Synthesis, Benzodiazepine Receptor Binding, and Anticonvulsant Activity of 2,3-Dihydro-3-oxo-5*H*-pyrido[3,4-*b*][1,4]benzothiazine-4-carbonitriles

Robert J. Chorvat,*[†] Bipin N. Desai,[†] Suzanne Evans Radak,[†] James Bloss,[‡] James Hirsch,[‡] and Stanley Tenen[‡]

Departments of Medicinal Chemistry and Biological Research, G. D. Searle and Co., Chicago, Illinois 60680.
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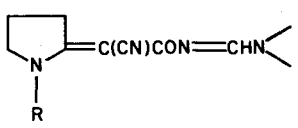
A series of oxopyridobenzothiazines (azaphenothiazines) were prepared and evaluated for binding to the benzodiazepine receptor, anticonvulsant activity in the pentylenetetrazole-induced convulsion assay, and, in two cases, ability to increase punished responding in a standard conflict test. While parent compound **1a** showed binding affinity comparable to chlorodiazepoxide (CDP), its potency in the anticonvulsant assay and the anticonflict test was considerably weaker than CDP. Of the variety of derivatives synthesized, only the 7-chloro compound **1b** showed receptor affinity comparable to **1a** with slightly improved in vivo activity. The poor correlation between receptor binding and in vivo activity may be due to variability in absorption or pharmacological responses unrelated to affinity for the benzodiazepine receptor.

The tricyclic phenothiazines constitute a major class of pharmaceutical agents with beneficial antipsychotic, CNS depressant, and antihistaminic properties.[1] While most compounds prepared in these series do not contain a heteroatom in either aromatic ring, various monoazaphenothiazines are known,[2] with several being currently marketed as drugs.[3] In view of the medical importance of this class of compounds, we investigated our previously described α-pyridone annulation reaction with the benzothiazine system.[4,5] This union rendered heretofore unknown oxopyridobenzothiazines[6] (1), potential precursors for a variety of central nitrogen alkylated analogues. We found, however, that the parent compound possessed properties similar to the benzodiazepines in both in vitro binding and in vivo assays. In light of these findings, we pursued modification of this structure with the intention of fully exploiting these unexpected characteristics.

Chemistry. 2*H*-1,4-Benzothiazine-3(4*H*)-thiones (2)[7] were converted to cyanoacetamide adducts **4** via treatment of the readily derived thiolactim ethers **3** with the sodium salt of cyanoacetamide in DMF as shown in Scheme I. We initially found that treatment of **4a** with greater than 2 equiv of *N*,*N*-dimethylformamide diethyl acetal in DMF at 95–100 °C resulted in the formation of the bis(dimethylaminomethylene) adduct **6a**. The carboxamide was readily liberated through hydrolysis with ammonium hydroxide solution, and continued heating produced the tricyclic α-pyridone **1a**.

We subsequently found that treatment of **4a** with 1 equiv of the acetal reagent in DMF at room temperature gave the monoadduct **5a**. This compound was then cyclized to **1a** by heating in DMF at 145 °C, a result contrasting earlier reports on an analogous cyclization by Glushkov and co-workers.[9,10] In their work on pyrrolidine I, the ring-alkylated nitrogen was necessary for thermal



I

cyclization to produce the annulated pyridone. The unsubstituted (I, R = H) system afforded an annulated pyrimidone.[9] This suggested that the enhanced nucleophilicity of the carbon adjacent to sulfur directed cyclization, via an enamine intermediate formed upon double-bond isomerization, to the pyridone 1.[6] When *N*,*N*-dimethylacetamide dimethyl acetal was used to form the monoadduct **5e**, heating afforded the corresponding methylpyridone **1e**.

Since addition of an electronegative substituent to the fused benzene ring of the benzodiazepine series favorably alters biological activity,[11] the effect of these and other substituents on the benzene nucleus of the title series was also studied. Incorporation of chlorine at both the 7- and 8-positions of **1** was accomplished via the previously described thermal cyclization pathway by using 6-chloro-2*H*-1,4-benzothiazin-3(4*H*)-one[12] or 7-chloro-2*H*-1,4-benzothiazin-3(4*H*)-one,[13] respectively, as precursors to starting material **2**.[14] The 7,8-dimethoxypyridone **1d** was synthesized from 6,7-dimethoxy-2*H*-1,4-benzothiazin-3-(4*H*)-one.[15]

The corresponding sulfoxides and sulfones of several tricyclic pyridones were formed through oxidation with peracetic acid. Thus, the sulfoxides **7a** and **7c** were prepared with the peracid at room temperature. Heating the sulfides or sulfoxides at 60–75 °C in the presence of excess

[†] Department of Medicinal Chemistry.
[‡] Department of Biological Research.

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(2) Petrow, V. A.; Rewald, E. L. *J. Chem. Soc.* **1945**, 591. Takahashi, T.; Yoshii, E. *Pharm. Bull.* **1954**, *2*, 382. Yale, H. L.; Sowinski, F. *J. Am. Chem. Soc.* **1958**, *80*, 1651. Gennaro, A. R. *J. Org. Chem.* **1959**, *241*, 1156. Schuler, W. A.; Klebe, H. *Ann. Chem.* **1962**, *653*, 172.
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(6) Chorvat, R. J.; Radak, S. Evans *Tetrahedron Lett.* **1980**, 421.
(7) Prasad, R. N. *J. Med. Chem.* **1969**, *12*, 290.
(8) These exo adducts appeared to be a single isomer from both ^1H and ^{13}C NMR spectroscopy, suggesting that the hydrogen-bonded structure shown in **4** was present. Previous examples of cyclic unsaturated systems where hydrogen bonding also provided energy barriers favoring a single isomer at room temperature have been reported, e.g., Shvo, Y.; Belsky, I. *Tetrahydron* **1969**, *25*, 290.
(9) Azimov, V. A.; Granik, V. G.; Glushkov, R. G.; Yakhonto, L. N. *Khim. Geterosikl. Soedin.* **1978**, 355.
(10) Granik, V. G.; Marchenko, N. B.; Vlasova, T. F.; Glushkov, R. G. *Khim. Geterosikl. Soedin.* 1976, 1509.
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(15) Baldick, K. J.; Lions, F. *J. Proc. R. Soc. N.S.W.* **1938**, *71*, 112.

