

Synthesis of New Benzimidazoles as Potential Therapeutic Agents—III Preparation of bis-Benzimidazoles

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Summary: Preparation, physical properties, chromatographic behavior, mass spectral fragmentation pattern and proton magnetic resonance spin pattern of 1,3-bis-(2-benzimidazolyl)-1-methyl-propane (1), 1,3-bis-(2-benzimidazolyl)-2-methyl-propane (2) and 1,3-bis-(2-benzimidazolyl)-1,1-dimethyl-propane (3) are described.

Introduction

The programme of research for the synthesis of new benzimidazoles [1,2] including bis-benzimidazoles, having different substituents at position 2- of benzimidazole nucleus has been undertaken with a view to evaluate their biological activity, since substituted benzimidazoles have found [3] extensive use as pharmaceuticals, veterinary anthelmintics, and fungicides. The present paper describes the preparation, physical properties, chromatographic behaviour, mass-spectral fragmentation patterns and proton magnetic resonance spin pattern of three bis-benzimidazoles, namely 1,3-bis-(2-benzimidazolyl)-1-methyl-propane (1) (Fig. 1), 1,3-bis-(2-benzimidazolyl)-2-methyl-propane (2) (Fig. 2) and 1,3-bis-(2-benzimidazolyl)-1,1-dimethyl-propane (3) (Fig. 3).

