POTENTIAL ANTIDEPRESSANTS: 1-(4-(AMINOALKOXY)PHENYL)-2-PROPYLAMINES

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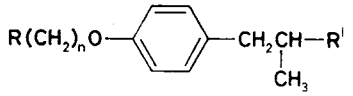
1-(4-Hydroxyphenyl)-2-propylamine (*X*) and its N-monomethyl (*XI*) and N,N-dimethyl (*XII*) derivatives were O-alkylated with six tert.aminoalkyl chlorides to aminoalkyl ethers *Ia*–*VIc*. In cases of *X* and *XI* the reactions were complicated by O,N-dialkylation leading to isolation of triamino ethers *XVI* and *XVII*. 1-(4-Hydroxyphenyl)propan-2-one was alkylated with 2-dimethylaminoethyl chloride and the ether *XIII* was obtained. An attempt to transform 4-(2-dimethylaminoethoxy)benzaldehyde to the 1-aryl-2-nitropropene *XIV* by heating with nitroethane in acetic acid in the presence of ammonium acetate resulted in the formation of 4-(2-dimethylaminoethoxy)benzonitrile (*XV*). In the form of salts the amino ethers prepared were tested for antidepressant activity but proved little active or inactive.

The aryloxyalkylamine fragment occurs rather often in molecules of antidepressant agents[1–11]. On the other hand, the well known central stimulant 1-phenyl-2-propylamine (amphetamine) "is fairly well accepted for being used as an antidepressant" (ref.[12]). In this situation we considered worthwhile to create molecules containing the aryloxyalkylamine as well as the amphetamine fragments. In the present paper a series of 1-(4-(aminoalkoxy)phenyl)-2-propylamines *Ia*–*VIc* is described.

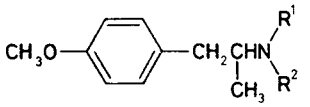


I, R = $N(CH_3)_2$; n = 2 — *IV*, R = N⬡; n = 2
II, R = $N(CH_3)_2$; n = 3 — *V*, R = N⬡; n = 2
III, R = $N(C_2H_5)_2$; n = 2 — *VI*, R = N⬡; n = 3

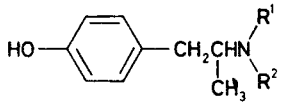
In formulae *I*–*VI*: *a*, $R^1 = NH_2$ *b*, $R^1 = NHCH_3$ *c*, $R^1 = N(CH_3)_2$

1-(4-Methoxyphenyl)-2-nitro-1-propene[13] was the almost universal intermediate in the present study. Its reduction with lithium aluminium hydride[14] resulted in the formation of 1-(4-methoxyphenyl)-2-propylamine which was formylated by heating with ethyl formate in autoclave to 120–130°C to *VII* whose preparation by a dif-

ferent route[15,16] was described and for which the melting point of 35°C was given. In our hands, the compound melted at 56–57°C and its characterization, therefore, is included in the Experimental. Formamide *VII* was reduced with lithium aluminium hydride in ether to give N-methyl derivative *VIII*, obtained previously[17–19] by different methods. Compound *VIII* was transformed to N,N-dimethyl derivative *IX* (prepared differently[20,21]) by the Eschweiler–Clarke reaction[22], i.e. by refluxing with a mixture of 80% formic acid and 36% formaldehyde. 1-(4-Methoxyphenyl)-2--propylamine and its N-methylated derivative *VIII* and *IX* were O-demethylated by refluxing with 47% hydrobromic acid[17,19,21,23,24] to the phenolic amines *X*–*XII* which were isolated in the form of hydrobromides.



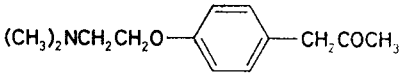
VII, $R^1 = H$; $R^2 = CHO$
VIII, $R^1 = H$; $R^2 = CH_3$
IX, $R^1 = R^2 = CH_3$



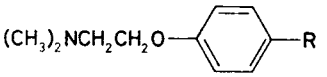
X, $R^1 = R^2 = H$
XI, $R^1 = H$; $R^2 = CH_3$
XII, $R^1 = R^2 = CH_3$

In a similar connection, 1-(4-hydroxyphenyl)propan-2-one[25] was prepared by the described procedure and was reacted in boiling butan-2-one with 2-dimethylaminoethyl chloride hydrochloride in the presence of potassium carbonate to give *XIII*, isolated and characterized in the form of hydrochloride. The released base was transformed to the hydrogen maleate. In the effort to transform the known 4-(2-dimethylaminoethoxy)benzaldehyde[26] to *XIV* by refluxing in acetic acid with nitroethane in the presence of ammonium acetate (for the method, cf.[27]) a mixture was obtained from which the major, less polar component was isolated by chromatography on aluminium oxide, transformed to crystalline hydrogen maleate and identified, surprisingly, as the nitrile *XV* (analysis and mass spectrum: $C_{11}H_{14}N_2O$; band of ArCN at 2 230 cm^{-1} in the IR spectrum; only signals of hydrogens of 2-dimethylaminoethoxy and 4 ArH in the ^1H NMR spectrum). Its formation is in agreement with the recent announcement[28] of a one-step conversion of aromatic aldehydes into nitriles by refluxing with nitroethane in acetic acid in the presence of sodium acetate. The authors[28] stated that the use of ammonium acetate in place of sodium acetate results in the formation of the expected 1-aryl-2-nitropropenes which is evidently incorrect. Our case shows that it is not easy to predict whether the nitrile or the nitropropene will be formed. Also the explanation of the formation of nitriles is not quite easy. It is necessary to assume the following steps: (i) rearrangement of nitroethane to ethanehydroxamic acid by the acid present, (ii) cleavage of the ethanehydroxamic acid to hydroxylamine, (iii) formation of the oxime of the starting aldehyde, (iv) dehydration of the oxime. What is strange is the fact that for the first

two steps "hot and concentrated acids" are required[29]. In our case the whole chain of reactions proceeded under rather mild conditions (boiling acetic acid).



