Journal of Medicinal Chemistry

VOLUME 8, NUMBER 6 OCTOBER 27, 1965

Synthesis of Potential Anticancer Agents. XXXIV. Fluorobenzimidazoles and Fluorobenzotriazoles[1]

JOHN A. MONTGOMERY AND KATHLEEN HEWSON

Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama

Received June 28, 1965

5-Fluorobenzimidazole (IV), 4,6-difluorobenzimidazole (V), 4,6-difluorobenzotriazole (VI), 4,5,7-trifluorobenzimidazole (VII), 4-amino-5,7-difluorobenzimidazole (XIX), and 4-amino-5,7-difluorobenzotriazole (XX) were synthesized and evaluated for cell culture cytotoxicity. Compounds IV, V, and XIX were also evaluated for their ability to inhibit the Friend virus leukemia and were found to be inactive.

The antiviral activity of benzimidazoles is well known,[2] and among the benzimidazoles certain chlorobenzimidazoles (and also certain chlorobenzotriazoles) have shown activity.[3] Furthermore, more than 30 animal neoplasms are known to be virus induced, and a number of human viruses have been shown to be oncogenic in experimental animals.[4] Virus etiology of some human cancers is possible if not likely. For these reasons we undertook the synthesis and biological evaluation of a series of fluorobenzimidazoles and fluorobenzotriazoles.

Many of the fluoroanilines necessary for the synthesis of the desired fluorobenzimidazoles have been described in the literature, prepared by a series of Schiemann reactions.[5,6] Reduction of 4-fluoro-2-nitroaniline (I),[5] 2,4-difluoro-6-nitroaniline (II),[7] and 3,4,6-trifluoro-2-nitroaniline (III)[6a] to the corresponding *o*-phenylenediamines was accomplished catalytically at atmospheric pressure. The crude diamines were isolated with as little exposure to air as possible and allowed to react immediately with diethoxymethyl acetate[8] to give the desired benzimidazoles: 5-fluorobenzimidazole (IV),[9] 4,6-difluorobenzimidazole (V), and 4,5,7-trifluorobenzimidazole (VII). 4,6-Difluorobenzotriazole (VI) was also prepared, by the reduction of II followed by the treatment of the resultant *o*-phenylenediamine with sodium nitrite in aqueous acetic acid solution.

Another difluorobenzimidazole that we desired to prepare is 5,6-difluorobenzimidazole, a precursor of which is 4,5-difluoro-2-nitroaniline (X). The preparation of X was attempted by the amination of 2,4,5-trifluoronitrobenzene (VIII),[6] since it is known that the chlorine *ortho* to the nitro group of 2,4,5-trichloronitrobenzene reacts preferentially with ammonia to give 4,5-dichloro-2-nitroaniline[10] and that the *ortho* fluorine of 2,4-difluoronitrobenzene is preferentially replaced.[11] The reaction of VIII with ammonia, however, gave a mixture of 2,5-difluoro-4-nitroaniline (IX) and X, in which the approximate ratio of *para*:*ortho* displacement was 6:1, making this approach to the preparation of any quantity of 5,6-difluorobenzimidazole impractical. The identity of IX was established by a comparison of its melting point with the value reported for authentic 2,5-difluoro-4-nitroaniline,[6a] by the fact that it could not be distilled with steam, and by the fact that reduction and reaction of the resultant phenylenediamine with formic acid gave a diformyl derivative rather than a benzimidazole. The diformyl derivative on refluxing with acid (conditions that have been used to effect ring closure to benzimidazoles) gave 2,5-difluoro-*p*-phenylenediamine[6a] dihydrochloride.

Another benzimidazole desired for biological evaluation was 4-amino-5,7-difluorobenzimidazole (XIX), a compound that might be considered to be an analog of adenine. The preparation of this benzimidazole was approached by the amination of 3,4,6-trifluoro-2-nitroacetanilide (XI)[6a] which gave 3-amino-4,6-di-

(1) This work was supported by funds from the C. F. Kettering Foundation and the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. PH-43-64-51.