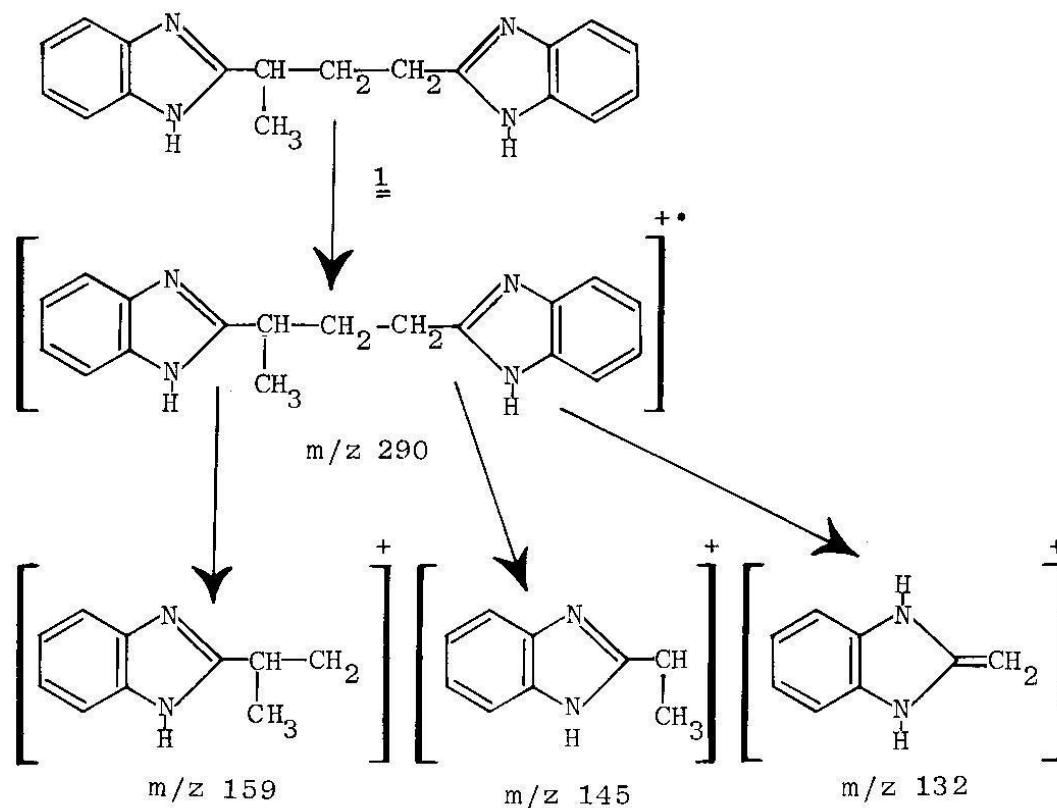
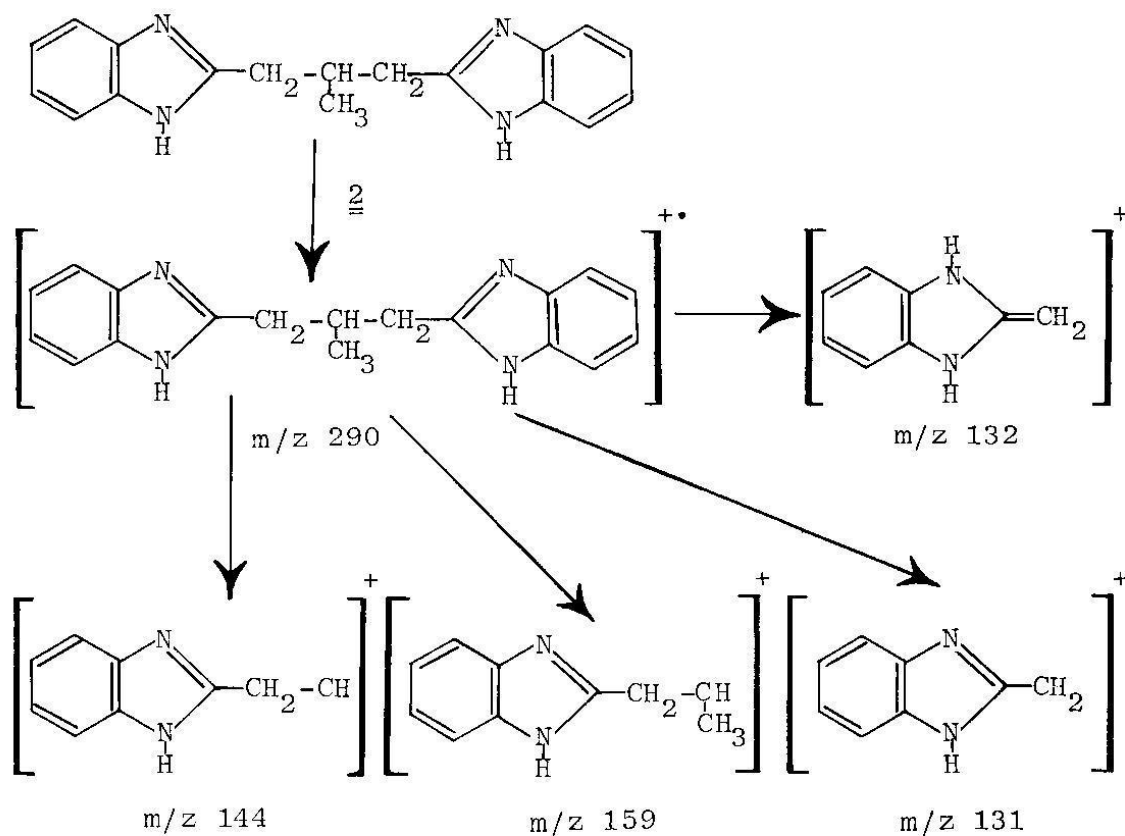
Results and Discussion

These benzimidazoles were prepared by condensation of two moles of o-phenylene-diamine with one mole each of dibasic acids [4]. It has been found that the melting points of these compounds are much higher (Table 1) than those of benzimidazoles [1,2,5]. Results of thin layer chromatography

reveal that R_f values of bis-benzimidazoles are lower than those of benzimidazoles [5] measured under similar conditions. It has also been observed that R_f values increase with increasing methyl substitution in the side chain of bis-benzimidazoles i.e. R_f value of (3) is higher than that of 1 or 2 (Table II). Retention times in high performance liquid chromatography (HPLC) shown in Table III and Fig. 4 also increase in the same order.

Mass-spectral fragmentation patterns of 1, 2 and 3 shown in Fig. 1, 2 and 3 are similar to those of 2-alkyl substituted benzimidazoles. Characteristic peak at m/e 132 is visible in all the spectra.

