Table IV. Anticonvulsant Testing in Rats

	ip			po		
compd	MES ED_{50}, mg/kg	ND_{50}, mg/kg	PI	MES ED_{50}, mg/kg	ND_{50}, mg/kg	PI
5	1.7 (0.6-6.6)[a]	>100	>59	26 (13-39)	>100	>3.8
9	5.5 (2.9-19)	>100	>18	>30		
14				52 (31-105)	>100	>1.9
15	3.1 (1.2-6.2)	53 (35-83)	17			
19	4.5 (1.5-6.7)	41 (29-57)	9.1	10 (4.5-19)	>300	>30
24	7.8 (5.3-12)	44 (26-92)	5.6	22 (11-42)	~200	~9
36	5.9 (3.8-8.4)	>60	>10	25 (15-36)	>100	>4.0
39				54 (33-115)	>100	>1.8
40	6.2 (2.2-14)	32 (17-63)	5.2[b]			
42	24 (14-33)	153 (119-211)	6.4	62 (30-125)	>300	>4.8
43	3.8 (2.2-5.3)	46 (31-78)	12	13 (7.3-20)	>100	>7.7
51	14 (8.0-23)	>100	>7.1	53 (34-83)	>100	>1.9
phenytoin	21 (13-32)	>300	>14	85 (51-154)	>300	>3.5

[a] 95% confidence limits are included in parentheses. [b] Stimulation.

treated with *m*-chloroperbenzoic acid (85%; 1.52 g, 0.0075 mol) in methylene chloride (30 mL) for 2 h at room temperature. After workup and extraction as above, the hydrochloride was precipitated and recrystallized from acetone–MeOH to give 0.66 g (65%) of **54**, mp 199–202 °C dec. Anal. ($C_{16}H_{17}ClN_2O_2S$) C, H, N.

Maximal Electroshock Assay. Groups of 8–10 male Hilltop ICR-derived mice weighing 19–30 g or Simonsen Sprague–Dawley derived rats weighing 80–110 g were dosed with compound or aqueous vehicle prior to the administration of a transcorneal electroshock. The mice received 50 mA while rats received 150 mA of a 60-Hz current for 0.2 s. The shock was delivered after testing for a neurological deficit as described below. The pretreatment times were 15 min following ip administration and 30 min following oral administration. The times were fixed since the large number of compounds to be tested did not allow determination of peak activity for each compound.

Immediately prior to the administration of the electroshock, each animal was placed on a 16-gauge, 65-cm long copper wire suspended 40 cm above the table. The ability of a mouse to remain on the wire for 10 s (rat, 8 s) was determined. The quantal data were used to estimate a dose of compound causing a neurological deficit in 50% of the animals (ND_{50}).

The LD_{50} values were estimated from the 5-day survivals of mice subjected to a behavioral screen. Compounds were administered ip in increasing doses to groups of three male Simonsen ICR-derived mice weighing 16–24 g. Deaths were determined on the 5th day.

All quantal data were evaluated by the method of Litchfield and Wilcoxon.[18] The protective index (PI) is the ratio of the deficit-producing dose (ND_{50}) to the anticonvulsant dose (ED_{50}).

Acknowledgment. We thank Margery Schuler, Margie McMahon, Karen Peterson, Charlene Schulz, Charlotte Rogers, and particularly Linda Hedley for expert technical assistance and the Syntex Analytical Department for analytical support.

(18) J. T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).

Novel Tetracyclic Spiropiperidines. 1. 3-Aryl-1,3-dihydrospiro[benzo[*c*]thiophene-1,4′-piperidines] as Potential Antidepressants[1a]

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A series of 3-aryl-1,3-dihydrospiro[benzo[*c*]thiophene-1,4′-piperidine] derivatives was synthesized and evaluated pharmacologically for potential psychotropic activity. Potent antidepressant-like activity was noted throughout the series, as assessed by tetrabenazine (TBZ) ptosis prevention in mice and potentiation of 5-hydroxytryptophan (5-HTP) induced behavioral effects in rats. A possible therapeutic advantage of the title compounds appears to be the overall low anticholinergic potential in comparison with the classic tricyclic antidepressants. Several congeners with nuclear halogen substitution also exhibited CNS stimulant properties, as evidenced by their ability to induce a dopamine agonist-like stereotypy and to increase the spontaneous motor activity in mice.

