had ir and uv spectra in agreement with its assigned structure; purity was confirmed by tlc using Brinkmann silica gel GF. Melting points are uncorrected and were taken in capillary tubes on a Mel-Temp block.

α-(2-Chloro-4-nitrophenoxy)-*m*-toluic acid, a precursor for the synthesis of inhibitors **34–40,** has already been described.[8] The base-catalyzed ester hydrolysis was modified by using aqueous DMSO in place of aqueous MeOH. In this medium the reaction was essentially complete in 1 hr at 80–85°, with yields of up to 79% being obtained.

***N*-Arylamides (Method A).** Conversion of the nitro-substituted acid to the acid chloride and condensation with the arylamine in toluene at reflux was performed as previously described.[8] Compounds prepared in this manner are listed in Table IV.

***N,N*-Dialkylamides (Method B). *N,N*-Diethyl-*p*-nitrophenoxyacetamide (54).** A mixture of 983 mg (5.0 mmol) of *p*-nitrophenoxyacetic acid, 4 ml of $SOCl_2$, and 8 ml of C_6H_6 was stirred under reflux for 4.5 hr, then cooled, and spin evaporated *in vacuo*. The residual oil was dissolved in 8 ml of CH_2Cl_2 and cooled in an ice bath. The cold solution of acid chloride was added slowly with stirring to a chilled solution of 802 mg (11 mmol) of Et_2NH in 10 ml of CH_2Cl_2. Stirring was continued under protection from moisture for 10 min, while maintaining the temperature below 10°. Next, the mixture was diluted with 35 ml of CH_2Cl_2 and shaken with 50 ml of H_2O. The organic layer was washed with 1% HCl (1 × 50 ml) and 5% Na_2CO_3 (3 × 50 ml), then dried ($MgSO_4$), and evaporated to dryness. Upon trituration with petroleum ether (bp 30–60°) and scratching, the residual oil solidified. Recrystallization from EtOAc–petroleum ether (bp 65–110°) afforded 1.01 g (80%) of very pale yellow crystals, mp 64–65° (tlc in 1:1 EtOAc–petroleum ether). *Anal.* ($C_{12}H_{16}N_2O_4$) C, H, N. For additional compounds prepared by this method, see Table IV.

2-Chloro-4-nitrophenyl Benzyl Ethers (80–82) (Method C). The α-bromination of substituted toluenes and subsequent reaction with 2-chloro-4-nitrophenol were carried out in the usual manner.[8] Physical properties of the ethers are given in Table IV.

The reaction of *N,N*-dimethyl-*p*-toluenesulfonamide with NBS was complicated by side reactions, resulting in a low overall yield of **81.** A possible alternative route to compound **76,** involving α-bromination of *N,N*-diethyl-*m*-toluamide followed by reaction with 2-chloro-4-nitrophenol, was unsuccessful on account of the mixture of products formed when the diethyltoluamide was treated with NBS.

4,6-Diamino-1,2-dihydro-2,2-dimethyl-*s*-triazine Ethanesulfonates (5–43) (Methods D–F). The nitro intermediates **45–82** were hydrogenated over PtO_2 (Method D), Raney Ni (Method E), or 5% Pd/C (Method F); the resulting crude amines were condensed with cyanoguanidine and Me_2CO[16] in the presence of $EtSO_3H$ as previously described.[8] Compounds obtained by this procedure are shown in Table V.

Acknowledgments. We wish to thank Dr. Florence White of Drug Research and Development, National Cancer Institute, for supplying the cell culture and *in vivo* testing data. In addition, we wish to acknowledge the assistance of Mrs. Julie Beardslee and Mrs. Janet Wood in performing the enzyme assays.

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Studies on Psychotropic Drugs. 18.[1] Synthesis and Structure–Activity Relationships of 5-Phenyl-1,3-dihydro-2*H*-thieno[2,3-*e*][1,4]diazepin-2-ones

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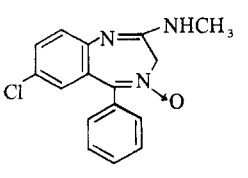
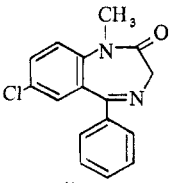
Received July 3, 1972

A series of 5-phenyl-1,3-dihydro-2*H*-thieno[2,3-*e*][1,4]diazepin-2-ones was synthesized and evaluated for CNS depressant activity. Structure–activity relationships were discussed.

It is well known that a number of 1,4-benzodiazepine derivatives show potent antianxiety activity.[2] From the standpoint of bioisosterism, we synthesized a series of thienodiazepine derivatives, which have a thieno moiety in place of the benzo moiety of the benzodiazepine ring system, starting from readily obtainable 2-amino-3-benzoylthiophenes according to Gewald, *et al.*[3] 5-Phenyl-1,3-dihydro-2*H*-thieno[2,3-*e*][1,4]diazepin-2-ones thus synthesized were pharmacologically screened and, as was expected, several compounds in this series **(84, 109,** and **110)** were found to show higher CNS depressant activity than CDP and not less than DZP. These compounds were observed to have similar low toxicity to CDP and DZP.



chlordiazepoxide (CDP)



