

ALKYLATION AND ARALKYLATION OF N-HETEROCYCLES

IV. Methylation and Benzylation of 5 (or 6)-Nitro Benzimidazoles

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ABSTRACT

Methylation and benzylation of 5 (or 6)-nitro benzimidazoles have been carried out under uniform conditions and the structures of the products obtained have been established by comparison with authentic samples prepared by standard methods. In each case a mixture of 1, 5- and 1, 6-isomers has been obtained, the former being comparatively in larger proportion. The results are explained on the basis of tautomer stabilisation by and the deactivating influence of nitro group.

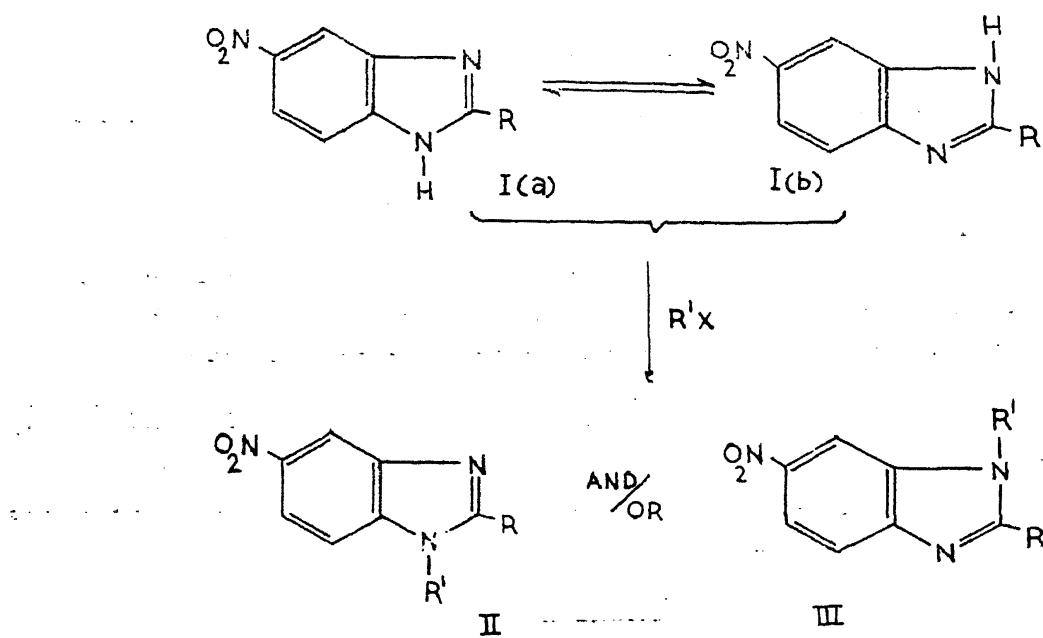
THE study of the tautomeric behaviour of 5 (or 6)-nitro benzimidazoles (I) was first made by Phillips.¹ Results of these studies, together with those obtained more recently by others under various experimental conditions, are summarised in Table I.

TABLE I

Results of N-substitution in tautomeric 5 (or 6)-nitro benzimidazoles (I)

Sl. No.	R (in I)	Reagent	Product		Reference
			Ratio of 1, 5- to 1, 6-isomer		
1	H	KO-SO ₃ CH ₃ +OH ⁻	15:1		2
2	CH ₃	(CH ₃) ₂ SO ₄	1:100		1
3	CH ₃	(CH ₃) ₂ SO ₄ +OH ⁻	1:5		1
4	CH ₃	HCl in CH ₃ OH	1, 6-isomer only		1
5	CH ₃	(CH ₃) ₂ SO ₄	1:1		3, 4
6	CH ₃	(CH ₃) ₂ SO ₄ + OH ⁻	1:1		3, 4
7	CH ₃	(C ₂ H ₅) ₂ SO ₄ + OH ⁻	1:8		5
8	C ₆ H ₅	C ₆ H ₅ CH ₂ Cl, CH ₃ COONa + I ₂	2:1		6

By heating 5 (or 6)-nitro-2-methyl benzimidazole (I, $R = CH_3$) with methanolic hydrogen chloride in a sealed tube Phillips¹ obtained 1, 2-di-methyl-6-nitro benzimidazole (III; $R = R' = CH_3$) as the exclusive product. Methylation by methyl sulphate, however, gave a mixture of 1, 5- and 1, 6-isomers (II and III, $R = R' = CH_3$) in 1:100 proportion. When alkali was used along with methyl sulphate 1, 5- and 1, 6-isomers were obtained in 1:5 proportion.



