POTENTIAL GANGLIONIC AND NEUROMUSCULAR BLOCKING AGENTS: 1-ARYL-4-METHYL-4-SUBSTITUTED PIPERAZINIUM IODIDES*

Z. KOPICOVÁ, J. NĚMEC and M. PROTIVA

Research Institute of Pharmacy and Biochemistry, 130 00 Prague 3

Received May 14th, 1975

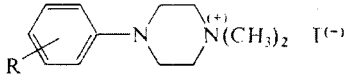
Addition of 1-phenylpiperazine and of its *o*-, *m*-, and *p*-methyl, *o*-fluoro, *o*- and *m*-chloro, and *m*-trifluoromethyl derivatives to acrylonitrile, acrylamide and ethyl acrylate yielded 1,4-disubstituted piperazines *II*—*IV* which reacted with methyl iodide to the monoquaternary piperazinium iodides *V*—*VII*. The compounds have the character of peripheral myorelaxants, depress briefly the blood pressure of normotensive rats and show a positive inotropic effect on isolated rabbit atrium.

1,1-Dimethyl-4-phenylpiperazinium iodide[1] (DMPP, *Ia*) has aroused the interest of pharmacologists some time ago when it was found to stimulate sympathetic as well as parasympathetic ganglia[2-4], to be suitable for testing the effect of ganglioplegics[5] but under certain conditions to display a ganglioplegic effect[6]. Its typical effects on heart inotropy and frequency have also been described[7]. Its *o*-methyl derivative (*Ib*) has an analogous gangliostimulating effect while the *o,o'*-dimethyl derivative is practically ineffective[8]. The carba analogue of *Ia*, *i.e.* 1,1-dimethyl-4-phenylpiperidinium iodide, shows also a powerful stimulating effect on autonomic ganglia[9]; replacement of one of the methyls with isopropyl, resulting in 1-isopropyl-1-methyl-4-phenylpiperidinium iodide, causes the reversal of the action and the product becomes a ganglioplegic[9]. In connection with our systematic studies in the field of structure-activity relationships of piperazine derivatives[10-13] we describe now the preparation and the results of pharmacological screening of the series of 1-alkyl-4-aryl-1-methylpiperazinium iodides *V*—*VII*, substituted in the alkyl residue with a functional group, *i.e.* cyano (*V*), aminocarbonyl (*VI*) and ethoxycarbonyl (*VII*). In connection with the case cited[9] one could expect in the substances a ganglioplegic rather than a gangliostimulating activity.

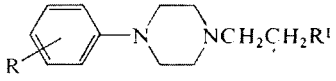
1-Phenylpiperazine[14-16] and its *o*-, *m*-, and *p*-methyl[17], *o*-fluoro[18], *o*- and *m*-chloro[17,19] and *m*-trifluoromethyl[20] derivatives were added to acrylonitrile, acrylamide and ethyl acrylate, yielding 1,4-disubstituted piperazines *II*—*IV*. The nitriles *II*

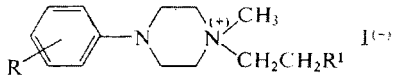
* Part XCV in the series Neurotropic and Psychotropic Agents; Part XCIV: This Journal *41*, 443 (1976).

were prepared according to the literature: *IIa–d* (ref.[21]), *IIf* (refs[19,22]), *IIg* (ref.[21]) (see also ref.[23]), *IIh* (ref.[20]). The hitherto undescribed *o*-fluoro derivative *IIe* was obtained analogously (method[21]) and was converted to the methiodide in the crude state. Amides *IIIa–IIId* and *IIIg* and esters *IVe* and *IVf* were prepared by addition



I





II, $R^1 = CN$
III, $R^1 = CONH_2$
IV, $R^1 = COOC_2H_5$

V, $R^1 = CN$
VI, $R^1 = CONH_2$
VII, $R^1 = COOC_2H_5$

In all formulae: *a*, R = H; *b*, R = *o*-CH_3; *c*, R = *m*-CH_3; *d*, R = *p*-CH_3; *e*, R = *o*-F; *f*, R = *o*-Cl; *g*, R = *m*-Cl; *h*, R = *m*-CF_3.

of the corresponding arylpiperazines to acrylamide and to ethyl acrylate, respectively, dissolved in tert-butyl alcohol at 50–60°C in the presence of benzyltriethylammonium hydroxide as catalyst. All the amides shown are known compounds and had been prepared by hydration of the corresponding nitriles with sulfuric acid[21] but the esters are novel compounds. All the ditertiary bases *II–IV* underwent addition of methyl iodide in ethanol or methanol or best without any solvent. The yields of the monomethiodides *V–VII* were 60–95% as shown in Table I.