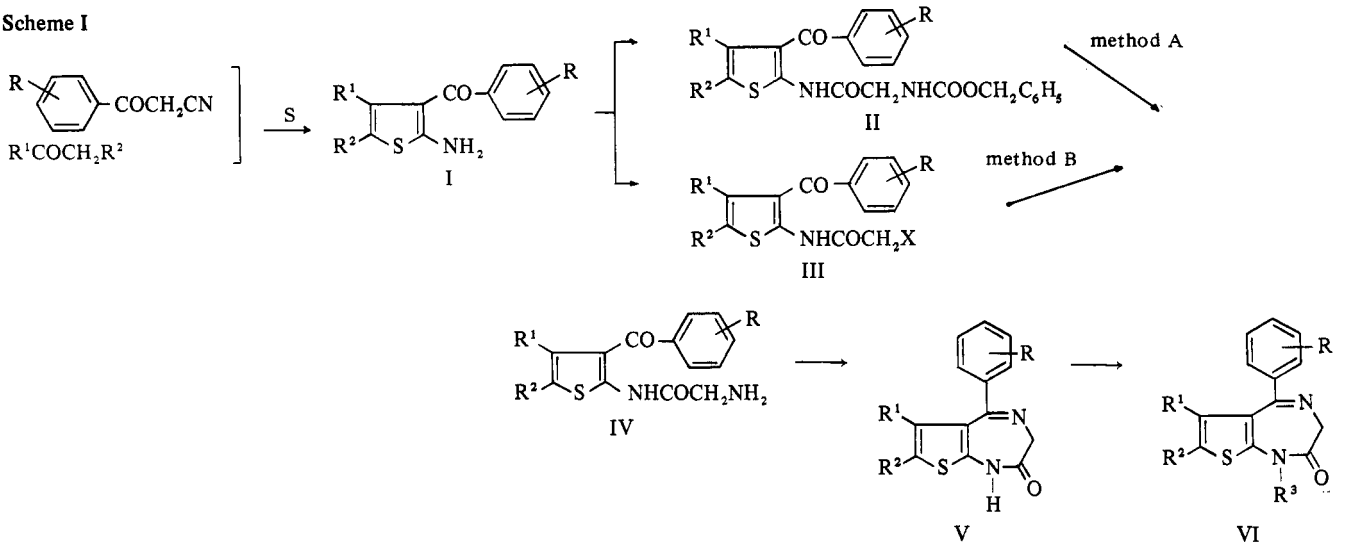
diazepam (DZP)

Chemistry. The synthetic route to thienodiazepine derivatives is shown in Scheme I.

Starting materials, 2-amino-3-benzoylthiophenes (I), were prepared by the reaction of ω-cyanoacetophenone with aldehyde or ketone and sulfur in the presence of catalytic amine (Table I). Compounds of type I were converted into corresponding aminoacetamide derivatives IV *via* methods A and B, respectively.

Method A. Benzyloxycarbonylaminoacetamide intermediates II were synthesized by condensation of I with benzyloxycarbonylaminoacetyl chloride in $CHCl_3$ at low

Scheme I



temperature (Table II). Then II was deprotected with HBr-AcOH to give IV.

Method B. Haloacetamide intermediates III (Table III) were ammonolyzed by passing NH_3 gas in $CHCl_3$–MeOH solution to give IV (Table IV). Chloro- or bromoacetamides were obtained by the corresponding halogenoacetylation of I in boiling $CHCl_3$, and iodoacetamides were prepared by the reaction of chloroacetamides, which could only be ammonolyzed with difficulty, with NaI in boiling Me_2CO.

The ring-closure reaction of IV to 5-phenyl-1,3-dihydro-2*H*-thieno[2,3-*e*][1,4]diazepin-2-ones (V) was carried out by refluxing a mixture of IV and equimolar AcOH in pyridine–C_6H_6 solution with azeotropic removal of water. Finally, compounds V were alkylated to give the corresponding 1-substituted derivatives VI.

Results and Discussion

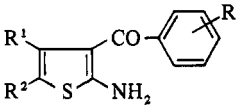
In Table V, the results of two preliminary screening tests for thienodiazepine derivatives are summarized in comparison with those of CDP and DZP.

Generally, it is said that in the benzodiazepine series, the C-7 substitution with an electron-releasing group results in a withdrawal of the potency and the introduction of a halogen atom in the ortho position of a C-5 phenyl or methylation at the 1 position potentiates the activity.[4]

In order to study the structure-activity relationships in thienodiazepine series, first of all, we varied the substituents at C-6 from H to *i*-Pr, at C-7 from H to *n*-Bu (**81**, **83**, **90**, **91**, **95**, and **96**), and the combined alkylene linkage at C-6 and C-7 from 3 to 5 methylenes (**97**, **98**, **103**, and **104**). Several compounds (**81**, **83**, and **91**) showed potent activity by this modification. Among them, compound **83** which possesses an ethyl group at C-7 and a H atom at C-6 was found to impart optimum activity. Increasing the bulkiness of the substituents at C-6 and/or C-7 seemed to decrease the activity. However, introduction of an alkylene linkage between C-6 and C-7 (**97** and **98**) still afforded slightly lower activity than **83**.

