Chem., 38, 2363 (1960); (c) E. L. Stogryn, J. Med. Chem., 12, 185 (1969).
(14) T. S. Osdene, P. B. Russell, and L. Rane, J. Med. Chem., 10, 431 (1967).
(15) M. E. King, A. M. Shefner, and M. D. Schneider, Proc. Helminthol. Soc. Wash., 39, 288 (1972).
(16) L. Rane and D. S. Rane, Proc. Helminthol. Soc. Wash., 39, 283 (1972).
(17) (a) W. Peters, "Chemotherapy and Drug Resistance in Malaria," Academic Press, New York, N. Y., 1970, p 106; (b) L. H. Schmidt, Trans. Roy. Soc. Trop. Med. Hyg., 67, 446 (1973).
(18) A. Muller and P. Kraus, Monatsh. Chem., 61, 219 (1932).
(19) H. B. Donahoe, R. J. Seiwald, Sr. M. M. C. Neumann, and K. K. Kimura, J. Org. Chem., 22, 68 (1957).
(20) (a) J. Cason and D. J. McLeod, J. Org. Chem., 23, 1497 (1958); (b) S. Swann, Jr., R. Oehler, and R. J. Buswell, "Organic Syntheses," Collect. Vol. II, A. H. Blatt, Ed., Wiley, New York, N. Y., 1943, p 276.
(21) N. L. Drake, J. V. Hook, J. A. Garman, R. Hayes, R. Johnson, G. W. Kelley, S. Melamed, and R. M. Peck, J. Amer. Chem. Soc., 68, 1529 (1946).
(22) E. B. Hartshorn and S. L. Baird, Jr., J. Amer. Chem. Soc., 68, 1562 (1946).

Synthesis and Pharmacological Evaluation of 2,3-Dihydro-1*H*-thieno[2,3-*e*][1,4]diazepines

Francis J. Tinney,* Joseph P. Sanchez, and Joan A. Nogas

Chemistry Department, Research and Development Division, Parke, Davis and Company, Ann Arbor, Michigan 48106.
Received August 7, 1973

A series of 2,3-dihydro-1*H*-thieno[2,3-*e*][1,4]diazepines was synthesized and evaluated for CNS activity. A new antianxiety screen for benzodiazepine-like drugs was used along with the standard anticonvulsant test. Structure-activity relationships were discussed. One compound, 1,3,6,7,8,9-hexahydro-5-phenyl-2*H*-[1]benzothieno[2,3-*e*][1,4]diazepin-2-one monosulfate (CI-718), is undergoing clinical studies in man.

During the past decade members of the 1,4-benzodiazepine class of compounds have generated considerable interest in the CNS field as psychotherapeutic agents.[1,2] Our laboratories' interest has been mainly centered on the fusion of heterocyclic rings to the seven-member diazepine ring system thus resulting in novel hetero 1,4-diazepines.

Scheme I

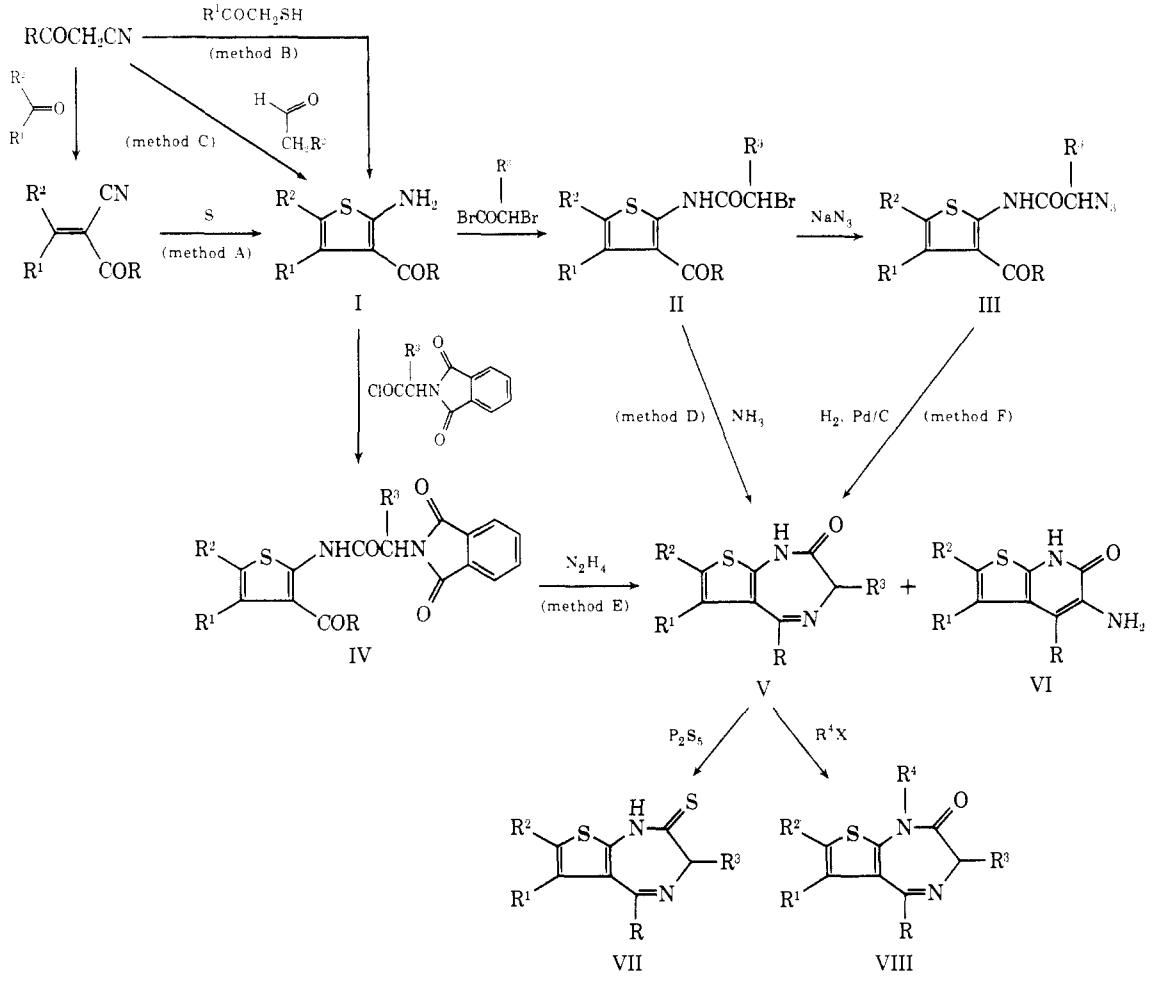
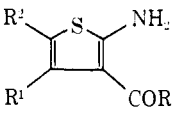


