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N-Substituted 3-Azabicyclo [3. 2. 1] octanes *

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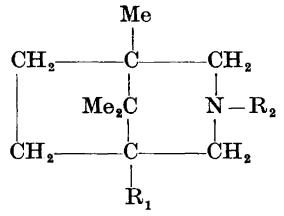
A number of N-substituted camphidine derivatives are reported. Most of them have biological activity, either as depressants of the central nervous system, or as hypotensive, ganglion blocking agents. Structure activity relations are discussed.

A preceding paper[1] reported ganglion blocking agents of the non-symmetric bis-quaternary type having one nitrogen atom form part of a camphidine ring.

In view of this action and of the similarity of the camphidine ring to tropane, the parent N-methylcamphidine (I)[2] was chosen as an interesting point of departure for further work towards structures with pharmacological action on the autonomic nervous system.

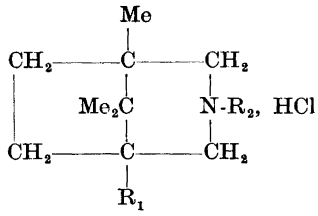
Because of a certain structural similarity to 3-methylaminoisocamphane (mecamylamine), a potent non-quaternary ganglion blocking agent, N-methylcamphidine (I) itself and a number of other simple N-substituted camphidines were examined for effect on synaptic transmission and blood pressure. These compounds are represented by the general formula (see Table 1):



I, R_1 = H, R_2 = Me
II, R_1 = Cl, R_2 = Me
III, R_1 = H, R_2 = Et
IV, R_1 = H, R_2 = *n*-Pr
V, R_1 = H, R_2 = CH_2OH

* Terpene amines II. Part I of this series: K. Rubinstein, K. Hermansen and N. Elming. *Acta Chem. Scand.* 2061 **17** (1963) 2061.

Table 1. N-Alkyl-camphidines.



Compound	R_1	R_2	Method	M.p. °C	Recryst. solvent	Yield %	Formula	Chlorine (ionic) %	
								calc.	found
I	H	Me	*a*	224–226[b]	EtOH-ether	39	$C_{11}H_{22}ClN$	17.4	17.3
II	Cl	Me	*c*	265–267	»	34	$C_{11}H_{21}Cl_2N$	14.9	14.9
III	H	Et	*d*	283–285[g]	»	27	$C_{12}H_{24}ClN$	16.3	16.4
IV	H	n-Pr	*e*	275–276[h]	EtOH	31	$C_{13}H_{26}ClN$	15.2	15.3
V	H	CH_2OH	*f*	232–233	MeCN	17	$C_{11}H_{22}ClNO$	16.2	16.2

a) From N-methyl-camphorimide [6] by reduction with lithium aluminium hydride essentially as described in the Experimental Part for the reduction of camphorimide. The hydrochloride was obtained by adding gaseous hydrogen chloride to an etheral solution of the base. *b*) Previously found [2] 226–227°. *c*) As method *a*, using N-methyl-5-chloro-camphorimide (prepared by methylation of 5-chlorocamphorimide) (*cf.* Ref.[7]) followed by reduction with lithium aluminium hydride. *d*) As method *a*, using N-ethyl-camphorimide (prepared analogously to N-methyl-camphorimide) (*cf.* Ref.[6]). *e*) As method *a*, using N-propyl-camphorimide (prepared analogously to N-methyl-camphorimide). *f*) As method *a*, using N-carbethoxycamphorimide which was prepared from N-silver-camphorimide [8] and chloroformic acid ethyl ester in a benzene suspension (shaking at room temperature for 18 h) followed by isolation by distillation. *g*) Previously found [9] 274°. *h*) Previously found [9] 278–279°.

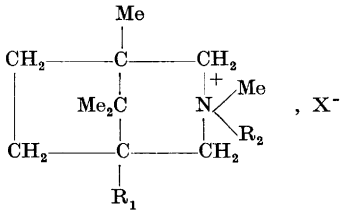
Compounds corresponding to this structure were indeed found to have some hypotensive action, apparently exerted through blockade of sympathetic synaptic transmission. This observation takes on added significance when viewed in the light of the recent observation by Edge *et al.*[3], that substituted 3-azabicyclo [3.2.1] octanes are by-products, by a unique ring expansion reaction, in the preparation of various terpene amines similar to mecamylamine. The camphidine ring thus formed a basis for the development of the polyalkyl-piperidine series of ganglion blocking agents (pempidine).[3]

Quaternization with methyl halides (see Table 2) of the N-alkyl camphidines in some cases increased the blocking effect on ganglia (VI and VII) (see Table 6).

