POTENTIAL NEUROLEPTICS OF THE ORTHOPRAMIDE SERIES; SYNTHESIS OF HETEROCYCLIC 5-AMINO-2-METHOXYBENZAMIDES AND OF SOME RELATED COMPOUNDS

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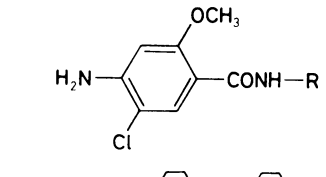
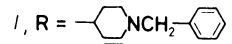
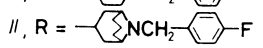
2-Methoxy-5-nitrobenzoyl chloride was reacted with 2-(aminomethyl)-1-ethylpyrrolidine, 3-amino-1-ethylpiperidine, 4-amino-1-benzylpiperidine, 1-benzylpiperazine, and 1-amino-4-benzylpiperazine and gave the N-substituted 2-methoxy-5-nitrobenzamides *VIa*—*VIe*. Their reduction with hydrazine hydrate and Raney nickel in ethanol afforded the corresponding 5-amino-2-methoxybenzamides *VIIa*—*VIIe*. The amino amides *VIIb* and *VIIc* were transformed to methylamino compounds *XIb* and *XIc* via the 4-toluenesulfonamides *VIIIb* and *VIIIc* and the N-methyl-4-toluenesulfonamides *Xb* and *Xc*. The N-(1-benzyl-4-piperidinyl)amides *VIc*, *VIIc*, and *XIc* were found to be mild neuroleptics having antiapomorphine, some cataleptic and some ataxic activity.

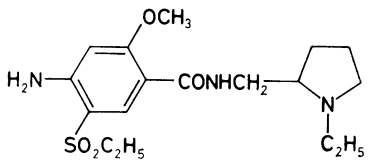
In the group of orthopramide (2-methoxybenzamide) neuroleptic agents several interesting compounds carry in their molecules the aromatic amino or methylamino group in *p*-position towards the carboxamido fragment. Compounds *I*—*V* have to be mentioned as examples. Compound *I* is known under the generic name "clebopride" and it is an antidopaminergic agent with rather important antagonistic activities against aphetamine-induced stereotypic behaviour and apomorphine-induced gnawing behaviour in rodents, being at the same time rather low-cataleptic[1,2]. The side chain analogue *II* ("BRL 34778") is a selective dopamine antagonist; it is rather strongly cataleptic but has enormous antiapomorphine activity in the test of apomorphine climbing behaviour in mice[3]. The sulfone *III* ("amisulpride", Socian^{R}) is a noncataleptic neuroleptic agent lacking the activity against the apomorphine-induced stereotypies which, nevertheless, found practical use in psychiatric pharmacotherapy[4,5]. The methylamino compounds *IV* and *V* are the Japanese experimental neuroleptic agents[6] YM-08050 and YM-09152-2. The former (*IV*) is a low-cataleptic neuroleptic[7] whose further development was probably discontinued (last reports in 1980 (ref.[8])). On the other hand, the latter compound (*V*) is the object of much interest[9–11]; its cataleptic activity is two times higher than that of haloperidol but its antagonistic activity towards amphetamine stereotypies is 5 times

higher. Continuing our studies in the orthopramide series[12,13], we have now prepared several heterocyclic amides of 5-amino-2-methoxybenzoic acid, their 5-nitro analogues (as intermediates) and two of the 5-(methylamino) analogues. Description of the syntheses and some preliminary pharmacological data are the object of the present communication.

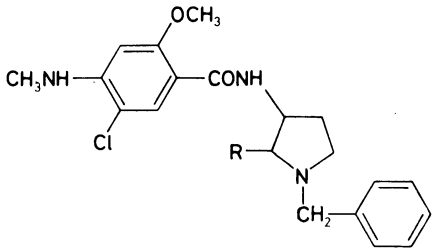


I, R = 

II, R = 



III

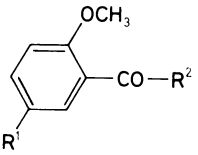


IV, R = H

V, R = CH_3

The syntheses started from 2-methoxy-5-nitrobenzoyl chloride[14] which was reacted with 2-(aminomethyl)-1-ethylpyrrolidine[12], 3-amino-1-ethylpiperidine[15], 4-amino-1-benzylpiperidine[16,17], 1-benzylpiperazine[18], and 1-amino-4-benzylpiperazine[19] in boiling chloroform (method *A*). The hydrochlorides of *VIa*–*VIe* formed could either be directly isolated or they were first transformed to crystalline bases and these were neutralized with hydrogen chloride in mixtures of ethanol and ether. All bases *VIa*–*VIe* were crystalline and were characterized by UV, IR and ^{1}H NMR spectra. The first two amides *VIa* and *VIb* were mentioned in patents[20,21]; the hydrochlorides were not described. The used 4-amino-1-benzylpiperidine has been prepared not only by the methods described (reduction of 1-benzyl-4-piperidone oxime[22] with sodium and ethanol[23] or with lithium aluminium hydride[16,17]) but also by making use of the Leuckart reaction[24]. 1-Benzyl-4-piperidone was reacted with formamide and formic acid at 170°C and the obtained oily 1-benzyl-4-(formamido) piperidine was hydrolyzed with ethanolic potassium hydroxide without characterization. 4-Amino-1-benzylpiperidine, obtained in a good yield, was transformed to the dihydrochloride monohydrate and sulfate monohydrate (mass spectrum confirmed the composition of the base) which were found identical with the salts of 4-amino-1-benzylpiperidine, prepared by the ways described[16,17,23].

The nitro amides *VIa*–*VId* and the hydrazide *VIe* were reduced to the amino compounds *VIIa*–*VIIe* with hydrazine hydrate and Raney nickel in ethanol (method[25–29]) (general method *B*). With the exception of *VIIa*, the bases were crystalline and spectra of all bases *VIIa*–*VIIe* were registered. The base *VIIe* crystallized as a 6 : 1 solvate with benzene which was confirmed by the mass spectrum. The bases *VIIa*–*VIIe* were transformed to salts (hydrochlorides, oxalates), all of which were solvated with water. Compounds *VIa*–*VIe* and *VIIa*–*VIIe*, which were prepared by the general methods *A* and *B*, are assembled in Table I with the usual experimental data. The preparations of *VIc* and *VIIc* are described in the Experimental as the examples. Spectra of compounds of Table I are assembled in Table II.