Attention was then turned to the substituent effect on the C-5 phenyl moiety. The introduction of a halogen atom,

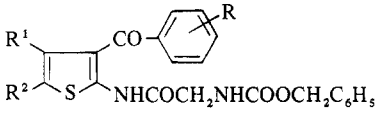
Table I. 2-Amino-3-benzoylthiophenes (I)



No.	R^1	R^2	R	Mp, °C	Yield, %	Crystn solvent[a]	Formula[b]
1	H	CH_3	*o*-Cl	160–162	75	E	$C_{12}H_{10}ClNOS$
2	H	C_2H_5	H	87–88	70	H/E	$C_{13}H_{13}NOS$
3	H	C_2H_5	*o*-F	114–116	68	H	$C_{13}H_{12}FNOS$
4	H	C_2H_5	*o*-Cl	132–133	61	H/E	$C_{13}H_{12}ClNOS$
5	H	C_2H_5	*o*-Br	123–125	60	H/C	$C_{13}H_{12}BrNOS$
6	H	C_2H_5	*o*-CH_3	110–112	58	H/E	$C_{14}H_{15}NOS$
7	H	C_2H_5	*o*-OCH_3	145–147	73	E	$C_{14}H_{15}NO_2S$
8	H	*i*-C_3H_7	*o*-Cl	*c*			
9	H	*n*-C_4H_9	H	*c*			
10	CH_3	CH_3	H	140–141	72	E	$C_{13}H_{13}NOS$
11	CH_3	CH_3	*o*-Cl	151–152	59	E	$C_{13}H_{12}ClNOS$
12	CH_3	CH_3	*p*-Cl	127–129	52	E	$C_{13}H_{12}ClNOS$
13	CH	CH_3	*m*-CF_3	*c*			
14	CH_3	*n*-C_3H_7	H	*c*			
15	*i*-C_3H_7	H	H	*c*			
16	-$(CH_2)_3$-		H	176–177	51	E	$C_{14}H_{13}NOS$
17	-$(CH_2)_4$-		*p*-Cl	138–139	68	E	$C_{15}H_{14}ClNOS$
18	-$(CH_2)_4$-		*o*-OCH_3	181–182	71	E	$C_{16}H_{17}NO_2S$
19	-$(CH_2)_4$-		*m*-CF_3	123–124	60	E	$C_{16}H_{14}F_3NOS$
20	-$CH_2CH_2CH(CH_3)CH_2$-		H	118–119	67	E	$C_{16}H_{17}NOS$
21	-$(CH_2)_5$-		H	115–116	58	E	$C_{16}H_{17}NOS$

[a] E, EtOH; H, hexane; C, EtOAc. [b] Analyzed for C, H, and N. [c] Not isolated and used crude in next step.

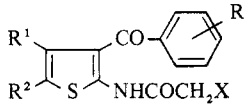
Table II. 2-Benzyloxycarbonylaminoacetamido-3-benzoylthiophenes (II)



No.	R^1	R^2	R	Mp, °C	Yield, %	Crystn solvent[a]	Formula[b]
22	H	CH_3	*o*-Cl	153–154	70	E	$C_{22}H_{19}ClN_2O_4S$
23	H	C_2H_5	H	100	73	E	$C_{23}H_{22}N_2O_4S$
24	H	C_2H_5	*o*-Cl	118–119	61	E	$C_{23}H_{21}ClN_2O_4S$
25	H	C_2H_5	*o*-CH_3	128–129	70	E	$C_{24}H_{24}N_2O_4S$
26	H	C_2H_5	*o*-OCH_3	77–78	62	E	$C_{24}H_{24}N_2O_5S$
27	H	*i*-C_3H_7	*o*-Cl	112–114		E	$C_{24}H_{23}ClN_2O_4S$
28	H	*n*-C_4H_9	H	91–92		E	$C_{25}H_{26}N_2O_4S$
29	CH_3	CH_3	H	145–146	67	E	$C_{23}H_{22}N_2O_4S$
30	CH_3	CH_3	*p*-Cl	157–159	74	E	$C_{23}H_{21}ClN_2O_4S$
31	CH_3	CH_3	*m*-CF_3	125–126		E	$C_{24}H_{21}F_3N_2O_4S$
32	CH_3	*n*-C_3H_7	H	97–98		E	$C_{25}H_{26}N_2O_4S$
33	*i*-C_3H_7	H	H	*c*			
34	$-(CH_2)_3-$		H	114–115	72	E	$C_{24}H_{22}N_2O_4S$
35	$-(CH_2)_4-$		*p*-Cl	124–125	73	E	$C_{25}H_{23}ClN_2O_4S$
36	$-(CH_2)_4-$		*o*-OCH_3	*c*			
37	$-(CH_2)_4-$		*m*-CF_3	135	68	E	$C_{26}H_{23}F_3N_2O_4S$
38	$-CH_2CH_2CH(CH_3)CH_2-$		H	139–140	71	E	$C_{26}H_{26}N_2O_4S$
39	$-(CH_2)_5-$		H	140–141	67	E	$C_{26}H_{26}N_2O_4S$

[a] E, EtOH. [b] Analyzed for C, H, and N. [c] Not isolated and used crude in next step.

Table III. 2-Haloacetamido-3-benzoylthiophenes (III)