The introduction of aralkyl groups as substituents on nitrogen led to compounds which were weak hypotensive agents. In some cases this action could be restored by methylating up to the methonium stage (VIII and IX) (see Table 6).

However, in the course of the pharmacological investigation of the tertiary N-substituted camphidines it was observed that the aralkyl-compounds produced a peculiar cataleptic syndrome in animals.[4] Hence further structural variants (X–XXVIII) were prepared and studied (see Table 3):

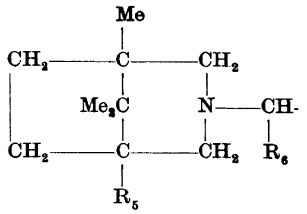
Table 2. N,N-Dialkyl-camphidines.



Compound	R_1	R_2	X	Method	M.p. °C	Recryst. solvent	Yield %	Formula	Chlorine %		Iodine %	
									calc.	found	calc.	found
VI	H	Me	I	*a*	subl. at 260[e]	EtOH-ether	72	$C_{12}H_{24}IN$			41.0	40.4
VII	Cl	Me	I	*b*	234	EtOH	38	$C_{12}H_{23}ClIN$			37.0	37.0
VIII	H	*p*-chloro-benzyl	Cl	*c*	163—166	Me_2CO-ether	27	$C_{18}H_{27}Cl_2N$	10.8	11.1		
IX	H	*o*-chloro-benzyl	I	*d*	177—179	MeCOEt-ether	25	$C_{18}H_{27}ClIN$			30.2	31.0

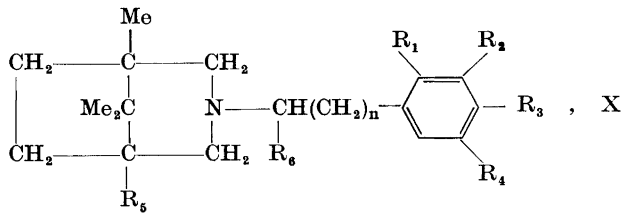
a) From an alcoholic solution of I (free base) and MeI at room temperature. *b*) From an alcoholic solution of II (free base) and MeI at 120° for 15 h. *c*) From an alcoholic solution of I (free base) and *p*-chlorobenzyl chloride [21] (reflux for 24 h). *d*) As method *a*, using XI (free base) (see Table 3) instead of I. *e*) Previously found [2] > 300° and [9] 271—273°.

Table 3. N-Aralkyl-camphidines.



