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

BENZIMIDAZOLE STUDIES. I. THE MECHANISM OF BENZIMIDAZOLE FORMATION FROM *O*-PHENYLENEDIAMINE

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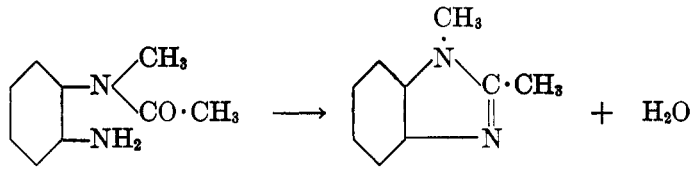
Although benzimidazoles have been known for a long time, the mechanism of the reaction by which they are formed from *o*-phenylenediamine has not been clearly established. Phillips (1) carried out a series of reactions which were intended to throw some light on this question. He concluded that the monoacyl derivative of *o*-phenylenediamine was the necessary intermediate for the reaction. Monoacyl-*o*-phenylenediamines when heated with 4 *N* hydrochloric acid passed readily into the corresponding benzimidazoles. He also noted that the diacyl-*o*-phenylenediamines yielded benzimidazoles, when treated under the same conditions. He concluded that the latter action involved, as the first step, the formation of the monoacyl derivative which subsequently underwent ring closure with the splitting out of a molecule of water. The fact that it was difficult to obtain any 2-methylbenzimidazole when *o*-phenylenediamine was heated with excess acetic anhydride served to confirm his conclusion that the diacyl derivative did not yield the benzimidazole directly.

Phillips further noted the formation of 1,2-dimethylbenzimidazole when *o*-amino-N-methylacetanilide was heated with dilute hydrochloric acid.

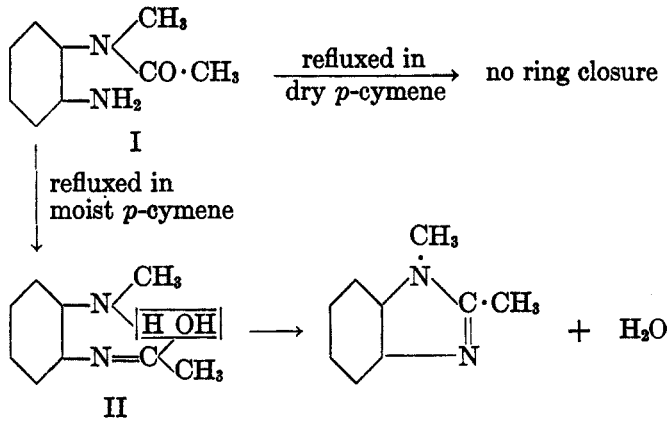


He did not draw any definite conclusions from this reaction, but it seemed that the reaction might be explained in one of two ways. It might be inferred that the ring closure proceeded by the splitting out of water with both hydrogen atoms coming from the same nitrogen atom. However it might be assumed that the aqueous medium used first hydrolyzed the acetyl derivative. Reacetylation might then occur on the other nitrogen atom, followed by ring closure. In this case the two hydrogens would have come from the adjacent nitrogen atoms.

In order to study this ring closure more carefully, it was decided to carry out a series of reactions in dry organic solvents, thereby eliminating the possibility that hydrolysis might play a part in the reactions. These reactions were designed for two purposes: (A) to test Phillips' conclusion that the monoacyl derivative was the necessary intermediate; and (B) to determine the source of the two hydrogen atoms which split out to form water. The experimental conditions used to effect ring closure were similar to those described by Chatterjee (2).

N,N'-Diacetyl-*o*-phenylenediamine was refluxed in dry xylene (b.p. 140°) and also in dry *p*-cymene. No trace of 2-methylbenzimidazole was found in either case. In comparison with the behavior of the diacyl compound, it was found that the monoacetyl-*o*-phenylenediamine gave a quantitative yield of 2-methylbenzimidazole when refluxed in dry xylene. These results were in agreement with Phillips' conclusions.

