bath. The precipitate was recrystallized from MeCN to give 17 (0.19 g).

Ethyl 4-Amino-2-(2-isopropoxyphenyl)pyrimidine-5-carboxylate (44). Method A. Ethyl ethoxymethylenecyanoacetate (0.855 g, 5.05 mmol) was added with stirring to an ice-cold solution of 2-isopropoxybenzamidine[1] (1.66 g, 9.3 mmol) in ethanol (10 mL). The solution was allowed to stand at 0–5 °C for 17 h. The solution was cooled (dry ice/2-propanol), and 44 (0.6 g, 39.5%), mp 132–134 °C, was collected by filtration. Recrystallization from MeCN gave an analytical sample, mp 133–135 °C. Anal. ($C_{16}H_{19}N_3O_3$) C, H, N.

Method B. Sodium azide (0.54 g, 8.3 mmol) was added to a solution of $AlCl_3$ (0.37 g, 2.78 mmol) in THF (16.5 mL).[18] The mixture was stirred under reflux for 0.5 h. The mixture was cooled to −45 °C, and the cyanoacrylate 43 (0.69 g, 2.3 mmol) was added in small portions. After 1 h at −45 °C, followed successively by 1 h at 5 °C, 1 h at 25 °C, and 18 h at reflux, the mixture was cooled and poured onto ice-water (400 mL). The mixture was acidified to pH 3 with 6 N HCl and then filtered. The pH of the filtrate was adjusted to 6 with saturated $NaHCO_3$ solution. After the solution was cooled, stirred, and triturated for 2 h, the resultant solid (0.355 g, 51%) was collected by filtration and recrystallized from toluene–Skellysolve B to give 44, mp 129–134 °C.

Acknowledgment. We thank Dr. Paul Siminoff and Fred Reed for kindly providing us with all the rat PCA data and the Analytical Research and Development Department for their services.

Tricyclics with Analgesic and Antidepressant Activity. 2. [[(Alkylamino)ethyl]thio]dibenzo[*b,f*]thiepins and 10,11-Dihydro Derivatives[1]

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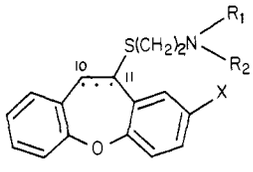
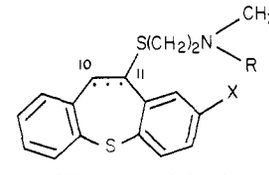
A series of [[(alkylamino)ethyl]thio]dibenz[*b,f*]thiepins (III) and their 10,11-dihydro derivatives (IV) was synthesized and subjected to broad analgesic/CNS screening. Preliminary results indicated a combination of analgesic/antidepressant profiles, similar to that observed for the [[(alkylamino)ethyl]thio]dibenz[*b,f*]oxepins (I) and their corresponding dihydro derivatives (II). The most active congener from the present series, **10b**, shows an antinociceptive potency in the pentazocine range as assessed by phenyl-*p*-quinone-induced writhing (PQW) and tail flick in mice. It is also more than twice as active as imipramine in preventing tetrabenazine-induced ptosis (TBZ), a test widely recognized to be of predictive value for clinically efficacious antidepressants.

A previous publication[1] from these laboratories has described a series of [[(alkylamino)ethyl]thio]dibenz[*b,f*]oxepins (I) and their 10,11-dihydro derivatives (II) as



