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SYNTHESIS AND CHARACTERIZATIONS OF SOME SELECTED ALKYL-2,2'-BIIMDAZOLE *USED* AS AN AGENT OF ANTI-MALARIA

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ABSTRACT

Malaria is one of the most important life-threatening infectious diseases in the tropics. In spite of the effectiveness of existing drugs, reports on reduced sensitivity of the parasite to these drugs warrants synthesizing an improved anti-malarial drugs. Imidazole and its derivatives are of great significance due to their importance roles in biological systems particularly in enzymes as proton acceptors or proton donors. In this study, the literature of the derivatives of imidazole such as 2.2,-biimidazole together with its alkyl substituted and application as an anti-malarial drug was discussed. The experimental which involves the synthesis and properties of alkyl substituted-2,2-biimidazole based were investigated and discussed, their applications in various aspects of life such as medicine, were also considered. The synthesized alkylated 2,2'-biimidazole compounds were confirmed using various analytical techniques such as melting point, Fourier transform infrared, X-Ray structures etc. The anti-bacterial activity of the complexes of the imidazole in general and the ant-malarial activity of the 2,2-biimidazole in particular were also compared in this paper.

Keywords: ***2,2-Biimidazole, Alkyl-2,2-Biimidazole, Bacteria, Malaria***

INTRODUCTION

African countries carry a disproportionately high percentage of cases and death causes by malarial. About 95% malaria cases, 96% death 80% and children under 5years account for about 80%. The highest percentage were accounted by four countries Nigeria (31.3%) Congo (12.6%), Tanzania (4.1%) and Niger (3.9%) (WHO, 2023).

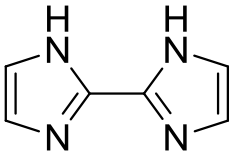
Reactions of carbonyl containing compounds like glyoxal with ammonia, amines and their derivatives are important for gaining nitrogen-containing heterocyclic substances such as azoles, pyridines etc. These products were for instance used in drugs, insecticides, various dyes and polymers. (Josef, 2020). Imidazole derivatives possess different kinds of bioactivity: anti-inflammatory, enzyme inhibition, analgesic, anti-neoplastic, anti-anthelmintic, anti-viral, anti-ulcer, anti-fungal, anti-filarial, anti-cancer, cardiovascular activity, anti-malaria, and many others. Compounds and the possibility of new discoveries attract the minds of researchers in this field.

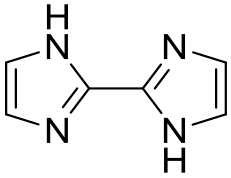
Since the first synthesis of 2,2'-bisimidazole in 1927, this molecule was researched in many different areas of chemistry **(**Lehmstedt, 1927) and (Dervisi, 2012). Most of the applications of 2,2'-bisimidazole are associated with its metal complexes. For example, several applications within biochemistry, catalysis (water splitting), and magnetic materials exist where 2,2'-bisimidazole itself is used as the sole ligand in homoleptic complexes, or as a co-ligand in heteroleptic complexes.

2,2'-bisimidazole is typically synthesized from an ammonium acetate and glyoxal (oxaldehyde) aqueous solution. (Steffens, 1986). Alternatively, as described in the original syntheses, ammonium acetate is produced in-situ by bubbling ammonia gas through the reaction mixture containing acetic acid. The synthesis of 2,2'-bisimidazole is very cheap and could easily be scaled up if necessary. However, the yields according to Decurtins, *et al* (1985), are notoriously poor, hovering around 35% with even the most optimized conditions. Strides towards optimizing the synthesis of 2,2' biimidazole from commercial reagents has been carried out among several research groups a hundred years ago with some more recent success using unconventional starting materials. Lewczuk *et al*, (2017) and Zhou, (2002).

2,2'-Biimidazole

2,2-biimidazole with molecular formula ($C_6H_8N_4$) is one of the derivatives of imidazole, it is obtained by coupling two imidazole rings (Favre, 2013), therefore it is expected to have similarities in both their physical and chemical properties. *Cui, et al (2007).* The two possible structural isomers of 2,2-biimidazole are:





cis- *trans-*

2,2-biimidazole

MATERIALS AND METHODS

Reagents and Materials: The reagents and materials used in this research such as ammonium chloride, glyoxal, sodium hydroxide, magnesium sulphate, diethyl ether bromomethane, bromobutane, bromohexane SiO_2, petroleum ether, THF etc., were obtained from various chemical shops in and outside the country which are all of analytical grade and most of which were used without further treatment.

