Synthesis and Mass-Spectral Studies of New Benzimidazoles

M.AMJAD,FARZANA LATIF,MASHOODA HASAN*
AND NAEEMA KHAN
Department of Chemistry,
Quaid-i-Azam University,
Islamabad, Pakistan.

(Received 27th October,1983)

Summary: Synthesis, chromatographic behaviour and mass spectral fragmentation pattern of some 2-substituted 4/5-nitrobenzimidazoles are described. The mass-spectral data of these benzimidazoles, in conjunction with mass-spectral data obtained for corresponding 2-substituted benzimidazoles having no nitrosubstituent in benzene ring, show that fragments at m/e 103, 91, 90, 64 and 63 are diagnostic for benzimidazole nucleus.

Introduction

In view of the interesting pharmacological properties of nitro derivatives of certain alkaloidal bases [1,2] and hypertensive and hypotensive activities [3] of certain dinitro-substituted amino-benzimidazoles, it was considered of interest to extend these studies to mono-nitro benzimidazoles. Thus, the programme of the synthesis of differently substituted mono-nitro benzimidazoles was directed to the synthesis of six new 2-substituted 4/5-nitro-benzimidazoles (6-11) (Table 1).

Compounds (7) and (8) were prepared by condensing different γ-lactones with 4-nitro-o-phenylenediamine in the presence of 4N hydrochloric acid. For the preparation of compounds (9-11) substituted acetic acids were used in place of γ-lactones. However, 3-nitro-o-phenylenediamine was condensed with γ-butyrolactone under similar conditions for the preparation of compound (6). Structural elucidation was done by mass-spectrometric analysis. Yields and physical properties of these compounds are shown in Table 1.

A study of mass-spectral fragmentation of benzimidazoles (6-11), which is shown in Table II and Figure 1, reveals that fragmentation occurs through six different modes. Mode A represents the fragmentation of side chain without loss of nitro-group. Mode B is the loss of nitro-group from molecular ion, and is present only in 10 and 11 where side chains are small. Mode C represents the loss of nitro-group from different fragments. Mode D is the enlargement of imidazole ring after the loss of nitro-group, whereas mode E is the contraction of the same ring. Mode F is cleavage of imidazole ring.

Benzimidazoles (6-9) show peaks at m/e 177 (base peak) and at m/e 311, showing a possibility of intramolecular hydrogen transfer [4] through a cyclic transition state. These peaks are not present in the spectra of 10 and 11 where the side chains are small and intramolecular hydrogen transfer through cyclic tranistion state is not possible.

Table 1: Physical Data of Nitrobenzimidazoles

No.	Name of the Benzimidazole	Structure of the side chain at position 2	Yield %	MF	Mol. Wt.	Solubility	m.p. °C/* solvent for cryst	Colour	R_f TLC (Ethyl-acetate)
(6)	4-Nitro-2(3-hydroxypropyl) -benzimidazole	$-CH_2CH_2-CH_2-OH$	33	$C_{10}H_{11}N_3O_3$	221	MeOH, acetone	140/ acetone	dark brown	0.55
(7)	5-Nitro-2(3-hydroxypropyl) -benzimidazole	$-CH_2-CH_2CH_2-OH$	50	$C_{10}H_{11}N_3O_3$	221	MeOH, acetone, ethanol	159-60/ benzene	Colour-less	0.16
(8)	5-Nitro-2(3-butyl)-benzi-m.dazole	$-CH_2-CH_2-CH(OH)CH_3$	40	$C_{11}H_{13}N_3O_3$	235	MeOH, acetone	153-4/ H_2O	Pale yellow	0.26
(9)	5-Nitro-2-ethoxy -methyl benzimi-dazole.	$-CH_2OC_2H_5$	30	$C_{10}H_{11}N_3O_3$	221	MeOH, EtOH, acetone	91/H_2O	Colour-less	0.74
(10)	5-Nitro-2(chloro -methyl)benzi-midazole	$-CH_2Cl$	45	$C_8H_6N_3O_2Cl$	221	MeOH, acetone	174-5/ H_2O	Pale yellow	0.53
(11)	5-Nitro-2(diflou -romethyl) benzimidazole	$-CHF_2$	56	$C_8H_5N_3O_2F_2$	213	MeOH, EtOH, acetone	177-8/ H_2O	Colour-less	0.62

*All melting points have been recorded in open capillaries on Gallenkamp melting point apparatus, and are uncorrected.

