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Racemisation of *R*-Bupivacaine: A Key Factor in the Integrated and Economic Process for the Production of Levobupivacaine

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Abstract:

Two methods for the racemisation of nonracemic bupivacaine and 2′,6′-pipecoloxylidide, a key intermediate in the synthesis of bupivacaine, are described. One uses carboxylic acids at high temperature and the other uses water and a cosolvent. The product obtained from the carboxylic acid racemisation is of suitable quality to generate commercial levobupivacaine hydrochloride (Chirocaine) 1[*S*], a less cardiotoxic alternative to bupivacaine hydrochloride (Marcaine) 1[*R*,*S*].

Introduction

Racemic bupivacaine hydrochloride (Marcaine) **1[*R*,*S*]** is currently used as an epidural anaesthetic during labour and for ulna nerve block for local anaesthesia in minor operations. At high doses however, it is potentially hazardous due to cardiotoxicity problems. A clinical study was carried out to compare the racemate with the (*S*)-isomer.[1] It was found that the myocardial contractility index and the stoke index were reduced by a greater degree with racemic bupivacaine than with levobupivacaine. No significant effects on ECG were detected with levobupivacaine; it was known at the time that racemic bupivacaine produces both mechanical depression and small but statistically significant ECG alterations. This evidence confirmed that levobupivacaine is less cardiotoxic in man, making it significantly safer than racemic bupivacaine.

Following this study, the requirement for quantities of high quality chiral levobupivacaine hydrochloride **1[*S*]** increased. An economically competitive route to **1[*S*]** was therefore needed.

A number of synthetic routes to levobupivacaine hydrochloride **1[*S*]** were investigated. These included the resolution of racemic bupivacaine **2**, which is readily available, and 2′,6′-pipecoloxylidide, **3**, a precursor of bupivacaine. Resolution methods for both of these compounds had previously been documented in the literature.[2,3] The method described for the resolution of **2** used at least 0.5 equiv of tartaric acid. In the initial experiments we carried out, 0.5 equiv of tartaric acid were used in 10 vols of propan-2-ol, providing (*S*)-enriched bupivacaine tartrate in 90% ee. The tartrate salt was then treated with base, and the (*S*)-enriched bupivacaine free base was recrystallised twice from isopropyl acetate to give (*S*)-bupivacaine in 99% ee. This method was developed such that when 0.25 equiv of D-tartaric acid is used with 2% water and 6 vols of propan-2-ol, the product salt crystallises out as a 2:1 bupivacaine:tartrate salt in 98% ee.[4] The (*R*)-bupivacaine remains in the mother liquor as the free base. This improvement leads to an overall yield of approximately 35−40% high purity **1**.

A method for resolving **3** was also in the literature;[2,3] this method used dibenzoyl-D-tartaric acid which crystallised as the (*R*)-2′,6′-pipecoloxylidide-dibenzoyl-D-tartrate salt. By switching to dibenzoyl-L-tartaric acid, the desired (*S*)-2′,6′-pipecoloxylidide-dibenzoyl-L-tartrate salt crystallises from solution, and the desired isomer is therefore more easily isolated and obtained with a higher enantiomeric excess. This improvement to the literature method and the filtration of the product at 50 °C lead to the desired isomer crystallising in greater than 98% diastereomeric excess.

Butylation of the secondary amine of the isolated (*S*)-isomer of **3** can be achieved using butyl bromide and a suitable base such as potassium carbonate[2,5] or by reductive amination using butyraldehyde[3,6] to give (*S*)-bupivacaine.

1 can therefore be made via two resolution routes. One method involves the resolution on the final compound and the other on a late-stage intermediate. Despite the two resolution methods being highly efficient, by the very nature of a resolution process, two-thirds of the high value material would be wasted if the (*R*)-isomer could not be recycled. Therefore, to improve the economics of the overall process, the (*R*)-isomer needed to be racemised and the racemic mixture obtained recycled into the resolution process, as depicted in Scheme 1.