Proton magnetic resonance spectra of 1, 2 and 3 are shown in Fig. 6, 7 and 8, and data are listed in Table IV, V and VI respectively. They are in conformity with their structures. The benzene protons show A_2B_2 pattern. Two sets are visible in 1 and 3, because of their unsymmetrical structure. The methylene groups in 2 have diastereotopic protons. Methylene protons H_1 and H_2 in 1

FIG. I FRAGMENTATION PATTERN OF 1FIG. II FRAGMENTATION PATTERN OF 2

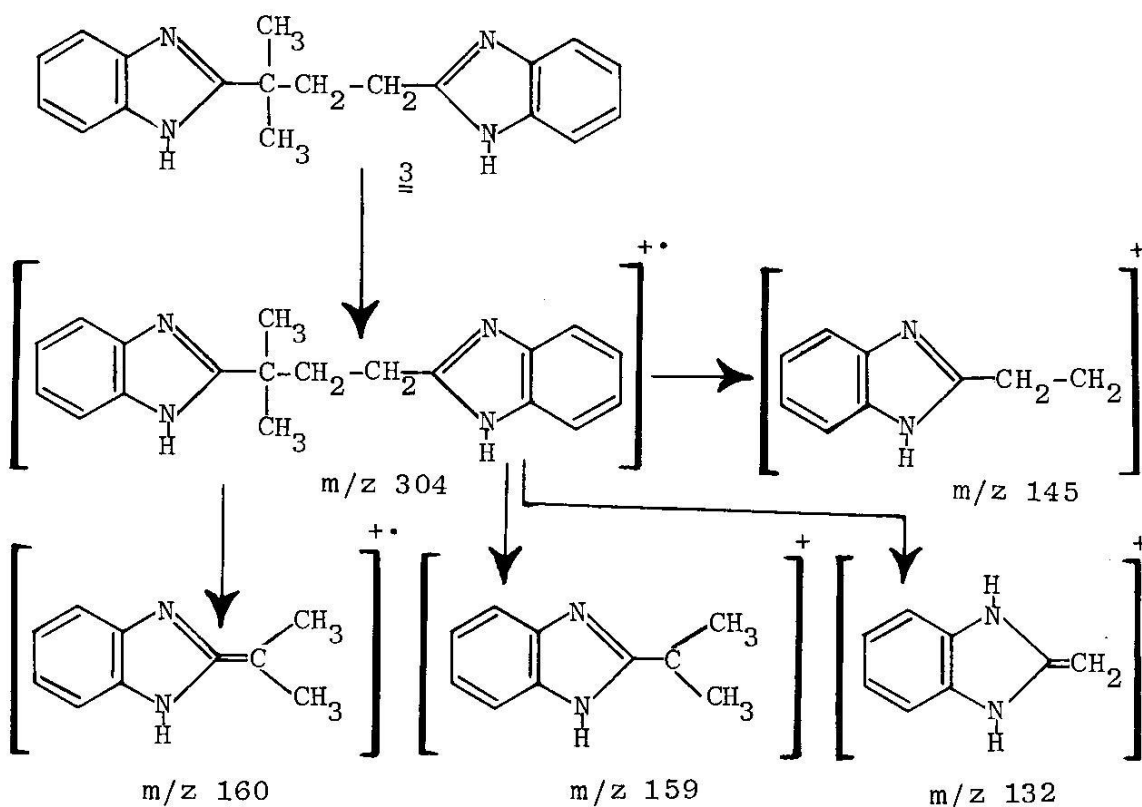
FIG. III FRAGMENTATION PATTERN OF 3

Table-1: Yield, Physical Properties and Mass Spectral Data of Bis-Benzimidazoles

Bis-benzimidazole	Carboxylic Acid used	m.p. °C	Solvent use for recrystallization	Yield %	Molecular Formula	Mass Spectra data
<u>1</u>	2-Methyl-glutaric acid	(Darkens at 240) 249-250	MeOH/H ₂ O	30	C ₁₈ H ₁₈ N ₄	290,159,145 132
<u>2</u>	3-Methyl-glutaric acid	239-240	MeOH/H ₂ O	30	C ₁₈ H ₁₈ N ₄	290,159, (base) 144,132,131.
<u>3</u>	2,2-Dimethyl-glutaric acid	285-286	MeOH/H ₂ O	25	C ₁₉ H ₂₀ N ₄	304,160 (base) 145,132.