VI, $R^1 = NO_2$ *IX*, $R^1 = N(SO_2{-}C_6H_4{-}CH_3)_2$

VII, $R^1 = NH_2$ *X*, $R^1 = NSO_2{-}C_6H_4{-}CH_3$ (CH_3)

VIII, $R^1 = NHSO_2{-}C_6H_4{-}CH_3$ *XI*, $R^1 = NHCH_3$

In formulae *VI*–*XI*: *a*, $R^2 = NHCH_2$–(N-C_2H_5) *b*, $R^2 = NH$–(N-C_2H_5)

c, $R^2 = NH$–(piperidine)–NCH_2–C_6H_5 *d*, $R^2 = N$(piperidine)–NCH_2–C_6H_5

e, $R^2 = NH$–N(piperidine)–NCH_2–C_6H_5

Only in series *b* and *c* the preparation of methylamino compounds (*XIb* and *XIc*) was carried out. Reactions of *VIIb* and *VIIc* with 4-toluenesulfonyl chloride gave mixtures of the desired N-tosyl compounds *VIIIb* and *VIIIc* and of the N,N-ditosyl compounds *IXb* and *IXc* which were separated by crystallization. Reaction conditions determined the predomination of one or the other type of products. The following conditions were used: (i) reaction of the components in pyridine at room temperature, (ii) reaction of the components in dichloromethane in the presence of sodium hydrogen carbonate, and (iii) reaction of the components in dichloromethane in the presence of sodium hydroxide in water with vigorous stirring. The most reliable conditions for obtaining the desired *VIIIb* and *VIIIc* proved those under (ii). Reactions under conditions (iii) where 4-toluenesulfonyl chloride and sodium hydroxide were added in several portions, were favourable for the formation of *IXb* and *IXc*. Further step was the methylation of *VIIIb* and *VIIIc* to *Xb* and *Xc* which was carried out with dimethyl sulfate in dichloromethane in the presence of aqueous potassium hydroxide

TABLE I

N-Substituted 2-Methoxy-5-nitro(and amino)benzamides *VIa*—*VIe* and *VIIa*—*VIIe*

Compound (Method, yield %)	M.p., °C (solvent)	Formula (M.w.)	Calculated/Found		
			% C	% H	% N
VIa-HCl	159·5—161	$C_{15}H_{22}ClN_3O_4$[a]	52·40	6·45	12·22
(*A*, 81)	(acetone–2-propanol–ether)	(343·8)	52·29	6·50	12·50
VIb	108—110	$C_{15}H_{21}N_3O_4$	58·62	6·89	13·67
(*A*, 81)	(benzene–cyclohexane–hexane)	(307·3)	58·45	6·77	13·60
VIb-HCl[b]	176—176·5	$C_{15}H_{22}ClN_3O_4$[c]	49·79	6·69	11·61
	(ethanol–ether)	+ H_2O	50·01	6·45	11·62
		(361·8)			
VIc[d]	131—134	$C_{20}H_{23}N_3O_4$	65·02	6·28	11·38
(*A*, 100)	(benzene–light petroleum)	(369·4)	64·80	6·05	11·18
VIc-HCl[b]	145·5—148·5	$C_{20}H_{24}ClN_3O_4$[e]	56·66	6.19	9·91
	(ethanol–ether)	+ H_2O	56·63	6·08	9·92
		(423·9)			
VId	140—143	$C_{19}H_{21}N_3O_4$	64·21	5·96	11·82
(*A*, 85)	(benzene–hexane)	(355·4)	64·23	5·94	11·75
VId-HCl	228	$C_{19}H_{22}ClN$[f]	58·23	5·66	10·72
	(ethanol–acetone–ether)	(391·9)	58·35	5·75	10·63
VIe	150—151	$C_{19}H_{22}N_4O_4$	61·60	5·99	15·13
(*A*, 86)	(benzene–light petroleum)	(370·4)	61·26	5·98	14·94
VIe-HCl[g]	153·5—155	$C_{19}H_{24}Cl_2N_4O_4$[h]	54·87	5·82	13·47
	(ethanol–acetone)	+ 0·5 H_2O	54·59	5·78	13·27
		(415·9)			
VIIa-SO[i]	130—133	$C_{18}H_{26}N_3O_8$	51·30	6·46	9·97
(*B*, 82)	(aqueous ethanol–acetone)	+ 0·5 H_2O	51·60	6·49	9·67
		(421·4)			
VIIb	102·5—104·5	$C_{15}H_{23}N_3O_2$	64·95	8·36	15·15
(*B*, 82)	(benzene–light petroleum)	(277·4)	64·88	8·36	15·14
VIIb-2HCl[b]	209—212[j]	$C_{15}H_{25}Cl_2N_3O_2$[k]	48·91	7·39	11·40
	(ethanol–acetone–ether)	+ H_2O	48·52	7·19	11·17
		(368·3)			
VIIc[d]	131—133	$C_{20}H_{25}N_3O_2$	70·77	7·42	12·38
(*B*, 76)	(benzene–cyclohexane)	(339·4)	70·52	7·54	12·16
VIIc-2HCl[l]	183—185	$C_{20}H_{27}Cl_2N_3O_2$[m]	54·67	6·88	9·56
	(ethanol–acetone)	+ 1·5 H_2O	54·69	6·71	9·58
		(439·4)			

TABLE I
(*Continued*)

Compound (Method, yield %)	M.p., °C (solvent)	Formula (M.w.)	Calculated/Found		
			% C	% H	% N
VIId	115–116·5	$C_{19}H_{23}N_3O_2$	70·13	7·12	12·91
(*B*, 75)	(benzene–light petroleum)	(325·4)	69·95	6·98	12·83
VIId-SOH[n]	132–135	$C_{22}H_{26}N_3O_8$	56·28	5·80	8·95
	(ethanol–acetone)	+ 0·5 H_2O	56·34	5·50	8·87
		(469·5)			
VIIe[o]	157–158	$C_{19}H_{24}N_4O_2$	67·96	7·13	15·91
(*B*, 83)	(benzene)	+ 1/6 C_6H_6	67·70	6·94	16·04
VIIe-2HCl[l]	229–231	$C_{19}H_{26}Cl_2N_4O_2$[p]	51·82	6·64	12·72
	(ethanol)	+ 1·5 H_2O	52·06	6·39	12·42
		(440·4)			

