Preparation, Physical Properties and Nuclear Magnetic Resonance Spectral Studies of Isomeric 2 [Hydroxypropyl]-Benzimidazoles

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Summary: Preparation, physical properties and nuclear magnetic resonance spectral (^{1}H and ^{13}C) data of 2-[2-hydroxypropyl]-and 2-[3-hydroxypropyl]-benzimidazoles (1) and (2) have been described.

Two isomeric benzimidazoles, namely 2 [2-hydroxypyropyl]-1 and 2 [3-hydroxypropyl] - (2) [1] have been prepared and their physical properties and ^{1}H and ^{13}C nuclear magnetic resonance spectral behaviour have been studied. It seems that higher polarity of 3-hydroxybutyric acid as compared to 4-hydroxybutyric acid has led to higher yield of (1) (Table 1). Compound (1) shows higher R_f value and smaller retention time because of higher polarity of its side chain as shown in Table 1. Mass-spectral data given in Table I confirm the molecular formulae of (1) and (2) and also exhibit a fragment at m/e = 132, characteristic of benzimidazole nucleus [1-5].

Proton magnetic resonance spectra of (1) and (2) are shown in Fig. 1 (a and b) and 2 respectively, and data are listed in Table II and III. These data are in conformity with the expected structure.

Methylene protons of (1) appeared as doublet of doublet at δ2.99 ppm, when proton magnetic resonance spectrum was measured at 90 MHz (Fig. 1a and Table II). However, when the same spectrum was measured at 300 MHz (Fig. 1b), these protons appeared as multiplet at about δ2.98 ppm., in accordance with the diastereotopic nature of these protons. Moreover, small additional peaks became visible on both the sides of the multiplet close to it, indicating unequal population of different conformers.

^{13}C magnetic resonance spectra of (1) and (2) are shown in Fig. 3 (a and b), and 4 respectively, whereas data are recorded in Tables IV and V. Assignment of peaks to benzimidazole portion has been made on the basis of data available in the literature [6] on unsubstituted benzimidazole.

Experimental

Preparation (1)

A mixture of 5.4 g (0.05 mole) of o-phenylenediamine and 5.2 g (0.05 mole) of 3-hydroxybutyric acid (Fluka) was refluxed in 25 ml. 4 N hydrochloric acid with good stirring for eight hours. The reaction mixture was cooled to O°C and nutralized with sodium carbonate. The product was collected

