ALKYLATION AND ARALKYLATION OF N-HETEROCYCLES

Part III. Methylation and Benzylation of 5 (or 6)-Chloro Benzimidazoles

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ABSTRACT

Methylation and benzylation of 5 (or 6)-chloro 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 unambiguous methods. The results are explained on the basis of inductive (−I) and resonance (+M) effects of chlorogroup and the tautomer stabilisation.

INTRODUCTION

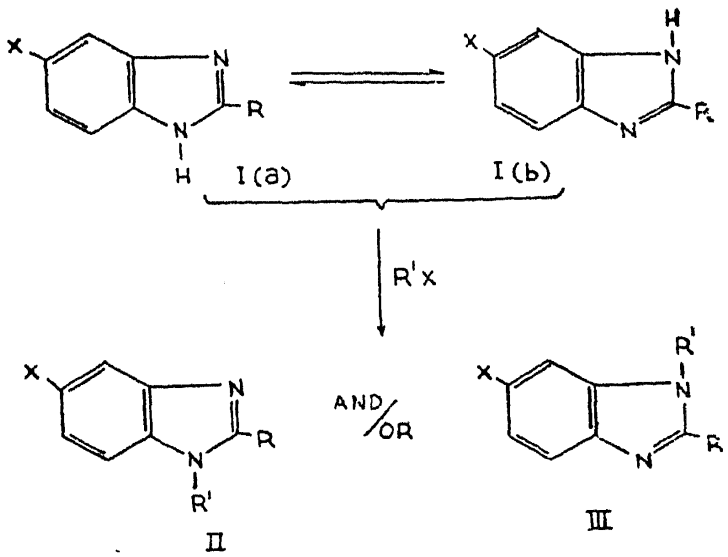
THE methylation of tautomeric halo benzimidazoles under different conditions, was first studied by Fischer and co-workers,[1, 2] later by Phillips[3] and more recently by Ridd and co-workers.[4] Their results are summarised in Table I.

Phillips concluded that the formation of 1, 6-isomer (III) is favoured when methyl sulphate is the methylating agent. In the presence of alkali, however, the proportion of 1, 6-isomer was observed to be reduced. Results obtained by the repetition of Phillips experiments by Smith and Ridd[4] suggested that the almost exclusive formation of 1, 6-isomer must be incorrect. Quite recently, Aliprandi *et al.*[5] obtained exclusively 1, 5-isomer (II) by the alkylation of 5 (or 6)-chloro benzimidazole (I; X = Cl; R = H) with potassium alkyl sulphates under alkaline conditions. Rao and Ratnam[6] reported the formation of 1, 5-isomer (II; X = Cl, R = C_6H_5 and R′ = $C_6H_5CH_2$) by refluxing 5 (or 6)-chloro-2-phenyl benzimidazole (I; X = Cl; R = C_6H_5) with 2 moles of benzyl chloride in the presence of fused sodium acetate and a speck of iodine.

TABLE I

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

Sl. No.	X	R	Reagent	Product — Ratio of 1, 5 to 1, 6-isomer	Reference
1	Cl	H	CH_3I in CH_3OH	Methiodide of 1, 6-isomer	1
2	Cl	H	$KOSO_3CH_3 + OH^-$	1, 5-isomer only	5
3	Cl	H	$(C_2H_5)_2SO_4 + OH^-$	,,	5
4	Cl	CH_3	CH_3I	Methiodide of 1, 5-isomer	2
5	Br	H	CH_3I	,,	2
6	Br	CH_3	CH_3I	,,	2
7	Br	CH_3	$(CH_3)_2SO_4$	1 : 50	3
8	Br	CH_3	$(CH_3)_2SO_4 + OH^-$	1 : 2	3
9	Br	CH_3	$(CH_3)_2SO_4$	1 : 1	4
10	Br	CH_3	$(CH_3)_2SO_4 + OH^-$	5 : 6	4
11	Br	CH_3	CH_3I in CH_3OH	1, 6-isomer only	3
12	Cl	C_6H_5	$C_6H_5CH_2Cl$, $CH_3COONa + I_2$	1, 5-isomer only	6



X = Cl or Br

The results obtained by earlier workers are so varying that no positive conclusions regarding the influence of substituents can be drawn. Hence it was considered desirable, in continuation of our studies of methylation and benzylation of 5 (or 6)-methyl benzimidazoles,[7] to carry out a systematic study of methylation and benzylation of 5 (or 6)-chloro benzimidazoles (I; X = Cl, R = H, CH_3 and C_6H_5).

