vent gave the pure product, m.p. 165–167°. The yield was 8 g. (39%).

Compounds XII, XIII and XV were similarly prepared by substituting ethyl chloroacetate, chloroacetaldehyde dimethyl acetal and β-chloroethyl β-hydroxyethyl ether, respectively, for the β-chloroethyl vinyl ether in the above synthesis.

α-Methyl-4-{3-[2-(trifluoromethyl)-10-phenothiazinyl]-propyl}-piperazinemethanol Dimaleate (VIII) (A).—A mixture of 19.8 g. (0.05 mole) of IV, 12.4 g. (0.1 mole) of β-chloroethyl carbamate, 6.9 g. (0.05 mole) of anhydrous potassium carbonate and 100 ml. of anhydrous toluene was stirred and refluxed for 18 hours, filtered, and the filtrate concentrated to dryness on the steam-bath *in vacuo*. To the residual oil in 250 ml. of warm acetonitrile was added a solution of 13.4 g. of maleic acid in 150 ml. of warm acetonitrile. The mixture was warmed for 0.5 hr., cooled and the solid filtered. It weighed 5 g. A recrystallization from water gave 3.5 g. (10% yield) of product, m.p. 210–212° dec. A mixture m.p. with Ia was 160–200°.

The above **dimaleate** was dissolved in a minimum amount of warm water and the **base** liberated with an excess of 20% aqueous potassium hydroxide solution. **The base** was extracted into ether, the ether solution was washed with water and dried. The filtered ether solution was cooled and treated with a slight excess of ethereal hydrogen chloride. The very hygroscopic **salt** which separated was filtered and recrystallized from absolute ethanol to give the pure **dihydrochloride**; m.p. 205–208°.

(B).—A mixture of 3.9 g. (0.01 mole) of IV, 1.32 g. (0.03 mole) of acetaldehyde and 100 ml. of anhydrous toluene sealed in a Carius tube was heated 18 hours at 93°. The tube was cooled, opened and the toluene solution concentrated *in vacuo* to give a black tar. This was extracted with 50 ml. of boiling acetonitrile, and the acetonitrile solution decanted from the insoluble material. To the acetonitrile solution was added a solution of 2.32 g. (0.02 mole) of maleic acid in 20 ml. of warm acetonitrile. The dark tan solid which separated on cooling was filtered and washed with a little acetonitrile. The solid weighed 1.0 g., m.p. 188–190°. Recrystallization first from 95% ethanol and then from water gave 0.3 g. of material, m.p. 210–212° dec. A mixture m.p. with VIIIa was 210–212° dec., and the infrared spectra of the two compounds were identical.

Anal. Calcd. for $C_{22}H_{26}F_3N_3OS \cdot 2C_4H_4O_4$: N, 6.28; S, 4.79. Found: N, 6.56 S, 4.97.

4-{3-[2-(Trifluoromethyl)-10-phenothiazinyl]-propyl}-piperazine-ethanol 5-Oxide Hydrochloride.—Four and one-half grams (0.01 mole) of I in 200 ml. of 95% ethanol and a solution of 1.8 g. of oxalic acid in 50 ml. of 95% ethanol were mixed rapidly. Subsequently, the mixture was heated under reflux for 0.5 hr., cooled, and the **dioxalate** filtered. It was an extremely insoluble compound, m.p. 215–217° dec. One recrystallization from 95% ethanol raised the m.p. to 220–221° dec. This **dioxalate**, 250 ml. of 95% ethanol, 100 ml. of water and 1.3 g. of 30% hydrogen peroxide were refluxed for 24 hours, then concentrated *in vacuo* on the steam-bath. The residual yellow gum was dissolved in water, and the solution treated with an excess of 10% aqueous sodium hydroxide solution. The liberated **base** was insoluble in ether but could be extracted with chloroform. The chloroform extracts were dried and concentrated. The residual oil was dissolved in 10 ml. of isopropyl alcohol and the solution treated with ethereal hydrogen chloride. The crystalline solid which separated was filtered and recrystallized from chlorobenzene to give 2 g. (40% yield) of product, m.p. 213–215°.

Anal. Calcd. for $C_{22}H_{26}F_3N_3O_2S \cdot HCl$: C, 53.92; H, 5.56; N, 8.58; Cl, 7.24; S, 6.54. Found: C, 53.85; H, 5.46; N, 8.43; Cl, 7.28; S, 6.71.

4-{3-[10-(7-Nitro-2-trifluoromethyl)-phenothiazinyl]-propyl}-1-piperazine-ethanol Dimaleate (X).—A mixture of 31.2 g. (0.1 mole) of 7-nitro-2-(trifluoromethyl)-phenothiazine, 4.3 g. (0.11 mole) of sodium amide and 300 ml. of diethylene glycol dimethyl ether was heated to 90° and 18.9 g. of trimethylene chlorobromide added dropwise. The mixture was then stirred and heated for 18 hours at 145°, cooled and to it was added 22.5 g. of sodium iodide and 26 g. of 1-piperazine-ethanol. Subsequently, the reaction was allowed to proceed for 18 hours at 115°, the mixture diluted with 300 ml. of anhydrous xylene and filtered. The filtrate was concentrated on the steam-bath *in vacuo*, and the residue, in acetonitrile, converted to the maleic acid salt. The crude salt was twice recrystallized from 95% ethanol to give 12 g. (17% yield) of pure product, m.p. 185–187° dec.

