acetylation is transformed smoothly to 2,3-ditosyl-4,7-anhydro-D-gluco-D-gulo-heptosan <1,5> β <1,6>, a sugar derivative containing one six-atom ring and two five-atom rings fused together in a novel manner.

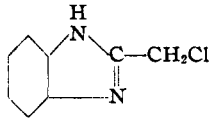
BETHESDA, MARYLAND RECEIVED JUNE 24, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

The Allylic Character of 2-(α-Chloroalkyl)-benzimidazoles[1]

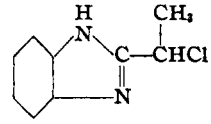
BY HERMAN SKOLNIK,[2] JOHN G. MILLER AND ALLAN R. DAY

Previous work[3] has indicated that the chlorine atoms in 2-chloromethylbenzimidazole and 2-(α-chloroethyl)-benzimidazole are highly reactive. This was shown by the extreme ease with which these compounds reacted with primary or secondary amines. Structurally they are similar to allyl chloride and benzyl chloride, and so might be expected to show some similarity in chemical behavior. The fact that they appeared to be more active prompted the present study of the activating effect of the benzimidazole group on the chlorine atom in several types of 2-(α-chloroalkyl)-benzimidazoles.



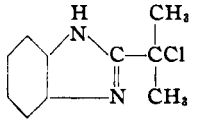
I

2-Chloromethyl-benzimidazole



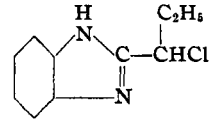
II

2-(α-Chloroethyl)-benzimidazole



III

2-(α-Chloroisopropyl)-benzimidazole



IV

2-(α-Chloro-*n*-propyl)-benzimidazole

This selection of 2-α-chloroalkyl derivatives not only permitted a study of the labilizing influence of the benzimidazole nucleus but the effect of the nature of the α-carbon atoms as well. It will be noted that compound I is a primary halide, II and IV are secondary halides, while III is a tertiary halide.

Numerous studies have been published concerning the effect of labilizing groups on halogen atoms. In many cases only qualitative information has been reported, such as the conditions under which certain metathetic reactions occur or whether the reaction proceeds at all. In other cases quantitative data resulting from reaction studies have been reported. In the present investigation both the qualitative and quantitative methods have been employed. The results from both methods point to the fact that the 2-α-chloroalkyl benzimidazoles are more reactive than the usual allyl halide type. No work has been reported previously on this grouping, $-N=\overset{|}{C}-\overset{|}{C}HCl$. Only the qualitative data are included in this paper.

It was no great surprise to encounter certain anomalies in the chemical investigation undertaken to establish the allylic character of compounds I, II, III and IV. These derivatives have more functional groups than allyl chloride, which results in greater complexity of activity. For example, the benzimidazole ring system contains two nitrogen atoms, one a tertiary basic nitrogen and the other attached to an active hydrogen atom. In solution such compounds are probably highly associated through hydrogen bonding.[4]

Since allyl chloride is known to react with Grignard reagents, it was expected that 2-chloromethylbenzimidazole would react similarly with phenylmagnesium bromide. However, no identifiable products could be isolated.

Greater success resulted from a study of hydrolysis reactions. The 2-chloromethyl compound was hydrolyzed almost quantitatively by boiling with water for thirty to sixty minutes. The 2-(α-chloroethyl) and 2-(α-chloro-*n*-propyl) compounds gave similar results in a somewhat shorter time and the 2-(α-chloroisopropyl) derivative was completely hydrolyzed by water at room temperature. The greater ease of hydrolysis of the secondary and tertiary chlorides was to be expected, but it must

(1) Presented at the Detroit meeting of the American Chemical Society in April, 1943.

(2) Present address, Hercules Powder Co., Wilmington, Del.

(3) Bloom and Day, *J. Org. Chem.*, **4**, 14 (1939); Roeder and Day, *ibid.*, **6**, 25 (1941).

