1-(3-DIMETHYLAMINO-1-PHENYLPROPYL)PIPERAZINES AND RELATED COMPOUNDS: SYNTHESIS AND PHARMACOLOGICAL SCREENING*

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Substitution reactions of N,N-dimethyl-3-chloro-3-phenylpropylamine with 1-methylpiperazine and a series of analogues afforded 1-(3-dimethylamino-1-phenylpropyl)piperazines *I*— *V*. A similar substitution with piperidine resulted in the diamine *VIII*. Hydrolysis of the carbamate *V* gave the secondary amine *VI* which was transformed by alkylation with cyclopropylmethyl bromide to compound *VII*. 3-Dimethylamino-3-phenylpropanol was treated with thionyl chloride to give N,N-dimethyl-3-chloro-1-phenylpropylamine (*IX*) which reacted with 1-methylpiperazine and afforded the triamine *X*. The maleates of the amines prepared exhibited hypotensive effects of short duration (*III*, *IV*, *VI*, *VII*, *X*) and moderate antiarrhythmic effects (*V*— *VIII*). The phenylpiperazine derivative *III* showed a significant antiarrhythmic action and a a high local anaesthetic activity.

Several reports[1-4] described 1-benzylpiperazine as a central stimulant and 1-(3,4-methylenedioxybenzyl)-4-(4-chlorophenoxyacetyl)-piperazine (fipexide, ref.[5]) likewise was characterized as a psychotonic with antireserpine and central stimulant activity. A certain degree of the central stimulant activity of 1-benzylpiperazine was confirmed by our group[6] and the same type of activity was found with some derivatives of 1-benzylpiperazine substituted in the benzene nucleus[6-8]. Derivatives of 1-benzylpiperazine with bulky substituents in *ortho*-position of the benzene nucleus showed rather central depressant than stimulant properties[9] and 1-benzylpiperazine derivatives with an arylthiomethyl as substituent on the benzyl α-carbon were almost devoid of central activity[10]. The purpose of the present paper was to study the influence of 2-dimethylaminoethyl as a substituent on the benzyl α-carbon in a series of 1-benzylpiperazine derivatives on the central activity. To this end, a series of the title compounds *I* – *VII* has been prepared.

The known N,N-dimethyl-3-chloro-3-phenylpropylamine hydrochloride[11-13] was subjected to reactions with 1-methylpiperazine, 1-(3-hydroxypropyl)piperazine[14], 1-phenylpiperazine[15], 1-benzylpiperazine and 1-(ethoxycarbonyl)piperazine in boiling

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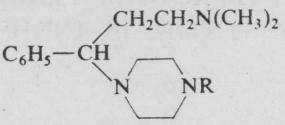
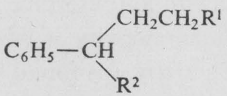
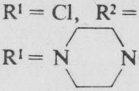


I, R = CH_3 *IV*, R = $CH_2C_6H_5$
II, R = $(CH_2)_3OH$ *V*, R = $COOC_2H_5$
III, R = C_6H_5 *VI*, R = H
VII, R = CH_2– 

acetone and in the presence of potassium carbonate (method *A*); 1,4-disubstituted piperazines *I* – *V* were obtained in this way. The carbamate *V* was hydrolyzed with potassium hydroxide in a small volume of ethanol and converted to the secondary amine *VI* which was alkylated with cyclopropylmethyl bromide in 1-butanol in the presence of potassium carbonate at 120°C and gave the compound *VII*. Method A and the use of piperidine led to the diamine *VIII*. For preparing the isomer of compound *I* with reversed residues of dimethylamine and methylpiperazine, *i.e.* compound *X*, 3-dimethylamino-3-phenylpropanol[16] was used as the starting material. Its reaction with thionyl chloride in chloroform gave N,N-dimethyl-3-chloro--1-phenylpropylamine hydrochloride (*IX*). In spite of the fact that the halogen atom in this compound is relatively little reactive, we succeeded in carrying out its reaction with 1-methylpiperazine using the conditions of method *A* and obtained the desired compound *X* in a satisfactory yield. Compounds prepared by method *A* are assembled in Table I with the usual experimental data.