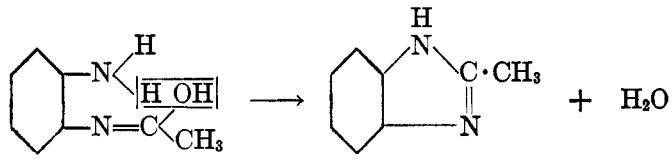
The starting compounds for the second phase of the work were *o*-amino-N-methylacetanilide (I) and N-methyl-N'-acetyl-*o*-phenylenediamine (II). When pure samples of I were refluxed in dry xylene or in dry *p*-cymene, only the starting material could be recovered. Under fairly vigorous conditions (temperatures of 140° and 176° respectively) this compound showed no tendency to undergo ring closure. It was noted that when the sample was refluxed with moist *p*-cymene, a small amount of 1,2-dimethylbenzimidazole was formed. This can be explained only on the assumption that some hydrolysis occurred, followed by acetylation of the other nitrogen atom. The latter derivative, having hydrogen attached to each of the nitrogen atoms, then underwent ring closure to form the benzimidazole.



In contrast to the behavior of I, the isomeric form N-methyl-N'-acetyl-*o*-phenylenediamine (II) was found to undergo ring closure very readily. When refluxed in dry xylene, it gave quantitative yields of the correspond-

ing benzimidazole. Ring closure was observed to occur at temperatures far below that of boiling xylene. When the compound was dried at 50–60°, ring closure slowly took place. Accurate melting point determination was found to be impossible because of this change. Melting started at a low temperature but complete melting occurred only near the melting point of the dimethylbenzimidazole, except in those cases where the melting point was rapidly determined.

The results of these experiments showed that the ring closure produced by the action of organic acids on *o*-phenylenediamine proceeds through the monoacyl derivative. The latter then probably splits out water by losing the oxygen of the acyl group and one hydrogen from each of the two nitrogen atoms. The reaction for the ring closure, involving the monoacyl-*o*-phenylenediamine, may be formulated as follows:



This mechanism, if extended, should be useful in determining the orientation of the imidazole ring relative to the aromatic ring. This work is being continued by Day and co-workers.

EXPERIMENTAL

I. *Preparation of starting compounds*

Diacetyl-o-phenylenediamine. *o*-Phenylenediamine (10.8 g., 0.1 mole) was dissolved in 3 *N* hydrochloric acid (0.2+ mole) and the solution diluted to 250 cc. Acetic anhydride (23.6 cc., 0.25 mole) and 34 g. (0.25 mole) of sodium acetate were added. When all of the sodium acetate had dissolved, the mixture was cooled and the product removed by filtration. Yield 15.36 g. (80%), m.p. 188.2–188.7° (corr.).

o-Aminoacetanilide. *o*-Nitroaniline (55.25 g., 0.4 mole) and 75.5 cc. (0.8 mole) of acetic anhydride were refluxed for 2 hours. The solution was slowly poured into water and after cooling the acetylated product was removed by filtration. It was recrystallized from hot water. Yield 97%, m.p. 93° (corr.).

Ten grams of *o*-nitroacetanilide was dissolved in 200 cc. of alcohol, 3 g. of 10% palladium on charcoal was added and the mixture shaken in an atmosphere of hydrogen until the theoretical amount was absorbed. The catalyst was removed and the filtrate evaporated under reduced pressure. The crude *o*-aminoacetanilide was recrystallized from benzene, m.p. 132.8–133.5° (corr.). This method was superior to that used by Phillips who reduced the acetylated nitroaniline with iron and acetic acid. The latter method was tried several times, but yielded mostly 2-methylbenzimidazole. To avoid the formation of benzimidazole, the reduction should be carried out under neutral conditions and preferably at room temperature.

o-Amino-N-methylacetanilide. N-*o*-Nitrophenyl-*p*-toluene sulfonamide was prepared by the method of Usherwood and Whitely (3). A solution of 250 g. (1.8 moles)

of *o*-nitroaniline and 345 g. (1.8 moles) of *p*-toluenesulfonyl chloride in 246 cc. of pyridine was heated on the water-bath for 5 hours. The mixture was poured into water and stirred until crystallization occurred. The product was recrystallized from alcohol. Yield 413.7 g. (78%), m.p. 111–113° (corr.).

This compound was methylated by the method of Usherwood and Whitely as modified by Phillips. Four hundred and ten grams (1.4 moles) was suspended in 342 cc. of 4 *N* sodium hydroxide and 103 cc. (1.08 moles) of methyl sulfate added. The mixture was boiled gently and alkalinity to phenolphthalein was maintained by adding 10 *N* sodium hydroxide as needed. More methyl sulfate (153 cc.; 1.61 moles) was then added and the above treatment repeated. This mixture was cooled and filtered. The crude N-*o*-nitrophenyl-N-methyl-*p*-toluenesulfonamide was recrystallized from alcohol. Yield 387 g. (90%), m.p. 131.7–132.8° (corr.).

o-Nitromethylaniline was obtained by heating the above product with a mixture of glacial acetic acid (193.6 cc.) and concentrated sulfuric acid (436.4 cc.) on the water-bath for 1½ hours (method of Usherwood and Whitely). The solution was poured into water and allowed to stand overnight. The product was recrystallized from warm alcohol. Yield 89%, m.p. 33–34.5° (corr.).