(2) R. L. Thompson in "Advances in Chemotherapy," Vol. 1, A. Goldin and F. Hawking, Ed., Academic Press Inc., New York, N. Y., 1964, p. 85.

(3) I. Tamm, R. Bablanian, M. M. Nemes, C. H. Shunk, F. M. Robinson, and K. Folkers, *J. Exptl. Med.*, **113**, 625 (1961).

(4) J. J. Trentin, Y. Yabe, and G. Taylor, *Science*, **137**, 835 (1962); R. J. Huebner, W. P. Rowe, and W. T. Love, *Proc. Natl. Acad. Sci. U. S.*, **48**, 2051 (1962).

(5) F. Swarts, *Rec. trav. chim.*, **35**, 131 (1915).

(6) (a) G. C. Finger, F. H. Reed, D. M. Burness, D. M. Fort, and R. K. Blough, *J. Am. Chem. Soc.*, **73**, 145 (1951); (b) F. Wegand, R. Lowenfeld, and E. F. Moller, *Ber.*, **84**, 108 (1951).

(7) G. C. Finger, F. H. Reed, and J. F. Finnerty, *J. Am. Chem. Soc.*, **73**, 153 (1951).

(8) J. A. Montgomery and L. B. Holum, *ibid.*, **80**, 404 (1958).

(9) (a) W. T. Smith and E. C. Steinle, *ibid.*, **75**, 1293 (1953); (b) E. C. Fisher and M. M. Joullie, *J. Org. Chem.*, **23**, 1944 (1958).

(10) F. Beilstein and A. Kurbatous, *Ann.*, **196**, 214 (1879).

(11) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 273 (1951). The reaction of VIII with galactosylamine has been reported.[6b] Although the authors claim displacement of the fluorine *ortho* to the nitro group, they offer no proof to support their claim. The fact that they were unable to prepare an isoalloxazine from the diamine from their product suggests that, in reality, *para* displacement may have occurred.

fluoro-2-nitroacetanilide (XII) and an approximately equal amount of 4,6-difluoro-2-nitro-*m*-phenylenediamine (XIII), which resulted from concomitant deacetylation and amination of XI. Catalytic reduction of XIII to 4,6-difluoro-1,2,3-benzenetriamine followed by immediate reaction of the benzenetriamine with diethoxymethyl acetate gave the benzimidazole XIX, but it could not be freed of colored impurities resulting from the oxidation of the very unstable benzenetriamine. Consequently, 3-amino-4,6-difluoro-2-nitroacetanilide (XII) was reduced catalytically to 2,3-diamino-4,6-difluoroacetanilide (XIV), which on treatment with diethoxymethyl acetate gave 4-acetamido-5,7-difluorobenzimidazole (XVII). Hydrolysis of XVII in aqueous hydrochloric acid gave the hydrochloride of 4-amino-5,7-difluorobenzimidazole (XIX). Since other attempts to utilize XIII by various reduction-cyclization procedures resulted only in low yields of XIX, we studied the acetylation of XIII to give XII. Various acetylation conditions were used, but the best conditions found gave a mixture of three products: XII, N,N'-(4,6-difluoro-2-nitro-*m*-phenylene)bisacetamide (XV), and a material tentatively identified as N-(3-amino-4,6-difluoro-2-nitrophenyl)diacetamide (XVI) on the basis of its infrared spectrum. From this mixture pure XII was obtained in 25% yield.

Reduction of XII followed by immediate reaction of the resultant diamine XIV with sodium nitrite in aqueous acetic acid gave 4-acetamido-5,7-difluorobenzotriazole (XVIII), which was hydrolyzed in aqueous hydrochloric acid to 4-amino-5,7-difluorobenzotriazole (XX).

Attempts to convert XIX to 4-chloro-5,7-difluorobenzimidazole by a Sandmeyer reaction resulted instead in the isolation of what appears to be a zwitterionic diazonium salt (XXI), although an analytical sample of XXI was not prepared. The structure XXI is supported by its infrared spectrum and by the fact that the same compound was isolated from the diazotization of XIX in either concentrated hydrochloric acid or 48% fluoroboric acid. Furthermore, XXI was found to give a positive Bratton–Marshall test.[12,13] The coupling product of XXI and β-naphthol, a deep red compound, was prepared, and its infrared spectrum shows the conversion of the diazonium group of XXI to an azo group. It has not been possible to replace the diazonium group of XXI by halogens.

