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Studies on the Methylation of 5-Nitro-benzimidazoles

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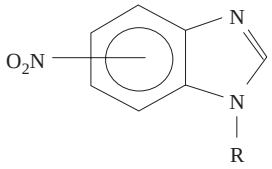
Methylation of 2H, 5-nitro- **(1)** and 2-ethyl, 5-nitro- **(2)** benzimidazoles separately with methyl iodide in acetone in the presence of potassium carbonate yielded 2H, 5/6-nitro-**(3A** and **3B)** and 2-ethyl, 5/6-nitro- **(4A** and **4B)** methylbenzimidazoles respectively. Methylation of **1** and **2** in dimethylformamide in place of acetone yielded not only **3A**, **3B** and **4A, 4B** respectively, but in addition 1,3-dimethyl-5-nitro-benzimidazol-2-one **(5)** was also obtained in each case. The structure of the synthesized compounds was determined with the help of mass and ^{1}H NMR spectroscopic analysis.

Introduction

The benzimidazole ring structure is of particular interest especially within the realm of medicinal chemistry. Many of these compounds display a broad range of biological properties including antibacterial, anthelmintic, antiinflammatory, anticancer, and antiviral activity. There is still interest in the synthesis of benzimidazole derivatives for obtaining new biologically active compounds[1]. Benzimidazolone derivatives are also medicinally important. They exhibit a wide variety of interesting biochemical and pharmacological properties[1]. They antagonize neurotransmitters[2], inhibit aldose reductase[3], show antiulcer and antisecretory properties[4], enhance pulmonary surfactant secretion[5] and modulate ion channels[6].

During the current literature survey it was found that the unsymmetrical nitrobenzimidazoles **a** and **b** shown in Fig. 1 were prepared as potential anti-viral agents[7] as analogs of acyclovir and ganciclovir. These compounds were tested in the form of a mixture of regioisomers and no attempt was made to separate the isomers. My research group has already succeeded[8] in preparing and separating several pairs of unsymmetrical 2H- and 2-alkyl, 5/6-nitro, 5/6-chloro- and 5/6-methyl p-touene-sulphonylbenzimidazoles respectively. "Cis" and "trans" configurations could be assigned to the synthesized isomers on the basis of their respective ^{1}H NMR data, particularly NOE studies.

