Synthesis, Characterization and Structural elucidation of some di-substituted 2-(α-hydroxy benzyl) Bezimidazole derivatives.

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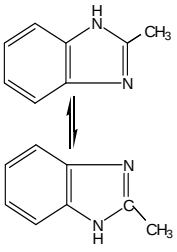
Abstract:

Benzimidazoles are known to possess wide variety of chromatographic agents and it is a class of medicinal chemistry. Among these benzimidazoles HBB is found to be a very useful molecules in terms of various biological activities. In the present work, two series of HBB analogs were synthesized; characterized and structural elucidation has done by analytical methods like IR, NMR and MASS spectroscopy.

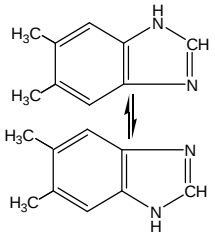
Key word: Synthesis, Characterization, Structural Elucidation, Benzimidazole Derivatives.

Introduction:

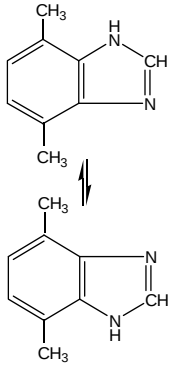
Literatures survey that benzimidazole derivatives can be synthesized by various routes. Synthesis of new benzimidazoles of new compounds that can be used as medicines for prophylamine and curing diseases.
Benzimidazole nucleus has been reported to posses antimicrobial and antifungal activities. This benzimidazole possessing free imino hydrogen are tautomeric systems. The two possible tautometic forms of benzimidazoles(and of those of its derivatives possessing a plane of symmetry) are identical and a definite assignment of structure is possible.
Examples are 2-methyl, 5,6-dimethyl and 4,7-dimethyl benzimidazoles



2, Methyl Benzimidazole



5,6 dimethyl Benzimidazole



4,7 dimethyl Benzimidazole

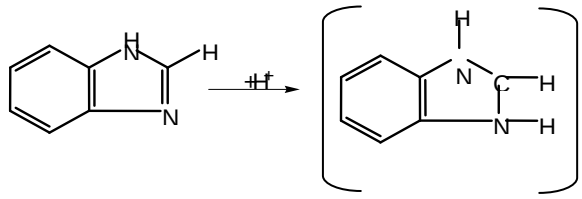
The benzimidazoles are high melting and high boiling solids. The parent compound melts at 170°C. They are soluble in polar solvents and sparingly soluble in non polar solvents.

The pseudo acidic character of benzimidazole and many of its derivatives is reflected in the ability to form salts with metals.The ability to react with Grignard reagents to give the acidic nature of the benzimidazole and 2-substitution of the imino hydrogen eliminates the pseudoacidic character. A number of crystalline salts (such as lithium, sodium, potassium and barium salts have been prepared by the addition of the appropriate metal amide to a solution of benzimidazole in liquid ammonia. These salts hydrolyze upon exposure to water with the regeneration of benzimidazole.

Electronegative groups increase the acidic nature of the benzimidazoles. The nitrobenzimidazoles are strong enough acids to dissolve in sodium carbonate of ammonia. 2-methyl-4,6 (or) 5,7-dinitro benzimidazole forms a stable ammonia salt.

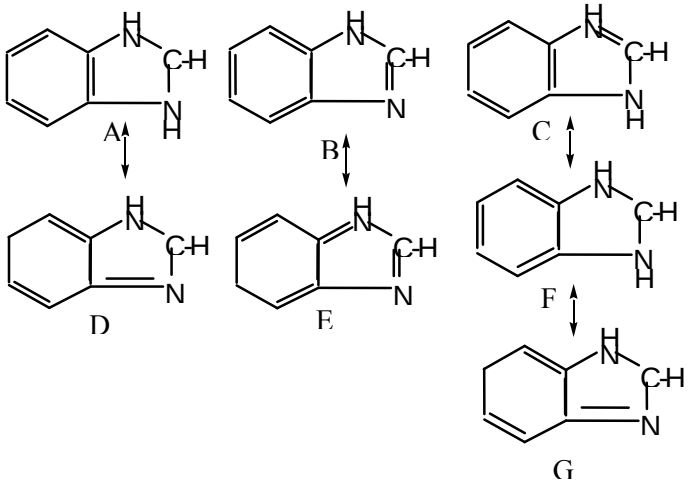
Basic Strength and Electronic Structure:

The benzimidazoles are predominantly basic compounds having the ability to form salts with acids.



Benzimidazole (pK α 5.5) is a basic considerably weaker than the imidazole (pK α 7.0**).** This difference in the basic strength is a reflection of the conjugation between the imidazole and benzene rings.

Conjugation increases the number of contributing states in the resonance sense, thus enhancing the chemical stability of the molecule.Thus decreasing its proton structures. A to G represent the major contributions to the state of benzimidazole system.