Previous publications from these laboratories[2-5] have documented the pharmacologically diverse responses evoked by structurally varied 3-aryl-1,3-dihydrospiro[isobenzofuran-1(3*H*),4′-piperidines] (I). Marked antide-

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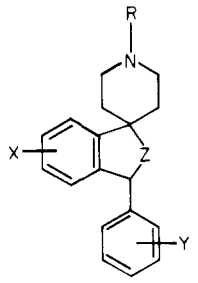


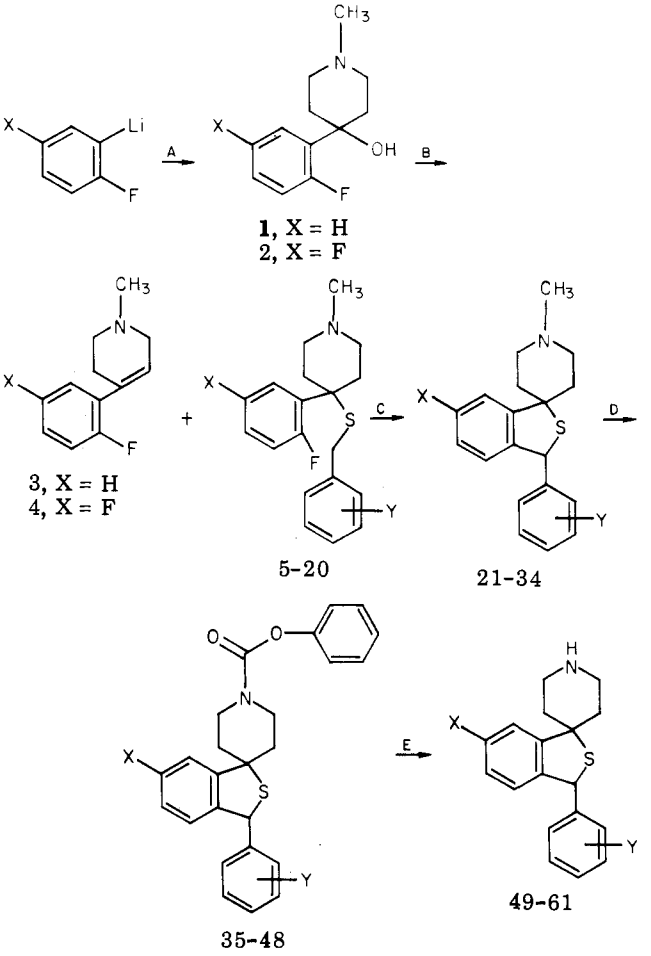
I, Z = O
HRP 197, R = X = H; Y = 4-CH_3
HP 505, R = X = H; Y = H

II, Z = S
21-34, R = CH_3
49-61, R = H

pressant, neuroleptic, hypotensive, as well as diuretic properties were observed in various animal models, and two congeners of this chemical class, HP 505 and HRP 197, are of clinical interest as psychoactive agents. As part of a program aimed at discovering novel tetracyclic spiropiperidines of potential therapeutic use, we have undertaken the study of a series of isosteric 3-aryl-1,3-dihydrospiro[benzo[*c*]thiophene-1,4′-piperidines] (II), and the present paper describes the synthesis and biological evaluation of those analogues bearing N-substituents considered most relevant to the antidepressant profile: a methyl radical or a hydrogen. It is worth noting that, in addition to the enhanced lipophilicity, subtle changes in drug-receptor events might also be expected from the replacement of oxygen with sulfur, due to the sharpened angle formed by carbon-sulfur bonds within the sterically constrained spirobenzothiophene system.

Chemistry. The synthetic sequences leading to target compounds **21–34** and **49–61** are outlined in Scheme I. 2-Fluorophenyllithium, prepared conveniently from 2-bromofluorobenzene and *n*-butyllithium at −70 °C or lower,[6] reacted readily with *N*-methyl-4-piperidinone to give amino alcohol **1** in good yields (method A). Similarly prepared was the 5-fluoro analogue, **2**, using 1-bromo-2,5-difluorobenzene as the starting material. Condensation of **1** or **2** with benzyl mercaptans was best carried out under acidic conditions with boron trifluoride etherate in glacial acetic acid (method B), and the desired sulfides, **5** and **6**, could be readily separated from byproducts **3** and **4**, arising, respectively, from the dehydration of **1** and **2**. The general applicability of this condensation is reflected by the large number of nuclear substituted sulfides[7] listed

Scheme I



1, X = H
2, X = F

3, X = H
4, X = F

5–20

21–34

35–48

49–61

in Table I. It is interesting to note that an alternative approach (in fact, the more frequently used one) to **5**, involving a coupling reaction between the tosylate of **1** and the sodium salt of benzyl mercaptan, has led to **3** exclusively as a result of elimination. For the cyclization of **5** to **21** and of **6–18** to **22–34**, we adopted the very versatile intramolecular fluorine-displacement reaction,[8a,b] employing a carbanion generated at the benzyl carbon by a strong base, such as sodium methylsulfinylmethide (dimsyl sodium), prepared by the procedure of Corey et al.[9a,b] (method C). In general, ring closures occurred instantaneously at room temperature, giving rise to dihydrospiro[benzo[*c*]thiophenes] **21–34** in good to excellent yields (Table II). The only benzyl sulfides which failed to cyclize were **19** and **20**, both carrying a nitro group on the benzyl moiety. It is quite conceivable, in retrospect, that the combined electron-withdrawing and delocalization effect elicited by a nitro group had rendered the carbanion too stable—thus much less nucleophilic—for the displacement to take place. For the preparation of secondary amines, compounds **21–34** were converted to phenyl carbamates **35–48** (method D), which were then subjected to alkaline hydrolysis (method E) to afford **49–61**, without complications arising from the often susceptible trifluoromethyl group or the nuclear halogens. Another attempt to de-