[a] Calculated: 10·31 % Cl, found: 10·60 % Cl; [b] monohydrate; [c] calculated: 9·80 % Cl, found: 10·09 % Cl; [d] see Experimental; [e] calculated: 8·36 % Cl, found: 8·62 % Cl; [f] calculated: 9·05 % Cl, 9·28 % Cl; [g] hemihydrate; [h] calculated: 8·53 % Cl, found: 8·57 % Cl; [i] SO sesquioxalate; [j] with decomposition; [k] calculated: 19·25 % Cl, found: 19·49 % Cl; [l] sesquihydrate; [m] calculated: 16·14 % Cl, found: 16·28 % Cl; [n] SOH sesquioxalate hemihydrate; [o] 6 : 1 solvate with benzene; [p] calculated: 16·10 % Cl, found: 15·87 % Cl.

(vigorous stirring) and tetrabutylammonium hydrogen sulfate as the phase-transfer catalyst. All the intermediates *VIIIb*, *VIIIc*, *Xb*, and *Xc*, as well as the by-products *IXb* and *IXc* were crystalline and their identity was confirmed by spectra. The final step was the detosylation of *Xb* and *Xc* which was carried out with 90% sulfuric acid first at low temperature, finally at 70–80°C (for analogy, cf. ref.[6]). The products *XIb* and *XIc* were obtained as crystalline bases and spectra confirmed their structures. The salts of these bases did not crystallize and for pharmacological testing aqueous solutions of the methanesulfonates had to be used.

Compounds *VIa*–*VIe*, *VIIa*–*VIIe*, *XIb*, and *XIc* were pharmacologically tested as potential neuroleptics of the orthopramide series. They were administered orally in the form of salts described in Table I (*XIb* and *XIc* in the form of aqueous solutions of methanesulfonates) and the doses were calculated per bases. Acute toxicity in mice, LD_{50} in mg/kg: *VIa*, 194; *VIe*, 602; *VIIa*, 218; *VIIc*, 148; *XIc*, 212; *XIb*, 250 mg/kg was lethal for 100% of the animals.

Affinity to the dopamine-D_2 receptors evaluated by inhibition of binding of 0·5 nM [^{3}H] spiperone in rat corpus striatum in vitro, IC_{50} in nmol l^{-1}: *VIa*–*VIe*, *VIIa*–*VIIe*, *XIb*, and *XIc*, >1 000. The affinity could not be proven at all.

TABLE II

Spectra of N-substituted 2-methoxy-5-nitro(and amino)benzamides *VIa*–*VIe* and *VIIa*–*VIIe*[a]

Compound	Spectrum	Data
VIa	UV	296 (4·12)
	IR	830, 900 (2 adjacent and solitary Ar–H); 1 015, 1 247, 2 895 ($ArOCH_3$); 1 350, 1 511 ($ArNO_2$); 1 611, 3 005, 3 085, 3 113 (Ar); 1 511, 1 653 (ArCONHR); 2 768 (CH_2–N); 3 360 (NH
	^{1}H NMR	1·15 t, 3 H (CH_3 of ethyl, J = 7·0); 1·50–4·00 m, 11 H ($CH_2CHCH_2CH_2CH_2NCH_2$); 4·10 s, 3 H (OCH_3); 7·10 d, 1 H (H-3, J = 8·5); 8·25 bs, 1 H (CONH); 8·30 dd, 1 H (H-4, J = 8·5; 3·0); 9·10 d, 1 H (H-6, J = 3·0)
VIb	UV	297 (4·02)
	IR	830, 878 (2 adjacent and solitary Ar–H); 1 022, 1 273, 2 800 ($ArOCH_3$); 1 340, 1 520 ($ArNO_2$); 1 480, 1 580, 3 020, 3 035, 3 090, 3 120 (Ar); 1 520, 1 655 (ArCONHR); 2 750, 2 780 (CH_2–N); 3 295 (NH)
	^{1}H NMR	1·10 t, 3 H (CH_3 of ethyl, J = 7·0); 1·70 m, 4 H (2 × H-4 and 2 × H-5 of piperidinyl); 2·00–2·80 m, 6 H (CH_2N of ethylamino and CH_2NCH_2); 4·10 s, 3 H (OCH_3); 4·30 bm, 1 H (H-3 of piperidinyl); 7·10 d, 1 H (H-3, J = 9·0); 8·30 bs, 1 H (CONH); 8·30 dd, 1 H (H-4, J = 9·0; 3·0); 9·02 d, 1 H (H-6, J = 3·0)
VIc	UV	300 (4·04)
	IR	700, 740, 750, 825, 830, 890 (5 and 2 adjacent and solitary Ar–H); 1 020, 1 240, 2 815 ($ArOCH_3$); 1 357, 1 520 ($ArNO_2$); 1 520, 1 660 (ArCONHR); 1 615, 3 090 (Ar); 3 407 (NH)
	^{1}H NMR	1·30–3·00 m, 8 H (4 × CH_2 of piperidinyl); 3·50 s, 2 H ($ArCH_2N$); 4·00 s, 3 H (OCH_3); 4·00 bm, 1 H (H-4 of piperidinyl); 7·00 d, 1 H (H-3, J = 8·0); 7·25 s, 5 H (C_6H_5); 7·52 bd, 1 H (CONH, J = 8·0); 8·21 dd, 1 H (H-4, J = 3·0, 8·0); 8·98 d, 1 H (H-6, J = 3·0)
VId	UV	infl. 235 (4·04), 302 (4·02)
	IR	701, 743, 833, 863 (5 and 2 adjacent and solitary Ar–H); 1 025, 1 271, 2 813 ($ArOCH_3$); 1 345, 1 512 ($ArNO_2$); 1 480, 1 587, 3 075 (Ar); 1 637 (ArCON); 2 765, 2 800 (CH_2–N)
	^{1}H NMR	2·50 m, 4 H ($CH_2N^4CH_2$ of piperazine); 3·55 s, 2 H ($ArCH_2N$); 3·20 m and 3·85 m, 2 and 2 H ($CH_2N^1CH_2$ of piperazine); 3·95 s, 3 H (OCH_3); 7·00 d, 1 H (H-3, J = 9·0); 7·30 s, 5 H (C_6H_5); 8·20 d, 1 H (H-6, J = 3·0); 8·28 dd, 1 H (H-4, J = 9·0, 3·0)

