

1-1-2000

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MASHOODA HASAN

FARZANA SHAHEEN

UZMA YUNUS

SHAZIA MUNIR

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Preparation of Optically Active Amino Acid Derivatives of Some Methylated 5-Amino-Azaheterocycles

Mashooda HASAN, Farzana SHAHEEN, Uzma YUNUS and Shazia MUNIR
*Department of Chemistry, Quaid-i-Azam University,
Islamabad-PAKISTAN*

Received 23.10.1998

The present paper describes the reduction of 1-methyl-5-nitro-benzimidazoles (**1A**, **2A**) and 1,3-dimethyl-2H-5-nitro-benzimidazol-2-one (**3**) to 5-aminobenzimidazoles (**4A**, **5A**) and 1,3-dimethyl-2H-5-amino-benzimidazol-2-one (**6**) respectively with hydrazine hydrate in absolute ethanol in the presence of graphite. Compounds **5A** and **6** were converted to 2-ethyl-5-(phthaloyl-L-phenylalanyl)amino-1-methylbenzimidazole (**7**) and 1,3-dimethyl-5-(phthaloyl-L-phenylalanyl)aminobenzimidazol-2-one (**8**). Characterization of the synthesized compounds was done with the help of mass spectrometry and ¹H NMR spectroscopic studies. Optical activity of the amino acid derivatives **7** and **8** was also recorded.

Introduction

Since numerous benzimidazole¹ and benzimidazolone² derivatives have found use as valuable pharmaceuticals, it was considered worthwhile to prepare new compounds by coupling these nuclei with amino acids. Such coupled derivatives are expected to exhibit novel and interesting pharmacological activities. For this purpose, methylated benzimidazoles and benzimidazolone having a nitro-substituent in their benzene ring which had previously been prepared³ by our research group working on the methylation of benzimidazoles were considered suitable starting materials. The plan was to reduce the nitro group present in these compounds to an amino group, and to couple the 5-amino-substituted heterocycles with a suitably protected amino acid derivative to yield the target molecules.

Results and Discussion

The first step in the present work was to reduce the 5-nitro-azaheterocycles 2H- (**1A**), 2-ethyl- (**2A**) 5-nitro-1-methylbenzimidazoles and 1,3-dimethyl-2H-5-nitro-benzimidazol-2-one (**3**) to corresponding 5-amino compounds, i.e. 5-amino-2H- (**4A**), 5-amino-2-ethyl- (**5A**) 1-methylbenzimidazoles and 5-amino-1,3-dimethyl-2H-benzimidazol-2-one (**6**).

The reduction of 5-nitro compounds **1A**, **2A** and **3** to respective 5-amino compounds **4A**, **5A** and **6** was carried out using hydrazine hydrate/graphite in absolute ethanol. This method gave pure amino

compounds in high yield (>90%) and was also found to be selective because compound **3** was reduced to compound **6** without affecting the C=O group (Figure 1). The characterization of the products was done with the help of ^1H NMR and mass spectral studies.

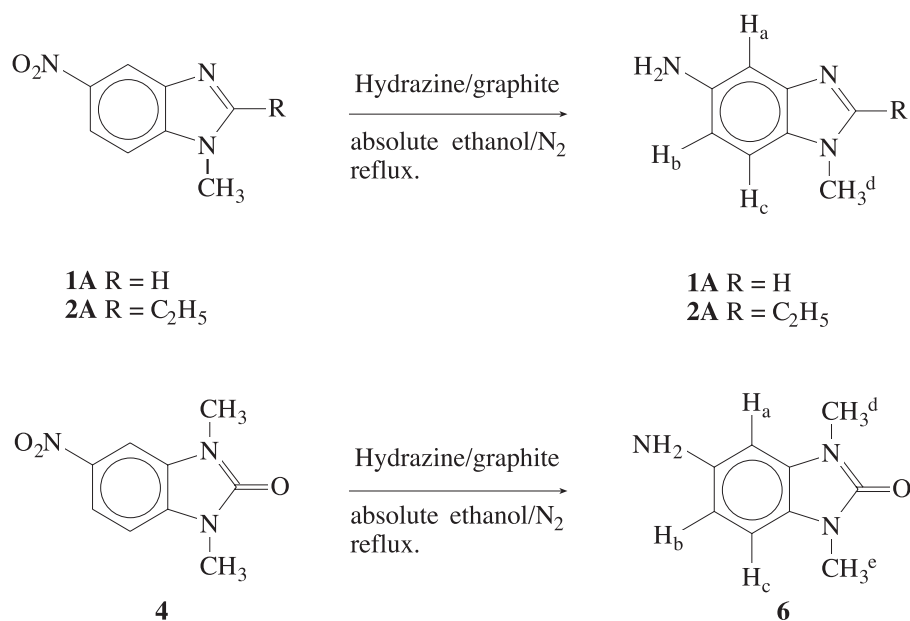


Figure 1. Reduction of methyl nitrobenzimidazoles and 1,3-dimethyl nitrobenzimidazol-2-one.

When the quantity of reducing agent and solvent was used in the same proportion as given in the literature⁴, only 50% reaction took place in two hours. The reflux time had to be increased from two hours to ten hours and the quantity of hydrazine and graphite was doubled in order to complete the reduction. Interesting results were obtained when a mixture of **1A**, its 6-nitro-isomer **1B** and **3** were subjected to reduction using the method described above. It was found that the complete reduction to amino compounds **4A**, **4B** and **6** required only four hours. Similarly a mixture of **2A**, its 6-nitro-isomer **2B**, and **3** could be completely reduced to a mixture of corresponding amino compounds **5A**, **5B** and **6** in six hours. When compounds **1A**, **2A** and **3** were separately reduced, complete reduction in each case took more than ten hours. It seems that these compounds are assisting each other in the process of reduction.