Anal. Calcd. for $C_{22}H_{25}F_3N_4O_3S \cdot 2C_4H_4O_4$: C, 50.42; H, 4.65; N, 7.84. Found: C, 50.41; H, 4.85; N, 7.61.

10-[3-(4-Methyl-1-piperazinyl)-propyl]-7-nitro-2-(trifluoromethyl)-phenothiazine (XI).—A mixture of 31.2 g. (0.1 mole) of 7-nitro-2-(trifluoromethyl)-phenothiazine, 4.3 g. (0.11 mole) of sodium amide and 300 ml. of diethylene glycol dimethyl ether was heated to 90° and treated dropwise with 21.2 g. of 4-methyl-1-piperazinepropyl chloride. The mixture was then heated to 135° and maintained for four hours at this temperature, cooled, and filtered. The filtrate was concentrated on the steam-bath *in vacuo*. When the residual oil was treated with acetonitrile, crystallization occurred. The solid was filtered to give 31 g. of crude product, m.p. 124–126°. After one recrystallization from hexane, there was obtained 23 g. (51% yield) of pure product, m.p. 127–128°.

Anal. Calcd. for $C_{21}H_{23}F_3N_4O_2S$: C, 55.73; H, 5.12; N, 12.38. Found: C, 55.99; H, 5.00; N, 12.04.

NEW BRUNSWICK, N. J.

[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

6-(Trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide and Related Compounds

BY HARRY L. YALE, KATHRYN LOSEE AND JACK BERNSTEIN

RECEIVED AUGUST 21, 1959

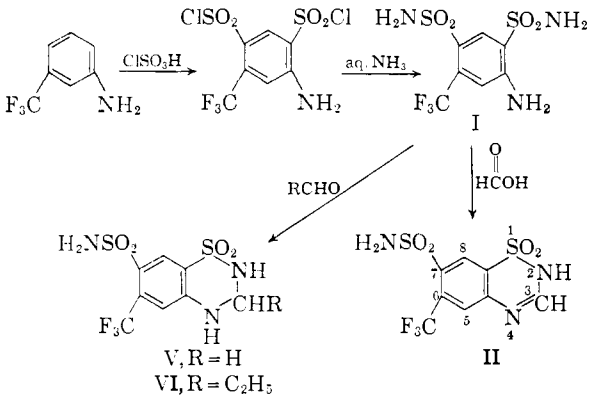
The synthesis of 6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide (II) and its 3-methyl- (XIII) and 3-ethyl- (XV) derivatives, 3,4-dihydro-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide (V) and its ethyl derivative (VI), as well as 3-oxo-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide (XXIII) is described. Both II and V have demonstrated clinical usefulness as diuretic agents. The effect on the diuretic activity of these compounds caused by the replacement of a benzene by a pyridine nucleus has also been ascertained by synthesizing 1,2,4-pyrido[2,3-e]thiadiazine-7-sulfonamide-1,1-dioxide (XVIII), 3,4-dihydro-1,2,4-pyrido[2,3-e]thiadiazine-7-sulfonamide-1,1-dioxide (XIX) and 6-methyl-1,2,4-pyrido[2,3-e]thiadiazine-7-sulfonamide-1,1-dioxide (XX). Elucidation of the structures of the acetyl and propionyl derivatives of 5-amino-α,α,α-trifluoro-2,4-toluenedisulfonamide (I), precursors, respectively, of XIII and XV, has involved to a considerable extent a study of the infrared spectra of these derivatives. These data are presented and discussed.

The clinical effectiveness of 6-chloro-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide[1a] as a diuretic agent[1b,c] suggested to us the synthesis of the corresponding 6-(trifluoromethyl) derivative. This reasoning was based on the observation that the

(1) (a) F. C. Novello and J. M. Sprague, THIS JOURNAL, **79**, 2028 (1957); (b) R. V. Ford and C. L. Spurr, *Southern Soc. Clin. Research Meeting*, **1**, 26 (1957), through *Am. J. Med.*, **22**, 965 (1957); (c) R. V. Ford, J. H. Moyer and C. L. Spurr, *A.M.A. Arch. of Int. Med.*, **100**, 582 (1957).

substitution of a chlorine atom by a trifluoromethyl group in various classes of organic compounds has led to a number of clinically useful drugs.[2] We are now reporting the synthesis of 6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide[3] (II) which has been found to be a useful diuretic agent.[4a,b,c] In addition, we have prepared 3,4-dihydro-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide (V),[5] which has been reported to possess similar pharmacological activity,[6] along with its 3-ethyl derivative VI. These compounds were obtained by the sequence of reactions shown in Chart I.