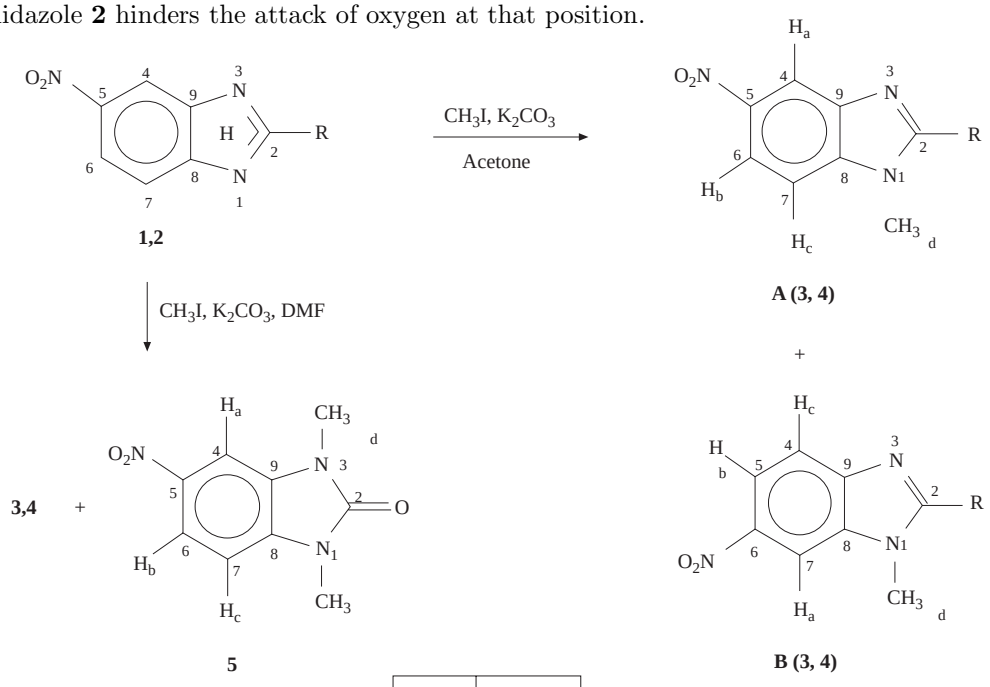


R = $CH_2OCH_2CH_2OH$ **(a)**
R = $CH_2OCH(CH_2OH)_2$ **(b)**

Figure 1.

In the light of the foregoing it seemed worthwhile to prepare more regioisomeric mixtures. Once ample data on the separation, characterization and identification of the structure of regioisomers become available, a systematic study of the dependence of biological activity on the regioisomeric structure might form an important area of research for such compounds.

For this purpose 2H, 5-nitro- **(1)** and 2-ethyl, 5-nitro- **(2)** benzimidazoles were separately methylated with methyl iodide in the presence of anhydrous potassium carbonate using acetone as solvent. The product obtained from **(1)** after the usual work up could be separated into two compounds on fractional crystallization from ethanol. They were found to be the expected regioisomers 2H, 5-nitro- **(3A)** and 2H, 6-nitro- **(3B)** methylbenzmidazoles. Their structure was determined on the basis of their mass and ^{1}H NMR spectral studies, which are to be discussed later. The product obtained from **(2)** on methylation under the same conditions could be separated into two regioisomeric compounds **4A** and **4B** on similar work up. Their structure was found to be 2-ethyl, 5-nitro- and 2-ethyl, 6-nitro-methylbenzimidazoles respectively on the basis of their mass and ^{1}H NMR spectral studies, which will be described in the following section. However, when the same two methylations were carried out using dimethylformamide as solvent in place of acetone, an additional compound identified as 1,3-dimethyl-5-nitro-benzimidazol-2-one **(5)** was formed in both cases in addition to the respective regioisomeric compounds described earlier Fig. 2. These results show that some oxidation had occurred at 2-position in 5/6-nitro-subtituted benzimidazole ring after methylation in the presence of dimethylformamide. The formation of **5** in these experiments may be due to the attack of atmospheric oxygen. Moreover, the amount of **5** obtained during the methylation of **1** was much greater than that formed in the methylation of **2**. It seems that the presence of bulky alkyl group at 2-position in the benzimidazole **2** hinders the attack of oxygen at that position.



	R
1, 3	H
2, 4	C_2H_5

Figure 2. Methylation of Benzimidazoles **1** and **2**

Further investigations, such as methylation of **1** and **2** in dimethylformamide under nitrogen atmosphere, will be carried out in order to study the role of atmospheric oxygen if any in the formation of **5**. Moreover, methylation of 2H- and 2-alkylbenzimdiazoles having no nitro-substituent in the benzene ring of benzimidazoles will also be studied under similar conditions to see the effect of the nitro group on the results of these reactions.

Spectral Studies

Mass spectral data

Mass spectral data of compounds **3, 4** and **5**, which are in full agreement with their excepted structure, are given in the Experimental section.

