

## Photochemistry of Diazonium Salts. II. Synthesis of 2-Fluoro-L-histidine and 2-Fluorohistamine, and the Halogen Lability of 2-Fluoroimidazoles

Kenneth L. Kirk, Wakatu Nagai,<sup>1</sup> and Louis A. Cohen\*

Contribution from the Laboratory of Chemistry, National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, Bethesda, Maryland 20014. Received April 12, 1973

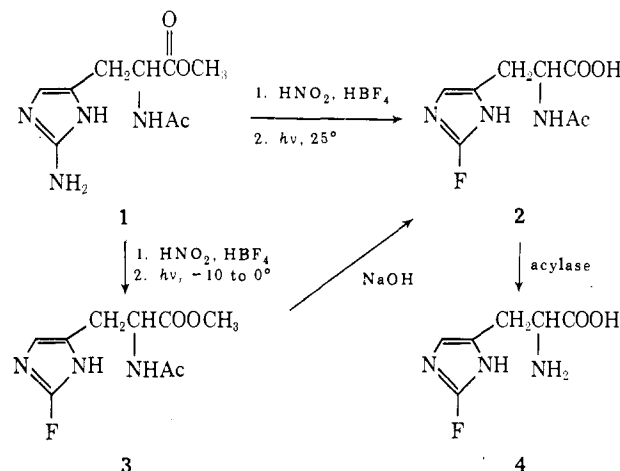
**Abstract:** Irradiation of diazotized  $\alpha$ -N-acetyl-2-amino-L-histidine methyl ester in tetrafluoroboric acid solution, at  $-10$  to  $0^\circ$ , provides the 2-fluoroimidazole derivative in 32% yield; 2-fluoro-L-histidine is obtained after ester hydrolysis and enzymatic deacylation of the latter derivative. An analogous approach to 2-fluorohistamine failed because of decomposition during acid or alkaline hydrolysis of the N-acetyl group. The histamine analog was obtained, however, by use of the more labile trifluoroacetyl group for protection of the side-chain amine. In contrast to the very high degree of stability of 4-fluoroimidazoles, the 2-fluoro isomers are subject to fluorine displacement (*via* an addition-elimination mechanism) by a variety of nucleophiles under mild reaction conditions. 2-Fluoroimidazoles also differ markedly from other haloimidazoles, both in degree of reactivity and in mechanism of dehalogenation. 2-Fluoroimidazole, itself, undergoes oligomerization to a cyclic trimer, which may possess heteroannular resonance stabilization. This unexpected lability suggests that 2-fluoro analogs of biologically important imidazoles may serve as affinity labels and inactivators of receptor sites and enzymes.

In paper I of this series, we described a general method for the introduction of fluorine into aromatic and heteroaromatic rings, based on irradiation of the corresponding diazonium ion in tetrafluoroboric acid solution.<sup>2</sup> Initial studies on the enzymatic and *in vivo* properties of 4-fluoro-L-histidine and 4-fluorohistamine, synthesized by this method, provided results of sufficient interest<sup>3</sup> to stimulate our pursuit of the corresponding 2-fluoro series. The requisite precursors to this series are 2-amino-L-histidine and 2-aminohistamine (with their side chain functional groups suitably protected); synthesis of these compounds and their derivatives has already been described.<sup>4</sup> The present report is concerned with the synthesis of the 2-fluoro analogs of histidine and histamine, and with the unexpected lability of the halogen in 2-fluoroimidazoles.

Irradiation of the diazonium salt of **1**, in the manner previously described ( $25^\circ$ , 10–16 hr),<sup>2</sup> resulted in introduction of fluorine at C-2, but also in extensive hydrolysis of the ester function. The product **2**, formed in low yield, was not only difficult to recover from the reaction mixture but, following recovery, was also difficult to purify satisfactorily. Acid hydrolysis of **2**, according to the procedure used for the 4-fluoro analog,<sup>2</sup> resulted in complete loss of Pauly-positive material.<sup>5</sup> Although this crude preparation of **2** was deacylated by hog kidney acylase, the resulting amino acid **4** could not be purified effectively.

