

# ALKALOIDS

M.Sc (SEM IV)  
Elective Course 1c  
Organic Chemistry Special

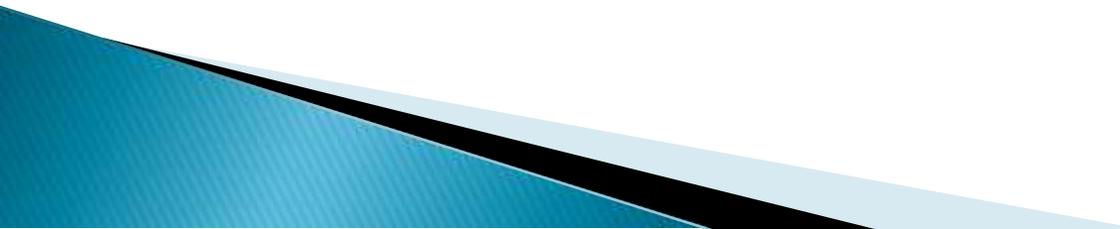
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# Introduction

- ▶ Term introduced by German chemist Carl F.W Meissnerin (1819). Alkaloids are “Alkali Like” (derived from the word Alkali).
- ▶ Definition:
- ▶ The name alkaloid was given to all organic bases isolated from plants.
- ▶ **Konigs(1880)** suggested that alkaloids should be defined as **naturally occurring organic bases which contain a pyridine ring**. This definition further modified by **Ladenburg**, who purposed to define alkaloids as **natural plants compound having a basic character and containing at least one nitrogen atom in a heterocyclic ring**.
- ▶ One must admit that even today it is still difficult to define an alkaloid. The term is generally limited to organic bases formed in plants. Those alkaloids obtained from plants are specified as **plant alkaloids (or vegetable alkaloids)**.

- ▶ Alkaloids are defined mainly as **“Group of naturally occurring organic compounds which are basic in nature, contain one or more nitrogen atoms normally of heterocyclic nature & posses specific physiological action on human or animal body”**.
  - ▶ On the whole, alkaloids are very poisonous but are used medicinally in very small quantities. Thus we find that the basic properties, (usually) complex structures, physiological action and plant origin are the main characters which define plant alkaloids.
  - ▶ Alkaloids are found abundantly in higher plants usually in seeds, roots, leaves or bark of the plants. Also occur as salts of various plant acids. Example- acetic acid, citric acid, etc.
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▶ **Properties:**

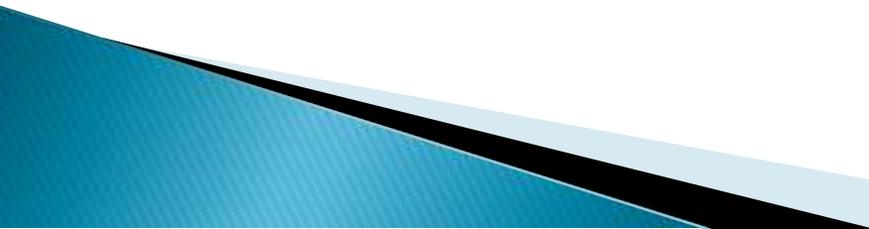
- ▶ Alkaloids are usually colorless, crystalline, non-volatile solids which are insoluble in water but soluble in ethanol, ether, etc.
- ▶ Some alkaloids are liquids, soluble in water.  
    Ex: Nicotine
- ▶ Most alkaloids have a bitter taste and are optically active (laevorotatory).

▶ **Clinical Use:**

- ▶ Analgesic – Morphine (in opium)
- ▶ Antimalarial - Quinine (in cinchona)

# Classification

Alkaloids are mainly categorized in 4 ways:-

1. **Biosynthetic classification** :- Based on types of precursor used for alkaloid biosynthesis in plants.
  2. **Pharmacological classification** :- Based on pharmacological response or use.
  3. **Taxonomical classification** :- Based on their distribution in various plant.
  4. **Chemical classification** :- It is probably most satisfactory way to classify the alkaloids.
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## ▶ Chemical Classification:

Here, the alkaloids are classified according to the nature of heterocyclic ring.

