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.

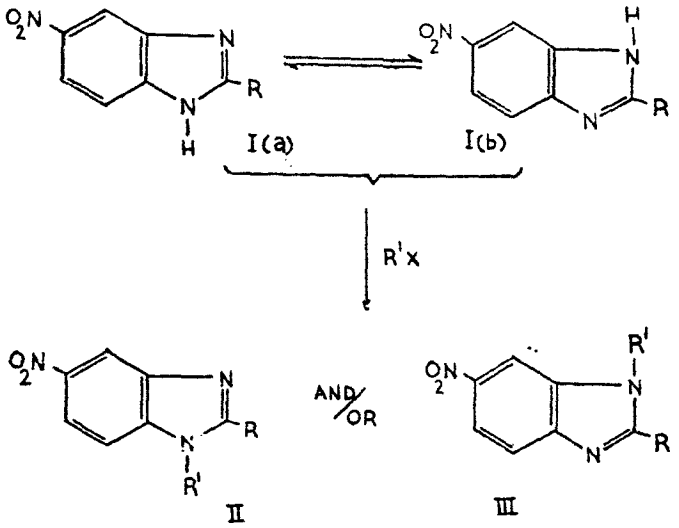
The study of the tautomeric behaviour of 5 (or 6)-nitro benzimidazoles (I) was first made by Phillips.[1] Results of these studies, together with those obtained more recently by others under various experimental conditions, are summarised in Table I.

Table I

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

Sl. No.	R (in I)	Reagent	Product: Ratio of 1, 5- to 1, 6-isomer	Reference
1	H	$KO-SO_3CH_3+OH^-$	15:1	2
2	CH_3	$(CH_3)_2SO_4$	1:100	1
3	CH_3	$(CH_3)_2SO_4+OH^-$	1:5	1
4	CH_3	HCl in CH_3OH	1, 6-isomer only	1
5	CH_3	$(CH_3)_2SO_4$	1:1	3, 4
6	CH_3	$(CH_3)_2SO_4 + OH^-$	1:1	3, 4
7	CH_3	$(C_2H_5)_2SO_4 + OH^-$	1:8	5
8	C_6H_5	$C_6H_5CH_2Cl$, $CH_3COONa+I_2$	2:1	6

By heating 5 (or 6)-nitro-2-methyl benzimidazole (I, R = CH_3) with methanolic hydrogen chloride in a sealed tube Phillips[1] obtained 1, 2-dimethyl-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-workers[3] 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 Ratnam[6] 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 method[8] 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_3I, potassium carbonate in acetone, 40 hr.	60	35
2	CH_3	do.	45	50
3	C_6H_5	do.	60	35–40
4	H*	$C_6H_5CH_2Cl$, 170–180°, CH_3COONa, I_2, 12 hr.	55	25
5	CH_3†	do. do. 12 hr.	55	35
6	C_6H_5	do. do. 9 hr.	65	35

* 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*-phenylenediamine[9] (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 Reade[11] by different method,

N^2-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 N^2-methyl-4-nitro-*o*-phenylenediamine (3 g.), yellow plates, m.p. 184°, identical with that prepared by Phillips[1] by different method.

1-*Methyl-2-phenyl-6-nitro benzimidazole.*—A mixture of N^2-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; $C_{14}H_{11}N_3O_2$ requires C, 66·4; H, 4·4; N, 16·6%).

N^2-Benzyl-4-nitro-o-phenylenediamine.— N-Benzyl-2,5-dinitro aniline[12] (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; $C_{13}H_{13}N_3O_2$ requires C, 64·2; H, 5·4; N, 17·3%).

1-*Benzyl-6-nitro benzimidazole.*—N^2-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; $C_{14}H_{11}N_3O_2$ requires C, 66·4; H, 4·4; N, 16·6%).

1-*Benzyl-2-methyl-6-nitro benzimidazole.*—N^2-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 carbonate 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-nitro[13]-and 1-methyl-5-nitro[14] 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-nitro[3]- and 1, 2-dimethyl-5-nitro[10] 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.