2-(PIPERAZINOMETHYL)-6,7,8,9-TETRAHYDRO-5*H*-BENZOCYCLOHEPTENES*

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Substitution reactions of 2-chloromethyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene with 1-methylpiperazine, 1-arylpiperazines *XVI*—*XIX*, 1-(arylmethyl)piperazines *XX*—*XXIII* and 1-ethoxycarbonylpiperazine yielded 1,4-disubstituted piperazines *I*—*X*. Alkaline hydrolysis of the ethoxycarbonyl derivative *X* yielded the secondary amine *XI* which was converted to *XII*-*XIV*. Reaction of the amine *XI* with acetic anhydride and acetic acid leads to acetylation to the amide *XV* but mostly to an acetolysis to 2-(acetoxymethyl)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XXVII*). While with the arylpiperazine derivatives *II*—*V* the central depressant activity is most noticeable, the benzylpiperazines *VI*—*IX* are clearly anticonvulsant. Of the secondary amines, particularly *XX* and *XXI* show central stimulation while the carbamates *XXIV*—*XXVI* are central depressants.

In the preceding part of this series[1] we described the synthesis of 2-piperazino-6,7,8,9-tetrahydro-5*H*-benzocycloheptene and of several of its *N*-substitution derivatives which displayed various types of neurotropic and cardiovascular activity of moderate degree. In the present communication, the preparation and pharmacology of the derivatives of homologous 2-(piperazinomethyl)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene *I*—*XV* are taken up. The common parent compound of the whole study was 2-chloromethyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene[2] which was heated with excess 1-methylpiperazine, 1-arylpiperazines *XVI*—*XIX*, 1-benzylpiperazines *XX*—*XXIII* and 1-ethoxycarbonylpiperazine[3] (method *A*) to convert it in good yields to the desired 1,4-disubstituted piperazines *I*—*X* shown in Table I. The starting 1-arylpiperazines *XVI*—*XIX* were prepared by the described procedure[4,5] by heating the hydrochlorides of the corresponding aromatic amines with diethanolamine hydrochloride (method *B*). They were characterized as maleates (prepared in this laboratory by Dr I. Červená) and are also shown in Table I. 1-Benzylpiperazine (*XX*) was obtained through the reaction of piperazine with benzyl chloride[6]. Table I shows the appropriate hydrogen tartrate[7]. 1-(Subst-benzyl) piperazines *XXI*—*XXIII* were prepared by hydrolysis of the carbamates *XXIV*—*XXVI* using a highly concentrated ethanolic solution of potassium hydroxide (method *C*).

* Part XI in the series Benzocycloheptenes and Heterocyclic Analogues as Potential Drugs; Part X: This Journal *38*, 2989 (1973).

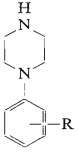
The *o*-methoxybenzyl derivative *XXII* is new while the preparation of *XXI* and *XXIII* had been described[8–10] in analogy to the preparation of *XX* (ref.[6]). Only the 4-methoxybenzyl derivative *XXIII* was prepared also by hydrolysis[11] of carbamate *XXVI*, carried out in a different way. The carbamates *XXIV–XXVI* were obtained by heating 4-chlorobenzyl chloride (commercial product), 2-methoxybenzyl chloride[12] and 4-methoxybenzyl chloride[12,13] with excess 1-ethoxycarbonylpiperazine[3] (method *D*). The first two are new, the preparation of *XXVI* was described using a different method[11]. The 4-methoxybenzyl alcohol required for the preparation of 4-methoxybenzyl chloride was obtained in a novel way, employing reduction of anisic methyl ester[14] with sodium bis(2-methoxyethoxy)dihydroaluminate[15].