The irradiation procedure was then modified by reduction in temperature to  $-10$  to  $0^\circ$ , and by use of a more efficient cell to shorten irradiation time. Under

these conditions, the ester group proved resistant to hydrolysis; furthermore, complete decomposition of the diazonium ion was now achieved in 0.5–1 hr. The fluoroester **3** was readily isolated in 32% yield. Saponification of **3** and enzymatic deacylation of the resulting acid **2** (without isolation) provided the desired amino acid **4** in 77% yield from **3**.



Irradiation of the diazonium salt of  $\alpha$ -N-acetyl-2-aminohistamine (**9a**),<sup>4</sup> at  $25^\circ$ , provided the expected 2-fluoro analog **10a**. As had already been observed with **2**, **10a** underwent decomposition (with loss of Pauly test) under the minimal acid or alkaline conditions necessary to effect hydrolysis of the amide linkage. This lability was circumvented, in the case of **2**, by use of enzymatic deacylation of the  $\alpha$ -acetamido acid. Rather than attempt to develop an enzymatic system for the hydrolysis of acetylated histamines, we chose to repeat the entire sequence with the use of a more labile  $\alpha$ -N-acyl derivative. Coupling of  $\alpha$ -N-trifluoroacetylhistamine (**5b**) with *p*-carbomethoxyphenyldiazonium ion provided the 2-aryloxy derivative **7b**, which was separated chromatographically from smaller quantities of the 4-aryloxy isomer **8b** and the 2,4-bisaryloxy deriva-

(1) Associate in the Visiting Program, U. S. Public Health Service, 1971–1973.

(2) K. L. Kirk and L. A. Cohen, *J. Amer. Chem. Soc.*, **95**, 4619 (1973). For a preliminary communication, see K. L. Kirk and L. A. Cohen, *ibid.*, **93**, 3060 (1971).

(3) See, e.g., B. M. Dunn, C. DiBello, and I. M. Chaiken, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **32**, 541 (1973). Reports of other studies are in preparation.

(4) W. Nagai, K. L. Kirk, and L. A. Cohen, *J. Org. Chem.*, **38**, 1971 (1973).

(5) K. Hofmann, "Imidazole and Its Derivatives," Interscience, New York, N. Y., 1953, p 136.

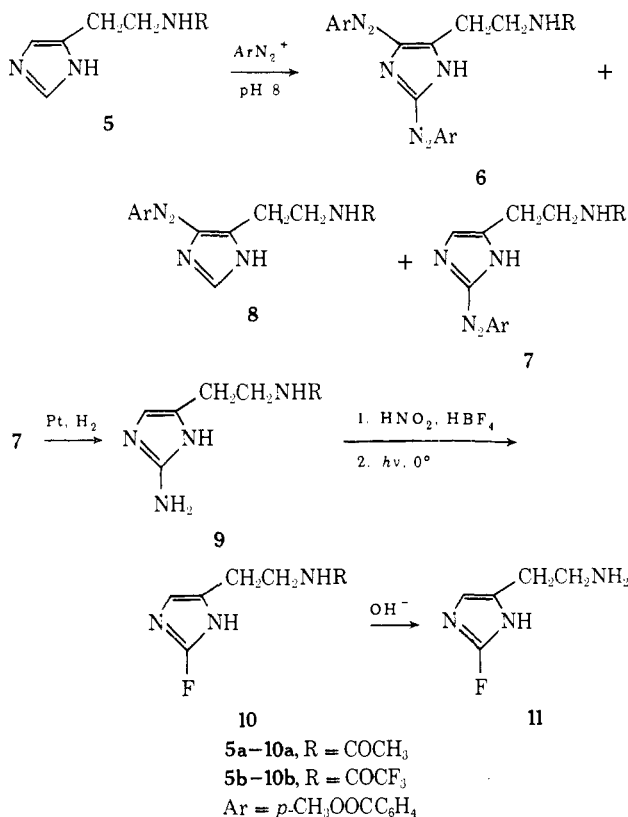
Table I. Partial Nmr Data for Imidazole Derivatives<sup>a</sup>