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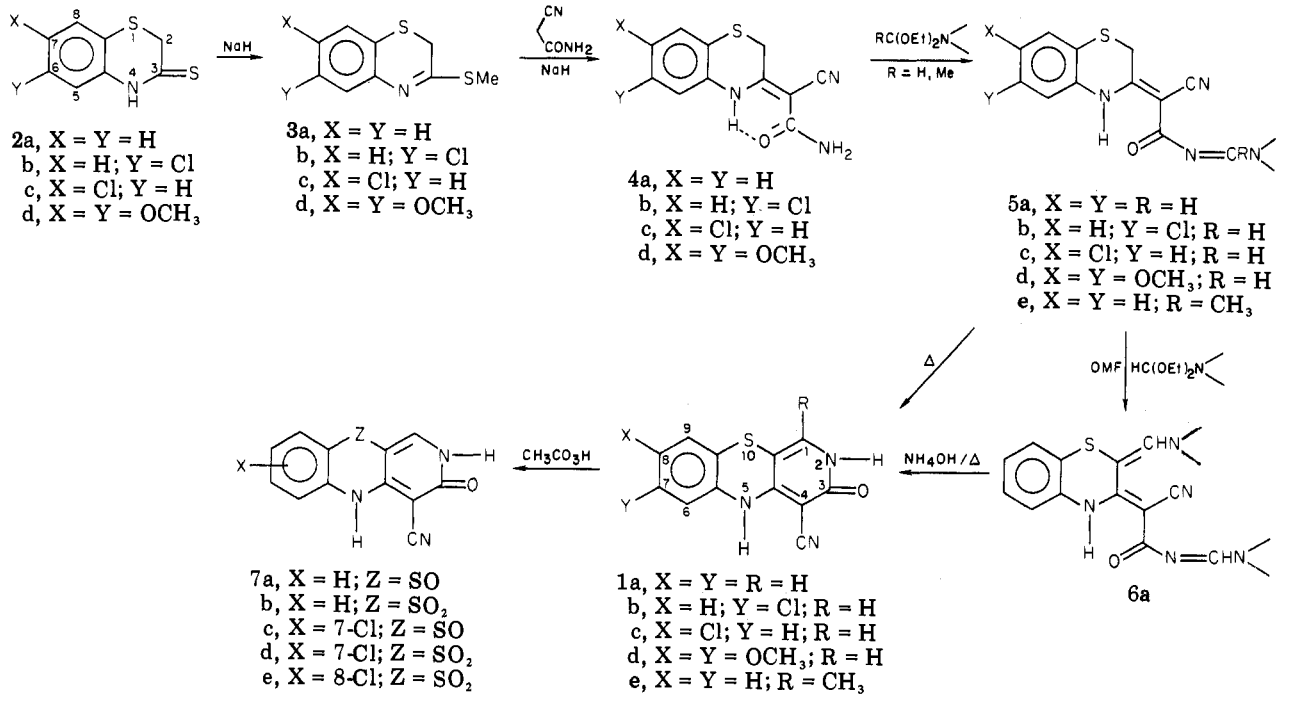
Scheme I



2a, X = Y = H
b, X = H; Y = Cl
c, X = Cl; Y = H
d, X = Y = OCH_3

3a, X = Y = H
b, X = H; Y = Cl
c, X = Cl; Y = H
d, X = Y = OCH_3

4a, X = Y = H
b, X = H; Y = Cl
c, X = Cl; Y = H
d, X = Y = OCH_3

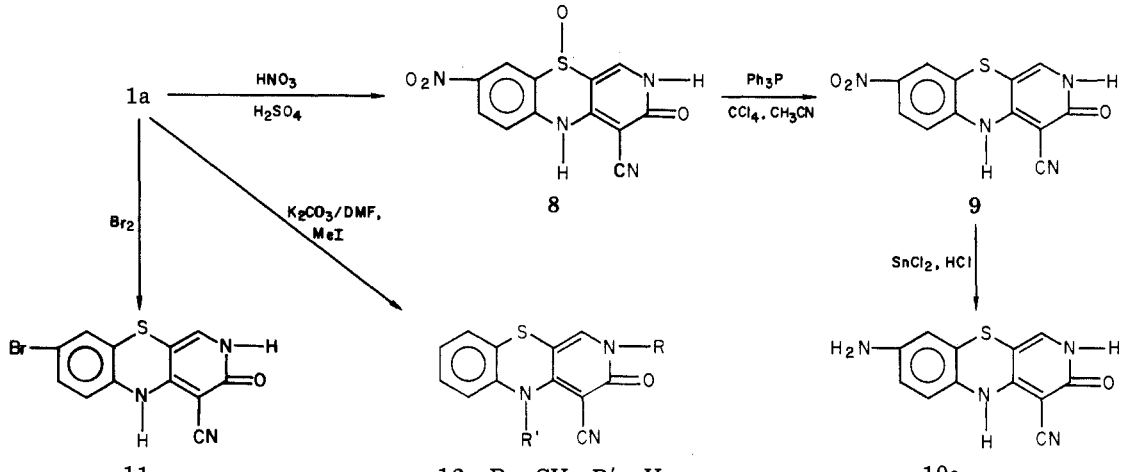
5a, X = Y = R = H
b, X = H; Y = Cl; R = H
c, X = Cl; Y = H; R = H
d, X = Y = OCH_3; R = H
e, X = Y = H; R = CH_3

6a

1a, X = Y = R = H
b, X = H; Y = Cl; R = H
c, X = Cl; Y = H; R = H
d, X = Y = OCH_3; R = H
e, X = Y = H; R = CH_3

7a, X = H; Z = SO
b, X = H; Z = SO_2
c, X = 7-Cl; Z = SO
d, X = 7-Cl; Z = SO_2
e, X = 8-Cl; Z = SO_2

Scheme II



8

9

11

12a, R = CH_3; R' = H
b, R = R' = CH_3

10a
10b, ·HCl

peracid gave sulfones **7b,d,e**.

Other substituents were incorporated at the 8-position of the tricyclic system through electrophilic aromatic substitution reeactions (Scheme II). Thus, nitration of **1a** gave nitro derivative **8**, which was also oxidized to its corresponding sulfoxide during this reaction.[16] Reduction of sulfoxide **8** to sulfide **9** was best accomplished by following the procedure of Szmant with triphenylphosphine and carbon tetrachloride in acetonitrile.[17] Treatment of **9** with stannic chloride in HCl afforded the 8-amino tricyclic pyridone **10a** or its hydrochloride salt **10b**. In addition, treatment of **1a** in HOAc with Br_2 afforded the 8-bromo derivative **11**.