1. Heterocyclic Alkaloid (Typical alkaloid):- Containing N-atom in the heterocyclic ring.
  - a. Pyrrolidine – Ex: Hygrine
  - b. Piperidine – Ex: coniine
  - c. Pyridine-piperidine- Ex: Anabesine
  - d. Quinoline – Ex: quinine, quinoline
  - e. Isoquinoline – Ex: papavarine
  - f. Indole – Ex: Lysergic acid
  - g. Pyrrolidine - Pyridine – Ex: Nicotine
  - h. Phenanthrene – Ex: Morphine
  - i. Tropane – Ex: Atropine
  - j. Purine – Ex: Caffeine

2. Non-heterocyclic Alkaloid (Atypical alkaloid):-

- a. Phenylethyl amine (Amino alkaloid) – Ex: Ephedrine
- b. Tropolone – Ex: Colchicine

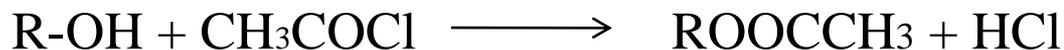
- ❑ It should be noted that in many cases different alkaloids obtained from the same plant often have similar chemical structures, and so sometimes the source of the alkaloids may indicate chemical similarity.

# General methods for determining structure of alkaloids

1. **Molecular Formula:** The first step in structure elucidation is the determination of molecular formula and optical rotatory power. Elemental composition and hence the empirical formula is found by combustion analysis.
2. **Determination of Unsaturation:** The unsaturation can be determined by adding bromine, halogen acids or by hydroxylation with  $\text{KMnO}_4$  or by reduction.
  - ▶ Number of double bond:- Number of rings present in an alkaloids can be determine by following formula:  $\text{C}_a\text{H}_b\text{N}_c\text{O}_d$
  - ▶ Number of double bond present =  $a - b/2 + c/2 + 1$

**3. Functional group determination:** When an alkaloid contains oxygen, the functional nature of the element is determined.

**a. Hydroxyl group** – The presence of this group may be ascertained by the action of acetic anhydride, acetyl chloride or benzoyl chloride on the alkaloid leads to formation of acetate.



The number of hydroxyl group is further estimated by acetylation.

The next problem is to decide whether the hydroxyl group is alcoholic or phenolic. It is phenolic if the alkaloid is soluble in sodium hydroxide and reprecipitated by carbon dioxide, also a coloration with ferric chloride will indicate the presence of phenolic group.

**b. Carboxyl group** – The solubility of alkaloid in aqueous sodium carbonate or ammonia, also treatment with alcohol form ester.

**c. Oxo group** – The presence of an oxo group is readily ascertained by the formation of an oxime, semicarbazone and phenylhydrazone.

**d. Methoxyl group** – Zeisel Method is used for determination of methoxyl group. In this method, the alkaloid is heated with concentrated hydriodic acid at 126 degree C ; the methoxyl groups are thereby converted into methyl iodide, which is then absorbed by ethanolic silver nitrate and silver iodide is weighed.

**e. Methylene dioxyl group (-OCH<sub>2</sub>O-)** – Formaldehyde is formed when alkaloid is heated with hydrochloric acid or sulphuric acid.

## ▶ The functional nature of the nitrogen:

- ▶ General reactions of alkaloids with acetic acid, methyl iodide and nitrous acid indicates the nature of nitrogen. If all reactions are negative - nitrogen probably tertiary.
- ▶ Nature and Number of alkyl group attached to nitrogen – Distillation with aqueous KOH formation of methylamine, dimethylamine and trimethylamine (volatile products).
- ▶ Aliphatic amino acid group react with nitrous acid to give a primary alcohol with the evolution of nitrogen gas.
- ▶ If it is aromatic it form diazonic salt by diazocoupling reaction.
- ▶ If secondary, amino group react with nitrous acid to form nitrosamine.
- ▶ If it is tertiary then it react with methyl iodide to form quaternary salt.
- ▶ Herzig - Mayer method :-Presence and number of N-methyl group.  
$$(\text{C}_8\text{H}_{16}\text{O}_4)\text{NCH}_3 + \text{HI} \longrightarrow (\text{C}_8\text{H}_{16}\text{O}_4)\text{NH} + \text{CH}_3\text{I}$$