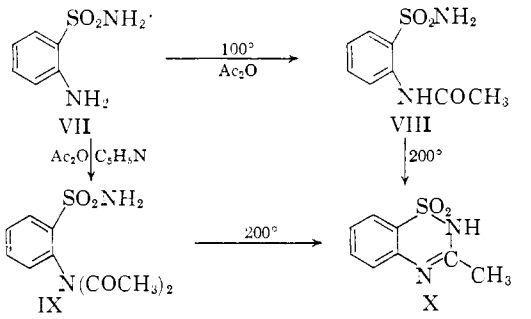
CHART I



The synthesis of 3-methyl- and 3-ethyl-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide required a less direct procedure, namely, the acylation of I, followed by pyrolysis to effect ring closure. Only two pertinent reports of this procedure are to be found in the literature and both are concerned with the acetylation of *o*-aminobenzenesulfonamide (VII). The latter with acetic anhydride at 100° gave *o*-acetamidobenzenesulfonamide (VIII),[7] while with acetic anhydride in pyridine at room temperature it gave *o*-diacetamidobenzenesulfonamide (IX)[8]; both VIII and IX at 200° gave 3-methyl-1,2,4-benzothiadiazine-1,1-dioxide (X) (Chart II).

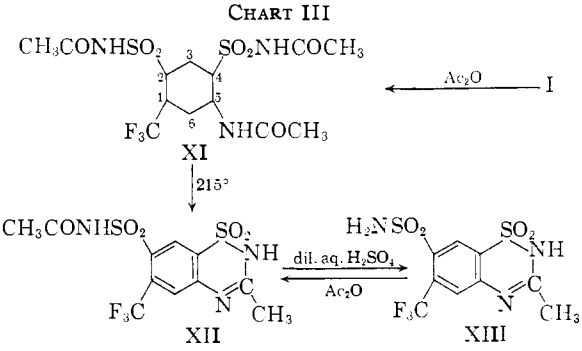
When heated at reflux temperature for two hours, Compound I and a large excess of acetic anhydride gave a **triacetyl derivative XI.** The structure of XI was elucidated as follows: Pyrolysis of XI in the dry state or in Dowtherm A at 215–225° gave a **monoacetyl-3-methyl-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide (XII).** —XIII and an excess of acetic anhydride at reflux temperature gave only XII. Since 6-(trifluoro-

CHART II



methyl)-1,2,4-benzothiadiazine-1,1-dioxide[9] was recovered unchanged from a similar treatment with acetic anhydride, the acetylation could not have occurred in the thiadiazine ring but rather at the 7-position in XIII. These reactions are summarized in Chart III.

CHART III



The structures assigned to XI and XII are consistent with their infrared spectra. Thus, XI shows bands at 6.03–6.05 and 6.6–6.5 μ due to the 5-CH_3CONH–group; the absorption at 5.92–5.95 μ is due to the 4-$CH_3CONHSO_2$–group; the 5.8–5.85 band (the shift being due to the proximity of the $-CF_3$ group) is due to the 2-$CH_3CONHSO_2$–group; and the lack of absorption at 5.74 μ indicates the absence of any $(CH_3CO)_2N$– grouping at the 2-, 4- or 5- positions; XII exhibits medium intensity bands at 6.15, 6.24 and 6.30 and strong absorption at 6.60 μ characteristic of the basic ring structure.[10] In addition, XII possesses a 5.83 μ band characteristic of the 7-$CH_3CONHSO_2$– group adjacent to the $-CF_3$ group. Confirmation for this assignment of the latter band is found in the observation that while it is missing in the spectrum of XIII, it is restored when XIII is treated with acetic anhydride to give XII.

A monoacetyl derivative of I could be obtained by heating I with one or two equivalents of acetic anhydride in acetic acid, under reflux. In the infrared this derivative absorbs at 6.04 and 6.64 μ due to the 5-CH_3CONH– group; neither of the bands due to the 2- or 4-$CH_3CONHSO_2$ groups is seen. On pyrolysis, either in the dry state or in Dowtherm A, this derivative gave only XIII.

(2) H. L. Yale, *J. Med. Pharm. Chem.*, **1**, 121 (1959).

(3) This product is registered by E. R. Squibb & Sons under the name Ademol.

(4) (a) J. H. Moyer, M. Fuchs, S. Irie and T. Bodi, *Am. J. Cardiol.*, **3**, 113 (1959); (b) A. C. Montero, J. B. Rochelle and R. V. Ford, *Am. Heart J.*, **57**, 484 (1959); (c) *Monographs on Therapy*, **4**, **1**, April (1959).

(5) The corresponding 6-chloro derivative has been described by G. de Stevens, L. H. Werner, A. Halamandaris and S. Ricca, Jr., *Experientia*, **14**, 463 (1958).

(6) W. Kobinger and F. Lund, *Ugeskrift for Laeger*, **120**, 1583 (1958); N. Bobolth, K. Thomsen, P. From Hansen, N. R. Hagenson and J. Opresnik, *ibid.*, **120**, 1585 (1958).

(7) A. Ekbom, *Bihang till Svenska Vet. Akad. Handl.*, **27**, II, No. 1, 3 (1902); "Beilstein", 4th Ed., Vol. 27, p. 570; Vol. 14, p. 682.

(8) D. V. Parke and R. T. Williams, *J. Chem. Soc.*, 1760 (1950).

