Short Communication

An Efficient Synthesis of a New, Chiral 2′,6′-Pipecoloxylidide Local Anaesthetic Agent

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Federsel, H.-J., Jaksch, P. and Sandberg, R., 1987. An Efficient Synthesis of a New, Chiral 2′,6′-Pipecoloxylidide Local Anaesthetic Agent. – Acta Chem. Scand., Ser. B 41: 757–761.

The finding that enantiomers of 2′,6′-pipecoloxylidide derivatives show significant differences with respect to their local anaesthetic action dates back to the late 1960's. Thus, in 1969 Luduena[1] reported that (*S*)-mepivacaine (**1a**) and (*S*)-bupivacaine (**1b**) (Scheme 1) were significantly longer-acting than their *R*-enantiomers. This observed difference in anaesthetic activity confirmed the results which had been obtained a few years earlier from studies on the enantiomers of prilocaine (**2**).[2] Investigations were subsequently performed in order to find out whether therapeutic advantages would result from using enantiomerically pure local anaesthetics instead of racemates.[3]

Recently, (*S*)-(−)-1-propyl-2′,6′-pipecoloxylidide (**1c**), which has been given the generic name ropivacaine, was found to have interesting properties as a local anaesthetic.[4] Clinical tests are currently being performed with this compound in order to evaluate its therapeutic potential. A multistep synthesis of ropivacaine · HCl (**6**) starting with the resolution of (±)-pipecolinic acid has been described.[5] This route, which affords the product in rather low yield (14 % of theory), suffers from a number of severe drawbacks mainly attributable to the reaction conditions and work-up procedures in the various steps. Furthermore, the product obtained has an optical purity of only 80 % ee, which is significantly lower than the desired value of >95 % ee. Our main objective was thus to find an alternative synthesis which would afford **1c** with the desired optical purity and, hopefully, in considerably better overall yield.

We now report an efficient method for the synthesis of ropivacaine · HCl · H_2O (**7**) based on a resolution method published by Tullar[6] some 15 years ago. Thus, Tullar found that (±)-2′,6′-pipecoloxylidide (**3**) could be resolved by using (−)-dibenzoyl-L-tartaric acid (natural isomer), thereby making virtually any member of the series of *N*-substituted enantiomeric derivatives (e.g. **1**) available via a subsequent alkylation step.

Results and discussion

The reaction conditons, yields and optical purities in the synthesis of ropivacaine · HCl · H_2O (**7**) are shown in Scheme 1, in which unisolated intermediates are indicated by an asterisk.

Fractional crystallization of **3** using (−)−*O*,*O*′-dibenzoyl-L-tartaric acid was performed in accordance with the previously mentioned literature procedure,[6] except for slight changes in relative amounts, concentrations and temperatures. The use of 2-propanol (H_2O content <0.1 %) as solvent in this step led to immediate onset of crystallization of the 2:1 dibenzoyltartrate salt **4** during or directly after the addition of dibenzoyltartaric acid, even at reflux temperature (i.e. ca. 80 °C). The solubility of a purified sample of **4** under these conditions was found to be 5 mg

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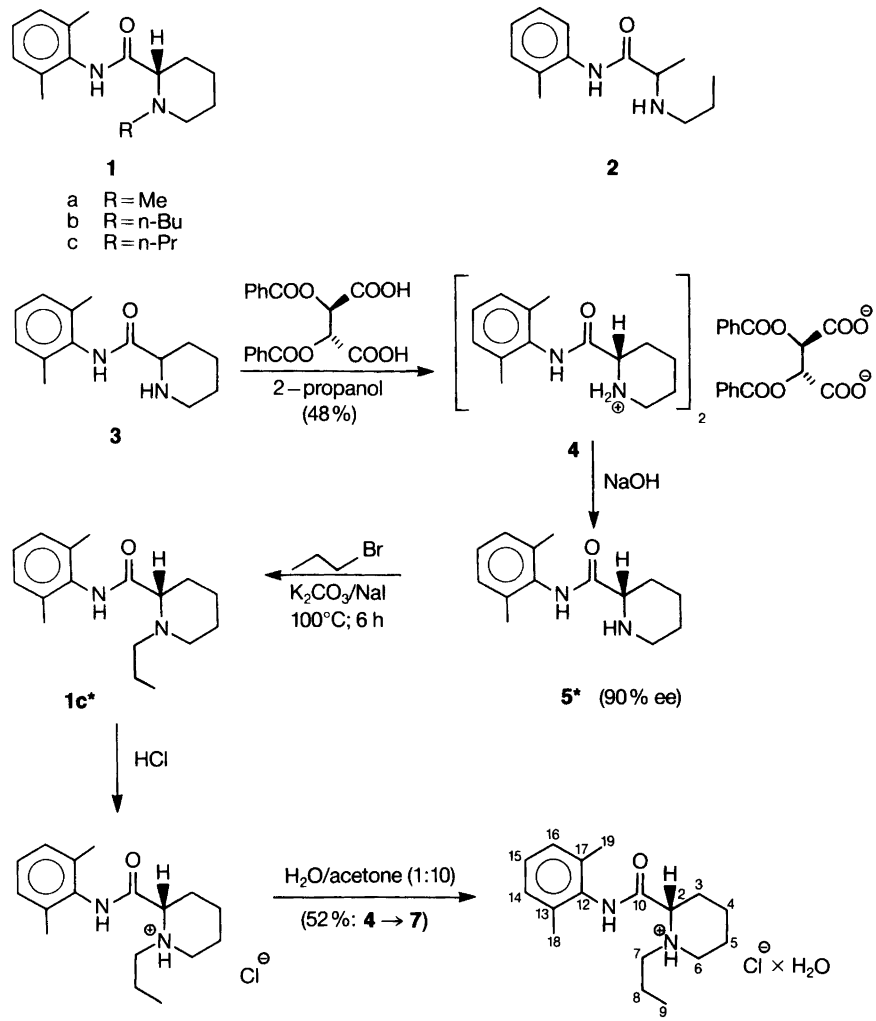

