POTENTIAL ANTIDEPRESSANTS: 3-ARYL-3-(ARYLTHIO)PROPYLAMINES AS SELECTIVE INHIBITORS OF 5-HYDROXYTRYPTAMINE RE-UPTAKE IN THE BRAIN

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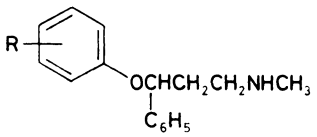
4-(Triffuoromethyl)thiophenol, 2-methylthiophenol, 2-methoxythiophenol, and 1-naphthalenethiol were transformed by reactions with N,N-dimethyl-3-chloro-3-phenylpropylamine to N,N-dimethyl-3-aryl-3-(arylthio)propylamines *IVa*—*VIIa*. These afforded the secondary amines *IVb*—*VIIb* by treatment with ethyl chloroformate and by the following hydrolysis and decarboxylation of the primarily formed N-(methyl)-N-(ethoxycarbonyl) analogues. Reaction of 1-naphthalenethiol with the 4-toluenesulfonic ester *X* in situ gave the thiophene analogue *VIIIa* which was similarly demethylated to *VIIIb*. Some of the prepared compounds (*IVa*, *IVb*, *Va*, *VIIIa*) were found to be selective inhibitors of 5-hydroxytryptamine re-uptake in the rat brain synaptosomes which indicates their potential antidepressant activity.

A number of novel nontricyclic potential antidepressants has been described in the literature in the last 15 years. These compounds, called sometimes „antidepressants of the second generation" (refs[1-3]), were developed and in some cases introduced to therapeutic practice with the aim at using agents with diminished anticholinergic, sedative and cardiovascular side effects, typical for the classical antidepressants[4-6]. In this connection, a great attention has recently been devoted to substances with specific mechanisms of action and in the first line to those which potentiate the 5-hydroxytryptamine (5-HT) transmission. Compounds of this type inhibit the 5-HT re-uptake on synaptic terminals or influence the serotonergic functions by different regulation mechanisms; the re-uptake of noradrenaline (NA) (probably connected with the cardiovascular side-effects) on the other hand, is only slightly influenced.

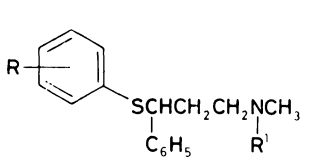
Selective inhibitors of 5-HT re-uptake belong to most diverse structures. One of the important type are 3-aryl-3-(aryloxy)propylamines[7] out of which three were tested with much care. Fluoxetine (*I*), which already has been introduced to clinical practice as an antidepressant[8], is a real selective inhibitor of 5-HT re-uptake. Small modifications of the structure of this compound resulted in important changes in pharmacological effects: the 3-(2-tolyloxy) analogue *II* (tomoxetine[9-11]) and the 3-(2-methoxyphenoxy) analogue *III* (nisoxetine[12-14]) are selective inhibitors of the

NA re-uptake. An attempt to explain this phenomenon was made on the basis of conformation energy minima calculations. It was found that the preferred conformations of nisoxetine and fluoxetine differ greatly[15].

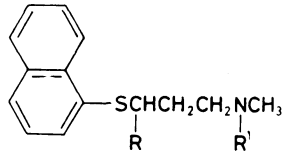


I, R = 4-CF_3
II, R = 2-CH_3
III, R = 2-OCH_3

It seemed worthwhile to ascertain the pharmacological profile of isosteric compounds derived from the 3-aryl-3-(aryloxy)propylamines by substitution of oxygen atom by sulfur which now have been synthesized. The synthesis of the first three compounds *IVa*–*VIa* started from 4-(trifluoromethyl)thiophenol[16], 2-methylthiophenol[17] and 2-methoxythiophenol[18] which were subjected in the form of sodium salts to treatment with N,N-dimethyl-3-chloro-3-phenylpropylamine[7] in ethanol (method *A*). The resulting oily bases *IVa*–*VIa* were transformed for characterization and for pharmacological testing to crystalline salts. The identity of the products was further corroborated by analyses and spectra. Further three substances (*IVb*–*VIb*) were obtained by demethylation of *IVa*–*VIa*. Reactions with ethyl chloroformate in benzene gave the corresponding N-monodemethylated N-(ethoxycarbonyl) analogues which were not isolated but directly hydrolyzed and decarboxylated by heating with potassium hydroxide in ethanol (method *B*). The oily bases *IVb*–*VIb* were likewise transformed to salts and characterized by analyses and spectra.



