anhydrous sodium sulfate, and concentration by distillation afforded 160 mg of a pale yellow liquid. Final purification by preparative gas chromatography afforded 2-*endo*-phenylbornane (**18**) as a colorless liquid: λ_{max} 6.22, 12.92, 13.68, and 14.28 μ; nmr spectrum τ 2.88 (br s, 5, C_6H_5), 7.01 (quartet of doublets, 1, J = 11.2, 5.5, and 2.1 Hz, CH-2), 7.87 (triplet of triplets, 1, J = 12.2 and 3.5 Hz, CH-3), and 8.98, 9.07, and 9.28 (3 s, 9, $3CH_3$); *m/e* 214.1724 (calcd for $C_{16}H_{22}$, 214.1721).

1-Phenyl-2-*endo*-3,3-trimethylnorbornane (24). A solution containing 227 mg (1.07 mmol) of 1-phenylcamphene (**20**) in 10 ml of ethanol was stirred over 10 mg of 10% palladium on charcoal in an atmosphere of hydrogen. Absorption ceased after 1.1 equiv. Removal of the catalyst by filtration and of the solvent by distillation afforded a colorless liquid which was further purified by short-path distillation at 91–92° (0.55 mm) to afford a colorless liquid which exhibited a single peak on gas chromatographic analysis: λ_{max} 6.22, 13.23, and 14.27 μ; nmr spectrum τ 2.91 (s, 5, C_6H_5), 7.83 (br d, 1, J = 9.5 Hz, CH-4), 8.98 and 9.17 (2 s, 6, $2CH_3$), and 9.36 (d, 3, J = 7.5 Hz, CH_3-2); *m/e* 214.1725 (calcd for $C_{16}H_{22}$, 214.1721).

Acknowledgment. The author is indebted to H. J. Krauss, R. S. Payne, J. Alvis, and T. H. Jones for able technical assistance. Partial support of this work by the U. S. Army Research Office–Durham is gratefully acknowledged.

Photochemistry of Diazonium Salts. I. Synthesis of 4-Fluoroimidazoles, 4-Fluorohistamine, and 4-Fluorohistidine[1]

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Abstract: Imidazolediazonium ions, prepared by diazotization of aminoimidazoles in tetrafluoroboric acid solution and irradiated *in situ*, decompose with formation of fluoroimidazoles in 30–40% yield. This procedure has been applied to the synthesis of 2-fluoroimidazole, 4-fluoroimidazole, and ethyl 4-fluoroimidazole-5-carboxylate. The ester, in turn, has served as the starting point for various transformations, including the synthesis of 4-fluorohistamine and 4-fluorohistidine. The fluorinated amino acid parallels histidine as a substrate for several enzymes and, in the case of histidine–ammonia lyase, serves as a competitive inhibitor. To date, fluorinated imidazoles have been obtained only by the photochemical method.

A wide variety of fluorinated analogs of biologically significant compounds have been synthesized and studied as potential enzyme inhibitors and as therapeutic agents.[2] Of the possible replacements for hydrogen in carbon–hydrogen bonds, fluorine offers the unique advantage of effecting a marked change in electron density distribution and related properties, but with a minimal change in molecular size or shape.[3] This combination of properties is proposed to be the basis for the effectiveness of drugs such as fluorouracil and the fluorosteroids.[2] While numerous ring-fluorinated aromatic and heteroaromatic systems have been prepared and studied as biochemical analogs, ring-fluorinated imidazoles have not been accessible for this purpose.[4] Since the imidazole ring plays a key role in biological structure and function (histidine, histamine, purine precursors, etc.), we were prompted, some years ago, to initiate a study of synthetic approaches to fluoroimidazoles.

In our hands, the more obvious synthetic routes[5] to fluoroimidazoles afforded only negative results, *e.g.*, (1) reaction of 4-bromo-5-nitroimidazole or of 4-bromo-5-carbethoxyimidazole with potassium fluoride, cesium fluoride,[6] or silver fluoride[7] gave either no halogen exchange or tarry polymers (at elevated temperatures);[8] (2) formation of the imidazole ring by reaction of acyclic α-fluoro-α-bromo ketones with formamide[9] failed; (3) thermal decomposition of imidazolediazonium fluoroborates,[10] such as **2**, with or without solvent and with or without metal catalysis, resulted either in no reaction or in intractable tars.

The diazonium fluoroborate **2** shows exceptional stability; in fact, treatment of the compound with mild base provides a colorless, neutral, *sublimable* material, which may be formulated as **3a** or, preferably, as **3b** (Scheme I).[11] Since diazo compounds are known to undergo facile photoextrusion of nitrogen,[12] we were

(1) (a) This work was presented in part at a Symposium on Fluorine in Medicinal Chemistry, 162nd National Meeting of the American Chemical Society, Washington, D. C., Sept 1971. (b) For a preliminary communication, see K. L. Kirk and L. A. Cohen, *J. Amer. Chem. Soc.*, **93**, 3060 (1971).

(2) (a) P. Goldman, *Science*, **164**, 1123 (1969); (b) F. Weygand and W. Oettmeier, *Usp. Khim.*, **39**, 622 (1970); *Russ. Chem. Rev.*, 290 (1970); (c) D. F. Loncrini and R. Filler, *Advan. Fluorine Chem.*, **6**, 43 (1970).

(3) Generally accepted van der Waals radii are 1.20 Å for hydrogen and 1.35 Å for fluorine. A fluorine atom attached to an sp^2 carbon is probably somewhat smaller.

