SYNTHESIS AND CHARACTERIZATION OF SEVERAL LOCAL ANAESTHETICS

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A dissertation submitted in partial fulfillment of the
requirements for the award of the degree of
Master of Science (Chemistry)

Faculty of Science
Universiti Teknologi Malaysia

2013

Specially dedicated to my parents, husband

ACKNOWLEDGEMENT

First and foremost, I would like to acknowledge the lessons, support and guidance of my supervisor, Prof. Dr. Hasnah Mohd Sirat. Her continuous commitments to research studies ensure not only constant results but also have granted her the respect of all her students. I thank her for giving me the opportunity to carry out this research in the field of local anaesthetics.

My words of gratitude also go to all the lecturers, laboratory officers and research officers from the Department of Chemistry and Universiti Teknologi Malaysia. My sincere appreciation also extends to my parents, husband, brothers, sisters and sons for their support, encouragement, care and love. Besides, I'd like to thank to all my friends; especially Tan Ke Xin, for their valuable experience and opinions along this study.

Last but not least, for anyone I've forgotten that has involved directly or indirectly in completing this project, thank you.

ABSTRACT

Three local anaesthetics, tetracaine, lidocaine and benzocaine were synthesized and characterized. Tetracaine or 2-(diethylamino)ethyl 4-butylaminobenzoate was synthesized using two approaches. The first approach was a direct esterification of 4-butylaminobenzoic acid with 2-(diethylamino)ethanol in the presence of boron trifluoride etherate as catalyst to afford 2-(diethylamino)ethyl 4-butylaminobenzoate. The second approach involved two step reactions. Treatment of 4-butylaminobenzoic acid with ethanol in the presence of boron trifluoride etherate afforded ethyl 4-butylaminobenzoate in the first step, followed by, transesterification of ethyl 4-butylaminobenzoate with 2-(diethylamino)ethanol to afford 2-(diethylamino)ethyl 4-butylaminobenzoate in the second step. Lidocaine or 2-(diethylamino)-*N*-(2,6-dimethylphenyl)acetamide was synthesized from 2,6-dimethylaniline, α-chloroacetyl chloride, diethylamine, with α-chloro-2,6-dimethylacetanilide being intermediate in the synthesis. Benzocaine or ethyl-4-aminobenzoate was synthesized by Fischer esterification of 4-aminobenzoic acid with absolute ethanol. The intermediates and products were characterized by using infrared (IR), proton nuclear magnetic resonance (^{1}H NMR), and carbon nuclear magnetic resonance (^{13}C NMR) spectroscopies.

ABSTRAK

Tiga anestetik setempat, iaitu tetrakaina, lidokaina, dan benzokaina telah disintesis dan dicirikan. Tetrakaina atau 2-(dietilamino)etil 4-butilaminobenzoat telah disintesiskan melalui dua pendekatan. Pedekatan pertama adalah pengesteran secara terus antara asid 4-butilaminobenzoik dengan 2-(dietilamino)etanol bermangkinkan boron trifluorida eterat untuk memperolehi 2-(dietilamino)etil 4-butilaminobenzoat. Pendekatan kedua melibatkan tindak balas dua langkah. Tindak balas antara asid 4-butilaminobenzoik dengan etanol dengan kehadiran boron trifluorida eterat menghasilkan etil 4-butilaminobenzoat dalam langkah pertama, seterusnya diikuti dengan pentransesteran 4-butilaminobenzoat dengan 2-(dietilamino)etanol bagi menghasilkan 2-(dietilamino)etil 4-butilaminobenzoat pada langkah kedua. Lidokaina atau 2-(dietilamino)-*N*-(2,6-dimetilfenil)asetamida telah disintesis daripada 2,6-dimetilanilina, α-kloroasetil klorida, dietilamina, dengan α-kloro-2,6-dimetilasetanilida sebagai perantara dalam proses sintesis tersebut. Benzokaina atau etil-4-aminobenzoat telah disintesis secara pengesteran langsung asid 4-aminobenzoik bersama-sama etanol mutlak. Bahan perantara dan produk telah dicirikan dengan menggunakan spektroskopi inframerah, resonans magnet nukleus (^{1}H dan ^{13}C).

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LIST OF ABBREVIATIONS

δ	chemical shift
Hz	hertz
mL	milliliter
g	gram
EtOAc	ethyl acetate
PE	petroleum ether
HPLC	high performance liquid chromotography
GC	gas Chromatography
h	hour
IUPAC	International Union of Pure and Applied Chemistry
R_f	retention factor
NMR	nuclear magnetic resonance
ppm	parts per million
RT	room temperature
br	broad
d	doublet
DEPT	distortionless enhancement of polarization transfer
J	coupling constant
q	quartet
s	singlet
sext	sextet
TLC	thin layer chromatography
PABA	*para*-aminobenzoic acid
EMLA	lidocaine/prilocaine
IVRA	intravenous regional anaesthesia
v/v	volume/volume
IR	infrared

EtOAc	ethyl acetate
t	triplet
v	frequency
M	molar
INN	International Neoproprietary Name

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CHAPTER 1

INTRODUCTION

1.1 Background of Study

An anaesthesia is one of the most significant developments of modern medicine because it allows once unbearable medical procedures to be performed while the patient is relaxed and asleep. There are three main types of anaesthesia: general anaesthetic - putting someone to sleep and keeping them asleep for surgery or other medical procedures, regional anaesthetic – numbing an area of the body, local anaesthetic – numbing only a small part of body [1].

