POTENTIAL ANTIDEPRESSANTS: 4-(THIOARYLOXY)PIPERIDINES

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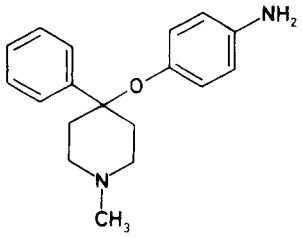
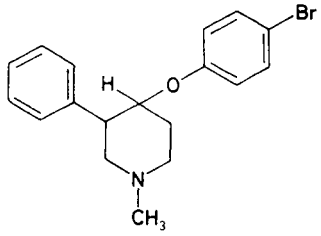
Nucleophilic substitution reactions of a series of thio-substituted fluoroarenes with 1-methyl-4--piperidinol, 1-benzyl-4-piperidinol, and 1-methyl-4-phenyl-4-piperidinol in the presence of sodium hydride in dimethylformamide gave the title compounds *V*—*XI* and *XIII*. The salts of these bases were pharmacologically tested and salts of compounds *V*, *XI*, and *XIII* showed in behavioural tests properties which are indicative of antidepressant activity.

The 4-(aryloxy)piperidine fragment occurs rather frequently in molecules of antidepressant compounds. The example are the structures of the experimental drugs B 777–81 (*I*) (refs[1–3]), HRP 803 (*II*) (ref.[4]), and "ifoxetine" (CGP 15 210G) (*III*) (refs[5–9]) (cf. also ref.[10]). Some time ago we were also engaged in this series of compounds; our work was strictly limited to substances having a sulfur(sulfide)-con-



I



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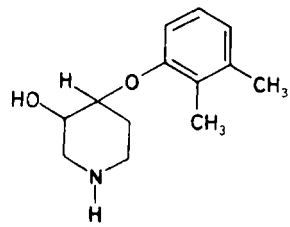

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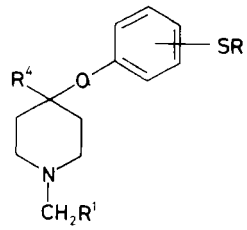


IV

taining substituent in the 4-(aryloxy) group, i.e. to compounds of the general formula *IV*. For maintaining similar lipophilicity like in the model compounds *I* and *II*, the molecules of our substances contained a second aryl residue as R,R^1 or R^4. The present communication deals with the synthesis and pharmacology of several compounds *IV*.

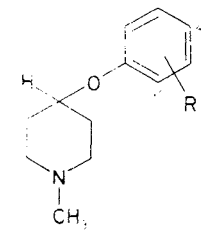
In preparing compounds *IV* we used as the general method the nucleophilic displacement of atom of fluorine in the thio substituted fluoroarenes by 4-hydroxypiperidines. This method proved very useful in our previous work[11-16]. This reaction proceeds in dimethylformamide in the presence of sodium hydride. As 4-hydroxypiperidines 1-methyl-4-piperidinol, 1-benzyl-4-piperidinol[17], and 1-methyl-4-phenyl-4-piperidinol[18] were used. The following thio substituted fluoroarenes were involved in this investigation: 2-fluorothioanisole[19,20], 4-fluorothioanisole[21], 2-fluorodiphenyl sulfide[16], 4-fluorodiphenyl sulfide[22], 2-fluoro-2'-(trifluoromethyl)diphenyl sulfide, 2-fluoro-4'-(trifluoromethyl)diphenyl sulfide, and 4-fluoro-4'-(trifluoromethyl)di-