Compd	Solvent	δ, ppm	
		H <sub>2</sub>	H <sub>3</sub> <sup>b</sup>
3	CD <sub>3</sub> OD		6.55
4	D <sub>2</sub> O		6.69
5b <sup>c</sup>	CD <sub>3</sub> COOD	8.83 (d, <i>J</i> = 1.5 Hz)	7.43
	DMSO- <i>d</i> <sub>6</sub>	8.70 (d, <i>J</i> = 1.0 Hz)	7.43
7b	CD <sub>3</sub> COOD		7.36
8b	CD <sub>3</sub> COOD	8.43 (s)	
9b	CD <sub>3</sub> COOD		6.70
	DMSO- <i>d</i> <sub>6</sub>		6.63
10b	CD <sub>3</sub> COOD		6.53
	DMSO- <i>d</i> <sub>6</sub>		6.55
11	CD <sub>3</sub> OD		6.57
12	D <sub>2</sub> O		7.24, 7.71 <sup>d</sup>

<sup>a</sup> Spectra were recorded on a Varian A-60 spectrometer. <sup>b</sup> All H<sub>2</sub> signals appear as singlets. <sup>c</sup> As the trifluoroacetate salt. <sup>d</sup> Assignments as H<sub>1</sub> and H<sub>3</sub> uncertain.

time **6b**. The distribution of products, their chromatographic behavior, and their nmr spectra (Table I; on which structural assignments to **7b** and **8b** are based) are consistent with the results obtained previously in the *N*-acetyl series (**6a–8a**).<sup>4</sup> Catalytic hydrogenolysis of **7b** provided the aminoimidazole **9b**. The diazonium salt obtained from **9b** was irradiated at 0° to provide the fluoroimidazole **10b** in 37% yield. There was no evidence for hydrolysis of the trifluoroacetyl group during irradiation or isolation. Finally, the trifluoroacetyl group was removed from **10b** in 0.5 *N* sodium hydroxide at 25° to produce 2-fluorohistamine (**11**).

The isomeric 2-fluoro- and 4-fluoroimidazoles show significant differences in both physical and chemical properties. For example, 2-fluoroimidazole<sup>2</sup> dissociates to its anion with a *pK*<sub>a</sub> value of 10.5, whereas

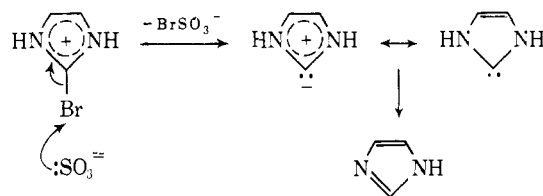


4-fluoroimidazole shows no evidence of dissociation up to pH 11.7.<sup>6</sup> We attribute this difference, primarily, to

the fact that the anion of 2-fluoroimidazole is more symmetrical, and hence more effectively stabilized by resonance, than is the anion of 4-fluoroimidazole. While 4-fluoroimidazoles have been found stable to the action of acid, alkali, or strong nucleophiles. 2-fluoroimidazoles show a significant tendency toward loss of the halogen atom.

To understand the behavior of 2-fluoroimidazoles, it is first necessary to clarify some seeming contradictions in the chemistry of other haloimidazoles. The classical studies of Pyman and of others<sup>7a</sup> have shown that: (a) bromo- and iodoimidazoles are stable to acid, alkali, and most nucleophiles;<sup>6b</sup> (b) these haloimidazoles are attacked by the powerful nucleophile, sulfite ion, to effect reductive dehalogenation; (c) halogen at C-2 is far more reactive toward sulfite ion than is halogen at C-4;<sup>7b</sup> (d) bromine can be replaced slowly by chlorine in hot, concentrated hydrochloric acid;<sup>8</sup> and (e) chloroimidazoles are unreactive toward sulfite ion, or any other nucleophiles.<sup>8</sup> Since imidazolesulfonic acids are fully stable under the conditions of sulfite reduction,<sup>9</sup> it is clear that such acids cannot be intermediates in reductive dehalogenation, and that the reaction does not follow the usual aromatic S<sub>N</sub> (addition–elimination) mechanism.<sup>10</sup> As an alternative, we suggest that the soft nucleophile,<sup>11</sup> sulfite ion, attacks the soft halogen rather than carbon, with the imidazolium carbanion (= carbene) as a leaving group (Scheme I).<sup>12</sup> Since imidazolium ion undergoes deu-

