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# SYNTHESIS AND ALKALINE HYDROLYSIS OF (PENTAFLUOROETHYL)-IMIDAZOLES

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SUMMARY

Photochemical ring substitution of the N-trifluoroacetyl derivatives of histamine and of L-histidine methyl ester by pentafluoroethyl radical provides the corresponding 2- and 4-pentafluoroethylated products in yields of 19% and 27%, respectively. Alkaline hydrolysis converts the 2-pentafluoroethyl group to trifluoroacetyl. The reaction mechanism, involving a diazafulvene intermediate, is analogous to that elucidated for (trifluoromethyl)imidazoles; however, the pentafluoroethyl group is markedly more reactive to hydrolysis than the trifluoromethyl group. For imidazole derivatives, the ratio of reactivities is 75 at C-2 and 40 at C-4. The hydrolysis of 4-(pentafluoroethyl)histamine affords the bicyclic product, 4-(trifluoromethyl)-6,7-dihydro-1H-imidazo[4,5-c]-pyridine in 65.4% yield.

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## INTRODUCTION

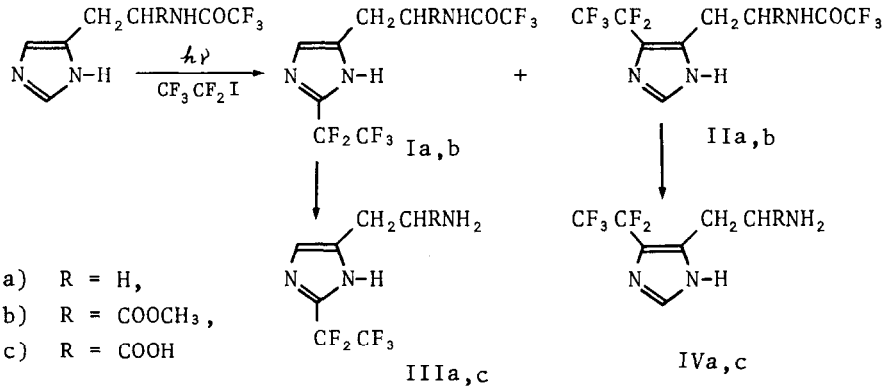
We have recently described facile, general syntheses of ring-trifluoromethylated imidazoles [1~3]. Under mild alkaline conditions, these compounds eliminate hydrogen fluoride to form transient difluorodiaza-fulvenes, and the latter species react rapidly with a variety of nucleophiles [4]. This property suggested to us the possibility that appropriate (trifluoromethyl)imidazoles might serve as covalent affinity labels in biological systems. Additionally, various transformations of the trifluoromethyl group provided new synthetic routes to biologically significant imidazole derivatives [5].

(Trifluoroacetyl)imidazoles are also of potential biological interest. Thus, 2-(trifluoroacetyl)imidazole bears both a structural and electronic resemblance to 2-nitroimidazole (the antibiotic, azomycin). Furthermore, the great avidity of the carbonyl group for nucleophilic addition suggests that such compounds may form strong covalent bonds to biological nucleophiles. N-Methyl-2-(trifluoroacetyl)imidazole has been prepared in reasonable yield by N to C migration in an ylid intermediate [6a]. This approach was also used with N-(methoxymethyl)imidazole and, after acid hydrolysis of the protecting group, provided a series of 2-acylimidazoles [6b]. Efforts to produce 2-(trifluoroacetyl)imidazole or 2-(trifluoroacetyl)-histidine by the latter method were unsuccessful [7]. Equally unsuccessful was our attempt to oxidize 2-(1' -hydroxy-2',2',2' -trifluoroethyl)imidazole [8]. It was logical to expect the chemistry of (pentafluoroethyl)imidazoles to show some similarity to that of the trifluoromethyl series and, since we had already prepared the former compounds [2], we investigated alkaline hydrolysis as a route to the trifluoroacetyl derivatives. Analogous studies were undertaken with the histamine and histidine derivatives.