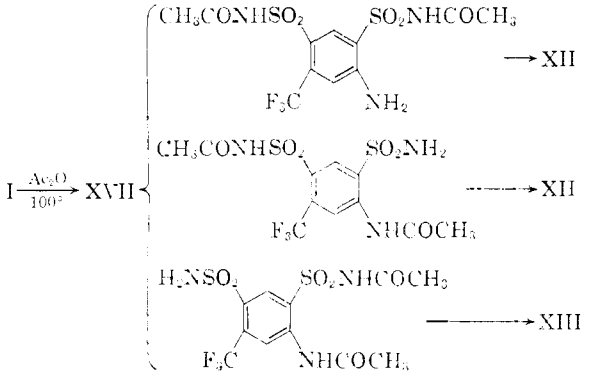
(9) C. T. Holdrege, R. B. Babel and L. C. Cheney in a paper presented before the A.C.S. Meeting in Boston, Mass., April 5–10, 1959, reported the synthesis of this compound.

(10) It is interesting to note that the hydrogenation of the 3,4-positions alters the basic ring absorption. Thus, II shows medium absorption at 6.15, 6.24, 6.4 and strong absorption at 6.6 μ, while V exhibits two strong bands at 6.2 and 6.55 and a weaker band at 6.42 μ.

The structure of the monoacetyl derivative is thus established as 5-acetamido-α,α,α-trifluoro-2,4-toluenedisulfonamide.

Efforts to prepare a diacetyl derivative of I resulted in the isolation of a mixture of diacetyl derivatives (XVII). The pyrolysis of XVII in the dry state or in Dowtherm A at 215–225° gave a mixture of XII and XIII. These observations, along with the infrared spectrum,[11] would indicate that XVII was a mixture; the source of the pyrolysis products is shown in Chart IV.

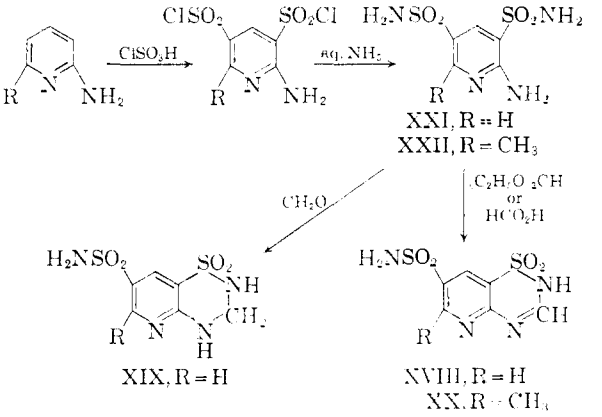
CHART IV



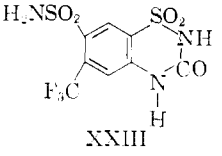
When Compound I and a large excess of propionic anhydride were heated under reflux for two hours a mixture of **tripropionyl derivatives XIV** was obtained.[11] In contrast to XI, preliminary experiments with XIV showed unexpected sensitivity to pyrolysis; the dry pyrolysis at 225 or 250° gave black tars while the pyrolysis in Dowtherm A at 210–225° gave a reaction product from which only 3- ethyl-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide (XV) was isolated by the usual recrystallization procedure. It was subsequently found that pyrolysis of XIV for only a few minutes rather than the usual two hours at 200–210° gave 3-ethyl-7-propionylsulfamyl-6-(trifluoromethyl)-1,2,4 - benzothiadiazine - 1,1 - dioxide (XVI) (prolonging the heating time or raising the temperature resulted in increased tar formation). Moreover, fractional crystallization of the reaction product from the pyrolysis of XIV in Dowtherm A at 200–210° proved it to be a mixture of XV and XVI; XV with a large excess of propionic anhydride gave only XVI.

Since the replacement, in certain prototype molecules, of the benzene nucleus by pyridine has led to a number of clinically useful drugs,[12-14] the study of the effect of this change in the benzothiadiazine-1,1-dioxides has been initiated with the synthesis of 1,2,4-pyrido[2,3-e]thiadiazine-7-sulfonamide-1,1-dioxide (XVII), 3,4-dihydro-1,2,4-pyrido[2,3-*e*]-thiadiazine-7-sulfonamide-1,1-dioxide (XIX) and 6 - methyl - 1,2,4 - pyrido[2,3 - e] - thiadiazine - 7-sulfonamide-1,1-dioxide (XX).[15]

These compounds were prepared by a sequence of reactions similar to those used with compounds II and V, with the exception that the cyclization of the intermediate disulfonamides XXI and XXII with formic acid required a temperature of about 140° in a sealed tube; XXI and XXII were more conveniently cyclized with ethyl orthoformate.[16]



The fusion of 5-amino-α,α,α-trifluoro-2,4-toluenedisulfonamide with urea at 200° gave 3-oxo-6-(trifluoromethyl)-1,2,4-benzothiadiazine - 7 - sulfonamide-1,1-dioxide (XXIII).



XXIII

Acknowledgment.—The authors are grateful to Dr. N. Coy and Miss B. Keeler for the infrared and ultraviolet spectra and for the discussions which aided in their interpretation. The microanalyses were carried out by Mr. J. F. Alicino and his associates.

Experimental Part

All melting points are uncorrected.