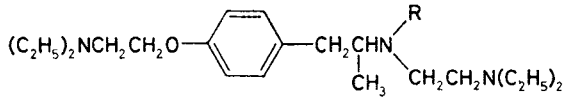
XIII



XIV, R = CH=C(CH$_3$)NO$_2$

XV, R = CN

Hydrobromides of *X* and *XII* and the base *XI* were alkylated by heating with hydrochlorides of 2-dimethylaminoethyl chloride, 3-dimethylaminopropyl chloride, 2-diethylaminoethyl chloride, 2-pyrrolidinoethyl chloride, 2-piperidinoethyl chloride, and 3-piperidinopropyl chloride in 2-propanol to 90°C in the presence of 50% sodium hydroxide (general method). The bases *Ia*–*VIc* were oily and were transformed to crystalline salts. The structures were confirmed by recording the mass spectra (mostly with the salts) and by ^{1}H NMR spectra of the released bases. The products obtained by this general method are assembled in Table I with the usual experimental data. The spectra of these compounds are assembled in Table II. Preparation of *Ic* is described in the Experimental as an example. In the case of the primary amine *X* and the secondary amine *XI* there we could see the tendency to N-alkylation in addition to the desired O-alkylation. In fact, the crude products, obtained from *X* and *XI*, have to be considered mixtures of the O-monoalkylated and O,N-dialkylated products, from which the O-alkylated products are isolated by crystallization of the salts. Separation of the dialkylated products was successful in two cases (*XVI*, *XVII*) and is described in the Experimental separately.



XVI, R = H

XVII, R = CH$_3$

Most of the compounds prepared were pharmacologically tested as potential antidepressants. They were administered orally in the form of salts, described in Table I and in the Experimental; the doses given were calculated per bases.

Acute toxicity in mice (LD_{50} in mg/kg): *Ia*, 563; *Ib*, 386; *Ic*, >1 000; *IIa*, 306; *IIb*, 302; *IIc*, 194; *IIIa*, 626; *IIIc*, 247; *IVb*, 490; *IVc*, 492; *Va*, 426; *Vb*, 289; *Vc*, 273; *VIa*, 201; *VIb*, 264; *VIc*, 186; *XIII*, 50 (i.v.); *XVII*, 696.

Antireserpine activity (antagonization of reserpine hypothermia in mice; dose with significant effect ED in mg/kg): *Ia*, 10; *Ib*, 10; *Ic*, 10; *IIa*, >10; *IIb*, >10; *IIc*, potentiates the reserpine hypothermia in the dose of 10 mg/kg; *IIIa*, >10; *IIIc*,

TABLE I

1-(4-(Aminoalkoxy)phenyl)-2-propylamines *Ia*—*VIc*

Compound[a] (yield %)	M.p., °C (solvent) or b.p., °C/kPa	Formula (M.w.)	Calculated/Found			
			% C	% H	% Cl	% N
Ia·2 HCl	250—251	$C_{13}H_{24}Cl_2N_2O$	52·88	8·19	24·02	9·49
(45)	(aqueous 2-propanol)	(295·3)	52·54	8·26	24·17	9·41
Ib	162—165/0·4	$C_{14}H_{24}N_2O$	70·52	10·46	—	12·11
(53)		(231·4)	70·57	10·44	—	12·01
Ib·BHO[b]	154—156[c]	$C_{18}H_{28}N_2O_9.H_2O$	49·76	6·96	—	6·45
	(aqueous ethanol)	(434·4)	49·72	6·70	—	6·85
Ic·2 HCl[d]	235—237	$C_{15}H_{28}Cl_2N_2O$	55·72	8·73	21·93	8·66
(56)	(ethanol–ether)	(323·3)	55·35	8·64	21·78	8·55
IIa·2 HCl	233—235	$C_{14}H_{26}Cl_2N_2O$	—	—	22·93	9·06
(56)	(ethanol)	(309·3)	—	—	23·30	9·09
IIb·2 HCl	212—214	$C_{15}H_{28}Cl_2N_2O$	55·72	8·73	21·93	8·66
(52)	(ethanol–acetone)	(323·3)	55·77	8·41	21·97	8·23
IIc·2 HCl	259—261	$C_{16}H_{30}Cl_2N_2O$	56·96	8·96	21·02	8·30
(49)	(ethanol–ether)	(337·3)	56·58	8·99	21·17	8·22
IIIa·BHO[b,e]	135—137	$C_{19}H_{30}N_2O_2$	53·01	7·03	—	6·51
(54)	(ethanol)	(430·5)	53·18	7·00	—	6·52
IIIa—2 P[f]	181—183	$C_{27}H_{32}N_8O_{15}$	45·76	4·55	—	15·82
	(ethyl acetate)	(708·6)	45·50	4·59	—	15·57
IIIb·2 P[f,g]	160—162	$C_{28}H_{34}N_8O_{15}$	46·54	4·74	—	15·51
(46)	(ethyl acetate)	(722·6)	46·52	4·88	—	15·20
IIIc·2 HCl	177—179	$C_{17}H_{32}Cl_2N_2O$	58·12	9·18	20·18	7·97
(58)	(ethanol–ether)	(351·4)	57·78	9·02	20·41	7·49
IVa·2 HCl	208—210	$C_{15}H_{26}Cl_2N_2O$	—	—	22·07	8·72
(49)	(ethanol)	(321·3)	—	—	22·44	8·67
IVb·BHO[b]	145—147[h]	$C_{20}H_{30}N_2O_9.$	53·20	6·92	—	6·22
(59)	(aqueous 2-propanol)	$.0{\cdot}5\ H_2O$	52·60	6·93	—	6·52
		(451·5)				
IVc·2 HCl	221—222[c]	$C_{17}H_{30}Cl_2N_2O.H_2O$	55·57	8·78	19·30	7·62
(58)	(ethanol–ether)	(367·4)	55·56	8·43	19·62	7·98
Va·2 HCl	214—216[h]	$C_{16}H_{28}Cl_2N_2O.$	55·81	8·52	20·60	8·14
(48)	(ethanol–acetone)	$.0{\cdot}5\ H_2O$	56·27	8·51	20·28	8·48
		(344·3)				
Vb	175—178/0·15	$C_{17}H_{28}N_2O$	73·86	10·21	—	10·14
(48)		(276·4)	74·40	10·34	—	10·15