5 (or 6)-Chloro- and 5 (or 6)-chloro-2-methyl banzimidazoles have been prepared from 4-chloro-*o*-phenylenediamine by Phillips method.[8] 5 (or 6)-Chloro-2-phenyl benzimidazole was obtainad by heating 4-chloro-*o*-phenylenediamine with benzoic acid under pressure.[9] To characterise the products of methylation and benzylation of these tautomeric benzimidazoles, the required N-substituted-5-chloro and 6-chloro benzimidazoles (II and III) have been obtained by unambiguous methods. Methylation and benzylation has been carried out as described earlier.[7] The mixtures obtained on benzylation of 5 (or 6)-chloro and 5 (or 6)-chloro-2-methyl benzimidazoles could not completely be separated into the components. However, they could be separated as methiodides by fractional precipitation. The results of methylation and benzylation are summarised in Table II.

TABLE II

Results of methylation and benzylation of 5 (or 6) Chloro Benzimidazoles (I)

Sl. No.	X	R	Conditions	Relative percentage yields of		
				1, 5-isomer	1, 6-isomer	Quaternary salt
1	Cl	H	CH_3I in acetone, potassium carbonate, 40 hours	100	..	..
2	Cl	CH_3	do.	100	..	..
3	Cl	C_6H_5	do.	50	..	50
4	Cl	H	$C_6H_5CH_2Cl$, CH_3COONa, I_2, 15 hrs., 170–180°C.	34	66	..
5	Cl	CH_3	do.	63	37	..
6	Cl	C_6H_5	do. 9 hr., 160–180°	100	..	..

In general, on methylation and benzylation of tautomeric halo benzimidazoles, the formation of 1, 5-isomer seems to be favoured.

It is well known that halogen atoms can exert inductive (—I) and mesomeric (+M) effects that oppose each other. By a study of pK_a values it has been shown[10–12] that all halo benzimidazoles are less basic than

benzimidazole regardless of position of substituent. The halogen atom must, therefore, exhibit a predominantly base-weakening effect (−I). The order of basicity for the halo benzimidazoles has been shown to be F>I>Cl>Br. Thus chlorine and bromine show a smaller mesomeric effect (+M) and their inductive effect (−I) is more noticeable. While pK_a values show that halogen atoms exert predominantly an inductive effect, the ultraviolet data[11] support the existence of resonance e ects similar to those observed for the halogenated benzenes.

In 5 (or 6)-chloro benzimidazoles (I; X = Cl; R = alkyl and aryl) if the electron attracting character of the chloro group predominates the tautomer (I *b*) is stabilised which reacts with the alkylating agent by S_E 2′-mechanism, resulting in the formation of 1, 5-isomer (II). But due to electromeric effects tautomer (I *a*) is likely to be stabilised leading to the formation of 1, 6-isomer (III). Normally, one would expect mixtures of 1, 5- and 1, 6-isomers to be obtained in the chloro compounds unless one of the effects is predominant. Since 1, 5-isomer is obtained exclusively on methylation, the inductive effect seems to be dominating. On benzylation of 5 (or 6)-chloro and 5 (or 6)-chloro-2-methyl benzimidazoles, mixtures of 1, 5- and 1, 6-isomers have been obtainad in 1 : 2 and 2 : 1 proportions respectively. These results indicate that both inductive and electromeric effects are operating. In the case of 5 (or 6)-chloro-2-phenyl benzimidazole, 1, 5-isomer alone has been obtained as reported by Rao and Ratnam.[6]

Experimental

1, 2-*Dimethyl-5-chloro benzimidazole*

N^1-Methyl-4-chloro-*o*-phenylenediamine[13] (1·2 g.) was condensed with acetic acid by refluxing in 4 N hydrochloric acid (25 ml.) for two hours. The reaction mixture was diluted, filtered free from solid impurities and basified with dilute ammonia when an almost colourless solid (1 g.) melting at 69–70° was obtained. This was dried at 110° for one hour and crystallised from benzene-petroleum ether to get pure 1, 2-dimethyl-5-chloro benzimidazole as colourless rectangular plates, m.p. 132–33° C. (Found: C : 59·5; H : 5·2; N : 15·6; $C_9H_9ClN_2$ requires C : 59·8; H : 5·0; N: 15·5%).

