NEUROTROPIC AND PSYCHOTROPIC COMPOUNDS. L.*
DERIVATIVES OF 1-(2-PHENYLTHIOBENZYL)PIPERAZINE AND 1-(2-BENZYLBENZYL)PIPERAZINE

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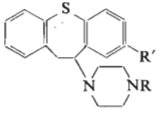
Proceeding from 2-(phenylthio)benzyl bromide and 2-benzylbenzyl bromide, substitution reactions with 1-methylpiperazine and 1-(ethoxycarbonyl)piperazine yielded *III*, *IV*, *VIII* and *IX*. The ethoxycarbonyl derivatives *IV* and *IX* were converted by hydrolysis to 1-(2-phenylthiobenzyl)-piperazine (*V*) and 1-(2-benzylbenzyl)piperazine (*X*). From these two secondary amines, alkylation, addition, acylation and other reactions led to derivatives *VI*, *VII* and *XI*–*XXX*. The central depressant activity of these compounds is very weak, in some cases they show a potentiation of thiopental sleep (*XVIII*, *XX*, *XXII*, *XXX*). A common property of the derivatives is a slight hypotensive activity, in some cases protracted.

In the preceding papers of this series (for a review see[1]) we described the high degree of central depressant and neuroleptic activity of 10-piperazino derivatives of 10,11-dihydrodibenzo[*b*,*f*]thiepins (*I*) and 10,11-dihydrodibenzo[*a*,*d*]cycloheptenes (*II*). In connection with the examination of one type of open-ring models of these compounds we prepared a number of derivatives of 1-(2-phenylthiobenzyl)piperazine (*III* – *VII*) and 1-(2-benzylbenzyl)piperazine (*VIII* – *XXX*) which are described here.

As starting compounds we used 2-(phenylthio)benzyl bromide, prepared by a reaction of 2-(phenylthio)benzyl alcohol[2] with hydrobromic acid, and the known 2-benzylbenzyl bromide[3]. The required 2-benzylbenzyl alcohol[2] was prepared by reduction of 2-benzylbenzoic acid[4] with sodium bis(2-methoxyethoxy)dihydroaluminate[5].



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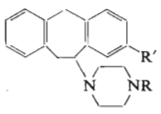

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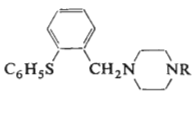

III, R = CH_3 *V*, R = H
IV, R = $COOC_2H_5$ *VI*, R = $C(=NH)NH_2$
VII, R = SO_2CH_3

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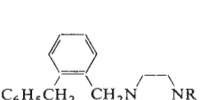
Substitution reactions of 2-(phenylthio)benzyl bromide and 2-benzylbenzyl bromide with 1-methylpiperazine[6] and 1-(ethoxycarbonyl)piperazine[7] ("method A") yielded 1,4-disubstituted piperazines *III*, *IV*, *VIII* and *IX*. The ethoxycarbonyl derivatives *IV* and *IX* were converted by alkaline hydrolysis ("method B") to the secondary amines *V* and *X* which served as intermediates for further work. 1-(2-Benzylbenzyl)piperazine (*X*) was alkylated with isopropyl bromide, n-butyl bromide, allyl bromide and propargyl bromide in boiling toluene in the presence of slight excess of triethylamine ("method C"), or with benzyl chloride in ethanol in the presence of sodium bicarbonate; this yielded the ditertiary amines *XI*–*XV*. Other 1,4-disubstituted piperazines *XVI*–*XVIII* were prepared by addition of acrylonitrile, acrylamide or methyl acrylate to 1-(2-benzylbenzyl)piperazine (*X*) under catalysis with sodium hydroxide ("method D"). The acetyl derivative *XIX* was obtained from the secondary amine *X* by heating with a mixture of acetic acid and acetic anhydride. Similarly, treatment with succinic anhydride in chloroform resulted in the 3-carboxypropionyl derivative *XX* and the action of benzoyl chloride in ether in the presence of potassium carbonate in the benzoyl derivative *XXI*. Reduction of the adduct *XVIII* with lithium aluminium hydride in ether resulted in the 3-hydroxypropyl derivative *XXII*. Analogous reduction of succinamic acid *XX* in tetrahydrofuran yielded the 4-hydroxybutyl derivative *XXIII*. The reaction of 1-(2-phenylthiobenzyl)piperazine with S-methylisothiourea sulfate in aqueous ethanol produced directly the sulfate of the guanidine derivative *VI*. Reaction of the amines *V* and *X* with methanesulfonyl chloride or with 4-toluenesulfonyl chloride in pyridine ("method E") led to the sulfonamides *VII*, *XXIV* and *XXV*. Reaction of 1-(2-benzylbenzyl)piperazine (*X*) with nitrous acid produced the nitrosamine *XXVI* which was reduced with lithium