Hydrolysis of carbamate *X* using method *C* resulted in the secondary amine *XI* which served as the parent substance for several further transformations. Alkylation with propargyl bromide in boiling 1-butanol in the presence of potassium carbonate yielded the propargyl derivative *XII*. Reaction of amine *XI* with 1,2-epoxypropane in methanol resulted in the aminoalcohol *XIII*. Reaction of amine *XI* with methanesulfonyl chloride in boiling benzene in the presence of pyridine led to the sulfonamide *XIV*. On the other hand, application of a boiling mixture of acetic anhydride and acetic acid resulted in a mixture of two products which were separated by distillation. The expected amide *XV* is the higher boiling product and is formed in a lesser degree. The principal product is a nitrogen-free compound which was identified as 2-(acetoxymethyl)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XXVII*). Under the drastic conditions employed, acetylation is thus dominated by acetolysis, accompanied by splitting the benzyl-N bond. The 1,4-diacetylpiperazine which is probably formed as a by-product, was not detected. In the reaction of amine *XI* with acetyl chloride in boiling benzene in the presence of pyridine, the amide *XV* is the main product. All the piperazine derivatives prepared are shown together with the experimental data in Table I while the experimental section contains only examples of preparation of the compounds by common methods *A – D* and full descriptions of preparations in which other methods were used.

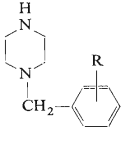
I, R = CH_3
II, R = C_6H_5
III, R = 3-$C_6H_4CH_3$
IV, R = 4-$C_6H_4CH_3$
V, R = 3-C_6H_4Cl
VI, R = $CH_2C_6H_5$
VII, R = 4-$CH_2C_6H_4Cl$
VIII, R = 2-$CH_2C_6H_4OCH_3$

IX, R = 4-$CH_2C_6H_4OCH_3$
X, R = $COOCH_2CH_3$
XI, R = H
XII, R = $CH_2C{\equiv}CH$
XIII, R = CH_2CHCH_3 (OH)
XIV, R = SO_2CH_3
XV, R = $COCH_3$

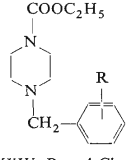
Most of the piperazine derivatives prepared were tested pharmacologically in the form of salts by methods of general screening. The results are shown in Table II, giving in the first place the mode of application, further the value of orientative acute toxicity for mice and also the dose at which the compound was applied in a series of principal *in vivo* tests. It follows from the results that the arylpiperazine derivatives *II*–*V* display the spectrum of effects of mild central depressants. In this respect the most pronounced effects were found with the phenylpiperazine derivative *II* unsubstituted in the ring. With the benzylpiperazine derivatives *VI*–*VIII*, the central depressant activity recedes somewhat in the background while an anticonvulsant activity appears, mainly again with the compound not substituted in the ring, *viz. VI*. With the benzylpiperazine intermediates, in particular *XX* and *XXI*, high doses bring about an excitatory, and convulsant effect. At *D* doses, an increased locomotor and exploratory activity can be observed. Both compounds showed antireserpine activity but only as regards the effect on reserpine hypothermia, having no effect on reserpine ptosis. The observed activity of *XX* hardly warrants its clinical applicability as an antidepressant as claimed in the patent[7]. The carbamates *XXIV*–*XXVI* display again a slight central depressant activity. With many compounds, especially following intravenous administration, a hypotensive and adrenolytic activity was found which is manifested by a deep and brief drop of blood pressure in normotensive rats (*X*, *XI*, *XXV*) or by a slight but protracted drop of blood pressure (*XV*, *XXIV*, *XXVI*). Structurally nonspecific types of activity were also encountered, such as locally anaesthetic (*X*, *XV*), spasmolytic of papaverine type (*XV*), mydriatic (*I*, *XI*). In no case were the effects such as to warrant detailed examination.



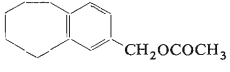
XVI, R = H
XVII, R = 3-CH_3
XVIII, R = 4-CH_3
XIX, R = 3-Cl