I, 10,11-dehydro
II, 10,11-dihydro

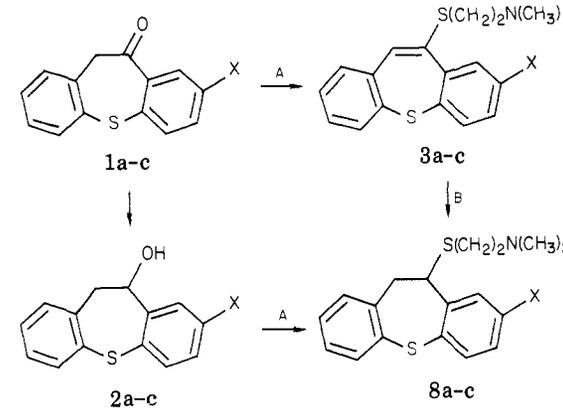


III, 10,11-dehydro
IV, 10,11-dihydro

potential analgesic agents. Results from animal studies indicated that these compounds, in general, showed a low propensity for addiction and tolerance, and many congeners, especially those bearing a fluorine substituent at the C-2 position, further displayed a unique pharmacological profile that combines the desired analgesic activity with an added component of antidepressant-like properties. The latter feature would seem particularly attractive in view of the growing body of clinical evidence[3–5] that implicates the close relationship between chronic pain and depression and the demonstrated effectiveness of many tricyclic antidepressants in alleviating pain associated with a variety of conditions. In this paper we report the synthesis and preliminary pharmacology of a related series of [[(alkylamino)ethyl]thio]dibenzo[*b,f*]thiepins (III) and the corresponding 10,11-dihydro derivatives (IV).[6]

Chemistry. The initial target compounds, i.e., **3a–c** and **8a–c**, were synthesized according to the procedures outlined in Scheme I. Dehydrative coupling of ketones

Scheme I[a]



[a] a, X = H; b, X = F; c, X = Cl.

1a–c[7] with β-(dimethylamino)ethanethiol in the presence of boron trifluoride etherate and glacial acetic acid (method A) afforded vinyl sulfides **3a–c** (type III) in good yields.

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[‡] Department of Biological Sciences.

(1) For paper 1, see Ong, H. H.; Profitt, J. A.; Anderson, V. B.; Spaulding, T. C.; Wilker, J. C.; Geyer, H. M. III *J. Med. Chem.* **1980**, *23*, 494.
(2) Present address: Miles Laboratories, Elkhart, IN.
(3) Moore, D. *J. Am. Med. Assoc.* **1980**, *73*, 1585.
(4) Ward, N. G.; Bloom, V. L.; Friedel, R. O. *Pain* **1979**, *7*, 331.
(5) Shimm, D. S.; Logue, G. L.; Maltbie, A. A.; Dugan, S. *J. Am. Med. Assoc.* **1979**, *241*, 2408.
(6) After our study had been completed, the synthesis of **10c** was reported via a different synthetic scheme: see Bartl, V.; Nemec, J.; Bartosova, M.; Protiva, M. *Collect. Czech. Chem. Commun.* **1978**, *43*, 2427.
(7) Jilek, J. O.; Metysova, J.; Pomukacek, J.; Protiva, M. *Collect. Czech. Chem. Commun.* **1968**, *33*, 1831.

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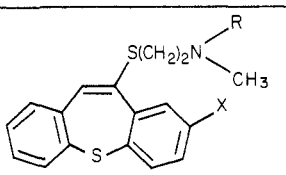
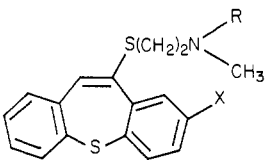
Table I. 11-[(β-Aminoethyl)thio]dibenzo[b,f]thiepins and Dihydro Derivatives[a]



3-6



8 and 10

compd	R	X	method	yield,[b] %	mp, °C	recrystn solvent[c]	formula	anal.
3a	CH_3	H	A	57.0	216-218	M-E	$C_{18}H_{19}NS_2 \cdot HCl$	C, H, N
3b	CH_3	F	A	45.4	209-211	M-A-E	$C_{18}H_{18}FNS_2 \cdot HCl$	C, H, N
3c	CH_3	Cl	A	42.6	219-221	M-A-E	$C_{18}H_{18}ClNS_2 \cdot HCl$	C, H, N
4a	$C(=O)OC_6H_5$	H	C	67.5	109-110	E-H	$C_{24}H_{21}NO_2S_2$	C, H, N
4b	$C(=O)OC_6H_5$	F	C	86.0	87-89	H	$C_{24}H_{20}FNO_2S_2$	C, H, N
4c	$C(=O)OC_6H_5$	Cl	C	48.8	*d*	*e*	$C_{24}H_{20}ClNO_2S_2$	C, H, N
5a	H	H	D	81.0	156-157	M-E	$C_{17}H_{17}NS_2 \cdot C_4H_4O_4$[f]	C, H, N
5b	H	F	D	37.0	170-171	M	$C_{17}H_{16}FNS_2 \cdot C_4H_4O_4$[f]	C, H, N
5c	H	Cl	D	44.3	194-196	M-A-E	$C_{17}H_{16}ClNS_2 \cdot HCl$	C, H, N
5d	H	OH	D	77.0	147-149	A-H	$C_{17}H_{17}NOS_2$	C, H, N
6b	C≡N	F	E	60.0	101-103	A-H	$C_{18}H_{15}FN_2S_2$	C, H, N
8a	CH_3	H	F	81.0	177-179	M-E	$C_{18}H_{21}NS_2 \cdot HCl$	C, H, N
			B	72.0				
8b	CH_3	F	F	54.6	155-158	A-E	$C_{18}H_{20}FNS_2 \cdot HCl$	C, H, N
8e	CH_3	Cl	F	37.9	99-101	A-E	$C_{18}H_{20}ClNS_2 \cdot C_4H_4O_4$[f]	C, H, N
10a	H	H	F	65.3	117-119	M-E	$C_{17}H_{19}NS_2 \cdot HCl$	C, H, N
10b	H	F	F	75.6	114-116	A-E	$C_{17}H_{18}FNS_2 \cdot C_4H_4O_4$[f]	C, H, N
10c	H	Cl	F	60.4	110-112	A-E	$C_{17}H_{18}ClNS_2 \cdot C_4H_4O_4$[f]	C, H, N

