recovery), mp 273–274° dec. The $CHCl_3$ extracts were concentrated *in vacuo* and the concentrate was dissolved in hot MeOH, treated with dry HCl, and diluted with EtOAc. The solid was recrystallized (aqueous MeOH–DMF); yield 23.1 g, mp 227–229° dec. A sample of the hydrochloride was converted to the free base and the solid was recrystallized (aqueous MeOH–DMF); mp 152–153°. The ir absorption bands of the salt and free base were as expected.

Acknowledgment.—The authors wish to thank Dr. D. A. Stauffer's analytical chemistry section for their services.

7-Trifluoromethoxy and 7-Trifluoromethylthio Derivatives of 1,4-Benzodiazepines

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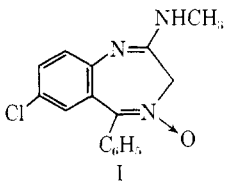
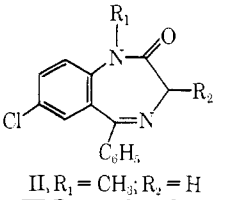
Replacement of halogen by "pseudohalogens" in compounds of medicinal interest often results in the formation of agents possessing therapeutic efficacy. In this regard the effectiveness of the trifluoromethyl group suggested that other highly fluorinated moieties might serve as pseudohalogens. The trifluoromethoxy and trifluoromethylthio groups seemed particularly interesting, since (1) these groups are inert to a variety of chemical reagents,[1] (2) their attachment to molecules of pharmaceutical interest has received little attention,[2] and (3) appropriate starting materials are available.[3] Sheppard has shown that the trifluoromethoxy group acts as a halogen in that it deactivates benzene systems by inductive electron withdrawal and donates electrons by resonance, whereas the trifluoromethylthio group deactivates such systems by both inductive and resonance mechanisms.[4] Accordingly, we have prepared representative 7-trifluoromethoxy- and 7-trifluoromethylthio-1,4-benzodiazepines, since compounds I–III are important psychotherapeutic agents, and all contain a 7-chloro substituent.[5]



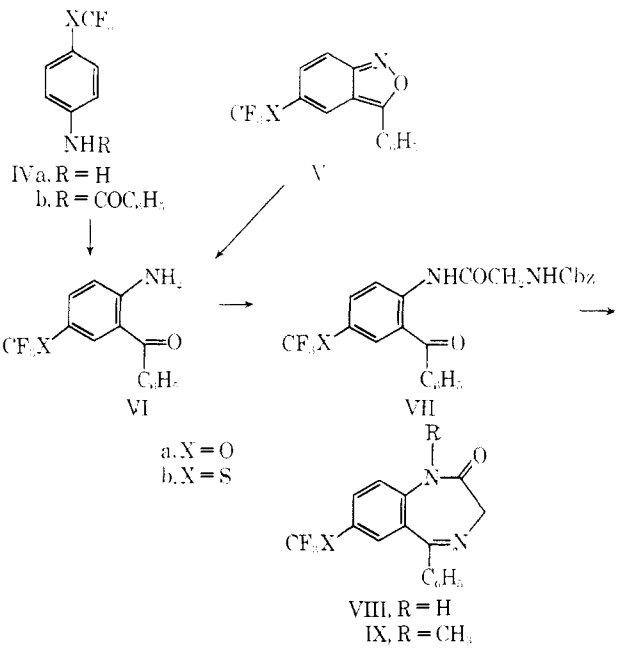
I



II, $R_1 = CH_3$; $R_2 = H$
III, $R_1 = H$; $R_2 = OH$

For the preparation of the desired 1,4-benzodiazepines in the 7-trifluoromethoxy series, *p*-trifluoromethoxyaniline (IVa)[1a] was converted smoothly into *o*-aminobenzophenone (VIa) by treatment with $ZnCl_2$ and PhCOCl as described previously (see Scheme I).[5]

