. H. Jones for carrying out this reaction.

(31) R. L. Frank, R. E. Berry, and O. L. Shotwell, *J. Am. Chem. Soc.*, **71**, 3889 (1949).

(32) E. J. Salmi, *Chem. Ber.*, **71**, 1803 (1938).

(33) M. Sulzbacher, E. Bergmann, and E. R. Pariser, *J. Am. Chem. Soc.*, **70**, 2827 (1948).

(34) E. G. Howard, U. S. Patent 2,790,810 and 2,790,811 (1957).

(35) E. J. Cragoe, Jr., J. A. Nicholson, and J. M. Sprague, *J. Med. Pharm. Chem.*, **4**, 369 (1961).

Anal. Calcd. for $C_8H_4F_5NO_2$: C, 39.84; H, 1.67; N, 5.81. Found: C, 40.21; H, 1.90; N, 5.69.

3. *m*-(Pentafluoroethyl)aniline (VIII) was prepared by dissolving VII (110 g., 0.457 mole) in ethanol (450 ml.) and hydrogenating[30] for 5 hr. at 162 kg./cm.^{2} and 30° using Raney nickel. The catalyst was removed by filtration and the filtrate fractionally distilled using a 35.6 cm. Vigreux column. The yield was 87 g. (95%), b.p. 80–82° (14 mm.); $n^{25}D$ 1.4478.

Anal. Calcd. for $C_8H_6F_5N$: C, 45.50; H, 2.86; N, 6.63. Found: C, 45.88; H, 2.90; N, 6.44.

4. 4-Amino-6-(pentafluoroethyl-1,3-benzenedisulfonamide (XII).—Method 1. —Under anhydrous conditions, chlorosulfonic acid (177 g., 100 ml., 1.52 moles) was mechanically stirred and VIII (20 g., 0.095 mole) was added at room temperature over a 20 min. period. Sodium chloride (90 g., 1.55 mole) was added, portionwise, over a period of 90 min. Considerable foaming occurred, particularly during the early part of the addition. The temperature was raised to 150° over 30 min. and maintained for 2 hr. During the heating period, the contents of the reaction vessel solidified. The mixture was cooled, quenched with ice water (500 ml.) and extracted with ether (300 ml.). The ether extract was washed with water, dried over sodium sulfate, concentrated to 100 ml. and added to liquid ammonia (250 ml.). The solid that formed upon evaporation of the volatile material was triturated with boiling benzene (two 100 ml. portions) and recrystallized from water. The yield of XII was 19.7 g. (56%), m.p. 247.5–248°.

Method 2, Step 1.—2-Amino-4-pentafluoroethylbenzenesulfonic Acid (IX).— In a flask equipped with a thermometer, mechanical stirrer and reflux condenser protected with a drying tube, a stirred solution of VIII (10.5 g., 0.05 mole) in *s*-tetrachloroethane (100 ml.), was cooled in an ice bath and a solution of chlorosulfonic acid (6 g., 0.05 mole) in *s*-tetrachloroethane (25 ml.) was added over a period of 15 min. The mixture was heated via an oil bath at 125° for 3 hr., cooled and filtered. The solid was washed with a little *s*-tetrachloroethane and dried. The yield of IX was 14.1 g. (98%) and the purity was adequate for use in the next step. A small sample was purified by dissolving in aqueous sodium carbonate and precipitating with dil. hydrochloric acid; m.p. 357.5–358.5°.

Anal. Calcd. for $C_8H_6F_5NO_3S$: C, 33.00; H, 2.08; N, 4.81. Found: C, 32.90; H, 2.27; N, 4.70.

Step 2.—4-Amino-6-pentafluoroethyl-1,3-benzenedisulfonamide (XII).—Chlorosulfonic acid (185 g., 105 ml., 1.6 mole) was placed in a 1-l. flask, the stirrer was started, cooled in an ice bath and IX (46.4 g., 0.16 mole) was added gradually over 15 min. The ice bath was removed and sodium chloride (98 g.) was added, portionwise, over 1 hr. using vigorous stirring. The temperature was rapidly raised to 150° where it was maintained for 1.5 hr. The solid reaction mass was cooled, quenched with ice water (700 ml.) and filtered. The gummy product was dissolved in aqueous ammonia (300 ml. of sp. gr. 0.89), then heated on a steam bath for 2.5 hr. and cooled. The crystalline solid that formed was removed by filtration, dried and triturated with two 100 ml. portions of boiling benzene (the benzene extracts were saved). The product was dried and recrystallized from water. The yield of XII was 9.6 g. (16%), m.p. 247.5–248°.

