4-Piperazinyl-10*H*-thieno[2,3-*b*][1,5]benzodiazepines as Potential Neuroleptics[1]

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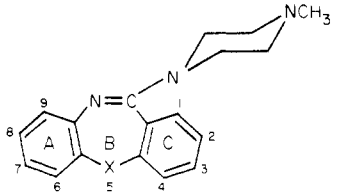
A series of 4-substituted 10*H*-thieno[2,3-*b*][1,5]benzodiazepines has been synthesized. These compounds have been assessed for their ability to block a conditioned avoidance response (CAR) and to produce catalepsy in rats and have been compared with several typical and atypical neuroleptics. The compounds which inhibit CAR at doses which produce no catalepsy are believed to cause less extrapyramidal side effects in the clinic. A number of compounds (**9**, **12**, **17**, **29**, and **34**) show potent neuroleptic activity, yet maintain a favorable separation of activity on these two parameters. Three 5-piperazinyl-10*H*-thieno[2,3-*b*][1,4]benzodiazepine derivatives (**46**–**48**) analogous to compounds in the [1,5] series have been prepared for comparison and were found to be inactive.

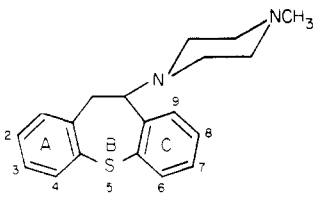
The incidence of extrapyramidal side effects in the management of psychotic disorders with neuroleptic drugs is an inherent problem. These adverse reactions, as well as the beneficial antipsychotic actions, are believed to be due to the blockade of dopamine receptors in the brain. Until recently, the therapeutic efficacy of the neuroleptics was considered to be closely associated with the extrapyramidal motor action and was evaluated in terms of their ability to produce a characteristic catalepsy in animals. It is, however, now believed that the extrapyramidal dysfunction is caused by blockade of the dopamine receptors in the striatum,[2] whereas the antipsychotic activity is due to a similar interaction in the mesolimbic area[3] of the brain. Thus, a compound with a more specific action on the dopaminergic receptors in the mesolimbic system would be expected to produce less catalepsy in animals and less undesirable extrapyramidal symptoms in man.

During recent years a number of antipsychotic agents belonging to the chemical class of dibenzoepines have been introduced. Some of these are powerful neuroleptics of the classical type (i.e., loxapine and clothiapine), but clozapine is an exception, since it is an effective antipsychotic compound which produces minimal extrapyramidal side effects. Clozapine differs from typical neuroleptics in its pharmacological, biochemical, and clinical actions.[4] The results from recent studies[5] suggest that it is more active in the mesolimbic than in the striatal system.

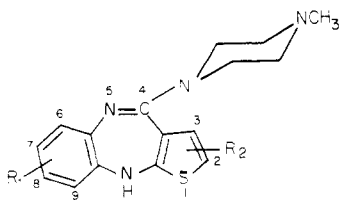


	X	substituent
loxapine	O	2-Cl
clothiapine	S	2-Cl
HF-2046	NH	2-Cl
clozapine	NH	8-Cl

Chemically, clozapine differs from the other neuroleptics of the dibenzoepine series in having a distinct substitution with a chlorine atom in position 8 (ring A), but not in position 2 (ring C). It is noncataleptogenic and does not antagonize apomorphine-induced stereotypies in animals, whereas its (ring C substituted) 2-chloro isomer HF-2046 behaves like a classical neuroleptic in these respects.[6] A similar change in activity profile has also been reported in the cases of octoclothepin and doclothepin. Octoclothepin, bearing an 8-chloro substituent in ring C, is a typical antipsychotic agent in its pharmacological and clinical effects, whereas its (ring A substituted) 2-chloro isomer doclothepin has a very similar pharmacological action to clozapine.[7] There is no definitive explanation as to how the transposition of this halogen substitution can result in a profound change in activity. Molecular topography of clozapine and HF-2046, as determined by X-ray crystallography,[8] does not reveal any significant difference. Electron transfer reactions have been often implicated in reversible attachment of biologically active molecules at a receptor site. Such a shift in nuclear substitution, as above, can contribute to the electronic imbalance between the two benzene rings of the asymmetrical tricyclic system. Similar effects can also be achieved by replacing one of the benzene rings with suitable heteroarene groups; thus, it would be of interest to examine whether compounds such as I, where the benzene ring (C)



