

THE ADDITION PRODUCTS OF β -METHYL- β -NITROSTYRENE
DERIVATIVES WITH 2-MERCAPTOMETHYLBENZIMIDAZOLE AND
THEIR NMR STUDIES⁺

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Key Word Index

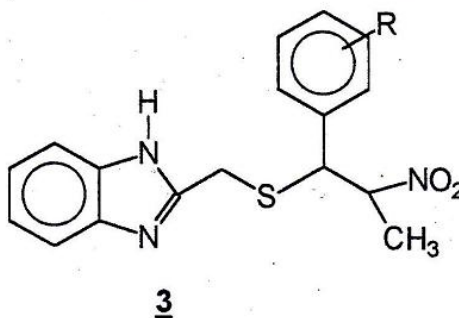
β -Methyl- β -nitrostyrenes, 2-Mercaptomethylbenzimidazole,
Nitropropane derivatives.

ABSTRACT

2[(2-nitro-1-phenyl-propyl) thiomethyl] benzimidazole **3** derivatives have been synthesized starting from β -methyl- β -nitrostyrenes **1** and 2-mercaptomethylbenzimidazole **2** and their structures have been elucidated. According to the ¹H-NMR spectra, the products are the mixtures of two rotamers (A and B) in varying proportions.

INTRODUCTION

As a continuation of our research¹⁻⁵, the reaction of thiol groups with β -nitrostyrene has been further studied. The biological activity of the compounds will be reported later with the QSAR studies. All the derivatives in this study are reported first time.



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(+) This study is a part of Semra Özgüçlü's dissertation for MSc degree in Pharmaceutical Chemistry at. The Institute of Health Sciences, Gazi University.

EXPERIMENTAL

Melting points: Electrothermal 9200, uncorrected. IR spectra: Perkin Elmer 1330 IR-SPetrophotometer. ^1H -NMR and ^{13}C -NMR spectra: Jeol 500MHz spectrometer (Chemical shifts in δ units (ppm)). Elemental analysis: Carlo-Erba 1106 elemental analyser.

METHODS

Synthesis of β -methyl- β -nitrostyrenes 1

The derivatives of β -methyl- β -nitrostyrene were synthesized according to literature methods^{1,6-10}.

Synthesis of 2-mercaptomethylbenzimidazole 2

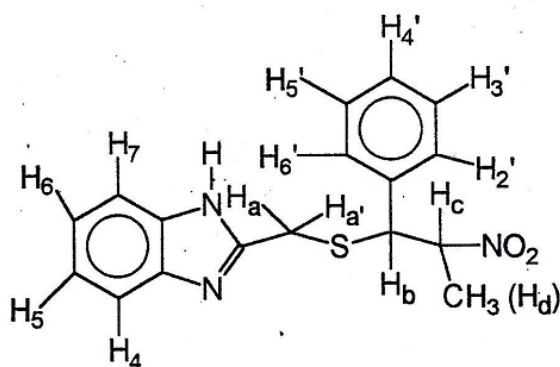
The synthesis of 2-mercaptomethylbenzimidazole **2** has been made according to literature methods^{4, 11, 12}.

Synthesis of 2-[(2-Nitro-1-(4-substituted phenyl)-propyl)-thiomethyl]- benzimidazole 3

General Method

0.005 Mole 2-mercaptomethylbenzimidazole **2** and 0.005 mole appropriate β -methyl- β -nitrostyrene **1** derivative have been stirred in 10 mL ethanol for 2 h at room temperature and left in the refrigerator for 24 h, after adding few mL of water the precipitated crystals have been filtered.

In NMR spectra of these compounds, signals of some protons have been determined separately. Therefore these protons have been assigned as follows:



2-[(2-Nitro-1-phenyl-propyl)thiomethyl]benzimidazole 3a

Yield: 52%, m.p.: 147.5 °C Anal. C₁₇H₁₇N₃O₂S (327.41)

Calc. (%): C :62.37 , H : 5.23 , N : 12.83

Found.(%): C :61.98 , H : 5.16 , N : 12.92

IR (KBr): $\nu(\text{cm}^{-1})$ =1540,1360 (NO₂).