VIII, R = CH_3
IX, R = $COOC_2H_5$
X, R = H
XI, R = $CH(CH_3)_2$
XII, R = $(CH_2)_3CH_3$
XIII, R = $CH_2CH{=}CH_2$
XIV, R = $CH_2C{\equiv}CH$
XV, R = $CH_2C_6H_5$
XVI, R = CH_2CH_2CN
XVII, R = $CH_2CH_2CONH_2$
XVIII, R = $CH_2CH_2COOCH_3$

XIX, R = $COCH_3$
XX, R = $CO(CH_2)_2CO_2H$
XXI, R = COC_6H_5
XXII, R = $CH_2CH_2CH_2OH$
XXIII, R = $CH_2CH_2CH_2CH_2OH$
XXIV, R = SO_2CH_3
XXV, R = 4-$SO_2C_6H_4CH_3$
XXVI, R = NO
XXVII, R = NH_2
XXVIII, R = $N{=}CHC_6H_5$
XXIX, R = 4-$N{=}CHC_6H_4Cl$

XXX, R = $N{=}CH$–

aluminium hydride in ether to the hydrazine derivative *XXVII*. On heating this compound with benzaldehyde, 4-chlorobenzaldehyde, or with 3,4-dimethoxybenzaldehyde in ethanol ("method F") we obtained the corresponding hydrazones *XXVIII* to *XXX*. A survey of all the piperazine derivatives prepared may be found in Table I.

The following substances were tested pharmacologically in a wider set of tests of general screening (the way of administration, the acute toxicity value for mice LD_{50} in mg/kg, and finally the dose in mg/kg, used in most *in vivo* tests, are shown): *V*-mesylate (*i.v.*, 43·7, 9·0), *VI*-hemisulfate (*p.o.*, > 150), *VIII*-maleate (*i.v.*, 50, 10), *VIII*-methiodide (*i.v.*, 2·5, 0·5), *IX*-hydrogen maleate (*i.v.*, 200, 40), *X*-maleate (*i.v.*, 50, 10), *XI*-maleate (*i.v.*, 30, 6), *XII*-di(hydrogen maleate) (*i.v.*, 37·5, 7), *XIII*-di(hydrogen maleate) (*i.v.*, 45, 9), *XIV*-di(hydrogen maleate) (*i.v.*, 87·5, 17), *XV*-di(hydrogen maleate) (*p.o.*, 1 500, 300), *XVI*-maleate (*i.v.*, 100, 20), *XVII*-maleate (*i.v.*, 87·5, 17), *XVIII*-maleate (*p.o.*, 1 500, 300), *XIX*-hydrogen maleate (*i.v.*, 62·5, 12), *XX*-hydrogen maleate (*i.v.*, 225, 45), *XXI*-hydrogen maleate (*p.o.*, >2500, 300), *XXII*-maleate (*i.v.*, 65, 13), *XXIV*-hydrogen maleate (*p.o.*, > 2 500, 300), *XXV*-hydrogen maleate (*p.o.*, >2 500, 300), *XXVI*-hydrogen maleate (*p.o.*, 1 000, 200), *XXVII*-di(hydrogen maleate) (*i.v.*, 125, 25), *XXVIII*-maleate (*p.o.*, >2 500, 300), *XXIX*-maleate (*p.o.*, 1 500, 300), *XXX*-maleate (*p.o.*, > 2 500, 300).

The central depressant activity is found in slight indications with *XV*, *XVIII*, *XXIV* and *XXVI*. In several cases, a mild to pronounced potentiation of thiopental sleep in mice (*XVIII*, *XX*, *XXII*, *XXX*) and a slight to pronounced hypothermic effect in rats (*XVIII*, *XX*, *XXVI*) was recorded. Compounds *XI* and *XXVI* showed anticonvulsant activity toward pentazol in mice, compound *XXX* also against electro-shock. Compounds *V*, *XIV*, *XX*, in high doses, display excitatory activity, at the normal doses used an antireserpine activity in the ptosis test in mice (*V*, *XX*) or potentiation of phenmetrazine in mice (*XX*). With compound *V* a local anaesthetic activity was found in the test of infiltration anaesthesia in guinea pigs which was more pronounced than the effect of "procaine". However, the compound causes also irritation. Compound *V* has a spasmolytic effect on rat duodenum against acetylcholine contractions of a degree similar to that of "adiphenine". This activity is shown in a similar extent by the methiodide of *VIII*. This compound has also a myorelaxant activity of the curare type toward the neuromuscular preparation of rat gastrocnemius muscle *in vivo*. Compound *XVIII* showed a considerable antihistamine activity in the detoxication test in guinea pigs.