Racemisation of Enriched (*R*)-Bupivacaine and Its Precursor, Enriched (*R*)-2′,6′-Pipecoloxylidide. We have found two racemisation methods for both **1[*R*]** and **3[*R*]**. The first method uses an acid such as a carboxylic acid,[7] and the second method uses water and a cosolvent.[8]

Racemisation Using a Carboxylic Acid. The racemisation of L-proline and (*R*)-2-piperidinecarboxylic acid using butanal

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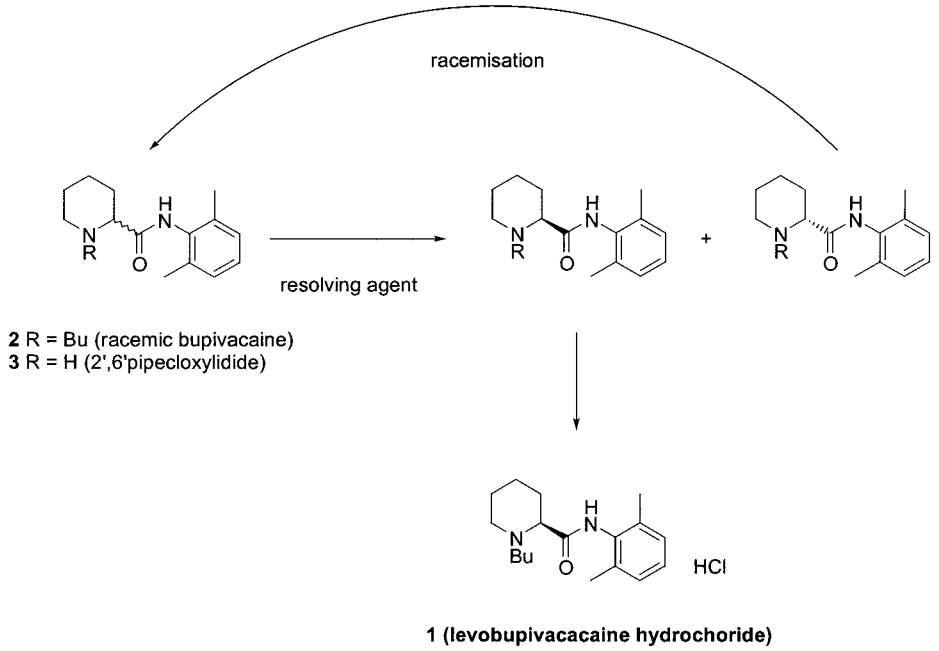
Scheme 1. **Overall process for the synthesis of levobupivacaine 1**



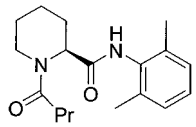


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Figure 1. **Structure of butyrylamide.**

and salicyaldehyde in the presence of an organic acid such as formic, acetic, propanoic, or butanoic acid was already known.[9] In these racemisations the first step is the reaction between the aldehyde and amino acid to form the Schiff base, which has a positive charge on the nitrogen. The second step is proton abstraction from the α-carbon by the carboxylate anion. On the basis of this information, single isomer **3** was heated at 118 °C in butyric acid containing salicyaldehyde; racemisation did occur, but approximately 30% of *N*-butyrylamide **4** also formed (Figure 1).

It was subsequently found that the prescence of the aldehyde was not necessary for racemisation to occur; this suggests a different reaction mechanism takes place in the absence of the aldehyde. Unfortunately the butanoic acid still reacted with the secondary amine of **3**, generating **4**. We concluded that if the Schiffs base is not required as an intermediate in the racemisation, then the single isomer tertiary amine **2** could possibly undergo racemisation and would not form the amide by-product. This was confirmed when it was heated in butanoic acid; racemisation took place without the formation of any undesirable impurity. A number of conditions were investigated including the use of an inert solvent such as toluene and xylene. The results are summarised in Table 1.