SCHEME I



Transformation of VIa into benzodiazepine VIIIa was effected by acylation with carbobenzyloxyglycine and dicyclohexylcarbodiimide, removal of the blocking group in the resulting VIIa with HBr–AcOH, and heating of the derived glycinamido ketone.[7]

In the 7-trifluoromethylthio series reduction of a mixture of *o*- and *p*-nitrophenyl trifluoromethyl sulfides, obtained by nitration of phenyl trifluoromethyl sulfide,[1b] gave the corresponding anilines. Fractional crystallization of the derived benzanilides afforded the pure *para* isomer IVb in 25% over-all yield. Treatment of IVb with $ZnCl_2$ and PhCOCl[6] proved an unreliable method for the preparation of the desired ketone VIb, the yield ranging from 0–14%. This difficulty was circumvented by condensation[8] of phenylacetonitrile with the mixed nitrophenyl trifluoromethyl sulfides. Chromatography of the products afforded 35% of anthranil Vb, which was converted quantitatively into benzophenone VIb by catalytic hydrogenation.[9,10] In contrast to the trifluoromethoxy series, acylation of VIb with carbobenzyloxyglycine and dicyclohexylcarbodiimide proceeded slowly and produced VIIb in poor yield. The product was highly contaminated with benzyl (2,4-dicyclohexylallophanoylmethyl)carbamate. This crude material, however, could be converted into the desired 7-trifluoromethylthio-1,4-benzodiazepine VIIIb by removal of the blocking group and cyclization as described above.

Methylation of VIIIa and VIIIb furnished the 1-methyl-1,4-benzodiazepin-2-ones IXa and IXb, respectively. As in the acylation of ketones VIa and

(1) (a) W. A. Sheppard, *J. Org. Chem.*, **29**, 1 (1964); (b) *ibid.*, **29**, 895 (1964). These papers also review the earlier contributions of L. M. Yagupolsky and his collaborators.

(2) (a) 2-Trifluoromethylthiophenothiazines: E. A. Nodiff, S. Lipschutz, P. N. Craig, and M. Gordon, *ibid.*, **25**, 60 (1960); (b) *p*-trifluoromethoxyphenyl- and *p*-trifluoromethylthiophenylsulfonylureas: B. Blank and J. F. Kerwin, U. S. Patent 3,021,368 (1962).

(3) S. Andreades, J. F. Harris, Jr., and W. A. Sheppard, *J. Org. Chem.*, **29**, 898 (1964).

(4) W. A. Sheppard, *J. Am. Chem. Soc.*, **85**, 1314 (1963).

(5) (a) S. J. Childress and M. I. Gluckman, *J. Pharm. Sci.*, **53**, 577 (1964); (b) L. H. Sternbach, L. O. Randall, R. Banziger, and H. Lahr in "Drugs Affecting the Central Nervous System," A. Burger, Ed., Marcel Dekker, Inc., New York, N. Y., 1968, p 237.

(6) L. H. Sternbach, R. I. Fryer, W. Metlesics, G. Sach, and A. Stempel, *J. Org. Chem.*, **27**, 3781 (1962).

(7) A. Stempel and F. W. Landgraf, *ibid.*, **27**, 4675 (1962).

(8) R. B. Davis and L. C. Pizzini, *ibid.*, **25**, 1884 (1960).

(9) G. N. Walker, *ibid.*, **27**, 1929 (1962).

(10) *p*-Nitrophenyl trifluoromethyl ether[2a] was converted into anthranil Va in a similar manner. However, use of Va for the preparation of benzophenone VIa was not investigated, since the yield of Va was inferior to that of ketone VIa as prepared by the Friedel–Crafts procedure.