XX, R = H
XXI, R = 4-Cl
XXII, R = 2-OCH_3
XXIII, R = 4-OCH_3



XXIV, R = 4-Cl
XXV, R = 2-OCH_3
XVI, R = 4-OCH_3



XXVII

The compounds prepared were also tested for their antimicrobial activity *in vitro* at the bacteriological department of this institute (Dr J. Turinová, Dr A. Čapek). Some were inhibitory toward *Mycobacterium tuberculosis* H37Rv (the inhibitory concentration in μg/ml is shown): *III*, 50; *VI*, 100; *VIII*, 50; *IX*, 25; *X*, 50; *XII*, 100; *XXV*, 100; *XXVI*, 100. Three compounds were inhibitory toward *Streptococcus β-haemolyticus* (*IX*, 25; *X*, 50; *XXV*, 100), two were active against *Staphylococcus pyogenes aureus*, including a penicillin-resistant strain (*IX*, 50—100; *X*, 50). Some of the compounds have antifungal activity; thus, *II*, *III*, *IV*, *IX* and *XIV* inhibit growth of *Trichophyton mentagrophytes* at a concentration of 125 μg/ml.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected. The samples were dried in the usual way. The NMR spectra in $CDCl_3$ were recorded in a ZKR-60 (Zeiss-Jena) spectrometer. The homogeneity of the compounds was tested by thin-layer chromatography on silica gel.

2-(4-Phenylpiperazinomethyl)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*II*) (Method *A*)

A mixture of 8·0 g 2-chloromethyl-6,7,8,9-tetrahydro-5*H*-benzocycloheptene[2] and 13·3 g 1-phenylpiperazine[4] was heated under stirring for 1 h to 100°C. After cooling to 60°C, 60 ml warm water was added together with 100 ml benzene and the mixture was stirred until the solids dissolved. After separation, the benzene layer was washed with water and extracted with a mixture of 25 ml concentrated hydrochloric acid and 80 ml water. The separated oily hydrochloride was combined with the acid aqueous phase, treatment with ammonia liberated the bases which were isolated by extraction with ether. After drying the extract with anhydrous K_2CO_3, ether was evaporated and distillation *in vacuo* applied to removing the fractions boiling below 220°C/1 Torr, containing mainly the starting *XVI*. Base *II* was obtained in a yield of 11·0 g (84%) as an oil boiling at 222°C/1 Torr. Neutralization with maleic acid in hot ethanolic solution yields a maleate melting at 192 to 193°C (methanol–ether). Analytical data for the base as well as for the maleate are shown in Table I. The bases *I* and *III*—*X* (Table I) were prepared in a similar way.

1-(2-Methoxybenzyl)piperazine (*XXII*) (Method *C*)

A mixture of 53 g carbamate *XXV* and 50 ml ethanol was combined with 50 g KOH and the mixture was refluxed for 3 h (a 110°C bath). After cooling, it was dissolved in 300 ml water, the solution was saturated with potassium carbonate and the product was isolated by extraction with ether. Distillation yielded 31·2 g (79%) of base *XXII* boiling at 134—136°C/2 Torr or 124—126°C/1·8 Torr. Neutralization of a base sample with maleic acid in ethanol yielded a maleate melting at 137—139°C (ethanol). The analytical data for the base and the maleate are shown in Table I. Bases *XI*, *XXI* and *XXIII* were prepared similarly.

4-Methoxybenzyl Alcohol

A mixture of 200 g methyl ester of 4-methoxybenzoic acid[14] and 900 ml benzene was stirred at room temperature while 580 ml 50% benzene solution of sodium bis (2-methoxyethoxy)dihydroaluminate were added dropwise over the period of 1 h.[15] The turbid solution was heated for 30 min under stirring to 60°C and then stirred for 2 h at room temperature. Under external cooling with water, it was decomposed by slowly adding 1 200 ml 10% NaOH, the benzene layer was separated, washed with water, dried with K_2CO_3 and distilled; 124 g (75%), b.p. 125—127°C/10 Torr. Ref.[16] reports a b.p. of 130°C/8 Torr for a product prepared in a different way.

