[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

The Alkylation of 6-(Trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide 1,1-Dioxide and Related Compounds. A New Reaction of *ortho* Esters with Sulfonamides[1]

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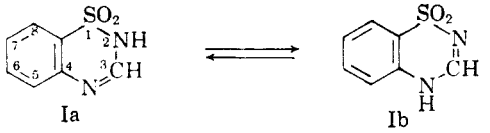
A new reaction of ortho esters with 1,2,4-benzothiadiazine 1,1-dioxides and pyridothiadiazine 1,1-dioxides is described. These react at 150° to give a mixture of the 2- and 4-alkylated derivatives, thus confirming for the first time the previously postulated existence of mobile hydrogen atom tautomerism and, consequently, an unsymmetrical triad system in this class of heterocyclic compounds. The reaction is generally applicable but will proceed to completion only when (a) the volatile products, b.p. 50–80°, are allowed to distill, (b) the internal temperature exceeds 130–135°, and (c) a homogeneous reaction mixture is obtained. 3,4-Dihydro-1,2,4-benzothiadiazines do not react since they do not possess mobile hydrogen atom tautomerism. When the reactant has an $-SO_2NH_2$ which is not *ortho* to an amino group, reaction to form an $-SO_2N{=}CHO$-Alkyl group occurs. *N*-Acetylbenzenesulfonamide, which can tautomerize to an unsymmetrical triad system, gives both *O*- and *N*-alkylated derivatives.

Reaction of 6-(trifluoromethyl)-1,2,4-benzothiadiazine 1,1-dioxide with dialkylaminoalkyl chlorides in the presence of sodamide gives 4-(dialkylaminoalkyl) derivatives. The synthesis of the isomeric 2-(dialkylaminoalkyl) derivatives, by an indirect procedure, is also described.

Although the existence of a tautomeric equilibrium in the benzothiadiazine 1,1-dioxides which still retain a mobile hydrogen atom (Ia, b) has been demonstrated by physical measurements,[2]



Ia

1,2,4-Benzothiadiazine 1,1-dioxide

Ib

1,4,2-Benzothiadiazine 1,1-dioxide

up to the present time, derivatives of both forms have not been isolated from an alkylation reaction. Thus, in his pioneering work with the 1,2,4-benzothiadiazine 1,1-dioxide nucleus Ekbom[3] reported that methyl iodide in methanolic potassium hydroxide gave the 4-methyl derivative. More recently, Novello *et al.*[2] found that monoalkylation of 6-chloro-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (II) gave the corresponding 4-alkyl derivative when treated with allyl bromide in ethanolic sodium ethoxide or with methyl sulfate in aqueous sodium hydroxide.

As the 1,2,4-benzothiadiazine 1,1-dioxides possess one of the classical examples of an unsymmetrical triad system,[4] $-NH-C{=}N \rightleftharpoons -N{=}\overset{|}{C}-NH-$, the base-catalyzed alkylation should have led to both 2- and 4-alkyl derivatives. It must be assumed that in the reactions discussed above the 4-alkylated derivatives were the preponderant reaction products and, consequently, the only ones isolated; that no 2-alkylated derivatives were isolated (although small amounts may have been present) must be attributed to the dominant influence of the $-SO_2-$ group on the triad system, under these alkylating conditions.

Under more favorable experimental conditions, however, it should be possible to confirm the existence of the tautomeric equilibrium postulated with this class of compounds. The new reaction we are reporting, namely the alkylation of benzothiadiazine and pyridothiadiazine 1,1-dioxides by means of trialkyl orthoformates does precisely this, as it leads to the simultaneous formation of both 2- and 4-monoalkylated derivatives. Thus, when 6-(trifluoromethyl)-1,2,4-benzothiadiazine 1,1-dioxide (III) and triethyl orthoformate (TOF) were heated for about three hours in an oil bath at 150° so that volatile products, b.p. 50–80°, distilled, two products, 4-ethyl-6-(trifluoromethyl)-1,4,2-benzothiadiazine 1,1-dioxide (IV), and 2-ethyl-6-(trifluoromethyl)-1,2,4-benzothiadiazine 1,1-dioxide (V) were obtained in 40% and 19% yields, respectively.[4] The structures of these isomers were established by hydrolyzing IV and V to 5-(ethylamino)-α,α,α-trifluoro-*p*-toluenesulfonamide (VI) and 2-amino-*N*-ethyl-α,α,α-trifluoro-*p*-toluenesulfonamide (VII), respectively; VI and VII were then shown to be identical with authentic specimens of these com-

(1) Presented before the Division of Medicinal Chemistry, at the 138th Meeting of the American Chemical Society, New York, September 11–16, 1960.

(2) F. C. Novello, S. C. Bell, E. L. A. Abrams, C. Ziegler, and J. M. Sprague, *J. Org. Chem.*, **25**, 970 (1960). The report by L. H. Werner, A. Halamandaris, S. Ricca, L. Dorfman, and G. de Stevens, *J. Am. Chem. Soc.*, **82**, 1161 (1960), that II and dimethyl sulfate in aqueous sodium hydroxide gave the 7-methylsulfamoyl derivative may be incorrect.

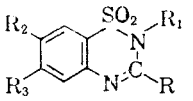
(3) Ekbom, *Bih. Svensk Vetenskakad Handl.*, **27**, II, 3 (1902); *Beilstein*, 4th Ed., **27**, 570; **14**, 682.

(4) C. K. Ingold in *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, pp. 543–575, has summarized the literature and shown the development of the ionic theory of mobile hydrogen tautomerism or prototropy. Symmetrical triad systems would give only one alkylated derivative.

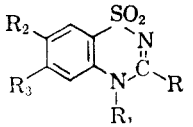
(5) No example of *N*-alkylation by means of a trialkyl orthoformate has been found in the literature.

TABLE I

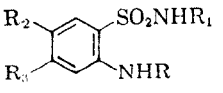
TABULATION OF STRUCTURES OF COMPOUNDS DESCRIBED



II.	R, R_1 = H; R_2 = H_2NSO_2; R_3 = Cl
III.	R, R_1, R_2 = H; R_3 = F_3C
V.	R, R_2 = H; R_1 = C_2H_5; R_3 = F_3C
VIII.	R, R_1 = H; R_2 = H_2NSO_2; R_3 = F_3C
X.	R = H; R_1 = C_2H_5; R_2 = $C_2H_5OCH{=}NSO_2$; R_3 = F_3C
XII.	R = H; R_1 = C_2H_5; R_2 = H_2NSO_2; R_3 = F_3C
XVII.	R = CH_3; R_1 = H; R_2 = H_2NSO_2; R_3 = F_3C
XIX.	R, R_1 = H; R_2 = $C_2H_5OCH{=}NSO_2$; R_3 = Cl
XXI.	R = H; R_1 = C_2H_5; R_2 = $C_2H_5OCH{=}NSO_2$; R_3 = Cl
XXV.	R, R_1 = H; R_2 = $C_2H_5OCH{=}NSO_2$; R_3 = F_3C
XXVI.	R, R_1 = H; R_2 = $CH_3OCH{=}NSO_2$; R_3 = F_3C
XLVII.	R, R_2 = H; R_1 = $(C_2H_5)_2NCH_2CH_2$; R_3 = F_3C
XLIX.	R, R_2 = H; R_1 = $(CH_3)_2N(CH_2)_3$; R_3 = F_3C



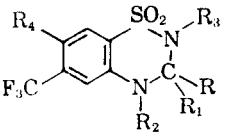
IV.	R, R_2 = H; R_1 = C_2H_5; R_3 = F_3C
IX.	R = H; R_1 = C_2H_5; R_2 = $C_2H_5OCH{=}NSO_2$; R_3 = F_3C
XI.	R = H; R_1 = C_2H_5; R_2 = H_2NSO_2; R_3 = F_3C
XX.	R = H; R_1 = C_2H_5; R_2 = $C_2H_5OCH{=}NSO_2$; R_3 = Cl
XXII.	R = H; R_1 = C_2H_5; R_2 = H_2NSO_2; R_3 = F_3C
XXVII.	R = H; R_1 = CH_3; R_2 = H_2NSO_2; R_3 = F_3C
XXVIII.	R = H; R_1 = CH_3; R_2 = CH_2NHSO_2; R_3 = F_3C
XLV.	R, R_2 = H; R_1 = $(C_2H_5)_2NCH_2CH_2$; R_3 = F_3C
XLVI.	R, R_2 = H; R_1 = $(CH_3)_2N(CH_2)_3$; R_3 = F_3C



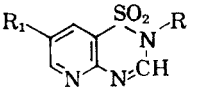
VI.	R_1, R_2 = H; R = C_2H_5; R_3 = F_3C
VII.	R, R_2 = H; R_1 = C_2H_5; R_3 = F_3C
XIII.	R = CHO; R_1 = C_2H_5; R_2 = H_2NSO_2; R_3 = F_3C
XIV.	R = H; R_1 = C_2H_5; R_2 = H_2NSO_2; R_3 = F_3C
XV.	R = C_2H_5; R_1 = H; R_2 = H_2NSO_2; R_3 = F_3C
XVIII.	R = CH_3CO; R_1 = C_2H_5; R_2 = H_2NSO_2; R_3 = F_3C
XXIII.	R = H; R_1 = C_2H_5; R_2 = H_2NSO_2; R_3 = Cl
XXIV.	R, R_1 = H; R_2 = H_2NSO_2; R_3 = F_3C
XXIX.	R = CHO; R_1 = CH_3; R_2 = H_2NSO_2; R_3 = F_3C

TABLE I (*Continued*)

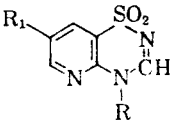
XLVIII.	R, R_2 = H; R_1 = $(C_2H_5)_2NCH_2CH_2$; R_3 = F_3C
L.	R, R_2 = H; R_1 = $(CH_3)_2N(CH_2)_3$; R_3 = F_3C



XVI.	R, R_1, R_2 = H; R_3 = C_2H_5; R_4 = H_2NSO_2
XXX.	R, R_1, R_2, R_3 = H; R_4 = H_2NSO_2
XXXI.	R, R_2, R_3 = H; R_1 = $C_6H_5CH_2$; R_4 = H_2NSO_2
XXXII.	R, R_1, R_2, R_3 = H; R_4 = $C_2H_5OCH{=}NSO_2$
XXXIII.	R, R_2, R_3 = H; R_1 = $C_6H_5CH_2$; R_4 = $C_2H_5OCH{=}NSO_2$
XXXIV.	R + R_1 = 0; R_2, R_3 = H; R_4 = H_2NSO_2
XXXV.	R + R_1 = 0; R_2 = C_2H_5; R_3 = H; R_4 = H_2NSO_2
XXXVI.	R + R_1 = 0; R_2 = H; R_3 = C_2H_5; R_4 = H_2NSO_2
XLIII.	R, R_2 = H; R_1 = $C_6H_5CH_2$; R_3 = C_2H_5; R_4 = H_2NSO_2
XLIV.	R, R_1, R_3 = H; R_2 = C_2H_5; R_4 = H_2NSO_2



XXXVII.	R = H; R_1 = H_2NSO_2



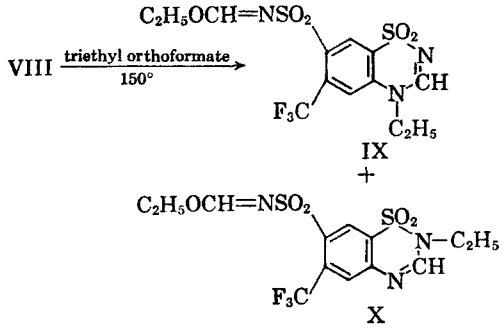
XXXVIII.	R = C_2H_5; R_1 = $C_2H_5OCH{=}NSO_2$
XXXIX.	R = C_2H_5; R_1 = H_2NSO_2

pounds synthesized as described in the Experimental.