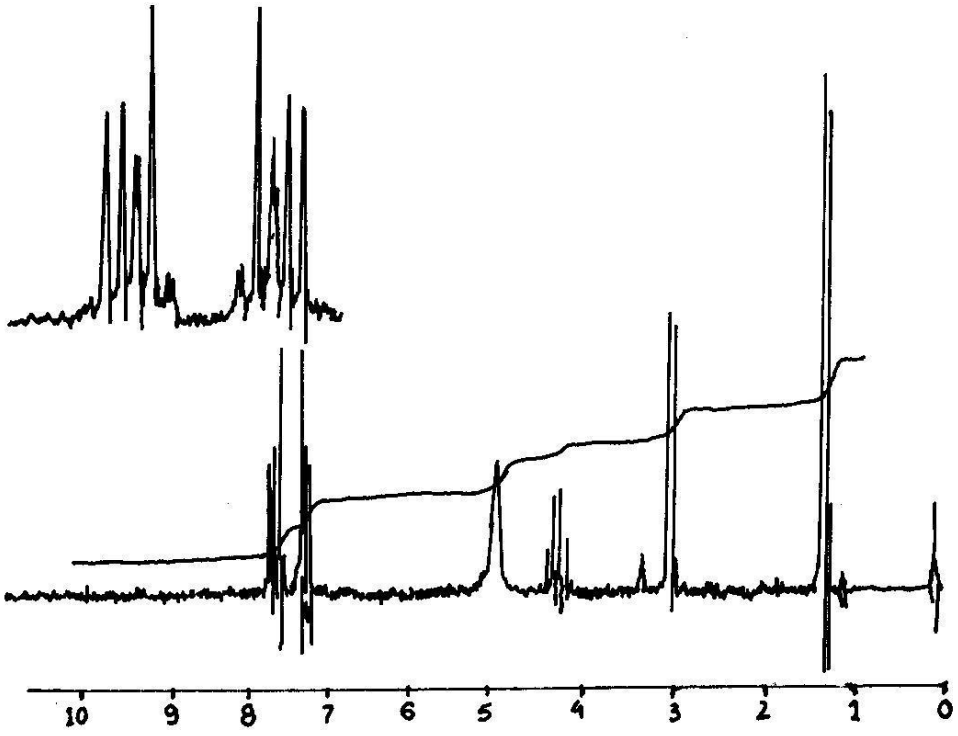


Fig. 1a

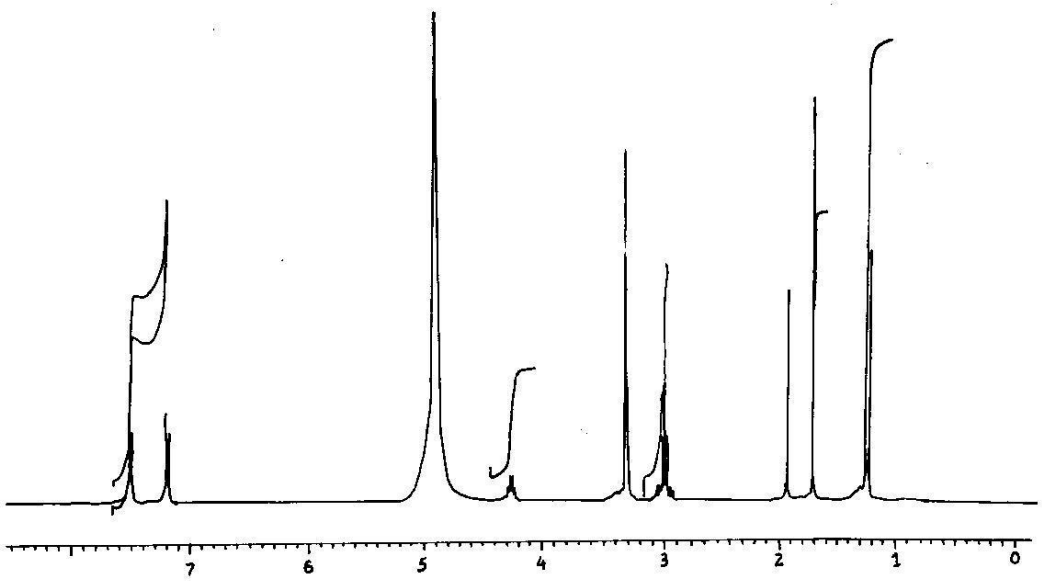


Fig. 1b

Table-I

Number	Benzimidazole	M.P. °C	Solvent used for crystallization	Yield %	Molecular Formula and Molecular Mass	Mass Spectral Fragments	TLC R_f-value $x10^2$	HPLC (retention time). min.
(1)	2[2-Hydroxypropyl]-	185	MeOH/H_2O	75	$C_{10}H_{12}N_2O$ 176	M^+=176 m/e = 132 (base peak)	5.3	14
(2)	2[3-Hydroxypropyl]	160	EtOH/pet.ether	40	$C_{10}H_{12}N_2O$ 176	M^+=176 m/e = 132 (base peak)	3.9	17

