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Research Article

SYNTHESIS AND SPECTRAL STUDIES OF 6-HYDROXY (3,2-a) PYRIDOBENZIMIDAZOLE AND ITS QUARTERNARY SALT

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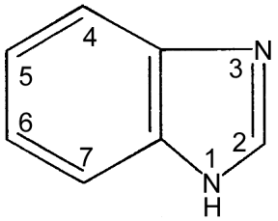
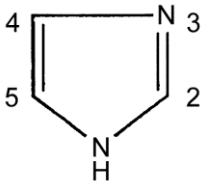
ABSTRACT
6-Hydroxy-(3,2-a) Pyridobenzimidazole has been synthesized and spectral studies of its quaternary methiodide has been discussed with a view to ascertain the position of hydroxyl group on benzimidazole nucleus. This spectral property reveals its internal charge transfer nature. This compound shows beautiful fluorescence and a study of its fluorescence spectra has been carried out.

Key Words: *6-Hydroxy-(3,2-a) Pyridobenzimidazole, Benzimidazoles*

INTRODUCTION

Benzimidazoles contain a benzene ring fused to an imidazole ring as indicated in the structure of benzimidazole. The heterocyclic portion of the benzimidazole ring system has been referred as glyoxaline imidazole 1,3 diazole and imidazole (Hantzsch, 1888) Imidazole, which is the term used most frequently, indicates a five membered heterocyclic ring system containing an imino group and a tertiary nitrogen.





The imidazole nucleus is found in a number of important products (natural) such as histidine (a normal constituent of most proteins) and the purines. 5,6 dimethy 1-1-(d-D-ribofuranosy1) benzimidizole is an integral part of the structure of vit B_{12} (Bonnett,1963). Consequently a massive research effort has been expanded upon the chemistry of the Imidazoles and Benzimidazoles with the emphasis on the synthesis of new compounds for pharmacological screening and the discovery of a new antibacterial viz,2-nitro imidazole and anthelmintic angents eg 2(4-thiazolyl) benzimidozolo.

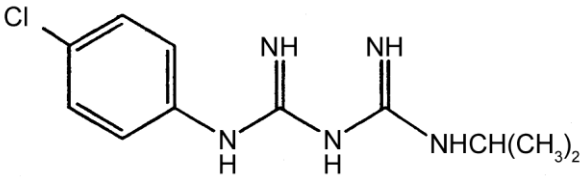
Benzimidazole inhibits the growth of certain yeasts and bacteria. The action is reversed by the addition of adenine or guanine. It was noted, however, the adenine does not prevent "benzimidazole anesthesia" in mice, so that the latter effect is apparently not related to purine utilization. Substitution of an amino group in the benzene nucleus of benzimidazole does not appear to affect the inhibiting action to any extent. Benzimidazole derivatives were tested initially as antivirals because of their structural similarity to the benzimidazole moiety in vit. B_{12} (5,6-dimethy 1-1-(α-Dribofuranosy1) benzimidazole. Alky1 substituted benzimidazoles have been found to inhibit the multiplication of influenza β virus, Lee Strain (Tamm 1953).

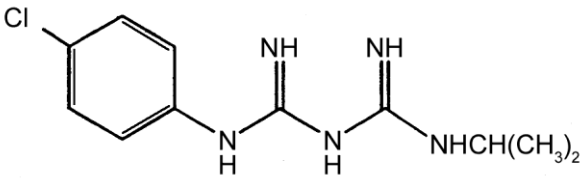
These are better antithyroid agent in rats than pheny1 thiourea (Bywater, 1945). The 2-alky1-aminomethy1 and 2-dialky1-aminomethyl benzimidazoles possess local anaesthetic activity (Roeder and Day, 1941).

Shealy *et al.,* (1962) reported that some 5-substituted triazino imidazole-4-carboximides have been found to be potential anticancer agents.