6-(Trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide (II).—To 100 ml. of 99% chlorosulfonic acid in a 1-l. 3-necked flask, at room temperature, was added 20 g. of *m*-aminobenzotrifluoride, dropwise, with stirring. To the resultant yellow solution was added slowly 90 g. of sodium chloride, and when this addition was completed, the mixture was heated for two hours by means of an oil-bath maintained at 175–180°. The solid reaction mixture was then cooled and treated rapidly with 500 ml. of crushed ice and water followed by 300 ml. of ether; the mixture was stirred vigorously and allowed to stratify. The ether layer, which contained the **5-amino-α,α,α-trifluoro-2,4-toluenedisulfonyl chloride**, was separated, washed with 15 ml. of water, dried and concentrated to about 50 ml. on the steam-bath. The cooled ether solution was added dropwise and with stirring to 50 ml. of aqueous ammonia (d. 0.7), the mixture was heated for one hour on the steam-bath, cooled, and the solid filtered. The crude, air-dried **5-amino-α,α,α-trifluoro-2,4-toluenedisulfonamide (I)** weighed 8 g. (20% yield), m.p. 232–236°. An analytical sample, recrystallized from water, melted at 236–238°. *Anal.* Calcd. for $C_7H_8F_3N_3O_4S_2$: C, 26.33; H, 2.53; S, 20.09. Found: C, 26.07; H, 2.64; S, 19.89. The crude disulfon-

(11) The spectrum of XVII shows no band at 5.7 μ, but bands at 5.81, 5.88, 5.93, 6.05 and 6.64 μ are present, indicating acetylation at the 2-, 4- and 5-positions, respectively.

(12) H. L. Yale, K. Losee, J. Martins, M. Holsing, F. M. Perry and J. Bernstein, THIS JOURNAL, **75**, 1933 (1953).

(13) A. von Schlichtegroll, *Arzneimittel-Forsch.*, **7**, 237 (1957).

(14) A. D. Spielman, *N. Y. State J. Med.*, **57**, 3329 (1957).

(15) When tested orally in the dog, compounds XVIII, XIX and XX were found to be somewhat less potent diuretic agents than the corresponding benzene derivatives.

(16) Ethyl orthoformate at 110–130° can effect cyclization of *o*-aminobenzenesulfon-*o*-toluide while 98–100% formic acid at reflux temperature gave only the intermediate *formamido derivative;* removal of the ethanol formed is essential; *cf.* J. H. Freeman and E. C. Wagner, *J. Org. Chem.*, **16**, 815 (1951).

amide, 8 g., and 100 ml. of 98–100% formic acid were heated under reflux for four hours, concentrated to about two-thirds volume and cooled. The crude product crystallized from the cooled concentrated reaction mixture; this, when filtered and washed with 10 ml. of cold water, melted at 301–303°. Recrystallization from water gave 5.9 g. (70% yield) of **6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide**, m.p. 305–306°.

Anal. Calcd. for $C_8H_8F_3N_3O_4S_2$: C, 29.20; H, 1.84; N, 12.76; S, 19.48. Found: C, 29.23; H, 2.03; N, 12.58; S, 19.28.

1,2,4-Pyrido[2,3-e]thiadiazine-7-sulfonamide-1,1-dioxide (XVIII).—The intermediate disulfonamide XXI, m.p. 222–223° after recrystallization from water, was prepared in 11% yield by the procedure described for I. *Anal.* Calcd. for $C_5H_6N_4O_4S_2$: N, 22.22; S, 25.38. Found: N, 22.04; S, 25.57.

Cyclization Method A.—A mixture of 2.52 g. (0.01 mole) of XXI and 10 ml. of redistilled ethyl orthoformate in an open flask was stirred and heated for three hours by means of an oil-bath at 110–130°. The cooled semi-solid mass was triturated with ether and filtered to give 2.5 g. of material, m.p. 215–220°. A recrystallization from water gave 1.3 g. (50% yield) of XVIII, m.p. 332–334° dec. *Anal.* Calcd. for $C_6H_6N_4O_4S_2$: C, 27.47; H, 2.30; S, 24.44. Found: C, 27.55; H, 2.29; S, 24.10.

Cyclization Method B.—A mixture of 7 g. (0.028 mole) of XXI and 70 ml. of 98–100% formic acid was heated for four hours in a sealed tube at 140°. The tube was cooled and carefully opened since there was considerable internal pressure. The reaction mixture was concentrated to dryness *in vacuo*, the residue was triturated with 50 ml. of water and the solid filtered (for filtrate, see below). It weighed 2 g.; recrystallization from water gave 1.5 g. (21% yield) of product, m.p. 332–334° dec. A mixture m.p. of the two products was 332–334° dec. and the infrared spectra were identical.

The aqueous filtrate from the trituration was adjusted to *p*H 5; the solid which separated was filtered and shown to be unreacted XXI, by m.p. and mixture m.p. The recovery was 3.5 g. (50%).

6-Methyl-1,2,4-pyrido[2,3-e]thiadiazine-7-sulfonamide-1,1-dioxide (XX).—The intermediate disulfonamide XXII, m.p. 235–236° dec. after recrystallization from water, was prepared in 15% yield by the procedure described for I. *Anal.* Calcd. for $C_6H_{10}N_4O_4S_2$: N, 21.04; S, 24.11. Found: N, 20.92; S, 24.01. A mixture of 10 g. (0.037 mole) of XXII and 50 ml. of redistilled ethyl orthoformate was treated as above. The yield of crude product, m.p. 210–220° dec., was 10 g.; recrystallization from water gave 7 g. (70% yield) of product, m.p. 309–310°. *Anal.* Calcd. for $C_7H_8N_4O_4S_2$: C, 30.42; H, 2.91; N, 20.28. Found: C, 30.71; H, 3.08; N, 20.01.