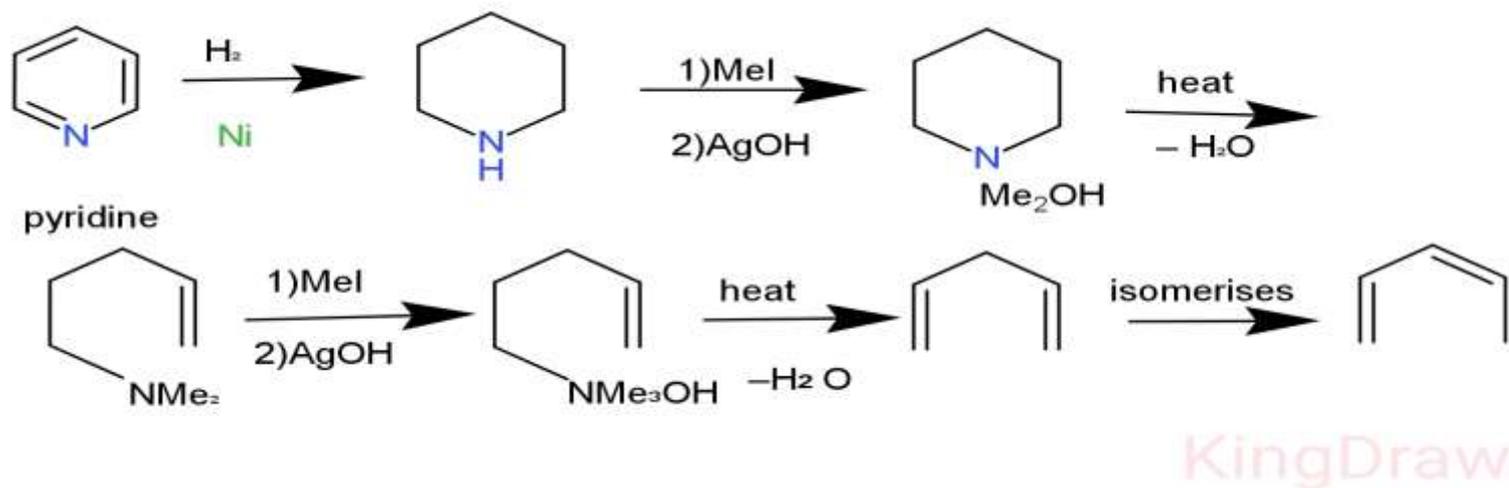
## 4. Degradation of alkaloids:-

Study of degradation of alkaloids gives rise to some identifiable products of known structure.

a. **Hoffman Exhaustive Methylation method (HEM):-** The method was applied by Willstater in 1870 and was further developed by Hoffmann.

Heterocyclic rings are opened with elimination of nitrogen and the nature of the carbon skeleton can be obtained.

- Hydrogenation of heterocyclic ring (if it is unsaturated)
- Convert the saturated compound to the quaternary methylammonium hydroxide which is then heated.
- In this stage, a molecule of water is eliminated, a hydrogen atom in the beta position with respect the N-atom combining with –OH group.
- The ring is opened at the N atom on the same side as the beta hydrogen atom eliminated.
- This process is repeated on the same product. This resulted in the complete removal of N atom from the molecule, leaving an unsaturated hydrocarbon, which is isomerises to a conjugated diene

