1-(2,4,6-TRIMETHYLBENZYL)PIPERAZINE AND SOME OF ITS 4-SUBSTITUTED DERIVATIVES: SYNTHESIS AND PHARMACOLOGICAL SCREENING*

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Reactions of 2,4,6-trimethylbenzyl chloride with 1-methyl-, 1-(2-hydroxyethyl)-, 1-phenyl- and 1-(ethoxycarbonyl)piperazine yielded 1,4-disubstituted piperazines *I*—*IV*, of which carbamate *IV* was hydrolyzed to the secondary amine *V*. This was converted to the guanidine derivative *VI* and to nitrosamine *VII*. Reduction produced the hydrazine derivative *VIII* which was transformed to aminoguanidine *IX* and to hydrazones *X*—*XII*. Central neurotropic effects are brought about only by high doses of the compounds; with some it is excitation (*I*, *II*, *VIII*), with most it is depression (*IV*, *VII*, *X*—*XII*), in one case it is a pronounced anticonvulsant effect (*XI*). Some effects not specific to structure were also observed: local anaesthetic, antiarrhythmic, myotropically spasmolytic (*IV*—*VI*) and briefly hypotensive (*I*, *II*, *IV*—*VI*, *VIII*).

In the context of our systematic studies of pharmacodynamically active piperazine derivatives, especially of the relatively simple substituted N-benzylpiperazines[1-4] we carried out the present study focussing on 2,4,6-trimethylbenzyl as the N-substituent of piperazine. The study included the synthesis and the pharmacological screening of *I*—*XII*.

The synthesis of *I*—*XII* proceeded from 2,4,6-trimethylbenzyl chloride[5] which underwent substitution reactions (method *A*) with 1-methylpiperazine, 1-(2-hydroxyethyl)piperazine, 1-phenylpiperazine[6] and 1-(ethoxycarbonyl)piperazine[7] to the 1,4-disubstituted piperazines *I*—*IV*. Alkaline hydrolysis of carbamate *IV* using a high concentration of potassium hydroxide yielded the parent secondary amine *V*. This reacted with S-methylisothiourea sulfate[8] in aqueous ethanol (method *B*)[4] to yield the N-guanyl derivative[9] *VI*. Treatment with nitrous acid converted *V* to nitrosamine *VII* which was reduced with lithium aluminium hydride in ether to the hydrazine derivative *VIII*. Application of method *B* to this compound resulted in the aminoguanidine derivative *IX*. Reaction of the hydrazine derivative *VIII* with benzaldehyde, 4-chlorobenzaldehyde and salicylaldehyde in boiling ethanol (method *C*) produced hydrazones[10] *X*—*XII*. All the bases prepared were converted to salts for pharmacolog-

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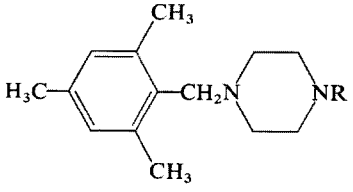
ical tests. Both the bases and the salts are summarized in Table I which includes the usual experimental data.



I, R = CH_3
II, R = CH_2CH_2OH
III, R = C_6H_5
IV, R = $COOC_2H_5$
V, R = H
VI, R = $C(=NH)NH_2$
VII, R = NO
VIII, R = NH_2
IX, R = $NHC(=NH)NH_2$
X, R = $N=CHC_6H_5$
XI, R = 4-$N=CHC_6H_4Cl$
XII, R = 2-$N=CHC_6H_4OH$

