Synthesis and Antidepressant Activity of 4-Aryltetrahydrothieno[2,3-*c*]pyridine Derivatives

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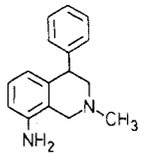
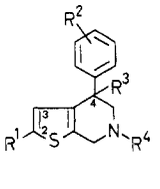
A series of substituted 4-aryltetrahydrothieno[2,3-*c*]pyridines was prepared by acid-catalyzed cyclization of 1-aryl-2-[(2-thienylmethyl)amino]ethanol derivatives. The compounds were examined for their antidepressant activity, as demonstrated by their ability to inhibit the uptake of norepinephrine (NE) and serotonin (5-HT) and to prevent tetrabenazine-induced ptosis (TBZ) in mice. Significant inhibition of both neurotransmitters is observed for several of the tested compounds, while some of them are selective inhibitors of either NE or 5-HT uptake. Optimal activity is associated with the introduction of lipophilic substituents into the 4-position of the phenyl ring and less lipophilic substituents into the 2-position of the thiophene ring (**11**, **23**). Compound **33** bearing substituents in positions 2 and 6 of the phenyl ring is inactive. This might be a consequence of an out of plane conformation of this compound.

Tricyclic antidepressants such as imipramine or amitriptyline are most frequently used in the treatment of endogenous depression.[1-3] Their ability to inhibit the uptake of norepinephrine (NE) and 5-hydroxytryptamine (5-HT) into the presynaptic nerve terminal has generally been predictive of antidepressant action in man.[4,5] However, these drugs have undesirable anticholinergic[6] or cardiotoxic side effects[7-9] that seem to be related to their tricyclic structure.

Nomifensine,[10] a nontricyclic antidepressant, strongly inhibits NE uptake and is a novel antidepressant without cardiotoxic effects.[11,12] During the past 5 years, we have been synthesizing structurally related 4-aryltetrahydrothieno[2,3-*c*]pyridines as potential antidepressants.[13] We now report on syntheses and pharmacological and biochemical evaluation of these compounds shown by formula I.



Nomifensine

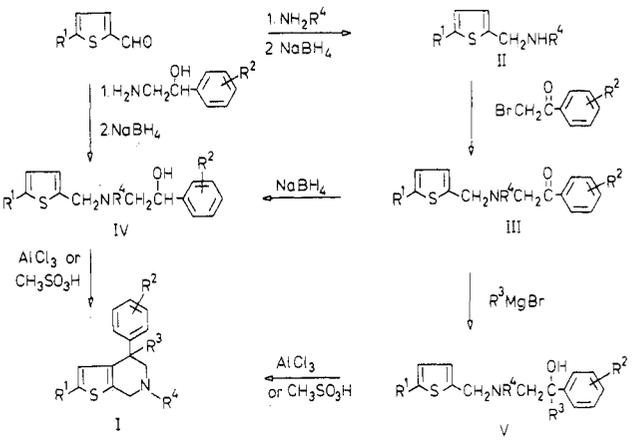


I

Chemistry. The individual compounds I shown in Table I were synthesized as outlined in Scheme I.

Key intermediates were the 1-aryl-2-[(2-thienylmethyl)amino]ethanols IV and V that yielded the corresponding compounds I by ring closure. One of the latter compounds (**36**) had been prepared previously in this way with use of polyphosphoric acid for the cyclization.[14]

Scheme I



Similar cyclizations in the tetrahydroisoquinoline series have been effected with various other acids.[15] In our hands, $AlCl_3$ (method A) or methanesulfonic acid (method B) gave rather good yields of the desired compounds I.

Some of the compounds I prepared in this manner were modified by introduction or alteration of substituents in positions 2 and 3. Introduction of a *tert*-butyl group into position 2 was effected by alkylation with *tert*-butyl alcohol/BF_3[16] (compound **13**). 2-Nitro groups were introduced (compounds **7** and **16**) and optionally reduced to amino groups (compounds **8**, **17**, and **19**), employing conventional methods. The 2-hydroxymethyl group of compound **23** was generated by reduction of the corresponding 2-formyl analogue, which was obtained by condensation of the lithium salt of V (R^1 = Li) with dimethylformamide. Treatment of **9** with bromine and $AlBr_3$ yielded the 3-bromo-substituted compound **34**.

The intermediates 1-aryl-2-[(2-thienylmethyl)amino]-ethanols IV (R^4 = H) were prepared by reaction of 2-amino-1-arylethanol with the appropriate 2-thiophenecarbaldehyde to give the corresponding imino derivative, which was not isolated but directly reduced to give IV.

Another procedure was utilized to prepare the aminoethanols IV and V bearing an alkyl group at the nitrogen. Reaction of a primary amine with 2-thiophenecarbaldehyde followed by borohydride reduction gave the 2-(aminomethyl)thiophenes II,[7] which were alkylated with the appropriate phenacyl bromides to afford the amino ketones III. The latter were either reduced with $NaBH_4$ or treated with Grignard reagents to give the aminoethanols IV or V.

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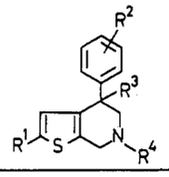
Table I. 4-Aryl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridines I