When the reaction was carried out between 6-(trifluoromethyl) - 1,2,4 - benzothiadiazine - 7 - sulfonamide 1,1 - dioxide (VIII) and triethyl orthoformate, the anticipated 4- and 2-alkylation occurred, but in addition, the 7-sulfamoyl group also reacted to give the *N*-ethoxymethylenesulfamoyl substituent.[6] The yields of the two products, IX

(6) Novello *et al.* (ref. 2) reported that II and triethyl orthoformate heated *under reflux* for twenty-four hours gave an 87% yield of 6-chloro-*N*-ethoxymethylene-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide; 6-chloro-2-methyl-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide and 6-chloro-3,4-dihydro-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide were also reported to give the corresponding *N*-ethoxymethylenesulfamoyl derivatives. It is apparent that under reflux, however prolonged, no alkylation occurred. Novello reported that mild alkaline hydrolysis of the *N*-ethoxymethylenesulfamoyl derivatives regenerated the parent compound. Under the conditions employed in our investigation, II undergoes alkylation as well.

and X, were 39% and 57%, respectively.[7] Both IX and X were stable compounds which could be recrystallized from nonhydroxylated solvents; recrystallization from boiling aqueous isopropyl alcohol led, in each instance, to the formation of new products: thus, IX gave 4-ethyl-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (XI) while X gave 6′-(ethylsulfamoyl)-α,α,α-tri-



IX

+

X

fluoro-4′-sulfamoyl-*m*-formotoluidide (XIII) and 6′-(ethylsulfamoyl)-α,α,α-trifluoro-4′-sulfamoyl-*m*-toluidide (XIV). While 2-ethyl-6-(trifluoromethyl-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (XII) has not been isolated, it is presumed to be the precursor of XIII and XIV, as 2-alkyl-1,2,4-benzothiadiazine 1,1-dioxides have shown a characteristic instability toward recrystallization from boiling aqueous alcohol.[8]

The structure of XI was established by demonstrating that upon hydrolysis it gave a disulfonamide identical with authentic 5-(ethylamino)-α,α,α-trifluoro-2,4-toluene-disulfonamide (XV) synthesized as described in the Experimental. Furthermore, XI was identical with the product from the monoalkylation of VIII with ethyl iodide in ethanolic sodium hydroxide, thus establishing the structure of that reaction product as the 4-ethyl derivative, also. In addition, it was shown that XV and triethyl orthoformate at 150° regenerated IX.

The structure of XIV (and indirectly XII and XIII) was confirmed by reaction with formaldehyde to give a product identical with 3,4-dihydro-2-ethyl-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (XVI), synthesized from 3,4-dihydro-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (XXX) and diethyl sulfate in aqueous sodium hydroxide.[9]

Under the experimental conditions employed in this reaction, the unchanged benzothiadiazine 1,1-dioxide was insoluble in the triethyl orthoformate. During the course of the heating by means of an oil bath maintained at 150°, it was observed that a vigorous reaction occurred when the internal temperature reached 130–135°; while the volatile products (b.p. 50–80°) were collected, the internal temperature gradually rose. The reaction was complete in about three hours when a clear solution was formed and the internal temperature reached 145–150°. 3-Methyl-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (XVII) and triethyl formate, however, reacted sluggishly, presumably because of to the blocking effect of the 3-methyl group, and even after prolonged heating the XVII was largely undissolved. When the hot triethyl orthoformate solution was decanted, concentrated to dryness and the residual oil dissolved in boiling water, there was isolated, in small yield, 6′-(ethylsulfamoyl)-α,α,α-trifluoro-4′-sulfamoyl-*m*-acetotoluidide (XVIII), arising from the hydrolytic ring opening of 2-ethyl-3-methyl-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.

As noted above, Novello *et al.*[2] reported that II and triethyl orthoformate heated under reflux[10] for twenty-four hours gave the *N*-ethoxymethylene derivative (XIX); they mentioned no other product and apparently observed no other reaction. Under the alkylation conditions employed in our work, II

(7) In the ultraviolet, VIII [$\lambda_{max}^{C_2H_5OH}$ 278 (ϵ 9200) and a shoulder at 295 mμ] and IX [$\lambda_{max}^{C_2H_5OH}$ 288 (ϵ 11,900) and a shoulder at 300 mμ] have similar spectra; X, with the double bond in the 3,4- position has a different spectra, $\lambda_{max}^{C_2H_5OH}$ 273, 310 mμ (ϵ 11,200, 12,800) and no shoulder in the 300-mμ region. From this data, the conclusion to be drawn is that VIII exists predominantly with the double bond in the 2,3-positon, similar to IX. Novello *et al.* (ref. 2) arrived at the same conclusion regarding the position of the double bond in II.

(8) Novello *et al.* (ref. 2) have reported that recrystallization of 2-methyl-1,2,4-benzothiadiazine 1,1-dioxide and 6-chloro-*N*,2-dimethyl-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide from boiling aqueous alcohol involved ring scission and gave 2′-(methylsulfamoyl)formanilide and 5′-chloro-2′,4′-bis(methylsulfamoyl)formanilide, respectively. The formation of XIV above arises by further hydrolysis of XIII (see Experimental).

(9) 6-Chloro-3,4-dihydro-2-methyl-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide was obtained by treating 6-chloro-3,4-dihydro-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide with (a) methyl sulfate in aqueous sodium hydroxide [L. H. Werner *et al.*, *J. Am. Chem. Soc.*, 82, 1161 (1960)] or (b) methyl iodide and sodium hydride in *N,N*-dimethylformamide [W. J. Close *et al.*, *J. Am. Chem. Soc.*, 82, 1132 (1960)]. Actually, when dialkylation occurs, the 2- and 7-positions are involved (see Experimental for details).

The structure of XVI has been further confirmed by Drs. A. Cohen and N. Coy of these laboratories as a result of their studies of this and related compounds in the near infrared; their results will be published shortly. In this connection, it should be stated that the generalization made by L. H. Werner *et al.*, that sulfonamides with a free $-SO_2NH_2$ group will show characteristic absorption at 2.98 and 3.08 μ is of questionable value in assigning structure. Thus, we have observed that 3,4-dihydro-*N*-2-dimethyl-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, which lacks an $-SO_2NH_2$ group, shows absorption at 2.98 and 3.02 μ; while 3,4-dihydro-2-methyl- and 3,4-dihydro-2-ethyl-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, which have $-SO_2NH_2$ groups, absorb at 3.02 and 3.08 μ and 2.97 and 3.05 μ, respectively. The overlap in the absorption of these three compounds in the 3-μ region does not afford a rigorous basis for structure assignment.

(10) We have repeated this experiment and have observed that the maximum internal temperature under these conditions is 125°. It would appear, therefore, that the alkylation reaction has very critical temperature requirements.

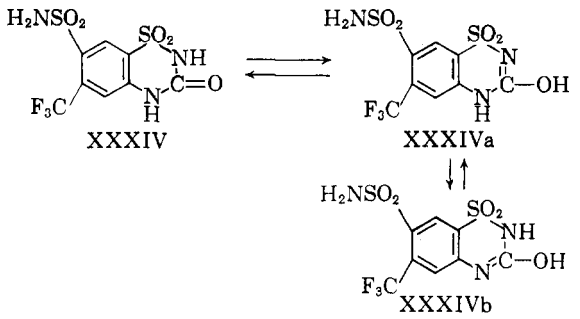
reacted sluggishly to give a 55% yield of XIX and a 43% combined yield of *N*-ethoxymethylene-4-ethyl- (XX) and *N*-ethoxymethylene-2-ethyl-6-chloro-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (XXI). By increasing the amount of triethyl orthoformate and prolonging the reaction time it was possible to alkylate II completely to give a mixture of XX and XXI, which were separated by fractional crystallization. While XX was stable and could be purified, XXI could not, and was, therefore, identified by hydrolysis to give 6′-(ethylsulfamoyl)-4′-sulfamoyl-*m*-chloroanilide (XXIII). Recrystallization of XIX from aqueous isopropyl alcohol regenerated II; a similar treatment of XX gave 4-ethyl-6-chloro-1,4,2-benzothiadiazine-7-sulfonamide 1,1-dioxide (XXII).

A mixture of 5-amino-α,α,α-trifluoro-2,4-toluenedisulfonamide (XXIV) and triethyl orthoformate heated for two hours at 120° resulted only in cyclization and in the formation of the *N*-ethoxymethylene derivative of VIII (XXV); at 150°, the same reactants underwent cyclization, *N*-ethoxymethylene formation and alkylation to give IX and X. Ethyl formate and XXIV at 150° did not react.

The slow distillation of a mixture of VIII and trimethyl orthoformate gave only the *N*-methoxymethylene derivative of VIII (XXVI); in a sealed tube at 150°, the same reactants gave the expected mixture of methylated derivatives as a noncrystalline gum. Separation was effected by treatment with boiling aqueous isopropyl alcohol to give two products, 4-methyl-6-(trifluoromethyl)-1,4,2-benzothiadiazine-7-sulfonamide 1,1-dioxide (XXVII) (identical with the product from the reaction of VIII with methyl iodide in ethanolic sodium hydroxide[11]) and 6′-(methylsulfamoyl)-α,α,α-trifluoro-4′-sulfamoyl-*m*-formotoluidide (XXIX).