Salts of the piperazine derivatives *I*–*XII* were subjected to a general pharmacological screening, the results of which appear in Table II. With the exception of the guanidine derivative *VI* the compounds are not particularly toxic (acute toxicity was determined in mice), the effects of which appeared only at relatively high doses. As to the central neurotropic activity, there are signs of excitation (compounds *I*, *II*, *VIII*), in one case (*I*) with a slight antireserpine action, as well as signs of central depression which were apparent mostly only at high doses by inhibition of mouse motility (*IV*, *VII*, *X*–*XII*), in one case by potentiation of thiopental sleep (*VII*) and, in the case of hydrazones *X*–*XII*, by a hypothermic effect. In no case could we demonstrate at the doses shown an incoordinating effect in the rotating-rod test in mice. In the case of *XI* there was a significant anticonvulsant activity. With half of the substances (*I*, *II*, *IV*–*VI*, *VIII*) a brief hypotensive effect was observed in normotensive rats, probably based on a slight α-sympatholytic effect. Contrary to expectation, however, the aminoguanidine derivative *IX*, at a relatively high oral dose, had no effect on the blood pressure of hypertensive rats. The structurally little specific locally anaesthetic effect which was tested only with compounds readily soluble in water, was observed in *IV*–*VI* (most pronounced with aminocarbamate *IV*). This was accompanied in part by an antiarrhythmic effect (*VI*) and in all cases by a myotropic spasmolytic activity in the *in vitro* test (with respect to barium chloride contractions), in an extent resembling papaverine. The hypoglycaemic effect of nitrosamine *VII* should also be mentioned. All the compounds were ineffective as analgesics, anticholinergics, antiinflammatory agents, antihistamines and with respect to heart inotropy and frequency.

All the compounds were tested for antimicrobial activity *in vitro* toward a standard set of microorganisms (Dr J. Turinová, Department of Bacteriology of this Institute). With the exception of *IX* which had an antibacterial effect with a relatively broad spectrum (Table II), and of the specifically oriented *IV* and *VII*, none of the compounds showed antimicrobial activity.

TABLE I

Piperazine Derivatives *I*—*XII*

Compound[a]	Method (yield, %)	B.p., °C/Torr or m.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found		
				% C	% H	% N
I	*A*[b] (78)	127—129/2·5	$C_{15}H_{24}N_2$ (232·4)	77·53 77·11	10·41 10·47	12·06 12·13
I-2 M	—	184—187 (ethanol)	$C_{23}H_{32}N_2O_8$ (464·5)	59·47 59·73	6·94 7·02	6·03 6·00
II	*A* (77)	82—84[c] (benzene–light petroleum)	$C_{16}H_{26}N_2O$ (262·4)	73·24 73·13	9·99 10·19	10·68 10·26
II-M	—	118—120 (ethanol)	$C_{20}H_{30}N_2O_5$ (378·5)	63·47 63·50	7·99 8·08	7·40 7·57
III	*A* (66)	81—82 (ethanol)	$C_{20}H_{26}N_2$ (294·4)	81·58 81·51	8·90 9·00	9·52 9·57
III-M	—	150—151 (ethanol)	$C_{24}H_{30}N_2O_4$ (410·5)	70·22 70·25	7·37 7·36	6·82 6·94
IV	*A* (88)	156—158/0·8	—	—	—	—
IV-M	—	166—167 (ethanol)	$C_{21}H_{30}N_2O_6$ (406·5)	62·05 62·17	7·44 7·41	6·89 6·86
V	[b]	99—100 (ethanol)	$C_{14}H_{22}N_2$ (218·3)	77·01 77·23	10·16 10·22	12·83 12·63
V-M	—	176—178 (aqueous ethanol)	$C_{18}H_{26}N_2O_4$ (334·4)	64·64 64·63	7·84 7·96	8·38 8·20
VI-HS[d]	*B* (60)	234—237 (aqueous ethanol)	$C_{16}H_{28}N_4O_{2.5}S_{0.5}$ (332·4)	57·81 57·96	8·48 8·44	16·86 16·86
VII-M	[b]	141—143 (ethanol)	$C_{18}H_{25}N_3O_5$ (363·4)	59·49 59·63	6·93 7·12	11·56 11·70
VIII	[b]	73—74 (light petroleum)	$C_{14}H_{23}N_3$ (233·3)	72·05 72·54	9·93 10·04	18·01 17·99
VIII-2 MS	—	219—221 (ethanol–ether)	$C_{16}H_{31}N_3O_6S_2$[e] (425·6)	45·15 45·11	7·34 7·48	9·87 9·85
IX-HS[f]	*B* (50)	236—239 (aqueous ethanol)	$C_{15}H_{28}N_5O_3S_{0.5}$[g] (342·4)	52·61 52·92	8·24 8·18	20·45 20·28
X	*C*[b] (88)	99—101 (ethanol)	$C_{21}H_{27}N_3$ (321·5)	78·46 78·34	8·47 8·65	13·07 13·18

TABLE I
(*Continued*)