Nonracemic **2** and **3** can be heated in, for example, propionic acid or butanoic acid, with or without the an inert solvent, such as toluene or xylenes, and undergo racemisation. On a small scale, the racemic product can be easily isolated by extraction using suitable pH adjustments.

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Table 1. **Comparison of reaction conditions using different carboxylic acids to racemise single isomer bupivacaine and the results obtained**

carboxylic acid	solvent	temperature/ °C	time/ h	enantiomeric excess/%	yield/ %
acetic		110	22	56	86
propionic		120	18	9	88
butyric		120	23	3	91
butyric	toluene	110	22	87	85
butyric	xylene	140	18	54	96

Table 2. **Comparison between the carboxylic acid pK_a values**

acid	pK_a at 25 °C
acetic acid	4.76[10]
propionic acid	4.87[10]
butanoic acid	4.82[10]
tartartic acid	3.04 step 1[10]
	4.37 step2[10]
camphor sulfonic acid	2[11]
hydrochloric acid	−6.2[12]

The racemisation of bupivacaine salts in propionic acid was also investigated. (*R*)-bupivacaine tartrate, (*R*)-bupivacaine camphor sulphonic acid, and (*S*)-bupivacaine hydrochloride were heated at reflux in propionic acid. The hydrochloride salt did not racemise, while the camphor sulphonate did so slowly; 80% ee was obtained after 22 h. Over the same period of time the tartrate salt had completely racemised. The difference in the rate of the racemisation was thought to be due to the pK_a values of the acids. These values are shown in Table 2.

The carboxylic acid used in the racemisation should ideally have a pK_a in the range 4.7−5.0. Following the resolution of **2**, the mother liquor consists of enriched (*R*)-

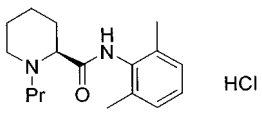

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Figure 2. **Structure of ropivacaine hydrochloride.**

bupivacaine, tartartic acid, and wet propan-2-ol. To ease processing on a larger scale the solvent is exchanged with toluene that is in turn replaced with propionic acid. The use of toluene minimises the reaction between propan-2-ol and propionic acid occurring. It was found that if 2 vols of propionic acid are used and the reaction is heated at reflux (150−154 °C), the racemisation is complete in only 2 h. After the mixture is cooled to 70−90 °C, a further volume of propionic acid is added, to ensure the suspension remains mobile throughout. Hydrogen chloride is then added which eases processing dramatically. The product **1[*R,S*]** crystallises out of solution on cooling to room temperature and is simply filtered. In early experiments **2[*R,S*]** was extracted out of the mixture as the bupivacaine base; however, it was found that by direct gassing of the reaction with hydrogen chloride, a higher yield is obtained and the product has less impurities. Racemic bupivacaine hydrochloride crystallises while cooling to room temperature. Toluene is added, and the product filtered and washed with propan-2-ol. The product obtained is of suitable quality to be resolved with D-tartaric acid, which leads to high grade **1**. A study was carried out which generated five batches of levobupivacaine hydrochloride starting from 1 kg bupivacaine hydrochloride monohydrate. The first batch was generated solely from pharmacopoeial grade material. Four subsequent batches were generated from 100% racemised bupivacaine. After the five loops were complete, 74% of the bupivacaine had been isolated. The five batches of levobupivacaine hydrochloride were all high purity.

Racemisation Using Water and a Cosolvent. The second method involves heating **3** in water or in the case of **2**, water and a cosolvent such as an alcohol or a polyol. In the case of **3**, this method has an advantage over the carboxylic acid racemisation method in that *N*-acylation does not occur. The racemisation of optically enriched ropivacaine hydrochloride **5** (Figure 5) in dilute aqueous solution (100 vols) at pH 1−6 and 80−130 °C had been previously reported.[13] Under these conditions the racemisation of single isomer bupivacaine is very slow.

