36. *Nucleophilic Substitution Reactions of 2-Chlorobenzimidazoles. Part I. Formation of Benzimidazolin-2-ones and 2-Alkoxybenzimidazoles.*

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The preparation of two new 2-chlorobenzimidazoles is described. The reactions of 2-chlorobenzimidazoles with sodium alkoxides, aqueous sodium hydroxide, hydrochloric acid, and glacial acetic acid have been studied. The ease of displacement of chlorine from these compounds depends on whether they are present in the reaction mixture largely as the anion, the cation, or the neutral molecule. Steric effects are apparent in the behaviour of the 1-substituted compounds.

CONFLICTING statements have been made about the ease of nucleophilic displacement of the halogen atom from 2-chlorobenzimidazoles.[1] Previous studies [2] have been limited to reactions with ammonia, amines, and hydrazine. The present work aims to extend the range of nucleophiles examined and to investigate possible preparative uses of these reactions.

The preparation of several 2-chlorobenzimidazoles has been described previously,[3] and in addition two new compounds have been prepared for the present study. 2-Chloro-1-isopropylbenzimidazole and 2-chloro-5,6-dinitrobenzimidazole were obtained by the action of phosphoryl chloride on the appropriate benzimidazolin-2-one.

In nitrogen heterocyclic compounds the ring carbon atoms may be classified as π-excessive or π-deficient.[4] For benzimidazole, calculations [5] suggest that whilst the 4-, 5-, 6-, and 7-positions are π-excessive, the 2-position is π-deficient. In most nucleophilic substitutions of heterocyclic compounds which occur under moderate conditions, the group displaced is attached originally to a π-deficient carbon atom. However, in studying the reactivity of the 2-chlorobenzimidazoles, factors other than the electron density at the 2-position must be considered. The 2-chlorobenzimidazoles are amphoteric compounds, and in solution, cations, anions, and neutral molecules are present, their relative concentrations being determined by the pH of the medium. Substituents in the benzene ring (and in the 1-position) may modify the apparent ease of displacement of the halogen both by their effect on the electron density at the ring carbon atom concerned, and by altering the pK_a values and hence the position of the acid-base equilibria. The latter determines the predominant species available for nucleophilic attack. It would be expected that for a particular compound, the ease of nucleophilic substitution would

[1] Hofmann, " The Chemistry of Heterocyclic Compounds. Imidzole and its Derivatives, Part I," Interscience Publ. Inc., New York, 1953, p. 302; Schipper and Day, " Heterocyclic Compounds," ed. Elderfield, Wiley, New York, 1956, Vol. V, p. 285.

[2] Hunger, Kebrle, Rossi, and Hofmann, *Helv. Chim. Acta*, 1961, **44**, 1273; James and Turner, *J.*, 1950, 1515; Bednyagina and Postovskii, *Zhur. obshchei Khim.*, 1960, **30**, 1431; Efros, Porai-Koshits, and Farbenstein, *ibid.*, 1953, **23**, 1691.

[3] Harrison, Ralph, and Smith, *J.*, 1963, 2930.

[4] Albert, " Heterocyclic Chemistry," Athlone Press, London, 1959, p. 31.

[5] Brown and Heffernan, *J.*, 1956, 4288.

decrease in the order cation > neutral molecule > anion. For 1-substituted 2-chlorobenzimidazoles, as for 2-chlorobenzoxazoles and 2-chlorobenzothiazoles, the situation is simplified as only cations or neutral molecules may be present. Thus when these compounds are treated with solutions of sodium alkoxides it may be assumed that the species attacked is the neutral molecule. But for the corresponding reaction of 2-chlorobenzimidazoles without 1-substituents, all of which have pK_a values (proton loss) of less than 10, the substrate will be almost entirely present as the anion which is very resistant to nucleophilic attack. In agreement with this, it is found that the powerful nucleophilic reagents OR^- (R = Me, Et, or t-Bu) fail to displace chlorine from 2-chlorobenzimidazole, 2-chloro-5-methylbenzimidazole, 2-chloro-5-nitrobenzimidazole, or 2-chloro-5,6-dinitrobenzimidazole, although in the last two compounds the electron density at the 2-position must be greatly reduced by the influence of the nitro-groups. 2-Chloro-1-methylbenzimidazole however, like 2-chlorobenzothiazole,[6] reacts readily with solutions of sodium methoxide or ethoxide in the corresponding alcohol yielding 2-alkoxy-compounds. Even this reaction has limitations, for 2-chloro-1-isopropylbenzimidazole reacts very slowly with sodium methoxide or ethoxide, and 2-chloro-1-methylbenzimidazole gave no alkoxy-compound with sodium t-butoxide. These observations suggest that steric hindrance may reduce the reactivity even where other factors are favourable.