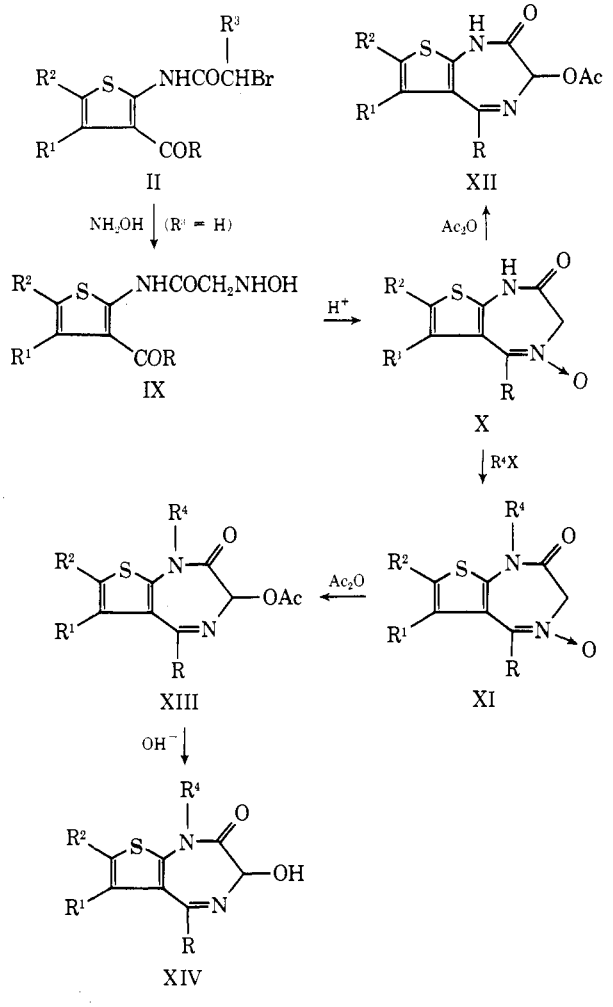
Table I. 2-Aminothiophenes (I)



No.	R^1	R^2	R	Method	Mp, °C	Yield, %	Crystn solvent[a]	Formula[b]
1	$-(CH_2)_4-$		C_6H_4-2-F	A	176–179	47.5	T–P	$C_{15}H_{14}FNOS$
2	$-(CH_2)_4-$		C_6H_4-2-Cl	A	155–157	37	M–W	$C_{15}H_{14}ClNOS$
3	$-(CH_2)_4-$		C_6H_4-2-CH_3	A	149–151	81	E	$C_{16}H_{17}NOS$
4	$-(CH_2)_4-$		C_6H_4-3-Cl	A	108–110	46	M–W	$C_{15}H_{14}ClNOS$
5	$-(CH_2)_4-$		C_6H_4-3-OCH_3	A	122–124	64	A	$C_{16}H_{17}NO_2S$
6	$-(CH_2)_4-$		C_6H_4-4-OCH_3	A	180–184	90.5	E–W	$C_{16}H_{17}NO_2S$
7	$-(CH_2)_4-$		2-Naphthyl	A	c			
8	$-(CH_2)_4-$		2-Thienyl	A	131–133	76	E–W	$C_{13}H_{13}NOS_2$
9	$-(CH_2)_4-$		2-Furyl	A	122–124	77	T	$C_{13}H_{13}NO_2S$
10	$-(CH_2)_4-$		C_6H_{11}	A	150–152	95	T	$C_{15}H_{21}NOS$
11	$-CH_2CH_2N(CO_2C_2H_5)CH_2-$		C_6H_5	A	160–161.5	72	M–W	$C_{17}H_{18}N_2O_3S$
12	$-CH_2CH_2N(COC_6H_5)CH_2-$		C_6H_5	A	244–247	53	A	$C_{21}H_{18}N_2O_2S$
13	$-CH_2CH_2SCH_2-$		C_6H_5	A	123–124.5	56	E	$C_{14}H_{13}NOS_2$
14	$-(CH_2)_6-$		C_6H_5	A	c			
15	H	H	C_6H_5	B	151–152	27	M	$C_{11}H_9NOS$
16	CH_3	H	2-Thienyl	B	121–123	48	M	$C_{10}H_9NOS_2$
17	H	CH_3	C_6H_5	C	c			
18	C_2H_5	CH_3	C_6H_5	A	127.5–129	65	E	$C_{14}H_{15}NOS$
19	C_3H_7	C_2H_5	C_6H_5	A	133–134.5	79	E	$C_{16}H_{19}NOS$
20	H	C_6H_5	C_6H_5	C	169–171	86	E	$C_{17}H_{13}NOS$
21	C_6H_5	H	C_6H_5	A	154–156	37	E	$C_{17}H_{13}NOS$

[a]A, MeCN; E, EtOH; M, MeOH; P, petroleum ether; T, toluene; W, water. [b]Satisfactory analyses for C, H, and N were obtained. [c]Not isolated and used crude in next step.

Scheme II



At the outset of our investigations in 1967, pyrido[1,4]diazepines had been described by Littel and Allen.[3] Subsequently the synthesis of 5-phenyl-1,3-dihydro-2*H*-thieno[2,3-*e*][1,4]diazepin-2-ones was published by Nakanishi, *et al.*,[4] following an earlier report[5] from our laboratory in this area. We now present our synthesis and pharmacological results with the 2,3-dihydro-1*H*-thieno[2,3-*e*][1,4]diazepines. This work has resulted in the development of 1,3,6,7,8,9-hexahydro-5-phenyl-2*H*-[1]benzothieno[2,3-*e*][1,4]diazepin-2-one monosulfate (CI-718, 63) which is presently undergoing clinical studies in man. Other work in our laboratories has resulted in the synthesis of pyrazolo[1,4]diazepines.[6-10]

Chemistry. Thienodiazepines were prepared according to the routes shown in Schemes I and II using a variety of procedures.[2]

The starting 2-aminothiophenes (I, Table I) were readily obtained by methods analogous to those described by Gewald, *et al.*[11] (methods A–C). Bromoacetamide intermediates (II, Table II) were converted in methanolic ammonia to aminoacetamides which readily cyclized *in situ* to 1,3-dihydro-2*H*-thieno[2,3-*e*][1,4]diazepin-2-ones (V, method D). Bromoacetamides (II) were prepared by acylation of I with bromoacetyl bromide. The 2-phthalimido intermediates (IV, Table III) were hydrazinolyzed with anhydrous hydrazine to aminoacetamides which readily cyclized *in situ* to V (method E). Phthalimido derivatives IV were prepared by acylation of I with phthalimidoacetyl chloride.

