POTENTIAL NEUROLEPTICS OF THE ORTHOPRAMIDE SERIES; SYNTHESIS OF N-(3-(TERT.AMINO)PROPYL)-5-SULFAMOYL-2--METHOXYBENZAMIDES

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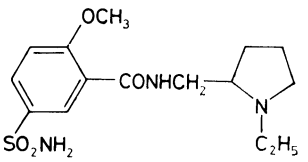
Received June 8, 1989
Accepted June 21, 1989

Heating ethyl 5-sulfamoyl-2-methoxybenzoate with a series of twelve 3-(tert.amino)propylamines (*IIIa*—*IIIl*) afforded the title compounds *IIa*—*IIl* which were transformed to salts and subjected to pharmacological screening as potential neuroleptics of the sulpiride series. Only compounds *IId* (hydrogen oxalate, VÚFB-15 453) and *IIg* (methanesulfonate, VÚFB-15 397) showed indications of the desired psychotropic activity.

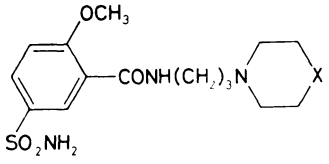
Some time ago, several N-substituted 5-sulfamoyl-2-methoxybenzamides were described[1] as analogues of the atypical neuroleptic agent "sulpiride" (*I*) (refs[2,3]). Two further analogues of a similar type were described earlier in patents[4]. The present paper represents a continuation of our earlier investigation[1] and deals with the title compounds *IIa*—*IIl*.



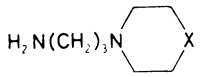
I

Compounds *IIa*—*IIl* were obtained by heating equimolecular quantities of ethyl 5-sulfamoyl-2-methoxybenzoate[1,5] and the diamines *IIIa*—*IIIl* to 100°C (general method). Crystallization of the solidified melts from ethanol or methanol afforded the crystalline bases *IIa*—*IIl* which were characterized by spectra. They were transformed to crystalline salts (hydrochlorides, methanesulfonates etc.) which were used for pharmacological testing. Out of the starting diamines *III* the following were described in the literature and have now been prepared by the methods described: *IIIa* (ref.[6]), *IIIb* (ref.[7]), *IIIc* (ref.[8]), *IIId* (ref.[9]), *IIIe* (ref.[9]), and *IIIf* (ref.[9]). Diamine *IIIg* was obtained from the nitrile *IVg* (ref.[10]) by reduction with lithium aluminium hydride in ether (it was prepared earlier[11] by hydrogenation of *IVg* on

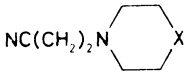
Raney nickel). Synthesis of *IIIh* started from 1-(4-ethylphenyl)piperazine (cf. also ref.[12]) which was obtained by heating a mixture of hydrochlorides of 4-ethylaniline and diethanolamine to 200–220°C (method[13]). Addition reaction of 1-(4-ethylphenyl)piperazine to acrylonitrile (method[10]) gave *IVh* which was reduced with lithium aluminium hydride to *IIIh*; the oily base was characterized by the ^{1}H NMR spectrum and was transformed to crystalline monopicrate and trihydrochloride, Diamine *IIIi* was prepared by similar reduction of *IVi* (ref.[10]); synthesis if *IIIi* by a different method was mentioned in a patent[14]. 1-(2-Methoxyphenyl)piperazine was prepared by reaction of 2-anisidine with bis(2-chloroethyl)amine hydrochloride[15,16] in refluxing 1-butanol in the presence of potassium carbonate (a similar synthesis from bis(2-bromoethyl)amine hydrobromide in methanol was described[17]). The following addition to acrylonitrile afforded *IVj* which was earlier prepared by alkylation with 3-chloropropionitrile[18]. Reduction of *IVj* with lithium aluminium hydride gave *IIIj* which had been earlier prepared by different methods[14,18]. 1-(3-Methoxyphenyl)piperazine was prepared from 3-anisidine similarly like the 2-methoxy analogue (cf. also ref.[19]) and was added to acrylonitrile to give *IVk* (cf. ref.[18]). Similar reduction gave *IIIk* (cf. ref.[18]), characterized as the trihydrochloride. The synthesis of *IIIl* (cf. ref.[11]) proceeded similarly via 1-(4-methoxyphenyl)piperazine (cf. ref.[20]) and via *IVl* (cf. ref.[11]). Our synthesis of the four N-monosubstituted piperazines, further *IVh*, *IVj*, *IVk*, *IVl*, and *IIIg*–*IIIl* is being described in the Experimental. The final compounds *II*, prepared by the mentioned general method, are assembled in Table I with the usual experimental data. The preparation of *IIe* is described in the Experimental as an example. The spectra of compounds *II* are assembled in Table II.