3,4-Dihydro-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (XXX) and its 3-benzyl derivative (XXXI) and triethyl orthoformate under alkylation conditions gave only the corresponding *N*-ethoxymethylene derivatives XXXII and XXXIII, respectively.[12] The failure to alkylate is due, of course, to the absence of a triad system in this class of compounds.

3-Oxo-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (XXXIV), which might be considered a 3,4-dihydro derivative, can also exist as the tautomerides XXXIVa, b. As anticipated, XXXIV was alkylated by triethyl orthoformate to give a mixture of 2- and 4-ethylated compounds as their *N*-ethoxymethylene derivatives; the mixture could not be separated. Boiling



aqueous isopropyl alcohol effected separation into the 4-ethyl- (XXXV) (24% yield) and 2-ethyl-3-oxo-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (XXXVI) (34% yield). The alkylation of XXXIV by ethyl iodide, in *N,N*-dimethylformamide, in the presence of sodium hydride, also gave XXXV and XXXVI.[13]

The reaction between triethyl orthoformate and 1,2,4-pyrido[2,3-e]thiadiazine-7-sulfonamide 1,1-dioxide (XXXVII) at 150° gave only the *N*-ethoxymethylene-4-ethyl derivative (XXXVIII); a careful search failed to uncover any 2-ethyl derivative. Recrystallization of XXXVIII from boiling aqueous isopropyl alcohol gave 4-ethyl-1,4,2-pyrido[2,3-e]-thiadiazine-7-sulfonamide 1,1-dioxide (XXXIX).

DISCUSSION

Certain generalizations are possible from the data presented above, regarding the behavior of triethyl orthoformate at 150° with representatives of the three principal classes of compounds—*e.g.* VIII (which possesses an unsymmetrical triad system), XXX (the 3,4-dihydro derivative which is incapable of forming a triad system), and XXXIV (which appears to be a 3,4-dihydro derivative, but which can form an unsymmetrical triad system through the oxygen atom at position 3). All three compounds first react to form *N*-ethoxymethylene derivatives; this derivative of VIII is also alkylated at the 2- and 4-positions; this derivative of XXX undergoes no additional reaction; and this derivative of XXXIV is also further alkylated at the 2- and 4-positions. A further reasonable generalization, based on the observation that the alkylation reactions require several hours of heating at elevated temperature, is that an S_N2 process is involved.[14]

(11) It was of interest that this reaction gave beside unchanged VIII, a small yield of *N*,4-dimethyl-6-(trifluoromethyl)-1,4,2-benzothiadiazine-7-sulfonamide 1,1-dioxide (XXVIII) (see Experimental).

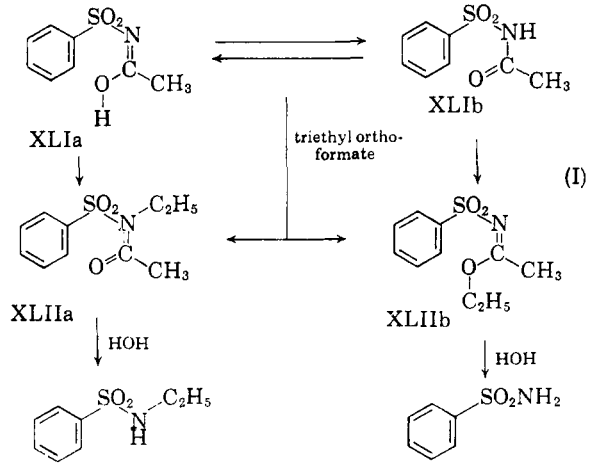
(12) Novello, *et al.* (ref. 2) reported that 6-chloro-3,4-dihydro-1,2,4-benzothiadiazine-7-sulfonamide and triethyl orthoformate under reflux gave the *N*-ethoxymethylene derivative.

(13) W. J. Close, L. R. Swett, L. E. Brady, J. H. Short, and M. Vernsten, *J. Am. Chem. Soc.*, **82**, 1132 (1960) have reported that 6-chloro-3-oxo-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide and ethyl iodide under similar conditions gave a 95% yield of the 2-ethyl derivative. Their product, as described, was not purified other than by washing with water. It is reasonable to assume that some 4-ethyl derivative was also present.

(14) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland [*J. Am. Chem. Soc.*, **77**, 6269 (1955)] have reviewed the literature on the contrasting alkylation of other unsymmetrical triad systems (ambident anions), and have classified those alkylations as S_N1 or S_N2 types.

Reactions of triethyl orthoformate with simple sulfonamides. Primary sulfonamides—*e.g.*, benzenesulfonamide—reacted with triethyl orthoformate under alkylation conditions, to give only ethoxymethylene derivatives. Secondary sulfonamides—*e.g.*, *N*-ethylbenzenesulfonamide—did not react with triethyl orthoformate, nor did they react if a catalytic amount of *p*-toluenesulfonic acid was added. Interestingly enough, if *N*-ethylbenezenesulfonamide and triethyl orthoformate were heated so that the triethyl orthoformate distilled during a three-hour period, a quantitative yield of *N*-ethyl-*N*-(phenylsulfonyl)formamide diethyl acetal (XL) was obtained.

A related example of the alkylation reaction was found in the behavior of triethyl orthoformate with *N*-acetylbenzenesulfonamide (XLI). It was assumed that XLI would give both *O*- and *N*-alkylation, as it can exist as the tautomerides (XLIa b), and that hydrolysis of the reaction mixture should give benzenesulfonamide and *N*-ethylbenzenesulfonamide. The reaction was carried out and gave as product a noncrystalline *oil;* in the infrared, the *oil* showed no absorption in the=NH, but did absorb in the C=O and C=N regions, thus confirming the presence of XLIIa and XLIIb.



From the hydrolysis of the *oil*, benzenesulfonamide was obtained in 9% yield and *N*-ethylbenzenesulfonamide in 59% yield.

Alkylation of 6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide (III) *with dialkylaminoalkyl halides in the presence of sodamide.* It was anticipated, and subsequently demonstrated, that the alkylation of III with a dialkylaminoalkyl halide in the presence of sodamide would lead to 4-substitution. The isomeric 2-dialkylaminoalkyl derivatives were synthesized by an indirect procedure. The details of these syntheses are described in the Experimental.

Miscellaneous syntheses. The reaction of XIV with phenylacetaldehyde dimethyl acetal in aqueous alcoholic hydrochloric acid gave 3-benzyl-3,4-dihydro-2-ethyl-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (XLIII).

5-Ethylamino-α,α,α-trifluoro-2,4-toluenedisulfonamide (*via* the hydrolysis of XI) and formaldehyde gave 3,4-dihydro-4-ethyl-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (XLIV).

EXPERIMENTAL

All melting points are uncorrected.

Allkylation of 6-(trifluoromethyl)-1,2,4-benzothiadiazine 1,1-dioxide (III) *by triethyl orthoformate.* A mixture of 19.0 g. (0.076 mole) of III and 150 ml. of triethyl orthoformate reacted vigorously when placed in an oil bath preheated to 150°. The oil bath temperature was kept at 150–155° during the reaction. The distillate collected during 3 hr., b.p. 50–80°, weighed 37.5 g.[15] No solid separated from the reaction mixture on cooling. Concentration to dryness *in vacuo* gave a residual oil which solidified. Recrystallization from 80 ml. of isopropyl alcohol gave 9.8 g. of solid, m.p. 130–150° (for filtrate, see below). This solid was triturated with 150 ml. of anhydrous ether and filtered; the solid now weighed 9.3 g., m.p. 146–148°. Recrystallization from isopropyl alcohol gave 8.4 g. (40% yield) of IV, m.p. 153–155°, λ (no =NH or —NH_2 absorption) 6.15, 6.20, 6.38, 6.85–6.90 μ (doublet).

Anal. Calcd. for $C_{10}H_9F_3N_2O_2S$: C, 43.19; H, 3.27; N, 10.07; S, 11.52. Found: C, 43.46; H, 3.40; N, 10.13; S, 11.76.

The original isopropyl alcohol filtrate was concentrated to dryness to give 9.5 g. of solid. This material was washed with 200 ml. of anhydrous ether; the insoluble solid weighed 1.9 g. (10% recovery) of III, m.p. and mixture m.p. 261–263° dec. The ether washings were evaporated to give 6.82 g. of solid, m.p. 63–65°. Recrystallization from ligroin and then from hexane gave 4.1 g. (19% yield) of V, m.p. 71–73°, λ (no =NH or —NH_2 absorption) 6.15, 6.27, 6.40, 6.83, 6.97 μ.

Anal. Calcd. for $C_{10}H_9F_3N_2O_2S$: C, 43.19; H, 3.27; N, 10.07. Found: C, 43.01; H, 3.15; N, 10.28.

Hydrolysis of IV. A solution of 1.6 g. of IV, 5 ml. of 10% aqueous sodium hydroxide and 15 ml. of water was refluxed for 3 hr., cooled and acidified with dilute hydrochloric acid. The precipitated solid was filtered and recrystallized from 35% isopropyl alcohol–65% water to give 5-(ethylamino)-α,α,α-trifluoro-*p*-toluenesulfonamide (VI), m.p. 186–188°, λ 2.92, 2.97, 3.05, 6.15, 6.20, 6.32, 6.55, 6.75, 6.90 μ.

Anal. Calcd. for $C_9H_{11}F_3N_2O_3S$: N, 10.42; S, 11.95. Found: N, 10.48; S, 11.93.

Hydrolysis of V. A similar hydrolysis of V gave VII, m.p. 75–77°, λ 2.88, 2.95, 3.05, 6.12, 6.35, 6.68, 6.90 μ.

Anal. Calcd. for $C_9H_{11}F_3N_2O_3S$: N, 10.42; S, 11.95. Found: N, 10.63; S, 11.85.

Reaction between 6-(trifluoromethyl)-1,2,4-benzothiadiazine 7-sulfonamide 1,1-dioxide (VIII) *and triethyl orthoformate.* A mixture of 30.0 g. (0.091 mole) of VIII and 300 ml. of triethyl orthoformate was treated as in the above example. Complete solution occurred in about 3 hr. and coincided with the cessation of distillation. The distillate weighed 35 g. The reaction mixture was allowed to cool to room temperature, the crystalline product which separated was filtered (for filtrate, see below), washed with a little anhydrous ether, and dried; it weighed 13.6 g. (39% yield), m.p. 175–177°. An analytical sample of IX after two recrystallizations from triethyl orthoformate melted at 179–180°, λ (no =NH or —NH_2 absorption), 6.20, 6.40, 8.58–8.80 (broad), 9.0, 9.45 μ.

Anal. Calcd. for $C_{13}H_{14}F_3N_3O_5S_2$ C, 37.76; H, 3.42; N, 10.17. Found: C, 37.50; H, 3.55; N, 10.43.