¹H-NMR (DMSO -d₆) : δ (ppm) = 1.26 (d, J_{d,c}= 6.72 Hz, 3H, CH₃ of B), 1.55 (d, J_{d,c}= 6.10 Hz, 3H, CH₃ of A), 3.70 (d, J_{a,a'}= 14.00 Hz, 1H, H_a of B), 3.74 (d, J_{a,a'}= 14.65 Hz, 1H, H_a of A), 3.84 (d, J_{a',a}= 14.65 Hz, 1H, H_{a'} of B), 3.90 (d, J_{a',a}= 14.04 Hz, 1H, H_{a'} of A), 4.52 (d, J_{b,c}= 9.77 Hz, 1H, H_b of A and B), 5.27-5.36 (m, 1H, H_c of A and B), 7.15 -7.16 (br. s, 2H, H₄+H₇ of A and B), 7.25-7.47 (m, 5H, aromatic protons of A and B), 7.50-7.64 (m, 2H, H₅+H₆), 12.42 (s, 1H, NH).

¹H-NMR (CDCl₃) : δ (ppm) = 1.32 (d, J_{d,c}= 6.71 Hz, 3H, CH₃ of B), 1.71 (d, J_{d,c}= 6.72 Hz, 3H, CH₃ of A), 3.73 (d, J_{a,a'}= 15.87 Hz, 1H, H_a of A and B), 3.90 (d, J_{a',a}= 15.87 Hz, 1H, H_{a'} of A and B), 4.09 (d, J_{b,c}= 10.99 Hz, 1H, H_b of B), 4.35 (d, J_{b,c}= 9.16 Hz, 1H, H_b of A), 4.89-4.94 (m, 1H, H_c of A and B), 7.02 -7.63 (m, 9H, aromatic protons of A and B).

2-[(2-Nitro-1-(4-chlorophenyl)propyl)thiomethyl]benzimidazole 3b

Yield: 75%, m.p.: 82-83 °C Anal. C₁₇H₁₆ClN₃O₂S (361.86)

Calc. (%): C : 56.43, H: 4.43, N : 11.61

Found.(%): C : 56.13, H: 4.32, N : 11.30

IR (KBr): $\nu(\text{cm}^{-1})$ = 1540,1360 (NO₂).

¹H-NMR (DMSO -d₆) : δ (ppm) = 1.27 (d, J_{d,c}= 6.72 Hz, 3H, CH₃ of B), 1.54 (d, J_{d,c}= 6.11 Hz, 3H, CH₃ of A), 3.70 (d, J_{a,a'}= 14.04 Hz, 1H, H_a of B), 3.75 (d, J_{a,a'}= 14.04 Hz, 1H, H_a of A), 3.84 (d, J_{a',a}= 14.04 Hz, 1H, H_{a'} of B), 3.70 (d, J_{a',a}= 14.65 Hz, 1H, H_{a'} of A), 4.54 (d, J_{b,c}= 9.15 Hz, 1H, H_b of A and B), 5.26 - 5.34 (m, 1H, H_c of A and B), 7.13-7.16 (m, 2H, H₃+H₅ of A and B), 7.24-7.47 (m, 2H, H₂+H₆ of A and B), 7.36-7.40 (m, 2H, H₄+H₇ of A and B), 7.44-7.49 (br.s, 2H, H₅+H₆ of A and B), 12.34 (s, 1H, NH).

2-[(2-Nitro-1-(4-nitrophenyl)propyl)thiomethyl]benzimidazole 3c

Yield: 80%, m.p.: 65-68 °C Anal. C₁₇H₁₆N₄O₄S (372.41)

Calc. (%): C : 54.83, H: 4.33, N : 15.04

Found.(%): C : 54.50, H: 4.06, N : 14.84

IR (KBr): $\nu(\text{cm}^{-1})$ = 1540,1360 (NO₂).