II



III



IV

In formulae *II*–*IV*: *a*, X = —; *b*, X = CH_2; *c*, X = O; *d*, X = NCH_3; *e*, X = NC_6H_5; *f*, X = N(2-$CH_3C_6H_4$); *g*, X = N(4-$CH_3C_6H_4$); *h*, X = N(4-$C_2H_5C_6H_4$); *i*, X = N(3-ClC_6H_4); *j*, X = N(2-$CH_3OC_6H_4$); *k*, X = N(3-$CH_3OC_6H_4$); *l*, X = N(4-$CH_3OC_6H_4$)

TABLE I

N-(3-(Tert.amino)propyl)-5-sulfanoyl-2-methoxybenzamides *II*

Compound[a] Yield, %	M.p., °C Solvent	Formula M.w.	Calculated/Found				
			% C	% H	% Cl	% N	% S
IIa	156—159	$C_{15}H_{23}N_3O_4S$	52·76	6·79	—	12·31	9·39
34	ethanol–toluene	341·4	52·52	7·09	—	12·09	9·19
IIa-HCl	241—244	$C_{15}H_{24}ClN_3O_4S$	47·67	6·40	9·38	11·12	8·49
	ethanol	377·9	47·33	6·39	9·24	11·21	8·69
IIb	173—175	$C_{16}H_{25}N_3O_4S$	54·06	7·09	—	11·82	9·02
60	ethanol	355·5	53·93	7·15	—	11·79	8·88
IIb-HCl	215·5—216·5	$C_{16}H_{26}ClN_3O_4S$	49·03	6·69	9·05	10·72	8·18
	ethanol–acetone	391·9	48·99	6·73	9·07	10·56	8·19
IIc	153—157	$C_{15}H_{23}N_3O_5S$	50·40	6·49	—	11·76	8·97
48	ethanol	357·4	50·55	6·50	—	11·51	8·92
IIc-HFU	194—195·5	$C_{15}H_{23}N_3O_5S$	49·14	6·07	—	10·11	7·72
	ethanol	+ 0·5 $C_4H_4O_4$	48·83	6·11	—	10·09	8·12
		415·5					
IId-HH	168—170	$C_{16}H_{26}N_4O_4S$	50·64	7·17	—	14·76	8·45
89[b]	ethanol–acetone	+ 0·5 H_2O	50·54	7·19	—	14·42	8·34
		379·5					
IId-BHO-HH	190—191	$C_{20}H_{30}N_4O_{12}S$	42·93	5·58	—	10·01	5·73
	dimethylformamide–-ethanol–acetone	+ 0·5 H_2O	43·07	5·71	—	10·29	5·64
		559·6					
IIe[c]	220—221	$C_{21}H_{28}N_4O_4S$	58·31	6·52	—	12·95	7·41
63	dimethylformamide–-ethanol	432·5	58·41	6·69	—	12·95	7·59
IIe-MS	221—223	$C_{22}H_{32}N_4O_7S_2$	49·98	6·10	—	10·60	12·13
	ethanol–ether	528·6	50·06	6·20	—	10·66	12·04
IIf	194—196	$C_{22}H_{30}N_4O_4S$	59·17	6·77	—	12·55	7·18
32	ethanol–toluene	446·6	59·50	6·79	—	12·53	7·36
IIf-HCl	229—231	$C_{22}H_{31}ClN_4O_4S$	54·70	6·47	7·34	11·60	6·64
	ethanol	483·0	54·67	6·52	7·60	11·66	6·80
IIg	203—205	$C_{22}H_{30}N_4O_4S$	59·17	6·77	—	12·55	7·18
51	ethanol–toluene	446·6	59·07	6·79	—	12·71	7·50
IIg-MS	221—223	$C_{23}H_{34}N_4O_7S_2$	50·90	6·31	—	10·33	11·82
	ethanol	542·7	50·50	6·35	—	10·59	11·89
IIh	194	$C_{23}H_{32}N_4O_4S$	59·97	7·00	—	12·16	6·96
50	dimethylformamide–-ethanol	460·6	59·83	7·02	—	12·10	7·17

TABLE I
(*Continued*)

Compound[a] Yield, %	M.p., °C Solvent	Formula M.w.	Calculated/Found				
			% C	% H	% Cl	% N	% S
IIh-MS	136–138	$C_{24}H_{36}N_4O_7S_2$	51·78	6·52	—	10·07	11·52
	aqueous ethanol	556·6	51·53	6·66	—	9·64	11·26
IIi	219–220	$C_{21}H_{27}ClN_4O_4S$	54·01	5·83	7·59	12·00	6·87
50	dimethylformamide–ethanol	467·0	54·13	5·87	7·79	11·81	6·77
IIi-MS	212–214	$C_{22}H_{31}ClN_4O_7S_2$	46·92	5·55	6·30	9·95	11·39
	ethanol–ether	563·1	46·58	5·61	6·54	9·65	11·39
IIj	222–224	$C_{22}H_{30}N_4O_5S$	57·12	6·54	—	12·11	6·93
52	dimethylformamide–methanol	462·6	56·89	6·57	—	12·18	7·15
IIj-MS	185–187	$C_{23}H_{34}N_4O_8S_2$	49·44	6·13	—	10·03	11·48
	ethanol	558·7	49·72	6·25	—	10·10	11·28
IIk	180–181·5[d]	$C_{22}H_{30}N_4O_5S$	57·12	6·54	—	12·11	6·93
46	ethanol	462·6	57·03	6·67	—	12·19	7·03
IIk-MS-HH	174–176	$C_{23}H_{34}N_4O_8S_2$	48·66	6·21	—	9·87	11·30
	95% ethanol	+ 0·5 H_2O	48·33	6·19	—	9·64	11·16
		567·7					
IIl	217·5–219	$C_{22}H_{30}N_4O_5S$	57·12	6·54	—	12·11	6·93
25	dimethylformamide–methanol	462·6	57·29	6·60	—	12·33	7·19
IIl-MS	144–146	$C_{23}H_{34}N_4O_8S_2$	49·44	6·13	—	10·03	11·48
	95% ethanol	558·7	49·68	6·43	—	9·82	11·26

[a] BHO bis(hydrogen oxalate), HFU hemifumarate, HH hemihydrate, MS methanesulfonate; [b] crude product; [c] see Experimental; [d] crystallized only after chromatography on neutral Al_2O_3 (activity II).