TABLE I
BIOLOGICAL ACTIVITIES OF REPRESENTATIVE BENZO-1,4-DIAZEPINES

Compd	Median effective dose, mg/kg ip: Ataxia[a]	Motor act. decrease[a]	Antielec shock[b]	Antistrych[c]	Lethality
7-Chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide (I)[d]	16	28	15	5	280
7-Chloro-1-methyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (II)[e]	8	9	11	3	>800 (20)[f]
1,3-Dihydro-1-methyl-5-phenyl-7-trifluoromethoxy-2H-1,4-benzodiazepin-2-one bisulfate (IXa)	23	22	20	5	259
2,3-Dihydro-5-phenyl-7-trifluoromethoxy-1H-1,4-benzodiazepine (XI)	82	>50	>50 (40)[f]	8.5	328 (60)[f]
1,3-Dihydro-3-hydroxy-5-phenyl-7-trifluoromethoxy-2H-1,4-benzodiazepin-2-one (XVb)	>100	>50	>50 (0)[f]	27	>270 (0)[f]

[a] Determined as described by W. B. Wright, Jr., H. J. Brabander, R. A. Hardy, Jr., and A. C. Osterberg, *J. Med. Chem.*, **9**, 852 (1966). [b] Determined as described by E. A. Swinyard, W. C. Brown, and L. S. Goodman, *J. Pharmacol. Exptl. Therap.*, **106**, 319 (1952). [c] Determined by a modification of method of H. M. Hanson and C. A. Stone in "Animal and Clinical Pharmacological Techniques in Drug Evaluation," Vol. I, J. H. Nodine and P. E. Siegler, Ed., Yearbook Medical Publishers Inc., Chicago, Ill., 1964, p 317. [d] Librium®. [e] Valium®. [f] Figure in parentheses gives percentage of mice affected at highest test dose.

TABLE II
7-TRIFLUOROMETHOXY- AND 7-TRIFLUOROMETHYLTHIO-1,4-BENZODIAZEPINES AND INTERMEDIATES IN THEIR PREPARATION

No.	Compd	Yield, %	Recrystn solvent	Mp, °C	Formula	Analyses
VIa	2-Amino-5-trifluoromethoxybenzophenone[a]	82	EtOH–H_2O	91–92	$C_{14}H_{10}F_3NO_2$	C, H, F, N
VIb	2-Amino-5-trifluoromethylthiobenzophenone[b]	100	EtOH–H_2O	67–68	$C_{14}H_{10}F_3NOS$	C, H, F, N, S
VIIa	Benzyl (2-benzoyl-4-trifluoromethoxyphenylcarbamoylmethyl)carbamate[c]	49	C_6H_6–hexane	117–119	$C_{24}H_{19}F_3N_2O_5$	C, H, F, N
VIIIa	1,3-Dihydro-5-phenyl-7-trifluoromethoxy-2H-1,4-benzodiazepin-2-one[c]	75	Me_2CO–hexane	157–158	$C_{16}H_{11}F_3N_2O_2$	C, H, F, N
VIIIb	1,3-Dihydro-5-phenyl-7-trifluoromethylthio-2H-1,4-benzodiazepin-2-one[c]	18	Me_2CO–hexane	176–178	$C_{16}H_{11}F_3N_2OS$	C, H, F, N; S[d]
IXa	1,3-Dihydro-1-methyl-5-phenyl-7-trifluoromethoxy-2H-1,4-benzodiazepin-2-one bisulfate[e]	85	Me_2CO–hexane	234–236	$C_{17}H_{13}F_3N_2O_2 \cdot H_2SO_4$	C, H, F, N, S
IXb	1,3-Dihydro-1-methyl-5-phenyl-7-trifluoromethylthio-2H-1,4-benzodiazepin-2-one bisulfate[e]	61	Me_2CO–hexane	181–184 (gas)	$C_{17}H_{13}F_3N_2OS \cdot H_2SO_4$	C, H, F, N
Xa	1,3-Dihydro-5-phenyl-7-trifluoromethoxy-2H-1,4-benzodiazepine-2-thione[f]	46	Et_2O–petr ether	187–188	$C_{16}H_{11}F_3N_2OS$	C, H, F, N, S
Xb	1,3-Dihydro-1-methyl-5-phenyl-7-trifluoromethoxy-2H-1,4-benzodiazepine-2-thione[f]	47	Et_2O–petr ether[g]	175–176	$C_{17}H_{13}F_3N_2OS$	C, H, F, N, S
XI	2,3-Dihydro-5-phenyl-7-trifluoromethoxy-1H-1,4-benzodiazepine[h]	43	CH_2Cl_2–Et_2O	117–118	$C_{16}H_{13}F_3N_2O$	C, H, F, N
XII	2-Methylmercapto-5-phenyl-7-trifluoromethoxy-3H-1,4-benzodiazepine[f]	90	MeOH–H_2O	82–84	$C_{17}H_{13}F_3N_2OS$	C, H, N
XIII	2-Methylamino-5-phenyl-7-trifluoromethoxy-3H-1,4-benzodiazepine[f]	80	Me_2CO–H_2O	176–178	$C_{17}H_{14}F_3N_3O$	C, H, F, N
XIV	1,3-Dihydro-5-phenyl-7-trifluoromethoxy-2H-1,4-benzodiazepin-2-one 4-oxide[i]	87	Me_2CO–hexane	197–198	$C_{16}H_{11}F_3N_2O_3$	H, F, N; C[j]
XVa	3-Acetoxy-1,3-dihydro-5-phenyl-7-trifluoromethoxy-2H-1,4-benzodiazepin-2-one[k]	71	Me_2CO–hexane	153–155	$C_{18}H_{13}F_3N_2O_4$	H, F, N; C[l]
XVb	1,3-Dihydro-3-hydroxy-5-phenyl-7-trifluoromethoxy-2H-1,4-benzodiazepin-2-one[k]	79	Me_2CO–hexane	201–202	$C_{16}H_{11}F_3N_2O_3$	C, H, F, N