The *o*-nitromethylaniline was acetylated by a modification of Phillips' method. Forty-nine grams (0.32 mole) was suspended in 98.5 cc. of acetic anhydride and 0.2 cc. of concentrated sulfuric acid was added. The mixture was warmed until solution was complete and then poured slowly into water. The acetylated product did not separate, as reported by Phillips, even on long standing. The solution was almost neutralized with ammonium hydroxide and extracted with benzene. The *o*-nitro-*N*-methylacetanilide was isolated by evaporation of the benzene extract. Yield 36 g. (73%), m.p. 71.2–71.4° (corr.).

o-Amino-N-methylacetanilide was prepared by the catalytic hydrogenation of the above nitro compound, by the same procedure used for *o*-aminoacetanilide; m.p. 149.9–150.3° (corr.). Phillips reported the melting point 67–68° for this compound.

Anal. Calc'd for $C_9H_{12}N_2O$: N, 17.06. Found: N, 17.03.

N-Methyl-N'-acetyl-o-phenylenediamine. Ten grams (0.065 mole) of *o*-nitromethylaniline was dissolved in alcohol containing 12 cc. of concentrated hydrochloric acid. Hydrogenation was carried out as previously described. The crude *o*-aminomethylaniline dihydrochloride was recrystallized from alcohol and ether. Yield 92%, m.p. 177° (corr.).

The acetylation of *o*-aminomethylaniline proved to be troublesome because of the tendency of the acetylated product to pass into the corresponding benzimidazole. The acylation was first attempted by the method which Hempel (4) used for acetylating *o*-aminoethylaniline. *o*-Aminomethylaniline dihydrochloride (8.57 g.; 0.044 mole) was placed in a separatory funnel and covered with water and ether. The free base was liberated by the addition of sodium hydroxide and the ether extract dried over sodium hydroxide. To the dry ether solution was added 3.9 cc. of acetic anhydride and the solution was allowed to stand overnight. On evaporation of the ether under reduced pressure, 8.67 g. of a white solid was obtained. This proved to be the acetate of 1,2-dimethylbenzimidazole. It was converted to the free base by treatment with dilute ammonium hydroxide and recrystallized from water; m.p. 111.4–111.8° (corr.).

Anal. Calc'd for $C_9H_{10}N_2$: N, 19.16. Found: N, 19.12.

The acetylation was finally effected by slowly adding the acetic anhydride in dry ether to the dry ether solution of the free base, in the presence of sodium bicarbonate and with constant stirring. The mixture was allowed to stand for 1½ hours, filtered, and the ether removed under reduced pressure. The residue was then extracted twice with 200 cc. of petroleum ether at room temperature. The extracts were evaporated to small volume by bubbling nitrogen through the solution. An almost colorless crystalline product was obtained. Yield 20%, m.p. 71.5–79.5° (corr.).

Anal. Calc'd for $C_9H_{12}N_2O$: N, 17.06. Found: N, 17.37.

II. *Ring Closure*

Five grams of diacetyl-*o*-phenylenediamine was refluxed for 4 hours in 80 cc. of dry xylene. The diacetyl derivative was recovered quantitatively, m.p. 188–188.7° (corr.).

One gram of the diacetyl compound was refluxed for 2 hours in 30 cc. of dry *p*-cymene. Recovery of the starting material was practically quantitative, m.p. 188–188.7° (corr.).

One gram of *o*-aminoacetanilide was refluxed for 2 hours in 30 cc. of dry xylene. The solution was cooled and filtered. Yield 0.88 g. of 2-methylbenzimidazole. It was recrystallized from water, m.p. 175.9–176.9° (corr.).