octoclothepin, 8-Cl
doclothepin, 2-Cl

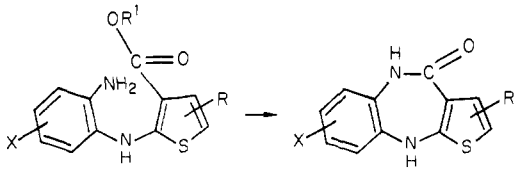


I

(1) Part 3 of the series Heteroarenobenzodiazepines; J. K. Chakrabarti and D. E. Tupper, British Patent Application 51 240, 1974; Belgium Patent 835 932, 1976. For part 2, see ref 12.
(2) O. Hornykiewicz, "Handbook of Neurochemistry", A. Lajtha, Ed., Plenum Press, New York, 1973, pp 465–502.
(3) N. E. Anden and C. Stock, *J. Pharm. Pharmacol.*, **25**, 346 (1973); G. Bertholini, *ibid.*, **28**, 429 (1976).
(4) F. Hunziker, E. Fisher, and J. Schmutz, *Helv. Chim. Acta*, 50, 1588 (1967); G. Stille, H. Lauener, and E. Eichenberger, *Farmaco, Ed. Prat.*, **26**, 603 (1971); H. Gross and E. Langner, *Wien. Med. Wochenschr.*, **166**, 814 (1966); J. Angst, D. Bente, P. Berner, H. Heimann, H. Helmchen, and H. Hippius, *Pharmakopsychiat./Neuro-Psychopharmakol.*, **4**, 201 (1971).
(5) J. L. Howard, B. T. Large, S. Wedley, and I. A. Pullar, *Life Sci.*, **23**, 599 (1978).
(6) J. Schmutz, *Arzneim.-Forsch. (Drug Res.)*, **25**, 712 (1975).
(7) J. O. Jilek, K. Sidelar, M. Rajsner, A. Dlabac, J. Metysova, and M. Protiva, *Act. Nerv. Super.*, 11, 215 (1975).
(8) T. J. Petcher and H. P. Weber, *J. Chem. Soc., Perkin Trans. 2*, 1415 (1976).

0022-2623/80/1823-0878$01.00/0

Scheme I



nearer to the basic piperazine ring is replaced with a relatively electron-rich thiophene ring, would produce a biological response similar to nonclassical neuroleptics.

In this paper, we report the synthesis of a series of 4-substituted 10*H*-thieno[2,3-*b*][1,5]benzodiazepines.[9] In order to investigate structure–activity relationships, modifications to the substituents on the phenyl as well as thiophene ring and suitable changes of the basic side chain have been made. To compare the activity, some analogous 5-piperazinyl-substituted 4*H*-thieno[2,3-*b*][1,4]benzodiazepines have also been made. The gross CNS activity of these compounds was established by studying the effects on the behavior of mice. Neuroleptic activity was evaluated in terms of their ability to produce hypothermia in mice and to block a conditioned avoidance response and produce catalepsy in rats. They have been compared with various types of antipsychotic drugs, e.g., clozapine, haloperidol, thioridazine, and *cis*-flupenthixol.

Chemistry. The amidines (Table I) were synthesized by reacting the corresponding diazepinones (Table II) with an appropriate amine in the presence of $TiCl_4$ and anisole (method A). Alternatively, the diazepinones were converted into the diazepinethiones, which on reaction with an amine gave the desired amidine (method B). The intermediate diazepinones were prepared by intramolecular cyclization of the corresponding diamino esters, as in Scheme I, with sodium methylsulfinylmethanide as described in our previous paper.[10] However, it was later found[11] that the diamino esters can be reacted directly with *N*-methylpiperazine, $TiCl_4$, and anisole at a higher temperature (160–180 °C) to give the desired amidines (**7**, **11**, and **18**) (method C). Various N-substituted piperazinyl compounds were obtained using method A. For certain modification of the distal N, the *N*-(carboethoxy) derivatives were hydrolyzed (method D) to give the corresponding N-unsubstituted piperazines, which were then appropriately alkylated to give the desired products (method E).

The preparation of 7-chloro-2-ethyl-4*H*-thieno[2,3-*b*]-[1,4]benzodiazepin-5-one and its dechloro analogue was reported earlier.[12] The respective amidines (**46**–**48**) were obtained by method A.

Structure–Activity Relationships. With respect to neuroleptic activity, it will be evident that a basic piperazine ring attached to the thienobenzodiazepine ring at position 4 is essential. The presence of a distal nitrogen with respect to the tricyclic system also seems critical, since compounds which are similarly substituted with a piperidine (**49**) or morpholine (**50**) ring, where this nitrogen is absent, are less effective. Compounds substituted with aminoalkylamines (Table I, section C), where the conformational freedom of these chains is greater than that of the piperazine ring, are also less effective. This suggests that a certain conformational state of the distal nitrogen atom of the piperazine ring is required for neuroleptic activity. 4′-(*N*-Methylpiperazinyl) compounds are most active. Higher alkyl (Et, *n*-Pr) substitution (**31**–**33**) leads to a reduction in activity. However, compounds (**34**–**36**) with 4′-[*N*-(hydroxyalkyl)] groups (2-hydroxyethyl, 3-hydroxypropyl) retain good activity. Compounds with electron-withdrawing substituents on this nitrogen are less effective. The 4′-*N*-oxides **10** and **14**, metabolites derived from **9** and **12**, respectively, showed similar or slightly lower activity than their parent compounds. The activity of these *N*-oxides, which are expected to be inactive due to the lone pair of electrons of the nitrogen being bonded to oxygen, can be explained by their in vivo enzymatic reduction to the parent compounds. Similar phenomena have been demonstrated by other psychotropic drugs, such as clozapine,[16] chlorpromazine, and imipramine.[17] These *N*-oxides are, as expected, inactive in in vitro [^{3}H]-spiroperidol binding tests involving central neuroleptic receptors.[18] In view of the above, it would appear that the position of the distal nitrogen with certain orientation of its lone pair of electrons plays a vital role in determining the neuroleptic activity.[16] The substitution of the phenyl ring with a halogen atom (Cl, F) at position 7 enhanced the activity. Although the 7,8-difluoro compound (**29**) retained good activity, the positional isomers 8-fluoro (**27**) and 6,8-difluoro (**30**) compounds showed diminished activity. The 8-methyl derivative (**28**) was moderately active, whereas substitution at position 7 with NO_2, SCH_3, SO_2CH_3, and SO_2NMe_2 gave no advantage.

