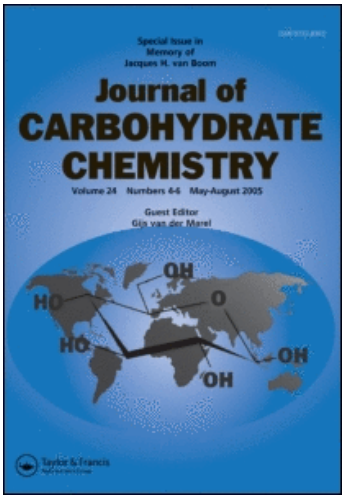

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Mass Spectra of 2-(Aldo-Polyhydroxyalkyl)-Benzimidazoles and 5,6-Dimethylbenzimidazole Analogs

Mohammed A. E. Sallam[a]; Suzan S. Saudi[a]
[a] Department of Chemistry, Faculty of Science Alexandria University, Alexandria, Egypt

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MASS SPECTRA OF 2-(ALDO-POLYHYDROXYALKYL)-BENZIMIDAZOLES AND 5,6-DIMETHYLBENZIMIDAZOLE ANALOGS

Mohammed A. E. Sallam* and Suzan S. Saudi

Department of Chemistry
Faculty of Science
Alexandria University
Alexandria, Egypt.

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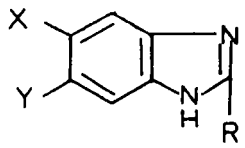
ABSTRACT

The mass spectra of a series of 2-(aldo-polyhydroxyalkyl)benzimidazoles and 5,6-dimethylbenzimidazole analogs are reported and discussed. They showed common fragmentation patterns. The most important fragmentation pathway, involves the common fragments BCH_2OH and BCHOH which were obtained by McLafferty rearrangement as the most abundant peaks in the spectra and can be used for the identification of 2-(aldo-polyhydroxyalkyl)benzimidazole analogs.

INTRODUCTION

Aldonic acids or their lactones are identified by electron-impact mass spectrometry as appropriate derivatives. The benzimidazole derivatives of carbohydrates are in general more superior to osazone derivatives for purposes of characterization. The mass spectra of benzimidazoles[1,2] and 2-alkylbenzimidazoles[3,4] show characteristic fragments which can be used for the identification of 2-(aldo-polyhydryxoalkyl)



1, X=Y=H, R=R_1=D-gluco-1,2,3,4,5-pentahydroxypentyl
2, X=Y=H, R=R_2=D-gulo-1,2,3,4,5-pentahydroxypentyl
3, X=Y=H, R=R_3=D-galacto-1,2,3,4,5-pentahydroxypentyl
4, X=Y=H, R=R_4=D-glycero-D-gulo-1,2,3,4,5,6-hexahydroxyhexyl
5, X=Y=CH_3, R=R_1
6, X=Y=CH_3, R=R_2
7, X=Y=CH_3, R=R_3
8, X=Y=CH_3, R=R_4
9, X=Y=CH_3, R=CH_2OH

analogs. In the present work the electron-impact induced fragmentation of a series of 2-(aldo-polyhydroxyalkyl) benzimidazoles and their 5,6-dimethylbenzimidazole analogs were studied. The general fragmentation behavior of these molecules is discussed.

The mass spectra of 2-(aldo-polyhydroxyalkyl)benzimidazoles 1 - 3 showed molecular ions of low intensity at m/z 268, and for the higher analog 4 at m/z 298. These compounds also showed common fragmentation patterns. The initial fragmentation represents a loss of the primary carbon atom giving M - CH_2OH fragment. Further fragmentation was shown as a gradual loss of secondary carbon atoms (Figure 1). The m/z 177 peak corresponding to (BCHOHCHOH) is formed by Y-cleavage of the polyhydroxyalkyl chain and showed relative abundance compared to the higher masses fragments (Table 1). Further fragmentation afforded a group of peaks at m/z 161, 160, 159, and 158. The peak M - H_2O characteristic for the fragmentation of alcohols, was