No.	R^1	R^2	R	X	Mp, °C	Yield, %	Crystn solvent[a]	Formula[b]
40	H	CH_3	*o*-Cl	Cl	127–128	85	M	$C_{14}H_{11}Cl_2NO_2S$
41	H	C_2H_5	H	Cl	114–115	89	M	$C_{15}H_{14}ClNO_2S$
42	H	C_2H_5	*o*-F	Cl	87–88	82	E	$C_{15}H_{13}ClFNO_2S$
43	H	C_2H_5	*o*-Cl	Cl	99–100	81	E	$C_{15}H_{13}Cl_2NO_2S$
44	H	C_2H_5	*o*-Br	Cl	90–91	78	E	$C_{15}H_{13}BrClNO_2S$
45	H	C_2H_5	*o*-CH_3	Cl	78–79	80	M	$C_{16}H_{16}ClNO_2S$
46	H	C_2H_5	*o*-OCH_3	Cl	141–142	82	M	$C_{16}H_{16}ClNO_3S$
47	CH_3	CH_3	*o*-Cl	Cl	182–183	87	M	$C_{15}H_{13}Cl_2NO_2S$
48	$-(CH_2)_3-$		H	Cl	121–122	82	E	$C_{16}H_{14}ClNO_2S$
49	$-(CH_2)_5-$		H	Cl	119–120	86	E	$C_{18}H_{18}ClNO_2S$
50	H	C_2H_5	*o*-Cl	Br	105–106	78	E	$C_{15}H_{13}BrClNO_2S$
51	CH_3	CH_3	H	Br	106–107	81	M	$C_{15}H_{14}BrNO_2S$
52	H	CH_3	*o*-Cl	I	140–142	87	E	$C_{14}H_{11}ClINO_2S$
53	H	C_2H_5	H	I	87–88	88	M	$C_{15}H_{14}INO_2S$
54	H	C_2H_5	*o*-F	I	96–97	89	H	$C_{15}H_{13}FINO_2S$
55	H	C_2H_5	*o*-Cl	I	100–101	86	E	$C_{15}H_{13}ClINO_2S$
56	H	C_2H_5	*o*-Br	I	94–96	87	H/E	$C_{15}H_{13}BrINO_2S$
57	H	C_2H_5	*o*-CH_3	I	78–79	81	E	$C_{16}H_{16}INO_2S$
58	H	C_2H_5	*o*-OCH_3	I	115–117	83	E	$C_{16}H_{16}INO_3S$
59	CH_3	CH_3	*o*-Cl	I	140–141	87	E	$C_{15}H_{13}ClINO_2S$

[a] M, MeOH; E, EtOH; H, hexane. [b] Analyzed for C, H, and N.

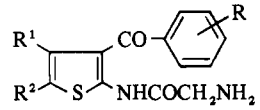
especially a fluorine atom (**84**), in the ortho position very strongly enhanced the activity (**84–86** and **99**), while the methoxy group at the ortho position (**88** and **101**) or any substituent at the meta or para positions (**93**, **94**, **100**, and **102**) was unfavorable.

It is of interest to consider whether the substitution at N-1 affords any influence on the activity. The regular tendency on the effect of N-1 methylation was not recognized. Thus, the activity was increased by N-1 methylation of 7-ethyl-5-*o*-chloro- or -bromophenyl derivatives (**109** and **110**), but no remarkable effect was observed in the 7-ethyl-5-*o*-fluorophenyl compound **108**. N-1 methylation of the alkylene linkaged compounds (**114–116** and **118**) caused potentiation only in anti Met activity. As for the other compounds (**105–107** and **111**), reduction of both activities was observed. Introduction of more bulky substituents than the methyl group at N-1 seemed to lower the activity (**119–121** and **122**).

From these results, some compounds (**83–85**, **108**, and **109**) were selected and their general pharmacological properties were studied in some detail. As shown in Table VI, the prototype **83** had comparable activity with CDP, but it was found to be slightly toxic. However, potentiation of activity was found to occur by halogen substitution at the ortho position in the C-5 phenyl moiety of **83**, not only in the two main activities discussed previously but also in other properties shown in Table VI. Furthermore, toxicity was lowered to some extent. Compounds **84**, **108**, and **109** had comparable activities with DZP in anticonvulsant, muscle-relaxant activities and taming effect but lower activity in narcosis potentiation. Compound **85**, on the other hand, displayed comparable activities with DZP except taming effect.

Turning attention again to N-1 substituion, it was observed that the taming effect was increased by N-1 methylation (compare **84** with **108** and **85** with **109**). However,

Table IV. 2-Aminoacetamido-3-benzoylthiophenes (IV)



No.	R^1	R^2	R	Method[a]	Mp, °C	Yield, %	Crystn solvent[b]	Formula[c]
60	H	CH_3	*o*-Cl	A, B	183–186	83[d]	E	$C_{14}H_{13}ClN_2O_2S$
61	H	C_2H_5	H	A, B	169–171	72[e]	E	$C_{15}H_{16}N_2O_2S \cdot HBr$
62	H	C_2H_5	*o*-F	B	145–147	75	H/E	$C_{15}H_{15}FN_2O_2S$
63	H	C_2H_5	*o*-Cl	A, B	148–149	85[d]	E	$C_{15}H_{15}ClN_2O_2S$
64	H	C_2H_5	*o*-Br	B	160–161	76	E	$C_{15}H_{15}BrN_2O_2S$
65	H	C_2H_5	*o*-CH_3	A, B	175–177	67[e]	E	$C_{16}H_{18}N_2O_2S \cdot HBr$
66	H	C_2H_5	*o*-OCH_3	A, B	185–186	70[d]	E	$C_{16}H_{18}N_2O_2S$
67	H	*i*-C_3H_7	*o*-Cl	A	127–128	42	E	$C_{16}H_{17}ClN_2O_2S$
68	H	*n*-C_4H_9	H	A	*f*			
69	CH_3	CH_3	H	A	213–215	69	E	$C_{15}H_{16}N_2O_2S \cdot HBr$
70	CH_3	CH_3	*o*-Cl	B	147–148	73	H/E	$C_{15}H_{15}ClN_2O_2S$
71	CH_3	CH_3	*p*-Cl	A	225–227	75	E	$C_{15}H_{15}ClN_2O_2S \cdot HBr$
72	CH_3	CH_3	*m*-CF_3	A	234–235[g]	53	E	$C_{16}H_{15}F_3N_2O_2S \cdot HBr$
73	CH_3	*n*-C_3H_7	H	A	170–173	64	E	$C_{17}H_{20}N_2O_2S$
74	*i*-C_3H_7	H	H	A	*f*			
75	$-(CH_2)_3-$		H	A, B	130–131	73[d]	E	$C_{16}H_{16}N_2O_2S$
76	$-(CH_2)_4-$		*p*-Cl	A	158–159	62	E/T	$C_{17}H_{17}ClN_2O_2S$
77	$-(CH_2)_4-$		*o*-OCH_3	A	134–135		E	$C_{18}H_{20}N_2O_3S$
78	$-(CH_2)_4-$		*m*-CF_3	A	163	73	E	$C_{18}H_{17}F_3N_2O_2S$
79	$-CH_2CH_2CH(CH_3)CH_2-$		H	A	156–157	69	E	$C_{18}H_{20}N_2O_2S$
80	$-(CH_2)_5-$		H	A, B	185–186	72[e]	E	$C_{18}H_{20}N_2O_2S \cdot HBr$

