Inhibitors of Platelet Aggregation. 1. 5,10-Dihydro-3-(phenyl, thienyl, and furyl)thiazolo[3,2-*b*][2,4]benzodiazepines and Related Compounds

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Various 5,10-dihydro-3-phenylthiazolo[3,2-*b*][2,4]benzodiazepines (IV) and 5,10-dihydro-3-thienylthiazolo-[3,2-*b*][2,4]benzodiazepines (V) were synthesized in 29–90% yield by the condensation of 1,2,4,5-tetrahydro-3*H*-2,4-benzodiazepine-3-thione (III) with the requisite 2-haloacetophenone or bromomethyl thienyl ketone in 2-methoxyethanol. 3-(2-Furyl)-5,10-dihydrothiazolo[3,2-*b*][2,4]benzodiazepine (VI), 5,10-dihydro-3-(2-naphthyl)thiazolo[3,2-*b*][2,4]benzodiazepine (VII), and 5,10-dihydro-2-methyl-3-phenylthiazolo[3,2-*b*][2,4]benzodiazepine (VIII) were prepared similarly. Several 3-(benzylthio)-2,5-dihydro-1*H*-2,4-benzodiazepines (IX) were obtained by the treatment of III with the appropriate benzyl chloride in 2-methoxyethanol. Six of the 5,10-dihydro-3-phenylthiazolo[3,2-*b*][2,4]benzodiazepines (IV) with H, OH, or MeO substituents on the 3-Ph group caused >50% inhibition of ADP-induced platelet aggregation *in vitro* at concentrations of 10^{-5} to 5×10^{-5} *M*. 5,10-Dihydro-3-(*o*-methoxyphenyl)thiazolo[3,2-*b*][2,4]benzodiazepine (**7**) also inhibited ADP-induced platelet aggregation in plasma from rabbits given single iv doses ranging from 1.5 to 6 mg/kg. Several 3-(hydroxy and methoxyphenyl)-5,10-dihydrothiazolo[3,2-*b*][2,4]benzodiazepines (**4**, **7**, **11**) caused a significant increase in either primary or secondary bleeding time from a micropuncture wound in the mouse mesentery 4 hr after a single oral 50 mg/kg dose.

There is strong evidence that platelet aggregation is a fundamental event in the formation of hemostatic plugs and thrombi.[1-7] Moreover, aggregation of blood platelets occurs in association with a variety of clinical disorders and experimental conditions where there is vascular injury.[5] These include thrombosis, atherosclerosis, thrombotic thrombocytopenic purpura, the Arthus reaction, the Shwartzman reaction, and renal transplants. There is also good evidence that adenosine diphosphate (ADP) is the principal factor that causes platelets to adhere to each other, although the mechanism by which ADP induces platelets to aggregate is not yet clear.[3-8] This nucleotide's key role in platelet function stimulated the search for inhibitors of ADP-induced platelet aggregation in the hope that such agents might prove to be useful in the prevention and management of thrombosis and embolism.[1-7] Known inhibitors include compounds structurally related to ADP such as adenosine, adenosine monophosphate (AMP), 2-chloroadenosine, and 5'-adamantoyl adenosine;[3,9-12] prostaglandin E_1;[13] antihistaminics;[10,11,14] antimalarials;[14] tricyclic antidepressants;[15] dipyridamole and related pyrimidopyrimidines;[16,17] antiinflammatory and fibrinolytic agents;[11,18] *p*-toluenesulfonyl-L-arginine Me ester (TAME) and related amino acid derivatives;[19,20] guanidine derivatives;[21] SH inhibitors;[22] and glyceryl guaiacolate.[23]