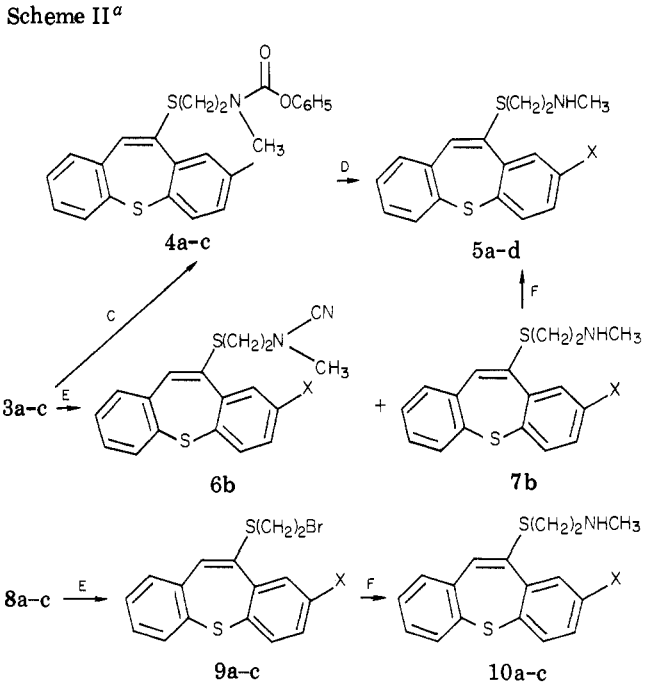
[a] All compounds exhibited IR, ^1H NMR, and MS spectra consistent with the structures. [b] Isolated yield; no efforts were made to optimize these yields. [c] A = acetone; E = ethyl ether; H = hexane; M = methanol. [d] Isolated as a heavy oil. [e] Purified by column chromatography over silica gel, dichloromethane as eluent. [f] Acid maleate salt.

In a similar manner, the corresponding 10,11-dihydro derivatives (type IV), **8a–c**, could be prepared in up to 81% yield from alcohols **2a–c**,[7] which were readily obtained from reduction of **1a–c** with sodium borohydride. An alternative route to **8a–c** was via the direct reduction of **3a–c** with magnesium in methanol (method B) as recently described by Profitt and Ong.[1,8]

Since previous SAR studies on the analogous [[(alkylamino)ethyl]thio]dibenz[b,f]oxepins (types I and II) indicated that optimal analgesic and antidepressant activity were associated, in both cases, with small substituents at the nitrogen terminal of the side chain, we decided in the present study to limit the structural modification involving the basic nitrogen to a simple replacement of one of the methyl groups with a hydrogen radical. Thus, as elaborated in Scheme II, **3a–c** were first converted to phenoxycarbonyl derivatives **4a–c** with phenyl chloroformate (method C); this was followed by alkaline hydrolysis with potassium hydroxide in ethylene glycol (method D). While **5a** and **5c** were obtained in good yields and high purity by this procedure, alkaline treatment of **4b** under similar conditions led to only a small yield of **5b**, accompanied by a major byproduct, **5d**, characterized as the hydroxy analogue of **5a–c**. The intermediacy of **5b** in the formation of **5d** was unambiguously established by effecting the alkaline hydrolysis under more strenuous conditions, which led to **5d** exclusively. A preferred method for demethylation of **3b**, therefore, involved treatment of the latter with cyanogen bromide (method E) to give an "abnormal" cleavage product, **7b**, in addition to the "normal" cyanamide **6b**. Analogous to what was observed for the dibenz[b,f]oxepins, conversion of **7b** to **5b** could be accomplished readily with methylamine in DMF (method F).