(4) Fluorobenzimidazoles, in which the fluorine is attached to the benzene ring, have been reported: (a) K. L. Kirk and L. A. Cohen, *J. Org. Chem.*, **34**, 384 (1969); (b) E. C. Fisher and M. M. Joullié, *ibid.*, **23**, 1944 (1958).

(5) (a) M. Hudlicky, "Organic Fluorine Chemistry," Plenum Press, New York, N. Y., 1970; (b) A. E. Pavlath and A. J. Leffler, "Aromatic Fluorine Compounds," Reinhold, New York, N. Y., 1962.

(6) N. N. Vorozhtsov, Jr., and G. G. Yakobson, *Zh. Obshch. Khim.*, **31**, 3705 (1961).

(7) A. G. Beaman and R. K. Robins, *J. Org. Chem.*, **28**, 2310 (1963).

(8) Studies were also conducted with various imidazoles in which one ring-nitrogen atom carried a reversible protecting group; however, no blocking group was found capable of surviving the conditions needed for halogen exchange.

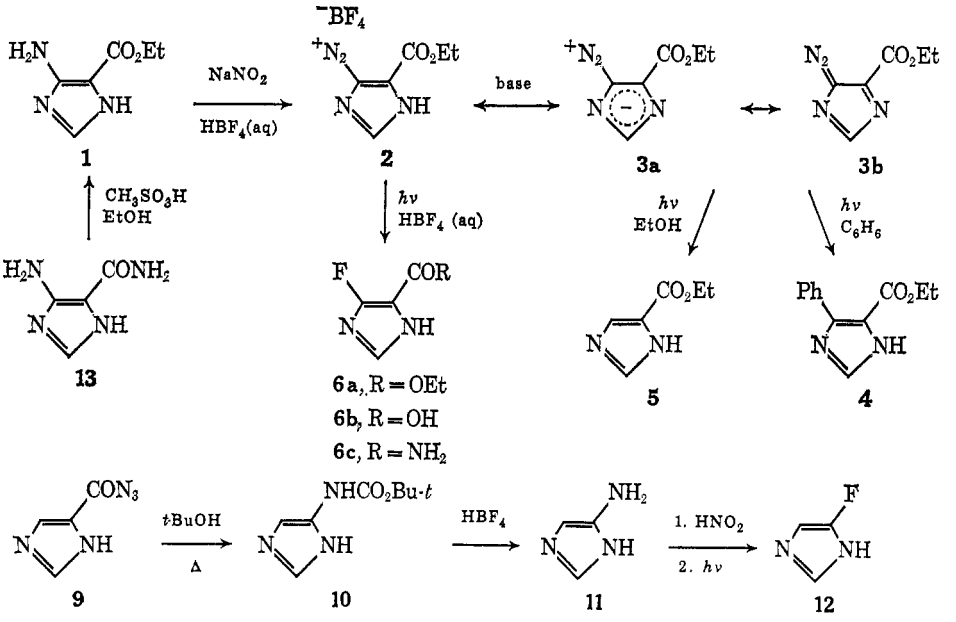
(9) H. Brederick and G. Theilig, *Chem. Ber.*, **86**, 88 (1953).

(10) A. Roe, *Org. React.*, **5**, 193 (1949).

(11) *Cf.* 5-diazoimidazole-4-carboxamide: Y. F. Shealy, R. F. Struck, L. B. Holum, and J. A. Montgomery, *J. Org. Chem.*, **26**, 2396 (1961).

(12) J. G. Calvert and J. N. Pitts, Jr., "Photochemistry," Wiley, New York, N. Y., p 471.

Scheme I

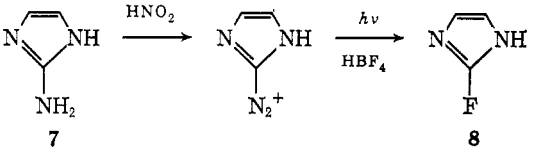


hopeful that a reactive species, photogenerated from **3**, could be trapped. Indeed, solutions of **3** in several solvents exhibited, under the influence of a mercury arc lamp, a brisk evolution of nitrogen which terminated within 1 hr. Irradiation of **3** in benzene provided a modest yield of ethyl 4-phenylimidazole-5-carboxylate (**4**), while irradiation in ethanol led to the formation of ethyl imidazole-4-carboxylate (**5**). The courses of these reactions permit no decision as to the nature of the intermediates involved,[13] although radical species seem preferable.[14]

The above reactions of **3**, upon irradiation, suggested that a fluorine atom might also be captured by the reactive intermediate, if the concentration of the halogen in the medium were sufficiently high.[13b,15] Accordingly, a solution of **2** in 50% aqueous tetrafluoroboric acid was irradiated until evolution of gas had ceased; following neutralization and ethyl acetate extraction of the reaction mixture, a single product was obtained in 40% yield. The nmr spectrum (Table I), mass spectrum, and elemental analysis identified the material as ethyl 4-fluoroimidazole-5-carboxylate (**6a**). For larger scale preparations, isolation of the intermediate diazonium fluoroborate was found to be unnecessary; when a solution of the amine **1** in 50% fluoroboric acid was treated with 1.1 equiv of concentrated, aqueous sodium nitrite, and the resulting mixture was irradiated, comparable yields of **6a** were obtained. Application of the latter procedure to a wide variety of aromatic and heteroaromatic amines has demonstrated both its generality and convenience.[16,17] While the yields of **6a**, and those of other fluoroimidazoles, have been consistently limited to 30–40%, the extraction procedure leads to material which is notably free of contaminants. Hydroxyimidazoles (imidazolones), the most likely alternative products of the irradiation, would either be insoluble in ethyl acetate or would decompose to even more polar materials.