The position of the nitro and bromo substituents in **8** and **11**, respectively, was established through their ^1H NMR spectra. The bromo compound **11** showed a spectrum that was similar to that of the 8-choro compound **1c**, where the position of the substituent was unequivocally established (vide supra). The three benzene ring protons of both **1c** and **11** were overlapped and formed a complex pattern centered at 7.15 and 7.25 ppm, respectively. The 8- and 9-protons of the 7-choro compound **1b** were partially overlapped and centered at 7.04 ppm, with the signal due to its 6-proton located about 0.4 ppm further downfield. We anticipated that if bromine were at the 7-position in **11** it would exert an even greater deshielding effect on the 6-proton.[18]

Assignment of the position of the nitro group in **8** was based on a comparison of the proton shifts of **8** with those of its corresponding nitro sulfide **9**. The position of the 1-proton in **8** is shifted downfield by 1.43 ppm from that in **9** due to the deshielding effect of the sulfoxide. In the nitrated ring, a downfield shift of 0.95 ppm was also observed for the proton showing only meta coupling (3 Hz).

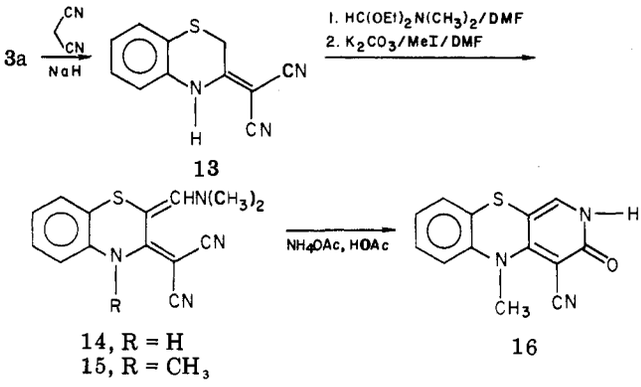
(16) If a single equivalent of nitric acid was used, the unsubstituted sulfoxide was the preponderant product.
(17) Castrillon, J. P. A.; Szmant, H. H. *J. Org. Chem.* **1965**, *30*, 1338.
(18) For a discussion on the effects of substituents on the chemical shifts of benzene protons, see Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: 1969; pp 201–204.

Table I. Binding Affinities and Anticonvulsant Activity of 2,3-Dihydro-3-oxo-5*H*-pyrido[3,4-*b*][1,4]benzothiazine-4-carbonitriles

compd	IC_{50},[a] [^{3}H]DZM, $\times 10^{-7}$ M	anti-PTZ assay[b] 30 min[c] 4[d]	30 min[c] 64[d]	60 min[c] 10[d]	60 min[c] 64[d]	60 min[c] 100[d]
1a	4.50	0/10[e] (62)[f]	4/10	0/10	1/10	
1b	4.00	2/10 (26)[f]	9/10	1/10 (32)[f]	10/10	
1c	3.20	NT[g]				2/10
1d	1000	0/10	2/10	1/10	2/10	
1e	17.0	0/10	1/10			2/10
7a	42.5	0/10	4/10	3/10[h] (41)[f]		8/10
7b	110	1/10	2/10		2/10	
7c	350	0/10	2/10	0/10		6/10
7d	76.0	0/10	4/10			5/20
7e	6.34	1/10	5/10	NT		
9	8.00	0/10	6/10	1/10		2/10
10	9.10	2/10	5/10		7/20	
11	80.0	0/10	5/10	0/10		2/10
12a	170	0/10	1/10			2/10
12b	1000	0/10	5/10	NT		
16	3.14	0/10	0/10		0/10	
chlordiazepoxide	4.42	(1.25)[f]				

[a] Concentration of drug inhibiting binding of tritiated diazepam to rat brain homogenates by 50%.[19-22] [b] Determination of the ability of the compound to inhibit pentylenetetrazole (PTZ) induced convulsions in mice.[2] [c] Time interval between administration of PTZ and test compound. [d] Dose administered in milligrams per kilogram. [e] Number of animals protected from convulsant per number of animals challenged. [f] ED_{50} in milligrams per kilogram, determined in a separate set of experiments. [g] Not tested. [h] Response at 25 mg/kg.

Scheme III



This deshielding effect established the C-9 position of the proton; the coupling pattern established the nitro group at the 8-position.

Compounds having an alkyl group on the pyridone, as well as the central, nitrogen of the tricyclic molecules were also prepared. Treatment of **1a** with 1 equiv of potassium carbonate and 1 equiv of methyl iodide in DMF gave *N*-methylpyridone **12a**. With 2 or more equiv of base and excess alkyl halide, the dialkylated material **12b** resulted. Since the central nitrogen alkylated derivative **16** was also desired, but not accessible through a direct alkylation route, an alternate approach was developed (Scheme III). Malononitrile derivative **13** was formed from thiolactim ether **3a** in a manner similar to that previously described for **4**. Treatment of **3** with *N*,*N*-dimethylformamide diethyl acetal in DMF to give **14**, followed by alkylation with methyl iodide in the presence of K_2CO_3 in DMF, afforded **15**, which was then converted to the α-pyridone **16** with ammonium acetate in acetic acid.

Biology. In 1977, Squires and Braestrup[19] first reported the existence of a specific, high-affinity, saturable binding site for benzodiazepines in the membrane fraction of rat brain, a phenomenon soon corroborated by other groups.[20-22] The highly significant correlations between the ability of members of this series to displace radiolabeled diazepam from these sites in vitro and their clinical potency strongly suggested that these sites were receptors mediating the pharmacological effects of the benzodiazepines. In addition, this in vitro binding technique provided a facile means of identifying structurally unrelated molecules with binding properties similar to those of the benzodiazepines.