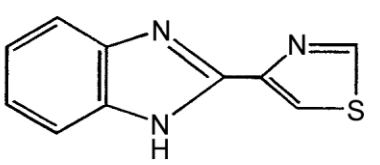
Okamato *et al.,* (1955) have reported that benzimidazole nucleus it self high antidiabetic activity. A large number of benzimidazole derivatives are reported to possess trypanosomicidal and spirocheticidal action and are active against diseases caused by protozoa. A number of benzimidazoles related to the active

antimalarial, paludrine have been prepared (King *et al.,* 1948). These may be looked upon as closed ring analogues of paludrine.

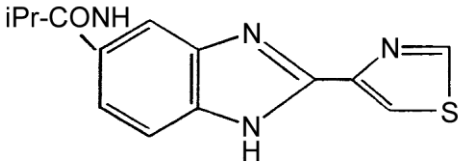




The most successful drugs "Thiabendazole" and "Carbendazole" which have been found of wide use as anthelmintic agents for both human and veterinary purposes.

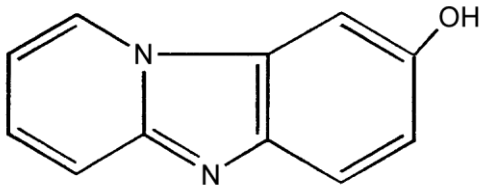


Thiabendazole

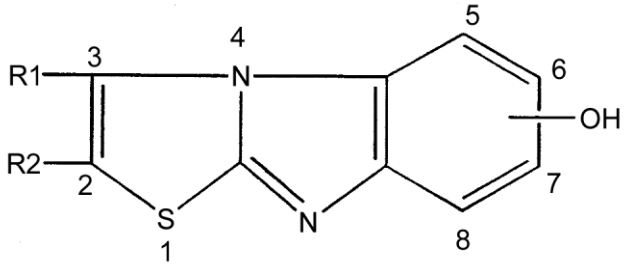


Carbendazole

6-hydroxy 1',2'-1, 2-pyridobenzimidazole (IV) can be obtained by treating p-benzoquinone with 2-amino pyridine. However, similar reaction carried out with 1,4-naphthoquinone did not yield any product.



Similarly some 6(7) – hydroxy thiazole (3-2a) – benzimidazole can be synthesized by condensing 2-amina-thiazoles with p-benzoquinones having the general structure.



6(7)-hydroxy thiazole (3-2a)-benzimidazole with uncertain hydroxy1 group
Where R_1 and R_2 are H, lower alky1, lower alkoxy or pheny1 nucleus.
However the preparation of their quaternary derivatives has not been reported and also there is no compete study which have a bearing on their finer structure, particularly with regards to the position of phenolic OH group, which could be either on 6^{th} or 7^{th} carbon. The synthesis of 6 hydroxy (1,3,4) thiadiazole 2,3,-b) benzimidazoles has also been reported (Soni and Sexena,1982), which were obtained

