

## Synthesis of Bis Pyridyl -3-Methyl Amine (A Potential Anti- Hypertensive Agent)

\* Salau R.B. and Jacob J.O.

Department of Chemistry,  
Federal University of Technology, Minna, Nigeria

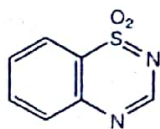
### Abstract

Bis Pyridyl - 3 - methyl amine was synthesized. It is an amino compound which could be screened for its bio-activity. This is against the backdrop that certain amines had positive actions as anti-hypertensive agents especially their roles as anti-depressant and inhibitors of monoamine oxidase (MAOI). The starting material was pyridine 3-carboxylic acid which was converted to pyridine - 3- carbonyl chloride, Bis pyridine -3- carbonyl amine and finally to the desired product. The reagent for the conversions were thionyl chloride, concentrated ammonia and clemmenson reduction reactions respectively.

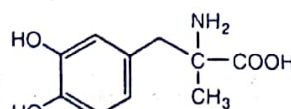
### Introduction

The modern era of organic synthesis has paved way for unlimited development of new drugs. Structure- Activity Relationship study of the new drugs started becoming a field of knowledge to be accorded paramount attentions. The newly synthesized derivatives of these compounds examined for their added advantages or disadvantages relative to the existing drugs. Exploration of homologous series<sup>1</sup> in particular, has been given more focus in the recent years by the development of a method called **Quantitative structure - Activity Relationship (QSAR)**. This method combines the study of biological activity with some physical properties, which are estimated by measurement or calculation.

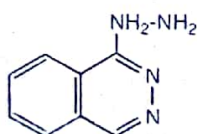
Hypertension is the clinical condition of elevated systolic or diastolic arterial blood pressure. Normotensive state of the blood pressure is given as 120-160/ 180-90 mmHg. Anti-hypertensive agents are the chemical substances of therapeutic potentiality employed in the management of hypertension. The origin of the application of nitrogenous anti-hypertensive agents can be traced to the work of Paton and Zamis<sup>2</sup> who described the pharmacological activities of the compound: Polymethylene bis trimethyl ammonium which competitively inhibited acetylcholine neurotransmitter. Variety of other nitrogenous compounds have been variously classified<sup>3,4,5</sup> depending on their mode of anti-hypertensive activities. They include **diuretic class** e.g hydrochlorthiazide (A), the **inhibitors/retardant** of noradrenaline transmitter e.g.  $\alpha$ -methyl dopa (B), the relaxant of arteriolar vesicular smooth muscle which are also referred to as **vasodilator** e.g. hydrallazine (C), the haemodynamic regulator or inhibitors of renin-angiotensin system e.g. claptopril (D).



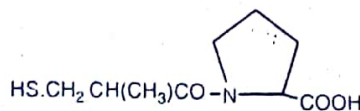
A



B



C



D

Mono Amine Oxidase Inhibitor (MAOI)<sup>6</sup> which has also been in use in the blood pressure regulation as anti-depressant. These compounds are also of amino nature. The Mono Amine Oxidase (MAO) enzymes are implicated for their activities of inactivating endogenous pressor amines (such as noradrenaline tyramine etc). Inhibition of the MAO enzyme by the MAOI has the effect of increasing the availability of the biogenic amines.

The aim of the study is to synthesis amino compound analogous to the existing anti-hypertensive agents, which are also nitrogenous in nature. The synthesized product is hence, expected to be subjected to screening for its bioactivity and physico-chemical properties based on structure- activity relationship for the prospect of a new drug.

### Material and Method

Pyridine - 3 - carbonyl chloride (II) was synthesized from pyridine - 3 - carboxylic acid (I). [20g, 0.163 mole] of finely powdered pyridine - 3- carboxylic acid was distilled with 50cm<sup>3</sup> of redistilled thionyl chloride. This was refluxed for sixty minutes to distill excess thionyl chloride at 78°C. Cotton wool was corked to the drying tube containing calcium chloride to exclude moisture. *The yellow, crystalline residue of pyridine - 3 - carbonyl chloride was obtained. (20.5g, 89.1% yield), melting point (160 - 162°C).*

In conversion to bis pyridine - 3- carbonyl amine (III), (10g, 0.07 mole) pyridine - 3 - carbonyl chloride (II) was dissolved in 50ml chloroform for refluxing to be carried out for ten minutes. (0.6cm<sup>3</sup>, 0.035 mole) concentrated ammonia solution was then added and refluxed for thirty minutes. The chloroform solvent was evaporated. *A vague fragrant smelling, pale yellow crystalline solid (12g, 64.5% yield) with melting point (249° - 251°C) was obtained.*