Table 2: TLC of Bis-Benzimidazoles on Silica Gel. Results Are R_f Values $\times 10^2$

Benzimidazole	Solvent System						
	1	2	4	5	6	7	
<u>1</u>	1	54	13	45	10	58	73
<u>2</u>	1	58	14	40	12	53	74
<u>3</u>	2	81	30	32	16	50	75

a) Solvent System 1 = Acetone : Pet. ether (1:4); 2 = Acetone : Pet. ether (4:1); 3 = Ethylacetate; 4 = Ethylacetate: MeOH (19:1); 5=MeOH:H₂O (1:10)
6 = Acetone: Pet. ether (9:1); 7 = Toluene: Ethylacetate: Ethanol: Ammonia (60, 10, 30, 2).

Table 3: HPLC of Bis-Benzimidazoles: Results are Retention Time (Minutes)

Benzimidazole	Solvent System		
	1*	2*	2**
<u>1</u>	4	4'20	5'30
<u>2</u>	4	4'35	5'0
<u>3</u>	4	5'05	6'20

1* = MeOH : H₂O (1:1), 2* = CHCl₃, flow rate = 0.5 ml min⁻¹

2** CHCl₃, flow rate = 0.4 ml min⁻¹

show a complex signal, and the two c protons show a broad quartet; whereas methylene protons c and c in 3 show triplets, where splitting of each triplet with the appearance of three additional small peaks in visible. The integration is however not disturbed. This points to the presence of another less populated conformer (b), in addition to (a) in 1 and 3 as shown in Fig. 8.

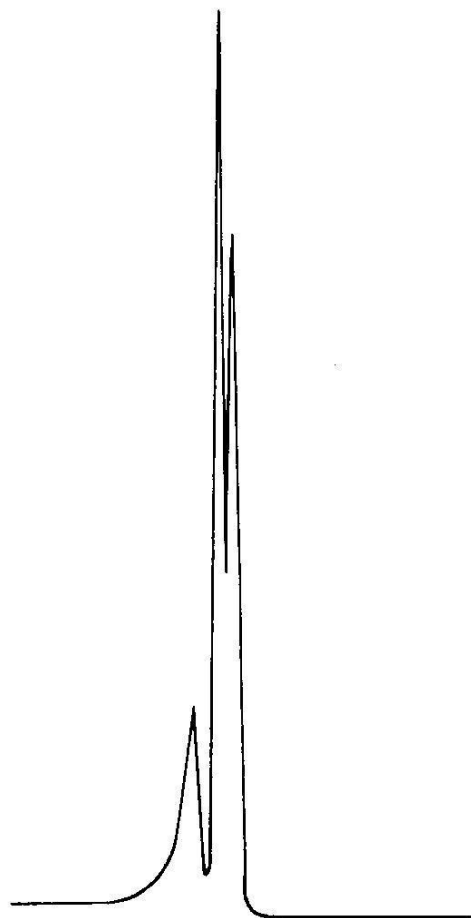


Fig.4: A typical chromatogram of a mixture of bis-benzimidazoles on 1D ultrasphere ODS column in chloroform at ambient temperature. Pressure = 1,000 - 11,000 psi, sensitivity = 0.16 AUFS, flow rate = 0.5 ml min⁻¹, chart speed = 5 mm min⁻¹, sample size = 10 μ l.

Experimental

Preparation of 1: A mixture of 2.9 g (1.0 mole) of 2-methyl glutaric acid, 4.3 g (2.0 moles) of o-phenylene diamine and 50 ml. of 4N hydrochloric acid were refluxed with good stirring for eight hours. The reaction mixture was then cooled to 0°C and neutralized with sodium carbonate. The product was collected on a filter, washed with