IV, R = 4-CF_3
V, R = 2-CH_3
VI, R = 2-OCH_3



VII, R = C_6H_5
VIII, R =

In compounds *IV*–*VII*: *a*, R^1 = CH_3 *b*, R^1 = H

The last compounds prepared were the 1-naphthyl and 2-thienyl analogues. Compound *VIIa* was prepared by method *A*, i.e. by reaction of 1-naphthalenethiol[19] with N,N-dimethyl-3-chloro-3-phenylpropylamine[7]. The demethylation of *VIIa* by method *B* led to the secondary amine *VIIb*. In the thiophene series, a different procedure had to be used because in the attempt at preparing the starting N,N-

TABLE I

3-Aryl-3-(arylthio)propylamines

Compound	Method (Yield, %)	M.p., °C (Solvent)	Formula (M.w.)	Calculated/Found				
				% C	% H	% F	% N	% S
IVa	*A*	173–175[a]	$C_{20}H_{22}F_3NO_4S$	55·93	5·16	13·27	3·26	7·47
	(72)	(2-propanol–ether)	(429·5)	55·93	5·12	13·41	3·32	7·56
IVb	*B*	220[a]	$C_{19}H_{20}F_3NO_4S$	54·93	4·85	13·72	3·37	7·72
	(56)	(aqueous ethanol)	(415·5)	54·93	4·83	13·97	3·24	7·99
Va	*A*	98·5–100·5[b]	$C_{22}H_{27}NO_4S$	65·80	6·78	—	3·49	7·98
	(85)	(2-propanol–ether)	(401·5)	65·66	7·02	—	3·50	8·12
Vb	*B*	96–97·5[b]	$C_{21}H_{25}NO_4S$	65·09	6·50	—	3·62	8·27
	(56)	(2-propanol–ether)	(387·5)	64·86	6·64	—	3·48	8·22
VIa	*A*	114–115·5[b]	$C_{22}H_{27}NO_5S$	63·28	6·52	—	3·35	7·68
	(82)	(2-propanol–ether)	(417·5)	63·24	6·80	—	3·33	7·80
VIb	*B*	147–148[b]	$C_{21}H_{25}NO_5S$	62·51	6·24	—	3·47	7·95
	(75)	(2-propanol)	(403·5)	62·24	6·34	—	3·05	8·12
VIIa	*A*	114–115[b]	$C_{25}H_{27}NO_4S$	68·62	6·22	—	3·20	7·33
	(76)	(2-propanol)	(437·6)	68·60	6·26	—	3·20	7·43
VIIb	*B*	105–107[b]	$C_{24}H_{25}NO_4S$	68·06	5·95	—	3·30	7·57
	(84)	(2-propanol–ether)	(423·5)	67·77	5·91	—	2·92	7·67
VIIIa	*C*	103–105[b]	$C_{23}H_{25}NO_4S_2$	62·26	5·68	—	3·16	14·46
	(56)	(2-propanol–ether)	(443·7)	62·04	5·67	—	3·29	14·46
VIIIb	*B*	105·5–108·5[b]	$C_{22}H_{23}NO_4S_2$	61·55	5·39	—	3·27	14·93
	(77)	(2-propanol–ether)	(429·6)	61·29	5·43	—	2·98	15·02
XI	—[d]	118–119[c]	$C_{13}H_{17}NO_4S$	55·10	6·05	—	4·94	11·32
	(61)	(2-propanol–ether)	(283·4)	54·82	6·07	—	5·03	11·40

[a] Hydrogen oxalate; [b] hydrogen maleate; [c] hydrogen fumarate; [d] in Experimental.