By a similar route, **8a–c** were demethylated to **10a–c** with greater efficiency; treatment of **8a–c** with cyanogen

Scheme II[a]



[a] a, X = H; b, X = F; c, X = Cl; d, X = OH.

bromide yielded almost exclusively the corresponding bromoethythio derivatives **9a–c**, which were then converted by method F to the secondary amines, **10a–c**, in high yields.

Pharmacological Results and Discussion

The title compounds were tested in a battery of pharmacological assays to assess their potential analgesic/CNS activity; highlights of these results are summarized in Table II. Additional biological data for selected compounds showing marked activity in the primary screens will also be presented in conjunction with SAR discussions.

(8) Profitt, J. A.; Ong, H. H. *J. Org. Chem.* **1979**, *44*, 3972.

Table II. Pharmacology of [[(Alkylamino)ethyl]thio]dibenzo[b,f]thiepins and 10,11-Dihydro Derivatives[d]

compd[a]	PQW writhing:[e] ED_{50}, mg/kg sc	tail flick: ED_{50}, mg/kg sc	TBZ ptosis:[b] ED_{50}, mg/kg po	5-HTP potentiation:[g] ED_{50}, mg/kg ip
3a	64% @ 10	>25	>20	>10
3b	>10	>25	3.6 (3.3-3.8)	>10
3c	14.6 (14.3-14.9)	>25	3.7 (2.9-4.9)[b]	>10
5a	58% @ 10	>25	23.9 (19.8-30.0)	>10
5b	8.9 (7.9-9.8)	50% @ 25	5.2 (4.7-5.9)	>10
5c	12.5 (12.0-13.1)	>25	4.6 (3.9-5.5)	>10
			0.55 (0.40-0.72)[b]	
5d	>10	>25	2.0 (1.5-2.6)	>10
8a	3.3 (3.1-3.5)	60% @ 25[c]	60% @ 20[b]	>10
8b	9.0 (7.7-10.9)	>25	1.2 (1.1-1.4)	>10
			0.91 (0.80-1.0)[b]	
8c	>10	>25	7.4 (6.6-8.3)	>10
			1.7 (1.5-2.0)[b]	
10a	4.2 (4.1-4.4)	60% @ 25[c]	8.0 (6.8-9.7)	>10
10b	2.9 (2.5-3.3)	60% @ 25[c]	1.5 (1.3-1.7)	8.1 (4.8-13.9)
			0.28 (0.25-0.31)[b]	
10c	4.4 (3.9-5.0)	63.6 (15.2-265.6)	2.0 (1.6-2.4)	50% @ 10
			0.50 (0.45-0.56)[b]	
pentazocine	2.4 (2.1-2.9)	14.6 (7.4-24.4)		
imipramine	10.7 (8.8-13.3)	>25	2.8 (2.5-3.0)	>10
			1.3 (1.2-1.4)	

[a] The vehicle control used in all four biological tests consists of distilled water and a few drops of Tween 80. [b] Determined after intraperitoneal administration. [c] ED_{50} value was not determined due to variability in dose-range studies. [d] ED_{50} values were calculated by a linear-regression analysis with 95% confidence limits given in parentheses. [e] Phenyl-p-quinone-induced writhing in mice. [f] Inhibition of tetrabenazine-induced ptosis in mice. [g] Potentiation of 5-hydroxytryptophan-induced stereotypy in rats.

Analgetic activity was determined by measuring the inhibition of phenyl-*p*-quinone-induced writhing (PQW) and the delay in response to noxious heat stimuli in mice (D'Amour–Smith tail-flick method). The PQW test is used to detect both weak and strong analgesics, while the tail-flick assay is sensitive to the opiate-like, strong analgesics.