3,4-Dihydro-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide (V).—A mixture of 32 g. (0.1 mole) of 5-amino-α,α,α-trifluoro-2,4-toluenedisulfonamide, 10 g. (0.12 mole) of 37% formalin solution and 400 ml. of 95% ethanol was heated under reflux for two hours and concentrated to dryness *in vacuo* on the steam-bath. The residual oil crystallized on cooling and this was recrystallized from water to give 29 g. (87% yield) of product, m.p. 264–265°.

Anal. Calcd. for $C_8H_8F_3N_3O_4S_2$: C, 29.00; H, 2.43; N, 12.69; S, 19.36; F, 17.20. Found: C, 29.19; H, 2.48; N, 12.76; S, 19.54; F, 17.57.

3-Ethyl-3,4-dihydro-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide (VI).—Into each of two Carius tubes was placed the following mixture: 4 g. (0.025 mole) of 5-amino-α,α,α-trifluoro-2,4-toluenedisulfonamide, 1.5 g. (0.025 mole) of propionaldehyde and 50 ml. of absolute ethanol. The tubes were sealed and heated for two hours at 86°. The cooled tubes contained a crystalline product which was filtered and recrystallized from aqueous acetone to give 8 g. (89% yield) of product, m.p. 266–267° dec.

Anal. Calcd. for $C_{10}H_{12}F_3N_3O_4S_2$: C, 33.42; H, 3.37; N, 11.70. Found: C, 33.95; H, 3.63; N, 11.37.

3,4-Dihydro-1,2,4-pyrido[2,3-e]thiadiazine-7-sulfonamide-1,1-dioxide (XIX).—A mixture of 1.5 g. (0.06 mole) of XXI, 0.44 g. of 37% formalin and 50 ml. of 95% ethanol were heated under reflux for 3 hours and then concentrated to dryness *in vacuo*. The residue was a clear viscous oil. This was extracted repeatedly with small portions of boiling water. The combined aqueous extracts were cooled and the solid which separated was filtered. It weighed 0.2 g., m.p. 264–266°. A recrystallization from water raised the m.p. to 269–270°.

Anal. Calcd. for $C_6H_8N_4O_4S_2$: C, 27.27; H, 3.05; N, 21.21. Found: C, 27.33; H, 3.06; N, 20.84.

7-Acetylsulfamyl-3-methyl-6-(trifluoromethyl)-1,2,4-benzothiadiazine-1,1-dioxide (XII).—A mixture of 25 g. (0.078 mole) of 5-amino-α,α,α-trifluoro-2,4-toluenedisulfonamide and 100 g. (0.91 mole) of acetic anhydride was heated under reflux for two hours, cooled, and the crystalline solid filtered on a sintered glass funnel. Recrystallization from aqueous acetonitrile (2:1) gave the **triacetyl derivative**, m.p. 200–202°; the clear melt on continued heating underwent decomposition at 228° and resolidification at 257°.

Anal. Calcd. for $C_{15}H_{14}F_3N_3O_7S_2$: N, 8.95; acetyl value, 27.51. Found: N, 8.95; acetyl value, 26.06.

The triacetyl derivative, 15 g., was pyrolyzed for two hours in an oil-bath at 215–225°. The pyrolysis product was dissolved in 500 ml. of boiling acetone, the solution was decolorized with Darco, filtered and the filtrate concentrated to dryness. The residual white solid was recrystallized from aqueous isopropyl alcohol (1:1) to give 4.5 g. (36% yield) of 7-acetylsulfamyl-3-methyl-6-(trifluoromethyl)-1,2,4-benzothiadiazine-1,1-dioxide, m.p. 285–287°.

Anal. Calcd. for $C_{11}H_{10}F_3N_3O_5S_2$: C, 34.28; H, 2.62; N, 10.91; acetyl value, 11.17. Found: C, 34.21; H, 2.99; N, 10.58; acetyl value, 10.90.

3-Methyl-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide (XIII).—One gram of the 7-acetylsulfamyl derivative XII, 500 ml. of water and five drops of concentrated sulfuric acid were heated under reflux for 24 hours, cooled and the crystalline product filtered. The product weighed 0.59 g. (66% yield), m.p. 335–337° dec. A recrystallization from aqueous isopropyl alcohol raised the m.p. to 338–340° dec.

Anal. Calcd. for $C_9H_8F_3N_3O_4S_2$: C, 31.49; H, 2.36; N, 12.24. Found: C, 31.82; H, 2.64; N, 11.93.

A mixture of 2.1 g. of XIII and 75 ml. of acetic anhydride was heated under reflux for two hours, cooled and the solid filtered. A recrystallization from aqueous isopropyl alcohol gave 1.5 g. (84% yield) of **acetylated product**; a m.p. and mixture m.p. with XII was 285–287°. The infrared spectra of the two compounds were identical.

Anal. Calcd. for $C_{11}H_{10}F_3N_3O_5S_2$: C, 34.28; H, 2.62; N, 10.91. Found: C, 34.11; H, 2.88; N, 10.96.