Structure D, E and G depicts the conjugation between the imidazole and benzene portions which may be responsible for the difference in basic strength between imidazole and benzimidazole.

Symmetry consideration may offer a plausible explanation for the observation that a methyl group in the 1 position fails to increase the basic strength of benzimidazole.

METERIALS AND METHODS

Step-1: Synthesis of 2-(α-hydroxy benzyl) benzimidazole[1,2]

Method 1:

In a 500ml of round bottom flask, equimolar amount of o-phenylene diamine (0.01 mol) and Mandelic acid (0.01 mol) were placed. 18 ml of 4n HCL was than added followed by a few porcelain chips and the mixture was refluxed gently on an oil-bath at 135-140°C for 2 hours. The reaction mixture was then allowed to cool to room temperature, which was further neutralized with 20% Na_2CO_3 solution and was kept overnight. The crude product filtered at the vacuum pump, was recrystallized from ice-cold water or acetone. The formation of 2-(α-hydroxy benzyl) benzimidazole was confirmed by comparing its melting point with that reported in the literature, by thin layer chromatography and spectral analysis.

Method 2:

2-(α-hydroxy benzyl) benzimidazole was synthesized in the following manner,

o-phenylene diamine(15 mmol) and Mandlic acid(30 mmol) were stirred in 4N HCL(40ml) under reflux for 3 hours. After cooling at room temperature, the pH was adjusted to 7.0 with NaOH(Solid). The resulting brown solid was filtered, washed with cold water, dried in vacuum pump and recrystallized from acetone.

Both the methods for the synthesis of 2-(α-hydroxy benzyl) benzimidazole were standardized to maximize the yield by changing one parameter at a time keeping others constant. The yield of HBB was maximized to the extent of 39-40% from the previously reported 30% utilizing the procedure reported in the literature.

Step II: Synthesis of 2-(α-bromo benzyl) benzimidazole[3]

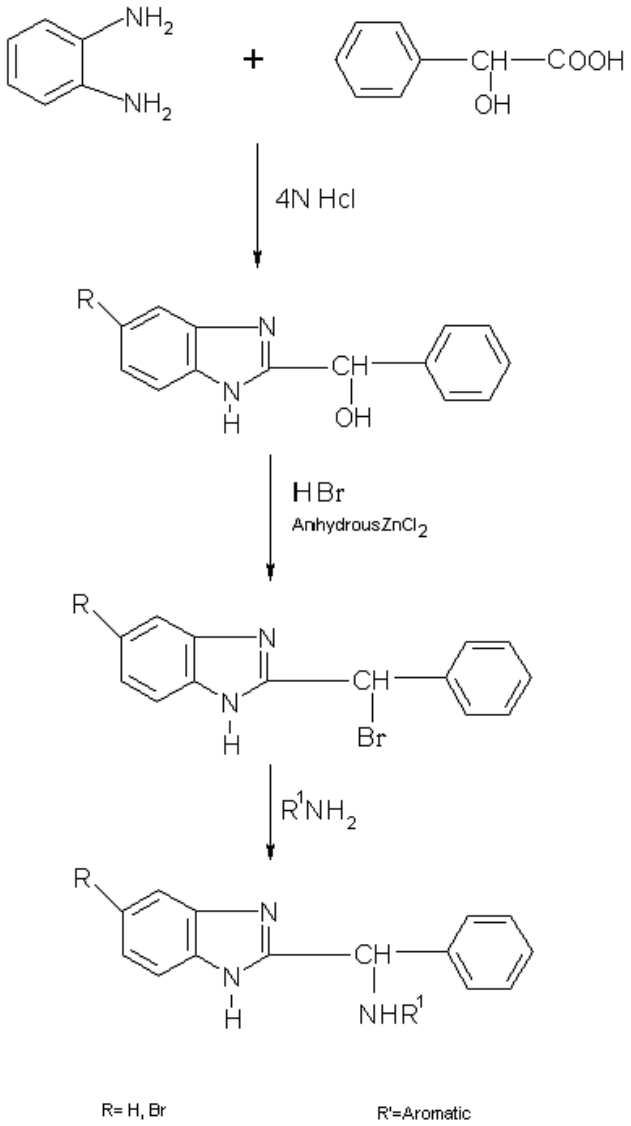
In a 250ml round bottom flask fitted with a reflux condenser, (the top of which is connected to a device for absorbing hydrogen chloride gas) Zinc chloride (o.5 mole) and HBr(3ml) were placed and 2-(α-hydroxy benzyl) benzimidazole(0.25 mol) was added. The mixture was refluxed gentlu at 125-130°C for 3 hours on an oil bath. The reaction mixture was then allowed to cool and the resulting bromide compound was separated. Refrigerated overnight and recrystallized successively from ice-cold water or acetone.