compd	R^1	R^2	R^3	R^4	mp (solv),[a] °C	method[b]	yield, %	formula	anal.[c]
1	2-Br	H	H	CH_3	210–212 (A)	B	44	$C_{14}H_{14}BrNS\cdot HCl$	CHN
2	2-Cl	H	H	CH_3	223–225 (A)	A	52	$C_{14}H_{14}ClNS\cdot HCl$	CHN
3	2-CH_3	H	H	CH_3	226–228 (A)	A	38	$C_{15}H_{17}NS\cdot HCl$	CHN
4	2-Br	4′-Br	H	CH_3	122–123 (B)	*d*	42	$C_{14}H_{13}Br_2NS$	CHNBr
5	2-Cl	4′-Br	H	CH_3	257–259 (A)	B	76	$C_{14}H_{13}BrClNS\cdot HCl$	CHN
6	2-Cl	4′-Br	H	H	283–285 (A)	B	85	$C_{13}H_{11}BrClNS\cdot HCl$	CHNBr
7	2-NO_2	4′-Br	H	CH_3	205–207 (A)	*b*	65	$C_{14}H_{13}BrN_2O_2S\cdot HCl$	CHNBr
8	2-NH_2	4′-Br	H	CH_3	145–147 (A)	*b*	57	$C_{14}H_{15}BrN_2S\cdot C_4H_4O_4$	CHN[f]
9	2-CH_3	4′-Br	H	CH_3	>260 (A)	B	49	$C_{15}H_{16}BrNS\cdot HCl$	CHN
10	2-CH_3	4′-Br	H	H	282–283 (A)	B	76	$C_{14}H_{14}BrNS\cdot HCl$	CHN
11	2-CH_2OCH_3	4′-Br	H	CH_3	167–168 (A)	*b*	45	$C_{16}H_{18}BrNOS\cdot CH_3SO_3H$	CHNBr
12	2-$CH_2CH_2CH_3$	4′-Br	H	CH_3	246–248 (A)	A	82	$C_{17}H_{20}BrNS\cdot HCl$	CHN
13	2-*t*-C_4H_9	4′-Br	H	CH_3	290–292 (B)	*b*	61	$C_{18}H_{22}BrNS\cdot HCl$	CHNBr
14	H	4′-Cl	H	*n*-C_4H_9	169–170 (A)	B	38	$C_{17}H_{20}ClNS\cdot HCl$	CHN
15	2-Cl	4′-Cl	H	CH_3	226–228 (A)	A	56	$C_{14}H_{13}Cl_2NS\cdot HCl$	CHN
16	2-NO_2	4′-Cl	H	CH_3	147–149 (C)	*b*	85	$C_{14}H_{13}ClN_2O_2S$	CHNCl
17	2-NH_2	4′-Cl	H	CH_3	165–166 (A)	*b*	60	$C_{14}H_{15}ClN_2S\cdot C_4H_4O_4$	CHNCl
18	2-CH_3	4′-Cl	H	CH_3	254–255 (A)	A	56	$C_{15}H_{16}ClNS\cdot HCl$	CHN
19	2-NHAc	4′-Cl	H	CH_3	227–229 (D)	*b*	78	$C_{16}H_{17}ClN_2OS$	CHNCl
20	2-$CH_2CH_2CH_3$	4′-F	H	CH_3	228–230 (A)	A	80	$C_{17}H_{20}FNS\cdot HCl$	CHN
21	2-Br	4′-CH_3	H	CH_3	264–266 (A)	A	52	$C_{15}H_{16}BrNS\cdot HCl$	CHN
22	2-Cl	4′-CH_3	H	CH_3	260–262 (A)	B	64	$C_{15}H_{16}ClNS\cdot HCl$	CHN
23	2-CH_2OH	4′-CH_3	H	CH_3	238–239 (A)	*b*	45	$C_{16}H_{19}NOS\cdot HCl$	CHN
24	2-CH_2CH_3	4′-CH_3	H	CH_2CH_3	231–232 (A)	B	51	$C_{18}H_{23}NS\cdot HCl$	CHN
25	2-CH_3	4′-CF_3	H	CH_3	273–274 (A)	A	48	$C_{16}H_{16}F_3NS\cdot HCl$	CHN
26	2-CH_3	4′-OH	H	CH_3	221–223 (E)	*b*	58	$C_{15}H_{17}NOS$	CHN
27	2-CH_3	4′-OCH_3	H	CH_3	236–238 (A)	A	40	$C_{16}H_{19}NOS\cdot HCl$	CHN
28	2-CH_3	4′-Br	CH_3	CH_3	263–265 (A)	A	82	$C_{16}H_{18}BrNS\cdot CH_3SO_3H$	CHNBr
29	2-CH_3	4′-Br	CH_2CH_3	CH_3	187–188 (A)	A	78	$C_{17}H_{20}BrNS\cdot CH_3SO_3H$	CHNBr
30	2-Cl	3′-OH	H	H	188–189 (E)	A	48	$C_{13}H_{12}ClNOS$	CHN
31	2-CH_3	3′-CF_3	H	CH_3	246–248 (A)	A	46	$C_{16}H_{16}F_3NS\cdot HCl$	CHN
32	H	2′,4′-Cl_2	H	CH_3	250–251 (A)	A	38	$C_{14}H_{13}Cl_2NS\cdot HCl$	CHNCl
33	2-CH_3	2′,6′-Cl_2	H	CH_3	235–237 (A)	A	54	$C_{15}H_{15}Cl_2NS\cdot HCl$	CHN
34	2-CH_3, 3-Br	4′-Br	H	CH_3	261–262 (A)	*b*	49	$C_{15}H_{15}Br_2NS\cdot HCl$	CHN
35	H	3′,4′-$(OCH_3)_2$	H	CH_3	114–115 (A)	A	50	$C_{16}H_{19}NO_2S\cdot HCl$	CHNCl
36[e]	H	H	H	H	193–199 (A)	B	51	$C_{13}H_{13}NS\cdot HCl$	

[a] Recrystallization solvent: A = EtOH, B = MeOH, C = THF, D = CH_3CN, E = AcOEt. [b] See Experimental Section. [c] Elemental analyses are within ±0.4% of the calculated values unless otherwise noted. [d] Cyclization was carried out in H_2SO_4. [e] Described in ref 13. [f] Calcd, 6.38; found, 5.83.

Results and Discussion

Most of the compounds examined are potent inhibitors of the uptake of NE and 5-HT in vitro and show antitetrabenazine (TBZ) activity in vivo (Table III). Substitution of position 2 of the fused thiophene ring and a para-substituted phenyl ring are most favorable for high potency and, to some extent, for the selectivity of these compounds.

