PREPARATION OF RACEMIC *cis*- AND *trans*-2-(2-ALKOXYPHENYL-CARBAMOYLOXY)CYCLOHEPTYLMETHYLPIPERIDINIUM CHLORIDES

Fridrich GREGAN[a], Viktor KETTMANN[b], Pavol NOVOMESKY[b] and Julius SIVY[b]

[a] *Department of Organic and Inorganic Chemistry, Faculty of Pharmacy, Comenius University, 832 32 Bratislava, The Slovak Republic*

[b] *Department of Analytical Chemistry, Faculty of Pharmacy, Comenius University, 832 32 Bratislava, The Slovak Republic*

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The synthesis of two pairs of the title diastereomers, which represent conformationally constrained analogues of the phenylcarbamate local anesthetics, is described. The synthesis was accomplished by starting from cycloheptanone and 2-alkoxyanilines and the intermediate diastereomers of 2-amino-methylcycloalkanols (*VI*, *VII*) were separated as their 4-nitrobenzoyl derivatives (*IV*, *V*) by extraction and fractional crystallization. The prepared compounds (*VIIIa*, *VIIIb*, *IXa*, and *IXb*) are assumed to be of help in interpreting the structure–activity relationships within this class of drugs.

This work is part of a project aiming at an understanding of some of the structural and physicochemical determinants of local anesthetic and related (including antiarrhythmic and anticonvulsant) activity of phenylcarbamate (pentacaine) derivatives (esters of alkoxyphenylcarbamoic acid with amino alcohols)[1]. Common structural features of the active compounds of this type are a phenylcarbamate function, a tertiary amine, and hydrophobic groups attached to the phenyl ring and the amine nitrogen. The phenylcarbamate and the amine moieties, which are connected via a linking chain (this typically consists of 2 or 3 carbon atoms), are assumed to participate directly in the drug-receptor interaction and hence constitutes two major pharmacophores[2–4].

Previous results have shown that the in vivo and in vitro activity of these compounds is dependent upon the molecular lipophilicity (as modelled by log *P* and related parameters)[5–7] as well as upon the spatial distribution of the two pharmacophores[7,8]. While the role of the molecular lipophilicity in eliciting the activity is well established, with the maximum activity corresponding to $(\log P)_{opt} \approx 4.0$ (ref.[7]), the spatial requirements are still poorly understood. This is caused by the fact that previous structure–activity relationship studies were based on flexible (open-chain) analogues so that the question of the bioactive conformation remained unanswered. The only exception is the semirigid, 1,2-disubstituted cyclohexane derivative reported by Benes et al.[8] in which the two pharmacophores are attached directly to the cyclohexane ring. To extend these studies, aiming at better understanding the spatial requirements of the local anesthetic

activity, we prepared two pairs of *cis* and *trans* isomers of another semirigid analogue which differs from the above cyclohexane derivative in using a cycloheptane ring and in attaching the amino function to the ring through a methylene group so that the linking chain consists of 3 carbon atoms.

In general, the phenylcarbamate local anesthetics are prepared by addition of amino alcohols to arylisocyanates; in the case of the semirigid (cyclic) analogues, the corresponding 2-aminocycloalkanols which are used in the addition reaction may exist in various diastereomeric forms. These may in principle be prepared either by a stereospecific reaction[9,10] or by a non-stereospecific reaction followed by separation of the diastereomers[11,12]. In the present work the latter approach was used.