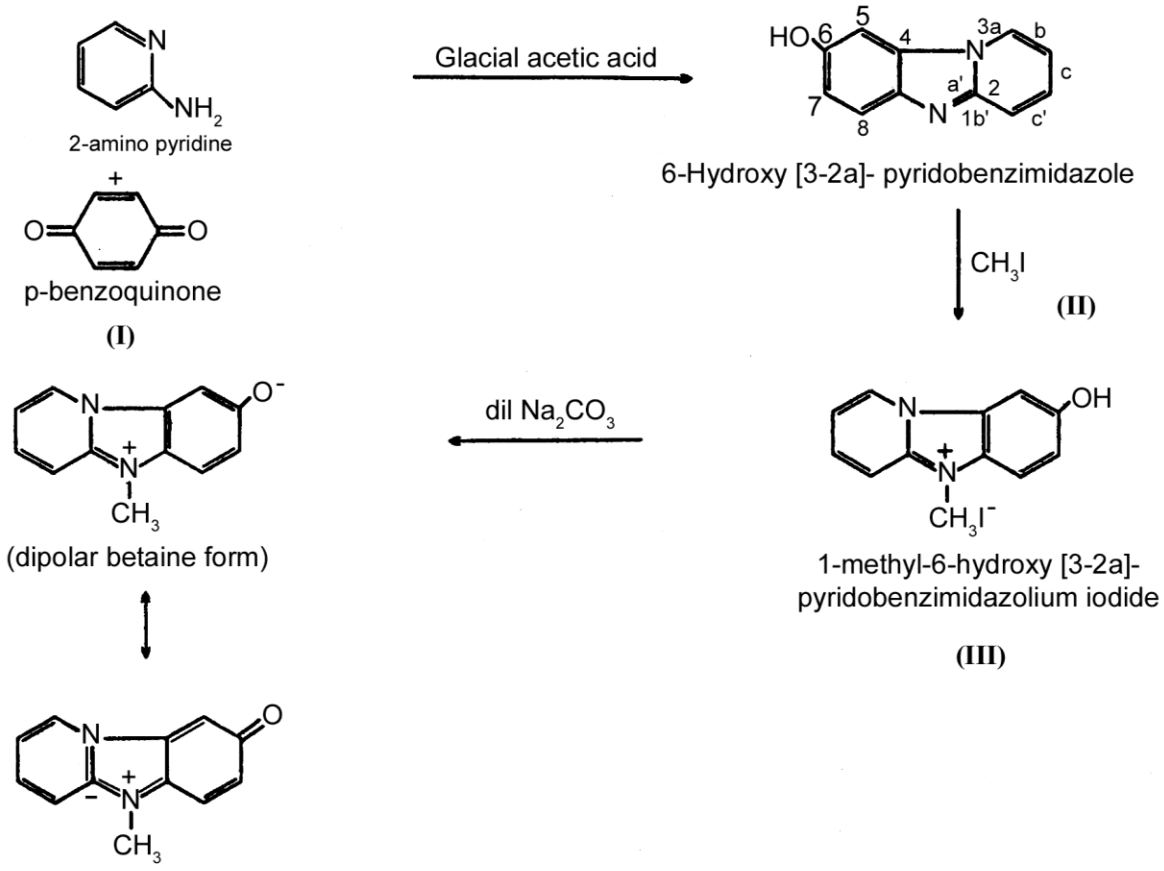
by the condensation of 2 amino 1,3,4-thiadiazoe with p-benzoquinone. They further reported (Soni and Sexena, 1979) the study of the reaction of 2-amino benzothiazole with p-benzoquinone, and they obtained 9-hydroxy benzimidazole (2,1-b) benzithiazoles.

Keeping in view of the antiviral activity (Eggers and Tamim, 1961) benzimidozole systems, e.g. thiabenzimidazole 2-(4-thiazoly 1) benzene diazole) which is well known for its use as leading anthelminthic for the control of most gastrointestinal nematodes of man, with the exception of trichuris species (Brown *et al.*, 1961; Douglas and Baker, 1968; Cuckler and Mezey, 1964), it was thought worthwhile to synthesize some new compounds containing benzimidazole moiety and to study their mode of formation through spectral data. Hence in this paper we report synthesis of 6 hydroxy (3-2a) pyridobenzimidazole(A) by the reaction of p-benzoquinone with 2-amino pyridine. Quaternisation of (1) with methyliodide yield compound(B). 1 -Methyl-6-hydroxy(3,2a)-pyridobenzimidazolium Iodide as evidenced by the work of Paudler and Blewitt, for the site of protonation and N methylation of imidazo(1,2-a)pyridines. Compound (11) gave intense yellow colour with dil. Alkali due to the formation of the phenol betaines,(internal charge transfer system).

MATERIALS AND METHODS

Experimental

All the reagents were thoroughly dried and purified before use. All melting points were determined on Kofler instrument. IR spectra were recorded on a Perkin-Elmer 577 spectrophotometer in KBr. UV absorption spectra were scanned on a Beckman Spectrophotometer, modelDU-2 using ion path length quartz cells. Fluoroscence spectra were recorded on fluorescence spectrophptometer Model204A.