A short alkyl substitution (Me, Et, *i*-Pr) at position 2 of the thiophene ring seems to increase the activity. Compounds with a bulky *t*-Bu group or a long *n*-hexane chain at this position, or with 3-methyl or 2,3-dialkyl substituents, showed only minimal activity. Of the two metabolic products derived from the oxidation[19] of the ethyl side chain of **12**, compound **15**, with a 1′-hydroxylethyl chain, maintained moderate activity, whereas the other compound (**16**), with an electron-withdrawing acetyl group, was inactive. A phenyl substitution at the 2 position also removed activity. The corresponding compounds **47** and **46** in the 1,4 series with a 2-ethyl chain and with or without a 7-chloro substitution were also found to be inactive.

The tests reported here correlate with the ability of compounds to block dopamine receptors. This is demonstrated by the high degree of activity shown by the potent neuroleptic compound *cis*-flupenthixol, compared with the relative lack of activity displayed by its trans isomer, a compound which does not interact significantly with do-

(9) During the final stage of the preparation of our manuscript, a paper reporting 10-(alkylamino)-4*H*-thieno[3,4-*b*][1,5]benzodiazepines as potential neuroleptic agents [J. B. Press, C. M. Hofmann, N. H. Eudy, W. J. Fanshawe, I. P. Day, E. N. Greenblatt, and S. R. Safir, *J. Med. Chem.*, **22**, 725 (1979)] came to our notice. The results of our observation on this series of compounds, as well as on the 10-piperazinyl-4*H*-thieno[3,2-*b*][1,5]benzodiazepines and their [1,4] isomers, are described in the following paper.

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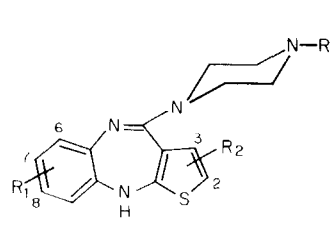
(18) J. L. Howard, S. Wedley, and I. A. Pullar, unpublished observations.

(19) D. E. Tupper and J. Fairhurst, to be published.

Table I[a]



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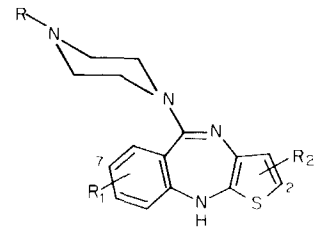
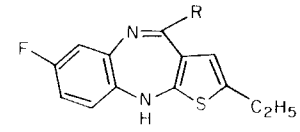


46-48



49-59

compd	R	R_1	R_2	% yield (method)	mp, °C	recrystn solvents	formula	anal.	mouse LD_{50},[b] mg/kg po	mouse hypothermia ED_{min},[c] mg/kg po	rat CAR,[d] po	rat catalepsy,[e] po
				A. 4-Piperazinylthieno[2,3-*b*][1,5]benzodiazepines								
1	H	H	2-C_2H_5	51 (D)	170-171	EtOAc-*n*-hexane	$C_{17}H_{20}N_4S$	C, H, N, S	800	100	0 (50)	NT
2	H	7-F	2-CH_3	74 (D)	111-112	CCl_4	$C_{16}H_{17}FN_4S$	C, H, N, F, S	400	100	1 (50)	NT
3	H	7-F	2-C_2H_5	90 (D)	162-163	CCl_4	$C_{17}H_{19}FN_4S$	C, H, N, F, S	NT	NT	1 (20 ip)	2 (60)
4	H	7-F	2-C_2H_5	85 (D)	166-169	EtOH-Et_2O	$C_{17}H_{19}FN_4S$ $C_4H_4O_4$	C, H, N, F, S	>800	100	1 (30 ip)	1 (30 sc)
5	H	7-Cl	2-C_2H_5	21 (D)	167-169	C_6H_6-*n*-hexane	$C_{17}H_{19}ClN_4S$	C, H, N, Cl, S	>400	50	0 (50)	0 (50)
6	CH_3	H	2-C_2H_5	64 (A)	186-188	EtOH-Et_2O	$C_{18}H_{22}N_4S$ $C_4H_4O_4$	C, H, N, O, S	150	25	2 (10)	1 (16)
7	CH_3	H	2-*t*-C_4H_9	34 (C)	211	CH_3CN	$C_{20}H_{26}N_4S$	C, H, N, S	400	12.5	0 (10)	NT
8	CH_3	7-F	H	74 (A)	228-230	CH_2Cl_2-*n*-hexane	$C_{16}H_{17}FN_4S$	C, H, N, F, S	>200	25	5 (30)	NT
9	CH_3	7-F	2-CH_3	35 (A)	168-170	EtOAc-*n*-hexane	$C_{17}H_{19}FN_4S$	C, H, N	200	3	4 (8)	1 (8)
10	CH_3 4'-oxide	7-F	2-CH_3	82[f]	235-237	$CHCl_3$	$C_{17}H_{19}FN_4OS$	C, H, N, F, S	200	6.25	3 (10)	2 (10)
11	CH_3	7-F	3-CH_3	11, 28 (A, C)	209-210	CH_3CN	$C_{17}H_{19}FN_4S$	C, H, N, F, S	>200	25	0 (25)	NT
12	CH_3	7-F	2-C_2H_5	85, 47 (A, B)	161-163	CCl_4	$C_{18}H_{21}FN_4S$	C, H, N, F, S	>200	6.25	3 (6)	2 (12)
13	CH_3	7-F	2-C_2H_5	58 (A)	125-127	*i*-PrOH-*n*-hexane	$C_{18}H_{21}FN_4S \cdot C_4H_4O_4$	C, H, N, F, S	200	6.25	2 (8)	1 (8)
14	CH_3 4 -oxide	7-F	2-C_2H_5	27[f]	205-210	CH_2Cl_2-Et_2O	$C_{18}H_{21}FN_4OS \cdot H_2O$	C, H, N, F, S	200	25	4 (12.5)	1 (10)
15	CH_3	7-F	2-$CHOHCH_3$	57[f]	189-191	EtOAc	$C_{18}H_{21}FN_4OS$	C, H, N, F, S	>400	25	4 (50)	1 (50)
16	CH_3	7-F	2-$COCH_3$	64[f]	276-279	EtOAc	$C_{18}H_{19}FN_4OS$	C, H, N, F, S	200	12.5	0 (20)	2 (50)