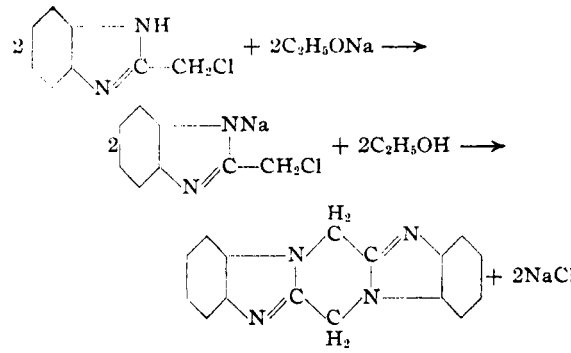
(4) Hunter and Marriot, *J. Chem. Soc.*, 777 (1941).

be noted that even the primary chloride underwent hydrolysis more readily than allyl chloride or benzyl chloride. The latter are best hydrolyzed by heating in an alkaline medium.

The Finklestein reaction,[5] involving the interaction of an organic chloride with potassium iodide in acetone solution, has been widely used to test for halogen reactivity. When 2-chloromethylbenzimidazole was treated with potassium iodide in acetone solution, a quantitative reaction (based on the amount of potassium chloride formed) apparently resulted. However, due to the instability of 2-iodomethylbenzimidazole in the presence of water, only 30% of the pure product could be isolated. Since this reaction proceeds rapidly without any observable side-reactions, it was adopted for the quantitative measurements involving reaction rate studies. In dry acetone solution, the medium used in the following paper, the iodides were stable and showed no tendency to liberate iodine.

Reactive organic chlorides ordinarily react readily with potassium cyanide to yield nitriles. All attempts to prepare the nitrile from 2-chloromethylbenzimidazole resulted in the formation of resinous materials. It was thought that the presence of active hydrogen in the —NH— group of the benzimidazole might be responsible for the anomalous nature of the reaction products. This assumption was confirmed by treating 1-methyl-2-chloromethylbenzimidazole with potassium cyanide. Potassium chloride separated in quantitative amounts and a crystalline product was isolated from the filtrate in good yields. This product proved to be 1-methyl-2-benzimidazoleacetamide. Evidently the nitrile had formed, but due to the mild basicity of the solution had been hydrolyzed to the corresponding amide.

The Williamson reaction with 2-chloromethylbenzimidazole also proved to be extremely interesting. When the 2-chloro compound was treated with sodium ethylate, an immediate reaction occurred even in the cold, as evidenced by the rapid precipitation of sodium chloride. However, the product isolated from this reaction had none of the properties of 2-ethoxymethylbenzimidazole, an authentic sample of which was prepared by a different method. Analyses of the reaction product agreed very well for dibenzamido-(1,2-a,1′,2′-d)-piperazine. The formation of such a compound follows logically fron the reactions



Although the reactivity of the —NH— group prevented the normal Williamson reaction, the speed with which the reaction proceeded gave further indication of the reactivity of the halogen atom. As a final qualitative check on the reactivity of the halogen, it was decided to determine whether or not these halogen compounds were active enough to react with primary alcohols. The reactivity of trityl chloride has been utilized for the preparation of ethers from primary alcohols.

$$(C_6H_5)_3CCl + RCH_2OH \longrightarrow RCH_2OC(C_6H_5)_3 + HCl$$

The hydrogen chloride is usually absorbed by carrying out the reaction in the presence of pyridine. This reaction has been particularly useful for determining the primary nature of an alcohol group and also for protecting (blocking) a primary alcohol group to prevent it from reacting further in any given reaction. The reactivity of the chlorine atom in trityl chloride in this reaction may be considered to be derived from two sources: (1) it is a tertiary halide; and (2) the chlorine atom may be said to be attached to the terminal carbon atom of three allylic systems. It will be noted that of the four 2-(α-chloroalkyl)-benzimidazoles studied in the present investigation, the 2-(α-chloroisopropyl) compound most closely resembles trityl chloride, in that it is a tertiary halide besides containing an allylic system. When 2-(α-chloroisopropyl)-benzimidazole was refluxed in dry alcohol solution, in the presence of pyridine, a good yield of 2-(α-ethoxyisopropyl)-benzimidazole was obtained. The other halides in this series (I, II and IV) do not react with ethyl alcohol under these conditions.