RESULTS AND DISCUSSION

Synthesis of (pentafluoroethyl)histamines and histidines

Photochemical perfluoroalkylation [2] was used to introduce the pentafluoroethyl group into the imidazole rings of histamine and L-histidine. Attack by the pentafluoroethyl radical on the N-trifluoroacetyl derivatives of histamine and L-histidine methyl ester parallels the results with trifluoromethylation [3]. The isomeric products (I and II) were separated without difficulty by silica gel chromatography and are readily differentiated on the basis of their $^1$H NMR spectra. The imidazole-ring proton at C-2 usually appears at lower field than that at C-4(5). The yields (Ia 18.8%, IIa 26.6%, Ib 18.9%, IIb 26.9%) and the ratios (Ia/IIa = 41/59, Ib/IIb = 45/55) show that the 4-pentafluoro-ethyl products are somewhat favored over the 2-isomers. Direct analyses of the reaction mixtures by GC-MS and




$^{19}$F NMR showed no significant signals of other products than I and II.

Protective groups were removed by acid hydrolysis [3] to provide the 2- and 4-pentafluoroethyl derivatives of histamine (IIIa and IVa) and of L-histidine (IIIc and IVc) as their dihydrochlorides.

Alkaline hydrolysis of 2-(pentafluoroethyl)imidazole (V)

In preliminary studies [8], 2-(trifluoroacetyl)imidazole (VII) could not be isolated from the alkaline hydrolysis of V.

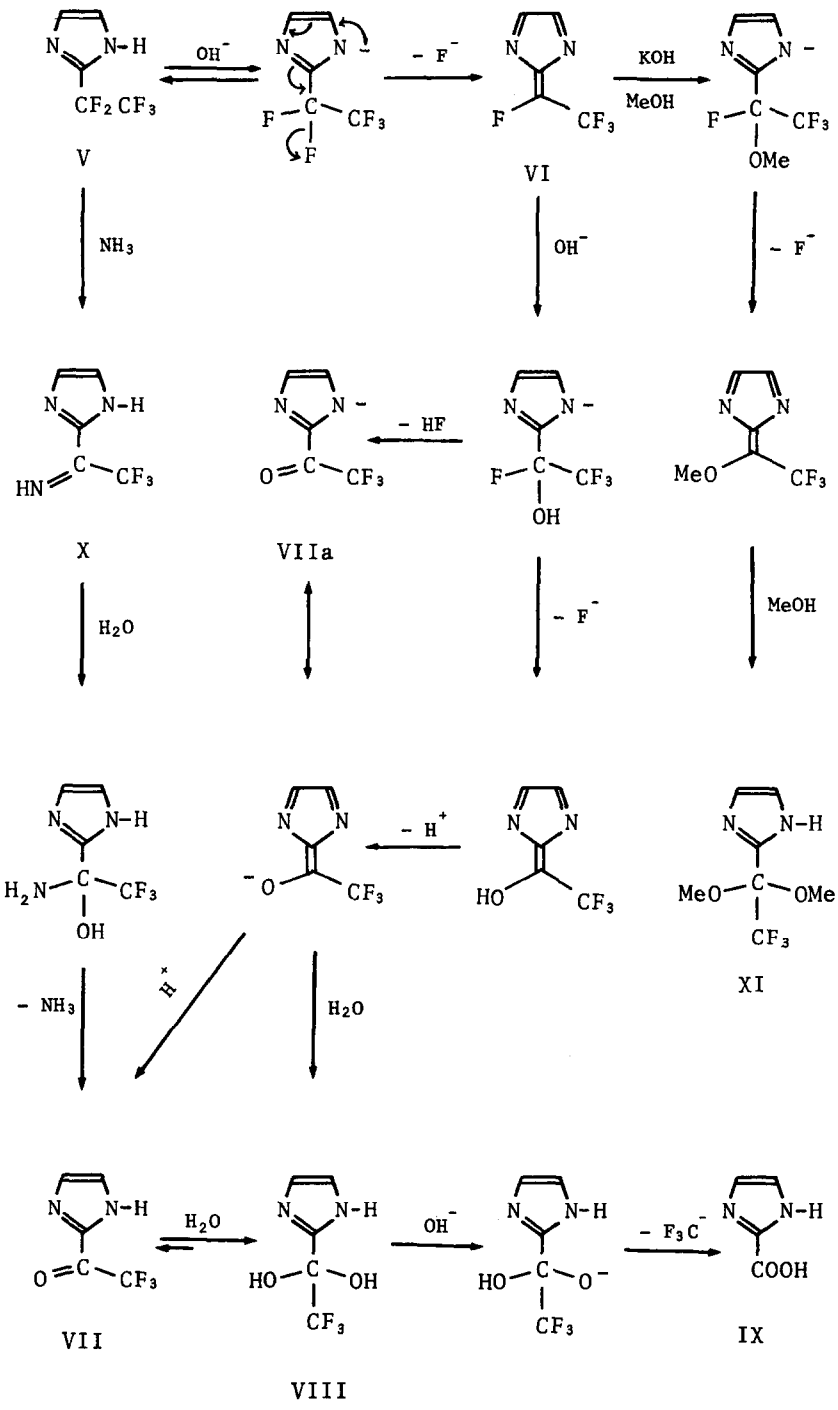
We have now reinvestigated the hydrolysis more quantitatively by UV spectroscopy. Although VII should show strong UV absorption, the hydrolysis of V ($\lambda_{max}$226 nm in 0.1N NaOH) results in a decrease in absorption at $\lambda_{max}$ without the appearance of any new peaks. The loss of absorption was followed at 230 nm and obeyed good first-order kinetics. The rate constant ($k_{obsd}$) for the hydrolysis is a function of the degree of NH ionization (Figure 1). The kinetic $pK_2$ value, 10.29 (30°C), is consistent with the value of 10.11 found for 2-(trifluoromethyl)imidazole [4]. At high pH, the limiting rate constant ($k'_{obsd} = k_{obsd}/f_{Im^-}$) for the consumption of V at 30°C is 0.151 $min^{-1}$($t_{1/2}$= 4.6 min).