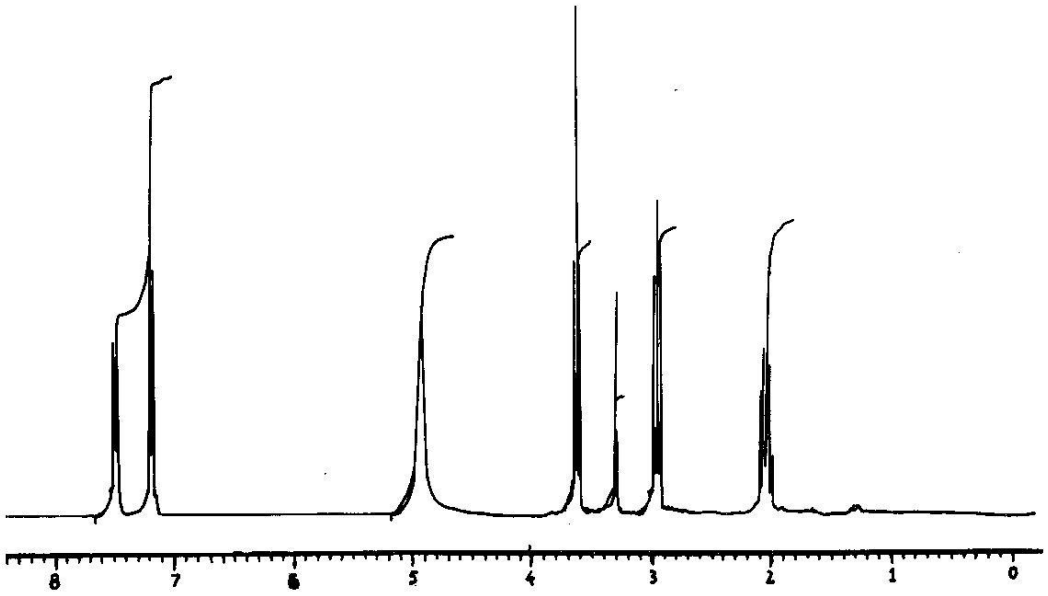


Fig. 2

on a filter, washed with cold water, and recrystallized from a mixture of methanol and water, yielding colourless needles. Melting point, precentage yield, R_f value and retention time are recorded in Table I. Mass-spectral measurements confirmed the molecular formula, showing molecular ion peak at m/e 176 and base peak at m/e 132.

Preparation of (2)

This compound was prepared by refluxing equimolar mixture of γ-butyrolactone and o-phenylenediamine in 4 N hydrochloric acid as already reported [1]. Melting point, percentage yield, R_f value and retention time are listed in Table I.

