N-(PIPERAZINOACYL) AND N-(PIPERAZINOALKYL) DERIVATIVES OF 4-CYCLOPENTYLANILINE AND RELATED COMPOUNDS: SYNTHESIS AND PHARMACOLOGICAL SCREENING

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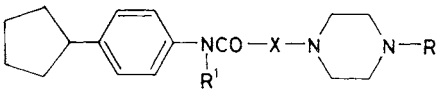
Received November 21st, 1985

Five N-(4-cyclopentylphenyl)haloalkanecarboxamides were reacted with 1-methylpiperazine and 1-(2-hydroxyethyl)piperazine to give the corresponding N-(4-cyclopentylphenyl)piperazinoalkanecarboxamides *Iab*—*Vab*. Their reduction with lithium aluminium hydride afforded the triamines *VIIab*—*XIab*. Acylation of the N-(4-methylpiperazino)alkyl-4-cyclopentylanilines *Xa* and *XIa* with propionyl chloride resulted in the propionanilides *XIVa* and *XVa*, whereas a similar reaction of the N-(4-(2-hydroxyethyl)piperazino)alkyl-4-cyclopentylanilines *VIIb* and *IXb*—*XIb* produced the propionoxypropionanilides *XIIc*—*XVc*. Ethanolysis of these compounds afforded corresponding hydroxypropionanilides *XIIb*—*XVb*. Many of the basic amides showed local anaesthetic and papaverine-like antispasmodic activity. The propionanilides *XIIb*, *XIVc*, and *XVa* proved interesting analgesic effects in the peritoneal test in mice.

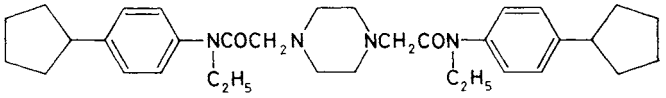
In a previous communication[1] we described synthesis and results of the pharmacological screening of a series of N-(aminoacyl) and N-(aminoalkyl) derivatives of 4-cyclopentylaniline. This investigation was continued by using the piperazine moiety as the amino group and the synthesis of these new compounds, as well as the results of their pharmacological screening, are the objects of the present communication.

The syntheses started from N-(4-cyclopentylphenyl)chloroacetamide, N-(4-cyclopentylphenyl)-N-ethylchloroacetamide, N-(4-cyclopentylphenyl)-3-chloropropionamide, N-(4-cyclopentylphenyl)-4-chlorobutyramide and N-(4-cyclopentylphenyl)-2-bromo-4-methylvaleramide, described previously[1]. These haloalkanecarboxamides were reacted with 1-methylpiperazine and 1-(2-hydroxyethyl)piperazine (100% excess at least) in boiling benzene (6 h refluxing) (method A) and afforded mostly in good yields the amides *Iab*—*Vab*. N-(4-Cyclopentylphenyl)-4-chlorobutyramide[1], however, proved under these conditions a little reactivity. The conditions were modified by using boiling toluene (16 h refluxing) and a different isolation procedure (method B); in this way the amides *IVa* and *IVb* were obtained in reasonable yields. The bases *Iab*—*Vab* were mostly crystalline and their identity was corroborated by spectra (IR, ^{1}H NMR); they were transformed to salts (mostly hydrochlorides). During preparation of the compound *IIa* a minor by-product was isolated on the basis of insolubility of its hydrochloride in water. The mass spectrum of the crystalline base

(*m/z* 544) indicated the composition $C_{34}H_{48}N_4O_2$ which was in agreement with the analyses of the base and of the hydrochloride. The ^1H NMR spectrum showed the presence of two N-ethyl-4-cyclopentylaniline residues per one piperazine moiety and structure *VI* was assigned to the by-product. The explanation of the formation of this compound consists in the presence of a small amount of piperazine as impurity in the 1-methylpiperazine used (it was prepared by methylation of piperazine monohydrochloride with dimethyl sulfate[2]).