Somewhat different results were reported by Le Bris and Wahl.⁴ They observed only a slight decrease in the proportion of 1, 6-isomer when methylation was carried out under alkaline conditions. By heating 5 (or 6)-nitro benzimidazole (I, $R = H$) with potassium methyl sulphate in the presence of alkali, Aliprandi *et al.*² observed the preferential formation of 1, 5-isomer. Recently, Grimison and co-workers³ established that on methylation of tautomeric nitro-benzimidazoles by methyl sulphate with or without alkali, the two N-methyl isomers are obtained almost in equal proportion in addition to quaternary salt. Rao and Ratnam⁶ obtained a mixture of two N-benzyl derivatives by heating 5 (or 6)-nitro-2-phenyl benzimidazole with two moles of benzyl chloride. They obtained 1, 5- and 1, 6-isomers in 2:1 proportion.

The results obtained by Phillips are at variance with those obtained by later workers. In continuation of our study of tautomerism in benzimidazoles,⁷ we have undertaken a systematic study of methylation and benzylation of tautomeric 5 (or 6)-nitro benzimidazoles (I, $R = H, CH_3$ and C_6H_5) under more or less identical experimental conditions with a view to evaluate

the effect of substituents on the results of N-substitution and to evolve a satisfactory method of separation of isomeric N-substituted nitro benzimidazoles.

5 (or 6)-nitro and 5 (or 6)-nitro-2-methyl benzimidazoles have been obtained by the condensation of 4-nitro-*o*-phenylenediamine with formic and acetic acids by Phillips method⁸ and 5 (or 6)-nitro-2-phenyl benzimidazole has been obtained by the condensation of 4-nitro-*o*-phenylenediamine with benzoic acid in the presence of polyphosphoric acid. These tautomeric nitro benzimidazoles have been methylated and benzylated by the general methods.⁷ To characterise the products of methylation and benzylation, the required isomeric benzimidazoles (II, III) have been prepared by definite synthetic methods.

The results of methylation and benzylation are presented in Table II.

TABLE II
Results of methylation and benzylation of 5 (or 6)-nitro benzimidazoles (I)

Sl. No.	R (in I)	Conditions	Relative percentage yield of products	
			1, 5-isomer	1, 6-isomer
1	H	CH ₃ I, potassium carbonate in acetone, 40 hr.	60	35
2	CH ₃	do.	45	50
3	C ₆ H ₅	do.	60	35-40
4	H*	C ₆ H ₅ CH ₂ Cl, 170-180°	55	25
5	CH ₃ †	do.	12 hr.	55
6	C ₆ H ₅	do.	9 hr.	65

* Quaternary salt was obtained in about 15-20% yield.

† Quaternary salt was obtained in 10-15% yield.

No quaternary salt formation was observed on methylation of 5 (or 6)-nitro benzimidazoles. Benzylation by heating with one mole of benzyl chloride gave resinous products in addition to the mixtures of isomeric

N-benzyl-nitro benzimidazoles. Attempts to improve the yield of N-benzyl derivatives by using two moles of the reagent has resulted in the formation of quaternary salts as the sole products. The mixtures of isomers obtained on methylation and benzylation could be separated satisfactorily into the components by column chromatography using alumina as the adsorbant.

In 5 (or 6)-nitro benzimidazoles, the electronegative nitro group should stabilise the tautomer (I b), which favours the formation of 1, 5-isomer on N-alkylation and N-aralkylation by S_E2' mechanism. On methylation and benzylation of 5 (or 6)-nitro benzimidazoles mixtures of 1, 5- and 1, 6-isomers have been obtained, the former (II) being comparatively in larger proportion. However, due to general deactivating influence of the nitro group the nucleophilic power of the tertiary nitrogen in tautomer (I b) is considerably reduced. And the tautomer (I a) to the extent present, decidedly being more reactive species, can readily react leading to the formation of 1, 6-isomer. The formation of mixtures of 1, 5- and 1, 6-isomers on methylation and benzylation of tautomeric nitro-benzimidazoles can be explained on the basis of these two effects.