The final product bis pyridine - 3 - methyl amine (IV) was obtained via the reaction with the prepared zinc-mercury amalgam. 32g of zinc metal was added to 2.4g of mercury chloride, followed by 1.6 cm<sup>3</sup> of concentrated hydrochloric acid and 40cm<sup>3</sup> of water. The shiny zinc-mercury amalgam obtained was covered with 25cm<sup>3</sup> of concentrated hydrochloric acid. To this was added to (4.15g, 0.183mole) Bis pyridine - 3 - carbonyl amine and boiled under reflex for eight hours. On further addition of 18.3cm<sup>3</sup> of concentrated Hydrochloric acid, another eight hours of reflux was carried out. The content was cooled over night. A floating solid product on the liquid layer in the flask together with undissolved amalgamated zinc was obtained. The undissolved amalgamated zinc was extracted with two 30cm<sup>3</sup> portions of hot benzene. The benzene layer was removed into the beaker and evaporated. *A colourless gelatinous solid (1.1g, 30.2% yield, melting point 40-42°C) solid with a characteristic odour was obtained.*

### Result and discussion

#### Spectroscopic data for bis pyridine 3 - carbonyl amine compound (III).

NMR (D<sub>2</sub>O): singlet 5.0 ppm (CO-NH), triplet 8.22 ppm (Ar - H)

quintet 9.2ppm (CO-N-H-CO)

IR  $\nu$  (cm<sup>-1</sup>) Nujol mull: 3400 (N - H), 3100 (C-H) aromatic, 1710 (C - O)

1630 (C-C) aromatic, 1290 (C - N) aromatic, 1160 (C - N) aliphatic

#### Spectroscopic data for bis pyridyl -3- methyl amine compound (IV)

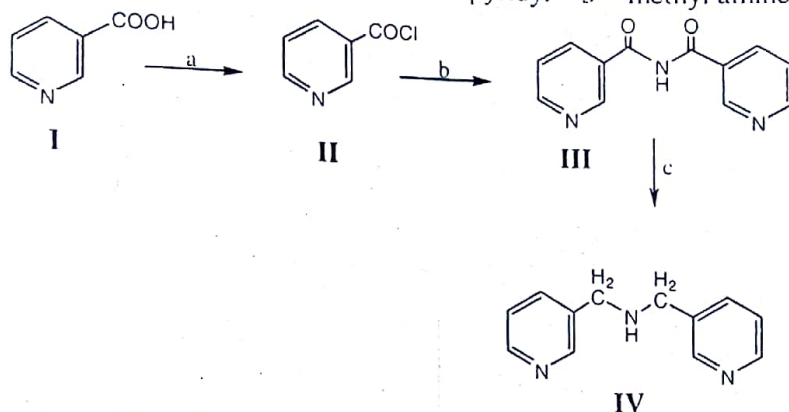
IR  $\nu$  (cm<sup>-1</sup>) Neat: 3500 (N - H), 2910 (C - H) aliphatic, 1625 (C - C) aromatic,

1380 (C - N) aromatic, 1150 (C - N) aliphatic

IR  $\nu$  (cm<sup>-1</sup>) Nujol mull: 3450 (N - H) 2900 (C - H) aliphatic, 1625 (C - C) aromatic,

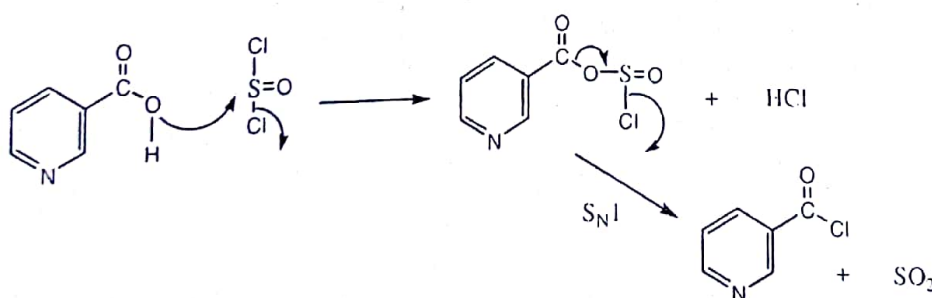
1380 (C - N) aromatic, 1155 (C - N) aliphatic.