(1) Presented in part before the Division of Medicinal Chemistry at the 178th National Meeting of the American Chemical Society. See Martin, L. L.; Ong, H. H.; Allen, R. C.; Bauer, V. J.; Kosley, R. W.; Klioze, S. S.; Shutske, G. M.; Profitt, J. A.; Worm, M. "Abstracts of Papers", 178th National Meeting of the American Chemical Society, Washington, D.C., Sept 1979; American Chemical Society: Washington, D.C., 1979; MEDI 25. (b) Miles Laboratories, Elkhart, Ind. (c) Visiting Senior Pharmacologist from Hoechst AG, Frankfurt, West Germany.

(2) Bauer, V. J.; Duffy, B. J.; Hoffman, D.; Klioze, S. S.; Kosley, R. W. Jr.; McFadden, A. R.; Martin, L. L.; Ong, H. H. *J. Med. Chem.* **1976**, *19*, 1315.

(3) Klioze, S. S.; Bauer, V. J.; Geyer, H. M. III *J. Med. Chem.* **1977**, *20*, 610.

(4) Klioze, S. S.; Novick, W. J. Jr. *J. Med. Chem.* **1978**, *21*, 400.

(5) Allen, R. C.; Bauer, V. J.; Kosley, R. W., Jr.; McFadden, A. R.; Shutske, G. M.; Cornfeldt, M. L.; Fielding, S.; Geyer, H. M. III; Wilker, J. C. *J. Med. Chem.* **1978**, *21*, 1149.

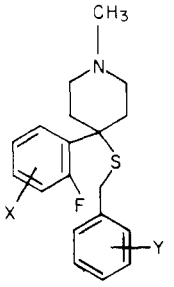
(6) At temperatures above −60 °C, benzyne formation became pronounced; as a result, both the purity and yields of **1** and **2** decreased drastically.

(7) The only difficulty we experienced in effecting this condensation involved *p*-methoxybenzyl mercaptan. For reasons not clearly understood, dehydration occurred predominately.

(8) (a) Helsley, G. C.; Strupczewski, J.; Woodward, D. L. *J. Med. Chem.* **1978**, *21*, 309. (b) Helsley, G. C. U.S. Patent 3 794 542 (1970).

(9) (a) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 866. (b) Corey, E. J.; Chaykovsky, M. *ibid.* **1965**, *87*, 1345.

Table I. 4-Benzyl-4-(2-fluorophenyl)-1-methylpiperidine Derivatives[a]



compd	X	Y	starting material	method	mp, °C	yield,[b] %	recrystn solvent[c]	formula	anal.
5	H	H	1	B	182-184	74	A-E	$C_{19}H_{22}FNS\cdot HCl$	C, H, N, S
6	F	H	2	B	164-166	37	A-E	$C_{19}H_{21}F_2NS\cdot C_4H_4O_4$[d]	C, H, N, S
7	H	2-CH_3	1	B	206-208	46	A-E	$C_{20}H_{24}FNS\cdot HCl$	C, H, N
8	H	3-CH_3	1	B	145-146	47	A-E	$C_{20}H_{24}FNS\cdot HBr$	C, H, N
9	H	4-CH_3	1	B	182-184	35	E-G	$C_{20}H_{24}FNS\cdot HBr$	C, H, N
10	H	2-F	1	B	153-155	41	E-G	$C_{19}H_{21}F_2NS\cdot C_4H_4O_4$[d]	C, H, N
11	H	3-F	1	B	178-180	34	A-E-G	$C_{19}H_{21}F_2NS\cdot HBr$	C, H, N
12	H	4-F	1	B	123-125	50	E-G	$C_{19}H_{21}F_2NS\cdot C_4H_4O_4$[d]	C, H, N
13	H	2-Cl	1	B	175-177	43	A-E	$C_{19}H_{21}ClFNS\cdot HCl$	C, H, F, N
14	H	3-Cl	1	B	195-197	46	A-E-G	$C_{19}H_{21}ClFNS\cdot HBr$	C, H, N
15	H	4-Cl	1	B	164-166	57	A	$C_{19}H_{21}ClFNS\cdot HCl$	C, H, F, N
16	H	2,4-Cl_2	1	B	210-212	40	A-E-G	$C_{19}H_{20}Cl_2FNS\cdot HBr$	C, H, N
17	H	3,4-Cl_2	1	B	188-190	47	A-E	$C_{19}H_{20}Cl_2FNS\cdot HCl$	C, H, Cl, N
18	H	3-CF_3	1	B	176-177	30	A	$C_{20}H_{21}F_4NS\cdot HBr$	C, H, N
19	H	2-NO_2	1	B	141-143	57	A-E	$C_{19}H_{21}FN_2O_2S\cdot HCl$	C, H, Cl, N
20	H	4-NO_2	1	B	209-210	42	A-E-G	$C_{19}H_{21}FNO_2S\cdot HCl$	C, H, N

[a] All compounds exhibited IR, MS, and ^1H NMR spectra consistent with the structures. [b] Isolated yield; no efforts were made to optimize these yields. [c] A = acetone; B = benzene; C = cyclohexane; D = water; E = ethyl ether; F = ethanol; G = methanol; H = hexane; I = pentane. [d] Acid maleate salt.

methylate **21** by the classic von Braun procedure has resulted in a cyanamide brominated at the methine (C-3) position.