In recent communications from these laboratories the synthesis of an array of 5,10-dihydro- and 2,3,5,10-tetrahydrothiazolo[3,2-*b*][2,4]benzodiazepines (I, R_1, R_2 = H, alkyl, OH, CO_2Et)[24] and 5,6-dihydro-6-methylthiazolo[2,3-*b*][1,3]benzodiazepines (II, R_1, R_2 = H, alkyl, Ph, OH, CO_2Et) was reported.[25] However, each of these substances lacked appreciable biological activity when tested in a variety of test systems. Moreover, none of them, including 5,6-dihydro-6-methyl-3-phenylthiazolo[2,3-*b*][1,3]benzodiazepine (II,

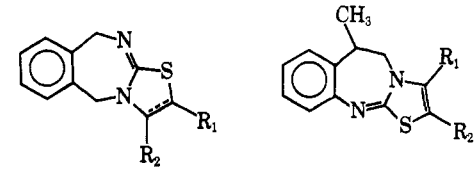

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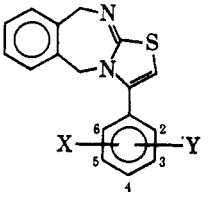
TABLE I

5,10-DIHYDRO-3-PHENYLTHIAZOLO[3,2-*b*][2,4]BENZODIAZEPINES[a]



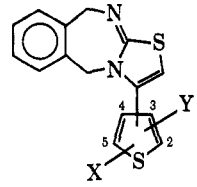
No.	X, Y	Mp, °C	Yield purified, %	Purifcn solvent	Formula	Inhibition of platelet aggregation *in vitro* Molar concn[b] × 10^{-5}	% inhibition[c]
1	4-Br	257–260	74	MeOH	$C_{17}H_{13}BrN_2S \cdot HBr$	50	19
2	4-Cl	250–251	68	*i*-PrOH	$C_{17}H_{13}ClN_2S \cdot HBr$	50	11
3	4-NO_2	282–285	63	EtOH–H_2O	$C_{17}H_{13}N_3O_2S \cdot HBr$	<50	0
4	2-OH	273	60	MeCN	$C_{17}H_{14}N_2OS \cdot HBr$	10	93
						5	73
						1	53
5	3,4-$(OH)_2$	258–259	29	$CH_3O(CH_2)_2OH$	$C_{17}H_{14}N_2O_2S \cdot HCl$	5	60, 42
						1	49, 0
6	H	256–257	90	MeCN	$C_{17}H_{14}N_2S \cdot HBr$	10	81
						1	79, 57
7	2-OCH_3	243	55	C_6H_6	$C_{18}H_{16}N_2OS \cdot HBr$	5	100, 80, 73
						1	44, 43, 39
8	3-OCH_3	252–254	71	H_2O	$C_{18}H_{16}N_2OS \cdot HBr$	10	69
						5	54
						1	59
9	4-OCH_3	244	78	H_2O	$C_{18}H_{16}N_2OS \cdot HBr$	5	32
10	4-$NHCOCH_3$	262–263 dec	68	EtOH	$C_{19}H_{17}N_3OS \cdot HCl$	5	22
						1	0
11	2,5-$(OCH_3)_2$	248	63	H_2O	$C_{19}H_{18}N_2O_2S \cdot HBr$	50	91
						10	56, 54
						5	64
						1	13
12	2,4-$(CH_3)_2$	259–260	76	*i*-PrOH	$C_{19}H_{18}N_2S \cdot HCl$	50	85
						10	31
						1	2
13	4-$O(CH_2)_3N(CH_3)_2$	263–264	80	EtOH	$C_{22}H_{25}N_3OS \cdot 2HBr$[d]	1	13
14	4-C_6H_5	217–220	53	EtOH	$C_{23}H_{18}N_2S \cdot HBr \cdot 0.8H_2O$[e]	<50	0
15	4-$O(CH_2)_3N$⟨⟩	255 dec	55	EtOH	$C_{24}H_{27}N_3OS \cdot 2HBr \cdot 0.33H_2O$[f]	5	48
						1	22
	Methapyrilene·HCl					100	42
						50	25
						10	17
	Adenosine					10	61
						1	25
	N^2-(*p*-Tolylsulfonyl)-L-arginine ethyl ester·HCl; TAME·HCl					500	80
						50	53

[a] Compounds analyzed for C, H, N. [b] Concns given as less than (<) indicate insol compounds. These were tested as filtrates of suspensions of the indicated concns. [c] Each entry is an average of 2 values obtained in separate platelet preparations. [d] S: calcd, 5.92; found, 5.80. [e] H_2O: calcd, 3.20; found, 3.29. [f] H_2O: calcd, 1.04; found, 1.14.

