ALKYLATION AND ARALKYLATION OF N-HETEROCYCLES

Part II.* Methylation and Benzylation of 5 (or 6)-Methyl Benzimidazoles

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Received August 10, 1968

ABSTRACT

Methylation and benzylation of 5 (or 6)-methyl benzimidazoles has been carried out under uniform conditions. The structures of the products obtained have been established by comparison with authentic samples prepared by unambiguous methods. The results obtained are explained on the basis of inductive effect of the methyl group and the relative basicity of the two nitrogen atoms.

INTRODUCTION

THE tautomeric character of 5 (or 6)-methyl benzimidazoles was first established by Fischer and co-workers.[1–3] Methylation of 2, 5 (or 6)-dimethyl benzimidazole[2] (I, R = CH_3) with methyl iodide was reported to give a separable mixture of 1, 2, 5- (II, R=R′ = CH_3) and 1, 2, 6- (III, R, R′=CH_3) trimethyl benzimidazoles in almost equal proportion in addition to 1, 2, 3, 5-tetramethyl benzimidazolium iodide (IV, R = R′ = CH_3). It was also shown that (II) and (III) with excess of methyl iodide gave the same methiodide[3] (IV), thus indicating the possibility of formation of isomeric benzimidazoles from tautomeric benzimidazoles by N-substitution and the formation of one and the same benzimidazolium salt on quaternisation of either isomer.

The benzimidazole obtained by Bamberger and Lorenzen[4] by the action of methyl iodide on the sodium and silver salts of 2, 5 (or 6)-dimethyl benzimidazole was assigned the structure (II, R, R′ = CH_3) by Phillips.[5] The results obtained by Phillips and more recently by others are summarised in Table I.

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* Part I: Rao and Ratnam, *J. Chem. Soc.*, 1959, p. 3087.

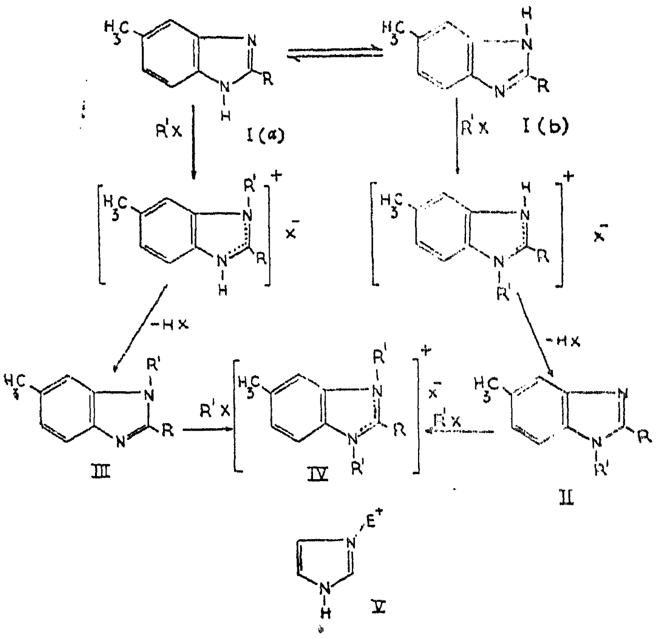

TABLE I

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

S.No.	R (in I)	Reagent	Product	Reference
			Ratio of 1, 5- to 1, 6-isomer	
1.	H	CH_3I in CH_3OH.	1, 6-isomer only	5
2.	H	$(CH_3)_2SO_4$	1 : 10	5
3.	H	$(CH_3)_2SO_4+OH^-$	1 : 1	5
4.	H	$CH_3SO_3-OK+OH^-$	9 : 1	6
5.	CH_3	CH_3I in CH_3OH	1, 2, 5-isomer and its methiodide	5
6.	CH_3	$(CH_3)_2SO_4$	1 : 10	5
7.	CH_3	$(CH_3)_2SO_4+OH^-$	1 : 1	5
8.	C_6H_5	$C_6H_5CH_2Cl$, $CH_3COONa+I_2$	1, 2, 6-isomer only	7

The results obtained by Fischer do not throw sufficient light on the tautomeric behaviour of 5 (or 6)-methyl benzimidazoles, since in most cases the products of alkylation were quaternary salts. The results obtained by Phillips indicate that the course of N-substitution to a large extent depends on the experimental conditions of alkylation. The oily product obtained on methylation of 5 (or 6)-methyl benzimidazole[5] by methyl iodide was presumed to be 1, 6-isomer (III, $R = H, R' = CH_3$), without establishing its identity with an authentic sample. Further, the position of methyl group in " 2, 2′-dimethyl-3′-benzyl benzimidazole " obtained by Bamberger and Lorenzen[4] by allowing benzyl chloride to react with 2, 5 (or 6)-dimethyl benzimidazole in ethanolic sodium ethoxide is left undecided.