TABLE I

Piperazine Derivatives *I*—*XXVI*

Compound[a]	Method (% yield)	B.p., °C/Torr or m.p., °C (solvent)	Formula (m. w.)	Calculated/Found		
				% C	% H	% N
I	*A* (80)	150/1	$C_{17}H_{26}N_2$ (258·4)	79·00 79·14	10·15 10·11	—
I-2HM	—	196—197 (methanol–ether)	$C_{25}H_{34}N_2O_8$ (490·5)	61·21 61·14	6·99 7·20	5·71 5·56
II	*A*[b] (84)	222/1	$C_{22}H_{28}N_2$ (320·5)	82·45 82·62	8·81 8·88	
II-M	—	192—193 (methanol–ether)	$C_{26}H_{32}N_2O_4$ (436·5)	71·53 71·49	7·39 7·62	6·42 6·38
III	*A* (87)	222/1	$C_{23}H_{30}N_2$ (334·5)	82·58 82·58	9·04 9·15	8·38 8·13
III-M	—	161—162 (methanol–ether)	$C_{27}H_{34}N_2O_4$ (450·6)	71·97 71·76	7·61 7·78	6·22 6·31
IV	*A* (66)	225/1	$C_{23}H_{30}N_2$ (334·5)	82·58 83·01	9·04 8·95	8·38 8·21
IV-M	—	169—170 (methanol–ether)	$C_{27}H_{34}N_2O_4$ (450·6)	71·97 71·81	7·61 7·70	6·22 6·07
V	*A* (77)	232/1	$C_{22}H_{27}ClN_2$ (354·9)	74·44 75·09	7·67 7·72	7·90[c] 7·76
V-M	—	170—171 (ethanol–ether)	$C_{26}H_{31}ClN_2O_4$ (471·0)	66·30 66·11	6·63 6·69	5·95[d] 5·81
VI	*A* (96)	215/1	$C_{23}H_{30}N_2$ (334·5)	82·58 82·88	9·04 9·17	8·38 8·23
VI-2HM	—	198—200 (methanol–ether)	$C_{31}H_{38}N_2O_8$ (566·6)	65·70 65·70	6·77 6·81	4·95 5·13
VII	*A* (79)	235/1	$C_{23}H_{29}ClN_2$ (368·9)	74·87 74·90	7·92 7·84	7·60[e] 7·50
VII-2HM	—	206—207 (methanol–ether)	$C_{31}H_{37}ClN_2O_8$ (601·1)	61·94 62·00	6·20 6·13	4·66[f] 4·70
VIII	*A* (92)	235/1	$C_{24}H_{32}N_2O$ (364·5)	79·07 79·31	8·85 9·12	7·69 7·52
VIII-2HM	—	180—181 (methanol–ether)	$C_{32}H_{40}N_2O_9$ (596.7)	64·41 64·74	6·76 6·85	4·70 4·68
IX	*A* (89)	235/1	$C_{24}H_{32}N_2O$ (364.5)	79·07 79·34	8·85 8·97	7·69 7·43

TABLE I
(*Continued*)

Compound[a]	Method (% yield)	B.p., °C/Torr or m.p., °C (solvent)	Formula (m. w.)	Calculated/Found % C	% H	% N
IX-2HM	—	202—203 (methanol–ether)	$C_{32}H_{40}N_2O_9$ (596·7)	64·41 64·41	6·76 6·92	4·70 4·60
X	*A* (81)	192/0·5[g]	$C_{19}H_{28}N_2O_2$ (316·4)	72·12 72·12	8·92 8·78	— —
X-HM	—	129—130 (ethanol–ether)	$C_{23}H_{32}N_2O_6$ (432·5)	63·86 63·93	7·46 7·68	6·48 6·43
XI	*C* (91)	160/2 59—60 (hexane)	$C_{16}H_{24}N_2$ (244·4)	78·63 78·69	9·91 9·96	11·46 11·22
XI-2HM	—	166—167 (methanol–ether)	$C_{24}H_{32}N_2O_8$ (476.5)	60·49 60·93	6·77 6·88	5·88 5·88
XII	[b]	178/0·5	$C_{19}H_{26}N_2$ (282·4)	80·80 80·59	9·28 9·38	9·92 9·80
XII-2HM	—	163—164 (ethanol)	$C_{27}H_{34}N_2O_8$ (514·6)	63·02 62·59	6·66 6·70	5·44 5·33
XIII	[b]	184/0·5	$C_{19}H_{30}N_2O$ (302·5)	75·45 75·95	10·00 10·19	9·26 8·95
XIII-2HM	—	177—178 (ethanol)	$C_{27}H_{38}N_2O_9$ (534·6)	60·65 60·42	7·17 7·34	5·24 5·13
XIV	[b]	89—90 (benzene–light petroleum)	$C_{17}H_{26}N_2O_2S$ (322·4)	63·31 63·63	8·13 8·24	8·69[h] 8·47
XV	[b]	200/1	$C_{18}H_{26}N_2O$ (286·4)	75·48 75·61	9·15 9·23	— —
XV-HM	—	144—145 (ethanol–ether)	$C_{22}H_{30}N_2O_5$ (402·5)	65·65 65·86	7·51 7·53	6·96 6·63
XVI-M	*B*[4] (42)	145—147·5 (ethanol)	$C_{14}H_{18}N_2O_4$ (278·3)	60·42 60·24	6·52 6·69	10·07 10·10
XVII-M	*B*[5] (58)	136—138 (ethanol)	$C_{15}H_{20}N_2O_4$ (292·3)	61·62 61·97	6·90 7·28	9·58 9·83
XVIII-M	*B*[5] (55)	148—150 (ethanol)	$C_{15}H_{20}N_2O_4$ (292·3)	61·62 61·64	6·90 7·06	9·59 9·72
XIX-M	*B*[5] (59)	148 (ethanol)	$C_{14}H_{17}ClN_2O_4$ (312·8)	53·76 53·87	5·48 5·61	8·96[i] 9·07