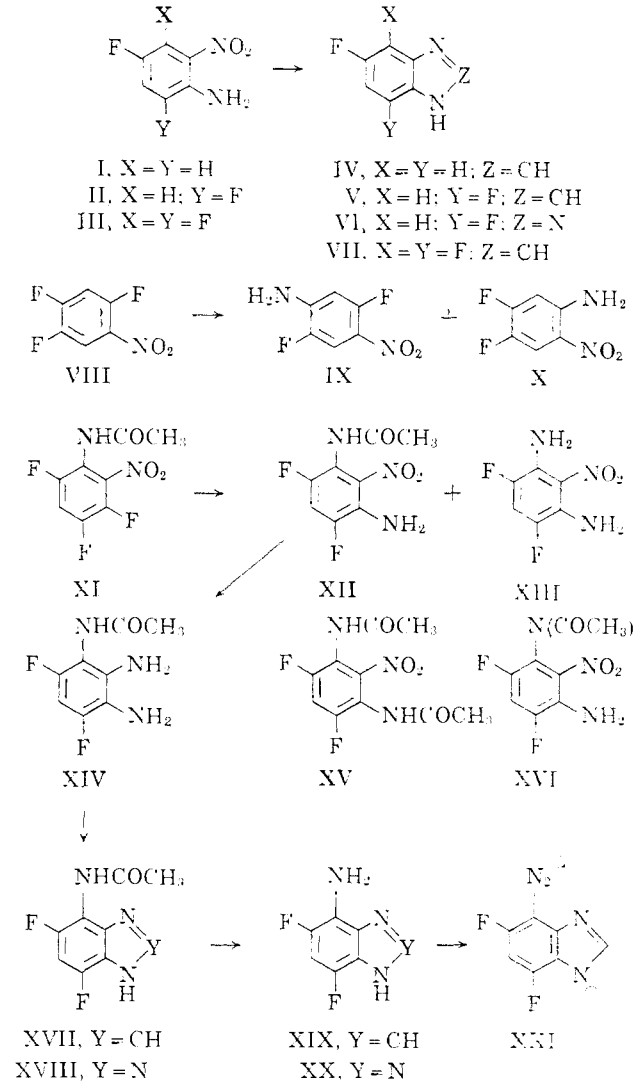
Biological Evaluation.—All of the benzimidazoles and benzotriazoles prepared were evaluated for cell culture cytotoxicity.[14] The results, which show these compounds to be relatively noncytotoxic, are given in Table I. 5-Fluorobenzimidazole, 4,6-difluorobenzimidazole, and 4-amino-5,7-difluorobenzimidazole were also evaluated for activity against the Friend virus leukemia,[17] to assess their potential to inhibit a virus-induced cancer. All three compounds were essentially inactive.

TABLE I

CELL CULTURE CYTOTOXICITY

Compd.	ED_{50}[a]
IV	56
V	26
VI	34
VII	>100
XVII	>100
XVIII	>100
XIX	100
XX	34

[a] The concentration in γ/ml. required to inhibit the growth of KB cells in culture to 50% of controls.[15]



Experimental Section

Except where specified, the melting points reported were determined on a Kofler Heizbank apparatus and are corrected. The ultraviolet spectra were determined in aqueous and ethanol solution with a Cary Model 14 spectrophotometer. The infrared spectra were determined in pressed KBr disks with a Perkin-Elmer Model 221-G spectrophotometer. Except where indicated the R_f values were determined from paper chromatograms run in the descending manner on Whatman No. 1 filter paper using water-saturated butanol as eluent.

5-Fluorobenzimidazole (IV).—Platinum dioxide catalyst (400 mg.) was prereduced in ethanol (100 ml.) and 4-fluoro-2-nitroaniline[5] (I, 4.0 g., 25.6 mmoles) added. The resulting mixture was stirred at atmospheric pressure until the theoretical amount of hydrogen (76.3 mmoles) was consumed (*ca.* 1 hr. at 24°). The catalyst was removed by filtration through dry Celite in a

(12) A. C. Bratton and E. K. Marshall, Jr., *J. Biol. Chem.*, **128**, 537 (1939).