Scheme I



terium exchange much more readily at C-2 than at C-4,<sup>13</sup> the C-2 carbanion is clearly the more stable and the better leaving group, accounting for the greater lability of halogen at C-2. According to the addition–elimination mechanism, chloroimidazoles should be at least as reactive (if not more so) as their bromo counterparts. The stability observed for chloroimidazoles toward sulfite ion<sup>8</sup> strengthens our denial of the aromatic S<sub>N</sub> mechanism; the absence of effective interaction between soft sulfite and moderately hard chlorine follows from

(6) (a) The ionization process was followed by changes in <sup>19</sup>F nmr signals as a function of pH, full titration curves being obtained; this technique will be described in detail separately (with H. J. Yeh), together with other physical properties of the isomeric series. (b) The same *pK*<sub>a</sub> order has been found for 2-bromoimidazole (11.03) and for 4-bromoimidazole (12.32): G. B. Barlin, *J. Chem. Soc. B*, 641 (1967).

(7) (a) For a review of the earlier literature, see ref 5, Chapter 4. (b) Initial conclusions regarding differences in reactivity between 2-bromo- and 2-iodoimidazoles are invalid, because of incorrect structural assignments. This question has been clarified recently by nmr studies: M. S. R. Naidu and H. B. Bensusan, *J. Org. Chem.*, **33**, 1307 (1968).

(8) A. W. Lutz and S. DeLorenzo, *J. Heterocycl. Chem.*, **4**, 399 (1967).

(9) Reference 5, Chapters 4 and 6.

(10) J. Miller, "Aromatic Nucleophilic Substitution," Elsevier, New York, N. Y., 1968.

(11) R. G. Pearson, *J. Amer. Chem. Soc.*, **85**, 3533 (1963); R. G. Pearson and J. Songstad, *ibid.*, **89**, 1827 (1967).

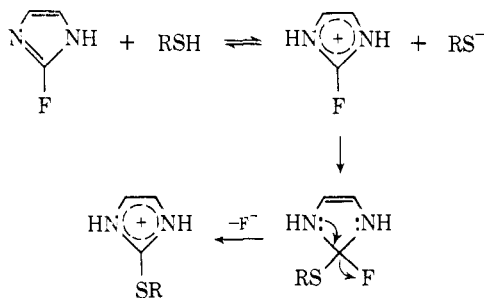
(12) This reaction may be compared with that between picryl chloride and iodide ion to form 1,3,5-trinitrobenzene: A. H. Blatt and R. W. Tristram, *ibid.*, **74**, 6273 (1952); see also ref 10, p 382.

(13) T. M. Harris and J. C. Randall, *Chem. Ind. (London)*, 1728 (1965), and references cited therein.

generalized hard-soft principles.<sup>11</sup> The slow replacement of bromine by chlorine in bromoimidazolium ions<sup>5</sup> may, however, follow a true addition-elimination mechanism, such as that observed in the interaction of halonitroimidazoles<sup>6b,14</sup> or of 2-chlorobenzimidazoles<sup>15</sup> with a variety of nucleophiles.