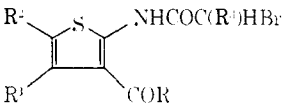
The azidoacetamide intermediates (III, Table III) were hydrogenated in the presence of Pd/C to give V (method F). The azidoacetamides III were prepared by reaction of II with NaN_3 in DMSO.

In the preparation of V, an occasional isolated by-product, aminothieno[2,3-*b*]pyridinone (VI), occurred in several instances.† A similar six-member ring formation was observed with benzodiazepine compounds.[2]

Compounds V could be converted in the presence of P_2S_5 and pyridine to the thiones VII. Compounds V were

†The structure for this type of compound was supported by spectral and analytical data.

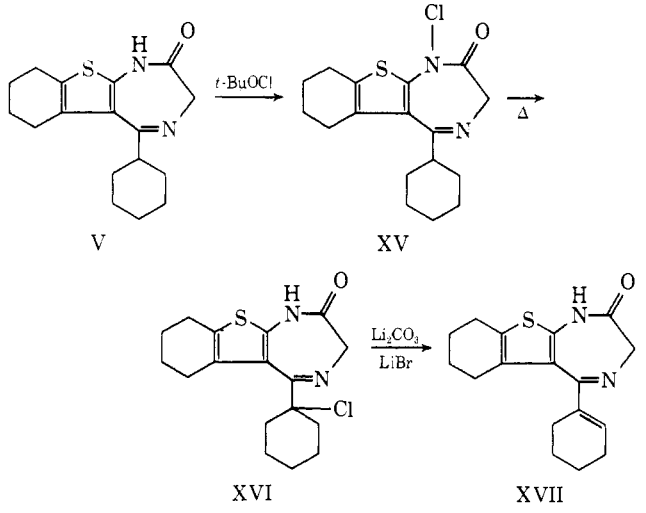
Table II. 2-(2-Bromoacetamido)thiophenes (II)



No.	R^1	R^2	R	R^3	Mp, °C	Yield, %	Crystn solvent[a]	Formula[b]
22	$-(CH_2)_3-$		C_6H_5	H	112–114	93	M	$C_{16}H_{14}BrNO_2S$
23	$-(CH_2)_4-$		C_6H_5	H	109–111	88	M	$C_{17}H_{16}BrNO_2S$
24	$-(CH_2)_4-$		C_6H_4-2-F	H	133–136	71	T–P	$C_{17}H_{15}BrFNO_2S$
25	$-(CH_2)_4-$		C_6H_4-2-Cl	H	162–164	82	M	$C_{17}H_{15}BrClNO_2S$
26	$-(CH_2)_4-$		C_6H_4-2-CH_3	H	131–134	67	A	$C_{18}H_{18}BrNO_2S$
27	$-(CH_2)_4-$		C_6H_4-2-OCH_3	H	218.5–220	67	A	$C_{18}H_{18}BrNO_3S$
28	$-(CH_2)_4-$		C_6H_4-3-Cl	H	148–150	47	T	$C_{17}H_{15}BrClNO_2S$
29	$-(CH_2)_4-$		C_6H_4-3-OCH_3	H	101–103	96	T–P	$C_{18}H_{18}BrNO_3S$
30	$-(CH_2)_4-$		C_6H_4-4-Cl	H	137–140	93	A	$C_{17}H_{15}BrClNO_2S$
31	$-(CH_2)_4-$		C_6H_4-4-OCH_3	H	172–174	98	T	$C_{18}H_{18}BrNO_3S$
32	$-(CH_2)_4-$		2-Naphthyl	H	138–140	16	M	$C_{21}H_{18}BrNO_2S$
33	$-(CH_2)_4-$		2-Thienyl	H	154–155	98	T	$C_{15}H_{14}BrNO_2S_2$
34	$-(CH_2)_4-$		2-Furyl	H	125–126	97	T	$C_{15}H_{14}BrNO_3S$
35	$-(CH_2)_4-$		C_6H_{11}	H	96.5–98	95	T	$C_{17}H_{22}BrNO_2S$
36	$-CH_2CH_2N(CO_2C_2H_5)CH_2-$		C_6H_5	H	121–123	83	B–C	$C_{19}H_{19}BrN_2O_4S$
37	$-CH_2CH_2N(COC_6H_5)CH_2-$		C_6H_5	H	214–216	91	M	$C_{23}H_{19}BrN_2O_3S$
38	$-CH_2CH_2SCH_2-$		C_6H_5	H	150–157.5	88	M	$C_{16}H_{14}BrNO_2S_2$
39	$-CH_2CH_2CH(CH_3)CH_2-$		C_6H_5	H	129–132	74	M	$C_{18}H_{18}BrNO_2S$
40	$-(CH_2)_5-$		C_6H_5	H	91–93	87	M	$C_{18}H_{18}BrNO_2S$
41	$-(CH_2)_6-$		C_6H_5	H	138–140	41	M	$C_{19}H_{20}BrNO_2S$
42	$-(CH_2)_4-$		C_6H_5	CH_3	119.5–121.5	85	M	$C_{18}H_{18}BrNO_2S$
43	H	H	C_6H_5	H	141–143	62	M	$C_{13}H_{10}BrNO_2S$
44	CH_3	H	C_6H_5	H	120–122	81	M	$C_{14}H_{12}BrNO_2S$
45	CH_3	H	2-Thienyl	H	94.5–96.5	83	M	$C_{12}H_{10}BrNO_2S_2$
46	H	CH_3	C_6H_5	H	127–128	54	M	$C_{14}H_{12}BrNO_2S$
47	C_2H_5	CH_3	C_6H_5	H	115–116.5	80	M	$C_{16}H_{16}BrNO_2S$
48	C_3H_7	C_2H_5	C_6H_5	H	*c*			
49	H	C_6H_5	C_6H_5	H	152–155	96	E	$C_{19}H_{14}BrNO_2S$
50	C_6H_5	H	C_6H_5	H	107–109	77	E	$C_{19}H_{14}BrNO_2S$

[a] A, MeCN; B, PhH; C, cyclohexane; E, EtOH; M, MeOH; P, petroleum ether; T, toluene; W, water. [b] Satisfactory analyses for C, H, and N were obtained. [c] Not isolated and used crude in next step.