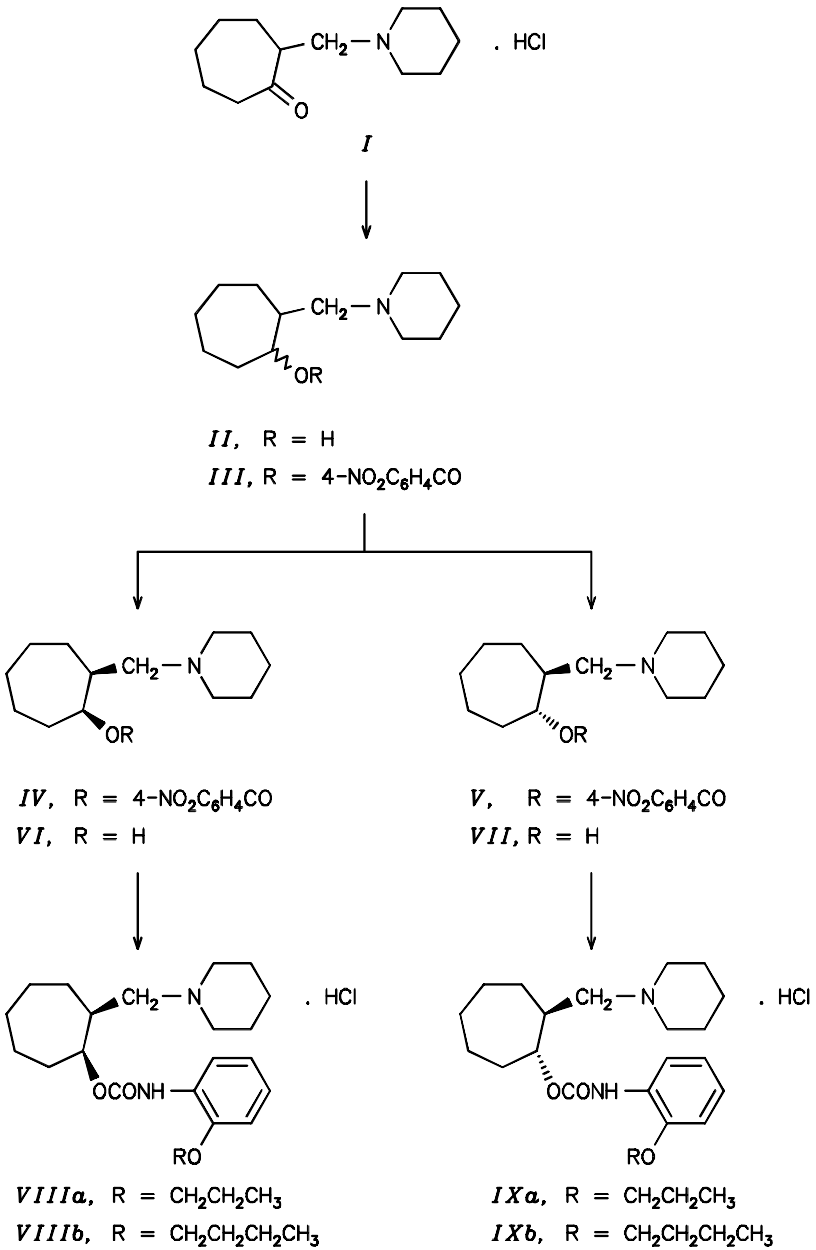
Final products *VIIIa*, *VIIIb*, *IXa*, and *IXb* (Table I) were prepared as racemates by the routes depicted in Scheme 1. Based on the known dependence of the in vivo activity on molecular lipophilicity[7], the alkoxy group (–OR) on the phenyl ring is presented by a propoxy and a butoxy group, in order to achieve the maximum activity.

The structure of the final compounds was proved by IR, ^{1}H and ^{13}C NMR spectra (Tables II – IV) and, for the butoxy derivatives (*IXa* and *IXb*), also by a single-crystal X-ray diffraction[13].

The starting 2-alkoxyphenylisocyanates were freshly prepared from 2-alkoxyanilines by reaction with phosgene according to the published method[14]. These compounds were in turn prepared by starting from *N*-(2-hydroxyphenyl)acetamide, which was first allowed to react with 1-bromoalkane in the presence of sodium ethoxide and subsequent hydrolysis of the so obtained *N*-(2-alkoxyphenyl)acetamides[15,16] with dilute hydrochloric acid gave the corresponding 2-alkoxyanilines[17,18].

The synthesis of 2-(piperidinomethyl)cycloheptanol *II* has already been described in the literature[12]; in the present paper we describe a new modification of the preparation procedure which involves the Mannich reaction of cycloheptanone with formaldehyde and piperidinium chloride[19] followed by reduction of the obtained 1-(2-oxocycloheptylmethyl)piperidinium chloride (*I*) with sodium borohydride in water. The amino alcohol *II* prepared in this manner is a mixture of two racemic diastereomers – *cis* (*VI*) and *trans* (*VII*) – so that they had to be separated. To achieve this, we first prepared the corresponding isomers (*IV* . HCl and *V* . HCl) of a solid derivative, 2-(4-nitrobenzoyloxy)cycloheptylmethylpiperidinium chloride (*III*), which were subsequently separated by extraction and fractional crystallization. Hydrolysis of *IV* . HCl and *V* . HCl with dilute hydrochloric acid followed by a treatment with sodium hydroxide gave the free bases *VI* and *VII*.