Compounds *IIa*–*IIl* (in the form of salts described in Table I) were subjected to a preliminary pharmacological screening. They were administered orally (unless otherwise stated) and the doses given were calculated per bases. Acute toxicity in mice, approximate values of LD_{50} in mg/kg: *IIb* 30 i.v.; *IId*, 150 i.v.; *IIe*, 125 i.v.; *IIg*, 150 i.v.; *IIi*, >2 500. In the rotarod test in mice doses of 500 mg/kg were administered and per cent of animals responding by ataxia are given: *IId*, 20; *IIg*, 70; *IIh*, 40; *IIi*, 30; *IIj*, 30; the remaining compounds were inactive (for sulpiride (*I*), ED_{50} c. 500 mg/kg). The same doses were administered in the test of inhibition of

the climbing behaviour of mice which was induced by apomorphine (2 mg/kg s.c.): only *IId* and *IIg* showed activity comparable to that of sulpiride (PD_{50} 340 mg/kg (ref.[3])), the other compounds were inactive. For estimating the influence on the adrenaline toxicity in mice, the doses of 250 mg/kg were administered (per cent of protected animals given): *IIf*, 100; *IIg*, 40; *IIj*, 50; the other compounds were inactive. The same doses were used for establishing the influence on the lethal action of noradrenaline in rats (per cent of protected animals given): *IIe*, 70–100; *IIf*, 70–100; *IIg*, 70–100; *IIj*, 80; *III*, 30; the other compounds were inactive. In conclusion, only compounds *IId* (hydrogen oxalate, VÚFB-15 453) and *IIg* (methanesulfonate, VÚFB-15 397) showed indications of psychotropic activity of the neuroleptic type.

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} (log ε)) were 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, and ^1H NMR spectra (in CD_3SOCD_3 unless otherwise stated, δ in ppm, J in Hz) with a Tesla BS 487C (80 MHz) spectrometer. 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 $MgSO_4$, Na_2SO_4 or K_2CO_3 and evaporated under reduced pressure on a rotary evaporator.

1-(4-Ethylphenyl)piperazine

A mixture of 85 g 4-ethylaniline, 74 g diethanolamine and 140 g hydrochloric acid was heated and water was distilled off. The residue was then heated for 4 h to 200°C, for 1 h to 200–220°C and for 2·5 h to 235°C (bath temperature). The melt was cooled to 60°C and was slowly treated under external cooling with a solution of 65 g NaOH in 100 ml water. The separated product was extracted with benzene, the extract was washed with 5M-NaOH and water, and processed by distillation; 63·8 g (48%), b.p. 160–163°C/1·5 kPa. Ref.[12], b.p. 130–134·5°C/0·17 kPa (different synthetic procedure).

1-(2-Methoxyphenyl)piperazine

A mixture of 61·6 g 2-anisidine, 300 ml 1-butanol, 98·3 g bis-(2-chloroethyl)amine hydrochloride[15,16], and 34·6 g K_2CO_3 was stirred and refluxed for 20 h. Further 34·6 g K_2CO_3 were added, 40 ml 1-butanol were distilled off and the residue was heated for 5 h to 130°C (bath temperature). Most of the 1-butanol was evaporated in vacuo and the cooled residue was treated with 200 ml 2·5M-NaOH. The oily product was extracted with ether, the extract was processed and the residue was distilled; 56·5 g (59%), b.p. 124°C/0·1 kPa. ^1H NMR spectrum ($CDCl_3$): 1·65 s, 1 H (NH); 3·04 s, 8 H (4 × CH_2N); 3·85 s, 3 H (OCH_3); 6·90 s, 4 H (ArH). For $C_{11}H_{16}N_2O$ (192·3) calculated: 68·71% C, 8·39% H, 14·57% N; found: 68·44% C, 8·59% H, 14·58% N. Ref.[17], b.p. 130–133°C/13 Pa (different synthetic procedure).

Dihydrochloride, m.p. 212–215°C (ethanol). For $C_{11}H_{18}Cl_2N_2O$ (265·2) calculated: 26·74% Cl, 10·57% N; found: 26·50% Cl, 10·93% N.