TABLE II
Spectra of 3-aryl-3-(arylthio)propylamines

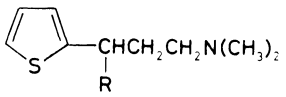
Compound	Spectrum	Data
IVa	IR[a]	700, 753, 760, 833 (5 and 2 adjacent Ar-H); 1 130, 1 166, 1 175, 1 320 (Ar-CF_3); 1 492, 1 603, 3 030, 3 040, 3 050 (Ar); 1 723 (COOH)
	^{1}H NMR[c]	7·00—7·50 m, 9 H (Ar); 4·40 m, 1 H (CH); 2·18 s, 1·90—2·20 m, $\sum$10 H (CH_2CH_2, NCH_3)
	^{13}C NMR[c]	141·56 s (C-1); 140·95 s (C-1′); 130·27 d, 2 C; 128·63 d, 2 C; 128·36 s, (C-4′, J_{FC} = 28·0); 127·80 d, 2 C; 127·43 d (C-4); 125·41 d, 2 C (C-3′, C-5′, J_{FC} = 4·0); 124·18 s (CF_3, J_{FC} = 272·0); 56·92 t (CH_2N); 50·12 d (SCH); 45·41 q (NCH_3); 34·58 t ($CHCH_2CH_2$)
IVb	MS[a]	325 (M^+, 0·6), 115 (1), 104 (2·3), 91 (2), 77 (1·4), 44 (100)
	^{1}H NMR[c]	7·00—7·50 m, 9 H (Ar); 4·40 t, 1 H (SCH); 2·62 t, 2 H (CH_2N); 2·40 s, 3 H (NCH_3); 2·14 m, 2 H (CCH_2C); 2·32 bs, 1 H (NH)
Va	MS[b]	285 (3·4), 117 (1), 91 (3·4), 77 (1·6), 58 (100), 45 (5·5), 44 (6)
	^{1}H NMR[c]	7·00—7·40 m, 9 H (Ar); 4·20 t, 1 H (SCH); 2·30 s, 3 H (CCH_3); 2·20 m, 4 H (CH_2CH_2); 2·16 s, 6 H (NCH_3)
	^{13}C NMR[c]	142·07 s (C-1); 139·98 s (C-1′); 134·30 s (C-2′); 132·73 d, 130·05 d, 127·65 d, 126·09 d (C-2′, C-3′, C-4′, C-5′); 128·25 d (C-2, C-6); 127·65 d (C-4); 126·98 d (C-3, C-5); 57·14 t (CH_2N); 50·64 d (SCH); 45·41 q (NCH_3); 34·21 t ($CHCH_2CH_2$); 20·54 q (Ar-CH_3)
Vb	MS[b]	271 (2·7), 148 (2), 115 (1·3), 98 (2), 91 (1), 44 (100)
	^{1}H NMR[c]	7·20 s, 5 H (Ar-H of phenyl); 7·00 m, 4 H (Ar-H of 2-tolyl); 4·18 t, 1 H (SCH); 2·60 bt, 2 H (CH_2N); 2·38 s, 3 H (CCH_3); 2·30 s, 3 H (NCH_3); 2·14 m, 2 H (CCH_2C); 2·24 bs, 1 H (NH)
VIa	MS[b]	162 (1), 117 (1), 115 (1), 91 (3), 58 (100), 44 (4)
	IR[b]	700, 733, 762 (4 and 5 adjacent Ar-H); 1 070, 1 237 (ArOR); 1 354, 1 573 (COO^-); 1 615 (C=C); 1 700 (COOH); infl. 3 050, 3 340 (COOH); 2 420, 2 600 (NH^+); 3 010, 3 053, 3 075 (Ar)
	^{1}H NMR[c]	7·12 s, 5 H (Ar-H of phenyl); 6·60—7·20 m, 4 H (Ar-H of 2-methoxyphenyl); 4·35 bt, 1 H (SCH); 3·85 s, 3 H (OCH_3); 2·20 m, 4 H (CH_2CH_2); 2·20 s, 6 H (NCH_3)
VIb	MS[b]	287 (2·6), 148 (2), 140 (3·4), 91 (3), 65 (2), 44 (100)
	IR[b]	700, 733, 761 (5 and 4 adjacent Ar-H); 1 070, 1 239 (ArOR); 1 350, 1 580, (COO^-); 2 485, 2 740 (NH^+); 3 060, 3 350 (NH)
	^{1}H NMR[c]	7·20 s, 6·60—7·20 m, $\sum$ 9 H (Ar-H); 4·35 t, 1 H (SCH); 3·82 s, 3 H (OCH_3); 2·60 t, 2 H (CH_2N); 2·35 s, 3 H (NCH_3); 2·14 m, 2 H (CCH_2C); 1·23 bs, 1 H (NH)
VIIa	MS[b]	321 (1·9), 162 (1·4), 115 (5), 91 (1·7), 58 (100)
	^{1}H NMR[c]	8·45 m, 1 H (H-8 of naphthyl); 7·20—7·90 m, 6 H (remaining Ar-H of naphthyl); 7·18 s, 5 H (Ar-H of phenyl); 4·22 bt, 1 H (SCH); 2·20 m, 4 H (CH_2CH_2); 2·14 s, 6 H (NCH_3)