The overall yield of the two diastereomers *IV* . HCl and *V* . HCl in their separation was 49%, with the predominant isomer obtained from the mixture being the *cis* (*IV* . HCl) isomer (41% vs 8%). While melting points of *IV* . HCl and *V* . HCl are sufficiently different (see Experimental) boiling points of the amino alcohols *VI* and *VII* are practically the same; the larger differences between the latter isomers were found in


CH2—N
. HCl
O
I
OR
II, R = H
III, R = 4-NO2C6H4CO
IV, R = 4-NO2C6H4CO
VI, R = H
V, R = 4-NO2C6H4CO
VII, R = H
OCONH
RO
VIIIa, R = CH2CH2CH3
VIIIb, R = CH2CH2CH2CH3
IXa, R = CH2CH2CH3
IXb, R = CH2CH2CH2CH3

SCHEME 1

the n_D^{20} and R_F values. As to the final products, the physicochemical properties of the two diastereomers differ only marginally (Table I). On the other hand, preliminary in vivo tests have revealed significant differences in the local anesthetic activity between the two geometrical isomers as well as between the propoxy and butoxy derivatives so that the compounds described here are expected to be of value in analyzing the structural requirements of the anesthetic receptor.

EXPERIMENTAL

The melting points were determined on a Kofler block and are uncorrected. All compounds were checked for purity by TLC on silica gel Silufol UV-254 (Kavalier) plates impregnated with 5% solution of silicon oil in heptane, using 1 M HCl–acetone (1 : 1) as the mobile phase (detection by 254 nm UV light and iodine vapours). The presented R_F values are averages of 4 independent measurements. IR spectra were measured with a M-80 spectrophotometer (Zeiss, Jena) in chloroform. NMR spectra (^1H at 299.93 MHz and ^{13}C at 75.43 MHz) were obtained on a Varian VXR-300 spectrometer in $CDCl_3$ solution using tetramethylsilane as an internal standard.

1-(2-Oxocycloheptylmethyl)piperidinium Chloride (*I*)

To a mixture of cycloheptanone (67.2 g, 0.60 mol), 30% aqueous formaldehyde (40.2 g, 0.40 mol) and triethylamine (1 ml) piperidinium chloride (48.6 g, 0.40 mol) was added successively (within 5 min) with stirring at room temperature. Then the stirring mixture was heated in CO_2 atmosphere for 3.5 h in a boiling water bath. After cooling the mixture was taken up in ether (to remove the excess cycloheptanone), the aqueous layer was evaporated to dryness and the solid residue was crystallized from acetone–ethanol (10 : 1); yield 50.2 g (52%), m.p. 173 – 174 °C; ref.[14] gives m.p. 152 °C. For $C_{13}H_{24}ClNO$ (245.8) calculated: 63.64% C, 9.84% H, 5.70% N; found: 62.68% C, 10.12% H, 6.05% N.

TABLE I
Yields, melting points, chromatographical and analytical data of compounds *VIIIa*, *VIIIb*, *IXa*, and *IXb*

Compound	M.p., °C Yield, %	TLC R_F	Formula (M.w.)	Calculated/Found		
				% C	% H	% N
VIIIa	191	0.38	$C_{23}H_{37}ClN_2O_3$	64.99	8.78	6.59
	56		(425.0)	65.30	8.53	6.69
VIIIb	194	0.42	$C_{23}H_{37}ClN_2O_3$	64.99	8.78	6.59
	54		(425.0)	65.22	9.04	6.74
IXa	173	0.33	$C_{24}H_{39}ClN_2O_3$	65.66	8.95	6.38
	48		(439.0)	65.88	8.62	6.09
IXb	175	0.34	$C_{24}H_{39}ClN_2O_3$	65.66	8.95	6.38
	50		(439.0)	66.00	8.61	6.50

TABLE II
Infrared spectra ($CHCl_3$, wavenumbers in cm^{-1}) of compounds *VIIIa*, *VIIIb*, *IXa*, and *IXb*

Compound	ν(N–H)	ν(N^+–H)	ν(C=O)	ν(C=C)	δ(C–N–H)
VIIIa	3 432	2 464	1 724	1 604	1 526
VIIIb	3 432	2 452	1 726	1 604	1 525
IXa	3 433	2 463	1 724	1 604	1 526
IXb	3 433	2 451	1 725	1 604	1 525