1-*Methyl-2-phenyl-5-chloro benzimidazole*

A mixture of N^1-methyl-4-chloro-*o*-phenylenediamine (1·5 g.) and benzaldehyde (1 g.) in alcohol (15 ml.) and nitrobenzene (10 ml.) was heated on a steam bath for two hours. After evaporation of the alcohol, the

reaction mixture was steam distilled to remove nitrobenzene and aldehyde. The dark brown residue (1 g.) was dried and recrystallised from alcohol and then repeatedly from benzene-petroleum ether to give pure 1-methyl-2-phenyl-5-chloro benzimidazole, m.p. 139-40° C. colourless plates (Found: C : 69·6; H : 4·9; N : 11·2; $C_{14}H_{11}ClN_2$ requires C : 69·3; H : 4·5; N : 11·5%).

1-Methyl-2-phenyl-6-chloro benzimidazole

Condensation of N^2-methyl-4-chloro-*o*-phenylenediamine[13] (1·5 g.) with benzaldehyde (0·9 g.) in alcoholic nitrobenzene and working out the reaction mixture gave a brown solid (1·1 g.). On recrystallisation from benzene-petroleum ether pure 1-methyl-2-phenyl-6-chloro benzimidazole was obtained as bushy needles, m.p. 124° (Found : C : 69·4; H : 4·8; N : 11·6; $C_{14}H_{11}ClN_2$ requires C : 69·3; H : 4·5; N : 11·5%).

The following methiodides were obtained by leaving over-night the appropriate 1-benzyl benzimidazole with methyliodide in benzene solution. The solid separated was filtered, washed with dry ether.

(*a*) 1-Benzyl-5-chloro benzimidazole methiodide; m.p. 215° (Found : C: 46·4; H : 3·9; N : 7·0; $C_{15}H_{14}Cl\,IN_2$ requires C : 46·8; H : 3·6; N : 7·3%).

(*b*) 1-Benzyl-2-methyl-5-chloro benzimidazole methiodide, m.p. 225° (Found : C : 48·6; H : 3·9; N : 7·2; $C_{16}H_{16}Cl\,IN_2$ requires C : 48·2; H : 4·0; N : 7·0%).

(*c*) 1-Benzyl-6-chloro benzimidazole methiodide; m.p. 182–83° (Found: C : 46·3; H : 3·3; N : 7·5; $C_{15}H_{14}Cl\,IN_2$ requires C : 46·8; H : 3·6; N : 7·3%).

(*d*) 1-Benzyl-2-methyl-6-chloro benzimidazole methiodide; m.p. 219–220° (Found : C : 47·9; H : 4·2; N : 7·4; $C_{16}H_{16}Cl\,IN_2$ requires C : 48·2; H : 4·0; N : 7·0%).

Methylation of 5 (or 6)-chloro benzimidazole

A solution of 5 (or 6)-chloro benzimidazole[1] (0·92 g.) and methyl-iodide (0·9 g.) in dry acetone (50 ml.) was gently refluxed over anhydrous potassium carbonate for forty hours. Acetone was evaporated, the residue was treated with cold water (100 ml.) and extracted with chloroform. The chloroform extracts were evaporated when a low melting solid (0·8 g.) was obtained. This was dissolved in dry acetone saturated with hydrogen chloride gas. The precipitated hydrochloride was filtered, washed with

benzene and recrystallised from ethanol-ether mixture giving colourless needles, m.p. 238° C. This was found to be identical in all respects with an authentic sample of 1-methyl-5-chloro benzimidazole hydrochloride[13] (m.p. 240–41°) and their mixed melting point was found to be undepressed.

Methylation of 2-*methyl*-5 (*or* 6)-*chloro benzimidazole.*

Methylation of 2-methyl-5 (or 6)-chloro benzimidazole[2] (0·68 g.) gave a low melting solid. This was dissolved in dry chloroform and saturated with hydrogen chloride gas and the precipitated hydrochloride (m.p. 273°) was filtered and decomposed by the addition of ammonia when a compound (0·55 g.), m.p. 65° was obtained. This was dried at 110° for one hour and recrystallised from benzene-petroleum ether giving colourless rectangular rods, m.p. 132°. By comparison with synthesised 1, 2-dimethyl-5-chloro and 6-chloro[13] benzimidazoles this compound was found to be identical with the former. Its mixed melting point with 1, 2-dimethyl-5-chloro benzimidazole was undepressed (131°) whereas that with 1, 2-dimethyl-6-chloro benzimidazole was depressed (90–102°).