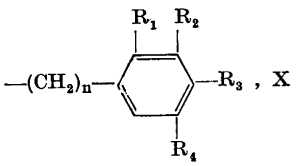
Compound	R_1	R_2	R_3	R_4	R_5	R_6	n	X	Method	M.p. °C	Recryst. solvent	Yield %	Formula
X	H	H	H	H	H	H	0	HCl	B	220–221	iPrOH-ether	19[a]	$C_{17}H_{26}ClN$
XI	Cl	H	H	H	H	H	0	HBr	B	146–147	Me_2CO-ether	61[b]	$C_{17}H_{25}BrClN$
XII	Cl	H	H	H	H	H	1	HCl	B	208–209	EtOH-ether	20[a]	$C_{18}H_{27}Cl_2N$
XIII	Cl	H	H	H	H	H	2	HCl	C	202–204	iPrOH-ether	81[b]	$C_{19}H_{29}Cl_2N$
XIV	H	Cl	H	H	H	H	0	HCl	A	234–236	EtOH-ether	69[b]	$C_{17}H_{25}Cl_2N$
XV	H	Cl	H	H	Cl	H	0	HCl	B	244–245	MeOH	73[b]	$C_{17}H_{24}Cl_3N$
XVI	H	H	Cl	H	H	H	0	HCl	B	227–229	EtOH-ether	24[a]	$C_{17}H_{25}Cl_2N$
XVII	Cl	H	Cl	H	H	H	0	HCl	A	205–207	MeCN	68[b]	$C_{17}H_{24}Cl_3N$
XVIII	NO_2	H	H	H	H	H	0	HCl	A	215–216	MeCN	46[b]	$C_{17}H_{26}ClNO_2$
XIX	H	Me	H	H	H	H	0	HCl	A	199–200	iPrOH	82[b]	$C_{18}H_{18}ClN$
XX	OMe	H	H	H	H	H	0	H_2SO_4	A	165–167	iPrOH-ether	47[b]	$C_{18}H_{29}NO_5S$[c]
XXI	OMe	H	H	H	H	H	1	HCl	C	206–207	EtOH-ether	50[b]	$C_{19}H_{30}ClNO$
XXII	H	OMe	H	H	H	H	0	HCl	A	225–227	EtOH-ether	93[b]	$C_{18}H_{28}ClNO$
XXIII	H	OMe	H	H	H	H	1	HCl	C	219–221	EtOH-ether	65[b]	$C_{19}H_{30}ClNO$
XXIV	H	OMe	OMe	H	H	H	1	HCl	C	224–226	iPrOH-ether	58[b]	$C_{20}H_{32}ClNO_2$
XXV	H	OMe	OMe	OMe	H	H	0	HCl	B	170–172	EtOH-ether	16[a]	$C_{20}H_{32}ClNO_3$
XXVI	NH_2	H	H	H	H	H	0	2HBr	(A)[e]	240–270	MeOH-ether	22[h]	$C_{17}H_{28}Br_2N_2$
XXVII	H	OH	H	H	H	H	0	HCl	(A)[f]	202–204	MeOH-ether	89[i]	$C_{17}H_{26}ClNO$
XXVIII	H	Cl	H	H	H	C_6H_5	0	HBr	A	237–239	MeOH	44[b]	$C_{23}H_{29}BrClN$

a. From the imide. *b*. From the corresponding free base. *c*. Calc. S, 8.6, Found: S, 8.7. *e*. Prepared from XVIII. *f*. Prepared from XXII. *g*. Amine nitrogen. *h*. From XVIII. *i*. From XXII. *j*. Ionic chlorine.

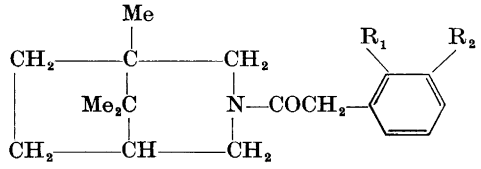


n = 0, 1 or 2
R_1, R_2, R_3, R_4, R_5 and R_6 represent H, Cl, NO_2, Me, OMe, NH_2, OH or Ph in various combinations
X = HCl, HBr or H_2SO_4

The structural variations were extended to amides exemplified by the following phenylacetylcamphidides (XXIX and XXX) (see Table 4):