The reaction conditions were developed such that when (*S*)-bupivacaine is heated in 10 vols of ethylene glycol containing 10% v/v water at 138 °C for 9 h, racemisation is complete. The use of a cosolvent allows solutions of higher concentration to be used than without cosolvent, since bupivacaine is then in solution. The racemic product can be either isolated by crystallisation from the aqueous media or by extraction into an organic solvent such as ethyl acetate and then by evaporation of the solvent.

Table 3. **Racemisation of nonracemic 2 under different conditions using 10 vols of solvent**

alcohol	amount alcohol (mL)	amount water (mL)	temperature/ °C	time/ h	% ee
ethylene glycol	2.5	2.5	120	24	68
1-butanol	2.5	2.5	reflux	24	94
ethylene glycol	4.5	0.5	138	9	4
1,2-butanediol	15	1.5	122	19	72
propan-2-ol	53	1.2	123 (70 psi)	20	91

A number of conditions were tried and are summarised in Table 3. The results clearly show that the rate of reaction is temperature-dependent. The racemisation was also investigated in the presence of tartaric acid. A mixture of (*S*)-bupivacaine and (*S*)-bupivacaine-D-tartrate were heated in propan-2-ol and water in a 1:1 ratio at 150 °C in a sealed vessel. After 22 h 26% ee was achieved.

In summary, two methods for the racemisation of bupivacaine have been demonstrated. This allows material left in the mother liquors of the resolution process to be racemised and used to generate high quality levobupivacaine hydrochloride, thereby reducing the overall cost.

Experimental Section

The ^{1}H NMR spectra were determined using a Bruker AC-200 instrument in the solvent noted.

Resolution of Racemic Bupivacaine 2. To MTBE (780 g) and water (300 g) was added racemic bupivacaine hydrochloride monohydrate (200 g). The mixture was warmed to 45 °C and treated with 46/48% w/w sodium hydroxide (54.1 g) solution. The lower aqueous phase (pH 14) was removed and the organic layer washed with water (200 g). After the aqueous layer was removed, the organic layer was concentrated by atmospheric distillation. MTBE (642 g) was then removed and propan-2-ol (800 g) added; the distillation was continued. A further 529 g of solvent was distilled. Propan-2-ol (385 g) was then added, bringing the solvent volume to 6 vols with respect to **2[*R,S*]**. When the internal temperature was adjusted to 75 °C, water (20 g) was added followed by D-(−)-tartaric acid (21.8 g). The mixture was brought back to reflux and then allowed to cool to room temperature over 3 h. After 1 h at this temperature the suspension was filtered. The solid was returned to the vessel and stirred with propan-2-ol (314 g) for 10 min. It was then filtered and washed with propan-2-ol (24 g). The di-bupivacaine tartrate salt was dried to give 84.9 g of product with >99% ee. ^{1}H NMR (CD_3OD) δ 1.0 (t, 6H), 1.4 (m, 4H), 1.8 (brm, 14H), 2.2 (s, 12H), 2.3 (m, 2H), 3.0 (brm, 6H), 3.6 (m, 2H), 3.9 (m, 2H), 4.4 (s, 2H, tartaric acid), 7.1 (s, 6H).

Racemisation Using Acid. The mother liquors from the above resolution process, which contained approximately 94 g of bupivacaine in 969 g of propan-2-ol, were concentrated by atmospheric distillation. When 756 g of solvent had been