Biological Results and Discussion

The title compounds were evaluated in a battery of assays for broad CNS screening. Not surprisingly, potent antidepressant-like properties emerged as the most prominent features of the activity spectrum, as assessed by the inhibition of tetrabenazine (TBZ) ptosis in mice and the potentiation of head twitching induced by 5-hydroxytryptophan (5-HTP) in pargyline-pretreated rats (Table III). While most clinically efficacious antidepressants have shown activity in the TBZ model, attenuation of 5-HTP-induced stereotypy is thought to be associated selectively with agents acting via the serotonergic mechanism.

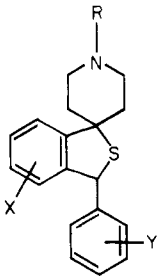
With respect to anti-TBZ activity, the spiro[benzo[*c*]-thiophene-1,4′-piperidines] (II) are, in general, equipotent to (or slightly less active than) their oxygen isosteres (I) where direct comparison is possible.[2] Similar to what was observed with the spiro[isobenzofuran-1,4′-piperidines] (I), nuclear substitution(s) on the pendant aromatic ring frequently exerted differential effects upon the secondary and tertiary amines, reflecting, perhaps, significant differences in absorption, distribution, metabolism, or drug–receptor interactions.[2] Among the tertiary amines studied (**21–34**), enhancement of anti-TBZ activity was usually seen with the introduction of a nuclear substituent of $+\pi$ value (Hansch hydrophobic substituent parameter) as illustrated by **23**, **26–32**, and **34**, whereas the outcome of disubstitution was not always favorable (**33**). In the case of secondary amines (**49–61**), the unsubstituted compound, **49**, was among the most active congeners of this series, being approximately equipotent to desipramine when given orally or by intraperitoneal administration. Monosubstitution, surprisingly, no longer elicited a uniformly beneficial effect. It is also worth noting that, with either secondary or tertiary amines, there appears to be no discernible pattern regarding the optimum position(s) of substitution in so far as the pendant ring is concerned.

By contrast, the presence as well as the position of nuclear substitution appears to be crucial to 5-HTP potentiation. A para group on the pendant ring almost invariably increased potency (**25**, **28**, **31–33**, **52**, **55**, **58–60**), an ortho group was often detrimental (**23**, **26**, **29**, **53**, and **56**), and the results produced by meta substituents were frequently unpredictable (**26**, **27**, **34**, **54**, and **61**). The most dramatic augmentation of activity was seen among the secondary amines, where the introduction of a 4-chloro group into the pendant ring was accompanied by a 100-fold increase in potency; the resultant compound, **58**, was found to be far more active than chlorimipramine or fluoxetine, both of which are widely recognized as potent blockers of presynaptic neuronal uptake of serotonin. It is also interesting to note that incorporation of a 6-fluoro substituent into the fused aromatic ring (**22**), while improving the anti-TBZ activity, virtually abolished the potentiating effect on 5-hydroxytryptophan.

A possible therapeutic advantage which sets the title compounds apart from the tricyclic antidepressants is their relatively low anticholinergic potential as assessed by the prevention of physostigmine lethality in mice.[10] Other characteristic features of this series include a behavioral effect (licking, gnawing, and sniffing) evoked by many congeners (**28**, **31**, **33**, **54**, and **58**), somewhat reminiscent of the stereotypic behavior caused by dopamine agonists and by the nontricyclic antidepressant nomifensine.[11a,b]

(10) Of the 13 compounds tested in this model (**21**, **23**, **25**, **28**, **31–33**, **49**, **51**, **52**, **55**, **58**, and **60**), only **25** and **52** showed marginal response at 50 mg/kg ip; the others were inactive at this dose. By contrast, the corresponding ED_{50} values for desipramine and amitryptyline were 40.4 and 8.1 mg/kg ip, respectively.