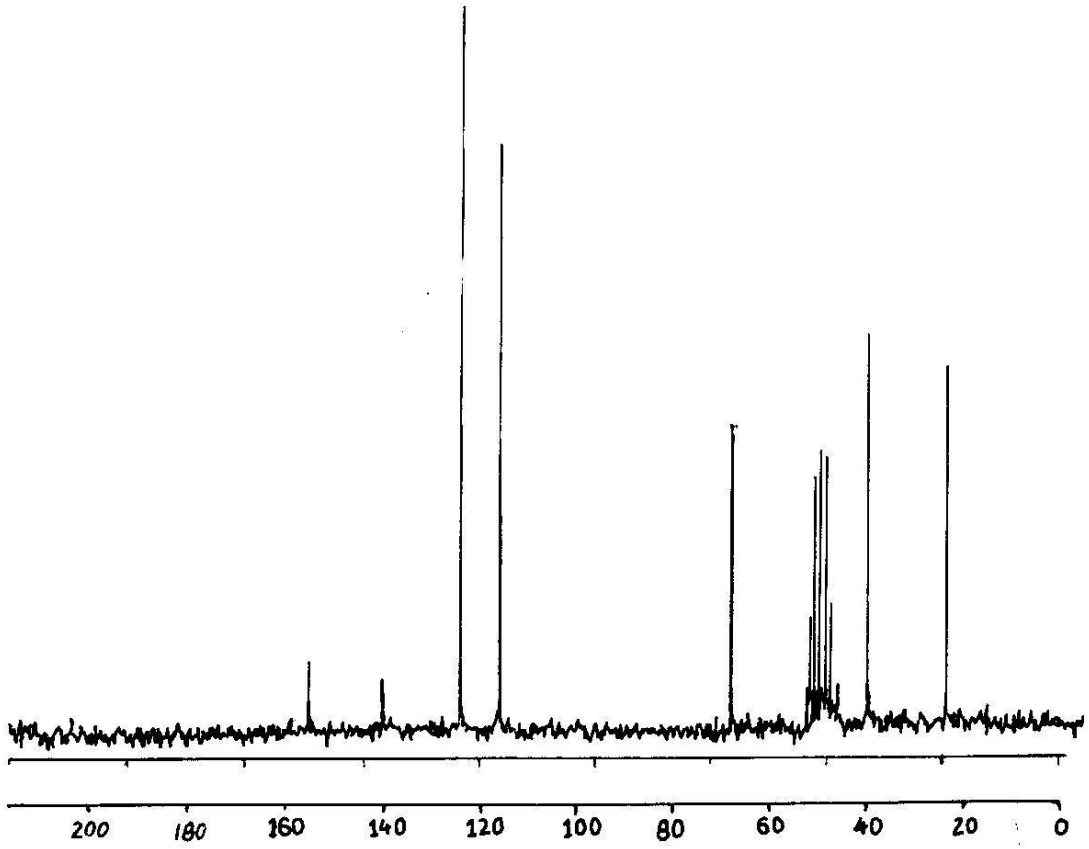


Fig. 3a

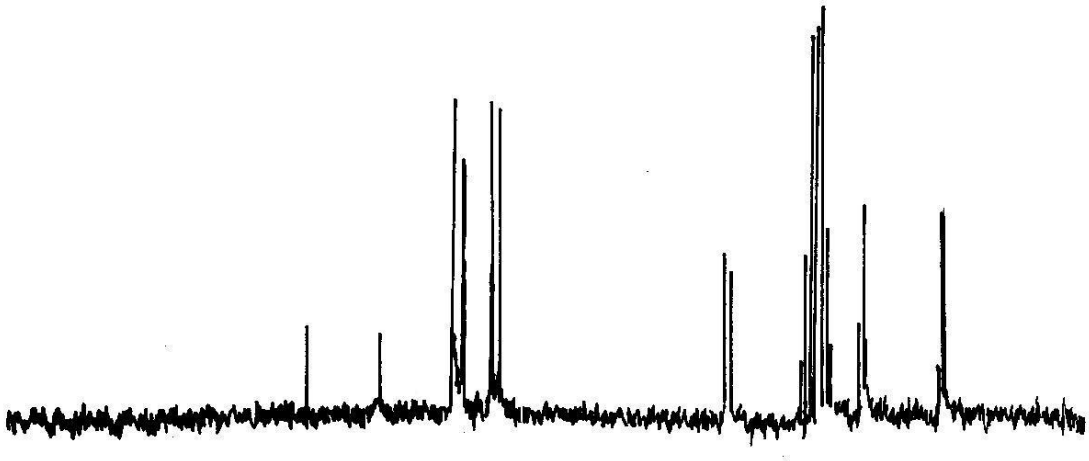
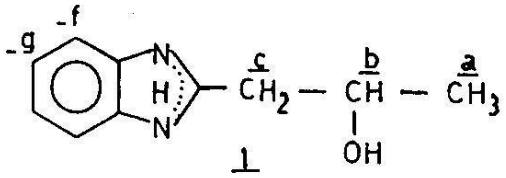


Fig. 3b

Table-II Types of Protons and ^{1}H-Magnetic Resonance Spectral Data of (1) Measured at 90 MHz

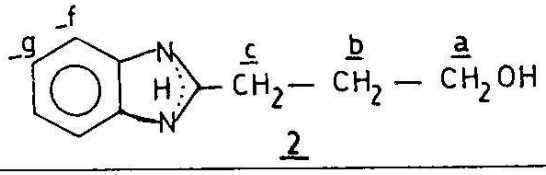


1

Protons	Chemical shift (ppm)	Peaks Pattern	Coupling Constants (Hz)
3H<u>a</u>	1.23	d*	$J_{a,b}$ = 6.
1H<u>b</u>	4.29	dq***	$J_{a,b}=J_{b,c}=6$
2H<u>c</u>	2.99	dd**	$J_{c,b}=6$, $J_{c,c}$=v.small.
2H<u>f</u>	7.5	**dd A_2B_2	Jortho=6.2, Jmeta=3
2H<u>g</u>	7.15	**dd	

* = doublet.
** = doublet of doublet.
*** = doublet of quartet.

Table-III Types of Protons and ^{1}H Magnetic Resonance Spectral Data of (2) Measured at 300 MHz.



2

Protons	Chemical Shift (ppm)	Peak Pattern	Coupling Constants (Hz)
2H<u>a</u>	3.62	t*	$J_{a,b}$ = 6.3
2H<u>b</u>	2.03	m**	$J_{a,b}$=6.3, $J_{c,b}$=7.6
2H<u>c</u>	2.95	t*	$J_{c,b}$ = 7.6
2H<u>f</u>	7.47	dd***	J_{ortho} = 5.9
2H<u>g</u>	7.16	dd*** A_2B_2	J_{meta} = 3.1

* = Triplet
** = Multiplet
*** = Doublet of doublet.