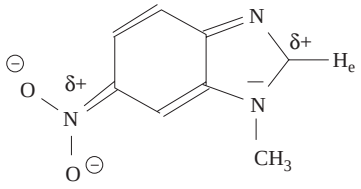
^{1}H NMR spectral studies

Compound **5:** The structure of **5** has been confirmed with the help of ^{1}H NMR spectral measurements. Proton magnetic resonance data of the compound are listed in the experimental. Five sets of peaks were visible in the ^{1}H NMR spectrum of **5**. The two singlets present at δ=3.40 and δ=3.45 were assigned to two N-CH_3 protons. Protons H_a and H_b are ortho to nitro group, and hence they are more deshielded than H_c, which is meta to the NO_2-group, so H_a and H_b were shifted downfield as compared to H_c. The lowest field doublet of doublet at δ=8.06 was assigned to H_b, which had ortho coupling with H_c (J_{bc}=8.6 Hz) and meta coupling with H_a (J_{ba}=2.1 Hz). A doublet at δ=7.84 was due to H_a, which showed meta coupling with H_b (J_{ab}=2.1 Hz). The proton H_c showed the highest field resonance of all aromatic protons and appeared at δ=6.99.

Structure assignment of 3A and 3B "Trans" and "cis" assignment to pure regioisomers was made on the basis of ^{1}H NMR spectral studies. Complete ^{1}H NMR data of regioisomers **3A** and **3B** are given in the experimental.

It is the relative chemical shifts of the aromatic proton signals that distinguish **3A** and **3B**. By looking at the "trans" and "cis" structure, one can understand that only H_a in both regio-isomers has meta coupling. In the "trans" regioisomer **3A**, H_a is ortho to NO_2- and meta to N-CH_3. In the cis regioisomer **3B** H_a is ortho to both NO_2- and N-CH_3 groups. Thus H_a in **3A** is more deshielded than H_a in **3B**. That is, H_a in **3A** should be shifted downfield as compared to H_a in **3B**. In **3A** H_a showed a doublet with meta coupling (J_{ab}=2.1) at δ=8.71, which is downfield as compared to the doublet with meta coupling (J_{ab}=2.1) shown by H_a at δ=8.37 in **3B**.

The other proton that plays a decisive role in "trans" and "cis" assignments to these structures is the one attached to the 2-position of **3A** and **3B**, i.e., He. Of all the resonance forms that can be written for **3B**, one has a positive charge at 2-position while no such resonance form is possible for **3A**. Thus, H_e in **3B** should be shifted downfield as compared to the same proton H_e in **3A**. In ^{1}H NMR spectra of **3B**, H_e showed a singlet at δ=8.11, which is downfield as compared to the singlet shown by H_e at δ=8.05 in **3A**. In **3B**, H_b showed a doublet of doublet at δ=8.25 due to ortho and meta coupling with H_c and H_a protons respectively. Similarly, H_b in **3A** showed a doublet of doublet at δ=8.22. A singlet at δ=3.92 in **3A** and at δ=3.95 in **3B** was assigned to N-CH_3 protons.

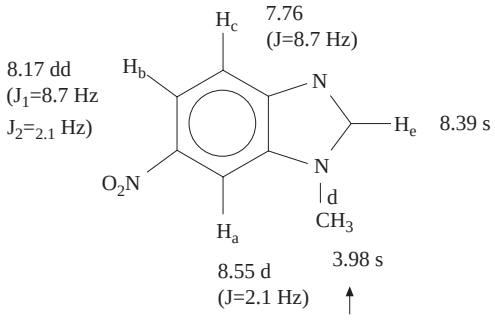


Structure assignment of 4A and 4B ^{1}H NMR data of compounds **4A** and **4B** are given in the Experimental section. The proton H_a in both **4A** and **4B** has meta coupling with H_b (J_{ab}=2.2 Hz) and its chemical shifts play a key role in trans and cis assignment to these structures. This proton in **4A** exhibited a doublet at δ=8.62 that was shifted downfield as compared to the doublet of H_a at δ=8.28 in **4B**. In **4A** and **4B** the proton H_b showed a doublet of doublet at δ=8.20 and δ=8.19 respectively. A quartet at δ=3.0 was assignable to -CH_2 and a triplet at δ=1.5 was assigned to CH_3 protons in the side chain. A singlet at δ=3.81 was assigned to N-NH_3 in **4A** and at δ=3.84 was assigned to N-CH_3 protons in **4B**.