Table II. 3-Aryl-1,3-dihydrospiro[benzo[*c*]thiophene-1,4'-piperidines][a]



compd	X	Y	R	starting material	method	mp, °C	yield,[b] %	recrystn solvent[c]	formula	anal.
21	H	H	CH_3	5	C	120-121	67	E-H	$C_{19}H_{21}NS$	C, H, N, S
22	F	H	CH_3	6	C	136-137	52	E-I	$C_{19}H_{20}FNS$	C, H, F, N, S
23	H	2-CH_3	CH_3	7	C	132-134	75	E-H	$C_{20}H_{23}NS$	C, H, N
24	H	3-CH_3	CH_3	8	C	262-264	59	G	$C_{20}H_{23}NS \cdot HBr$	C, H, N
25	H	4-CH_3	CH_3	9	C	121-122	43	E-H	$C_{20}H_{23}NS$	C, H, N
26	H	2-F	CH_3	10	C	263-265	83	E-G	$C_{19}H_{20}FNS \cdot HBr$	C, H, F, N
27	H	3-F	CH_3	11	C	139-141	65	A-E	$C_{19}H_{20}FNS \cdot C_4H_4O_4$[d]	C, H, F, N
28	H	4-F	CH_3	12	C	109-110	83	E-I	$C_{19}H_{20}FNS$	C, H, F, N
29	H	2-Cl	CH_3	13	C	178-179	64	A	$C_{19}H_{20}ClNS \cdot C_4H_4O_4$[d]	C, H, Cl, N
30	H	3-Cl	CH_3	14	C	236-237	71	A-E	$C_{19}H_{20}ClNS \cdot HBr$	C, H, N
31	H	4-Cl	CH_3	15	C	121-123	89	E-I	$C_{19}H_{20}ClNS$	C, H, Cl, N
32	H	2,4-Cl_2	CH_3	16	C	260-261	34	A-E-G	$C_{19}H_{19}Cl_2NS \cdot HBr$	C, H, Cl, N
33	H	3,4-Cl_2	CH_3	17	C	212-213	76	A-E-G	$C_{19}H_{19}Cl_2NS \cdot C_4H_4O_4$[d]	C, H, Cl, N
34	H	3-CF_3	CH_3	18	C	186-187	57	A	$C_{20}H_{20}F_3NS \cdot C_4H_4O_4$[d]	C, H, N
35	H	H	C(=O)OC_6H_5	21	D	171-173	93	B-H	$C_{25}H_{23}NO_2S$	C, H, N
36	F	H	C(=O)OC_6H_5	22	D	156-158	75	E-I	$C_{26}H_{22}FNO_2S$	C, H, N
37	H	2-CH_3	C(=O)OC_6H_5	23	D	*e*	63	*f*	$C_{26}H_{25}NO_2S$	C, H
38	H	3-CH_3	C(=O)OC_6H_5	24	D	157-160	60	B-H	$C_{26}H_{25}NO_2S$	C, H, N
39	H	4-CH_3	C(=O)OC_6H_5	25	D	179-180	36	B-H	$C_{26}H_{25}NO_2S$	C, H, N
40	H	2-F	C(=O)OC_6H_5	26	D	122-123	72	A-I	$C_{25}H_{22}FNO_2S$	C, H, N
41	H	3-F	C(=O)OC_6H_5	27	D	144-146	79	B-H	$C_{25}H_{22}FNO_2S$	C, H, N
42	H	4-F	C(=O)OC_6H_5	28	D	200-201	87	A-I	$C_{25}H_{22}FNO_2S$	C, H, N
43	H	2-Cl	C(=O)OC_6H_5	29	D	*e*	73	*f*	$C_{25}H_{22}ClNO_2S$	H, N; C[g]
44	H	3-Cl	C(=O)OC_6H_5	30	D	168-170	79	A	$C_{25}H_{22}ClNO_2S$	C, H, N
45	H	4-Cl	C(=O)OC_6H_5	31	D	211-212	81	B-H	$C_{25}H_{22}ClNO_2S$	C, H, N
46	H	2,4-Cl_2	C(=O)OC_6H_5	32	D	*e*	77	*f*	$C_{25}H_{21}Cl_2NO_2S$	C, H, N
47	H	3,4-Cl_2	C(=O)OC_6H_5	33	D	200-201	93	A-I	$C_{25}H_{21}Cl_2NO_2S$	C, H, N
48	H	3-CF_3	C(=O)OC_6H_5	34	D	127-129	65	H	$C_{26}H_{22}F_3NO_2S$	C, H, N
49	H	H	H	35	E	142-144	94	A-H	$C_{18}H_{19}NS$	C, H, N, S
50	H	2-CH_3	H	37	E	178-179	54	E-G	$C_{19}H_{21}NS \cdot C_4H_4O_4$[d]	C, H, N
51	H	3-CH_3	H	38	E	175-176	58	A	$C_{19}H_{21}NS \cdot C_4H_4O_4$[d]	C, H, N
52	H	4-CH_3	H	39	E	214-215	37	E-G	$C_{19}H_{21}NS \cdot C_4H_4O_4$[d]	C, H, N
53	H	2-F	H	40	E	186-187	81	A-E-G	$C_{18}H_{18}FNS \cdot C_4H_4O_4$[d]	C, H, F, N
54	H	3-F	H	41	E	188-189	56	A-E-G	$C_{18}H_{18}FNS \cdot C_4H_4O_4$[d]	C, H, F, N
55	H	4-F	H	42	E	259-260	70	A-E-G	$C_{18}H_{18}FNS \cdot HCl$	C, H, F, N
56	H	2-Cl	H	43	E	173-174	68	A-E-G	$C_{18}H_{18}ClNS \cdot C_4H_4O_4$[d]	C, H, N
57	H	3-Cl	H	44	E	190-191	53	A-E-G	$C_{18}H_{18}ClNS \cdot C_4H_4O_4$[d]	C, H, N
58	H	4-Cl	H	45	E	138-140	78	A-H	$C_{18}H_{18}ClNS$	C, H, Cl, N
59	H	2,4-Cl_2	H	46	E	172-173	72	A-E-G	$C_{18}H_{17}Cl_2NS \cdot C_4H_4O_4$[d]	C, H, Cl, N
60	H	3,4-Cl_2	H	47	E	192-193	77	E-G	$C_{18}H_{17}Cl_2NS \cdot C_4H_4O_4$[d]	C, H, Cl, N
61	H	3-CF_3	H	48	E	183-184	40	A	$C_{19}H_{18}F_3NS \cdot C_4H_4O_4$[d]	C, H, N