TABLE I
4-(Thioaryloxy)piperidines

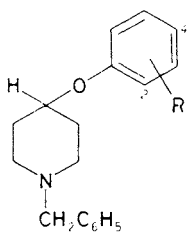
Compound[a] (Yield, %)[b]	M.p., °C (solvent)	Formula (M.w.)	Calculated/Found				
			% C	% H	% Hal	% N	% S
V-HO[c]	158·5—159·5	$C_{20}H_{23}NO_5S$	61·68	5·95	—	3·60	8·23
(79)	(ethanol–acetone)	(389·5)	61·62	5·88	—	3·53	8·47
VI-HCl	157·5—158·5	$C_{18}H_{22}ClNOS$	64·36	6·60	10·56[d]	4·17	9·55
(94)	(ethanol–ether)	(335·9)	64·43	6·50	10·62	4·40	9·76
VII-HO	102·5—104	$C_{21}H_{22}F_3NO_5S$	55·13	4·85	12·46[e]	3·06	7·01
(26)	(ethanol–ether)	(457·5)	54·75	5·02	12·33	3·05	7·19
VIII-HO	178·5—179·5	$C_{21}H_{22}F_3NO_5S$	55·13	4·85	12·46[e]	3·06	7·01
(27)	(ethanol)	(457·5)	55·08	4·99	12·56	2·99	7·30
IX-HO	194—195	$C_{21}H_{22}F_3NO_5S$	55·13	4·85	12·46[e]	3·06	7·01
(23)	(ethanol)	(457·5)	55·30	4·92	12·18	3·11	7·05
X-HCl	189—197	$C_{19}H_{24}ClNOS$	65·22	6·91	10·13[d]	4·00	9·16
(72)	(ethanol–ether)	(349·9)	64·73	7·01	10·18	4·28	9·48
XI-HCl	198—203	$C_{19}H_{24}ClNOS$	65·22	6·91	10·13[d]	4·00	9·16
(62)	(ethanol)	(349·9)	65·13	6·92	10·03	3·88	9·41
XIII-HO	201—202	$C_{21}H_{25}NO_5S$	62·51	6·25	—	3·47	7·95
(36)	(ethanol–acetone)	(403·5)	62·38	6·44	—	3·73	8·22

[a] HO hydrogen oxalate; [b] yields of crude oily bases; [c] see Experimental; [d] Cl; [e] F.

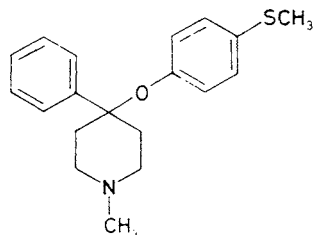
phenyl sulfide[23]. The synthesis of some of these compounds, which are either new or whose preparation was described in the literature differently or unsatisfactorily, is described in Experimental. The bases of the final products *V*–*XI* and *XIII*, which were prepared by the mentioned general method, were oily and were transformed to crystalline salts whose spectra were recorded. The salts of *V*–*XI* and *XIII* are assembled in Table I with the usual experimental data; their spectra are assembled in Table II. Preparation of *V* is used as the example of the general method and is described in Experimental. A special case was the attempt to prepare *XII* by a similar reaction of 1-benzyl-4-piperidinol[17] with 4-chlorophenyl trifluoromethyl sulfide[24]. The yield of this reaction was very poor and the product was so lipophilic that its hydrochloride remained in the organic layer from which it was attempted to extract it to 10% hydrochloric acid. It was obtained by crystallization from this organic layer. The base which was isolated from the aqueous layer and transformed to the hydrogen oxalate, was identified as the starting 1-benzyl-4-piperidinol. This experiment is also included in the Experimental.



V, R = 2-SC_6H_5
VI, R = 4-SC_6H_5
VII, R = 2-S-(3-CF_3-phenyl)
VIII, R = 2-S-(4-CF_3-phenyl)
IX, R = 4-S-(4-CF_3-phenyl)



X, R = 2-SCH_3
XI, R = 4-SCH_3
XII, R = 4-SCF_3



XIII

Compounds *V*–*XI* and *XIII* were pharmacologically examined in tests indicative of antidepressant activity. They were tested in the form of salts, described in Table I, and they were administered orally (the doses in mg/kg were calculated per bases).

Antireserpine activities: (i) Inhibition of reserpine-induced ptosis in mice (ED, effective doses in mg/kg with statistically significant effect): *V*, 100; *VI*, >100; *VII*, 100; *VIII*, >30; *IX*, 500; *X*, 30; *XI*, 30; *XIII*, 30. (ii) Antagonization of reserpine hypothermia in mice (ED, effective doses in mg/kg with statistically significant effect): *V*, 25; *XIII*, 10.

Potentiation of yohimbine toxicity in mice (ED_{50} in mg/kg): *V*, 52·6, *VI*, 100; *VII*, >100; *VIII*, >50; *IX*, 356; *X*, >50; *XI*, 63; *XIII*, 32·3.