TABLE I
(*Continued*)

Compound[a]	Method (% yield)	B.p., °C/Torr or m.p., °C (solvent)	Formula (m. w.)	Calculated/Found		
				% C	% H	% N
XX-T	ref.[6,7]	155·5—156·5 (aq. ethanol)	$C_{15}H_{22}N_2O_6$ (326·4)	55·20 54·87	6·80 6·91	8·58 8·46
XXI	*C* (88)	160—162/12[j]	$C_{11}H_{15}ClN_2$ (210·7)	62·70 61·85	7·17 7·24	13·30[k] 12·76
XXI-MS	—	181—182 (ethanol)	$C_{12}H_{19}ClN_2O_3S$ (306·8)	46·97 47·23	6·24 6·24	9·13[m] 8·74
XXII	*C*[b] (79)	134—136/2	$C_{12}H_{18}N_2O$ (206·3)	69·87 69·20	8·80 8·88	— —
XXII-M	—	137—139 (ethanol)	$C_{16}H_{22}N_2O_5$ (322·3)	59·61 59·94	6·88 7·03	8·69 8·72
XXIII	*C* (92)	180—182/12[n]	—	—	—	—
XXIV	*D* (88)	180—182/2·5	$C_{14}H_{19}ClN_2O_2$ (282·8)	59·46 59·44	6·77 6·84	9·91[o] 9·66
XXIV-HM	—	160—161 (ethanol)	$C_{18}H_{23}ClN_2O_6$ (398·8)	54·20 54·50	5·81 5·84	7·02[p] 6·71
XXV	*D*[b] (88)	170—173/1·3	$C_{15}H_{22}N_2O_3$ (278·3)	64·72 64·52	7·97 8·05	10·07 9·88
XXV-HM	—	141—142 (ethanol)	$C_{19}H_{26}N_2O_7$ (394·4)	57·86 58·36	6·64 6·71	7·10 7·13
XXVI	*D* (87)	178—184/1·7[q]	—	—	—	—
XXVI-HM	—	143—144 (ethanol)	$C_{19}H_{26}N_2O_7$ (394·4)	57·86 57·87	6·64 6·75	7·10 6·89