TABLE I
(*Continued*)

Compound[a] (yield %)	M.p., °C (solvent) or b.p., °C/kPa	Formula (M.w.)	Calculated/Found			
			% C	% H	% Cl	% N
Vb·2 HCl	140—142[c]	$C_{17}H_{30}Cl_2N_2O.H_2O$	55·57	8·78	19·30	7·63
	(ethanol–acetone)	(367·4)	55·51	8·51	19·24	7·63
Vc·2 HCl	236·5—238·5[h]	$C_{18}H_{32}Cl_2N_2O.$	58·05	8·93	19·04	7·52
(58)	(ethanol–ether)	$.0{\cdot}5\ H_2O$	57·69	8·74	19·37	7·63
		(372·4)				
VIa·2 HCl	265—267[c]	$C_{17}H_{30}Cl_2N_2O.H_2O$	55·58	8·78	19·30	7·63
(56)	(ethanol)	(367·4)	55·61	9·09	19·20	7·70
VIb·2 HCl	236—238	$C_{18}H_{32}Cl_2N_2O$	59·49	8·88	19·52	7·71
(53)	(ethanol–acetone)	(363·4)	58·99	8·86	19·70	7·71
VIc·2 HCl	253—255[h]	$C_{19}H_{34}Cl_2N_2O.$	59·05	9·13	18·35	7·25
(55)	(ethanol- ether)	$.0{\cdot}5\ H_2O$	59·22	8·99	18·57	7·43
		(386 4)				

[a] The compounds were prepared by the "general method" (cf. Experimental); [b] bis(hydrogen oxalate); [c] monohydrate; [d] see Experimental; [e] see Experimental under *XVI*; [f] dipicrate; [g] see Experimental under *XVII*; [h] hemihydrate.

potentiates reserpine hypothermia at 10 mg/kg; *IVb*, >10, *IVc*, >10; *Va*, >10; *Vb*, >10; *Vc*, 10; *VIa*, >10; *VIb*, >10; *VIc*, 10; *XXVII*, potentiates reserpine hypothermia at 10 mg/kg.

Antireserpine activity (ptosis in mice): *IIIc* inhibits significantly the reserpine ptosis at 25 mg/kg; at the same dose *Ia*, *Ic*, *IIa*, *IIb*, *IIc*, *IIIa*, *IVb*, *IVc*, *Va*, *Vb*, *Vc*, *VIa*, *VIb*, *VIc* and *XXVII* are inactive; *XIII* is significantly active at 300 mg/kg.

Antireserpine activity, antagonization of the ulcerogenic effects of reserpine in rats (dose ED in mg/kg which significantly antagonizes the ulcerogenic effects of reserpine): *Ia*, 50; *Ib*, *Ic*, *IIIa*, *IIIc*, *Vb*, *Vc*, *VIc*, all >50; *XVII*, 50.

Potentiation of yohimbine toxicity in mice: *XIII* at 500 mg/kg potentiates the toxicity slightly.

Inhibition of binding of 4 nmol l^{-1} [^{3}H]imipramine and [^{3}H]desipramine in the rat hypothalamus: IC_{50} for all compounds tested are above 100 nmol l^{-1}. None of the compounds did inflence the binding of 0·5 nmol l^{-1} [^{3}H]spiperone in the rat brain striatum in the concentration of 200 nmol l^{-1} (no dopaminergic activity).

Inhibition of spontaneous locomotor activity in mice (test of Dews): Compounds *Ia*, *Ib*, *Ic*, *IIa*, *IIb*, *IIIa*, *IIIc*, *IVb*, *IVc*, *Va*, *Vb*, *Vc*, *VIa*, *VIb*, and *VIc* inhibit mildly