Anal. Calcd. for $C_8H_8F_5N_3O_4S_2$: C, 26.02; H, 2.18; N, 11.38; S, 17.91. Found: C, 26.59; H, 2.29; N, 11.26; S, 17.50.

The combined benzene extracts were concentrated and cooled whereby **2-amino-4-(pentafluoroethyl)benzenesulfonamide** (XIII), 12.5 g. (26%) separated.

After recrystallization from benzene, the m.p. was 110.5–111.5°.

Anal. Calcd. for $C_8H_7F_5N_2O_2S_2$: C, 33.11; H, 2.43; N, 9.65. Found: C, 33.53; H, 2.49; N, 9.57.

II. 3,3-Spiro Derivatives of 3,4-Dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxides. Method A. General.—The required 4-amino-1,3-benzenedisulfonamide derivative (0.02 mole) and ketone (0.06 mole) were dissolved in dimethylformamide (50 ml.) and heated on a steam bath under anhydrous conditions for 12 to 48 hr. The product was usually isolated by precipitation from the reaction mixture. Water, petroleum ether[36] or acetic acid proved to be the most satisfactory for this purpose. In some cases, the addition of methanol or ethanol prior to treatment with the precipitating solvent produced a more satisfactory separation of the product.

Trituration of the precipitated material with an appropriate solvent (usually petroleum ether) frequently improved the quality of the product. Purification was effected by recrystallization from the selected solvent or solvent pair.

Some compounds of this type undergo appreciable hydrolysis in hot aqueous media; therefore, recrystallizations involving a water component usually were done at room temperature or below. The substance was usually dissolved in the organic solvent, cooled, stirred and water added very slowly. Under these conditions, the product often separated in crystalline form with high purity.

When non-aqueous solvents were employed, recrystallizations were carried out in the conventional manner at elevated temperatures. Example: **4′-*sec*-Butyl-6-trifluoromethylspiro-[2H-1,2,4-benzothiadiazine-3(4H)-1′-cyclohexane]-7-sulfonamide-1,1-dioxide (compound 27).**—4-Amino-6-trifluoromethyl-1,3-benzenedisulfonamide (6.4 g., 0.02 mole) and 4-*sec*-butylcyclohexanone (6.1 g., 0.04 mole) were dissolved in dimethylformamide (25 ml.) and heated on a steam bath for 48 hr. The reaction mixture was cooled, treated with methanol (100 ml.) and then water (300 ml.) was gradually added with stirring. The aqueous layer was decanted and the viscous, oily product triturated with petroleum ether (100 ml.). The resulting solid was removed by filtration and dried. The crude material was dissolved in methanol (25 ml.), stirred and a few ml. of water added. The small amount of oil that separated was removed by filtration. The filtrate was stirred and water (75 ml.) gradually added whereby the pure crystalline product separated.

Method B. General.—This procedure is identical with Method A except that 2.32 g. (0.04 mole) of anhydrous potassium fluoride is added initially to the reaction mixture and then removed by filtration at the end of the reaction period. Example: **3′-Methyl-6-chlorospiro[2H-1,2,4-benzothiadiazine-3(4H),1′-cyclohexane]-7-sulfonamide-1,1-dioxide (compound 12).**—4-Amino-6-chloro-1,3-benzenedisulfonamide (5.7 g., 0.02 mole) and 3-methylcyclohexanone (7 g., 0.06 mole) were dissolved in dimethylformamide (30 ml.). Anhydrous potassium fluoride (2.32 g., 0.04 mole) was added and the mixture heated on a steam bath under anhydrous conditions for 20 hr. The solution was filtered and extracted with three 50 ml. portions of petroleum ether. The lower, dimethylformamide, layer was concentrated to a small volume at reduced pressure, diluted with ethanol (20 ml.) and precipitated by the slow addition of water (150 ml.). The solid that separated was removed by filtration, dried and recrystallized by dissolving in acetone and slowly adding water. A second recrystallization from methanol–water gave pure material.