Since for the uptake studies synaptosomal preparations of the whole rat brain minus cerebellum were used, [^{3}H]NE uptake might also occur into dopaminergic synaptosomes to a smaller extent. Nomifensine exhibits a well-known inhibition of dopamine uptake[18] that, measured with striatal synaptosomes, is about one-tenth that of NE uptake inhibition presented in this paper. Thus, with regard to nomifensine IC_{50} values, a minor interference only can occur by effecting dopaminergic uptake process.

Br, Cl, and CH_3 substituents in the thiophene 2-position (**1–3**) increase the NE uptake inhibiting activity of the corresponding compounds correlating with their decrease in lipophilicity.[19] Their influence on the 5-HT uptake process, however, is weak. Introduction of a *tert*-butyl group into the thiophene ring (**13**) leads to a decrease in potency in comparison with the 2-methyl-substituted compound **9**.

Uptake inhibition is increased by substitution of the para position of the phenyl ring with halogen, methyl, or methoxy groups but not with trifluoromethyl. This increase is not equally pronounced for NE and 5-HT activity. Thus, the *p*-bromo derivatives of the compounds **2** and **3** (**5**, **9**) are over 10 times more active on 5-HT inhibition than **2** and **3**, whereas the *p*-methyl derivative of compound **1** (**21**) and the *p*-chloro derivative of compound **3** (**18**) are 3 times more active with respect to NE inhibition than **1** and **3**.

Beside the para substituent, a comparably less lipophilic group in the 2-position is necessary to enhance both neurotransmitters. So the amino, the hydroxymethyl, and the methoxymethyl derivatives (**8**, **23**, and **11**, respectively) are the most active compounds.

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Figure 1. Coplanar arrangement of the phenyl ring and the protonated amino group.

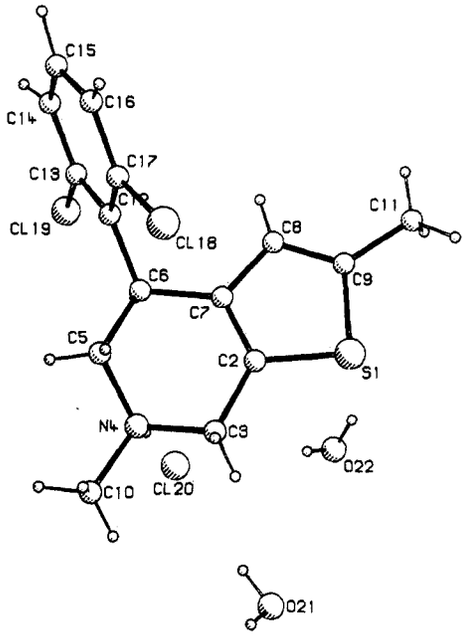

Figure 2. Molecular structure of compound **33**. Dihedral angle τ(C5–C6–C12–C13) = −118°.

Generally, the compounds I are more potent on NE than on 5-HT uptake inhibition. **2** and **3** bearing no substituent at the phenyl ring, the 3-phenyl-substituted derivatives **30** and **31**, and the *p*-methyl compound **22**, however, showed a fairly selective NE uptake inhibition. On the other hand, the 3,4-dimethoxy analogue **35** displays 5-HT selectivity. Of these compounds, only **3** and **22** show an anti-TBZ activity. Compounds with substituents in the thiophene 3-position (**34**) or in the phenyl ring 2- and 6-position (**32** and **33**) are less active with respect to uptake inhibition as well as to anti-TBZ activity.

From NE uptake inhibition studies with α-alkyl-substituted phenethylamines and with rigid analogues of amphetamines, it has been established that the pharmacophoric conformation at the uptake sites involves a more or less coplanar arrangement of the phenyl ring and the protonated amino group (Figure 1).[20]

Our results confirm these observations. As shown by X-ray crystallography (Figure 2), the phenyl ring in compound **33** is forced out of the plane. This out of plane phenyl ring conformation is due to the steric hindrance by the two ortho chlorine atoms, which do not allow proper fit of this molecule to the active site. This might be also true for compound **34** and, to some extent, for the compounds **32** and **29**.

A therapeutic advantage of the title compounds compared with imipramine and amitriptyline is their relatively low anticholinergic and cardiotoxic potential as their weak affinity to the specific [^{3}H]QNB binding sites[21,22] and low cardiodepressive effects might indicate. At concentrations up to 10^{-4} g/mL, compounds **15** and **23** moderately decrease contractility and frequency of isolated atria of guinea pigs.[23] At the same concentrations, nomifensine and particularly amitriptyline show marked cardiodepressive effects.[24a,b]

Experimental Section

Chemistry. Melting or decomposition points were determined in a Büchi 510 apparatus in open capillary tubes and are uncorrected. Microanalyses agree, unless otherwise stated, with calculated values within ±0.4%. IR and NMR spectra are consistent with assigned structures.

2-Thiophenecarbaldehydes. 5-Bromo-, 4-chloro-, and 5-methyl-2-thiophenecarbaldehyde were commercially available. 5-Ethyl- and 5-propyl-2-thiophenecarbaldehyde were prepared according to procedures described in the literature.[25]

2-(Aminomethyl)thiophenes II were prepared by borohydride reduction of the corresponding imines by using the methods of Schellenberg[26] and Horii et al.:[27] 2-[(methylamino)methyl]-thiophene hydrochloride,[17] yield 86%, mp 196–198 °C; 5-methyl-2-[(methylamino)methyl]thiophene,[28] yield 91%, bp 83–84 °C (10 mm); 5-bromo-2-[(methylamino)methyl]thiophene, yield 76%, bp 127–128 °C (10 mm); 5-chloro-2-[(methylamino)-methyl]thiophene, yield 78%, bp 100–102 °C (10 mm); 5-propyl-2-[(methylamino)methyl]thiophene, yield 86%, bp 116–117 °C (10 mm); 5-ethyl-2-[(ethylamino)methyl]thiophene, yield 88%, bp 105–108 °C (10 mm); 2-[(butylamino)methyl]thiophene hydrochloride, yield 90%, mp 224–226 °C.

