Sedative, Antiadrenergic, and Hypotensive 2-Substituted 2H-1,2,4-Benzothiadiazin-3(4H)-one 1,1-Dioxides

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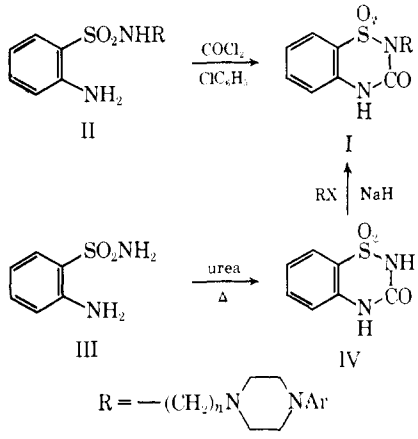
It has been reported that 3-substituted 2,4(1H,3H)-quinazolinediones, particularly 3-[ω-(4-aryl-1-piperazinyl)alkyl]-2,4(1H,3H)-quinazolinediones,[2] showed sedative and hypotensive activities in experimental animals. These findings led us to prepare analogous 2-substituted 2H-1,2,4-benzothiadiazin-3(4H)-one 1,1-dioxides.[3]

Preparation of 2H-1,2,4-benzothiadiazin-3(4H)-one 1,1-dioxide[4,5] and its 2-methyl and 2-benzyl derivatives[4,5] and 2,4-dimethyl-2H-1,2,4-benzothiadiazin-3-(4H)-one 1,1-dioxide[6] has been reported, but no pharmacological data have been given.

The reaction of *o*-nitrobenzenesulfonyl chloride with amines gave *o*-nitrobenzenesulfonamides which were hydrogenated to *o*-aminobenzenesulfonamides (II). The cyclization of II was carried out by treatment with phosgene in boiling chlorobenzene to give 2H-1,2,4-benzothiadiazin-3(4H)-one 1,1-dioxides (I) (Scheme I).

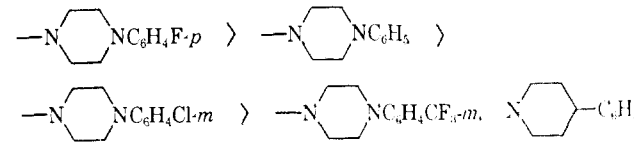
SCHEME I



Similarly, unsubstituted III was cyclized with urea at 200° or with phosgene in boiling chlorobenzene to give IV which was then alkylated to obtain I.

Pharmacology.—These compounds showed varying degrees of sedative and hypotensive activities. One of the best compounds as a potential psychosedative was **5**·HCl. Its activity in experimental animals was comparable to that of chlorpromazine hydrochloride and 3-[3-(4-*m*-chlorophenyl-1-piperazinyl)propyl]-2,4-(1H,3H)-quinazolinedione hydrochloride (V).[3] This was shown by the following tests: (1) a blind cross-over behavioral study[7] in dogs and cats, (2) the rotarod test,[8] (3) locomotor activity using activity cages[9] in mice, (4) hexobarbital sleeping time prolongation[10] in mice, and (5) lowering the threshold electric current for psychomotor seizure[11] in mice (minimal electroshock threshold test). In the blind cross-over behavioral study in dogs and cats, **5**·HCl at 15 mg/kg *po* produced sedation equal to that produced by chlorpromazine and V. In the hexobarbital sleeping time test, **5**·HCl was about two-thirds as potent as chlorpromazine at 5 mg/kg ip (mice). In the rotarod test, the ED_{50} of **5**·HCl was 4.2 mg/kg ip (mice), while those of chlorpromazine and V were 1.6 and 2.9 mg/kg, respectively. The minimal electroshock threshold test showed that **5**·HCl had an ED_{50} of 6.0 mg/kg, while chlorpromazine and V had an ED_{50} of 3.2 and 8.9 mg/kg, respectively. There was no protection against maximal electroshock or against pentylenetetrazole- or tremorine-induced tremors.

When X = H and n = 3 the following sedative activity–structure relationships were observed. Other than **5**·HCl, the compounds in this series showed weaker sedative and hypotensive activities than the corresponding 3-substituted 2,4(1H,3H)-quinazolinediones.