[a-d] See corresponding footnotes to Table I. [e] A colorless oil. [f] Purified by column chromatography over silica gel, CH_2Cl_2 as eluant. [g] C: calcd, 68.88; found, 69.36.

Additional evidence for the CNS stimulant component was provided by the observation that the aforementioned compounds, at 15 mg/kg po, also significantly increased the spontaneous motor activity in mice.

In summary, the 3-aryl-1,3-dihydrospiro[benzo[*c*]-thiophene-1,4'-piperidines] represent a novel class of potential antidepressants of a unique profile. In depth studies are now underway to further elucidate the underlying mechanisms of their pharmacological actions.

Experimental Section

The structure 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 analysis were indicated only by symbols of the elements, the analytical results obtained for those elements (performed by Micro-Tech Laboratories, Skokie, Ill.) were within 0.4% of theoretical values.

4-(2-Fluorophenyl)-4-hydroxy-1-methylpiperidine (1). Method A. To a solution of 2-bromofluorobenzene (17.5 g, 0.1 mol) in 50 mL of anhydrous THF was added, at −70 °C and under nitrogen, 46 mL of *n*-butyllithium (2.4 M, Alfa Chemical Co.) over a period of 15 min. The tan-colored solution wa stirred at −70 °C for an additional hour before 11.3 g (0.1 mol) of freshly distilled 1-methyl-4-piperidinone in 20 mL of THF was added at a rate so that the internal temperature remained below −60 °C (20 min). Following total addition, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature.

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Table III. Pharmacology of 3-Aryl-1,3-dihydrospiro[benzo[c]thiophene-1,4'-piperidines]

compd[a]	tetrabenazine ptosis: ED_{50}, mg/kg po	5-HTP potentiation: ED_{50}, mg/kg ip
21	4.6 (3.8-6.0) 2.5 (2.1-2.9)[b]	3.4 (1.4-8.7)
22	2.8 (2.5-3.1) 1.8 (1.5-2.1)[b]	>10
23	1.3 (1.1-1.6) 0.77 (0.69-0.83)[b]	>10
24	~20[b,f]	>2[c]
25	~3[b,f]	1.0 (0.85-1.24)
26	2.1 (1.9-2.2) 3.0 (2.3-4.1)[b]	>10
27	3.3 (3.1-3.6) 0.83 (0.63-1.07)[b]	>10
28	3.1 (2.9-3.4) 1.4 (1.3-1.7)[b]	1.5[f]
29	3.6 (2.9-4.7) 0.6 (0.5-0.7)[b]	10.1 (9.4-11.9)
30	1.3 (1.1-1.5) 0.9 (0.8-1.1)[b]	[d]
31	1.4 (1.3-1.6) 1.3 (1.2-1.4)[b]	0.40 (0.25-0.94)
32	3.8 (3.5-4.0) 1.6 (1.5-1.8)[b]	0.91 (0.52-1.60)
33	6.1 (4.9-7.8) 3.5 (2.8-4.3)[b]	0.58 (0.51-1.4)
34	1.6 (1.5-1.8) 0.73 (0.53-0.96)[b]	0.52 (0.27-1.01)
49	1.3 (1.0-1.6) 1.1 (0.9-1.2)[b]	~3[f]
50	1.4 (1.2-1.5)	2.8 (2.7-3.0)
51	2.9 (2.6-3.0) 1.9 (1.7-2.1)[b]	0.71 (0.53-0.95)
52	3.6 (3.1-4.0) 0.69 (0.58-0.82)[b]	~0.16[b]
53	6.6 (5.6-8.0) 0.78 (0.6-1.0)[b]	3.9 (2.7-5.6)
54	3.1 (2.9-3.4)	0.16 (0.065-0.38)
55	2.1 (1.8-2.6) 0.67 (0.58-0.76)[b]	0.32 (0.27-1.0)
56	2.2 (2.0-2.3)	4.4 (2.8-6.9)
57	1.8 (1.6-2.0) 0.52 (0.40-0.64)[b]	[d]
58	1.6 (1.5-1.8) 2.1 (1.7-2.4)[b]	0.03 (0.02-0.096) 0.78 (0.32-1.65)[e]
59	3.8 (3.5-4.1) 2.4 (2.2-2.6)[b]	2.2 (1.4-3.4)
60	0.82 (0.67-0.97)	~0.4[f]
61	1.7 (1.5-1.8) 1.2 (1.0-1.4)[b]	[d]
desipramine	1.6 (1.4-1.8) 0.8 (0.6-0.9)[b]	>10
amitriptyline	7.8 (7.1-8.7) 1.5 (1.1-1.9)[b]	7.1 (3.9-9.1)
chlorimipramine	3.5 (2.9-4.3) 0.73 (0.25-1.2)[b]	3.1 (1.5-4.7)
fluoxetine	[g]	0.6 (0.3-1.6)