R_1 = H; R_2 = C_6H_5) and 5,6-dihydro-2-(*o*-methoxyphenyl)-6-methylthiazolo[2,3-*b*][1,3]benzodiazepine (II, R_1 = H; R_2 = *o*-$OCH_3C_6H_4$), displayed significant effects on the inhibition of ADP-induced platelet aggregation *in vitro*.[24,25] We now wish to report the preparation of a novel group of 5, 10-dihydro-3-(phenyl, thienyl, and furyl)thiazolo[3,2-*b*][2,4]-benzodiazepines that are effective inhibitors of ADP-induced platelet aggregation and represent a new class of antithrombotic agents.

Chemistry.—The condensation of 1,2,4,5-tetrahydro-3*H*-2,4-benzodiazepine-3-thione (III)[24] with an appropriately substituted 2-haloacetophenone or bromomethyl thienyl ketone in 2-methoxyethanol gave the corresponding 5,10-dihydro-3-phenylthiazolo[3,2-*b*]-[2,4]benzodiazepines (IV) (**1–15**, Table I) and 5,-10-dihydro-3-thienylthiazolo[3,2-*b*][2,4]benzodiazepines (V) (**16–20**, Table II) in 29–90% yield (procedures I–III). 3-(2-Furyl)-5,10-dihydrothiazolo[3,2-*b*]-[2,4]benzodiazepine (VI) (39%), 5,10-dihydro-3-(2-naphthyl)thiazolo[3,2-*b*][2,4]benzodiazepine (VII) (67%), and 5,10-dihydro-2-methyl-3-phenylthiazolo-[3,2-*b*][2,4]benzodiazepine (VIII) (61%) were prepared in a similar manner from 1,2,4,5-tetrahydro-3*H*-benzo[2,4]diazepine-3-thione (III) and bromomethyl 2-furyl ketone, 2-bromo-2′-acetonaphthone, and 1-bromo-1-phenyl-2-propanone, respectively. Benzylation of 1,2,4,5-tetrahydro-3*H*-benzo[2,4]diazepine-3-thione (III) with α-chlorotoluene, *o*,α-dichlorotoluene, and 2-(chloromethyl)-1,4-dimethylbenzene in 2-methoxyeth-

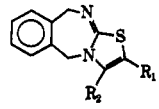
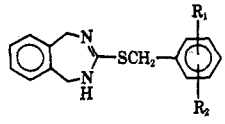
TABLE II
5,10-DIHYDRO-3-THIENYLTHIAZOLO[3,2-*b*][2,4]BENZODIAZEPINES[a]