The reaction scheme for the synthesis of Bis pyridyl - 3 - methyl amine is as follows:



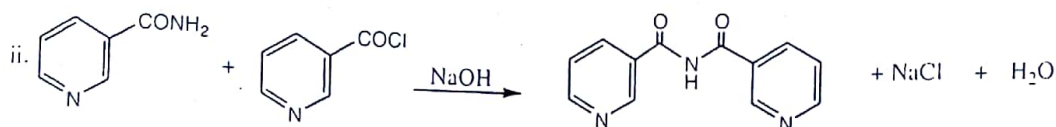
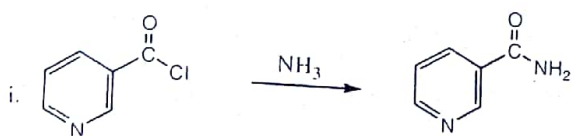
a = Thionyl chloride  $\text{SOCl}_2$     b = ammonia ( $\text{NH}_3$ ) in 1:2 to compound (II)  
 c = zinc/mercury amalgam in conc.  $\text{HCl}$ .

The first compound formed, pyridine - 3 - carbonyl chloride (II), was a highly fuming compound found to melt at  $160-162^\circ\text{C}$ . It was insoluble in water but soluble in tetra chloromethane. To achieve the product, a choice of thionyl chloride was made<sup>7</sup> because of its amenability to pyridine derivative<sup>7</sup> of organic acid as well as its convenience of separability. The other by gaseous products ( $\text{HCl}$  and  $\text{SO}_2$ ) formed were responsible for easy separation of the acyl chloride. Other possible reagents that can be used are  $\text{PCl}_3$ ,  $\text{PCl}_5$  ( $\text{COCl}_2$ ) and  $\text{Ph}_3\text{P}$  in  $\text{CCl}_4$ . These cannot be compared with the convenience in the use of thionyl chloride in terms of the isolation of the acyl chloride product. The boiling point of thionyl chloride was  $78^\circ\text{C}$  compared to phosphoryl chloride  $107^\circ\text{C}$ . It is thus easier to distill off excess thionyl chloride. This is because its temperature is far lower than that of the acyl chloride compound (II). The thionyl chloride was expected to yield higher than others<sup>8</sup>. However, the shortcoming of the thionyl chloride route lie in its choking odour as well as possible explosive reaction when in contact with water. The reaction mechanism<sup>9</sup> is proposed thus:

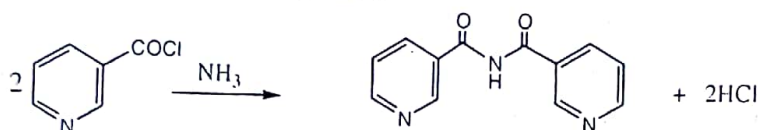


The first step is fast

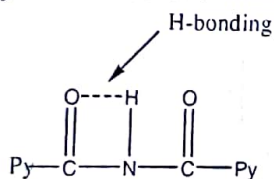
Bis pyridine - 3 - carbonyl amine compound (III) was obtained by the reaction of the Bis pyridine - 3 - carbonyl chloride compound (II) with concentrated ammonia solution. Two routes using concentrated ammonia were possible. There is possibility of 1:1 mole ratio in *Schotten Bauman* way<sup>9</sup>.



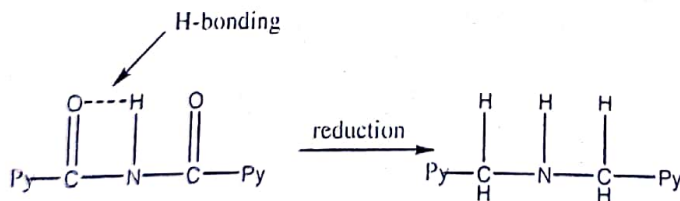
The reaction above was dropped for an alternative 2:1 route of acyl chloride: ammonia reaction due to the disadvantage of difficulty of separation of the compound (III) from product mixture. Both products are water soluble. The adopted method, on the other hand, has gaseous HCl by - product as shown below.