¹H-NMR (DMSO -d₆) : δ (ppm) = 1.29 (d, J_{d,c}= 6.10 Hz, 3H, CH₃ of B), 1.57 (d, J_{d,c}= 6.10 Hz, 3H, CH₃ of A), 3.78 (d, J_{a,a'}= 14.64 Hz, 1H, H_a of B), 3.83 (d, J_{a,a'}= 14.04 Hz, 1H, H_a of A), 3.90 (d, J_{a',a}= 14.04 Hz,

^1H , H_{a} of B), 3.95 (d, $J_{\text{a},\text{a}'} = 14.64$ Hz, 1H, H_{a} of A), 4.70 (d, $J_{\text{b},\text{c}} = 6.72$ Hz, 1H, H_{b} of B), 4.72 (d, $J_{\text{b},\text{c}} = 7.32$ Hz, 1H, H_{b} of A), 5.35-5.38 (m, 1H, H_{c} of B), 5.40-5.44 (m, 1H, H_{c} of A), 7.10-7.13 (m, 2H, $\text{H}_4 + \text{H}_7$ of A and B), 7.44-7.50 (m, 2H, $\text{H}_5 + \text{H}_6$ of A and B), 7.61-7.66 (m, 2H, $\text{H}_2 + \text{H}_6$ of A and B), 8.09-8.11 (m, 2H, $\text{H}_3 + \text{H}_5$ of A and B), 12.42 (s, 1H, NH).

2-[(2-Nitro-1-(4-tolyl)propyl)thiomethyl]benzimidazole 3d

Yield: 75%, m.p.: 63-65°C Anal. $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_2\text{S}$ (341.43)

Calc. (%): C: 63.32, H: 5.61, N: 12.31

Found. (%): C: 63.00, H: 5.51, N: 12.00

IR (KBr): ν (cm^{-1}) = 1540, 1360 (NO_2).

^1H -NMR ($\text{DMSO}-d_6$): δ (ppm) = 1.26 (d, $J_{\text{d},\text{c}} = 3.30$ Hz, 3H, CH_3 of B), 1.54 (d, $J_{\text{d},\text{c}} = 3.00$ Hz, 3H, CH_3 of A), 2.26 (s, 3H, CH_3 of A), 2.27 (s, 3H, CH_3 of B), 3.68 (d, $J_{\text{a},\text{a}'} = 14.65$ Hz, 1H, H_{a} of B), 3.72 (d, $J_{\text{a},\text{a}'} = 14.04$ Hz, 1H, H_{a} of A), 3.82 (d, $J_{\text{a},\text{a}'} = 14.04$ Hz, 1H, H_{a} of B), 3.87 (d, $J_{\text{a},\text{a}'} = 14.04$ Hz, 1H, H_{a} of A), 4.46 (d, $J_{\text{b},\text{c}} = 4.27$ Hz, 1H, H_{b} of B), 4.48 (d, $J_{\text{b},\text{c}} = 4.27$ Hz, 1H, H_{b} of A), 5.23-5.30 (m, 1H, H_{c} of A and B), 7.11-7.16 (m, 4H, aromatic protons of A and B), 7.24-7.29 (m, 2H, $\text{H}_4 + \text{H}_7$ of A and B), 7.49-7.50 (br.s, 2H, $\text{H}_5 + \text{H}_6$ of A and B), 12.35 (s, 1H, NH).

2-[(2-Nitro-1-(4-methoxyphenyl)propyl)thiomethyl]benzimidazole 3e

Yield: 54%, m.p.: 137-139 °C Anal. $\text{C}_{18}\text{H}_{19}\text{N}_3\text{O}_3\text{S}$ (357.44)

Calc. (%): C: 60.49, H: 5.36, N: 11.76

Found. (%): C: 60.14, H: 5.35, N: 11.56

IR (KBr): ν (cm^{-1}) = 1540, 1360 (NO_2).

^1H -NMR ($\text{DMSO}-d_6$): δ (ppm) = 1.26 (d, $J_{\text{d},\text{c}} = 6.72$ Hz, 3H, CH_3 of B), 1.54 (d, $J_{\text{d},\text{c}} = 6.71$ Hz, 3H, CH_3 of A), 3.71 (s, 3H, OCH_3 of A), 3.73 (s, 3H, OCH_3 of B), 3.68 (d, $J_{\text{a},\text{a}'} = 14.03$ Hz, 1H, H_{a} of B), 3.72 (d, $J_{\text{a},\text{a}'} = 14.04$ Hz, 1H, H_{a} of A), 3.81 (d, $J_{\text{a},\text{a}'} = 14.03$ Hz, 1H, H_{a} of B), 3.86 (d, $J_{\text{a},\text{a}'} = 14.04$ Hz, 1H, H_{a} of A), 4.46 (d, $J_{\text{b},\text{c}} = 9.77$ Hz, 1H, H_{b} of A), 4.47 (d, $J_{\text{b},\text{c}} = 9.76$ Hz, 1H, H_{b} of B), 5.25-5.28 (m, 1H, H_{c} of A and B), 6.86-6.91 (m, 2H, $\text{H}_3 + \text{H}_5$ of A and B), 7.13-7.16 (m, 2H, $\text{H}_2 + \text{H}_6$ of A and B), 7.29-7.34 (m, 2H, $\text{H}_4 + \text{H}_7$ of A and B), 7.50 (br.s, 2H, $\text{H}_5 + \text{H}_6$ of A and B), 12.37 (s, 1H, NH).