Scheme III



alkylated in the presence of NaH to give the corresponding 1-substituted derivatives VIII.

The 4-oxides X were obtained by acidic ring closure of 2-(hydroxyamino)acetamide derivatives IX. The 2-(hydroxyamino)acetamide intermediates IX could be obtained from II by a modification of the procedure of Bell, *et al.*,[12] used for benzodiazepine-type structures.

Compounds X underwent a Polonovski type rearrangement in Ac_2O to give the 3-acetate esters XII. Attempted conversion of XII to the 3-hydroxy derivatives was unsuccessful. Compounds X could be converted to the 1-substituted compounds XI which could then be rearranged in Ac_2O to XIII. Basic hydrolysis of XIII gave XIV (Table IV).

The synthetic route to the 5-(1-cyclohexenyl) derivative XVII is shown in Scheme III. Compound V underwent N^1 chlorination in the presence of *t*-BuOCl to give XV which was isolated but not vigorously purified. Compound XV when heated in ethyl acetate rearranged to XVI. Dehydrohalogenation of XVI with a mixture of lithium carbonate and bromide afforded XVII.

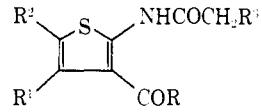
Results and Discussion

In the pharmacological screening of the thienodiazepines, we have made use of a new simple, rapid, and specific screen for benzodiazepine-like drugs developed by Poschel.[13] It is believed that this is the first screen that can differentiate benzodiazepine-like drugs from mere sedatives and anticonvulsants. The demonstration of activity for diazepam and chlordiazepoxide indicates the validity of the test procedure for determining antianxiety activity.

The anticonvulsant activity of the compound was measured in a standard test that is carried out essentially as described by Chen, *et al.*[14-16] The results of these two screening tests for the thienodiazepines, as compared to diazepam and chlordiazepoxide, are summarized in Table V.

Various modifications of the thienodiazepine ring system were made in order to study the relationship between chemical structure and biological activity. Substituents at C-7 were varied from H to Et and Ph, and at C-6 from H to *n*-Pr and Ph. The combined alkylene linkage at C-6 and C-7 was varied from three to six methylenes, and var-

Table III. 2-Azidoacetamido- and 2-Phthalimidoacetamidothiophenes (III and IV)



No.	R¹	R²	R	R³	Mp, °C	Yield, %	Crystn solvent[a]	Formula[b]
51	$-CH_2CH_2N(CO_2C_2H_5)CH_2-$		C_6H_5	N_3	[c]			
52	$-CH_2CH_2N(COC_6H_5)CH_2-$		C_6H_5	N_3	[c]			
53	$-CH_2CH_2CH(CH_3)CH_2-$		C_6H_5	N_3	163–165	89	M	$C_{18}H_{15}N_4O_2S$
54	H	C_6H_5	C_6H_5	N_3	[c]			
55	C_6H_5	H	C_6H_5	N_3	160–162	71	M	$C_{19}H_{14}N_4OS_2$
56	$-(CH_2)_3-$		C_6H_5	Phthalimido	266–268	84	EA	$C_{24}H_{18}N_2O_4S$
57	$-(CH_2)_4-$		C_6H_4-2-Cl	Phthalimido	[c]			
58	$-(CH_2)_4-$		C_6H_4-2-CH_3	Phthalimido	[c]			
59	$-(CH_2)_4-$		C_6H_4-2-OCH_3	Phthalimido	[c]			
60	H	C_6H_5	C_6H_5	Phthalimido	240–242	83	EA	$C_{27}H_{18}N_2O_4S$

[a]EA, EtOAc; M, MeOH. [b]Satisfactory analyses for C, H, and N were obtained. [c]Not isolated and used crude in next step.

ious N and S insertions in this unit were prepared. Generally, groups larger than Me at either C-6 or C-7 decreased potency, whereas a 4-carbon methylene bridge between C-6 and C-7 showed the greatest activity. The most active compounds were **62, 63, 78, 96, 98,** and **99.**

Next, the substituent at C-5 was varied to include cycloalkyl, cycloalkenyl, phenyl, substituted phenyl, naphthyl, and various heterocycles. The greatest potency was found when C-5 was either phenyl, *o*-fluorophenyl, or 2-thienyl. The most active compounds were **62–64, 73,** and **97.**

The hydrogen at N-1 was replaced with alkyl, cycloalkylmethyl, allyl, and alkylaminoalkyl. Of these substituents, the Me group had the greatest potency. The most active compounds were **84, 94,** and **104.**

The C-3 position was substituted with alkyl, acetate, and hydroxy groups. The most active compounds were **84, 94,** and **104.** The six-member ring structure VI showed marginal activity in both test procedures.

From the numerous structural changes that we have made in the thienodiazepine ring system, we feel that the most potent antianxiety agent has a 4-carbon methylene linkage between C-6 and C-7, is unsubstituted at N-1, has either a phenyl, *o*-fluorophenyl, or 2-thienyl group at C-5, and has an oxygen function at C-2.

From the group, compound **63** (CI-718) was chosen for additional studies.‡ Compared to chlordiazepoxide and diazepam, **63** was generally found to be more potent as an antianxiety agent than chlordiazepoxide but less potent than diazepam. However, at effective antianxiety doses **63** appeared to produce less sedation than either chlordiazepoxide or diazepam. At relatively high doses **63** produced marked increases in locomotor activity, unlike the two reference agents. This compound is presently undergoing clinical studies in man.

Experimental Section

Synthetic Procedures. The melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. A Beckman IR-9 spectrophotometer was used to determine the infrared spectra. The nuclear magnetic resonance spectra were obtained with a Varian A-60 spectrometer.

