Studies on Carbanilic Acid Esters of Cyclic Amino Alcohols. 5. Local Anesthetic Potency of the Enantiomers of Two *N*-Butyl-3-piperidyl Carbanilates[1]

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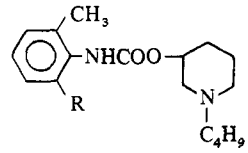
We have recently reported the synthesis and the local anesthetic potency of a number of carbanilic acid esters of cyclic amino alcohols.[1] Some of the compounds were more potent than lidocaine in experimental animals and two of them (**1** and **2**) were found interesting enough to merit further evaluation. Findings in animals† and preliminary results in man‡ indicate that **1** especially possesses good local anesthetic properties, characterized by long duration of action.



1, R = Cl
2, R = CH_3

Studies on the local anesthetic properties of the enantiomers of prilocaine,[2] mepivacaine,[3,4] and bupivacaine[4] have been reported, and it has been found that the enantiomers differ in their local anesthetic effect. Whether an enantiomer has advantages of clinical importance over its corresponding racemate remains yet to be proven. Studies on enantiomers may also contribute to the understanding of the mechanism of action of local anesthetics.[5,6]

We therefore decided to prepare the enantiomers of compounds **1** and **2** and determine their absolute configuration. Comparison of the local anesthetic activities was made with (*R*)-(+)- and (*S*)-(−)-bupivacaine (*N*-butyl-2′,6′-pipecoloxylidide).

Chemistry. Several attempts to resolve the racemic phenylcarbamates **1** and **2** using a variety of optically active acids were unsuccessful. However, the amino alcohol (±)-*N*-butyl-3-hydroxypiperidine (**3**) could be resolved using the (+) and (−) forms of 4-chlorotartranilic acid, as described by Montzka, *et al.*[7] Compounds (+)-**3** and (−)-**3** were then allowed to react with 2-chloro-6-methylphenyl isocyanate and 2,6-dimethylphenyl isocyanate, respectively, yielding the enantiomers of **1** and **2**.

A stereospecific synthesis of (*S*)-(−)-3-hydroxypiperidine with mannitol as starting material has recently been reported by Deane and Inch.[8] We resolved (±)-3-hydroxypiperidine using (−)-4-chlorotartranilic acid and obtained (*S*)-(−)-3-hydroxypiperidine having the reported physical data.[8] Alkylation of this compound with BuI in BuOH afforded (+)-*N*-butyl-3-hydroxypiperidine thus establishing the *S* configuration for this compound [(*S*)-(+)-**3**]. (*S*)-(+)-**3** was then allowed to react with 2-chloro-6-methylphenyl isocyanate yielding (*S*)-(−)-**1**, which in all respects was identical with (−)-**1** obtained by coupling 2-chloro-6-methylphenyl isocyanate with (+)-**3**, prepared by direct resolution of (±)-**3**.

Table I. Physical Data of the Optical Isomers of 1 and 2

Compd	Mp, °C	$[\alpha]^{20}D$,[a] deg
(*R*)-(+)-**1**	98–99.5	+12.9 (*c* 1.15)
(*S*)-(−)-**1**	98–99.5	−12.7 (*c* 1.5)
(*R*)-(+)-**2**	88.5–89.5	+15.5 (*c* 1.0)
(*S*)-(−)-**2**	89–89.5	−15.4 (*c* 1.0)

[a] In EtOH.

Physical data of the optical isomers of **1** and **2** are recorded in Table I.

Pharmacological Results. The methods used in the pharmacological evaluations of the compounds have been published.[1] (*R*)-(+)-**1** and (*R*)-(+)-**2** produced a longer duration of corneal anesthesia in the rabbit and a greater depth of block of the evoked action potential in isolated sciatic nerve of the frog than the corresponding *S*-(−) forms (Table II). The *R*-(+) forms of **1** and **2** were also more toxic (iv; mice) than the *S*-(−) forms. These findings and the results of a more detailed study† suggest differences in the potency of the enantiomers with regard to local anesthetic action, as well as differences in toxicity.