As the 2-chlorobenzimidazoles are stable in cold or hot water, their behaviour with aqueous acids and alkalies merited investigation. 2-Chlorobenzimidazole, 2-chloro-5-methylbenzimidazole, and 2-chloro-1-methylbenzimidazole are not affected by prolonged action of aqueous hydrochloric acid or sodium hydroxide of any concentration at temperatures up to the boiling point. The failure of the 1-methyl compound to react with aqueous sodium hydroxide, although reaction with sodium methoxide or ethoxide occurs readily, is probably a result of decreased nucleophilic power of the attacking reagent (OH^-) as compared with OR^-. The 2-chlorobenzimidazoles with *Bz*-nitro-substituents are also inert to aqueous alkali, but the 5-nitro-compound is converted into the benzimidazolin-2-one by mineral acid more readily than has previously been supposed,[7] and the 5,6-dinitro-compound undergoes a similar reaction on gentle warming with dilute hydrochloric acid. The behaviour of the 2-chlorobenzimidazoles is thus very different from that of 2-chlorobenzoxazole which is converted into benzoxazolin-2-one even by warm water.[8]

Although aqueous hydrochloric acid does not convert 2-chlorobenzimidazole into benzimidazolin-2-one, we have previously [3] shown that this change can be effected by the action of hot glacial acetic acid. As the other 2-chlorobenzimidazoles behave similarly, this reaction is a convenient one for converting a 2-chlorobenzimidazole into the corresponding benzimidazolin-2-one. The rate of displacement of chlorine in this reaction decreases in the order: 2-chloro-5,6-dinitrobenzimidazole > 2-chloro-5-nitrobenzimidazole ~ 2-chloro-1-methylbenzimidazole > 2-chlorobenzimidazole > 2-chloro-5-methylbenzimidazole.

Experimental

2-Chloro-1-isopropylbenzimidazole.—1-Isopropylbenzimidazolin-2-one [9] (5 g.) dissolved readily in cold, freshly distilled phosphoryl chloride (50 ml.). The solution was boiled under reflux for 3 hr. Removal of the excess of phosphoryl chloride at *ca.* 40 mm., followed by addition of ice–water to the residue, gave a clear solution showing that no unchanged 1-isopropylbenzimidazolin-2-one was present. Basification precipitated a brown tar which was extracted with ether (3 × 50 ml.) and the combined extracts dried (anhydrous Na_2SO_4) and evaporated. The yellow residue was distilled at 2—3 mm. and the fraction of b. p. 130—140°

[6] Gilman, Lentz, and Beel, *J. Amer. Chem. Soc.*, 1952, **74**, 1081; Todesco and Vivarelli, *Gazzetta*, 1962, **92**, 1221.
[7] Kym and Ratner, *Ber.*, 1912, **45**, 3238.
[8] Seidel, *J. prakt. Chem.*, 1890, **42**, 445.
[9] Davoll, *J.*, 1960, 308.

was collected. This soon solidified, and after further purification by dissolution in ethanol and precipitation by water, gave 2-*chloro*-1-*isopropylbenzimidazole* (3·25 g.) as a white solid, m. p. 47—48° to a viscous liquid which undergoes a further change to a clear liquid at 54—56° (Found: C, 61·8; H, 6·1; Cl, 17·7; N, 14·2. $C_{10}H_{11}ClN_2$ requires C, 61·7; H, 5·7; Cl, 18·2; N, 14·4%). The *picrate* (yellow leaflets from ethanol) had m. p. 164—165° (Found: C, 45·6; H, 3·3; Cl, 8·4; N, 16·9. $C_{16}H_{14}ClN_5O_7$ requires C, 45·4; H, 3·3; Cl, 8·4; N, 16·5%).

5,6-*Dinitrobenzimidazolin*-2-*one*.—This was obtained by the action of fuming nitric acid and sulphuric acid on benzimidazolin-2-one [10] and had m. p. ~320° (decomp.). The 1,3-*diacetyl derivative*, prepared by the method given previously,[3] formed needles (from ethanol), m. p. 264—266° (Found: C, 42·9; H, 2·7; N, 18·4. $C_{11}H_8N_4O_7$ requires C, 42·9; H, 2·6; N, 18·2%).

