decomposed with 10 ml. of water, and then 10 ml. of 10% sulfuric acid was added to decompose the complex. The light yellow ether solution was separated, washed with two 50 ml. portions of water, dried over sodium sulfate, filtered, and evaporated to dryness. The crude product was recrystallized from a mixture of 15 ml. of ligroin (b.p. 65–110°) and 25 ml. of dioxane. The product weighed 0.25 g. (4.93% yield), m.p. 158.0–158.8°.

Anal. Calcd. for $C_{11}H_{12}N_2O_4$: N, 11.87. Found: N, 11.71.

α-Dichloroacetamido-p-nitrocinnamyl alcohol (XIV). To a solution of 5 ml. of acetic anhydride and 2.5 ml. of glacial acetic acid was added, with stirring, 0.75 g. of pulverized cupric nitrate trihydrate. A temperature of 30–35° was maintained. After the exothermic reaction had ceased there was added 0.75 g. of α-dichloroacetamidocinnamyl alcohol portionwise during 20 min. at 10–20°. The temperature was allowed to rise to room temperature during 10 min. and then poured into 100 g. of ice and water. A yellow oil separated which crystallized. The nitro derivative was purified by recrystallization from petroleum ether. The colorless needles which separated were filtered and dried *in vacuo* at 25° over phosphorus pentoxide, m.p. 94–98°.

Anal. Calcd. for $C_{11}H_{10}Cl_2N_2O_4$: H, 3.28; Cl, 23.28; N, 9.18. Found: H, 3.61; Cl, 23.01; N, 9.05.

Infrared analysis demonstrated the presence of a *p*-nitrophenyl group. Qualitative tests for a double bond and a hydroxyl group were positive.

Ethyl α-dichloroacetamido-p-nitrocinnamate (XV). This compound was prepared by the nitration of ethyl α-dichloroacetamidocinnamate (X). The nitration reagent was prepared in the same manner as that described above. A mixture of 10 ml. of acetic anhydride, 5 ml. of glacial acetic acid, and 1.5 g. of cupric nitrate was used. To it was added 1.8 g. of (X) portionwise at 25–30°. The mixture was stirred for 0.5 hr. and then poured into 50 g. of ice and water. The oil which separated was dissolved in ether, dried over sodium sulfate, and the ether evaporated. The semi-crystalline residue of (XV) was used directly without purification in the lithium aluminum hydride reduction step described below. This compound has been described by Huebner and Scholz.[2]

α-Dichloroacetamido-p-nitrocinnamyl alcohol (XIV). To a solution of 1.2 g. of impure (XV) described above in 50 ml. of anhydrous ether there was added dropwise during 30 min., a lithium aluminum hydride solution consisting of 0.1040 g. lithium aluminum hydride ether. The mixture was stirred 10 min. and then stirred with 50 ml. of 10% sulfuric acid. The ether layer was washed with water, dried with sodium sulfate and then evaporated to dryness under reduced pressure. The residue was dissolved in carbon tetrachloride and precipitated by adding excess petroleum ether. The colorless crystalline product weighed 0.65 g., m.p. 96°.

Anal. Calcd. for $C_{11}H_{10}Cl_2N_2O_4$: N, 9.18. Found: N, 9.17.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF PENNSYLVANIA]

Preparation of 5(6)-Fluorobenzimidazole and 4(7)-Fluorobenzimidazole

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5(6)-Fluorobenzimidazole and 4(7)-fluorobenzimidazole have been prepared by the Schiemann reaction from the corresponding amino compounds. The infrared and ultraviolet absorption spectra and *p*Ka values have been determined for both compounds.