TABLE II
Spectra of compounds *Ia*—*VIc*

Compound	Spectrum	Data
Ia	^{1}H NMR	1·10 d, 3 H (C–CH_3, J = 6·0); 1·60 bs, 2 H (NH_2); 2·60 s, 6 H ($N(CH_3)_2$); 2·60—3·10 m, 5 H (CH_2N and $ArCH_2CHN$); 4·03 t, 2 H (CH_2O); 6·80 d, 2 H (H-3, 5 of Ar, J = 8·5); 7·09 d, 2 H (H-2, 6 of Ar, J = 8·5)
Ia·2 HCl	MS	CI: 222 (M^+, $C_{13}H_{22}N_2O$); EI: 179 (23), 115 (10), 73 (17), 72 (27), 58 (100), 45 (28), 44 (51)
Ib	^{1}H NMR	1·05 d, 3 H (C–CH_3, J = 6·0); 1·98 s, 1 H (NH); 2·30 s, 6 H ($N(CH_3)_2$); 2·38 s, 3 H (NCH_3); 2·70 m, 5 H (NCH_2 and $ArCH_2CHN$); 4·02 t, 2 H (CH_2O, J = 6·0); 6·80 d, 2 H (H-3, 5 of Ar, J = 8·5); 7·08 d, 2 H (H-2, 6 of Ar, J = 8·5)
Ic	^{1}H NMR	0·95 d, 3 H (C–CH_3, J = 7·0); 2·30 s, 12 H (2 $N(CH_3)_2$); 2·40—3·10 m, 3 H ($ArCH_2CHN$); 2·72 t, 2 H (NCH_2, J = 7·0); 4·06 t, 2 H (CH_2O, J = 7·0); 6·82 d, 2 H (H-3, 5 of Ar, J = 8·5); 7·10 d, 2 H (H-2, 6 of Ar, J = 8·5)
Ic·2 HCl	MS	250 (M^+, $C_{15}H_{26}N_2O$, 0·1), 72 ($C_4H_{10}N$, 100), 58 (C_3H_8N, 17)
	IR	769, 820 (2 adjacent Ar–H); 1 030, 1 240 (ArOR); 1 512, 1 582, 1 608 (Ar); 2 455, 2 565 (NH^+)
IIa	^{1}H NMR	1·10 d, 3 H (C–CH_3); 1·70 bs, 2 H (NH_2); 2·00 m, 2 H (CH_2 in position 2 of propyl); 2·21 s, 6 H ($N(CH_3)_2$); 2·40—3·10 m, 5 H (CH_2N and $ArCH_2CHN$); 3·98 t, 2 H (OCH_2); 6·80 d, 2 H (H-3, 5 of Ar, J = 8·5); 7·08 d (H-2, 6 of Ar, J = 8·5)
IIa·2 HCl	IR	796, 812, 840 (2 adjacent Ar–H); 1 052, 1 240 (ArOR); 1 512, 1 605, 3 005 (Ar); 2 470, 2 510, 2 660 (NH^+); 3 280, 3 360 (NH_2)
	^{1}H NMR (D_2O)	1·25 d, 3 H (C–CH_3, J = 6·5); 2·15 bm, 2 H (CH_2 in position 2 of propyl); 2·88 s, 6 H ($N(CH_3)_2$); 2·50—3·50 m, 5 H (CH_2N and $ArCH_2CHN$); 4·12 t, 2 H (CH_2O, J = 6·0); 6·95 d, 2 H (H-3, 5 of Ar, J = 8·5); 7·23 d, 2 H (H-2, 6 of Ar, J = 8·5)
IIb	IR (film)	836 (2 adjacent Ar–H); 1 245 (ArOR); 1 510, 1 580, 1 610, 3 055 (Ar); 2 760, 2 780, 2 810 (N–CH_3); 3 300 (NH)
	^{1}H NMR	1·02 d, 3 H (C–CH_3); 1·65 bs, 1 H (NH); 1·95 m, 2 H (CH_2 in position 2 of propyl); 2·20 s, 6 H ($N(CH_3)_2$); 2·31 s, 3 H (NCH_3); 2·40—3·10 m, 5 H (CH_2N and $ArCH_2CHN$); 3·95 t, 2 H (CH_2O, J = 6·5); 6·85 d, 2 H (H-3, 5 of Ar, J = 8·5); 7·00 d, 2 H (H-2, 6 of Ar, J = 8·5)
IIb·2 HCl	IR	800, 810 (2 adjacent Ar–H); 1 240, 1 250, 1 260 (ArOR); 1 512, 1 610 (Ar); 2 520, 2 620 (NH^+); 3 390 (NH)

TABLE II
(*Continued*)

Compound	Spectrum	Data
IIc	^{1}H NMR	0·95 d, 3 H (C–CH_3, J = 7·0); 2·00 m, 2 H (CH_2 in position 2 of propyl); 2·25 s, 6 H ($N(CH_3)_2$ of dimethylaminopropoxy); 2·34 s, 6 H (remaining $N(CH_3)_2$); 2·40—3·10 m, 5 H (CH_2N and $ArCH_2CHN$); 4·02 t, 2 H (CH_2O, J = 7·0); 6·82 d, 2 H (H-3, 5 of Ar, J = 8·5); 7·10 d, 2 H (H-2, 6 of Ar, J = 8·5)
IIc·2 HCl	MS	CI: 264 (M^+, $C_{16}H_{28}N_2O$); EI: 193 (1), 86 (2), 72 (100), 58 (14)
IIIa	^{1}H NMR	1·04 t, 6 H (2 CH_3 of ethyls); 1·10 d, 3 H (remaining C–CH_3); 1·40 bs, 2 H (NH_2); 2·55 m, 2 H ($ArCH_2$); 2·60 q, 4 H (CH_2NCH_2 of diethylamino); 2·88 t, 2 H (remaining CH_2N); 3·10 m, 1 H (CH–N); 4·00 t, 2 H (CH_2O, J = 6·0); 6·81 d, 2 H (H-3, 5 of Ar, J = 9·0); 7·09 d, 2 H (H-2, 6 of Ar, J = 9·0)
IIIa-BHO[a]	MS	CI: 250 (M^+, $C_{15}H_{26}N_2O$)
IIIb	^{1}H NMR	1·08 d, 3 H (C–CH_3); 1·10 t, 6 H (2 CH_3 of ethyls, J = 7·0); 1·40 bs, 1 H (NH); 2·40 s, 3 H (NCH_3); 2·50—3·00 m, 9 H (3 CH_2N and $ArCH_2CHN$); 4·02 t, 2 H (CH_2O, J = 6·0); 6·82 d, 2 H (H-3, 5 of Ar, J = 8·5); 7·09 d, 2 H (H-2, 6 of Ar, J = 8·5)
IIIc	^{1}H NMR	0·95 d, 3 H (C–CH_3, J = 7·0); 1·19 t, 6 H (2 CH_3 of ethyls, J = 7·0); 2·32 s, 6 H ($N(CH_3)_2$); 2·40—3·20 m, 3 H ($ArCH_2CHN$); 2·65 q, 4 H (CH_2NCH_2 of diethylamino, J = 7·0); 2·89 t, 2 H (remaining CH_2N, J = 7·0); 4·03 t, 2 H (CH_2O, J = 7·0); 6·80 d, 2 H (H-3, 5 of Ar, J = 8·5); 7·10 d, 2 H (H-2, 6 of Ar, J = 8·5)
IIIc·2 HCl	MS	CI: 278 (M^+, $C_{17}H_{30}N_2O$); EI: 207 (2), 100 (3), 86 (8), 72 (100)
IVa	UV (CH_3OH)	λ_{max} 278 nm (log ε 3·21), 284·5 nm (3·13)
	IR (film)	805 (2 adjacent Ar–H); 1 245 (ArOR); 1 510, 1 583 (Ar); 2 780, 2 850 (NH^+); 3 280, 3 350 (NH_2)
	^{1}H NMR	1·09 d, 3 H (C–CH_3, J = 6·0); 1·50 bm, 4 H (CH_2CH_2 in positions 3, 4 of pyrrolidine); 2·05 bs, 2 H (NH_2); 2·10—3·20 m, 7 H (CH_2NCH_2 of pyrrolidine and $ArCH_2CHN$); 2·72 t, 2 H (remaining CH_2N, J = 6·0); 4·05 t, 2 H (CH_2O, J = 6·0); 6·80 d, 2 H (H-3, 5 of Ar, J = 8·5); 7·06 d, 2 H (H-2, 6 of Ar, J = 8·5)
IVb	^{1}H NMR	1·03 d, 3 H (C–CH_3); 1·45 m, 4 H (CH_2CH_2 in positions 3, 4 of pyrrolidine); 2·39 s, 3 H (NCH_3); 2·60 m, 7 H (CH_2NCH_2 of pyrrolidine and $ArCH_2CHN$); 2·88 t, 2 H (remaining CH_2N); 4·08 t, 2 H (CH_2O, J = 6·0); 6·80 d, 2 H (H-3, 5 of Ar, J = 8·5); 7·09 d, 2 H (H-2, 6 of Ar, J = 8·5)
IVb-BHO[a,b]	MS	CI: 262 (M^+, $C_{16}H_{26}N_2O$)