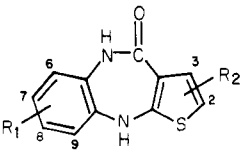
17	CH_3	7-F	2-*i*-C_3H_7	57 (A)	132–135	EtOAc–*n*-hexane	$C_{19}H_{23}FN_4S$	C, H, N, F, S	50	6.25	4 (10)	2 (10)
18	CH_3	7-F	2-*t*-C_4H_9	27 (C)	167–173	CH_3CN	$C_{20}H_{25}FN_4S$	C, H, N, F, S	>400	12.5	1 (10)	1 (10)
19	CH_3	7-F	2-*n*-C_6H_{14}	62 (A)	101–105	cyclohexane–*n*-hexane	$C_{22}H_{29}FN_4S$	C, H, N, F, S	>400	100	0 (50)	NT
20	CH_3	7-F	2-C_6H_5	25 (A)	235–240	MeOH	$C_{22}H_{21}FN_4S\cdot 2HCl\cdot H_2O$	C, H, N	>400	50	0 (50)	0 (50)
21	CH_3	7-F	2,3-$(CH_2)_4$–	56 (A)	196–199	cyclohexane–*n*-hexane	$C_{20}H_{23}FN_4S$	C, H, N, F, S	>400	100	0 (50)	NT
22	CH_3	7-Cl	2-C_2H_5	36 (A)	119–121	EtOH–Et_2O	$C_{18}H_{21}ClN_4S\cdot C_4H_4O_4$	C, H, N, Cl, O	50	6.25	2 (8)	1 (8)
23	CH_3	7-NO_2	2-C_2H_5	10 (A)	110	EtOAc–*n*-hexane	$C_{18}H_{21}N_5O_2S$	C, H, N, O, S	>400	50	0 (25)	NT
24	CH_3	7-SCH_3	2-C_2H_5	40 (A)	174–175	CCl_4	$C_{19}H_{24}N_4S_2$	C, H, N	>200	100	0 (50)	NT
25	CH_3	7-SO_2CH_3	2-C_2H_5	32 (A)	132–135	pet. ether (40–60 °C)	$C_{19}H_{24}N_4O_2S_2$	C, H, N, S	>400	>400	0 (50)	NT
26	CH_3	7-$SO_2N(CH_3)_2$	2-C_2H_5	68 (A)	225–227	EtOAc–*n*-hexane	$C_{20}H_{27}N_5O_2S_2$	C, H, N, O, S	>800	>800	0 (50)	NT
27	CH_3	8-F	2-C_2H_5	61 (A)	125–127	EtOH–Et_2O	$C_{18}H_{21}FN_4S\cdot C_4H_4O_4$	C, H, N, F, S	150	12.5	1 (4)	1 (8)
28	CH_3	8-CH_3	2-C_2H_5	68 (A)	168–171	EtOAc–*n*-hexane	$C_{19}H_{24}N_4S$	C, H, N, S	150	50	2 (25)	2 (50)
29	CH_3	7,8-F_2	2-C_2H_5	41 (A)	172	CCl_4–*n*-hexane	$C_{18}H_{20}F_2N_4S$	C, H, N, F, S	300	6.25	3 (10)	3 (25)
30	CH_3	6,8-F_2	2-C_2H_5	78 (A)	122–124	EtOH–Et_2O	$C_{18}H_{20}F_2N_4S\cdot C_4H_4O_4$	C, H, N, F, S	600	25	1 (50)	1 (50)
31	C_2H_5	H	2-C_2H_5	47 (E)	169–170	EtOAc–*n*-hexane	$C_{19}H_{24}N_4S$	C, H, N, S	200	50	2 (10)	1 (10)
32	*n*-C_3H_7	H	2-C_2H_5	20 (E)	102–103	EtOAc–*n*-hexane	$C_{20}H_{26}N_4S$	C, H, N, S	>200	25	0 (10)	2 (20)
33	*n*-C_3H_7	7-F	2-C_2H_5	58 (E)	163–164	EtOAc–*n*-hexane	$C_{20}H_{25}FN_4S$	C, H, N, F, S	>100	6.25	0 (10)	NT
34	$(CH_2)_2OH$	H	2-C_2H_5	38 (E)	175–176	EtOAc–*n*-hexane	$C_{19}H_{24}N_4OS$	C, H, N, O, S	>400		4 (20)	2 (20)
35	$(CH_2)_2OH$	7-F	2-C_2H_5	67 (E)	173–175	EtOH–Et_2O	$C_{19}H_{23}FN_4OS\cdot 2C_4H_4O_4$	C, H, N, F, S	400	50	4 (20)	1 (10)
36	$(CH_2)_3OH$	7-F	2-C_2H_5	63 (E)	145–148	CH_2Cl_2–*n*-hexane	$C_{20}H_{25}FN_4OS$	C, H, N, F, S	400	25	2 (10)	2 (12.5)
37	$COOC_2H_5$	H	2-C_2H_5	63 (A)	169–170	CH_2Cl_2–*n*-hexane	$C_{20}H_{24}N_4O_2S$	C, H, N, O, S	>400	50	0 (50)	NT
38	$COOC_2H_5$	7-F	2-CH_3	90 (A)	187–188	EtOAc–cyclohexane	$C_{19}H_{21}FN_4O_2S$	C, H, N, F, S	400	>400	0 (50)	NT
39	$COOC_2H_5$	7-F	2-C_2H_5	78 (A)	149–151	*i*-PrOH–*n*-hexane	$C_{20}H_{23}FN_4O_2S\cdot C_4H_4O_4$	C, H, N, F, S	>800	100	0 (50)	0 (50)
40	C_6H_5	7-F	2-C_2H_5	27 (A)	154–156	CH_2Cl_2–*n*-hexane	$C_{23}H_{24}FN_4S$	C, H, N, F, S	>400	>400	0 (50 ip)	NT
41	3′-C_6H_4Cl	7-F	2-C_2H_5	44 (B)	250–255	EtOAc–CH_2Cl_2	$C_{23}H_{22}ClFN_4S\cdot HCl$	C, H, N	>400	>400	0 (50 ip)	NT
42	3′-$C_6H_4CF_3$	7-F	2-C_2H_5	67 (B)	184–186	EtOAc–$CHCl_3$	$C_{24}H_{22}F_4N_4S\cdot HCl$	C, H, N, Cl	400	>400	0 (50 ip)	NT
43	$CH_2C_6H_5$	H	2-C_2H_5	32 (E)	79–80	amorphous	$C_{24}H_{26}N_4S$	C, H, N	>400	200	4 (50)	2 (50)
44	$CH_2C_6H_5$	7-F	2-C_2H_5	36 (E)	265–270	EtOH–Et_2O	$C_{24}H_{25}FN_4S\cdot 2HCl$	C, H, N, Cl, F, S	>400	200	1 (40)	2 (25)
45	CH_2-4′-C_6H_4Cl	7-F	2-C_2H_5	59 (E)	166–168	CH_2Cl_2–*n*-hexane	$C_{24}H_{24}ClFN_4S$	C, H, N, Cl, F, S	>400	>400	0 (50)	0 (50)