TABLE II

UV, IR and ^{1}H NMR spectra of compounds *IIa*–*IIl*

Compound	Spectrum	Data
IIa	UV	264 (4·00), 326 (3·62)
	IR	830, 860 (2 adjacent and solitary Ar–H); 1 140, 1 152, 1 310 (SO_2NH_2); 1 250 ($ArOCH_3$); 1 550, 1 633 (ArCONHR); 3 290, 3 580 (NH_2)
IIb	UV	231 (4·17), 288 (3·34)
	IR	840, 885 (2 adjacent and solitary Ar–H); 1 185, 1 340 (SO_2NH_2); 1 240, 1 290 ($ArOCH_3$); 1 484, 1 590 (Ar); 1 550, 1 618 (ArCONHR); 3 100, 3 280, 3 370 (NH_2)
	^{1}H NMR	1·50 bm, 6 H (3 × CH_2 in positions 3,4,5 of piperidine); 1·70 m, 2 H (CH_2 in position 2 of propyl); 2·30 bm, 6 H (3 × CH_2 around the piperidine N); 3·30 m, 2 H (the remaining CH_2N); 3·94 s, 3 H (OCH_3); 7·20 d, 1 H (H-3 of benzoyl, J = 8·0); 7·25 bs, 2 H (SO_2NH_2); 7·82 dd, 1 H (H-4 of benzoyl, J = 8·0; 2·0); 8·10 d, 1 H (H-6 of benzoyl, J = 2·0); 8·18 bt, 1 H (CONH)
IIc	UV	233 (4·12), 289 (3·33)
	IR	840, 870 (2 adjacent and solitary Ar–H); 1 111 (C–O–C); 1 242 ($ArOCH_3$); 1 170, 1 340 (SO_2NH_2); 1 481, 1 586 (Ar); 1 550, 1 617 (ArCONHR); 3 100, 3 240, 3 370 (NH, NH_2)
	^{1}H NMR	1·70 m, 2 H (CH_2 in position 2 of propyl); 2·45 bm, 6 H (3 × CH_2 around the morpholine N); 3·30 m, 2 H (remaining CH_2N); 3·60 m, 4 H (CH_2OCH_2 of morpholine); 3·94 s, 3 H (OCH_3); 7·20 d, 1 H (H-3 of benzoyl, J = 8·0); 7·25 bs, 2 H (SO_2NH_2); 7·82 dd, 1 H (H-4 of benzoyl, J = 8·0; 2·0); 8·10 d, 1 H (H-6 of benzoyl, J = 2·0); 8·22 bt, 1 H (CONH)
IId-HH[a]	UV	263 (4·03), 322 (3·64)
	IR	840, 880, 900 (2 adjacent and solitary Ar–H); 1 143, 1 310 (SO_2NH_2); 1 240 ($ArOCH_3$); 1 560 (Ar); 1 610, 2 700–3 200 (H_2O); 3 140, 3 315 (NH_2)
IIe	UV	239 (4·38), 287 (3·54)
	IR	688, 752, 805, 827, 863, 880 (5 and 2 adjacent and solitary Ar–H); 1 125, 1 150, 1 170, 1 330 (SO_2NH_2); 1 500, 1 592 (Ar); 1 532, 1 630 (ArCONHR); 3 160, 3 368 (NH_2)
	^{1}H NMR	1·70 bm, 2 H (CH_2 in position 2 of propyl); 2·50 bm, 6 H (3 CH_2 around the piperazine N^1); 3·10 bm, 4 H ($CH_2N^4CH_2$ of piperazine); 3·40 bm, 2 H (remaining CH_2N); 3·90 s, 3 H (OCH_3); 6·60–7·30 m, 6 H (C_6H_5 and H-3 of benzoyl); 7·30 s, 2 H (SO_2NH_2); 7·88 dd, 1 H (H-4 of benzoyl, J = 8·5; 2·0); 8·20 d, 1 H (H-6 of benzoyl, J = 2·0); 8·28 bt, 1 H (CONH, J = 5·0)