(I) 2-Aminothiophenes. Method A (Table I, 1–14, 18, 19, and 21). 2-Amino-3-(o-fluorobenzoyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene (1). A mixture consisting of 196 g (1.2 mol) of (o-fluorobenzoyl)acetonitrile,[5] 130 g (1.32 mol) of cyclohexanone, 10.5 g (0.12 mol) of β-alanine, 150 ml of AcOH, and 1 l. of C_6H_6 was heated under reflux under a water separator for 19 hr. After cooling, the resulting solution was washed with water (3 × 300 ml), dried (Na_2SO_4), and evaporated under reduced pressure to yield, after distillation, 207 g (71% yield) of α-(*o*-fluorobenzoyl)-$\Delta^{1,\alpha}$-cyclohexaneacetonitrile, bp 145–162° (0.35–0.9 mm). This intermediate, 207 g (0.85 mol), was suspended in 500 ml of EtOH and 27.5 g (0.85 mol) of sulfur was added. Then diethylamine, 212 ml, was added. The mixture was stirred at room temperature for 1 hr and cooled and the precipitate was collected and recrystallized from toluene–petroleum ether to yield 132 g of **1**, mp 176–179°.

Method B (Table I, 15 and 16). 2-Amino-4-methyl-3-(2-thenoyl)thiophene (16). Triethylamine (12 ml) was added to a mixture of 46 g (0.51 mol) of mercaptoacetone and 77 g (0.51 mol) of 2-thenoylacetonitrile [prepared analogously to (*o*-fluorobenzoyl)acetonitrile] in 300 ml of EtOH. The mixture was warmed to 60° for 45 min and cooled and the precipitate collected. Recrystallization from MeOH yielded 55 g of **16**, mp 121–123°.

Method C (Table I, 17 and 20). 2-Amino-5-phenyl-3-benzoylthiophene (20). To a suspension of benzoylacetonitrile, 72.5 g (0.5 mol), and sulfur, 16 g (0.5 mol), in 100 ml of DMF was added 38 ml of triethylamine followed by 60 g (0.5 mol) of phenylacetaldehyde. The solution was stirred at room temperature for 1 hr and then poured into 2 l. of water and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water (2 × 500 ml), dried (Na_2SO_4), and evaporated under reduced pressure to yield, after crystallization from EtOH, 120 g of **20**, mp 169–171°.

(II) 2-(2-Bromoacetamido)thiophenes (Table II, 22–50). 2-(2-Bromoacetamido)-3-(*o*-fluorobenzoyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene (24). Bromoacetyl bromide, 80 g (0.40 mol), was added dropwise to a stirred solution of 91 g (0.33 mol) of **1** and 26.5 g (0.33 mol) of pyridine in 1.5 l. of Et_2O. The resulting suspension was stirred at room temperature for 3 hr and then filtered. The filtrate was washed with water (2 × 250 ml) and the ethereal layer separated, dried (Na_2SO_4), and evaporated under reduced pressure to yield 92 g of **24** after crystallization from toluene–petroleum ether, mp 133–136°.

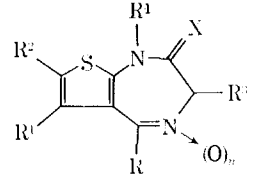
(III) 2-(2-Azidoacetamido)thiophenes (Table III, 51–55). 2-Azido-*N*-(3-benzoyl-4-phenyl-2-thienyl)acetamide (55). To a suspension of 7.3 g (0.112 mol) of NaN_3 in 50 ml of DMSO was added 32 g (0.08 mol) of **50**. The suspension was stirred at room temperature for 2 hr and then poured into 2 l. of water. The precipitate was collected and recrystallized from MeOH to yield 205 g of **55**, mp 160–162°.

(IV) 2-(2-Phthalimidoacetamido)thiophenes (Table III, 56–60). *N*-(3-Benzoyl-5-phenyl-2-thienyl)-1,3-dioxo-2-isoindolineacetamide (60). Phthalimidoacetic acid, 21 g (0.1 mol), was added to 50 g (0.42 mol) of $SOCl_2$ and the mixture heated on a steam bath for 1 hr. The excess $SOCl_2$ was evaporated under reduced pressure and the residue added to a solution of 31 g (0.1 mol) of **20** in 2 l. of CH_2Cl_2 and 16 g (0.2 mol) of pyridine. After stirring at room temperature overnight, a precipitate formed that was collected and recrystallized from EtOAc to yield 39 g of **60**, mp 240–242°.

(V) 2,3-Dihydro-1*H*-thieno[2,3-*e*][1,4]diazepines. Method D (Table IV, 62, 64, 68–75, 80, 82, 83, 89, 95–101). 1,3,6,7,8,9-Hexahydro-5-phenyl-2*H*-[1]benzothieno[2,3-*e*][1,4]diazepin-2-one (62). A solution of 80 g of NH_3 in 1 l. of MeOH was added to a suspension of 76 g (0.2 mol) of **23** in 1 l. of Et_2O. The resulting so-

‡A full report on the pharmacology and clinical studies with this compound will be presented at a later date.

Table IV. 2,3-Dihydro-1*H*-thieno[2,3-*e*][1,4]diazepines (V, VII, VIII, X–XIV, XVII)