(13) Y. F. Shealy, R. F. Struck, L. B. Holum, and J. A. Montgomery, *J. Org. Chem.*, **26**, 2396 (1961).

(14) These growth inhibition studies were carried out by the procedure of Eagle and Foley[15] as modified by the Cancer Chemotherapy National Service Center.[16]

(15) H. Eagle and G. E. Foley, *Cancer Res.*, **18**, 1017 (1958).

(16) *Cancer Chemotherapy Rept.*, **1**, 63 (1959).

(17) C. Friend, *J. Exptl. Med.*, **105**, 307 (1957).

nitrogen atmosphere, and the filtrate was evaporated to dryness *in vacuo*. The solid residue was dissolved, with evolution of heat, in diethoxymethyl acetate (15 ml.) and the resulting solution was allowed to stand at room temperature overnight before it was evaporated to dryness *in vacuo*. An ethanol solution of the residue was evaporated to dryness twice and then a solution of the residue in 3 *N* NH_4OH was evaporated to dryness twice, before it was dissolved in a minimum of boiling water. After Norit treatment, the solution was allowed to stand until crystallization was complete; yield 950 mg. (27%), m.p. 129–130° (lit. 132°,[9b] 137–137.5°[9a]). Thin layer chromatography on silica gel H (chloroform–methanol 9:1) showed one homogeneous fluorescent spot; λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1—271 (6.58), 277.5 (6.28), pH 7—242 (5.43), 274.5 (5.38), pH 13—280 (6.44).

4,6-Difluorobenzimidazole (V).—2,4-Difluoro-6-nitroaniline[7] (II, 348 mg., 2 mmoles) in absolute ethanol (15 ml.) was reduced as described above (35 mg. of PtO_2 catalyst). After the reduction was complete (10 min.), the catalyst was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. The white solid diamine was immediately dissolved in diethoxymethyl acetate (3 ml.) and the solution was allowed to stand at room temperature for 3 hr. before it was evaporated to dryness *in vacuo*. The oily residue was evaporated twice with ethanol before the semisolid mass was dissolved in a hot water–ethanol solution. On standing overnight at 4°, the solution deposited a solid which was collected by filtration and dried; yield 200 mg. A second crop of crude product was obtained from the filtrate and the samples were combined and recrystallized from water (80 ml.) to give a total of 90 mg. (28%) of purified product. An analytical sample was prepared by subliming the purified product at 0.1–0.05 mm. (bath 100–110°); yield 62 mg. (20%); sublimes >190°; R_f 0.89; λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1—240 (3.78), 263.5 (4.15), 271 (3.48), pH 7—237.5 (5.23), 263 (3.20), 267.5 (3.08), 271.5 (3.18), pH 13—257 (5.13), 269 (5.46); $\bar{\nu}_{max}$ in cm.$^{-1}$, 3420, 3180, 3100, 2900, 2780, 2560 (NH, CH), 1625, 1605, 1535 (C=C, C=N).

Anal. Calcd. for $C_7H_4F_2N_2$: C, 54.55; H, 2.62; N, 18.19. Found: C, 54.44; H, 2.98; N, 18.25.

4,6-Difluorobenzotriazole (VI).—2,4-Difluoro-6-nitroaniline[7] (II, 696 mg., 4 mmoles) in 30 ml. of absolute ethanol was reduced as described above (70 mg. of PtO_2 catalyst), the reaction mixture was then filtered to remove the catalyst, and the filtrate was evaporated to dryness *in vacuo*. The solid residue obtained was immediately dissolved in glacial acetic acid (0.46 ml., 8 mmoles), diluted with 1.2 ml. of water, and cooled in an ice bath. An aqueous solution of $NaNO_2$ (300 mg., 4.36 mmoles, in 0.48 ml. of water) was added to the cold acid reaction solution. The reaction mixture was removed from the ice bath and stirred gently. The temperature rose to 70–80° and the solution solidified. The solid was triturated with cold water and the resulting suspension was allowed to stand in an ice bath for 1 hr. before the solid was removed by filtration, washed with fresh water, and dried *in vacuo* to give 482 mg. of crude material, m.p. 155°.