[a] See Experimental Section. [b] E, EtOH; H, hexane; T, toluene. [c] Analyzed for C, H, and N. [d] Yield per cent by method B. [e] Yield per cent by method A. [f] Not isolated and used crude in next step. [g] Decomposed.

while N-1 methylation of 5-*o*-fluorophenyl derivative caused an increase in narcosis potentiation and a decrease in anticonvulsant and muscle-relaxant activities, N-1 methylation of the 5-*o*-chlorophenyl derivative resulted in a reverse change in all these properties.

In conclusion, the present results suggest the following matter: in this thienodiazepine series an ethyl group at C-7 is the most favorable substituent for the activity. It is possible to increase the potency by the introduction of a halogen atom in the ortho position of a C-5 phenyl, as the case of the benzodiazepine series. The effect of N-1 methylation depends on the property of the individual compound.

Experimental Section

Pharmacology Methods. The animals used were dd-strain mice weighing 20–25 g and Wistar rats weighing 140–170 g.

1. Inhibition of Fighting Behavior (FE). Fighting episodes were induced by the method of Tedeschi, *et al.*[5] Groups of 12 female mice (six pairs) each were given the test compounds orally 60 min prior to receiving foot shock (530 V, 1.3 mA, 10 cps). The ED_{50}, the dose which inhibited the fighting in 50% pairs according to the same criterion of the Tedeschi, *et al.*,[5] was determined graphically.

2. Antipentetrazole Activity (Met).[6] Groups of five or seven male mice each were given the test compounds intraperitoneally 15 min prior to the treatment with pentetrazole, 150 mg/kg (sc). The ED_{50}, the dose which prevented the lethality within 3 hr in 50% of the animals, was calculated by the probit method.

3. Anti-MES Activity. Maximal electroshock (MES) was induced by the method of Nakanishi, *et al.*[7] Groups of five or seven male mice each were challenged with a maximal electroshock (ac 2000 V, 12.5 mA, 0.2 sec) applied by the corneal electrodes 1 hr after the administration of the test compounds. The ED_{50} values which prevented the tonic extensor of the hind limb in 50% of the animals were determined by the graphical interpolation or by the probit method.

4. Antibemegride-Induced Convulsions. Groups of five or seven male mice each were challenged with bemegride, 50 mg/kg (ip), 60 min after the treatment of the test compounds. The 50% effective dose (ED_{50}) in the prevention of the tonic extensor convulsion was determined by the graphical interpolation or by the probit method.

5. Effects on Motor Coordination. Groups of five female mice each were placed on a horizontal rotating cage[8] and a horizontal rotating rod.[9] The test compounds were given intraperitoneally 1 hr before the tests. The ED_{50}, the dose which dropped 50% of the animals from the apparatus within 1 min, was calculated by the probit method.

6. Narcosis Potentiation. Groups of seven male mice each were given the test compounds, intraperitoneally 30 min prior to the treatment with subnarcotic dose of hexobarbital (40 mg/kg, ip) or orally 30 min after the treatment of chlorprothixene hydrochloride (25 mg/kg, po). The animals were kept in a chamber at 26° and the righting reflex was checked 15 and 30 min after the treatment of hexobarbital or 60 and 90 min after the treatment of chlorprothixen The PD_{50}, the dose which resulted in loss of the righting reflex for more than 30 sec in 50% of the animals, was determined graphically.

7. Taming Effects in Olfactory Bulb-Removed Rats. Groups of three female olfactory bulb-removed rats (O.B. rats)[10] each were orally given the test compounds. The hyperemotionality of the animals was hourly scored for 6 hr by the rating scale method previously reported by the authors.[8] The ED_{50}, the dose for 50% inhibition of the hyperemotionality, was determined graphically from the inhibitory rate at the most effective time.

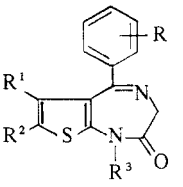
8. Acute Toxicity. Groups of ten male mice each were given the test compounds intraperitoneally or orally. The 50% lethal dose (LD_{50}) was calculated by the probit method.