In view of the varying results obtained under different conditions of alkylation, a study of methylation and benzylation of tautomeric 5 (or 6)-methyl benzimidazoles (I, $R = H$, CH_3 and C_6H_5) has been undertaken, adopting throughout the same experimental conditions in order to evaluate the possible influence of substituents on the course of N-substitution.

5 (or 6)-Methyl[5]-, 2, 5 (or 6)-dimethyl[5]-, and 2-phenyl-5 (or 6)-methyl[8] benzimidazoles have been prepared by standard methods. To characterise the products of N-substitution the required N-substituted 5-methyl and 6-methyl benzimidazoles have been obtained by unambiguous methods.[9] In addition, 1, 5-dimethyl-2-phenyl and 1, 6-dimethyl-2-phenyl benzimidazoles have now been prepared for this purpose. Methylation and benzylation have been carried out using only one mole of the reagent under mild alkaline conditions to minimise the chances of quaternisation. Methylations have been carried out by refluxing the benzimidazole for several hours with methyl iodide in dry acetone in the presence of anhydrous potassium carbonate. The benzimidazoles have been benzylated using freshly distilled benzyl chloride in the presence of fused sodium acetate and a speck of iodine.[7] The results of methylation and benzylation are included in Table II.

In the methylation of all the three benzimidazoles used, formation of quaternary salt (IV) was noticed. Benzylation of 5 (or 6)-methyl benzimidazole at 100° led to the formation of quaternary salt in considerable quantities. However, on benzylation at 170–80° no quaternary compounds were isolated. In the case of 2, 5 (or 6)-dimethyl benzimidazole benzylation above 100° seems to resinify the product. At 100° a good yield of N-benzyl derivative together with some quaternary salt has been obtained. Quaternary salts could be separated from the free bases taking advantage of the insolubility of the former in dry benzene. The N-methyl isomers obtained on methylation of 5 (or 6)-methyl benzimidazole were separated by chromatography over alumina. The mixture of N-benzyl isomers obtained on benzylation, however, could be satisfactorily separated into its components by fractional crystallisation from aqueous ethanol,

TABLE II

Results of methylation and benzylation of 5 (*or* 6)-*methyl benzimidazoles* (*I*)

S.No.	R (in I)	Conditions	Relative percentage yield of Products		
			1, 5-isomer	1, 6-isomer	Quaternary salt
1.	H	CH_3I in acetone, potassium carbonate, 40 hrs.	23	47	30
2.	CH_3	CH_3I in acetone, potassium carbonate, 40 hrs.	55	..	45
3.	C_6H_5	CH_3I in acetone, potassium carbonate, 40 hrs.	50	..	50
4.	H	$C_6H_5CH_2Cl$, CH_3COONa I_2, 12 hrs., 170—180°	37	63	..
5.	CH_3	$C_6H_5CH_2Cl$, CH_3COONa, I_2, 12 hrs., 100°	..	64	36
6.	C_6H_5	$C_6H_5CH_2Cl$, CH_3COONa, I_2, 10 hrs., 170°	..	100	..

The orientation of N-substitution in imidazole derivatives depends on the mechanism and type of species involved. Under neutral conditions methylation of imidazoles was shown to involve the neutral molecule by S_E2'-mechanism,[10, 11] *i.e.*, attack by the electrophilic reagent (E^+) at the tertiary nitrogen atom of the ring followed by the proton loss from the imino group (V). The same mechanism can be extended to 5 (or 6)-sustituted benzimidazoles. Unlike in imidazole, the problem is not so simple in 5 (or 6)-methyl benzimidazoles, since they can exist as a mixture of two tautomers (I *a* and I *b*). The electron release by the methyl group in the benzene ring would be expected to increase the electron density, at the nitrogen para to the methyl group. If tautomer ratio is the measure of relative basicity of two nitrogen atoms, structure (I *a*) would be more stable and predominant. Methylation of 5 (or 6)-methyl benzimidazole gave a mixture of 1, 5- and 1, 6-isomers, the latter being obtained comparatively in larger proportion. The formation of 1, 6-isomer can be expected by the attack of the alkylating agent at the tertiary nitrogen atom in the tautomer