Since the qualitative data uniformly indicated a high order of reactivity for the halogen atom in 2-(α-chloroalkyl)-benzimidazoles, it was decided at this point in the investigation that the accumulation of more qualitative information would be of little value. Consequently the remaining part of

(5) Finklestein, *Ber.*, **43**, 1528 (1910).

the work was devoted to a quantitative study of the potassium iodide reaction (see following paper).

Experimental

Melting Points.—The melting points recorded are corrected values and agree with literature values unless otherwise stated. New compounds are designated by the notation (NC), immediately following the name of the compound.

2-Chloromethylbenzimidazole.—The Phillips method[6] as modified by Bloom and Day[3] was used for preparing 2-chloromethylbenzimidazole. The yields of crude product after washing with water and drying varied from 78 to 86%. The pure compound was obtained as colorless plates by recrystallization from dry acetone and decolorization with the aid of Darco. The pure product melted at 159–160° when the rate of heating did not exceed 1° per minute. When the rate of heating is rapid (2° or more per minute), the compound changes to a yellow solid at about 140° which does not melt below 250°. This transition is probably due to polymerization.

Anal. Calcd. for C_8H_7ClN: N, 16.83. Found: N, 16.79.

2-Hydroxymethylbenzimidazole (reference compound).—This compound was prepared from *o*-phenylenediamine and glycolic acid, according to the Phillips procedure.[6] The crude product was recrystallized from hot water with the aid of Darco; yields 75–85%; m. p. 170.5–171.5°.

2-Ethoxymethylbenzimidazole (NC), (reference compound).—2-Ethoxymethylbenzimidazole was prepared by Phillips' method from *o*-phenylenediamine and ethoxyacetic acid.[7] It was obtained as colorless needles from 10% alcohol; yield, 88%; m. p. 154.5–155°.

Anal. Calcd. for $C_{10}H_{12}ON_2$: C, 68.15; H, 6.87; N, 15.90. Found: C, 68.04; H, 6.91; N, 15.87.

2-(α-Chloroethyl)-benzimidazole.—This compound was prepared according to the method of Roeder and Day.[3] The crude product, after being thoroughly dried, was purified by adding it in small amounts to hot benzene and separating the supernatant liquid from the gums which always formed. The excess benzene was evaporated by means of a fan; yields 55–60%; m. p. 134–135°.

2-(α-Hydroxyethyl)-benzimidazole (reference compound).—It was prepared from *o*-phenylenediamine and lactic acid by the procedure described for 2-hydroxymethylbenzimidazole. The yield of pure product was 75%; m. p. 178.5–179.5°.

2-(α-Hydroxyisopropyl)-benzimidazole (NC), (an intermediate for the preparation of 2-(α-chloroisopropyl)-benzimidazole).—The preparation of this derivative from *o*-phenylenediamine and α-hydroxyisobutyric acid followed the procedure described for 2-hydroxymethylbenzimidazole. The product was recrystallized from 5% ethyl alcohol, with the aid of Darco; yield, 65%; m. p. 227.5–228°.

Anal. Calcd. for $C_{10}H_{12}ON_2$: C, 68.15; H, 6.87; N, 15.90. Found: C, 67.99; H, 6.80; N, 15.80.