1-(4-Chlorophenyl)-2-[[(5-chloro-2-thienyl)methyl]-methylamino]ethanol Hydrochloride (37). To a solution of 5-chloro-2-[(methylamino)methyl]thiophene (57.4 g, 0.355 mol) in 500 mL of dry EtOH were added K_2CO_3 (55.2 g) and *p*-chlorophenacyl bromide (82.9 g, 0.355 mol) with stirring. After continuous stirring at ambient temperature for 2 h, 16.9 g of $NaBH_4$ was added in small portions at about 5 °C. The mixture was stirred at ambient temperature for 2 h and then poured into 1.5 L of ice–water. The organic material was extracted with CH_2Cl_2. The combined extracts were dried ($MgSO_4$) and evaporated in vacuo, giving an oil of the crude reaction product, which was chromatographed on a silica gel column with cyclohexane–EtOAc (1:1) as eluent. The colorless, oily base was converted into its hydrochloride salt, yielding 96.2 g (80 %) of pure **37**, mp 161–162 °C. Compound **38–56** were prepared in a similar manner by using the appropriately substituted 2-(aminomethyl)thiophenes and phenacyl bromides. The results are shown in Table II.

2-[[(5-Chloro-2-thienyl)methyl]amino]-1-(3-hydroxy-phenyl)ethanol Oxalate (57). A mixture of 5-chloro-2-thiophenecarbaldehyde (14.6 g, 0.1 mol), 2-amino-1-(3-hydroxyphenyl)ethanol hydrochloride (19 g, 0.1 mol), K_2CO_3 (14 g), and 0.2 mL of trifluoroacetic acid in 200 mL of benzene was refluxed for 4 h until 1.8 mL of water had separated. After cooling, a solution of 4.2 g of $NaBH_4$ in 100 mL of MeOH was added at about 5 °C. The mixture was stirred for 30 min and then evaporated. The residue was taken up in CH_2Cl_2, hydrolyzed with 50 mL of

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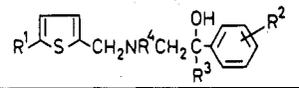
Table II. 1-Aryl-2-[(2-thienylmethyl)amino]ethanols IV and V



compd	R^1	R^2	R^3	R^4	mp, °C	yield, %	formula	anal.
37	Cl	4-Cl	H	CH_3	161–162	80	$C_{14}H_{15}Cl_2NOS\cdot HCl$	CHN
38	Cl	H	H	CH_3	103–104	86	$C_{14}H_{16}ClNOS\cdot HCl$	C[b]HNCl
39	CH_3	H	H	CH_3	111–112	80	$C_{15}H_{19}NOS\cdot C_2H_2O_4$	CHN
40	Br	4-Br	H	CH_3	176–178	64	$C_{14}H_{15}Br_2NOS\cdot HCl$	CHN
41	Cl	4-Br	H	CH_3	169–170	78	$C_{14}H_{15}BrClNOS\cdot HCl$	CHN
42	CH_3	4-Br	H	CH_3	41–42	92	$C_{15}H_{18}BrNOS$	CHNBr
43	n-C_3H_7	4-Br	H	CH_3	165–166	88	$C_{17}H_{22}BrNOS\cdot HCl$	CHN
44	H	4-Cl	H	n-C_4H_9	58–60	74	$C_{17}H_{22}ClNOS\cdot C_2H_2O_4\cdot {}^1/_2H_2O$	CHN
45	Br	H	H	CH_3	117–118	77	$C_{14}H_{16}BrNOS\cdot HCl$	CHNCl
46	CH_3	4-Cl	H	CH_3	149–150	76	$C_{15}H_{18}ClNOS\cdot HCl$	CHNCl
47	n-C_3H_7	4-F	H	CH_3	120–121	86	$C_{17}H_{22}FNOS\cdot HCl$	CHN
48	Br	4-CH_3	H	CH_3	145–146	76	$C_{15}H_{18}BrNOS\cdot HCl$	CHN
49	Cl	4-CH_3	H	CH_3	115–116	78	$C_{15}H_{18}ClNOS\cdot HCl$	CHN
50	CH_3CH_2	4-CH_3	H	CH_3CH_2	111–112	71	$C_{18}H_{25}NOS\cdot C_2H_2O_4$	CHN
51	CH_3	4-CF_3	H	CH_3	182–183	69	$C_{16}H_{18}F_3NOS\cdot HCl$	CHN
52	CH_3	4-OCH_3	H	CH_3	158–159	63	$C_{16}H_{21}NO_2S\cdot C_2H_2O_4$	CHN
53	CH_3	3-CF_3	H	CH_3	162–164	71	$C_{16}H_{18}F_3NOS\cdot HCl$	CHN
54	H	2,4-Cl_2	H	CH_3	130–131	44	$C_{14}H_{15}Cl_2NOS\cdot C_2H_2O_4$	CHN
55	CH_3	2,6-Cl_2	H	CH_3	[a]	66	$C_{15}H_{17}Cl_2NOS$	[c]
56	H	3,4-$(OCH_3)_2$	H	CH_3	173–174	70	$C_{16}H_{21}NO_3S\cdot HCl$	CHN
57	Cl	3-OH	H	H	174–176	78	$C_{13}H_{14}ClNO_2S\cdot C_2H_2O_4$	CHN
58	Cl	4-Br	H	H	206–208	57	$C_{13}H_{13}BrClNOS\cdot HCl$	CHN
59	CH_3	4-Br	H	H	105–106	68	$C_{14}H_{16}BrNOS$	CHN
60	CH_3	4-Br	CH_3	CH_3	172–174	42	$C_{16}H_{20}BrNOS\cdot HCl$	CHN
61	CH_3	4-Br	CH_3CH_2	CH_3	100–101	48	$C_{17}H_{22}BrNOS\cdot C_2H_2O_4\cdot H_2O$	CHN

[a] Isolated as an oil. [b] Calcd, 52.83; found, 52.14. [c] Structure confirmed by ^1H NMR ($CDCl_3$) δ 2.40 (s, NCH_3, $ThCH_3$), 2.48–3.31 (m, CH_2), 3.80 (d, CH_2), 5.50 (m, CH), 6.57–6.68 (m, Th, 2 H), 6.95–7.40 (m, Ph, 3 H).