The common property of almost the whole series of the new compounds is a hypotensive effect in the test with rats. Short-time drops of blood pressure (*VIII*-CH_3I, *X*, *XIII*, *XVI*, *XXVI*, *XXIX*) as well as protracted slight depressions (*V*, *VIII*, *IX*, *XIV*, *XVII*, *XIX*, *XX*, *XXV*) were observed. With the guanidine derivative *VI*, a qualitatively similar activity spectrum as with guanethidine was found; the hypotensive effect of the compound in the test using narcotized cats is much weaker. Compound *XVIII* brings about a drop of blood pressure only after 24 h following application. With compound *XIX*, detailed experiments on rats with experimental hypertension (DOCA) did not confirm the hypotensive effect found in normotensive rats and the compound does not bring about a drop of pressure in monkeys with normal pressure. Similarly, the hypotensive effect of *XXV* was not confirmed in a test with rats with experimental hypertension. Compound *XXVII* applied to rats brings about a short-period drop of blood pressure which is followed by a rise. A slight hypertension effect was observed with *XXVIII*. Compound *VIII* shows a coronary dilation in a Langendorf preparation. Antiarrhythmic effect (toward aconitine) in rats was recorded with compounds *V* and *VIII*. Compound *V*, at the same time, is a cardiodepressant for isolated rabbit auricle. Compound *XVII* shows a negative chronotropic effect and compound *XXII* shows a negative inotropic as well as chronotropic effect. Some compounds

TABLE I

Piperazine Derivatives *III*—*XXX*

Compound[a]	Method (yield, %)	M.p., °C (solvent) and/or b.p., °C/Torr	Formula (m.w.)	Calculated/Found			
				% C	% H	% N	% S(Cl)
III-M	A	160·5—162·5	$C_{22}H_{26}N_2O_4S$	63·75	6·32	6·76	7·72
	(92)	(ethanol)	(414·5)	63·66	6·32	6·98	7·86
IV	A[b]	232—234/2	$C_{20}H_{24}N_2O_2S$	67·38	6·79	7·86	8·99
	(91)		(356·5)	67·40	6·90	7·97	8·97
V	B[b]	194—195/2	$C_{17}H_{20}N_2S$	71·80	7·09	9·85	11·25
	(87)		(284·3)	71·60	7·17	9·92	11·24
V-MS	—	118—120	$C_{18}H_{24}N_2O_3S_2$	56·81	6·36	7·36	16·85
		(acetone)	(380·5)	56·88	6·31	7·28	16·95
VI-½ H_2SO_4	[b]	237—238	$C_{18}H_{22}N_4S$	57·57	6·17	14·92	12·81
		(50% ethanol)	½ H_2SO_4	57·41	6·04	14·58	12·45
			(375·5)				
VII[c]	E	75—77	$C_{18}H_{22}N_2O_2S_2$	58·19	6·24	7·54	—
	(94)	(benzene–light petroleum)	. ½ H_2O	57·95	6·20	7·60	
			(371·5)				
VIII-M	A	162—164	$C_{23}H_{28}N_2O_4$	69·67	7·13	7·06	—
	(88)	(ethanol)	(396·5)	69·60	7·19	7·02	
VIII-CH_3I	—	243—245	$C_{20}H_{27}IN_2$	56·87	6·44	6·63	30·05[d]
		(95% ethanol)	(422·3)	56·82	6·46	6·64	29·97
IX-HM	A	139—140	$C_{25}H_{30}N_2O_6$	66·05	6·65	6·16	—
	(89)	(ethanol)	(454·5)	65·82	6·54	6·17	
X[e]	B	59—61	$C_{18}H_{22}N_2$	81·16	8·33	—	—
	(87)	(light petroleum) 164—167/1·5	(266·4)	80·63	8·27		
X-M	—	157—158	$C_{22}H_{26}N_2O_4$	69·09	6·85	7·33	—
		(ethanol)	(382·4)	69·03	6·86	7·21	
X-P	—	171—172·5	$C_{24}H_{25}N_5O_7$	58·17	5·09	14·14	—
		(ethanol)	(495·5)	58·28	5·24	14·29	
XI-M	C	169—171	$C_{25}H_{32}N_2O_4$	70·72	7·60	—	—
		(ethanol)	(424·5)	70·30	7·57		
XII-2 HM	C[b]	180—181·5	$C_{30}H_{38}N_2O_8$	64·96	6·91	5·05	—
	(79)	(acetone)	(554·6)	64·92	6·89	5·14	
XIII-2 HM[f]	C	171—173	$C_{29}H_{34}N_2O_8$	64·67	6·36	5·20	—
	(70)	(ethanol)	(538·6)	64·64	6·42	5·23	
XIV-2 HM[g]	C	154—156	$C_{29}H_{32}N_2O_8$	64·91	6·01	5·22	—
	(29)	(ethanol)	(536·6)	64·94	6·04	5·35	
XV	[b]	65·5—67·5	$C_{25}H_{28}N_2$	84·22	7·93	7·86	—
		(ethanol)	(356·5)	84·75	7·94	7·68	