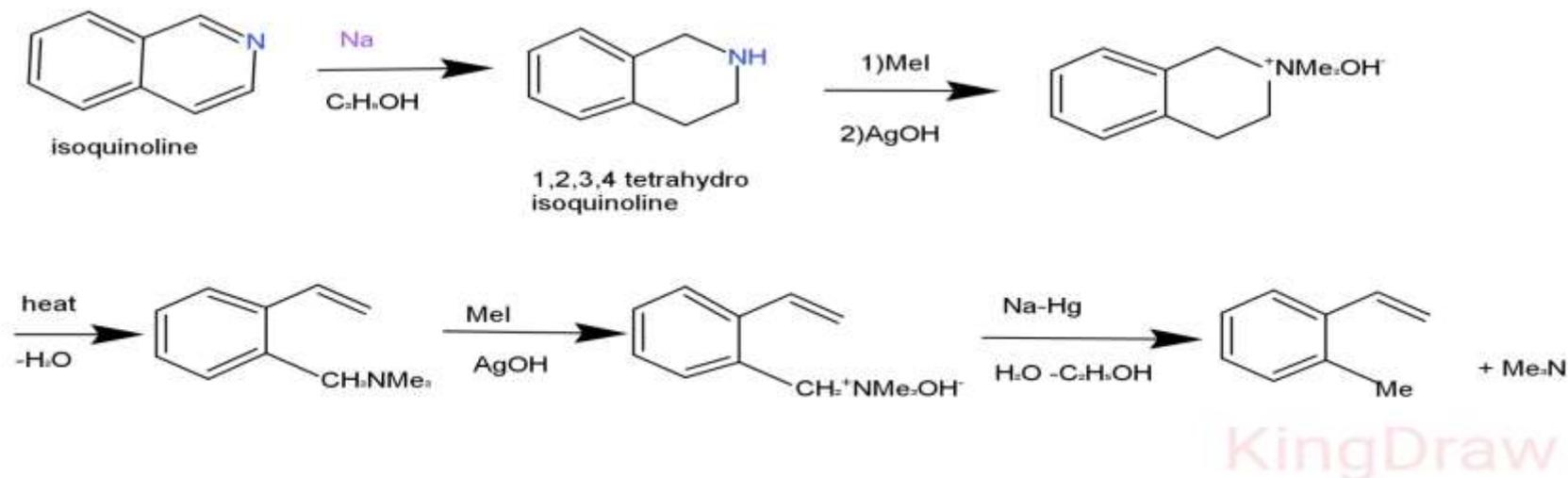


- ▶ HEM fails if there is no beta hydrogen available for elimination as water. In such case the Emde modification may be used. Ex- Isoquinoline
- ▶ Even though the compound contains a beta hydrogen atom, the exhaustive methylation method may fail. Ex- Tetrahydroquinoline.

**b. Emde's method:** Emde's modification may be used in the above two cases, where HEM failed.

In this method, quaternary ammonium halide is reduced with sodium amalgam in aqueous ethanol or catalytically hydrogenated.

Ex- Isoquinoline



- **Other methods for degradation of alkaloids are also known**

- Von Braun's method

- Oxidation

- Zinc distillation

- Alkali fusion

5. **Physical Methods:** The important physical methods used in the structure elucidation of alkaloids are as follows;

- ▶ IR Spectroscopy – Identify functional groups
- ▶ UV spectroscopy – Characteristic of chromophoric system
- ▶ NMR Spectroscopy – Detects the type of protons
- ▶ Mass Spectroscopy – Know molecular weight and fragments
- ▶ X -Analysis – Distinguish the various possible structures
- ▶ Optical rotatory dispersion (ORD) and circular dichromism – Optically active stereoisomers
- ▶ Conformational Analysis – Stereochemistry

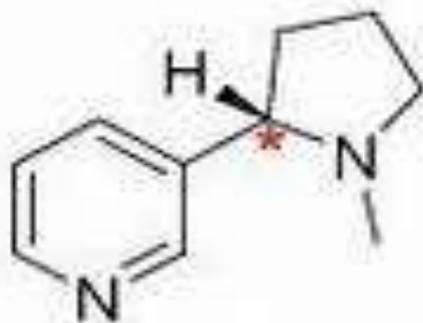
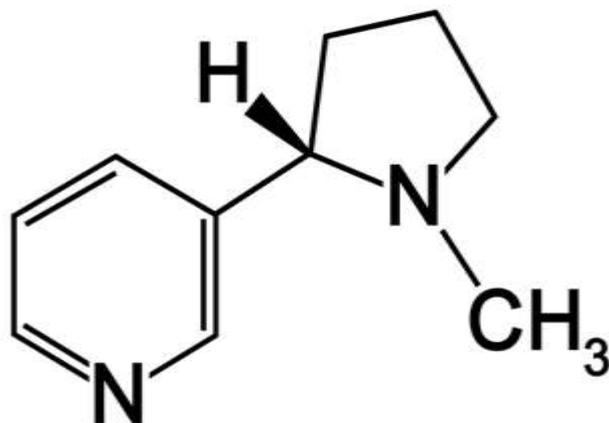
6. **Synthesis:**

- ▶ The above mentioned chemical and analytical work helps to propose a tentative structure of the alkaloid under investigation.
- ▶ Synthesis always gives additional evidence for the assigned structure even though the physical method provide final proof of the proposed structure.

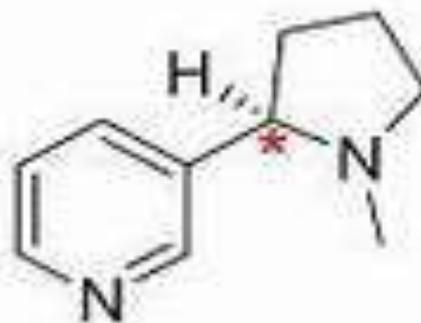
# NICOTINE

- Nicotine is the chief alkaloid of tobacco plant.
- IUPAC name 3-(1-methyl-2-pyrrolidinyl) pyridine.
- It is a bicyclic compound with a pyridine cycle and a pyrrolidine cycle. The molecule possess an asymmetric carbon and so exists in two enantiomeric compounds.
- It occurs in the plant leaves as salts of malic acid and citric acid to the extent of 4 to 5 percent. The alkaloid was named after the Frenchman NICOT who introduced tobacco in France in 1560.