[a] Method A, ref 6. [b] Reference 9. [c] Reference 7. [d] S: calcd, 9.53; found, 10.02. [e] L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961). [f] Reference 11. [g] Eluted by hexane–CH_2Cl_2 (1:9). [h] Reference 12. [i] S. C. Bell, T. S. Sulkowski, C. Gochman, and S. J. Childress, *J. Org. Chem.*, **27**, 562 (1962). [j] C: calcd, 57.15; found, 56.68. [k] Reference 13. [l] C: calcd, 57.15; found, 56.67.

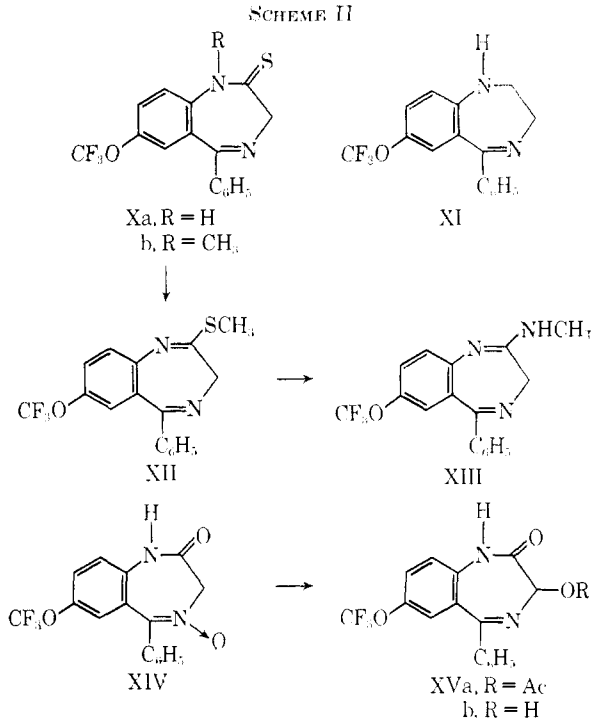
VIb, this reaction was superior in the 7-trifluoromethoxy series. These results with VI and VIII suggest a reduced nucleophilicity for the nitrogen functions in the trifluoromethylthio series, an observation qualitatively in accord with the behavior predicted by the substituent constants for the OR_F and SR_F groups.[4] In view of these synthetic difficulties other 1,4-benzodiazepines were prepared only in the 7-trifluoromethoxy series.