[a] The vehicle control used in both of the biological tests consists of distilled water and a few drops of Tween 80. [b] Determined by intraperitoneal administration. [c] Toxic effects required a lower screening dose. [d] Seizures before 5-HTP dosing. [e] Determined by oral administration. [f] Estimated graphically without statistical analysis. [g] Inactive at the screening dose of 20 mg/kg ip.

Water was then added (200 mL), the layers were separated, and the aqueous phase was extracted 3 times with ether. The combined organic solution was shaken with a large excess of 2 N HCl, and basification of the acidic solution with concentrated ammonia yielded a heavy oil which solidified on standing. Recrystallization of the crude amino alcohol from benzene–hexane gave 14 g (67%) of 1 as colorless prisms, mp 127–129 °C. Anal. ($C_{12}H_{16}FNO$) C, H, F, N.

4-(2,5-Difluorophenyl)-4-hydroxy-1-methylpiperidine maleate (2) was prepared from 2-bromo-1,4-difluorobenzene in 56% yield by method A, mp 160–162 °C. Anal. ($C_{12}H_{15}F_2NO \cdot C_4H_4O_4$) C, H, N, S.

4-(Benzylthio)-4-(2-fluorophenyl)-1-methylpiperidine Hydrochloride (5). Method B. A mixture of 1 (4.5 g, 21.5 mmol), 8 mL of benzyl mercaptan, and 10 mL of boron trifluoride in 10 mL of glacial acetic acid was stirred at 60 °C for 15 h. The excess reagents were removed at 60 °C under reduced pressure, and the residue was equilibrated with a mixture of 50 mL of ether and 50 mL of 2 N hydrochloric acid. After the mixture was stirred in cold (0–5 °C) for 2 h, the crude crystalline **5** was filtered off and air-dried. Recrystallization from acetone-ether gave 5.6 g (74%) of **5**. Properties of **5**, and of **6–20** prepared in a similar manner, are included in Table I.

4-(2-Fluorophenyl)-1,2,3,6-tetrahydro-1-methylpyridine Maleate (3). The aqueous filtrate, after the removal of crude **5**, was basified to pH 9–10 with concentrated ammonia. The liberated amine was extracted into ether, washed (H_2O), and dried ($MgSO_4$). Evaporation of solvent in vacuo left a colorless oil which, upon treatment with ethereal maleic acid, afforded 1.66 g (25%) of **3**. Compound **3** was recrystallized from acetone–ether to give

fine needles: mp 148.5–149.5 °C. Anal. ($C_{16}H_{16}FNO_4$) C, H, N.

4-(2,5-Difluorophenyl)-1,2,3,6-tetrahydro-1-methylpyridine maleate (4) was prepared in a similar manner as **3** from **2** (2.3 g of the free base, 10 mmol). After **6** was removed by filtration, the aqueous filtrate was basified with concentrated ammonia and the liberated amine was extracted into ether. Treatment of the ether solution with ethereal maleic acid gave 1.6 g (50%) of **4**, which was recrystallized from acetone–ether to give fine needles, mp 163–164 °C. Anal. ($C_{16}H_{17}F_2NO_4$) C, H, N.

1,3-Dihydro-1′-methyl-3-phenylspiro[benzo[*c*]thiophene-1,4′-piperidine] (21). Method C. A solution of sodium methylsulfinylmethide was prepared by heating 0.45 g of sodium hydride in 20 mL of anhydrous Me_2SO at 80–85 °C under N_2 for 30 min. The mixture was cooled to room temperature and to it, over 10–15 min, was added a solution of **5** (4.9 g of the free base, 15.6 mmol) in 10 mL of Me_2SO. The reaction mixture turned brownish red and, after stirring at room temperature for 1 h, it was poured onto 200 g of ice–water. The solid was filtered off, washed (H_2O), and air-dried. Recrystallization of the crude product from ether–hexane gave 3.1 g (67%) of **21** as colorless prisms. Properties of **21**, and of **22–34** prepared in a similar manner, are included in Table II.

1,3-Dihydro-1′-(phenoxycarbonyl)-3-phenylspiro[benzo-[*c*]thiophene-1,4′-piperidine] (35). Method D. A mixture of **21** (2.3 g, 7.8 mmol), 1.4 g of phenyl chloroformate, and 0.5 g of sodium bicarbonate in 40 mL of CH_2Cl_2 was stirred at room temperature for 4 h. The inorganic salts were filtered, and the filtrate was washed with dilute NaOH (5%) and water and dried ($MgSO_4$). Removal of solvent under reduced pressure left an off-white solid, which was recrystallized from benzene–hexane to give 3.0 g (93%) of **35** as rosettes. Properties of **35**, and of **36–48** prepared in a similar manner, are included in Table II.