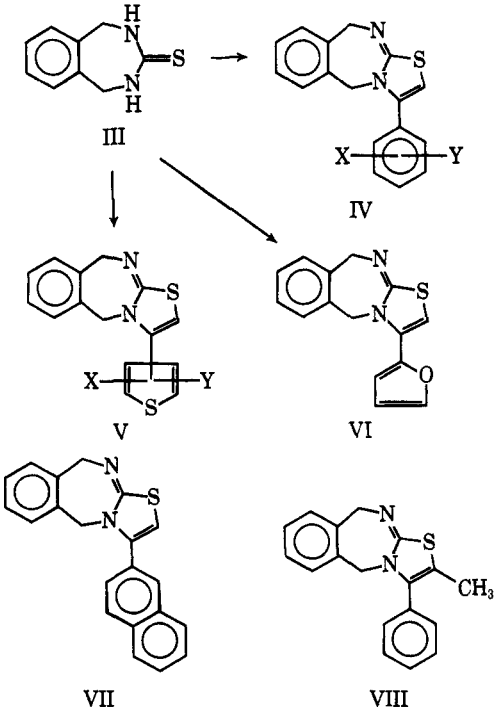
No.	Position of thiophene attachment	X, Y	Mp, °C	Yield purified, %	Purifcn solvent	Formula	Inhibition of platelet aggregation *in vitro* Molar concn[b] × 10^{-5}	% inhibition[c]
16	3	2,5-Cl_2	249–252	55	EtOAc–MeOH	$C_{15}H_{10}Cl_2N_2S_2 \cdot HBr$	5	41, 0
							1	38, 0
17	2	5-Br	253–255 dec	38	MeOH	$C_{15}H_{11}BrN_2S_2 \cdot HBr$	<10	0
18	2	5-Cl	248–249 dec	48	$CH_3O(CH_2)_2OH$	$C_{15}H_{11}ClN_2S_2 \cdot HBr$	<10	0
19	2	H	232–233	52	EtOH–Et_2O	$C_{15}H_{12}N_2S_2 \cdot HBr$	<50	68
							10	73
							1	20
20	2	5-CH_3	223–226	49	EtOH	$C_{16}H_{14}N_2S_2 \cdot HBr$	<10	0

[a–c] See footnotes *a–c*, Table I.

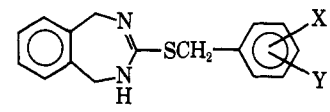
TABLE III
INHIBITION OF PLATELET AGGREGATION BY OTHER 5,6-DIHYDRO-3-SUBSTITUTED-THIAZOLO[3,2-*b*][2,4]BENZODIAZEPINES AND 3-(BENZYLTHIO)-2,5-DIHYDRO-1*H*-2,4-BENZODIAZEPINES

No.	Structure	R_1	R_2	Inhibition of platelet aggregation *in vitro* Molar concn[a] × 10^{-5}	% inhibition[b]
VI		H	2-Furyl	5	62, 29
				1	46, 22
VII		H	2-Naphthyl	<50	18
VIII		CH_3	Phenyl	10	34
IXb		2-Cl	H	<50	27
IXa		H	H	1	47
IXc		2-CH_3	5-CH_3	1	0

[a,b] See footnotes *b* and *c*, Table I.



anol afforded the "open chain" analogs 3-(benzylthio)-2,5-dihydro-1*H*-2,4-benzodiazepine (IXa) (70%), 3-[(*o*-chlorobenzyl)thio]-2,5-dihydro-1*H*-2,4-benzodiazepine (IXb) (61%), and 3-[(2,5-dimethylbenzyl)-thio]-2,5-dihydro-1*H*-2,4-benzodiazepine (IXc) (62%), respectively.



IXa, X = H; Y = H
b, X = 2-Cl; Y = H
c, X = 2-CH_3; Y = 5-CH_3

Biology.—The 5,10-dihydro-3-substituted-thiazolo-[3,2-*b*][2,4]benzodiazepines (IV–VIII) (Tables I–III) and 3-(benzylthio)-2,5-dihydro-1*H*-2,4-benzodiazepines (IXa–c) (Table III) were tested as inhibitors of ADP-induced platelet aggregation *in vitro* utilizing a modification of the method of Born and Cross.[3] In principle, when ADP is added to platelet-rich plasma (PRP) and the PRP is gently agitated, the individual platelets aggregate, or stick together, to form clumps. Each clump contains a large number of platelets. The con-

sequent decrease in the number of particles in suspension causes a decrease in the optical density of the PRP. Compounds that inhibit platelet aggregation minimize or prevent this decrease in the optical density. Colorimetric measurements afford a quantitative measure of the amount of aggregation of the platelets.