2-*Chloro*-5,6-*dinitrobenzimidazole*.—5,6-Dinitrobenzimidazolin-2-one (5·0 g.) was boiled under reflux with freshly-distilled phosphoryl chloride (100 ml.) for 6 hr. Excess of phosphoryl chloride was removed at *ca.* 40 mm., the yellow residue was cooled thoroughly in a bath of solid CO_2 and ethanol, and ice-cold water was added. A vigorous reaction at this stage must be avoided, otherwise reconversion of the chloro-compound into the benzimidazolin-2-one may occur. During the addition of ice–water, a yellow solid mixed with brown tar was formed, but on continual agitation this was completely converted into a yellow solid. The solid was collected, washed thoroughly with water (1000 ml.), and dried, giving crude 2-*chloro*-5,6-*dinitrobenzimidazole* (2·5 g.), shown by infrared spectroscopy to contain very little of the benzimidazolin-2-one. Recrystallisation from water (1000 ml.) gave glittering yellow leaflets (1·9 g., 35%), which had m. p. 188—189° and on further heating, bubbled and resolidified. The sample for analysis was crystallised from aqueous ethanol and had m. p. 190—191° (Found: C, 33·6; H, 1·8; Cl, 14·1; N, 22·45. $C_7H_3ClN_4O_4,0{\cdot}5H_2O$ requires C, 33·4; H, 1·6; Cl, 14·1; N, 22·3%). Attempts to obtain the anhydrous compound were unsuccessful. The yields obtained from this preparation were variable, the maximum being 40%. Neither of the methods used previously [3] to separate 2-chloro-5-nitrobenzimidazole from 5-nitrobenzimidazolin-2-one, *i.e.*, chromatography on alumina and fractional precipitation from acid solution, was satisfactory in the present case. The method described above depends on the difference in water solubility of the chloro-compound and of the benzimidazolin-2-one.

Action of Sodium Alkoxides on 2-*Chlorobenzimidazoles*.—The 2-chlorobenzimidazole (1·0 g.) was added to a solution of sodium (0·5 g.) in methanol, ethanol, or t-butanol (40 ml.). The mixture was boiled under reflux for 3 hr., a clear solution forming rapidly, although in some cases separation of solid commenced after a short time. Solids were isolated at one or more of the following stages of the working up: *A*, Filtration of the hot reaction mixture; *B*, Evaporation of the filtrate to dryness (reduced pressure), addition of water (25 ml.), and strong cooling; *C*, Neutralisation with 4N-hydrochloric acid. A solid was isolated at stage *A* only in the reactions of 2-chloro-1-methylbenzimidazole with sodium methoxide or ethoxide (identified as sodium chloride), and of 2-chlorobenzimidazole and 2-chloro-5-methylbenzimidazole with sodium t-butoxide (identified as the sodium salt of the chloro-compound). In the reactions of 2-chloro-1-methylbenzimidazole a solid was isolated at stage *B*; this was either the 2-alkoxy-compound (see below) or in the case of sodium t-butoxide, the unchanged chloro-compound. In the other reactions, the chloro-compound was recovered in good yield at stage *C* where no appreciable reaction had occurred.

The following 2-alkoxy-compounds were obtained from the appropriate chloro-compounds (1 g.):

2-*Methoxy*-1-*methylbenzimidazole* (0·6 g.), white needles from aqueous methanol, m. p. 40° (Found: N, 16·9. $C_9H_{10}N_2O$ requires N, 17·3%); *picrate*, needles from ethanol, m. p. 137—138° (Found: C, 46·2; H, 3·2; N, 18·2. $C_{15}H_{13}N_5O_8$ requires C, 46·0; H, 3·3; N, 17·9%).

2-*Ethoxy*-1-*methylbenzimidazole* (0·8 g.), white solid with m. p. too slow for satisfactory purification; characterised as the *picrate*, needles from ethanol, m. p. 152—153° (Found: C, 47·7; H, 3·9; N, 17·2. $C_{16}H_{15}N_5O_8$ requires C, 47·4; H, 3·7; N, 17·3%).

[*Note*. 2-Chloro-1-methylbenzimidazole formed a *picrate*, m. p. 167—168° (Found: C, 42·7; H, 2·9; Cl, 8·9; N, 17·7. $C_{14}H_{10}ClN_5O_7$ requires C, 42·5; H, 2·6; Cl, 9·0; N, 17·7%)].