I, X = CH_2; R^1 = H *III*, X = $(CH_2)_2$; R^1 = H
II, X = CH_2; R^1 = C_2H_5 *IV*, X = $(CH_2)_3$; R^1 = H
V, X = $>CHCH_2CH(CH_3)_2$; R^1 = H



VI

In formulae *I*–*V* and *VII*–*XV* *a*, R = CH_3 *b*, R = CH_2CH_2OH
c, R = $CH_2CH_2OCOC_2H_5$

The amides *Iab*–*Vab* were reduced with lithium aluminium hydride in mixtures of ether and benzene (method C) to give the amines *VIIab*–*XIab*. The bases obtained were mostly oily (with the exception of *IXb*) and were transformed to salts (hydrochlorides, maleates). Treatment of the amines *Xa* and *XIa* with a slight excess of propionyl chloride in boiling chloroform and in the presence of potassium carbonate (method D) resulted in the propionanilides *XIVa* and *XVa*. A similar reaction of the amino alcohols *VIIb* and *IXb*–*XIb* gave the propionoxypropionanilides *XIIc*–*XVc* which were transformed to the hydroxypropionanilides *XIIb*–*XVb* by treatment with boiling ethanol in the presence of a small amount of sodium ethoxide (method E). The bases of the propionanilides were oily but afforded crystalline salts (hydrochlorides, maleates). All compounds prepared are assembled in Table I with the usual experimental data while the Experimental describes only examples of the syntheses.

Most of the compounds prepared were subjected to the general pharmacological screening in the form of salts described in the Experimental and in Table I. In the

first line acute toxicity in mice (LD_{50} in mg/kg) and the doses (D in mg/kg), which were used in the screening, are given. Compounds which were administered intravenously: *Ia*, 150, 30; *Ib*, 175, 35; *IIIa*, 150, 30; *IIIb*, 150, 30; *Va*, 27·5, 5; *Vb*, 37·5, 7; *VIIa*, 200, 40; *VIIb*, 175, 35; *VIIIa*, 125, 25; *IXa*, 150, 30; *IXb*, 175, 35; *XIIb*, 100,

TABLE I

4-Cyclopentylaniline derivatives *Iab*—*Vab* and *VIIab*—*XVabc*

Compound[a]	Method (yield, %)	M.p., °C (solvent)	Formula (mol. wt.)	Calculated/found			
				% C	% H	% Cl	% N
Ia[b]	A (86)	70—71 (hexane)	$C_{18}H_{27}N_3O$ (301·4)	71·72 71·74	9·03 8·87	— —	13·94 13·90
Ia·2 HCl		204—205 (aqueous ethanol)	$C_{18}H_{29}Cl_2N_3O$ (374·4)	57·74 57·17	7·81 8·09	18·94 18·77	11·23 11·14
Ib	A (86)	81—82[c] (benzene–hexane)	$C_{19}H_{29}N_3O_2$ (331·5)	68·85 68·75	8·82 8·95	— —	12·68 12·58
Ib·2 HCl		194—195 (aqueous ethanol)	$C_{19}H_{31}Cl_2N_3O_2$ (404·4)	56·42 56·32	7·73 7·82	17·55 17·48	10·39 10·46
IIa·2 HM[b]	A (82)	158—159 (ethanol)	$C_{28}H_{39}N_3O_9$ (561·6)	59·88 60·07	7·00 7·07	— —	7·48 7·36
IIIa	A (89)	122—123[d] (benzene–hexane)	$C_{19}H_{29}N_3O$ (315·5)	72·33 72·60	9·27 9·11	— —	13·32 13·13
IIIa·2 HCl		221—222 (aqueous ethanol)	$C_{19}H_{31}Cl_2N_3O$ (388·4)	58·75 58·43	8·05 7·83	18·26 18·18	10·82 10·43
IIIb	A (95)	119—120[e] (benzene–hexane)	$C_{20}H_{31}N_3O_2$ (345·5)	69·53 69·71	9·05 9·06	— —	12·16 12·20
IIIb·2 HCl		223—225 (aqueous ethanol)	$C_{20}H_{33}Cl_2N_3O_2$ (418·4)	57·42 57·24	7·95 8·01	16·94 16·89	10·04 9·91
IVa	B (41)	82—83 (benzene–hexane)	$C_{20}H_{31}N_3O$ (329·5)	72·91 73·01	9·48 9·55	— —	12·75 12·56
IVb[b]	B (39)	99—100 (benzene–hexane)	$C_{21}H_{33}N_3O_2$ (359·5)	70·16 69·94	9·25 9·28	— —	11·69 11·69
IVb·2 HCl		222—223 (aqueous ethanol)	$C_{21}H_{35}Cl_2N_3O_2$ (432·4)	58·32 58·56	8·16 8·28	16·40 16·20	9·72 9·67
Va	A (87)	95—96[f] (hexane)	$C_{22}H_{35}N_3O$ (357·5)	73·90 73·73	9·87 9·90	— —	11·75 11·66
Va·2 HCl[g]		218—220 (aqueous ethanol–ether)	$C_{22}H_{37}Cl_2N_3O$ + 0·5 H_2O (439·5)	60·17 60·68	8·69 8·66	16·13 15·93	9·56 9·65