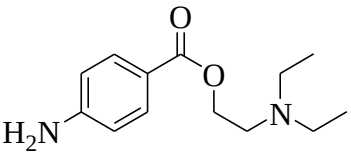
A local anaesthesia**,** is given through various medications and dosages in the form of epidurals, pudendal blocks, and spinal blocks. It is also given near the end of birth for an episiotomy, to relieve the discomfort of the perineum stretching and also after birth to repair tears and episiotomies. When used at the end of birth or after birth, medication such as procaine (Novocain) **(1)**, lidocaine (Dalcaine, Dilocaine, L-Caine, Nervocaine, Xylocaine) **(2)**, and tetracaine (Pontocaine) **(3)**, is injected into the skin, muscle, or cervix for the fast, temporary relief of pain in the perineal area [2].

Chemically, all local anaesthetics have an intermediate chain linking an amine on one end to an aromatic ring on the other. The amine end is hydrophilic, and the aromatic end is lipophilic. Difference of the amine or aromatic ends changes the chemical activity of the drug. There are two basic classes of local anaesthetics i.e, the amino amides and the amino esters. Amino amides have an amide link between the

intermediate chain and the aromatic end, whereas amino esters have an ester link between the intermediate chain and the aromatic end [3]. Amino esters and amino amides differ in several respects. Amino esters are metabolized in the plasma *via* pseudocholinesterases, whereas amino amides are metabolized in the liver. Amino esters are unstable in solution, but amino amides are very stable in solution. Amino esters are much more likely to cause allergic hypersensitivity reactions than amino amides.

Lidocaine **(2)** is one of the local anaesthetics of the amino amides group, which has molecular formula $C_{14}H_{22}N_2O$ with 234.34 g/mol molecular mass. The IUPAC name for this compound is 2-(diethylamino)-*N*-(2,6-dimethylphenyl)acetamide[4] . It is used topically to relieve itching, burning and pain from skin inflammations, injected as a dental anesthetic or as a local anaesthetic for minor surgery. Lidocaine is the first amino amide-type local anaesthetic[5].

Tetracaine **(3)** is one of the local anaesthetics of the amino ester group, which has molecular formula $C_{15}H_{24}N_2O_2$ with 264.363 g/mol molecular mass. The IUPAC name for this compound is 2-(diethylamino)ethyl 4-(butylamino)benzoate. Also known as amethocaine; trade name Pontocaine and Dicaine. It is mainly used topically in ophthalmology and as an antipruritic, and it has been used in spinal anesthesia [6]. Benzocaine **(4)** is one of the local anaesthetics of the amino ester group, which has molecular formula $C_9H_{11}NO_2$ with 165.189 g/mol molecular mass. The IUPAC name for this compound is ethyl *p*-aminobenzoate. It is commonly used as a topical pain reliever [7].



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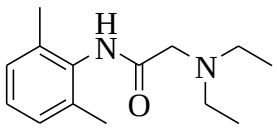

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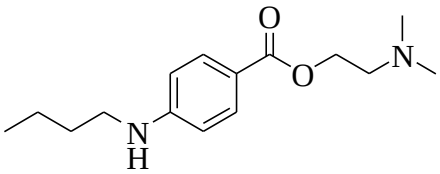

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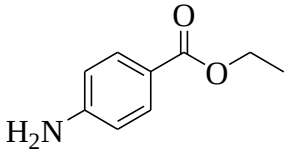

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1.2 Objectives of Study

The main objectives of the research are:

i. To synthesize local anaesthetic, tetracaine **(3)** or 2-(dimethylamino)ethyl 4-(butylamino)benzoate. lidocaine **(2)** or 2-(diethylamino)-*N*-(2,6-dimethylphenyl)acetamide, benzocaine **(4)** and ethyl *p*-aminobenzoate.

ii. To characterize the products and intermediates using spectroscopic techniques.

1.3 Scope of Study

Three local anaesthetics, tetracaine, lidocaine and benzocaine are synthesized and characterized. Tetracaine or 2-(diethylamino)ethyl 4-butylaminobenzoate is synthesized using two approaches. The first approach is a direct esterification of 4-butylaminobenzoic acid with 2-(diethylamino)ethanol in the presence of boron trifluoride etherate as catalyst to afford 2-(diethylamino)ethyl 4-butylaminobenzoate. The second approach involves two step reactions. Treatment of 4-butylaminobenzoic acid with ethanol in the presence of boron trifluoride etherate afforded ethyl 4-butylaminobenzoate in the first step, followed by, transesterification of ethyl 4-butylaminobenzoate with 2-(diethylamino)ethanol to afford 2-(diethylamino)ethyl 4-butylaminobenzoate. Lidocaine or 2-(diethylamino)-*N*-(2,6-dimethylphenyl)acetamide is synthesized from 2,6-dimethylaniline, α-chloroacetyl chloride, diethylamine, with α-chloro-2,6-dimethylacetanilide being intermediate in the synthesis. Benzocaine or ethyl-4-aminobenzoate is synthesized by Fischer esterification of 4-aminobenzoic acid with absolute ethanol. The intermediates and products are characterized by using infrared (IR), proton nuclear magnetic resonance (^{1}H NMR), and carbon nuclear magnetic resonance (^{13}C NMR) spectroscopies.

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