Table I (*Continued*)

compd	R	R_1	R_2	% yield (method)	mp, °C	recrystn solvents	formula	anal.	mouse LD_{50},[b] mg/kg po	mouse hypothermia ED_{min},[c] mg/kg po	rat CAR,[d] po	rat catalepsy,[e] po
				B. 5-Piperazinylthieno[2,3-*b*][1,4]benzodiazepines								
46	CH_3	H	2-C_2H_5	31 (A)	190–193	EtOAc–*n*-hexane	$C_{18}H_{22}N_4S$	C, H, N, S	>200	100	0 (25)	NT
47	CH_3	7-Cl	2-C_2H_5	36 (A)	208–210	MeOH–H_2O	$C_{18}H_{21}ClN_4S$	C, H, N, Cl, S	>100	50	0 (50)	NT
48	CH_3	H	2-$COCH_3$	6 (A)	222–223	EtOAc–CCl_4	$C_{18}H_{20}N_4OS$	C, H, N, S	>400	200	1 (40)	NT
				C. 4-Aminothieno[2,3-*b*][1,5]benzodiazepines								
49	c-NC_5H_{10}			22 (A)	165–170	CH_2Cl_2–*n*-hexane	$C_{18}H_{20}FN_3S$	C, H, N	>200	12.5	0 (50)	NT
50	c-$N(CH_2CH_2)_2O$			44 (A)	171–173	CH_2Cl_2–*n*-hexane	$C_{17}H_{18}FN_3OS$	C, H, N	>400	>400	0 (50)	NT
51	$NH(CH_2)_2OH$			34 (B)	196–198	EtOH–*n*-hexane	$C_{15}H_{16}FN_3OS \cdot C_4H_4O_4$	C, H, N, F, S	>800	200	0 (50)	0 (50)
52	$NH(CH_2)_3OH$			72 (B)	174–175	EtOH–*n*-hexane	$C_{16}H_{18}FN_3OS \cdot C_4H_4O_4$	C, H, N, F, S	400	>200	0 (40 ip)	NT
53	$NH(CH_2)_2N(CH_3)_2$			9 (B)	183–184	EtOH–*n*-hexane	$C_{20}H_{25}FN_4S \cdot 1.5C_4H_4O_4$	C, H, N, F, S	400	200	1 (40 ip)	NT
54	$NH(CH_2)_3N(CH_3)_2$			19 (B)	193–195	*i*-PrOH–*n*-hexane	$C_{25}H_{28}FN_5S \cdot 2C_4H_4O_4$	C, H, N	>800	>400	1 (50 ip)	NT
55	$NH(CH_2)_2$-c-$N(CH_2CH_2)_2O$			71 (B)	189–203	EtOH–EtOAc	$C_{19}H_{23}FN_4OS \cdot C_4H_4O_4$	C, H, N, F, S	400	200	0 (50 ip)	NT
56	$NH(CH_2)_3$-c-$N(CH_2CH_2)_2O$			57 (B)	182–186	*i*-PrOH–*n*-hexane	$C_{20}H_{25}FN_4OS \cdot 2C_4H_4O_4$	C, H, N	800	400	0 (50 ip)	NT
57	$NH(CH_2)_2$-c-NC_5H_{10}			54 (B)	184–185	EtOH–EtOAc	$C_{20}H_{25}FN_4S \cdot 1.5C_4H_4O_4$	C, H, N, F, S	>400	200	2 (20 ip)	0 (50)
58	$NH(CH_2)_2$-c-$N(CH_2CH_2)_2N$-C_6H_5			25 (B)	168–170	EtOAc–*n*-hexane	$C_{25}H_{28}FN_5S$	C, H, N, F	>800	>400	0 (50)	0 (50)
59	$NH(CH_2)_3$-c-$N(CH_2CH_2)_2N$-CH_3			48 (B)	181	EtOAc–*n*-hexane	$C_{21}H_{28}FN_5S$	C, H, N, F, S	400	200	2 (50 ip)	NT
clozapine									150	50	3 (30)	2 (80)
haloperidol									>100	3.00	3 (1.25)	3 (1.25)
chlorpromazine									400	6.25	3 (10)	1 (10)
thioridazine									400	25	3 (50)	1 (25)
cis-flupenthixol									300	3.00	2 (2.5)	4 (2.5)
trans-flupenthixol									>400	>400	1 (50)	0 (50)