Compound[a]	Method (yield, %)	B.p., °C/Torr or m.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found		
				% C	% H	% N
X-MS	—	194—197 (ethanol)	$C_{22}H_{31}N_3O_3S$[h] (417·5)	63·29 63·43	7·48 7·64	10·07 10·11
XI	*C* (90)	123—125[i] (ethanol)	$C_{21}H_{26}ClN_3$[j] (355·9)	70·87 70·70	7·36 7·46	11·81 11·86
XI-MS	—	209—211 (ethanol)	$C_{22}H_{30}ClN_3O_3S$[k] (452·0)	58·46 58·22	6·69 6·71	9·30 9·41
XII	*C* (94)	120—122[m] (ethanol)	$C_{21}H_{27}N_3O$ (337·5)	74·74 74·68	8·06 8·35	12·45 12·53
XII-MS	—	212—215 (ethanol)	$C_{22}H_{31}N_3O_4S$[n] (433·6)	60·94 60·51	7·21 7·26	9·69 9·56

[a] M maleate, HS hemisulfate, MS methanesulfonate. [b] See Experimental. [c] ^{1}H-NMR spectrum: δ 6·83 (s, 2 H, aromatic protons), 3·58 (t, 2 H, CH_2O), 3·43 (s, 2 H, $ArCH_2N$), 2·92 (s, 1 H, OH), 2·00—2·85 (m, 10 H, 5 NCH_2), 2·34 (s, 6 H, 2,6-$Ar(CH_3)_2$), 2·25 (s, 3 H, 4-$ArCH_3$). [d] Solvate with one-half-molecule of ethanol. [e] Calculated: 15·07% S; found: 14·94% S. [f] Monohydrate. [g] Calculated: 4·68% S; found: 4·96% S. [h] Calculated: 7·67% S; found: 7·84% S. [i] UV spectrum: λ_{max} 297·5 nm (log ε 4·30); IR spectrum: 822, 855, 900 (2 adjacent and solitary Ar—H), 1491, 1559, 1598 (Ar), 1612 cm^{-1} (C=N); ^{1}H-NMR spectrum: δ 7·50 (mcd, J = 9·0 Hz, 2 H, 3,5-H_2 of 4-chlorophenyl), *c.* 7·40 (1 H, ArCH=), 7·25 (mcd, J = 9·0 Hz, 2 H, 2,6-H_2 of 4-chlorophenyl) 6·84 (s, 2 H, 3,5-H_2 of subst. benzyl), 3·46 (s, 2 H, $ArCH_2N$), 3·06 and 2·62 (2 t, 8 H, 4 NCH_2 of piperazine), 2·32 (s, 6 H, 2,6-$Ar(CH_3)_2$), 2·24 (s, 3 H, 4-$ArCH_3$). [j] Calculated: 9·96% Cl; found: 10·13% Cl. [k] Calculated: 7·84 Cl, 7·09% S; found: 8·01% Cl, 7·30% S. [m] UV spectrum: λ_{max} 285 nm (log ε 4·21), 312 nm (4·17); IR spectrum (Nujol): 751, 852 (4 adjacent and solitary Ar—H), 1129, 1270 (Ar—OH), 1597 (Ar), 1620 cm^{-1} (C=N). [n] Calculated: 7·39% S; found: 7·52% S.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* at about 0·5 Torr over P_2O_5 at room temperature or at 77°C. The UV spectra (in methanol) were recorded in a Unicam SP 700 spectrophotometer, IR spectra (in KBr unless stated otherwise) in a Unicam SP 200G spectrophotometer and NMR spectra (in $CDCl_3$) in a ZKR 60 (Zeiss, Jena) spectrometer. The analyses are shown in Table I.

1-Methyl-4-(2,4,6-trimethylbenzyl)piperazine (*I*) (Method *A*)

A mixture of 12·6 g 2,4,6-trimethylbenzyl chloride[5] (b.p. 108—112°C/8—10 Torr, m.p. 35—36°C) and 15·0 g 1-methylpiperazine was heated for 2·5 h at 100—110°C. After cooling, it was decomposed with 60 ml water and extracted with benzene. The extract was shaken with dilute hydro-

TABLE II

Pharmacological Screening of Piperazine Derivatives *I*—*XII* (doses in mg/kg)