Preparation of Some Standard Solutions: Standard solutions of many reagents used in the research such as slurry of ammonium chloride, 20% glyoxal and 35% sodium hydroxide etc and the ligands were prepared and synthesized.

Preparation of 20wt% Glyoxal solution

20wt% of glyoxal was prepared by adding 10g of glyoxal to 50cm^3 of distilled water.

Synthesis of 2,2'-biimidazole

50g of 20wt% aqueous glyoxal (3.45mol) was then slowly added drop wise to the resulting slurry of ammonium chloride for three hours with vigorously stirring. The resulting reaction mixture was additionally stirred for five hours at room temperature and then neutralized with distilled water to adjust the pH of the solution to 5-7. The produced brown coloured crystals was filtered and washed with distilled water several times. The product was dried over magnesium sulphate $MgSO_4$. According to Lin, (1997), the N-alkylation of 2,2'-biimidazole is usually convenient. However competing reactions such as elimination of halides, reactions of multi-position selectivity, steric hindrance to multisubstitution, quaternisation and product decomposition by moisture may lead to poor yields. The reaction conditions have a significant influence on the selectivity. The reaction of 2,2'-biimidazole with dihaloalkanes usually leads to N,N'-bridged derivatives, Thummel, (1989) The yields of compounds the low isolated yield of 2,2'-biimidazole can be attributed to decomposition by moisture and steric hindrance to substitution.

Synthesis of 1,1´-dimethyl-2,2´-biimidazole:

A mixture of (0.26g, 1.9mmol) 2,2´-biimidazole, 8cm^3 diethyl ether and 35% aqueous solution of sodium hydroxide were stirred under nitrogen for one hour. (0.65 g, 4.0mmol) bromomethane and 1cm^3 diethyl ether were mixed together and added drop-wise over 20 min and refluxed for 1h. Two phases were formed distilled water were added to the diethyl ether phase. Then the other phase was washed with distilled water, filtered (evaporated) and dried over $MgSO_4$. It was then subjected to column chromatography (SiO_2, petroleum ether/THF=3/1) which gave a pale yellow crystalline solid, yield 70.2%. m.p. 143-145°C (Cho, 2004).

Synthesis of 1,1´-dibutyl-2,2´-biimidazole: A mixture of (0.26g, 1.9 mmol) 2,2´-biimidazole, 8cm^3 diethyl ether and 35% aqueous solution of sodium hydroxide were stirred under nitrogen for one hour. (0.97g, 4.0mmol) 1-bromobutane and 1cm3 diethyl ether were mixed together and added drop-wise over 20 min and refluxed for 6 h. Two phases were formed distilled water were added to the diethyl ether phase. Then the other phase was washed with distilled water, filtered (evaporated) and dried over MgSO4. The product was then subjected to column chromatography (SiO_2, petroleum ether/THF=3/1) which gave a light green crystalline solid, yield 68% (Cho, 2004).

Synthesis of 1,1´-dihexyl-2,2´-biimidazole:

A mixture of (0.26g, 1.9 mmol) 2,2´-biimidazole, 8cm^3diethyl ether and 35 % aqueous solution of sodium hydroxide were stirred under nitrogen for one hour. (1.21g, 4.0 mmol) 1-bromohexane and 1cm3 diethyl ether were mixed together and added drop-wise over 20 min and refluxed for 6 h. Two phases were formed distilled water were added to the diethyl ether phase. Then the other phase was washed with distilled water, filtered (evaporated) and dried over MgSO4, then subjected to column chromatography (SiO_2, petroleum ether/THF=3/1) which gave a brown crystalline solid, yield 68% (Cho, 2004).

Chemical Analysis

Thermogravimetric analysis (TGA)

The TGA results were obtained by using Mettler Toledo simultaneous thermogravimetric analyzer at a heating rate of 5°C/min from room temperature to 400°C under air atmosphere (sample mass 5-10 mg on aluminium pan) (Trivedi, et al, 2018).

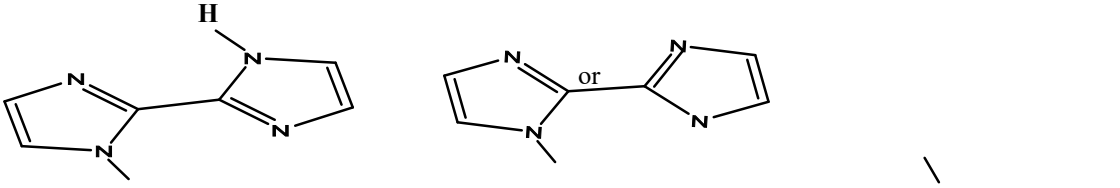
The infrared spectra*:*
The FTIR were analyzed using KBr pellets and an Agilent spectrometer, with a measurement range of 4000-500 cm^{-1}.
UV-Vis spectroscopy