TABLE I
(*Continued*)

Compound[a]	Method (yield, %)	M.p., °C (solvent) and/or b.p., °C/Torr	Formula (m.w.)	Calculated/Found			
				% C	% H	% N	% S(Cl)
XV-2 HM	—	189—191·5 (95% ethanol)	$C_{33}H_{36}N_2O_8$ (588·6)	67·33 67·09	6·16 6·32	4·76 5·05	—
XVI	D[b] (84)	94·5—95·5 (ethanol)	$C_{21}H_{25}N_3$ (319·4)	78·96 78·92	7·89 8·07	13·16 12·86	—
XVI-M	—	143—145·5 (ethanol)	$C_{25}H_{29}N_3O_4$ (435·5)	68·94 68·68	6·71 6·78	9·65 9·87	—
XVII[h]	D (78)	103·5—105·5 (benzene)	$C_{21}H_{27}N_3O$ (337·5)	74·74 75·13	8·07 8·24	12·45 12·68	—
XVII-M	—	169—171 (ethanol)	$C_{25}H_{31}N_3O_5$ (453·5)	66·20 66·19	6·89 7·00	9·27 8·95	—
XVIII-M	D (93)	149—152 (95% ethanol)	$C_{26}H_{32}N_2O_6$ (468·5)	66·65 66·47	6·88 7·00	5·98 5·98	—
XIX	[b]	79—81 (ether–light petroleum)	$C_{20}H_{24}N_2O$ (308·4)	77·88 77·95	7·84 8·04	9·08 9·24	—
XIX-HM	—	161—163 (ethanol)	$C_{24}H_{28}N_2O_5$ (424·5)	67·90 67·74	6·65 6·72	6·60 6·72	—
XX[c]	[b]	124—125 (ethanol)	$C_{22}H_{26}N_2O_3 . \frac{1}{2} H_2O$ (375·5)	70·37 70·03	7·25 7·16	7·46 7·13	—
XX-HM[c]	—	143—146 (ethanol–ether)	$C_{26}H_{30}N_2O_7 . \frac{1}{2} H_2O$ (490·5)	63·66 63·56	6·16 6·08	5·71 5·66	—
XXI	[b]	105—108 (ethanol)	$C_{25}H_{26}N_2O$ (370·5)	81·04 81·12	7·07 7·15	7·56 7·12	—
XXI-HM	—	161—163 (ethanol)	$C_{29}H_{30}N_2O_5$ (486·6)	71·58 71·62	6·22 6·24	5·76 5·54	—
XXII	[b]	81—83 (light petroleum)	$C_{21}H_{28}N_2O$ (324·5)	77·73 77·93	8·70 8·53	8·63 8·92	—
XXII-M	—	123—124 (ethanol)	$C_{25}H_{32}N_2O_5$ (440·5)	68·16 68·31	7·32 7·34	6·36 6·54	—
XXIII	[b]	72—73 (benzene–light petroleum)	$C_{22}H_{30}N_2O$ (338·5)	78·06 77·86	8·93 8·99	8·28 8·25	—
XXIII-HM[c]	—	161—167 (ethanol)	$C_{30}H_{38}N_2O_9 . \frac{1}{2} H_2O$ (579·6)	62·16 62·24	6·78 6·54	4·83 4·64	—

TABLE I
(*Continued*)