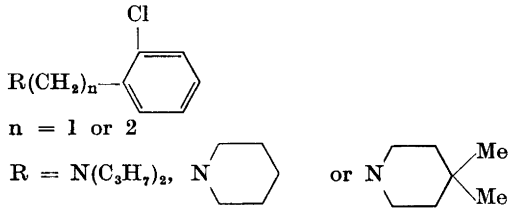


Carbon %		Hydrogen %		Nitrogen %		Chlorine %		Free base			
Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found	B.p. o/mm Hg	n_D^{25}	Nitrogen % Calc.	Nitrogen % Found
72.9	73.1	9.4	9.5	5.0	4.9	12.7	12.9	not isolated			
56.9	57.5	7.0	7.2	3.9	3.9			not isolated			
65.7	65.8	8.2	8.3	4.4	4.3	10.7	10.8[j]	not isolated			
66.6	66.9	8.5	8.7	4.1	4.1	10.4	10.3[j]	166–167/1–0	1.5310	4.6	4.5
64.9	64.7	8.0	7.9	4.5	4.4	11.3	11.3[j]	124–128/0.3	1.5351	5.0	5.0
58.5	58.6	6.9	7.0	4.0	4.1	30.5	29.6	128–132/0.04	M.p.62–64	4.5	4.4
64.9	64.6	8.0	8.1	4.5	4.4	22.6	22.3	not isolated			
58.5	58.1	6.9	6.7	4.0	4.2	10.2	10.1[j]	147–149/0.1	1.5460	4.5	4.5
62.9	62.9	7.7	7.8	8.6	8.7	10.9	10.8		M.p.69–71	4.9	4.8[g]
73.6	73.5	9.6	9.6	4.8	4.8	12.1	12.3	120–125/0.05	1.5242	5.4	5.5
58.2	58.0	7.9	7.9	3.8	3.7			140–142/1.1	1.5313	5.1	5.1
70.5	70.6	9.4	9.4	4.3	4.2	11.0	11.0	135–150/0.1	1.5295	4.9	4.7
69.8	69.7	9.1	9.1	4.5	4.5	11.4	11.7	142–145/1.0	1.5289	5.1	5.1
70.5	70.6	9.4	9.4	4.3	4.3	10.5	11.0	156–159/1.0	1.5282	4.9	4.7
67.9	67.8	9.1	8.8	4.0	3.9	10.0	10.0	179–182/0.8	1.5328	4.4	4.4
64.9	64.8	8.7	9.0	3.8	3.6	9.6	9.6	Not isolated			
48.6	48.7	6.7	6.8	6.7	6.8			Not isolated			
69.0	69.0	8.9	8.8	4.7	4.7	12.0	12.0	Not isolated			
63.5	63.5	6.7	6.7	3.2	3.2			180–185/0.3	1.5733	4.0	3.8



XXIX, R_1 = OMe, R_2 = H
XXX, R_1 = H, R_2 = OMe

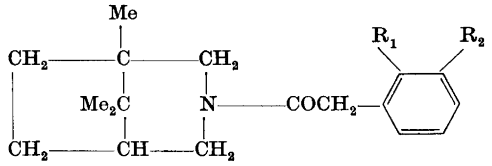
and a few derivatives containing a simple ring-system (piperidine) or an aliphatic tertiary amine (XXXI–XXXIV) (see Table 5):



n = 1 or 2

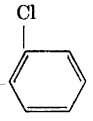
R = $N(C_3H_7)_2$, or

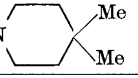
Table 4. Substituted phenylacetcamphidides.



Compound	R_1	R_2	Method	B.p. o/mm Hg	n_D^{25}	Yield %	Formula	Carbon %		Hydrogen %		Nitrogen %	
								calc.	found	calc.	found	calc.	found
XXIX	OMe	H	C	168–170/0.3	1.5420	38[a]	$C_{19}H_{27}NO_2$	75.7	75.9	9.0	9.1	4.7	4.5
XXX	H	OMe	C	175–177/0.3	1.5441	50[b]	$C_{19}H_{27}NO_2$	75.7	75.2	9.0	9.1	4.7	4.6

a. From *o*-methoxyphenylacetyl chloride. *b.* From *m*-methoxyphenylacetyl chloride.

Table 5. Substituted aralkylamines. R—$(CH_2)_n$—  , X

Compound	R	n	X	M.p. °C	Recryst. solvent	Yield %	Formula	Carbon %		Hydrogen %		Nitrogen %	
								calc.	found	calc.	found	calc.	found
XXXI	$N(n\text{-}C_3H_7)_2$	2	HBr	113–115	MeCN-ether	15[a]	$C_{14}H_{23}BrClN$	52.4	51.9	7.2	7.0	5.4	4.4
XXXII	$N(n\text{-}C_3H_7)_2$	1	HCl	142–144	iPrOH-ether	52[a]	$C_{13}H_{21}Cl_2N$	59.5	59.6	8.1	7.9	5.3	5.4
XXXIII		1	HCl	192–193	MeCN	35[a]	$C_{12}H_{17}Cl_2N$	58.5	58.9	7.0	7.0	5.7	5.7
XXXIV		1	HCl	263–264	EtOH	68[a]	$C_{14}H_{21}Cl_2N$	61.2	61.4	7.7	7.7	5.1	5.1

a. Overall yield from the corresponding aralkyl chloride.

The similarity of these latter compounds and the central nervous system depressant piperazine derivatives described by Mills *et al.*[5] should be noted.