TABLE I
(*Continued*)

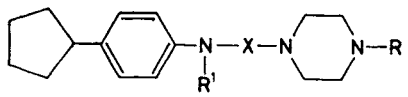
Compound[a]	Method (yield, %)	M.p., °C (solvent)	Formula (mol. wt.)	Calculated/found			
				% C	% H	% Cl	% N
Vb-2 HCl[g]	A (72)	228–230 (aqueous ethanol)	$C_{23}H_{39}Cl_2N_3O_2$ + 0·5 H_2O (469·5)	58·85 59·35	8·58 8·61	15·10 15·03	8·95 9·06
VIIa-3 HCl	C (96)	224–226 (ethanol–ether[h])	$C_{18}H_{32}Cl_3N_3$ (396·8)	54·48 54·22	8·14 8·15	26·79 26·68	10·59 10·93
VIIb-2 HCl	C (93)	213–214 (aqueous ethanol)	$C_{19}H_{33}Cl_2N_3O$ (390·4)	58·46 58·56	8·52 8·72	18·16 17·98	10·76 10·55
VIIIa-3 HCl	C (94)	205–206 (ethanol–ether[h])	$C_{20}H_{36}Cl_3N_3$ (424·9)	56·55 56·46	8·54 8·25	25·02 24·71	9·89 9·88
IXa-3 HCl	C (91)	243–245 (aqueous ethanol–ether[h])	$C_{19}H_{34}Cl_3N_3$ (410·9)	55·55 55·46	8·34 8·18	25·88 25·86	10·23 10·16
IXb[b]	C (90)	75–76 (benzene–hexane)	$C_{20}H_{33}N_3O$ (331·5)	72·48 72·67	10·03 10·13	— —	12·66 12·78
IXb-3 HCl		231–232 (ethanol[h])	$C_{20}H_{36}Cl_3N_3O$ (440·9)	54·51 55·01	8·23 8·03	24·11 24·34	9·53 9·64
Xa-3 HCl	C (94)	215–216 (aqueous ethanol[h])	$C_{20}H_{36}Cl_3N_3$ (424·9)	56·55 56·20	8·54 8·40	25·02 24·78	9·89 9·60
Xb-3 HCl[g]	C (94)	223–224 (aqueous ethanol[h])	$C_{21}H_{38}Cl_3N_3O$ + 0·5 H_2O (463·9)	54·36 54·00	8·48 8·28	22·93 22·96	9·06 8·92
XIa-1·5 M[i]	C (95)	168–169 (aqueous ethanol–ether)	$C_{29}H_{43}N_3O_6$ + 1·5 H_2O (556·7)	62·56 62·32	8·33 8·04	— —	7·55 7·62
XIb-1·5 M[i]	C (86)	160–161 (98% ethanol–ether)	$C_{30}H_{45}N_3O_7$ + 1·5 H_2O (586·7)	61·44 61·74	8·24 8·05	— —	7·16 7·22
XIIb-2 HCl	E (80)	157–159 (ethanol–ether)	$C_{22}H_{37}Cl_2N_3O_2$ (446·5)	59·18 58·50	8·35 8·18	15·89 15·98	9·41 9·49
XIIc-2 HCl[j]	D (81)	172–173 (ethanol–ether)	$C_{25}H_{41}Cl_2N_3O_3$ + H_2O (520·5)	57·68 57·68	8·34 8·64	13·63 13·82	8·07 7·94
XIIIb-2 HCl[b]	E (88)	201–202 (ethanol–ether)	$C_{23}H_{39}Cl_2N_3O_2$ (460·5)	59·99 59·39	8·54 8·54	15·40 15·46	9·12 9·12

TABLE I
(*Continued*)