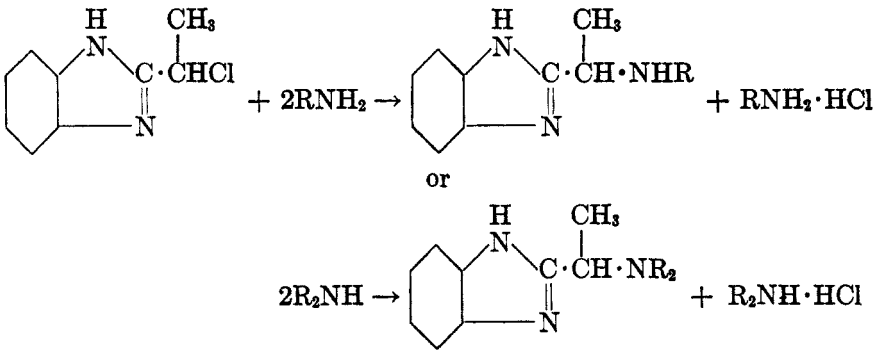
One gram of *o*-amino-N-methylacetanilide was refluxed in 30 cc. of dry xylene for 2 hours. The material recovered from the solution weighed 0.99 g. and melted at 149–149.4° (corr.), indicating that ring closure had not occurred. Another sample was refluxed in dry *p*-cymene, but again only the starting material was recovered.

Samples (0.25 g.) of N-methyl-N′-acetyl-*o*-phenylenediamine were refluxed in dry xylene (8 cc.) for 2 hours. The 1,2-dimethylbenzimidazole was precipitated from the warm solution by the addition of petroleum ether, and recrystallized from water, m.p. 111.5–111.9° (corr.). The conversions were practically quantitative.

II. PREPARATION OF 2-(α-ALKYLAMINOETHYL)-BENZIMIDAZOLES

Recent work (5) in the field of 2-substituted benzimidazoles has shown that 2-alkylaminomethyl benzimidazoles possess interesting local anesthetic properties. For example a 0.5% solution of the dihydrochloride of 2-(di-*n*-butylaminomethyl)benzimidazole was tested for corneal anesthesia and found to be about as effective as 1% cocaine solution. Similarly a 1% solution was found to be as effective as a 1% procaine solution in producing intradermal anesthesia. The compounds in this series, however, possessed some undesirable properties. The free bases were insoluble in water and their dihydrochlorides were too acidic in solution to be practical as local anesthetics. Attempts were made to prepare the monohydrochlorides but only the dihydrochlorides could be isolated.

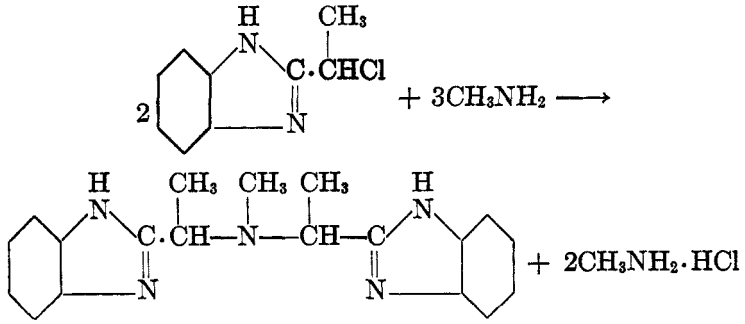
It was therefore considered advisable to extend this work in the hope of eliminating the undesirable properties. 2-(α-Chloroethyl)benzimidazole, prepared by Phillips' method (6) from *o*-phenylenediamine, was condensed with a series of primary and secondary amines.



The conditions for the condensations varied considerably depending on the particular amine which was used.

The condensations with secondary amines were normal in all cases, yielding the corresponding 2-(α-dialkylaminoethyl)benzimidazoles. Two of the latter were appreciably soluble in water at room temperature, the morpholine derivative dissolving to the extent of 2% and the dimethylamine derivative about 1%. These benzimidazoles formed only dihydrochlorides when treated with hydrogen chloride under various conditions. The 2% aqueous solutions of these dihydrochlorides were quite acidic (pH about 3).

The condensations with primary amines, above methylamine, yielded 2-(α-alkylaminoethyl)benzimidazoles. These compounds formed monohydrochlorides on treatment with hydrogen chloride. The aqueous solutions of the hydrochlorides were much less acidic (pH 6–7) than the dihydrochloride solutions noted above. When ammonia or methylamine was used, two moles of the chloroethylbenzimidazole reacted with one of the base to yield disubstituted derivatives.



These compounds formed only dihydrochlorides when treated with hydrogen chloride. This might indicate that the aliphatic nitrogen atom present in the molecule did not take part in salt formation, either through lack of

basicity or due to steric hindrance. The aqueous solutions of these salts were weakly acidic (pH 5).

