Design, Synthesis, Characterization and Spectral Analysis Of 2(4-Chloro Acetamido) Benzoic Acid

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Abstract: - Medicinal chemistry is the study of how novel drugs can be designed and developed. This process is helped immeasurably by a detailed understanding of the structure and function of the molecular targets that are present in the body. The medicinal chemist attempts to design and synthesize a pharmaceutical agent that has a desired biological effect on human body or some other living system. In this study, Local anesthetic activity was investigated with an assumed hypothesis that the essential alkyl substituted nitrogen having strong ionization characteristics (pKa in basic side) generally found in local anesthetics can be replaced by amide nitrogen, having chloro methyl group attached to the carbonyl carbon of amide. In this type of arrangement, the inductive effect exerted by chlorine provided enough ionization character to amide nitrogen. Eight esters, ten amides and one imidazole derivatives of 4-(2-chloroacetamido) benzoic acid were synthesized by Fischer's esterification, Schotten-Baumann and substitution reactions. Local anesthetics are the drugs which produce reversible block of nerve damage without loss of consciousness and with loss of pain sensation.

Key Words: ***Molecular targets, alkyl substituted nitrogen, ionization, chloro-methyl group, carbonyl carbon of amide, fisher's esterification, substitution reactions.***

I. INTRODUCTION

The major drug targets are normally large molecules (macromolecules), such as proteins and nucleic acids. Knowing the structures, properties and functions of these macromolecules is crucial if we are to design new drugs [1]. Once the target and a testing system have been chosen, the next stage is to find a lead compound- a compound which shows the desired pharmacological activity.

Manuscript revised January 25, 2023; accepted January 26, 2023. Date of publication January 27, 2023.

This paper available online at www.ijprse.com

ISSN (Online): 2582-7898; SJIF: 5.59

Now a days, structure determination is a relatively straight forward process and it is only when the natural product is obtained in minute quantities that a full synthesis required to establish its structure. Many naturally occurring drugs have been obtained and their structures were determined (e.g. morphine from opium, cocaine from coca leaves, quinine from the bark of the cinchona tree) [2]. In recent years, medicinal chemistry has undergone the revolutionary change. Rapid advances in the biological sciences have resulted in a much better understanding of how the body functions at the cellular and molecular levels.

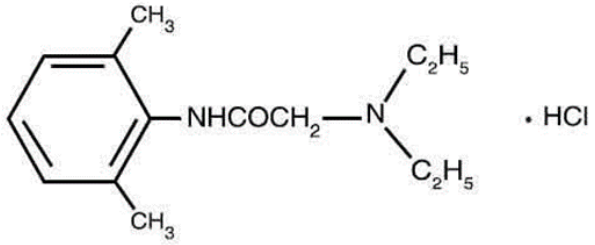

Fig.1. Structure of amithocaine

Local anesthetics are widely used to prevent and relieve pain during surgical procedures, acute pains and in the management of chronic pain. Local anesthetics are used in labour pain, post operative pain and post trauma pain. It should be absorbed at the site of action and it should have a low degree of systemic toxicity. Local anesthetics should be non-irritating and should not cause any damage of nerve and other tissues) [3]. Local anesthetics that are used in dentistry is procaine, monocaine, epinephrine, cobefrin, neosynephrin.