By looking at the ^{1}H NMR spectra of compounds **5, 3A, 3B, 4A** and **4B** it becomes clear that the peak pattern of the aromatic protons is diagnostic for the two classes of closely related medicinal compounds, i.e., substituted benzimidazolone and benzimidazoles. There are three sets of peaks: the two doublets, one due to H_a and the other due to H_c, and the third doublet of doublet due to H_b, which exhibits both ortho and meta coupling. This doublet of doublet is in the middle of the two doublets in **3A, 3B, 4A** and **4B** (benzimidazoles), whereas it appears at the lowest field in benzimidazolone.

To sum up, the "trans" regioisomers **3A** and **4A** are formed in higher yield and have higher melting points as compared to the respective "cis" isomers.

NOE difference experiment NOE Difference was performed on **3B** in order to establish the position of the nitro group with respect to the methyl group present at position 1. For this purpose, **3B** was dissolved in deuterated methanol and its ^{1}H NMR spectrum was measured. The chemical shifts of **3B** in CD_3OD are listed in the Experimental section. Irradiation of methyl protons (3.98 ppm) at N-1 resulted in the enhancement of the H_a (8.55 ppm) signal and not of the H_c (7.76 ppm) doublet. This experiment unequivocally determined the "cis" structure of **3B**.



It also interesting to note that the difference in the chemical shift of H_a in **3A** and **3B** is exactly the same as that in **4A** and **4B**, i.e., 0.34 ppm, the singlet for the "trans" **(A)** isomer appearing in the lower field in both cases. Another interesting point is that the chemical shift difference of the three methyl protons (N-CH_3) between **3A** and **3B** is 0.03 ppm, which is exactly the same as that between **4A** and **4B**. Here the singlet for **A** appears at a higher field in both sets.

Experimental

All the solvents were distilled before use and dried as per requirement. The progress of the reactions was monitored by thin-layer chromatography using pre-coated silica-gel 60HF_{254} plates of 0.2 mm thickness

(E. Merck).

Solvent systems used

a = $CHCl_3$: MeOH (9:1)

b = CH_2Cl_2 : MeOH (40:1)

c = EtOAc : Pet-ether (4:1)

Melting points were recorded on a Gallenkamp melting point apparatus (design No. 889339) and are uncorrected. ^{1}H NMR spectra of the synthesized compounds were scanned in $CDCl_3$ solution unless otherwise indicated, with a Bruker machine at the HEJ Research Institute of Chemistry, University of Karachi. Chemical shifts are given in δ-scale (ppm). Mass spectra (low resolution) of the synthesized compounds were recorded at MAT 120 at the HEJ Research Institute of Chemistry, University of Karachi.

2H, 5-Nitrobenzimidazole **(1)** was prepared by the known procedure, i.e., refluxing 1,2-diamino-4-nitrobenzene with formic acid in 4N HCl and the usual work up. 2-Ethyl, 5-nitro-benzimidazole **(2)** was prepared with the same procedure using propionic acid in place of formic acid.

Preparation of 1-methyl-5/6-nitro-benzimidazoles (3A and 3B)

Compound **1** (4g; 0.024M), methyl iodide (1.51ml; 0.02M) and anhydrous potassium carbonate (3.3g; 0.023M) were refluxed in dry acetone (200ml) for four hours. Removal of solvent under reduced pressure yielded the yellow solid (3.0g), which showed a single spot on thin-layer chromatography plate (R_f =0.72^a, 0.45^b, 0.20^c).

Separation of 3a and 3b

Mixture of **3A** and **3B** (3.0g) was dissolved in a minimum amount of ethanol and kept overnight. The next day colourless crystals were formed. After filtration the mother liquor was concentrated and kept overnight. The crystals so obtained were filtered. The process was repeated. The three crops of crystals showing the same melting point were combined to give **3B** (2.1g). The solvent was removed from the mother liquor in vacuo and the dry residue was recrystallized from acetone, yielding brown crystals of **3B** (0.6g).