# Structure of Nicotine



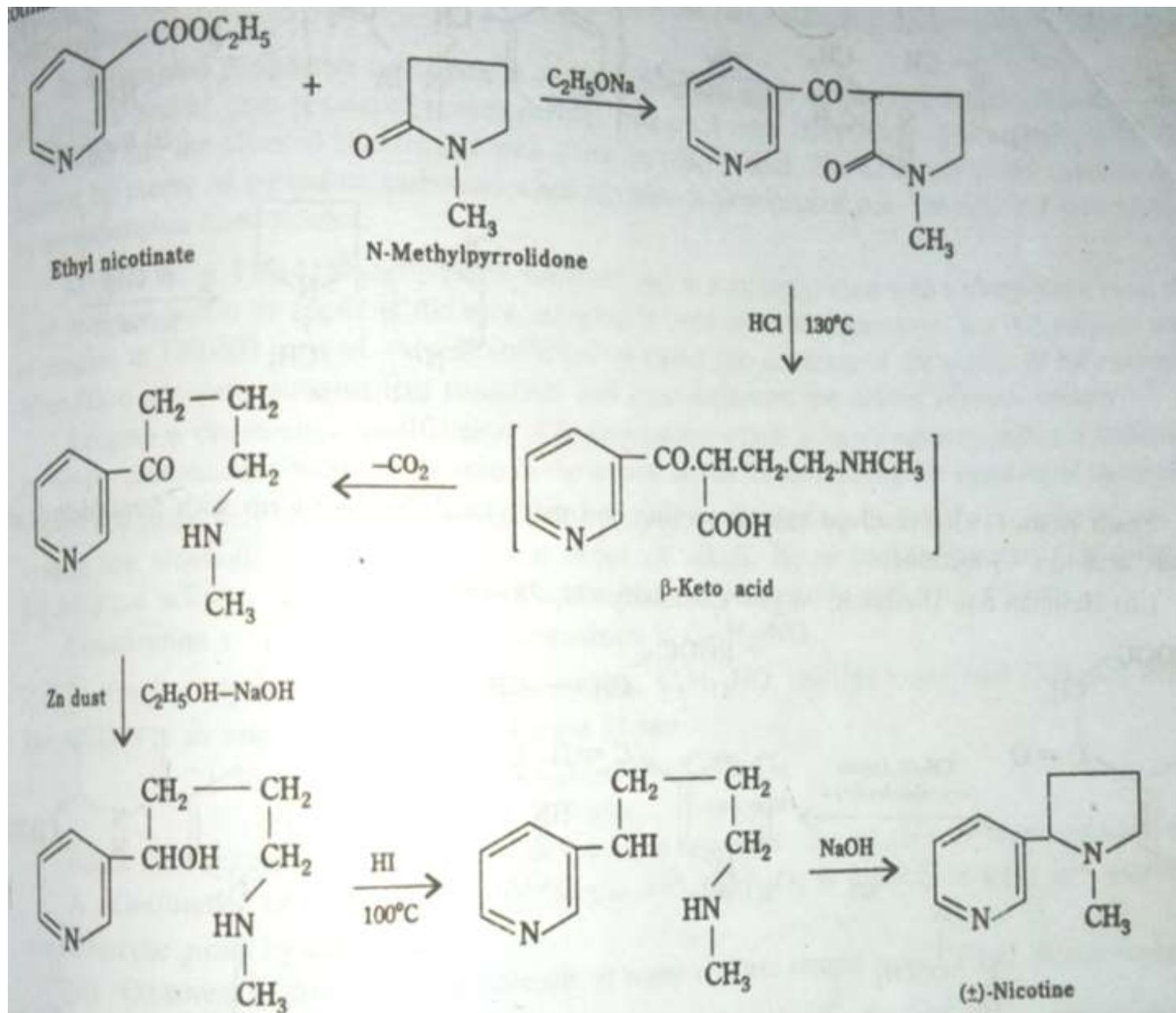
(S)-Nicotine



(R)-Nicotine

# SYNTHESIS

- The structure of nicotine was confirmed by the following synthesis accomplished by Spath(1928). This synthesis also confirms pinners formula for nicotine. (scheme given in the next slide)
- The racemic alkaloid obtained is resolved by means of (+)-tartaric acid to get (-)-nicotine which is found to be identical with the natural alkaloid.



# Synthesis of Nicotine

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### Books recommended

1. IL Finar; Organic Chemistry volume 2.
2. Bahl and Bahl; Advance organic Chemistry
3. OP Agarwal; organic chemistry, volume 1 natural products.

**THANK YOU**

