Agricultural Division American Cyanamid Company

# Novel Halogenated Imidazoles. Chloroimidazoles.

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With one exception chloroimidazoles containing an unalkylated ring nitrogen have been ignored. Procedures are described using hypochlorite solution that permit the synthesis of 4,5-dichloroimidazole and 2,4,5-trichloroimidazole. Various bromoimidazoles are also converted to chloroimidazoles in refluxing hydrochloric acid.

Although the literature is replete with examples of direct bromination and iodination of imidazoles containing an unalkylated ring nitrogen, there is no mention of chlorination attempts, either successful or unsuccessful (2). Indeed, only one ring-chlorinated imidazole with an unalkylated ring nitrogen [2,4-dichloroimidazole (3)] has been cited in the literature (4), and the purity of this compound is questionable.

All of our efforts in using chlorine as the chlorinating agent have led to undesired products containing carbonyl groups. Nevertheless, we have found three instances where an imidazole can be directly chlorinated. Imidazole itself under certain narrowly defined conditions will react with sodium hypochlorite to give 4,5-dichloroimidazole (I). Increasing or decreasing the recommended amount of hypochlorite solution does not favor trichlorination or monochlorination, but merely lowers the yield and quality of I. The assignment of the chlorine positions was made by n.m.r. spectral comparisons with various bromoimidazoles of unambiguous structure (see Table I).

The fact that dichlorination is preferred and occurs almost entirely in the 4,5 positions (5) is signally different from the bromination or iodination of imidazole. When imidazole is allowed to react with bromine, the trisubstituted compound is the only significant product. With iodine mono, di and triiodinated imidazoles can be prepared. Hypochlorite chlorination of 4-bromoimidazole (V) gives only 4-bromo-5-chloroimidazole (VI), no 2-chloro product being found.

Attempts to prepare 2,4,5-trichloroimidazole (II) by reacting I with hypochlorite solution were not very successful since poor yields were obtained. To obtain any product at all appears to depend on a narrow set of conditions (see "Experimental").

2-Alkylimidazoles (VIIa,b) also can be converted to 4,5-dichloro derivatives, as demonstrated by the facile chlorination of 2-methyl and 2-ethylimidazole (IXa,b).