The rate-limiting step, as already shown for (trifluoromethyl)imidazoles [4], should be the internal elimination of fluoride ion to form a transient diazafulvene (VI). Surprisingly, V is 75-fold as reactive as 2-(trifluoromethyl)imidazole. It seems unreasonable that the trifluoromethyl group could promote the departure of fluoride ion from anion of V, and the enhanced reactivity may be due to better stabilization of the olefinic system of VI by $CF_3$ than by F.

During the hydrolysis, very weak UV absorption was observed at 320 ~ 330 nm, which disappeared by the end of the reaction. This absorption may be due to 2-(trifluoroacetyl)imidazolate ion (VIIa), which undergoes rapid hydration to VIII. The equilibrium lies so far to the side of the hydrate that only one signal is observed by $^{19}F$ NMR, at - 5.56 ppm in water ( at - 5.08 ppm in 0.2N NaOH).

In 1N NaOH at 30°C, VIII is converted slowly to imidazole-2-carboxylic acid (IX) as shown by increasing UV absorption at 247 nm. In media less basic than 0.2N NaOH, the conversion is negligibly slow. The alkaline degradation of perfluoroalkyl ketones, via the haloform (fluoroform) reaction, has been described for several cases [9]; further studies on the reaction are in progress.

On the basis of the information obtained from UV kinetic analysis, optimum conditions were determined for the preparation of VII. Thus, hydrolysis of V in 0.2N NaOH (2h at ambient temperature) gave VII in 46.3%yield. Although VII exists overwhelmingly as its hydrate in aqueous solution, evaporation


OH⁻
- F⁻
KOH
MeOH
V
VI
NH₃
OH⁻
- F⁻
- HF
X
VIIa
H₂O
- F⁻
MeOH
- H⁺
XI
- NH₃
H⁺
H₂O
VII
VIII
H₂O
OH⁻
- F₃C⁻
IX

to dryness evidently results in dehydration to the ketone.

Hydrolysis of V in aqueous ammonia provided VII in 96.3% yield. The anticipated ketimine (X) product was observed by UV spectroscopy as an intermediate. In 4.4% ammonia solution at 30°C, absorption at $\lambda_{max}$ (312 nm) increased rapidly, reached a maximum after 7 min, and then began to decrease slowly. As shown in Figure 2, $k_{obsd}$ for the consumption of V increases with a decrease in the concentration of ammonia. The trend continues until the pH of the solution is too low to effect extensive ionization of V, at which point, $k_{obsd}$ begins to decrease. The same phenomenon had already been described for the ammonolysis of 2-(trifluoromethyl)imidazole [4] and has been attributed to the strong requirement for unbound water to solvate the departing fluoride ion.

In the reaction of V with methanolic KOH, the dimethyl ketal (XI) was obtained in 94.0% yield. Although the methanolysis could not be monitored by UV spectroscopy, it was evident that the rate of fulvene formation was markedly slower than in water. The critical role of solvation in facilitating the departure of fluoride ion has been described previously [4]. The dimethyl ketal is not formed from VII and VIII in methanolic base and must, therefore, be generated directly by successive methanol additions to the fulvene.