Scheme 1.

ml^{-1}, which is a considerably lower value than the concentration range of ca. 90 mg ml^{-1} used in the crystallization process. Consequently, the crystallization system is strongly over-saturated and the efficiency of the resolution was found to depend both on the rate of cooling and on the total crystallization time. Thus, when the mixture (or solution) under reflux was cooled to 20 °C within 0.5–1 h after completing the addition of dibenzoyltartaric acid, (+)-2′,6′-pipecoloxylidide (**5**) was obtained in an optical purity of 95 % (*S*).[§]

This rather high level of enantiomeric purity was obtained simultaneously with an excellent yield of ca. 92 % (based on the theoretical amount of (*S*)-enantiomer). Optical purities of ca. 98 % (*S*) could be obtained if the crystallization process was interrupted after less than 0.5 h. After a prolonged crystallization time (i.e. several hours), however, an equilibrium point was reached with a stable composition containing only 65–70 % of the desired (*S*)-enantiomer.

Fractional crystallizations of diastereomeric salts are known to be affected by the presence of water in the solvents used. The influence of water has been ascribed to its greater tendency to form

[§]The (*S*)-configuration of **5** was established by reference to an authentic sample of the (*R*)-enantiomer.[6]

Table 1. Resolution of (±)-2′,6′-pipecoloxylidide. The influence of various H_2O-contents on the optical purity and enantiomeric yield.

H_2O-Content in 2-propanol/%[a]	Optical purity /% (*S*)	Enantiomeric yield/%
0.1	95	92[b]
2	74	55[b]
10	98	30[c]

[a]Determined by Karl Fischer titration. [b]Crystallization time 0.5–1 h. [c]Crystallization time 2 h.

solvates than alcohols and other solvents.[7] In Table 1 we have summarized our findings, which clearly show that changes in the water content give substantial variations in optical purity and enantiomeric yield. Furthermore, the composition of the isolated dibenzoyltartrate salt changes from the 2:1 ratio in **4** to 1:1 in the presence of 10 % H_2O.

The *N*-alkylation of the resolved pipecoloxylidide base **5** was conducted under fairly standard conditions. Thus, by using an excess of 1-bromopropane and a catalytic amount of NaI in the presence of K_2CO_3, the conversion of starting material was >99.5 % in a variety of solvents. The use of water-miscible solvents (e.g. acetonitrile, ethanol) caused difficulties in the subsequent work-up procedure; these could be avoided by using 4-methyl-2-pentanone (isobutyl methyl ketone; MIBK). In this case, inorganic salts could be efficiently separated off in the aqueous phase after adding water to the reaction mixture. The HCl-salt **6** could then simply be precipitated from the organic phase by adding hydrochloric acid. No loss in optical purity in the product thus isolated could be detected.

Further studies on this reaction system revealed that the amount of water in the solvent has a profound influence on the reaction time. Thus, decreasing the H_2O content from the normal level of 3 mg ml^{-1} (reagent grade quality) to 0.2 mg ml^{-1} increased the alkylation time from 6 to 17 h, whereas higher water levels (e.g. 15 mg ml^{-1}) were found to have no effect on the reaction time. It can thus be concluded that a certain minimum amount of water has to be present in the solvent in order to ensure some solubilization of the heterogeneous base K_2CO_3. Changing to a completely homogeneous system by using triethylamine resulted in a decrease in reaction time from 6 to 4 h accompanied by a slight increase in yield (ca. 2 %). In this case, however, the isolated product had a distinctly inferior chemical purity.