[a] M maleate, HM hydrogen maleate, T tartrate, MS methanesulfonate. [b] See experimental. [c] Calculated: 9·99% Cl; found: 10·20% Cl. [d] Calculated: 7·53% Cl; found: 7·53% Cl. [e] Calculated: 9·61% Cl; found: 9·77% Cl. [f] Calculated: 5·90% Cl; found: 5·87% Cl. [g] NMR spectrum: δ 7·00 (s, 3 H, aromatic protons), 4·10 (q, J = 7·0 Hz, 2 H, OCH_2), 3·43 (s, 2 H, $ArCH_2N$), 3·60—3·10 (m, 4 H, $CH_2N^4CH_2$), 2·75 (m, 4 H, CH_2—Ar—CH_2 in a ring), 2·34 (t, 4 H, $CH_2N^1CH_2$), 1·71 (bs, 6 H, 3 CH_2 in positions 6, 7, 8), 1·23 (t, J = 7·0 Hz, 3 H, C—CH_3). [h] Calculated: 9·94% S; found: 10·10% S. [i] Calculated: 11·34% Cl; found: 11·13% Cl. [j] For the product prepared in a reaction of piperazine with 4-chlorobenzyl bromide[8,9] or with 4-chlorobenzyl chloride[10], b.p. of 140—142°/2·5 Torr; 132—134°C/1·4 Torr; 122—126°C/0·8 Torr have been reported. [k] The product is apparently not completely pure; calculated: 16·83% Cl; found: 16·58% Cl. [m] Calculated: 11·56% Cl; 10·45% S; found: 11·20% Cl, 10·17% S. [n] M.p. 28—31°C; preparation

1-(2-Methoxybenzyl)-4-(ethoxycarbonyl)piperazine (*XXV*)
(Method *D*)

A mixture of 43 g 2-methoxybenzyl chloride[12] (b.p. 104–105°C/10 Torr) and 86 g 1-(ethoxycarbonyl)piperazine[3] was heated for 2 h to 100°C. After cooling, the mixture was combined with 220 ml water and the product was isolated by extraction with benzene. The extract was washed with water and extracted with excess dilute hydrochloric acid (240 ml, 1 : 3). The aqueous solution of the hydrochloride was shaken with excess 15% NaOH to liberate the base which was isolated by extraction with benzene; 67 g (88%), b.p. 170–173°C/1·3 Torr. Neutralization of the base with maleic acid in ethanol yielded the hydrogen maleate melting at 141–142°C (ethanol). The analytical data are shown in Table I. The carbamates *XXIV* and *XXVI* were prepared in a similar way.

2-(4-Propargylpiperazinomethyl)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XII*)

A solution of 8·2 g base *XI* in 50 ml 1-butanol was combined with 5·7 g K_2CO_3 and 4·8 g propargyl bromide and the mixture was refluxed under stirring for 12 h. After cooling, it was filtered, the filtrate was evaporated and the remaining oil was dissolved in a mixture of benzene and ether. The solution was shaken with 100 ml dilute hydrochloric acid (1 : 2), the separated hydrochloride was combined with the acid–aqueous phase and treatment with 20% NaOH liberated the base. Extraction with benzene and distillation yielded 5·8 g (62%) product, boiling at 178°C/0·5 Torr. Di(hydrogen maleate), m.p. 163–164°C (ethanol). The analytical data are shown in Table I.

2-[4-(2-Hydroxypropyl)piperazinomethyl]-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XIII*)

A solution of 7·0 g base *XI* in 15 ml ethanol was combined with slowly added 3·0 g 1,2-epoxypropane, the mixture was stirred for 2 h at room temperature and, after adding further 2·0 g epoxypropane, it was stirred for 1 h at room temperature and for 1 h at 40–50°C. After standing overnight, the mixture was distilled; 8·6 g (99%) base, b.p. 184°C/0·5 Torr. NMR spectrum: δ 7·05 (s, 3 H, aromatic protons), 3·80 (m, 1 H, CH—O), 3·44 (s, 2 H, $ArCH_2N$), 3·40 (bs, 1 H, OH), 2·80 (m, 4 H, CH_2—Ar—CH_2 in the ring), 2·10–2·60 (m, 10 H, 5 NCH_2), 1·75 (m, 6 H, 3 CH_2 in positions 6,7,8), 1·12 (d, J = 6·0 Hz, 3 H, CH_3). Di(hydrogen maleate), m.p. 177–178°C (ethanol). Analytical data in Table I.