(I *a*) followed by dehydrohalogenation. However, the expected relation between the basicity of nitrogen and its nucleophilic power suggests that the tautomer (I *b*) present in low concentration will have the higher rate coefficient for substitution by S_E2'-mechanism. Thus the tautomer (I *b*) to the extent it is present is likely to be more reactive and can form 1, 5-isomer. Thus the formation of 1, 5- and 1, 6-isomers can be explained. On methylation of 2, 5 (or 6)-dimethyl benzimidazole and 5 (or 6)-methyl-2-phenyl benzimidazole besides 1, 5-isomer considerable amounts of quaternary salts are formed. During the alkylation if quaternary salt is formed it is difficult to interpret, as it might have been formed from 1, 6-isomer or 1, 5-isomer. In the case of 5 (or 6)-methyl benzimidazoles it may be expected that 1, 6-isomer is formed first and that it undergoes quaternisation later. The substituent in 2-position of tautomeric benzimidazole does not seem to have any significant effect in tautomer stabilisation, since it is symmetrically situated with respect to both nitrogens. In this respect benzylation experiments are more helpful as the quaternary salts are not formed in two cases and the formation of 1, 6-isomer in larger amounts on benzylation is in accordance with the mechanism proposed earlier.[7]

EXPERIMENTAL

1, 5-*Dimethyl-2-phenyl benzimidazole*.—To N^1-methyl 4-methyl-*o*-phenylenediamine[12] (1·5 g.) in alcohol (15 ml.) was added benzaldehyde (1·2 g.) and nitrobenzene (15 ml.) and refluxed for two hours. The solution remaining after the evaporation of alcohol was steam-distilled to remove nitrobenzene and unreacted aldehyde. The residue (1·0 g.) after crystallisation from dilute alcohol and finally from petroleum ether gave 1, 5-dimethyl-2-phenyl benzimidazole as colourless needles, m.p. 131° (Found: C : 81·3; H : 6·5; N : 12·3. $C_{15}H_{14}N_2$ requires C : 81·1; H : 6·3; N : 12·6%).

1, 6-*Dimethyl-2-phenyl benzimidazole*.—Condensation of N^2-methyl-4-methyl-*o*-phenylene-diamine[12] (1·2 g.) with benzaldehyde in alcoholic nitrobenzene gave crude 1, 6-dimethyl-2-phenyl benzimidazole (0·75 g.). On crystallisation first from alcohol and finally from ethyl acetate-petroleum ether mixture the pure benzimidazole was obtained as colourless bushy needles, m.p. 138° (Found : C : 81·3; H : 6·6; N : 12·4. $C_{15}H_{14}N_2$ requires C : 81·1; H : 6·3; N : 12·6%).

Methylation of 5 (*or* 6)-*methyl benzimidazole*.—A mixture of 5 (or 6)-methyl benzimidazole (1·3 g.) and methyl iodide (1·5 g.) in dry acetone (50 ml.) was refluxed over anhydrous potassium carbonate for forty hours. After evaporation of acetone, water (100 ml.) was added to the residue and extracted with several small portions of chloroform. The chloroform extracts were dried and evaporated. The gummy residue obtained was treated with dry benzene (50 ml.) when the insoluble quaternary salt (0·25 g.) separated out. It crystallised from alcohol in needles, m.p. 227° and analysed for 1, 3, 5-trimethyl benzimidazolium iodide (Found: C : 41·5; H: 4·8; N : 9·5. $C_{10}H_{13}IN_2$ requires C : 41·7; H : 4·5; N : 9·7%).

The low melting solid obtained on evaporation of filtrate was dissolved in benzene (15 ml.) and chromatographed over alumina. The yellow band separated was eluted with benzene. First elutions gave compound (A), colourless needles from petroleum ether (40–60°), m.p. 74°. The final elutions with benzene-ethyl acetate mixture (2 : 1) gave compound (B), colourless needles from benzene-petroleum ether, m.p. 95°. The middle fractions gave an oil, which on resubmitting to chromatography gave further quantities of (A) and (B). The yields of (A) and (B) were 0·4 g. and 0·2 g. respectively. (A) and (B) have been found to be identical in all respects with 1, 6-dimethyl[13] and 1, 5-dimethyl[14] benzimidazoles respectively, synthesised by unambiguous methods.