In the PQW assay, optimal activity was found in **8a** and **10a–c**, all of which belong to the dihydrodibenzo[*b,f*]-thiepin series (type IV). It is worth noting that the most active compound, **10b**, also possesses the same structural parameters (i.e., a methylaminoethylthio side chain on the tricyclic framework and a 2-fluoro substituent) as the most active congener in the corresponding dibenz[*b,f*]oxepin series (type II: R = H; X = F). Overall, there appears to be no discernible pattern regarding the effect of halogen substitution on the antiwrithing activity. In the tail-flick assay, only marginal or low potency was observed for the title compounds, except for **5b**, **8a**, and **10a,b**, which were moderately active. Compounds **8a** and **10a** had similar potency as pentazocine in the Haffner's tail-clip model,[9] having ED_{50} values of 24.9 and 23.0 mg/kg sc, respectively, compared to 23.3 mg/kg sc obtained for pentazocine.

Antidepressant activity of the title compounds was determined by measuring their ability to prevent tetrabenazine-induced ptosis (TBZ) in mice and the potentiation of head twitching induced by 5-hydroxytryptophan (5-HTP) in pargyline-pretreated rats (Table II). With respect to anti-TBZ activity, the dihydro congeners, **8a–c** and **10a–c**, were generally more active than their dehydro counterparts, **3a–c** and **5a–c**. Two of the most active analogues in this model, **10b** and **10c**, also displayed moderate potency in potentiating 5-HTP-induced stereotypy, implying a possible involvement of the serotonergic pathway. In general, introduction of a 2-halo substituent greatly enhances the anti-TBZ activity; a similar effect was also observed for the 2-hydroxy substituent ($-\pi$ value, Hansch hydrophobic substituent parameter) as illustrated by **5d**.

(9) Haffner, F. *Dtsch. Med. Wochenschr.* **1929**, *55*, 731.

Antipsychotic activity was assessed by inhibition of apomorphine-induced mouse climbing[10a–c] and/or by antagonism of amphetamine aggregation toxicity.[11] Analogous to what was observed for the dibenz[*b,f*]oxepins, none of the title compounds from either type III or type IV series showed any significant activity.

Thus, the replacement of oxygen with sulfur in [[(alkylamino)ethyl]thio]dibenz[*b,f*]oxepins and their 10,11-dihydro derivatives has resulted in a series of compounds with reduced analgesic activity and modified antidepressant profile (i.e., the emergence of 5-HTP potentiation activity). The results further demonstrate that a seemingly minor isosteric substitution can bring about significant changes in biological activity due to subtle differences in lipophilicity, bond angles, and metabolic fate.

Experimental Section

The structures of all compounds are supported by their IR (Perkin-Elmer 457) and ^1H NMR (JEOLCO C60HL; tetramethylsilane) spectra. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Mass spectral data were determined with a Finnigan Model 4000 GC–MS equipped with a INCOS data system. Where analyses are indicated only by symbols of the elements, the analytical results obtained for those elements (performed by Micro-Tech Laboratories, Skokie, IL) were within 0.4% of theoretical values.

10-[[β-(Dimethylamino)ethyl]thio]dibenzo[*b,f*]thiepin Hydrochloride (3a). Method A. A mixture of **1a** (9.0 g, 41.6 mmol) and 8.0 g of β-(dimethylamino)ethylthiol hydrochloride in 100 mL of glacial acetic acid containing 52 mL of boron trifluoride etherate was stirred at 60 °C for 16 h. The cooled solution was poured onto 1 kg of crushed ice and, without delay, was

(10) (a) At the screening dose of 10 mg/kg ip, compounds **3a,c**, **5a,b,d**, **8a**, and **10a,c** were either inactive or marginally active; by comparison, chlorpromazine had an ED_{50} of 1.3 (1.1–1.6) mg/kg ip. (b) Costall, B.; Naylor, R. J.; Nohria, V. *Eur. J. Pharmacol.* **1978**, *50*, 39.

(11) In this model, only compound **3b** exhibited moderate activity with an ED_{50} value of 28.0 (15.3–50.9) mg/kg ip. When administered orally, however, **3b,c**, **5c**, **8a–c**, and **10b** all had ED_{50}'s much greater than 20 mg/kg. By comparison, the value obtained for chlorpromazine was 2.8 mg/kg po.

basified with a large excess of 40% sodium hydroxide. The basic material was extracted into ether, washed, dried, and concentrated to a reddish oil. The crude amino sulfide was purified by column chromatography over silica gel; elution with 10% methanol–CH_2Cl_2 (v/v) afforded a pale yellowish oil, which was converted to a crystalline hydrochloride (**3a**) in ether. Properties of **3a**, and of **3b,c** prepared in a similar manner, are included in Table I.