From the chemical standpoint, the aims of this work have been realized. Benzimidazole derivatives, similar in structure to those known to possess local anesthetic activity but lacking their undesirable properties, have been prepared. They are being pharmacologically tested and the results of these tests will be reported later.

EXPERIMENTAL

Analyses. The semi-micro Kjeldahl method was used for the determination of nitrogen in all cases, except for the piperidine derivatives. For the latter the semi-micro Dumas method was used. The chlorine analyses were carried out by the Volhard method. The chloroethyl compound was decomposed for chlorine analysis by sodium peroxide fusion in a Parr bomb.

Melting points. The melting points recorded are corrected values. Most of the dihydrochlorides melted over a wide range. This is accounted for by the fact that they lose hydrogen chloride when heated. In order to achieve uniformity the melting points were taken with the temperature rising about 1 degree per minute.

I. *2-(α-Chloroethyl)benzimidazole.* *o*-Phenylenediamine (21.63 g., 0.2 mole) and 32.56 g. (0.3 mole) of α-chloropropionic acid were refluxed in 200 cc. of 5 *N* hydrochloric acid for 3 hours. The solution was allowed to stand overnight, filtered, and the filtrate cooled by the addition of ice. It was then neutralized by the careful addition of solid sodium bicarbonate with stirring. The product was removed by filtration, washed with water and dried. Yields 61–64%. It was found advisable to recrystallize the crude product from benzene before using it in the subsequent condensations. The recovery was 70–80%. The product was obtained as colorless needles from hot benzene, using decolorizing carbon, m.p. 134.7–135.4°.

Anal. Calc'd for $C_9H_9ClN_2$: C, 59.83; H, 5.02; Cl, 19.63; N, 15.51.
Found: C, 59.68; H, 5.04; Cl, 19.55; N, 15.46.

A series of reactions was carried out to determine the best conditions for the preparation of this compound. The best yields were obtained in 4 *N* to 6 *N* hydrochloric acid when refluxed for 3 hours. Above 6 *N* or below 4 *N* the yields dropped rapidly. The yields also dropped when the refluxing period was reduced to 1–2 hours. These facts suggested that the reaction might be reversible. Consequently samples of pure 2-(α-chloroethyl)benzimidazole were refluxed with hydrochloric acid, but no evidence was obtained which indicated that this compound was hydrolyzed under the experimental conditions used.

Reactions of 2-(α-chloroethyl)-benzimidazole with amines. One equivalent of the chloroethyl derivative was added gradually to a cold, dry alcohol or alcohol-ether solution containing 2 equivalents of the amine. After heating on the water-bath, the amine hydrochloride was precipitated by the addition of dry ether and removed by filtration. The amine hydrochlorides were recovered in yields varying from 73 to 98%. The benzimidazole derivatives could not all be isolated by the same general method from the alcohol-ether filtrates. The derivatives of the secondary amines (II to VII) and of two of the primary amines (IX and XII) were isolated by evaporating the filtrates to small volume. The solids obtained were broken up, stirred with water, and filtered. The dried products were then recrystallized from suitable solvents. The free bases were converted into the corresponding hydrochlorides by treating their cold ether or alcohol-ether solutions with dry hydrogen chloride. The

salts were filtered and recrystallized from suitable solvents. The hydrochlorides of these bases could also be obtained by treating the cold filtrates from the original reaction-mixtures with dry hydrogen chloride.

Two of the primary amine derivatives (X and XI) were most readily isolated by treating the cold filtrates from the original reaction-mixture with dry hydrogen chloride. The precipitated hydrochlorides were recrystallized from alcohol and acetone until pure. The free bases were obtained by adding sodium hydroxide pellets or solid sodium bicarbonate to aqueous solutions of the hydrochlorides. They were then recrystallized from suitable solvents.

The product formed by the interaction of the chloroethylbenzimidazole and ammonia was worked up by a third method. The filtrate from the reaction-mixture was evaporated almost to dryness. The solid residue was dissolved in concentrated hydrochloric acid and the hydrochloride precipitated by the addition of water.

The following experimental conditions include only those which gave the best yields. In every case several preliminary runs were made to determine the optimum conditions.

II. *2 - (α - Dimethylaminoethyl)benzimidazole.* 2 - (α - Chloroethyl)benzimidazole (5.91 g.; 0.032 mole) was added to 15 cc. of dry alcohol containing 2.95 g. (0.065 mole) of dimethylamine. After standing overnight, the solution was heated on the water-bath for 1½ hours. Sixty cubic centimeters of dry ether was added to the cold solution and the dimethylamine hydrochloride removed by filtration. The product can be isolated from the filtrate by the general method described above. Due to the solubility of this compound in water, it was simpler to recrystallize, from hot water in the presence of decolorizing carbon, the residue from the original filtrate; colorless plates, yield 66%, m.p. 208–210° (decomp.).