[a] A limited dose–response curve was run in the CAR and catalepsy experiments. The maximum dose used was half the ED_{50} for disrupting the ability of rats to remain on a rotating rod. The doses quoted in the table were selected to allow, where possible, a comparison to be made between a compound's ability to produce catalepsy and to inhibit CAR. [b] Figures represent approximate LD_{50} (mg/kg po) in mice; NT = not tested. [c] See pharmacological methods; NT = not tested. [d] Activity: 0 = no significant effect (0–25% block); 1 = 26–30% block; 2 = 31–50% block; 3 = 51–75% block; 4 = 76–99% block; 5 = complete block of conditioned and unconditioned response. Numbers in parentheses = dose, mg/kg, po, unless otherwise stated. [e] Activity: 0 = no significant effect (group score 0–3); 1 = group score 4–7; 2 = group score 8–15; 3 = group score 16–30; 4 = group score 31–40. Numbers in parentheses = dose, mg/kg, po, unless otherwise stated. NT = not tested. [f] Reference 19.

Table II. 5,10-Dihydro-4*H*-thieno[2,3-*b*][1,5]benzodiazepin-4-ones



no.	R_1	R_2	yield, %	mp, °C	crystn solv	formula	anal.
60	H	2-C_2H_5	79	218–220	$CHCl_3$	$C_{13}H_{12}N_2OS$	C, H, N, O, S
61	7-F	2-C_2H_5	60	210–212	EtOH	$C_{13}H_{11}FN_2OS$	C, H, N, F, S
62	8-F	2-C_2H_5	88	255–257	EtOAc	$C_{13}H_{11}FN_2OS$	C, H, N, F, S
63	8-CH_3	2-C_2H_5	74	205–207	EtOAc	$C_{14}H_{14}N_2OS$	C, H, N, O, S
64	6,8-F_2	2-C_2H_5	83	230–232	$CHCl_3$	$C_{13}H_{10}F_2N_2OS$	C, H, N, F, S
65	7,8-F_2	2-C_2H_5	78[a]				
66	7-Cl	2-C_2H_5	54	216–218	EtOAc	$C_{13}H_{11}ClN_2OS$	C, H, N, Cl, O, S
67	7-NO_2	2-C_2H_5	75[a]				
68	7-SCH_3	2-C_2H_5	40	171–172	EtOAc	$C_{14}H_{14}N_2OS_2$	C, H, N, O, S
69	7-SO_2CH_3	2-C_2H_5	74	219–221	EtOAc	$C_{14}H_{14}N_2O_3S_2$	C, H, N, O, S
70	7-$SO_2N(CH_3)_2$	2-C_2H_5	70	258–260	EtOAc	$C_{15}H_{17}N_3O_3S_2$	C, H, N, O, S
71	7-F	H	33	235–240	CCl_4–*n*-hexane	$C_{11}H_7FN_2OS$	C, H, N, F, S
72	7-F	2-CH_3	68	250–252	EtOAc	$C_{12}H_9FN_2OS$	C, H, N
73	7-F	2-*i*-C_3H_7	14	234–236	EtOAc	$C_{14}H_{13}FN_2OS$	C, H, N, F, S
74	7-F	2-*n*-C_6H_{14}	44	151–152	EtOAc–CCl_4	$C_{17}H_{19}FN_2OS$	C, H, N, F, S
75	7-F	2-C_6H_5	72	250–255	EtOAc	$C_{17}H_{11}FN_2OS$	C, H, N, F
76	7-F	2,3-$(CH_2)_4$–	36	237–240	EtOAc	$C_{15}H_{13}FN_2OS$	C, H, N, F, S

[a] Crude product used for next stage without purification.

pamine receptors and which has no antipsychotic activity. Unlike the standard neuroleptics tested, clozapine blocks the conditioned avoidance response in rats at doses which are very much lower than those required to produce catalepsy. It is thought that this profile of activity is associated with the relative lack of extrapyramidal side effects produced by this compound in the clinic. A number of compounds in the present series, e.g., **9**, **12**, **17**, **29**, and **34**, have been found to be more potent than clozapine and show a similar, if less marked, separation of activity in these two tests. This profile of activity needs further development of this class of compounds.

Experimental Section

Melting points were determined with a Köfler hot stage apparatus and are uncorrected. All the compounds were characterized by physical methods using IR, UV, and NMR. $MgSO_4$ was used as a drying agent. Microanalyses were within ±0.4% of the calculated values unless noted otherwise.