Methylation of 2, 5 (*or* 6)-*dimethyl benzimidazole*.—Methylation of 2, 5 (or 6)-dimethyl benzimidazole (1·6 g.) with methyl iodide (1·6 g.) in acetone over potassium carbonate gave a low melting solid. This was triturated with benzene (75 ml.) and the insoluble quaternary salt was filtered (0·5 g). It crystallised from alcohol as rectangular rods, m.p. 165–66°, and analysed for 1, 2, 3, 5-tetramethyl benzimidazolium iodide (Found: C : 43·5; H : 5·2; N : 9·1; $C_{11}H_{15}IN_2$ requires C : 43·7; H : 5·0; N: 9·3%). The residue obtained on evaporation of the filtrate (0·6 g.) was recrystallised from petroleum ether (40–60°) giving colourless needles, m.p. 140°. This compound was found to be identical in all respects with a synthetic sample of 1, 2, 5-trimethyl benzimidazole.[12] Its mixed melting point with 1, 2, 6-trimethyl benzimidazole[12] was depressed (80–98°).

Methylation of 5 (*or* 6)-*methyl-2-phenyl benzimidazole*.—Methylation of 5 (or 6)-methyl-2-phenyl benzimidazole (0·65 g.) with methyl iodide (0·5 g.) in dry acetone over potassium carbonate gave a solid. This was treated with dry benzene (50 ml.). The benzene insoluble compound (0·2 g.), crystallised from acetone petroleum ether in colourless needles, m.p. 215° and analysed for 1, 3, 5-trimethyl-2-phenyl benzimidazolium iodide (Found : C : 52·4; H : 4·9; N : 7·4. $C_{16}H_{17}IN_2$ requires C : 52·7; H : 4·6; N : 7·7%). The filtrate was passed over a column of alumina. Elution with benzene gave a compound (A; 0·2 g.), colourless plates m.p. 130°, from benzene petroleum ether. Final elutions with ethylacetate-benzene gave a compound (B; 0·12 g.), m.p. 242°. By comparison with authentic samples A and B were found to be identical with 1, 5-dimethyl-2-phenyl and 5 (or 6)-methyl-2-phenyl benzimidazoles repectively.

Benzylation of 5 (*or* 6)-*methyl benzimidazole.*—A mixture of 5 (or 6)-methyl benzimidazole (0·95 g.), freshly-distilled benzyl chloride (0·9 g.), fused sodium acetate (1·0 g.) and a speck of iodine was heated on an oil-bath maintained at 170–80° for twelve hours. The reaction mixture while still hot was poured into crushed ice with vigorous stirring and the solid (0·9 g.) separated was filtered and recrystallised from alcohol giving a colourless solid, m.p. 120–30°. Crystallisation of this from dilute alcohol (1 : 2) gave a compound m.p. 170° rectangular rods (A; 0·5 g.) and the filtrate on concentration gave a compound, m.p. 140° (B; 0·3 g.), colourless rectangular plates. A and B were identical with 1-benzyl-6-methyl and 5-methyl benzimidazoles respectively by comparison with synthetic samples.[9]

Benzylation of 2, 5 (*or* 6)-*dimethyl benzimidazole.*—Benzylation of 2, 5 (or 6)-dimethyl benzimidazole (0·6 g.) with benzyl chloride (0·55 g.) in the presence of fused sodium acetate and iodine on water-bath for twelve hours gave a low melting solid. It was washed several times with cold water and then with cold petroleum ether. The residue was treated with dry benzene (50 ml.) and the benzene-insoluble compound (0·2 g.) was filtered and recrystallised from alcohol in hexagonal plates, m.p. 261–62°. This analysed for 1, 3-dibenzyl-2, 5-dimethyl benzimidazolium chloride (Found: C : 75·9; H : 6·2; N : 7·5. $C_{23}H_{23}ClN_2$ requires C : 76·1; H: 6·2; N : 7·7%). The solid obtained on evaporation of the benzene solution was purified by recrystallisation from aqueous ethanol (1 : 2) giving colourless plates (0·35 g.), m.p. 141°. This was found to be 1-benzyl-2, 6-dimethyl benzimidazole by comparison with synthetic samples of 1-benzyl-2, 5- and 2, 6-dimethyl benzimidazoles.[9]

Benzylation of 5 (*or* 6)-*methyl-2-phenyl benzimidazole.*—5 (or 6)-Methyl-2-phenyl benzimidazole (1·5 g.) was benzylated by heating with benzyl chloride (0·8 g.) in the presence of sodium acetate and iodine, at 170–80° for twelve hours. The reaction mixture was added to excess of crushed ice when a resinous solid separated out which when treated with a little alcohol gave a granular solid (1·39 g.). This was filtered and recrystallised from alcohol and benzene yielding colourless prismatic rods, m.p. 195°. This was found to be identical with an authentic sample of 1-benzyl-2-phenyl-6-methyl benzimidazole.[7]

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