2-[(2-Nitro-1-(4-hydroxy-3-methoxyphenyl)propyl)thiomethyl]benzimidazole 3f

Yield: 47%, m.p.: 85 - 87°C Anal. $\text{C}_{18}\text{H}_{20}\text{N}_3\text{O}_4\text{S}$ (374.44)

Calc. (%): C: 57.90, H: 5.13, N: 11.25

Found. (%): C: 57.54, H: 5.01, N: 10.86

IR (KBr): ν (cm^{-1}) = 1540, 1360 (NO_2).

¹H-NMR (DMSO -d₆) : δ (ppm) = 1.26 (d, J_{d,c} = 6.11 Hz, 3H, CH₃ of B), 1.56 (d, J_{d,c} = 6.71 Hz, 3H, CH₃ of A), 3.65 (s, 3H, OCH₃ of A), 3.69 (s, 3H, OCH₃ of B), 3.71-3.89 (m, 2H, H_a+H_{a'} of A+B), 4.37 (d, J_{b,c} = 10.37 Hz, 1H, H_b of B), 4.40 (d, J_{b,c} = 9.15 Hz, 1H, H_b of A), 5.24-5.26 (m, 1H, H_c of B), 5.27-5.30 (m, 1H, H_c of A), 6.68 (dd, 1H, H_{5'} of A), 6.71 (dd, 1H, H_{5'} of B), 6.75 (dd, 1H, H_{6'} of A), 6.77 (dd, 1H, H_{6'} of B), 7.11-7.19 (m, 2H, H₄+H₇ of A and B), 7.42 (br. s, 2H, H₅+H₆ of A), 7.58 (br. s, 2H, H₅+H₆ of B), 9.05 (s, 1H, OH, of A), 9.08 (s, 1H, OH, of B), 12.37 (s, 1H, NH).

2-[(2-Nitro-1-(4-ethoxyphenyl)propyl)thiomethyl]benzimidazole 3g

Yield: 34%, m.p.: 128-130 °C Anal. C₁₉H₂₁N₃O₃S (371.47)

Calc. (%): C: 61.44, H: 5.70, N: 11.31

Found. (%): C: 61.31, H: 5.58, N: 11.08

IR (KBr): ν (cm⁻¹) = 1540, 1360 (NO₂).

¹H-NMR (DMSO -d₆) : δ (ppm) = 1.26 (d, J_{d,c} = 6.72 Hz, 3H, H_d of B), 1.53 (d, J_{d,c} = 6.71 Hz, 3H, H_d of A), 1.29 (t, 3H, CH₃, of B), 1.30 (t, 3H, CH₃ of A), 3.87 - 3.66 (m, 2H, H_a+H_{a'} of A and B), 3.95 - 4.00 (m, 2H, CH₂, of A and B), 4.46 (d, J_{b,c} = 9.16 Hz, 1H, H_b of B), 4.46 (d, J_{b,c} = 9.16 Hz, 1H, H_b of A), 5.29 - 5.20 (m, 1H, H_c of A and B), 6.85 (d, 2H, H₃+H_{5'} of B), 6.88 (d, 2H, H₃+H_{5'} of A), 7.16 - 7.13 (m, 2H, H₄+H₇ of A and B), 7.28 (d, 2H, H₂+H_{6'} of B), 7.31 (d, 2H, H₂+H_{6'} of A), 7.50 (br. s, 2H, H₅+H₆ of A and B), 12.36 (s, 1H, NH).