Anal. Calc'd for $C_{11}H_{15}N_3$: C, 69.80; H, 7.98; N, 22.20.
Found: C, 69.67; H, 8.06; N, 22.15.

The dihydrochloride was prepared from a dry alcohol-ether solution of the base. Recrystallization from 95% alcohol and acetone gave colorless prisms of the monohydrate, m.p. (range) 125.5–191°.

Anal. Calc'd for $C_{11}H_{15}N_3 \cdot 2HCl \cdot H_2O$: N, 15.00; Cl, 25.31.
Found: N, 15.01; Cl, 25.22.

III. *2-(α-Diethylaminoethyl)benzimidazole.* Five grams (0.027 mole) of 2-(α-chloroethyl)benzimidazole was added to a solution of 4.5 g. (0.06 mole) of diethylamine in 6 cc. of dry alcohol and 5 cc. of dry ether. The solution was refluxed for 3 hours, cooled, diluted with 10 cc. of dry ether, and filtered. The condensation-product, obtained in 88.7% yield from the filtrate, was recrystallized from ligroin, m.p. 177.5–178°. This compound formed very light greenish-yellow plates.

Anal. Calc'd for $C_{13}H_{19}N_3$: C, 71.85; H, 8.81; N, 19.34.
Found: C, 71.81; H, 8.84; N, 19.40.

The dihydrochloride was prepared from a dry alcohol-ether solution of the base and recrystallized from dry alcohol and ether; colorless prisms, m.p. (range) 137.5–185°.

Anal. Calc'd for $C_{13}H_{19}N_3 \cdot 2HCl$: N, 14.48; Cl, 24.43.
Found: N, 14.49; Cl, 24.45.

IV. *2-(α-Di-n-butylaminoethyl)benzimidazole.* 2-(α-Chloroethyl)benzimidazole (4.72 g., 0.026 mole) was added to a solution of 6.75 g., (0.052 mole) of di-*n*-butylamine in 25 cc. of dry alcohol. The solution was refluxed for 1 hour, cooled, diluted with 25 cc. of dry ether, and filtered. The filtrate gave a 75.5% yield of the product. It was recrystallized from acetone and water; colorless needles, m.p. 139.1–139.3°.

Anal. Calc'd for $C_{17}H_{27}N_3$: C, 74.67; H, 9.94; N, 15.37.
Found: C, 74.49; H, 10.08; N, 15.30.

The dihydrochloride was prepared from a dry ether solution of the base and recrystallized from dry alcohol and acetone; colorless prisms, m.p. (range) 132.5–175°.

Anal. Calc'd for $C_{17}H_{27}N_3 \cdot 2HCl$: N, 12.13; Cl, 20.48.
Found: N, 12.08; Cl, 20.45.

V. *2-(α-Dibenzylaminoethyl)benzimidazole.* Five grams (0.027 mole) of 2-(α-chloroethyl)benzimidazole was added to a solution of 10.92 g. (0.055 mole) of dibenzylamine in 25 cc. of dry alcohol. The solution was refluxed for 3 hours, cooled, diluted with 75 cc. of dry ether, and filtered. In this case most of the condensation-product precipitated with the benzylamine hydrochloride. A small amount of solid recovered from the filtrate was added to the first precipitate, and the total solid extracted twice with water and dried. The residue was recrystallized from acetone and water; colorless needles, yield 65.4%, m.p. 222.3–223.2°.

Anal. Calc'd for $C_{23}H_{23}N_3$: C, 80.90; H, 6.78; N, 12.31.
Found: C, 80.71; H, 6.70; N, 12.23.

The dihydrochloride was obtained from a dry alcohol-ether solution of the base and recrystallized from alcohol and water; colorless prisms, m.p. (range) 183.3–208°.

Anal. Calc'd for $C_{23}H_{23}N_3 \cdot 2HCl$: N, 10.14; Cl, 17.11.
Found: N, 10.02; Cl, 16.95.

VI. *2-(α-Morpholinoethyl)benzimidazole.* 2-(α-Chloroethyl)benzimidazole (10.8 g., 0.06 mole) was added to a solution of 10.42 g. (0.12 mole) of morpholine in 40 cc. of dry alcohol. The solution was allowed to stand overnight, diluted with 145 cc. of dry ether and filtered. The product isolated from the filtrate was recrystallized from water (use of decolorizing carbon was necessary in some cases); colorless plates, yields 55–64%, m.p. 196.8–197°.