2-(α-Chloroisopropyl)-benzimidazole (NC).—A solution of 21.5 cc. of thionyl chloride in 31 cc. of chloroform was added gradually to 17.6 g. (0.10 mole) of 2-(α-hydroxyisopropyl)-benzimidazole and the mixture refluxed for two hours on the water-bath. After the initial reaction the solution became clear. The chloroform and excess thionyl chloride were removed at room temperature under reduced pressure. The residue was dissolved in water filtered and the cold solution (0°) was gradually neutralized with sodium bicarbonate. The crude product was removed, washed with ice water and dried. Colorless plates were obtained by recrystallization from petroleum ether; yield, 48%; m. p. 135.5–136.6°.

Anal. Calcd. for $C_{10}H_{11}ClN_2$: C, 61.69; H, 5.70; N, 14.39. Found: C, 61.64; H, 5.83; N, 14.28.

α-Hydroxy-*n*-butyric Acid (an intermediate for the preparation of 2-(α-hydroxy-*n*-propyl)-benzimidazole).—Propionaldehyde cyanohydrin[8] was hydrolyzed to α-hydroxy-*n*-butyric acid according to the procedure of Przibytek.[9] Concentrated hydrochloric acid was added to the cyanohydrin and the mixture allowed to stand for three days and finally heated for one hour at 60–70°. The hydroxy acid was extracted with ether and dried over sodium sulfate. Evaporation of the ether left a viscous liquid which was used for the next preparation without further purification.

2-(α-Hydroxy-*n*-propyl)-benzimidazole (NC), (an intermediate for the preparation of 2-(α-chloro-*n*-propyl)-benzimidazole).—This product was prepared from *o*-phenylenediamine and α-hydroxy-*n*-butyric acid by the procedure described for 2-hydroxymethylbenzimidazole. The product was obtained as colorless needles by recrystallization from 15% ethyl alcohol, with the aid of Darco; yield, 63%; m. p. 220–221°.

Anal. Calcd. for $C_{10}H_{12}ON_2$: C, 68.15; H, 6.87; N, 15.91. Found: C, 68.09; H, 6.83; N, 15.84.

2-(α-Chloro-*n*-propyl)-benzimidazole (NC).—A solution of 14.5 cc. of thionyl chloride in 21.5 cc. of chloroform was added gradually to 11.9 g. (0.0675 mole) of 2-(α-hydroxy-*n*-propyl)-benzimidazole and treated further as described under the preparation of 2-(α-chloroisopropyl)-benzimidazole. The compound was obtained as colorless needles by recrystallization from petroleum ether; yield, 66%; m. p. 144.5–145.5°.

Anal. Calcd. for $C_{10}H_{11}ClN_2$: C, 61.69; H, 5.70; N, 14.39. Found: C, 61.57; H, 5.78; N, 14.30.

1-Methyl-2-chloromethylbenzimidazole (NC).—N-Methyl-*o*-phenylenediamine dihydrochloride (16.9 g., 0.087 mole) (3) and 11.87 g. (0.13 mole) of chloroacetic acid were dissolved in 87 cc. of 2 *N* hydrochloric acid and refluxed for three hours. After standing overnight the solution was filtered, cooled in ice and gradually neutralized with sodium bicarbonate. The crude product was removed, washed with 200 cc. of ice water and dried. It is quite soluble at room temperature in acetone, ether, benzene, toluene, xylene, ethyl acetate, dioxane and the common alcohols. It was best purified by dissolving in dilute hydrochloric acid and decolorizing with Darco. The filtrate was neutralized with sodium bicarbonate and ex-

(6) Phillips, *J. Chem. Soc.*, 2393 (1928).

(7) The ethoxyacetic acid was prepared according to Sommelet, *Ann. chim. phys.*, [8] **9**, 489 (1906).

(8) "Organic Syntheses," John Wiley & Sons, Inc., N. Y., **20**, 42 (1940).

(9) Przibytek, *J. Russ. Chem. Gesell.*, **8**, 335 (1887).

tracted with ether. Most of the ether was removed by evaporation and the product filtered. When these operations were repeated three times, a colorless crystalline solid was obtained; yield, 58%; m. p. 94.5–95.5°.