Compound[a]	Method (yield, %)	M.p., °C (solvent) and/or b.p., °C/Torr	Formula (m.w.)	Calculated/Found			
				% C	% H	% N	% S(Cl)
XXIV	E	91—92·5	$C_{19}H_{24}N_2O_2S$	66·26	7·02	8·13	9·30
	(79)	(ethanol)	(344·4)	65·70	6·96	8·42	9·48
XXIV-HM	—	163—165	$C_{23}H_{28}N_2O_6S$	59·99	6·13	6·08	6·95
		(ethanol)	(460·5)	59·96	6·05	6·02	7·14
XXV	E[b]	151—154	$C_{25}H_{28}N_2O_2S$	71·39	6·71	6·66	7·62
	(94)	(ethanol)	(420·6)	71·39	6·74	6·60	7·88
XXV-HM	—	190·5—193·5	$C_{29}H_{32}N_2O_6S$	64·90	6·01	5·22	6·02
		(90% ethanol)	(536·6)	64·92	5·98	5·01	6·08
XXVI-HCl	[b]	188	$C_{18}H_{22}ClN_3O$	—	—	12·64	—
		(ethanol)	(331·8)			12·31	
XXVI-M	—	117	$C_{22}H_{25}N_3O_5$	64·22	6·12	10·21	—
		(ethanol)	(411·4)	64·03	6·46	9·96	
XXVII-2 HM	[b]	158—160	$C_{26}H_{31}N_3O_8$	60·81	6·08	8·18	—
		(ethanol)	(513·5)	60·87	6·22	8·62	
XXVIII	F[b]	85·5—88	$C_{25}H_{27}N_3$	81·26	7·37	11·37	—
	(98)	(ethanol)	(369·5)	81·24	7·37	11·46	
XXVIII-M	—	161—164	$C_{29}H_{31}N_3O_4$	71·72	6·44	8·65	—
		(ethanol)	(485·6)	71·79	6·44	8·50	
XXIX	F	94·5—95·5	$C_{25}H_{26}ClN_3$	74·33	6·49	10·40	8·78
	(88)	(ethanol)	(403·9)	74·59	6·62	10·32	8·98
XXIX-M	—	164—167	$C_{29}H_{30}ClN_3O_4$	66·98	5·82	8·08	6·82
		(90% ethanol)	(520·0)	67·36	5·96	7·98	6·67
XXX	F	103—104	$C_{27}H_{31}N_3O_2$	75·49	7·27	9·78	—
	(100)	(ether–light petroleum)	(429·5)	75·51	7·25	9·58	
XXX-M	—	148—150	$C_{31}H_{35}N_3O_6$	68·24	6·47	7·70	—
		(ethanol)	(545·6)	68·22	6·52	7·73	

[a] M maleate, MS methanesulfonate, HM hydrogen maleate, P picrate. [b] See the Experimental section. [c] Hemihydrate. [d] Iodine content. [e] NMR spectrum: δ 7·21 (singlet, 9 H of aromatic rings), 4·16 (singlet, 2 H of the diphenylmethane CH_2 group), 3·39 (singlet, 2 H of the benzylamine CH_2 group), 2·60—3·00 (multiplet, 4 H of the CH_2 groups in the piperazine ring in the vicinity of NH), 2·10—2·55 (multiplet, 4 H of the remaining CH_2 groups of the piperazine ring), 2·24 (singlet, 1 H of the NH group, disappears on deuterization). [f] Crude base boils at 178—180°C/1·5 Torr. [g] Crude base boils at 185—195°C/0·8 Torr. [h] NMR spectrum: δ 7·20 (singlet, 9 H of aromatic rings), 8·15 and 5·80 (singlets, 2 H of the $CONH_2$ group), 4·14 (singlet 2 H of the diphenylmethane CH_2 group), 3·40 (singlet, 2 H of the benzylamine CH_2 group), 2·00—2·80 (multiplet, 12 H of the remaining CH_2 groups).

displayed a diuretic effect on mice (*XII*, *XVIII*, *XXV*, *XXVIII*) and a hypoglycaemic effect on rats (*XII*, *XXVII*).

In several cases, a more pronounced antimicrobial activity was observed *in vitro* (the minimum inhibitory concentration in μg/ml is shown) using *Mycobacterium tuberculosis* H 37 Rv (*IX*, 12·5; *XII*, 25; *XV*, 25), *Streptococcus β-haemolyticus* (*VI*, 12·5; *XXV*, 25) and *Staphylococcus pyogenes aureus* (*XXV*, 25).