The fluorine atom in **6a** is not subject to facile nucleophilic displacement. Thus, **6a** is readily converted to the corresponding acid **6b** with aqueous alkali or to the amide **6c** with ammonia, in each case without detectable loss of fluorine.

By diazotization and irradiation, 2-aminoimidazole (**7**) was converted into 2-fluoroimidazole (**8**) in 30% yield.[18] The corresponding transformation of 4-aminoimidazole (**11**) to 4-fluoroimidazole (**12**) required a modified approach, since 4-aminoimidazoles (which have no electron-withdrawing group at C-5) are generally too unstable for isolation. Imidazole-4-carbonyl azide (**9**)[19a] was rearranged thermally in *tert*-butyl alcohol to give the *tert*-butyl carbamate **10**.[19b] Solution of this compound in cold tetrafluoroboric acid resulted in immediate gas evolution, indicative of removal of the blocking group. The resulting 4-aminoimidazole was diazotized and irradiated to provide a 41% yield of 4-fluoroimidazole. The same product was obtained, although in significantly lower yield, when **11** was generated *in situ* by reduction of 4-nitroimidazole with zinc dust in tetrafluoroboric acid.



(13) (a) T. DoMinh, O. P. Strausz, and H. E. Gunning, *J. Amer. Chem. Soc.*, **91**, 1261 (1969); (b) E. S. Lewis, R. E. Holliday, and L. D. Hartung, *ibid.*, **91**, 430 (1969).

(14) Mechanistic and synthetic aspects of the thermal and photochemical breakdown of **3** are under investigation.

(15) W. E. Lee, J. G. Calvert, and E. W. Malmberg, *J. Amer. Chem. Soc.*, **83**, 1928 (1961).

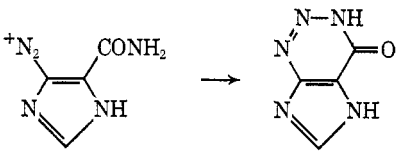
(16) The photoconversion of thin films of aryldiazonium fluoroborates to aryl fluorides has recently been reported: R. C. Petterson, A. DiMaggio, A. L. Hebert, T. J. Haley, J. P. Mykytka, and I. M. Sarkar, *J. Org. Chem.*, **36**, 631 (1971).

(17) Application to the preparation of fluorotriazoles and fluorothiazoles will be reported in the near future.

(18) In the absence of irradiation, none of the diazonium fluoroborates examined provided detectable quantities of fluorinated imidazoles, either in solution or under pyrolytic conditions. Thermal decomposition of imidazole-2-diazonium fluoroborate in tetrafluoroboric acid leads exclusively to 2-azidoimidazole; the mechanism of formation of the azido derivative is under investigation.

(19) (a) I. E. Balaban, *J. Chem. Soc.*, 268 (1930); (b) *cf.* K. L. Kirk and L. A. Cohen, *J. Org. Chem.*, **34**, 395 (1969).

Projected syntheses of 4-fluorohistidine and of 4-fluorohistamine were based on elaboration of the side chain of the fluoro ester **6a** and depended, therefore, on the availability of the amino ester **1**. The preparation of bulk quantities of **1** by published procedures[20] proved extremely time-consuming. Efforts to incorporate fluorine into the commercially available 4-aminoimidazole-5-carboxamide (**13**) were thwarted by the fact that cyclization of the diazonium salt **14** to 2-aza-

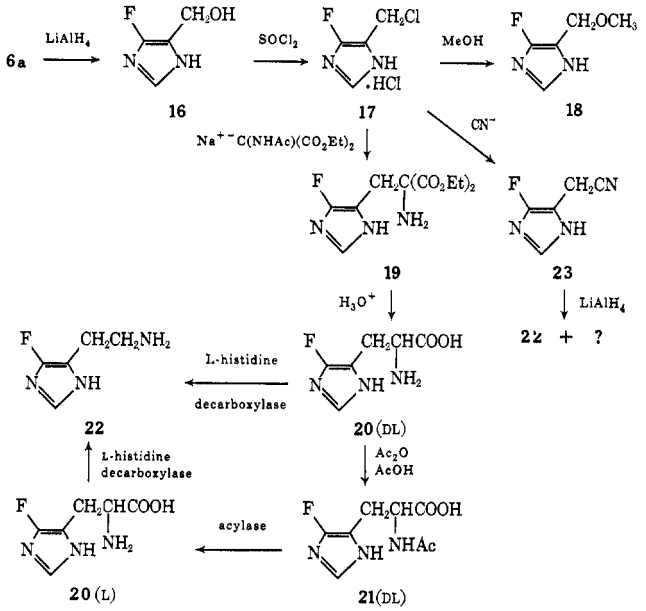


14 **15**

hypoxanthine (**15**)[11] occurred faster than photofluorination. Accordingly, considerable attention was given to the development of a practical method for the conversion of **13** to the ester **1**. The procedure finally adopted consists of exposure of the amide to 5–10 equiv of anhydrous methanesulfonic acid in refluxing ethanol for 2–3 weeks. By this method, **1** was obtained from commerical **13** in 50–60% yield, in runs yielding 50–100 g of material. The remainder of the starting material could not be accounted for as an imidazole derivative; apparently, some degradation of the imidazole ring in **1** or **13** is possible under the strong acid conditions used.