Methylation of 2H- and 2-ethyl 5-nitro-benzimidazoles separately as described in our earlier paper³ with methyl iodide in the presence of anhydrous potassium carbonate using anhydrous dimethylformamide as the solvent led to the formation of a mixture of corresponding 5- and 6-nitro-methylbenzimidazoles **1A**, **1B** and **2A**, **2B** respectively. In each case a third compound, 1,3-dimethyl-2H-5-nitro-benzimidazol-2-one (**3**) was also formed. The three compounds in each case were first separated and then subjected to reduction as described. Keeping in mind the consistent results described in the preceding para it seems a better idea in terms of time to first reduce the mixture of nitro compounds obtained through the synthesis and then to separate and purify the amino compounds so obtained.

Mass fragmentation pattern of **4A** and **5A** shown in Figures 2 and 3 respectively show similarities. Data are listed in the experimental also. Molecular ion peaks are visible in both the spectra. The molecular ion I in **5A** loses a $-\text{CH}_3$ radical to produce a peak at $m/z=160$ (fragment VII) and a C_2H_5 radical to give a peak at $m/z=146$ (fragment VIII). Loss of the C_2H_4 molecule from the molecular ion in **5A** gave fragment

I at $m/z=147$. Further fragmentation of I then led to II-VI as shown in Figure 3. It is interesting to note that the mass spectral fragmentation pattern of **4A** shown in Figure 2 which starts with the formation of the molecular ion at $m/z=147$, is exactly identical to the fragmentation of the fragment II at $m/z=147$ in **5A**.

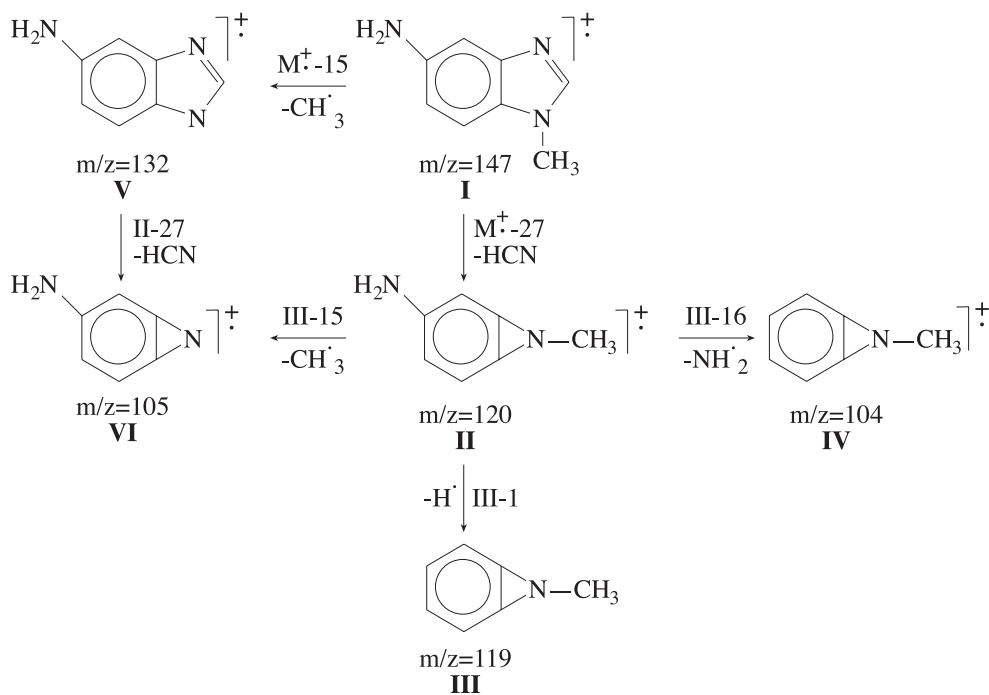


Figure 2. Mass fragmentation pattern of **4A**.

The 1H NMR spectral data of compounds **4A** and **5A** are given in the experimental section. In both these spectra, H_a and H_b are shifted upfield due to the enhanced mesomeric effect of NH_2 at ortho position, whereas H_c resonated at the lower field of all three aromatic protons. The proton H_c showed a doublet whereas H_b exhibited a doublet of doublet. A singlet at $\delta=3.75$ was due to $N-CH_3$ protons in **4A** and at $\delta=3.6$ in **5A**. A singlet at $\delta=7.71$ in **4A** is assigned to H_e . A quartet at $\delta=2.18$ in **5A** is due to H_e and H_f showed a triplet at $\delta=1.40$.

The mass fragmentation pattern of compound **6** is given in Figure 4. Molecular ion gave base peak at $m/z=177$ which corresponded to its molecular weight. Fragments II, III and IV were formed due to loss of CH_3 radical, the CO and $Me-N=C=O$ molecules from the molecular ion respectively. Fragment V was the result of the loss of CH_3 radical from fragment III and fragment VI was through the loss of CH_3 from fragment IV.

1H NMR spectral data of **6** is given in the experimental section. Three sets of peaks were visible in the aromatic region. Proton H_c appeared as a doublet at the lowest field at $\delta=6.73$ and exhibited an ortho coupling with H_b . The electron donating effect of NH_2 group was more at ortho position which resulted in H_a and H_b being shifted towards a higher field compared with H_c . The proton H_b showed a doublet of doublet due to ortho and meta coupling with H_c and H_a respectively at $\delta=6.43$, whereas H_a appears as a doublet at $\delta=6.35$. The two methyl groups d and e appeared as singlets at $\delta=3.35$ and 3.34 respectively.