Methylation of 5 (*or* 6)-*chloro-2-phenyl benzimidazole*

Methylation of 2-phenyl-5 (or 6)-chloro benzimidazole[9] (0·8 g.) with methyl iodide (0·7 g.) gave a solid (0·8 g.). This was triturated with dry banzene (100 ml.) and the insoluble compound (0·4 g.) was filtered. It recrystallised from benzene-alcohol mixture as colourless needles, m.p. 236–38° and analysed for 1, 3-dimethyl-2-phenyl-5-chloro benzimidazolium iodide (Found: C : 46·5; H : 3·9; N : 7·0; $C_{15}H_{14}Cl\,IN_2$ requires C: 46·8; H : 3·7; N : 7·3%). The residue (0·4 g.) obtained on evaporation of the benzene solution, crystallised from benzene petroleum ether mixture as colourless plates, m.p. 140°. This was found to be identical with a synthetic sample of 1-methyl-2-phenyl-5-chloro benzimidazole in crystalline shape and their mixed melting point was undepressed. However, it differed from 1-methyl-2-phenyl-6-chloro benzimidazole in crystalline shape and their mixed melting point was depressed (88–102°).

Benzylation of 5 (*or* 6)-*chloro benzimidazole*

5 (or 6)-Chloro benzimidazole (1·5 g.), freshly distilled benzyl chloride (1·2 g.) fused sodium acetate and a speck of iodine were thoroughly mixed and heated for fifteen hours on an oil-bath maintained at 170–80°. The reaction mixture while still hot was poured into crushed ice with vigorous stirring. The solid obtained was filtered and washed repeatedly with cold

petroleum ether. On crystallisation from dilute alcohol a colourless solid (1·7 g.) melting at 80–100° was obtained. Its mixed melting point with authentic samples of 1-benzyl-5-chloro[14] and 1-benzyl-6-chloro[13] benzimidazoles was undepressed. This could not be separated into the components directly. 0·5 g. of the benzylation product was converted into methiodide (m.p. 160–170°) by leaving overnight its benzene solution with methyl iodide. The mixture of methiodides thus obtained was dissolved in chloroform and fractional precipitation by the addition of small quantities of petroleum ether (60–80°) gave compound A (0·23 g.) m.p. 214° in the first fractions, whereas last fractions gave compound B (0·45 g.) m.p. 180°. The compounds (A) and (B) were found to be methiodides of 1-benzyl-5-chloro and 1-benzyl-6-chloro benzimidazole respectively by comparison with authentic samples.

Benzylation of 2-methyl-5 (or 6)-chloro benzimidazole

Benzylation of 2-methyl-5 (or 6)-chloro benzimidazole (1·2 g.) by general method gave a colourless compound (1·3 g.), m.p. 85–102°, indicating it to be a mixture. This could be resolved into its components by converting 0·5 g. of the material into methiodides (m.p. 200–10°) and by fractional precipitation from the acetone solution by the addition of small quantities of petroleum ether. Compound A (0·42 g.) m.p. 224° obtained in the first fractions and compound B (0·25 g.), m.p. 220° from the last fractions were found to be identical in all respects with authentic samples of 1-benzyl-2-methyl-5-chloro and 6-chloro benzimidazole methiodides respectively.

Benzylation of 2-phenyl-5 (or 6)-chloro benzimidazole

Benzylation of 2-phenyl-5 (or 6)-chloro benzimidazole (1·0 g.) at 160–80° for nine hours by the general method, gave a resinous solid which on treatment with a little alcohol gave a granular solid (0·88 g). This was recrystallised from alcohol yielding prismatic rods, m.p. 170°, found to be identical with synthesised 1-benzyl-2-phenyl-5-chloro benzimidazole[15] in crystalline shape and melting point. Their mixed melting point was found to be undepressed; whereas its mixed melting point with 1-benzyl-2-phenyl-6-chloro benzimidazole[15] was depressed (45–50°).

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