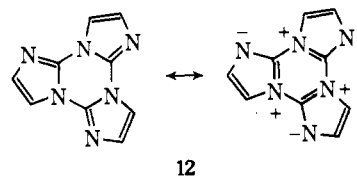
With such data at hand, it seemed unlikely that the fluorine in a fluoroimidazole could serve as a site for attack by sulfite, both because of the degree of hardness of the fluorine atom and because of the strength of the heteroaryl-fluorine bond; nor did an addition-elimination mechanism seem likely in the absence of a strong electron-delocalizing group (such as nitro). To our surprise, the fluorine atom in 2-fluoroimidazoles was found subject to replacement by water, sulfur nucleophiles, and even an imidazole nitrogen atom.<sup>16</sup> In strongly acidic, aqueous media, the 2-fluoroimidazolium ion shows a slow release of fluoride ion. The 2-fluoroimidazole anion, formed in alkaline media, is stable toward nucleophiles under mild conditions; this stability is due, presumably, to the increased electron density in the ring, to electrostatic repulsion between two negatively charged species, and to the difficulty of stabilizing a second negative charge in the addition complex. Since the  $pK_a$  value of 2-fluoroimidazolium ion is *ca.* 2.7,<sup>2</sup> the greatest sensitivity to nucleophilic attack may be expected between pH 2 and 7; in this region there exists the greatest opportunity for co-existence of the imidazolium cation and a nucleophilic anion.<sup>17</sup> Thus, 2-fluoroimidazole is stable to aqueous sulfite ion at 50° but is attacked rapidly by bisulfite ion at 30° (with formation of the sulfonic acid). Sulfur nucleophiles, such as thiophenol, thiolacetic acid, and 2-mercaptoethanol rapidly replace the fluorine atom with formation of the corresponding 2-mercaptoimidazole derivatives (Scheme II). Similar behavior is

Scheme II



found for 2-fluorohistamine and 2-fluorohistidine; on the other hand, no instance of replacement of a 4-fluoro substituent has yet been observed.

At 100°, 2-fluoroimidazole undergoes self-condensation (*via* autocatalysis) to the cyclic trimer **12**, a process which also occurs slowly during the storage of the monomer in a deep freeze. The possibility that this heteroannulene possesses resonance stabilization in



excess of that of imidazole, itself, is suggested by its ultraviolet spectrum, and by its exceptionally low basicity (first  $pK_a < 2.0$ ). Further studies with this compound are in progress.

Clearly, the unique ability of 2-fluoroimidazoles, in contrast to the other haloimidazoles, to engage in an addition-elimination mechanism must be attributed to the much higher electronegativity of fluorine. In addition to the theoretical and synthetic implications of this observation, there exist the intriguing possibilities that 2-fluoro analogs of biologically important imidazoles may serve as affinity labels and inactivators of specific membrane receptor sites and enzymes; these avenues are under investigation.

### Experimental Section<sup>18</sup>

**Irradiation Procedure.** The radiation source was a Hanovia 450-W, medium-pressure mercury vapor lamp, equipped with a Corex filter, and placed in a quartz immersion well. The solution to be irradiated was contained in a Pyrex cylindrical vessel (usually of 200 ml capacity) which surrounded the quartz vessel.<sup>19</sup> The concentric cylinders provided a solution thickness of 5–7 mm. The entire apparatus was immersed in an ice-salt bath and the temperature was maintained at –10 to 0° during irradiation. Mixing of the solution was achieved with a stream of nitrogen.

**$\alpha$ -N-Acetyl-2-fluoro-L-histidine Methyl Ester (3).** To 100 ml of 50% aqueous tetrafluoroboric acid was added, at –10°, 2.26 g (8.6 mmol) of  $\alpha$ -N-acetyl-2-amino-L-histidine methyl ester (1, as the dihydrate).<sup>4</sup> To the resulting solution was added a solution of 0.80 g (12 mmol) of sodium nitrite in 5 ml of water. The solution of diazonium salt was diluted with 100 ml of cold tetrafluoroboric acid and the mixture was subjected to irradiation at 0°. After 1 hr, ultraviolet absorption at 320 nm (due to the diazonium imidazole chromophore) had disappeared completely. The reaction mixture was neutralized to pH 6 with cold, concentrated sodium hydroxide, and was subjected to continuous extraction with ethyl acetate for 24 hr. The ethyl acetate extract was dried ( $Na_2SO_4$ ) and concentrated to 50 ml. This solution was chromatographed on a short silica gel column (to remove salts); the Pauly-positive fractions were pooled and evaporated to give 0.63 g (32%) of an oil, which soon crystallized. The product was recrystallized from ethyl acetate, mp 127–128°.

*Anal.* Calcd for  $C_9H_{12}N_3O_3F$ : C, 47.16; H, 5.28; N, 18.33. Found: C, 47.15; H, 5.29; N, 18.23.