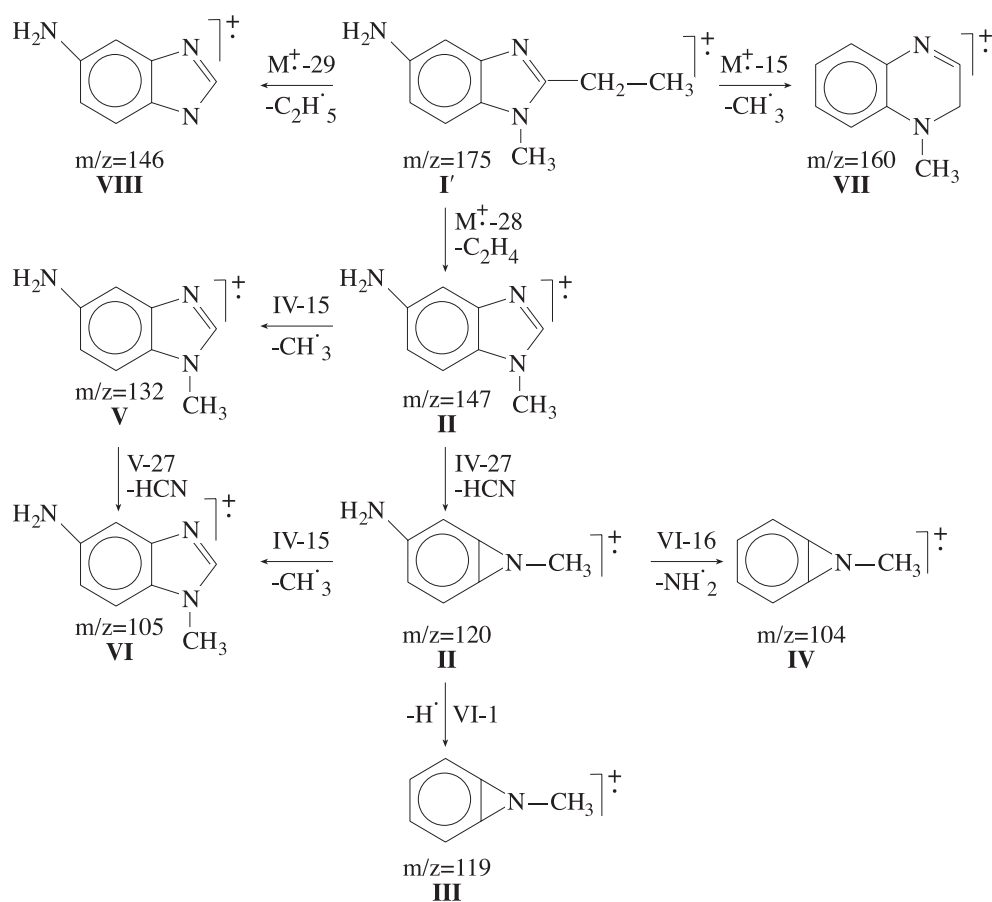


Figure 3. Mass fragmentation pattern of 5A.

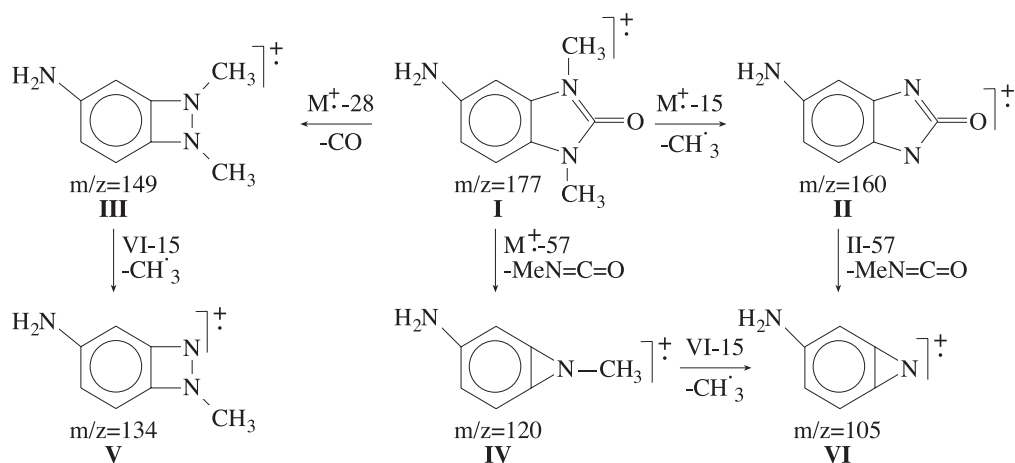


Figure 4. Mass fragmentation pattern of 6.

The next step in the synthesis of optically active amino acid derivatives was to couple the 5-amino-substituted heterocycles **4A**, **5A** and **6** separately with phthaloyl-L-phenylalanyl chloride.

The phthaloyl-L-phenylalanyl chloride was prepared as described in the literature^{5a} and was coupled^{5b} separately with **4A**, **5A** and **6** (Figures 5 and 6). Coupling of **5A** and **6** led to the formation of the desi-