The reaction of 2-chloro-1-isopropylbenzimidazole with sodium ethoxide, carried out by the standard method but with a longer period of heating (24 hr.), afforded an oil at stage *B*. This was extracted with ether and the residue obtained by evaporation of the extract was treated with a solution of picric acid in ethanol. The solid which separated was collected, and after

[10] Efros and Eltsov, *Zhur. obshchei Khim.*, 1957, **27**, 127.

recrystallisation from ethanol gave 2-*ethoxy*-1-*isopropylbenzimidazole picrate* (0·8 g., 36%), m. p. 132—133° (Found: C, 50·0; H, 4·5; N, 16·5. $C_{18}H_{19}N_5O_8$ requires C, 49·9; H, 4·4; N, 16·2%). However, when the normal period of heating (3 hr.) was used, the picrate isolated in this way had m. p. 164—165° after recrystallisation, and was shown by mixed m. p. and analysis to be the picrate of 2-chloro-1-isopropylbenzimidazole.

When 2-methoxy-1-methylbenzimidazole (0·25 g.) was boiled under reflux with 4N-hydrochloric acid (10 ml.) for 0·5 hr., a solid separated on cooling which was identified as 1-methylbenzimidazolin-2-one (0·2 g.) by m. p. and mixed m. p. 190—192°. Since 2-methoxybenzothiazole is reported [11] to be converted into 1-methylbenzothiazolin-2-one by strong heating, the effect of heating 2-methoxy-1-methylbenzimidazole at 190° for 3 hr. was examined. The methoxy-compound was recovered in good yield, and no evidence was found for the formation of 1,3-dimethylbenzimidazolin-2-one.

Action of Aqueous Hydrochloric Acid on 2-Chlorobenzimidazoles.—2-Chlorobenzimidazole (1·0 g.) dissolved readily in hydrochloric acid (25 ml. of N-, 6N-, or 12N-) but was recovered in good yield after boiling the solutions for 3 hr., cooling, and neutralising with dilute ammonia solution. Similar results were obtained in experiments using 2-chloro-1-methyl- and 2-chloro-5-methyl-benzimidazoles.

From solutions of 2-chloro-5-nitrobenzimidazole in 3N- or 6N-hydrochloric acid which had been boiled for 30 min., the solid recovered on cooling and neutralisation was entirely 5-nitrobenzimidazolin-2-one, but when N-, 9N-, or 12N-acid was used some unchanged chloro-compound was present. By ultraviolet spectroscopy, using a method described previously,[3] 2-chloro-5-nitrobenzimidazole was shown to constitute about 75% of the recovered material when N-hydrochloric acid was used and about 25% for the more concentrated acids. Even after heating with 18N-sulphuric acid at 160° for 30 min., the recovered material contained about 50 % of unchanged chloro-compound. Since the chloro-compound must be completely protonated in the more concentrated acids, the increase in stability may be due to a decrease in the concentration of the effective nucleophile, in this case " free " water molecules.

2-Chloro-5,6-dinitrobenzimidazole was converted completely into 5,6-dinitrobenzimidazolin-2-one (identified by infrared spectrum) by warming with 4N-hydrochloric acid for a short time.

Action of Aqueous Sodium Hydroxide on 2-Chlorobenzimidazoles.—After the 2-chlorobenzimidazoles (1·0 g.) had been boiled under reflux with sodium hydroxide solution (25 ml.) (various concentrations up to 12N), they were recovered in good yield although sometimes contaminated with silica from the glass. Since 2-chloro-1-methylbenzimidazole is insoluble in aqueous sodium hydroxide, diethylene glycol and aqueous dioxan were also tried as reaction media, but no evidence of the liberation of chloride ion was found.

Action of Acetic Acid on 2-Chlorobenzimidazoles.—The formation of benzimidazolin-2-one by boiling a solution of 2-chlorobenzimidazole in glacial acetic acid, evaporation, and purification of the residue, has been previously described.[3] The other 2-chlorobenzimidazoles, including those with 1-substituents, have now been shown to behave similarly.

The effect of substituents on the rate of this reaction was studied by the following method.[12] The chloro-compound (1·0 g.) in glacial acetic acid (50 ml.) was boiled under reflux, and the hydrogen chloride evolved was trapped in a known volume of standard silver nitrate solution which was finally combined with the main reaction mixture for back titration of the unused silver nitrate. The following values were obtained for the extent of decomposition after various reaction times:

2-Chlorobenzimidazole	78% after 15 min.; 96% after 30 min.; complete after 45 min.
2-Chloro-5-methylbenzimidazole...	67% after 15 min.; 90% after 30 min.; 96% after 45 min.; complete after 60 min.
2-Chloro-5-nitrobenzimidazole ...	94% after 15 min.; complete after 30 min.
2-Chloro-1-methylbenzimidazole...	92% after 15 min.; complete after 30 min.
2-Chloro-5,6-dinitrobenzimidazole	Complete after 15 min.

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[11] Davies and Sexton, *J.*, 1942, 304.
[12] Ralph, M.Sc. Thesis, University of Leicester, 1963.