IIf	UV	235 (4·28), 284 (3·43)
	IR	761, 849, 890 (4 and 2 adjacent and solitary Ar–H); 1 140, 1 340 (SO_2NH_2); 1 229, 1 241 ($ArOCH_3$); 1 490, 1 591, 3 075 (Ar); 1 535, 1 630 (ArCONHR); 3 380 (NH, NH_2)
	^{1}H NMR	1·75 bm, 2 H (CH_2 in position 2 of propyl); 2·20 s, 3 H ($ArCH_3$); 2·50 bm, 6 H (3 × CH_2 around the piperazine N^1); 2·80 bm, 4 H ($CH_2N^4CH_2$ of piperazine); 3·35 m, 2 H (remaining CH_2N); 3·94 s, 3 H (OCH_3); 7·00 m, 4 H (4 × ArH of tolyl); 7·20 d, 1 H (H-3 of benzoyl, J = 8·0); 7·28 bs, 2 H (SO_2NH_2); 7·84 dd, 1 H (H-4 of benzoyl, J = 8·0; 2·0); 8·15 d, 1 H (H-6 of benzoyl, J = 2·0); 8·22 bt, 1 H (CONH)
IIg	UV	238 (4·41), 287·5 (3·54)
	IR	800, 810, 830, 860 (2 adjacent and solitary Ar–H); 1 168, 1 340 (SO_2NH_2); 1 240 ($ArOCH_3$); 1 480, 1 510, 1 595, 3 030, 3 054, 3 095 (Ar); 3 240, 3 380 (NH_2)
	^{1}H NMR	1·75 m, 2 H (CH_2 in position 2 of propyl); 2·18 s, 3 H ($ArCH_3$); 2·50 bm, 6 H (2 × CH_2 around the piperazine N^1); 3·00 bm, 4 H ($CH_2N^4CH_2$ of piperazine); 3·35 m, 2 H (remaining CH_2N); 3·90 s, 3 H (OCH_3); 6·70 d, 2 H (H-2 and H-6 of tolyl, J = 8·0); 6·97 d, 2 H (H-3 and H-5 of tolyl, J = 8·0); 7·20 d, 1 H (H-3 of benzoyl, J = 8·0); 7·26 bs, 2 H (SO_2NH_2); 7·82 dd, 1 H (H-4 of benzoyl, J = 8·0; 2·0); 8·14 d, 1 H (H-6 of benzoyl, J = 2·0); 8·20 bt, 1 H (CONH)
IIh	UV	238 (4·43), 287·5 (3·55)
	IR	826, 841, 888 (2 adjacent and solitary Ar–H); 1 187, 1 189, 1 340 (SO_2NH_2); 1 241 ($ArOCH_3$); 1 513, 1 590 (Ar); 1 550, 1 620 (ArCONHR); 2 773, 2 810 (CH_2N); 3 115, 3 275, 3 370 (NH_2)
	^{1}H NMR	1·11 t, 3 H (CH_3 of ethyl, J = 7·0); 1·70 bm, 2 H (CH_2 in position 2 of propyl); 2·50 bm, 8 H (3 × CH_2 around the piperazine N^1 and $ArCH_2$); 3·02 bm, 4 H ($CH_2N^4CH_2$ of piperazine); 3·40 m, 2 H (remaining CH_2N); 3·90 s, 3 H (OCH_3); 6·88 d and 7·00 d (ABq), 2 and 2 H (4 × ArH of ethylphenyl, J = 9·0); 7·20 d, 1 H (H-3 of benzoyl, J = 9·0); 7·30 bs, 2 H (SO_2NH_2); 7·88 dd, 1 H (H-4 of benzoyl, J = 9·0; 2·5); 8·18 d, 1 H (H-6 of benzoyl, J = 2·5); 8·28 bt, 1 H (CONH, J = 5·0)
IIi	UV	240 (4·35), 289 (3·63)
	IR	766, 780, 802, 827, 880 (3 and 2 adjacent and solitary Ar–H); 1 125, 1 150, 1 170, 1 320 (SO_2NH_2); 1 250 ($ArOCH_3$); 1 535, 1 630 (CONH); 1 560, 1 590 (Ar); 3 170, 3 368 (NH_2)
	^{1}H NMR	1·70 bm, 2 H (CH_2 in position 2 of propyl); 2·50 m, 6 H (3 × CH_2 around the piperazine N^1); 3·15 bm, 4 H ($CH_2N^4CH_2$ of piperazine); 3·40 bm, 2 H (remaining CH_2N); 3·90 s, 3 H (OCH_3); 6·60—7·30 m, 5 H (4 × ArH of chlorophenyl and H-3 of benzoyl); 7·30 s, 2 H (SO_2NH_2); 7·88 dd, 1 H (H-4 of benzoyl, J = 8·5; 2·0); 8·20 d, 1 H (H-6 of benzoyl, J = 2·0); 8·25 bt, 1 H (CONH, J = 5·0)

TABLE II
(*Continued*)