The adrenergic blocking actions of the compounds were assessed by their ability to antagonize (a) the pressor response to epinephrine and to carotid occulsion in the anesthetized dog, (b) the cat nictitating membrane response to epinephrine and to preganglionic sympathetic nerve stimulation, and (c) the rabbit aortic strip response to epinephrine. The acute hypotensive effect was evaluated in anesthetized normotensive dogs and rats. Administration was made intravenously, except for compounds in which poor solubility precluded the use of this route, in which case the compounds were administered intraduodenally in dogs and intracecally in rats. The antiadrenergic and hypotensive activities of the benzothiadiazinone studies is shown in Table I. It is apparent that the unsubstituted phenylpiperazine and phenylpiperidine derivatives (**1**, **6**, **8**) had greater activity than compounds with substituents in the phenyl ring. It should be mentioned, however, that **1**, the most active of the series, was also the only one soluble in water, a fact which may point toward differences in ease of penetration to active sites, rather than to differences in activity, among the different compounds.

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(3) For some of the compounds see S. Hayao, U. S. Patent 3,267,096 (1966).

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(9) C. A. Winter, and L. Flataker, *J. Pharmacol. Exptl. Therap.*, **103**, 93 (1951).

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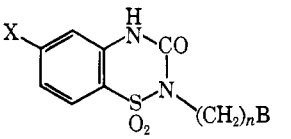
TABLE I



No.	X	n	B	Mp, °C	Formula	Analyses	Adrenergic blocking and hypotensive action (rel potency)[h]
1	H	3	—N⟨⟩NC$_6$H$_5$	152–153	$C_{20}H_{24}N_4O_3S$	C, N; H[c]	
				256–257 dec	$C_{20}H_{24}N_4O_3S \cdot CH_4O \cdot HCl$[a]	C, H, N	++++
2	H	3	—N⟨⟩NC$_6$H$_4$Cl-*m*	149–150	$C_{20}H_{23}ClN_4O_3S$	N; C,[d] H[e]	
				224–226	$C_{20}H_{23}ClN_4O_3S \cdot HCl$	C, H, N	0
3	H	3	—N⟨⟩NC$_6$H$_4$CF$_3$-*m*	158–159	$C_{21}H_{23}F_3N_4O_3S$	C, H, N	
				262–263 dec	$C_{21}H_{23}F_3N_4O_3S \cdot HCl$	C, H, N	++
4	H	3	—N⟨⟩NC$_6$H$_4$F-*m*	148–149	$C_{20}H_{23}FN_4O_3S$	C, H, N	
				257–258 dec	$C_{20}H_{23}FN_4O_3S \cdot HCl$	C, H; N[f]	Not tested
5	H	3	—N⟨⟩NC$_6$H$_4$F-*p*	165–167	$C_{20}H_{23}FN_4O_3S$	C, H, N	
				228–230	$C_{20}H_{23}FN_4O_3S \cdot HCl$	C, H, N	++
6	H	3	—N⟨⟩NC$_6$H$_5$	161–162	$C_{21}H_{25}N_3O_3S$	C, H, N	
				219–220 dec	$C_{21}H_{25}N_3O_3S \cdot CH_4O \cdot HCl$[a]	C, H, N	+++
7	H	4	—N⟨⟩NC$_6$H$_4$Cl-*m*	161–163 dec	$C_{21}H_{25}ClN_4O_3S \cdot C_4H_4O_4$[b]	C, H, N	++
8	H	5	—N⟨⟩NC$_6$H$_5$	190 dec	$C_{22}H_{28}N_4O_3S \cdot 2HCl$	C, H, N	+++
9	Cl	3	—N⟨⟩NC$_6$H$_5$	152–153	$C_{20}H_{23}ClN_4O_3S$	H, N; C[g]	Not tested

[a] Methanolate. [b] Maleate. [c] H: calcd, 6.00; found, 6.45. [d] C: calcd, 55.4; found, 54.8. [e] H: calcd, 5.30; found, 5.85. [f] N: calcd, 12.3; found 11.8. [g] C: calcd, 55.2; found, 54.7. [h] Salt.