Alkaline hydrolysis of 4-(pentafluoroethyl)imidazole (XII)

In contrast to V, XII shows UV absorption only below 220 nm, and its rate of hydrolysis was followed by the rate of formation of XIII at 297 nm ($\lambda_{max}$). As with V, $k_{obsd}$ increases with the fraction of anion present, providing a kinetic $pK_2$ = 11.74 and a limiting rate constant ($k'_{obsd}$) = 0.680 $min^{-1}$ at 30°C ($t_{1/2}$ = 1 min). Thus, XII is 4.6-fold as reactive as V, paralleling our earlier observations with the (trifluoromethyl)-imidazole isomers [4].

It is somewhat surprising that 2-(trifluoroacetyl)imidazole (VII) prefers the fully hydrated form in aqueous solution while the 4-isomer (XIII) exists in equilibrium with its hydrate (XIV); $^{19}F$ NMR of XIII in water showed two peaks at 5.26 ppm, XIII, and at - 5.60 ppm, XIV, in the ratio 4 : 6. Since the

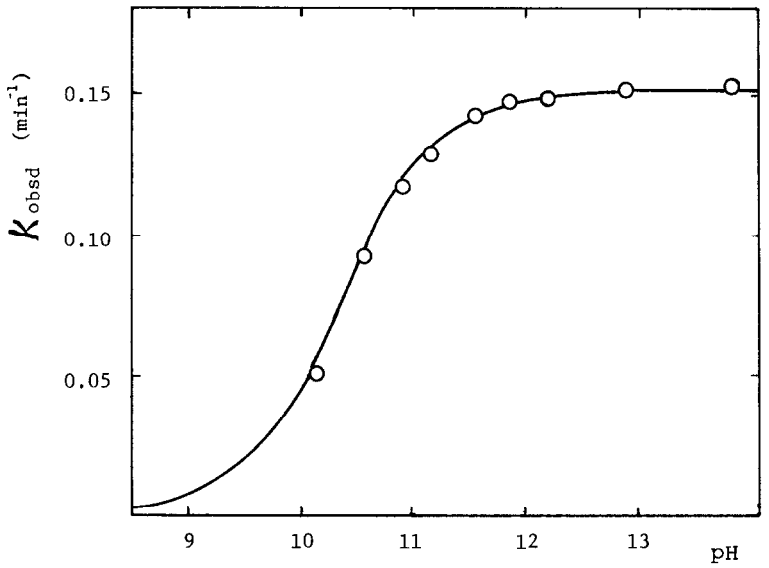



Fig. 1. pH dependence for the hydrolysis of V at 30°C. Solid line represents the calculated curve based on $pK_2$ = 10.29 and $k'_{obsd}$ = 0.151 min.$^{-1}$

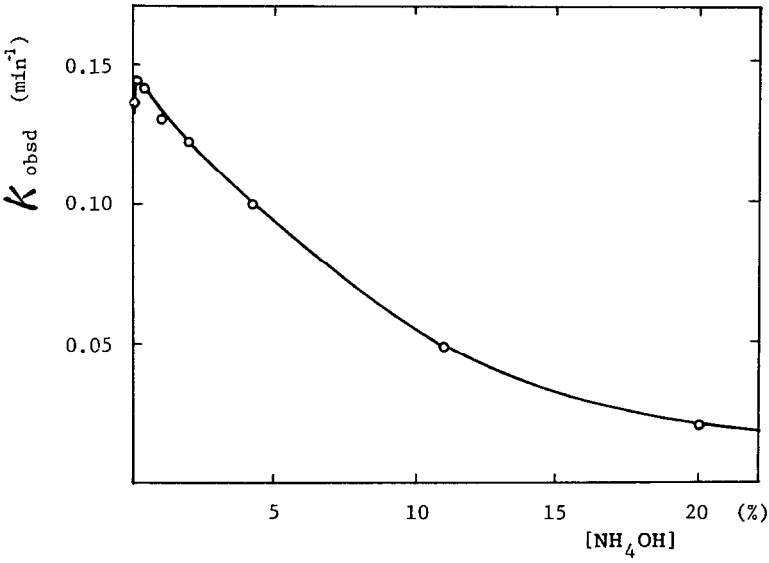
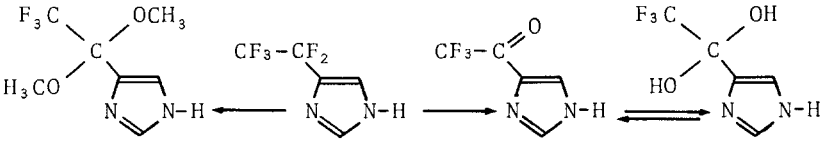
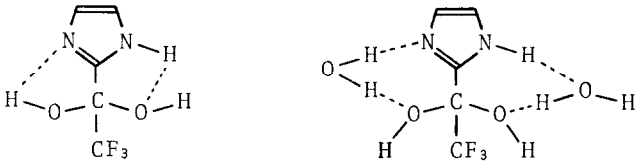