TABLE II
(*Continued*)

Compound	Spectrum	Data
IVc	^{1}H NMR	0·95 d, 3 H (C–CH_3, J = 7·0); 1·85 bm, 4 H (CH_2CH_2 in positions 3, 4 of pyrrolidine); 2·32 s, 6 H ($N(CH_3)_2$); 2·40—3·20 m, 7 H (CH_2NCH_2 of pyrrolidine and $ArCH_2CHN$); 2·90 t, 2 H (remaining CH_2N, J = 7·0); 4·10 t, 2 H (CH_2O, J = 7·0); 6·82 d, 2 H (H-3, 5 of Ar, J = 8·5); 7·10 d, 2 H (H-2, 6 of Ar, J = 8·5)
IVc-2 HCl[c]	MS	CI: 276 (M^+, $C_{17}H_{28}N_2O$); EI: 205 (2), 98 (2), 84 (6), 72 (100), 56 (4)
Va	^{1}H NMR	1·10 d, 3 H (C–CH_3); 1·30—1·80 m, 6 H (3 CH_2 in positions 3, 4, 5 of piperidine); 2·00—3·00 m, 9 H (CH_2NCH_2 of piperidine, further CH_2N and $ArCH_2CHN$); 4·09 t, 2 H (CH_2O, J = 6·0); 6·81 d, 2 H (H-3, 5 of Ar, J = 8·5); 7·00 d, 2 H (H-2, 6 of Ar, J = 8·5)
Va-2 HCl	MS	CI: 262 (M^+, $C_{16}H_{26}N_2O$); EI: 219 (8), 155 (12), 112 (10), 98 (100), 85 (14), 55 (9), 44 (22)
Vb	IR (film)	805 (2 adjacent Ar–H); 1 035, 1 240 (ArOR); 1 510, 1 580, 1 609, 3 020 (Ar); 2 780 (N-CH_3, N–CH_2); 3 320 (NH)
	^{1}H NMR	1·00 d, 3 H (C–CH_3, J = 6·5); 1·50 bm, 7 H (3 CH_2 in positions 3, 4, 5 of piperidine and NH); 2·32 s, 3 H (NCH_3); 2·20—2·90 m, 9 H (CH_2NCH_2 of piperidine, further CH_2N and $ArCH_2CHN$); 4·01 t, 2 H (CH_2O, J = 6·0); 6·72 d, 2 H (H-3, 5 of Ar, J = 8·5); 7·00 d, 2 H (H-2, 6 of Ar, J = 8·5)
Vb-2 HCl	MS	CI: 276 (M^+, $C_{17}H_{28}N_2O$); EI: 219 ($C_{14}H_{21}NO$, 16), 113 ($C_7H_{15}N$, 9); 112 ($C_7H_{14}N$, 8), 98 ($C_6H_{12}N$, 54), 84 ($C_5H_{10}N$, 47), 58 (C_3H_8N, 100)
	IR	800 (2 adjacent Ar–H); 1 246 (ArOR); 1 510, 1 580, 1 610 (Ar); 2 640, 2 715 (NH^+); 3 410 (NH)
	^{1}H NMR (D_2O)	1·25 d, 3 H (C–CH_3, J = 6·5); 1·85 bm, 6 H (3 CH_2 in positions 3, 4, 5 of piperidine); 2·70 s, 3 H (NCH_3); 2·80—3·80 m, 9 H (CH_2NCH_2 of piperidine, further CH_2N and $ArCH_2CHN$); 4·35 t, 2 H (CH_2O, J = 6·0); 6·98 d, 2 H (H-3, 5 of Ar, J = 8·5); 7·25 d, 2 H (H-2, 6 of Ar, J = 8·5)
Vc	^{1}H NMR	0·95 d, 3 H (C–CH_3, J = 7·0); 1·60 bm, 6 H (3 CH_2 in positions 3, 4, 5 of piperidine); 2·35 s, 6 H ($N(CH_3)_2$); 2·40—3·20 m, 7 H (CH_2NCH_2 of piperidine and $ArCH_2CHN$); 2·80 t, 2 H (further CH_2N, J = 7·0); 4·11 t, 2 H (CH_2O, J = 7·0); 6·82 N, 2 H (H-3, 5 of Ar, J = 8·5); 7·10 d, 2 H (H-2, 6 of Ar, J = 8·5)