No.	R^1	R^2	R	R^3	R^4	*n*	X	Method[a]	Mp, °C	Yield, %	Crystn solvent	Formula[c]
61[d]	$-(CH_2)_3-$		C_6H_5	H	H	0	O	E	251–253			
62	$-(CH_2)_4-$		C_6H_5	H	H	0	O	D	249–250	60	A	$C_{17}H_{16}N_2OS$
63	$-(CH_2)_4-$		C_6H_5	H	H	0	O		278–279	98	E–ET	$C_{17}H_{16}N_2OS \cdot H_2SO_4$
64	$-(CH_2)_4-$		C_6H_4-2-F	H	H	0	O	D	234–236	16	E–W	$C_{17}H_{15}FN_2OS$
65	$-(CH_2)_4-$		C_6H_4-2-Cl	H	H	0	O	E	267–269	11	E–W	$C_{17}H_{15}ClN_2OS$
66	$-(CH_2)_4-$		C_6H_4-2-CH_3	H	H	0	O	E	275–276	22	A	$C_{18}H_{18}N_2OS$
67[d]	$-(CH_2)_4-$		C_6H_4-2-OCH_3	H	H	0	O	E	245–246			
68	$-(CH_2)_4-$		C_6H_4-3-Cl	H	H	0	O	D	189–191	8	M	$C_{17}H_{15}ClN_2OS$
69	$-(CH_2)_4-$		C_6H_4-3-OCH_3	H	H	0	O	D	183–186	20	A	$C_{18}H_{18}N_2O_2S$
70[d]	$-(CH_2)_4-$		C_6H_4-4-Cl	H	H	0	O	D	263–264			
71	$-(CH_2)_4-$		C_6H_4-4-OCH_3	H	H	0	O	D	256–258	42	M	$C_{18}H_{18}N_2O_2S$
72	$-(CH_2)_4-$		2-Naphthyl	H	H	0	O	D	249–250	15	A	$C_{21}H_{18}N_2OS$
73	$-(CH_2)_4-$		2-Thienyl	H	H	0	O	D	252–254	15	A	$C_{15}H_{14}N_2OS_2$
74	$-(CH_2)_4-$		2-Furyl	H	H	0	O	D	233–235	26	A	$C_{15}H_{14}N_2O_2S$
75	$-(CH_2)_4-$		C_6H_{11}	H	H	0	O	D	242–244	31	T	$C_{17}H_{22}N_2OS$
76	$-(CH_2)_4-$		1-Cyclohexenyl	H	H	0	O		225–227	4	T–P	$C_{17}H_{20}N_2OS \cdot 0.5H_2O$
77	$-(CH_2)_4-$		C_6H_5	H	H	0	S		265–266	50	M	$C_{17}H_{16}N_2S_2$
78	$CH_2CH_2N(CO_2C_2H_5)CH_2$		C_6H_5	H	H	0	O	F	223–225	61	T–C	$C_{18}H_{19}N_3O_3S$
79	$CH_2CH_2N(COC_6H_5)CH_2$		C_6H_5	H	H	0	O	F	213–215	19	T–C	$C_{23}H_{19}N_3O_2S$
80	$CH_2CH_2SCH_2$		C_6H_5	H	H	0	O	D	256–259	18	M	$C_{16}H_{14}N_2OS_2$
81[d]	$CH_2CH_2CH(CH_3)CH_2$		C_6H_5	H	H	0	O	F	227–229			
82[d]	$-(CH_2)_5-$		C_6H_5	H	H	0	O	D	233.5–235			
83	$-(CH_2)_6-$		C_6H_5	H	H	0	O	D	191–192	20	E–W	$C_{19}H_{20}N_2OS$
84	$-(CH_2)_4-$		C_6H_5	H	CH_3	0	O		129–131	70	H	$C_{18}H_{18}N_2OS$
85	$-(CH_2)_4-$		C_6H_5	H	$-CH_2$-c-C_3H_5	0	O		170–172	55	T–P	$C_{21}H_{22}N_2OS$
86	$-(CH_2)_4-$		C_6H_5	H	$-(CH_2)_3N(CH_3)_2$	0	O		137–140	94	E	$C_{22}H_{27}N_3OS \cdot 2HClO_4 \cdot 0.5H_2O$
87	$-(CH_2)_4-$		C_6H_5	H	$-(CH_2)_2N(C_2H_5)_2$	0	O		259–261	95	E	$C_{23}H_{29}N_3OS \cdot 2HClO_4$
88	$-(CH_2)_4-$		2-Furyl	H	$-(CH_2)_2N(C_2H_5)_2$	0	O		228–230	56	I–M	$C_{21}H_{27}N_3O_2S \cdot 2HClO_4$
89	$-(CH_2)_4-$		C_6H_5	CH_3	H	0	O	D	231–233.5	26	A	$C_{18}H_{18}N_2OS$
90	$-(CH_2)_4-$		C_6H_5	H	H	1	O		277–278	62	M	$C_{17}H_{16}N_2O_2S$
91	$-(CH_2)_4-$		C_6H_5	H	CH_2	1	O		177–179	77	C	$C_{18}H_{18}N_2O_2S$
92	$-(CH_2)_4-$		C_6H_5	$-OCOCH_3$	H	0	O		288–290	14	M	$C_{19}H_{18}N_2O_3S$
93	$-(CH_2)_4-$		C_6H_5	$-OCOCH_3$	CH_3	0	O		182–184.5	83	C	$C_{20}H_{20}N_2O_3S$

94	$-(CH_2)_4-$		C_6H_5	OH	CH_3	0	O	185–186	64	M	$C_{18}H_{18}N_2O_2S$
95	H		C_6H_5	H	H	0	O	198–200	15	A	$C_{13}H_{10}N_2OS$
96	CH_3		C_6H_5	H	H	0	O	248.5–249.5	60	M	$C_{14}H_{12}N_2OS$
97	CH_3		2-Thienyl	H	H	0	O	211–213	30	M	$C_{12}H_{10}N_2OS$
98[e]	H	CH_3	C_6H_5	H	H	0	O	213–215			
99[d]	CH_3	CH_3	C_6H_5	H	H	0	O	241–243			
100	C_2H_5	CH_3	C_6H_5	H	H	0	O	218.5–220	40	M	$C_{16}H_{16}N_2OS$
101	C_3H_7	C_2H_5	C_6H_5	H	H	0	O	193–195	32	A	$C_{18}H_{20}N_2OS$
102	H	C_6H_5	C_6H_5	H	H	0	O	230–232	40	A	$C_{19}H_{14}N_2OS$
103	C_6H_5	H	C_6H_5	H	H	0	O	251–253	23	A	$C_{19}H_{14}N_2OS$
104	CH_3	H	C_6H_5	H	CH_3	0	O	202–203	83	M	$C_{15}H_{14}N_2OS$
105	CH_3	H	C_6H_5	H	C_2H_5	0	O	158–160	80	M	$C_{16}H_{16}N_2OS$
106	CH_2	H	C_6H_5	H	$-CH_2CH=CH_2$	0	O	116.5–118	74	C	$C_{17}H_{16}N_2OS$
Chlordiazepoxide											
Diazepam											

[a]See Experimental Section. [b]A, MeCN; C, cyclohexane; E, EtOH; ET, Et_2O; H, hexane; I, *i*-PrOH; M, MeOH; P, petroleum ether; T, toluene; W, water. [c]Satisfactory analyses for C, H, and N were obtained. [d]See ref 4. [e]Invag A.G., British Patent 1,256,548 (1971).