Synthetic Methods. Melting points were taken in a capillary tube and are uncorrected. The structures of all compounds were supported by ir, nmr, and mass spectra. The spectra were obtained from a Jasco Model IR-G spectrophotometer for the ir, by a Jeol Model PS-100 for the nmr, and by a Jeol Model JMS-01SG for the mass spectra. Analytical results obtained were within ±0.4% of the theoretical values. Representative procedures for the preparation of the compounds are illustrated below.

(I) 2-Amino-3-benzoylthiophenes. (a) From Aldehydes (Table I, 1-9). 2-Amino-3-*o*-chlorobenzoyl-5-ethylthiophene (4). A solution of butyraldehyde (7.2 g, 0.1 mol) in EtOH (5 ml) was added dropwis to a stirred mixture of *o*-chloro-ω-cyanoacetophenone (18.0 g, 0.1 mol), powdered sulfur (3.5 g, 0.11 g-atom), DMF (30 ml), and triethylamine (8 ml) at 45–50° during 30 min. After stirring below 60° for an additional 1 hr, a suspension of the mixture in water was extracted with EtOAc. The extract was washed with 10% HCl, Na_2CO_3 solution, and water, successively, dried (Na_2SO_4), and then concentrated under reduced pressure. Recrystallization of the residue from hexane–EtOH gave 16.2 g of **4**, mp 132–133°.

(b) From Ketones (Table I, 10-21). 2-Amino-3-*o*-chlorobenzoyl-4,5-dimethylthiophene (11). A mixture of methyl ethyl ketone (7.2 g, 0.1 mol), *o*-chloro-ω-cyanoacetophenone (18.0 g, 0.1 mol), powdered sulfur (3.5 g, 0.11 g-atom), and morpholine (10 ml) in EtOH (50 ml) was stirred under reflux for 3 hr, cooled, and then concentrated under reduced pressure. The extract of the residue with

Table V. 5-Phenyl-1,3-dihydro-2*H*-thieno[2,3-*e*][1,4]diazepin-2-ones (V and VI)



No.	R^1	R^2	R^3	R	Mp, °C	Yield, %	Crystn solvent[a]	Formula[b]	Pharmacological data (1)[c] FE	Met
81[d]	H	CH_3	H	H	207-210				8	17
82	H	CH_3	H	*o*-Cl	212-213	74	H/E	$C_{14}H_{11}ClN_2OS$	15	0.9
83	H	C_2H_5	H	H	194-195	70	T	$C_{15}H_{14}N_2OS$	7	3.1
84	H	C_2H_5	H	*o*-F	178-180	82	H/E	$C_{15}H_{13}FN_2OS$	0.4	0.3
85	H	C_2H_5	H	*o*-Cl	204-206	81	T	$C_{15}H_{13}ClN_2OS$	5	3.3
86	H	C_2H_5	H	*o*-Br	208-209	79	H/E	$C_{15}H_{13}BrN_2OS$	4.5	3.6
87	H	C_2H_5	H	*o*-CH_3	182-183	76	T	$C_{16}H_{16}N_2OS$		8
88	H	C_2H_5	H	*o*-OCH_3	168-169	64	T	$C_{16}H_{16}N_2O_2S$	19	17
89	H	*i*-C_3H_7	H	*o*-Cl	243-246[e]	84	E	$C_{16}H_{15}ClN_2OS$	20	10
90	H	*n*-C_4H_9	H	H	163-164		I	$C_{17}H_{18}N_2OS$	>80 (0)	>160 (16.7)
91	CH_3	CH_3	H	H	236-237	75	D/W	$C_{15}H_{14}N_2OS$	20	15
92	CH_3	CH_3	H	*o*-Cl	251	72	T/E	$C_{15}H_{13}ClN_2OS$	10.5	47.0
93	CH_3	CH_3	H	*p*-Cl	243-245[e]	80	H/E	$C_{15}H_{13}ClN_2OS$	>160 (0)	
94	CH_3	CH_3	H	*m*-CF_3	220-222	75	H/E	$C_{16}H_{13}F_3N_2OS$	>160 (0)	>160 (0)
95	CH_3	*n*-C_3H_7	H	H	207-208	70	E	$C_{17}H_{18}N_2OS$	120	>160 (16.7)
96	*i*-C_3H_7	H	H	H	230-232		H/E	$C_{16}H_{16}N_2OS$	>160 (25)	130
97	-$(CH_2)_3$-		H	H	243[e]	76	E	$C_{16}H_{14}N_2OS$	30	30
98[f]	-$(CH_2)_4$-		H	H	247-249[e]				20	35
99[f]	-$(CH_2)_4$-		H	*o*-Cl	260-263[e]				10	20
100	-$(CH_2)_4$-		H	*p*-Cl	253-254[e]	77	D/W	$C_{17}H_{15}ClN_2OS$	>160 (0)	>160 (0)
101	-$(CH_2)_4$-		H	*o*-OCH_3	241-242[e]	58	H/E	$C_{18}H_{18}N_2O_2S$	>80 (25)	80
102	-$(CH_2)_4$-		H	*m*-CF_3	217	69	E	$C_{18}H_{15}F_3N_2OS$	160	>160 (0)
103	-$CH_2CH_2CH(CH_3)CH_2$-		H	H	224-225[e]	83	H/C	$C_{18}H_{18}N_2OS$	60	80
104	-$(CH_2)_5$-		H	H	228-229[e]	75	M	$C_{18}H_{18}N_2OS$	70	>160 (0)
105	H	CH_3	CH_3	H	234-235[e]	70	C/E	$C_{15}H_{14}N_2OS \cdot HCl$	40	>160 (0)
106	H	CH_3	CH_3	*o*-Cl	232-234[e]	68	C/E	$C_{15}H_{13}ClN_2OS \cdot HCl$	25	2.1
107	H	C_2H_5	CH_3	H	103-104	64	E	$C_{16}H_{16}N_2OS \cdot HCl$	30	10
108	H	C_2H_5	CH_3	*o*-F	203-204[e]	68	A/E	$C_{16}H_{15}FN_2OS \cdot HCl$	0.6	0.4
109	H	C_2H_5	CH_3	*o*-Cl	105-106	88	H	$C_{16}H_{15}ClN_2OS$	2.9	0.5
110	H	C_2H_5	CH_3	*o*-Br	100-102	80	H/E	$C_{16}H_{15}BrN_2OS$	1.2	0.3
111	CH_3	CH_3	CH_3	H	121	70	H/E	$C_{16}H_{16}N_2OS$	36	15
112	CH_3	CH_3	CH_3	*o*-Cl	235-236	83	E	$C_{16}H_{15}ClN_2OS \cdot HCl$	12	12.5
113	CH_3	CH_3	CH_3	*p*-Cl	182-184	76	H/E	$C_{16}H_{15}ClN_2OS$	>80 (0)	>160 (0)
114[f]	-$(CH_2)_4$-		CH_3	H	128-129[e]				35	15
115	-$(CH_2)_4$-		CH_3	*o*-Cl	137	87	I	$C_{18}H_{17}ClN_2OS$	30	3.7
116	-$(CH_2)_4$-		CH_3	*o*-OCH_3	148-149	88	E	$C_{19}H_{20}N_2O_2S$	>80 (0)	16
117	-$(CH_2)_4$-		CH_3	*m*-CF_3	141-141.5	77	E	$C_{19}H_{17}F_3N_2OS$		>160 (0)
118	-$(CH_2)_5$-		CH_3	H	150-151	72	E	$C_{19}H_{20}N_2OS$	120	>160 (16.7)
119	-$(CH_2)_4$-		-$CH_2CH{=}CH_2$	H	139-140	71	H/E	$C_{20}H_{20}N_2OS$	>160 (25)	>160 (16.7)
120	-$(CH_2)_4$-		-$CH_2C{\equiv}CH$	H	137-138	70	I	$C_{20}H_{18}N_2OS$	>160 (25)	>160 (0)
121	-$(CH_2)_4$-		*n*-C_4H_9	H	101-102	82	H/E	$C_{21}H_{24}N_2OS$	>160 (0)	>160 (0)
122	-$(CH_2)_4$-		-$CH_2C_6H_5$	H	121-122	84	I	$C_{24}H_{22}N_2OS$	>160 (25)	>160 (0)
Cf. CDP									14.7	4.6
Cf. DZP									1.6	0.9

