

**Preparation of New Benzimidazoles as
Potential Therapeutic Agents-IV**

MASHOODA HASAN*, FARNAZ MALIK, MARIA C.

* GARCIA ALVAREZ AND ZAHIDA MAQBOOL**
Department of Chemistry, Quaid-i-Azam University,
Islamabad, Pakistan.

** Pinstech, Nilore.

(Received 16th November, 1985, Revised 18th February, 1986)

Summary: Preparation, physical properties, chromatographic behaviour, mass-spectral fragmentation pattern and ^1H n.m.r. spectra of 4-(2-benzimidazolyl)-4-methyl pentanoic acid (3a) and 1,3-bis (2-benzimidazolyl)-2,2-dimethyl propane (4) are described.

The previous [1] paper of the series described the preparation and properties of 1,3-bis (2-benzimidazolyl)-1-methyl-propane (1), 1,3-bis-2(2-benzimidazolyl)-2-methyl propane (2) and 1,3-bis-(2-benzimidazolyl)-1,1-dimethyl propane (3). These three compounds were sent to National Institute of Health, Bethesda, U.S.A. for anti-tumor testing. Compound (3) is now to be synthesized in larger amounts in National Institute of Health, Bethesda, U.S.A. for further testing.

In view of the foregoing, it was considered worthwhile to synthesize more compounds of the series. As a result, 1,3-bis(2-benzimidazolyl)-2,2-dimethyl propane (4) has been synthesized by the reaction of 3,3-dimethylglutaric acid with o-phenylenediamine in 1:2 molar ratio in 4N hydrochloric acid. Structure determination was done on the basis of mass and ^1H - n.m.r spectral data. Percentage yield, solvent for recrystallization, melting point, and mass spectral data are

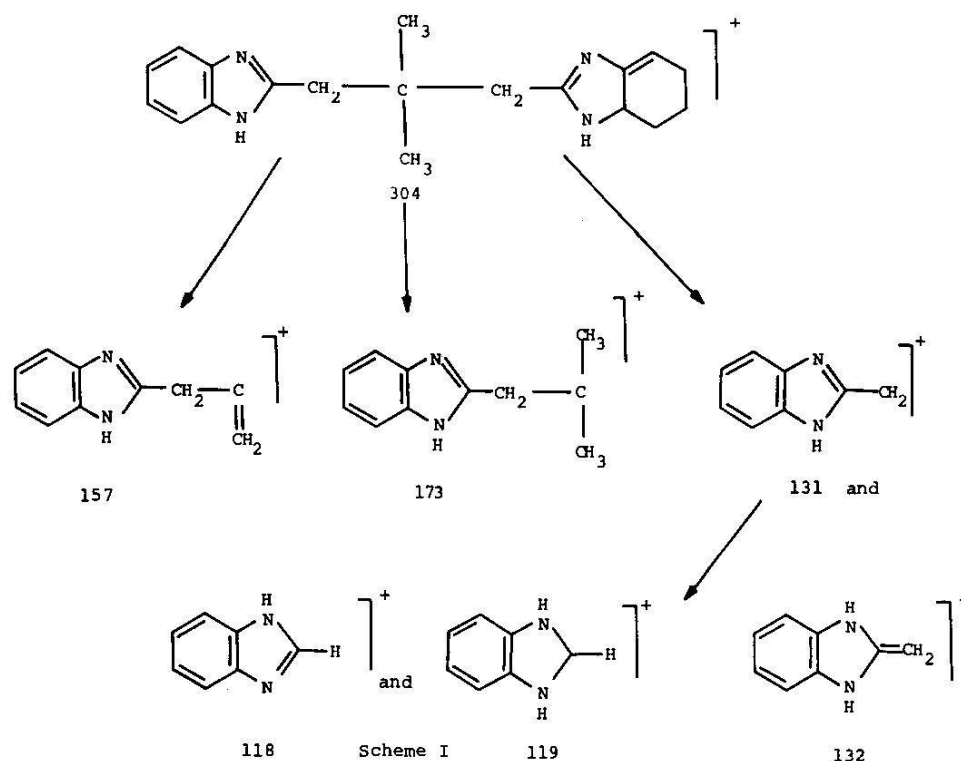
Table-I: Yield, physical properties and mass spectral data of benzimidazoles