These compounds absorb UV light due to the presence of conjugated pi (π) bonding systems (π - π^* transition) and nonbonding electron system (n - π^* transition). There are certain energy gaps between π - π^* and n - π^* orbitals. It was observed that negligible structural changes occurred 2.2,-biimidazole as compared to the alkylated 2.2,-biimidazole, which was not sufficiently large to alter UV-Visible spectral properties in solution state. They all exhibited hypsochromic effect (1 nm change) in absorbance maxima (λ_{max}) at 207 nm compared. Whereas, the alkylated2.2,-biimidazole exhibited bathochromic shift at the absorbance maxima (λ_{max}) 206 nm (Trivedi, et al, 2018).

RESULTS AND DISCUSSION

Some physical properties of 2,2′-biimidazole and alky-2,2′-biimidazole

The 2,2′-biimidazole been prepared, the colour is brownish crystals, the decomposition temperature: was 348-351^{0}C and the molecular weight is 134g/mol. The expected structure may be of two isomers. Lastly the percentage yield of the synthesized compounds were also calculated:



Trans structure **Cis structure**

Some physical properties of the product:

Molecular weight is 162g/mol, the colour is pale yellow crystals, decomposition temperature: 240^{0}C to 241^{0}C. Reaction for the preparation of 1,1'- dimethyl-2,2′-biimidazole:

Some physical properties of 1,1′-dibutyl-2,2′-biimidazole:

The molecular weight is 246g/mol, the is colour is light green crystals, decomposition temperature: 274^{0}C.

Some physical properties of 1,1′-dihexyl-2,2′-biimidazole:

Molecular weight is 302g/mol, colour is brown crystals, the melting Point: 241^{0}C. Some of the physical properties of the synthesized compounds were listed in Table 2 below:

Table 1: Physical Properties of the synthesized compounds

COMPOUND	COLOUR	APPEARANCE	% YIELD	TGA
2.2,-biimidazole	Brownish	Crystals	33%	349^{0}C
1,1'-dimethyl-2.2,-biimidazole	Pale Yellow	Crystals	70.2%	241^{0}C
1,1'-dibutyl-2.2,-biimidazole	Dark Yellow	Crystals	68%	274^{0}C
1,1'-dihexyl-2.2,-biimidazole	Brown	Crystals	74%	243^{0}C

As can be seen on Table 2 above which contain some physical properties of the synthesized compounds, all the four compounds being synthesized were found to be solid and crystalline substances of different colours as expected from the literature. The 2.2,-biimidazole was shinny and brownish crystalline solid with the percentage yield of 33% and melted at 349^{0}C. The 1,1'-dimethyl-2.2,-biimidazole was found to be Pale Yellow crystalline solid with percentage yield of 70.2% and melted at 241^{0}C. The 1,1'-dibutyl-2.2,-biimidazole was found to be light-green crystalline solid with percentage yield of 68% and boiled at 274^{0}C. The 1,1'-dihexyl-2.2,-biimidazole was found to be brown crystalline solid with percentage yield of 74% and boiled at 243^{0}C.

UV-Vis spectroscopy

It was observed that negligible structural changes occurred 2.2,-biimidazole as compared to the alkylated 2.2,-biimidazole, which was not sufficiently large to alter UV-Visible spectral properties in solution state. They all exhibited hypsochromic effect (1 nm change) in absorbance maxima (λ_{max}) at 207 nm compared. Whereas, the alkylated2.2,-biimidazole exhibited bathochromic shift at the absorbance maxima (λ_{max}) 206 nm.

The Fourier Transform Infrared

The Fourier Transform Infrared of the compounds were measured and the stretching vibration of the possible bonds were obtained and presented in table:

Table 2: Fourier Transform Infrared of the synthesized compounds

Compound	(Ar) N-H (cm^{-1})	(Al) C-H (cm^{-1})	(Ar) C=N (cm^{-1})	(Ar) C-C (cm^{-1})	(Ar) C-N (cm^{-1})	(Ar) C=C (cm^{-1})	(Ar) C-H (cm^{-1})
2.2,-biimidazole	3315.04	--	2769.07	1619.61	1228.72	1722.60	672.43
1,1'-dimethyl-2.2,-biimidazole	3312.34	2891.89	2762.41	1609.27	1226.16	1728.01	846.22
1,1'-dibutyl-2.2,-biimidazole	3315.29	2892.01	2766.42	1612.33	1221.02	1723.92	797.86
1,,1'-dihexyl-2.2,-biimidazole	3318.32	2892.55	2764.34	1609.11	1220.49	1726.17	812.52

The Fourier Transform Infrare* (*FTIR) analysis

Table 1 provides a complete account of the observed IR and the theoretical IR vibrations. The comparison. Theoretical and experimental wavenumbers exhibit a reasonable level of concurrence, and the allocation of wavenumbers to distinct functional groups is expounded upon in the subsequent discussion, Ramya, (2013).