2-(4-Methanesulfonylpiperazinomethyl)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XIV*)

Four ml pyridine were added to a solution of 6·0 g base *XI* in 40 ml benzene and 3·0 g methanesulfonyl chloride in 10 ml benzene was then added dropwise under stirring. The mixture was refluxed under stirring for 6 h, cooled and 250 ml benzene was then added and the whole mixture washed several times with water. The benzene solution was dried with K_2CO_3 and evaporated. The residue was recrystallized from a mixture of ethanol and light petroleum; 5·8 g (74%), m.p. 89–90°C (benzene–light petroleum). Analytical data in Table I.

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of the compound has been described through a reaction of piperazine with 4-methoxybenzyl bromide[8,9] or with 4-methoxybenzyl chloride[10], or else by a different modification of the present method *C* (ref.[11]); the boiling points reported are 150°C/2·5 Torr, 130–136°C/1·5 Torr, 106 to 108°C/0·05 Torr, 128–130°C/1·5 Torr. [o] Calculated: 12·54% Cl; found: 12·45% Cl. [p] Calculated: 8·89% Cl; found: 8·72% Cl. [q] Ref.[11] reports a b.p. of 159–161°C/0·5 Torr for the base obtained by reductive alkylation of 1-ethoxycarbonylpiperazine with anisaldehyde on Raney nickel.

TABLE II

Pharmacological Properties of Piperazine Derivatives

Compound[a] Application[b]	LD_{50}[c] D[d]	Effect observed
I-2HM *p.o.*	1 500 300	At doses above D it increases motility of mice, *i.e.* shows signs of central stimulant activity. At dose D it prolongs slightly thiopental sleep (*i.e.* a sign of depressant activity); a slight mydriatic effect on mice.
II-M *p.o.*	2 000 300	At dose D it displays signs of central depression in mice; it potentiates markedly the thiopental sleep in mice; it decreases the rectal temperature in rats; it has a miotic effect on mice and a peripheral vasodilating effect on guinea-pigs.
III-M *p.o.*	2 500 300	At doses above D there are signs of central depression in mice; at dose D it potentiates thiopental sleep in mice; it increases blood pressure in rats.
IV-M *p.o.*	>2 500 300	The same as with *III*.
V-M *p.o.*	>2 500 300	Central effects the same as with *III* and *IV*; it decreases slightly the blood pressure of rats.
VI-2HM *p.o.*	1 500 300	It potentiates very slightly the thiopental sleep in mice; at dose D it has an anticonvulsant effect toward pentetrazol in mice, at dose D/2 insignificant. Only a sign of anticonvulsant activity in the electro-shock test in mice.
VII-2HM *p.o.*	2 000 300	At dose D and higher it increases mouse motility; at the same time slight potentiation of thiopental sleep in mice and a slight hypothermic effect in rats; a slight anticonvulsant effect toward pentetrazol and electro-shock.
VIII-2HM *p.o.*	1 000 200	It potentiates thiopental sleep in mice and has an anticonvulsant effect toward pentetrazol in mice; slightly decreases rat blood pressure.
IX-2HM *p.o.*	1 500 300	At doses above D there are signs of central stimulation in mice; otherwise no typical effects.
X-HM *i.v.*	50 10	Symptoms of central depression in mice; a locally anaesthetic effect on rabbit cornea about the magnitude as with cocaine but it irritates; a brief drop of blood pressure of rats and inhibition of adrenaline pressor response (α-sympatholytic effect); it decreases markedly the blood sugar level in rats; it is negatively inotropic and chronotropic toward the isolated rabbit auricle.
XI-2HM *p.o.*	750 150	At high doses it inhibits the exploratory activity of mice; a slight mydriatic effect in mice.