Carboxylic acid used.	Name of Benzimidazole	M.P.°C	Solvent use for recrystallization	M.F.	%Yield	Mass Spectral data
2,2-Dimethyl-glutaric acid	4-(2-benzimidazolyl)-4-methyl pentanoic acid (3a)	218-220	H ₂ O	C ₁₃ H ₁₆ N ₂ O ₂	20%	232,204,187,171 159,145(base peak) 132,131,119,118.
3,3-Dimethyl-glutaric acid	1,3-bis(2-benzimidazolyl)-2,2-dimethyl-Propane (4)	292-293	MeOH/H ₂ O	C ₁₉ H ₂₀ N ₄	17%	304,173(base peak) 157,132,131,118,119

Table-II: TLC of Benzimidazoles on silica gel. Results are R_f values $\times 10^2$

Benzimidazole	Solvent System*						
	1	2	3	4	5	6	7
(3a)	0	37	23	50	84	52	8
(4)	16	62	15	47	7	68	43

* 1 = Acetone : Pet.ether (1:4) 2 = Acetone : Peter.ether (4:1)
 3 = Ethyl acetate 4 = Ethyl acetate: MeOH (19:1)
 5 = MeOH : H₂O (1:10) 6 = Acetone : Pet. ether (9:1)
 7 = Toluene : Ethyl acetate : Ethanol : Ammonia (60, 10, 30, 2).



shown in Table 1. R_f values in different solvents are listed in Table-II. Scheme I shows detailed mass-spectral fragmentation pattern of (4) and ^1H n.m.r. data are listed in Table-III.

Furthermore, during the preparation and purification of (3) through crystallization as described in the previous paper [1], it was noted that the

mother liquor contained another compound having lower R_f value than (3) (Table-II). Mother liquor was evaporated and the residue was recrystallized from water, yielding shining crystals of pure (3a). Percentage yield, melting points and mass spectral data are listed in Table-1. Mass spectral data shown in Scheme II suggested that the compound was a benzimidazole, rather than

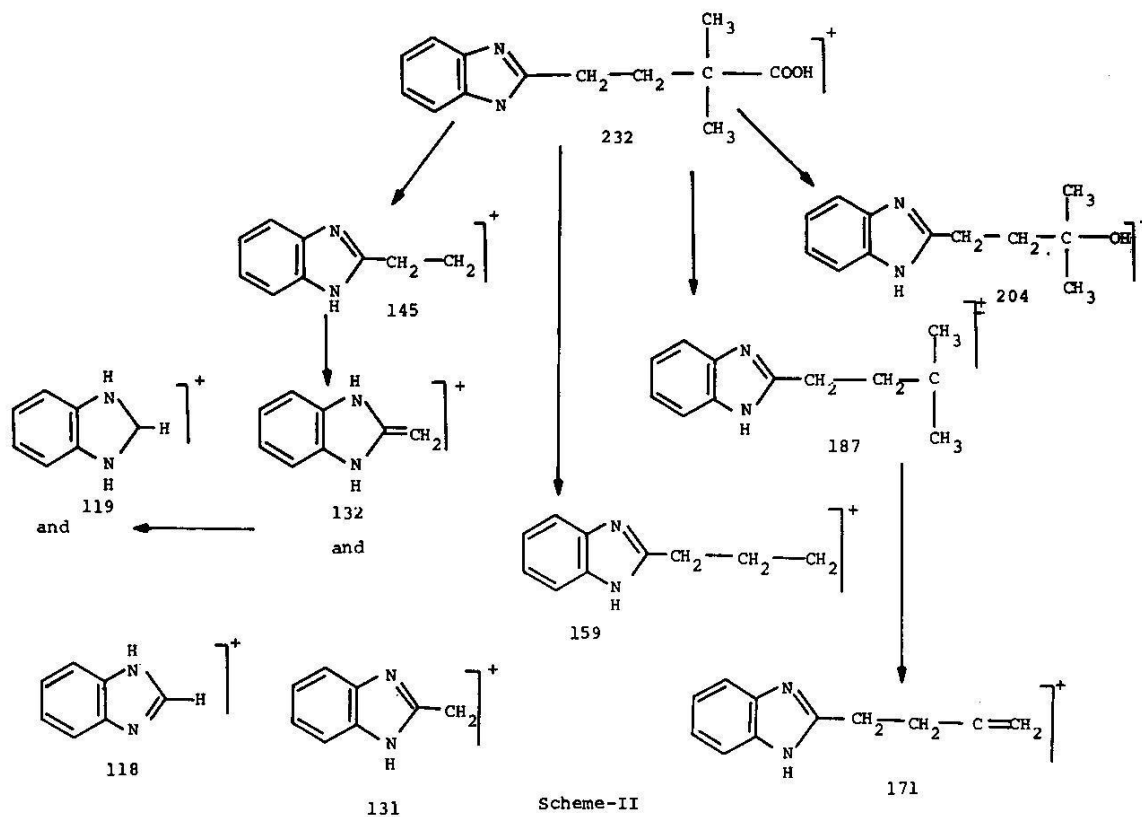
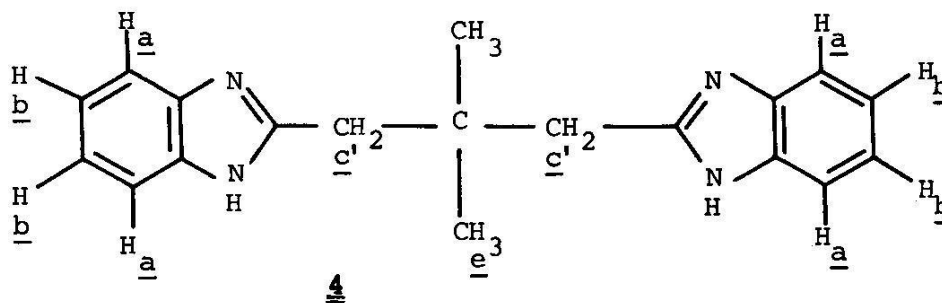
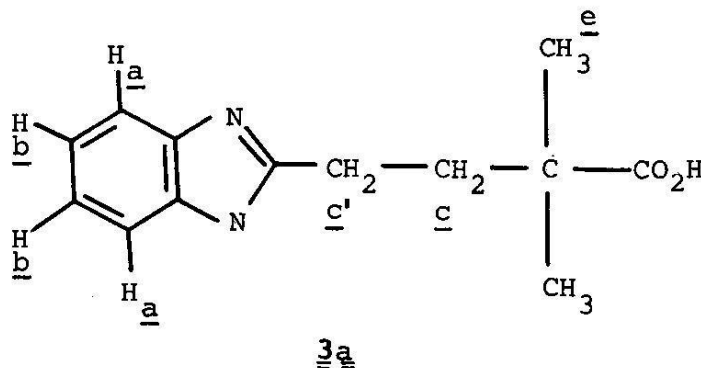