TABLE III
^1H NMR chemical shifts (ppm, δ-scale, in $CDCl_3$) of compounds *VIIIa*, *VIIIb*, *IXa*, and *IXb*

Proton	*VIIIa*	*VIIIb*	*IXa*	*IXb*
H-1	5.17	4.63	5.17	4.64
H-2	2.44	2.34	2.44	2.34
H-3 to H-7	1.5 – 2.1	1.45 – 1.9	1.5 – 2.1	1.45 – 1.9
H-8	2.99, 3.03	2.93	2.99, 3.03	2.93
H-9	11.90	11.88	11.79	11.93
H-10,14	2.67, 2.71 3.48, 3.55	2.55, 2.73 3.48, 3.62	2.68, 2.72 3.49, 3.56	2.52, 2.72 3.48, 3.62
H-11,13	1.80, 2.40	1.80, 2.40	1.80, 2.40	1.80, 2.40
H-12	1.42, 1.85	1.42, 1.85	1.42, 1.85	1.42, 1.85
H-3′	6.88	6.87	6.88	6.88
H-4′	7.01	7.01	7.01	7.01
H-5′	6.94	6.95	6.94	6.95
H-6′	8.02	8.02	8.02	8.03
H-7′	7.25	7.29	7.25	7.26
H-9′	4.02	4.01	4.06	4.06
H-10′	1.89	1.88	1.84	1.84
H-11′	–	–	1.51	1.50
H-12′	1.06	1.06	1.01	1.01

2-(Piperidinomethyl)cycloheptanol (*II*)

Compound *I* (49.2 g, 0.20 mol) was dissolved in water (200 ml) and sodium borohydride (30.2 g, 0.80 mol) was added successively (within 50 min) under stirring and cooling. The mixture was allowed to stand for 12 h at room temperature and then was heated for 1 h at 70 °C with stirring. After cooling, the mixture was acidified to pH 3 – 4 by dilute hydrochloric acid and again was heated for 1 h at 70 °C. After cooling, the mixture was made alkaline (pH 12) by addition of dilute sodium hydroxide. The separated product was repeatedly extracted with ether, the organic layer was dried over anhydrous sodium sulfate, the inorganic material was filtered off and the filtrate was distilled to give a residue which was purified by distillation under reduced pressure; yield 22.0 g (52%), b.p. 105 °C/106 Pa, n_D^{20} 1.4905; ref.[9] gives b.p. 147 – 151 °C/1.06 kPa.

TABLE IV
^{13}C NMR chemical shifts (ppm, δ-scale, in $CDCl_3$) of compounds *VIIIa*, *VIIIb*, *IXa*, and *IXb*

Carbon	*VIIIa*	*VIIIb*	*IXa*	*IXb*
C-1	76.2	78.1	76.2	78.1
C-2	38.5	40.3	38.6	40.3
C-3 to C-7	22.1, 25.8 27.4 , 28.3 32.0	22.6, 26.0 28.8, 29.6 32.7	22.1, 25.8 27.4, 28.3 32.0	22.6, 26.0 28.8, 29.5 32.7
C-8	60.9	61.9	60.9	61.9
C-10,14	52.5, 55.4	52.5, 55.8	52.6, 55.3	52.5, 55.8
C-11,13	22.2	22.0	22.3	22.0
C-12	22.0	21.9	22.0	21.9
C-1′	127.3	127.3	127.3	127.2
C-2′	147.1	147.1	147.2	147.1
C-3′	111.2	111.1	111.1	111.0
C-4′	123.2	123.2	123.2	123.2
C-5′	120.9	120.9	120.9	120.9
C-6′	118.3	118.3	118.3	118.3
C-8′	152.9	152.9	153.0	153.0
C-9′	70.2	70.1	68.5	68.4
C-10′	22.5	22.5	31.1	31.2
C-11′	–	–	19.3	19.3
C-12′	10.5	10.6	13.9	13.9

cis-[2-(4-Nitrobenzoyloxy)cycloheptylmethyl]piperidinium Chloride (*IV* . HCl)
and *trans*-[2-(4-Nitrobenzoyloxy)cycloheptylmethyl]piperidinium Chloride (*V* . HCl)

A mixture of compound *II* (88.8 g, 0.42 mol) and anhydrous chloroform (400 ml) was added within 30 min under stirring and cooling to a solution of 4-nitrobenzoyl chloride (74.4 g, 0.40 mol) so as to maintain the temperature of the mixture within 20 – 30 °C. Then the mixture was stirred at room temperature for additional 2 h and the solvent was evaporated in vacuo on a rotatory evaporator. The oily residue was mixed with ether (100 – 200 ml) until the product becomes solid. Then the product *III* was mixed with ether–acetone (3 : 1), filtered and dried; yield 141 g (85%), m.p. 117 – 120 °C.