10,11-Dihydro-10-[[β-(methylamino)ethyl]thio]dibenzo-[b,f]thiepin Hydrochloride (8a). Method A. A solution of **2a** (15 g, 65 mmol) and 13 g of β-(dimethylamino)ethylthiol hydrochloride in 80 mL of glacial acetic acid and 80 mL of boron trifluoride etherate was stirred at 20 °C for 72 h. The cooled mixture was poured onto a large excess of ice-cold 15% sodium hydroxide, and the emulsion was filtered. The organic material was extracted into ether, washed, dried, and concentrated to a reddish oil. The crude product was purified by column chromatography over silica gel packed in CH_2Cl_2; elution with 10% methanol–CH_2Cl_2 (v/v) yielded a colorless oil, which was converted to a crystalline hydrochloride (**8a**) in ether. Properties of **8a**, and of **8b,c** prepared in a similar manner, are included in Table I.

Method B. Alternatively, **8a** was prepared by reduction of **3a** with magnesium in methanol. To 3.13 g (10 mmol) of the free base from **3a** in 50 mL of anhydrous methanol (Mallinckrodt, Karl Fischer) was added, at 0–5 °C, 1.8 g (75 mmol) of mangnesium shavings. The reaction mixture was stirred at 10 °C for 1 h and allowed to warm to room temperature. The methanolic solution was then decanted from the unreacted magnesium and acidified cautiously with a large excess of 3 N hydrochloric acid. The acidic mixture was extracted three times with 50-mL portions of $CHCl_3$, and the combined organic solution was washed with water, dried ($MgSO_4$), and concentrated to a brownish oil. The crude product was converted to 2.53 g (72%) of **8a**, which was identical with an authentic sample prepared by method A.

10-[[β-[N-Methyl-N-(phenoxycarbonyl)amino]ethyl]-thio]dibenzo[b,f]thiepin (4a). Method C. A solution of 6.26 g (20 mmol) of the free base from **3a** in 40 mL of CH_2Cl_2 was stirred at room temperature with 7.0 g of potassium carbonate while 3.8 g of freshly distilled phenyl chloroformate in 30 mL of CH_2Cl_2 was added dropwise over 30 min. The mixture was stirred at room temperature for an additional 16 h and then filtered, and the filtrate was diluted with 150 mL of ether. The organic solution was washed with 10% sodium hydroxide and water and dried over $MgSO_4$ overnight. Removal of the solvents under reduced pressure left a dark oil, which was purified by passing through a short column of silica gel packed in ether; elution with a large excess of ether afforded 5.66 g (67.5%) of **4a** of analytical purity. Properties of **4a**, and of **4b,c** prepared in a similar manner, are included in Table I.

10-[[β-(Methylamino)ethyl]thio]dibenzo[b,f]thiepin Maleate (5a). Method D. A mixture of **4a** (5.4 g, 12.9 mmol) and 10.5 g of potassium hydroxide in 80 mL of ethylene glycol was heated at 165 °C for 1 h, during which a clear solution was formed. The cooled solution was diluted with water (200 mL) and extracted thrice with ether (100 mL portions), and the combined ether solution was dried over anhydrous K_2CO_3. Removal of the solvent under reduced pressure left a pale yellowish oil, which was converted to a crystalline maleate (**5a**) in ether. Properties of **5a**, and of **5c** prepared in a similar manner, are included in Table I.

2-Hydroxy-11-[[β-(methylamino)ethyl]thio]dibenzo[b,-f]thiepin (5d). Method D. A mixture of **4b** (7.0 g, 16 mmol) and 40 g of 85% potassium hydroxide in 150 mL of ethylene glycol was stirred at 160–170 °C for 2 h. The cooled mixture was diluted with 300 mL of water, and the clear solution was acidified with concentrated hydrochloric acid. Rebasification with 6 N ammonium hydroxide (to pH 9–10) led to the precipitation of an off-white solid. The air-dried product was recrystallized twice from acetone to give 3.9 g (77%) of pure **5d**. Properties of **5d** are included in Table I.