(15) This is a typical distillate. Gas chromatography indicated that the principal components were ethanol (*ca.* 87%), and ethyl formate (*ca.* 3%).

Recrystallization of the entire IX from 20% isopropyl alcohol-80% water gave 7.2 g. (60% yield based on IX) of XI, m.p. 279–280°, λ 2.98, 3.05, 6.13, 6.25, 6.47, 6.78, 6.93, 8.80, 9.05, 9.45 μ.

Anal. Calcd. for $C_{10}H_{10}F_3N_3O_4S_2$: C, 33.60; H, 2.83; N, 11.76. Found: C, 33.72; H, 3.01; N, 12.03.

The original triethyl orthoformate filtrate was concentrated *in vacuo* until a crystalline solid began to separate. The mixture was then cooled, the solid filtered and dried; it weighed 20.0 g. (57% yield), m.p. 140–142°. An analytical sample of X, after two recrystallizations from petroleum ether (b.p. 100–140°) melted at 143–145°, λ (no =NH or —NH_2 absorption), 6.30, 6.40, 6.50, 6.8–6.85 (doublet), 8.48, 8.67, 8.85, 9.05, 9.20 μ.

Anal. Calcd. for $C_{13}H_{14}F_3N_3O_3S_2$: C, 37.76; H, 3.42; N, 10.17. Found: C, 37.96; H, 3.65; N, 10.44.

Recrystallization of the entire X from 20% isopropyl alcohol–80% water gave 12.0 g. (70% yield) of XIII, m.p. 182–184°, λ 2.95, 3.03, 5.95, 6.35, 6.57 μ.

Anal. Calcd. for $C_{10}H_{12}F_3N_3O_3S_2$: C, 32.00; H, 3.23; N, 11.20; S, 17.09. Found: C, 32.49; H, 3.20; N, 11.56; S, 17.42.

The aqueous isopropyl alcohol mother liquors from the XIII were concentrated to two-thirds volume and cooled. The solid which separated was filtered and recrystallized from water. The product crystallized initially as a hydrate, m.p. 104–106° but on drying at 56° lost 3.3% of its weight and gave anhydrous XIV, m.p. 112–114°, λ 2.95, 3.05, 6.13, 6.43, 6.93 μ. The yield was 4.4 g. (22%).

Anal. Calcd. for $C_9H_{12}F_3N_3O_4S_2$: C, 31.12; H, 3.49; N, 12.10. Found: C, 31.18; H, 3.68; N, 12.11.

Hydrolysis of XIII. (a) Crude XIII, 14.0 g. (0.38 mole), 15.0 g. (0.38 mole) of sodium hydroxide pellets, and 750 ml. of water were refluxed for 2 hr., cooled and the solution treated with an excess of solid carbon dioxide; the solid which separated was filtered and dried to give 10.0 g. (76% yield) of XIV, m.p. 102–104°. Recrystallization from water raised the m.p. to 104–106°; a mixture melting point with the product described directly above was 104–106°.

(b) A mixture of 0.5 g. XIII and 20 ml. of 20% isopropyl alcohol–80% water was heated to dryness on the steam bath. The residual solid was unchanged starting material, m.p., 180–182°; when the same mixture was refluxed for 2 hr. and then heated to dryness on the steam bath, there was obtained 0.43 g. of XIV, m.p. 104–106°.

Hydrolysis of XI. A solution of 11.0 g. (0.03 mole) of XI, 100 ml. of water, and 2.4 g. (0.06 mole) of sodium hydroxide was refluxed for 2 hr., cooled, and treated with an excess of solid carbon dioxide. The precipitated solid was filtered and dried; it weighed 10 g. (96% yield) and melted at 212–214°. Recrystallization from isopropyl alcohol or from a large volume of water gave 8 g. (77% yield) of XV, m.p. 218–220°, λ 2.97, 3.05, 6.20, 6.40, 6.96 μ.

Anal. Calcd. for $C_9H_{12}F_3N_3O_4S_2$: C, 31.12; H, 3.49; N, 12.10. Found: C, 31.27; H, 3.67; N, 12.05.

Cyclization of XV. A solution of 0.5 g. of XV and 10 ml. of triethyl orthoformate was heated for 3 hr. at 150°, cooled, the precipitated solid filtered, washed with a little ether, and dried to give 0.4 g. of IX, m.p. and mixture m.p., 179–180°. The filtrate was concentrated *in vacuo* to give an additional 0.070 g. of impure IX, m.p. 166–168°. Each product was recrystallized separately from 20% isopropyl alcohol–80% water and gave XI in each instance, m.p. and mixture m.p. 279–280°.

When 0.5 g. of XV was heated under reflux with 15 ml. of 98–100% formic acid for 4 hr., XV was recovered unchanged.

Authentic 5-(ethylamino)-α,α,α-trifluoro-p-toluenesulfonamide (VI) *and 5-(ethylamino)-α,α,α-trifluoro-2,4-toluenedisulfonamide* (XV). To a vigorously stirred solution of 161.0 g. (1.0 mole) of α,α,α-trifluoro-*m*-toluidine in 85 ml. (1.0 mole) of concd. hydrochloric acid and 1 l. of water, at room temperature, was added, in one portion, 102.0 g. (1.0 mole) of acetic anhydride. The acetyl derivative separated rapidly, was filtered, and dried to give 158.4 g. (78% yield) of *α,α,α-trifluoro-m-acetotoluidide*, m.p. 95–97°. An analytical sample from hexane melted at 100–102°.

Anal. Calcd. for $C_9H_8F_3NO$: C, 53.20; H, 3.97; N, 6.90. Found: C, 53.18; H, 3.91; N, 6.93.

The acetyl derivative, 158.0 g., 1 l. of dry benzene and 33.5 g. (0.081 mole) of sodamide were stirred and heated under reflux for 4 hr., cooled to room temperature, and 150.0 g. (1.1 moles) of ethyl iodide was added. The mixture was heated again under reflux with stirring for 4 hr., cooled, 50.0 g. of ethyl iodide added, and the heating and stirring continued for 18 hr. The usual work-up gave 135.7 g. (59% yield) of *N-ethyl-α,α,α-trifluoro-m-acetotoluidide*, b.p. 130–135° (15 mm.), n_D^{24} 1.4700.

Anal. Calcd. for $C_{11}H_{12}F_3NO$: C, 57.14; H, 5.23; N, 6.06. Found: C, 57.66; H, 5.53; N, 6.04.

The *N-ethyl derivative*, 135.5 g., 500 ml. of 95% ethanol, and 50 ml. of concd. hydrochloric acid were refluxed for 8 hr. and the alcohol was distilled. The residue was treated with an excess of 40% aqueous sodium hydroxide and the liberated oil extracted with ether. The ether extracts were dried, concentrated, and the residue distilled to give 72.0 g. (65% yield) of *N-ethyl-α,α,α-trifluoro-m-toluidine*, b.p. 82° (4 mm.), n_D^{24} 1.4770.

Anal. Calcd. for $C_9H_{10}F_3N$: C, 57.13; H, 5.33; N, 7.40. Found: C, 56.74; H, 5.29; N, 7.32.

The residue from the distillation weighed 33.0 g. (25% recovery of *N*-ethyl-α,α,α-trifluoro-*m*-acetotoluidine). To 23.2 g. (0.12 mole) of *N*-ethyl-α,α,α-trifluoro-*m*-toluidine in 320 ml. of tetrachloroethane, was added, with cooling, 15 g. (0.13 mole) of chlorosulfonic acid, dropwise, then 8.4 g. (0.14 mole) of sodium chloride. The mixture was heated slowly to reflux, maintained at reflux for 1 hr., cooled, and poured on ice. The solid which separated was filtered to give 12 g. of crude *2-(ethylamino)-α,α,α-trifluoro-p-toluenesulfonic acid*,[16] m.p. 198–200° dec.; recrystallization from *n*-propyl alcohol gave 6.0 g. (19% yield) of pure *acid*, m.p. 210–212° dec.

Anal. Calcd. for $C_9H_{11}F_3NO_3S$: C, 39.97; H, 4.11; N, 5.19; S, 11.87; neut. equiv., 270. Found: C, 40.04; H, 4.00; N, 5.45; S, 11.87; neut. equiv., 271.

To 25 ml. of chlorosulfonic acid at 0° was added, in portions, the above 6 g. of acid. The mixture was heated at 150° (oil bath temperature), kept at 150° for 3 hr., cooled to room temperature, 10 ml. of purified thionyl chloride added dropwise, and the mixture warmed carefully by means of a steam bath, heated for 1 hr. on the steam bath, and poured on ice. The precipitated material was filtered, washed with a little water and heated on the steam bath for 1 hr. with 100 ml. of concd. aqueous ammonia. The solid in the cooled reaction mixture was filtered, dried and extracted with 100 ml. of boiling benzene. The hot benzene solution was decanted leaving behind 1.4 g. of crude XV. Recrystallization from water gave 0.62 g. of pure XV, m.p. 218–220°; a mixture melting point with the hydrolysis product from XI, was 218–220° and their infrared spectra were identical.

Anal. Calcd. for $C_9H_{12}F_3N_3O_4A_2$: C, 31.12; H, 3.49; N, 12.10. Found: C, 31.17; H, 3.66; N, 12.06.

The benzene solution was concentrated to dryness to give 0.35 g. of solid; recrystallization from 20% isopropyl alcohol–80% water gave 5-(ethylamino)-α,α,α-trifluoro-*p*-toluenesulfonamide (VI), m.p. 184–186°; a mixture melting point with the hydrolysis product from IV was 184–186° and their infrared spectra were identical.

2-Amino-N-ethyl-α,α,α-trifluoro-p-toluenesulfonamide (VII). 2-Nitro-α,α,α-trifluoro-*p*-toluenesulfonyl chloride, 0.2 mole, in toluene, was added to 300 ml. of 33% aqueous monoethylamine, with stirring. The mixture was then

(16) The chlorosulfonation of *m*-aminobenzotrifluoride has been shown recently to occur *ortho* to the amino group [see H. L. Yale and F. Sowinski, *J. Org. Chem.*, 25, 1824 (1960); and F. C. Novello, S. C. Bell, E. L. A. Abrams, C. Ziegler, and J. M. Sprague, *J. Org. Chem.*, 25, 965 (1960)].

heated for 3 hr. on the steam bath, cooled, the solid filtered, and recrystallized twice from petroleum ether (b.p. 100–140°) to give 38 g. (65% yield) of *N-ethyl-2-nitro-α,α,α-trifluoro-p-toluenesulfonamide*, m.p. 88–90°.