VIII, $R^1 = N(CH_3)_2$, $R^2 =$ 
IX, $R^1 = Cl$, $R^2 = N(CH_3)_2$
X, $R^1 =$  NCH_3, $R^2 = N(CH_3)_2$

Compounds *I* – *VIII* and *X* were pharmacologically tested in the form of hydrogen maleates (Table I) using a general screening program; they were administered intravenously. Numbers of compounds, values of acute toxicities in mice (LD_{50} in mg/kg), the doses used for the screening (D in mg/kg) and the effects found are given: *I*, 100, 20 no significant effects; *II*, 87·5, 18, mild and brief drops of blood pressure in normotensive rats, a mild positive effect on the inotropy of the isolated rabbit heart atrium; *III*, 5, 1, significant and brief drops of blood pressure, a significant antiarrhythmic effect towards ventricular extrasystoles in rats elicited with aconitine (more active

TABLE I

1-(3-Dimethylamino-1-phenylpropyl)piperazines and the related compounds prepared by the method *A*

Compound[a] (% yield)	B.p., °C/Pa or m.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found		
			% C	% H	% N
I	125/50[b]	$C_{16}H_{27}N_3$	73·51	10·41	16·08
(60)		(261·4)	73·56	10·47	15·77
I-3 HM	164—165	$C_{28}H_{39}N_3O_{12}$	55·16	6·45	6·89
	(ethanol)	(609·6)	55·39	6·56	7·00
II	170/40	$C_{18}H_{31}N_3O$	70·78	10·23	12·76
(69)		(305·5)	71·13	10·20	13·27
II-3 HM	142—143	$C_{30}H_{43}N_3O_3$	55·12	6·63	6·43
	(ethanol)	(653·7)	55·57	6·55	6·39
III-2 HM	173—174	$C_{29}H_{37}N_3O_8$	62·69	6·71	7·56
(83)	(aqueous ethanol)	(555·6)	62·96	6·84	7·66
IV-3 HM	166—168	$C_{34}H_{43}N_3O_{12}$	59·55	6·32	6·13
(81)	(aqueous ethanol)	(685·7)	59·39	6·40	6·11
V	175/80	$C_{18}H_{29}N_3O_2$	67·58	9·15	13·15
(87[c])		(319·4)	67·21	9·33	12·93
V-2 HM	105—107	$C_{26}H_{37}N_3O_{10}$	56·61	6·76	7·62
	(ethanol)	(551·6)	56·54	7·05	7·57
VIII	109/50[d]	$C_{16}H_{26}N_2$	77·99	10·64	11·37
(98)		(246·4)	77·89	10·68	11·20
VIII-2 HM	162—163	$C_{24}H_{34}N_2O_8$	60·24	7·16	5·85
	(ethanol)	(478·5)	60·47	7·41	5·92
X	124—125/70	$C_{16}H_{27}N_3$	73·51	10·41	16·08
(67)		(261·4)	73·55	10·37	15·77
X-3 HM	163—164	$C_{28}H_{39}N_3O_{12}$	55·16	6·45	6·89
	(aqueous ethanol)	(609·6)	54·97	6·45	6·86

[a] HM hydrogen maleate. [b] ^{1}H-NMR spectrum: δ 7·28 (s, 5 H, C_6H_5), 3·31 (t, J = 6·0 Hz, 1 H, ArCH), 2·42 (s, 4 H, CH_2CH_2N of the side chain), 2·22 (s, 3 H, NCH_3), 2·15 (s, 6 H, CH_3NCH_3), 2·00—2·40 (m, 8 H, 4 NCH_2 of piperazine). [c] See Experimental. [d] ^{1}H-NMR spectrum: δ 7·28 (s, 5 H, C_6H_5), 3·35 (t, J = 6·0 Hz, 1 H, ArCH), *c.* 2·30 (m, 3 H, CH_2CH_2N of the side chain), 2·15 (s, 6 H, CH_3NCH_3), *c.* 2·15 (m, 4 H, CH_2NCH_2 of piperidine), 1·40 (m, 6 H, remaining 3 CH_2 of piperidine).

than quinidine and procainamide used as standards), in a concentration of 1% it brings about a complete and long-lasting anaesthesia in the test of infiltration anaesthesia in guinea-pigs (equipotent with procaine), an important negative effect on the inotropy of the isolated rabbit heart atrium; *IV*, 25, 5, mild and brief drops of blood pressure. a negative effect on the heart inotropy; *V*, 125, 25, brief drops of blood pressure, a mild antiarrhythmic effect towards ventricular fibrillations elicited by inhalation of chloroform in mice, a slight negatively inotropic effect; *VI*, 100, 20, brief drops of blood pressure, a mild effect towards chloroform arrhythmia in mice and a slight positively inotropic effect; *VII*, 87·5, 17, brief drops of blood pressure, antiarrhythmic effect towards chloroform in mice; *VIII*, 75, 15, significant and brief drops of blood pressure, a mild antiarrhythmic effect against chloroform in mice; *X*, 150, 30, brief drops of blood pressure. None of the compounds showed typical central effects (neither depressant not stimulant).