EXPERIMENTAL

5 (or 6)-nitro-2-phenyl benzimidazole.—Polyphosphoric acid was prepared by careful addition of phosphoric acid (6 ml.) to phosphorus pentoxide (10 g.) in a round bottomed flask. The flask was stoppered and heated on a boiling water-bath for four hours, when a syrupy liquid was obtained. This was mixed intimately with a finely powdered mixture of 4-nitro-*o*-phenylenediamine⁹ (4.6 g.) and benzoic acid (3.7 g.) and heated for another two hours. The reaction mixture was treated with cold water and the solid obtained was filtered, washed several times with sodium bicarbonate solution. The residue was extracted with 5% potassium hydroxide solution and the extracts on acidification gave a pale yellow solid (5 g.). Recrystallisation from alcohol gave almost a colourless compound, m.p. 203°, identical with 5 (or 6)-nitro-2-phenyl benzimidazole prepared by other method.¹⁰

N-methyl-2, 5-dinitro aniline.—2, 5-dinitro aniline (10 g.) was refluxed with methyl sulphate (10 g.) in dry acetone over anhydrous potassium carbonate on a steam-bath for forty hours. The residue obtained after the removal of acetone from the reaction mixture was washed with 10% sodium hydroxide solution, then with water and recrystallised from methanol, giving N-methyl-2, 5-dinitro aniline (6 g.) as dark red needles, m.p. 163°, identical with that obtained by Macmillan and Read¹¹ by different method.

N²-methyl-4-nitro-o-phenylenediamine.—Hydrogen sulphide was passed into a suspension of N-methyl-2, 5-dinitro aniline (5 g.) in alcohol (35 ml.) and liquor ammonia (20 ml.), maintaining the temperature at 50°. The reduction was complete in thirty minutes and the solution was left overnight in an ice-chest. The separated solid was filtered, washed with cold water and crystallised from benzene giving pure N²-methyl-4-nitro-o-phenylenediamine (3 g.), yellow plates, m.p. 184°, identical with that prepared by Phillips¹ by different method.

1-Methyl-2-phenyl-6-nitro benzimidazole.—A mixture of N²-methyl-4-nitro-o-phenylenediamine (1 g.), benzaldehyde (0.6 g.), alcohol (15 ml.) and nitrobenzene (15 ml.) was heated on a steam-bath for two hours. After the removal of alcohol, the reaction mixture was steam-distilled to remove nitrobenzene and unreacted aldehyde. The residue was washed several times with cold petroleum ether, recrystallised first from dilute alcohol and subsequently from acetone-petroleum ether yielding the pure 6-nitro benzimidazole, rectangular plates, m.p. 196° (Found: C, 66.2; H, 4.6; N, 16.7; C₁₄H₁₁N₃O₂ requires C, 66.4; H, 4.4; N, 16.6%).

N²-Benzyl-4-nitro-o-phenylenediamine.—N-Benzyl-2,5-dinitro aniline¹² (6.5 g.) was suspended in alcohol (60 ml.) and liquor ammonia (25 ml.) and reduced by passing a slow stream of hydrogen sulphide gas. The starting material went into solution in about half-an-hour and a dark red crystalline solid started separating out. The reduction was complete in about half-an-hour, reaction mixture was cooled to 0° and the diamine (3.5 g.) filtered and recrystallised from dilute alcohol giving dark red rectangular rods, m.p. 135° (Found: C, 63.8; H, 5.2; N, 17.1; C₁₃H₁₃N₃O₂ requires C, 64.2; H, 5.4; N, 17.3%).