Compound **3A**: Yield 2.1g (64%); m.p. = 200° (ethanol), R_f =0.72^a, 0.45^b, 0.20^c. ^{1}H-NMR: δ=8.71 (d, H_a, 1H, J_{ab}=2.1 Hz); δ=8.25 (dd, H_b, 1H, J_{bc}=8.25, J_{ba}=2.1); δ=8.05 (s, H_e, 1H); δ=7.45 (d, H_a, 1H, J_{cb}=8.9 Hz); δ=3.92 (s, H_d, 3H). MS: 177(100) [$M^{+\cdot}$]; 147(11.43), 131(44), 120(6.1), 104(35), 91(3.3), 75(5.3).

Compound **3B**: Yield 0.6g (8%); m.p. = 133° (ethanol), R_f =0.72^a, 0.45^b, 0.20^c. ^{1}H-NMR: δ=8.37, 8.55* (d, H_a, 1H, J_{ab}=2.1 Hz); δ=8.22, 8.17* (dd, H_b, 1H, J_{cb}=8.9, J_{ba}=2.2 Hz); δ=8.11, 8.39* (s, H_e, 1H); δ=7.85, 7.76* (d, H_c, 1H, J_{cb}=8.7 Hz); δ=3.95, 3.98* (s, H_d, 3H). MS: same as for **3A**.

* Measured in CD_3OD

Preparation of 2-ethyl-1-methyl-5/6-nitro-benzimidazoles (4A and 4B): Compound **2** (4g, 0.02M), methyl iodide (1.29ml, 0.02M) and anhydrous potassium carbonate (2.87g, 0.02M) were refluxed in dry acetone (250ml) for six hours. After the removal of the solvent, the yellow solid of the regioisomeric mixture **4A** and **4B** was obtained, which gave a single spot in thin-layer chromatograph (R_f =0.87^a, 0.41^b, 0.33^e).

Separation of 4A and 4B:

Separation of **4A** and **4B** was achieved through fractional crystallization as described for **3A** and **3B**.

Compound **4A**: Yield 1.9g (69%); m.p. = 182° (ethanol), R_f =0.87^a, 0.41^b, 0.33^e. ^{1}H-NMR: δ=8.62 (d, 1H, J_{ab}=2.1 Hz); δ=8.20 (dd, H_b, 1H, J_{bc}=8.9 Hz, J_{ba}=2.2 Hz); δ=7.34 (d, H_c, 1H J_{cb}=8.9 Hz); δ=3.81 (s, H_d, 3H); δ=2.99, (q, H_e, 2H, $J_{e,b}$=7.5 Hz); δ=1.50 (t, H_f, 3H, $J_{e,f}$=7.5 Hz). MS: 205(100) [$M^{+\cdot}$],

204(64), 190(4.7), 177(2.3), 176(5.05), 175(1.89), 147(2.42), 131(5.2), 91(6.04), 75(4.5).

Compound **4B**: Yield =0.5g (18%); m.p. = 133° (acetone); R_f=0.87^a, 0.41^b, 0.33^e. ^{1}H-NMR: δ=8.28 (d, H_a,1H, J_{ab}=2.1 Hz); δ=8.19 (dd, H_b, 1H, J_{bc}=8.9 Hz, J_{ba}=2.2 Hz); δ=7.17 (d, H_c, 1H J_{cb}=8.9 Hz); δ=3.84 (s, H_d, 3H); δ=3.0, (q, H_e, 2H, $J_{e,f}$=7.5 Hz); δ=1.5 (t, H_f, 3H, $J_{e,f}$=7.5 Hz). MS: same as for **4A**.