TABLE II
(*Continued*)

Compound	Spectrum	Data
Vc-2 HCl[b]	MS	CI: 290 (M^+, $C_{18}H_{30}N_2O$); EI: 219 (1), 156 (2), 112 (3), 98 (100), 72 (51), 58 (20)
VIa	^{1}H NMR	1·03 d, 3 H (C–CH_3); 1·20–3·00 m, 17 H (CH_2CH_2N, 5 CH_2 of piperidine, $ArCH_2CHN$); 3·98 t, 2 H (CH_2O, J = 6·0); 6·80 d, 2 H (H-3, 5 of aryl, J = 8·5); 7·09 d, 2 H (H-2, 6 of Ar, J = 8·5)
VIa-2 HCl[c]	IR	800, 815 (2 adjacent Ar–H); 1 250 (ArOR); 1 512, 1 607, 3 030 (Ar); 2 400, 2 480, 2 540, 2 640 (NH^+); 3 290, 3 350 (NH_2, H_2O)
	^{1}H NMR (D_2O)	1·30 d, 3 H (C–CH_3); 1·80 bm, 6 H (3 CH_2 in positions 3, 4, 5 of piperidine); 2·20 bm, 2 H (CH_2 in position 2 of propyl); 3·20 bm, 9 H (CH_2NCH_2 of piperidine, further CH_2N and $ArCH_2CHN$); 4·18 t, 2 H (CH_2O, J = 6·0); 7·00 d, 2 H (H-3, 5 of Ar, J = 8·5); 7·29 d, 2 H (H-2,6 of Ar, J = 8·5)
VIb	^{1}H NMR	1·05 d, 3 H (C–CH_3); 1·50 m, 6 H (3 CH_2 in positions 3, 4, 5 of piperidine); 2·00 m, 2 H (CH_2 in position 2 of propyl); 2·40 m, 6 H (3 CH_2N); 2·65 m, 3 H ($ArCH_2CHN$); 3·98 t, 2 H (CH_2O, J = 6·0); 6·80 d, 2 H (H-3, 5 of Ar, J = 8·5); 7·08 d, 2 H (H-2, 6 of Ar, J = 8·5)
VIb-2 HCl	MS	290 (M^+, $C_{18}H_{30}N_2O$), 289 (M-1), 233 (8), 127 (3), 126 (3), 98 (48), 84 (5), 58 (100)
	IR	810 (2 adjacent Ar–H); 1 245 (ArOR); 1 475, 1 514, 1 580, 1 610 (Ar); 2 530, 2 625, 2 730 (NH^+, NH_2^+)
	^{1}H NMR (D_2O)	1·30 d, 3 H (C–CH_3, J = 7·0); 1·80 bm, 6 H (3 CH_2 in positions 3, 4, 5 of piperidine); 2·20 m, 2 H (CH_2 in position 2 of propyl); 2·78 s, 3 H (NCH_3); 2·80–3·80 m, 9 H (CH_2NCH_2 of piperidine, further CH_2N, and $ArCH_2CHN$); 4·20 t, 2 H (CH_2O, J = 6·0); 7·02 d, 2 H (H-3, 5 of Ar, J = 8·5); 7·30 d, 2 H (H-2, 6 of Ar, J = 8·5)
VIc	^{1}H NMR	0·95 d, 3 H (C–CH_3, J = 7·0); 1·60 bm, 6 H (3 CH_2 in positions 3, 4, 5 of piperidine); 2·00 m, 2 H (CH_2 in position 2 of propyl); 2·32 s, 6 H ($N(CH_3)_2$); 2·40–3·00 m, 9 H (3 CH_2N and $ArCH_2CHN$); 4·00 t, 2 H (CH_2O, J = 7·0); 6·82 d, 2 H (H-3, 5 of of Ar, J = 8·5); 7·10 d, 2 H (H-2, 6 of Ar, J = 8·5)
VIc-2 HCl[b]	MS	304 (M^+, $C_{19}H_{32}N_2O$), 303 (M-1); 233 (2), 126 (2), 98 (9), 72 (100).

[a] Bis(hydrogen oxalate); [b] hemihydrate; [c] monohydrate.

the activity in the dose of 10 mg/kg; at the same dose, *IIc* inhibits by 51%; *XIII* at 300 mg/kg inhibits to 72%.

Ataxic activity in the rotarod test in mice: *XIII* at 500 mg/kg brings about ataxia in 40% of the mice. The same compound at 300 mg/kg is inactive in the test of apomorphine-induced climbing behaviour in mice and inactive at 250 mg/kg in the test of catalepsy in rats.

In conclusion, none of the compounds prepared did show the profile of potential antidepressant which would warrant further study.

EXPERIMENTAL

The melting points of analytical samples were determined in the Kofler block and were not corrected. The samples were dried in vacuo of about 60 Pa over P_2O_5 at room temperature or at a suitably elevated temperature. The UV spectrum was recorded at a Unicam SP 8 000 spectrophotometer, the IR spectra (mostly in Nujol, ν in cm^{-1}) were recorded with the Perkin–Elmer 298 spectrophotometer, ^1H NMR spectra (in $CDCl_3$ unless stated otherwise, δ, J in Hz) with a Tesla BS 487C (80 MHz) spectrometer, and the mass spectra with MCH 1 320 and Varian MAT 44S spectrometers (m/z, fragments and/or % given). The homogeneity of the substances and composition of the mixtures were checked by thin-layer chromatography (TLC) on silica gel (Silufol). The extracts were dried with $MgSO_4$ or K_2CO_3 and evaporated under reduced pressure at the rotary evaporator.