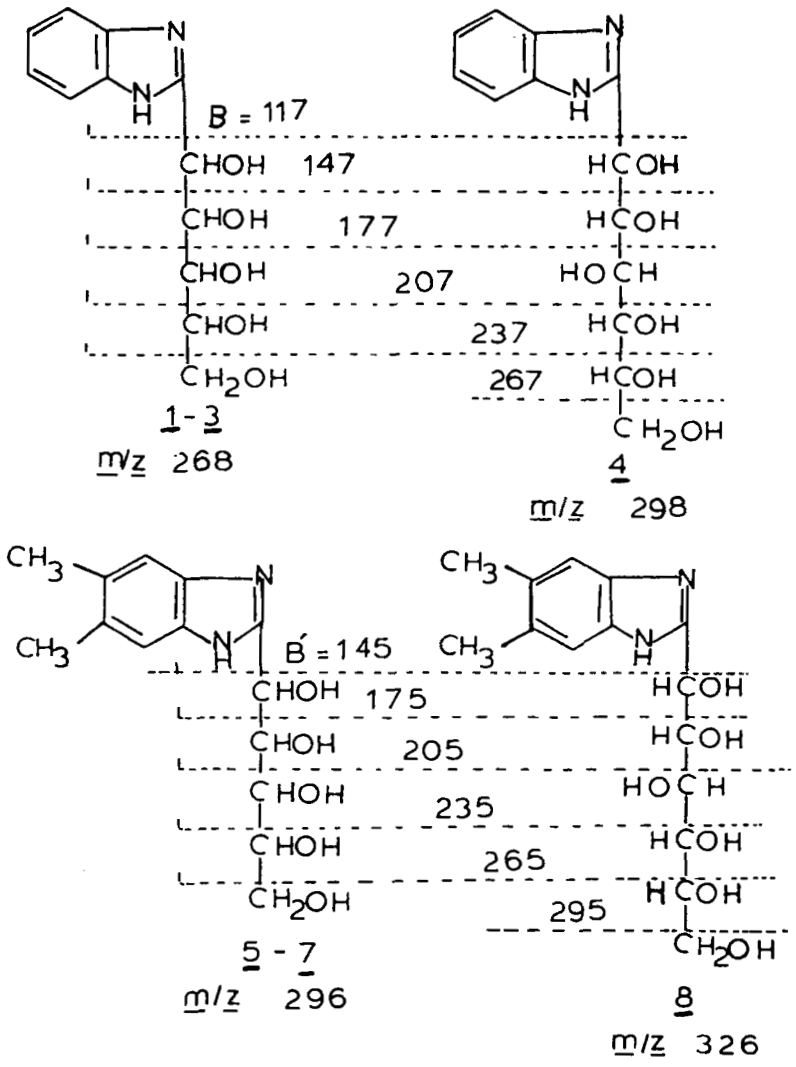


FIG. 1

TABLE 1. Mass Spectra of Compounds 1 - 4

m/z	Intensity % 1	2	3	4	Fragment
63	14	10	15	22	B - HCN - HCN
64	26	18	26	24	BH - HCN - HCN
65	30	22	28	54	BH_2 - HCN - HCN
77	6	5	7	13	Ph
90	14	9	15	16	B - HCN
91	30	20	29	35	BH - HCN
92	27	20	24	51	BH_2 - HCN
103	5	4	5	6	PhCN
104	3	2	3	5	PhCNH
117	10	6	10	5	B
118	32	21	31	37	BH
119	34	26	30	57	BH_2
130	6	4	5	2	$BCH_2OH - H_2O$
131	10	7	10	15	BCH_2 or (A)
132	6	4	6	13	BCH_3
146	40	27	40	10	BCHO
147	100	92	100	93	BCHOH
148	99	100	78	100	BCH_2OH
149	11	10	8	18	$BHCH_2OH$
158	3	2	4	1	BCHO
159	6	4	6	8	BCHCHO
160	12	7	12	5	BCHCHOH
161	15	10	13	24	
176	10	5	10	1	BCHOHCHO
177	13	8	13	15	BCHOHCHOH
207	5	3	5	5	$B(CHOH)_3$
236	1	0.4	0.4	-	M - H - CH_2OH
237	1	0.5	1	-	M - CH_2OH
250	0.1			-	M - H_2O
267	-	-	-	1	(M - CH_2OH)
268	1	0.1	1	-	M
298	-	-	-	0.02	(M)