**2-Fluoro-L-histidine (4).** A solution of 229 mg (1 mmol) of **3** in 3 ml of 0.5 *N* sodium hydroxide was stored at ambient temperature. After 4 hr, tlc (1-butanol-ethyl acetate-acetic acid-water, 1:1:1:1) indicated complete saponification of the ester. The pH of the solution was adjusted to 7, the volume was increased to 10 ml, and 5 mg of hog kidney acylase I (Sigma Chemical Co.) was added. The pH was maintained at *ca.* 7 by addition of 0.1 *N* sodium hydroxide. After 2 hr, an additional 2 mg of enzyme was added. The reaction mixture was stirred overnight, the pH was then adjusted to 5 with 1 *N* hydrochloric acid, and the solution was filtered and lyophilized. The residue was dissolved in a minimum volume of water and the solution was applied to a cold Dowex 50 ( $H^+$  form) column (3–4 ml wet volume). The column was washed with water to neutrality and the amino acid was eluted with 3% ammonium hydroxide.<sup>20</sup> The Pauly-positive fractions were pooled;

(14) F. Koehler, *J. Prakt. Chem.*, **21**, 50 (1963); L. A. Cohen, *Annu. Rev. Biochem.*, **37**, 718 (1968).

(15) Reference 5, p 302.

(16) In view of the chemical and biological significance of these observations, preliminary results are presented here without experimental detail. Kinetic and mechanistic studies are in progress, and will be reported in full at a later date.

(17) This combination is favored because it provides the most effective nucleophile, the most electrophilic substrate, and a neutral addition intermediate. In the case of halogen acid media, these species also exist at any acid concentration below pH 2.

(18) 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. Wherever possible, identity and homogeneity of each compound were confirmed by nmr and mass spectra, and by tlc.

(19) For reaction volumes of less than 200 ml, the bottom of the reaction flask was filled with glass beads.

(20) The chromatographic column was encased in a cold water jacket.

the solution was placed on a rotary evaporator for 0.5 hr at 30° (to remove ammonia) and was then lyophilized. The residue, which was homogeneous by tlc, was crystallized from methanol to provide 130 mg (77%) of the amino acid **4**;  $[\alpha]^{25D} -31.0^\circ$  (*c* 0.4, H<sub>2</sub>O).

*Anal.* Calcd for C<sub>6</sub>H<sub>9</sub>N<sub>3</sub>O<sub>3</sub>F: C, 41.62; H, 4.66; N, 24.27. Found: C, 41.80; H, 4.84; N, 24.47.

**$\alpha$ -N-Acetyl-2-fluorohistamine (10a).** A solution of 250 mg (1.5 mmol) of  $\alpha$ -N-acetyl-2-aminohistamine (**9a**)<sup>4</sup> in 50 ml of 50% tetrafluoroboric acid was diazotized with 150 mg of sodium nitrite in 5 ml of water at -10°. The solution was irradiated for 15 hr, by use of the original procedure.<sup>2</sup> The reaction mixture was neutralized to pH 6 and was subjected to continuous extraction with ether for 24 hr. The ether extract was dried and evaporated to an oil, which crystallized upon trituration with 6% methanol-ethyl acetate. The mixture was diluted to turbidity with ether and was chilled overnight; 125 mg of pale brownish crystals, mp 143–146°, was obtained. Identity was confirmed by nmr and mass spectra.

**Attempted Deacetylation of 10a. A. By Acid Hydrolysis.** A solution of 43 mg of **10a** in 20 ml of 6 N hydrochloric acid was heated on steam overnight. Evaporation of the solvent provided a brown oil, which failed to give a Pauly test directly, or following tlc. A similar result was obtained following exposure of **10a** to methanolic hydrogen chloride for 3 days at 25°.

**B. By Alkaline Hydrolysis.** A solution of 60 mg of **10a** in 6 ml of 1 N potassium hydroxide was stored at 25° for several days, the course of deacetylation being followed by tlc. Work-up and chromatography provided a trace of Pauly-positive material together with considerable tar.