EXPERIMENTAL

The melting points of analytical samples were determined in Kofler's block and the samples were dried in the usual way. Analyses of all the piperazine derivatives and of their salts are shown in Table I. The NMR spectra (in deuteriochloroform) were recorded in a ZKR 60 (Zeiss, Jena) spectrometer, the IR spectra (in Nujol) using a Unicam SP 200G spectrophotometer and the one UV spectrum (in methanol) using a Unicam SP 700 spectrophotometer.

2-(Phenylthio)benzyl Bromide

A mixture of 100 g 2-(phenylthio)benzyl alcohol[2] and 320 ml 48% hydrobromic acid was refluxed under stirring for 3 h. After cooling, it was diluted with 1·5 liter water and extracted with chloroform. The extract was washed with water, dried with magnesium sulfate and distilled: 121 g (94%), b.p. 162–164°C/2 Torr. For $C_{13}H_{11}BrS$ (279·2) calculated: 55·92% C, 3·97% H, 28·63% Br, 11·48% S; found: 55·94% C, 3·75% H, 28·37% Br, 11·27% S.

2-Benzylbenzyl Alcohol

Sodium bis(2-methoxyethoxy)-dihydroaluminate[5] (162 ml 50% benzene solution) was added dropwise under stirring to a solution of 42·4 g 2-benzylbenzoic acid[4] in 300 ml benzene at 45 to 50°C. The mixture was stirred for 3 h at room temperature, decomposed under cooling with cold water by adding dropwise 280 ml 10% sodium hydroxide, the benzene layer was separated, washed with water, dried (K_2CO_3) and distilled: 30·1 g (76%), b.p. 132°C/1 Torr. For the product obtained by analogous reduction with lithium aluminium hydride we published[2] a b.p. of 128 to 130°C/2 Torr.

1-(2-Phenylthiobenzyl)-4-(ethoxycarbonyl)piperazine (*IV*) ("Method A")

A mixture of 25·0 g 2-(phenylthio)benzyl bromide and 42·8 g 1-(ethoxycarbonyl)piperazine[7] was heated under stirring for 3 h at 120°C. After cooling, it was mixed with 130 ml 10% solution of sodium hydroxide and, after shaking, extracted with ether. The extract was washed with water, dried (K_2CO_3) and distilled: 29·0 g (91%), b.p. 232–234°C/2 Torr. Compounds *III*, *VIII* and *IX* shown in Table I were prepared similarly.

1-(2-Phenylthiobenzyl)piperazine (*V*) ("Method B")

Solid sodium hydroxide (22·7 g) was added to a solution of 29·0 g compound *IV* in 23 ml ethanol and the mixture was refluxed at 110–120°C. After cooling, it was diluted with 100 ml water and extracted with benzene. The extract was dried (K_2CO_3) and distilled: 20·2 g (87%), b.p. 194 to 195°C/2 Torr. NMR spectrum: δ 7·25 (singlet, 5 H of phenyl), 7·00–7·60 (multiplet, 4 H of disubstituted benzene ring), 3·61 (singlet, 2 H of the benzyl CH_2 group), 2·80 (multiplet, 4 H of the CH_2 groups of the piperazine ring vicinal to the NH group), 2·45 (multiplet, 4 H of the remaining CH_2 groups of the piperazine ring), 1·62 (singlet, 1 H of the NH group, disappears on deuterization). On neutralization with methanesulfonic acid in ethanol the base yields a monomethanesulfonate, m.p. 118–120°C (acetone). Compound *X* was obtained in a similar way.

1-(2-Benzylbenzyl)-4-(n-butyl)piperazine (*XII*) ("Method C")

Triethylamine (7·0 ml) and 5·0 g n-butyl bromide were added to a solution of 7·8 g amine *X* in 50 ml toluene and the mixture was refluxed for 12 h in a 110°C bath. After cooling, 75 ml benzene and 100 ml water were added and, after shaking, the benzene layer was separated, washed with water, dried with K_2CO_3 and treated by distillation; 7·5 g (79%), b.p. 177—182°C/1 Torr, m.p. 38—40°C. The crude base was neutralized with maleic acid in ethanol to the di(hydrogen maleate), m.p. 180—181·5°C (acetone). A similar procedure was used for the preparation of *XI*, *XIII* and *XIV*.