EXPERIMENTAL *

1. N-Alkyl-camphidines (see Table 1)
2. N,N-Dialkyl-camphidines (see Table 2)
3. N-Aralkyl-camphidines (see Table 3)

Method A

The compounds XIV, XVII, XVIII, XIX, XX, XXII and XXVIII were prepared from *d*-camphidine and the appropriate substituted benzyl chlorides (*m*-chlorobenzyl chloride [10], 2,4-dichlorobenzylchloride [11], *o*-nitrobenzyl chloride [12], *m*-methylbenzyl chloride [13], *o*-methoxybenzyl chloride [14], *m*-methoxybenzyl chloride [15] and *m*-chlorobenzhydryl chloride [16]).

d-Camphidine was obtained from camphorimide by reduction with lithium aluminium hydride. This method gives better yields than the methods previously described [17,18].

d-Camphidine hydrochloride. A solution of *d*-camphorimide [19] (268 g) in anhydrous ether (5.9 l) was added during 5 h (under nitrogen) to a suspension of lithium aluminium hydride (140 g) in anhydrous ether (2.1 l). The mixture was then heated under reflux for 24 h and cooled. Water (174 ml) was added dropwise, followed by 15 % sodium hydroxide (174 ml) and water (327 ml). After 1 h the precipitate was removed by filtration and washed with ether (6 × 500 ml). The filtrate was extracted with 3 N hydrochloric acid (1 l) and the aqueous extract evaporated to dryness in a vacuum. The residue was dissolved in 3 N sodium hydroxide (600 ml) and the mixture steam distilled. The distillate (3 l) was collected in 3 N hydrochloric acid (500 ml). From time to time it was necessary to add a little methanol in order to remove camphidine from the condenser. The distillate was evaporated to dryness in a vacuum and the residue dried. The yield of *d*-camphidine hydrochloride was 187 g (67 %); m.p. 280–282°; $[\alpha]_D^{25}$ + 15° (*c* = 2, water). (Found: Cl 18.9. Calc. for $C_{10}H_{20}ClN$: Cl 18.7).

The preparation of XIV is given as an example of method A. A mixture of *d*-camphidine hydrochloride (60 g), *m*-chlorobenzyl chloride (53.4 g), anhydrous sodium carbonate (100.5 g) and ethanol (500 ml) was heated under reflux with stirring for 4 h. After cooling, the mixture was filtered and the filtrate distilled in a vacuum. The yield of N-(*m*-chlorobenzyl)-camphidine was 80.6 g (92 %). N-(*m*-chlorobenzyl)-camphidine (79.6 g) was dissolved in anhydrous ether (400 ml) and gaseous hydrogen chloride was added. After filtration and washing with ether the crude product (87 g) was dissolved in ethanol (400 ml) and precipitated with anhydrous ether (200 ml) and the precipitate then crystallized from isopropyl alcohol (750 ml).

XXVI was prepared from XVIII by reduction with iron and hydrochloric acid. XVIII (5 g) was dissolved in 6 N hydrochloric acid (30 ml) and iron powder (5 g) was gradually added during 20 min. After standing at room temperature for 3 h with frequent shaking 6 N hydrochloric acid (20 ml) was added and the mixture left standing overnight. The precipitate was removed by filtration and washed with water (25 ml). 30 % sodium hydroxide was added and the alkaline solution was diluted to 300 ml and extracted continously with ether for 4 h. The ether layer was separated and extracted three times with 20 ml of 10 % hydrobromic acid and the aqueous layer separated and evaporated in a vacuum. Crystallization from methanol-ether gave 1.6 g of XXVI.

XXVII was prepared by demethylation of XXII. A mixture of XXII (15 g) and hydrobromic acid (150 ml) was heated under reflux for 8 h and then evaporated in a vacuum. 5 % sodium hydrogen carbonate (600 ml) was added and the mixture heated to boiling, cooled and extracted with ether (3 × 200 ml). The ether extract was washed with water

* All melting points are uncorrected. Microanalyses by Dr. W. Kirsten and his staff, Institute of Medical Chemistry, University of Uppsala, Sweden.