1,3-Dihydro-3-phenylspiro[benzo[*c*]thiophene-1,4′-piperidine] (49). Method E. A mixture of **35** (3.0 g, 7.5 mmol) and 8.5 g of 85% potassium hydroxide pellets in 50 mL of ethylene glycol was stirred at 155 °C for 30 min. The mixture was cooled, diluted with water, and extracted 3 times with $CHCl_3$ (100-mL portions). The combined organic solution was washed exhaustively with H_2O (to remove ethylene glycol) and dried over K_2CO_3. Removal of solvent under reduced pressure left a solid residue which was recrystallized from acetone–hexane to give 1.95 g (94%) of **49**. Properties of **49**, and of **50–61** prepared in a similar manner, are included in Table II.

Antagonism of Tetrabenazine-Induced Ptosis in Mice.[12] The test compound was administered per os or by intraperitoneal injection (ip) to male mice (Charles River CD-1), weighing 20 to 30 g, in groups of five. Tetrabenazine methansulfonate (40 mg/kg, ip) was administered 30 min after ip or 60 min after po administration, and after another 30 min the mice were placed in individual containers. Ptosis was then evaluated on a three-point scale: eyes closed = 2; eyes half-opened = 1; eyes open = 0. A linear-regression analysis of the ptosis scores was used to compute ED_{50} values and 95% confidence intervals.

5-Hydroxytryptophan Potentiation in Rats.[13a,b] Groups of six male Wistar rats weighing 150–200 g were used in this test procedure. Four hours prior to testing, pargyline hydrochloride was prepared and administered by subcutaneous injection at 75 mg/kg in 1% saline and at a dosage volume of 1.25 mL/kg. Thirty minutes before testing, drugs were prepared (distilled water and a few drops of Tween 80) and administered intraperitoneally at a dosage volume of 10 mL/kg. L-5-Hydroxytryptophan (1.0 mg/kg, ip) was administered in volumes proportional to 10 mL/kg, and 5 min after 5-HTP administration the animals were observed for 15 min. A compound was considered to potentiate 5-HTP activity if the animals exhibited head twitching accompanied by course tremors. Potentiation was expressed as normalized percent potentiation relative to vehicle control. Dose-range studies were performed in a similar manner, except that 10 animals per dose group were tested. ED_{50} values were calculated by a linear-regression analysis and presented with 95% confidence limits.

Physostigmine Lethality in Mice. Groups of ten male (Charles River CD-1) mice weighing 18–25 g were administered the test compound (ip or po) at the dosage volume of 10 mL/kg. Control group received vehicle (distilled water and a few drops of Tween 80). At 30, 60, and 120 min after administration of the test compound, an injection of physostigmine sulfate at 2.5 mg/kg, ip, was given to the individual animals. One hour after physostigmine administration, the drug group was checked for deaths. Surviving mice were considered protected. The time period with the greatest protection was the peak time of drug activity. A dose-range study was performed in a similar manner, except that all animals were tested at the peak time of drug activity and five groups of ten animals were employed (four drug groups and one vehicle control). ED_{50} values were calculated by a linear-regression analysis and presented with 95% confidence limits.

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Synthesis and Stereochemistry of 7-Phenyl-2-propionanilidobenzo[*a*]quinolizidine Derivatives. Structural Probes of Fentanyl Analgesics

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The four diastereomers of *N*-(1,3,4,6,7,11b-hexahydro-7-phenyl-2*H*-benzo[*a*]quinolizin-2-yl)-*N*-phenylpropanamide (**7c**, **7d**, **9c**, and **9d**), which are conformationally restricted analogues of fentanyl, were synthesized and separately tested for analgesic activity and affinity for the opiate receptor of rat brain. Stereochemical assignments for **7c**, **7d**, **9c**, and **9d** were deduced from NMR spectral analyses. Conformational analysis revealed that the 2α isomers (**7d** and **9d**) exist in solution as mixtures of cis- and trans-fused conformers with ca. 90 and 45% cis form, respectively. Other compounds (**12a**, **12b**, and **14**) related to these propionanilides were also prepared, stereochemically characterized, and tested. Weak analgesic activity was observed for **7d**, and both **7d** and **9d** bound to the opiate receptor with an I_{50} of ca. 1100 and 1500 nM, respectively (ca. 0.5% of fentanyl and 2% of morphine). The analgesic activity of **7d** was abolished by the opiate antagonist naloxone.

The 4-propionanilidopiperidines represent a class of potent, morphine-like analgesics.[1-4] Fentanyl (**1a**),[2] its *cis*-(+)-3-methyl analogue (**1b**),[3a] and sufentanil (**2**)[4] are typical structures of this series with potent analgesic

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