Evaluation of the parent tricyclic pyridone **1a** in this binding assay disclosed that this compound bound to the benzodiazepine receptor with an IC_{50} of 4.5×10^{-7} M (Table I). In vivo testing of **1a** in the pentylenetetrazole (PTZ) induced seizure assay, a standard pharmacological test for anticonvulsant activity,[23] showed that this compound could block the convulsant properties of PTZ in a dose-responsive fashion ($ED_{50} \approx 60$ mg/kg) when it was administered to mice 30 min before the convulsant (Table I). Administration of **1a** 1 h before PTZ, however, had little effect in blocking convulsions. These data suggested a rapid onset of activity and/or short half-life for this compound. Other members of this series were generally tested at these two time intervals before PTZ administration so that variations in these properties among members of this series could be observed. In addition, **1a** was evaluated for its ability to increase punished responding in a standard conflict test.[24] In this assay (Vogel test), antianxiety activity is indicated by an increased response that is periodically punished by shock. Again, **1a** showed activity in this paradigm with a minimum effective dose (MED) of 60 mg/kg (ip).

To gain some understanding of the structural features of **1a** that were necessary for optimal binding to the dia-

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(20) Mohler, H.; Okada, T. *Science* **1977**, *198*, 849.
(21) Speth, R. C.; Wastek, G. J.; Johnson, P. C.; Yamamura, H. I. *Life Sci.* **1978**, *22*, 859.
(22) Mackerer, C. R.; Kochman, R. L.; Bierschenk, B. A.; Bremner, S. S. *J. Pharmacol. Exp. Ther.* **1978**, *206*, 405.
(23) Goodman, L. S.; Grewald, M. S.; Brown, W. C.; Swinyard, E. A. *J. Pharm. Exp. Ther.* **1953**, *108*, 168.
(24) Vogel, J. R.; Beer, B.; Clody, D. E. *Psychopharmacologia* **1971**, *21*, 1.

zepam receptor,[19-22] as well as highest potency in the anticonvulsant assay, we initially studied the effect of methylation of its pyridone ring. This modification on the C atom of the pyridone heterocycle **1e** or on its N-atom **12a** diminished both binding and anti-PTZ activity. The *N,N'*-dimethylated analogue **12b** showed very weak binding to the receptor but had good anti-PTZ activity at 64 mg/kg when administered 30 min before PTZ, a response that may not be related to its binding affinity. The compound with only the central nitrogen alkylated (**16**) possessed binding comparable to **1a**, indicating the necessity of the unsubstituted pyridone nitrogen for optimal receptor recognition. This compound, however, was devoid of anti-PTZ activity, which again suggested that receptor binding and anti-PTZ activity do not correlate in this series.

The effect of benzene-ring substitutents on binding and in vivo activity was also determined. Addition of a chloro substituent to either the 7- or 8-position of the tricyclic system did not significantly alter binding (**1b** and **1c**, respectively). However, **1b** possessed greater and dose-response anti-PTZ activity at both time intervals. Moreover, the MED of this compound in the Vogel assay was 18 mg/kg, a significant increase in potency over **1a**. The limited anticonvulsant testing of **1c** indicated diminished activity in comparison to **1b**. Substituting an 8-bromo substituent (**11**) for the chloro group diminished binding, but **11** had significant activity at 64 mg/kg at the 30-min interval in the anti-PTZ assay. This was also true of the 8-nitro compound **9** and 8-amino compound **10** at this dose and time interval, though binding affinities were less than **1a**. The dimethoxy compound **1d** showed diminished binding and little in vivo activity, a result consistent with the effect of electron-donating substituents in the benzodiazepine series.[11]

The effect of oxidation of the sulfur atom was also evaluated in the unsubstituted and the chloro-substituted series. In general, oxidation diminished the affinity of all compounds for the receptor, with no consistent pattern for the relative binding affinities of sulfoxides and sulfones in each series. In the anticonvulsant assay, the sulfoxide in the unsubstituted series (**7a**) showed good activity at both 30 and 60 min, with better potency at the longer time interval. However, in the 7-chloro series, the sulfoxide **7c** was active only at 100 mg/kg at the 60-min time interval.[25] The sulfone **7b** in the unsubstituted series showed little in vivo activity, whereas in both chloro series some anticonvulsant activity was manifested by sulfones **7d** and **7e** at high doses.

While correlation between in vitro binding and in vivo anticonvulsant or anticonflict activity in the benzodiazepine series is generally very good,[26] this correlation in the oxopyridobenzothiazine series has been absent. The extreme insolubility of these high-melting compounds may result in poor absorption and bioavailability and could contribute, to some degree, to the unpredictable responses among members of this series. Another possibility is that the biological properties of these compounds are unrelated to their receptor affinity and result from other, possibly novel, mechanisms of action.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were taken on a Varian A60-A or T-60 spectrometer with Me_4Si as an internal standard. UV spectra were obtained on a Beckman DK-2A by the group of A. J. Damascus; when extinction coefficients are omitted, compound solubility precluded recording of accurate values. Mass spectra were determined on a AEI MS 30 by Dr. J. Hribar and asssociates. Compounds were subjected to elemental analysis by the group of E. Zielinski, and the results were within ±0.4% of theoretical values unless indicated.

2*H*-1,4-Benzothiazine-3(4*H*)-thiones (2) were prepared according to the procedure of Prasad.[7]

Compound 2a: recrystallized from EtOH; mp 128–128.5 °C; UV (MeOH) max 275 nm (ε 20 800); NMR ($CDCl_3$) δ 3.83 (2 H, s, CH_2), 6.83–7.43 (4 H, m, aromatic H's). Anal. ($C_8H_7NS_2$) C, H, N.

Compound 2b: recrystallized from EtOH; mp 204.5–210 °C; UV (MeOH) max 280 nm (ε 24 300); NMR (Me_2SO-d_6) δ 3.90 (2 H, s, CH_2), 7.00–7.50 (3 H, m, aromatic H). Anal. ($C_8H_6NS_2Cl$) C, H, N.

Compound 2c: recrystallized from EtOH/EtOAc; mp 196–199 °C; UV (MeOH) max 280 nm (ε 24 200); NMR (Me_2SO-d_6) δ 3.95 (2 H, s, CH_2), 7.25 (2 H, m, aromatic H), 7.47 (1 H, m, aromatic H). Anal. Calcd for $C_8H_6NS_2Cl$: C, 44.54; H, 2.80; N, 6.49; S, 29.72. Found: C, 44.92; H, 2.87; N, 7.09; S, 29.36.

Compound 2d: recrystallized from MeOH; mp 197–199 °C; UV (MeOH) max 285 nm (ε 28 900); NMR ($CDCl_3$) δ 3.83 (8 H, s, 2-OCH_3's and CH_2), 6.62 (1 H, s, aromatic H), 6.75 (1 H, s, aromatic H). Anal. ($C_{10}H_{11}NO_2S_2$) C, H, N.