Thus, treatment of the 1,4-benzodiazepin-2-ones VIIIa and IXa with P_2S_5 in pyridine[11] gave the 2-thiones Xa and Xb, respectively (Scheme II). Methylation of Xa furnished the 2-methylmercapto derivative XII, which reacted with methylamine to furnish XIII.[11] Reduction of VIIIa with $LiAlH_4$[12] afforded the 2,3-dihydro-1H-1,4-benzodiazepine XI. Finally, oxidation of VIIIa with *m*-chloroperbenzoic acid gave the N-oxide XIV, which was readily transformed by the Polonovski reaction into the 2-acetoxy derivative XVa and then to the 2-hydroxy derivative XVb.[13]

Pharmacology.—Representative compounds were tested for their ability to induce ataxia, to decrease locomotor activity, and to afford protection against electroshock-induced and strychnine-induced convulsions in mice. The activities of our most interesting compounds are given in Table I; comparable data for the 7-chloro derivatives I and II are included. These limited tests indicate compound IXa to have activity, potency, and acute toxicity similar to that of the clinically effective compound I.

(11) G. A. Archer and L. H. Sternbach, *J. Org. Chem.*, **29**, 231 (1964).
(12) L. H. Sternbach, E. Reeder, and G. A. Archer, *ibid.*, **28**, 2456 (1963).
(13) S. C. Bell and S. J. Childress, *ibid.*, **27**, 1691 (1962).

SCHEME II



Xa, R = H
b, R = CH_3

XI

XII

XIII

XIV

XVa, R = Ac
b, R = H

Experimental Section

Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Procedures used for the preparation of new compounds are indicated by the appropriate reference; when chromatography was required for the isolation of pure materials, as confirmed by thin layer chromatography, the details are summarized. All chromatography was conducted on a synthetic magnesia–silica gel adsorbent. The petroleum ether used was the fraction boiling at 30–60°. Where analyses are indicated only by symbols of the elements, analytical results were within ±0.4% of the theoretical values.

3-Phenyl-5-trifluoromethoxyanthranil (Va) was prepared by condensation of *p*-nitrophenyl trifluoromethyl ether[1b] with $PhCH_2CN$.[8,9] The product was eluted with petroleum ether–CH_2Cl_2 (3:1) and recrystallized (Me_2CO–H_2O) with difficulty; 20% yield, mp 87–89°. *Anal.* ($C_{14}H_8F_3NO_2$) C, H, N.

3-Phenyl-5-trifluoromethylthioanthranil (Vb).—Phenyl trifluoromethyl sulfide (34.5 g, 0.194 mole) was nitrated as described previously.[1b] Distillation of the crude product (28 g) with a spinning-band column gave 47% of a mixture of *o*- and *p*-nitrophenyl trifluoromethyl sulfides. Condensation of 15.3 g of this mixture with $PhCH_2CN$ was effected with methanolic KOH.[8,9] The product, isolated with ether, was dissolved in petroleum ether–CH_2Cl_2 (3:1) and chromatographed. The material eluted by petroleum ether–CH_2Cl_2 (3:1) was rechromatographed to furnish 7.34 g (36%) of yellow crystals. A sample recrystallized from MeOH–H_2O had mp 97–98°. *Anal.* ($C_{14}H_8F_3NOS$) C, H, N, S.

The remaining new compounds are given in Table II.

Acknowledgment.—Microanalyses were furnished by Mr. L. Brancone and his staff.