C–N vibration

Identifying the C–N vibration poses a significant challenge due to the potential for the mixing of many vibrations within this Spectral area.

Generally, the C–N stretching vibration of **1335 to 1250** cm^{-1} is found aromatic rings. **2.2,-biimidazole** exhibits a C–N stretching vibration which is detected in the infrared (IR) spectrum at wavenumbers of 1228.72 cm^{-1} and the theoretical values observed in the region of **1335 to 1250** cm^{-1}. The C–C stretching vibrational range from 1600 to 1585 cm^{-1}. In this compound the observed C–C stretching vibration is detected at 1619.61cm^{-1}. The molecule under investigation exhibits a C–C stretching vibration (simulated) detected at **1600–1585** cm^{-1}. The N–H stretching vibration of **3400–3250** cm^{-1} is found aromatic rings. **2.2,-biimidazole** exhibits a N–H stretching vibration which is detected in the infrared (IR) spectrum at wavenumbers of 3315.04 cm^{-1} and the theoretical values observed in the region of **3400–3250** cm^{-1}. The C–H stretching vibrational range from **900–675** cm^{-1}. In this compound the observed C–H stretching vibration is detected at 672.43 cm^{-1}. The molecule under investigation exhibits a C–H stretching vibration (simulated) detected at **900–675** cm^{-1}. The C=N stretching vibration of **2830–2695** cm^{-1} is found aromatic rings. **2.2,-biimidazole** exhibits a C=N stretching vibration which is detected in the infrared (IR) spectrum at wavenumbers of 769.07 cm^{-1} and the theoretical values observed in the region of **2830–2695** cm^{-1}. The C=C stretching vibration of **1730–1720** cm^{-1} is found aromatic rings. **2.2,-biimidazole** exhibits a C=C stretching vibration which is detected in the infrared (IR) spectrum at wavenumbers of 1722.60 cm^{-1} and the theoretical values observed in the region of **1730–1720** cm^{-1}.

C–H vibration (Alkyl)

Alkyl groups on aromatic compounds display many different spectral bands within the range of 3000–2500 cm^{-1}(for 1,1'-dimethyl-2.2,-biimidazole, 1,1'-dibutyl-2.2,-biimidazole and 1,1'-dihexyl-2.2,-biimidazole), which can be attributed to the stretching vibrations of alkyl group attached to aromatic compound (C–H) bonds. The C-H stretching vibrations of the titled compound are experimentally observed at 3312.34, 3315.29, 3318.32cm^{-1}. The theoretically observed C–H stretching vibrations are 3000–2500 cm^{-1}.

C–H vibration (Aromatic)

Aromatic compounds display many different spectral bands within the range of **900–675** cm^{-1}, which can be attributed to the stretching vibrations of aromatic carbon-hydrogen Ar(C–H) bonds. The ArC-H stretching vibrations of the compounds (**2.2,-biimidazole,** 1,1'-dimethyl-2.2,-biimidazole, 1,1'-dibutyl-2.2,-biimidazole and 1,1'-dihexyl-2.2,-biimidazole) are experimentally observed at 846.22, 797.80 and 812.52 cm^{-1} respectively. The theoretically observed ArC–H stretching vibrations are 900 to 675 cm^{-1}.

C–N vibration (Aromatic)

Aromatic compounds display many different spectral bands within the range of **1335–1250** cm^{-1}, which can be attributed to the stretching vibrations of aromatic carbon-hydrogen Ar(C–N) bonds. The ArC-N stretching vibrations of the compounds (**2.2,-biimidazole,** 1,1'-dimethyl-2.2,-sbiimidazole, 1,1'-dibutyl-2.2,-biimidazole and 1,1'-dihexyl-2.2,-biimidazole) are experimentally observed at 1226.16, 1221.02 and 1220.49 cm^{-1} respectively. The theoretically observed ArC–N stretching vibrations are **1335–1250** cm^{-1}.