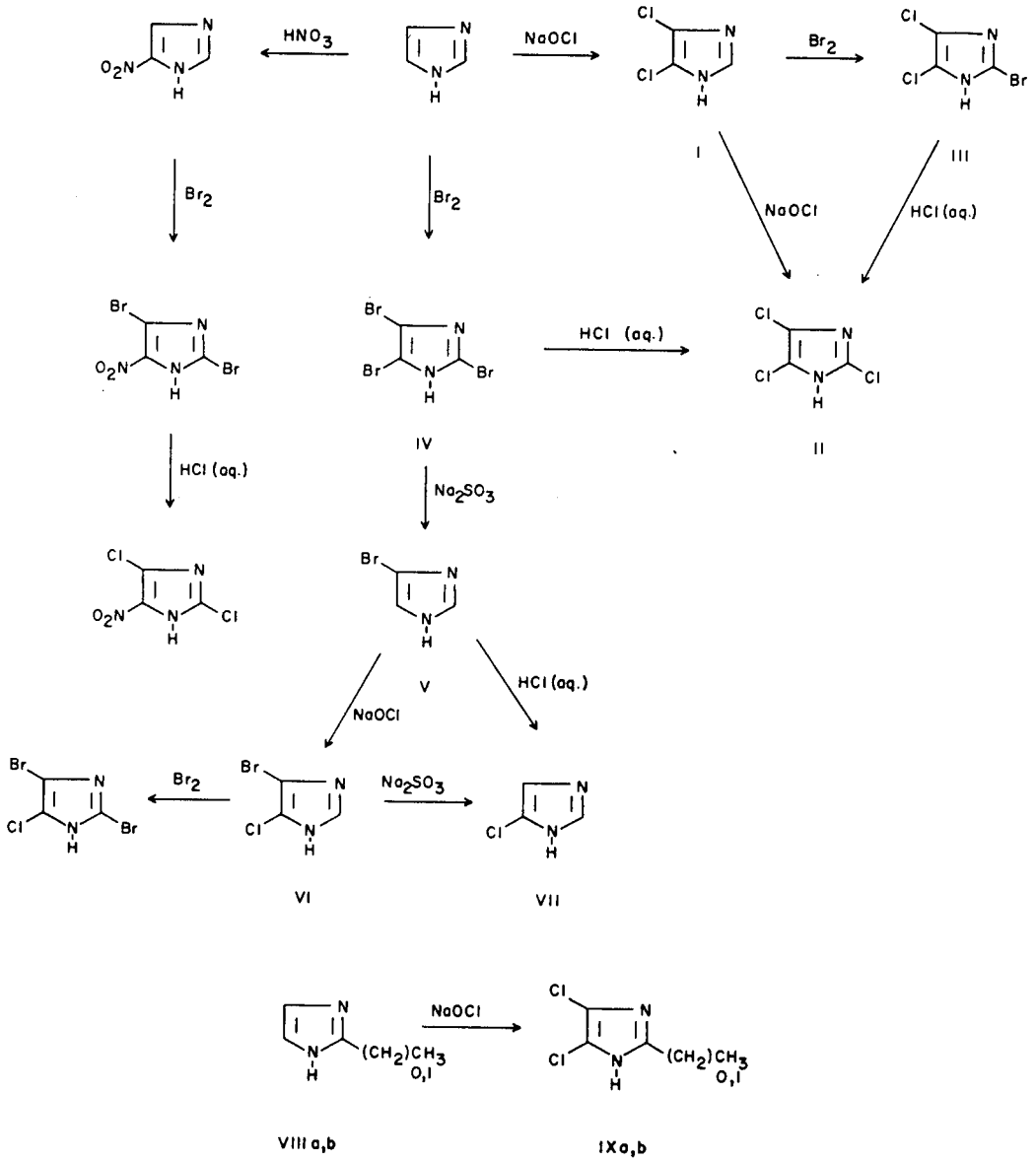
Two other pathways to II have been devised, each superior to the method just described. Either 2-bromo-4,5-dichloroimidazole (III) or 2,4,5-tribromoimidazole (IV) is converted to II by simply heating the appropriate bromo compound in concentrated hydrochloric acid under reflux.

The formation of II is conveniently followed by the appearance in the infrared spectrum of three bands in the 600-700 $cm^{-1}$ region (Experimental). These approaches were based on a report by King and Murch (4) that 2,4-dichloroimidazole is obtained from the treatment of 2,4-dibromo-5-imidazolecarboxylic acid *p*-bromoanilide with concentrated hydrochloric acid at 150°. This method of substitution of chlorine for bromine atoms appears to be general, and a variety of chlorinated imidazoles not obtainable by other means are shown in Chart I.

Ironically, when the work of King and Murch was repeated or with the modification just described, no pure 2,4-dichloroimidazole could be isolated. Elemental analyses of the products showed the presence of varying amounts of bromine-containing compounds, and mass spectral data indicated the existence of monobromo, bromochloro, dichloro, dibromo, and trichloroimidazoles. Although King and Murch suggested that they had this compound in 95% purity, based on nitrogen and halogen analyses, they did not exclude the possibility of the existence of a mixed bromochloroimidazole.

It is known (2) that sulfite ion will reductively remove both bromine and iodine atoms from an appropriately substituted imidazole. However, chlorine atoms appear to be resistant to removal in boiling sodium sulfite solutions. For example, a sample of II contaminated with a tenacious impurity of some brominated imidazole was upgraded in purity by heating the compound in refluxing sulfite solution (from 4.4% Br to 2.3% Br after two hours and 1.1% Br after 18 hours). Although prolonged heating (77 hours) of I in sulfite solution failed to remove either of the chlorine atoms (starting material recovered in 92% yield), 4-bromo-5-chloroimidazole was (VI) smoothly debrominated to the novel 4-chloroimidazole (VII). Compound VII was also prepared from V by treatment with

CHART I
Preparation of Chlorinated Imidazoles




VIII a,b IX a,b

hydrochloric acid, but the transformation required the more vigorous conditions of a sealed tube at 150° for 72 hours.