Anal. Calcd. for $C_9H_9ClN_2$: C, 59.83; H, 5.02; N, 15.51. Found: C, 59.72; H, 4.95; N, 15.47.

1-Methyl-2-(α-hydroxyethyl)-benzimidazole (NC), (an intermediate for the preparation of 1-methyl-2-(α-chloroethyl)-benzimidazole).—It was prepared from N-methyl-*o*-phenylenediamine dihydrochloride (16.9 g., 0.087 mole) and 11.70 g. (0.13 mole) of lactic acid by the procedure described for the preparation of 2-hydroxymethylbenzimidazole. The product was obtained as colorless needles by recrystallizing from water, with the aid of Darco; yield, 89%; m. p. 59.6–61°.

Anal. Calcd. for $C_{10}H_{12}ON_2$: C, 68.15; H, 6.87; N, 15.91. Found: C, 67.95; H, 6.91; N, 15.79.

1-Methyl-2-(α-chloroethyl)-benzimidazole (NC).—A solution of 11.5 cc. of thionyl chloride in 16 cc. of chloroform was added gradually to 1-methyl-2-(α-hydroxyethyl)-benzimidazole (8.8 g., 0.05 mole) and treated further as described under the preparation of 2-(α-chloroisopropyl)-benzimidazole. The crude product was recrystallized several times from dry ether; yield, 64%; m. p. 64–65°.

Anal. Calcd. for $C_{10}H_{11}ClN_2$: C, 61.69; H, 5.70; N, 14.39. Found: C, 61.51; H, 5.67; N, 14.24.

Reactions of 2-(α-Chloroalkyl)-benzimidazoles

(I) 2-Chloromethylbenzimidazole

(a) **With Phenylmagnesium Bromide.**—To a solution of phenylmagnesium bromide (2.72 g., 0.015 mole) in dry ether was added 2.5 g. (0.015 mole) of 2-chloromethylbenzimidazole dissolved in the minimum amount of dry xylene. The solution was then refluxed for one hour with stirring. After cooling, the magnesium salt was removed by filtration and the filtrate evaporated. Only intractable, gummy materials were obtained.

(b) **With Water.**—2-Chloromethylbenzimidazole (5 g., 0.03 mole) was refluxed with 175 cc. of water for forty-five minutes before solution was complete. The solution was cooled and neutralized with sodium bicarbonate. The crude 2-hydroxymethylbenzimidazole was recrystallized from water; yield, 94%; m. p. 169.5–170.5°.

Anal. Calcd. for $C_8H_8ON_2$: N, 18.92. Found: N, 18.79.

(c) **With Potassium Iodide.**—2-Chloromethylbenzimidazole (5 g., 0.03 mole) in 100 cc. of acetone was added to a solution of potassium iodide (5 g., 0.03 mole) in 50 cc. of acetone and refluxed for two hours. The yield of potassium chloride, obtained by filtering the cooled mixture, was almost quantitative. This filtrate was evaporated to small volume, cooled and filtered. The crude 2-iodomethylbenzimidazole (NC) was washed with water and recrystallized from acetone. It was obtained as light yellow needles; yield, 31%; m. p. 137–139° (dec.). Free iodine was observed to form at the decomposition point. The pure product in dry acetone solution appears to be stable and the usual tests for free iodine were negative.

Anal. Calcd. for $C_8H_7IN_2$: C, 37.23; H, 2.73; N, 10.86. Found: C, 37.08; H, 2.81; N, 10.79.

(d) **With Potassium Cyanide.**—Potassium cyanide (2.6 g., 0.04 mole) in 2.5 cc. of water was added to 5 g. (0.03 mole) of 2-chloromethylbenzimidazole dissolved in the minimum amount of dry alcohol. The mixture was heated for two hours on the water-bath, cooled and the potassium chloride removed by filtration. The chloride was isolated in practically theoretical yield. The filtrate on evaporation yielded only intractable gums. Although several runs were made under various conditions, no solid material could be isolated.