TABLE II
(*Contined*)

Compound	Spectrum	Data
VIe	MS	370 (M^+, $C_{19}H_{22}N_4O_4$, 0·3), 266 ($C_{12}H_{16}N_3O_4$, 3·5), 190 ($C_{11}H_{16}N_3$, 3·2), 175 ($C_{11}H_{15}N_2$, 23), 91 (C_7H_7, 100)
	UV	298 (4·03)
	IR	697, 736, 750, 830, 900 (5 and 2 adjacent and solitary Ar–H), 1 002, 1 245, 1 278, 2 800 ($ArOCH_3$); 1 350, 1 519 ($ArNO_2$); 1 539, 1 670 (ArCONH); 1 613, 3 025, 3 080, 3 115 (Ar); 2 760 (CH_2–N); 3 320 (NH)
	^{1}H NMR	2·65 m, 4 H ($CH_2N^4CH_2$ of piperazine), 3·00 m, 4 H ($CH_2N^1CH_2$ of piperazine); 3·58 s, 2 H ($ArCH_2N$); 4·10 s, 3 H (OCH_3); 7·08 d, 1 H (H-3, J = 9·0); 7·30 s, 5 H (C_6H_5); 8·30 s, 1 H (CONH); 8·30 dd, 1 H (H-4, J = 9·0, 3·0); 9·00 d, 1 H (H-6, J = 3·0)
VIIa	IR	816, 876 (2 adjacent and solitary Ar–H); 1 240, 2 810 ($ArOCH_3$); 1 492, 1 582, 3 080 (Ar); 1 512, 1 645 (CONH); 3 155, 3 410 (NH)
	^{1}H NMR	1·10 t, 3 H (CH_3 of ethyl, J = 7·0); 1·40–3·70 m, 13 H ($CH_2CHCH_2CH_2CH_2NCH_2$ and NH_2); 3·80 s, 3 H (OCH_3); 6·70 m, 2 H (H-3 and H-4); 7·50 bs, 1 H (H-6); 8·40 bs, 1 H (CONH)
VIIb	UV	243 (4·07), 324 (3·46)
	IR	820, 880 (2 adjacent and solitary Ar–H); 1 020, 1 265, 2 810 ($ArOCH_3$); 1 483, 1 580, 1 586, 3 000, 3 040, 3 065 (Ar); 1 515, 1 641 (ArCONHR); 1 605 ($ArNH_2$); 2 770 (CH_2–N); 3 220, 3 325, 3 360, 3 440 (NH, NH_2)
	^{1}H NMR	1·03 t, 3 H (CH_3 of ethyl, J = 7·0): 1·60 bm, 4 H (2 × H-4 and 2 × H-5 of piperidine); 2·32 q, 2 H (NCH_2 of N-ethyl, J = 7·0); 2·50 bm, 4 H (CH_2NCH_2 of piperidine); 3·60 bs, 2 H ($ArNH_2$); 3·85 s, 3 H (OCH_3); 4·22 bm, 1 H (H-3 of piperidinyl); 6·75 bs, 2 H (H-3 and H-4); 7·52 bs, 1 H (H-6); 8·48 bd, 1 H (CONH, J = 8·0)

TABLE II
(*Continued*)

Compound	Spectrum	Data
VIIc	UV	328 (3·47)
	IR	705, 750, 823, 880 (5 and 2 adjacent and solitary Ar–H); 1 030, 1 184, 1 227, 2 805 ($ArOCH_3$); 1 500, 1 584, 3 015, 3 030, 3 045 (Ar); 1 545, 1 650 (ArCONHR); 1 610 ($ArNH_2$); 2 765 (CH_2–N); 3 375, 3 340, 3 415 (NH, NH_2)
	^{1}H NMR	1·30–3·00 m, 8 H (4 × CH_2 of piperidinyl); 3·48 s, 2 H ($ArCH_2N$); 3·55 bs, 2 H ($ArNH_2$); 3·80 s, 3 H (OCH_3); 3·98 bm, 1 H (H-4 of piperidinyl); 6·70 m, 2 H (H-3 and H-4); 7·25 s, 5 H (C_6H_5); 7·50 bs, 1 H (H-6); 7·90 bd, 1 H (CONH, J = 8·0)
VIId	UV	233 (4·13), 312 (3·46)
	IR	700, 741, 811, 880 (5 and 2 adjacent and solitary Ar–H); 1 022, 1 230, 2 845 ($ArOCH_3$); 1 500, 1 590, 3 000 (Ar); 1 604 ($ArNH_2$); 1 623 (ArCON); 2 765 (CH_2–N); 3 240, 3 335, 3 400 (NH_2)
	^{1}H NMR	2·50 bm, 4 H ($CH_2N^4CH_2$ of piperazine); 3·50 bs, 2 H ($ArNH_2$); 3·52 s, 2 H ($ArCH_2N$); 3·72 s, 3 H (OCH_3); 3·21 m and 3·80 m, 2 and 2 H ($CH_2N^1CH_2$ of piperazine); 6·60 m, 3 H (H-3, H-4, and H-6); 7·30 s, 5 H (C_6H_5)
VIIe[b]	MS	340 (M^+, $C_{19}H_{24}N_4O_2$, 2) 175 ($C_{11}H_{15}N_2$, 35), 150 ($C_8H_8NO_2$, 40), 91 (C_7H_7, 100)
	UV	326 (3·47)
	IR	706, 750, 780, 817, 878 (5 and 2 adjacent and solitary Ar–H); 1 009, 1 220, 1 242, 1 270, 2 820 ($ArOCH_3$); 1 500, 1 583, 1 616, 3 025 (Ar); 1 525, 1 662 (ArCONHR); 1 640 ($ArNH_2$); 2 805 (CH_2–N); 3 210, 3 295, 3 330, 3 445 (NH_2, NH)
	^{1}H NMR	2·60 m, 4 H ($CH_2N^4CH_2$ of piperazine); 2·90 m, 4 H ($CH_2N^1CH_2$ of piperazine); 3·50 s, 2 H ($ArCH_2N$); 3·56 bs, 2 H ($ArNH_2$); 3·80 s, 3 H (OCH_3); 6·70 m, 2 H (H-3 and H-4); 7·25 s, 6 H (C_6H_5 and 1/6 C_6H_6); 7·48 bs, 1 H (H-6); 8·65 bs, 1 H (CONH)

[a] In cases of noncrystalline bases, oily bases were used for recording the spectra and were prepared by decomposition of the purified crystalline salts with NH_4OH, extraction with dichloromethane and evaporation of the solvent; [b] 6 : 1 solvate with benzene.