2 M HCl, and then made alkaline. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined CH_2Cl_2 phases were dried ($MgSO_4$) and evaporated. Precipitation as oxalate gave 22.1 g (78 %) of pure **57**, mp 174–176 °C. The following two compounds were prepared similarly.

1-(4-Bromophenyl)-2-[[(5-chloro-2-thienyl)methyl]amino]ethanol (58). Compound **58** was obtained from 5-chloro-2-thiophenecarbaldehyde and 2-amino-1-(4-bromophenyl)ethanol hydrochloride: yield 57%, mp 206–208 °C.

1-(4-Bromophenyl)-2-[[(5-methyl-2-thienyl)methyl]amino]ethanol (59). Compound **59** was obtained from 5-methyl-2-thiophenecarbaldehyde and 2-amino-1-(4-bromophenyl)ethanol hydrochloride: yield 68%, mp 105–106 °C.

2-(4-Bromophenyl)-1-[[(5-methyl-2-thienyl)methyl]methylamino]-2-propanol Hydrochloride (60). 5-Methyl-2-[(methylamino)methyl]thiophene (5.64 g, 0.04 mol), p-bromophenacyl bromide (11.12 g, 0.04 mol), and 5.5 g of K_2CO_3 were stirred in 100 mL of dry Et_2O for 4 h. The mixture was filtered and added to a solution of methylmagnesium bromide (0.04 mol) in 30 mL of dry Et_2O. The mixture was refluxed for 1 h and then poured on 200 g of ice and extracted with EtOAc. The organic phase was dried ($MgSO_4$) and concentrated, giving a yellow oil, which was chromatographed on a silica gel column with cyclohexane–EtOAc (1:1) as eluent and converted into the hydrochloride salt, giving 6.32 g (42 %) of **60**, mp 172–174 °C.

4-Aryl-4,5,6,7-tetrahydrothieno[2,3-c]pyridines (I). Method A (General Procedure). To a solution of 0.05 mol of the carbinol IV or V (Table I) in 150 mL of 1,2-dichloroethane was added anhydrous $AlCl_3$ (14.7 g, 0.11 mol) at 10 °C. The mixture was stirred for 10 min and then poured on 200 g of ice. The acid solution was made alkaline. The phases were separated, and the organic layer was dried ($MgSO_4$) and concentrated. The crude oil of the base was chromatographed on a silica gel column with cyclohexane–EtOAc (1:1) and converted to the desired salts. The products were recrystallized from EtOH, if not otherwise stated.

Method B (General Procedure). The carbinol IV (0.05 mol) (Table II) was added to 50 mL of methanesulfonic acid, and the mixture was heated at 70 °C for 30 min and then poured on 200 g of ice. The acid solution was made alkaline and extracted three times with EtOAc. The organic phase was worked up according to method A. The results are shown in Table I.

4-(4-Bromophenyl)-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine. 2-[(Methylamino)methyl]thiophene (5.5 g, 0.044 mol), p-bromophenacyl bromide (12.23 g, 0.044 mol), and 6 g of K_2CO_3 were allowed to react in 100 mL of EtOH, reduced with 1.6 g of $NaBH_4$, and worked up as described above (**37**), yielding 11.34 g (79%) of 1-(4-bromophenyl)-2-[(2-thienylmethyl)methylamino]ethanol as an oil. The aminoethanol (11.34 g, 0.034 mol) was treated with 50 mL of methanesulfonic acid and worked up according to method B. The residual oily base (8 g, 59.9%) was suitable for the use in the following step.

4-(4-Bromophenyl)-6-methyl-2-nitro-4,5,6,7-tetrahydrothieno[2,3-c]pyridine Hydrochloride (7). To a solution of crude 4-(4-bromophenyl)-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine (8 g, 0.026 mol) in 30 mL trifluoroacetic acid was added 100 mL of fuming nitric acid at about 15 °C. After stirring for 1 h, the reaction mixture was poured on 300 g of ice, made alkaline, and extracted with CH_2Cl_2. The organic layer was washed with water, dried ($MgSO_4$), and concentrated, giving 6.6 g (65%) of **7**, mp 205–207 °C.

2-Amino-4-(4-bromophenyl)-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine Maleate (8). A solution of $SnCl_2$ (20 g) in 40 mL of concentrated HCl was added to 4 g (0,01 mol) of **7** in 20 mL of glacial acetic acid. The mixture was stirred for 15 min, poured on 300 g of ice, made alkaline, and extracted twice with Et_2O. The Et_2O phase was dried ($MgSO_4$) and evaporated to yield 2.9 g (72.5%) of the base as a yellow oil. Conversion into the maleate and recrystallization from EtOH gave 2.5 g (57%) of **8**, mp 145–147 °C.

4-(4-Bromophenyl)-2-*tert*-butyl-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine Hydrochloride (13). This compound was prepared from 4-(4-bromophenyl)-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine (4 g, 0.013 mol) and *tert*-butyl alcohol in the presence of BF_3 dissolved in 1,2-dichloroethane as described by McKenna et al.[16] The oily base was converted into the hydrochloride, giving 3.2 g (61%) of **13**, mp 290–292 °C (MeOH).

4-(4-Bromophenyl)-2-(methoxymethyl)-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine Methanesulfonate (11). 4-(4-Bromophenyl)-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]-pyridine (4 g, 0.013 mol), 100 mL of concentrated HCl, and aqueous formaldehyde solution (30%, 30 mL) were heated at 50 °C with stirring for 1 h. After cooling, the precipitate was filtered off and washed with ice–water and acetone, giving 4.1 g (82%) of 4-(4-bromophenyl)-2-(chloromethyl)-6-methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine hydrochloride, mp 249–250 °C.