Anal. Calcd. for $C_9H_9F_3N_2O_4S$: C, 36.23; H, 3.05; N, 9.39. Found: C, 36.35; H, 3.15; N, 9.64.

The nitro compound, 4 g., 100 ml. of absolute ethanol and 0.5 g. of 5% palladium on charcoal catalyst were subjected to 50 p.s.i. of hydrogen at room temperature; reduction was complete in 0.5 hr. The catalyst was filtered and the filtrate concentrated to dryness; the residual solid, 3.6 g., melted at 72–73°. Recrystallization from petroleum ether (b.p. 100–140°) and then from hexane gave 2.5 g. (71% yield) of VII, m.p. 75–77°; a mixture melting point with the hydrolysis product from V was 75–77° and their infrared spectra were identical.

3,4-Dihydro-2-ethyl-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (XVI). (a) To 21 g. (0.064 mole) of XXX, 5.1 g. (0.128 mole) of sodium hydroxide and 500 ml. of water was added slowly 9.8 g. (0.064 mole) of purified diethyl sulfate. A solid began to separate immediately. The mixture was stirred overnight at room temperature, the solid filtered and dried; it weighed 12.7 g. One recrystallization from 25% ethanol-75% water gave 8.5 g. (37% yield) of XVI, m.p. 224–226°, λ 2.98, 3.05, 6.17, 6.40, 6.58 μ.

Anal. Calcd. for $C_{10}H_{12}F_3N_3O_4S_2$: C, 33.41; H, 3.37; N, 11.70; S, 17.84. Found: C, 33.98; H, 3.48; N, 12.02; S, 17.80.

The filtrate was treated with an excess of solid carbon dioxide; the solid which separated was shown to be unchanged XXX.

(b) A solution of 0.93 g. (0.0027 mole) of 5-amino-*N*-ethyl-α,α,α-trifluoro-2,4-toluenedisulfonamide (XIV), 0.21 g. of 37% formalin solution and 1.0 ml. 10% hydrochloric acid in 10 ml. 95% ethanol was refluxed for 2 hr. and then concentrated to dryness. The residual solid was recrystallized from water to give 0.72 g. (74% yield) of XVI, melting point and mixture melting point with the product from (a), 222–224°. The infrared spectra of the two products were identical.

Reaction of 3-methyl-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (XVII) *and triethyl orthoformate.* A mixture of 8.1 g. (0.023 mole) of XVII and 160 ml. of triethyl orthoformate was treated in the usual manner. The hot triethyl orthoformate solution was decanted from the solid and concentrated to dryness *in vacuo*. The residue was recrystallized from water to give 0.52 g. of solid, m.p. 202–204°. A second recrystallization gave XVIII, m.p. 204–206°, λ 2.98, 3.10, 5.85, 6.30, 6.57 μ.

Anal. Calcd. for $C_{11}H_{14}F_3N_3O_5S_2$: C, 33.93; H, 3.63; N, 10.79; Acetyl value, 11.05. Found: C, 33.65; H, 3.63; N, 10.79; Acetyl value, 10.28.

Reaction of 6-chloro-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (II) *with triethyl orthoformate.* (a) A mixture of 10.0 g. (0.033 mole) of II and 100 ml. of triethyl orthoformate was treated under the usual alkylation conditions. Some insoluble material was present even after 3 hr. of heating. The cooled mixture was filtered and the solid washed with dry ether. The dried solid weighed 6.5 g. (55% yield as XIX), softens at 185°, m.p. 207–209°,[17] λ 3.05, 6.13, 6.30, 6.65, 8.48, 8.56, 8.67, 8.73, 8.95, 9.15 μ. The strong absorption band at 6.3, characteristic of the C=N band of the N-$C_2H_5OCH{:}NSO_2$ group, and the fact that recrystallization from hot aqueous isopropyl alcohol gave II, established this material as XIX. The triethyl orthoformate filtrate was concentrated to dryness *in vacuo* to give 5.5 g. (43% yield as XX + XXI) of solid; recrystallization from 25% isopropyl alcohol 75% water gave a product, m.p. 266–268° (for filtrate, see below); a second recrystallization from water raised the m.p. to 277–279° and was unchanged after an additional recrystallization from water. The yield of XXII was 3.5 g. (74% based on XX + XXI), λ 2.95, 3.05, 6.12, 6.27, 6.4, 6.8, 6.95μ.

Anal. Calcd. for $C_9H_{10}ClN_3O_4S_2$: C, 33.38; H, 3.08; N, 12.97; N-C_2H_5, 8.98. Found: C, 33.75; H, 3.27; N, 12.69; N-C_2H_5, 9.35.

The aqueous isopropyl alcohol filtrate from above was concentrated to a small volume and cooled. The solid which separated was filtered and dried. It weighed 0.5 g., m.p. 97–99° dec. Recrystallization from water gave XXIII, m.p. 142–144°, and this was unchanged after another recrystallization from water.

Anal. Calcd. for $C_8H_{12}ClN_3O_4S_2$: C, 30.62; H, 3.85; N, 13.41. Found: C, 30.66; H, 3.87; N, 13.56.

(b) A mixture of 10.5 g. of II and 200 ml. of triethyl orthoformate was heated and stirred under alkylation conditions for 4 hr. by means of an oil bath at 150°. The oil bath was removed and the heating continued by means of a Glascol mantle so that during 5 hr., 70 ml. of triethyl orthoformate distilled. This prolonged heating resulted in a clear solution. The solution was concentrated *in vacuo;* when about 50 ml. of triethyl orthoformate had been collected, a solid began to separate. The mixture was cooled and the solid filtered (for filtrate, see below). The solid (crude XX), weighed 2.3 g. (17% yield), m.p. 166–170°; recrystallization from dry toluene and drying at 78° *in vacuo* gave a toluene solvate of XX, m.p. 164–166°.

Anal. Calcd. for $C_{12}H_{14}ClN_3O_5S_2 \cdot 0.75\ C_6H_5CH_3$: C, 46.16; H, 4.50; N, 9.36; S, 14.28. Found: C, 46.40; H, 4.52; N, 9.56; S, 14.28.

Solvate-free XX was obtained by drying at 110° *in vacuo*, m.p. 168–170°.

Anal. Calcd. for $C_{12}H_{14}ClN_3O_5S_2$: C, 37.92; H, 3.71; N, 11.06. Found: C, 38.14; H, 3.88; N, 11.08.

Recrystallization of the XX from water gave XXII, m.p. 277–279°; the infrared spectra of this product and the product from (a) above, were identical.

The triethyl orthoformate filtrate from the XX was concentrated *in vacuo* to a semisolid mass. Attempts to purify this material by recrystallization were unsuccessful, since no material of constant melting point could be isolated. A small portion, hydrolyzed by solution in boiling aqueous isopropyl alcohol, gave XXIII, melting point and mixture melting point with the XXIII obtained in (a) above, 142–144°.

Reaction of 5-amino-α,αα,-trifluoro-2,4-toluenedisulfonamide (XXIV) *and triethyl orthoformate.* (a) *Cyclization at 120°.* A mixture of 10.0 g. (0.31 mole) of XXIV and 100 ml. of triethyl orthoformate was heated for 2 hr. in an oil bath maintained at 120°, allowing the volatile products to distill. No solid separated from the pale yellow solution even after prolonged cooling. The mixture was concentrated to dryness *in vacuo* and the residue kept at room temperature until crystallization occurred. The *N*-ethoxymethylene derivative of VIII weighed 9.0 g. Recrystallization from water gave 7.0 g. (67% yield) of VIII, m.p. and mixture m.p. 290–292°.

(b) *Cyclization and alkylation at 150°.* The same quantities of reactants as in (a), were heated for 3 hr. at 150° under alkylation conditions, cooled to room temperature and the crystalline crude IX which separated was filtered and dried; it weighed 2.0 g., m.p. 163–165°. Recrystallization from 20% isopropyl alcohol–80% water gave 1.0 g. (9% yield) of XI, m.p. 275–277°; a mixture melting point with the product, m.p. 278–280°, described above was 276–278°.

The triethyl orthoformate filtrate was concentrated to dryness *in vacuo*. The residue slowly solidified to a mixture of two products; one had crystallized on the walls of the flask and was readily removable, while the other substance was gummy and had concentrated at the bottom. The crystalline solid weighed 8.0 g. and recrystallization from water yielded 5.0 g. (48% yield) of VIII, m.p. and mixture m.p. 290–292°. The gummy solid weighed 3.0 g.; two recrystallizations from water gave 1.0 g. (9% yield) of XIV, m.p. and mixture m.p. 104–106°.

(17) Ref. 2 states that XIX softens at 195°, m.p. 207–210°

5-Amino-α,α,α-trifluoro-2,4-toluenedisulfonamide (XXIV) *and ethyl formate at 150°*. The disulfonamide, 5 g., and 50 ml. of ethyl formate, in a sealed tube, were heated for 4 hr. at 150°. The cooled tube was opened, the small amount of solid filtered and the filtrate concentrated to dryness. The filtered solid and the residual solid from the concentration were shown by melting point and mixture melting point (235–237°) to be unchanged XXIV.

Reaction of 6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (VIII) *and trimethyl orthoformate.* (a) A mixture of 20.0 g. (0.061 mole) of VIII and 150 ml. of trimethyl orthoformate was distilled slowly so that *ca.* 80 ml. distilled in about 6 hr. The reaction mixture was kept at room temperature until crystallization occurred. The filtered, dried XXVI weighed 23.0 g. (100% yield), m.p. 208–210° dec., λ 3.05, 6.13, 6.25, 6.65, 8.5–8.75 (broad), 9.1, 9.2 μ.

Anal. Calcd. for $C_{10}H_8F_3N_3O_5S_2$: C, 32.34; H, 2.17; N, 11.32. Found: C, 32.63; H, 2.55; N, 11.51.

(b) A mixture of 5.0 g. (0.015 mole) of VIII and 75 ml. of trimethyl orthoformate was heated for 3 hr. in a sealed tube at 150°. The clear solution was concentrated to dryness *in vacuo* to give a sticky gel. This was dissolved at the boiling point in 100 ml. of 20% isopropyl alcohol–80% water and the solution cooled to give 2.1 g. of solid, m.p. 244–246°. A recrystallization from the same solvent raised the m.p. to 256–258° and this melting point was unchanged after another recrystallization from the same mixture of solvents, λ 2.98, 3.05, 6.1, 6.25, 6.45, 6.73, 6.85, 6.93, 7.0 μ. The yield of XXVII was 1.0 g. (20%).

Anal. Calcd. for $C_9H_8F_3N_3O_4S_2$: C, 31.48; H, 2.36; N, 12.24; S, 18.70. Found: C, 31.67; H, 2.64; N, 12.66; S, 18.93.