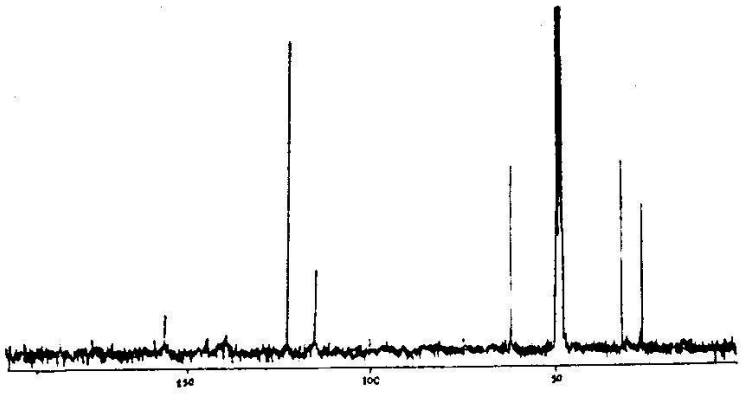
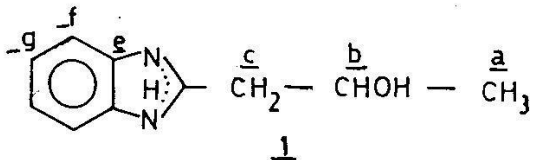


Fig. 4

Table-IV: Types of Carbon Atoms and ^{13}C Magnetic Resonance Spectral Data (OFF-Resonance (1))

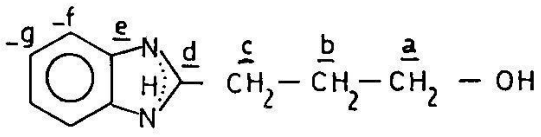


1

Carbon Atom	Chemical Shift (ppm)	Peak Pattern
1C-a	23.3	**** q
1C-b	67.4	** d
1C-c	39.4	*** t
1C-d	154.2	* s
2C-e	139.5	** d
2C-f	115.4	** d
2-g	123.7	** d

* = Singlet
** = Doublet
*** = Triplet
**** = Quartet

Table-V: Types of Carbon Atoms and ^{13}C Magnetic Resonance Spectral Data of (2)



2

Carbon Atoms	Chemical Shifts (ppm)	Peak Pattern
1C-a	62.1	t
1C-b	26.39	t
1C-c	32.01	t
1C-d	156.59	s
2C-e	139.68	s
2C-f	115.31	d
2C-g	123.14	d

Chromatography of (1) and (2)

Thin layer chromatography of (1) and (2) was carried out on 0.25 mm thick 20x20 cm chromoplates of silica gel HF_{254} (Fluka) in a mixture of 9:1 chloroform and methanol. The results are recorded in Table I.

High performance liquid chromatography was done on 25 cm x 46 cm 1D ultrasphere ODS (C_{18}) reversed phase prepacked steel column using isocratic liquid chromatograph (Altex model 330A). Column effluent was monitored with an analytical UV detector (Altex model 110A) at 254 nm for the detection of benzimidazoles. Samples were dissolved in a mixture of 1:1 methanol and water. Sample volumes of 10 µl were injected for analysis. Attenuation was 0.16 AUFS during all measurements. Chart speed was 1mm min^{-1} on XY recorded. (Kippe and Zonen BD 40). Pressure varied from 1,000 - 1,200 Psi. Flow measurements were made at ambient temperature. Solvent used was of HPLC grade (Fluka). Retention time of the two benzimidazoles is listed in Table I.

Nucelar Magnetic Resonance Spectroscopy

Proton magnetic resonance spectra of (1) were recorded at 300 as well as 90 MHz in MeOH-d_4, whereas that of (2) at 300 MHz in the same solvent. ^{13}C magnetic resonance spectrum of (1) was measured 20-15 MHz in CD_3OD using internal standard CD_3OD (49.0), and that of (2) was recorded at 75 MHz using same internal standard.

Acknowledgement

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