Among the 5,10-dihydro-3-phenylthiazolo[3,2-*b*][2,-4]benzodiazepines (IV) (Table I), 6 compounds (**4**–**8**, **11**) caused >50% inhibition at concentrations of 10^{-5} to 5×10^{-5} *M*. Each of these substances contained H, OH, or MeO substituents on the benzene ring. The introduction of halogen (**1**, **2**), acetamido (**10**), Me (**12**), or dialkylaminoalkoxy (**13**, **15**) substituents on the benzene ring at position 3 abolished or reduced activity (Table I), as did the insertion of a Me group (VIII) at position 2 adjacent to the benzene ring (Table III). 5,10-Dihydro-3-(2-thienyl and 2-furyl)thiazolo[3,2-*b*]-[2,4]benzodiazepine (**19**, Table II, and VI, Table III) and 2-(benzylthio)-2,5-dihydro-1*H*-2,4-benzodiazepine (IXa) produced 47–73% inhibition at concentrations ranging from 10^{-5} to 10^{-4} *M* (Tables II, III).

5,10-Dihydro-3-(*o*-methoxyphenyl)thiazolo[3,2-*b*]-[2,4]benzodiazepine·HBr (**7**) also inhibited platelet aggregation in PRP taken from rabbits that had been given a single iv dose of the drug 30–60 min prior to blood sampling. In this apparent *in vitro–in vivo* study, drug doses of 1.5–6.0 mg/kg caused variable inhibition of platelet aggregation ranging from 28 to 62% and 0 to 62% at posttreatment periods of 30 and 60 min, respectively (Table IV).

TABLE IV

INHIBITION OF PLATELET AGGREGATION IN PLASMA FROM RABBITS DOSED WITH 5,10-DIHYDRO-3-(*o*-METHOXYPHENYL)THIAZOLO[3,2-*b*][2,4]-BENZODIAZEPINE·HBr

Single dose (mg of base/kg) iv	% inhibition of platelet aggregation at posttreatment periods[a] 30 min	60 min
6.0	44	0
	28	21
3.0	52	62
	39	52
1.5	30	22
	62	18
	41	47

[a] Each entry was obtained utilizing separate platelet preparations.

Increases in bleeding time are observed with drugs that interfere with platelet function and/or the coagulation mechanism. In a recent report Herrmann, *et al.*,[11] described a new technique for studying platelet aggregation which depends on the formation of a hemostatic platelet plug following a micropuncture wound in a small vein of the mouse mesentery. The effects of *o*-(5,10-dihydrothiazolo[3,2-*b*][2,4]benzodiazepin-3-yl)-phenol·HBr (**4**), 5,10-dihydro-3-(*o*-methoxyphenyl)thiazolo[3,2-*b*][2,4]benzodiazepine·HBr (**7**), and 3-(2,5-dimethoxyphenyl)-5,10-dihydrothiazolo[3,2-*b*][2,4]-benzodiazepine·HBr (**11**) on mouse mesentery puncture bleeding time were studied utilizing a modification of the above technique. An increase in both the primary and secondary bleeding time was observed 4 hr after a single oral 50 mg/kg dose of each substance. The effects of **4** on primary bleeding and of **7** and **11** on secondary bleeding were statistically significant ($P < 0.05$) (Table V).

Experimental Section[26,27]

Inhibition of Platelet Aggregation *in Vitro*.—Female New Zealand white rabbits were anesthetized with Na pentobarbital, and blood was collected from the carotid artery through a plastic cannula into 0.1 vol of 3.8% Na citrate, pH 7.0. Throughout the test, platelets were handled in either plastic or silicon-coated glass apparatus. Platelet-rich plasma (PRP) obtained by centrifugation was adjusted to pH 6.5 and stored for periods up to 45 min. Just before use the PRP was adjusted to pH 7.0.