TABLE II
(Continued)

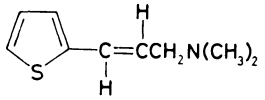
Compound	Spectrum	Data
VIIb	MS[b]	307 (0·7), 160 (3), 148 (2), 115 (6), 98 (7), 88 (3), 60 (3·7), 57 (5), 44 (100)
	^{1}H NMR[c]	8·45 m, 1 H (H-8 of naphtyl); 7·20–7·80 m, 6 H (remaining Ar-H of naphtyl); 7·18 s, 5 H (Ar-H of phenyl); 4·23 t, 1 H (SCH); 2·68 t, 2 H (CH_2N); 2·32 s, 3 H (NCH_3); 2·16 m, 2 H (CCH_2C); 1·12 bs, 1 H (NH)
VIIIa	MS[b]	327 (0·7), 168 (1·3), 129 (1·4), 115 (4), 73 (4), 71 (3), 58 (100)
	^{1}H NMR[c]	6·50–8·50 nm, 10 H (naphtyl, thienyl); 4·60 t, 1 H (SCH); 2·30 m, 4 H (CH_2CH_2); 2·16 s, 6 H (NCH_3)
	^{13}C NMR[c]	146·18 s (C-1 of thienyl); 134·42 s, 134·00 s (C-1 and C-4a of naphtyl); 131·69 s (C-8 of naphtyl); 133·03 d, 128·85 d, 128·48 d, 126·53 d, 126·09 d, 2 C; 125·71 d, 125·34 d, 2 C; 124·29 d (=CH); 57·07 t (CH_2N); 46·83 d (SCH); 45·41 q (NCH_3); 35·48 t ($CHCH_2CH_2$)
VIIIb	MS[b]	313 (M^+, 1); 44 (100)
	^{1}H NMR[c]	8·45 m, 1 H (H-8 of naphtyl); 7·20–7·90 m, 6 H (remaining Ar-H of naphtyl); 7·12 bd, 1 H (H-5 of thienyl); 6·76 t, 1 H (H-4 of thienyl); 6·58 bd, 1 H (H-3 of thienyl); 4·58 t, 1 H (SCH); 2·68 t, 2 H (CH_2N); 2·35 s, 2 H (CCH_2C); 2·20 m, 3 H (NCH_3); 1·14 bs, 1 H (NH)
XI	^{1}H NMR[c]	6·90–7·20 m, 3 H (thienyl); 6·66 bd, 1 H (H-1 of 1-propenyl, J = 16·0); 6·10 dt, 1 H (H-2 of 1-propenyl, J = 16·0, 7·0); 3·05 bd, 2 H (CH_2N); J = 7·0; 2·26 s, 6 H (NCH_3)
	^{13}C NMR[c]	142·07 s (C-2 of thienyl); 127·13 d, 127·13 d, 125·49 d, 125·04 d, 123·77 d (=CH); 61·62 t (CH_2N); 45·12 q ($N(CH_3)_2$)

[a] Hydrogen oxalate; [b] hydrogen maleate; [c] base.