Compound[a]	Method (yield, %)	M.p., °C (solvent)	Formula (mol. wt.)	Calculated/found			
				% C	% H	% Cl	% N
XIIIc·2 HCl[j]	D (90)	177—178 (98% ethanol–ether)	$C_{26}H_{43}Cl_2N_3O_3 + H_2O$ (534·6)	58·43 58·30	8·48 8·36	13·26 13·20	7·86 7·99
XIVa·2 HCl[b,g]	D (93)	211—213 (98% ethanol)	$C_{23}H_{39}Cl_2N_3O + 0{\cdot}5\ H_2O$ (453·5)	60·92 61·03	8·89 8·98	15·64 15·52	9·26 9·20
XIVb·2 HCl[j]	E (92)	145—146 (98% ethanol–ether)	$C_{24}H_{41}Cl_2N_3O_2 + H_2O$ (492·5)	58·53 58·72	8·80 8·66	14·40 14·65	8·53 8·72
XIVc·2 HCl[k]	D (94)	170—171 (98% ethanol–ether)	$C_{27}H_{45}Cl_2N_3O_3 + 2\ H_2O$ (566·6)	57·26 57·56	8·69 8·26	12·51 12·77	7·42 7·54
XVa·M	D (85)	139—140 (ethanol–ether)	$C_{29}H_{45}N_3O_5$ (515·7)	67·54 67·24	8·80 9·05	— —	8·15 8·30
XVb·M[g]	E (90)	69—72 (98% ethanol–ether)	$C_{30}H_{47}N_3O_6 + 0{\cdot}5\ H_2O$ (554·7)	64·94 64·60	8·75 9·01	— —	7·55 7·01
XVc·2 HM[j]	D (92)	88—89 (98% ethanol–ether)	$C_{37}H_{55}N_3O_{11} + H_2O$ (735·8)	60·38 59·96	7·80 7·70	— —	5·71 5·79

[a] M = maleate, 2 HM = bis(hydrogen maleate), 1·5 M = sesquimaleate. [b] See Experimental. [c] IR spectrum: 825 (2 adjacent Ar—H), 1 060 (CH_2OH), 1 520, 1 684 (NHCO), 1 588 (Ar), 3 340 cm^{-1} (OH, NH); ^1H NMR spectrum: δ 8·95 (bs, 1 H, NH), 7·40 (d, J = 8·0 Hz, 2 H 2, 6-H_2 of aniline), 7·10 (d, J = 8·0 Hz, 2 H, 3, 5-H_2 of aniline), 3·60 (t, 2 H, CH_2O), 3·10 (s, 2 H, $COCH_2N$), 2·75 (bs, 1 H, OH), c. 2·55 (m, 11 H, remaining 5 CH_2N and ArCH of cyclopentyl), 1·30—2·20 (m, 8 H, 4 CH_2 of cyclopentyl). [d] IR spectrum (KBr): 804, 825, 833 (2 adjacent Ar—H), 1 514, 1 536, 1 656 (NHCO), 1 604 (Ar), 3 255, 3 290 cm^{-1} (NH); ^1H NMR spectrum: δ 10·75 (bs, 1 H, NH), 7·40 (d, J = 8·0 Hz, 2 H, 2, 6-H_2 in aniline), 7·12 (d, J = 8·0 Hz, 2 H, 3, 5-H_2 in aniline), 2·40—3·00 (m, 13 H, 5 CH_2N, CH_2CO, ArCH of cyclopentyl), 2·28 (s, 3 H, CH_3N), 1·40—2·20 (m, 8 H, 4 CH_2 of cyclopentyl). [e] IR spectrum: 822 (2 adjacent Ar—H), 1 075 (CH_2OH), 1 514, 1 532, 1 688 (NHCO), 1 600 (Ar), 3 115, 3 190 (NH), 3 265 cm^{-1} (OH). [f] IR spectrum: 832 (2 adjacent Ar—H), 1 518, 1 530, 1 533, 1 659 (NHCO), 1 598 (Ar), 3 310 cm^{-1} (NH); ^1H NMR spectrum: δ 9·05 (bs, 1 H, NH), 7·40 (d, J = 8·0 Hz, 2 H, 3, 5-H_2 of aniline), 7·10 (d, J = 8·0 Hz, 2 H, 2, 6-H_2 of aniline), 3·00 (m, 1 H, ArCH of cyclopentyl), 2·30—2·90 (m, 12 H, 4 CH_2N of piperazine and $NCHCH_2CH$), 2·20 (s, 3 H, CH_3N), 1·20—2·10 (m, 8 H, 4 CH_2 of cyclopentyl), 0·90 (d, J = 6·0 Hz, 6 H, CH_3—C—CH_3 of isobutyl). [g] Hemihydrate. [h] Containing HCl. [i] Sesquihydrate. [j] Monohydrate. [k] Dihydrate.