2-[(2-Nitro-1-(4-dimethylaminophenyl)propyl)thiomethyl]benzimidazole 3h

Yield: 31%, m.p.: 126 - 128°C Anal. C₁₉H₂₂N₄O₂S (370.42)

Calc. (%): C: 61.60, H: 5.99, N: 15.22

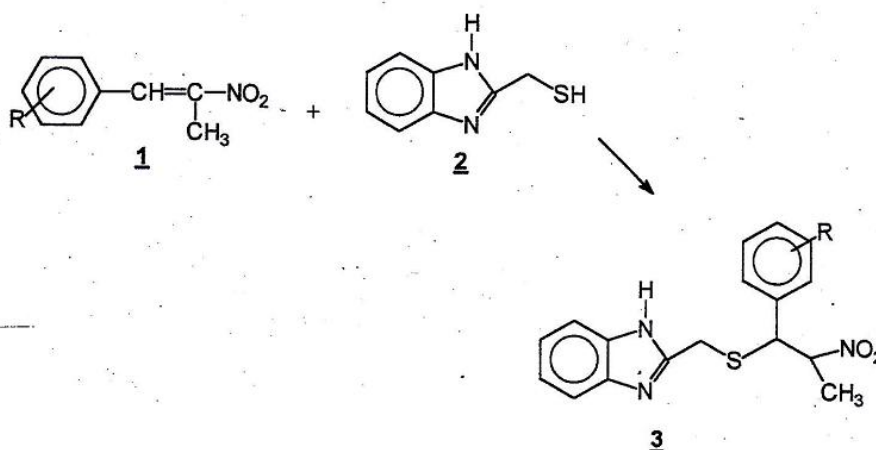
Found. (%): C: 61.70, H: 5.80, N: 14.91

IR (KBr): ν (cm⁻¹) = 1540, 1360 (NO₂).

¹H-NMR (DMSO -d₆) : δ (ppm) = 1.26 (d, J_{d,c} = 6.11 Hz, 3H, CH₃ of B), 1.52 (d, J_{d,c} = 6.71 Hz, 3H, CH₃ of A), 2.86 (s, 6H, N(CH₃)₂ of B), 2.88 (s, 6H, N(CH₃)₂ of A), 3.65-3.85 (m, 2H, CH₂ of A and B), 4.38 (d, J_{b,c} = 6.11 Hz, 1H, H_b of B), 4.40 (d, J_{b,c} = 6.10 Hz, 1H, H_b of A), 5.16-5.23 (m, 1H, H_c of A and B), 6.63-6.68 (m, 2H, H₃+H_{5'} of A and B), 7.14 - 7.21 (m, 4H, H₄+H₇+H₂+H_{6'} of A and B), 7.51-7.49 (br. s, 2H, H₅+H₆ of A and B), 12.32 (s, 1H, NH).

RESULTS AND DISCUSSION

The title compounds have been synthesized by the addition of 2-Mercaptomethylbenzimidazole **2** on appropriate β -methyl- β -nitrostyrenes **1**. Synthesis pathway of the addition product has been given in Scheme 1. The derivatives of **1** which are the starting material have been synthesized according to literature methods^{1,6-10} using proper benzaldehyde and nitroethane. Compounds **3** have been obtained by stirring ethanolic solution of 2-Mercaptomethylbenzimidazole **2** with the ethanolic solution of β -methyl- β -nitrostyrenes **1** at room temperature. As discussed in previous papers¹⁻⁵ the addition proceeds over thiol group.



Scheme 1: Synthesis of compound **3**.

Two doublets have been observed on the $^1\text{H-NMR}$ spectra of Compound **3** derivatives belonging to the protons of methyl group (H_d) located at β -position to nitro group approximately at $\delta=1.26$ ppm and $\delta=1.54$ ppm. According to the results of homonuclear spin decoupling spectra these two signals belong to two different compounds and in order to differentiate these two compounds the one with the methyl group signal at lower field ($\delta=1.54$ ppm) will be called as Compound A and the other ($\delta=1.26$ ppm) as Compound B.