1-(2-Benzylbenzyl)-4-benzylpiperazine (*XV*)

Sodium bicarbonate (8·4 g) was added to a solution of 13·3 g amine *X* in 100 ml ethanol (50°C), followed by a dropwise addition of 7·6 g benzyl chloride. The mixture was heated for 3 h to 75°C, cooled and, after standing overnight, the inorganic salts were removed by filtration. The filtrate was evaporated in a rotary evaporator at reduced pressure. The yield of the base (17·7 g) corresponded to the theoretical. M.p. 65·5—67·5°C (ethanol). The di(hydrogen maleate) was prepared in the usual way: m.p. 189—191·5°C (95% ethanol).

1-(2-Benzylbenzyl)-4-(2-cyanoethyl)piperazine (*XVI*) ("Method D")

A solution of 4·5 g acrylonitrile in 15 ml tert butyl alcohol was added dropwise over 30 min to a solution of 15·0 g amine *X* in 70 ml tert butyl alcohol at 50°C. The solution was stirred for 2 h at room temperature; after 1 h 0·4 g solid sodium hydroxide was added. Stirring continued for 3 h at 50—60°C, the mixture was left at room temperature overnight and the solvent was evaporated at reduced pressure. The residue was dissolved in 250 ml benzene, the solution was washed with water, dried with $MgSO_4$ and evaporated. The residue (15·1 g, 84%) is the required base, m.p. 94·5—95·5°C (ethanol). NMR spectrum: δ 7·60—6·85 (deformed singlet, 9 H of aromatic rings), 4·15 (singlet, 2 H of diphenylmethane CH_2), 3·40 (singlet, 2 H of benzylamine CH_2), 2·90—2·15 (multiplet, 12 H of CH_2 groups of the piperazine ring and the side chain). The usual procedure was applied for the preparation of maleate, m.p. 143—145·5°C (ethanol). Compounds *XVII* and *XVIII* were prepared similarly.

1-(2-Benzylbenzyl)-4-acetylpiperazine (*XIX*)

A mixture of 13·9 g amine *X*, 70 ml acetic acid and 10·5 g acetic anhydride was heated for 2 h to 70°C and refluxed for further 2 h. The volatile components were evaporated at reduced pressure, the residue was mixed with 100 ml water and 10 ml concentrated aqueous ammonia and the mixture was extracted with 150 ml benzene. The extract was washed with water, dried (K_2CO_3) and evaporated: 15·9 g (98%), m.p. 79—81°C (ether–light petroleum). UV spectrum: λ_{max} 262 nm (log ε 2·740), 269 nm (2·635). IR spectrum: 700, 749 and 753 (monosubstituted and 1,2-disubstituted benzene), 1635 cm^{-1} (—CONRR'). Hydrogen maleate was prepared in the usual manner, m.p. 161—163°C (ethanol).

1-(2-Benzylbenzyl)-4-(3-carboxypropionyl)piperazine (*XX*)

A mixture of 16·0 g amine *X*, 6·0 g succinic anhydride and 450 ml chloroform was refluxed for 10 h. Succinic anhydride (3·0 g) was then added and refluxing continued for further 7 h. After cooling, the mixture was filtered, the filtrate evaporated and the residue recrystallized from 55 ml benzene; 17·7 g (80%), hemihydrate of the base melted at 124—125°C. The hydrogen maleate prepared in the usual way also crystallizes as hemihydrate, m.p. 143—146°C (ethanol–ether).

1-(2-Benzylbenzyl)-4-benzoylpiperazine (*XXI*)

Anhydrous potassium carbonate (13·8 g) was added to a solution of 8·0 g amine *X* in 70 ml ether and this was followed with 4·3 g benzoyl chloride. The mixture was stirred for 2 h at room temperature and then refluxed for 2 h. After evaporation of ether the residue was shaken with 200 ml water and 200 ml chloroform. The organic layer was washed with water, dried ($MgSO_4$) and evaporated; 10·3 g (92%), m.p. 105–108°C (ethanol). Hydrogen maleate was prepared in the usual way, m.p. 161–163°C (ethanol).

1-(2-Benzylbenzyl)-4-(3-hydroxypropyl)piperazine (*XXII*)