Reaction of Cyanogen Bromide with 11-[[β-(Dimethylamino)ethyl]thio]-2-fluorodibenzo[b,f]thiepin (3b). Method E. A solution of the free base from **3b** (8.5 g, 25.6 mmol) in 50 mL of $CHCl_3$ was added dropwise to a solution of 2.5 g of cyanogen bromide in 30 mL of the same solvent. After stirring at room temperature for 2 h, the solution was concentrated in vacuo to a yellowish residue, which by TLC (silica gel F-254, CH_2Cl_2) was found to be a 2:1 mixture of two components. The crude products were thus separated by column chromatography over silica gel packed in CH_2Cl_2; elution with a large excess of CH_2Cl_2 gave, first, 2.9 g (31%, R_f 0.89) of **7b** as a pale yellowish oil. Anal. ($C_{16}H_{12}BrFS_2$) C, H. Further elution with CH_2Cl_2 gave 5.14 g (60%) of **6b** with a R_f value of 0.42. Properties of **6b** are included in Table I.

2-Fluoro-11-[[β-(methylamino)ethyl]thio]dibenzo[b,f]-thiepin (5b). Method F. A solution of **7b** (1.4 g, 3.8 mmol) in 30 mL of anhydrous dimethylformamide was bubbled with a stream of methylamine for 30 min. The warm solution was tightly stoppered and allowed to stand at room temperature overnight. Water (200 mL) was added; the organic product was extracted thrice with ether (150 mL portions), and the combined ethereal solution was washed exhaustively with water to remove the unreacted methylamine. The dried solution was then treated with a large excess of ethereal maleic acid to give, after trituration with acetone, 750 mg (37%) of **5b** as fine crystalline needles. Properties of **5b** are included in Table I.

10-[(β-Bromoethyl)thio]-10,11-dihydrodibenzo[b,f]thiepin (9a). Method E. To 11.5 g (36.5 mmol) of the free base from **8a** in 50 mL of $CHCl_3$ was added dropwise to 4.62 g of cyanogen bromide in 50 mL of the same solvent. After stirring at room temperature for 10 min, the solution was evaporated under reduced pressure to dryness, and the oil residue was purified by column chromatography over silica gel packed in CH_2Cl_2. Elution with CH_2Cl_2 gave 10.8 g (84%) of **9a**: mp 60–62 °C; fluffy needles from hexane. Anal. ($C_{16}H_{15}BrS_2$) C, H.

2-Fluoro-11-[(β-bromoethyl)thio]-10,11-dihydrodibenzo-[b,f]thiepin (9b) was obtained from **8b** in 92% yield by method E to give a colorless oil. Anal. ($C_{16}H_{14}BrFS_2$) C, H.

2-Chloro-11-[(β-bromoethyl)thio]-10,11-dihydrodibenzo-[b,f]thiepin (9c) was obtained from **8c** in 67% yield by method E to give a yellowish gum. Anal. ($C_{16}H_{14}BrClS_2$) C, H.

10,11-Dihydro-10-[[β-(methylamino)ethyl]thio]dibenzo-[b,f]thiepin Hydrochloride (10a). Method F. Anhydrous methylamine was bubbled through a solution of **9a** (3.5 g, 10 mmol) in 30 mL of DMF containing a few crystals of KI until it became saturated. The solution was stoppered and allowed to stand at room temperature for 16 h before 350 g of ice–water was added. The organic materials were extracted with three 100-mL portions of ether, and the combined ether solution was washed four times with water to remove the bulk of DMF and excess of methylamine. After drying over $MgSO_4$, the ether solution was treated with an ethereal solution of hydrogen chloride to give a gummy precipitate. Trituration of the crude product with methanol gave 2.2 g (65.3%) of **10a** as colorless prisms. Properties of **10a**, and of **10b,c** prepared in a similar manner, are included in Table I.

Pharmacological Methods. Procedural details for the inhibition of phenyl-*p*-quinone-induced writhing,[1] D'Amour–Smith tail-flick analgesia,[1] prevention of tetrabenazine-induced ptosis,[12] potentiation of 5-hydroxytryptophan-induced stereotypy,[12] and amphetamine aggregation toxicity[1] were previously reported. The antagonism of apomorphine-induced mouse climbing was carried out by a modification of the procedure developed by Costall and co-workers.[10b]

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