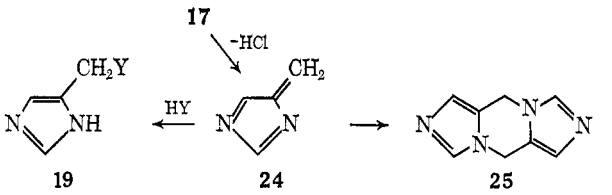
Elaboration of the amino acid side chain proceeded without major difficulty. The fluoro ester **6a** was reduced with lithium aluminum hydride to 4-fluoroimidazole-5-methanol (**16**) (Scheme II). Reaction of

Scheme II



this alcohol with thionyl chloride led to 4-fluoro-5-chloromethylimidazole hydrochloride (**17**). This material was found to be exceedingly reactive, as evidenced by its rapid solvolysis in water or alcohol; however, alkylation of **17** with sodium diethyl acetamidomalonate in ethanol proceeded to **19** in reasonable yield without

(20) (a) A. H. Cook, A. C. Davis, I. Heilbron, and G. H. Thomas, *J. Chem. Soc.*, 1071 (1949); (b) L. P. Kulev and V. R. Koroleva, *Zh. Obshch. Khim.*, **29**, 2401 (1959).



19 **24** **25**

significant competitive solvolysis. The use of dimethylformamide as solvent failed to increase the yield, nor did alkylation with the formamidomalonate offer any advantage. The alkylation reaction probably occurs by nucleophilic addition to the double bond of **24**, rather than by SN1 or SN2 displacement on the chloride.[21] A competing side reaction may be dimerization of **24** to **25**, a pathway which has been observed with some analogs of **24**.[22] Acid hydrolysis of the alkylation product, followed by ion-exchange chromatography, gave the desired 4-fluoro-DL-histidine (**20**).

α-*N*-Acetyl-4-fluoro-DL-histidine was prepared by acetylation of the DL-amino acid with acetic anhydride in acetic acid. Without purification, this material was treated with hog kidney acylase I, and the free L-amino acid was recovered. To demonstrate the stereochemical homogeneity of the product, a sample was subjected to the action of L-histidine decarboxylase. Essentially complete decarboxylation to 4-fluorohistamine (**22**) occurred, as shown by tlc. The N-acylated D isomer, which survived the action of acylase, was either hydrolyzed to the D-amino acid or was racemized to generate more of the DL compound. The racemic amino acid is also subject to oxidative deamination with D-amino acid oxidase; on a preparative scale, however, resolution by means of acylase is preferable.

In addition to serving as a substrate for the three enzymes mentioned, 4-fluorohistidine is deaminated slowly by histidine–ammonia lyase to 4-fluorourocanic acid. In this case, the fluorinated amino acid also serves as a competitive inhibitor for the deamination of L-histidine.[23]

4-Fluorohistamine (**22**) was obtained by enzymatic decarboxylation (with L-histidine decarboxylase) of either 4-fluoro-DL-histidine or of 4-fluoro-L-histidine. With respect to ease of recovery of the product, use of the L enantiomer was found preferable to that of the DL mixture. The more obvious route to the histamine analog, *via* **17** and **23**, proved disappointing: not only was the cyanomethyl intermediate **23** obtained in relatively poor yield, but its subsequent reduction (with lithium aluminum hydride) provided only a trace of the desired amine **22** and, principally, an oily material yet to be characterized.

All of the 4-fluoroimidazoles prepared, to date, have been found stable to loss of halogen over a wide pH range and in the presence of various strong nucleophiles. 2-Fluoroimidazole, on the other hand, appears to be fairly stable in alkaline media but loses halogen slowly at low pH.[24] 4-Fluoroimidazolium ion shows a pK_a of 2.5 while that of the 2-fluoro isomer is *ca.* 2.7. On the basis of electronic considerations, the 2-fluoro-

(21) T. C. Bruice and J. L. Herz, *J. Amer. Chem. Soc.*, **86**, 4109 (1964).

(22) L. A. Cohen, unpublished observations.

(23) Studies with histidine–ammonia lyase were performed by Dr. C. B. Klee of this Institute; detailed results will be reported separately.

(24) Studies on the synthesis and properties of a variety of 2-fluoroimidazoles will be reported separately.

imidazolium ion should be the more acidic; this reversal in behavior may be due to the greater symmetry of the 2-fluoroimidazolium ion over that of the 4-fluoro isomer.[25]

Structures were assigned to the various imidazoles partly on the basis of their nmr spectra (Table I). While

Table I. Partial Nmr Data for Fluoroimidazoles[a]

Compd	Solvent	δ_{H_2}, ppm	J_{H_2-F}, Hz
6a	CD_3OD	7.39 (d)[b]	1.6
6c	CD_3OD	7.47 (d)	1.5
10	$CDCl_3$	7.18 (b)[c]	*d*
13[e]	CD_3OD	7.15 (d)	1.5
16	CD_3OD	7.18 (d)	1.5
19	$CDCl_3$	7.18 (b)	*d*
20	D_2O	7.35 (d)	1.5

[a] Spectra were recorded on a Varian A-60 spectrometer. [b] d = doublet, b = broad, unresolved singlet. [c] The H_4 signal appears as a symmetrical quartet at 6.50 ppm; J_{H_4-F} = 8 Hz. [d] Resolution was too poor to measure the coupling constant. [e] As the hydrochloride.

the chemical shift of the C-2 hydrogen reflects, in general, the electronic influence of the substituent at C-5, its coupling to the fluorine at C-4 remains fairly constant at 1.5 Hz.