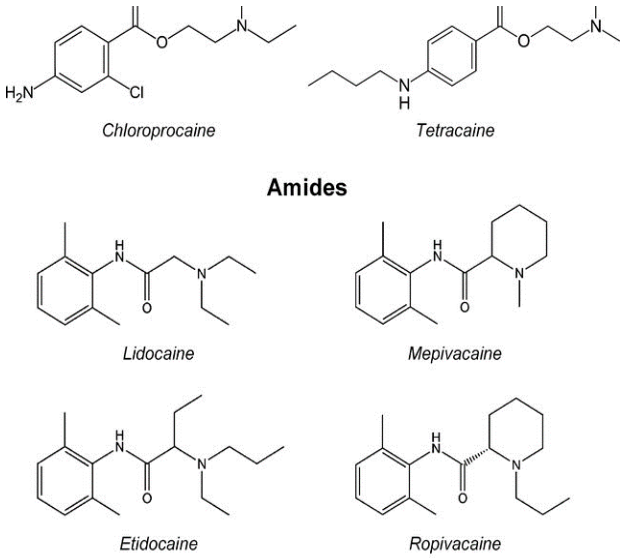

Fig.2. Structure of local anesthetics

II. LITERATURE

2.1 History of Local Anesthetics:

The first local anesthetic in the 19th century was cocaine which was first isolated from the leaves of coca shrub (Erythroxylon coca) by the chemist Albert Niemann in the year of 1860. Like him several chemists of that era has tasted his newly isolated compound and the isolated compound caused numbing of tongue [4]. The chemist Sigmund Frered has studied the physiological actions of cocaine.In the year of 1884, Carl Koller has introduced cocaine for a clinical practice and it was administered topically during ophthalmic surgery. And the chemist Halstead has used cocaine as infiltration conduction block anesthetics.

2.2 MOA Of Local Anesthetics

Local anesthetics acts at cell membrane and it inhibits the generation and conduction of nerve impulse. Local anesthetics with membrane proteins may blocks the potassium channel by the interaction of local anesthetics with potassium channel but the drawback is that it requires high conc. of drug [5]. If the local anesthetic agent is applied externally, it might first cross the membrane to exert blocking action. Actually, the sodium channels of mammalian brain complexes of glycosylated proteins with about 300,000 Daltons, which has 2 subunits, the large α subunit with about 260,000 Daltons and the β subunit with nearly 33,000 – 38,000 Daltons. A subunit with 4domain and 6 transmembrane segments with pore loop.

2.3 Chemistry of Local Anesthetics

The clinically useful local anesthetics fall into one of two chemical groups

1. Amino-esters
2. Amino-amides have an amide link between the aromatic end and the intermediate chain.

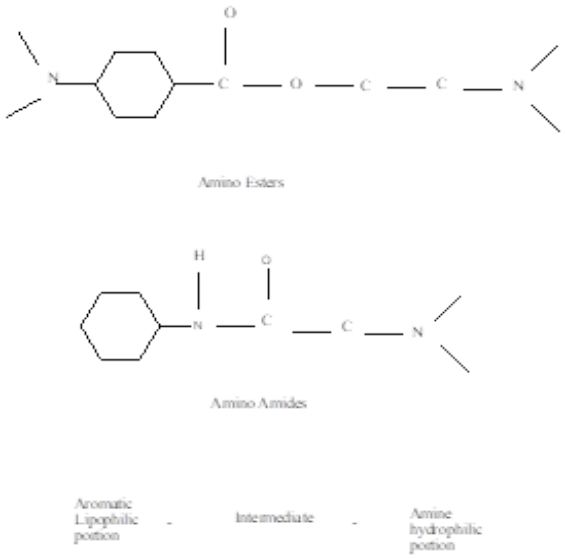

Fig.3. Chemical structure of ester and amides

Ester and amide groups are differed in terms of their stability in solution, metabolism and allergic potential. Amides are stable in solution and undergoes enzymatic degradation in liver and excreted in urine and it was not metabolized in PABA and rarely causes allergic reactions [6]. Esters are unstable in solution and hydrolyzed in plasma by the enzyme pseudo-cholinesterase which was metabolized to PABA but it may cause allergic to some patients. In this study 8 esters (-COO), 10 amines(-NH2) and 1 imidazole derivatives of 4-(2-chloroacetamido) benzoic acid was synthesized with an intention to study their local anesthetic activity.

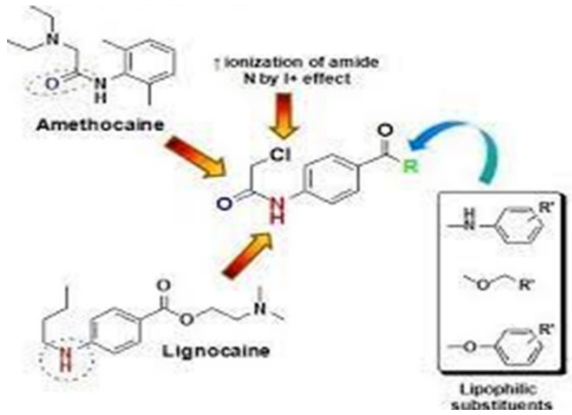

Fig.4. Ionization characteristics of amide

Form the literature survey, many of the local anesthetics such as Amithocaine and Lignocaine.