A solution of 14·0 g 1-(2-benzylbenzyl)-4-(2-methoxycarbonylethyl)piperazine (*XVIII*) in 100 ml ether was added under stirring to a suspension of 4·6 g lithium aluminium hydride in 100 ml ether. The mixture was stirred for 1 h at room temperature and refluxed for 3 h. After cooling, it was decomposed by adding dropwise 4·6 ml water, 4·6 ml 15% sodium hydroxide and 13·8 ml water, the mixture was filtered and the filtrate evaporated. The residue was dissolved in 100 ml chloroform, the solution was washed with water and evaporated again: 10·3 g (80%), m.p. 81–83°C (light petroleum). NMR spectrum: 7·18 (singlet, 9 H of aromatic rings), 4·11 (singlet, 2 H of the diphenylmethane CH_2 group), 3·76 (triplet, 2 H of the CH_2 group in CH_2OH), 3·38 (singlet, 2 H of the benzylamine CH_2 group), 2·20–2·74 (multiplet, 10 H of the other $—NCH_2$-groups), 1·40–1·94 (multiplet, 2 H of the middle CH_2 group of the aliphatic chain), 5·34–4·34 (broad singlet, 1 H of the OH group, disappears after deuterization). The compound can be converted to the maleate, melting at 123–124°C (ethanol).

1-(2-Benzylbenzyl)-4-(4-hydroxybutyl)piperazine (*XXIII*)

A solution of 7·3 g *XX* in 120 ml tetrahydrofuran was added dropwise under stirring to a solution of 2·8 g lithium aluminium hydride in 50 ml tetrahydrofuran. The mixture was refluxed for 10 h and, after cooling, it was decomposed and processed as in the preceding case. A total of 5·0 g (74%) crude base was obtained from which di(hydrogen maleate) was first prepared and purified by crystallization from ethanol. It crystallizes as hemihydrate melting at 161–167°C. From this the base was released by aqueous ammonia and isolated by extraction with benzene: m.p. 72 to 73°C (benzene–light petroleum). IR spectrum: 693, 732 and 752 (monosubstituted and 1,2-disubstituted benzene), 1071 (CH_2OH), 1600 (Ar), 2770 ($N\text{-}CH_2$), 3200 cm^{-1} (OH).

1-(2-Phenylthiobenzyl)-4-guanylpiperazine (*VI*)

A solution of 6·95 g S-methylisothiuronium sulfate in 10 ml water was added to a solution of 14·2 g amine *V* in 15 ml ethanol and the mixture was refluxed for 8 h. The hemisulfate of the product precipitated on standing overnight, was filtered and recrystallized from 50% ethanol: 8·5 g, m.p. 238–239°C.

1-(2-Benzylbenzyl)-4-(4-toluenesulfonyl)piperazine (*XXV*) ("Method E")

A solution of 5·8 g 4-toluenesulfonyl chloride in 10 ml benzene was added dropwise under stirring to a solution of 8·0 g amine *X* in 50 ml pyridine. The mixture was stirred for 2 h at room temperature and left to stand overnight. Then it was diluted with 200 ml benzene and washed several times with water, the solution was dried with K_2CO_3 and evaporated: 11·9 g (94%), m.p. 151–154°C (ethanol). Hydrogen maleate was prepared in the usual way: m.p. 193–195°C (90% ethanol). The sulfonamides *VII* and *XXIV* were prepared analogously.

1-(2-Benzylbenzyl)-4-nitrosopiperazine (*XXVI*)

Dilute (1 : 1) hydrochloric acid (30 ml) was added to a suspension of 13·3 g amine *X* in 100 ml water and, over a period of 15 min, a solution of 6·0 g sodium nitrite in 15 ml water was added dropwise at room temperature. The mixture was stirred while being heated to 60°C and then left at room temperature overnight. The precipitated hydrochloride of the product was filtered (the sample was recrystallized from ethanol, m.p. 188°C), was dissolved in hot water, made alkaline with 50% sodium hydroxide to release the base and this was isolated by extraction with benzene; 13·4 g (91%). The crude base was converted to hydrogen maleate, m.p. 117°C (ethanol).

1-(2-Benzylbenzyl)-4-aminopiperazine (*XXVII*)

A solution of 13·3 g base *XXVI* in 150 ml ether was added dropwise to a suspension of 6·8 g lithium aluminium hydride in 100 ml ether and the mixture was refluxed under stirring for 4 h. After cooling, it was decomposed with water and processed in the usual way. A total of 11·3 g (89%) crude base was obtained. The base was converted to di(hydrogen maleate), m.p. 158—160°C (ethanol).

1-(2-Benzylbenzyl)-4-(benzylideneamino)piperazine (*XXVIII*) ("Method F")

A solution of 5·35 g base *XXVII* and 2·12 g pure benzaldehyde in 25 ml ethanol was refluxed for 6 h. After standing overnight the precipitated product was filtered; 6·9 g (98%), m.p. 85·5 to 88°C (ethanol). Maleate can be prepared in the usual way: m.p. 161—164°C (ethanol). Compounds *XXIX* and *XXX* were prepared analogously.

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