Aliquots of 1.3 ml of PRP were added to 3 tubes contg 0.6 ml of incubation mixt, pH 7.0, contg 0.1 *M* $(HOCH_2)_3CNH_2$, 0.07 *M* NaCl, and 0.0003 *M* $CaCl_2$. A set of tubes containing the benzodiazepine dissolved in the incubation mixt was prepared for each concn of benzodiazepine tested.

The optical density of the tubes was read in a photoelectric colorimeter. A 0.1-ml aliquot of saline was added to 1 tube in each set and 0.1 ml of a soln of 20 μg/ml of ADP in saline, pH 6.5, was added to the other 2 tubes. The tubes were shaken on a rotating table for 8 min at 23 ± 2° and the optical density was read again.

The decrease in optical density produced by the ADP compared to saline was taken as a measure of the aggregating effect of ADP. The inhibition of aggregation caused by the benzodiazepine was calcd by comparison of the effects of ADP in the 2 sets of tubes. Thus, if the decrease of optical density caused by ADP in the set of tubes contg the benzodiazepine was 20% of the decrease in the set of control tubes, the test compd was considered to have caused an 80% inhibition of aggregation.

Inhibition of Platelet Aggregation in Plasma from Rabbits.—Female rabbits (New Zealand strain) weighing 3–6 kg were fed a diet of pellets and H_2O *ad lib*. The animals were anesthetized with Na pentobarbital (20 mg/kg iv) and Et_2O. Supplemental pentobarbital was administered when necessary to maintain light surgical anesthesia. Using polyethylene tubing, a jugular vein and a carotid artery were cannulated for drug administration and blood sampling, respectively. The drug was added to saline and injected in a vol of 20 ml during a 5-min period. Blood samples (9 ml of whole blood, 1 ml of 3.14% Na citrate, pH 7.2) were drawn prior to treatment and at 30- and 60-min intervals posttreatment. Each animal was dosed only once and was sacrificed at the termination of the test.

Platelet-rich plasma (PRP) was prepared as described above. An 0.35-ml aliquot of PRP was added to a tube contg 0.1 ml of 0.055 *M* $(HOCH_2)_3CNH_2$ in 0.1 *M* NaCl, pH 7.0. The mixt was stirred at 33° and 1000 rpm in a Bryston platelet aggregometer with continuous recording of the optical density. An aliquot of 0.05 ml of a soln of 2.5 μg/ml of ADP in saline was added and the decrease in optical density measured. The effect of the benzodiazepine on platelet aggregation by ADP was detd by comparing the values obtained with the pre- and posttreatment samples of PRP.

Mouse Mesentery Puncture Bleeding Time.—Groups of 9–18 fasted mice were anesthetized with Na amobarbital and were given a single oral dose of 5% acacia or the test drug in 5% acacia. Four hours posttreatment, a puncture 50 μ in diameter was made in a mesenteric vein 300–400 μ in diameter utilizing the technique of Herrmann, *et al.*[11] Primary bleeding time was defined as the number of seconds continuous bleeding was observed during a 5-min period following the puncture. Secondary bleeding was defined as the total number of seconds that bleeding occurred in the period after the termination of primary bleeding. To minimize uncontrolled variables, treated and control mice were alternated such that each test on a treated animal was followed immediately by a test on a control animal. In those instances where primary bleeding lasted throughout the 5-min period, the animal was excluded from consideration with regard to secondary bleeding.

5,10-Dihydro-3-(phenyl and thienyl)thiazolo[3,2-*b*][2,4]-benzodiazepines (1–20, Tables I, II). Procedure I.—To a soln

(26) Melting points (corrected) were taken on a Thomas-Hoover capillary melting point apparatus.