(3 × 150 ml) and then extracted with 3 N hydrochloric acid (3 × 150 ml). The aqueous layer was separated and evaporated in a vacuum. Two crystallizations from methanol-ether gave 12.8 g of XXVII.

Method B

X, XI, XII, XVI and XXV were prepared from *d*-camphorimide and the appropriate substituted aralkyl chlorides (benzyl chloride, *o*-chlorobenzyl chloride,[20] *β*-*o*-chlorophenylethyl chloride (see below), *p*-chlorobenzyl chloride,[21] and 3,4,5-trimethoxybenzyl chloride [22]), followed by reduction with lithium aluminium hydride of the imides.

The preparation of X is given as an example of method B.

A solution of N-benzylcamphorimide (25 g) (from potassium camphorimide and benzyl chloride, cf. Ref.[6]) in anhydrous ether (250 ml) was gradually added with stirring to a mixture of lithium aluminium hydride (8 g) in anhydrous ether (160 ml). After standing for 16 h at room temperature the mixture was heated under reflux for 4 h. After cooling, water (10 ml) was gradually added followed by 15 % sodium hydroxide (10 ml) and finally water (35 ml). After stirring for 1 ½ h the precipitate was removed by filtration and washed with ether (5 × 60 ml). After drying with magnesium sulfate and evaporation the residue was distilled. The yield of N-benzylcamphidine (b.p.$_1$ 113—114°) was 6.4 g (29 %). Dissolution in ether and addition of gaseous hydrogen chloride gave 6.5 g of crude product. The yield after crystallization from isopropyl alcohol-ether was 5 g of X.

XV was prepared similarly from 5-chlorocamphorimide.[1]

β-o-Chlorophenylethyl chloride.

A solution of *β*-(*o*-chlorophenyl)-ethanol in anhydrous chloroform (10 ml) was added during 1 h with heating under reflux to a solution of thionyl chloride (13.8 ml) in anhydrous chloroform (10 ml) and heating under reflux was continued for 4 h. After standing overnight at room temperature the mixture was distilled. The fraction (9.8 g) with b.p. $_{10-13}$ 138—162° was redistilled. The yield was 7.5 g (67 %) of *β*-*o*-chlorophenylethyl chloride (b.p.$_8$ 101—103°). (Found: Cl 40.4. Calc. for $C_8H_8Cl_2$: Cl 40.5).

Method C

This method which was used for the preparation of XIII, XXI, XXIII and XXIV consists of a condensation of *d*-camphidine with the appropriate substituted aralkanoyl chlorides (*o*-chlorohydrocinnamic acid chloride,[23] *o*-methoxyphenylacetyl chloride,[24] *m*-methoxyphenylacetyl chloride,[25] and 3,4-dimethoxyphenylacetyl chloride [26]), followed by reduction with lithium aluminium hydride.

The preparation of XIII is given as an example of method C.

d-Camphidine hydrochloride (38.9 g) was dissolved in water and 3 N sodium hydroxide (80 ml) was added. The camphidine was extracted with ether (4 × 50 ml), the ether layer separated, dried with magnesium sulfate and filtered. *o*-Chlorohydrocinnamic acid chloride [23] (20.3 g) was added under cooling to the ether extract, the mixture left standing for 4 h and the camphidine hydrochloride removed by filtration. Evaporating gave 27.9 g (81 %) of crude N-*β*-(*o*-chlorophenyl)-propiocamphidide, which was used directly in the next step, which consists of a reduction with lithium aluminium hydride.

A solution of crude N-*β*-*o*-(chlorophenyl)-propiocamphidide (24 g) in anhydrous ether (50 ml) was added dropwise during 1 h to a suspension of lithium aluminium hydride (2.85 g) in anhydrous ether (100 ml). After standing overnight at room temperature the mixture was heated under reflux for 4 h. After cooling, water (3.9 ml) was added dropwise followed by 15 % sodium hydroxide (3.9 ml) and water (12.5 ml). After standing for 1 h the precipitate was removed by filtration and washed with ether. The filtrate was dried with magnesium sulfate and distilled. The yield of N-*γ*-(*o*-chlorophenylpropyl)-camphidine was 76 %; b.p.$_1$ 166—167°; n_D^{25} 1.5310 (Found: N 4.5. Calc. for $C_{19}H_{28}ClN$: N 4.6). Dissolution in ether and addition of gaseous hydrogen chloride gave XIII which was crystallized from isopropyl alcohol-ether (yield 81 %).