Research Article

Preparation of 6-Hydroxy(3,2-a)-Pyridobenzimidazole

A solution of P-benzoquinone(0.01mol) was dissolved in minimum quantity of the glacial acetic acid. 2gm of 2-amino pyrimidine was dissolved in minimum quantity of the glacial acetic acid. The second solution was added gradually of the first with constant shacking and solution was warmed on a water bath for 2-3 minutes. The mixture was left to stand for 2 days. To this, 20 ml 50% HCl was added and the solution was diluted. It was extracted with either to remove unreacted quinone and hydroquinone. The resulting solution was made alkaline with sodium carbonate solution when the desired compound precipitated. After treatment with charcol in ethanol, the compound was recrystallised from ethanol and acetone.

Yield = 2.5 gms

m.p. = 320^0 C

Physical state = Light brown solid.

Analysis

	Found	N	=	23.00
	Calculated for	N	=	22.70

UV(in ethanol)

λ_{max} in nm	loge
260	2.05
330	2.83
350	3.30
370	3.50

In. 0.1 M HCl		In. 0.1 M NaOH	
λ_{max} in nm	loge	λ_{max} in nm	loge
300	2.09	290	2.10
345	2.75	332	2.79
370	3.41	362	3.31
395	3.79	385	3.82

IR	Phenolic OH	3220, 1210 cm^{-1}
	C=C,C=N	1610 cm^{-1}
	C-N	1270 cm^{-1}
	Aromatic ring	1475 cm^{-1}

Preparation of 1-Methyl -6Hydroxy (3-2a) -pyridobenzimidazolium iodide (B)

1 gm of this compound (1) was dissolved in 1:1 ethanol acetone solution and was boiled under reflux with excess of methyl iodide on a water bath for 1-3 hrs. When the desired N-methyl benzimidazolium iodide got partly separated out. Excess solvent was removed by distillation on a water bath and the product was recrystallised from acetone or ethanol.

m.p.	=	310^0C	
Yield	=	1 gm	
Physical state	=	Light yellow brown.	

Analysis

Found	N	=	13.0%	I	=	40.00%
Calculated	N	=	12.8%	I	=	38.83%

UV (in EtOH)

λ_{max} in nm	loge
250	2.50
300	2.75
360	3.42
375	3.80

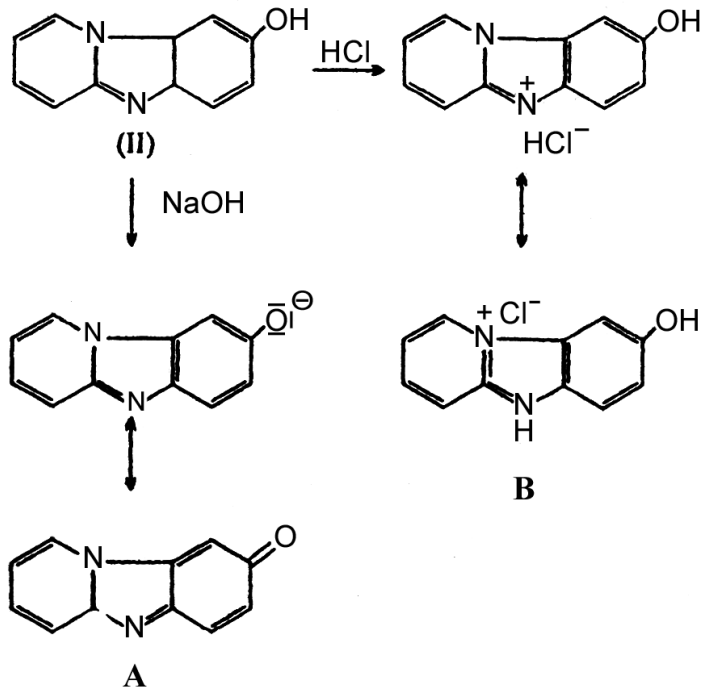
RESULTS AND DISCUSSION

The structure of the compounds has been determined on the basis of the IR, UV spectra and elemental analysis. The IR spectra of this compound showed bands at 1210 (Phenolic OH), 1625 (C=N), 1315 (C-N) and 1450 cm^{-1} (aromatic ring). Electronic absorption spectra of these compounds have been studied which has a bearing on their finer structure, particularly with regards to the position of phenolic hydroxyl group.