Compound	Spectrum	Data
IIj	UV	283·5 (saturated solution)
	IR	759, 817, 865 (4 and 2 adjacent and solitary Ar–H); 1 170, 1 339 (SO_2NH_2); 1 244 ($ArOCH_3$); 1 492 (Ar); 1 533, 1 638, 1 695 (ArCONHR); 3 180, 3 393 (NH, NH_2)
	^{1}H NMR	1·70 bm, 2 H (CH_2 in position 2 of propyl); 2·50 bm, 6 H (3 × CH_2 around the piperazine N^1); 2·95 bm, 4 H ($CH_2N^4CH_2$ of piperazine); 3·35 bm, 2 H (remaining CH_2N); 3·68 s and 3·92 s, 3 and 3 H (2 $ArOCH_3$); 6·90 bs, 4 H (4 ArH of *o*-methoxyphenyl); 7·25 d, 1 H (H-3 of benzoyl, J = 9·0); 7·30 bs, 2 H (SO_2NH_2); 7·90 dd, 1 H (H-4 of benzoyl, J = 9·0; 2·5); 8·20 d, 1 H (H-6 of benzoyl, J = 2·5); 8·30 bt, 1 H (CONH)
IIk	UV	infl. 236 (4·35), 287 (3·73)
	IR (KBr)	827, 882 (Ar–H); 1 170, 1 332 (SO_2NH_2); 1 249 ($ArOCH_3$); 1 494, 1 572, 1 592, 1 605 (Ar); 1 535, 1 629 (ArCONHR); 2 815 ($ArOCH_3$); 3 140, 3 370 (NH, NH_2)
	^{1}H NMR	1·71 m, 2 H (CH_2 in position 2 of propyl); 2·50 m, 6 H (3 × CH_2 around the piperazine N^1); 3·10 bm, 4 H ($CH_2N^4CH_2$ of piperazine); 3·39 m, 2 H (remaining CH_2N); 3·69 s and 3·92 s, 3 and 3 H (2 $ArOCH_3$); 6·40 m, 3 H (H-2, H-4 and H-6 of *m*-methoxyphenyl); 7·10 m, 1 H (H-5 of *m*-methoxyphenyl); 7·25 d, 1 H (H-3 of benzoyl, J = 9·0); 7·30 s, 2 H (SO_2NH_2); 7·90 dd, 1 H (H-4 of benzoyl, J = 9·0; 2·5); 8·21 d, 1 H (H-6 of benzoyl, J = 2·5); 8·29 bt, 1 H (CONH)
IIl	UV	238 (4·44), 291 (4·09)
	IR	814, 882 (2 adjacent and solitary Ar–H); 1 010, 1 243 ($ArOCH_3$); 1 159, 1 171, 1 333 (SO_2NH_2); 1 513, 1 594, 3 040, 3 080 (Ar); 1 537, 1 632 (ArCONHR); 3 150, 3 375 (NH)
	^{1}H NMR	1·70 m, 2 H (CH_2 in position 2 of propyl); 2·48 m, 6 H (3 × CH_2 around the piperazine N^1); 3·00 m, 4 H ($CH_2N^4CH_2$ of piperazine); 3·30 m, 2 H (remaining CH_2N); 3·65 s and 3·91 s, 3 and 3 H (2 $ArOCH_3$); 6·80 s, 4 H (4 × ArH of *p*-methoxyphenyl); 7·25 d, 1 H (H-3 of benzoyl, J = 8·5); 7·30 bs, 2 H (SO_2NH_2); 7·87 dd, 1 H (H-4 of benzoyl, J = 8·5; 2·0); 8·15 d, 1 H (H-6 of benzoyl, J = 2·0); 8·21 bt, 1 H (CONH)

[a] HH hemihydrate.

1-(3-Methoxyphenyl)piperazine

A similar reaction of 61·6 g 3-anisidine with 89·3 g bis(2-chloroethyl)amine hydrochloride[15,16] and 34·6 g + 34·6 g K_2CO_3 in 300 ml 1-butanol gave 61·5 g (67%) of the product, b.p. 130°C/67 Pa. ^{1}H NMR spectrum ($CDCl_3$): 1·65 s, 1 H (NH); 3·00 m, 8 H (4 CH_2N); 3·78 s, 3 H (OCH_3); 6·45 m, 3 H (H-2, H-4, H-6); 7·15 m, 1 H (H-5). For $C_{11}H_{16}N_2O$ (192·3) calculated: 68·71% C, 8·39% H, 14·57% N; found: 68·61% C, 8·54% H, 14·73% N. Ref.[19], b.p. 140—145°C/33 Pa.

1-(4-Methoxyphenyl)piperazine

A similar reaction of 37·0 g 4-anisidine with 53·5 g bis(2-chloroethyl)amine hydrochloride[15,16] and 20·8 g + 10·4 g K_2CO_3 in 200 ml 1-butanol gave 34·5 g (60%) of the product, b.p. 118°C/40 Pa, m.p. 82—86°C (cyclohexane–light petroleum). ^{1}H NMR spectrum ($CDCl_3$): 1·90 bs, 1 H (NH); 2·95 s, 8 H (4 CH_2N); 3·70 s, 3 H (OCH_3); 6·80 s, 4 H (ArH).

Monohydrochloride, m.p. 211—212°C (ethanol). UV spectrum: 241 (4·06), 295·5 (3·27). IR spectrum: 825 (2 adjacent Ar–H); 1 190, 1 240 ($ArOCH_3$); 1 510, 1 590, 1 610, 3 065, 3 105 (Ar); 2 500, 2 628, 2 700 (NH_2^+); 3 190 (NH). For $C_{11}H_{17}ClN_2O$ (228·7) calculated: 57·76% C, 7·49% H, 15·50% Cl, 12·25% N; found: 57·78% C, 7·38% H, 15·67% Cl, 12·52% N. Prelog and Blažek[20] described the hydrobromide, obtained by a different synthetic procedure.

3-(4-(4-Ethylphenyl)-1-piperazinyl)propionitrile (*IVh*)

Stirred 1-(4-ethylphenyl)piperazine (47·6 g) was treated at 30°C with 14·9 g acrylonitrile, added dropwise over 15 min. The temperature of the mixture rose spontaneously to 55°C, the mixture was stirred for 2 h and allowed to stand overnight at room temperature. The precipitated *IVh* was filtered; 60·5 g (99%), m.p. 60—61°C (ethanol). UV spectrum: 247·5 (4·12), 286·5 (3·14). IR spectrum: 825, 832 (2 adjacent Ar–H); 1 510, 1 609, 3 025 (Ar); 2243 (RCN); 2 695, 2 740 (CH_2N). ^{1}H NMR spectrum ($CDCl_3$): 1·19 t, 3 H (CH_3, J = 7·0); 2·30—2·80 m, 10 H (CH_2N^1. .CH_2, NCH_2CH_2CN and $ArCH_2$); 3·15 bt, 4 H ($CH_2N^4CH_2$); 6·81 d, 2 H (H-2 and H-6, J = 9·0); 7·10 d, 2 H (H-3 and H-5). For $C_{15}H_{21}N_3$ (243·4) calculated: 74·03% C, 8·70% H, 17·27% N; found: 74·31% C, 8·46% H, 16·98% N.