## EXPERIMENTAL

Melting points were taken on a Thomas-Hoover Capillary melting point apparatus and are uncorrected. Microanalyses were performed by Galbraith Laboratories in Knoxville, Tennessee. Infrared spectra were obtained on a Perkin-Elmer model 421 spectrometer using Nujol (R) mulls. The n.m.r. spectra were determined in deuterated dimethylsulfoxide with tetramethylsilane as the internal standard on a Varian A-60 spectrometer. The mass spectral data are given as mole per cent based on relative peak heights using appropriate compounds as standards.

4,5-Dichloroimidazole (I) (6).

Imidazole (68.0 g., 1.0 mole) was added all at once (in larger preparations aqueous solutions were used) to a solution of sodium hydroxide (40.0 g., 1.0 mole) in 5.25% sodium hypochlorite ("Chlorox", 2840 g., 2.0 mole) with stirring. In some runs the additional base was omitted without adversely affecting the result. The solution turned yellow, then deep orange and the temperature rose to 41°. After five minutes the *p*H (9-10) was adjusted to 4 with concentrated hydrochloric acid. The brown precipitate was collected, washed with water and dried under vacuum to give 96.0 g. of crude product. Concentration of the filtrate to half volume yielded after chilling another 10.0 g. of solid making a total crude yield of 106.0 g. (77.3%). A portion of the crude product (91.5 g.) was recrystallized from water (2 l.) after treatment with carbon (60 g.) to yield 65.2 g. (50.8%) of white product with

TABLE I

Ring Proton Chemical Shift Positions of Imidazoles

| Structure | Position ($\tau$) ppm 2H | 4H | 5H |
|---|---|---|---|
| 2-Br | | 2.96 | 2.96 |
| 2,4-$Br_2$ | | | 2.62 |
| 4,5-$Br_2$ | 2.19 | | |
| I 4,5-$Cl_2$ | 2.30 | | |
| VI 4-Br, 5-Cl | 2.30 | | |
| V 4-Br | 2.27 | | 2.70 |
| VII 4-Cl | 2.28 | | 2.75 |

m.p. 179-180°. The infrared spectrum shows strong absorption bands at 628, 660 and 810 $cm^{-1}$

*Anal.* Calcd. for $C_3H_2Cl_2N_2$: C, 26.30; H, 1.47; Cl, 51.78; N, 20.45. Found: C, 26.55; H, 1.52; Cl, 52.01; N, 20.62.

From a 3.68 mole preparation to prepare I, a small quantity of 2,4,5-trichloroimidazole (II) was also isolated as follows. The filtrate (*p*H 4) from which I was removed was further acidified to *p*H 2. After the resultant suspension was chilled for 48 hours, the precipitate was collected and dried to give crude II as an orange-brown solid with m.p. 180-197°. This solid was dissolved in 2*M* ammonium hydroxide, the *p*H adjusted to 6 and the solution chilled. An additional quantity of I separated. This solid was removed and the mother liquor adjusted with carbon, refiltered and reacidified to *p*H 2. The solid that now precipitated (2.3% yield) had m.p. 210-211°. After a recrystallization from water (carbon treatment), the product had m.p. 195-196°.

*Anal.* Calcd. for $C_3HCl_3N_2$: C, 21.02; H, 0.59; Cl, 62.05; N, 16.34. Found: C, 21.06; H, 0.66; Cl, 61.73; N, 16.32.

2,4,5-Trichloroimidazole (II).

A. From 2,4,5-tribromoimidazole (IV).

2,4,5-Tribromoimidazole (7) (100 g., 0.33 mole) was heated in 2500 ml. of boiling concentrated hydrochloric acid (foaming) for a period of 50 hours. After cooling and diluting with 2100 ml. of water, the reaction mixture was chilled overnight. The solids were removed by filtration, washed with 300 ml. of water, and dried in a vacuum oven at 90° for six hours. The product weighed 19.7 g. (35.2%) and had m.p. 212-213°. After recrystallization from water the m.p. was 195-196° and the microanalyses showed a 4.35% bromine content. Therefore, a 1.0 g. sample was heated under reflux in 20 ml. of 10% aqueous sodium sulfite for 18 hours. The solution was basified with ammonium hydroxide and then acidified to *p*H 3. The precipitate (0.6 g.) after recrystallization from ethyl acetate had m.p. 180-181°. The infrared spectrum shows medium absorption bands at 628, 633 and 670 $cm^{-1}$.