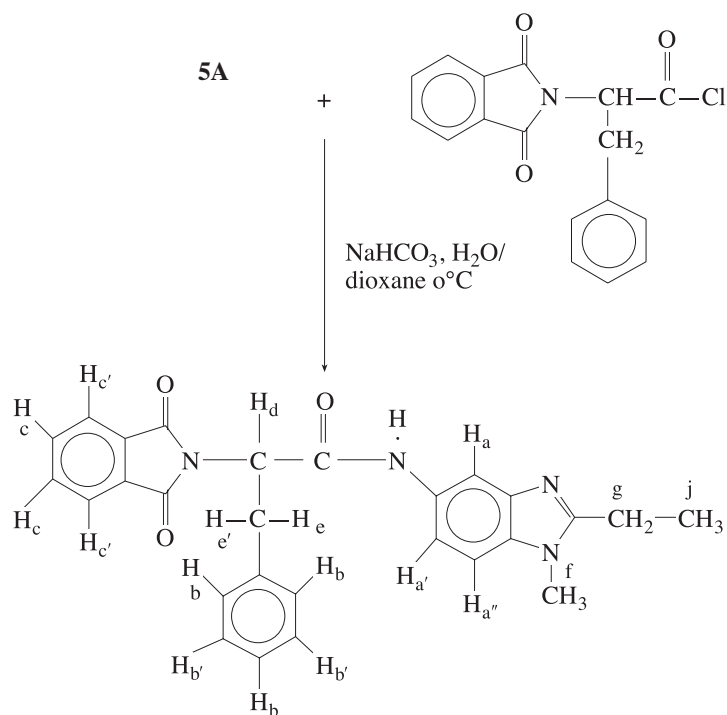


Figure 5. Preparation of 7.

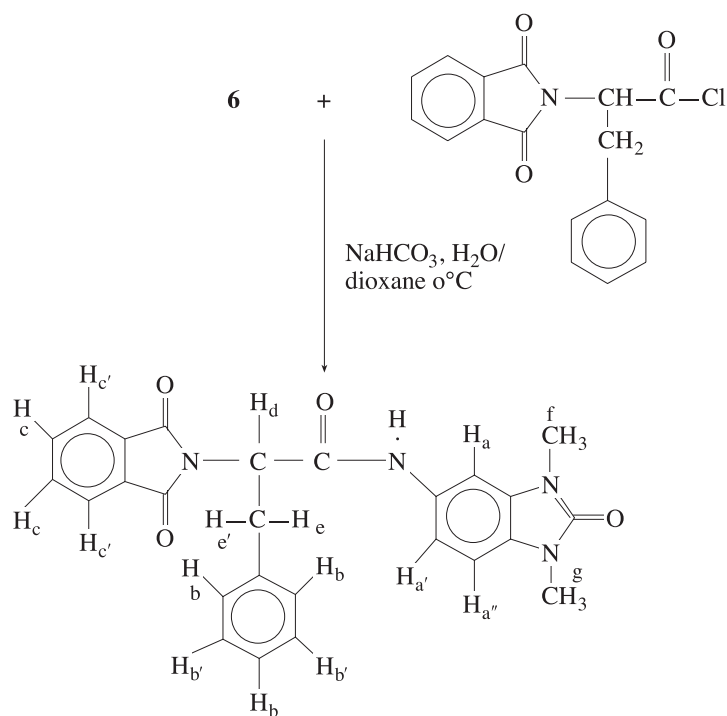


Figure 6. Preparation of 8.

red compounds 2-ethyl-5-(phthaloyl-L-phenylalanyl)amino-1-methyl-1-benzimidazole (7) and 1,3-dimethyl-5-(phthaloyl-L-phenylalanyl)amino-2H-benzimidazol-2-one (8) respectively in good yield. After recrystallization their melting points and specific rotation were recorded. Compound 4A failed to give the coupled

product with the acid chloride of phthaloyl-L-phenylalanine. Both compounds **7** and **8** showed negative rotation. The values of specific rotation are given in the experimental. The characterization of **7** and **8** was done with the help of mass and ^1H NMR spectra.