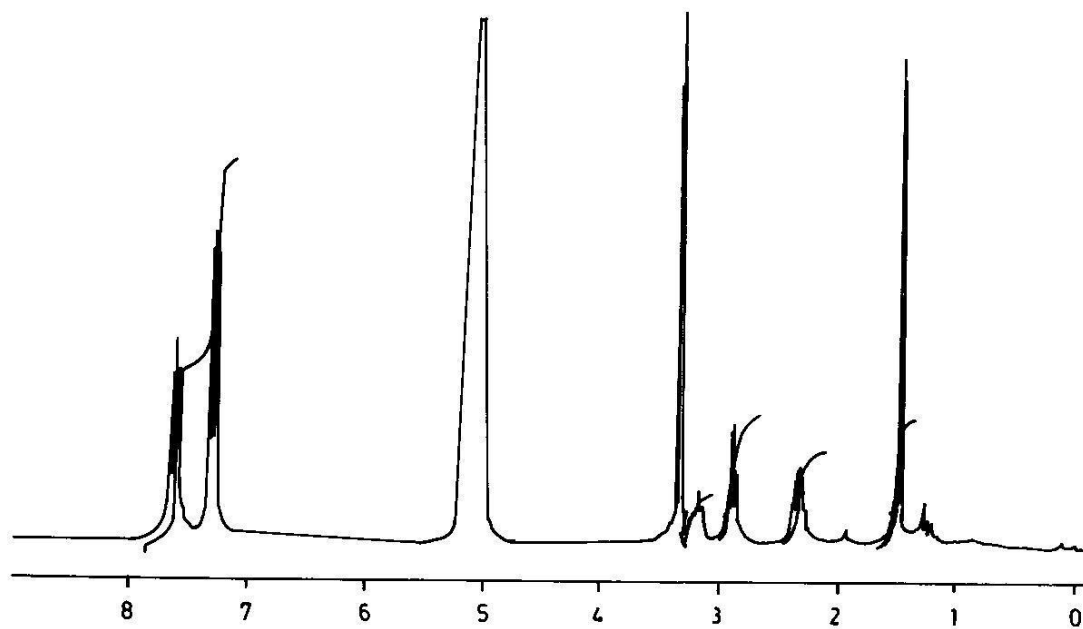


FIG. V PROTON MAGNETIC RESONANCE SPECTRUM OF 1

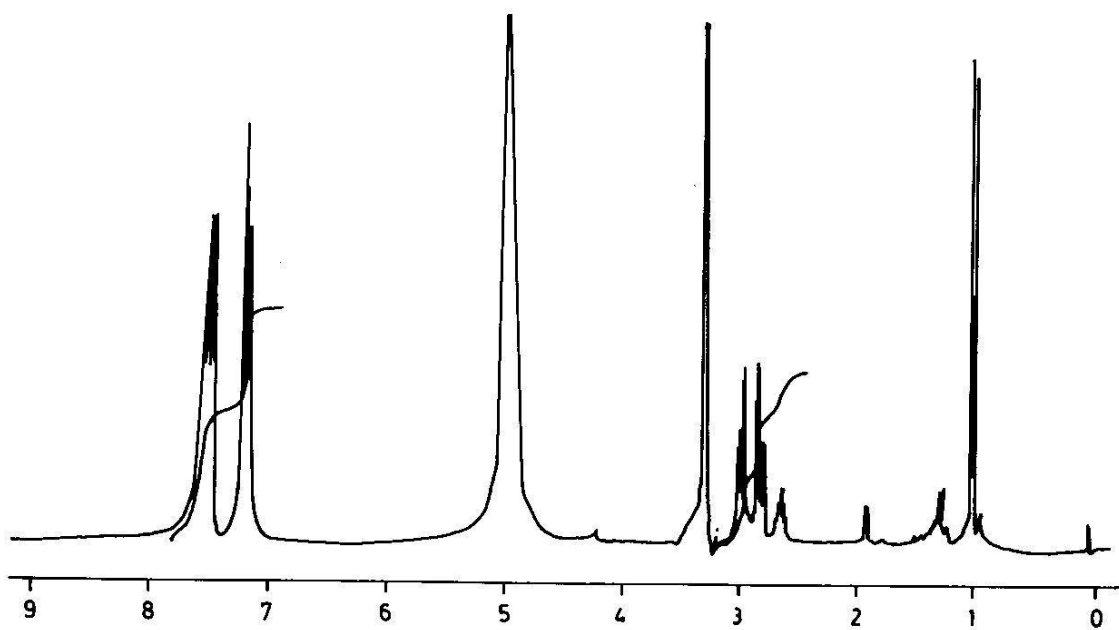
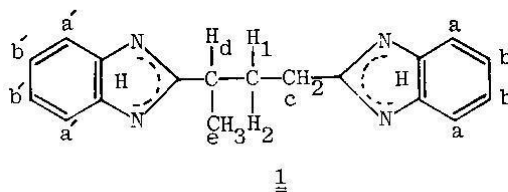