A fine powder of the product *III* (140 g, 0.32 mol) was extracted under reflux and rigorous stirring with acetone (3 200 ml) at the boiling temperature. The undissolved residue was filtered off and again was extracted with acetone (700 ml). Then the filtrates were combined, cooled and allowed to stand for 12 h. The separated solid was combined with the solid obtained from the preceding extractions and crystallized 2 times from ethanol–ethyl acetate (1 : 1) to obtain 57 g (41%) of the *cis* isomer *IV* . HCl, m.p. 236 – 237 °C, TLC: R_F 0.35; ref.[12] gives m.p. 230 – 232 °C. For $C_{20}H_{29}ClN_2O_4$ (396.9) calculated: 60.52% C, 7.36% H, 7.06% N; found: 61.14% C, 7.33% H, 6.88% N. Concentration of the filtrates afforded a solid which was purified by a repeated crystallization from 1-propanol–ethyl acetate (1 : 3) to obtain 11 g (8%) of the *trans* isomer (*V* . HCl), m.p. 140 – 141 °C, TLC: R_F 0.33; ref.[12] gives m.p. 160 – 161 °C. For $C_{20}H_{29}ClN_2O_4$ (396.9) calculated: 60.52% C, 7.36% H, 7.06% N; found: 59.71% C, 6.98% H, 6.99% N.

cis-2-(Piperidinomethyl)cycloheptanol (*VI*)

A mixture of compound *IV* . HCl (71.5 g, 0.18 mol) and 10% methanolic solution of potassium hydroxide (1 140 ml) was heated at the boil for 2 h under stirring. After filtration, the solvent was removed by distillation under reduced pressure, the solid residue was dissolved in water (500 ml), cooled and extracted with ether (3 × 50 ml). The combined ether layer was dried over anhydrous sodium sulfate, the sulfate was filtered off, the solvent distilled off and the residue was purified by distillation under reduced pressure. Yields 15.2 g (72%) of product *VI*, b.p. 158 °C/227 Pa, n_D^{20} 1.4995, TLC: R_F 0.16; ref.[12] gives b.p. 144 – 147 °C/1.07 kPa, n_D^{20} 1.4982. Hydrochloride of amino alcohol *VI* was prepared by treatment with ethereal solution of HCl, followed by crystallization from ethyl acetate–2-butanone (3 : 1), m.p. 214 – 215 °C.

trans-2-(Piperidinomethyl)cycloheptanol (*VII*)

Title compound was prepared from *V* . HCl (71.5 g, 0.18 mol) by the same procedure. Yield 14.3 g (68%) of *VII*, b.p. 156 °C/227 Pa, n_D^{20} 1.4946, TLC: R_F 0.35; ref.[12] gives b.p. 141 – 143 °C/1.07 kPa, n_D^{20} 1.4931. Hydrochloride: m.p. 196 – 197 °C.

General Procedure for Preparation of Compounds *VIIIa*, *VIIIb*, *IXa*, and *IXb*

A mixture of 2-alkoxyphenylisocyanate (30 mmol) and compound *VI* or *VII* (6.69 g, 32 mmol) in toluene (30 ml) and some drops od triethylamine was refluxed for 12 h. After cooling, an equal volume of petroleum ether was added and the mixture was allowed to stand overnight in a refrigerator. The solid by-product, *N*,*N*′-bis(2-alkoxyphenyl)urea, was filtered off and the toluene filtrate was extracted with 5% hydrochloric acid (3 × 50 ml). The aqueous layer was extracted with chloroform (3 × 40 ml) and the combined organic layer dried over anhydrous sodium sulfate. After the sulfate was removed by filtration and chloroform by distillation, the residual moisture was removed by azeotropic distillation with toluene. The solid residue was crystallized from ethyl acetate. Yields, analytical and spectral data are given in Tables I – IV.

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