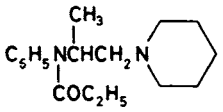
20; *XIIc*, 62·5, 12; *XIIIb*, 75, 15; *XIIIc*, 62·5, 12; *XIVa*, 56·3, 12; *XIVb*, 100, 20; orally administered compounds: *IIa*, 2 000, 300; *XVa*, 1 500, 300; *XVb*, 2 000, 300; *XVc*, 2 000, 300. Most of the compounds in doses above D brought about first excitation, followed by central depression, ataxia, tremor and convulsions. Discoordinating effect in the rotarod test in mice (*i.v.* doses in mg/kg bringing about ataxia in 50% animals) was rather rare: *VIIa*, 25–40; *VIIIa*, 25; *XIIb*, 10–20.



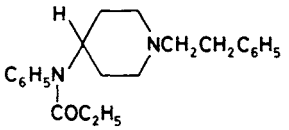
VII, X = $(CH_2)_2$; R^1 = H
VIII, X = $(CH_2)_2$; R^1 = C_2H_5
IX, X = $(CH_2)_3$; R^1 = H
X, X = $(CH_2)_4$; R^1 = H
XI, X = $-CH_2CH(CH_2CH(CH_3)_2)-$; R^1 = H
XII, X = $(CH_2)_2$; R^1 = COC_2H_5
XIII, X = $(CH_2)_3$; R^1 = COC_2H_5
XIV, X = $(CH_2)_4$; R^1 = COC_2H_5
XV, X = $-CH_2CH(CH_2CH(CH_3)_2)-$; R^1 = COC_2H_5

Local anaesthetic effect in the test of infiltration anaesthesia (concentration in % bringing about a complete anaesthesia in 50% guinea-pigs; for procaine, EC = 1%): 0·1–0·5 for compounds *Ia*, *Ib*, *IIIb*, *Va*, *Vb*, *XIIIb*, *XIVa*, and *XIVb*; in the test of corneal anaesthesia (concentration in % bringing about in 50% rabbits a complete anaesthesia of the eye cornea; for trimecaine, EC = 1%): 0·1–0·5 for compounds *Va*, *XIIIb*, *XIIIc*, *XIVa*. Spasmolytic (parasympatholytic) effect (concentrations in μg/ml exhibiting a reduction of the acetylcholine contractions of the isolated rat duodenum by 50%; for atropine, EC = 0·05): 1–10 for compounds *IIIa*, *Va*, *Vb*, *VIIIa*, *XIIc*, and *XIIIb*. Spasmolytic (musculotropic) effect (similar arrangement, barium chloride contractions; for papaverine, EC = 5): *IIIa*, 10; *Va*, 1–10; *Vb*, 1–10; *XIIc*, 10; *XIIIc*, 1–10; *XIVa*, 10. Deep drops of blood pressure in normotensive rats after *i.v.* administration of doses D: *Ia*, *VIIb*, *IXa*, *IXb*. Effect on heart inotropy (concentration in μg/ml eliciting a decrease of inotropy of the isolated rabbit heart atrium by 25%): *Ia*, 50; *Ib*, 50; *IIIa*, 10–50; *IIIb*, 25–50; *Va*, 10–50; *Vb*, 50; *VIIa*, 50; *VIIb*, 25–50; *IXa*, 50; *XIIIb*, 10–50; *XIIIc*, 50; *XIVa*, 50; *XIVb*, 10–50. Effect on heart frequency (similar arrangement): *Va*, 10–50; *VIIa*, 50; *IXa*, 50; *XIVa*, 50; *XIVb*, 10. Diuretic effect (oral dose in mg/kg increasing the diuresis in mice by 100% as compared with the control; for hydrochlorothiazide, ED = 100): *XIIb*, 100. Hyperglycaemic effect (oral dose in mg/kg increasing blood sugar in rats by 20%): *IIa*, 300; *XVa*, 300. Analgesic activity in mice using chemical stimulation (intraperitoneal administration of acetic acid), D_{50} in mg/kg orally: *XIIb*, c. 10; *XIVc*, 17·2; *XVa*, 2·4 (for comparison D_{50} of morphine 0·24, and meperidine 3·1). In oral doses of 10 mg/kg compounds *XIIb*, *XIVc*, and *XVa* were analgetical-

ly inactive in the Haffner test in mice (mechanical stimulation). It is worth mentioning that the propionanilide fragment appear in moledules of some potent analgetics, *e.g.* phenampromide (*XVI*) and fentanyl (*XVII*) (ref.[3]).