FIG. VI PROTON MAGNETIC RESONANCE SPECTRUM OF 2

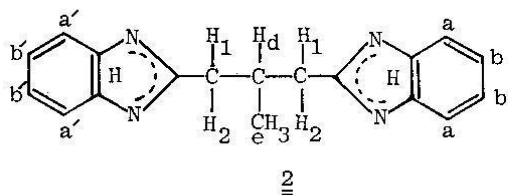
Table 4: Types of protons and proton-magnetic resonance data of 1

Proton	Chemical Shift (ppm)	Spin Pattern	Coupling Constant Hz	$W \frac{1}{2}$ (Hz)
$2H_a$	7.5	A_2B_2	-	-
$2H_b$	7.19		-	-
$2H_a^1$	7.45	A_2B_2	-	-
$2H_b^1$	7.15			
$3H_e$	1.47	d^*	$J_{e,d} = \text{ca } 1.2$	
$1H_1 + 1H_2$	2.30	Complex signal	-	-
$2H_c$	2.90	q^{**} (broad)	$J_{c,1} = 5.80$ $J_{c,2} = 8.27$	-
$1H_d$	2.64	m^{***}	-	8.98

* = doublet

** = quartet

*** = multiplet

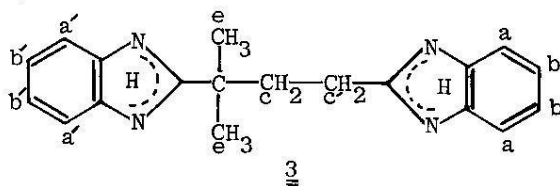
Table 5: Types of protons and proton-magnetic resonance data of 2

Protons	Chemical Shift (ppm)	Spin Pattern	Coupling Constants (Hz)	$W \frac{1}{2}$ (Hz)
$4H_a$	7.5	A_2B_2	-	-
$4H_b$	7.2	-	-	-
$3H_e$	0.98	d^*	$J_{e,d} = \text{Ca } 1.2$	-
$2H_1$	2.82	$d.d^{**}$	$J_{1,d} = 8.1$ $J_{1,2} = 14.2-$	
$2H_2$	2.98	$d.d^{**}$	$J_{2,d} = 6.3$ $J_{2,1} = 14.2$	
$1H_d$	2.64	m^{***}	-	15.2