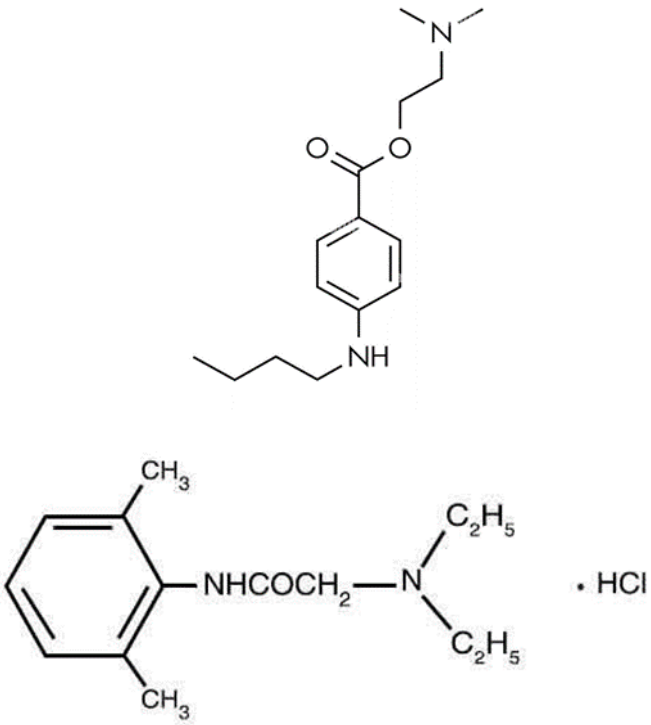

Fig.5. Structure of tetracaine and amithocaine

We have chosen 4-amino benzoic acid nucleus as parent compound, the essential alkyl substituted nitrogen possess strong ionization characteristics which was replaced by amide nitrogen. Carbonyl group was replaced rationally in order to improve the binding pockets for binding [7].

III. Materials And Methods

Amino benzoic acid, sodium hydroxide, tetrahydrofuran, chloroacetyl chloride, hydrochloric acid, ethanol-water mixture and pure ethanol were purchased from the where of analytical grade The Best Scientific Company, Pvt. Limited, Dharmapuri.

3.1 Experimental Section

3.1.1 Methodology:

PROCEDURE 1:

Weigh accurately about 1.37g of 4-aminobenzoic acid in a conical flask and it was dissolved with 35% of NaOH solution (35g of NaOH in 100 ml of distilled water) then chloroacetyl chloride was added in a drop wise manner at 4-10℃ with constant stirring and the mixture was shaken for 10mins to obtain a clear reaction mixture.