3-(Methylthio)-2*H*-1,4-benzothiazines (3). The preparation of the thiolactim ether from the unsubstituted benzothiazine is representative. To 3.0 g of a 57% NaH/mineral oil dispersion (70 mmol), previously washed with Skelly B to remove the mineral oil, in 150 mL of THF at room temperature in a nitrogen atmosphere was added in portions 9.05 g (50 mmol) of **2a** over a 15-min period. After the reaction mixture was stirred for an additional 10 min, 8.5 g (60 mmol) of methyl iodide in 10 mL of THF was added over a 2- to 3-min period. After the mixture was stirred for 15 min at room temperature, TLC (10% ethyl acetate/toluene; silica-coated microscope slide) indicated complete conversion to the thioether **3a**, and this solution was used in the subsequent reaction without isolation of this product: NMR ($CDCl_3$) δ 2.52 (3 H, s, S-CH_3), 3.20 (2 H, s, CH_2).

2-Cyano-2-(2,3-dihydro-4*H*-benzothiazin-3-ylidene)acetamides (4). The prepartion of the unsubstituted benzothiazine adduct is representative. To 3.2 g (79 mmol) of 57% NaH/mineral oil dispersion previously washed twice with Skelly B to remove the mineral oil and suspended in 125 mL of DMF at room temperature in a nitrogen atmosphere was added 6.3 g (75 mmol) of cyanoacetamide in portions over a 15-min period. After addition, the solution was stirred for 30 min before the previously prepared lactim ether solution of **3a** was added dropwise over a 10-min period. The reaction mixture was then heated at ca. 70 °C for 6 h and then cooled to ambient temperature before diluting the solution with ca. 200 mL of H_2O, followed by 1 N HCl solution until the pH of the solution was about 8. Additional H_2O (~150 mL) caused formation of a precipitate, which was collected, affording 10.0 g (87%) of **4a**. Recrystallization from DMF/H_2O (slight) gave pure compound **4a**: mp 267–268 °C (dec); UV (MeOH) max 276 nm (ε 25 000); NMR (Me_2SO-d_6) δ 3.88 (2 H, s, CH_2), 7.0–7.5 (4 H, m, aromatic H's). Anal. ($C_{11}H_9N_3OS$) C, H, N.

Compound 4b: recrystallized from DMF/H_2O: mp >300 °C; UV (MeOH/$CHCl_3$) max 282 nm (ε 29 800), 319 (17 000); NMR (Me_2SO-d_6) δ 3.93 (2 H, s, CH_2), 7.0–7.5 (3 H, m, aromatic H's). Anal. ($C_{11}H_8ClN_3OS$) C, H, N.

Compound 4c: recrystallized from DMF/H_2O; mp 150–160 °C (dec); UV (MeOH/$CHCl_3$) max 282 nm (ε 24 100); NMR (Me_2SO-d_6) δ 3.93 (2 H, s, CH_2), 7.2–7.6 (3 H, m, aromatic H's). Anal. ($C_{11}H_8ClN_3OS$) C, H, N.

Compound 4d: recrystallized from DMF/H_2O; mp 220–222 °C; UV (MeOH) max 286 nm (ε 28 400) 360 (15 700); NMR (Me_2SO-d_6) δ 3.73 (6 H, s, OMe's), 3.82 (2 H, s, CH_2), 6.92 (1 H, s, aromatic H), 6.97 (1 H, s, aromatic H). Anal. ($C_{13}H_{13}N_3O_3S$) C, H, N.

2-Cyano-2-(2,3-dihydro-4*H*-benzothiazin-3-ylidene)-*N*-[(dimethylamino)methylene]acetamides (5). The following two examples are representative.

(25) Due to the propensity of the sulfoxide of **1c** to oxidize to the sulfone **7e**, clean sulfoxide in this series was not prepared.

(26) Malick, J. B.; Enna, S. J. *Commun. Psychopharmacol.* **1979**, *3*, 245.

Compound 5a. To 2.5 g (10.8 mmol) of **4a** in 60 mL of dry DMF at room temperature in a nitrogen atmosphere was added 2.0 g (13.6 mmol) of *N,N*-dimethylformamide diethyl acetal. The reaction mixture was stirred overnight at room temperature and then poured onto 300 mL of H_2O and extracted with $CHCl_3$. The extracts were combined and concentrated in vacuo to give a brown syrup, which was crystallized from EtOAc to give 3.01 g (97%) of **5a**. A small sample was recrystallized from aqueous DMF and dried to give analytically pure **5a**: mp 157–158 °C; UV (MeOH) max 219, 240 shoulder on 219, 365 nm (ϵ 15 700); NMR ($CDCl_3$) δ 3.18 [6 H, s, N $(CH_3)_2$], 3.81 (2 H, s, CH_2), 6.83–7.4 (4 H, m, aromatic H's), 8.47 (1 H, s, =CH). Anal. ($C_{14}H_{14}N_4OS$) C, H, N.

Compound 5c. After the reaction mixture was stirred at room temperature overnight, a precipitate was isolated, washed with ethyl acetate, recrystallized from aqueous DMF, and dried to afford **5c**: mp 200–204 °C (softening from 196 °C); UV (MeOH) max 235, 365 nm (ϵ 30 600); NMR ($CDCl_3$) δ 3.20 [6 H, s, $N(CH_3)_2$], 3.83 (2 H, s, CH_2), 6.83–7.35 (3 H, m, aromatic H's), 8.50 (1 H, s, =CH). Anal. ($C_{14}H_{13}ClN_4OS$) C, H, N.

2,3-Dihydro-3-oxo-5*H*-pyrido[3,4-*b*][1,4]benzothiazine-4-carbonitriles (1) via the Monoadducts 5. The preparation of **1a** is representative. To 7.7 g (33.4 mmol) of **4a** in 150 mL of DMF at room temperature in a nitrogen atmosphere was added 5.7 g (40 mmol) of *N,N*-dimethylformamide diethyl acetal, and the reaction mixture was stirred at room temperature overnight. The cyclization of the monoadduct **5a** was accomplished by heating this reaction mixture at ca. 145 °C for 6 h and then cooling. The precipitate present was collected, washed with a small amount of ethyl acetate, and dried to afford 4.52 g (56%) of analytically pure **1a**: mp >305 °C; UV (MeOH) max 252 nm (ϵ 42 600); NMR (Me_2SO-d_6) δ 6.92–7.30 (4 H, m, aromatic H's), 7.32 (1 H, s, pyridone H). Anal. ($C_{12}H_7N_3OS$) C, H, N.