We have observed the same situation with the Compound **4** derivatives which we have done before and interpreted it as the signals of two diastereomers². However it was confusing that the formation energies had been so close to each. We had to think about other possibilities. One of the ways to elucidate why methyl group gives two different signals has been to record the $^1\text{H-NMR}$ spectra at different temperatures and to observe if there is any change at the proportion of these signals. The $^1\text{H-NMR}$

spectrum of Compound 3a which has the highest proportion between the signals has been recorded first at 24°C, then kept at 70°C for 20 minutes and recorded again. While the proportions have been as A: 75%, B: 25% at room temperature (24°C), they turned out to be as A: 47%, B: 53% after being kept at 70°C. In other words the proportions had the reverse values. Bringing the temperature up to 100°C and waiting for 20 minutes did not change the proportions. The same NMR solution has been kept at room temperature allowing to cool down then recorded again revealing values as A: 44%, B: 56% (Fig 1). The observation of two methyl signals indicates that Compound 3 is a mixture of A and B. The variation at the intensity of methyl signals should be interpreted as that A and B are not stereoisomers but rotamers because diastereomers can not be converted to each other with heat.

Also on the ^1H -NMR spectra of other derivatives of Compound 3 the ratio of A and B rotamers has been determined referring to the intensity of two signals given by the methyl group.

Table 1: The ratios of rotamers A and B in Compound 3 derivatives.

3	R	A%	B%
a	H	75	25
b	Cl	45	55
c	NO ₂	42	58
d	CH ₃	47	53
e	OCH ₃	73	27
f	OH, OCH ₃	43	57
g	OC ₂ H ₅	35	65
h	N(CH ₃) ₂	50	50

Besides the changes mentioned above some others have also happened on the spectra recorded at high temperatures as follows: New singlets have come out at $\delta = 2.39$, 4.20 and 8.10 ppm, and the signal belonging to the proton of -NH group at $\delta = 12.43$ ppm has decreased notably on the spectrum recorded at 70°C and disappeared totally on the spectrum recorded at 100°C. On the contrary the intensity of the new signals has increased reciprocally. On the spectrum which has been recorded after being kept at the room temperature for two hours the signal of the -NH proton is restored at low intensity and the intensity of the new signals decrease proportionally. The splitting mode of the signals of all the other protons change notably and when examined carefully changes in the chemical shifts have also been observed to some extent (Fig 1).

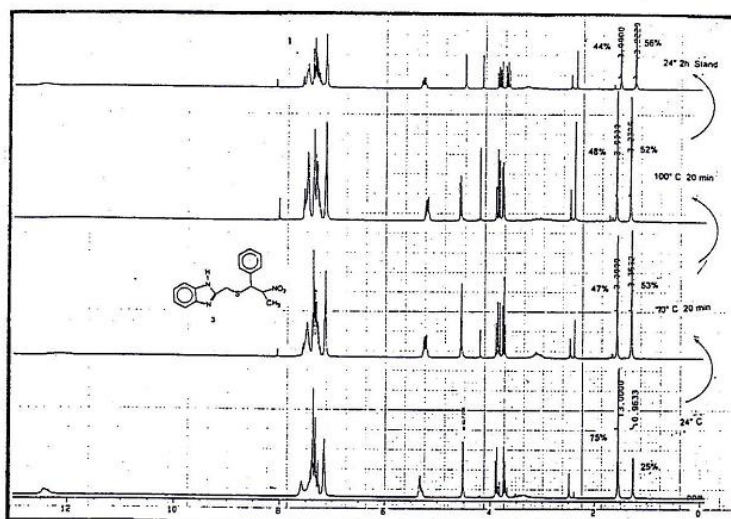
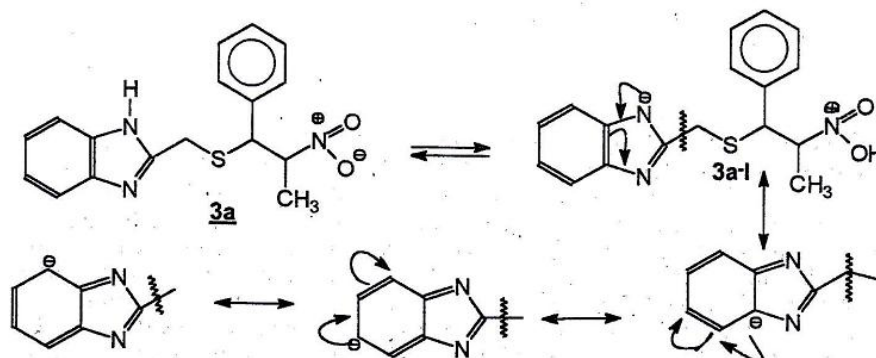


Figure 1: ^1H -NMR spectrum of compound **3a** recorded at different temperatures.