Method A. 2-Ethyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*][1,5]benzodiazepine Maleate (6). A solution of $TiCl_4$ (1.2 mL, 0.011 mol) in dry anisole (5 mL) was added to a stirred suspension of the diazepinone **60** (2.4 g, 0.01 mol) in *N*-methylpiperazine (10 mL). The mixture was stirred and heated to 120 °C for 2 h and then poured onto ice–water and extracted with CH_2Cl_2. The combined extracts were washed with water, dried, and evaporated under reduced pressure. Crystallization from *n*-hexane gave the free base (2.1 g, 64%; mp 195–197 °C), which was dissolved in ethanol, maleic acid was added, and the solution was boiled with ether until crystallization began. Filtration gave the salt as yellow crystals, mp 186–188 °C.

Method B. 2-Ethyl-7-fluoro-5,10-dihydro-4*H*-thieno[2,3-*b*][1,5]benzodiazepine-4-thione. Diazepinone **61** (20 g, 0.076 mol) was added to a stirred solution of P_2S_5 (17 g, 0.077 mol) in anhydrous pyridine (400 mL). The mixture was stirred at reflux for 1.5 h, poured onto ice–water, stirred for 1 h, filtered, and dried to give 19.7 g (93%). A portion was recrystallized from aqueous ethanol for analysis, mp 203–206 °C. Anal. ($C_{13}H_{11}FN_2S_2$) C, H, N, F, S.

2-Ethyl-7-fluoro-4-[(2-*N*-morpholinoethyl)amino]-10*H*-thieno[2,3-*b*][1,5]benzodiazepine (55). The above diazepinethione (1.85 g, 0.0066 mol) was stirred in 2-aminoethylmorpholine (8.5 g) under nitrogen at 60 °C for 2.25 h. The mixture was poured onto dilute aqueous maleic acid, washed twice with ether, and basified with 20 M ammonia solution. The product was extracted into EtOAc, washed twice with water, and dried, and the solvent was removed to leave the crude free base, 1.84 g (71%), which was converted into the maleate salt and crystallized from EtOH–EtOAc–*n*-hexane, mp 189–203 °C.

Method C. Ethyl 2-(4-fluoro-2-nitroanilino)-4-methylthiophene-3-carboxylate was prepared as in ref 10 from ethyl 2-amino-4-methylthiophene-3-carboxylate and 2,5-difluoronitrobenzene in Me_2SO using K_2CO_3 as a base in 27% yield, mp 125–127 °C (cyclohexane).

7-Fluoro-3-methyl-4-(4-methyl-1-piperazinyl)-10*H*-thieno[2,3-*b*][1,5]benzodiazepine (11). The above nitro ester (14.3 g, 0.044 mol) was hydrogenated in a mixture of EtOH and EtOAc with 10% Pd/C (1.6 g) at 60 psi. After removal of the catalyst, the solvent was evaporated and the crude diamino ester was dissolved in a mixture of anisole (215 mL) and *N*-methylpiperazine (55 mL). To the stirred solution under N_2 was added a solution of $TiCl_4$ (13.5 mL) in anisole (75 mL), and the mixture was heated for 4 h at 120 °C and then at reflux overnight. The solution was cooled to 70 °C, a mixture of 2-propanol (50 mL) and 20 M ammonia solution (50 mL) was added, and the mixture was filtered through Celite, washing with EtOAc. The combined filtrate and washings were washed with water and extracted into 2 N HCl. The acid solution was basified with 20 M ammonia solution and extracted with CH_2Cl_2. The organic phase was washed with water and then filtered through a short column of Florisil. The residue after evaporation of the solvent was crystallized from acetonitrile: yield 4.0 g (27.5%); mp 209–210 °C.

Method D. 2-Ethyl-7-fluoro-4-(1-piperazinyl)-10*H*-thieno[2,3-*b*][1,5]benzodiazepine (3). A solution of 2-ethyl-7-fluoro-4-[4-(carboethoxy)-1-piperazinyl]-10*H*-thieno[2,3-*b*]-[1,5]benzodiazepine (**39**; 10.0 g, 0.025 mol) and KOH (50 g) in 95% EtOH (250 mL) was heated under reflux in a N_2 atmosphere for 16 h. The solution was evaporated under reduced pressure and partitioned between water and CH_2Cl_2. The CH_2Cl_2 phase was washed with water, dried, and evaporated to a yellow amorphous solid. Crystallization from CCl_4 gave pure **3**: yield 7.3 g (90%); mp 162–163 °C.

Method E. 2-Ethyl-7-fluoro-4-[4-(3-hydroxypropyl)-1-piperazinyl]-10*H*-thieno[2,3-*b*][1,5]benzodiazepine (36). A solution of **3** (1.65 g, 0.005 mol), 3-bromo-1-propanol (1.4 g, 0.01 mol), and triethylamine (2.8 mL, 0.02 mol) in 90% EtOH (150 mL) was heated under reflux for 16 h. A further portion of 3-bromo-1-propanol (0.2 g) and triethylamine (0.5 mL) was added and the heating continued for a further 6 h. The solution was evaporated under reduced pressure and partitioned between water and CH_2Cl_2. The organic phase was washed with water, dried, and evaporated. Crystallization from CH_2Cl_2–*n*-hexane gave yellow crystals: yield 1.2 g (63%); mp 145–148 °C.

Pharmacological Methods. All compounds were dissolved in distilled water or suspended in 0.5% carboxymethylcellulose.

Solutions or suspensions were administered orally except where mentioned otherwise.

Acute Toxicity. The compounds were administered to three albino mice (CFW) weighing 19–21 g in doses up to 800 mg/kg orally. The mice were observed over 48 h for mortalities and other gross behavioral changes. LD_{50} values were approximated from the results.