Table II includes the results of orientative pharmacological screening of the piperazinium iodides *V–VII* prepared which, using *in vivo* tests, were administered intravenously. The compounds tested are all rather toxic. In normotensive rats they bring about a drop of blood pressure, apparently in consequence of ganglioplegic action[6,9]. All of them display a peripheral myorelaxant effect on the rat gastrocnemius muscle, mostly of brief duration. Using isolated rabbit atrium, heart inotropy and frequency were affected, a positive inotropic effect clearly predominating. When estimating the acute toxicity for mice, higher doses mostly brought about a central depression. None of the compounds was selected for detailed tests.

The compounds prepared were tested for antimicrobial activity *in vitro* (Dr J. Turinová, Dr A. Čapek) at the bacteriological department of this institute; in only two microorganisms and with but a few compounds an antimicrobial effect was established (species, compound and minimum inhibitory concentration in μg/ml are shown): *Mycobacterium tuberculosis* H37Rv: *Vd*, 50; *VIc*, 50; *Trichophyton mentagrophytes*: *Vc*, 125; *VIc*, 125; *VId*, 125; *VIIe*, 125.

TABLE I

1-Aryl-4-methyl-4-substituted Piperazinium Iodides *V*— *VII*

Compound	M.p., °C (solvent)	Formula (mol.wt.)	Calculated/Found			
			% C	% H	% N	% I
Va	166—167 (95% ethanol)	$C_{14}H_{20}IN_3$ (357·2)	47·07 47·02	5·64 5·68	11·76 11·75	— —
Vb	174·5—176·5 (aqueous ethanol)	$C_{15}H_{22}IN_3$ (371·3)	48·52 48·41	5·97 6·06	11·32 11·22	34·18 34·21
Vc	158—159 (aqueous ethanol)	$C_{15}H_{22}IN_3$ (371·3)	48·52 48·47	5·97 6·04	11·32 11·01	34·18 33·95
Vd	160·5—163 (95% ethanol)	$C_{15}H_{22}IN_3$ (371·3)	48·52 48·42	5·97 5·91	11·32 11·65	34·18 33·91
Ve	141—142 (95% ethanol)	$C_{14}H_{19}FIN_3$ (375·2)	44·81 44·86	5·10 5·30	5·06[a] 4·77	33·82 33·94
Vf	174—176·5 (aqueous ethanol)	$C_{14}H_{19}ClIN_3$[b] (391·7)	42·93 42·95	4·89 4·81	10·73 10·92	32·40 32·43
Vg	151—152 (aqueous ethanol)	$C_{14}H_{19}ClIN_3$[c] (391·7)	42·93 42·81	4·89 4·80	10·73 10·70	32·40 32·86
Vh	182—184 (95% ethanol)	$C_{15}H_{19}F_3IN_3$ (425·2)	42·36 42·21	4·50 4·43	— —	29·84 29·59
VIa	201—203 (aqueous ethanol)	$C_{14}H_{22}IN_3O$ (375·2)	44·81 44·81	5·91 5·98	11·20 11·05	33·82 33·69
VIb	224—225 (aqueous ethanol)	$C_{15}H_{24}IN_3O$ (389·3)	46·28 46·34	6·21 6·28	10·80 10·33	32·60 32·94
VIc	184—186 (95% ethanol)	$C_{15}H_{24}IN_3O$ (389·3)	46·28 46·34	6·21 6·26	10·80 10·47	32·60 32·70
VId	206·5—207·5 (95% ethanol)	$C_{15}H_{24}IN_3O$ (389·3)	46·28 46·29	6·21 6·11	10·80 10·65	32·60 32·52
VIg	155—156·5 (95% ethanol)	$C_{14}H_{21}ClIN_3O$ (409·7)	41·04 41·48	5·17 5·09	10·26 10·46	8·65[d] 8·76
VIIe	159—161 (acetone)	$C_{16}H_{24}FIN_2O_2$ (422·3)	45·51 45·74	5·73 5·74	4·50[a] 4·30	30·05 30·20
VIIf	124—126 (acetone)	$C_{16}H_{24}ClIN_2O_2$[e] (438·7)	43·80 43·54	5·51 5·45	6·39 6·39	28·92 29·01

[a] Content of fluorine. [b] Calculated: 9·05%; found: 9·20% Cl. [c] Calculated: 9·05% Cl; found: 9·27% Cl. [d] Content of chlorine. [e] Calculated: 8·27% Cl; found: 8·16% Cl.