We see from the data that the absorption spectra of this compound in ethanol at different pH show a characteristic bathochromic shift of the absorption. Maxima in the longer wavelengths in both acidic as well as alkaline medium. No zwitterionic structure is expected in strongly alkaline medium. The observed bathochromic shift may be explained on the basis of the following canonical quinoid structure is expected in strongly as one of the contributing form.

Table 1: (6-Hydroxy (3-2a) pyrimidobenzimidazole)

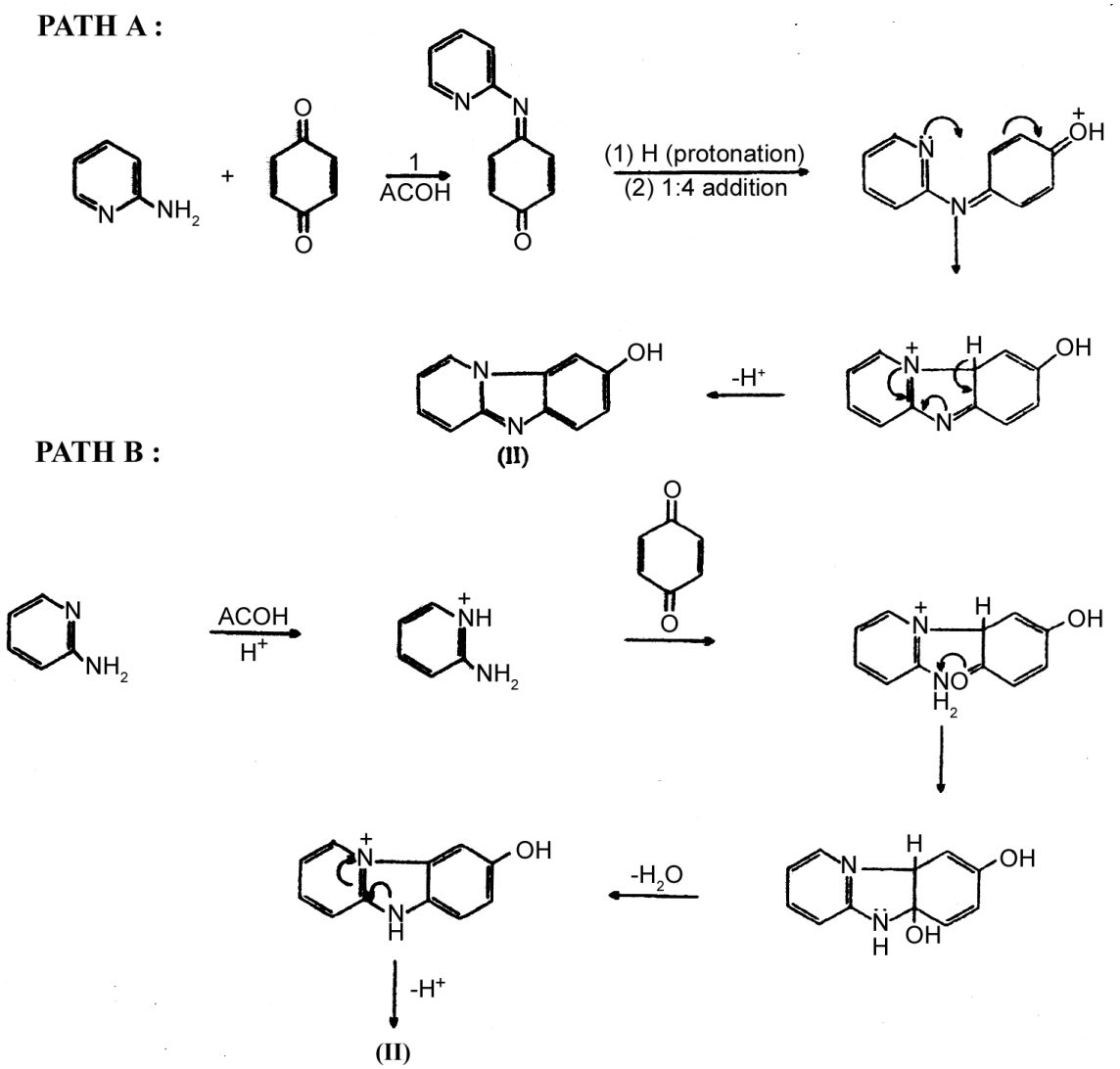
Compound	Molecular Formula	Mpt. ^0C	% Analysis		U.V. Spectra					
					Ethanol		0.1 M HCl		0.1 M NaOH	
			Calc	Found	λ_{max} in nm	loge	λ_{max} in nm	loge	λ_{max} in nm	loge
Compound II	$C_{10}H_7N_3O$	320	N,22.7	23	260	2.05	300	2.09	290	2.10
					330	2.83	345	2.75	332	2.79
					350	3.30	370	3.41	362	3.31
					370	3.50	395	3.79	385	3.82
Methiodide of Compound II	$C_{11}H_{10}N_3O_1$	310	N,12.8 I 38.83	13	250	2.50				
					300	2.75				
				40	360	3.42				
					375	3.80				