**$\alpha$ -N-Trifluoroacetylhistamine (5b).** In a 250-ml round-bottomed flask, equipped with reflux condenser and drying tube, was placed 35 ml of trifluoroacetic anhydride. The flask was chilled in an ice-salt bath and the liquid was stirred magnetically while 10 g (0.09 mol) of powdered histamine (free base) was added in one portion. The heat of reaction was sufficient to boil the solvent for several minutes. When the reaction had subsided, the ice bath was removed and stirring at ambient temperature was continued for 5 hr. The solvent was removed *in vacuo*, 50 ml of water was added to the residue, and the solvent was again removed *in vacuo*. This procedure was repeated three times with 50 ml of water and three times with 50 ml of ethanol, leaving a colorless, waxy material. The crude product was dissolved in 90 ml of hot ethyl acetate and the solution was diluted with 250 ml of ether. The crystalline product, which had separated overnight, was collected and dried, giving 27 g (93%) of the histamine derivative as its trifluoroacetate salt, mp 100–101°.

*Anal.* Calcd for C<sub>9</sub>H<sub>9</sub>N<sub>3</sub>O<sub>3</sub>F<sub>6</sub>: C, 33.65; H, 2.82; N, 13.08. Found: C, 33.37; H, 2.73; N, 12.71.

**$\alpha$ -N-Trifluoroacetyl-2-(*p*-carbomethoxyphenylazo)histamine (7b).** A solution of 13 g (0.19 mol) of sodium nitrite in 50 ml of water was cooled to 0–2° and was added gradually to a stirred, ice-cold solution of 20 g (0.13 mol) of methyl *p*-aminobenzoate in 70 ml of 6 N hydrochloric acid. The solution of diazonium salt was stored at ice temperature for 40 min and was then added gradually to a stirred, ice-cold solution of 40.6 g (0.13 mol) of  $\alpha$ -N-trifluoroacetylhistamine (trifluoroacetate) in 400 ml of 0.1 M borate buffer (final pH adjusted to 8.5). During addition of the diazonium salt, the pH was maintained at 8.0–8.4 with 1 N sodium hydroxide; the reaction mixture was refrigerated for 1 hr, and the orange-yellow precipitate was collected and dried (79 g). A solution of the crude product in the minimum volume of chloroform-methanol (15:1) was applied to a column of 5 kg of silicic acid (100 mesh), and the column was eluted with the same solvent system. The mixture of compounds was resolved into three colored bands: the fastest moving consisted of 3.31 g (8%)<sup>21</sup> of deep red crystals, mp 207–210° (CHCl<sub>3</sub>), which were identified as the 2,4-bisarylazo product **6b** by nmr and by elemental analysis.

*Anal.* Calcd for C<sub>23</sub>H<sub>20</sub>N<sub>7</sub>H<sub>5</sub>F<sub>3</sub>: C, 51.98; H, 3.79; N, 18.45. Found: C, 51.62; H, 3.44; N, 18.32.

(21) Based on total material recovered by chromatography.

The second fraction consisted of 30.4 g (72%) of deep yellow crystals, mp 183–184° (CHCl<sub>3</sub>), identified as the 2-arylazo derivative **7b** by nmr and mass spectra, and by elemental analysis.

*Anal.* Calcd for C<sub>15</sub>H<sub>14</sub>N<sub>3</sub>O<sub>3</sub>F<sub>3</sub>: C, 48.78; H, 3.82; N, 18.96. Found: C, 48.57; H, 3.64; N, 18.75.

The last fraction consisted of 8.6 g (20%) of light yellow crystals, mp 202–203° (CHCl<sub>3</sub>), identified as the 4-arylazo derivative **8b** by nmr and mass spectra, and by elemental analysis.

*Anal.* Calcd for C<sub>13</sub>H<sub>14</sub>N<sub>3</sub>O<sub>3</sub>F<sub>3</sub>: C, 48.78; H, 3.82; N, 18.96. Found: C, 48.92; H, 3.82; N, 19.08.