[a]H, hexane; E, EtOH; T, toluene; I, *i*-PrOH; D, DMF; W, H_2O; C, EtOAc; M, MeOH; A, Me_2CO. [b]Analyzed for C, H, and N. [c]FE, the inhibition of fighting episodes. Met, the antagonism of pentylenetetrazole. Values are ED_{50}'s expressed in mg/kg. Values in parentheses express inhibitory rate (%) at induced dose. [d]Invag A.G., Netherlands Patent 6,918,485 (1970). [e]Decomposed. [f]Park, Davis and Co., Belgium Patent 745,560 (1970).

Table VI. Pharmacological Data (2)[a]

	Anticonvulsant activity		Muscle-relaxant activity		Narcosis potentiation		Taming effect	Acute toxicity LD_{50}	
	Electroshock ED_{50}, ip	Bemegride ED_{50}, ip	Rotacage ED_{50}, ip	Rotarod ED_{50}, ip	Hexobarbital PD_{50}, ip	Chlorprothixene PD_{50}, po	(O.B. rats), ED_{50}, po	ip	po
83	12.0	5.3	32.4	31.0	2.9	17.6	34.0	300	480
84	3.9	0.4	4.2	3.5	2.1	3.5	12.4	330	580
85	7.0	1.3	17.2	6.4	0.6	0.2	64.0	410	670
108	4.6	0.5	9.7	6.3	1.3	0.8	9.3	390	640
109	8.0	0.6	8.1	3.3	1.5	0.5	16.1	440	636
CDP	16.0	3.3	19.2	14.2	1.6	9.2	80.0	380	950
DZP	7.0	0.7	7.2	5.3	0.5	0.5	14.6	410	740

[a]Values are expressed in mg/kg.

EtOAc was washed with water, 10% HCl, and Na_2CO_3 solution, successively, dried (Na_2SO_4), and then concentrated under reduced pressure. Recrystallization of the residue from EtOH gave 15.7 g of **11**, mp 151–152°.

(II) 2-Benzyloxycarbonylaminoacetamido-3-benzoylthiophenes (Table II, 22–39). 2-Benzyloxycarbonylaminoacetamido-3-*o*-chlorobenzoyl-5-ethylthiophene (24). Benzyloxycarbonylaminoacetyl chloride (27.3 g, 0.12 mol) was added, with ice cooling, to a solution of **4** (26.6 g, 0.1 mol) in $CHCl_3$ (150 ml). After standing overnight in an ice box, the mixture was concentrated under reduced pressure. Recrystallization of the residue from EtOH gave 27.9 g of **24**, mp 118–119°.