N-(1-(4-Methoxyphenyl)-2-propyl)formamide (*VII*)

A mixture of 35·0 g 1-(4-methoxyphenyl)-2-propylamine[14] and 85 ml ethyl formate was heated for 6 h in an autoclave to 120–130°C. Evaporation of the volatile components gave 40·0 g (theoretical) of a residue which represented the crude *VII* and which crystallized from a mixture of warm benzene and hexane, m.p. 56–57°C. IR spectrum: 818, 834 (2 adjacent Ar—H); 1 025, 1 245 ($ArOCH_3$); 1 460, 1 510, 1 610 (Ar); 1 565, 1 650 (RHNCHO); 2 740 (CHO); 3 205 (NH). ^1H NMR spectrum: 1·12 d and 1·22 d, $\sum$ 3 H (C—CH_3, J = 7·5); 2·70 m, 2 H ($ArCH_2$); 3·75 s, 3 H (OCH_3); 4·20 m, 1 H (CHN); 5·80 bs, 1 H (NH); 6·78 d, 2 H (H-3, 5 of Ar); 7·00 d and 7·04 d, $\sum$ 2 H (H-2, 6 of Ar); 7·70 d (J = 12·0) and 8·00 bs, $\sum$ 1 H (CHO). For $C_{11}H_{15}NO_2$ (193·3) calculated: 68·36% C, 7·84% H, 7·25% N; found: 68·85% C, 8·00% H, 7·41% N. Ref.[15], m.p. 35°C.

N-Methyl-1-(4-methoxyphenyl)-2-propylamine (*VIII*)

A solution of 75·0 g *VII* in 500 ml ether was added dropwise to a stirred solution of 35·0 g $LiAlH_4$ in 500 ml ether and the mixture was refluxed for 2 h. After cooling it was decomposed by a slow addition of 140 ml 20% NaOH, the mixture was stirred for 2 h and allowed to stand overnight. The solid was filtered off, washed with 500 ml ether and the filtrate was evaporated. The residue (68·5 g, 98%) represents the crude base *VIII*. A sample was characterized by transformation to the hydrochloride, m.p. 175°C (ethanol–ether). Refs[17,18], m.p. 176–177°C and 174°C, respectively.

N,N-Dimethyl-1-(4-methoxyphenyl)-2-propylamine (*IX*)

A mixture of 60·5 g 1-(4-methoxyphenyl)-2-propylamine[14], 90 ml water, 80 ml 80% formic acid, and 110 ml 36% formaldehyde was stirred and refluxed for 5 h (bath of 110–120°C). After

cooling, 100 ml hydrochloric acid were added under stirring and the mixture was evaporated in vacuo. The residue was dissolved in 180 ml water, 10 ml hydrochloric acid were added, and the solution was washed with a mixture 1 : 1 of benzene and ether. The aqueous solution was made alkaline with 20% NaOH and the base was extracted with a mixture 1 : 1 of benzene and ether. Processing of the extract and distillation of the residue gave 57·5 g (81%) of *IX*, b.p. 125 to 127°C/0·4 kPa, [n_D^{23}] 1·5132; hydrochloride, m.p. 160—162°C (ethanol–ether). Refs[20,21], b.p. 137°C/1·7 kPa and 130—132°C/1·3 kPa, respectively, and m.p. of the hydrochloride, 161—162°C.

1-(4-(2-Dimethylaminoethoxy)phenyl)propan-2-one (*XIII*)

A mixture of 15·0 g 1-(4-hydroxyphenyl)propan-2-one[25], 120 ml butan-2-one, 15·0 g 2-dimethylaminoethyl chloride hydrochloride, and 30 g K_2CO_3 was stirred and refluxed for 16 h. After cooling the solid was filtered off, washed with butan-2-one and the filtrate was evaporated. The residue was dissolved in ether and transformed by treatment with an ethereal solution of HCl to the crude hydrochloride (21·3 g). This was decomposed with 20 ml water with NH_4OH, the base was isolated by extraction with benzene and distilled; 7·9 g (36%), b.p. 135—142°C/70 Pa.

Hydrochloride, m.p. 146—148°C (ethanol). Mass spectrum: 221 (M^+, $C_{13}H_{19}NO_2$, 1), 72 ($C_4H_{10}N$, 4·5), 58 (C_3H_8N, 100). IR spectrum: 806, 855 (2 adjacent Ar–H); 1 055, 1 160, 1 236 (ArOR); 1 480, 1 512, 1 580, 1 605, 3 005 (Ar); 1 710 (RCOR·); 2 460 (NH^+). For $C_{13}H_{20}ClNO_2$ (257·8) calculated: 60·57% C, 7·82% H, 13·76% Cl, 5·43% N; found: 60·34% C, 7·84% H, 13·71% Cl, 5·58% N.

Hydrogen maleate, m.p. 81—83°C. For $C_{17}H_{23}NO_6$ (337·4) calculated: 60·52% C, 6·87% H, 4·15% N; found: 60·23% C, 6·79% H, 3·97% N.