(*S*)-(−) bupivacaine[9] has recently been reported[4] to be longer acting upon injection and less toxic than (*R*)-(+)-bupivacaine, which is possibly related to differences in the rate of absorption from the injection site. In experiments on frog sciatic nerve (Table II) the block (equilibrium) caused by (*R*)-(+)-bupivacaine was deeper than with (*S*)-(−)-bupivacaine. The *R*-(+) form of bupivacaine also tended to produce longer duration of corneal anesthesia than the *S*-(−) form. Iv LD_{50} values demonstrated a higher toxicity for the *R*-(+) form. The results indicate that bupivacaine has about the same potency as compounds **1** and **2**, and also that the enantiomers show differences in excitation block and toxicity. The more active enantiomers of the three pairs have the same steric configuration (*R*). The positive correlation between nerve blocking and toxic activities observed with these compounds agrees well with results of studies with other local anesthetics.[10] It is also consistent with previous findings[5,6] that suggest some stereoselectivity in the mechanism for excitation block by local anesthetics. The present observations that (*S*)-(−)-bupivacaine appears to be less active but, according to other authors,[4] longer acting upon injection may exemplify lack of correlation between local anesthetic activity and duration of action.[10] One conceivable explanation is that the enantiomers influence the different pharmacological actions of the compounds in different ways.

Experimental Section

Melting points were determined in an electrically heated metal block, using calibrated Anschütz thermometers. Microanalyses were performed by Dr. A. Bernhardt, Mülheim, Germany. Microanalytical results obtained for the elements indicated were within ±0.4% of the theoretical value. Ir spectra were run on a Perkin-Elmer 237 spectrophotometer with grating monochromator. Optical rotations were measured on a Perkin-Elmer 141 polarimeter.

Materials. (±)-*N*-Butyl-3-hydroxypiperidine was prepared as previously described.[1] (±)-3-Hydroxypiperidine was commercially available. 2-Chloro-6-methyl- and 2,6-dimethylphenyl isocyanate were prepared according to methods described in the literature.[11,12]

(−)-4-Chlorotartranilic acid was prepared by the method de-

†B. Åkerman, unpublished results.

‡Unpublished results by G. Bengberg, M. H. Holmdahl, and H. Edström, Department of Anesthesiology, University Hospital, Uppsala, Sweden.

Table II. Local Anesthetic Potency and Toxicity

Compd	Corneal anesthesia[a] Duration min ± SE	Corneal anesthesia[a] Relative activity	Sciatic nerve block *in vitro*[b] Depression of action potential, % ± SE	Sciatic nerve block *in vitro*[b] Relative activity	LD_{50},[c] iv mg/kg	LD_{50},[c] iv Relative toxicity
(*R*)-(+)-1	15.4 ± 1.8	1.0	96 ± 3	1.0	8	1.0
(*S*)-(−)-1	8.4 ± 0.9	0.5	44 ± 1	0.5	20	0.4
(*R*)-(+)-2	14.2 ± 0.9	0.9	87 ± 3	0.9	11	0.7
(*S*)-(−)-2	1.8 ± 0.6	0.1	50 ± 4	0.5	19	0.4
(*R*)-(+)-Bupivacaine	14.6 ± 1.8	1.0	87 ± 6	0.9	6	1.3
(*S*)-(−)-Bupivacaine	11.5 ± 1.5	0.7	48 ± 7	0.5	10	0.8

[a]Rabbit, 0.25%, 0.25 ml applied for 0.5 min, $N = 6$. [b]Frog, 0.1 m*M*, equilibrium block, $N = 4$. [c]Mice.

scribed for the (+) enantiomer,[7] mp 192–193.5° (from EtOH-H_2O), $[\alpha]^{20}D$ −105.1° (*c* 1.02, 95% EtOH). *Anal.* ($C_{10}H_{10}ClNO_5$) C, H, N.

Resolution of (±)-*N*-Butyl-3-hydroxypiperidine (3). To a solution of 26.1 g (0.083 mole) of (+)-4-chlorotartranilic acid[7] in warm 95% EtOH (175 ml) (±)-**3** (25 g, 0.166 mole) was added. The mixt was kept at room temp for 24 hr, and the formed salt was collected. Two recrystns from 95% EtOH and seeding with crystals from a previous experiment afforded 13.0 g of product, mp 151–153°, $[\alpha]^{20}D$ +63.5° (*c* 1.02, H_2O).

The optically active salt (5.8 g) was decomposed with 5 *N* NaOH, and the amino alcohol was extracted with Et_2O. After drying (Na_2SO_4) and evaporation of the solvent, 2.0 g of (+)-**3** was obtained, $[\alpha]^{20}D$ +4.0° (*c* 1.15, EtOH).