Among the aromatic protons particularly the signal of H_5+H_6 protons has shifted to $\delta = 7.50$ ppm from $\delta = 7.59$ ppm and splitting mode has also changed. With the signals of H_4+H_7 protons the change is observed as variation at splitting mode. The results which had been obtained from the spectra recorded at varying temperature can be interpreted as follows: With an increase at the temperature the proton sitting on -NH can be transferred onto the oxygen of nitro group providing a negative charge for the N-1 of benzimidazol ring and also creating an -OH instead of -NH (Scheme 2). It is thought that the signal appearing at $\delta = 8.10$ ppm belongs to -OH group. The variations of the signals of the protons belonging to benzimidazole ring can be attributed to the contribution of the negative charge to the delocalisation over the ring (Scheme 2).



Scheme 2: Probable structural formulae of Compound **3a** in DMSO-d_6 at elevated temperatures.

^1H -NMR and homonuclear spin decoupling spectra have been used for the structure elucidation of Compound 3 derivatives. When characteristic signals observed at the ^1H -NMR spectrum of Compound 3a are taken into consideration as an example, it can be said that methyl group (H_d) signals are observed as a doublet at $\delta = 1.26$ ppm (B) and $\delta = 1.55$ ppm (A). The doublets belonging to H_a and H_a' protons are observed for rotamer A at $\delta = 3.74$ ppm and 3.90 ppm and for rotamer B $\delta = 3.70$ and 3.84 ppm. With both of the rotamers only one doublet is observed for H_b at $\delta = 4.52$ ppm. The signal of H_c is observed as multiplet due to the fact that the signals of the rotamers mix each other (Fig. 2). Aromatic protons are observed at expected locations. Coupling constants of each compound have been calculated where possible and given in experimental section.

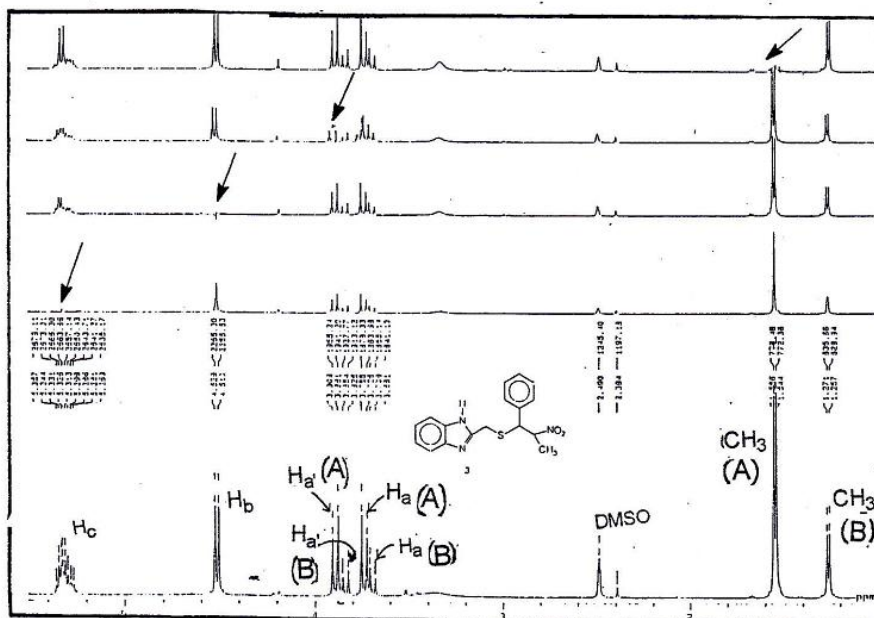


Figure2: ^1H -NMR spectrum of aliphatic protons and spin decoupling spectrum of 3a.

ACKNOWLEDGEMENTS

^1H -NMR spectra have been recorded by Shigeru ITO from Institute for Medical and Dental Engineering Tokyo Medical and Dental University, Tokyo-JAPAN.

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