Compound 1b: mp >300 °C; UV (MeOH) max 253 nm (ϵ 35 900); NMR (Me_2SO-d_6) δ 7.02 (1 H, dd, 8-H), 7.07 (1 H, d, 9-H), 7.35 (1 H, s, 1-H), 7.41 (1 H, m, 6-H). Anal. ($C_{12}H_6ClN_3OS$) C, H, N.

Compound 1c: recrystallized from DMF/H_2O; mp >300 °C; UV (MeOH) max 256 nm (ϵ 39 700); NMR (Me_2SO-d_6) δ 7.15 (3 H, m, 6-, 7-, and 9-H's), 7.33 (1 H, s, pyridone H). Anal. ($C_{12}H_6ClN_3OS$) C, H, N.

Compound 1d: mp >300 °C; UV (MeOH) max 251 nm (ϵ 46 400), 310 (5700); NMR (Me_2SO-d_6) δ 3.70 (6 H, s, OMe's), 6.67 (1 H, s, aromatic H), 7.17 (1 H, s, aromatic H), 7.30 (1 H, s, aromatic H).

Compound 1e: mp >305 °C; UV (MeOH/$CHCl_3$) max 254 nm. Anal. ($C_{13}H_9N_3OS$) C, H, N.

2-Cyano-2-[2-[(Dimethylamino)methylene]-3,4-dihydro-2*H*-1,4-benzothiazin-3-ylidene]-*N*-[(dimethylamino)-methylene]acetamide (6a). To 0.23 g (1 mmol) of **4a** in 2 mL of DMF was added 0.4 g (2.7 mmol) of dimethylformamide diethyl acetal, and the reaction mixture was heated on a steam bath for 2 h. The solvent was then removed (N_2 stream), leaving a solid residue. Recrystallization from CH_2Cl_2/Skelly B gave 340 mg (99%) of **6a**: mp 163–183 °C (slow dec); UV (MeOH) max 222 nm (ϵ 23 400), 272 (24 700), 379 (32 100); NMR ($CDCl_3$) δ 3.11 (3 H, s, N-CH_3), 3.15 (3 H, s, N-CH_3), 3.20 (6 H, s, N-CH_3's), 6.8–7.2 (4 H, m, aromatic H's), 7.41 (1 H, s, vinyl H), 8.47 (1 H, br s, HC=N). Anal. ($C_{17}H_{19}N_5OS$) C, H, N.

2,3-Dihydro-3-oxo-5*H*-pyrido[3,4-*b*][1,4]benzothiazine-4-carbonitrile (1a) via the Bisadduct 6a. To 460 mg (2.0 mmol) of **4a** in 5 mL of DMF was added 550 mg (3.8 mmol) of dimethylformamide diethyl acetal, and the reaction mixture was heated at ca. 100 °C for 3 h. After this time, TLC showed complete conversion of **4a** to **6a**. Concentrated ammonium hydroxide solution (2 mL) was then added, and heating was continued for 15 min. After the mixture was cooled, water was added followed by sufficient glacial acetic acid to acidify the solution. The precipitate that formed was collected, washed with a small amount of methanol and then ether, and dried to afford 340 mg of **1a** (71%). This product was identical with that obtained via the monoadduct **5a**. Anal. ($C_{12}H_7N_3OS$) C, H, N.

2,3-Dihydro-3-oxo-5*H*-pyrido[3,4-*b*][1,4]benzothiazine-4-carbonitrile 10-Oxides (7). The preparation of **7a** is representative. To 0.1 g of **1a** suspended in 2 mL of glacial HOAc at room temperature was added 0.5 mL of 40% peracetic acid solution, and the reaction mixture was stirred at ambient temperature for 1.5 h. The now faint yellow solid was collected, washed with a small amount of MeOH, and dried to give 90 mg (~85%) of **7a**: mp >300 °C; UV (MeOH) max 260 nm; NMR (Me_2SO-d_6) δ 7.16–8.08 (4 H, m, aromatic H's), 8.68 (1 H, s, 1-H). Anal. ($C_{12}H_7N_3O_2S$) C, H, N.

Compound 7c: recrystallized from DMF/H_2O; mp >300 °C; UV (MeOH) max 258 nm (ϵ 39 000); NMR (Me_2SO-d_6) δ 7.30 (1 H, d of d, 8-H), 7.80–8.10 (2 H, m, 6- and 9-H's), 8.77 (1 H, s, 1-H). Anal. ($C_{12}H_6N_3ClO_2S$) C, H, N.

2,3-Dihydro-3-oxo-5*H*-pyrido[3,4-*b*][1,4]benzothiazine-4-carbonitrile 10,10-Dioxides (7). The preparation of **7d** is representative. To 120 mg of **1b** in 4 mL of glacial HOAc was added 0.4 mL of 40% peracetic acid solution, and the reaction mixture was heated at ca. 95 °C for 2.5 h. The off-white crystalline solid was then collected and dried to give 104 mg (78%) of pure **7d**: mp >300 °C; UV (MeOH/$CHCl_3$) 256 nm; MS, *m/e* 307 (M^+); NMR (Me_2SO-d_6) δ 7.40 (1 H, d of d, 8-H), 7.80–8.10 (2 H, m, 6- and 9-H's), 8.60 (1 H, s, 1-H). Anal. ($C_{12}H_6ClN_3O_3S$) C, H, N.

Compound 7b: mp >300 °C; UV (MeOH) max 260 nm; NMR (Me_2SO-d_6) δ 7.2–8.1 (4 H, m, aromatic H's), 8.57 (1 H, s, 1-H). Anal. ($C_{12}H_7N_3O_3S$) C, H, N.

Compound 7e: mp >300 °C; UV (MeOH) max 265 nm; MS, *m/e* 307 (M^+); NMR (Me_2SO-d_6) δ 7.73–8.30 (3 H, m, aromatic H's), 8.83 (1 H, s, 1-H). Anal. ($C_{12}H_6ClN_3O_3S$) C, H, N.