XVI



XVII

The compounds prepared were also tested for antimicrobial activity *in vitro* (microorganisms and the minimum inhibitory concentrations in μg/ml are given unless they exceed 100 μg/ml): *Streptococcus β-haemolyticus, Ib* 100, *Va* 50, *Vb* 50, *VIIa* 100, *VIIb* 100, *IXa* 100, *Xa* 100, *Xb* 100, *XIa* 12·5, *XIb* 25, *XIIIc* 100, *XVa* 25, *XVb* 50, *XVc* 25; *Streptococcus faecalis, IXa* 100, *XIa* 50, *XIb* 50, *XVa* 50, *XVb* 100, *XVc* 100; *Staphylococcus pyogenes aureus, Va* 50, *Vb* 100, *XIa* 25, *XIb* 25, *XVa* 25, *XVb* 50, *XVc* 25; *Pseudomonas aeruginosa, Xa* 100, *Xb* 100, *XIb* 100; *Mycobacterium tuberculosis* H37Rv, *Ia* 100, *Ib* 100, *IIa* 50, *IIIa* 100, *IIIb* 100, *Va* 12·5, *Vb* 25, *VIa* 50, *VIIb* 50, *VIIIa* 12·5, *IXa* 25, *IXb* 100, *Xa* 25, *Xb* 100, *XIa* 6·25, *XIb* 12·5, *XIIb* 50, *XIIc* 100, *XIIIb* 100, *XIIIc* 50, *XIVa* 25, *XIVb* 25, *XIVc* 50, *XVa* 6·25, *XVb* 6·25; *Saccharomyces pasterianus, Ia* 100, *Ib* 100, *IIa* 50, *IIIa* 100, *IIIb* 100, *IVb* 50, *Vb* 50, *VIIa* 50, *VIIb* 100, *VIIIa* 25, *IXa* 100, *IXb* 100, *Xa* 50, *Xb* 50, *XIa* 50, *XIb* 50, *XIIb* 50, *XIIc* 100, *XIIIb* 50, *XIIIc* 50, *XIVa* 50, *XIVc* 50, *XVa* 50, *XVc* 25; *Trichophython mentagrophytes, Ia* 50, *Ib* 100, *IIa* 50, *IIIa* 100, *IIIb* 100, *IVb* 50, *Vb* 50, *VIIa* 25, *VIIb* 50, *VIIIa* 25, *IXa* 50, *IXb* 50, *Xa* 50, *Xb* 50, *XIa* 25, *XIb* 25, *XIIb* 50, *XIIc* 50, *XIIIb* 50, *XIIIc* 25, *XIVa* 25, *XIVb* 50, *XIVc* 50, *XVa* 25, *XVc* 12·5; *Candida albicans, Ia* 100, *Ib* 100, *IIIa* 100, *IIIb* 100, *VIIb* 100, *IXa* 100, *IXb* 100, *XIIc* 100, *XVc* 50; *Aspergillus niger, IIIa* 100, *IIIb* 100, *VIIb* 100, *IXa* 100, *IXb* 100, *XIIc* 100.

EXPERIMENTAL

The melting points of analytical samples were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* of about 60 Pa over P_2O_5 at room temperature or at 77°C. The IR spectra (mostly in Nujol) were recorded with a Unicam SP 200 G spectrophotometer, ^{1}H NMR spectra (in C^2HCl_3) with a Tesla BS 487 C (80 MHz) spectrometer, and the mass spectrum with MS 902 (AEI) spectrometer. The homogeneity of the compounds and composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol).

N-(4-Cyclopentylphenyl)-2-(4-methylpiperazino)acetamide (*Ia*) (Method A)

A solution of 11·0 g N-(4-cyclopentylphenyl)chloroacetamide[1] in 70 ml benzene was treated with 10·0 g 1-methylpiperazine, the stirred mixture was refluxed for 6 h, and allowed to stand overnight. The precipitated 1-methylpiperazine hydrochloride was filtered off, washed with benzene, the filtrate was washed with water, dried with Na_2SO_4 and evaporated *in vacuo*; 11·9 g (86%) *Ia*, m.p. 70–71°C (hexane). IR spectrum: 830 (2 adjacent Ar—H), 1 520, 1 688 (NHCO), 1 586, 1 610 (Ar), 3 335 cm^{-1} (NH). ^{1}H NMR spectrum: δ 8·95 (bs, 1 H, NH), 7·40 (d, J = = 8·0 Hz, 2 H, 2,6-H_2 in anilide), 7·10 (d, J = 8·0 Hz, 2 H, 3,5-H_2 in anilide), 3·02 (s, 2 H, $COCH_2N$), c. 2·90 (m, 1 H, ArCH in cyclopentyl), c. 2·50 (m, 8 H, 4 CH_2N of piperazine), 2·21 (s, 3 H, CH_3N), 1·40–2·10 (m, 8 H, 4 CH_2 of cyclopentyl). Neutralization of the base in ethanol

with a solution of HCl in ethanol and addition of ether gave the dihydrochloride which crystallized in leaflets from aqueous ethanol, m.p. 204–205°C (sintering at 180–190°C). Analyses of the base and of the dihydrochloride are included in Table I.