Attempted Acetylation of 6-(Trifluoromethyl)-1,2,4-benzothiadiazine-1,1-dioxide.—The synthesis of 6-(trifluoromethyl)-1,2,4-benzothiadiazine-1,1-dioxide has been reported[9]; it melts at 253–255°.

Anal. Calcd. for $C_8H_5F_3N_2O_2S$: C, 38.40; H, 2.01; N, 11.19. Found: C, 38.71; H, 2.09; N, 11.17.

A solution of 0.5 g. of this compound and 10 ml. of acetic anhydride was refluxed for two hours and concentrated to dryness. The m.p. of the residual solid and a mixture m.p. with the starting material was 253–255°.

7-Acetylsulfamyl-6-(trifluoromethyl)-1,2,4-benzothiadiazine-1,1-dioxide.—A mixture of 2.5 g. of 6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide and 150 ml. of acetic anhydride was refluxed for two hours, cooled and the solid filtered. It weighed 2.8 g., m.p. 292–293° dec. Recrystallization from aqueous ethanol gave a product m.p. 301–302° dec. A mixture m.p. with II was 280–284° dec.

Anal. Calcd. for $C_{10}H_8F_3N_3O_5S_2$: C, 32.34; H, 2.18; N, 11.33. Found: C, 32.09; H, 2.19; N, 11.42.

Reaction of 5-Amino-α,α,α-trifluoro-2,4-toluenedisulfonamide with Propionic Anhydride.—A mixture of 25 g. (0.08 mole) of 5-amino-α,α,α-trifluoro-2,4-toluenedisulfonamide and 104 g. (0.8 mole) of propionic anhydride was heated under reflux for two hours and then concentrated to dryness; the crude **tripropionyl derivative** melted at 218–220°. An analytical sample recrystallized from aqueous acetonitrile melted at 227–229°. In the infrared, the mixture shows no absorption in the region 6.0–6.3 μ; the 5.95 μ band is again due to a 4-$C_2H_5CONHSO_2$– group; the 5.74 μ band is attributed to a 5-$(C_2H_5CO)_2N^-$ group; and the 5.78 μ band is due to the 2-$C_2H_5CONHSO_2$– group.

Anal. Calcd. for $C_{16}H_{20}F_3N_3O_7S_2$: C, 39.42; H, 4.14; N, 8.63; propionyl value, 35.17. Found: C, 39.76; H, 4.14; N, 8.27; propionyl value, 33.95.

Pyrolysis of the Mixture of Tripropionyl Derivatives. A.—In the dry state, at 225 or 250°, only black tars were obtained. When 0.5 g. of the *mixture* was placed in a 6-inch test-tube and immersed in an oil-bath preheated to 210–215°, the solid, originally colorless, had become dirty gray in color in about 5 minutes and a black tarry melt was beginning to appear in about 10 minutes. The tube was removed from the oil-bath and the dark colored solid recrystallized from water to give 0.2 g. (46% yield) of 3-ethyl-7-propionylsulfamyl-6-(trifluoromethyl)-1,2,4-benzothiadiazine-1,1-dioxide (XVI), m.p. 282–283° dec.

Anal. Calcd. for $C_{13}H_{14}F_3N_3O_5S_2$: C, 37.77; H, 3.42; N, 10.17; propionyl value, 13.56. Found: C, 37.83; H, 3.37; N, 10.19; propionyl value, 14.06.

B.—The *tripropionyl mixture*, 31 g., was dissolved in 310 ml. of Dowtherm A preheated to 210°, the solution was kept two hours at 210–215°, cooled, and the crystalline solid filtered. The solid was washed with ethyl ether and recrystallized from aqueous isopropyl alcohol (1:1) to give 10 g. (42% yield) of 3-ethyl-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide (XV), m.p. 345–347° dec.

Anal. Calcd. for $C_{10}H_{10}F_3N_3O_4S_2$: C, 33.61; H, 2.83; N, 11.76; S, 17.94. Found: C, 33.22; H, 2.92; N, 11.57; S, 17.99.

Alternately, 5 g. of the **tripropionyl mixture** was dissolved in 50 ml. of Dowtherm A, preheated to 210°, the solution was kept two hours at 210–215°, cooled, the solid filtered and washed with hexane. The crude solid, 3.5 g., was stirred for one hour at room temperature with 200 ml. of ethyl acetate. The insoluble material weighed 2.0 g. and after recrystallization from water there was obtained 1.8 g. of product, m.p. 345–347° dec.; a mixture m.p. with XV obtained above was 345–347° dec. The infrared absorption curves of the two compounds were identical. The ethyl acetate filtrate concentrated to dryness gave 0.8 g. of residue; this was recrystallized from aqueous isopropyl alcohol to give 0.6 g. of product, m.p. 282–283° dec. A mixture m.p. with XVI obtained above was 282–283° dec. and the infrared absorption spectra of the two compounds were identical.

7-Acetylsulfamyl-3-ethyl-6-(trifluoromethyl)-1,2,4-benzothiadiazine-1,1-dioxide.—A mixture of 1.0 g. of XV and 40 ml. of acetic anhydride were refluxed for 2 hours, cooled, and the solid filtered. A recrystallization from aqueous ethanol gave the product, m.p. 296–297°. This compound again shows absorption at 5.77 μ.