Exploratory studies have indicated that the fluoro analogs of both histidine and histamine are valuable tools for the elucidation of enzyme and receptor mechanisms. The effect of the fluoro analog on the activities of various histidine containing polypeptide hormones and hormone-releasing factors is also of interest. Finally, 4-fluorohistidine, while nontoxic to mice, has been found to produce a mild soporific or anesthetic effect. A number of investigations in these directions have been initiated; their results will be reported separately.

Experimental Section[26]

Irradiation Procedure. In all photochemical reactions, the radiation source was an Hanovia 450-W, medium-pressure mercury vapor lamp, placed in a quartz immersion well. The sample was placed in an external quartz semicircular vessel positioned *ca.* 20 cm from the light source.[27] Even after prolonged use, the quartz vessels showed no evidence of etching. Reactions were run at ambient temperature; there was no evidence of excessive heating, nor was any effort made to maintain a constant temperature. Reaction mixtures were worked up when nitrogen evolution had ceased. In several runs, gas evolution was measured volumetrically, the total gas collected corresponding closely to the calculated value.

Ethyl 4-Aminoimidazole-5-carboxylate (1). To a suspension of 100 g (0.62 mol) of powdered 4-aminoimidazole-5-carboxamide hydrochloride (**13**) (Sigma or Aldrich Chemical Co.) in 1200 ml of absolute ethanol was added 500 g (5.2 mol) of methanesulfonic acid (96–98%). Following distillation of *ca.* 200 ml of ethanol at atmospheric pressure,[28] the mixture was refluxed for 15–18 days, at which point tlc showed the absence of starting material. After removal of most of the ethanol, the residual syrup was diluted with water and neutralized (pH 5) with cold, concentrated alkali. The mixture was extracted with three 200-ml portions of ethyl acetate, the extracts were dried and concentrated, and the residue was recrystallized from ethanol–ethyl acetate to give 45–55 g (47–57%) of the ester **1**, mp 178–180° (lit.[20a] mp 180–181°). The material is homogeneous according to tlc and of sufficient purity for further use.

Ethyl 4-Fluoroimidazole-5-carboxylate (6a). To a solution of 5 g (0.032 mol) of **1** in 125 ml of 50% aqueous fluoroboric acid, cooled to 0°, was added a solution of 2.8 g (0.041 mol) of sodium nitrite in the minimum amount of water. The solution was irradiated until evolution of nitrogen had ceased (12–20 hr). The mixture was chilled in ice and was neutralized with cold, concentrated sodium hydroxide (pH 5–6). The solution was then extracted with three 50-ml portions of ethyl acetate; the combined extracts were dried (Na_2SO_4) and evaporated to give a crystalline, almost colorless residue. Following ethyl acetate extraction, the aqueous layer gave a negative Pauly color test, showing that all imidazole-containing material had been removed. The crystalline product was purified by sublimation to give 2.0 g (39%) of **6a**, mp 147.5–148°.

Anal. Calcd for $C_6H_7FN_2O_2$: C, 45.57; H, 4.46; N, 17.72. Found: C, 45.86; H, 4.46; N, 17.96.

4-Fluoroimidazole-5-carboxylic Acid (6b). Ethyl 4-fluoroimidazole-5-carboxylate (**6a**, 0.80 g, 5 mmol) was added to 3 ml of 2.5 *N* sodium hydroxide. Solution was rapid and was followed by slow separation of the sodium salt as needles. At ambient temperature, complete saponification of **6a** required 10 days, progress of the reaction being followed by tlc. The mixture was adjusted to pH 2 with 2 *N* hydrochloric acid, the needles changing to plates in the process. The mixture was chilled and filtered, providing 468 mg (72%) of the acid, which was recrystallized from water, mp 211–212° (decomposition with gas evolution).

Anal. Calcd for $C_4H_3FN_2O_2$: C, 36.93; H, 2.33; N, 21.54. Found: C, 37.03; H, 2.48; N, 21.83.

4-Fluoroimidazole-5-carboxamide (6c). The ethyl ester **6a** (6.0 g, 0.038 mol) was dissolved in 50 ml of concentrated ammonium hydroxide. After storage of the mixture for 3 weeks at 25°, tlc showed complete conversion of the ester. The solution was evaporated almost to dryness, the residue was dissolved in a minimum amount of hot water, and the solution was filtered and chilled. The first crop of product consisted of 3.0 g (61%), mp 257–260°. Concentration of the mother liquors gave a total yield of 95%. A sample was sublimed for analysis.

Anal. Calcd for $C_4H_4FN_3O$: C, 37.21; H, 3.12; N, 32.57. Found: C, 37.10; H, 2.82; N, 32.79.

2-Fluoroimidazole (8). To a solution of 6.7 g (0.05 mol) of 2-aminoimidazolium sulfate[29] in 250 ml of 50% tetrafluoroboric acid was added, at −10°, a solution of 3.8 g (0.055 mol) of sodium nitrite in 5 ml of water. The mixture was irradiated until nitrogen evolution ceased (10 hr). The solution was cooled to 0° and was neutralized (pH 7) with cold, concentrated sodium hydroxide. This mixture was subjected to continuous extraction with ether for 18 hr; the ether extract was dried ($MgSO_4$) and evaporated to give a residue of oily crystals. This material was redissolved in ether and the solution was saturated with hydrogen chloride. The hydrochloride of **8** separated as colorless crystals, which were recrystallized from methanol–ether, mp 215–226°, 30% yield.