Inhibition of the apomorphine-induced climbing behaviour in mice; dose in mg/kg and response (per cent of positively reacting animals) given: *VIb*, 100, ineffective; *VIc*, 100, 70%; *VIa* and *VIIa*, 100, ineffective; *VIIc*, 100, 30%; *VIId* and *VIIe*, 100, ineffective; *XIc*, 100, 50%.

Cataleptic activity in rats, dose and response (per cent of cataleptic animals) given: *VIb*, *VIe*, *VIIa*, *VIId*, and *VIIe*, 100, ineffective; *VIc*, 100, 70%; *VIIc*, 100, 30%; *XIc*, 100, 50%.

Ataxic activity in the rotard test in mice, dose in mg/kg and response (per cent of animals with ataxia): *VIa*, 50, 30%; *VIb*, 250, 60%; *VIc*, 100, 80%; *VId*, 250, ineffective; *VIe*, 250, 80%; *VIIa*, 100, 40%; *VIIb*, 100, ineffective; *VIIc*, ED_{50} = 56; *VIId*, 250, 30%; *VIIe* and *XIc*, 100, 30%; *XIb*, 100, 20%. Influence on the lethal activity of adrenaline in mice: *VIa* – *VIc*, *VIIa*, *VIIc*, and *XIc*, ineffective at the dose of 100 mg/kg.

In conclusion, only *VIc* (VÚFB-16624), *VIIc* (VÚFB-16630), and *XIc* (VÚFB-17057) have the character of mild neuroleptic agents having antiapomorphine, some cataleptic and some ataxic activity; the lack of affinity to dopamine-D_2 receptors is surprising.

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. UV spectra (in methanol, λ_{max} in nm ($\log \varepsilon$)) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (in Nujol, ν in cm^{-1}) were recorded with the Perkin–Elmer 298 spectrophotometer, ^1H NMR spectra (in $CDCl_3$, δ in ppm, J in Hz) with a CW-NMR Tesla BS 487C (80 MHz) spectrometer, and the mass spectra (m/z, fragments and/or %) with MCH 1320 and Varian MAT 44S (GC-MS) spectrometers. 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 on a rotary evaporator.

4-Amino-1-benzylpiperidine

A mixture of 11·4 g 1-benzyl-4-piperidone, 40·5 g formamide, and 8·5 g formic acid was stirred for 30 min at 100–125°C and 5 h at 170°C (bath temperature 190°C). It was evaporated under reduced pressure (bath temperature until 145°C), the residue was dissolved in 70 ml benzene, the solution was washed with water, 1M-NaOH, and water, dried, and evaporated; 9·6 g (73%) of crude 1-benzyl-4-(formamido)piperidine. It did crystalline neither in the form of the base, nor as the oxalate. The crude intermediate (6·7 g) was disolved in 15 ml ethanol, 14 g KOH were added and the mixture was stirred and refluxed for 4 h. After cooling the mixture was diluted with 50 ml water and extracted with ether. Processing of the extract gave 5·7 g (97%) of crude 4-amino-1-benzylpiperidine which was distilled, b.p. 93–95°C/40 Pa. Ref.[17], b.p. 113–116°C/80 Pa (different method).

Dihydrochloride monohydrate, m.p. 265–267°C (ethanol). Ref.[16], m.p. 273–274°C.

Sulfate monohydrate, m.p. 257–259°C with decomposition (aqueous ethanol). Mass spectrum: 190 (M^+, $C_{12}H_{18}N_2$, 3·5), 173 ($C_{12}H_{15}N$, 21), 146 ($C_{10}H_{12}N$, 6), 118 (C_8H_8N, 7), 91 (C_7H_7,

100). For $C_{12}H_{20}N_2O_4S + H_2O$ (306·4) calculated: 47·04% C, 7·24% H, 9·15% N, 10·47% S; found: 47·06% C, 7·25% H, 9·07% N, 10·57% S.

N-(1-Benzyl-4-piperidinyl)-2-methoxy-5-nitrobenzamide (*VIc*) (Method *A*)

A solution of 3·5 g 2-methoxy-5-nitrobenzoyl chloride[14] in 15 ml chloroform was stirred and treated at 45—50°C over 1 h with a solution of 2·9 g 4-amino-1-benzylpiperidine in 12 ml chloroform, added dropwise. The mixture was refluxed for 1·5 h and evaporated in vacuo. The residue was dissolved in 50 ml benzene and the solution was shaken with 40 ml 5M-HCl. The precipitated hydrochloride was filtered, combined with the acid aqueous layer of the filtrate, the suspension was made alkaline with 250 ml 2M-NaOH and the base was extracted with benzene. Processing of the extract gave 5·6 g (theoretical) of crude crystalline *VIc*, m.p. 125—135°C. It was purified by crystallization from benzene; m.p. 131—134°C. Analysis and spectra are included in Tables I and II.

Hydrochloride monohydrate, m.p. 145·5—148·5°C (ethanol–ether). For analysis, cf. Table I.

N-(1-Benzyl-4-piperidinyl)-5-amino-2-methoxybenzamide (*VIIc*) (Method *B*)

A stirred solution of 4·5 g *VIc* in 70 ml ethanol was treated with 1·3 ml 99% $N_2H_4.H_2O$ and then slowly with 0·4 g Raney Ni. The mixture was stirred for 1·5 h at 60°C and after the addition of 1 g active carbon refluxed for 20 min. After cooling the mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was dissolved in 50 ml benzene, the solution was washed with water, dried, and evaporated; 3·1 g (76%) of *VIIc*, m.p. 122—128°C. Analytical sample, m.p. 131—133°C (benzene–cyclohexane).