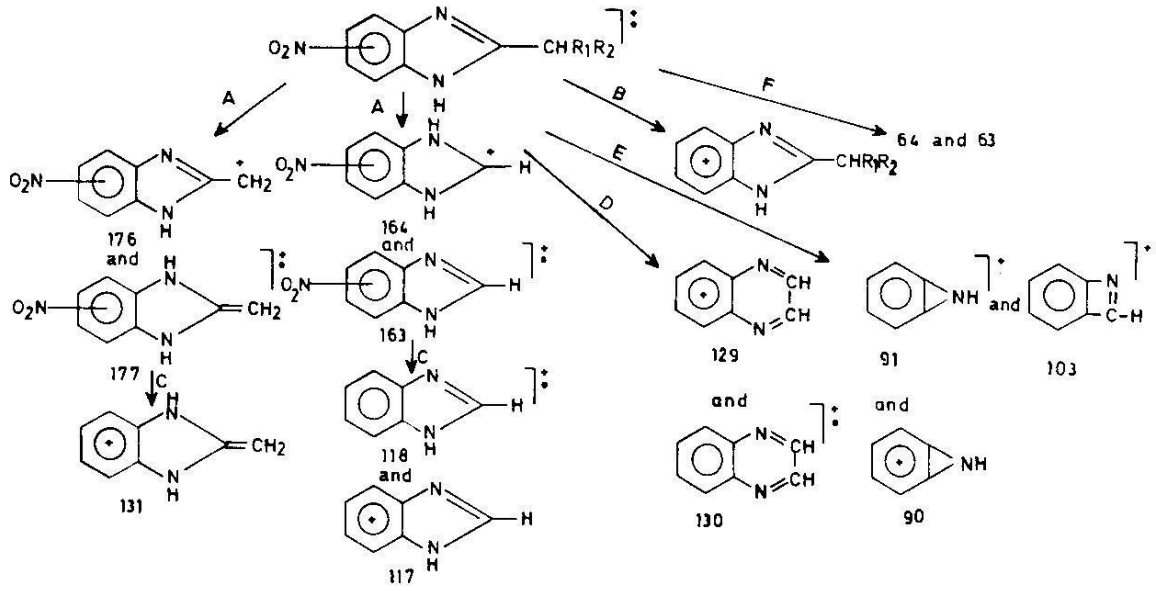

Fig.1: Modes of Fragmentation of Nitrobenzimidazoles and structures of some important fragments

Table-2 : Mass Spectral Data of Nitrobenzimidazoles

Compound	M^+	Mode A	Mode B	Mode C	Mode D	Mode E	Mode F
(6)	221	191,190 **177**	-	131,118	130,129	91,90	103,64, 63
(7)	221	191,190, **177**		131,118	130,129	90	103,64, 63
(8)	235	220,202, 191,190, **177**	-	131,118	130,129	90	103,64 63
(9)	221	192,**177**	-	131,118	130,129	91,90	103,64, 63
(10)	211 and 211+2	163	**176**	130,118	130,129	90	103,64, 63
(11)	**213**	155	167	117	-	90	103,64, 63

N.B. Base peaks have been underlined.

Fragments at m/e 130 and 129 are visible in (6-10) and are absent from the spectrum of (11), where their formation is not possible due to the non-availability of enough hydrogens in the molecule.

Characteristic peaks for benzimidazole nucleus are visible at m/e 103, 91, 90, 64 and 63 in all the spectra, and are diagnostic for benzimidazole nucleus, since these peaks are also present in corresponding benzimidazoles without nitro-group in benzene ring, synthesized in our laboratory. High resolution mass-spectral measurements, carried out by Dr.J. van Thuijl, Department of Chemistry, State University, Leiden, The Netherlands, on 2-ethoxy-methylbenzimidazole revealed the composition of the fragment at m/e 103 as C_7H_5N with an accurate mass of 103.0430. The structure of this fragment is shown in Fig.1.

Experimental

Preparation of 6: 2.0 ml (0.025 mole) of freshly distilled γ-butyrolactone was refluxed with 3.0 g. of 3-nitro-o-phenylenediamine in 100 ml of 4N hydrochloric acid for 10 hours. The dark red solution was cooled to O°C and then treated with excess of sodium carbonate. The precipitated crude product was separated, washed with cold water and purified by preparative thin-layer chromatography on silica-gel G and was recrystallized from acetone yielding dark brown needles in 33% yield (2.0 g), melting at 140°C. R_f was found to be 0.55 on thin-layer chromatography using silica-gel as adsorbent and ethylacetate as solvent.

Similarly compounds (7),(8), (9), (10) and (11) have been synthesized by refluxing appropriate γ-butyrolactone/ γ-methyl-γ-butyrolactone/ ethoxy acetic acid/chloroacetic acid/ difluoroacetic acid with 4-nitro-o-phenylenediamine in 100 ml of 4N hydrochloric acid for 8 hours. The compounds (7-11) were worked up and purified similarly as described for compound 6. The yields and physical data are cited in Table 1.

Mass spectra of the synthesized compounds were measured by H.E.J. Research Institute of Chemistry, University of Karachi. The project was financed by the University Research Fund.

In addition to mass-spectral studies, efforts are being made to arrange for the testing of the biological activities of the synthesized compounds in view of getting some newer therapeutic agents.

References

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