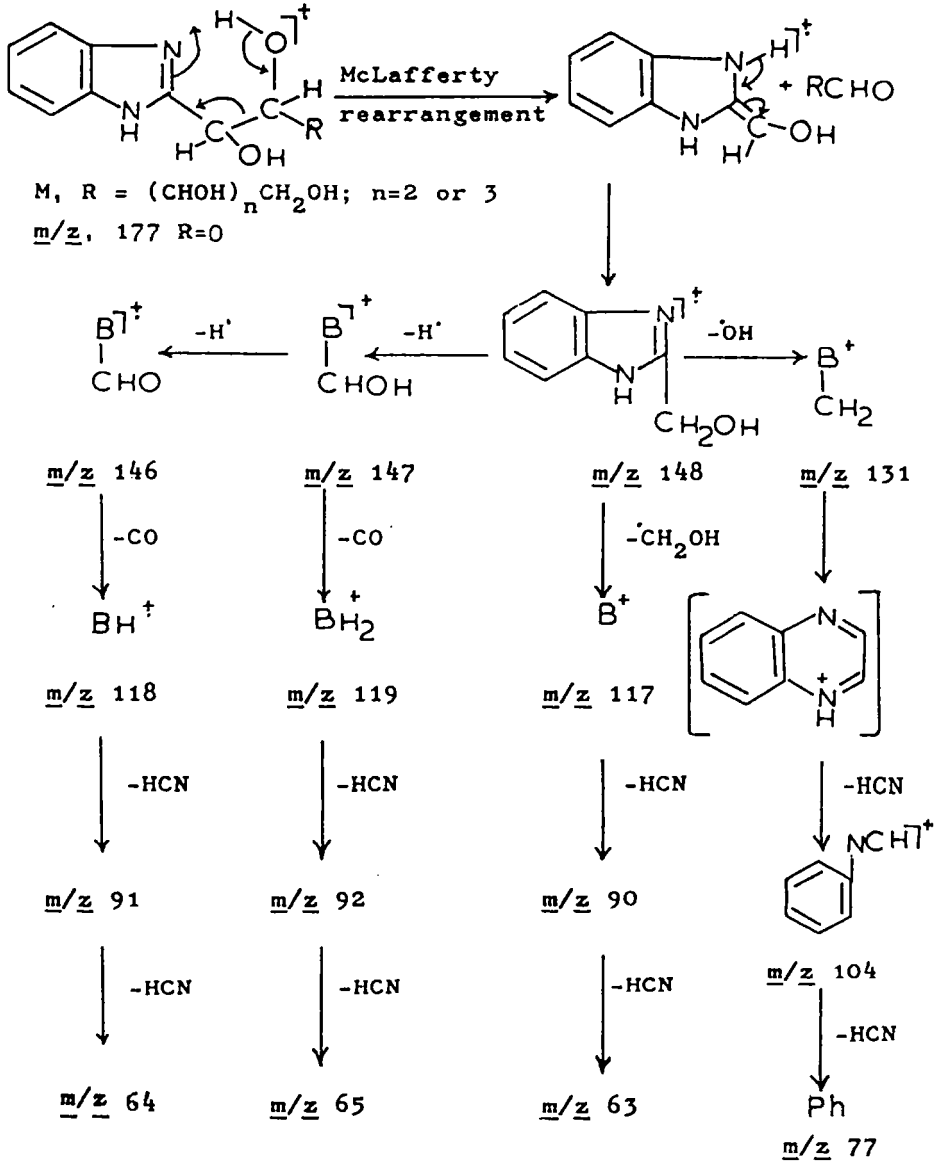
very weak or absent; only compound 1 showed low intensity peak at m/z 250. In addition, the peak M - HCN characteristic for the fragmentation of 2-alkylbenzimidazoles was absent due to the relative instability of the polyhydroxyalkyl chain compared to the base moiety. The most abundant peaks in the spectra of compounds 1 - 4 were shown at m/z 146, 147, and 148 probably corresponding to BCHO, BCHOH, and BCH_2OH, respectively. The base peaks at m/z 148 and 147 are likely formed by β-cleavage of the polyhydroxyalkyl chain by McLafferty rearrangement, either from the molecular ion M or the fragment at m/z 177 (Scheme 1). Benzimidazoles carrying long alkyl chains at position 2, produce[3,4] key fragments by McLafferty rearrangement and provide a means for the location of the alkyl side chain.[5] The peaks at m/z 148 and 147 can be used for the identification of the 2-(aldo-polyhydroxyalkyl) analogs. The peak at m/z 147 (BCHOH) is indicative of the carbon-carbon linkage between the polyhydroxyalkyl chain and the base moiety for C-nucleosides.[6]