N-(4-Cyclopentylphenyl)-N-ethyl-2-(4-methylpiperazino)acetamide (*IIa*)

A mixture of 17·1 g N-(4-cyclopentylphenyl)-N-ethylchloroacetamide[1], 120 ml benzene and 13·5 g 1-methylpiperazine was stirred and refluxed for 6 h. After standing overnight the benzene layer was decanted from the separated hygroscopic 1-methylpiperazine hydrochloride, it was washed with water and the bases were extracted with a solution of 30 ml hydrochloric acid in 300 ml water. The solid, separated from the aqueous layer, was filtered off, the filtrate was made alkaline with 20% NaOH and the oily *IIa* was isolated by extraction with a 3 : 1 mixture of benzene and ether; 17·3 g (82%). It was transformed to the bis(hydrogen maleate), m.p. 158–159°C (*cf.* Table I).

The solid (1·0 g), which was filtered off from the acid aqueous layer, was decomposed with NH_4OH and the base was isolated by extraction with benzene; 0·60 g 1,4-bis(N-ethyl-4-cyclopentylanilinocarbonylmethyl)piperazine (*VI*), m.p. 150–151°C (benzene–hexane). Mass spectrum, *m/z* (%): 544 (M^+ corresponding to $C_{34}H_{48}N_4O_2$), 328 (100), 299 (11·4), 286 (14·6), 273 (22·4), 228 (32·1), 111 (47·8), 98 (18·4), 70 (21·0), 69 (11·7), 56 (15·6), 42 (12·9), 41 (11·2). IR spectrum: 790, 843 (2 adjacent Ar—H), 1 505, 1 512, 1 602, 3 005, 3 030 (Ar), 1 672 cm^{-1} (CONRAr). ^1H NMR spectrum: δ 7·21 (d, J = 8·0 Hz, 4 H, 2,6,2′,6′-H_4 in anilines), 6·99 (d, J = 8·0 Hz, 4 H, 3,5,3′,5′-H_4 in anilines), 3·69 (q, J = 7·0 Hz, 4 H, 2 $CONCH_2$), c. 3·00 (m, 2 H, 2 ArCH of cyclopentyls), 2·80 (s, 4 H, 2 NCH_2CO), 2·42 (s, 8 H, 4 CH_2N of piperazine), 1·40–2·20 (m, 16 H, 8 CH_2 of two cyclopentyls), 1·06 (t, J = 7·0 Hz, 6 H, 2 C—CH_3). For $C_{34}H_{48}N_4O_2$ (544·8) calculated: 74·96% C, 8·88% H, 10·29% N; found: 74·71% C, 9·09% H, 10·15% N.

Dihydrochloride of *VI*, m.p. 229–230°C (97% ethanol). For $C_{34}H_{50}Cl_2N_4O_2$ (617·7) calculated: 66·11% C, 8·16% H, 11·48% Cl, 9·07% N; found: 66·39% C, 8·38% H, 11·63% Cl, 9·03% N.

N-(4-Cyclopentylphenyl)-4-(4-(2-hydroxyethyl)piperazino)-butyramide (*IVb*) (Method B)

A solution of 19·1 g N-(4-cyclopentylphenyl)-4-chlorobutyramide[1] in 150 ml toluene was treated with 19·5 g 1-(2-hydroxyethyl)piperazine and the mixture was refluxed for 16 h under stirring. After cooling it was diluted with benzene, washed thoroughly with water, dried and evaporated *in vacuo*. The residue was dissolved in 50 ml ethanol, the solution was neutralized with hydrochloric acid and evaporated *in vacuo*. The crude hydrochloride was dissolved in 130 ml water, the solution was treated with NH_4OH and allowed to stand overnight at 4°C. There were obtained 10·2 g (39%) crystalline *IVb*, m.p. 99–100°C (benzene–hexane). IR spectrum: 801, 829 (2 adjacent Ar—H), 1 069, 1 077 (CH_2OH), 1 160, 1 307 (C—O and O—H of alcohol), 1 511, 1 534, 1 690 (ArNHCO), 1 600 (Ar), 3 110, 3 190, 3 260 cm^{-1} (NH, OH). Dihydrochloride, m.p. 222–223°C (96% ethanol). Analyses of the base and of the dihydrochloride are included in Table I.