Several fluorine-containing compounds have been reported to have useful physiological properties. *p*-Fluorobenzoic acid inhibits the growth of *E. coli* and the inhibition is reversed by tyrosine but not by *p*-aminobenzoic acid.[1] *m*-Fluoro-*p*-aminobenzoic acid also inhibits the growth of *E. coli* and the inhibition is reversed by *p*-aminobenzoic acid.[2] A number of fluorinated phenylalanines and tyrosines have been tested as growth inhibitors and were found to be competitive inhibitors of their parent amino acids. The preparation and resolution of the three DL-monofluorophenylalanines have been carried out since the observation was made that *m*-fluoro-DL-phenylalanine effectively inhibits the metabolism of phenylalanine by a competitive process.[3] Recently the biological activity of three fluoro derivatives of pyrimidines has been reported. 5-Fluorouracil and 5-fluoroörotic acid have shown appreciable activity against a number of mouse and rat tumors.[4] Very recently, also, several 2-fluoropurines have been prepared and it is reported that 2-fluoroadenosine inhibits the growth of Human Epidermoid Carcinoma (HE2).[5]

Since the benzimidazole nucleus is present in several physiologically active compounds it was believed that the preparation of fluorobenzimidazoles might lead to some interesting compounds. In the present study the 5(6)-fluoro- and 4(7)-

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fluorobenzimidazoles have been prepared. These compounds are being tested in the antitumor program of the University of Pennsylvania and also by Smith Klein & French of Philadelphia, Pa. The results will be published elsewhere.

The 5(6)-isomer was previously prepared from 4-fluoro-*o*-phenylenediamine.[6] The preparation of 5(6)-fluorobenzimidazole has been reported quite recently by Japanese chemists.[7] They used a different route to 4-fluoro-*o*-phenylenediamine. However, we desired to use a more general method which would allow the introduction of fluorine into several substituted benzimidazoles. The Schiemann reaction was chosen as the procedure which would allow the most variety. Both fluorobenzimidazoles were prepared by the decomposition of the corresponding benzimidazolediazonium fluoborates.

The 5(6)-benzimidazolediazonium fluoborate was prepared from 5(6)-aminobenzimidazole which was made by a method similar to that described by Rabinowitz and Wagner.[8]

The 4(7)-benzimidazolediazonium fluoborate was prepared from 4(7)-aminobenzimidazole which was made by a method similar to that described by Van der Want.[9]

Potentiometric titration of 5(6)-fluorobenzimidazole and 4(7)-fluorobenzimidazole with hydrochloric acid in water gave pK_a values of 5.11 and 4.40,respectively. Under similar conditions benzimidazole has a pK_a value of 5.53. Thus 5(6)-fluorobenzimidazole is a somewhat weaker base than benzimidazole and 4(7)-fluorobenzimidazole is a weaker base than either one. Benzimidazole is a weaker base than is imidazole which has a pK_a value of 6.95. Conjugation of the benzene ring with the imidazole ring increases the number of extreme resonance structures in which electrons are withdrawn from the nitrogen atoms of the imidazole ring. This reduces the basicity of the imidazole ring. The presence of electron-attracting substituents in the benzene ring further reduces the basicity of the imidazole ring. Since fluorine can decrease the basicity only through an inductive effect this reduction is greatest when the fluorine occupies the 4(7)-position as expected. The difference in basicity between the two isomeric fluoro compounds is greater than the difference noted for 5(6)- and 4(7)-nitrobenzimidazoles.[8] The nitro compounds although weaker bases than the corresponding fluorobenzimidazoles, their pK_a values being 3.60 and 3.80, have about the same base strength. Unfortunately a direct comparison with the corresponding chlorobenzimidazoles is impossible, at the moment, since the reported literature values were made in 50% aqueous ethanol.[10]

The ultraviolet spectra of 5(6)- and 4(7)-fluorobenzimidazoles were measured in aqueous solution, 0.1*N* hydrochloric acid and 0.1*N* sodium hydroxide solutions. The ultraviolet spectrum of benzimidazole was also determined under the same conditions for direct comparison with these values. The ultraviolet spectrum of benzimidazole is reported in the literature in ethanol solution, in 0.1*N* hydrochloric acid and 0.1*N* sodium hydroxide solutions.[11] The data obtained in the present study are listed in Table I.

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA (λ IN mμ)

	Benzimidazole		5(6)-Fluorobenzimidazole		4(7)-Fluorobenzimidazole	
Solvent	λ	Log ε	λ	Log ε	λ	Log ε
Water	245	3.72	242	3.69	242	3.70
	271	3.79	273	3.69	273	3.26
	278	3.78				
0.1*N* HCl	267	3.88	271	3.88	263	3.76
	275	3.83	277	3.82	268	3.69
0.1*N* NaOH	271	3.88	275	3.87	263	3.84
	275	3.84				

Interpretation of these differences is not possible at the present time. A broad study of benzimidazoles and imidazoles is being started to obtain the data necessary to definitely assign the absorption bands, and to correlate ultraviolet and infrared data, pK_a data and molecular weights with the observed facts.