**$\alpha$ -N-Trifluoroacetyl-2-aminohistamine (9b).** A solution of 1.00 g (2.7 mmol) of **7b** in 100 ml of absolute ethanol containing 0.15 g of platinum oxide was subjected to catalytic hydrogenation at ambient temperature and at an initial hydrogen pressure of 40–45 psi (Parr bomb). A hydrogen pressure of 30–40 psi was maintained throughout the reduction process. After the reaction mixture had been shaken overnight, an additional 0.15 g of catalyst was added and the reduction continued for an additional 20 hr. The catalyst was removed by filtration and the solvent was evaporated *in vacuo*. The residual yellow oil was dissolved in 50 ml of water and the pH of the solution was adjusted to 2.5 with 0.5 ml of 50% tetrafluoroboric acid. Methyl *p*-aminobenzoate was removed by extraction of this solution with four 50-ml portions of ether and the aqueous layer was evaporated to dryness by lyophilization. The residual crystalline material (0.75 g, 90%) was recrystallized from a small volume of ethyl acetate to provide **9b** as its fluoroborate salt, mp 139–140°.

*Anal.* Calcd for C<sub>7</sub>H<sub>10</sub>N<sub>4</sub>OF<sub>7</sub>B: C, 27.12; H, 3.25; N, 18.07. Found: C, 26.81; H, 3.40; N, 18.33.

**$\alpha$ -N-Trifluoroacetyl-2-fluorohistamine (10b).** A solution of 5.76 g (18.5 mmol) of **9b** in 100 ml of 50% tetrafluoroboric acid was diazotized and the resulting diazonium salt was irradiated, as described above for **3**. After irradiation for 1 hr, absorption at 320 nm had disappeared. The dark red solution was neutralized to pH 6.0–6.5 with 230 ml of 20% sodium hydroxide (at -4°) and the mixture was extracted with four 125-ml portions of ether.<sup>22</sup> The combined ether extracts were dried and evaporated to give 1.69 g of a violet solid. This material was dissolved in 80 ml of ethyl acetate, the solution was applied to a column of 20 g of silicic acid (100 mesh), and the column was eluted with ethyl acetate. The initial fractions (Pauly positive) were combined and evaporated to give 1.54 g (37%) of an off-white crystalline product, mp 132–134°. This material was recrystallized from 500 ml of benzene, giving colorless prisms, mp 140–141°.

*Anal.* Calcd for C<sub>7</sub>H<sub>7</sub>N<sub>3</sub>OF<sub>4</sub>: C, 37.34; H, 3.13; N, 18.66. Found: C, 37.05; H, 3.16; N, 18.67.

**2-Fluorohistamine (11).** A solution of 240 mg (1.1 mmol) of **10b** in 4 ml of 0.5 N sodium hydroxide was stored under nitrogen (25°) for 4 hr. The solution was poured onto a column of Dowex 50 (H<sup>+</sup> form, 6 ml wet volume); the column was washed to neutrality and was eluted with dilute ammonium hydroxide.<sup>20</sup> The solution was concentrated *in vacuo* at 30° and was finally lyophilized to give 180 mg of a noncrystalline solid. The compound was unstable under the conditions of normal mass spectroscopy, but gave the expected M + 1 value by chemical ionization mass spectroscopy. All efforts to crystallize the material were fruitless. The amine picrate underwent partial solvolysis during crystallization from alcohol-containing solvent systems, but was obtained in pure form from acetonitrile alone, mp 119–122°.

*Anal.* Calcd for C<sub>11</sub>H<sub>11</sub>N<sub>3</sub>O<sub>7</sub>F: C, 36.88; H, 3.10; N, 23.46. Found: C, 36.91; H, 2.97; N, 23.21.

**Imidazole Cyclic Trimer (12).** 2-Fluoroimidazole (50 mg) was heated at 100° for 1 hr in a sublimation apparatus (no vacuum). The system was then evacuated, whereupon a colorless solid sublimed, 35 mg; mp 193–196°; uv max (C<sub>2</sub>H<sub>5</sub>OH) 228 nm ( $\epsilon$  33,300), 235 (31,500), 255 (inflection) (5850); mass spectrum *m/e* 198.

*Anal.* Calcd for C<sub>3</sub>H<sub>6</sub>N<sub>6</sub>: C, 54.54; H, 3.05; N, 42.41. Found: C, 53.90; H, 3.15; N, 42.38.

(22) Tlc showed that all Pauly-positive material had been removed from the aqueous layer.