Mouse Hypothermia. The rectal temperature of groups of three CFW mice was measured at 15 min, 2.5 h, and 5 h after administration of the compounds. In order to simplify the recording of hypothermia, the "temperature index" method of assessment[13] was used. Taking as a base the mean initial temperature of each group, the mean temperature changes from this figure at the three time intervals were summed and termed the "temperature index". The results are expressed as ED_{min} values, which are the minimum doses (mg/kg po) of the compounds giving a temperature index of at least 5 lower than that of a control group of animals.

Conditioned Avoidance Response (CAR) in Rats. The method was essentially that described by Jacobsen and Sonne.[14] Lilly Wistar rats (120–130 g) were trained to pass from one side of a shuttle box to the other on hearing a 5-s buzzer. Failure to respond within 1 s from the end of the buzzer resulted in the animals receiving a mild electric shock. The compound under tests was administered to only those animals which showed a high level of conditioned response. Groups of five animals were dosed orally 1 h 50 min prior to placing them individually in the shuttle boxes. After a 10-min habituation period, they were tested for 20 min. During this period the number of times the buzzer sounded, as well as the number of shocks received by the animal, was recorded. The degree of conditioned avoidance blockade was calculated by expressing the number of shocks received as a percentage of the number of stimuli presented.

Rat Catalepsy. The method used was essentially that described by Costall and Olley.[15] Groups of eight Lilly Wistar rats (180–190 g) were assessed for the presence of catalepsy at 0.5, 1, 1.5, 2, 3, 4, and 5 h after the oral administration of the compound. The front paws of each animal were placed on a wooden rod 1.5-cm in diameter suspended 7 cm above a table. The length of time the animal maintained this position was recorded up to a maximum of 20 min. Animals were considered to be noncataleptic if they removed their front paws from the bar within 10 s. Each cataleptic animal was assigned a score of from 0 to 5 depending on how long they maintained the imposed posture (0 = <10 s; 1 = 10 s–2.5 min; 2 = 2.5–5 min; 3 = 5–10 min; 4 = 10–20 min; 5 = >20 min). The maximum scores obtained for each animal, regardless of time after dosing, were summed, thus giving a maximum score of 40 for each group.

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10-Piperazinyl-4*H*-thieno[3,2-*b*][1,5]- and -[3,4-*b*][1,5]benzodiazepines as Potential Neuroleptics[1]

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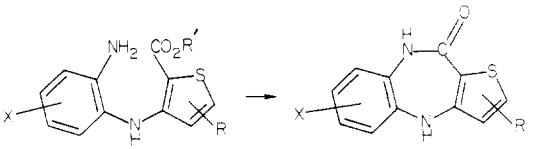
The synthesis of 10-piperazinyl-4*H*-thieno[3,2-*b*][1,5]- and -[3,4-*b*][1,5]benzodiazepines is described. The activity of these compounds has been assessed on the basis of their ability to produce hypothermia in mice and block a conditioned avoidance response (CAR) and produce catalepsy in rats, and the results are compared with various classical and nonclassical neuroleptic drugs. A number of compounds (**6**, **17**, **21**, and **22**) demonstrate potency greater than clozapine and also show low degree of catalepsy. It is believed that this profile of activity, unlike standard neuroleptics, is associated with the relative lack of extrapyramidal side effects in the clinic. The corresponding 9-piperazinyl-4*H*-thieno[1,4]benzodiazepines (**12** and **35**), limited analogues prepared in the respective series, were inactive.

In the previous paper in this issue,[2] we described the synthesis and evaluation of the neuroleptic activity of a series of 4-substituted 10*H*-thieno[2,3-*b*][1,5]benzodiazepines. This paper is concerned with the preparation of the other two isomeric 10-piperazinyl-4*H*-thieno[3,2-*b*][1,5]- and -[3,4-*b*][1,5]benzodiazepines.[3] The gross CNS activity of these compounds has been established by studying their effects on the behavior of mice. Neuroleptic activity has been examined in terms of their ability to produce hypothermia in mice and inhibit a conditioned avoidance response and produce catalepsy in rats. The results have been compared with various typical and atypical neuroleptics. The respective 9-piperazinyl-4*H*-thieno[1,4]benzodiazepines (**12** and **35**) in each series have also been prepared for comparison of activity.

Scheme I



Chemistry. 4*H*-Thieno[3,2-*b*][1,5]benzodiazepinones. The synthetic route to the diazepinones (**36–39**, Table II) using cyclization of the corresponding amino ester (Scheme I) was previously reported.[4]

4*H*-Thieno[3,4-*b*][1,5]benzodiazepinones. The route to the synthesis of the diazepinones (**40**, **43**, **45**, and **47**) using cyclization of the corresponding amino esters (Scheme I) was described in our earlier paper.[4] The amino

(1) Part 4 of the series: Heteroarenobenzodiazepines; J. K. Chakrabarti and D. E. Tupper, British Patent Application 51 240, 1974; Belgium Patent 835 932, 1976. For part 3, see ref 2.

(2) J. K. Chakrabarti, L. Horsman, T. M. Hotten, I. A. Pullar, D. E. Tupper, and F. C. Wright, *J. Med. Chem.*, preceding paper in this issue.

(3) During the final stage of preparation of our manuscript, a paper reporting 10-(alkylamino)-4*H*-thieno[3,4-*b*][1,5]benzodiazepines as potential neuroleptic agents [J. B. Press, C. M. Hofmann, N. H. Eudy, W. J. Fanshawe, I. P. Day, E. N. Greenblatt, and S. R. Safir, *J. Med. Chem.*, **22**, 725 (1979)] came to our attention. We describe here the different routes to the synthesis of this series of compounds and their pharmacological profile, which is at variance with their observation.

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