The BCH_2 ion at m/z 131 is common for 2-alkylbenzimidazoles and represents the postulated[3,4] ring-expanded quinoxalinium ion (A) which is formed by loss of hydrogen atom from the 2-alkyl group with concomitant ring expansion of the heteroaromatic ring. In a similar manner it is formed from compounds 1 - 4 by loss of a hydroxyl group from the abundant ion BCH_2OH with concomitant ring expansion.

The peaks at m/z 119, 118, and 117 corresponding to BH_2, BH, and B are obtained by α-cleavage of the polyhydroxyalkyl chain, and offer ready means for identifying the benzimidazole nucleus. Fragmentation of the base moiety takes place by twice loss of HCN molecule.

Electron-impact mass spectra for the 2-(aldo-polyhydroxyalkyl)-5,6-dimethylbenzimidazoles 5 - 8

SCHEME 1



were very similar, confirming the fragmentation pattern for compounds 1 - 4. The molecular ions M, M + 1, and M + 2 were of low intensity for these compounds, and the initial fragmentation by loss of the primary carbon atom afforded the ion at m/z 265 for compounds 5 - 7 and 295 for 8. The fragments corresponding to loss of secondary carbon atoms were observed at m/z 295, 265, 235, 205, and 175. In general the M - H_2O peak was of low intensity. The 5,6-dimethylbenzimidazole and o-xylene M - H peaks[3,5,7] were very weak or absent; only compound 7 showed weak M - 1 peak at m/z 295. The most abundant peaks for compounds 5 - 9, were at m/z 176 and 175 (Table 2) corresponding to B'CH_2OH and B'CHOH, respectively. These fragments are formed by β-cleavage of the polyhydroxyalkyl chain by McLafferty rearrangement. 5,6-Dimethyl-2-(hydroxymethyl)benzimidazole 9, showed the molecular ion M (B'CH_2OH) at m/z 176 as the base peak, confirming the β-cleavage by McLafferty rearrangement for compounds 1 - 8. The peaks M - 1 and M - 2 corresponding to B'CHOH and B'CHO, were seen at m/z 175 and 174, respectively. The M - CH_3 peak characteristic of the fragmentatation of 5,6-dimethylbenzimidazoles, was absent for compounds 5 - 8. However, fragments corresponding to the loss of CH_3 from the base peaks B'CH_2OH and B'CHOH are assigned to m/z 161 and 160, respectively. The abundance of the peak at m/z 159 for compounds 5 - 9 may be due to the contribution of the quinoxalinium ion (A) which is formed by ring expansion of the heterocyclic ring by a way similar to that of the corresponding ion at m/z 131 for compounds 1 - 4. Fragments obtained by α-cleavage of the polyhydroxyalkyl chain and those with subsequent hydrogen transfer to the base moiety were observed at m/z 145, 146, and 147, respectively.