Dihydrochloride sesquihydrate, m.p. 183—185°C (ethanol–acetone). Analyses and spectra are included in Tables I and II.

N-(1-Ethyl-3-piperidinyl)-2-methoxy-5-(N-(4-toluenesulfonyl)-amino)benzamide (*VIIIb*)

A) A stirred solution of 2·8 g *VIIb* in 5 ml pyridine was treated over 15 min at 5—15°C under stirring with 2·3 g 4-toluenesulfonyl chloride (freshly purified). The mixture was stirred for 1·5 h at room temperature, was allowed to stand overnight, and heated for 15 min to 60°C. After cooling the mixture was diluted with 50 ml water and extracted with 50 ml chloroform. The extract was washed with 1M-NaOH and water, was dried, and evaporated. The residue was crystallized from a mixture of cyclohexane and light petroleum; 1·8 g (42%) of *VIIIb*, m.p. 165—168°C (benzene–light petroleum). UV spectrum: 301 (3·47). IR spectrum: 882, 902 (2 adjacent and solitary Ar–H); 1 032, 1 265 ($ArOCH_3$); 1 170, 1 330 (SO_2NH); 1 480, 1 498, 1 587, 1 608, 3 060 (Ar); 1 540, 1 640 (ArCONHR); 2 810, 2 870 ($ArOCH_3$, CH_2–N); 3 140, 3 345 (NH). ^{1}H NMR spectrum: 1·01 t, 3 H (CH_3 of ethyl, J = 7·0); 2·20 s, 3 H ($ArCH_3$); 2·30 q, 2 H (NCH_2 of N–ethyl, J = 7·0); 1·30—3·00 m, 8 H ($CH_2NCH_2CH_2CH_2$ of piperidine); 3·88 s, 3 H (OCH_3); 4·48 bm, 1 H (H-3 of piperidinyl); 6·83 d, 1 H (H-3, J = 8·0); 7·00 d, 2 H (H-3 and H-5 of tosyl, J = 8·0); 7·55 dd, 1 H (H-4, J = 3·0, 8·0); 7·58 d, 2 H (H-2 and H-6 of tosyl, J = 8·0); 8·00 d, 1 H (H-6, J = 3·0); 8·60 flat band, 1 H (SO_2NH); 8·75 bd, 1 H (CONH, J = 8·0). For $C_{22}H_{29}N_3O_4S$ (431·5) calculated: 61·23% C, 6·77% H, 9·74% N, 7·43% S; found: 61·09% C, 7·03% H, 9·61% N, 7·48% S.

B) A stirred mixture of 6·0 g *VIIb*, 30 ml dichloromethane, and 3·3 g $NaHCO_3$ was treated dropwise with a solution of 4·6 g 4-toluensulfonyl chloride in 30 ml dichloromethane. The mixture was stirred for 3 h and allowed to stand overnight. After dilution with 30 ml dichloromethane the mixture was washed with 5% $NaHCO_3$ and water, dried, and evaporated in vacuo. The residue

was dissolved in 120 ml benzene and the solution was filtered with 1·5 g active carbon through a layer of 5 g Al_2O_3. The filtrate was evaporated to the volume of 50 ml and crystallization was induced by addition of light petroleum. After standing for 60 h at room temperature the product was filtered, washed with light petroleum, and dried in vacuo; 9·0 g (94%) of *VIIIb*, m.p. 163—169°C. The product was identical with that obtained under *A*.

N-(1-Benzyl-4-piperidinyl)-2-methoxy-5-(N-(4-toluenesulfonyl)amino)benzamide (*VIIIc*)

A stirred mixture of 3·4 g *VIIc*, 18 ml dichloromethane and 2·5 g $NaHCO_3$ was treated dropwise over 25 min with a solution of 1·9 g 4-toluenesulfonyl chloride in 10 ml dichloromethane and the mixture was stirred for 3 h at room temperature. Similar processing like in the preparation of *VIIIb* under *B* gave the crude product which was crystallized from a mixture of 25 ml toluene and 10 ml hexane; 4·7 g (96%) of *VIIIc*, m.p. 173—175°C (toluene). UV spectrum: 304 (4·10). IR spectrum: 699, 745, 809, 813, 899 (5 and 2 adjacent and solitary Ar–H); 1 161, 1 333 (SO_2NH); 1 290 ($ArOCH_3$); 1 482, 1 494, 1 581, 1 602, 3 030, 3 055, 3 085 (Ar); 1 548, 1 635 (ArCONH). ^{1}H NMR spectrum: 1·30—3·00 m, 8 H (4 × CH_2 of piperidine); 2·30 s, 3 H ($ArCH_3$); 3·50 s, 2 H ($ArCH_2N$); 3·90 s, 3 H (OCH_3); 4·30 bm, 1 H (H-4 of piperidinyl); 6·88 d, 1 H (H-3, J = 9·0); 7·05 d, 2 H (H-3 and H-5 of tosyl, J = 9·0); 7·25 s, 5 H (C_6H_5); 7·60 d, 2 H (H-2 and H-6 of tosyl, J = 9·0); 7·65 dd, 1 H (H-4, J = 9·0; 3·0); 8·00 d, 1 H (H-6, J = 3·0); 8·05 bd, 1 H (CONH); 8·60 flat band, 1 H (SO_2NH). For $C_{27}H_{31}N_3O_4S$ (493·6) calculated: 65·69% C, 6·33% H, 8·51% N, 6·50% S; found: 65·77% C, 6·50% H, 8·29% N, 6·71% S.