Compound[a]	Code No VÚFB	Application[b]	Acute toxicity LD_{50}	Dose tested D[c]	Effects observed
I-2 M	8·971	*i.v.*	75	15	*d, e, f*
II-M	8·972	*i.v.*	75	15	*d, e*
III-M	8·973	*p.o.*	2 500	300	*g*
IV-M	8·832	*i.v.*	50	10	*d, h, i, j, k*
V-M	8·837	*i.v.*	50	10	*d, i, l*
VI-HS[m]	8·839	*i.v.*	3·5	0·7	*d, i, l, n, o*
VII-M	9·011	*i.v.*	250	50	*p, q, r, s*
VIII-2 MS	9·015	*i.v.*	125	25	*d, e, t, u*
IX-HS[v]	9·068	*p.o.*	—	35	*w, x*
X-MS	9·007	*p.o.*	>2 500	300	*g, r*
XI-MS	9·072	*p.o.*	>2 500	300	*o, r, y, z*
XII-MS	9·073	*p.o.*	>1 500	300	*z*

[a] M maleate, HS hemisulfate, MS methanesulfonate. [b] *i.v.*, intravenously; *p.o.*, orally. [c] Basic dose in which the compound was applied *in vivo*. [d] With normotensive rats it brings about a brief drop of blood pressure. [e] At a dose greater than D it brings about symptoms of central excitation. [f] A sign of antireserpine effect in a test of eyelid ptosis and hypothermia in mice. [g] It brings about a rise in blood sugar level in rats by 20%. [h] In the infiltration anaesthesia test in guinea-pigs a 1% solution of the substance is more effective than a 1% solution of procaine; in the corneal anaesthesia test in rabbits the substance is similarly effective as cocaine. [i] It brings about inhibition of barium chloride contractions of isolated rat duodenum in an extent similar to that caused by papaverine. [j] Central depressant effect displayed by inhibition of motility of mice in known surroundings. [k] In tests done *in vitro* it inhibits growth of *Mycobacterium tuberculosis* H37Rv at the minimum concentration of 50 μg/ml and *Trichophyton mentagrophytes* 125 μg/ml. [l] It has a local anaesthetic effect in the test of infiltration and corneal anaesthesia but weaker than the standards used (procaine, cocaine). [m] Solvate with one-half molecule of ethanol. [n] It has a brief myorelaxant effect on rat gastrocnemius muscle. [o] An indication of antiarrhythmic effect toward ventricular fibrillation in mice as caused by chloroform. [p] It depresses the blood sugar level in mice by 20%; a slight effect observed even after oral administration. [q] It prolongs slightly thiopental sleep in mice. [r] At doses greater than D it brings about signs of central depression in mice. [s] It inhibits growth of *Trichophyton mentagrophytes* at 125 μg/ml. [t] It decreases slightly the pupil diameter in mice (miosis). [u] It increases slightly the skin temperature of guinea-pigs which suggests a vasodilating effect. [v] Monohydrate. [w] At the oral dose shown it does not affect blood pressure (estimated 3 h after application) in DOCA-hypertensive rats (Dr M. Vaněček, Pharmacological department of this Institute). [x] *In vitro*, the compound shows antimicrobial activity of a relatively wide spectrum (minimum inhibitory concentrations are shown, in μg/ml): *Streptococcus β-haemolyticus*, 12·5; *Staphylococcus pyogenes aureus*, 12·5; *Klebsiella pneumoniae*, 50; *Salmonella typhi abdominalis*, 50; *Mycobacterium tuberculosis* H37Rv, 50. [y] A significant anticonvulsant effect toward pentetrazol convulsions in mice; indication of anticonvulsant effect in the electro-shock test in mice. [z] It has a slight hypothermic effect in rats (rectal temperature).

chloric acid (1 : 3), the acid aqueous phase was separated, made alkaline with NH_4OH and the base was isolated by extraction with benzene; 13·5 g (78%), b.p. 127—129°C/2·5 Torr. ^{1}H-NMR spectrum: δ 6·86 (s, 2 H, aromatic protons), 3·44 (s, 2 H, $ArCH_2N$), 2·30—2·90 (m, 14 H, 4 NCH_2 and 2,6-$Ar(CH_3)_2$), 2·24 (s, 6 H, 4-Ar—CH_3, NCH_3). Neutralization of the base with maleic acid in boiling ethanol and standing overnight yielded the dimaleate, m.p. 184—187°C (ethanol).