TABLE 2. Mass spectra of Compounds 5 - 9

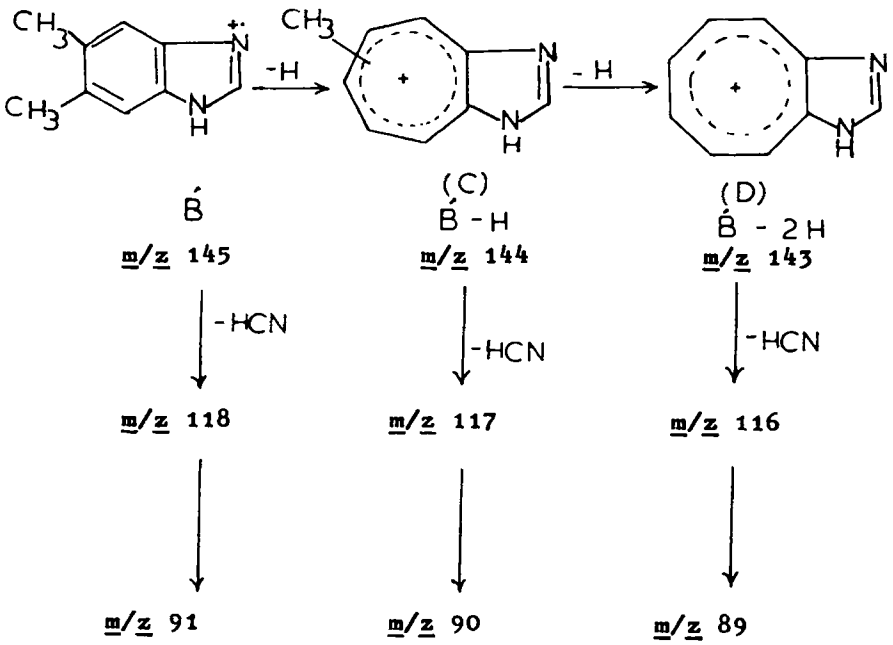
m/z	Intensity % 5	6	7	8	9	Fragment
77	9	9	16	7	14	Ph
89	4	4	6	3	9	B' - 2H - 2HCN
90	3	3	5	3	8	B' - H - 2HCN
91	12	12	20	10	22	B' - 2HCN
93	4	4	8	3	3	$B'H_2$ - 2HCN
104	4	4	8	4	7	B'H - HCN - CH_3
116	5	5	7	4	17	B' - 2H - HCN
117	5	5	7	4	14	B' - H - HCN
118	7	6	10	6	24	B' - HCN
119	3	3	5	2	4	B'H - HCN
120	6	5	10	4	4	$B'H_2$ - HCN
130	2	2	3	2	7	B' - CH_3
131	19	18	32	17	36	B'H - CH_3
132	12	11	22	9	15	$B'H_2$ - CH_3
143	3	2	4	2	26	B' - 2H
144	3	2	4	2	6	B' - H
145	17	16	27	18	16	B'
146	12	11	18	14	8	B'H
147	25	23	48	19	45	$B'H_2$
158	3	3	5	3	52	$B'CH_2OH$ - H_2O
159	14	15	21	15	24	$B'CH_2$
160	9	9	12	10	4	B'CHOH - CH_3
161	6	5	9	5	8	$B'CH_2OH$ - CH_3
174	15	15	29	16	3	B'CHO
175	75	69	100	56	41	B'CHOH
176	100	100	100	100	100	$B'CH_2OH$ (M)
177	11	11	18	12	12	$B'HCH_2OH$ (M + 1)
189	15	12	27	14		
205	11	10	28	10		B'CHOHCHOH
235	4	3	10	3		$B'(CHOH)_3$
265	1	1	2	0.1		M - CH_2OH