(36) Merck's "benzin," b.p. 30–60°.

Method C. General.—The 4-amino-1,3-benzenedisulfonamide derivative (0.02 mole) and ketone ethylene ketal (0.02 mole) were dissolved in 1-butanol (60 ml.) and concd. sulfuric acid (3 drops) was added. The mixture was refluxed and mechanically stirred under anhydrous conditions for 1 to 8 hr. During this time, the disulfonamide dissolved and the product separated. Purification was effected by recrystallization from the appropriate solvent or solvent mixture. Example: **6-Chlorospiro-[2H-1,2,4-benzothiadiazine-3(4H),5′-[m]dithiane]-7-sulfonamide-1,1-dioxide (compound 39).**—4-Amino-6-chloro-1,3-benzenedisulfonamide (2.85 g., 0.01 mole) and 1,4-dioxa-7,9-dithiaspiro[4.5]decane (1.8 g., 0.01 mole) were dissolved in 1-butanol (30 ml.) and concd. sulfuric acid (2 drops) was added. The mixture was stirred and refluxed under anhydrous conditions for 3.5 hr. During this time, the disulfonamide gradually dissolved and the product separated as a fine white solid. After separation by filtration, this material was washed with ethanol, then ether and dried. The product isolated in this manner was analytically pure.

Method D. General.—The 4-amino-1,3-benzenedisulfonamide derivative (0.02 mole), ketone (50 to 60 ml.) and *p*-toluenesulfonic acid (50 to 100 mg.) were refluxed under anhydrous conditions for 15 min. to 1 hr. The reaction mixture generally was treated with petroleum ether (400 to 500 ml.). The precipitated material was triturated with several portions of petroleum ether (50 ml.) and the product removed by filtration. After drying, purification was effected by recrystallization. Example: **4′-Methyl-6-chlorospiro-[2H-1,2,4-benzothiadiazine-3(4H)-1′-cyclohexane]-7-sulfonamide-1,1-dioxide (compound 13).** 4-Amino-6-chloro-1,3-benzenedisulfonamide (5.7 g., 0.02 mole), 4-methylcyclohexanone (60 ml.) and *p*-toluenesulfonic acid (50 mg.) were refluxed under anhydrous conditions for 15 min. After cooling, the reaction mixture was poured into petroleum ether (450 ml.), the upper layer was decanted and the residue treated with warm methanol (100 ml.). The solid which formed was removed by filtration and the filtrate was stirred and treated with water to give more solid. The second crop was removed by filtration and dried. The combined product was dissolved in 2-methoxyethanol (25 ml.), cooled, stirred and very slowly treated with cold water (240 ml.). The pure product separated in large white crystals.

Method E. General.—The 4-amino-1,3-benzenedisulfonamide derivative (0.02 mole), ketone (0.06 to 0.08 mole), *p*-dioxane (50 ml.) and *p*-toluenesulfonic acid (50 to 100 mg.) were mechanically stirred and refluxed under anhydrous conditions for 18 hr. The product was isolated either by the addition of water or by removing the solvent by reduced pressure distillation. The crude product was purified by trituration followed by recrystallization. Example: **2-Methyl-6-chlorospiro-[2H-1,2,4-benzothiadiazine-3(4H),1′-cyclobutane]-7-sulfonamide-1,1-dioxide (compound 2).**—2-Chloro-4-amino-5-methylsulfamoylbenzenesulfonamide (6 g., 0.02 mole), cyclobutanone (5.7 g., 0.08 mole) and *p*-toluenesulfonic acid (100 mg.) were suspended in dioxane (50 ml.) and the mixture was mechanically stirred and refluxed under anhydrous conditions for 18 hr. The resulting solution was cooled, stirred and very slowly treated with cold water until crystallization of the product was complete. The solid was removed by filtration, dried, dissolved in hot methanol (400 ml.), cooled and slowly treated with cold water (500 ml.). The resulting crystalline product was analytically pure.