N-(1-Ethyl-3-piperidinyl)-2-methoxy-5-(N,N-bis(4-toluenesulfonyl)amino)benzamide (*IXb*)

Emulsion obtained by vigorous stirring of 3·0 g *VIIb*, 15 ml dichloromethane, and 0·5 g NaOH in 6 ml water was treated over 30 min with a solution of 2·1 g 4-toluenesulfonyl chloride in 15 ml dichloromethane. The mixture was stirred for 1 h at room temperature and refluxed for 30 min. A solution of 0·5 g NaOH in 6 ml water was added followed by a solution of 2·1 g 4-toluenesulfonyl chloride in 15 ml dichloromethane, added dropwise over 20 min. After stirring for 30 min at 35°C the addition of 0·5 g NaOH in 6 ml water and 2·1 g 4-toluenesulfonyl chloride in 15 ml dichloromethane was repeated and the mixture was stirred and refluxed for 3 h. After cooling the mixture was washed with 1M-NaOH and water, dried, and evaporated. The residue was dissolved in 40 ml benzene, the solution was filtered with active carbon and the filtrate was induced to crystallize by addition of 60 ml light petroleum; 4·2 g (66%) of *IXb*, m.p. 160—163°C (benzene–light petroleum). UV spectrum: 235 (4·63), 275 (3·54), 280 (3·37). IR spectrum: 810, 885 (2 adjacent and solitary Ar–H); 1 172, 1 382 (SO_2N); 1 279, 2 800 ($ArOCH_3$); 1 525, 1 650 (ArCONHR); 3 365, 3 380 (NH). ^{1}H NMR spectrum: 1·03 t, 3 H (CH_3 of ethyl, J = 7·0); 1·60 bm, 4 H (2 × H-4 and 2 × H-5 of piperidine); 2·31, q, 2 H (NCH_2 of N-ethyl, J = 7·0), 2·40 s, 6 H (2 × $ArCH_3$); 2·40 bm, 4 H (CH_2NCH_2 of piperidine); 3·90 s, 3 H (OCH_3); 4·20 bm, 1 H (H-3 of piperidinyl); 6·84 d, 1 H (H-3, J = 8·0); 7·05 dd, 1 H (H-4, J = 3·0, 8·0); 7·25 d, 4 H (H-3, H-5, H-3′, and H-5′ of two tosyl groups, J = 8·0); 7·75 d, 4 H (H-2, H-6, H-2′, and H-6′ of two tosyl groups, J = 8·0); 7·88 d, 1 H (H-6, J = 3·0); 8·24 bd, 1 H (CONH, J = 8·0). For $C_{29}H_{35}N_3O_6S_2$ (585·7) calculated: 59·46% C, 6·02% H, 7·17% N, 10·95% S; found: 59·22% C, 6·17% H, 7·03% N, 11·01% S.

N-(1-Benzyl-4-piperidinyl)-2-methoxy-5-(N,N-bis(4-toluenesulfonyl)amino)benzamide (*IXc*)

The compound was prepared from *VIIc* similarly like the preceding product, m.p. 181—185°C (benzene–hexane). Mass spectrum (EI): 647 (M^+, $C_{34}H_{37}N_3O_6S_2$, 0·25), 278 (0·5), 246 (3),

139 (7), 123 (6), 91 (100). UV spectrum: 236 (4·56), 276 (3·51), 290 (3·37). IR spectrum: 703, 750, 815, 878 (5 and 2 adjacent and solitary Ar–H); 1 082, 1 280 ($ArOCH_3$); 1 165, 1 380 (SO_2N); 1 485, 1 595, 3 030, 3 055, 3 070 (Ar); 1 514, 1 644 (ArCONHR); 2 760, 2 800 (CH_2–N); 3 380 (NH). For $C_{34}H_{37}N_3O_6S_2$ (647·8) calculated: 63·03% C, 5·76% H, 6·49% N, 9·90% S; found: 63·13% C, 6·04% H, 6·69% N, 9·63% S.

N-(1-Ethyl-3-piperidinyl)-2-methoxy-5-
-(N-methyl-N-(4-toluenesulfonyl)amino)benzamide (*Xb*)

A vigorously stirred mixture of 7·6 g *VIIIb*, 40 ml dichloromethane, 3·5 g KOH in 24 ml water and 0·8 g tetrabutylammonium hydrogen sulfate was treated with a solution of 2·62 g dimethyl sulfate in 20 ml dichloromethane, added dropwise over 40 min. The mixture was stirred for 1 h at room temperature, the organic layer was separated, washed with 10% Na_2CO_3 and water, dried, and evaporated. The residue was crystallized from a mixture of 3 ml benzene and 20 ml hexane; 6·0 g (67%) of *Xb*, m.p. 94–98°C. Analytical sample, m.p. 99–101°C (benzene–cyclohexane–hexane). Mass spectrum, CI: 446 ($(M + 1)^+$, $C_{23}H_{31}N_3O_4S + H$); EI: 335 (0·3), 318 (0·6), 111 (100), 97 (82), 91 (28). UV spectrum: infl. 225 (4·45), 296 (3·43). IR spectrum: 817, 839, 869 (2 adjacent and solitary Ar–H); 1 024, 1 229, 2 820 ($ArOCH_3$); 1 160, 1 177, 1 351 (SO_2N); 1 490, 1 580, 1 602, (Ar); 1 527, 1 645 (ArCONHR); 2 780 (CH_2–N); 3 370 (NH). ^{1}H NMR spectrum: 1·10 t, 3 H (CH_3 of ethyl, J = 7·0); 1·65 bs, 4 H (2 × H-4 and 2 × H-5 of piperidine); 2·41 s, 3 H ($ArCH_3$); 2·45 bm, 6 H (NCH_2 of N-ethyl and CH_2NCH_2 of piperidine); 3·18 s, 3 H (NCH_3); 4·00 s, 3 H (OCH_3); 4·20 bm, 1 H (H-3 of piperidinyl); 6·98 d, 1 H (H-3, J = 8·5); 7·25 d, 2 H (H-3 and H-5 of tosyl, J = 8·5); 7·38 d, 2 H (H-2 and H-6 of tosyl, J = 8·5); 7·50 dd, 1 H (H-4, J = 8·5; 2·5); 7·68 d, 1 H (H-6, J = 2·5); 8·35 bd, 1 H (CONH, J = 8·0). For $C_{23}H_{31}N_3O_4S$ (445·6) calculated: 61·99% C, 7·01% H, 9·43% N, 7·20% S; found: 61·73% C, 7·14% H, 9·56% N, 7·32% S.

Hydrogen oxalate, m.p. 189–191·5°C (95% ethanol). For $C_{25}H_{33}N_3O_8S$ (535·5) calculated: 56·06% C, 6·21% H, 7·85% N, 5·99% S; found: 56·08% C, 6·35% H, 7·64% N, 6·26% S.