Treatment of (±)-3 with (−)-4-chlorotartranilic acid yielded similarly the enantiomeric salt, mp 151.5–153.5°, $[\alpha]^{20}D$ −63.7° (*c* 1.10, H_2O). Decomposition of the salt yielded (−)-3, $[\alpha]^{20}D$ −4.3° (*c* 1.38, EtOH).

Resolution of (±)-3-Hydroxypiperidine. (±)-3-Hydroxypiperidine (5.0 g, 0.05 mole) was treated with (−)-4-chlorotartranilic acid (6.5 g, 0.025 mole) in 95% EtOH as described for (±)-**3**. The salt obtained was recrystd twice from 95% EtOH affording 4.2 g of product, mp 152–153°, $[\alpha]^{20}D$ −77.6° (*c* 0.75, H_2O). The salt was stirred in a mixture of MeOH-PhMe (7:3) containing equivalent amounts of K_2CO_3. After filtrn and evapn, (*S*)-(−)-3-hydroxypiperidine was obtd, $[\alpha]^{20}D$ −8.0° (*c* 1.32, MeOH), lit.[8] $[\alpha]^{20}D$ −7.5° (*c* 2.0, MeOH).

(*S*)-(+)-*N*-Butyl-3-hydroxypiperidine [(*S*)-(+)-3]. (*S*)-(−)-3-Hydroxypiperidine (0.5 g, 5 mmoles), BuI (0.5 g, 6 mmoles), and K_2CO_3 (0.7 g, 5 mmoles) were mixed in BuOH (5 ml) and stirred at 80° for 5 hr. After filtration, evapn, and trituration with Et_2O, followed by filtration and evapn, 0.42 g (54%) of (*S*)-(+)-**3** was obtd, $[\alpha]^{20}D$ +4.2° (*c* 1.0, EtOH). Ir and tlc data were identical with those shown by (+)-**3** prepd by resoln of (±)-**3**.

Preparation of the Enantiomers of 1 and 2. The enantiomers of 1 and **2** were prepared from (+)-**3** and (−)-**3** and the appropriate isocyanate by the method described for the racemates.[1] Physical data for the optical isomers are given in Table I. When equivalent amounts of the appropriate pair of enantiomers were mixed and recrystd from ligroin, the observed mp were identical with, and did not depress, the mp of the racemic compounds. The ir spectra were also identical.

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Nitroheterocyclic Antimicrobial Agents. 1-Methyl-2-nitro-5-imidazolyl Derivatives

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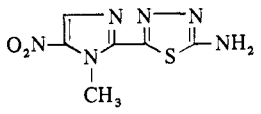
Since the discovery of the broad-spectrum antimicrobial activity of 2-amino-5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole (**1**),[1] a comparison of its activity with that of the corresponding 2-nitro isomer (**2**) was of interest, especially in view of the high antiprotozoal activities reported for both 5-nitro- and 2-nitroimidazoles.[2,3] In this report, the synthesis and antimicrobial activity of **2** and its amino-oxadiazole analog (**3**) are described.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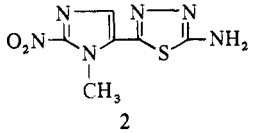
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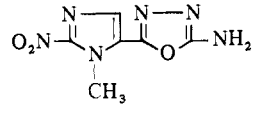
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1,5-Dimethyl-2-nitroimidazole (**4**)[3] appeared to be a potential intermediate for 1-methyl-2-nitroimidazole-5-carboxaldehyde (**5**). Probing experiments quickly revealed that oxidation of **4** to **5** with SeO_2 or CrO_3 proceeded only with considerable decomposition and that treatment of **4** with BuONO-HCl did not give the oxime of **5**. Condensation of **4** with benzaldehyde could be accomplished by using an excess of *tert*-BuOK and benzaldehyde to afford **6** in low yield. However, in subsequent experiments, the yield of **6** was improved by using a two-step synthesis† which involved addition of **4** to benzaldehyde in the presence of a catalytic amount of KOH in EtOH to give **7**, which was then dehydrated with H_2SO_4 to give **6**. The benzylidene derivative was easily ozonized to **5**, which was converted to the thiosemicarbazone **8**. The latter was oxidatively cyclized to give **2**.

A second approach was based on the method of imidazole

†We thank Drs. P. Miller and I. Starer of the Organic Chemicals Division (Bound Brook, N. J.) for providing information on this method, which they developed for the 5-nitroimidazole series.