The infrared spectra of the two isomeric fluorobenzimidazoles showed no significant differences from the infrared spectrum of benzimidazole itself.

EXPERIMENTAL

5(6)-Nitrobenzimidazole. It was prepared from 4-nitro-*o*-phenylenediamine and 98% formic acid.[12] The product was recrystallized from aqueous ethanol, yield 86%, m.p. 204–206°.

5(6)-Aminobenzimidazole. The 5(6)-nitrobenzimidazole was reduced with tin and hydrochloric acid as described by Staüble.[13] The yield was 72%. The anhydrous compound melted at 166-167°.

5(6)-Benzimidazolediazonium fluoborate. 5(6)-Aminobenzimidazole (6.63 g., 0.05 mole) was suspended in 100 ml. of 48% fluoboric acid solution. The mixture was cooled to 0° and diazotized by slowly adding, with stirring 3.51 g. (0.05 mole) of sodium nitrite dissolved in 6 ml. of water. The solution was stirred for an additional hour at 0°. The solid was

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removed by filtration and washed with cold fluoboric acid solution, cold dry ethanol, and anhydrous ether. On drying in a desiccator, over calcium chloride, it turned to a powdery white solid. The yield was 9.96 g. (86%). It decomposes at 195–200° with the evolution of boron trifluoride and nitrogen.

Unsuccessful attempts to decompose 5(6)-benzimidazolediazonium fluoborate. In 1956 a new method was reported for the decomposition of diazonium fluoborates using cuprous chloride.[14] Since the method appeared to be more convenient than thermal decomposition, it was tried first. A typical run is described below. 5(6)-Benzimidazolediazonium fluoborate (8.88 g., 0.038 mole) was dissolved in 500 ml. of water and the solution was stirred. Cuprous chloride (1 g.) was added to this solution in small portions and the mixture was heated on a steam bath for 2 hr. The copper was eliminated by passing hydrogen sulfide into the solution and removing the copper sulfide which formed. The filtrate was neutralized with solid sodium bicarbonate and a brown solid which formed was removed by filtration and dried (3.2 g.). The solid was extracted with ethyl acetate and the solvent was evaporated. The residue was dissolved in benzene, treated with decolorizing carbon and the solution was filtered. Petroleum ether (60–80°) was added until the solution became turbid. The material which separated was recrystallized several times by the same procedure but the melting point range of the compound remained large and could not be raised above 121°. Recently it has been found that the cuprous chloride method for decomposing diazonium fluoborates may lead to deamination or replacement by chlorine instead of fluorine.[15]This last reaction seems to have occurred in our case since the analytical data and melting point of our compound seem to be close to that of 5(6)-chlorobenzimidazole (m.p. 124–126°).

Anal. Calcd. for $C_7H_5N_2Cl$: C, 55.10; H, 3.30; N, 18.36. Found: C, 54.51; H, 3.25; N, 18.33.

5(6)-Fluorobenzimidazole. 5(6)-Benzimidazolediazonium fluoborate (9.96 g., 0.043 mole) was decomposed by heating at 195° until no more fumes appeared. The cooled residue was dissolved in 4*N* hydrochloric acid, treated with decolorizing carbon and filtered. The solution was then neutralized with solid sodium bicarbonate and the brown solid which formed was removed by filtration, washed with water, and dried (2.71 g.). The crude product was dissolved in benzene, treated with decolorizing carbon and the solution filtered. Petroleum ether (60–80°) was added to the filtrate until it became cloudy. On cooling, yellow crystals were obtained. This procedure was repeated several times until colorless crystals were obtained. The yield was 38%, m.p. 132°.

Anal. Calcd. for $C_7H_5N_2F$: C, 61.76; H, 3.70; N, 20.58. Found: C, 61.63; H, 3.56; N, 20.48.