3-(4-(2-Methoxyphenyl)-1-piperazinyl)propionitrile (*IVj*)

A similar reaction of 38·5 g 1-(2-methoxyphenyl)piperazine and 11·7 g acrylonitrile gave 44·8 g (91%) of *IVj*, m.p. 80·5—81·5°C (benzene–cyclohexane). IR spectrum: 750, 760, 770 (4 adjacent Ar–H); 1 240 ($ArOCH_3$); 1 500, 1 591, 3 050, 3 075 (Ar); 2 245 (RCN); 2 685, 2 735 ($ArOCH_3$, CH_2N). ^{1}H NMR spectrum ($CDCl_3$): 2·65 m, 8 H ($CH_2N^1CH_2$ and NCH_2CH_2CN); 3·10 m, 4 H ($CH_2N^4CH_2$); 3·85 s, 3 H (OCH_3); 6·90 bm, 4 H (ArH). For $C_{14}H_{19}N_3O$ (245·3) calculated: 68·54% C, 7·81% H, 17·13% N; found: 68·29% C, 7·89% H, 17·43% N. Ref.[18], m.p. 86—87°C (different synthetic method).

3-(4-(3-Methoxyphenyl)-1-piperazinyl)propionitrile (*IVk*)

A similar reaction of 53·8 g 1-(3-methoxyphenyl)piperazine and 16·5 g acrylonitrile gave 66·7 g (97%) of *IVk*, m.p. 102—104°C (benzene–cyclohexane). IR spectrum: 697, 774, 834, 860 (3 adjacent and solitary Ar–H); 1 173, 1 200, 1 211 ($ArOCH_3$); 1 490, 1 580, 1 601 (Ar); 2 690, 2 754, 2 788 ($ArOCH_3$ and CH_2–N); 2 240 (RCN). ^{1}H NMR spectrum ($CDCl_3$): 2·60 m, 8 H (CH_2N^1.

.CH_2 and NCH_2CH_2CN); 3·20 m, 4 H ($CH_2N^4CH_2$); 3·79 s, 3 H (OCH_3); 6·40 m, 3 H (H-2, H-4 and H-6); 7·15 m, 1 H (H-5 of methoxyphenyl). Ref.[18], m.p. 103—105°C (different method).

3-(4-(4-Methoxyphenyl)-1-piperazinyl)propionitrile (*IVl*)

A similar reaction of 32·6 g 1-(4-methoxyphenyl)piperazine and 10·1 g acrylonitrile gave 39·4 g (94%) of *IVl*, m.p. 78—79°C (aqueous ethanol). IR spectrum: 833 (2 adjacent Ar–H); 1 224, 1 243, 1 280, 1 298 ($ArOCH_3$); 1 510, 3 010, 3 040, 3 100 (Ar), 2 242 (RCN); 2 705 (CH_2N). ^{1}H NMR spectrum ($CDCl_3$): 2·65 m, 8 H ($CH_2N^1CH_2$ and NCH_2CH_2CN); 3·10 m, 4 H ($CH_2N^4CH_2$); 3·75 s, 3 H (OCH_3); 6·85 s, 4 H (ArH). Ref.[11], m.p. 80—81·5°C.

3-(4-(4-Methylphenyl)-1-piperazinyl)propylamine (*IIIg*)

A solution of 38·0 g *IVg* (ref.[10]) in 580 ml ether was added dropwise over 45 min to a stirred solution of 7·1 g $LiAlH_4$ in 100 ml ether and the mixture was refluxed for 9 h. After cooling it was decomposed under stirring and external cooling by slow addition of 7·1 ml water, 7·1 ml 20% NaOH, 14·2 ml water, and 7·1 g K_2CO_3. After standing for 30 min the solid was filtered off and the filtrate was processed by distillation; 27·6 g (70%) of *IIIg*, b.p. 156—160°C/80 Pa. Ref.[11], b.p. 158—162°C/0·12—0·19 kPa (different synthetic method).

3-(4-(4-Ethylphenyl)-1-piperazinyl)propylamine (*IIIh*)

Similar reduction of 60 g *IVh* with 11·5 g $LiAlH_4$ in 700 ml ether gave 43·0 g (71%) of *IIIh*, b.p. 160°C/67 Pa. ^{1}H NMR spectrum ($CDCl_3$): 1·11 t, 3 H (CH_3, J = 7·0); 1·28 bs, 2 H (NH_2); 1·60 m, 2 H ($CH_2\mathbf{CH_2}CH_2$); 2·20—2·80 m, 10 H ($CH_2N^1CH_2$, $\mathbf{CH_2}CH_2\mathbf{CH_2}$ and $ArCH_2$); 3·05 bm, 4 H ($CH_2N^4CH_2$); 6·72 d, 2 H (H-2 and H-6, J = 9·0); 6·99 d, 2 H (H-3 and H-5, J = 9·0). For $C_{15}H_{25}N_3$ (247·4) calculated: 72·82% C, 10·19% H, 16·99% N; found: 73·08% C, 9·98% H, 16·69% N.