(e) **With Sodium Ethylate. Preparation of Dibenzamido-(1,2-a,1′,2′-d)-piperazine** (NC).—Five grams (0.03 mole) of 2-chloromethylbenzimidazole, dissolved in dry alcohol, was added with stirring to a dry alcohol solution of sodium ethylate (0.69 g., 0.03 mole, in 125 cc. of dry alcohol). The mixture was heated on the water-bath for one hour, cooled and the sodium chloride removed by filtration. The filtrate was evaporated to small volume and cooled. The crude piperazine thus obtained was recrystallized from hot glacial acetic acid by the careful addition of water; colorless needles, m. p. above 300°; yield, 73%

Anal Calcd. for $C_{16}H_{12}N_4$: C, 73.83; H, 4.65; N, 21.54. Found: C, 73.79; H, 4.69; N, 21.51.

(f) **Attempted Reactions with Ethyl Alcohol.**—2-Chloromethylbenzimidazole was refluxed with dry alcohol both in the presence and absence of bases, such as dimethylaniline or pyridine. In every case the chloromethylbenzimidazole was recovered unchanged. The 2-(α-chloroethyl) compound behaved similarly.

II. 2-(α-Chloroethyl)-benzimidazole. With Water.—2-(α-Chloroethyl-benzimidazole (2.83 g., 0.0153 mole) was added to 75 cc. of boiling water. Within ten minutes all of the material was in solution, indicating that hydrolysis was complete. The cooled solution was neutralized with sodium bicarbonate and the crude 2-(α-hydroxyethyl)-benzimidazole removed by filtration. It was recrystallized from benzene; yield, 70.6%; m. p. 179–180°.

Anal. Calcd. for $C_9H_{10}ON_2$: N, 17.28. Found: N, 17.25.

The 2-(α-chloro-*n*-propyl)-benzimidazole gave almost identical results under the same conditions.

III. 2-(α-Chloroisopropyl)-benzimidazole. (a) **With Water.**—This compound is so susceptible to hydrolysis that by merely dissolving it in cold acetone containing a small amount of water, and evaporating rapidly by means of a fan, only 2-(α-hydroxyisopropyl)-benzimidazole is obtainable; m. p. 227–228°.

(b) **With Ethyl Alcohol. Preparation of 2-(α-Ethoxyisopropyl)-benzimidazole** (NC).—2-(α-Chloroisopropyl)-benzimidazole (1.5 g., 0.0077 mole) and 1 cc. of pyridine were dissolved in 60 cc. of dry alcohol and refluxed for six hours. Most of the alcohol was removed by evaporation, water added and the solution neutralized with sodium bicarbonate. The crude product was recrystallized from a 10% ethyl alcohol solution and obtained as colorless needles; yield, 56%; m. p. 203.7–204.4°. The analysis indicated the compound to be a monohydrate. The water was retained even after long drying at 130°.

Anal. Calcd. for $C_{12}H_{16}ON_2 \cdot H_2O$: C, 64.84; H, 8.06; N, 12.60. Found: C, 64.63; H, 8.18; N, 12.49.

IV. 1-Methyl-2-chloromethylbenzimidazole. With Potassium Cyanide (Preparation of 1-Methyl-2-benzimidaz-

oleacetamide).— 1-Methyl-2-chloromethylbenzimidazole (1.8 g., 0.01 mole) in 40 cc. of acetone was mixed with 0.65 g. (0.01 mole) of potassium cyanide dissolved in the least amount of water. The mixture was gently refluxed for six hours, filtered and the filtrate evaporated. The residue was treated with water and filtered. The crude product was recrystallized from acetone–water, with the aid of Darco; yield, 80%; m. p. 239–240°.

Anal. Calcd. for $C_{10}H_{11}ON_3$: C, 63.47; H, 5.86; N, 22.21. Found: C, 63.24; H, 5.73; N, 22.08.