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removed toluene (305 g) was added and the distillation continued. After the distillation of 447 g of solvent, propionic acid (309 g) was added, and the distillation was again continued. A further 186 g of propionic acid was removed, by which time the internal temperature was 152 °C. The mixture was heated for 2 h, by which time racemisation had occurred, and a further 93 g of propionic acid was then added. The solution was cooled to 70 °C, and hydrogen chloride (15.8 g) was added. The temperature was maintained between 70 and 90 °C. The mixture was stirred for a further hour and then cooled to room temperature over 2 h. Toluene (79 g) was added and the suspension stirred for 30 min. The suspension was filtered. The solid was returned to the vessel and slurried with propan-2-ol (77 g). It was filtered, washed with propan-2-ol (88 g), and dried under vacuum at 60 °C to constant weight to give racemic bupivacaine hydrochloride (95 g): mp 251−254 °C, 93% HPLC purity (remaining 7% due to propan-2-ol and ∼0.1 propionic acid), achiral chromatography: column, symmetry C18 (5 μm), 150 mm × 3.9 mm; mobile phase, acetonitrile 50%, pH 7 phosphate buffer 50%; wavelength, 210 nm; injection volume, 20 μL; flow rate, 1 mL/min; temperature, 40 °C; retention times: **1** 9.9 min. Chiral chromatography: column, pirkle L-phenylglycine, 250 mm × 4.6 mm; mobile phase, EtOH 15%, hexane 85%; wavelength, 220 nm; injection volume, 20 μL; flow rate, 1 mL/min; temperature, 40 °C; retention times: (*R*)-bupivacaine hydrochloride 7.4 min, (*S*)-bupivacaine hydrochloride 8.1 min. ^{1}H NMR (CD_3OD) δ 1.0 (t, 3H), 1.2 (d, propan-2-ol), 1.4 (m, 2H), 1.6−2.1 (m, 7H), 2.2 (s, 6H), 2.5 (m, 1H), 3.2 (m, 3H), 3.7 (br d, 1H), 4.0 (m, propan-2-ol), 4.2 (br d, 1H), 7.1 (m, 3H): loss on drying 7%.

Resolution of 3. Racemic **3** (20 g) was dissolved in ethanol (120 mL) and water (2 mL) and warmed. To the solution was added a warm solution of dibenzoyl-L-tartaric acid (15.4 g) in ethanol (210 mL). The mixture was heated to reflux and then allowed to cool. Crystallisation occurred at 69 °C, and the suspension was filtered at 50 °C. The di-2′,6′-pipecoloxylidide dibenzoyl-L-tartrate (10.3 g) salt was obtained in >99% ee. ^{1}H NMR δ 1.8 (brm, 10H), 2.2 (s, 12H), 2.4 (m, 2H), 3.1 (m, 2H), 3.3 (m, 2H), 4.2 (m, 2H), 5.0 (s, water), 5.9 (s, 2H, dibenzoyl-L-tartaric acid), 7.1 (m, 6H), 7.5 (t, 4H, dibenzoyl-L-tartaric acid), 7.6 (m, 2H, dibenzoyl-L-tartaric acid), 8.2 (d, 4H, dibenzoyl-L-tartaric acid).

To the pipecolamide tartrate salt (10 g) was added water (150 mL) and MTBE (200 mL). Sodium hydroxide (46/48% w/w, 5 mL) was added. The basic aqueous layer was removed, and the organic layer was washed with brine (50 mL), dried, and evaporated in vacuo to yield the free base as a white solid (6.1 g).

^{1}H NMR ($CDCl_3$) δ 1.6 (m, 5H), 1.8 (m, 1H), 2.1 (m, 1H), 2.2 (s, 6H), 2.8 (m, 1H), 3.15 (m, 1H), 3.4 (m, 1H), 7.1 (s, 2H), 7.3 (s, 1H), 8.2 (brs, 1H); chiral chromatography: column, D-phenylglycine, 250 × 4.6 mm; mobile phase, EtOH 1%, propan-2-ol 10%, *n*-heptane 89%; wavelength, 254 nm; flow rate, 2 mL/min; retention times: (*S*)-isomer 18.4 min, (*R*)-isomer 20.6 min.

Racemisation Using Water. A mixture of (*S*)-bupivacaine (>99% ee, 1.5 g, mmol), ethylene glycol (13.5 mL), and water (1.5 mL) was heated at 138 °C for 9 h. After the mixture cooled to ambient temperature, crystallisation of a solid occurred. The solid was filtered and dried to give a quantitative yield of bupivacaine that was shown by chiral HPLC analysis to be a 52:48 mixture of (*S*)-bupivacaine and (*R*)-bupivacaine.

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