TABLE II

Pharmacological Properties of Piperazinium Iodides *V— VII* (intravenous administration in tests *in vivo*; doses in mg/kg)

Compound	LD_{50}[a]	D[b]	Effect on blood pressure[c]	Myorelaxant effect[d]	Heart inotropy and frequency[e]	Other effects
Va	30·0	6·0	brief drop	brief effect	negatively inotropic	[f,g]
Vb	6·25	1·0	bried drop	significant effect[h]	—	
Vc	25·0	5·0	minute changes	brief effect	positively chronotropic	[f,g,i]
Vd	30·0	6·0	prolonged drop	brief effect	positively inotropic	[g]
Vf	6·25	1·0	prolonged drop	brief effect	positively inotropic	[f]
Vg	17·5	3·5	brief rise[j]	brief effect	—	[g]
Vh	17·0	3·5	brief rise	brief effect	—	[k]
VIb	7·5	1·5	prolonged drop	brief effect	positively inotropic	[g,m]
VIc	45·0	9·0	brief drop	brief effect	positively inotropic	[g]
VId	62·5	12·0	prolonged drop	brief effect	positively inotropic and chronotropic	[g]
VIg	25·0	5·0	brief drop	brief effect	—	[k]
VIIe	20·0	4·0	prolonged drop	brief effect	positively inotropic	
VIIf	12·5	2·5	brief drop	brief effect	positively inotropic and chronotropic	[g]

[a] Acute toxicity for mice on *i.v.* administration. [b] Dose at which the compound was applied *in vivo*. [c] Experiments were done with normotensive rats in pentobarbital narcosis; the blood pressure was measured with an electromanometer in the femoral artery. [d] Compounds were applied at $2LD_{50}$ *i.v.* to rats (the animal connected to a respiratory pump); the myorelaxing effect was evaluated from the inhibition of contractions of gastrocnemius muscle brought about by excitation of a severed sciatic nerve; doses D were usually without effect. [e] Isolated rabbit atrium was used for the tests; compounds applied at 50 μg/ml. [f] It brings about a brief hyperglycemia in rats. [g] In doses above D there are signs of central depression in rats. [h] At dose D a brief effect. [i] At dose D it potentiates thiopental sleep in mice. [j] At dose D/2 it brings about a brief drop of blood pressure followed by a hypertension reaction. [k] It extends significantly the survival of mouse myocard during asphyxia. [m] In an infiltration anaesthesia test (guinea-pigs) the compound shows a greater effect than procaine and in a test on rats it has an antiarrhythmic effect toward aconitine arrhythmia.

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 IR spectra (in Nujol) were recorded in a Unicam SP 200G spectrophotometer.

1-(2-Aminocarbonylethyl)-4-phenylpiperazine (*IIIa*)

A mixture of 10·6 g 1-phenylpiperazine[14], 25 ml tert-butyl alcohol and 1·5 ml 50% methanolic solution of benzyltriethylammonium hydroxide was heated to 50°C and, at that temperature, a solution of 5·0 g acrylamide in 20 ml tert-butyl alcohol was added dropwise over a period of 25 min. The mixture was stirred for 5 h at 50–60°C, left to stand overnight at room temperature, the precipitated product was filtered and washed with some ethanol and light petroleum; 11·2 g (74%), m.p. 166–168°C. Ref.[21] reports a m.p. of 170·7–171·6°C for an analytically pure product obtained by a different procedure.

An analogous method was used for the preparation of: 1-(2-aminocarbonylethyl)-4-(*o*-tolyl)-piperazine (*IIIb*) in a 52% yield, m.p. 132–135°C (ref.[21] reports a m.p. of 129·1–129·9°C); 1-(2-aminocarbonylethyl)-4-(*m*-tolyl)piperazine (*IIIc*), 66%, m.p. 139–145·5°C (ref.[21] reports 144·9 to 145·9°C); 1-(2-aminocarbonylethyl)-4-(*p*-tolyl)piperazine (*IIId*), 60%, m.p. 195–196°C (ref.[21] reports 191·5–192·5°C); 1-(2-aminocarbonylethyl)-4-(*m*-chlorophenyl)piperazine (*IIIg*), 57%, m.p. 141–145°C (ref.[21] reports 147·5–148·2°C).

1-(2-Ethoxycarbonylethyl)-4-(*o*-fluorophenyl)piperazine (*IVe*)

Like in the preceding case, 7·2 g 1-(o-fluorophenyl)piperazine[18] reacted with 8·7 ml ethyl acrylate in 12 ml tertiary butyl alcohol in the presence of 0·8 ml 50% methanolic solution of benzyltriethylammonium hydroxide. The tert-butyl alcohol was then evaporated at reduced pressure, the residue was mixed with some water and the product was isolated by extraction with ether. Distillation yielded 5·5 g (65%) product boiling at 173–176°C/3 Torr. IR spectrum: 750 (4 adjacent Ar—H), 1012 (C—F), 1240 (C—O of ester,) 1500, 1610 (Ar), 1736 cm^{-1} (RCOOR'). For $C_{15}H_{21}FN_2O_2$ (280·3) calculated: 64·26% C, 7·55% H, 6·78% F; found: 63·97% C, 7·19% H, 6·55% F.