Table III. Biological Activity of 4-Aryl-4,5,6,7-tetrahydrothieno[2,3-c]pyridines I

compd	inhibition of ^3H transmitter uptake: IC_{50},[a] μM, rat brain synaptosomes		antagonism of TBZ ptosis (mouse): ED_{50},[c] mg/kg po
	NE	5-HT	
1	2.3 (2.16–2.39)	>10 (30.3–43.1)[b]	6 (2.7–14.7)
2	1.4 (1.30–1.55)	>10 (23.3–36.1)[b]	>40
3	0.56 (0.50–0.63)	8 (6.29–11.71)	8.4 (5.7–13.5)
4	1.6 (1.34–1.95)	4.1 (3.95–4.24)	0.8 (0.6–1.3)
5	1.0 (0.64–1.37)	3.5 (2.97–4.39)	6.5 (3.3–14.2)
6	3.6 (2.65–3.92)	>10 (36.0–46.0)[b]	>40
7	0.45 (0.23–0.81)	2.45 (2.27–2.52)	3.6 (1.4–6.9)
8	0.13 (0.11–0.18)	0.09 (0.082–0.087)	7.4 (3.5–19.6)
9	0.5 (0.38–0.64)	0.54 (0.38–0.76)	2.6 (1.9–3.7)
10	0.76 (0.54–1.55)	1.8 (1.83–1.96)	>40
11	0.37 (0.32–0.42)	0.2 (0.15–0.28)	1.7 (0.9–2.9)
12	0.99 (0.74–1.26)	0.86 (0.46–0.61)	40[d]
13	1.74 (1.07–2.60)	5.7 (4.07–6.75)	7[d]
14	>10 (33.6–36.7)[b]	>10 (12.5–23.1)[b]	>40
15	1.6 (1.38–1.78)	5.4 (4.87–5.69)	2.2 (1.2–3.9)
16	0.8 (0.58–1.14)	3.35 (3.18–3.52)	>40
17	0.18 (0.11–0.26)	0.21 (0.15–0.25)	>40
18	0.19 (0.17–0.20)	3.55 (2.61–4.05)	>40
19	0.57 (0.43–0.70)	0.6 (0.46–0.82)	35[d]
20	1.1 (1.08–1.10)	0.78 (0.40–1.33)	13[d]
21	0.64 (0.62–0.65)	9.0 (6.25–19.6)	7.4[d]
22	0.9 (0.73–1.23)	>10 (42.2–49.4)[b]	5.9 (2.9–13.1)
23	0.05 (0.051–0.059)	1.2 (1.08–1.30)	0.7 (0.01–1.9)
24	0.27 (0.25–0.36)	1.8 (1.55–2.43)	>40
25	7.8 (6.52–8.51)	2.05 (1.17–3.01)	>40
26	0.25 (0.21–0.29)	0.46 (0.39–0.51)	10[d]
27	0.4 (0.34–0.49)	0.5 (0.48–0.51)	7.1 (4.4–10.5)
28	3.4 (3.30–3.49)	3.1 (3.05–3.24)	40
29	>10 (3.5–15.0)[b]	>10 (29.9–32.0)[b]	>40
30	3.2 (1.42–4.14)	>10 (21.5–29.9)[b]	>40
31	3.4	>10 (21.3–27.2)[b]	>40
32	>10 (37.5–44.1)[b]	3 (1.18–4.60)	>40
33	>10 (6.6–25.1)[b]	>10 (26.8–28.2)[b]	>40
34	7.8 (4.10–11.2)	>10 (7.2–16.9)[b]	>40
35	>10 (42.4)[b]	0.3 (0.25–0.34)	>40
36	3 (2.06–4.32)	>10 (9.1–24.5)[b]	>40
nomifensine	0.08 (0.06–0.09)	6.0 (5.15–6.12)	1.7 (0.7–3.0)
imipramine	5.0 (2.35–6.53)	0.23 (0.22–0.34)	2.3 (1.4–3.7)

[a] Mean of two to four separate experiments; range in parentheses. [b] Percent inhibition of transmitter uptake at 10^{-6} M drug concentration. [c] A least-square linear-regression analysis of the log dose as independent and the arc sin $\sqrt{\%/100}$ transformed scores as dependent variables was used to compute the ED_{50} values and 95% confidence intervals. [d] ED_{50} values are approximately estimated by a graphic method from the log dose–response curve on log probability paper.

The hydrochloride (4.1 g, 0.01 mol) was dissolved in MeOH (50 mL). $NaOCH_3$ (5.4 g, 0.1 mol) was added and the mixture refluxed for 1 h. After cooling and evaporation, the residue was taken up in water. The water layer was extracted with Et_2O. The Et_2O phase was washed with water, dried ($MgSO_4$), and evaporated. The residue was converted into the methanesulfonate and recrystallized from ethanol to give 2.0 g (44.5 %) of **11**, mp 167–168 °C.

4-(4-Chlorophenyl)-6-methyl-4,5,6,7-tetrahydrothieno-[2,3-*c*]pyridine. 2-[(Methylamino)methyl]thiophene (5.5 g, 0.044 mol), *p*-chloropenacyl bromide (10.3 g, 0.044 mol), and 6 g of K_2CO_3 were reacted in 100 mL of EtOH. The imine intermediate was reduced with 1.6 g of $NaBH_4$ and worked up as described above (**37**), yielding 1-(4-chlorophenyl)-2-[(2-thienylmethyl)-methylamino]ethanol as a colorless oil (10 g, 82%). The aminomethanol (10 g, 0.036 mol) was treated with 50 mL of methanesulfonic acid and worked up according to method B. The residual oily base (7 g, 73%) was suitable for the use in the following step.