C–C vibration (Aromatic)

Aromatic compounds display many different spectral bands within the range of **1600–1585** cm^{-1}, which can be attributed to the stretching vibrations of aromatic carbon-hydrogen Ar(C–C) bonds. The Ar(C-C) stretching vibrations of the compounds (**2.2,-biimidazole,** 1,1'-dimethyl-2.2,-biimidazole, 1,1'-dibutyl-2.2,-biimidazole and 1,1'-dihexyl-2.2,-biimidazole) are experimentally observed at 1609.27, 1612.33 and 1609.11 cm^{-1} respectively. The theoretically observed Ar(C–C) stretching vibrations are **1600–1585** cm^{-1}.

C=C vibration (Aromatic)

Aromatic compounds display many different spectral bands within the range of **1730–1720** cm^{-1}, which can be attributed to the stretching vibrations of aromatic carbon-hydrogen Ar(*C=C*) bonds. The Ar(*C=C)* stretching vibrations of the compounds (**2.2,-biimidazole,** 1,1'-dimethyl-2.2,-biimidazole, 1,1'-dibutyl-2.2,-biimidazole and 1,1'-dihexyl-2.2,-biimidazole) are experimentally observed at 1728.01, 1723.92 and 1726.17 cm^{-1} respectively. The theoretically observed Ar(*C=C)* stretching vibrations are **1730–1720** cm^{-1}.

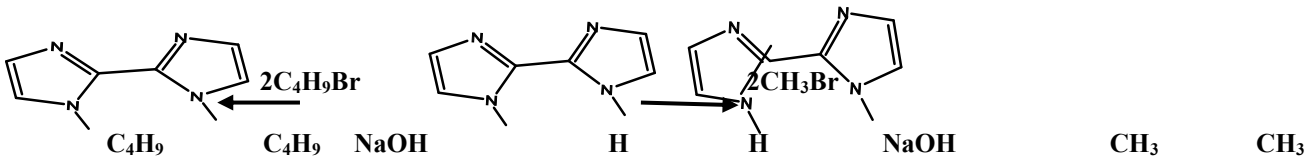
C=N vibration (Aromatic)

Aromatic compounds display many different spectral bands within the range of **2830–2695** cm^{-1}, which can be attributed to the stretching vibrations of aromatic carbon-hydrogen Ar(*C=C*) bonds. The Ar(*C=C)* stretching vibrations of the compounds (**2.2,-biimidazole,** 1,1'-dimethyl-2.2,-biimidazole, 1,1'-dibutyl-2.2,-biimidazole and 1,1'-dihexyl-2.2,-biimidazole) are experimentally observed at 2762.41, 2766.42, 2764.34 cm^{-1} respectively. The theoretically observed Ar(*C=C)* stretching vibrations are **2830–2695** cm^{-1}.

N–H vibration (Aromatic)

Aromatic compounds display many different spectral bands within the range of **3400–3250** cm^{-1}, which can be attributed to the stretching vibrations of aromatic carbon-hydrogen Ar(*N–H*) bonds. The Ar(*N–H*) stretching vibrations of the compounds (**2.2,-biimidazole,** 1,1'-dimethyl-2.2,-biimidazole, 1,1'-dibutyl-2.2,-biimidazole and 1,1'-dihexyl-2.2,-biimidazole) are experimentally observed at 3312.34, 3315.29, 3318.32 cm^{-1} respectively. The theoretically observed Ar(*N–H*) stretching vibrations are **3400–3250** cm^{-1}.

Alkylation of 2.2,-Biimidazole



1,1´-dibutyl-2,2´-biimidazole ***2,2´-biimidazole*** ***1,1´-dimethyl-2,2´-biimidazole***

1,1´-dihexyl-2,2´-biimidazole

CONCLUSIONS

In conclusion imidazole ring is a dynamic compound which can be used to synthesize many different compounds. The derivatives of imidazole are very important, it is used in many areas of chemistry and life in general especially in medicine. As reported in the literature, imidazole is used as an antibacterial and its antibacterial activity was reported to be altered by alkylating the imidazole ring, it was observed that, the antibacterial activity is increased with the increase in number of carbon atoms in the alkyl group. It was also reported that 2,2'-biimidazole is used as an antimalarial and it is a derivative of imidazole. As expected a derivative of a compound has similar chemical properties with the parent. Therefore the antimalarial activity of 2,2'-biimidazole is also improve by alkylating the imidazole. That means that, the antimalarial activity of 2,2'-biimidazole is less than that of1,1'-dimethyl-2.2,-biimidazole which is also less than that of1,1'-diethyl-2.2,-biimidazole. And the higher the number of carbon atoms in the alkyl group attached the greater the activity of the antimalarial of the 2.2,-biimidazole and the alkylated one.

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