(27) Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

TABLE V

EFFECTS OF 3-(HYDROXY AND METHOXYPHENYL)-5,10-DIHYDROTHIAZOLO[3,2-*b*][2,4]BENZODIAZEPINES ON MOUSE MESENTERY BLEEDING TIME

No.	Single oral dose, acacia or drug, mg of base/kg	Primary bleeding: No. of mice tested	Primary bleeding: Average bleeding time, sec	Primary bleeding: Significance, P^a	Secondary bleeding: No. of mice tested	Secondary bleeding: Average bleeding time, sec	Secondary bleeding: No. of mice with secondary bleeding	Secondary bleeding: Significance, P^a
4	Acacia	13	52		12	5	2	
	50	15	94	<0.05	12	28	7	>0.05
4	Acacia	10	78		9	10	2	
	25	10	165	>0.05	6	27	3	>0.05
4	Acacia	10	75		9	10	1	
	12.5	9	129	>0.05	7	16	1	>0.05
7	Acacia	18	66		16	15	6	
	50	17	77	>0.05	15	66	10	<0.05
11	Acacia	13	69		11	18	3	
	50	14	79	>0.05	13	62	8	<0.05

[a] Mann–Whitney U test.

of 10.0 g (0.056 mole) of 1,2,4,5-tetrahydro-3*H*-benzo[2,4]-diazepine-3-thione (III)[24] in 1 l. of boiling 2-methoxyethanol was added portionwise a soln of 12.4 g (0.062 mole) of 2-bromoacetophenone in 100 ml of 2-methoxyethanol over 5 min. The mixt was heated under reflux for 2.5 hr, and the solvent was removed *in vacuo*. The residue was triturated with EtOH and recrystd from MeCN to give 18.1 g (90%) of 5,10-dihydro-3-phenylthiazolo[3,2-*b*][2,4]benzodiazepine·HBr (**6**) as off-white crystals, mp 256–257°.

Procedure II.—Br_2 (10.2 g, 0.05 mole) in 50 ml of Et_2O was added dropwise over 10 min to a soln of 6.3 g (0.05 mole) of methyl 2-thienyl ketone in 50 ml of Et_2O. Decolorization was rapid, and the reaction was slightly exothermic. The mixt was stirred at room temp for 0.5 hr and volatile materials were removed *in vacuo*. The crude bromomethyl 2-thienyl ketone was dissolved in 100 ml of 2-methoxyethanol, and the soln was added portionwise to a soln of 7.1 g (0.04 mole) of 1,2,4,5-tetrahydro-3*H*-benzo[2,4]diazepine-3-thione (III)[24] in 700 ml of 2-methoxyethanol. The mixt was boiled under reflux for 1.5 hr, and the solvent was removed *in vacuo*. The residue was dissolved in EtOH (decolorizing charcoal), dild with Et_2O, and chilled. The product was collected by filtration and dried *in vacuo* at 70° for 18 hr. The 5,10-dihydro-3-(2-thienyl)thiazolo-[3,2-*b*][2,4]benzodiazepine·HBr (**19**) (7.6 g, 52%) was obtd as beige crystals, mp 232–233°.

Procedure III.—2′-Hydroxyacetophenone benzoate ester (4.8 g, 0.02 mole) was brominated according to procedure II, a soln of the crude 2-bromo-2′-hydroxyacetophenone benzoate ester in 2-methoxyethanol was added to 3.7 g (0.02 mole) of 1,2,4,5-tetrahydro-3*H*-benzo[2,4]diazepine (III)[24] in 400 ml of 2-methoxyethanol, and the mixt was heated under reflux for 2 hr. The reaction mixt was treated with decolorizing charcoal, the solvent was removed *in vacuo*, and the residue was dissolved in boiling MeCN. A precipitate appeared as heating was continued. The mixt was chilled and the product was collected by filtration. The *o*-(5,10-dihydrothiazolo[3,2-*b*][2,4]benzodiazepin-3-yl)phenol·HBr (**4**) (4.5 g, 60%) was isolated as off-white crystals, mp 273°.