4-(4-Chlorophenyl)-6-methyl-2-nitro-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine (16). This compound was prepared from 4-(4-chlorophenyl)-6-methyltetrahydrothieno[2,3-*c*]pyridine (7 g, 0.026 mol) as described above for compound **7**. Recrystallization from EtOH afforded **16** (1 g, 85%), mp 147–149 °C.

2-Amino-4-(4-chlorophenyl)-6-methyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine Maleate (17). A solution of **16** (7 g, 0.023 mol) in 70 mL of THF–EtOH (1:1) was transferred to a steel autoclave and shaken with 5% platinum on charcoal (700 mg) under 5 bars of hydrogen pressure at 25 °C for 2 h. The reaction mixture was filtered and evaporated. The maleate was prepared from the residual oily base. Recrystallization from EtOH afforded **17** (5.4 g, 60% yield), mp 165–166 °C.

2-(Acetylamino)-4-(4-chlorophenyl)-6-methyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine (19). The base (2 g, 0.009 mol) of **17** was prepared from its salt (see above) mixed with 10 mL of Ac_2O and stirred at 60 °C for 10 min. The mixture was evaporated, added to 100 g of ice, and made alkaline. The precipitation was extracted with CH_2Cl_2. Drying ($MgSO_4$) and evaporation of the extracts afforded 1.8 g (78.2%) of **19**, mp 227–229 °C (EtOAc).

2-Formyl-6-methyl-4-*p*-tolyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine. 2-[(Methylamino)methyl]thiophene (6.24 g, 0.049 mol), *p*-methylphenacyl bromide (11.5 g, 0.054 mol), and 6.7 g of K_2CO_3 were reacted in 100 mL of EtOH, reduced with 1.85 g of $NaBH_4$, and worked up as described above (**37**), giving 2-[(2-thienylmethyl)methylamino]-1-*p*-tolylethanol as a colorless oil (10.9 g, 85%). The aminoethanol (10.9 g, 0.042 mol) was dissolved in 1,2-dichloroethane, reacted with $AlCl_3$ (16.8 g), and worked up according to method A, giving 6-methyl-4-*p*-tolyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine (6.6 g, 65%) as a yellow oil, which was used in the next step without further purification.

The thienopyridine (6.6 g, 0.027 mol) was dissolved in 100 mL of dry Et_2O. Butyllithium (0.054 mol) in 35 mL of hexane was added under N_2 at −20 °C. The solution was stirred for 1 h at 0 °C, and DMF (4.38 g, 0.06 mol) was added at −20 °C. After stirring for 30 min, the mixture was poured on 200 g of ice and 5 mL of glacial acetic acid. The solution was neutralized and extracted with EtOAc. The organic layer was washed with water, dried ($MgSO_4$), and evaporated, giving 2-formyl-6-methyl-4-*p*-tolyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine (5.7 g, 77%) as a

yellow oil suitable for use in the following step.

2-(Hydroxymethyl)-6-methyl-4-*p*-tolyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine Hydrochloride (23). 2-Formyl-6-methyl-4-*p*-tolyl-tetrahydrothieno[2,3-*c*]pyridine (5.7 g, 0.021 mol) was dissolved in 100 mL of dioxane, and $NaBH_4$ (1.6 g) dissolved in 10 mL of water was added. After stirring for 2 h at ambient temperature, the mixture was treated with 20% HCl (10 mL) and concentrated. The residue was diluted with water and extracted with EtOAc. The aqueous phase was treated with concentrated ammonia and extracted with EtOAc. The organic layer was washed with water, dried ($MgSO_4$), and evaporated. The residue was converted into the hydrochloride and recrystallized from EtOH to give 3.65 g (44.6%) of **23**, mp 238–239 °C.

4-(4-Hydroxyphenyl)-2,6-dimethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine (26). A solution of **27** (3 g, 0.01 mol) in 63% aqueous HBr (60 mL) was standing at ambient temperature for 3 days. The mixture was poured on 200 g of ice, made alkaline, and extracted with CH_2Cl_2. The organic phase was washed with water, dried ($MgSO_4$), and evaporated, giving 1.5 g (57.7%) of **26**, mp 221–223 °C (EtOAc).

3-Bromo-4-(4-bromophenyl)-2,6-dimethyl-4,5,6,7-tetrahydrothieno[2,3-*c*]pyridine Hydrochloride (34). To a solution of **9** (3 g, 0.0084 mol) and anhydrous $AlBr_3$ (8 g, 0.03 mol) in 100 mL of glacial acetic acid was added Br_2 (1.4 g, 0.0084 mol). The mixture was stirred for 1 h and poured into 300 mL of ice water. The solution was made alkaline and extracted three times with EtOAc. The organic layer was washed with water, dried ($MgSO_4$), and evaporated. The residue was purified by chromatography on a silica gel column, eluting with CH_2Cl_2–MeOH (25:5), and converted into the hydrochloride, giving 1.8 g (49 %) of **34**, mp 261–262 °C.

Pharmacology. Uptake of (−)-[^{3}H]Norepinephrine and [^{3}H]Serotonin. According to Gray and Whittaker,[29] freshly prepared P_2-synaptosomal suspensions from total rat brain minus cerebellum were used (male SPF bred rats, strain Chbb:THOM, 200–350 g). The uptake assays were carried out within 2 h after synaptosomal preparation in the presence of pargyline as described.[4,30,31] The uptake process was terminated by rapid filtration and buffer washings under vacuum with use of Whatman GF/F filters. The energy-consuming active neurotransmitter uptake at 37 °C was determined from the total uptake by subtracting diffusion and unspecific binding measured at 0 °C in parallel. IC_{50} values were determined from log dose–response curves. They represent means of two to four separate experiments, each performed as duplicates.