Step III: Synthesis of title compounds[4]

2-(α-bromo benzyl) benzimidazole (0.01 mole) was dissolved in anhydrous dioxane (45 ml) and excess of various substituted aromatic amines were added. The reaction mixtures were allowed to stand overnight at room temperature, the solutions were evaporated to dryness and gummy solid obtained was washed with cold water. The solids were then extracted with 2M HCl. The acidic extracts were made alkaline with NH_4OH and the resultant products were recrystallized from ice-cold water or acetone. Some of these final derivatives were characterized as picrates. The melting points of all the title compounds were recrystallized by open capillary method and were found to be uncorrected. The compounds were obtained in comparatively good yield of 50-70%.

Similarly 2nd series of title compounds were synthesized using 4-bomo-1,2 phenylene diamine instead of o-phenylene diamine.

SCHEME OF THE SYNTHESIS



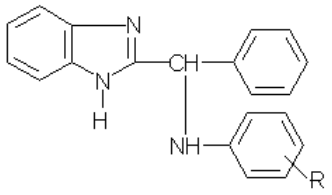
Spectral Analysis[5]

Infrared spectroscopy was done on Jasco FTIR-5300 instrument. H^1NMR spectra was recorded on Bruker 200. 13 MHz. Mass spectroscopy was done on QP 5000 GC/MS instrument.

Spectral Data of the Title Compounds of Series I and II	
I.R spectral Data showed Characteristic Absorption Peaks	Wavenumber (cm^{-1})
A. Hydrocarbon chromophore	
1. C-H stretching	1948.86
2. C-H bending	1295.99
3. C-H bending (Aromatic)	729.98
4. C-C multiple bond stretching aromatic	1581.27, 1586.82
B.	
1. N-H stretching vibrations	1953.13
2. N-H bending vibrations	1578.63
3. C-N vibrations aromatic	1188.64
C. C=C and C=N stretch	1022.34
D. Benzenoid ring breathing modes	890.32
E. Skeletal in-plane vibrations	1454.54
F. Heterocyclic ring breathing modes	788.34
	688.22
NMR spectral Data Showed different protons at	δ-value
Aromatic protons	7.2-7.8
C-H protons	1.4-2.0
N-H protons	1.0-3.2

Mass spectral date showed fragment ion peaks at excepted mass/charge ratio. Molecular ion peak was not obtained since the final derivatives are an adduct with picric acid held by charge transfer complex.

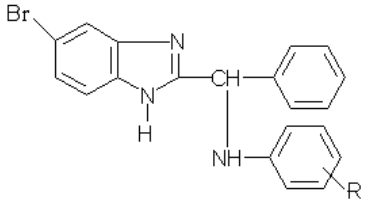
Table 1 – Physical and Analytical Data of Title compounds of series I



Sr.No.	R	Melting Point	%Yield	Complex/Free base
1.	m-chloro	145-150°C	62.05%	picrate
2.	o-chloro	120-135°C	58.12%	picrate
3.	3,4-dichloro	68°C	51.43%	Free base
4.	2,5-dichloro	98 -120°C	46.785%	picrate
5.	2,6-dichloro	90-128°C	56.37%	picrate
6.	m-nitro	70-180°C	58.55%	Free base
7.	o-nitro	89-95°C	40.58%	picrate
8.	2,4-dinitro	215-230°C	32.16%	picrate
9.	p-chloro o-nitro	95-110°C	41.05%	picrate
10	o-mehtyl	120-135°C	40.12%	picrate
11.	o-hydroxy	189°C	49.05%	picrate
12.	o-COOH	121°C	51.25%	picrate
13.	p-COOH	115°C	56.23%	picrate
14.	o-methoxy	154-165°C	47.36%	picrate

*This product was obtained by using Glacial Acetic Acid.

Table II – Physical and Analytical Data of Title compounds of series II



Sr.No.	R	Melting Point	%Yield	Complex/Free base
1.	3,4-dichloro	74-85°C	55.25%	Free base
2.	m-nitro	96-105°C	59/12%	Free base
3.	o-nitro	54-65°C	51.19%	Free base
4.	p-chloro o-nitro	109-115°C	55.23%	Free base
5.	α-naphthyl	102-106°C	42.14%	picrate

RESULTS

The resulting 2-(α-hydroxy benzyl) benzimidazole was converted to 2-(α-bromo benzyl) benzim idazole by reacting with HBr and Anhydrous $ZnCl_2$. Further attempts were made to synthesize two series of title compounds which were characterized by physical and instrumental analysis like recording their melting points in Open capillary tubes and by spectral studies such as IT, NMR and Mass spectroscopy.

DISCUSSIONS

The synthesis of HEB was standardized to maximize the yield to approximately 40% also, HBB was synthesized by new route using O-phenylene diamine and Mandelic acid in acidic medium and the maximization of yield was attained up to 36%.

This work thus confirms the better yield of HBB and simpler route for the synthesis of newer analogs of HBB.

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