TABLE II
(*Continued*)

Compound[a] application[b]	LD_{50}[c] D[d]	Effects observed
XII-2HM *i.v.*	100 20	At doses above D there are signs of excitation in mice; a deep and brief drop of rat blood pressure; a slight negatively inotropic effect on isolated rabbit auricle.
XIII-2HM *i.v.*	90 18	Identical with *XII*
XIV *p.o.*	2 500 300	No typical effects
XV-HM *i.v.*	75 15	At doses above D it depresses the locomotor and exploratory activity in mice; a locally anaesthetic effect on rabbit cornea; at a dose of D and D/2 a protracted drop of rat blood pressure and an adrenolytic effect; a spasmolytic effect of papaverine type toward barium chloride contractions on isolated rat duodenum.
XX–T *i.v.*	75 15	At doses above D a prolonged excitation in mice which gradually passes into convulsions with increasing dose, the animals perishing eventually. At dose D only a slight increase of locomotor and exploratory activity; it antagonizes the reserpine hypothermia in mice but does not affect ptosis and has no anticataleptic effect; it does not affect hypermotility after phenmetrazine but it potentiates its toxicity.
XXI-MS *i.v.*	55 11	At doses above D signs of excitation in mice; it antagonizes the reserpine hypothermia in mice but does not affect ptosis; central activity less pronounced than with *XX*
XXIII-M *i.v.*	62 12	No typical effects besides a myorelaxating effect on rat gastrocnemius.
XXIV-HM *i.v.*	150 30	At doses above D signs of excitation in mice; at dose D inhibition of exploratory activity and motility in familiar environment a protracted slight drop of rat blood pressure.
XXV-HM *i.v.*	150 30	It slightly potentiates thiopental sleep of mice and insignificantly decreases the body temperature of rats; briefly depresses the blood pressure of rats and causes brief bradycardia; shows a positively inotropic effect on rabbit auricle with simultaneous drop of heartbeat frequency.
XXVI-HM *i.v.*	175 35	At doses above D it shows symptoms of central depression in mice; potentiates pronouncedly thiopental sleep; slightly but protractedly decreases the blood pressure of rats and shows an adrenolytic effect.

[a] M maleate, HM hydrogen maleate, T tartrate, MS methanesulfonate. [b] *p.o.* per os, *i.v.* intravenously. [c] Acute toxicity for mice expressed by mean lethal dose in mg/kg. [d] Dose in mg/kg at which the compound was administered *in vivo*.

2-(4-Acetylpiperazinomethyl)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XV*)

A. A solution of 7·5 g base *XI* in 20 ml acetic acid was combined with 20 ml acetic anhydride and the mixture was refluxed for 4 h. After evaporation of the volatile fractions *in vacuo* the residue was decomposed with dilute NaOH and extracted with benzene. The extract was dried with K_2CO_3 and distilled. A total of 4·0 g fraction boiling at 125—126°C/0·5 Torr and 2·1 g fraction boiling at 200°C/1 Torr was obtained. The first fraction was identified as 2-(acetoxymethyl)-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (*XXVII*). NMR spectrum: δ 7·08 (s, 3 H, aromatic protons), 5·03 (s, 2 H, $ArCH_2O$), 2·80 (m, 4 H, CH_2—Ar—CH_2 in a ring), 2·08 (s, 3 H, CH_3), 1·72 (m, 6 H, 3 CH_2 in positions 6,7,8). For $C_{18}H_{26}N_2O$ (286·4) calculated: 75·48% C, 9·15% H; found: 75·61% C, 9·23% H. The second fraction is base *XV*, the analysis of which is included in Table I.

B. Three ml pyridine was added to a solution of 4·8 g base *XI* in 30 ml benzene, followed by a dropwise addition of 2 ml acetyl chloride and the mixture was refluxed for 1 h. After cooling, it was diluted with benzene, washed with water and the benzene solution was dried with K_2CO_3 and evaporated. A total of 4·2 g (75%) crude base *XV* was obtained, which was chromatographically identical with the product obtained under *A*. Hydrogen maleate, m.p. 144—145° (ethanol–ether). Analytical data in Table I.

The NMR spectra were recorded and interpreted by Dr B. Kakáč, and Dr J. Holubek at the physico-chemical department of this institute. The analyses were carried out at the analytical laboratory of the institute by Mr M. Čech, Mr K. Havel, Mrs J. Komancová, Mrs V. Šmídová and Mrs A. Slavíková. The technical cooperation of Mr F. Mikšík and Mrs P. Vejdělková is acknowledged.

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