Antagonism of Tetrabenazine-Induced Ptosis in Mice. The compounds were tested according to the method of Domenjoz et al.[32] in a modification of Vernier et al.[33] Ptosis of the eye lids occurred following the injection of 40 mg/kg tetrabenazine ip in mice (chbi:NMRI; 20–25 g). The test compounds were given orally as an aqueous solution or as a suspension in an aqueous 0.5% tylose solution (injection volume: 0.1 mL/10 g body weight) 1 h before tetrabenazine. Five animals per dose and at least three to five doses of each test compound were used. Ptosis was evaluated 75–120 min after the injection of tetrabenazine by using the score of Rubin et al.:[34] eyes closed = 100; eyes half-open = 50; eyes open = 0. For each dose, the mean of four observations in 15-min intervals was taken.

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Registry No. **1**, 82230-38-4; **1**·HCl, 70696-46-7; **2**, 90553-49-4; **2**·HCl, 70696-38-7; **3**, 90553-50-7; **3**·HCl, 70696-47-8; **4**, 82230-39-5; **5**, 70696-53-6; **5**·HCl, 70696-41-2; **6**, 90553-51-8; **6**·HCl, 73725-56-1; **7**, 88013-63-2; **7**·HCl, 88013-74-5; **7** (R^1 = H), 70696-52-5; **8**, 88013-36-9; **8**·maleate, 88013-37-0; **9**, 70696-56-9; **9**·HCl, 70696-50-3; **10**, 82230-50-0; **10**·HCl, 73725-57-2; **11**, 88013-55-2; **11**·CH_3SO_3H, 88013-56-3; **11**·HCl (R^1 = CH_2Cl), 90553-47-2; **12**, 90553-52-9; **12**·HCl, 90553-01-8; **13**, 90553-53-0; **13**·HCl, 90553-02-9; **14**, 90553-54-1; **14**·HCl, 90553-03-0; **15**, 70696-55-8; **15**·HCl, 70696-49-0; **16**, 88013-64-3; **16** (R^1 = H), 70696-54-7; **17**, 88013-26-7; **17**·maleate, 88013-27-8; **18**, 88013-66-5; **18**·HCl, 82230-41-9; **19**, 88013-38-1; **20**, 90553-55-2; **20**·HCl, 82230-45-3; **21**, 88013-69-8; **21**·HCl, 70696-42-3; **22**, 90553-56-3; **22**·HCl, 70696-43-4; **23**, 88013-73-4; **23**·HCl, 88013-31-4; **23** (R^1 = H), 90553-48-3; **23** (R^1 = CHO), 88013-68-7; **24**, 90553-57-4; **24**·HCl, 82230-43-1; **25**, 90553-58-5; **25**·HCl, 90553-04-1; **26**, 90553-05-2; **27**, 90553-59-6; **27**·HCl, 90553-06-3; **28**, 90553-60-9; **28**·CH_3SO_3H, 90584-07-9; **29**, 90553-07-4; **29**·CH_3SO_3H, 90553-08-5; **30**, 73731-41-6; **31**, 90553-61-0; **31**·HCl, 82230-46-4; **32**, 90553-62-1; **32**·HCl, 70696-44-5; **33**, 90553-63-2; **33**·HCl, 90553-09-6; **34**, 90553-64-3; **34**·HCl, 73725-55-0; **35**, 79599-91-0; **35**·HCl, 90553-10-9; **36**, 66200-59-7; **36**·HCl, 90553-11-0; **37**·HCl, 90553-12-1; **38**·HCl, 90553-13-2; **39**·$C_2H_2O_4$, 90553-15-4; **40**·HCl, 90553-16-5; **41**·HCl, 90553-17-6; **42**, 82230-37-3; **43**·HCl, 90553-18-7; **44**·$C_2H_2O_4$, 90553-20-1; **45**·HCl, 90553-21-2; **46**·HCl, 90553-22-3; **47**·HCl, 90553-23-4; **48**·HCl, 90553-24-5; **49**·HCl, 90553-25-6; **50**·$C_2H_2O_4$, 90553-27-8; **51**·HCl, 90553-28-9; **52**·$C_2H_2O_4$, 90553-30-3; **53**·HCl, 90553-31-4; **54**·$C_2H_2O_4$, 90553-33-6; **55**, 90553-34-7; **56**·HCl, 90553-35-8; **57**·$C_2H_2O_4$, 90553-37-0; **58**·HCl, 90553-38-1; **59**, 90553-39-2; **60**·HCl, 90553-40-5; **61**·$C_2H_2O_4$, 90553-42-7; II (R^1 = H, R^4 = CH_3), 7404-67-3; II (R^1 = R^4 = CH_3), 82230-49-7; II (R^1 = Br, R^4 = CH_3), 90553-43-8; II (R^1 = Cl, R^4 = CH_3), 70696-37-6; II (R^1 = $CH_2CH_2CH_3$, R^4 = CH_3), 90553-44-9; II (R^1 = CH_2CH_3, R^4 = CH_3), 90553-45-0; II (R^1 = H, R^4 = n-C_4H_9), 90553-46-1; [^{3}H]-NE, 62600-61-7; [^{3}H]-5-HT, 59969-33-4; 5-bromo-2-thiophenecarbaldehyde, 4701-17-1; 4-chloro-2-thiophenecarbaldehyde, 57500-51-3; 5-methyl-2-thiophenecarbaldehyde, 13679-70-4; 5-ethyl-2-thiophenecarbaldehyde, 36880-33-8; 5-propyl-2-thiophenecarbaldehyde, 35250-76-1; 5-chloro-2-thiophenecarbaldehyde, 7283-96-7; 2-amino-1-(3-hydroxyphenyl)ethanol hydrochloride, 4779-94-6; 2-amino-1-(4-bromophenyl)ethanol hydrochloride, 76008-53-2; *p*-chlorophenacyl bromide, 536-38-9; *p*-bromophenacyl bromide, 99-73-0; *p*-methylphenacyl bromide, 619-41-0.

Supplementary Material Available: Three tables are available with detailed dihedral angle and geometrical data for compound **33** (3 pages). Ordering information is given on any current masthead page.

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