2,3-Dihydro-8-nitro-3-oxo-5*H*-pyrido[3,4-*b*][1,4]benzothiazine-4-carbonitrile 10-Oxide (8). To 0.5 g (2.07 mmol) of **1a** dissolved in 5 mL of concentrated H_2SO_4 at ca. 0 °C was added dropwise 0.5 g (7.9 mmol) of HNO_3. after the mixture was stirred at the above temperature for 1 h, water was added, and the solid that formed was collected. Recrystallization from DMF/H_2O gave 0.53 g (68%) of **8** as the DMF solvate: mp >305 °C; UV (MeOH) max 245, 350 nm; NMR (Me_2SO-d_6) δ 2.70, 2.87 (DMF N-CH_3's), 8.17 (1 H, d, J = 8 Hz, 6-H), 8.47 (1 H, dd, J = 8 and 3 Hz, 7-H), 8.88 (1 H, s, 1-H), 8.85 (1 H, d, J = 3 Hz, 9-H). Anal. ($C_{12}H_6N_4O_4S{\cdot}C_3H_7NO$) C, H, N.

2,3-Dihydro-8-nitro-3-oxo-5*H*-pyrido[3,4-*b*][1,4]benzothiazine-4-carbonitrile (9). To 270 mg (1.03 mmol) of triphenylphosphine in 5 mL of a 1:1 CH_3CN/CCl_4 solution was added 120 mg (0.32 mmol) of **8**, and the reaction mixture was heated at reflux for 15 min. After the mixture was cooled the precipitate was collected and recrystallized from DMF/MeOH to give 55 mg (43%) of **9** as the hemisolvate (DMF): mp >305 °C; UV (MeOH) max 234, 295, 340 nm; NMR (Me_2SO-d_6) δ 2.70, 2.87 (DMF), 7.42 (1 H, s, 1-H), 7.43 (1 H, d, J = 9 Hz, 6-H), 7.93 (2 H, m, 7- and 9-H's). Anal. ($C_{12}H_6N_4O_3S{\cdot}0.5C_3H_7NO$) C, H, N.

6-Amino-2,3-dihydro-3-oxo-5*H*-pyrido[3,4-*b*][1,4]benzothiazine-4-carbonitrile (10). To 2.0 g (6.2 mmol) of **9** suspended in 70 mL of glacial HOAc was added 3.6 g (16 mmol) of stannic chloride dihydrate dissolved in 12 mL of concentrated hydrochloric acid solution and the reaction mixture was refluxed for 30 min. After the mixture was cooled the precipitate was collected, washed with additional HOAc, and dried before digesting into ca 150 mL of boiling MeOH. The hot solution was filtered, yielding 1.3 g of solid, which was digested again as above to afford 0.8 g of solid from this second portion of hot MeOH. This material was dissolved in 15 mL of Me_2SO and 2 mL H_2O, and the solution was basified to pH 8 with concentrated NH_4OH solution. The precipitate that formed was collected and dried to give 0.7 g (44%) of **10a** as the free base. Recrystallization from DMF/H_2O gave pure **10a**: mp >305 °C; UV (MeOH) 261, 320 nm; NMR (Me_2SO-d_6) δ 6.26 (1 H, d, 9-H), 6.35 (1 H, dd, 7-H), 7.00 (1 H, d, 6-H), 7.25 (1 H, s, 1-H); MS, *m/e* 256 (M^+). Anal. ($C_{12}H_8N_4OS$) C, H, N.

The MeOH filtrates were combined and concentrated to afford in three crops 0.75 g (40%) of amine hydrochloride salt **10b**. The second crop (0.22 g) proved to be analytically pure material: mp >300 °C; UV (MeOH) max 259 nm (ϵ 37 200). The other two crops analzyed ca. 1% low for C and showed UV spectra with ϵ 34 000, indicating about 90% of hydrochloride. Anal. ($C_{12}H_8N_4OS{\cdot}HCl$) C, H, N.

8-Bromo-2,3-dihydro-3-oxo-5*H*-pyrido[3,4-*b*][1,4]benzothiazine-4-carbonitrile (11). To 0.35 g (1.44 mmol) of **1a** in 50 mL of glacial HOAc was initially added 1 mL of a 1.09 M

Br_2/CCl_4 solution (2.18 mmol), and the reaction mixture was heated at ca. 100 °C for 1.5 h. A second 1.0-mL portion of the bromine solution was then added, and heating was continued at ca. 90 °C overnight. After the mixture was cooled, the precipitate present was collected and washed with a small amount of ethyl acetate, affording 380 mg (80%) of crude product. Recrystallization from DMF gave pure **11**: mp >305 °C; UV (MeOH) max 258 nm; NMR (Me_2SO-d_6) δ 7.25 (3 H, m, 6-, 7-, and 9-H), 7.32 (1 H, s, 1-H); MS *m/e* 320 (M^+). Anal. ($C_{12}H_6N_3OSBr$) C, H, N.

2,3-Dihydro-2-methyl-3-oxo-5*H*-pyrido[3,4-*b*][1,4]benzothiazine-4-carbonitrile (12a). To 240 mg (1 mmol) of **1a** in 5 mL of DMF at room temperature was added 140 mg (1 mmol) of K_2CO_3 and 140 mg of MeI (1 mmol), and the reaction mixture was stirred for 2.5 h. Addition of water caused formation of 0.18 g (70%) of monoalkylated product, which was collected and recrystallized from acetonitrile to give pure **12a**: mp 292–295 °C (dec); UV (MeOH) max 253 nm (ε 43 800), 300 (10 400); NMR (Me_2SO-d_6) δ 3.28 (3 H, s, N-CH_3), 6.9–7.4 (4 H, m, aromatic H's), 7.58 (1 H, s, 1-H). Anal. ($C_{13}H_9N_3OS$) C, H, N.

2,3-Dihydro-2,5-dimethyl-3-oxo-5*H*-pyrido[3,4-*b*][1,4]benzothiazine-4-carbonitrile (12b). To 1.0 g (4.1 mmol) of **1a** suspended in 10 mL of DMF were added 1.15 g (8.3 mmol) of anhydrous K_2CO_3 and 1.5 g (10.5 mmol) of MeI, and the reaction mixture was heated at ca. 100 °C for 2 h. After the mixture was cooled, water was added, and the solid was collected to afford 0.9 g (80%) of crude dialkylated product. Recrystallization from ethanol gave pure **12b**: mp 236–237 °C; UV (MeOH) max 250 nm; NMR (Me_2SO-d_6) δ 3.33 (3 H, s, 2-CH_3), 3.73 (3 H, s, 5-CH_3), 7.0–7.4 (4 H, m, aromatic H's), 7.66 (1 H, s, 1-H). Anal. ($C_{14}H_{11}N_3OS$) C, H, N.