The aqueous isopropyl alcohol mother liquors from the above recrystallizations were evaporated partially to give 0.52 g. of solid, m.p. 183–220° dec. Washing with diethyl ether left a residue of 0.26 g. of solid, m.p. 239–241°; when recrystallized from water, it melted at 255–257° and was identical with XXVII. The ether washings were evaporated to dryness to give 0.20 g. of solid, m.p. 194–196°. Recrystallization from 10% ethanol-90% water gave 0.1 g. of 6′-(methylsulfamoyl)-α,α,α-trifluoro-4′-sulfamoyl-*m*-formotoluidide (XXIX), m.p. 198–200°, λ 3.03, 3.13, 5.85, 6.33, 6.83, 6.90 μ.

Anal. Calcd. for $C_9H_{10}F_3N_3O_5S_2$: N, 11.63; S, 17.75. Found: N, 11.81; S, 17.45.

Reaction of 6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (VIII) *with methyl iodide in ethanol.* A solution of 22 g. (0.066 mole) of VIII in 100 ml. of 95% ethanol, 15 ml. of water, 2.4 g. (0.06 mole) of sodium hydroxide, and 6.5 ml. of methyl iodide was heated under reflux for a total of 18 hr.; a solid began to separate after about 2 hr. The cooled reaction mixture was filtered (for filtrate, see below) to give 10 g. of material, m.p. 238–244°. Recrystallization from 75% methanol-25% water gave 6.4 g. (31% yield) of XXVII, m.p. 256–258°; a mixture melting point with the XXVII from (b) in the above experiment was 256–258° and their infrared spectra were identical.

The filtrate from the above reaction product was concentrated to dryness to give a gummy residue consisting of unchanged VIII and XXVIII. This residue was boiled with 10 ml. of 10% aqueous hydrochloric acid and the hot extract decanted from the insoluble VIII.

The hydrochloric acid extract was evaporated to dryness and the residue recrystallized from water to give 0.7 g. of α,α,α-trifluoro-N^2-methyl-5-(methylamino)-2,4-toluenedisulfonamide arising from the hydrolysis of XXVIII, m.p. 166–168° dec., λ 2.95, 3.03, 6.18, 6.35, 6.6, 6.75, 6.85 μ. A mixture melting point with 5-amino-α,α,α-trifluoro-N^2,N^4-dimethyl-2,4-toluenedisulfonamide (see below) was 133–160°.

Anal. Calcd. for $C_9H_{12}F_3N_3O_4S_2$: C, 31.12; H, 3.49; N, 12.10; S, 18.46. Found: C, 30.87; H, 3.50; N, 12.29; S, 18.50.

Reaction of 6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (VIII) *with ethyl iodide in ethanol.* The reaction was carried out as described above between 6.5 g. (0.019 mole) of VIII, 50 ml. 95% ethanol, 0.6 g. (0.015 mole) of sodium hydroxide, and 2 ml. of ethyl iodide. The cooled reaction mixture was filtered (for filtrate, see below) to give 0.67 g. of solid, m.p. 250–260°; two recrystallizations from 75% methanol-25% water gave 0.38 g. (9% yield) of XI, melting point and mixture melting point with the XI obtained *via* the triethyl orthoformate reaction, 279–281°. The infrared spectra of both compounds were identical. Saponification of 0.24 g. of this product gave a quantitative yield of XV, melting point and mixture melting point with the XV obtained from XI *via* the triethyl orthoformate reaction, 216–218°; the infrared spectra of both compounds were identical.

The filtrate from the above 0.67 g. was concentrated to dryness to give 6.5 g. of solid, m.p. 248–270°. Recrystallization from water gave 4.7 g. of unreacted VIII.

3,4-Dihydro-N,2-dimethyl-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. 5-Amino-α,α,α-trifluoro-N^2,N^4-dimethyl-2,4-toluenedisulfonamide. To 75 ml. of 40% aqueous methylamine and 500 ml. of water, with stirring, was added approximately 0.2 mole of 5-amino-α,α,α-trifluoro-2,4-toluenedisulfonyl chloride. The mixture was stirred and heated for 2 hr. on the steam bath, cooled, the solid filtered, and recrystallized from water to give 37.2 g. (53% yield) of product, m.p. 162–164°.

Anal. Calcd. for $C_9H_{12}F_3N_3O_4S_2$: C, 31.12; H, 3.49; N, 12.10. Found: C, 31.09; H, 3.49; N, 12.02.

The *disulfonamide*, 8.7 g. (0.025 mole), 2.5 ml. of 37% formalin solution, 100 ml. of 95% ethanol, and 5 ml. of 10% hydrochloric acid were heated under reflux for 3 hr., the solution was concentrated to dryness and the residual solid recrystallized from 20% isopropyl alcohol–80% water to give 6 g. (67% yield) of product, m.p. 222–224°, λ 2.98, 3.02, 6.20, 6.45, 6.60, 6.88 μ.

Anal. Calcd. for $C_{10}H_{12}F_3N_3O_4S_2$: C, 33.36; H, 3.36; N, 11.67. Found: C, 33.59; H, 3.60; N, 11.41.

3,4-Dihydro-2-methyl-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide and 3,4-dihydro-N,2-dimethyl-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide. To 21 g. (0.064 mole) of 3,4-dihydro-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide dissolved in a solution of 5.1 g. (0.128 mole) of sodium hydroxide in 500 ml. of water was added dropwise 8 g. (0.064 mole) of purified methyl sulfate. The mixture was stirred for 72 hr. at room temperature and the solid which had separated was filtered and dried. It weighed 8.5 g., m.p. 189–190°. Recrystallization from 20% acetonitrile-80% water gave 5 g. (24% yield) of 3,4-dihydro-*N*,2-dimethyl-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, melting point and mixture melting point with the product above, 222–224°; their infrared curves were identical.

The alkaline filtrate from the above product was treated with an excess of solid carbon dioxide. The precipitated solid was filtered and dried; it weighed 9 g., m.p. 190–192°. Recrystallization from water gave 3,4-dihydro-2-methyl-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, microcrystals, m.p. 195–197°. The melting point was found to vary with the crystal structure; occasionally long needles, m.p. 204–206° were obtained; and a mixture of the two crystal forms melted at 203–205°.

Anal. Calcd. for $C_9H_{10}F_3N_3O_4S_2$: C, 31.30; H, 2.92; N, 12.17. Found: C, 31.60; H, 2.86; N, 12.21.

Reaction of 3,4-dihydro-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (XXX) *with triethyl orthoformate.* A mixture of 20 g. (0.06 mole) of XXX and 500 ml. of triethyl orthoformate was stirred and heated at 150° for 3 hr. The distillate, b.p. 50–80°, weighed 25 g. The reaction mixture was filtered, concentrated to dryness *in vacuo* and the residual oil desiccated *in vacuo* at 78° The *N*-ethoxymethylene derivative (XXXII), a pale yellow amorphous solid, sintered at 85° and melted at 97–99°,

λ 2.98, 3.05, 6.25, 6.58, 8.45–8.75 (broad), 9.0, 9.17, 9.5 μ. The yield was 14.0 g. (60%).

Anal. Calcd. for $C_{11}H_{12}F_3N_3O_5S_2$: C, 34.10; H, 3.13; N, 10.85. Found: C, 34.22; H, 3.60; N, 11.11.

Reaction of 3-benzyl-3,4-dihydro-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (XXXI) *with triethyl orthoformate.* A mixture of 10.0 g. (0.024 mole) of XXXI and 200 ml. of triethyl orthoformate were treated in the usual manner in an oil bath at 150°. A solid separated from the clear solution on cooling. The filtered, air-dried solid weighed 3.5 g., m.p. 223–225° dec. Recrystallization from triethyl orthoformate gave 2.0 g. (18% yield) of 3-benzyl-3,4-dihydro-*N*-ethoxymethylenesulfamoyl-6-(trifluoromethyl)-1,2,4-benzothiadiazine 1,1-dioxide (XXXIII), m.p. 232–234° dec., λ 2.95, 3.05, 6.08, 6.15, 6.25, 6.45, 6.88 μ.

Anal. Calcd. for $C_{18}H_{18}F_3N_3O_5S_2$: C, 45.28; H, 4.05; N, 8.80; S, 13.43. Found: C, 45.76; H, 3.57; N, 8.98; S, 13.43.

The above compound, 0.2 g., 4 ml. of 10% aqueous sodium hydroxide solution and 8 ml. of water were refluxed for 3 hr. during which the original yellow solution became colorless. The cooled reaction mixture was treated with an excess of dilute hydrochloric acid to give 0.075 g. of 5-amino-α,α,α-trifluoro-2,4-toluenedisulfonamide, m.p. and mixture m.p. 236–238°.

Reaction of 3-oxo-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (XXXIV) *with triethyl orthoformate.* The reaction at 150° between 5.7 g. (0.016 mole) of XXXIV and 100 ml. of triethyl orthoformate proceeded normally. The solution formed was concentrated to dryness *in vacuo* and the residue washed with 200 ml. of diethyl ether. The insoluble material, 1.84 g. was recrystallized from 20% isopropyl alcohol–80% water and melted at 258–259° dec.; the melting point was unchanged after two additional recrystallizations, λ 2.95, 3.03, 3.20, 5.88, 6.10, 6.25, 6.55 μ. The yield of XXXV was 1.44 g. (24%).

Anal. Calcd. for $C_{10}H_{10}F_3N_3O_5S_2$: C, 32.17; H, 2.71; N, 11.76. Found: C, 32.29; H, 2.84; N, 11.55.

The diethyl ether extract was evaporated to give 2.78 g. of solid. Recrystallization as above gave a product, m.p. 281–283° dec.; a second recrystallization raised the m.p. to 282–284° dec., λ 2.94, 3.02, 3.23, 5.90, 6.16, 6.25, 6.40, 6.6, 6.75, 6.80μ. The yield of XXXVI was 2.1 g. (34%).

Anal. Calcd. for $C_{10}H_{10}F_3N_3O_5S_2$: C, 32.17; H, 2.71; N, 11.76. Found: C, 32.31; H, 2.42; N, 11.32.

Saponification of 2.2 g. of XXXVI with 25 cc. of 20% aqueous sodium hydroxide gave 1.4 g. (69% yield) of XIV, m.p. and mixture m.p. 104–106°.