Sulfonylureas Having Diuretic Activity

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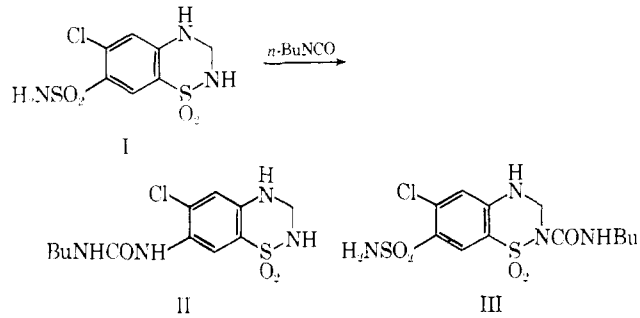
Received June 10, 1968

A patent[1] describing carbamoyl derivatives of 7-sulfamyl-3,4-dihydro-1,2,4-benzothiadiazine 1,1-dioxides prompts us to report our own findings with such preparations because, at least in one instance, our results differ.

When we treated hydrochlorothiazide (I) with butyl isocyanate, a single product was obtained, mp 156–157°, to which we have assigned structure II. In the patent cited above, under reaction conditions essentially identical with those which we have employed, the product obtained had a melting point of 174° and was assigned structure III.

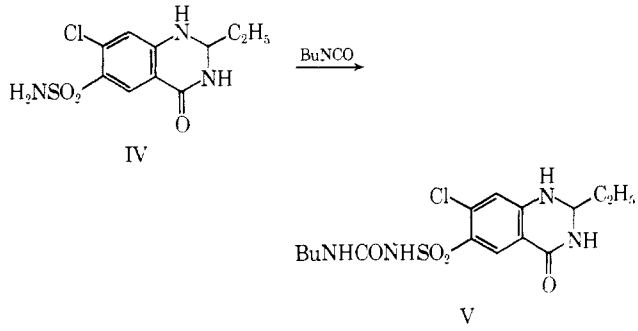


I

II

III

We have assigned structure II to our reaction product on the following basis: (a) it is reported that isocyanates do not react with *N*-substituted sulfonamides;[2] (b) the doublet at 2.95 and 3.05 μ in the ir spectra of I, characteristic of the unsubstituted 7-sulfamyl group, is no longer present in II; and (c) the related sulfamylquinazolone (IV), in which reaction at position II is unlikely, yields under comparable reaction conditions a monosulfonylurea derivative (V) of very similar structure to II. We are at a loss to explain the observed differences under what appears to be essentially identical reaction conditions.



IV

V

Compound II was devoid of hypoglycemic activity in the guinea pig but showed a diuretic potency in rats essentially equivalent to that of hydrochlorothiazide, but with a somewhat better Na/K ratio.[3] Compound V was much less potent than II as a diuretic agent.

Experimental Section[4]

6-Chloro-3,4-dihydro-7-(*N*-butylcarbamoyl)sulfamyl-2H-1,2,4-benzothiadiazine 1,1-Dioxide.—To a solution of 10.0 g (0.0336 mole) of 6-chloro-3,4-dihydro-7-sulfamoyl-2H-1,2,4-benzothiazine 1,1-dioxide (I) in 34 ml (0.0336 mole) of 1 *N* NaOH and 34 ml of Me_2CO at 10°, was added 3.32 g (0.0336 mole) of *n*-butyl

(1) G. deStevens and L. H. Werner, U. S. Patent 3,252,975 (1966).

(2) F. Kurzer in "Organic Sulfur Compounds," Vol. I, N. Kbarasch, Ed., Pergamon Press Inc., New York, N. Y., 1961, p 495.

(3) We are indebted to Dr. A Maass and Dr. D. Walz and their staffs, of these laboratories, for the biological test results. For the diuretic assay, the procedure of V. D. Wiebelhaus, F. T. Brennan, and G. F. Sosnowski, *Fed. Proc.*, **19**, 364 (1960), was used; the hypoglycemic activity was determined using the procedure described in the paper by B. Loev, K. M. Snader, and D. T. Walz, *J. Med. Chem.*, **6**, 506 (1963).

(4) All melting points are corrected; ir spectra were taken as Nujol mulls on a Perkin-Elmer Model 137 Infracord.