Table-III: Types of Protons and Proton Magnetic Resonance Data of (4)



Protons	Chemical shifts and peak pattern (ppm)	Coupling constants (Hz)
4H _c	2.8 (s)	
6H _e	1.15 (s)	
4H _a	7.68 (dd)	Jortho = 6.1
4H _b	7.29 (dd)	Jmeta = 3.1

Table-IV Types of Protons and Proton Magnetic Resonance Data of (3a)



Protons	Chemical Shifts and peak pattern (ppm)	Coupling constants (Hz)
2Hc	2.75 (m)	
2Hc	1.9 (m)	
6He	1.19 (s)	
2Ha	7.45 dd	Jortho = 6.1
2Hb	7.9 dd	Jmeta = 3.17

a bis-benzimidazole having a free carboxylic acid group. Presence of a free carboxylic acid group was confirmed by its solubility (with effervescence) in dilute NaHCO_3 solution. Decision between the two possible structures 4-(2-benzimidazolyl)-4-methyl pentanoic acid and 4-(2-benzimidazolyl)-2,2-dimethyl butane was made on the basis of ^1H n.m.r. data shown in Table-IV.

Methylene protons show a chemical shift of 2.75 ppm, which is identical with that exhibited by methylene protons (c) in (3) [1], which shows that methylene group carrying these

protons is directly attached to a benzimidazole nucleus. The methyl protons (e) however exhibit chemical shifts of 1.19 ppm, which is different from the same protons in (3) [1], which appear at 1.56 ppm. These results confirm that in spite of the experimental conditions chosen to prepare bis-benzimidazole (3) i.e. using dicarboxylic acid and o-phenylenediamine in 1:2 molar ratio, (3) could not be obtained in appreciable amount. The yield of (3) was the lowest of all other bis-benzimidazoles, i.e. (1) [1], (2), and (4) Table-1. This is most probably due to the steric hindrance offered by the two methyl groups present in the

vicinity of one of the carboxylic acid in 2,2-dimethyl glutaric acid to the attack of o-phenylenediamine. This is further supported by the fact that no similar beznimidazole has been detected in the mother liquors of (1), (2) and (4).

All melting points are uncorrected. ¹H n.m.r spectrum of (4) and (3a) was recorded in chloroform and dimethyl sulfoxide on 90 MHz Jeol

n.m.r. spectrometer respectively. Mass spectra of (4) and (3a) have been measured in HEJ Research Institute of Chemistry, University of Karachi.

References

1. Farzana Latif, Mashooda Hasan and Shagufta Zulifqar, *J.Chem.Soc.Pak.*, **6**, (3), 153 (1984).