1-(2,4,6-Trimethylbenzyl)piperazine (*V*)

A mixture of 54 g *IV* (Table I), 52 g solid KOH and 55 ml ethanol was refluxed under stirring for 4 h (a 110—120°C bath). After cooling, it was diluted with 80 ml water and the product was isolated by extraction with benzene; 28·5 g (70%), m.p. 99—100°C (ethanol). NMR spectrum: δ 6·83 (s, 2 H, aromatic protons), 3·39 (s, 2 H, $ArCH_2N$), 2·72 (m, 4 H, $CH_2N^4CH_2$ of piperazine), c. 2·40 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·34 (s, 6 H, 2,6-$Ar(CH_3)_2$), 2·24 (s, 3 H, 4-Ar—CH_3), 1·46 (s, 1 H, NH). Like in the preceding case, a maleate was prepared, m.p. 176 to 178°C (aqueous ethanol).

1-Guanyl-4-(2,4,6-trimethylbenzyl)piperazine (*VI*) (Method *B*)

A mixture of 10·9 g *V*, 7·0 g S-methylisothiourea sulfate[8], 12 ml ethanol and 10 ml water was refluxed for 8 h. Some 5 ml of the solvent was then distilled off, replaced with 5 ml acetone and the solution was left overnight in the refrigerator. A total of 9·5 g (60%) hemisulfate of *VI* solvated with one-half molecule of ethanol crystallized: m.p. 234—237°C (aqueous ethanol).

1-(2,4,6-Trimethylbenzyl)-4-nitrosopiperazine (*VII*)

Base *V* (12·2 g) was dissolved in a mixture of 16·5 ml dilute hydrochloric acid (1 : 1) and 8 ml water and a solution of 5·5 g $NaNO_2$ in 16 ml water was added dropwise over a period of 30 min under stirring at 75—80°C. The mixture was stirred at 80°C for 2 h, cooled, diluted with water, made alkaline with excess $NaHCO_3$ and the product was extracted with ether. After drying the extract with $MgSO_4$ and evaporation of the ether, 13·7 g (almost theoretical yield) crude base melting at 43—44°C (light petroleum) was obtained. Neutralization with maleic acid in ethanol yielded the maleate, melting at 141—143°C (ethanol).

1-Amino-4-(2,4,6-trimethylbenzyl)piperazine (*VIII*)

A solution of 24·7 g *VII* in 300 ml ether was added dropwise over 1 h to a stirred solution of 8·3 g $LiAlH_4$ in 200 ml ether. The mixture was left overnight at room temperature, decomposed under stirring by adding dropwise 8·5 ml water, 8·5 ml 15% NaOH and 25 ml water. After 1 h of stirring the solid was filtered and washed with ether. The filtrate crystallized on standing: 20·0 g (86%), m.p. 73—74°C (light petroleum). ^{1}H-NMR spectrum: δ 6·86 (s, 2 H, aromatic protons), 3·44 (s, 2 H, $ArCH_2N$), 2·95 (bs, 2 H, NH_2), 2·54 (bs, 8 H, 4 NCH_2 of piperazine), 2·34 (s, 6 H, 2,6-$Ar(CH_3)_2$), 2·25 (s, 3 H, 4-$ArCH_3$). Neutralization of the base with methanesulfonic acid in ethanol yielded dimethanesulfonate, m.p. 219—221°C (ethanol–ether).

1-(Benzylideneamino)-4-(2,4,6-trimethylbenzyl)piperazine (*X*) (Method *C*)

Benzaldehyde (4·0 g) was added to a solution of 8·2 g *VIII* in 60 ml ethanol and the mixture was refluxed for 3 h. Cooling led to 10·0 g (88%) product which was purified by crystallization from ethanol, m.p. 99—101°C. UV spectrum: λ_{max} 292 nm (log ε 4·23). IR spectrum: 698, 760, 886

(5 adjacent and solitary Ar—H), 1450, 1568, 1593 (Ar), 1614 cm^{-1} (C=N). ^{1}H-NMR spectrum: δ 7·10—7·70 (m, 6 H, C_6H_5—CH=), 6·84 (s, 2 H, 3,5-H_2 of subst. benzyl), 3·46 (s, 2 H, $ArCH_2N$), 3·06 (t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·62 (t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·32 (s, 6 H, 2,6-$Ar(CH_3)_2$), 2·24 (s, 3 H, 4-$ArCH_3$). Like in the preceding case, a methanesulfonate was prepared, m.p. 194—197°C (ethanol).

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