TABLE II

Spectra of 4-(thioaryloxy)piperidines

Compound[a]	Spectrum	Data
V-HO	MS	299 (M^+, $C_{18}H_{21}NOS$, 4), 190 (2), 98 (100), 96 (10), 70 (17), 55 (23)
	IR	695, 745, 770 (5 and 4 adjacent Ar–H); 1 153, 1 748, 2 725 (COOH); 1 580 (Ar)
VI-HCl	UV	230·5 (4·18), 248·5 (4·19), infl. 269 (3·93)
	IR	690, 743, 830 (5 and 2 adjacent Ar–H); 1 246 (Ar–O–R); 1 590, 3 075 (Ar); 2 480 (NH^+)
VII-HO	MS	367 (M^+, $C_{19}H_{20}F_3NOS$, 2·2), 249 (3), 200 (9), 171 (8), 98 (100), 96 (24), 70 (38), 55 (64)
VIII-HO	MS	367 (M^+, $C_{19}H_{20}F_3NOS$, 1·2); 348 (0·1), 270 (0·2), 98 (100), 70 (17), 55 (21)
IX-HO	MS	367 (M^+, $C_{19}H_{20}F_3NOS$, 0·8), 348 (0·3), 270 (0·4), 171 (1), 98 (100), 70 (16)
	IR	820, 829 (2 adjacent Ar–H); 1 120, 1 169, 1 328 ($ArCF_3$); 1 240 (Ar–O–R); 1 490, 1 590, 1 603, 3 020, 3 060 (Ar); 2 390 (NH^+)
	^{1}H NMR	2·00–3·50 m, 8 H (4 CH_2 of piperidine); 2·80 s, 3 H (NCH_3); 4·70 bs, 1 H (CH–O); 6·90 d (J = 8·5), 7·10 d (J = 8·5), and 7·40 d (J = 8·5), 2 + 2 + 4 H (ArH)
X-HCl	MS	313 (M^+, $C_{19}H_{23}NOS$, 2·3), 298 (0·4), 266 (0·7), 222 (0·6), 174 (39), 91 (100)
	IR	710, 744 (5 and 4 adjacent Ar–H); 1 233 (Ar–O–R); 1 575, 3 035, 3 050 (Ar); 2 435, 2 505, 2 575 (NH^+)
	^{1}H NMR	2·15 bs, 4 H (2 CH_2 in positions 3 and 5 of piperidine); 2·28 s, 3 H (SCH_3); 3·20 bs, 4 H (CH_2NCH_2 of piperidine); 4·30 s, 2 H ($ArCH_2N$); 4·80 bm, 1 H (CH–O); 7·10 m, 4 H (4 *ArH* of 1,2-disubstituted benzene); 7·30–7·80 m, 5 H (C_6H_5)
XI-HCl	IR (KBr)	701, 749, 815 (5 and 2 adjacent Ar–H); 1 038, 1 244 (Ar–O–R); 1 492, 1 567, 1 595, 3 035, 3 060 (Ar); 2 430, 2 490, 2 575, 2 665 (NH^+)
	^{1}H NMR	2·15 bs, 4 H (2 CH_2 in positions 3 and 5 of piperidine); 2·42 s, 3 H (SCH_3); 3·20 bs, 4 H CH_2NCH_2 of piperidine); 4·35 s, 2 H ($ArCH_2N$); 4·70 bm, 1 H (CH–O); 6·95 d, 2 H (H-2 and H-6 of phenoxy, J = 8·5); 7·21 d, 2 H (H-3 and H-5 of phenoxy, J = 8·5); 7·30–7·80 m, 5 H (C_6H_5)
XIII-HO	MS	313 (M^+, $C_{19}H_{23}NOS$, 0·5), 174 (90), 131 (10), 103 (20), 91 (10), 70 (78), 44 (100)

[a] HO hydrogen oxalate.

Inhibition of binding of 4 nmol l^{-1} [^{3}H]imipramine in the hypothalamus of the rat brain, IC_{50} in nmol l^{-1}: *VI*, 10 352; the other compounds, >100. Inhibition of binding of 4 nmol l^{-1} [^{3}H]desipramine in the rat hypothalamus (IC_{50} in nmol l^{-1}): *VI*, 177; the other compounds, >100.

In conclusion: Compounds *V* (VÚFB-17 023), *XI* (VÚFB-17 025), and *XIII* (VÚFB-17 024) showed in behavioural tests promising properties of potential antidepressants. Nevertheless, they did not warrant further studies.