Anal. Calcd. for $C_{12}H_{12}F_3N_3O_6S_2$: C, 36.08; H, 3.03; N, 10.52. Found: C, 35.99; H, 2.93; N, 10.71.

5-Acetamido-α,α,α-trifluoro-2,4-toluenedisulfonamide (XVII).—A mixture of 19.2 g. (0.06 mole) of 5-amino-α,α,α-trifluoro-2,4-toluenedisulfonamide, 12.2 g. (0.12 mole) of acetic anhydride and 100 ml. of glacial acetic acid was heated under reflux for 3 hours and then concentrated to dryness. The residual glass was warmed with 50 ml. of water until it solidified. The solid was filtered and air-dried to give 17 g. of material, m.p. 224–226° dec. Recrystallization from aqueous acetonitrile gave 14.5 g. (67% yield) of product, m.p. 234–236°.

Anal. Calcd. for $C_9H_{10}F_3N_3O_5S_2$: C, 29.91; H, 2.79; N, 11.63. Found: C, 30.53; H, 3.30; N, 11.71.

Two and one-half grams of XVII in a six-inch test-tube was placed in an oil-bath preheated to 200° and the temperature allowed to rise to 250° within a 2-hour period. No fusion was apparent, the white solid merely becoming gray in color and somewhat porous. This solid was recrystallized from water to give 1.5 g. (63% yield) of 3-methyl-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide (XIII), m.p. 338–340°.

Pyrolysis of 2.5 g. of XVII in 15 ml. of Dowtherm A at 210–215° gave a 47% yield of XIII, m.p. 338–340°.

Diacetyl Derivative of 5-Amino-α,α,α-trifluoro-2,4-toluenedisulfonamide (XVII).—A mixture of 5 g. (0.016 mole) of I and 15 ml. of acetic anhydride was heated on the steam-bath for one hour, cooled, the solid filtered and washed with ether. The yield was 6 g. (95%), m.p. 178–180° dec. An analytical sample recrystallized from aqueous ethanol melted unchanged at 178–180° dec.

Anal. Calcd. for $C_{11}H_{12}F_3N_3O_6S_2$: C, 32.75; H, 3.00; N, 10.42; acetyl, 21.34. Found: C, 33.09; H, 3.40; N, 9.88; acetyl, 21.89.

Pyrolysis of 3 g. of XVII in 15 ml. of Dowtherm A at 210–215° gave a product, m.p. 306–308° after recrystallization from water. The infrared spectrum of this material showed a weak band at 5.85 μ, indicative of the presence of XII, as well as bands at 6.15, 6.23, 6.30 and 6.62 μ. The analytical data obtained on this material (C, 32.06; H, 2.81; acetyl, 3.34) would indicate that about 25–35% of XII was present in the mixture.

3-Oxo-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide (XXI).—Three and two-tenths grams (0.01 mole) of 5-amino-α,α,α-trifluoro-2,4-toluenedisulfonamide and 0.6 g. of urea were ground thoroughly in a mortar and placed in an oil-bath preheated to 200°; the mixture fused and resolidified during 0.5 hour. The crude solid melted at 305–307° dec. A recrystallization from water containing several drops of dilute hydrochloric acid gave the pure product, m.p. 315–317° dec. The yield was 1.5 g. (28% yield). In the infrared, XXI showed a strong band at 5.82 μ and weaker bands at 6.22, 6.33 and 6.55 μ.

Anal. Calcd. for $C_8H_6F_3N_3O_5S_2$: C, 27.83; H, 1.75; N, 12.17. Found: C, 28.15; H, 2.11; N, 12.04.

NEW BRUNSWICK, N. J.

[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Benzacridines. IV.[1] 6,6-Dimethyl-11-keto-6,11-dihydrobenz[b]acridans

BY N. H. CROMWELL AND JOHN C. DAVID

RECEIVED SEPTEMBER 8, 1959

Catalytic hydrogenation and reaction with phenylmagnesium bromide converted 6,6-dimethyl-11-keto-6,11-dihydrobenz[b]acridine (I) into 6,6-dimethyl-11-keto-6,11-dihydrobenz[b]acridan (II) and 6,6-dimethyl-11-keto-12-phenyl-6,11-dihydrobenz[b]acridan (III), respectively. Dehydrogenation of II re-formed I while III produced the corresponding 12-phenyl derivative IV. Absorption spectra studies of II and III show them to have the expected characteristics of β-amino-α,β-unsaturated ketones when compared with an authentic member of this class of compounds, 1-phenyl-3-anilino-2-butene-1-one (V).

In a previous investigation[1] the hydrolysis of 6,6-dimethyl-11-bromo-6,11-dihydrobenz[b]acridine produced 6,6-dimethyl-11-hydroxy-6,11-dihydrobenz[b]acridine (A) which oxidized in the air to 6,6-dimethyl-11-keto-6,11-dihydrobenz[b]acridine (I). With the thought that better yields of A might be obtained by the hydrogenation of the readily available[1] keto compound I various hydrogenation experiments were carried out. No evidence for the formation of A was obtained using

(1) For paper III see, N. H. Cromwell and J. C. David, THIS JOURNAL, **81**, 1138 (1959).