1-(2-Ethoxycarbonylethyl)-4-(*o*-chlorophenyl)piperazine (*IVf*)

Like in the preceding case, 13·8 g 1-(*o*-chlorophenyl)piperazine[17] reacted with 15·2 ml ethyl acrylate in 25 ml tert-butyl alcohol in the presence of 1·5 ml catalyst. Further processing yielded 12·0 g (58%) product, most of which distilled at 193–195°C/2·9 Torr. For $C_{15}H_{21}ClN_2O_2$ (296·8) calculated: 60·70% C, 7·13% H, 11·95% Cl, 9·44% N; found: 60·68% C, 7·13% H, 12·28% Cl, 9·50% N.

1-(2-Ethoxycarbonylethyl)-4-(*o*-fluorophenyl)-1-methylpiperazinium Iodide (*VIIe*)

A mixture of 5·5 g base *IVe* with 20 ml methyl iodide was left to stand for 24 h at room temperature. The precipitated product was filtered and washed with ether: 7·9 g (95%), m.p. 147–157°, after recrystallization from acetone m.p. 159–161°C. IR spectrum: 770 (4 adjacent Ar—H), 1018 (C—F), 1210 (C—O of ester), 1500, 1610 (Ar), 1720 (RCOOR') cm^{-1}. The analysis is shown in Table I. If the analogous reactions were carried out in ethanol or methanol, a smaller excess of methyl iodide was used, as well as a longer reaction period (7 days) and lower yields were obtained (about 60%).

The authors are indebted to Dr E. Svátek (physico-chemical department of this institute) for measuring and interpreting the IR spectra, and to Mr M. Čech, Mrs J. Komancová, Mr K. Havel, Mrs V. Šmídová and Mrs J. Hrdá (analytical department of this institute) for carrying out the analyses.

REFERENCES

1. Weston A. W., Hamlin K. E. jr (Abbott Laboratories): U.S. 2 636 032 (21. IV. 1953); Chem. Abstr. *48*, 6474 (1954).
2. Chen G., Portman R., Wickel A.: J. Pharmacol. Exp. Ther. *103*, 330 (1951); Chem. Abstr. *46*, 1156 (1952).
3. Ambache N.: Arch. Int. Pharmacodyn. Ther. *97*, 427 (1954); Chem. Abstr. *48*, 11 638 (1954).
4. Gyermek L.: *Drugs Affecting the Peripheral Nervous System*, Vol. 1 (A. Burger, Ed.), p. 149, 183. Marcel Dekker, New York 1967.
5. Chen G. (Parke Davis & Co): U.S. 2 778 772 (22. I. 1957); Chem. Abstr. *51*, 6096 (1957).
6. Leach G. D. H.: J. Pharm. Pharmacol. *9*, 747 (1957); Chem. Abstr. *52*, 3139 (1958).
7. Soncin E., Maffii G.: Arch. Int. Pharmacodyn. Ther. *123*, 148 (1959); Chem. Abstr. *54*, 15 676 (1960).
8. Green A. L. Marshall I. G.: Nature *228*, 1211 (1970).
9. Chen G., Parcell R. F.: Arch. Int. Pharmacodyn. Ther. *97*, 186 (1954).
10. Kopicová Z., Šedivý Z., Hradil F., Protiva M.: This Journal *37*, 1371 (1972).
11. Kopicová Z., Protiva M.: This Journal *39*, 3147 (1974).
12. Kopicová Z., Svátek E., Protiva M.: This Journal, *40*, 1960 (1975).
13. Kopicová Z., Metyšová J., Protiva M.: This Journal *40*, 3519 (1975).
14. Pollard C. B., Mac Dowell L. G.: J. Amer. Chem. Soc. *56* 2199 (1934).
15. Prelog V., Dříza G. J.: This Journal *5*, 497 (1933).
16. Vejdělek Z. J., Metyš J., Hradil F., Protiva M.: This Journal *40*, 1204 (1975).
17. Pollard C. B., Wicker T. H. jr: J. Amer. Chem. Soc. *76*, 1853 (1954).
18. Ratouis R., Boissier J. R., Dumont C.: J. Med. Chem. *8*, 104 (1965).
19. Parcell R. F. (Parke, Davis & Co.): U.S. 2 833 770 (6. V. 1958); Chem. Abstr. *52*, 15 600 (1958).
20. May & Baker Ltd.: Neth Appl. 65/4788 (Brit. Appl. 14. IV. 1964); Chem. Abstr. *64*, 9744 (1966).
21. Pollard C. B., Rietz E. G., Robbins R.: J. Amer. Chem. Soc. *75*, 2989 (1953).
22. Hayao S., Schut R. N.: J. Org. Chem. *26*, 3414 (1961).
23. Najer H., Giudicelli J. F. (Synthelabo): Ger. Offen. 2 245 826 (Fr. Appl. 30. IX. 1971).

Translated by A. Kotyk.