Preparation of 1,3-dimethyl-2H-5-nitrobenzimidazol-2-one (5) and 1-methyl-2H-5/6 -nitro-benzimidazoles (3A and 3B) and separation of the two classes of compounds

Compound **1** (20g, 0.12M), methyl iodide (12.35ml, 0.24M) and anhydrous potassium carbonate (33g, 0.24M) were dissolved in dry N,N-dimethylformamide (250ml) and refluxed for 36 hours. After the completion of the reaction, the solvent was removed in vacuo. The residue was dissolved in water. The mixture was extracted in chloroform and chloroform layer washed thoroughly with water. The organic layer was then dried over anhydrous sodium sulphate, and the solvent was removed under vacuum, leaving, a crude brown solid. The mixture showed two spots on the thin layer chromatogram; **3**(R_f=0.72^a, 0.32^b) and **5**(R_f=0.93^a, 0.84^b). The crude mixture was recrystallized from methanol, yielding light yellow crystals of compound **5**. The thin-layer chromatogram of the mother liquor showed two spots corresponding to compounds **3** and **5** in almost equal amounts. The solvent was removed in vacuo and the residue was subjected to column chromatography using a gradient of n-hexane and ethylacetate. Fractions obtained with n-hexane : ethylacetate (7:3) gave pure **5**, and those with n-hexane : ethylacetate (1:1) contained a mixture of **3A** and **3B**.

Compound **5**: Yield =15g (59%); m.p. = 202° (methanol); R_f=0.936^a 0.84^b. ^{1}H-NMR: δ=8.06 (dd, H_b,1H, J_{bc}=6.32 Hz); δ=7.84 (d, H_a, J_{ab}=2.5 Hz; δ=6.99 (d, H_c, 1H J_{cb}=8.61 Hz); δ=3.40 (s, H_d, 3H); δ=3.45, (s, H_e, 3H). MS: 207(100) same as for **4A** [$M^+_\cdot$], 177(13.5), 161(51.5), 147(11.26), 133(7.46), 91(6.08), 75(3.2).

Compound **3** (**A** and **B**: Yield=1.5g(7%); m.p. =150°, R_f=0.72^a, 0.45^b. MS: 177(100) [$M^+_\cdot$], 147(18.44), 111(48.5), 104(24.06), 120(8.3), 91(2.1), 75(6.5).

Preparation of 5 and 2-ethyl-5-methyl-5/6-nitrobenzimidazoles (4A and 4B) and separation of the two classes of compounds

Compound **2** (3g, 0.15M), methyl iodide (1.94ml, 0.0314M) and anhydrous potassium carbonate (4.3g, 0.0314M) were dissolved in dry dimethylformamide (250ml) and refluxed for 36 hours. After the completion of the reaction, the solvent was removed in vacuo. The residue was dissolved in water. The mixture was extracted with chloroform, and the chloroform layer was washed thoroughly with water. The organic layer was then dried over anhydrous sodium sulphate and filtered. Removal of the solvent under reduced pressure gave a brown solid. A thin-layer chromatogram of this mixture showed two spots, one of compound **4**(R_f=0.87^a, 0.41^b) and the other of compound **5**(R_f=0.93^a, 0.84^b). The separation of **4** and **5** was achieved by subjecting it to column chromatography using a gradient of dichloromethane and methanol. Fractions obtained with dichloromethane: methanol (9:1) gave pure **5** and those with methylene chloride : methanol (2:1) gave a mixture of **4A** and **4B**.

Compound **5**: Yield=500mg(15%); m.p. =202° (methanol), R_f, ^{1}H NMR and MS: as already described.

Compound **4** (**A** and **B**): Yield=1.5g(47%), m.p. =140°, R_f=0.87^a, 0.41^b. MS: 205(100) [$M^+_\cdot$], 204(64.4), 190(4.8), 176(1.92), 170(4.03), 159(29), 147(3.15), 131(4.56), 104(11.7), 91(3.8), 75(4.8).

Compounds **1** and **2** were separately methylated in dry acetone in the presence of anhyd, potassium carbonate using double molar ratios of methyl iodide. Thin-layer chromatography of the product obtained after the usual work-up showed the absence of **5** in both experiments.

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