Monopicrate, m.p. 163—165°C (ethanol). For $C_{21}H_{28}N_6O_7$ (476·5) calculated: 52·93% C, 5·92% H, 17·64% N; found: 53·12% C, 5·92% H, 17·55% N.

Trihydrochloride, m.p. 203—205°C (ethanol–ether). For $C_{15}H_{28}Cl_3N_3$ (356·8) calculated: 50·49% C, 7·91% H, 29·81% Cl, 11·78% N; found: 50·74% C, 7·94% H, 29·78% Cl, 12·04% N.

3-(4-(3-Chlorophenyl)-1-piperazinyl)propylamine (*IIIi*)

Similar reduction of 57·1 g *IVi* (ref.[10]) with 12·5 g $LiAlH_4$ in 400 ml ether gave 35·7 g (63%) of *IIIi*, b.p. 179°C/0·12 kPa. ^{1}H NMR spectrum ($CDCl_3$): 1·65 m, 2 H ($CH_2\mathbf{CH_2}CH_2$); 2·20 bs, 2 H (NH_2); 2·30—2·90 m, 8 H ($CH_2N^1CH_2$, $\mathbf{CH_2}CH_2\mathbf{CH_2}$); 3·15 bm, 4 H ($CH_2N^4CH_2$); 6·50—7·20 m, 4 H (ArH). For $C_{13}H_{20}ClN_3$ (253·8) calculated: 61·52% C, 7·94% H, 13·97% Cl, 16·56% N; found: 61·84% C, 7·66% H, 13·67% Cl, 16·54% N. Ref.[14], b.p. 150—154°C/5 Pa (different method).

3-(4-(2-Methoxyphenyl)-1-piperazinyl)propylamine (*IIIj*)

Similar reduction of 44·0 g *IVj* with 8·6 g $LiAlH_4$ in 650 ml ether gave 24·9 g (56%) of *IIIj*, b.p. 152—155°C/80 Pa. Refs[14,18], b.p. 151—154°C/9 Pa and 140—155°C/20 Pa, respectively.

Trihydrochloride, m.p. 194—197°C (ethanol–5M-HCl). For $C_{14}H_{26}Cl_3N_3O$ (358·7) calculated 46·87% C, 7·31% H, 29·65% Cl, 11·71% N; found: 47·09 C, 7·44% H, 29·56% Cl, 11·72% N.

3-(4-(3-Methoxyphenyl)-1-piperazinyl)propylamine (*IIIk*)

Similar reduction of 66·5 g *IVk* with 14·0 g $LiAlH_4$ in 800 ml ether gave 43·9 g (65%) of *IIIk*, b.p. 173—175°C/80 Pa. Ref.[18], b.p. 155—165°C/20 Pa.

Trihydrochloride, m.p. 172—175°C (ethanol–hydrochloric acid). For $C_{14}H_{26}Cl_3N_3O$ (358·7) calculated: 46·87% C, 7·31% H, 29·65% Cl, 11·71% N; found: 46·85% C, 7·20% H, 29·31% Cl, 11·90% N.

3-(4-(4-Methoxyphenyl)-1-piperazinyl)propylamine (*IIIl*)

Similar reduction of 38·7 g *IVl* with 7·6 g $LiAlH_4$ in 650 ml ether gave 25·4 g (64%) of *IIIl*, b.p. 165—168°C/67 Pa. Ref.[11], b.p. 166—169°C/26 Pa (different method of reduction).

Trihydrochloride, m.p. 250—254°C with decomposition (ethanol–hydrochloric acid). For $C_{14}H_{26}Cl_3N_3O$ (358·8) calculated: 46·87% C, 7·31% H, 29·65% Cl, 11·71% N; found: 47·27% C, 7·45% H, 29·36% Cl, 11·88% N.

N-(3-(4-Phenyl-1-piperazinyl)propyl)-5-sulfamoyl-2-methoxybenzamide (*IIe*)
(General method)

A mixture 13·0 g ethyl 5-sulfamoyl-2-methoxybenzoate[1,5] and 11·0 g *IIIe* (ref.[9]) was stirred and heated for 14 h to 100°C. The solidified melt was disintegrated by refluxing with 100 ml ethanol for 1 h and after cooling the precipitated product was filtered, washed with ethanol, and dried in vacuo; 13·5 g (63%) of *IIe*, m.p. 220—221°C (dimethylformamide–ethanol). For analysis and spectra, cf. Tables I and II.

Methanesulfonate, m.p. 221—223°C (ethanol–ether), was prepared by neutralization with methanesulfonic acid in boiling ethanol and cooling of the solution obtained. The analysis is included in Table I.

The authors wish to thank their colleagues at the Research Institute for Pharmacy and Biochemistry for their contributions to the present study: Mrs J. Komancová, Mrs V. Šmídová, and Mrs J. Kropáčová (elemental analyses); Mrs A. Hrádková and Mrs E. Smetanová (recording of the UV *and* IR *spectra); Dr S. Wildt (acute toxicities).*

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Translated by the author (M.P.).