Reaction of XXIV, *ethyl iodide, and sodium hydride in N,N-dimethylformamide.* To 22 g. (0.064 mole) of XXIV in 75 ml. of *N,N*-dimethylformamide was added 3.1 g. (0.064 mole) of 50% sodium hydride in mineral oil, followed by 10.0 g. (0.065 mole) of ethyl iodide. The mixture was stirred at 70° for 1 hr. and poured into 1 l. of water. The precipitated solid was filtered and dried to give 13 g. of solid, m.p. 264–266° dec. Recrystallization from 50% aqueous ethanol gave 5.4 g. (22% yield) of XXXVI, melting point and mixture melting point with the triethyl orthoformate product, 282–284° dec.; their infrared spectra were identical. The aqueous ethanolic filtrate was concentrated to about 200 ml., cooled, the solid filtered and dried to give 4.0 g., m.p. 248–253°. This was recrystallized from 20% isopropyl alcohol–80% water to give an additional 2.2 g. (9% yield) of XXXVI; the mother liquors from this, concentrated to one-half volume gave 1.44 g. (6% yield) of XXXV, melting point and mixture melting point with the product from the triethyl orthoformate reaction, 259–261° dec. and their infrared spectra were identical.

Reaction of 1,2,4-pyrido[2,3-e]thiadiazine-7-sulfonamide 1,1-dioxide (XXXVII) *with triethyl orthoformate.* The reaction of 150° was carried out between 1.0 g. (0.004 mole) of XXXVII and 10 ml. of triethyl orthoformate. The cooled reaction mixture deposited 0.74 g. of solid, m.p. 142–186°. This was recrystallized from 25 ml. of triethyl orthoformate to give 0.23 g. of *N*-ethoxymethylenesulfamoyl-4-ethyl-1,4,2-pyrido[2,3-e]thiadiazine 1,1-dioxide (XXXVIII), m.p. 145–147°, λ (no =NH or —NH_2 absorption), 6.15, 6.25, 6.33, 6.80, 6.93, 8.78, 8.98, 9.07, 9.18 μ.

Anal. Calcd. for $C_{11}H_{14}N_4O_5S_2$: C, 38.14; H, 4.08; N, 16.17. Found: C, 37.97; H, 4.36; N, 16.21.

The triethyl orthoformate filtrate from the recrystallization was concentrated to dryness *in vacuo*. The residual solid weighed 0.12 g. This solid and the *N*-ethoxymethylene derivative above were recrystallized separately from water to give the same product, 4-ethyl-1,4,2-pyrido[2,3-e]thiadiazine-7-sulfonamide 1,1-dioxide (XXXIX), m.p. and mixture m.p. 247–249°, and with identical infrared spectra, λ 2.98, 3.07, 6.17, 6.32, 6.5, 6.8, 6.93 μ.

Anal. Calcd. for $C_9H_{10}N_4O_4S_2$: C, 33.11; H, 3.47; N, 19.31; S, 22.11; N—C_2H_5, 9.66. Found: C, 33.35; H, 3.47; N, 19.34; S, 22.26; N—C_2H_5, 9.02.

The original triethyl orthoformate filtrate was also worked up to give 0.12 g. of additional XXXIX. The reaction of 2-amino-3,5-pyridinedisulfonamide with triethyl orthoformate gave a 27% yield of XXXIX. The XXXIX, 0.5 g., was hydrolyzed with 10 ml. of 10% aqueous sodium hydroxide. The crude disulfonamide weighed 0.51 g. Recrystallization from water gave 2-ethylamino-3,5-pyridinedisulfonamide, m.p. 216–218°, λ 2.95, 3.0, 3.1, 6.25, 6.55 μ.

Anal. Calcd. for $C_7H_{12}N_4O_4S_2$: N, 19.99; S, 22.88. Found: N, 19.97; S, 22.36.

Reaction of arylsulfonamides with triethyl orthoformate at 150°. The following products were obtained in essentially quantitative yields: *N*-ethoxymethylenebenzenesulfonamide, m.p. 55–57° (recrystallized from petroleum ether [b.p. 100–140°]) (*Anal.* Calcd. for $C_9H_{11}NO_3S$: C, 50.69; H, 5.20; N, 6.57; S, 15.04. Found: C, 50.51; H, 5.07; N, 6.83; S, 15.19;) *N*-ethoxymethylene-α,α,α-trifluoro-*p*-toluenesulfonamide, m.p. 64–65° (recrystallized from hexane) (*Anal.* Calcd. for $C_{10}H_{10}F_3NO_3S$: C, 42.70; H, 3.59; N, 4.99. Found: C, 42.68; H, 3.98; N, 5.36) and *N*-ethoxymethylene-*o*-α,α,α-trifluoro-*o*-toluenesulfonamide, m.p. 77–79° (recrystallized from ligroin) (*Anal.* Calcd. for $C_{10}H_{10}F_3NO_3S$: C, 42.70; H, 3.59; N, 4.99. Found: C, 42.80; H, 3.40; N, 5.28). None of these compounds showed absorption in the =NH or —NH_2 region and all showed a strong band at 6.30 μ, characteristic of the C=N in the $C_2H_5OCH{:}NSO_2$— group.

Reaction of N-ethylbenzenesulfonamide and triethyl orthoformate at 150°. A solution of 3.35 g. (0.02 mole) of *N*-ethylbenzenesulfonamide in 50 ml. of triethyl orthoformate was heated so as to distill 25 ml. of triethyl orthoformate during 3 hr. The solution was concentrated to dryness *in vacuo* and the residue cooled to give a quantitative yield of *N*-ethyl-*N* (phenylsulfonyl) formamide diethyl acetal, m.p. 43–45°. An analytical sample, recrystallized from ligroin, melted at 45–47°, λ (no =NH or —NH_2 absorption), 6.83, 6.90, 8.65, 8.85, 9.05, 9.35, 9.62 μ.

Anal. Calcd. for $C_{13}H_{21}NO_4S$: C, 54.32; H, 7.37; N, 4.88; S, 11.15. Found: C, 54.55; H, 7.25; N, 5.03; S, 11.07.

When the above acetal was exposed for several days to normal laboratory atmosphere, it liquefied. When boiled with aqueous isopropyl alcohol, *N*-ethylbenzenesulfonamide was regenerated. In a screw cap sealed vial, the acetal remained unchanged even after several weeks.

Reaction of N-acetylbenzenesulfonamide with triethyl orthoformate. *N*-Acetylbenzenesulfonamide, 1.6 g., and 10 ml. of triethyl orthoformate were treated at 150° for 3 hr. The clear solution was concentrated to dryness *in vacuo* to give the mixture of products as an oil, λ (no =NH or —NH_2 absorption), 5.85, 6.20, 6.87, 7.48, 7.65, 8.0, 8.63, 8.90 μ.

Anal. Calcd. for $C_{10}H_{13}O_3NS$: C, 52.84; H, 5.77; N, 6.61. Found: C, 53.17; H, 5.81; N, 6.05.

The above oil, 1.0 g., was saponified by heating under reflux with a mixture of 20 ml. of 10% aqueous sodium hydroxide and 20 ml. of isopropyl alcohol for 0.5 hr. The isopropyl alcohol was distilled, the alkaline solution cooled and acidified to give 0.62 g. of solid. Extraction with boiling

ligroin left behind 0.14 g. (9% yield) of benzenesulfonamide, m.p. and mixture m.p. 147–149°. The ligroin extracts were evaporated to dryness to give 0.48 g. (59% yield) of *N*-ethylbenzenesulfonamide, m.p. 57–59° after recrystallization from ligroin; a mixture melting point with an authentic sample prepared from benzenesulfonyl chloride and monoethylamine, was 57–59°.

4-(2-Diethylaminoethyl)-6-(trifluoromethyl)-1,4,2-benzothiadiazine 1,1-dioxide (XLV) *monomaleate*. A mixture of 23.5 g. (0.093 mole) of 6-(trifluoromethyl)-1,2,4-benzothiadiazine 1,1-dioxide (III), 4.7 g. (0.12 mole) of sodamide, and 200 ml. of anhydrous bis-2-ethoxyethyl ether was stirred for 1 hr. at room temperature and then treated dropwise with 70 ml. of a 1.6*N* solution of 2-diethylaminoethyl chloride in dry toluene. The mixture was stirred and heated under reflux for 24 hr., cooled, filtered with suction, and the filtrate concentrated to dryness *in vacuo*. The residual gum was dissolved in 200 ml. of warm *n*-propyl alcohol and to this solution with stirring, was added a warm solution of 11.6 g. (0.1 mole) of maleic acid in 50 ml. of *n*-propyl alcohol. The crystalline product which separated on cooling was filtered and air dried; it weighed 20 g., m.p. 167–169°. Recrystallization from *n*-propyl alcohol gave 18 g. (41% yield) of product, m.p. 175–177°.

Anal. Calcd. for $C_{14}H_{18}F_3N_3O_2S \cdot C_4H_4O_4$: C, 46.45; H, 4.77; N, 9.04. Found: C, 46.85; H, 4.95; N, 8.78.

The maleate, 0.050 g., was dissolved in water and the *p*H adjusted to 7.6. The precipitated solid was filtered, washed with water and dried to give 0.038 g. of *base* (XLV), m.p. 115–117°, λ (no =NH or —NH_2 absorption), 6.15, 6.20, 6.40 μ.

Anal. Calcd. for $C_{14}H_{18}F_3N_3O_2S$: C, 48.18; H, 5.20. Found: C, 47.73; H, 5.49.

4-(3-Dimethylaminopropyl)-6-(trifluoromethyl)-1,4,2-benzothiadiazine 1,1-dioxide (XLVI) *maleate*. The reaction was carried out on the same scale as in the previous example, except for the substitution of 65 ml. of a 1.85*N* solution of 3-dimethylaminopropyl chloride. The crude base was isolated as a yellow glass; this, in 100 ml. of warm acetonitrile was treated with 11.6 g. (0.1 mole) of maleic acid in 100 ml. of acetonitrile. Since no solid separated, the mixture was concentrated to dryness *in vacuo*. The residual yellow glass was stirred with 100 ml. of water; partial solution was followed almost immediately by the separation of a solid. This solid was filtered and air dried; it weighed 8.5 g. and was unchanged III. The aqueous filtrate was concentrated *in vacuo* to a thick syrup which crystallized spontaneously. Recrystallization from *n*-propyl alcohol gave 10 g. (25% yield) of *maleate*, m.p. 179–181°; a mixture melting point with the 2-isomer (see below) was 108–160°.

Anal. Calcd. for $C_{13}H_{16}F_3N_3O_2S \cdot C_4H_4O_4$: C, 45.23; H, 4.47; N, 9.31. Found: C, 45.24; H, 4.44; N, 9.12.

When the purified maleate (0.025 g.) was dissolved in water and the solution adjusted to *p*H 7.6, a solid separated. It was filtered, washed with water, and dried to give 0.015 g. of *base* (XLVI), m.p. 133–135°.