Recrystallization of a sample (250 mg.) of the crude product from 15 ml. of boiling water with Norit treatment gave 150 mg. of pure product which was dried *in vacuo* overnight; yield 47%; m.p. 158°; R_f 0.93; λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1—259 (5.7), pH 7—266 (6.9), pH 13—267 (7.5), ethanol—265.5 (5.4), 263 (shoulder); $\bar{\nu}_{max}$ in cm.$^{-1}$, 3100–3090, 2920, 2780–2740 (CH, NH), 1620, 1605, 1535 (C=C, C=N), 1350, 1235, 1145.

Anal. Calcd. for $C_6H_3F_2N_3$: C, 46.55; H, 1.96; N, 27.10. Found: C, 46.45; H, 1.92; N, 26.89.

4,5,7-Trifluorobenzimidazole (VII).—2-Nitro-3,4-6-trifluoroaniline[6] (III, 520 mg., 2.7 mmoles) in absolute ethanol (15 ml.) was reduced as described above (50 mg. of PtO_2 catalyst), and after the hydrogenation was complete (10 min.), the catalyst was removed by filtration and the filtrate was evaporated to dryness. The resulting white residue was dissolved in diethoxymethyl acetate (5 ml.), and the solution was allowed to stand at room temperature overnight. Evaporation of the reaction mixture to dryness *in vacuo* and trituration of the resulting residue with water gave 380 mg. (83%) of crude product as a water-insoluble solid. Two recrystallizations of this product from acetone gave the pure material: yield 150 mg. (32%); sublimes at 210°; R_f 0.91; λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1—244 (3.3), pH 7—240 (5.1), pH 13—255 (4.8).

Anal. Calcd. for $C_7H_3F_3N_2$: C, 48.85; N, 1.76; N, 16.28. Found: C, 48.96; H, 2.15; N, 16.44.

2,5-Difluoro-4-nitroaniline (IX).[7]—A solution of 2,4,5-trifluoronitrobenzene[7] (VIII, 4.16 g.) in 100 ml. of ethanol saturated with NH_3 at 5° was allowed to stand at room temperature in a pressure bottle for 3 days. The excess NH_3 was removed from the orange reaction mixture under a stream of nitrogen before the mixture was filtered to remove insoluble inorganic salts. The ethanol filtrate was evaporated to dryness *in vacuo*, and the resulting residue was triturated thoroughly with water before it was dried *in vacuo* to give 3.96 g. of crude product. Recrystallization of the crude product from benzene (100 ml.) gave pure IX in the first crop; yield 2.14 g. (52%); m.p. 150° (lit.[7] 153–153.5°); λ_{max} in mμ ($\epsilon \times 10^{-3}$), ethanol—354–355 (14.9); $\bar{\nu}_{max}$ in cm.$^{-1}$, 3530, 3470 (NH), 1640 (primary amine), 1590, 1510 (phenyl), 1540, 1320–1310 (CNO_2).

Anal. Calcd. for $C_6H_4F_2N_2O_2$: C, 41.38; H, 2.32; N, 16.10. Found: C, 41.74; H, 2.50; N, 16.31.

Concentration of the filtrate from the isolation of IX gave impure 2-nitro-4,5-difluoroaniline (X) in two crops (925 mg.). Steam distillation of the crude isomer gave essentially pure material in the first 250 ml. of distillate; yield 359 mg. (9%); m.p. 140°; $\bar{\nu}_{max}$ in cm.$^{-1}$, 3490–3470, 3380 (NH), 1660 (primary amine), 1585 (C=C), 1530 (CNO_2), 1065, 655 (unassigned and not found in the infrared spectrum of the *para* isomer).

Anal. Calcd. for $C_6H_4F_2N_2O_2$: N, 16.10. Found: N, 16.15.