*Anal.* Calcd. for $C_3HCl_3N_2$: C, 21.02; H, 0.59; Cl, 62.05; N, 16.34. Found: C, 21.02; H, 0.55; Cl, 61.18; N, 16.27; Br, 1.10.

Mass spectral analysis indicated a purity of 97.3%.

B. From 2-Bromo-4,5-dichloroimidazole (III).

2-Bromo-4,5-dichloroimidazole (10.0 g., 0.047 mole) was heated in 250 ml. of concentrated hydrochloric acid under reflux for 72 hours. Initially a suspension existed and considerable foaming occurred. After approximately 8 hours the foaming had subsided and a clear solution was present. At the end of the reflux period, the reaction solution was filtered, diluted with 250 ml. of water and chilled. The precipitate was collected, washed with water and dried under vacuum to give 5.5 g. (69.2%) of product. After recrystallization from 500 ml. of water, a first crop (2.5 g., 31.4%) was taken with m.p. 180-181° and with an infrared spectrum identical to that of the compound prepared by method A. Mass spectral analysis indicated a purity of 98%.

C. From 4,5-dichloroimidazole (I).

To a solution of 4,5-dichloroimidazole (1.37 g., 0.01 mole) dissolved in 10 ml. of *N* sodium hydroxide (0.1 mole) was added all at once 10 ml. of *N* sodium hypochlorite solution. (Varying the order of addition or the rate of addition of reactant [dropwise *vs.* all at once] will cause the reaction to fail.) The reaction turned yellow and then dark brown with the temperature at 27°. At 30° ice (40 g.) was added to quench the reaction. The cold solution was treated with carbon, filtered, and acidified to precipitate a brown solid. This solid was dissolved in 60 ml. of 14% ammonium hydroxide, retreated with carbon, filtered, and acidified to *p*H 4. The product was recrystallized from water (carbon) to give 0.15 g. (8.9%) of white needles with m.p. 196-197°. The infrared spectrum was identical to those of the products obtained by methods A and B.

*Anal.* Calcd. for $C_3HCl_3N_2$; C, 21.02; H, 0.59; Cl, 62.05; N, 16.34. Found: C, 21.08; H, 0.60; Cl, 61.96; N, 16.31.

2-Bromo-4,5-dichloroimidazole (III).

4,5-Dichloroimidazole (1.36 g., 0.01 mole) was dissolved in 10 ml. of *N* sodium hydroxide (0.01 mole) and a solution of bromine (1.60 g., 0.01 mole) in 10 ml. chloroform added over a 10 minute period with stirring at 20-25°. The chloroform was removed *in vacuo* and the resulting aqueous solution acidified to *p*H 4 with hydrochloric acid. The precipitate was removed by filtration, washed with water, and dried to yield 1.63 g. (75.8%) of a brown product. Three recrystallizations from 20 ml. of 50% aqueous ethanol (carbon) gave 0.60 g. (27.9%) of white product with m.p. 219-220°. The infrared spectrum shows medium bands at 585 and 855 $cm^{-1}$ and a strong band at 660 $cm^{-1}$.

*Anal.* Calcd. for $C_3HBrCl_2N_2$: C, 16.75; H, 0.47; Br, 37.05; Cl, 32.85; N, 12.98. Found: C, 16.80; H, 0.55; Br, 36.76; Cl, 32.90; N, 13.09.

4-Bromo-5-chloroimidazole (VI).

4-Bromoimidazole (7) (35.0 g., 0.24 mole) was dissolved in 250 ml. of water containing 9.6 g. (0.24 mole) sodium hydroxide. 5.25% Sodium hypochlorite solution ("Chlorox", 18.6 g., 0.25 mole) was added all at once with good stirring. The reaction mixture became orange and the temperature rose to 40°. After clarifying the solution by a carbon treatment, the *p*H of the filtrate was adjusted to 3 with concentrated hydrochloric acid. The solid which precipitated was collected, washed with water and dried *in vacuo* to give 35.0 g. (81.4%) of product. Recrystallization of 20.0 g. from 1200 ml. water (carbon) gave 13.8 g. (56.2% adjusted) of product with m.p. 195-196°.