1-Benzyl-6-nitro benzimidazole.—N²-Benzyl-4-nitro-o-phenylenediamine (1 g.) and formic acid (2 ml.) were condensed in the presence of polyphosphoric acid as described under the preparation of 5 (or 6)-nitro-2-phenyl benzimidazole. The reaction mixture was diluted with ice-cold water and made ammoniacal. The solid obtained was filtered and recrystallised from dilute alcohol giving pure 1-benzyl-6-nitro benzimidazole (0.5 g.), rectangular rods, m.p. 155° (Found: C, 66.6; H, 4.6; N, 16.8; C₁₄H₁₁N₃O₂ requires C, 66.4; H, 4.4; N, 16.6%).

1-Benzyl-2-methyl-6-nitro benzimidazole.—N²-Benzyl-4-nitro-o-phenylenediamine (1 g.) was condensed with acetic acid (2 ml.) in the presence of polyphosphoric acid. The solid obtained was recrystallised from dilute alcohol giving 1-benzyl-2-methyl-6-nitro benzimidazole (0.6 g.), aggregates of needles,

m.p. 188° (Found: C, 67.6; H, 4.7; N, 16.1; $C_{15}H_{13}N_3O_2$ requires C, 67.4; H, 4.9; N, 15.7%).

Methylation of 5 (or 6)-nitro benzimidazole.—A solution of 5 (or 6)-nitro benzimidazole (1.55 g.) and methyl iodide (1.4 g.) in dry acetone (100 ml.) was gently refluxed over fused potassium carborate for forty hours. After the removal of acetone, the reaction mixture was treated with cold water (100 ml.) and the solid (1.5 g.) obtained was filtered and washed with 5% potassium hydroxide solution to remove the starting material. The residue (0.85 g.) after washing with water and crystallisation from ethanol gave a solid, m.p. 145–160°, indicating it to be a mixture. 0.5 g. of this was dissolved in benzene (20 ml.) and subjected to column chromatography over alumina, using benzene as the eluant. First fractions gave a compound, m.p. 180° (A); last fractions contained a compound, m.p. 209° (B). The middle fractions gave mixtures of (A) and (B) and were resubmitted to chromatography. The compounds (A; 0.18 g. and B; 0.30 g.) have been identified as 1-methyl-6-nitro¹³-and 1-methyl-5-nitro¹⁴ benzimidazoles respectively.

Methylation of 5 (or 6)-nitro-2-methyl benzimidazole.—5 (or 6)-nitro-2-methyl benzimidazole (0.85 g.) on methylation by the general method gave a solid. This was washed with 5% potassium hydroxide solution and crystallised from alcohol giving a compound, m.p. 180–200° indicating it to be a mixture. It was chromatographically separated into components by passing the benzene solution of the methylation product (0.5 g. in 20 ml.) over a column of alumina. The pale yellow band on elution with benzene gave a compound (A; 0.25 g.), m.p. 250°, and the last elutions with benzene-chloroform mixture (1:1) gave another compound (B; 0.22 g.), m.p. 226°. The compounds A and B were characterised as 1, 2-dimethyl-6-nitro³- and 1, 2-dimethyl-5-nitro¹⁰ benzimidazoles respectively by comparison with authentic samples.

Methylation of 5 (or 6)-nitro-2-phenyl benzimidazole.—Methylation of 5 (or 6)-nitro-2-phenyl benzimidazole (1.0 g.) gave a colourless crystalline solid (1.28 g.), m.p. 148–155°, insoluble in 5% potassium hydroxide solution. This mixture was dissolved in benzene and passed over a column of alumina when a yellow band appeared. Elution of the yellow band with benzene gave a compound, m.p. 195° (A) identified as 1-methyl-2-phenyl-6-nitro benzimidazole by comparison with an authentic sample. The last elutions with benzene and benzene-methanol mixture (2:1) gave a compound, m.p. 186° (B), identical with 1-methyl-2-phenyl-5-nitro benzimidazole.¹⁵ 1, 5- and 1, 6-isomers were obtained in 3:2 proportion.