2,5-Difluoro-*p*-N,N′-diformylphenylenediamine.—2,5-Difluoro-4-nitroaniline[7] (500 mg.) in 25 ml. of ethanol was reduced with 50 mg. of PtO_2. The catalyst was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. The yellow solid residue was dissolved in 20 ml. of 98% formic acid, and the solution was refluxed for 2 hr. Upon cooling, the solution deposited yellow needles which were removed by filtration, washed, and dried *in vacuo;* yield 300 mg.; m.p. 268° (capillary); λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 7—253 (15.4), 288 (9.3), pH 13—258 (12.4), 293 (8.5), ethanol—257 (19.1), 291 (12.4); $\bar{\nu}_{max}$ in cm.$^{-1}$, 3330–3290, 3130–3000 (CH), 1700 (C=O), 1675, 1590, 1575, 1510 (tetrasubstituted phenyl).

Anal. Calcd. for $C_8H_6F_2N_2O_2$: N, 14.00. Found: N, 14.11.

2,5-Difluoro-*p*-phenylenediamine Dihydrochloride.—A solution of difluoro-*p*-N,N′-diformylphenylenediamine (50 mg.) in 10 ml. of 4 *N* HCl was refluxed for 1 hr. Upon concentration of the solution white crystals formed. These crystals were removed by filtration and dried; yield 22 mg. (46%); sublimes >140°; λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1—231 (9.0), 284 (2.7), pH 7—231 (11.5), 299 (3.2), pH 13—231 (12.8), 297 (3.1), ethanol—238 (12.3), 295 (3.4); $\bar{\nu}_{max}$ in cm.$^{-1}$, 3490–3410 (NH), 2890–2760 (CH), 2800–2500 (acidic H), 1965, 1865, 1790, 1650–1610 (tetrasubstituted phenyl).

Anal. Calcd. for $C_6H_6F_2N_2 \cdot 2HCl$: C, 33.21; H, 3.72; N, 12.96. Found: C, 32.86; H, 4.08; N, 13.00.

3-Amino-4,6-difluoro-2-nitroacetanilide (XII).—3,4,6-Trifluoro-2-nitroacetanilide[6] (XI, 6.55 g., 23 mmoles) was dissolved in a cold solution of methanolic NH_3 (35 ml., saturated at 5°) in a Parr bomb. After solution was complete, the bomb was sealed and heated for 5 hr. at 120° before it was allowed to stand at room temperature overnight. The dark red solution was concentrated to a syrup in a stream of nitrogen before it was evaporated to dryness *in vacuo*. The resulting residue was triturated with ether and the filtrate was set aside. The ether-insoluble solid (4.0 g.) was dissolved in benzene (800 ml.), the resulting solution was filtered, and the filtrate was allowed to stand until crystallization was complete. The aminoacetanilide was isolated in two crops: yield 2.86 g. (44%), m.p. 180°. Recrystallization of a sample of the product from benzene gave the analytical sample: $\bar{\nu}_{max}$ in cm.$^{-1}$, 3480, 3390, 3220, 3010 (CH, NH), 1645, 1600 (amide C=O, NH), 1535, 1240 (CNO_2).

Anal. Calcd. for $C_8H_7F_2N_3O_3$: C, 41.57; H, 3.06; N, 18.09. Found: C, 41.94; H, 3.42; N, 18.15.

Evaporation of the ether filtrate to dryness gave 2.29 g. (43%) of crude 2,4-difluoro-5-nitro-*m*-phenylenediamine (XIII), which can be purified by trituration with petroleum ether (b.p. 30–60°). An analytical sample of the diamine was prepared by recrystallization of a sample of the crude product from benzene–petroleum ether; m.p. 170° dec.; $\bar{\nu}_{max}$ in cm.$^{-1}$, 3460, 3350 (NH), 1615, 1605, 1530 (NH_2, C=C, CNO_2), 1430 (CH), 1320, 1290 (CNO_2), 910 (phenyl).

Anal. Calcd. for $C_6H_5F_2N_3O_2$: C, 38.09; H, 2.67; N, 22.22. Found: C, 38.19; H, 2.41; N, 22.14.