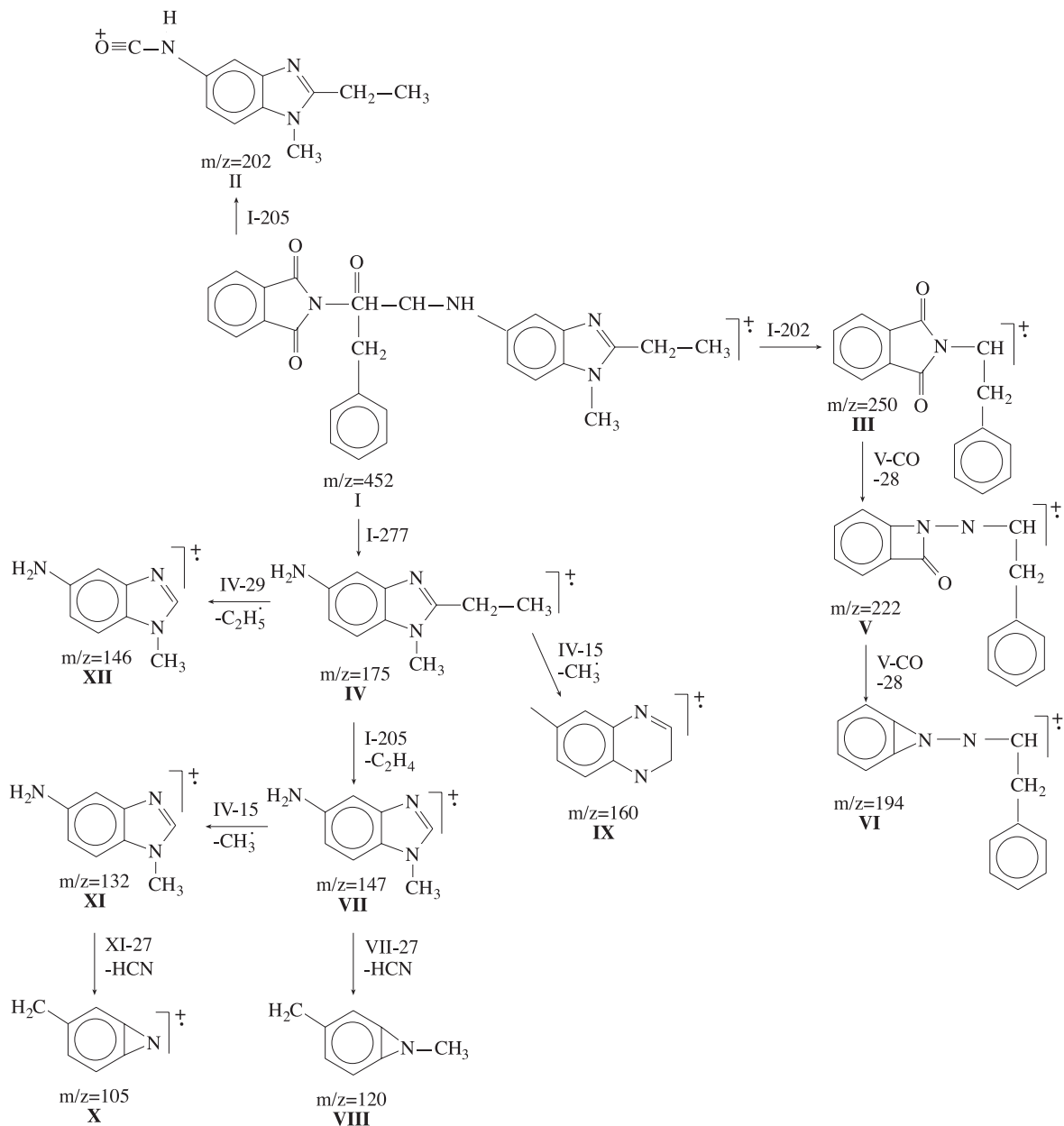


Figure 7. Mass fragmentation pattern of **7**.

Mass spectral fragmentation of **7** and **8** which are shown in Figures 7 and 8 follow a similar pattern. The molecular ion fragment **I** undergoes cleavage of C-C bond leading to the formation of fragments **II** at $m/z=202$ and 204 respectively and a fragment **III** at $m/z=250$ in both the cases. Further cleavage of fragment **III** to **V** and **VI** follows exactly the same course in both the compounds. Fragments **IV** at $m/z=175$ from **7** and at 177 from **8** are formed through the cleavage of C-N bonds in both the compounds through the same mechanism. Fragments **VIII** and **X** obtained by further cleavage of **IV** are visible in both the spectra.

Fragments IX at $m/z=160$ and 162 from IV in **7** and **8** respectively are obtained through the cleavage of a methyl radical.

The ^1H NMR data of compound **7** is given in the experimental section. The methyl group appeared as a triplet at $\delta=1.6$ and $-\text{CH}_2$ protons in the side chain showed a quartet at $\delta=2.1$. Proton H_d exhibited a doublet of doublet a $\delta=5.2$ due to coupling with diastereotopic H_e and $\text{H}_{e'}$ protons. Protons of group $-\text{CH}_2$ adjacent to the asymmetric center showed a multiplet at $\delta=3.52$. Due to nearly similar chemical shifts, H_a , $\text{H}_{a'}$, a'' and H_b , $\text{H}_{b'}$ protons showed a multiplet in the range of $\delta=7.19$ - 7.22 . The $\text{H}_{c'}$ protons showed resonance at a lower field than that of the H_c protons. Signals due to H_c and $\text{H}_{c'}$ are not clearly resolved, $\text{H}_{c'}$ protons showed a multiplet at $\delta=7.79$ and H_c protons exhibited a multiplet at $\delta=7.68$. A singlet at $\delta=3.4$ was assigned to $\text{N}-\text{CH}_3$ protons.