Table V. Pharmacological Data[a]

No.	AX: Minimally active dose	AX: Dose producing max effect[b]	PM, minimally active dose[c]
61	20 (C)	20 (C)	16
62	1.25	20	8
63	5	5	8
64	1.25	20	16
65	N	N	250
66	20 (C)	20 (C)	250
67	N	N	125
69	N	N	63
70	40 (C)	40 (C)	N
73	5	5	63
74	N	N	250
77	5 (C)	20 (C)	N
78	40	40	N
82	40 (C)	40 (C)	N
84	N	N	8
89	20 (C)	20 (C)	63
91	N	N	63
92	40 (C)	40 (C)	N
94	20	20	63
95	N	N	250
96	10	40	32
97	10	10	16
98	5	5	4
99	20	40	32
100	N	N	250
104	10	10	125
106	N	N	63
Chlordiazepoxide	10	20	4
Diazepam	1.25	20	8

[a]Full description of AX (antianxiety) and PM (anticonvulsant) test given in the Experimental Section; doses in mg/kg; N = inactive, C = marginal activity. [b]Dose at which greatest volume of milk was ingested (tested at 40 mg/kg or less). [c]Dose that gives a 4+ rating. All other compounds were evaluated in these tests and found to be inactive at doses of 500 mg/kg in the anticonvulsant screen and at 40 mg/kg in the antianxiety screen.

lution was stirred at room temperature overnight, the solvent evaporated under reduced pressure, and the residue dissolved in MeCN and warmed on a steam bath. Upon cooling, a precipitate formed and the resulting solid was recrystallized from MeCN to give 35 g of **62**, mp 249–250°. The monosulfate **63** was prepared from **62** and concentrated H_2SO_4, mp 278–279°.

Method E (Table IV, 61, 65–67). 1,3,6,7,8,9-Hexahydro-5-o-tolyl-2*H*-[1]benzothieno[2,3-*e*][1,4]diazepin-2-one (66). To a suspension of 57 g (0.124 mol) of **58** in 550 ml of MeOH was added 8 g (0.248 mol) of anhydrous hydrazine. The mixture was refluxed for 6 hr, cooled, and acidified with concentrated HCl. The solution was filtered, the filtrate evaporated under reduced pressure, and the residue dissolved in MeCN and cooled to yield 8 g of **66**, mp 275–276°.

Method F (Table IV, 78, 79, 81, 102, 103). 1,3-Dihydro-5,6-diphenyl-2*H*-thieno[2,3-*e*][1,4]diazepin-2-one (103). To a suspension of 1.0 g of 20% Pd/C in 500 ml of AcOH was added 15 g (0.041 mol) of **55**. The suspension was exposed to hydrogen for 2.5 hr and filtered, the solvent evaporated under reduced pressure, and the residue cyrstallized from MeCN to yield 2.9 g of **103**, mp 251–253°.

(VII) 1,3,6,7,8,9-Hexahydro-5-phenyl-2*H*-[1]benzothieno[2,3-*e*][1,4]diazepine-2-thione (Table IV, 77). A mixture of 15 g (0.051 mol) of **62** and 12.4 g (0.056 mol) of P_2S_5 in 150 ml of pyridine was refluxed for 1 hr. The mixture was cooled and poured into 375 ml of saturated NaCl solution and the precipitate filtered and washed with water (3 × 200 ml). Recrystallization from MeOH yielded 8 g of **77**, mp 265–266°.

(VIII) 1,3,6,7,8,9-Hexahydro-1-methyl-5-phenyl-2*H*-[1]benzothieno[2,3-*e*][1,4]diazepin-2-one (Table IV, 84). To a stirred solution of 5.0 g (0.017 mol) of **62** in 200 ml of DMF was added portionwise a 60.2% suspension of NaH in mineral oil (0.78 g, 0.019 mol). The resulting suspension was cooled to 10°, 2.8 g (0.02 mol)

of MeI was added dropwise, and the mixture obtained was stirred at room temperature for 45 min. The solvent was evaporated under reduced pressure. The residue obtained was dissolved in 100 ml of CH_2Cl_2 and the resulting solution was washed with water (2 × 100 ml), dried (Na_2SO_4), and evaporated under reduced pressure to yield after recrystallization from hexane, 2.5 g of **84**, mp 129–131°.

(X) 1,3,6,7,8,9-Hexahydro-5-phenyl-2*H*-[1]benzothieno[2,3-*e*][1,4]diazepin-2-one 4-Oxide (Table IV, 90). To a solution of 25 g (0.36 mol) of hydroxylamine hydrochloride in 70 ml of water was added 14.4 g (0.36 mol) of NaOH at 5°, followed by 500 ml of EtOH. To this mixture was added 34 g (0.09 mol) of **23** in 1 l. of EtOH. The solution was stirred for 2 days at room temperature and then evaporated under reduced pressure below 60°. The residue was washed with water (3 × 500 ml) and dried *in vacuo* at 80° to give 35 g of IX, mp 132–136°. The solid, without further purification, was suspended in 500 ml of *i*-PrOH and a saturated solution of HCl in *i*-PrOH added until the solution was acid to pH paper. The resulting solution was refluxed for 1 hr and the precipitate filtered and recrystallized from MeOH to yield 19.2 g of **90**, mp 277–278° dec.

(XI) 1,3,6,7,8,9-Hexahydro-1-methyl-5-phenyl-2*H*-[1]benzothieno[2,3-*e*][1,4]diazepin-2-one 4-Oxide (Table IV, 91). This was prepared from **90** by a similar procedure outlined for VIII.

(XII) 1,3,6,7,8,9-Hexahydro-3-hydroxy-5-phenyl-2*H*-[1]benzothieno[2,3-*e*][1,4]diazepin-2-one Acetate Ester (Table IV, 92). To 150 ml of Ac_2O was added 15.6 g (0.05 mol) of **90** and the mixture was heated on a steam bath for 2 hr. The Ac_2O was evaporated under reduced pressure and the residue was dissolved in MeOH and cooled to yield 2.5 g of **92**, mp 288–289°.