2-Cyano-2-(2,3-dihydro-4*H*-benzothiazin-3-ylidine)acetonitrile (13). The thiolactim ether **3a** was generated from 10.0 g (55 mmol) of thiolactam **2a**, 2.9 g (60 mmol) of 50% NaH dispersion, and 9.0 g (63 mmol) of CH_3I in 120 mL of THF as previously described. The anion of malononitrile was generated from 5.5 g (83 mmol) of the nitrile and 4.0 g (83 mmol) of 50% NaH dispersion in 200 mL of DMF as previously described. The solution of lactim ether was added to that of the malononitrile anion, and the resulting reaction mixture was heated at ca 85 °C for 5 h in a nitrogen atmosphere. After the mixture was cooled, the mixture was neutralized with glacial HOAc and diluted with water while cooling in an ice bath. The precipitate was collected, affording 8.38 g (71%) of analytically pure **13**: mp 250–252 °C (dec); UV (MeOH) max 279 nm (ε 21 400), 313 (14 600), 339 (15 500); NMR (Me_2SO-d_6) δ 3.83 (2 H, s, CH_2), 7.0–7.8 (4 H, br m, aromatic H's). Anal. ($C_{11}H_7N_3S$) C, H, N.

2-[2-[(Dimethylamino)methylene]-3,4-dihydro-2*H*-1,4-benzothiazin-3-ylidene]propanedinitrile (14). To 5.0 g (23.4 mmol) of **13** in 30 mL of DMF was added 4.5 g (30.6 mmol) of dimethylformamide diethyl acetal, and the reaction was heated at ca. 90 °C for 1 h in a nitrogen atmosphere. After cooling, the solution was diluted with water, and the yellow precipitate was collected, affording 5.67 g (90%) of **14**, which was suitable for the subsequent reaction. Recrystallization from DMF/H_2O gave pure **14** as golden needles: mp 236–238 °C (dec); UV (MeOH) max 220, 237 (sh), 274 (ε 21 400), 313, 339 nm; NMR ($CDCl_3$) δ 3.28 (6 H, s, N-CH_3's), 6.9–7.3 (4 H, m, aromatic H's), 7.40 (1 H, s, vinyl H); MS, *m/e* 268 (M^+). Anal. ($C_{14}H_{12}N_4S$) C, H, N.

2-[2-[(Dimethylamino)methylene]-3,4-dihydro-4-methyl-2*H*-1,4-benzothiazin-3-ylidene]propanedinitrile (15). To 1.0 g (3.7 mmol) of **14** in 20 mL of DMF were added 0.55 g (4.0 mmol) of anhydrous K_2CO_3 and 3.39 g (24 mmol) of MeI, and the reaction mixture was stirred at room temperature for 2 h. Dilution with water afforded 1.0 g (95%) of yellow solid, which was suitable for the subsequent reaction without further purification. Recrystallization from CH_2Cl_2/MeOH gave pure **15**: mp 240–241 °C; UV (MeOH) max 224 nm (ε 18 500), 276 (19 700), 348 (16 300); NMR ($CDCl_3$) δ 3.30 [6 H, s, N (CH_3)$_2$], 3.73 (3 H, s, N-CH_3), 7.15 (4 H, m, aromatic H's), 7.60 (1 H, s, olefinic H). Anal. ($C_{15}H_{14}N_4S$) C, H, N.

2,3-Dihydro-5-methyl-3-oxo-5*H*-pyrido[3,4-*b*][1,4]benzothiazine-4-carbonitrile (16). To 0.8 g (2.8 mmol) of **15** in 20 mL of glacial HOAc was added 1.0 g of ammonium acetate, and the reaction mixture was heated on the steam bath for 3 h. After the mixture was cooled, 514 mg (72%) of analytically pure **16** was collected in two crops: mp >300 °C; UV (MeOH) max 251 nm (ε 33 600); NMR (Me_2SO-d_6) δ 3.73 (3 H, s, N-CH_3), 7.45 (1 H, s, 1-H). Anal. ($C_{13}H_9N_3OS$) C, H, N.

Biological Testing Procedures. The benzodiazepine receptor binding assay was that described by Mackerer et al.[22] Six to eight concentrations of test drug were added to tubes containing rat brain membranes and [^{3}H]diazepam at a final concentration of 4 μM. After incubation at 30 °C for 10 min, followed by 4 °C for 20 min, reactions were terminated by vacuum filtration through Whatman GF/C glass-fiber filters. Nonspecific binding was determined in the presence of 4 μM unlabeled diazepam. The IC_{50} of a compound was that concentration resulting in 50% inhibition of [^{3}H]diazepam binding to the membrane fraction.

The anticonvulsant procedure followed that described by Goodman et al.[23] After the intraperitoneal administration of test compound suspended in saline containing 0.09 mL of a 1:1 mixture of propylene glycol/polysorbate 80 to groups of ten Charles River male albino mice (18–28 g), animals were challenged with an intravenous infusion of 35 mg/kg of pentylenetetrazole (PTZ) at 30- or 60-min intervals. Animals were observed for the appearance of clonic seizures, which occurred in all members of the control group of mice. Data were recorded as the number of mice protected from clonic seizures per number of mice tested. The method of Litchfield and Wilcoxson was used to determine ED_{50}'s at the reported times.[27]

The conflict procedure was adapted from that described by Vogel.[24] Twenty-four-hour water-deprived rats were placed individually into small plastic chambers containing a stainless-steel grid floor and a metallic drinking tube. Animals were permitted water ad libitum. After 20 licks, the animal received two electrical shocks (1.0 mA) on his next 2 licks. The number of shocks administered during a 3-min period commencing with the 20th lick was recorded. Drugs were administered intraperitoneally to test animals as a suspension in normal saline containing a drop of PG–Tween 80, and concentrations were adjusted so that all animals received 2 mL of drug suspension per kilogram of body weight. Animals were tested 40 min after injections, and the lowest dose that produced a statistically significant difference ($p \leq 0.05$, Mann Whitney *U* test) from the vehicle control group was described as the minimum effective dose (MED).

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(27) Litchfield, J. T.; Wilcoxson, F. *J. Pharm. Exp. Ther.* **1949**, *96*, 99.