Acetylation of 4,6-Difluoro-2-nitro-*m*-phenylenediamine.—To a solution of 4,6-difluoro-2-nitro-*m*-phenylenediamine (XIII, 1.89 g., 10 mmoles) in benzene (20 ml.) was added acetic anhydride (13 g., 128 mmoles), and the mixture was refluxed for 18 hr. The needles that formed during the reflux period were re-

moved by filtration, washed with benzene and ether, and recrystallized from a mixture of benzene and ethanol; yield of N,N'-(4,6-difluoro-2-nitro-*m*-phenylene)bisacetamide (XV), 470 mg. (17%); m.p. 298°; λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1, 7—311.5 (1.54), pH 13—275 (3.52), 342 (1.24); $\tilde{\nu}_{max}$ in cm.$^{-1}$, 3260–3220 (CH), 1670 (C=O), 1550, 1505 (phenyl, NO_2).

Anal. Calcd. for $C_{10}H_9F_2N_3O_4$: C, 43.95; H, 3.33; N, 15.40. Found: C, 43.89; H, 3.50; N, 15.30.

The benzene–acetic anhydride filtrate from above was evaporated to dryness *in vacuo*, and the gummy residue was triturated with a mixture of ethanol and ether and then with benzene. The yellow residue was identified as 3-amino-4,6-difluoro-2-nitroacetanilide (XII); yield 572 mg. (25%), m.p. 169–172° (one recrystallization gave pure XII).

The benzene filtrate yielded a third compound, 390 mg. (12%), m.p. 132–135°, whose infrared spectrum showed NH absorption at 3480 and 3380 cm.$^{-1}$ and C=O absorption at 1725 and 1650 cm.$^{-1}$ indicating that this material is N-(3-amino-4,6-difluoro-2-nitrophenyl)diacetamide (XVI).

4-Acetamido-5,7-difluorobenzimidazole (XVII).—3-Amino-4,6-difluoro-2-nitroacetanilide (XII, 2.06 g., 8.95 mmoles) in ethanol (75 ml.) was reduced as described above (206 mg. of PtO_2), and after the catalyst was removed by filtration the filtrate was evaporated to dryness *in vacuo*. The resulting residue was immediately dissolved in diethoxymethyl acetate (12 ml.) and the solution was allowed to stand at 40–50° for 30 min. before it was concentrated *in vacuo* to one-half volume. The residue was diluted with 5 ml. of diethoxymethyl acetate and allowed to stand at room temperature overnight. The reaction mixture was evaporated to dryness *in vacuo* and the residue was evaporated with ethanol until a hard glass was obtained. This crude product was dissolved in 25% ethanol (75 ml.), treated with Norit, and filtered, and the filtrate was allowed to stand until crystallization was complete; yield 1.07 g. (56%), m.p. 256–258°. An analytical sample was prepared by recrystallizing a small sample of the purified product from water; m.p. 258°; R_f 0.77; λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1—258 (6.5), pH 7—249 (7.7), pH 13—267 (8.1); $\tilde{\nu}_{max}$ in cm.$^{-1}$, 3240, 3170, 3110, 3030, 2790 (CH, NH), 1660 (amide carbonyl), 1650, 1630, 1615, 1540 (C=C, C=N, amide II), 1380, 1310, 1280, 1145, 835.

Anal. Calcd. for $C_9H_7F_2N_3O$: C, 51.18; H, 3.35; N, 19.90. Found: C, 51.18; H, 3.37; N, 20.13.