-dimethyl-3-chloro-3-(2-thienyl)propylamine from *IX* (ref.[20]) by treatment with thionyl chloride, the dehydration was the predominant reaction and the unsaturated amine *XI* ((*E*)-configuration according to the ^{1}H NMR spectrum) was obtained in a considerable yield. The amino alcohol *IX* was therefore treated with 4-toluenesulfonyl chloride in pyridine and the resulting 4-toluenesulfonic ester *X* was not isolated but reacted in situ with 1-naphthalenethiol[19] (method *C*) to give *VIIIa*. Demethylation to *VIIIb* was carried out by method *B*. Melting points of the salts, elemental analyses and spectral data of the compounds prepared are assembled in Tables I and II.



IX, R = OH
X, R = OSO_2–C$_6$H$_4$–CH_3



XI

Publication of the present communication was accelerated by the fact that there was a communication on similar sulfides presented at the 198th American Chemical Society National Meeting. According to the abstract available[21] it seems that overlapping relates only to compounds *IVa*, *IVb*, *Va*, and *Vb* (in the abstract without any experimental details).

Compounds described in the present communication were tested in the form of salts (cf. Experimental and Table I) by methods of biochemical pharmacology. Table III gives the code numbers of the compounds and the IC_{50} values characterizing *a*) the inhibition of binding of [^{3}H]imipramine in membranes of the rat brain cortex, *b*) inhibition of the [^{3}H]5-HT re-uptake in synaptosomes of the rat brain, and *c*) inhibition of re-uptake of [^{3}H]NA in the same brain structures. The tertiary amines show in most cases higher selectivity in the inhibition of re-uptake

TABLE III
Biochemical pharmacology of 3-aryl-3-(arylthio)propylamines including the standard *II*

Compound	Code number VÚFB-	IC_{50}, nmol l^{-1}		
		IMI[a]	5-HT[b]	NA[c]
IVa	18290	[d]	91·6	14 400
IVb	18291	[d]	31·5	4 350
Va	18275	37·2	41·4	1 520
Vb	18276	[d]	51·0	188
VIa	18265	370	111·1	2 025
VIb	18267	72·6	113·3	170
VIIb	18262	20·3	11·2	165
VIIIa	18271	19·1	14·7	1 930
VIIIb	18255	26·0	9·6	126
II[e]	18292	[d]	957·1	359

[a] Inhibition of binding of [^{3}H]imipramine in membranes of the rat brain cortex; [b] inhibition of [^{3}H]5-HT re-uptake in the synaptosomes in the rat brain; [c] inhibition of re-uptake of [^{3}H]NA in synaptosomes of the rat brain; [d] not determined; [e] tomoxetine[9–11].

of 5-HT in comparison with the secondary amines. An important selectivity was shown by compounds *IVa*, *IVb*, *Va*, and especially *VIIIa* (VÚFB-18271) with which the difference between the inhibition of 5-HT and NA re-uptake makes more than two orders of magnitude.

EXPERIMENTAL

The melting points were determined in the Koffer block; the samples were dried in vacuo of about 60 Pa over P_2O_5 at 80°C. IR spectra (NUJOL, γ in cm^{-1}) were recorded with a Perkin–Elmer 298 spectrophotometer, NMR spectra ($CDCl_3$, δ in ppm, J in Hz) with the FT-NMR spectrometer TESLA BS 567A (^1H at 100 MHz, ^{13}C at 25·14 MHz), and the mass spectra (m/z, %) with Varian MAT 44S (GC-MS) spectrometer. The homogeneity of the products and composition of the mixtures were checked by thin-layer chromatography (TLC) on silica gel (Silufol). The extracts were dried with $MgSO_4$, Na_2SO_4 or K_2CO_3 and evaporated under reduced pressure on a rotary evaporator.