4(7)-Nitrobenzimidazole. This compound was prepared from *o*-nitrochlorobenzene by a six-step process. The nitrochlorobenzene was sulfonated and then nitrated to give potassium 3,5-dinitro-4-chlorobenzenesulfonate.[16] The latter was converted to potassium 3,5-dinitro-4-aminobenzene sulfonate by treatment with ammonia. This compound was converted to 2,6-dinitroaniline by refluxing with 60% sulfuric acid for 3 hr.[17] The product crystallized on cooling. It was washed with water and recrystallized from ethanol. The yield was 70%, m.p. 138–139°.

2,6-Dinitroaniline has been reduced to 3-nitro-*o*-phenylenediamine by warming with sodium sulfide solution.[9] In the present study the reduction was effected by refluxing for 1 hr. with 2*N* ammonium sulfide while a slow stream of hydrogen sulfide was passed through the solution. The product which separated on cooling was removed by filtration and washed with water. It was converted to the corresponding hydrochloride by evaporation with 6*N* hydrochloric acid on a steam bath, yield 86%. The hydrochloride of 3-nitro-*o*-phenylenediamine was converted to 4(7)-nitrobenzimidazole by using modified Phillips conditions.[18] Since the melting point of the product was considerably higher than previously reported, the procedure is given here. The hydrochloride of 3-nitro-*o*-phenylenediamine (9.48 g., 0.05 mole) was dissolved in 100 ml. of 2*N* hydrochloric acid and 10 ml. of 98% formic acid added. The solution was heated on a steam bath for 1 hr., cooled, and neutralized slowly with concentrated ammonium hydroxide. The precipitate was removed, washed with water, dried, and recrystallized from 95% ethanol. Light peach colored needles were obtained, yield 92%, m.p. 248–249°. Earlier workers reported 238–239°[9] and 242°.[8]

4(7)-Aminobenzimidazole dihydrochloride. 4(7)-Nitrobenzimidazole was hydrogenated in dry ethanol with 10% palladium-on-charcoal as the catalyst. The theoretical amount of hydrogen was quickly absorbed. After removing the catalyst, the dihydrochloride was precipitated by the addition of an equal volume of concentrated hydrochloric acid and ether until no more precipitate formed. The yield of colorless needles was 89%, m.p. 247–249° (dec.). This agrees with the literature.[8]

4(7)-Benzimidazolediazonium fluoborate. 4(7)-Aminobenzimidazole dihydrochloride (10.03 g., 0.05 mole) was suspended in 100 ml. of 48% fluoboric acid solution and cooled to 0°. A solution of 3.51 g. (0.05 mole) of sodium nitrite in 6 ml. of water was added slowly to the cold stirred suspension. The reaction mixture was stirred for 0.5 hr. at 0°, and the solid then removed and washed with cold fluoboric acid solution, ethanol, and ether. The yield was 61%, m.p. 134° (dec.). This salt decomposes violently.

4(7)-Fluorobenzimidazole. 4(7)-Benzimidazolediazonium fluoborate (2 g., 0.0086 mole) was decomposed by carefully heating, in thin layers, at 130–140°. When no more boron trifluoride was given off, the brown residue was dissolved in ethanol, treated with decolorizing carbon, and the filtrate concentrated to a small volume. The addition of petroleum ether precipitated a gummy, brown product. This was dissolved in 1*N* hydrochloric acid, heated with decolorizing carbon, and the carbon removed by filtration. The filtrate was neutralized with solid sodium bicarbonate and concentrated to a small volume. On cooling, a brown crystalline product separated. The yield was 17%, m.p. 180–185°. This product was sublimed to give a colorless, crystalline product.

Anal. Calcd. for $C_7H_5N_2F$: C, 61.76; H, 3.70; N, 20.58. Found: C, 61.78; H, 3.82; N, 20.55.

Potentiometric titrations were carried out with a Beckmann *p*H meter, Model H 2. The fluorobenzimidazoles were used as 0.001*M* aqueous solutions. These solutions were titrated with 0.0053*N* hydrochloric acid.[19]

Ultraviolet absorption spectra were determined on 0.0001*M* solutions in water, 0.1*N* hydrochloric acid and 0.1*N* sodium hydroxide solutions with a Beckmann DU spectrophotometer equipped with a recorder model RS-3 from Process and Instruments Co., Brooklyn, N. Y.

Infrared spectra were determined with a Perkin-Elmer infrared spectrophotometer model 21.

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