We see from the data that absorption spectra of compound (II) in ethanol at different pH. It shows a characteristic bathochromic shift of the absorption maxima in longer wavelengths in both acidic as well as alkaline medium.

The compound showed λ_{ex} = 260 nm and λ_{em} = 370 nm in ethanol solution. The sensitivity μ was 0.3. In both acidic as well as basic medium the λ_{em} shifted towards the longer wave length side (red shift). Though the shift was more pronounced in the acidic medium than inalkaline medium. In alkaline medium this may be ascribed to the quinonoid structure (A). In acidic medium this should be attributed due to salt formation. The intensity of fluorescence however, decreased three times in the alkaline medium, while it remained almost the same in the acidic an neutral medium.

Fluorescence spectra of methiodide of compound showed a clear red shift of 10-15 nm in alkaline medium $\lambda_{em\ 450\ nm}$. The intensity of fluorescence indicated 3 times decrease from μ = 0.3 to 1. This may be attributed to salf formation and contribution of the dipolar betaine structure in ethanol.



It is therefore reasonably concluded that hybroxyI group is present at no.6 position in the compound. It being acidic, it causes the molecule to attain dipolar and quinonoid character through charge transfer, thus facilitating the absorption at the longer wave length. The formation of this compound can be explained by the following mechanism.

In these mechanisms cited here, the position of phenolic hydroxyl group remains ascertained as meta to the bridgehead nitrogen atom and para to second imidazole nitrogen through either of these routes.
In these mechanisms cited here, the position of phenolic hydroxyl group remains ascertained as meta to the bridgehead nitrogen atom and para to second imidazole nitrogen. Here 1:4 addition of 2-amino pyridine to p-benzoquinone will not take place in a manner analogous to aniline because in such systems the tertiary nitrogen is more basic and hence is a stronger nucleophile than primary amino group of the 2-amino pyridine and secondly the role of acetic acid as the medium of the reaction is not justifiable through this 1:4 addition mechanism .Moreover such a reaction would yield 7-hydroxy compound instead of the 6- Hydroxy product. Further 7-hydroxy would result into lesser canonical forms, thermodynamically unstable and as such it will not be consistent with the characteristic spectral behavior of the pronounced bathochromic shifting in the longer wavelengths on basification and quaternisation of this imidazole.

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