(III) 2-Haloacetamido-3-benzoylthiophenes. (a) Cl or Br Derivatives (Table III, 40–51). 2-Chloroacetamido-3-*o*-chlorobenzoyl-5-ethylthiophene (43). A solution of **4** (26.6 g, 0.1 mol) and chloroacetyl chloride (11.3 g, 0.11 mol) in $CHCl_3$ (130 ml) was refluxed for 1 hr. The solvent was concentrated under reduced pressure and the residue was recrystallized from EtOH to give 27.6 g of **43**, mp 99–100°.

(b) Iodo Derivatives (Table III, 52–59). 2-Iodoacetamido-3-*o*-chlorobenzoyl-5-ethylthiophene (55). Sodium iodide (16.5 g, 0.11 mol) was added to a stirred solution of **43** (34.2 g, 0.1 mol) in Me_2CO (200 ml) and the mixture was refluxed for 30 min. After cooling, the inorganic salt was filtered off and the filtrate was concentrated under reduced pressure. Recrystallization of the residue from EtOH gave 37.3 g of **55**, mp 100–101°.

(IV) 2-Aminoacetamido-3-benzoylthiophenes (Table IV, 60–80). Method A. 2-Aminoacetamido-3-*o*-chlorobenzoyl-5-ethylthiophene (63). A solution of **24** (45.7 g, 0.1 mol) in 20% HBr–AcOH (200 ml) was stirred at room temperature for 1 hr. Isopropyl ether (1 l.) was added to the mixture and the precipitated crystals were collected by filtration and washed with three 100-ml portions of isopropyl ether. A suspension of the crystals in water was made alkaline with $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and concentrated under reduced pressure. Recrystallization of the residue from EtOH gave 20.3 g of **63**, mp 146–148°.

Method B. 2-Aminoacetamido-3-*o*-bromobenzoyl-5-ethylthiophene (64). Ammonia gas was introduced, with ice cooling, to a solution of **56** (20 g, 0.042 mol) in $CHCl_3$ (50 ml) and MeOH (5 ml) during 2 hr. After stirring at room temperature for additional 2 hr, the mixture was washed with ice–water and $NaHCO_3$ solution, successively, dried (Na_2SO_4), and then concentrated under reduced pressure. Recrystallization of the residue from EtOH gave 11.7 g of **64**, mp 160–161°.

(V) 5-Phenylthieno[2,3-*e*][1,4]diazepines (Table V, 81–104). 5-*o*-Chlorophenyl-7-ethyl-1,3-dihydro-2*H*-thieno[2,3-*e*][1,4]diazepin-2-one (85). A solution of **63** (10.0 g, 0.031 mol) in a mixture of pyridine (50 ml), AcOH (1.9 g, 0.031 mol), and C_6H_6 (20 ml) was refluxed for 10 hr in a flask fitted with a water separator. The mixture was concentrated under reduced pressure. A suspension of the mixture in water was made alkaline with $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried (Na_2SO_4) and concentrated under reduced pressure. Crystallization of the residue from toluene gave 5.9 g of **85**, mp 204–206°.

(VI) 1-Substituted 5-Phenylthieno[2,3-*e*][1,4]diazepines (Table V, 105–122). 1-Methyl-5-*o*-chlorophenyl-7-ethyl-1,3-dihydro-2*H*-thieno[2,3-*e*][1,4]diazepin-2-one (109). A 50% suspension of NaH in mineral oil (2.9 g, 0.06 mol) was added portionwise to a solution of **85** (15.3 g, 0.05 mol) in DMF (100 ml). After stirring for 15 min at 50°, MeI (8.5 g, 0.06 mol) was added dropwise to the mixture with ice cooling and the solution was stirred for additional 30 min at room temperature. A suspension of the mixture in water was extracted with EtOAc. The extract was washed with water, dried (Na_2SO_4), and then concentrated under reduced pressure. Recrystallization of the residue from hexane gave 8.8 g of **109**, mp 105–106°.

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Centrally Acting Emetics. 7. Hofmann and Emde Degradation Products of Apomorphine†,[1]

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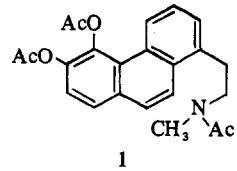
 Received August 14, 1972

Hofmann elimination of quaternary apomorphine derivatives has been studied with respect to direction of ring opening. Specificity of opening has been attained by choice of a suitable base, and some confusion and error existing in the older literature on the subject have been resolved. Emde degradations have been found to proceed smoothly and the structure of the product has been determined by nmr. Derivatives of the Hofmann and Emde products have been evaluated for emetic effects and these biological data have been rationalized on conformational grounds.

Tiffeneau and Porcher[2] first prepared "triacetylapomorphine" **1** by prolonged heating of apomorphine with excess acetic anhydride, and they reported it to be devoid of emetic activity; this observation was verified in this laboratory.[3] Since the diacetate ester **2** of apomorphine has emetic activity nearly identical with that of apomorphine itself,[3] it was



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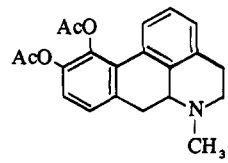

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speculated that the inactivity of triacetylapomorphine might be referrable, at least in part, to the masking of the basicity of the nitrogen by the amide link. The great differences in emetic activity produced by relatively minor

†This investigation was supported in part by Grants No. NS-04349 and NS-1396, National Institute of Neurological Diseases and Stroke. Abstracted in part from a thesis submitted by R. J. B. in partial fulfillment of the requirements for the Ph.D. degree, The University of Iowa, 1970.