Anal. Calcd for $C_3H_4ClFN_2$: C, 29.41; H, 3.29; N, 22.85; F, 15.51. Found: C, 29.47; H, 3.30; N, 22.60; F, 15.97.

***tert*-Butyl Imidazole-4-carbamate (10).** A solution of imidazole-4-carbonyl azide (**9**, 3.0 g, 0.022 mol)[19a] in 50 ml of dry *tert*-butyl alcohol was heated at reflux for 4 hr. The solvent was removed *in vacuo* and the residue was dissolved in a 1:1 mixture of ethyl acetate and ethanol. The solution was decolorized with charcoal and concentrated in a stream of nitrogen until crystallization began. The product, mp 195–201° dec, was obtained in 41% yield.

Anal. Calcd for $C_8H_{13}N_3O_2$: C, 52.44; H, 7.15; N, 22.94. Found: C, 52.18; H, 7.18; N, 23.19.

4-Fluoroimidazole (12). To 50 ml of cold, 50% tetrafluoroboric acid was added, in one portion, 0.73 g (4 mmol) of **10**. To the resulting solution was added dropwise a solution of 300 mg (4.3 mmol) of sodium nitrite in 1 ml of water. The mixture was stirred at 25° for 0.5 hr and then irradiated until nitrogen evolution ceased (10 hr). The product was recovered as described above for 2-fluoroimidazole. Evaporation of the dried ether extract gave

(25) G. W. Wheland, "Resonance in Organic Chemistry," Wiley, New York, N. Y., 1955, p 357.

(26) Melting points are uncorrected. Microanalyses, nmr, and mass spectral measurements were performed by the Microanalytical Services Section of this laboratory, under the direction of Dr. David F. Johnson. In addition to elemental analysis, identity and homogeneity of each compound were confirmed by nmr and mass spectrometry and by tlc.

(27) For large-scale runs, a number of cells can be placed around the light source.

(28) This distillation was performed to dehydrate the reaction mixture as much as possible.

(29) B. T. Storey, W. W. Sullivan, and C. L. Mayer, *J. Org. Chem.*, **29**, 3118 (1964).

140 mg (41%) of **12** as colorless crystals. The compound was further purified by sublimation, mp 101–104°.

Anal. Calcd for $C_3H_3FN_2$: C, 41.86; H, 3.51; N, 32.55. Found: C, 41.64; H, 3.45; N, 32.84.

4-Fluoroimidazole-5-methanol (16). To an ice-cold, rapidly stirred suspension of 1.4 g of powdered lithium aluminum hydride in 50 ml of anhydrous ether was added, over 0.5 hr, 4.0 g (0.025 mol) of powdered ethyl 4-fluoroimidazole-5-carboxylate (**6a**). The mixture was stirred an additional 0.5 hr at 25° and chilled, and the excess hydride was decomposed with 3.6 ml of water. The ether solution was filtered and the precipitate was suspended in 50 ml of methanol, previously saturated with carbon dioxide. The mixture was boiled briefly and filtered; the process was repeated 4–5 times with fresh solvent, or until the methanol extract showed, by tlc, that the precipitate was free of product. The combined methanol and ether extracts were evaporated; the residue was extracted with 50 ml of hot ethanol and, after filtration, the solution was evaporated to give **16**, as off-white crystals. Although the product, at this point, is contaminated with inorganic material, it is suitable for further work without purification. The pure compound was recovered in 40% yield by sublimation, mp 136-138°; this low recovery is due to partial decomposition during sublimation.

Anal. Calcd for $C_4H_5FN_2O$: C, 41.38; H, 4.34; N, 24.13. Found: C, 41.81; H, 4.43; N, 24.48.

5-Chloromethyl-4-fluoroimidazole Hydrochloride (17). Crude 4-fluoroimidazole-5-methanol (**16**, 15.8 g, 0.1 mol) was pulverized and added, in portions and with magnetic stirring, to 200 ml of cold thionyl chloride. Following addition, the mixture was stored for an additional 0.5 hr at 25°. Progress of the reaction was followed by the addition of small aliquots to methanol; tlc showed the fairly rapid disappearance of **16** and its replacement by **18**, formed by the methanolysis of **17**. Excess thionyl chloride was evaporated at reduced pressure and the residual yellow, glassy material was subjected to high vacuum overnight. Because of the extreme reactivity of **17**, no attempt was made at further purification.

4-Fluoro-5-methoxymethylimidazole (18). A sample of **17** was dissolved in methanol and the mixture was stored for 0.5 hr at 25°. Following removal of solvent, the residue was dissolved in water; the solution was neutralized with aqueous sodium bicarbonate and extracted with ether. The ether extract was dried ($MgSO_4$) and evaporated; the residual material was purified by sublimation, mp 52–53.5°.

Anal. Calcd for $C_5H_7FN_2O$: C, 46.15; H, 5.42; N, 21.53. Found: C, 46.51; H, 5.56; N, 20.93.