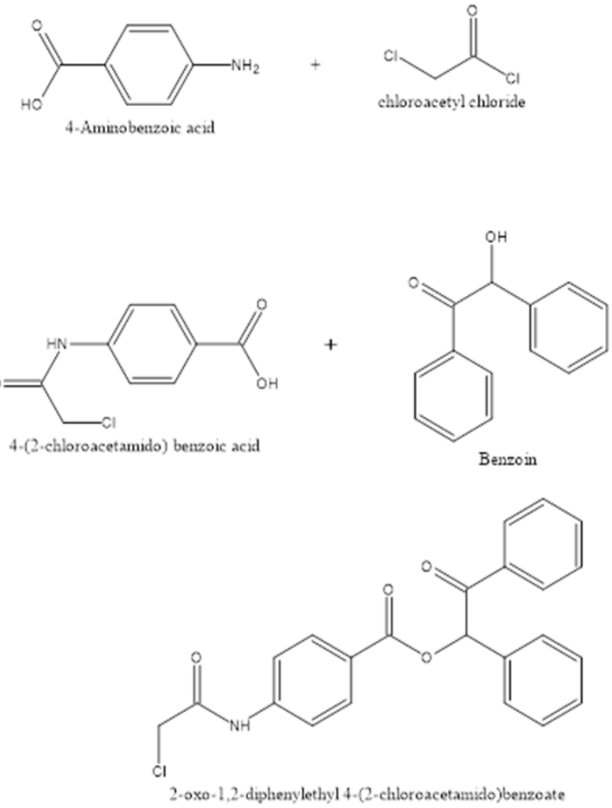

Fig.6. 4-aminobenzoic acid

Above content was acidified by drop wise addition of hydrochloric acid with constant stirring till the mixture turns slightly acidic which was confirmed by litmus paper (red-blue) and the product precipitates completely [7]. Few more drops of HCl was added and stirred. Finally, the compound was filtered, dried and crystallized using ethanol water mixture the compound was denoted as Int 1[8].

PROCEDURE 2:

Int 1 and benzoin was weighed in 1:2 ratio in a round bottom flask and few drops of conc. Sulphuric acid was added and now the solution was acidic in nature then 20ml of tetrahydrofuran was added into it then the solution was kept under refluxation for nearly about 4-6hrs.

Then the above content was poured into cold water and excess of acid was neutralized with NaOH to obtain the product precipitate [9]. Finally, the product was then filtered, dried and recrystallized with 75% ethanol.

Fig.7. Refluxation

IV. Result And Discussion

In an effort to develop novel substituted 4-2 chloroacetamido benzoic acid derivatives we finally synthesized a compound 2-oxo-1,2-diphenylethyl 4-(2-chloroacetamido) benzoate by the refluxing the int.1 with benzoin with tetrahydrofuran for nearly about 4-6hrs resulted in the formation of crude product by neutralizing it with NaOH and it was furtherly crystallized by using pure ethanol. Then the obtained compound was analyzed in UV- visible spectroscopy by using ethanol, methanol and water as a solvent at 200-400 nm –uv range and 400-800-visible range [10]. The absorbance peak was obtained between 200-800 nm. The peak was drawn using wavelength on x-axis and absorbance on Y-axis.

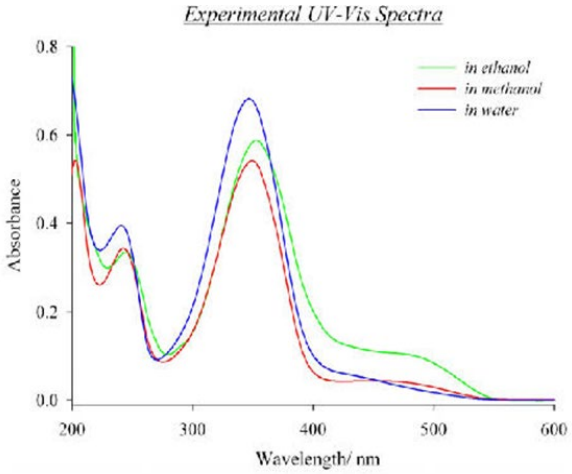

Fig.8. experimental UV-Visible spectra and the resultant product obtained was viewed in NMR spectroscopy.

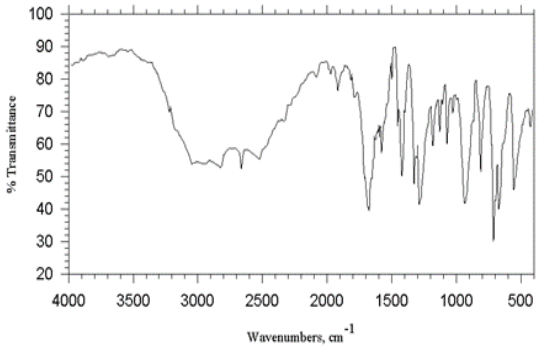

Fig.9. experimental NMR spectra

V. Conclusion

Through our studies, we have concluded the resultant product (Int.2) was synthesized by refluxing the Int.1 with benzoil along with tetrahydrofuran and hydrochloric acid for about 4 to 6 at 60^0 then it was neutralized by the addiction of alkali NaoH solution resulted in the formation of white precipetate with 78% of hield by recrystallization using ethanol.

The resultant product was analyzed in UV visible spectroscopy for its absorbance.

The maximum absorbance was studied at 254 nm using water ethanol and methanol (Fig:1).

The resultant product was also analyzed under NMR Spectroscopy. (Fig:2).

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