(XIII) 1,3,6,7,8,9-Hexahydro-3-hydroxy-1-methyl-5-phenyl-2*H*-[1]benzothieno[2,3-*e*][1,4]diazepin-2-one Acetate Ester (Table IV, 93). This was prepared from **91** by a similar procedure outlined for XII.

(XIV) 1,3,6,7,8,9-Hexahydro-3-hydroxy-1-methyl-5-phenyl-2*H*-[1]benzothieno[2,3-*e*][1,4]diazepin-2-one (Table IV, 94). To a solution of 3.7 g (0.01 mol) of **93** in 150 ml of EtOH, cooled to 5°, was added 0.4 g (0.01 mol) of NaOH in 15 ml of water. The solution was allowed to reach room temperature over 1 hr and then neutralized with solid CO_2. The solvents were evaporated under reduced pressure and the residue was dissolved in $CHCl_3$, washed with water (2 × 100 ml), and dried (Na_2SO_4). After evaporation of the solvent under reduced pressure, the residue was recrystallized from cyclohexane to yield 2.1 g of **94**, mp 185–186°.

(XVII) 5-(1-Cyclohexen-1-yl)-1,3,6,7,8,9-hexahydro-2*H*-[1]benzothieno[2,3-*e*][1,4]diazepin-2-one (Table IV, 76). To a mixture of 60 g (0.197 mol) of **75** in 300 ml of CH_2Cl_2 was added 23.6 g (0.217 mol) of *t*-BuOCl. The mixture was stirred 1 hr at room temperature and evaporated under reduced pressure to yield, after recyrstallization from CH_2Cl_2–Et_2O, 53 g (79% yield) of XV. Then XV, without further purification, was refluxed in 350 ml of EtOAc for 1 hr, cooled, and filtered to yield 49 g of XVI (90% yield), mp 119–122°. This intermediate was not further purified. To a mixture of 21.4 g (0.311 mol) of Li_2CO_3 and 11 g (0.127 mol) of LiBr suspended in 225 ml of DMF was added 48.5 g (0.144 mol) of XVI. The mixture was heated at 100° for 1.5 hr and then at 115° for 15 min and filtered. The solution was evaporated under reduced pressure and the residue was suspended in water and extracted with Et_2O. The Et_2O layer was separated, washed with water (1 × 200 ml), dried (Na_2SO_4), and evaporated under reduced pressure to yield, after recrystallization from toluene–petroleum ether, 1.6 g of **76**, mp 225–227°.

Pharmacology Tests. 1. Antianxiety Test (AX). After adjustment to the normal laboratory environment, each of a group of eight male Holtzman rats was given a measured dose of test compound, dissolved in water or suspended in 0.2% aqueous methocel, by oral intubation and was immediately placed in an individual metabolism cage. After a 30-min period, each animal was given access to a milk preparation. The total milk intake of each animal after 1 and 2 hr was recorded and compared with that of a group of eight untreated control animals. Greater than normal ingestion of milk by the treated animals was regarded as an indication that the test compound had suppressed the natural tendency of rodents to become immobilized in a novel, anxiety-producing situation as represented in the test by the isolation of the metabolism cage. A given dose of test compound was considered active if it caused a mean amount of ingestion greater than 5.0 ml per animal at the end of the first hour of the test.

2. Anticonvulsant Test (PM). In this test, each of a group of five rats was given a measured oral dose of a test compound, dissolved in water or suspended with acacia, followed 30 min later by a subcutaneous dose of 93 mg/kg of pentylenetetrazole. This quantity of pentylenetetrazole quickly produces convulsions in 98–100% of untreated control rats. The treated animals were then observed visually for 30 min following administration of pentylenetetrazole and anticonvulsant activity was judged by noting the time of onset and severity of clonic convulsive seizures and the number of animals completely protected from convulsions. The activity of a test compound at each dosage level was rated as follows: 4+, protection of all five rats; 3+, protection of three or four rats; 2+, protection of one or two rats; 1+, delay in onset; 0, no effect.

Acknowledgments. The authors wish to thank Drs. B. P. H. Poschel, D. A. McCarthy, G. M. Chen, and associates for the pharmacology. We would also like to express our appreciation to Mr. C. E. Childs and associates for the microanalyses, Dr. J. M. Vandenbelt and associates for the spectral data, Mr. W. M. Pearlman for catalytic hydrogenations, and Mr. H. D. Troutman and associates for preparation of certain starting materials.

References

(1) S. J. Childress and M. I. Gluckman, *J. Pharm. Sci.*, **53**, 577 (1964).
(2) G. A. Archer and L. H. Sternbach, *Chem. Rev.*, **68**, 747 (1968).
(3) R. Littell and D. S. Allen, Jr., *J. Med. Chem.*, **8**, 722 (1965).
(4) M. Nakanishi, T. Tahara, K. Araki, M. Shiroki, T. Tsumagari, and Y. Takigawa, *J. Med. Chem.*, **16**, 214 (1973).
(5) F. J. Tinney, Belgium Patent 745,560 (April 15, 1970).
(6) H. A. DeWald, U. S. Patent 3,557,095 (Jan 19, 1971).
(7) Y. J. L'Italien and I. C. Nordin, U. S. Patent 3,553,209 (Jan 5, 1971).
(8) H. A. DeWald and D. E. Butler, U. S. Patent 3,558,605 (Jan 26, 1971).
(9) I. C. Nordin, U. S. Patent 3,553,210 (Jan 5, 1971).
(10) I. C. Nordin, U. S. Patent 3,553,207 (Jan 5, 1971).
(11) K. Gewald, E. Schinke, and H. Böttcher, *Chem. Ber.*, **99**, 94 (1966).
(12) S. C. Bell, R. J. McCaully, and S. J. Childress, *J. Heterocycl. Chem.*, **4**, 647 (1967).
(13) B. P. H. Poschel, *Psychopharmacologia*, **19**, 193 (1971).
(14) G. Chen, C. R. Ensor, and I. G. Clarke, *AMA Arch. Neurol. Psychiat.*, **66**, 329 (1951).
(15) G. Chen, C. R. Ensor, and I. G. Clarke, *AMA Arch. Neurol. Psychiat.*, **68**, 498 (1952).
(16) G. Chen, R. Portman, C. R. Ensor, and A. C. Bratton, Jr., *J. Pharmacol. Exp. Ther.*, **103**, 54 (1951).