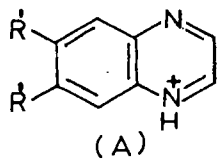
(continued)

TABLE 2- Continued

	Intensity %					
m/z	5	6	7	8	9	Fragment
278	0.1		0.2			M - H_2O
280	-	-	-	0.2		(M - CH_2OH)
295			0.1	-		M - 1
296	1	0.3	-			M
297	0.1		1			M + 1
326	-	-	-	0.2		(M)

SCHEME 2





(A)

m/z 131, R'=H

m/z 159, R'=CH_3

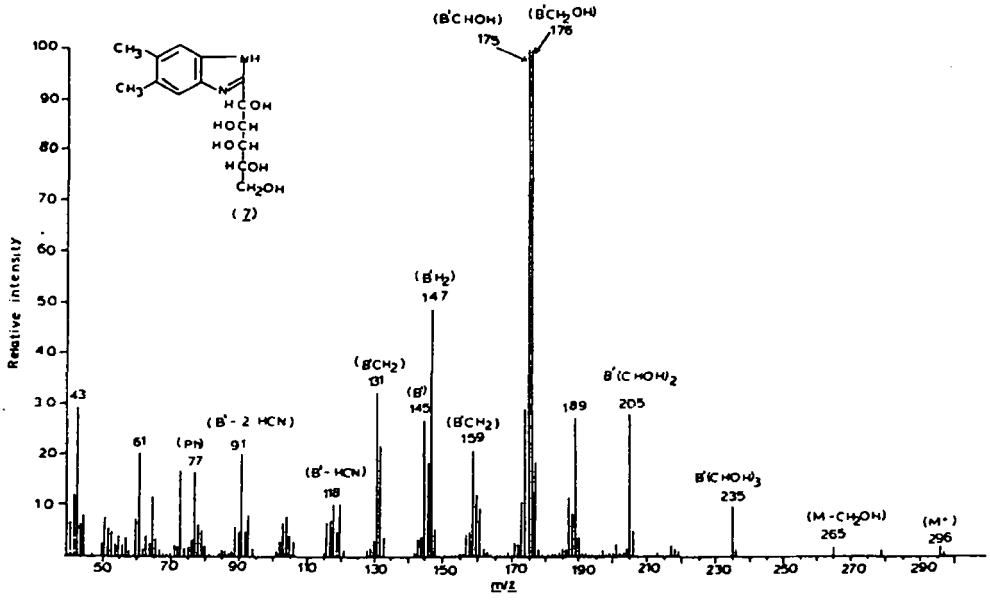


FIG. 2 Mass spectrum of 5,6-dimethyl-2-galacto-1,2,3,4,5-pentahydroxypentylbenzimidazole (7).

The mass spectra of compounds 5 - 9 showed characteristic peaks at m/z 144 and 143 corresponding to B' - H and B' - 2H which were absent for compounds 1 - 4. The existence of these peaks may be explained by the possible formation of the tropylium ions (C) and (D) by ring expansion of the carbocyclic ring of the benzimidazole nucleus (Scheme 2). The tropylium ion (C) at m/z 144 is formed by loss of hydrogen atom from one of the methyl substituents with concomitant ring expansion of the carbocyclic ring. Similar ring-expanded structures were postulated for 5(6)-methylbenzimidazole[3,8] and other heteroaromatics such as isomeric methyl quinolines.[9] Analogously, the tropylium ion (D) at m/z 143 is postulated by the expected loss of two hydrogen atoms from both methyl substituents with concomitant ring expansion.