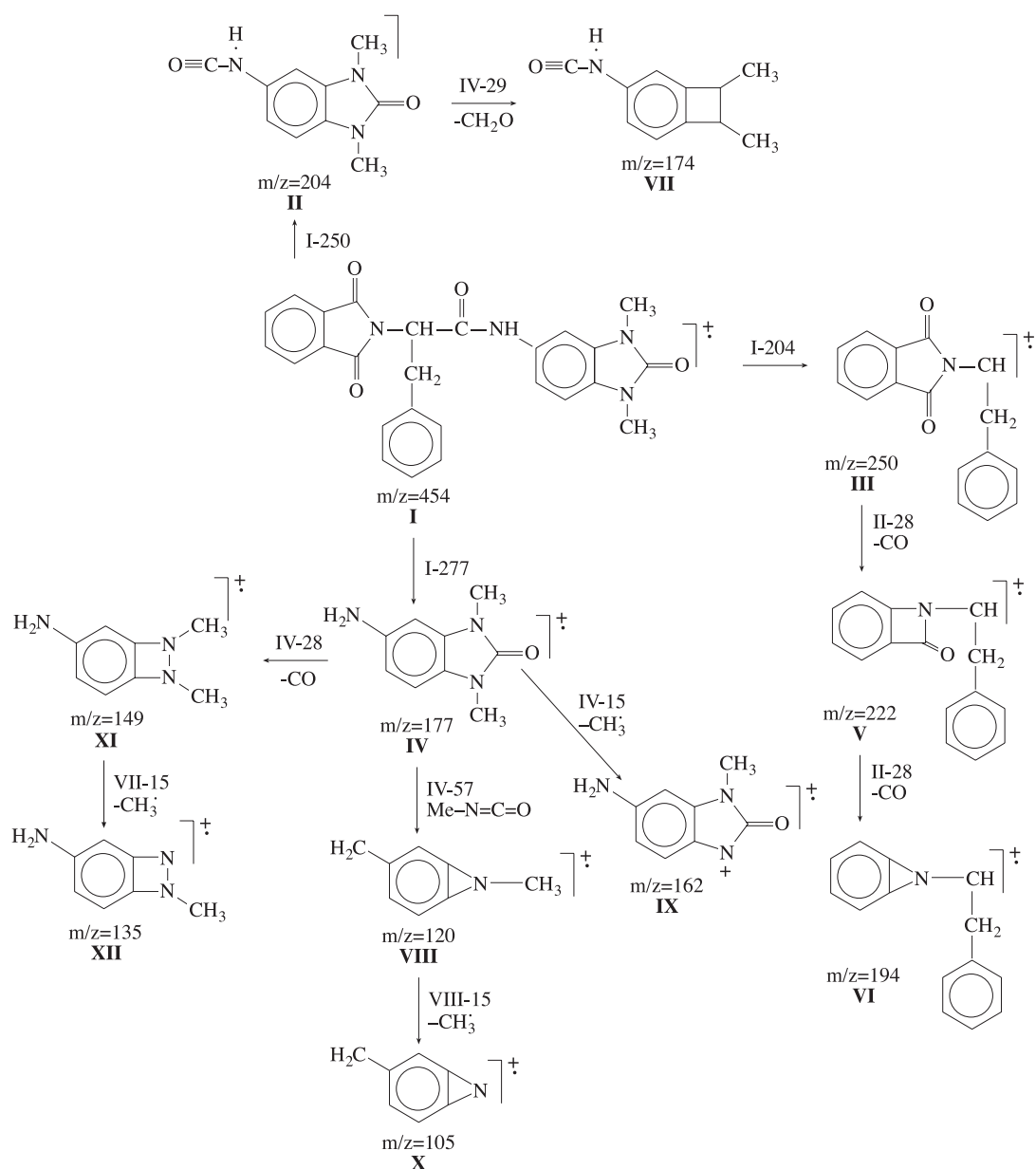


Figure 8. Mass fragmentation pattern of **8**.

¹H NMR data of compound **8** is given in the experimental section. In ¹H NMR spectrum of compound **8** two singlets at $\delta=3.35$ and at $\delta=3.37$ were due to two N-CH₃ protons. The two diastereotopic protons H_e and H_{e'} of the methylene group adjacent to the asymmetric center, showed a multiplet at $\delta=3.67$ due to vicinal and geminal coupling. Proton H_d showed a doublet of doublet at $\delta=5.31$ due to coupling with H_e and H_{e'}. Due to nearly similar chemical shifts H_a, H_{a'}, H_{a''} and H_b, H_{b'} protons showed a multiplet in the range of $\delta=7.16-7.22$. The H_{c'} protons are ortho to C=O group and therefore resonate at a lower field than H_c protons. The H_c protons exhibited a doublet of doublet at $\delta=7.71$ and H_{c'} protons showed a doublet of doublet at $\delta=7.81$.

Experimental

All solvents were distilled and dried where necessary before use. All the reactions were monitored with the help of thin-layer chromatography using precoated aluminum sheets with 60F₂₅₄ silica gel, 0.2 mm layer thickness (E. Merck). Various solvent systems used for developing the chromatograms were:

- a = chloroform : methanol (9:1),
- b = dichloromethane : methanol (40:1) and
- c = ethyl acetate : pet-ether (4:1).

Columns of different sizes packed with G₆₀ (70-230 mesh) silica gel were used for purification. Melting points of the synthesized compounds were recorded on the Gallenkamp (design No. 88 9339) melting point apparatus and are uncorrected. ¹H NMR spectra of the synthesized compounds were scanned in CDCl₃ with a Bruker machine operating at 500 MHz in H.E.J. Research Institute of Chemistry, University of Karachi. Chemical shifts are reported in δ scale (ppm). Mass spectra (low resolution) of the synthesized compounds were recorded at MAT 120 in H.E.J. Research Institute of Chemistry, University of Karachi. A Jasco J-20A automatic recording spectropolarimeter was used for the measurement of $[\alpha]_{589}^D$ of the optically active derivatives.

Compounds 2H- (**1A**), 2-ethyl- (**2A**) 1-methyl-5-nitro-benzimidazoles, their 6-nitro-isomers **1B**, **2B** and 1,3-dimethyl-2H-5-nitro-benzimidazol-2-one (**3**) were synthesized in our laboratory and the procedures are being published³. A brief description is given below:

2H- and 2-ethyl- 5-nitrobenzimidazoles were synthesized by the well known method, i.e. refluxing formic acid and propionic acid separately with 1,2-diamino-4-nitrobenzene in 4N hydrochloride acid and normal work-up. Both the compounds were then separately methylated with methyl iodide in the presence of anhydrous potassium carbonate using anhydrous dimethylformamide as the solvent. In both cases 1,3-dimethyl-benzimidazolone (**3** was obtained together with the respective regioisomeric 5- and 6-nitro-1-methylbenzimidazoles **1 (A and B)** and **2(A and B)**.

Compound **3** was separated from the mixture of 5- and 6- nitrobenzimidazoles through column chromatography. The regioisomers **A** and **B** in each case were separated through fractional crystallization. Their structure was determined with the help of mass, ¹H NMR spectral analyses and Nuclear Overhauser Effect measurement for **A** and **B**.

Preparation of 5-amino-1-methylbenzimidazole (**4A**)

Compound **1A** (1.0g, 5.6 mmol), hydrazine hydrate (1.15 ml, 10 mmol), graphite (3.0g) and absolute ethanol (100 ml) were refluxed for 12 hours under an atmosphere of nitrogen. After the completion of the reaction,

the contents were filtered and washed with ethanol. Removal of the solvent under reduced pressure gave compound **4B** which was recrystallized from ethyl acetate. Yield = 0.76g (94%); m.p. = 143°C; $R_f = 0.31^a$, 0.22^c . – $^1\text{H NMR}$ $\delta = 7.71$ (s, 1H, H_e), $\delta = 7.14$ (dd, 1H, H_c , $J_{cb} = 8.5$ Hz, $J_{ca} = 0.5$ Hz), $\delta = 7.07$ (dd, 1H, H_a , $J_{ab} = 2.1$ Hz, $J_{ac} = 0.5$ Hz), $\delta = 6.73$ (dd, 1H, H_b , $J_{bc} = 8.5$ Hz, $J_{ba} = 2.1$ Hz), $\delta = 3.75$ (s, 3H, N- CH_3). – MS = 147 (100) [M^+], 132 (26.1), 120 (2.5), 119 (8.7), 105 (14.4), 104 (0.61).