4. Substituted phenylacetcamphidides (see Table 4)

The two compounds of this series, XXIX and XXX were obtained as intermediates in method C mentioned above.

Table 6. Some pharmacological properties of substituted camphidines. (*cf.* Tables 1 and 2 for chemical formulas).

Compound	Anticholinergic effect % of atropine	Ganglion-blocking effect		BP action of 5—10 mg/kg[c]	LD 50 mg/kg mice[d]	
		P[a] % of C_6	S[b] % of C_6		i.p.	p.o.
I	0.005	150	15	↓	88	177
II	0.069	49	—	o	252	330
III	0.015	53	0	o	62	—
IV	0.028	36	—	o	69	—
V	0.0002	25	0	o	175	370
VI	0.017	174	—	↓	178	1420
VII	0.0005	143	—	↓	147	—
VIII	0.036	81	0	↑	245	—
IX	0	12	—	o	265	[e]

a) Parasympathetic ganglion blocking action (for details of technique see Ref.[28]).
b) Sympathetic ganglion blocking action (for details of technique see Ref.[28]).
c) ↑ indicates an increase, ↓ a decrease in blood pressure.
d) Mean lethal dose (intraperitoneal and oral route) (*cf.* Ref.[1]).
e) No acute deaths at 500 mg/kg. After a few days fatty infiltration of the liver in all animals.

5. Substituted aralkylamines (see Table 5)

The compounds XXXI—XXXIV were prepared by reaction of an excess of the appropriate amines (di-propyl amine, piperidine and 4,4-dimethyl-piperidine[27]), with β-*o*-chlorophenyl ethyl chloride (see under Method B) and *o*-chlorobenzyl chloride,[20] respectively.

The preparation of XXXI will be given as an example: A mixture of β-(*o*-chlorophenyl) ethyl chloride (10 g) and di-propylamine (14.5 g) was left standing at room temperature for 24 h and then heated under reflux for 20 h. Methanol was added, the solution evaporated in a vacuum and the residue dissolved in 30 % sodium hydroxide. The solution was extracted with ether (3 × 50 ml). Distillation gave 6 g (44 %) of β-(*o*-chlorophenyl) ethyl-N,N-di-propylamine ($b.p._{10}$ 135—145°). The hydrobromide was prepared in the usual way.

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The central nervous system depressant action of compounds X—XXXIV has already been reported and discussed.[4] Consequently, only compounds I—IX will be dealt with here. The substances were screened in the form of the salts reported in Tables 1 and 2 according to procedures outlined in the previous paper.[1]

Table 7. The effect of compounds I, II and mecamylamine on blood pressure (mm Hg) of hypertensive rats[a].

Compound	Dose mg/kg/day	Pre-drug period		Drug period		Post-drug period	
		Days	BP	Days	BP	Days	BP
I	29	15	160	10	151	7	151
II	29	12	161	9	146	10	160
Mecamylamine	3.5	14	143	9	116	9	139

a) The compounds were given mixed in the feed. *Cf.* Ref[1].

The results are summarized in Tables 6 and 7; the latter showing the effects of methyl-(I) and methyl-chlorocamphidine (II) upon the blood pressure of the unanesthetized, renal hypertensive rat.

The substances block autonomic ganglia to a certain degree. The tertiary amine of highest potency is I. Increasing bulk of the N-substituent decreases this action. Introduction of chlorine at position 5 also decreases potency. Since chlorine at this position is singularly unreactive, the substitution can be viewed as merely supplying bulk.

Quaternization of the active members does not abolish the blocking properties. In some cases it even enhances it (VI and VII as compared to the tertiary precursors I and II).

Considering the differences in technique and rating, the results as a whole correspond rather well with the values obtained with similar substances by Edge *et al.*[3]

As will appear from Table 7 neither compound I nor II exerted any appreciable effect upon blood pressure in the wake hypertensive rat. This is in contrast to results obtained in the acute experiment on anesthetized animals. Mecamylamine on the other hand does cause a marked reduction in blood pressure.

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