N-(1-Benzyl-4-piperidinyl)-2-methoxy-5-
-(N-methyl-N-(4-toluenesulfonyl)amino)benzamide (*Xc*)

A vigorously stirred mixture of a solution of 3·6 g *VIIIc* in 20 ml dichloromethane with a solution of 1·4 g KOH in 10 ml water and 0·3 g tetrabutylammonium hydrogen sulfate was treated with a solution of 1·01 g dimethyl sulfate in 13 ml dichloromethane, added dropwise over 10 min. The mixture was stirred for 1 h at room temperature, after dilution with 25 ml dichloromethane the organic layer was separated, washed with 10% $NaHCO_3$ and water, dried, and evaporated. The residue was crystallized from a mixture of benzene, cyclohexane and hexane; 3·0 g (77%) of 3 : 1 solvate of *Xc* with benzene, m.p. 62–64°C. Mass spectrum: 507 (M^+, $C_{28}H_{33}N_3O_4S$, 0·5) 376 (1), 335 (3), 318 (3), 173 (15), 91 (100), 82 (30); the presence of benzene was proven. UV spectrum: 295 (3·39). IR spectrum: 709, 740, 814, 832, 878 (5 and 2 adjacent and solitary Ar–H); 1 154, 1 173, 1 340, 1 348 (SO_2N); 1 237 ($ArOCH_3$); 1 488, 1 599 (Ar); 1 522, 1 645 (ArCONHR); 2 760 (CH_2–N); 3 375 (NH). ^{1}H NMR spectrum: 1·40–3·00 m, 8 H (4 × CH_2 of piperidine); 2·40 s, 3 H ($ArCH_3$); 3·15 s, 3 H (NCH_3); 3·53 s, 2 H ($ArCH_2N$); 3·98 s, 3 H (OCH_3); 4·05 bm, 1 H (H-4 of piperidinyl); 6·95 d, 1 H (H-3, J = 9·0); 7·30 m, 12 H (C_6H_5, C_6H_4 of tosyl, H-4 and 1/3 C_6H_6); 7·70 d, 1 H (H-6, J = 2·0); 7·80 bd, 1 H (CONH). For $C_{28}H_{33}N_3O_4S + 1/3\ C_6H_6$ (533·7) calculated: 67·51% C, 6·61% H, 7·87% N, 6·01% S; found: 67·75% C, 6·60% H, 7·79% N, 6·28% S.

N-(1-Ethyl-3-piperidinyl)-2-methoxy-5-(methylamino)benzamide (*XIb*)

A stirred and cooled solution of 4·45 g *Xb* in 100 ml ether was treated dropwise with 14 ml 90% H_2SO_4. Ether was slowly distilled off and the mixture was heated over 30 min from 40 to 75°C. It was stirred for 2·5 h at this temperature, after cooling it was diluted with 50 ml toluene and under cooling (ice and water) it was made alkaline with 40 ml NH_4OH. The separated organic layer was washed with water, dried, and evaporated in vacuo; 2·4 g (83%) of crystalline, almost homogeneous *XIb*, m.p. 124—127°C. Analytical sample, m.p. 125—127°C (benzene–hexane). UV spectrum: infl. 250 (4·04), 336 (3·49). IR spectrum: 811, 899 (2 adjacent and solitary Ar–H); 1 021, 1 178, 1 220, 2 813 ($ArOCH_3$); 1 498, 1 589, 1 611, 3 008 (Ar); 1 520, 1 646 (ArCONHR); 2 770, 2 795 (CH_2–N); 3 340, 3 360 (NH). ^{1}H NMR spectrum: 1·05 t, 3 H (CH_3 of ethyl, J = 7·0); 1·65 bs, 4 H (2 × H-4 and 2 × H-5 of piperidinyl); 2·40 m, 6 H (CH_2N of ethylamino and CH_2NCH_2 of piperidine); 2·80 s, 3 H (CH_3N); 3·69 bs, 1 H (ArNH); 3·88 s, 3 H (OCH_3); 4·25 bm, 1 H (H-3 of piperidinyl); 6·65 dd, 1 H (H-4, J = 8·5; 2·5); 6·88 d, 1 H (H-3, J = 8·5); 7·50 d, 1 H (H-6, J = 2·5); 8·50 bd, 1 H (CONH, J = 8·0). For $C_{16}H_{25}N_3O_2$ (291·4) calculated: 65·95% C, 8·65% H, 14·42% N; found: 65·71% C, 8·81% H, 14·27% N.

N-(1-Benzyl-4-piperidinyl)-2-methoxy-5-(methylamino)benzamide (*XIc*)

A stirred solution of 5·0 g *Xc* in 60 ml ether was treated over 7 min with 15·7 ml 90% H_2SO_4. The precipitated sulfate dissolved under refluxing of the mixture. Ether was distilled off and the residue was heated for 1 h to 70—80°C. After cooling the mixture was diluted with 50 ml ether and 20 ml benzene and under cooling it was made strongly alkaline with NH_4OH. The separated organic layer was washed with water, dried, and evaporated. The residue crystallized after trituration with hexane; 2·7 g (77%) of *XIc*, m.p. 100—104°C. Analytical sample, m.p. 105·5—107·5°C (benzene–hexane). UV spectrum: infl. 250 (3·98), 343 (3·42). IR spectrum: 700, 740, 805, 890 (5 and 2 adjacent and solitary Ar–H); 1 220, 2 805 ($ArOCH_3$); 1 490, 1 580, 1 610, 3 000, 3 025, 3 070 (Ar); 1 525, 1 649 (ArCONHR); 2 755 (CH_2–N); 3 330, 3 370 (NH). ^{1}H NMR spectrum: 1·40—3·00 m, (4 × CH_2 of piperidine); 2·80 s, 3 H (NCH_3); 3·50 s, 2 H ($ArCH_2N$); 3·60 bs, 1 H (ArNH); 3·80 s, 3 H (OCH_3); 4·00 m, 1 H (H-4 of piperidinyl); 6·62 dd, 1 H (H-4, J = 9·0, 2·5); 6·82 d, 1 H (H-3, J = 9·0); 7·25 s, 5 H (C_6H_5); 7·48 d, 1 H (H-6, J = 2·5); 8·00 bd, 1 H (CONH). For $C_{21}H_{27}N_3O_2$ (353·5) calculated: 71·36% C, 7·70% H, 11·89% N; found: 71·34% C, 7·60% H, 11·97% N.

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