The compounds prepared were also tested for antimicrobial activity in vitro (microorganism and the minimum inhibitory concentrations im mg/l – unless they exceed 100 mg/l – are given): *Streptococcus β-haemolyticus*, *VI* 25, *VII* 12·5, *VIII* 50, *XIII* 50; *Streptococcus faecalis*, *V* 50, *VI* 12·5, *VII* 12·5, *VIII* 12·5, *XIII* 25; *Staphylococcus pyogenes aureus*, *V* 50, *VII* 12·5, *VIII* 6·25, *XI* 100, *XIII* 100; *Escherichia coli*, *V* 50, *VI* 50, *VII* 50; *Proteus vulgaris*, *V* 50, *VI* 50, *VII* 25, *XIII* 50; *Saccharomyces pasterianus*, *VI* 50; *Trichophyton mentagrophytes*, *VI* 12·5, *VIII* 12·5, *X* 50, *XI* 12·5, *XIII* 50.

EXPERIMENTAL

The melting points of analytical samples were determined in the Mettler FP-5 melting point recorder; the samples were dried in vacuo of about 60 Pa over P_2O_5 at room temperature or at a suitably elevated temperature. UV spectra (in methanol, λ_{max} in nm (log ε)) were recorded with a Unicam SP 8 000 spectrophotometer, the IR spectra (mostly in Nujol, ν in cm^{-1}) were recorded with the Perkin–Elmer 298 spectrophotometer, ^{1}H NMR spectra in $CDCl_3$ unless stated otherwise, δ in ppm, J in Hz) with a Tesla BS 487C (80 MHz) spectrometer, and the mass spectra with Varian MAT 44S (GC-MS) spectrometer (*m/z* and % given). The homogeneity of the substances and composition of the mixtures were checked by thin-layer chromatography (TLC) on silica gel (Silufol). The extracts wee dried with $MgSO_4$ or K_2CO_3 and evaporated under reduced pressure on a rotary evaporator.

2-Fluorothioanisole (refs[19,20])

2-Fluorothiophenol[25] was added to a stirred solution of 18·7 g NaOH in 60 ml water and the solution was treated over 45 min at 50–60°C with 25·2 g dimethyl sulfate, added dropwise. The mixture was stirred for 4 h at 100°C, cooled, extracted with benzene, and the extract was processed; 43·7 g (88%), b.p. 69–70°C/1·3 kPa. Ref.[20], b.p. 51–55°C/0·23 kPa.

4-Fluorothioanisole (ref.[21])

4-Fluorothiophenol[26,27] (30·8 g) and 12·8 g NaOH in 45 ml water were similarly treated with 17·3 g dimethyl sulfate; 29·3 g (86%), b.p. 88–90°C/0·2 kPa. Ref.[21], b.p. 74°C/0·13 kPa.

4-Fluorodiphenyl Sulfide (ref.[22])

4-Fluorothiophenol[26,27] (19·4 g) was dissolved in 30 ml 1-methyl-2-pyrrolidone, the solution was treated with 23·5 g K_2CO_3, 0·5 g Cu, and 30·8 g iodobenzene and the mixture was refluxed under stirring for 10 h. After cooling it was distributed between 200 ml water and 150 ml benzene,

the mixture was filtered, the aqueous layer of the filtrate was extracted with benzene, the benzene layers were combined, washed with 100 ml 1M NaOH, 100 ml 5% hydrochloric acid, and water, dried, and distilled; 24·8 g (80%), b.p. 135–138°C/1·6 kPa. Ref.[22], b.p. 141–142°C/1·5 kPa.

2-Fluoro-2′-(trifluoromethyl)diphenyl Sulfide

A mixture of 36·2 g 2-fluorothiophenol[25], 60 ml dimethylformamide, 44·4 g K_2CO_3, and 51·1 g 2-chlorobenzotrifluoride was stirred and refluxed for 6·5 h. It was diluted with 400 ml water and extracted with benzene. The extract was washed with 1M NaOH, 5% hydrochloric acid, and water, dried, and distilled; 14·6 g (19%), b.p. 163–165°C/0·16 kPa. UV spectrum: 245 (3·98), 270 (3·74), 283 (3·73). IR spectrum (film): 756 (4 adjacent Ar—H); 1 130, 1 174, 1 311 ($ArCF_3$); 1 474, 1 542, 1 593, 3 070 (Ar). ^{1}H NMR spectrum: 6·90–7·60 m, 8 H (ArH). For $C_{13}H_8F_4S$ (272·3) calculated: 57·35% C, 2·96% H, 11·78% S; found: 57·44% C, 3·11% H, 12·28% S.