Anal. Calc'd for $C_{13}H_{17}N_3O$: C, 67.50; H, 7.40; N, 18.17.
Found: C, 67.34; H, 7.50; N, 18.3.

The dihydrochloride, obtained from a dry alcohol-ether solution of the base, was recrystallized from dry alcohol and ether; colorless prisms, m.p. (range) 140–214°.

Anal. Calc'd for $C_{13}H_{17}N_3O \cdot 2HCl$: N, 13.81; Cl, 23.31.
Found: N, 13.72; Cl, 23.21.

VII. *2-(α-Piperidinoethyl)benzimidazole.* Five grams (0.027 mole) of 2-(α-chloroethyl)benzimidazole was added to a solution of 4.71 g. (0.055 mole) of piperidine in 6 cc. of dry alcohol and 10 cc. of dry ether. The solution was refluxed for 2 hours, cooled, diluted with 75 cc. of dry ether, and filtered. The product was isolated from the filtrate in the usual way; yield 84%. It was recrystallized from ligroin; colorless needles, m.p. 167–167.2°.

Anal. Calc'd for $C_{14}H_{19}N_3$: C, 73.32; H, 8.35; N, 18.33.
Found: C, 73.34; H, 8.21; N, 18.29.

The dihydrochloride was prepared from a dry alcohol-ether solution of the base and recrystallized from dry alcohol and ether (or acetone); colorless prisms, m.p. (range) 168.5–214°.

Anal. Calc'd for $C_{14}H_{19}N_3 \cdot 2HCl$: N, 13.90; Cl, 23.46.
Found: N, 13.92; Cl, 23.43.

VIII. *Di-(α-benzimidazolylethyl)amine.* Dry ammonia was passed into a cooled solution of 6.11 g. (0.033 mole) of 2-(α-chloroethyl)benzimidazole in 22 cc. of dry alcohol and 22 cc. of dry ether. The mixture was allowed to stand for 2 days, cooled, and the ammonium chloride removed by filtration. The solid product, obtained

from the filtrate, was dissolved in concentrated hydrochloric acid and the dihydrochloride precipitated by the careful addition of water. The addition of too much water caused the precipitate to redissolve. The salt was purified by repeating the above treatment or by dissolving in water and reprecipitating it by the addition of concentrated hydrochloric acid until precipitation appeared to be complete; colorless needles, yields 36–42%, m.p. (range) 236–270°. Although this condensation was carried out under various conditions, only the disubstituted derivative could be isolated.

Anal. Calc'd for $C_{18}H_{19}N_5 \cdot 2HCl$: N, 18.51; Cl, 18.75.
Found: N, 18.50; Cl, 18.84.

The free base was prepared by neutralizing an aqueous solution of the hydrochloride with ammonium hydroxide. The base was dissolved in a mixture of benzene and acetone. The solution was evaporated to small volume and the product precipitated by the addition of ligroin; colorless prisms, m.p. 206.8–210.2°.

Anal. Calc'd for $C_{18}H_{19}N_5$: C, 70.79; H, 6.27; N, 22.94.
Found: C, 70.64; H, 6.43; N, 22.51.

IX. *Di-(α-benzimidazolylethyl)methylamine.* 2-(α-Chloroethyl)benzimidazole (5.64 g., 0.031 mole) was added to a solution of 1.94 g. (0.062 mole) of methylamine in 12 cc. of dry alcohol. The solution was refluxed for 1½ hours, cooled, diluted with 60 cc. of dry ether, and filtered. The product was obtained from the filtrate in yields of 81–90%. It was recrystallized from acetone and benzene; colorless needles, m.p. 205.1–205.9°. Even when a larger excess of methylamine was used, only the disubstituted product could be isolated.

Anal. Calc'd for $C_{18}H_{21}N_5$: C, 71.44; H, 6.62; N, 21.93.
Found: C, 71.28; H, 6.41; N, 21.87.

The dihydrochloride was prepared from a dry alcohol-ether solution of the base by treatment with dry hydrogen chloride. It was recrystallized from dry alcohol and acetone; colorless prisms, m.p. 234–237°.

Anal. Calc'd for $C_{18}H_{21}N_5 \cdot 2HCl$: N, 17.85; Cl, 18.08.
Found: N, 17.92; Cl, 18.23.