Summary

1. The following 2-α-chloroalkylbenzimidazoles have been prepared: 2-chloromethylbenzimidazole, 2-(α-chloroethyl)-benzimidazole, 2-(α-chloro-*n*-propyl)-benzimidazole (NC), 2-(α-chloroisopropyl)-benzimidazole (NC), 1-methyl-2-chloromethylbenzimidazole (NC), and 1-methyl-2-(α-chloroethyl)-benzimidazole (NC).

2. The labilizing effect of the benzimidazole nucleus on the chlorine atom in the above 2-α-chloroalkylbenzimidazoles has been studied. The results indicate that these halides are more active than the usual allyl halide type.

3. During the course of the investigation, the following new compounds were prepared: 2-ethoxymethylbenzimidazole, 2-(α-hydroxyisopropyl)-benzimidazole, 2-(α-hydroxy-*n*-propyl)-benzimidazole, 1-methyl-2-(α-hydroxyethyl)-benzimidazole, 2-iodomethylbenzimidazole, dibenzamido-(1,2-a,1′,2′-d)-piperazine, 2-(α-ethoxyisopropyl)-benzimidazole and 1-methyl-2-benzimidazoleacetamide.

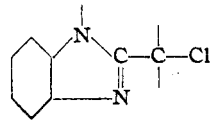
PHILADELPHIA, PA. RECEIVED MARCH 16, 1943

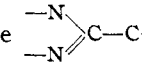
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

The Reaction of Some 2-(α-Chloroalkyl)-benzimidazoles with Potassium Iodide in Acetone Solution[1]

BY HERMAN SKOLNIK,[2] ALLAN R. DAY AND JOHN G. MILLER

The reaction of organic chlorides with potassium iodide in acetone solution, RCl + KI → RI + KCl, has been used frequently as a means of correlating the structures and reactivities of the chlorides.[3] This paper reports such a study applied to a series of 2-(α-chloroalkyl)-benzimidazoles whose preparation is described in a previous paper.[4] The series of six compounds was chosen to allow a thorough test of the labilizing influence of the benzimidazole grouping upon the chlorine atom situated as shown in the following skeleton common to the series



Despite unexpected complications met in the rate measurements, the results of this study show that the benzimidazole grouping in these compounds strongly enhances the reactivity of the chlorine, the  configuration in these compounds being the predominant activating structure discernible.

Experimental

Rate Measurements.—At the start of this work an attempt was made to follow the rates of reaction by measuring the fall in electrical conductance of the reaction system caused by the precipitation of the potassium chloride. This effort was abandoned because the specific rates measured in this way were very erratic, probably due to supersaturation.

The analytical method developed by Conant and co-workers[3a] was finally used. This method measures the extent of reaction by determining the amount of unreacted potassium iodide by titration with potassium iodate in cold hydrochloric acid solution. Chloroform is used as indicator, disappearance of color in the chloroform marking the end-point. Attempts to use other analytical methods failed. The procedure developed by Kolthoff, Laitinen and Lingane,[5] based on the iodoacetone method of Berg[6] employing

(1) Presented at the Detroit Meeting of the American Chemical Society in April, 1943.

(2) Present address, Hercules Powder Company, Wilmington, Del.

(3) See, for example: (a) Conant and Kirner, THIS JOURNAL, **46**, 246 (1924); Conant and Hussey, *ibid.*, **47**, 476 (1925); Conant, Kirner and Hussey, *ibid.*, **47**, 488 (1925); (b) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Company, New York, N. Y., 1940, pp. 152–156, 208.

(4) Skolnik, Miller and Day, THIS JOURNAL, **65**, 1854 (1943).

(5) Kolthoff, Laitinen and Lingane, THIS JOURNAL, **59**, 429 (1937).

(6) Berg, *Z. anal. Chem.*, **69**, 369 (1926).