4-Acetamido-5,7-difluorobenzotriazole (XVIII).—A solution of 3-amino-4,6-difluoro-2-nitroacetanilide (XIV, 3 g., 13 mmoles) in absolute ethanol (30 ml.) was reduced as described above and after removal of the catalyst by filtration under nitrogen atmosphere, the dark filtrate was evaporated to dryness *in vacuo*. The resulting residue was immediately mixed with glacial acetic acid (1.5 ml.) and the slurry was diluted with water (7.5 ml.). The mixture was shaken well and cooled in an ice bath before a solution of $NaNO_2$ (960 mg., 14.6 mmoles) in water (1.5 ml.) was added. The mixture was thoroughly shaken for a few minutes at about 50° (from heat of reaction) before it was allowed to stand in an ice bath for 1 hr. The dark solid that deposited was collected by filtration, washed on the funnel with a little cold water and ethanol, and finally dried by ether trituration to give 2.08 g. of crude product (76%). This crude product was sublimed at 0.1–0.05 mm. at 165° to give 1.7 g. of purified material which was triturated with warm ether and filtered, and the insoluble residue was dried *in vacuo* to give 95–98% pure product; yield 1.64 g. (60%), m.p. 250°.

The analytical sample was prepared from a previous run by water recrystallization of the purified material: m.p. 250°; R_f 0.73; λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1—265 (6.8), 270 (sh) (6.6), pH 7—272.5 (8.9), pH 13—272.5 (9.1); $\tilde{\nu}_{max}$ in cm.$^{-1}$, 1675 (C=O), 1645, 1615, 1545 (NH, C=C, C=N).

Anal. Calcd. for $C_9H_6F_2N_4O$: C, 45.29; H, 2.86; N, 26.42. Found: C, 45.43; H, 3.00; N, 26.69.

4-Amino-5,7-difluorobenzimidazole Hydrochloride (XIX).—A solution of 4-acetamido-5,7-difluorobenzimidazole (XVII, 1.07 g., 5.1 mmoles) in 4 *N* HCl (50 ml.) was heated at reflux for 3 hr. and the resulting dark red solution was treated with Norit and filtered, and the filtrate was evaporated to dryness *in vacuo*. The residue was triturated with ether, and the insoluble solid (1.22 g.) was sublimed at 0.05–0.1 mm. pressure in a 100–110° bath to give 809 mg. (78%) of purified product. Recrystallization of this sublimed material from absolute ethanol (50 ml.) gave pure XIX; yield 561 mg. (49%); m.p. >250° dec.; R_f 0.87; λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1—267 (3.2), 285 (3.2), pH 7—251 (5.7), pH 13—261 (6.5); $\tilde{\nu}_{max}$ in cm.$^{-1}$, 3500, 3350, 3215, 3100, 2970 (NH, CH), 2800–2500 (acidic H), 1650, 1615, 1550, 1510 (NH, C=C, C=N), 1415, 1125, 840 (unassigned).

Anal. Calcd. for $C_7H_5F_2N_3 \cdot HCl$: C, 40.97; H, 2.96; N, 20.48. Found: C, 40.57; H, 3.12; N, 20.13.

4-Amino-5,7-difluorobenzotriazole (XX).—A mixture of 4-acetamido-5,7-difluorobenzotriazole (XVIII, 1.6 g., 7.5 mmoles) in 4 *N* HCl (110 ml.) was refluxed for 1 hr. after solution was complete. The solution was concentrated to 15 ml. *in vacuo*, and the crystals that formed were collected by filtration, washed with water and ether, and dried *in vacuo* to give 1.16 g. (94%) of crude product. The crude product was twice recrystallized from water (*ca.* 150 ml.) and the final product was dried *in vacuo* at 61°; yield 0.77 g. (62%); m.p. 230°; R_f 0.40 (acetate buffer, pH 6.1); λ_{max} in mμ ($\epsilon \times 10^{-3}$), pH 1—258.5 (3.4), pH 7—272 (3.8), 293 (5.0), pH 13—272 (4.1), 292.5 (5.4); $\tilde{\nu}_{max}$ in cm.$^{-1}$, 3400 (OH), 3300 (NH), 3180–3000, 2800, 2600 (CH, acidic H), 1655, 1640, 1625, 1550, 1510 (NH, C=C, C=N).

Anal. Calcd. for $C_6H_4F_2N_4 \cdot {}^5/_6H_2O$: C, 38.95; H, 3.06; N, 30.25. Found: C, 38.90; H, 2.75; N, 29.87.

Acknowledgment.—The authors wish to express their appreciation to Dr. W. J. Barrett and his associates of the Analytical Section of this institute for the microanalytical and spectral determinations reported herein.