*Anal.* Calcd. for $C_3H_2BrClN_2$: C, 19.86; H, 1.11; Br, 44.04; Cl, 19.55; N, 15.44. Found: C, 19.63; H, 1.04; Br, 43.95; Cl, 19.74; N, 15.25.

4-Chloroimidazole (VII).

A. From 4-bromo-5-chloroimidazole (VI).

4-Bromo-5-chloroimidazole (15.0 g., 0.083 mole) was heated under reflux in 200 ml. of 10% aqueous sodium sulfite solution for 20 hours. The solution after its *p*H was adjusted to 2 with concen-

trated hydrochloric acid was taken to dryness on a rotary evaporator. The residual solid was extracted with three 200 ml. portions of boiling ethanol, the extracts combined and evaporated to dryness leaving a residue which was redissolved in water (100 ml.). After the solution was made basic with sodium carbonate, the precipitate which formed was collected and dried to yield 6.0 g., with m.p. 110-112°. Saturation of the filtrate with sodium sulfate followed by extraction with ether gave an additional 1.5 g. of product, m.p. 110-114°. The combined crops were recrystallized from water (50 ml.) to yield 6.6 g. (79.0%) of a white solid with m.p. 117-118°.

*Anal.* Calcd. for $C_3H_3ClN_2$: C, 35.14; H, 2.95; Cl, 34.59; N, 27.32. Found: C, 34.59; H, 2.91; Cl, 34.43; N, 27.10.

B. From 4-Bromoimidazole (V).

4-Bromoimidazole (2.0 g., 0.014 mole) was dissolved in concentrated hydrochloric acid and heated in a sealed tube for 72 hours at *ca.* 150° (oil bath temperature). After cooling the solution, it was basified with solid sodium carbonate and extracted with ether. The ether layers were washed, dried and stripped to give 0.80 g. of a solid with m.p. 112-115°. Recrystallization from 5 ml. water yielded 0.50 g. with m.p. 116-118°. The infrared spectrum was identical to the product obtained by method A.

*Anal.* Calcd. for $C_3H_3ClN_2$: C, 35.14; H, 2.95; Cl, 34.59; N, 27.32. Found: C, 33.86; H, 2.81; Cl, 30.70; Br, 5.77; N, 26.61.

Mass spectral analysis indicated a purity of 91.1% with 8.6% starting material still present.

2,4-Dibromo-5-chloroimidazole.

4-Bromo-5-chloroimidazole (10.0 g., 0.055 mole) was dissolved in 250 ml. of water containing 2.2 g. (0.055 mole) of sodium hydroxide. A solution of bromine (8.8 g., 0.055 mole) in 50 ml. chloroform was added over a 30-minute period. The temperature rose to 35° and the solution became black. After adjusting the *p*H to 7, the solution was diluted to 1000 ml. with water, boiled with 5.0 g. of carbon and filtered. The carbon treatment was repeated, the filtrate adjusted to *p*H 2, and the solution refrigerated overnight. The precipitate was collected and recrystallized two times from 1000 ml. water (carbon) to give 6.7 g. (46.7%) of a tan product, m.p. 218-220°.

*Anal.* Calcd. for $C_3HBr_2ClN_2$: C, 13.84; H, 0.39; Br, 61.39; Cl, 13.62; N, 10.76. Found: C, 14.03; H, 0.48; Br, 61.18; Cl, 13.71: N, 10.64.

2,4-Dibromo-5-nitroimidazole.