2-(4-(3-(4-Cyclopentylanilino)propyl)piperazino)ethanol (*IXb*) (Method C)

A solution of 22·0 g *IIIb* in 150 ml benzene (prepared by warming and then cooled) was slowly added to a stirred suspension of 8·0 g $LiAlH_4$ in 100 ml ether and the mixture was refluxed for 5 h. After cooling it was decomposed by a slow addition of 32 ml 20% NaOH, the precipitated

solid was filtered off, washed with benzene and the filtrate was evaporated *in vacuo*. The residue crystallized by standing; 18·9 g (90%), m.p. 75—76°C (benzene–hexane). ^{1}H NMR spectrum: δ 7·00 (d, J = 8·0 Hz, 2 H, 3,5-H_2 of aniline), 6·50 (d, J = 8·0 Hz, 2,6-H_2 of aniline), 3·60 (t, 2 H, CH_2O), c. 3·70 (bs, 1 H, NH), 3·10 (t, 2 H, CH_2NAr), 2·80 (m, 1 H, ArCH of cyclopentyl), c. 2·50 (m, 13 H, remaining 6 CH_2N and OH), 1·30—2·20 (m, 10 H, 4 CH_2 of cyclopentyl and CH_2 in the middle of the propane chain). Trihydrochloride, m.p. 231—232°C (ethanol containing HCl). Analyses of the base and of the trihydrochloride are included in Table I.

N-(4-Cyclopentylphenyl)-N-(4-(4-methylpiperazino)butyl)-propionamide (*XIVa*) (Method D)

A stirred mixture of 4·8 g *Xa*, 25 ml chloroform and 4·3 g K_2CO_3 was treated dropwise over 25 min with a solution of 1·7 g propionyl chloride in 20 ml chloroform, and refluxed for 2·5 h. After cooling it was washed several times with water, dried with Na_2SO_4 and evaporated; 5·3 g (93%) oily *XIVa*. It was dissolved in 80 ml ether and treated with 8 ml HCl solution in ethanol. The precipitated dihydrochloride crystallized from 98% ethanol as a hemihydrate, m.p. 211—213°C (in the capillary 223—225°C). IR spectrum: 798, 855 (2 adjacent Ar—H), 1 030, 1 043, 1 120, 1 183 (C—O), 1 265, 1 310, 1 370 (C—N), 1 400, 1 460 (C—H in CH_2CO), 1 510, 1 600 (Ar), 1 658 (NCO), 2 450 (NH^+), 3 400 cm^{-1} (H_2O). The analysis is included in Table I.

N-(4-Cyclopentylphenyl)-N-(3-(4-(2-hydroxyethyl)piperazino)-propyl)propionamide (*XIIIb*) (Method E)

A solution of 8·3 g *XIIIc* in 30 ml ethanol was added to a solution of sodium ethoxide, prepared from 70 ml ethanol and 0·4 g Na, and the mixture was allowed to stand at room temperature for 24 h. Addition of the calculated amount of HCl solution in ethanol resulted in precipitation of NaCl which was filtered off, the filtrate was evaporated, the residue was dissolved in chloroform, the solution was washed with water, dried and evaporated. The residue (7·25 g) is the oily base *XIIIb* which was dissolved in 20 ml ethanol and the solution was neutralized with a solution of HCl in 10 ml ethanol. Evaporation *in vacuo* gave the solid salt which was dissolved in 20 ml boiling ethanol, the solution was cooled and treated with 100 ml ether; 7·60 g (88%) dihydrochloride, m.p. 201—202°C (ethanol–ether). IR spectrum: 1 019, 1 078, 1 091 (C—O of CH_2OH), 1 271, 1 377, 3 355 (OH), 1 510, 1 603 (Ar), 1 650 (NCO), 2 400, 2 450 cm^{-1} (NH^+). The analysis is included in Table I.

The authors thank the following members of the research staff of the institute for co-operation: Mr L. Tůma (help with the synthesis), Drs J. Holubek, E. Svátek and M. Ryska (recording and interpretation of the spectra), Dr M. Bartošová (pharmacological screening), Dr J. Metyš (testing for analgesic activity), Dr J. Vintika (microbiological screening), and Mrs J. Komancová, Mrs V. Šmídová, Mrs J. Kropáčová, Mr M. Čech and Dr Z. Volková (elemental analyses).

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Translated by the author (M.P.).