Anal. Calcd. for $C_{13}H_{16}F_3N_3O_2S$: C, 46.57; H, 4.81; N, 12.53. Found: C, 46.38; H, 4.80; N, 12.33.

2-(2-Diethylaminoethyl)-6-(trifluoromethyl)-1,2,4-benzothiadiazine 1,1-dioxide (XLVII). *N-(2-Diethylaminoethyl)-α,α,α-trifluoro-2-Nitro-p-toluenesulfonamide*. To 80 ml. of 1.2*N* toluene solution of α,α,α-trifluoro-2-nitro-*p*-toluenesulfonyl chloride in 150 ml. of dry acetonitrile was added, dropwise, at room temperature, 11.6 g. (0.1 mole) of *N,N*-diethylethylenediamine in 50 ml. of dry acetonitrile. An exothermic reaction occurred, but no cooling was employed. The mixture was then stirred and heated under reflux for 1 hr. and concentrated *in vacuo*. The viscous residue was insoluble in water; a solution in aqueous potassium hydroxide was clarified with Hyflo and the filtrate treated with an excess of solid carbon dioxide. The oil which separated crystallized. This was filtered, air dried and recrystallized from hexane to give 22 g. (62% yield) of product, m.p. 64–66°. An analytical sample, recrystallized from ligroin, melted at 65–67°.

Anal. Calcd. for $C_{13}H_{18}F_3N_3O_4S$: C, 42.27; H, 4.92; N, 11.38. Found: C, 42.30; H, 5.17; N, 11.08.

2-Amino-N-(2-diethylaminoethyl)-α,α,α-trifluoro-p-toluenesulfonamide (XLVIII). The nitro compound 5.0 g. (0.014 mole), 1.0 g. of 5% palladium on charcoal catalyst and 200 ml. of absolute ethanol were hydrogenated at 50 p.s.i. and 50°, overnight. The cooled mixture was filtered from the catalyst and the filtrate concentrated to dryness under nitrogen. The residue crystallized to give essentially a quantitative yield of product, m.p. 59–61°; an analytical sample, recrystallized from ligroin, melted unchanged; and a mixture melting point with the nitro compound was 42–45°.

Anal. Calcd. for $C_{13}H_{20}F_3N_3O_2S$: C, 46.00; H, 5.95; N, 12.38. Found: C, 45.79; H, 6.01; N, 12.29.

2-(2-Diethylaminoethyl)-6-(trifluoromethyl)-1,2,4-benzothiadiazine 1,1-dioxide (XLVII). The product from the previous step and 200 ml. of triethyl orthoformate were placed in an oil bath preheated to 125°; the evolution of bubbles commenced promptly and ceased after 1.5 hr. The solution was concentrated *in vacuo* to give a residual oil which solidified, m.p. 79–82°. Recrystallization from ligroin gave 5.2 g. (essentially quantitative yield) of product, m.p. 87–88°, λ (no =NH or —NH_2 absorption), 6.18, 6.28, 6.40 μ.

Anal. Calcd. for $C_{14}H_{18}F_3N_3O_2S$: C, 48.14; H, 5.20; N, 12.03. Found: C, 48.58; H, 5.31; N, 11.76.

2-(3-Dimethylaminopropyl)-6-(trifluoromethyl)-1,2,4-benzothiadiazine 1,1-dioxide (XLIX) *maleate*. The above procedure gave a 65% yield of *N*-(3-dimethylaminopropyl)-α,α,α-trifluoro-2-nitro-*p*-toluenesulfonamide, m.p. 80–82° after recrystallization from hexane.

Anal. Calcd. for $C_{12}H_{16}F_3N_3O_4S$: C, 40.56; H, 4.54; N, 11.83. Found: C, 41.05; H, 4.43; N, 11.29.

The *2-amino derivative* (L) was obtained in 76% yield, m.p. 91–92°, after recrystallization from ligroin.

Anal. Calcd.: C, 44.30; H, 5.58; H, 12.91. Found: C, 44.29; H, 5.62; H, 12.61.

Cyclization of the amino compound with triethyl orthoformate gave a 93% yield of XLIX, m.p. 53–55°; this base could not be recrystallized since it was too soluble in all solvents. It was converted, in 50% yield, to a maleate, m.p. 141–143°, after recrystallization from isopropyl alcohol. A mixture melting point with the 4-isomer (see above) was 108–160°.

Anal. Calcd. for $C_{13}H_{16}F_3N_3O_2S$: C, 45.23; H, 4.47; N, 9.31. Found: C, 45.44; H, 4.74; N, 9.27.

3-Benzyl-2-ethyl-3,4-dihydro-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (XLIII). A solution of 3.5 g. (0.01 mole) of 6′-(ethylsulfamoyl)-α,α,α-trifluoro-4′-sulfamoyl-*m*-toluidide, 1.83 g. (0.011 mole) of phenylacetaldehyde dimethyl acetal, 2.5 ml. of 10% hydrochloric acid, and 25 ml. of 95% ethanol was heated under reflux for 2 hr., filtered hot, and the filtrate diluted with 27 ml. of hot water. The oil which separated solidified after keeping for several days at room temperature. The solid was dried thoroughly and recrystallized twice from toluene to give 1.2 g. (27% yield) of XLIII, m.p. 110–112°, λ 2.95–3.05, 6.17, 6.40, 6.65, 6.87, 7.35–7.55, 7.70, 7.88 μ.

Anal. Calcd. for $C_{17}H_{18}F_3N_3O_4S_2$: C, 45.42; H, 4.04; N, 9.35. Found: C, 45.62; H, 4.26; N, 9.66.

3,4-Dihydro-4-ethyl-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide (XLIV). 5-Ethylamino-α,α,α-trifluoro-2,4-toluenedisulfonamide (*via* the hydrolysis of XI), 5.43 g. (0.016 mole), 1.28 g. of 37% formalin solution, 50 ml. of 95% ethanol, and 2.5 ml. of 10% hydrochloric acid were heated under reflux for 2 hr. and the solution concentrated to dryness. The residual solid, m.p. 210–212°, when recrystallized from water gave XLIV, m.p. 217–219°, λ 2.97, 3.05, 6.13, 6.25, 6.48, 6.78, 6.93, 7.05, 7.40 μ. A mixture melting point with XVI was 183–195°.

Anal. Calcd. for $C_{10}H_{12}F_3N_3O_4S_2$: C, 33.42; H, 3.37; N, 11.70. Found: C, 33.22; H, 3.33; N, 12.05.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, CASE INSTITUTE OF TECHNOLOGY]

Reactions of 2-Chlorodioxene with Alcohols, Phenols, and Acids

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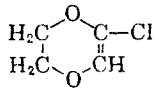
2-Chlorodioxene being an α-chloro and a vinyl ether may react with alcohols by replacement of the chlorine or by addition to the olefinic double bond. The products obtained can be accounted for if the first step involves addition to the double bond.

The olefinic bond in 2-chlorodioxene was found to possess unusual reactivity, adding alcohols, acids and phenols under mild conditions in the absence of added catalysts.

The products obtained from the reactions with alcohols were found to depend upon the general type of alcohol employed. Primary alcohols gave esters of 2-chloroethoxyacetic acid. Secondary alcohols gave a mixture of the ester, an alkyl chloride and *p*-dioxanone, while tertiary alcohols gave exclusively the corresponding alkyl chloride and *p*-dioxanone. Phenols reacted in the same manner as primary alcohols.

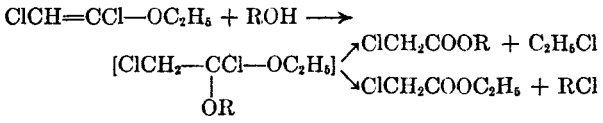
Acids were found to yield the corresponding acyl halide and *p*-dioxanone.

The chlorodioxene was obtained according to the method of Astle and Gergel[3] by the thermal dehydrohalogenation of 2,3-dichlorodioxane. It is a water-white liquid boiling at 145–147° at atmospheric pressure.

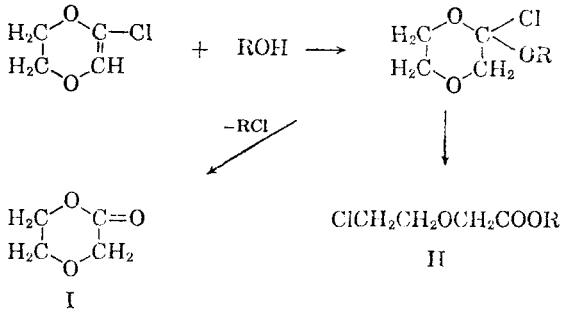


2-Chlorodioxene is an α-chloro ether as well as a vinyl ether. Although the chlorine would not be expected to have quite the activity found in most α-chloro ethers because of the inactivating effect of the double bond, the primary reaction may well involve replacement of this chlorine as the first step. As a vinyl ether the predominant reaction of active hydrogen compounds might be the addition to the double bond. Because of the difunctionality of this compound it was interesting to determine the nature of the reaction with a number of alcohols and acids.

Very little is found in the literature concerning the reactions of α-halovinyl ethers. Imbert[4] reports that reactions of α-halovinyl ethers with alcohols and acids give esters and acyl halides respectively. Cromptom and Vanderstichele[5] prepared chloro acetates and acid halides from α,β-dichlorovinyl ethyl ether. The reaction gives two distinct sets of products from a common intermediate formed by the addition of an alcohol to the double bond.



Applying this reaction sequence to chlorodioxene the products should be an alkyl chloride and dioxanone (I), or an ester of 2-chloroethoxyacetic acid (II).



I

II

EXPERIMENTAL

Four methods of reaction were employed in this investigation. Each method is illustrated.

Method A. This method involves simply refluxing the reactants in a suitable solvent for an appropriate length of time.

Chlorodioxene (120.5 g., 1.0 mole), 74.1 g. (1.0 mole) of butanol and 200 ml. of 1,4-dioxane were charged into a 500-ml. thermowell flask equipped with a thermometer and reflux condenser to which was attached a drying tube. The mixture was refluxed for 16 hr. with a pot temperature of 112°. A slight evolution of hydrogen chloride was noticed during this heating period. The reaction mixture was frac-

(1) From the M.S. thesis of John D. Welks.

(2) Present address: American Can Co., Barrington, Ill.

(3) M. J. Astle and W. C. Gergel, U. S. Patent 2,756,240 (July 4, 1956).

(4) G. Imbert, Ger. Patent 212,592 (Oct. 4, 1906).

(5) H. Crompton and P. L. Vanderstichele, *J. Chem. Soc.*, 691 (1920).