The preparation for this compound which follows is simpler than the one used by Balaban and Pyman (7). 4-Nitroimidazole (8) (3.0 g., 0.027 mole) was dissolved in 80 ml. of water containing sodium hydroxide (3.2 g., 0.080 mole). While maintaining the temperature of the reaction between 15-20°, bromine (8.5 g., 0.053 mole) was added dropwise to the stirred solution. After the addition was complete, the suspension was rebasified with 40 ml. of *N* sodium hydroxide to obtain a clear solution. The *p*H was adjusted to 3 and the precipitate collected and dried to give 4.0 g. of product. After a reprecipitation from 5% aqueous sodium carbonate (charcoal treated), the product weighed 3.0 g. (42.2%) with browning at 170°, m.p. >300° (lit. m.p. (7) >270° with blackening at 170°).

2,4-Dichloro-5-nitroimidazole.

2,4-Dibromo-5-nitroimidazole (19.0 g., 0.068 mole) was heated under reflux in concentrated hydrochloric acid (500 ml.) for six hours. After cooling to room temperature, the solution was diluted with water (500 ml.) and the resulting precipitate collected by filtration. The crude product was then recrystallized from 150 ml. of water to give 9.8 g. (79.1%) of a white product with m.p. 175-176°, identical to the m.p. and infrared spectrum of the analytical sample.

*Anal.* Calcd. for $C_3HCl_2N_3O_2$: C, 19.80; H, 0.55; Cl, 38.98; N, 23.09. Found: C, 19.69; H, 1.05; Cl, 34.63; N, 23.22, Br, 4.07.

Mass spectral data indicated the purity to be 87.1% with $C_3HBrClN_3O_2$ present to the extent of 9.5%.

4,5-Dichloro-2-methylimidazole (IXa).

2-Methylimidazole (Houdry Division, Air Products and Chemicals Company) (5.0 g., 0.06 mole) was dissolved in 6.1 ml. *N* sodium hydroxide (0.06 mole) solution and added all at once with good stirring to 5.25% sodium hypochlorite solution ("Chlorox"; 0.12 mole). The temperature rose to 43° while the reaction medium became a light orange in color. The solution was chilled, *p*H adjusted to 2 with concentrated hydrochloric acid, the resulting precipitate collected, water washed and dried to yield 4.95 g. (53.6%) of product with m.p. 245-250°. Recrystallization from water raised the m.p. to 251-252°.

*Anal.* Calcd. for $C_4H_4Cl_2N_2$: C, 31.82; H, 2.67; Cl, 46.96; N, 18.55. Found: C, 31.89; H, 2.67; Cl, 46.97; N, 18.51.

4,5-Dichloro-2-ethylimidazole (IXb).

This compound was prepared in a fashion similar to that for the 2-methyl homolog to give the crude product in 58.3% yield with m.p. 166-168°. Recrystallization from water gave the analytical sample with m.p. 170-171°.

*Anal.* Calcd. for $C_5H_6Cl_2N_2$: C, 36.40; H, 3.66; Cl, 42.96; N, 16.98. Found: C, 36.56; H, 3.30; Cl, 42.94; N, 17.09.

Acknowledgement

We are indebted to Mr. R. S. Wayne for the n.m.r. spectra and Mr. T. E. Mead for the mass spectral analyses.

## REFERENCES

(1) To whom correspondence should be addressed.

(2) K. Hofmann, "The Chemistry of Heterocyclic Compounds. Vol. VI. Imidazole and Its Derivatives, Part I," Interscience Publishers, Inc., New York, N. Y., 1953, p. 111.

(3) For simplicity, the existence of tautomeric structures will be ignored and only the tautomer with the lower numbering system will be named.

(4) H. King and W. O. Murch *J. Chem. Soc.*, 123, 621 (1923).

(5) On a large scale preparation, 2,4,5-trichloroimidazole (II) was isolated as a by-product in 2% yield.

(6) This chlorination must be run under basic conditions (*p*H 11), and sodium hypochlorite solution may be added slowly or rapidly to the imidazole solution without affecting the quality or yield of the product. However, when imidazole is added to the hypochlorite solution (the preferred way), it must be added all at once. If the addition is slow, foaming occurs, the *p*H drops rapidly to 8, and the yield becomes negligible.

(7) I. E. Balaban and F. L. Pyman, *J. Chem. Soc.*, 121, 947 (1922).

(8) R. G. Fargher and F. L. Pyman, *ibid.*, 115, 217 (1919).

Received March 10, 1967 Princeton, N. J. 08540