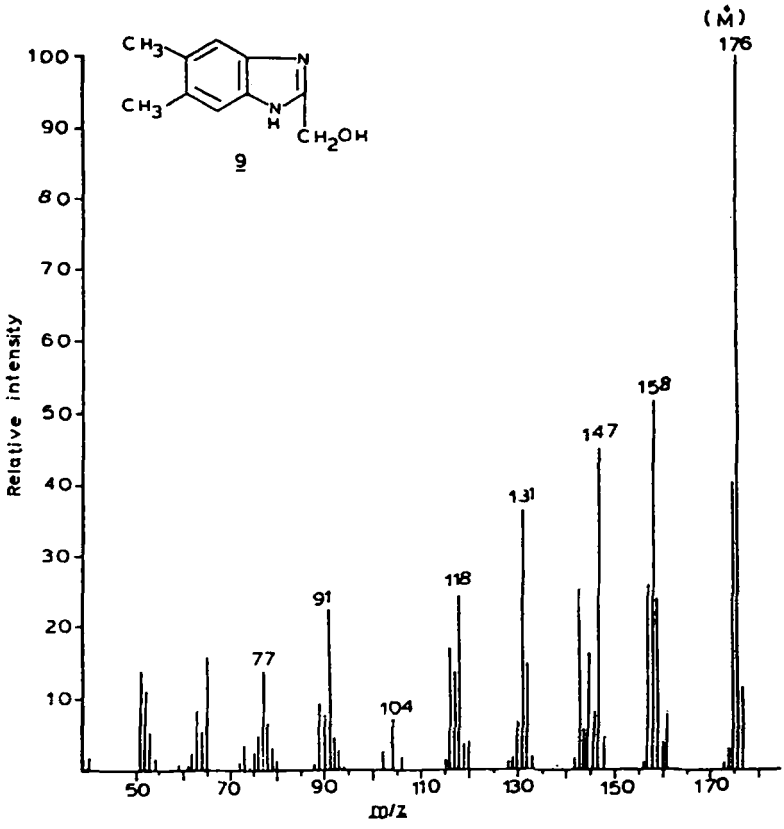


FIG. 3 Mass spectrum of 5,6-dimethyl-2-hydroxymethyl-benzimidazole (9).

In the fragmentation of the base nucleus B', two competitive mechanisms are expected; either a loss of CH_3 from the side chain of the carbocyclic ring[3] or a loss of HCN from the heterocyclic ring as that observed for benzimidazole.[5] The relative abundance of the peaks B' - CH_3, B'H - CH_3, and B'H_2 - CH_3 at m/z 130, 131, and 132, compared to the peaks B' - HCN, B'H - HCN, and B'H_2 - HCN at m/z 118, 119, and 120, supports the preferential loss of CH_3 from the carbocyclic ring. Successive loss of two molecules of HCN

from the fragments B', B' - H, B' - 2H affords the peaks at m/z 118, 117, 116 and 91,90, 89, respectively. On the other hand, loss of two molecules of HCN from the protonated base B'H and $B'H_2$ gives the peaks at m/z 119, 120, and 92, 93, respectively.

EXPERIMENTAL

Mass spectra were recorded by the direct insertion technique using Finnigan 6100 Data System Gas-Chromatograph/EI-CI spectrometer at 70 ev with a source temperature between 250 - 300° and that of the ion chamber at 200 - 220°. Compounds 1 - 4, were prepared by standard procedures, as cited in the literature.[10,11] Compounds 5 - 9 were prepared using the commercially available 4,5-dimethyl-o-phenylenediamine and the corresponding aldonolactone or aldonic acid. IR absorption spectra were recorded with a Unicum SP 1025 instrument. ^1H NMR spectra were recorded with a Varian EM-390 (90 MHz) instrument using tetramethylsilane as an internal standard. Deuteration of the OH and NH protons was carried out by addition of CD_3CO_2D to the samples. Combustion analyses were performed in the Department of Chemistry, Faculty of Science, Cairo University, Cairo, Egypt, and The Department of Chemistry, Purdue University, W. Lafayette IN. U.S.A.