In view of structural similarities between these compounds and the thiazide diuretics, some of them were tested for their effects on water, Na^+, K^+, and Cl^- excretion in the water-loaded rat. The compounds produced a small decrease, rather than an increase, in water and electrolyte excretion, this effect probably being related to a drug-induced lowering of blood pressure, and similar to the antidiuresis produced by other adrenergic blocking agents.[12]

At 5 mg/kg iv in an anesthetized, normotensive dog, **5**·HCl elicited a prompt reduction in mean blood pressure which reached a maximum of 48% in 20 min. Ninety minutes after drug administration, mean blood pressure was still 28% below control levels. The hypertensive response to epinephrine was partially blocked, while the hypotensive response to acetylcholine was unaffected. The acute and chronic effects of **5**·HCl were studied in hypertensive rats as described by Phillips and Kramer[13] for hydrochlorothiazide. Administration of 10 mg of **5**·HCl/kg orally once daily was followed by acute reduction in systolic blood pressure of 10–20%, persisting for 0.5–2 hr. No chronic reduction in blood pressure was observed.

Experimental Section[14]

1-Arylpiperazines[15] were prepared according to the procedure of Pollard. 4-Phenylpiperidine[16] was prepared as described in the literature.

4-(*m*-Fluorophenyl)-1-[3-(*o*-nitrobenzenesulfonamido)propyl]-piperazine.[17]—To an ice-cold solution of 1-(3-aminopropyl)-4-(*m*-fluorophenyl)piperazine (55 g, 0.232 mole) in 150 ml of C_6H_6 and 100 ml of 20% NaOH solution was added a solution of *o*-nitrobenzenesulfonyl chloride (51.3 g, 0.232 mole) in 150 ml of C_6H_6 during 15 min with vigorous stirring. The mixture was stirred at 25° for 2 hr, acidified with dilute HCl, and then made basic with NH_4OH to give a light yellow solid. The solid was collected and washed (H_2O, Et_2O); yield 64.2 g, mp 111–113°. The C_6H_6 layer was dried ($MgSO_4$) and concentrated *in vacuo* to an amber syrup which gave a bright yellow solid when triturated in C_6H_6–hexane; yield 28.7 g; mp 102–106°. The combined solids were recrystallized (C_6H_6–hexane); yield 78.8 g, mp 111–112°. Absorption bands of ir were as expected. *Anal.* ($C_{19}H_{23}FN_4O_4S$) C, H; N: calcd, 13.3; found, 12.6.

1-[3-(*o*-Aminobenzenesulfonamido)propyl]-4-(*m*-fluorophenyl)piperazine.—A solution of the above nitro compound (77.5 g, 0.184 mole) in 210 ml of AcOH was hydrogenated (3.5 kg/cm^2, 25°) using 5 g of 10% Pd–C as catalyst. The catalyst was filtered off and the solvent was removed *in vacuo*. The concentrate was treated with NH_4OH and the solid was collected and recrystallized (C_6H_4–hexane); yield 65.2 g. A sample was recrystallized (aqueous MeOH); mp 119–120°. *Anal.* ($C_{19}H_{25}FN_4O_2S$) N.

2-[3-(4-*m*-Fluorophenyl-1-piperazinyl)propyl]-2H-1,2,4-benzothiadiazin-3(4H)-one 1,1-Dioxide Hydrochloride (4).—To ice-cold C_6H_5Cl (250 ml) containing 50.9 g (0.515 mole) of $COCl_2$ was added the above amine (44.4 g, 0.113 mole). The suspension was stirred at 25° for 1 hr and refluxed for 1 hr. The solid that formed on cooling and addition of EtOAc was collected and twice recrystallized (aqueous MeOH–DMF); yield 39.0 g, mp 257–258° dec; ir absorption bands were as expected. The combined filtrates were concentrated *in vacuo* and made basic with NH_4OH. The solid free base was twice recrystallized (aqueous MeOH); yield 12.4 g, mp 148–149° (**4**).