N,N-Dimethyl-3-(2-methoxyphenylthio)-3-phenylpropylamine (*VIa*)

Method A. A stirred solution of sodium ethoxide (from 0·8 g Na and 20 ml ethanol) was treated with 4·9 g 2-methoxythiophenol[18] and the mixture was refluxed for 30 min. The solution was treated with 7·1 g N,N-dimethyl-3-chloro-3-phenylpropylamine[7], refluxed for 4 h and ethanol was distilled off. After cooling the reaction mixture was diluted with benzene and was made alkaline with 25 ml 2·5M NaOH. The separated aqueous layer was extracted with benzene, the organic layers were combined, dried, and evaporated. The oily residue, representing almost homogeneous *VIa* (9·8 g, 93%), was transformed to the hydrogen maleate, m.p. 114—115·5°C (2-propanol–ether). The analytical data and spectra are included in Tables I and II.

N-Methyl-3-(2-methoxyphenylthio)-3-phenylpropylamine (*VIb*)

Method B. A stirred solution of 5·9 g *VIa* in 30 ml benzene was treated over 30 min with a solution of 3·9 g ethyl chloroformate in 10 ml benzene and the mixture was refluxed for 8 h. After standing overnight, the mixture was diluted with 30 ml benzene, the solution was washed with 2·5M HCl (2 × 20 ml) and water (4 × 30 ml), dried and evaporated. The residue (6·6 g of the crude oily carbamate) was diluted with 10 ml ethanol, KOH (10·1 g) was added and the mixture was stirred and refluxed for 6 h (bath temperature 105°C). After standing overnight, ethanol was distilled off, the mixture was diluted with 25 ml water and extracted with benzene. Processing of the extract gave 4·8 g (91%) of oily *VIb* which was neutralized with 2·1 g maleic acid in 12 ml 2-propanol and gave 5·9 g of the hydrogen maleate melting at 147—148°C (2-propanol). The analytical data and spectra are included in Tables I and II.

N,N-Dimethyl-3-(1-naphthylthio)-3-(2-thienyl)propylamine (*VIIIa*)

Method C. A solution of 5·6 g *IX* (ref.[21]) in 30 ml pyridine was stirred, cooled, and treated under nitrogen over 20 min with 6·6 g 4-toluenesulfonyl chloride. The mixture was stirred for 4 h and allowed to stand overnight. The obtained solution of *X* was treated with a solution of 5·9 g 1-naphthalenethiol[19] in 40 ml triethylamine which was added dropwise under stirring during 15 min under external cooling. The mixture was refluxed for 11 h and after standing overnight it was evaporated in vacuo. The oily residue was distributed by shaking between 50 ml

10% Na_2CO_3 and 100 ml toluene, the organic layer was washed with water (2 × 100 ml), dried, and evaporated. The residue (12·1 g) was chromatographed on a column of 120 g silica gel. Elution with toluene separated first 5·1 g of less polar impurities and elution with a mixture of toluene and chloroform (1 : 1) and chloroform alone afforded 5·7 g (56%) of the homogeneous oily *VIIIa*. It was converted to the hydrogen maleate, m.p. 103—105°C (2-propanol–ether). Analytical data and spectra are included in Tables I and II.

(*E*)-N,N-Dimethyl-3-(2-thienyl)-2-propene-1-ylamine (*XI*)

A solution of 19·7 g *IX* (ref.[21]) in 60 ml chloroform was stirred and treated with 22·2 g $SOCl_2$, added dropwise over 20 min. The mixture was heated to 50°C, stirred for 1 h, volatile components were evaporated in vacuo, the residue was dissolved in 50 ml benzene and the evaporation was repeated. The residue was dissolved in 350 ml dichloromethane and the mixture was washed with 120 ml NH_4OH. Processing of the organic layer gave 17·5 g of crude *XI* which was transformed to the hydrogen fumarate, m.p. 118—119°C (2-propanol–ether). Analytical data and spectra are included in Tables I and II.

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