3-(2-Furyl)-5,10-dihydrothiazolo[3,2-*b*][2,4]benzodiazepine·HBr (VI).—2-Furyl methyl ketone (2.2 g, 0.02 mole) was brominated and condensed with 3.7 g (0.02 mole) of 1,2,4,5-tetrahydro-3*H*-benzo[2,4]diazepine-3-thione (III)[24] according to procedure II. The HBr salt of the product was obtained as beige crystals from MeOH–EtOAc (decolorizing charcoal), mp 207–209°, yield 2.7 g (39%). *Anal.* ($C_{15}H_{12}N_2OS$·HBr) C, H, N.

5,10-Dihydro-3-(2-naphthyl)thiazolo[3,2-*b*][2,4]benzodiazepine·HBr (VII).—2-Bromo-2′-acetonaphthone (3.0 g, 0.017 mole) and 1,2,4,5-tetrahydro-3*H*-benzo[2,4]diazepine-3-thione (III)[24] (4.2 g, 0.017 mole) were heated under reflux in 250 ml of 2-methoxyethanol for 1.5 hr, and the reaction mixt was worked up according to procedure I. The product (4.7 g, 67%) was isolated as off-white crystals from EtOH–Et_2O, mp 230–232°. *Anal.* ($C_{21}H_{16}N_2S$·HBr) C, H, N.

5,10-Dihydro-2-methyl-3-phenylthiazolo[3,2-*b*][2,4]benzodiazepine·HBr (VIII).—Utilizing procedure I, 4.3 g (0.02 mole) of 1-bromo-1-phenyl-2-propanone and 3.7 g (0.02 mole) of 1,2,4,5-tetrahydro-3*H*-benzo[2,4]diazepine-3-thione (III)[24] were condensed in 2-methoxyethanol to give 4.6 g (61%) of product as beige crystals from *i*-PrOH, mp 229–230°. *Anal.* ($C_{18}H_{16}N_2S$·HBr) C, H, N.

3-(Benzylthio)-2,5-dihydro-1*H*-2,4-benzodiazepine·HCl (IXa).—1,2,4,5-Tetrahydro-3*H*-benzo[2,4]diazepine-3-thione (III)[24] (10.0 g, 0.056 mole) was dissolved in 1 l. of boiling 2-methoxyethanol, and to it was added a soln of 8.5 g (0.067 mole) of α-chlorotoluene in 150 ml of 2-methoxyethanol over 15 min. The mixt was heated under reflux for 3 hr and volatile materials were removed *in vacuo*. The residue was triturated with Et_2O and allowed to stand at room temp under Et_2O for 72 hr. The crude product was collected by filtration and recrystd from *i*-PrOH–Et_2O to give 12.0 g (70%) of product as off-white crystals, mp 162–164°. *Anal.* ($C_{16}H_{18}N_2S$·HCl) C, H, Cl, N.

3-[(*o*-Chlorobenzyl)thio]-2,5-dihydro-1*H*-2,4-benzodiazepine·HCl (IXb).—*o*,α-Dichlorotoluene (3.5 g, 0.022 mole) and 1,2,4,5-tetrahydro-3*H*-benzo[2,4]diazepine-3-thione (III)[24] (3.7 g, 0.02 mole) were condensed in 250 ml of 2-methoxyethanol according to the procedure for IXa to give 4.1 g (61%) of product as beige crystals from *i*-PrOH, mp 209–211°. *Anal.* ($C_{16}H_{15}ClNS$·HCl) C, H, N.

3-[(2,5-Dimethylbenzyl)thio]-2,5-dihydro-1*H*-2,4-benzodiazepine·HCl (IXc).—Utilizing the procedure for IXa the reaction of 1,2,4,5-tetrahydro-3*H*-benzo[2,4]diazepine-3-thione (III)[24] (3.7 g, 0.02 mole) with 2-(chloromethyl)-*p*-xylene (3.1 g, 0.02 mole) in 2-methoxyethanol afforded 4.1 g (62%) of product as colorless crystals from *i*-PrOH, mp 216–218°. *Anal.* ($C_{18}H_{20}N_2S$·HCl) C, H, N.

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