6-Chloro-2-[3-(4-phenyl-1-piperazinyl)propyl]-2H-1,2,4-benzothiadiazin-3(4H)-one 1,1-Dioxide (9).—1-(3-Chloropropyl)-4-phenylpiperazine dihydrochloride (45.4 g, 0.146 mole) was added to a solution of 6-chloro-2H-1,2,4-benzothiadiazin-3(4H)-one 1,1-dioxide (34.1 g, 0.146 mole) and NaOMe (23.8 g, 0.44 mole) in 200 ml of absolute EtOH and 100 ml of DMSO. The mixture was heated under reflux for 20 hr, filtered, and concentrated *in vacuo*. The concentrate was suspended in $CHCl_3$ and washed with aqueous NaOH. The alkaline washings were acidified to give starting benzothiadiazinone, yield 14.0 g (41%

(12) R. Rodriguez, E. Hong, H. Vidrio, and E. G. Pardo, *J. Pharmacol. Exptl. Therap.*, **148**, 54 (1964).

(13) B. M. Phillips and D. L. Kramer, *J. Pharm. Sci.*, **54**, 1118 (1965).

(14) All melting points are corrected and were determined in a Büchi melting point apparatus. Ir spectra were determined with a Perkin-Elmer Model 237 grating spectrophotometer. Titrations were done with a Sargent Model D recording titrator. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(15) C. B. Pollard and L. B. MacDowell, *J. Am. Chem. Soc.*, **56**, 2199 (1934); **76**, 1853 (1954).

(16) P. A. J. Janssen, C. Van de Westeringh, A. H. M. Jageneau, P. A. J. Demoen, B. K. F. Hermans, G. H. P. VanDaele, K. H. L. Schellekens, C. A. M. Vander Eycken, and C. J. E. Niemegeers, *J. Med. Pharm. Chem.*, **1**, 281 (1959).

(17) Index name: Benzenesulfonamide, N-[3-(4-*m*-fluorophenyl-1-piperazinyl)propyl]-*o*-nitro-.

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.

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

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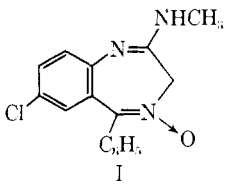
Replacement of halogen by "pseudohalogens" in compounds of medicinal interest often results in the formation of agents possessing therapeutic efficacy. In this regard the effectiveness of the trifluoromethyl group suggested that other highly fluorinated moieties might serve as pseudohalogens. The trifluoromethoxy 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.[1,3] 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]



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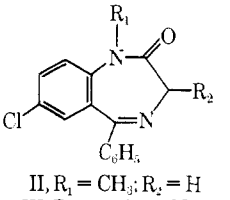
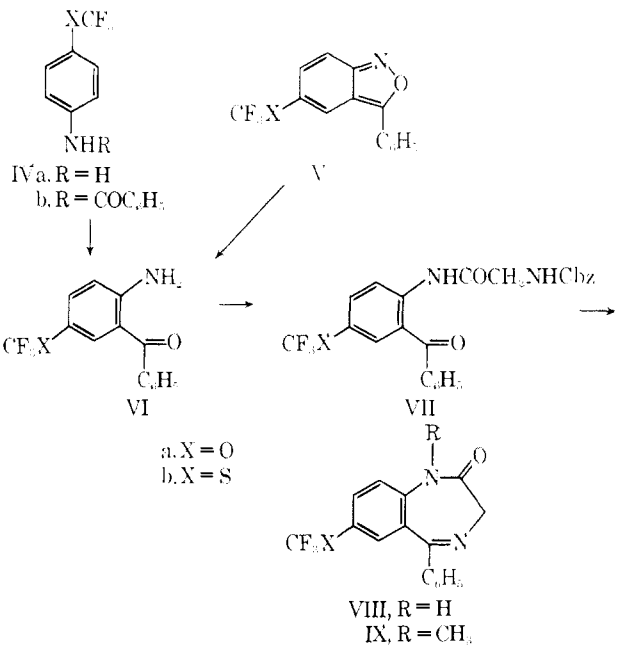


II, $R_1 = CH_3$; $R_2 = H$
III, $R_1 = H$; $R_2 = OH$

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).[6]

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.