2-(Aldo-polyhydroxyalkyl)-5,6-dimethylbenzimidazoles (5) - (9). 4,5-Dimethyl-o-phenylenediamine (0.01 mole), the corresponding lactone or acid; D-gluconic acid for 5, D-gulono-1,4-lactone for 6, D-galactono-1,4-lactone for 7, D-glycero-D-gulono-1,4-lactone for 8, and D-glycollic acid for 9 (0.009 mole) in water (4 mL), and concentrated hydrochloric acid (1.4 mL), were heated for 2 h on an oil bath at 135 ± 5°. The mixture was cooled and water (10 mL) was added to the warm solution. The diluted solution

TABLE 3. Microanalyses and IR Spectral Data for Compounds (5) - (9).

Compound	Crystallization solvent	M.P. (degrees)	Molecular formula	Calculated (%)			Found (%)			ν_{max}^{KBr} NH,OH
				C	H	N	C	H	N	
5	dil. EtOH	197-200	$C_{14}H_{20}N_2O_5$	56.8	6.8	9.5	57.0	6.9	9.6	3420-3220
6	water	158-160	$C_{14}H_{20}N_2O_5$	56.8	6.8	9.5	57.0	6.9	9.5	3440-3100
7	dil. EtOH	260-262	$C_{14}H_{20}N_2O_5$	56.8	6.8	9.5	56.8	6.9	9.1	3420-3300
8	dil. EtOH	209-210	$C_{15}H_{22}N_2O_6$	55.2	6.8	8.6	55.4	7.0	8.4	3420-3280
9	dil. MeOH	262-264	$C_{10}H_{12}N_2O$	68.2	6.9	15.9	68.3	6.9	16.0	3160-2640

TABLE 4. Chemical shifts (δ) and first-order coupling constants (J Hz) for Compounds (1) - (9) at 90 MHz in $(CD_3)_2SO$.

Compound	5,6-CH_3	2-polyhydroxyalkyl group H-2' - H-5' + OH	H-1'	OH-1'	Benzimidazole group H-5,6	H-4,7	NH
1		4.18 - 4.90m	3.82d $J_{1',2'}$ 6	5.73d J 7	7.00 - 7.22m	7.34 - 7.62m	12.20bs
2		3.17 - 5.00m	4.92d $J_{1',2'}$ 6	5.65m	6.98 - 7.23m	7.30 - 7.70m	12.19bs
3		3.20 - 5.00m	4.82d $J_{1',2'}$ 7	5.77d J 5	6.44 - 7.20m	7.33 - 7.60m	12.20bs
4		3.00 - 5.00m	4.80d $J_{1',2'}$ 7	5.78d J 6	6.97 - 7.20m	7.35 - 7.60m	12.20bs
5	2.30s	3.00 - 6.00m	4.80s	5.47s		7.23s	11.80bs
6	2.30s	3.00 - 5.80m	4.77d $J_{1',2'}$ 7	5.64d J 6		7.23s	11.85bs
7	2.30	3.10 - 5.90m	4.81d $J_{1',2'}$ 6	5.76d J 6		7.23s	11.80bs
8	2.30s	3.30 - 5.18m	4.92d $J_{1',2'}$ 6	5.84d J 7		7.27s	11.96bs
9	2.30s	4.58d (CH_2) $J_{1',OH}$ 7		5.48t $J_{1',1''}$ 12		7.23s	11.91bs

was treated with charcoal, filtered, the resultant mixture and filtrate made alkaline with ammonium hydroxide. The precipitate obtained was removed by filtration, washed with cold water, dried, and recrystallized from the appropriate solvent (Table 3). For ^{1}H NMR spectral data for compounds 1 - 9, see Table 4.

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