Preparation of 5-amino-2-ethyl-1-methylbenzimidazole (**5A**)

Compound **2A** (1.0g, 4.8 mmol), hydrazine hydrate (1.3 ml, 8.8 mmol), graphite (3.0g), ethanol (150 ml) were refluxed under nitrogen for 16 hours. The contents were filtered and washed with ethanol to remove the graphite. The solvent was removed under reduced pressure. The product thus obtained, was recrystallized from ethyl acetate to give compound **5**. Yield = 0.78g (91.7%); m.p. = 142°C; $R_f = 0.37^a$, 0.022^b , 0.041^c . – $^1\text{H NMR}$: $\delta = 7.46$ (d, 1H, H_c , $J_{cb} = 8.20$ Hz), $\delta = 6.60$ (dd, 1H, H_b , $J_{bc} = 8.2$ Hz, $J_{ba} = 2.1$ Hz), $\delta = 6.54$ (d, 1H, H_a , $J_{ab} = 2.1$ Hz), $\delta = 3.6$ (s, 3H, N- CH_3), $\delta = 2.18$ (q, H_e , 2H), $\delta = 1.40$ (t, 3H, H_f). – MS = 175 (100) [M^+], 174 (53.22), 160 (98.87), 147 (4.68), 146 (8.9), 132 (2), 120 (1.5), 119 (3), 105 (4), 104 (0.96).

Preparation of 5-amino-1,3-dimethylbenzimidazol-2-one (**6**)

Compound **3** (2.0g, 9.0 mmol), hydrazine hydrate (2.7 ml, 18 mmol), graphite (3.0g) were refluxed in absolute ethanol (250 ml) for 10 hours under nitrogen. After the completion of reaction, graphite was removed by filtration, the solvent was evaporated under reduced pressure, and the product thus obtained was recrystallized from benzene to give pure **6**. Yield = 1.6g (95%); m.p. = 145°C; $R_f = 0.65^a$, 0.43^b , 0.88^c . – $^1\text{H NMR}$: $\delta = 6.72$ (d, 1H, H_c , $J_{cb} = 8.1$ Hz), $\delta = 6.43$ (dd, 1H, H_b , $J_{bc} = 8.1$ Hz, $J_{ba} = 2.2$ Hz), $\delta = 6.35$ (d, 1H, H_a , $J_{ab} = 2.2$ Hz), $\delta = 3.35$ (s, 3H, N- CH_3), $\delta = 3.34$ (s, 3H, N- CH_3). – MS = 177 (100) [M^+], 162 (48), 149 (6), 134 (10.2), 120.9 (20), 105 (7), 65.9 (11).

Reduction of mixture of compounds **1A**, **1B** and **3**

A mixture of compound **1A**, **1B** and **3** (1.0g), hydrazine hydrate (1.15 ml, 10 mmol) and graphite (3.0g) was refluxed in absolute ethanol (100 ml) for 4 hours under nitrogen. After the completion of the reaction, the graphite was removed by filtration. Removal of the solvent under reduced pressure gave a product which was a mixture of compounds **4A**, **4B** and **6**. Compounds **4A** and **4B**, $R_f = 0.30^a$, 0.22^c . Compound **6**, $R_f = 0.65^a$, 0.42^b , 0.87^c .

Reduction of mixture of compounds **2A**, **2B** and **3**

A mixture of compounds **2A**, **2B**, and **3** was reduced as described for **1A**, **1B** and **3** above. Complete reduction required 4 hours and a mixture of **4A**, **4B** ($R_f = 0.65^a$, 0.41^b , 0.085^c) and **6** ($R_f = 0.65^a$, 0.42^b , 0.87^c) was formed.

Preparation of phthaloyl-L-phenylalanine^{4a}

A mixture of L-phenylalanine (4.9g, 30 mmol) and finely ground phthalic anhydride (4.4g, 30 mmol) was heated for 30 minutes with stirring in an oil bath at 145°-150°C. After cooling, the solid material was dissolved in hot methanol (20 ml). The filtered solution was diluted with water (20 ml) and the product was allowed to crystallize out slowly. Yield = 8.0g (81.1%), m.p. = 178°C, $R_f=0.18^a$, 0.27^b .

Preparation of phthaloyl-L-phenylalanyl chloride^{4b}

A mixture of phthaloyl-L-phenylalanine (7.0g, 22 mmol) and phosphorus pentachloride (4.5g, 22 mmol) in dry benzene (75 ml) was heated in an oil bath at 50-55° for one hour. The slightly yellowish solution was separated from the remaining phosphorus pentachloride by filtration. After concentration to dryness under reduced pressure, the solid was recrystallized from benzene: pet. ether and dried under reduced pressure. Yield=6.5g (87%); m.p. = 72°C; $R_f=0.92^a$, 0.45^b , 0.91^c .