* = doublet

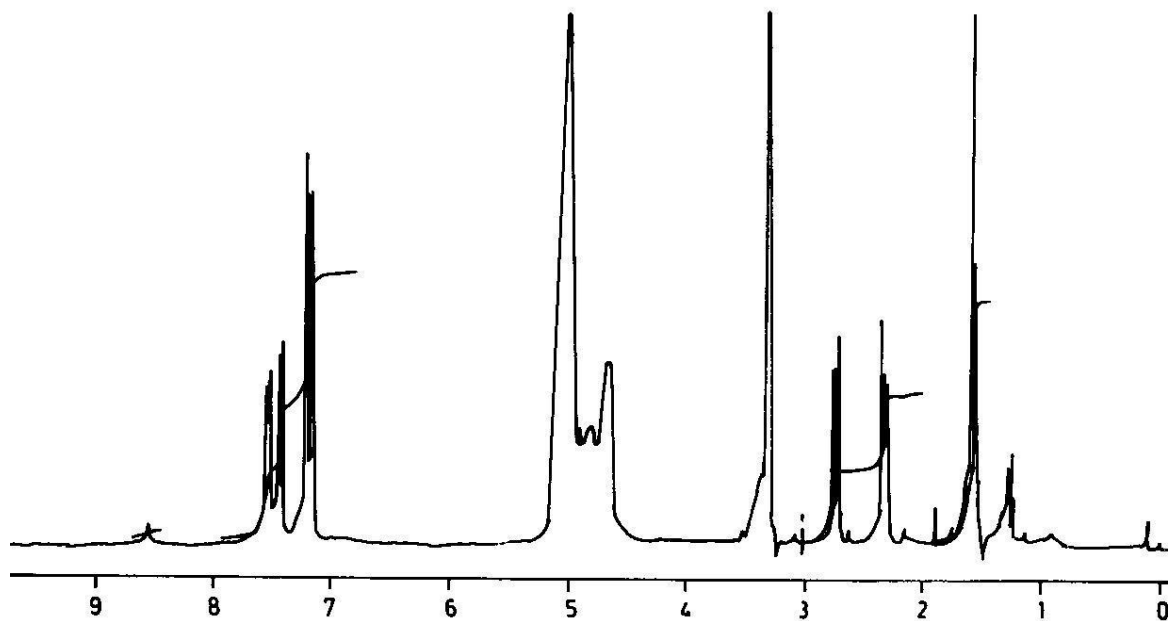
** = doublet of doublet

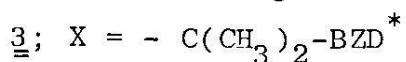
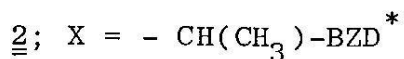
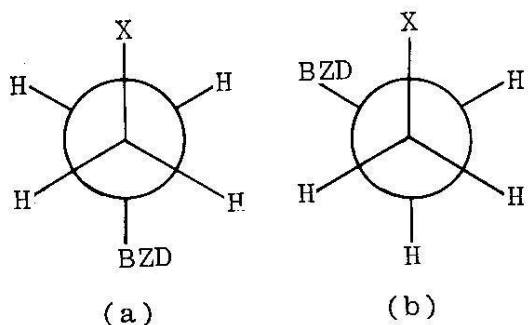
*** = multiplet

Table 6: Types of protons and proton-magnetic resonance data of 3

Protons	Chemical Shift (ppm)	Spin Pattern	Coupling Constants (Hz)	$W \frac{1}{2}$ (Hz)
$2H_a$	7.52	A_2B_2		
$2H_b$	7.19	A_2B_2		
$2H_b$	7.42	A_2B_2		
$2H_b$	7.14			
$6H_e$	1.56	*		
$2H_c$	2.31	** (splitting visible)		
$2H_c^1$	2.73	** (splitting visible)	$J_{c,c^1} = J_{c,c} = 8.5$	

* = singlet
** = triplet

FIG. VII PROTON MAGNETIC RESONANCE SPECTRUM OF 3



* = Benzimidazole nucleus

FIG.VIII

cold water and recrystallized with a mixture of methanol and water.

bis-Benzimidazoles 2 and 3 were prepared by the same procedure using 3-methyl glutaric acid (2.9 g) and 2,2-dimethyl glutaric acid (2.0 g) respectively.

Melting points and yields of these benzimidazoles are reported in Table 1.

Proton magnetic resonance spectra of 1, 2 and 3 were measured on a 300 MHz n.m.r. spectrometer in d₄-MeOH.

Chromatography

Thin layer chromatography (TLC) was carried out on 0.25 mm thick 20 x 20 cm chromatoplates of silica gel HF₂₅₄ (Fluka) with a series of solvents as recorded in Table II. Spots were made visible by fluorescence under ultraviolet light.

High performance liquid chromatography was done on 25 cm x 46 mm 1D Ultrasphere ODS (C₁₈) reversed

phase prepacked steel column using isocratic liquid chromatograph (Altex model 330 A). Column effluent was monitored with an analytical UV detector (Altex model 110 A) at 254 nm for the detection of bis-benzimidazoles. Samples were dissolved in the solvents shown in Table III and sample volumes of 10 μl were injected for analysis. Attenuation was 0.16 AUFS during all measurements. Chart speed was 5 mm min⁻¹ on an XY recorder (Kippe and Zonnen BD 40). Pressure varied from 1,000 - 1,200 psi during these measurements. All measurements were made at ambient temperature. Solvents used were of HPLC grade (Fluka). A typical chromatogram of a mixture of three bis-benzimidazoles is shown in Fig. 4. Retention times of the three bis-benzimidazoles are listed in Table III.

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