Benzylation of 5 (or 6)-nitro benzimidazole.—A mixture of 5 (or 6)-nitro benzimidazole (1.1 g.), freshly distilled benzyl chloride (0.8 g.), fused sodium acetate (1 g.) and a speck of iodine was heated on an oil-bath maintained at 160–180° for a period of twelve hours. The reaction mixture was treated with cold water, then triturated with 5% potassium hydroxide solution and filtered. The filtrate on acidification with acetic acid gave unreacted 5 (or 6)-nitro benzimidazole (0.15 g.), m.p. 203°. The residue (1.1 g.) from potassium hydroxide was washed with water, dried; 0.75 g. of the benzylation product was dissolved in benzene (15 ml.) and passed over a column of alumina and eluted with benzene when three products were obtained in the following order: Compound A (0.1 g.) prismatic rods from alcohol, m.p. 172–173°; Compound B (0.13 g.), rectangular rods from dilute alcohol, m.p. 155° and Compound C (0.27 g.), needles from dilute alcohol, m.p. 153°. On washing the column with benzene-ethanol (1:1) gave a resinous substance (0.2 g.) which did not crystallise. Product (A) analysed for 1:3 dibenzyl-5-nitro-benzimidazolium chloride (Found: C, 66.1; H, 4.9; N, 11.3; $C_{21}H_{18}ClN_3O_2$ requires C, 66.4; H, 4.7; N, 11.1%). Products (B) and (C) have been found to be identical in all respects with 1-benzyl-6-nitro and 1-benzyl-5-nitro¹⁶ benzimidazoles respectively, synthesised by unambiguous methods.

Benzylation of 5 (or 6)-nitro-2-methyl benzimidazole.—5 (or 6)-nitro-2-methyl benzimidazole (1.35 g.) was benzylated by the general method. The resinous solid obtained after washing with water was extracted with 5% potassium hydroxide solution till no more yellow colour was obtained. The alkali extracts on acidification with acetic acid gave (5 or 6)-nitro-2-methyl benzimidazole (0.2 g.), m.p. 220°. The alkali insoluble brown product was dried (1.3 g.). Benzene solution of 1.2 g. of the benzylation product was passed over a column of alumina and developed with benzene when four bands became visible. The yellow band on elution with benzene gave a compound (0.1 g.) tiny rods from alcohol, m.p. 208–209°. This analysed for 1, 3-dibenzyl-2-methyl-5-nitro benzimidazolium chloride (Found: C, 66.9; H, 5.5; N, 10.9; $C_{22}H_{20}ClN_3O_2$ requires C, 67.1; H, 5.2; N, 10.7%). The pale yellow band gave compound A (0.24 g.), aggregates of needles from alcohol, m.p. 188°, while the colourless zone gave compound B (0.36 g.), hexagonal plates from alcohol, m.p. 172°. Elution of the brownish-yellow zone at the top of the column with alcohol-benzene mixture gave a resinous substance (0.45 g.) which did not crystallise. The products A and B were identified as 1-benzyl-2-methyl-6-nitro- and 1-benzyl-2-methyl-5-nitro¹⁶ benzimidazoles respectively by comparison with synthetic samples.

Benzylation of 5 (or 6)-nitro-2-phenyl benzimidazole.—Benzylation of 5 (or 6)-nitro-2-phenyl benzimidazole (1 g.) by the general method gave a solid (0.85 g.), m.p. 140°, completely insoluble in 5% aqueous potash, thus clearly indicating that it was totally free from the starting material. The mixed melting point of the compound was found to be undepressed with the synthetic samples of 1-benzyl-2-phenyl-5-nitro- and 1-benzyl-2-phenyl-6-nitro benzimidazoles thereby indicating it to be a mixture. The mixture was separated by passing its benzene solution over a column of alumina. Elution with benzene gave a compound (A), m.p. 185°, yellow prismatic rods from acetone-petroleum ether mixture. The yellow band at the top of the column was eluted with benzene-alcohol mixture (1:1) when a compound (B) rectangular rods from acetone-petroleum ether, m.p. 159°, was obtained. The middle fractions contained the mixtures of (A) and (B) which could be resubmitted to chromatography. The compounds (A; 0.23 g. and B; 0.55 g.) have been found to be identical in all respects with 1-benzyl-2-phenyl-6-nitro- and 1-benzyl-2-phenyl-5-nitro benzimidazoles¹² respectively.

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