It is well known that the optical purity of partially resolved compounds can be improved in a final recrystallization.[8] In the present case, one recrystallization of the crude hydrochloride **6** from acetone/water (10:1) gave ropivacaine · HCl · H_2O (**7**) with an optical purity of >99.5 % ee.

Conclusion

Ropivacaine · HCl · H_2O (**7**) has been synthesized starting from (±)-2′,6′-pipecoloxylidide · HCl (**3** · HCl) in three steps (resolution, alkylation, final optical purification) and has been isolated in an overall yield of 50 % with an optical purity of >99.5 % ee.

Experimental

All chemicals used were of reagent grade. (±)-2′,6′-Pipecoloxylidide · HCl was purchased from Nobel Chemicals, Bofors, Sweden. Melting points were determined in capillary tubes on a Büchi 520 melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 298 spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a Jeol FX 200 instrument operating at 200 MHz and 50.10 MHz, respectively. Chemical shifts are reported in ppm on the δ scale relative to *t*-butyl alcohol (δ_H = 1.23 ppm and δ_{CH_3} = 30.6 ppm, respectively). Splitting patterns are designated as s (singlet), d (doublet), t (triplet) and m (multiplet). The assignments of the signals in the ^1H NMR spectrum of **7** were made on the basis of a ^1H–^{13}C correlated 2D spectrum recorded in C_6D_6/DMSO-d_6 (2.5:1). Mass spectra (electron impact, ionizing voltage 70 eV) were obtained on a LKB 9000 mass spectrometer or on a Hewlett-Packard Model 5970 A mass-selective detector, equipped with a Hewlett-Packard MS Chem Station. Optical rotations were measured on an Optical Activity Ltd. AA-100 polarimeter. Microanalyses were performed by *Analytische Laboratorien,* Engelskirchen, West Germany.

The optical purity of the resolved 2′,6′-pipecoloxylidide (**5**) was determined after derivatization with (−)-camphanic acid chloride (Fluka AG) in

pyridine (50 °C/20 min), using a Carlo Erba 2150 gas chromatograph equipped with a cross-linked quartz column (30 m × 0.2 mm, stationary phase J&W DB5) at 280 °C isothermal column-oven temperature, a flame-ionization detector, He as carrier gas and a LDC/Milton Roy CI-10 integrator. Using a carrier gas flow rate of 0.30 m s^{-1}, the retention times for the (*S*)- and (*R*)-enantiomers were ca. 9.2 min and 9.5 min, respectively. The determination of the enantiomeric purity of ropivacaine · HCl · H_2O (**7**) was performed by liquid chromatography (LC) using a chiral α_1-acid glycoprotein column (LKB Enantio Pac; 100 mm × 4 mm, particle size 10 μ). A Brownlee MPLC silica pre-column (30 mm × 4.6 mm) was used between the pump (LDC Constametric III) and the injector. Column eluates were monitored using an LDC Spectromonitor III (sensitivity 0.05 AUFS) at 220 nm. The eluent was composed of 2-propanol/phosphate buffer, pH 7.2, $I = 0.05$ (7:93), and with a flow rate of 0.30 ml min^{-1} the enantiomers were detected at retention times ~18 min (*R*) and ~28 min (*S*).

Bis[S-(+)-2′,6′-pipecoloxylidide] (−)-O,O′-dibenzoyl-L-tartrate (**4**). A mixture of (±)-2′,6′-pipecoloxylidide hydrochloride (**3** · HCl; 1.84 kg, 6.85 mol), water (6 l) and toluene (6 l) was heated to ca. 60 °C and pH was adjusted to >11 with 45 % NaOH (ca. 0.45 l). After separation, the organic phase was evaporated to dryness under reduced pressure and the residue was dissolved in 2-propanol (10 l) at 80 °C. A solution of (−)-*O,O′*-dibenzoyl-L-tartaric acid monohydrate (1.35 kg, 3.59 mol) in 2-propanol (4.3 l) was added while stirring and the mixture was then cooled to ca. 20 °C over a period of 1 h. The precipitated crystals were then filtered off, washed with 2-propanol (4 l) and dried to afford 1.36 kg (48.2 %) of the crystalline product **4**. Treatment of a sample of this material with base [e.g. NaOH (aq)] followed by a recrystallization from toluene gave (*S*)-(+)-2′,6′-pipecoloxylidide (**5**): m.p. 131–132 °C (lit.[6] m.p. 130–132 °C); $[\alpha]_D^{25}$ +49.0° (*c* 2.3, 1 M HCl) (lit.[6] +46.0); optical purity (GC) 95.0 % (*S*)-enantiomer; mass spectrum [*m/z* (% rel. int.)]: 232 (M^+, 0.4), 121 (6), 84 (100), 56 (10). Determination of solubility: A suspension of **4** (ca. 1 g) in 2-propanol (100 ml) was heated under reflux for 5 min. The resulting slurry was filtered while hot, and the clear filtrate was then evaporated to dryness under reduced pressure to afford 0.5 g of solid residue. Thus, the solubility of **4** is 0.5 g per 100 ml or 5 mg ml^{-1}.