Preparation of 2-ethyl-1-methyl-5(phthaloyl-L-phenylalanyl)-amino- benzimidazole(7)

Phthaloyl-L-phenylalanyl chloride (0.75g, 24 mmol) in dioxane (5ml) was added for 15 minutes to an ice-cooled solution of compound **2A** (0.5g, 24 mmol) and sodium bicarbonate (0.6g, 7.0 mmol) in 20 ml water. After stirring for 10 minutes, the suspension was acidified with 2N hydrochloric acid. The precipitate formed was filtered and recrystallized from ethanol. Yield = 1.0g (77.5%); m.p. = 224°C; $R_f = 0.37^a$, 0.022^b , 0.041^c , $[\alpha]_{589}^D = -4.5$ (CHCl₃). – ¹H NMR: $\delta = 7.79$ (m, 2H, H_{c'}), $\delta=7.68$ (m, 2H, H_c), $\delta = 7.22$ (m, 3H, H_a, H_{a'}, H_{a''}), $\delta = 7.19$ (m, 5H, H_b, H_{b'}), $\delta = 5.2$ (dd, 1H, H_d), $\delta = 3.52$ (m, 2H, H_e, H_{e'}), $\delta = 3.4$ (s, 3H, H_f), $\delta = 2.01$ (q, 2H, H_g), $\delta = 1.6$ (t, 3H, H_j). – MS = 452 (100) [M⁺], 160 (23), 250 (48), 222 (1.3), 175 (100), 147 (5), 146 (4), 132 (8), 120 (2), 202 (7), 194 (1.5), 105 (11).

Preparation of 1,3-dimethyl-5(phthaloyl-L-phenylalanyl)-amino-benzimidazol-2-one (8)

Compound **8** was prepared from phthaloyl-L-phenylalanyl chloride (1.5g, 4.8 mmol), compound **6** (1.0g, 48 mmol) and sodium bicarbonate (1.2g, 14 mmol) using the same procedure as described for the preparation of **7** above. Yield of **8** = 2.1g (78%); m.p. = 228°C; $R_f = 0.86^a$, 0.43^b , 0.31^c , $[\alpha]_{589}^D = -8.4$ (CHCl₃). – ¹H NMR: $\delta = 7.81$ (dd, 2H, H_{c'}, J_o = 5.3 Hz, J_m = 2.5 Hz), $\delta = 7.71$ (dd, 2H, H_c, J_o = 5.3 Hz, J_m = 2.5 Hz), $\delta = 7.22$ (m, 3H, H_a, H_{a'}, H_{a''}), $\delta = 7.16$ (m, 5H, H_b, H_{b'}), $\delta = 5.31$ (dd, 1H, H_d), $\delta = 5.69$ (dd, 2H, H_e, H_{e'}), $\delta = 3.37$ (s, 3H, N-CH₃, H_f), $\delta = 3.35$ (s, 3H, N-CH₃, H_g). – MS = 454 (100) [M⁺], 250 (58.5), 222 (1.6), 204 (7.14), 194 (1.1), 177 (100), 174 (2.03), 162 (18.5), 134 (1.67), 120 (1.4), 105 (13.6).

References

1. a) Nicolai, Eric; Goyard, Joel; Benchetrit, Thierry; Teulon, Jean Marie; Caussade, Francois; Virone, Angela; Delchambre, Chantal; Cloarec, Alex; *J. Med. Chem.*, 36(9), 1175-1187 (1993)
- b) Turconi, Marco; Nicola, Massimo; Gill Quintero, Myrna; Maiocchi, Luciano; Micheletti, Rosella; Giraldo, Ettore; Donetti, Arturo; *J. Med. Chem.*, 33 (8), 2101-2108 (1990).
- c) Kubo, Keiji; Inada, Yoshiyuki; Kohara, Yasuhisa; Sugiura, Yoshihiro; Ojima, Mami; Itoh, Katsuhiko; Furukawa, Yoshiyasu; Nishikawa, Kohei; Naka, Takehiko; *J. Med. Chem.* 36 (12), 1772-1784(1993)
- d) Kubo, Keiji; Kohara, Yasuhisa; Yoshimura, Yoshinobu; Inada, Yoshiyuki; Shibouta, Yumiko; Furukawa, Yoshiyasu; Kato, Takeshi; Nishikawa, Kohei; Naka, Takehiko; *J. Med. Chem.*, 36 (16), 2343-2349 (1993)
- e) Kubo, Keiji; Kohara, Yasuhisa; Imamiya, Eiko; Sugiura, Yoshihiro; Inada, Yoshiyuki; Furukawa, Yoshiyasu; Nishikawa, Kohei; Naka, Takehiko; *J. Med. Chem.*, 36 (15), 2182-2195 (1993)
- f) Ries, Uwe J.; Mihm, Gerhard; Narr, Berthold; Hasselbach, Kai M; Wittneben, Helmut; Entzeroth, Michael; Van Meel, Jacobus C.A.; Wienene, Wolfgang; Hanel, Nobert H.; *J. Med. Chem.*, 36 (25), 4040-4051 (1993)
2. a) Flynn, Daniel Lee; Moormann, Alan Edward; (G.D. Searle & Co) PCT Int. Appl. WO 9400, 449. (Cl.C07D 453/02), 06th Jan. 1994. US. Appl. 903, 833, 24th June 1992; 44 pp (CA.120; 245105) (US patent 5300512)
- b) Koeppe, Herbert; Mentrup, Anton; Reuth, Ernst Otto; Schromm, Kurt; Hoefke, Wolfgang; Muacevic, Gojko; *Can. CA* 1, 125, 751 (Cl.C07D205/04), 15th Jan. 1982, DE Appl. 2, 644, 833, 05th Oct. 1976, 80pp. Division of Can. Appl. No. 288, 058(CA.97:182415x)
3. Studies in the Methylation of 5-Nitrobenzimidazoles, Mashooda Hasan, Farzana Shaheen and Uzman Yunus, In press.
4. B.H. Han, D.H. Shin, S.Y. Cho, *Tetrahedron Letters*, 26, 50, 6233-6234 (1985).
5. a) Jesse P. Greenstein and Milton Winitz, *Chemistry of the Amino Acids*, Vol. 2, John Wiley and Sons, Inc. New York (1961), p. 902.
- b) *ibid*, p. 908.