4-(2-Dimethylaminoethoxy)benzonitrile (*XV*)

A mixture of 2·6 g 4-(2-dimethylaminoethoxy)benzaldehyde[26], 20 ml acetic acid, 1·6 g nitroethane, and 2·0 g ammonium acetate was stirred and refluxed for 4 h. Acetic acid was evaporated in vacuo, the residue was diluted with benzene, washed with saturated $NaHCO_3$ solution, and with water. Processing of the benzene solution gave 2·2 g of inhomogeneous residue which was chromatographed on 40 g neutral Al_2O_3 (activity II). Elution with benzene gave 1·1 g (40%) of homogeneous basic product which was identified as *XV*. It was transformed to the hydrogen maleate, m.p. 123—125°C (ethanol–ether). Mass spectrum: 190 (M^+, $C_{11}H_{14}N_2O$, 0·5), 119 (C_7H_5NO, 0·3), 102 (C_7H_4N, 1·5), 58 (C_3H_8N, 100). IR spectrum: 2 230 (Ar–CN). ^{1}H NMR spectrum (CD_3SOCD_3): 2·95 s, 6 H ($N(CH_3)_2$); 3·52 bt, 2 H (CH_2N); 4·40 bt, 2 H (CH_2O); 6·03 s, 2 H (CH=CH of maleic acid); 7·11 d, 2 H (H-3, 5 of Ar, J = 8·5); 7·75 d, 2 H (H-2, 6 of Ar, J = 8·5). For $C_{15}H_{18}N_2O_5$ (306·3) calculated: 58·81% C, 5·92% H, 9·15% N; found: 58·96% C, 5·83% H, 9·19% N.

N,N-Dimethyl-1-(4-(2-dimethylaminoethoxy)phenyl)-2-propylamine (*Ic*) (General Method)

A suspension of 5·2 g *XII* hydrobromide[21] in 30 ml 2-propanol was treated with a solution of 2·9 g NaOH in 3 ml water and the mixture was stirred for 30 min. 2-Dimethylaminoethyl chloride hydrochloride (2·9 g) was added and the mixture was stirred for 3 h at 90°C. The solvent was evaporated in vacuo, the residue was diluted with 10 ml water and extracted with benzene. The extract was washed with 5% NaOH and water, dried, and evaporated; 2·8 g (56%) of oily *Ic* which was transformed to the dihydrochloride and purified by its crystallization. A sample of the pure dihydrochloride was decomposed with NH_4OH and the released base, isolated by extraction with ether, was used for recording the ^{1}H NMR spectrum. For analysis and spectra, cf. Tables I and II.

N-(2-Diethylaminoethyl)-1-(4-(2-diethylaminoethoxy)phenyl)-2-propylamine (*XVI*)

A suspension of 10·5 g *X* hydrobromide[23] in 60 ml 2-propanol was treated with a solution of 5·4 g NaOH in 7 ml water, the suspension was stirred for 30 min, treated with 6·9 g 2-diethylaminoethyl chloride hydrochloride, and the mixture was stirred for 6 h at 90°C. Similar processing like in the preceding case gave 10·2 g mixture of bases which was chromatographed on 300 g neutral Al_2O_3 (activity II). Elution with benzene gave 5·55 g (35%) of homogeneous *XVI* which was transformed to the trihydrochloride, m.p. 187–189°C (ethanol–ether). ^{1}H NMR spectrum (D_2O): 1·00–1·50 m, 15 H (5 C—CH_3); 2·60–3·70 m, 17 H (7 CH_2N and $ArCH_2CHN$); 4·32 bt, 2 H (CH_2O); 7·00 d, 2 H (H-3, 5 of Ar, J = 8·0); 7·28 d, 2 H (H-2, 6 of Ar, J = 8·5). For $C_{21}H_{42}Cl_3N_3O$ (458·9) calculated: 54·95% C, 9·22% H, 23·18% Cl, 9·16% N; found: 54·92% C, 9·49% H, 22·90% Cl, 9·01% N.

From a sample of this salt the homogeneous oily base *XVI* was released and also used for recording the ^{1}H NMR spectrum: 0·80–1·20 m, 15 H (5 C—CH_3); 2·02 bs, 1 H (NH); 2·20 to 3·00 m, 17 H (7 CH_2N and $ArCH_2CHN$); 4·00 t, 2 H (CH_2O, J = 6·0); 6·80 d, 2 H (H-3, 5 of aryl, J = 8·0); 7·05 d, 2 H (H-2, 6 of aryl, J = 8·0).

The chromatography was continued by elution with chloroform which resulted in 6·15 g (54%) of *IIIa* (for further data, cf. Tables I and II).

N-(2-Diethylaminoethyl)-N-methyl-1-(4-(2-diethylaminoethoxy)phenyl)-2-propylamine (*XVII*)

A similar reaction of 3·70 g *XI* (refs[19,24]) with 5·4 g 2-diethylaminoethyl chloride hydrochloride and 3·20 g NaOH in 35 ml 2-propanol and 4 ml water as in the preceding case gave 5·4 g of oily mixture of bases which was chromatographed on 120 g neutral Al_2O_3 (activity II). Elution with a 1 : 1 mixture of benzene and light petroleum and benzene alone gave 1·75 g (22%) of oily *XVII*. ^{1}H NMR spectrum: 1·00 m, 15 H (5 C–CH_3); 2·30 s, 3 H (NCH_3); 2·40–3·00 m, 17 H (7 CH_2N and $ArCH_2CHN$); 4·00 t, 2 H (OCH_2, J = 6·0); 6·80 d, 2 H (H-3, 5 of Ar, J = 8·5); 7·09 d, 2 H (H-2, 6 of Ar, J = 8·5).

Tripicrate, m.p. 188–190°C (ethyl acetate). For $C_{40}H_{50}N_{12}O_{22}$ (1 050·9) calculated: 45·71% C, 4·80% H, 15·99% N; found: 45·63% C, 4·92% H, 15·73% N.

Continued elution with a mixture 3 : 7 of chloroform and benzene and then with chloroform alone afforded 2·7 g (46%) of *IIIb* (for further data, cf. Tables I and II).

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