X. *2-(α-Ethylaminoethyl)benzimidazole.* 2-(α-Chloroethyl)benzimidazole (10.26 g., 0.057 mole) was added to a solution of 5.2 g. (0.11 mole) of ethylamine in 20 cc. of dry alcohol and 10 cc. of dry ether. The solution was refluxed for 3 hours, cooled, diluted with 60 cc. of dry ether, and filtered. The cold filtrate was treated with dry hydrogen chloride and filtered. The crude monohydrochloride was recrystallized from dry alcohol and acetone; colorless needles, yields 40–44%, m.p. 225.7–226°.

Anal. Calc'd for $C_{11}H_{15}N_3 \cdot HCl$: N, 18.62; Cl, 15.71.
Found: N, 18.68; Cl, 15.71.

The free base was liberated from an aqueous solution of the hydrochloride by the addition of sodium hydroxide and extracted with benzene. The benzene solution was evaporated and the product recrystallized from benzene and ligroin; colorless plates, m.p. 149–149.3°.

Anal. Calc'd for $C_{11}H_{15}N_3$: C, 69.80; H, 7.98; N, 22.20.
Found: C, 69.68; H, 8.18; N, 22.21.

XI. *2-(α-n-Butylaminoethyl)benzimidazole.* Five grams (0.027 mole) of 2-(α-chloroethyl)benzimidazole in 10 cc. of dry alcohol was added to 4.05 g. (0.055 mole) of *n*-butylamine. The solution was allowed to stand overnight. It was then heated on the water-bath for 6 hours, cooled, diluted with 105 cc. of dry ether, and filtered. The monohydrochloride was obtained from the cold filtrate, as in the case of compound X; yield 91%. It was recrystallized from dry alcohol and acetone; colorless needles, m.p. 171.8–172.7°.

Anal. Calc'd for $C_{13}H_{19}N_3 \cdot HCl$: N, 16.56; Cl, 13.97.
Found: N, 16.62; Cl, 14.00.

The free base, obtained by adding sodium hydroxide to an aqueous solution of the hydrochloride, was recrystallized from ligroin; colorless needles, m.p. 120.3–121.7°.

Anal. Calc'd for $C_{13}H_{19}N_3$: C, 71.84; H, 8.81; N, 19.34.
Found: C, 71.75; H, 8.67; N, 19.32.

XII. *2-(α-Benzylaminoethyl)benzimidazole.* Five grams (0.027 mole) of 2-(α-chloroethyl)benzimidazole was added to a solution of 5.93 g. (0.055 mole) of benzylamine in 12 cc. of dry alcohol. The solution was refluxed for 3 hours, cooled, diluted with 60 cc. of dry ether, and filtered. A 92% yield of the product was obtained from the filtrate. It was recrystallized from acetone and water; colorless prisms, m.p. 155.5–156°.

Anal. Calc'd for $C_{16}H_{17}N_3$: C, 76.46; H, 6.81; N, 16.72.
Found: C, 76.31; H, 6.93; N, 16.59.

The monohydrochloride, obtained from a dry alcohol-ether solution of the base, was recrystallized from dry alcohol; colorless prisms, m.p. 218–220°.

Anal. Calc'd for $C_{16}H_{17}N_3 \cdot HCl$: N, 14.60; Cl, 12.32.
Found: N, 14.64; Cl, 12.38.

SUMMARY

1. Phillips' statement that the monoacyl-*o*-phenylenediamines were the necessary intermediates in the formation of benzimidazoles from *o*-phenylenediamine has been confirmed.

2. It has been shown that the monoacyl-*o*-phenylenediamines do not yield benzimidazoles, under anhydrous conditions, unless there is at least one hydrogen atom on each of the two nitrogen atoms.

3. 2-(α-Chloroethyl)benzimidazole has been prepared and the optimum conditions for the ring closure involved have been established.

4. 2-(α-Chloroethyl)benzimidazole has been condensed with six secondary amines to yield the corresponding 2-(α-dialkylaminoethyl)-benzimidazoles. The latter formed only dihydrochlorides.

5. 2-(α-Chloroethyl)benzimidazole has been condensed with three primary amines, above methylamine, to yield the corresponding 2-(α-alkylaminoethyl)benzimidazoles. These bases formed only monohydrochlorides. The condensation with ammonia and methylamine resulted in the formation of disubstituted derivatives which formed dihydrochlorides.

PHILADELPHIA, PA.

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