2-Fluoro-4′-(trifluoromethyl)diphenyl Sulfide

A solution of 12·9 g 2-fluorothiophenol[25] in 20 ml dimethylformamide was treated with 15·8 g K_2CO_3 and 22·6 g 4-bromobenzotrifluoride[28] and the mixture was refluxed for 6·5 h. Processing like in the preceding case gave 16·3 g (60%), b.p. 147–150°C/2 kPa. For $C_{13}H_8F_4S$ (272·3) calculated: 57·35% C, 2·96% H, 27·91% F, 11·78% S; found: 57·51% C, 2·98% H, 27·90% F, 12·10% S.

4-Fluoro-4′-(trifluoromethyl)diphenyl Sulfide (ref.[23])

A similar reaction of 19·3 g 4-fluorothiophenol[26,27] with 33·9 g 4-bromobenzotrifluoride[28] in 30 ml dimethylformamide in the presence of 23·5 g K_2CO_3 gave 19·6 g (48%) of product, b.p. 145–150°C/1·6 kPa. For $C_{13}H_8F_4S$ (272·3) calculated: 57·35% C, 2·96% H, 27·91% F, 11·78% S; found: 57·45% C, 3·06% H, 27·86% F, 12·20% S. Ref.[23], b.p. 94–95°C/50–65 Pa.

1-Methyl-4-(2-(phenylthio)phenoxy)piperidine (*V*) (General Method)

A solution of 5·8 g 1-methyl-4-piperidinol in 50 ml dimethylformamide was stirred and treated under nitrogen over 10 min with 1·6 g 80% NaH (suspension in oil). The mixture was stirred for 30 min at 50°C, was treated with 6·3 g 2-fluorodiphenyl sulfide[16], and heated under stirring for 5·5 h to 100°C. After standing overnight it was diluted with water and extracted with ether. The base was extracted from the ether solution into excessive dilute hydrochloric acid, the separated aqueous layer was made alkaline with 20% NaOH, and the base was isolated by extraction with benzene; 7·3 g (79%) of oily *V*. It was neutralized with oxalic acid dihydrate in acetone to give 8·75 g of hydrogen oxalate, m.p. 158·5–159·5°C. Analysis and spectra are included in Tables I and II.

1-Benzyl-4-(4-(trifluoromethylphenylthio)phenoxy)piperidine (*XII*)

A solution of 5·85 g 1-benzyl-4-piperidinol[17] in 30 ml dimethylformamide was treated under nitrogen with 1·2 g 80% NaH (suspension in oil), the mixture was stirred for 30 min, and treated with 6·5 g 4-chlorophenyl trifluoromethyl sulfide[24]. The mixture was then stirred for 6 h at 100°C. After cooling it was diluted with water and extracted with a 1 : 1 mixture of benzene and ether. The separated organic layer was shaken with excessive 10% hydrochloric acid, the acid aqueous layer was made alkaline with NH_4OH, and the base was isolated by extraction

with ether; 5·35 g of recovered 1-benzyl-4-piperidinol which afforded the hydrogen oxalate crystallizing from a mixture of ethanol, acetone, and ether as the hemihydrate, m.p. 65–69°C. Mass spectrum: 191 (M^+, $C_{12}H_{17}NO$), 190, 173, 114, 100, 91 (100). For $C_{14}H_{19}NO_5$ + 0·5 H_2O (290·3) calculated: 57·92% C, 6·94% H, 4·83% N; found: 57·66% C, 6·91% H, 4·49% N.

The original benzene–ether solution, which was washed with 10% hydrochloric acid, deposited on standing 0·48 g (4%) of *XII* hydrochloride, m.p. 224–227°C (benzene–ethanol). Mass spectrum: 367 (M^+, $C_{19}H_{20}F_3NOS$, 3), 290 (0·5), 276 (0·7), 174 (30), 91 (100). IR spectrum: 698, 750, 826 (5 and 2 adjacent Ar—H); 1 114 (SCF_3); 1 490, 1 591, 3 030 (Ar); 2 440, 2 510, 2 570 (NH^+). ^{1}H NMR spectrum: 2·00–3·50 m, 8 H (4 CH_2 of piperidine); 4·20 s, 2 H ($ArCH_2N$); 4·70 m, 1 H (CH–O); 6·88 d (J = 8·5) and 7·52 d (J = 8·5), 2 + 2 H (ArH of 1,4-disubstituted benzene); 7·30–7·70 m, 5 H (C_6H_5). For $C_{19}H_{21}ClF_3NOS$ (403·9) calculated: 56·50% C, 5·24% H, 8·78% Cl, 14·11% F, 3·47% N, 8·78% S; found: 57·05% C, 5·31% H, 8·67% Cl, 13·68% F, 3·80% N, 8·60% S.

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