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected. The samples were dried at about 50 Pa over P_2O_5 at room temperature or at 77°C. ^{1}H-NMR spectra (in C^2HCl_3) were recorded with a ZKR 60 (Zeiss, Jena) apparatus. The homogeneity of the compounds was checked by chromatography on thin layers of alumina.

1-(3-Dimethylamino-1-phenylpropyl)-4-(ethoxycarbonyl)piperazine (*V*) (Method *A*)

A mixture of 23·4 g N,N-dimethyl-3-chloro-3-phenylpropylamine hydrochloride[11–13] 39·5 g 1-(ethoxycarbonyl)piperazine, 200 ml acetone and 16·7 g K_2CO_3 was stirred and refluxed for 8 h. After standing overnight the inorganic salts were filtered off, the filtrate was evaporated, the residue dissolved in 200 ml benzene, the solution washed with water, dried with Na_2SO_4 and distilled; 27·7 g (87%), b.p. 175°C/80 Pa. Neutralization of the base with maleic acid in ethanol and addition of ether gave the bis(hydrogen maleate), m.p. 105—107°C (ethanol). Analyses of the base and of the salt were included in Table I.

1-(3-Dimethylamino-1-phenylpropyl)piperazine (*VI*)

A mixture of 20·5 g *V*, 10·3 g KOH and 20 ml ethanol was stirred and refluxed for 2·5 h in a bath of 120—125°C. After cooling the mixture was diluted with 150 ml water and extracted with benzene. The aqueous layer was saturated with K_2CO_3 and extracted with chloroform. The benzene and chloroform extracts were combined, dried with K_2CO_3 and distilled; 11·5 g (73%), b.p. 123°C/53 Pa. For $C_{15}H_{25}N_3$ (247·4) calculated: 72·81% C, 10·19% H; found: 72·48% C, 10·45% H.

Dimaleate, m.p. 156—159°C (ethanol). For $C_{23}H_{33}N_3O_8$ (479·5) calculated: 57·61% C, 6·94% H, 8·76% N; found: 57·57% C, 6·98% H, 8·80% N.

1-(3-Dimethylamino-1-phenylpropyl)-4-(cyclopropylmethyl)piperazine (*VII*)

A mixture of 7·1 g *VI*, 4·5 g K_2CO_3, 4·45 g cyclopropylmethyl bromide and 80 ml 1-butanol was stirred and heated for 20 h to 120—125°C. After cooling the salts were filtered off, the filtrate

was evaporated under reduced pressure and the residue was chromatographed on a column of 230 g neutral Al_2O_3 (activity II). Benzene eluted 3·0 g (35%) homogeneous oily base which was neutralized with 3·35 g maleic acid in 6 ml boiling ethanol. The addition of 20 ml ether and crystallization gave 5·3 g tris(hydrogen maleate), m.p. 141—143°C (acetone). For $C_{31}H_{43}N_3 \cdot O_{12}$ (649·7) calculated: 57·31% C, 6·67% H, 6·47% N; found: 57·34% C, 6·80% H, 6·28% N.

N,N-Dimethyl-3-chloro-1-phenylpropylamine (*IX*)

A solution of 9·0 g 3-dimethylamino-3-phenylpropanol (b.p. 134—136°C/1·1 kPa; lit.[16], b.p. 124—126°C/0·53 kPa) in 20 ml chloroform was added dropwise over 40 min to a stirred solution of 13 g $SOCl_2$ in 15 ml chloroform at room temperature. The mixture was refluxed for 2 h, allowed to stand overnight and evaporated under reduced pressure. There were obtained 10·6 g (90%) hydrochloride, m.p. 134—137°C. Analytical sample, m.p. 135—137°C (acetone–ether). For $C_{11}H_{17}Cl_2N$ (234·2) calculated: 56·42% C, 7·32% H, 30·28% Cl, 5·98% N; found: 56·15% C, 7·27% H, 30·15% Cl, 5·70% N.

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