Diethyl α-Acetamido-α-[4-fluoro-5-imidazolylmethyl]malonate (19). To 0.3 mol of sodium ethoxide (prepared from 7 g of sodium in 300 ml of ethanol) was added 45 g (0.2 mol) of diethyl acetamidomalonate. The solution was cooled to 5° and added, in one portion, to 0.1 mol of **17**, prepared as described above. The solution was stirred rapidly at ice temperature for 15 min, then at room temperature for 30 min. Most of the solvent was removed at reduced pressure and the residual material was taken up in a mixture of 100 ml of ethyl acetate and 100 ml of cold water. The ethyl acetate layer was separated and the aqueous layer was extracted with 5–6 additional 100-ml portions of ethyl acetate. The combined extracts were washed several times with small quantities of water, the aqueous fraction was reextracted once with ethyl acetate, the combined organic layers were dried (Na_2SO_4) and concentrated to 100 ml, and the solution was chromatographed on 500 g of silica gel. Excess acetamidomalonate was first removed by elution with ethyl acetate, and the product was eluted with 5% methanol–ethyl acetate. After evaporation of the solvent, the crystalline residue was recrystallized from ethyl acetate–ether to give 8.2 g (26%) of **19**, mp 138.5–139°. When the synthesis was performed with purified **16**, a similar yield was obtained.

Anal. Calcd for $C_{13}H_{18}FN_3O_5$: C, 49.51; H, 5.75; N, 13.33. Found: C, 49.53; H, 5.48; N, 13.10.

By use of diethyl formamidomalonate, the formamido analog of **19**, mp 120–122°, was obtained in comparable yield.

Anal. Calcd for $C_{12}H_{16}FN_3O_5$: C, 47.84; H, 5.35; N, 13.94; F, 6.31. Found: C, 47.81; H, 5.44; N, 13.65; F, 6.53.

4-Fluoro-DL-histidine (20). A solution of 10 g (0.032 mol) of **19** in 100 ml of 6 *N* hydrochloric acid was heated on steam for 10 hr. Evaporation of the solution *in vacuo* provided a hygroscopic glass. A concentrated, aqueous solution of this material was bound to a column of Dowex 50W-X4 and the free amino acid was eluted with dilute ammonium hydroxide. The eluate was evaporated and the residual crystals were dissolved in water; the solution was clarified with carbon, and the amino acid precipitated by addition of acetone and chilling. The yield was 4.5 g (82%) of colorless crystals.

Anal. Calcd for $C_6H_8FN_3O_2$: C, 41.62; H, 4.66; N, 24.27; F, 10.97. Found: C, 41.76; H, 4.67; N, 24.49; F, 10.59.

4-Fluoro-L-histidine (20). A solution of 3.5 g (0.018 mol) of 4-fluoro-DL-histidine in 50 ml of acetic acid and 3.4 ml of acetic anhydride was heated at 90° for 1 hr; at this point, tlc showed acetylation to be complete. Following removal of solvent *in vacuo*, the residue was dissolved in 50 ml of water, and the solvent again removed; this process was repeated five times. The final residue was dissolved in ethanol, the solution was decolorized with Norit, and the solvent was removed to give a colorless glass. This material was dissolved in 200 ml of water and the solution was adjusted to pH 7.0 with dilute ammonium hydroxide. To this solution was added 50 mg of hog kidney acylase I (powder, Sigma Chemical Co.), and deacylation was allowed to proceed at ambient temperature. The pH of the solution was maintained at 7 by addition of 1 *N* potassium hydroxide. After 12 hr, an additional 20 mg of acylase was added, and the solution was stored for an additional 2 hr. The solution was adjusted to pH 5 with dilute hydrochloric acid and was filtered through beds of Celite and Norit. The solution was then concentrated to 50 ml *in vacuo* and was added to a column of Dowex 50W-X4 (acid form, *ca.* 50 ml wet volume). The column was washed to neutrality with water and was eluted with dilute ammonium hydroxide until the eluate gave a negative Pauly test. The total eluate was evaporated to dryness and the residue was dissolved in the minimum volume of water. Upon addition of acetone to faint turbidity, the amino acid separated as colorless platelets. The material was twice recrystallized from water–acetone to give 1.14 g (73%) of the L-amino acid: $[\alpha]^{25}D$ −34.6° (*c* 0.4, H_2O).

Anal. Calcd for $C_6H_8FN_3O_2 \cdot H_2O$: C, 37.69; H, 5.27; N, 21.98. Found: C, 37.21; H, 5.20; N, 21.90.

4-Fluoro-D-histidine (20). The mother liquor from the first crystallization of the L isomer was evaporated to dryness. Trituration of the residue with ethanol gave colorless needles which were recrystallized from ethanol and proved to be the ammonium salt of the *N*-acetyl-4-fluoro-D-histidine (41% yield).

Anal. Calcd for $C_8H_{10}FN_3O_3 \cdot NH_3$: C, 41.38; H, 5.65; N, 24.13. Found: C, 41.24; H, 5.93; N, 23.97.

A 200-mg sample of the above salt was hydrolyzed by boiling its solution in 10 ml of 6 *N* hydrochloric acid overnight. The L-amino acid was recovered by ion-exchange chromatography, following the procedure given above for the DL-amino acid. The product was crystallized twice from water–acetone to give 72 mg (48%) of 4-fluoro-D-histidine: $[\alpha]^{25}D$ +31.4° (*c* 0.4, H_2O).

Anal. Calcd for $C_6H_8FN_3O_2$: C, 41.62; H, 4.66; N, 24.27. Found: C, 41.35; H, 4.81; N, 24.37.