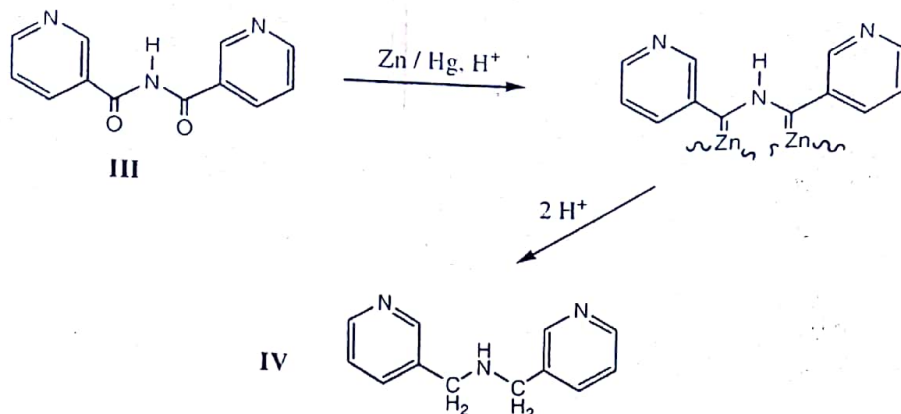
The bis pyridine - 3 - carbonyl amine compound (III) was soluble in water but insoluble in tetra chloromethane. The melting point was 249-251<sup>o</sup>C. This high melting point can be attributed to possibility of intra and intermolecular hydrogen bonding.



One outstanding spectral feature of the compound was the intense I.R absorption at 1710 cm<sup>-1</sup> which indicated the presence of two carbonyl functional groups. The other is the IR absorptions between 2850 cm<sup>-1</sup> and 2910 cm<sup>-1</sup> indicating the presence of intra and intermolecular hydrogen bonding.



The final compound, Bis pyridyl - 3 - methylamine (IV) was obtained by reduction of the carbonyl functional group. Clemmensen reduction route was chosen. The compound IV obtained was a colourless gelatinous solid which was insoluble in water, tri chloromethane and ethanol but soluble in benzene. The melting was 40-42<sup>o</sup>C. This was quite much lower than the preceding compound (III) practically due to loss of hydrogen bonding capability of compound (III) which was lost on its carbonyl reduction to compound (IV). The proposed mechanism<sup>10</sup> of the clemmensen was through zinc carbene intermediate.



One striking spectroscopic revelation of the compound (IV) formation was the disappearance of the I.R absorption at  $1710\text{cm}^{-1}$  for (C=O) which was a prominent feature of the preceding step for compound (III). This was an indication that (the carbonyl group) C = O actually converted to CH<sub>2</sub> (methylene group). Consequently, no further H-bonding trace in the IR absorption.

### Conclusion

The synthesized bis pyridyl – 3 – methylamine is essentially a nitrogenous compound. This forms a basis for relating it with other compound currently in use as anti-hypertensive agents. Further effort is to establish the potential of the compound towards the anticipated action.

### References

- A.S.V. Burgen and J. F. Mitchell 1985, *Gaaddum Pharmacology: Drug development and toxicology* 9<sup>th</sup> edition, London, Oxford University press pp223-226.
- Paiton and Zaimis 1949 *Britain Journal of pharmaceutical Chemotherapy* 4:381.
- Goodman, L.S., Gilman .A. and Gilman, L.S. (1980) (1975) *Pharmacological basis of herapeutics* 6<sup>th</sup> ed, London, Macmillan.
- O.O. Akinkugbe (Editor) ed. Bartrand 1975; *Hypertension in Africa*, Literamed Publication
- Budavari S. ed (1996). *The merck index: an encyclopaedia of chemicals, drugs and biological (Anti-hypertensives)* 12<sup>th</sup> ed, Rahway, New Jersey, Merck and Co Inc.
- Livingstone M. and Livingstone H. (1996); *Monoamine oxidase Inhibitor-An update of drug interactions. Drug safety Journal.* 14, 4: 219 – 227
- Chemical compounds retrieved Aug. 2006 *Encyclopaedia Britennica premium service:* <http://www.britanica.com/ed/ article 79728>
- I.L. Finar (1975) *organic chemistry* 6<sup>th</sup> ed. Vol. 1, English Language Book Society (ELBS), London, Longman pp158
- I.L. Finar (1975) *organic chemistry* 6<sup>th</sup> ed. Vol. 1, English Language Book Society (ELBS), London, Longman pp 761
- James Burdon and Robin I. Price (1986); 'Zinc carbene intermediate' *Journal of Chemical Society, Chemical Communications* 12 893