(S)-(−)-1-Propyl-2′,6′-pipecoloxylidide hydrochloride monohydrate (ropivacaine · HCl · H_2O) (**7**). A mixture of bis[(*S*)-(+)-2′,6′-pipecoloxylidide] dibenzoyltartrate (**4**; 100 g, 0.122 mol), 4-methyl-2-pentanone (MIBK; 600 ml), and water (400 ml) was made alkaline with 45 % NaOH (32 ml) at 60 °C. After separation, the organic phase was dried by azeotropically distilling off a volume of 200 ml to an H_2O content of ca. 3 mg ml^{-1} and the residue was then diluted with a corresponding amount (i.e. 200 ml) of MIBK. To this solution, K_2CO_3 (49.3 g, 0.357 mol), NaI (5.3 g, 0.035 mol) and 1-bromopropane (43.9 g, 0.357 mol) were added and the resulting mixture was allowed to react at 100 °C for 6 h with stirring. The temperature was reduced to 60 °C and the reaction mixture was washed with water (300 ml). After separation, the temperature of the organic phase was adjusted to 40 °C and conc. (ca. 36 %) aqueous HCl (17 ml) was added. The precipitate thus formed was filtered off after cooling the slurry to 20 °C; after drying, 54.4 g of crude product was obtained. Recrystallization was performed by dissolving the crude product (48 g) in a mixture of acetone (96 ml) and water (50 ml) under reflux, followed by adding more acetone (384 ml) and lowering the temperature. The crystals were filtered off at 20 °C; after drying, 37.0 g (52.5 %) of the product was obtained: m.p. 269.5–270.6 °C; H_2O-content (Karl Fischer titration) 5.4 % (theor. 5.5 %); $[\alpha]_D^{20}$ −7.28° (*c* 2, H_2O); optical purity (LC) 99.8 % (*S*)-enantiomer; IR (KBr disc): ν_{max} 3530 (amide N–H), 2660 and 2520 (amide salt NH^+), 1690 and 1660 (amide I), 1555 (amide II) and 785 (aromatic C–H) cm^{-1}; ^1H NMR (47 mg/1 ml D_2O): δ 0.95 (t, 3H, CH_3-9), 1.6–2.3 and 2.3–2.5 (m, 8H, CH_2-3, CH_2-4, CH_2-5, CH_2-8), 2.18 (s, 6H, aromatic CH_3-18, 19), 3.0–3.2 (m, 3H, CH_2-7, CH_a-6), 3.6–3.8 (brd, 1H, CH_e-6), 4.1–4.3 (dd, 1H, CH-2), 4.88 (s, 3H, H_2O, NH^+), 7.1–7.3 (m, 3H, aromatic CH-14, 15, 16); ^{13}C NMR (3 ml D_2O, saturated solution): δ 11.12 (C-9), 17.73 (C-8), 18.12 (C-18, C-19), 21.65 and 23.18 (C-4, C-5), 29.72 (C-3), 53.00 (C-6), 58.67 (C-7), 66.55 (C-2), 129.19 (C-14, C-16), 129.41 (C-15), 132.86 (C-12), 136.63 (C-13, C-17), 169.11 (C-10); mass spectrum [*m/z* (% rel. int.)]: 274 (M^+, 0.03), 245

($M^+-CH_2CH_3$, 0.2), 126 ($C_5H_9N^+C_3H_7$, 100), 84 ($C_5H_{10}N^+$, 7). Anal. $C_{17}H_{29}ClN_2O_2$; C, H, Cl, N, O.

Acknowledgement. The analytical work performed by Dr. Hans Malmberg and Mrs. Monica Widahl-Näsman, Analytical Department, Pharmaceutical Research and Development, and by Mr. Håkan Molin, Department of Antibacterial Chemotherapy, Astra Alab AB, is gratefully acknowledged.

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Received September 14, 1987.