4-Fluorohistamine (22). To a solution of 65 mg of 4-fluoro-L-histidine monohydrate in 50 ml of water was added 100 mg of L-histidine decarboxylase (crude acetone powder from *C. welchii*, Sigma Chemical Co.). The mixture was stored at ambient temperature, pH being maintained between 4.0 and 4.5 by addition of dilute hydrochloric acid. After 8 hr and after 16 hr, additional 100-mg portions of enzyme were added. After 2 days, tlc showed complete consumption of the amino acid. The solution was filtered through a bed of Celite and was added to a Dowex-50 column (acid form, 25 ml wet volume). The column was eluted with water to neutrality and the amine was eluted with dilute ammonium hydroxide. Fractions containing Pauly-positive material were combined and evaporated to dryness to give 50 mg of a semicrystalline solid. This material was dissolved in a small volume of ethanol and treated with 1 ml of a saturated solution of picric acid in ethanol. After refrigeration of the solution overnight, the picrate was collected and recrystallized from methanol to give 58 mg of 4-fluorohistamine picrate (43% yield), mp 189–200° dec.

Anal. Calcd for $C_{11}H_{11}FN_6O_7$: C, 36.88; H, 3.10; N, 23.46. Found: C, 36.95; H, 3.15; N, 23.60.

5-Cyanomethyl-4-fluoroimidazole (23). To an ice-cold solution of 0.85 g (5 mmol) of 5-chloromethyl-4-fluoroimidazole hydrochloride in 25 ml of dry dimethylformamide was added a cold solution of 0.80 g (18 mmol) of dry, powdered sodium cyanide in 30 ml of dimethylformamide. A mildly exothermic reaction ensued with gas evolution (probably hydrogen cyanide). The mixture was stirred overnight at room temperature, was then diluted with 200 ml of water, and was neutralized with sodium bicarbonate. The solution was saturated with sodium chloride and was extracted five times with 50-ml portions of ethyl acetate. The combined extracts were washed three times with water, dried (Na_2SO_4), and

concentrated to give a colorless, crystalline residue. This material was sublimed to give 110 mg (18%) of **23**, mp 149–151°. For analysis, a sample was recrystallized from methanol–water.

Anal. Calcd for $C_6H_4FN_3$: C, 48.00; H, 3.22; N, 33.59. Found: C, 47.71; H, 3.13; N, 33.75.

Hydride Reduction of 23. To a suspension of 150 mg of pulverized lithium aluminum hydride in 15 ml of tetrahydrofuran (purified by distillation from lithium aluminum hydride) was added a solution of 360 mg of **23** in 10 ml of tetrahydrofuran, dropwise with stirring and ice cooling. About 15 min after addition was completed, tlc showed the disappearance of the starting material and the appearance of a small amount of 4-fluorohistamine, together with a new Pauly-positive spot. The mixture was stirred at room temperature for 8 hr; an additional 150 mg of hydride was added and the mixture heated at reflux for 2 hr. Neither treatment effected any visible change (by tlc) in the composition of the reduction mixture. On the basis of tlc, the yield of **22** was judged too small to warrant work-up. Purification and structural studies on the major product of reduction are in progress.

Homolytic Aromatic Substitution. VIII. Phenylation of Polycyclic Aromatic Hydrocarbons[1,2]

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Abstract: Partial rate factors for homolytic phenylation at all sites in naphthalene, anthracene, biphenylene, and phenanthrene and two of the three positions in pyrene have been measured using the Meerwein reaction and *N*-nitrosoacetanilide as sources. Only phenanthrene exhibited a source effect, and both sets of reactivity data correlate with Hückel localization numbers. The reaction constants determined by the correlations are the lowest ever reported for an aromatic substitution reaction. Other sources were studied with phenanthrene, and 9-acetonylanthracene has been isolated.

The ultimate objective of this research was to test experimentally the correlations of structure and reactivity predicted by theory for homolytic phenylation of polycyclic aromatic hydrocarbons. The general concept, due primarily to Dewar, has been the subject of several reviews.[4–6] Prior to our studies, the molecular affinities of numerous polycyclic arenes for trichloromethyl,[7] methyl,[8a] and trifluoromethyl[8b] radicals had been measured and found to correlate with the lowest localization energy in the particular arene. In none of these studies were the alkylarenes isolated or measured directly. Thus, in making these correlations the total reactivity of every arene must be assigned to only the most reactive positions.[9] Under these circumstances, one is forced to cite the correlation in support of the measurements; nevertheless, the discovery of these relationships had a stimulating effect in this area of physical organic chemistry. In our investigations we have measured partial rate factors for phenylation at 14 sites in five polycyclic aromatic hydrocarbons with two different sources of phenyl radicals, the Meerwein reaction, and *N*-nitrosoacetanilide.

The mechanism of homolytic aromatic substitution, illustrated in eq 1 for the phenyl radical,[10] involves

$$C_6H_5\cdot + ArH \longrightarrow \underset{\mathbf{1}}{C_6H_5ArH\cdot} \longrightarrow C_6H_5Ar \qquad (1)$$

addition to the π system giving a cyclohexadienyl type of radical **1** which requires oxidation or dehydrogenation to produce biaryl. Experimental evidence for the formation and existence of the intermediate **1** includes the absence of primary isotope effects[11,12] and the isolation of dimers and disproportionation products of **1**.[13–15] Furthermore, addition of the phenyl radical to benzene has been shown to be irreversible,[16] *vide infra*.

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