Fig. 2. Dependence of $k_{obsd}$ for the ammonolysis of V on [$NH_4OH$] at 30°C.



XVI XII XIII XIV

equilibrium constant for hydration is favored by increased electron withdrawal [10], the combined effect of two nitrogen atoms acting on the carbonyl of VII may be sufficiently greater than that of one (XIII) to influence the position of equilibrium. Additionally, we suggest that VIII is preferentially stabilized by double hydrogen bonding, as in XVa or XVb. This issue is under further study.



XVa XVb

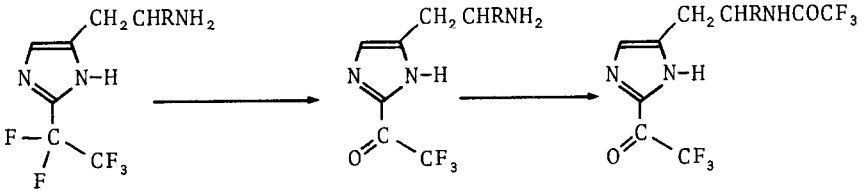
The ammonolysis of XII also provided XIII in 98.7% yield. The intermediate ketimine was observed by UV spectroscopy ($\lambda_{max}$ 287 nm in 4.4% ammonia solution). The relationship between the rate of ammonolysis of XII and ammonia concentration parallels the result with V. While the maximum rate of ammonolysis for V occurs in ca.0.5% ammonia (Figure 2), XII gives its maximum rate in 4-5% ammonia. This difference is a consequence of the higher $pK_2$ value for XII. Alkaline methanolysis of XII provides the dimethylketal (XVI) in 98.5% yield.

## Alkaline hydrolysis of pentafluoroethylhistamines and L-histidines

The pentafluoroethyl group of IIIa was converted to trifluoroacetyl (XVIIa) by alkaline hydrolysis, with $k_{obsd}$ = 1.25 $min^{-1}$ ($t_{1/2}$ = 0.55 min, 30°C, 0.1N NaOH). The 8-fold increase in

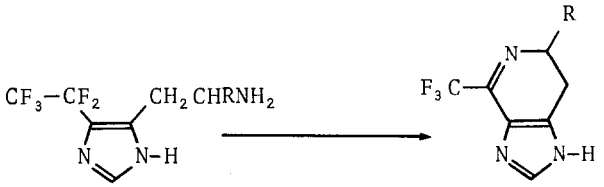
reactivity over that of V is probably due to the electron-releasing effect of the alkyl group at C-5; the 5-methyl group was also found to accelerate the alkaline hydrolysis of 2-(trifluoromethyl)imidazole [4]. As in the preceeding cases, the preparative reaction was performed in 4% aqueous ammonia, because of the higher yields and simplicity of procedure. The product was isolated as its N-trifluoroacetyl derivative (XVIIIa) in 75.9% yield. Compound Ia cannot be converted directly to XVIIIa because the N-trifluoroacetyl group would be lost in the basic medium.

The alkaline hydrolysis of IVa provided bicyclic condensation product XIXa. The primary amino group may add directly to the fulvene or may condense rapidly with a preformed carbonyl. In any event, formation of the first fulvene species should be the rate-limiting step [4]. It is surprising, therefore, that XIXa is formed only 1/7 as fast as XIII, with $k_{obsd} = 9.8 \times 10^{-2}$ $min^{-1}$ ($t_{1/2}$ = 7.1 min, 30°C, 0.1N NaOH). The 5-methyl group increases the rate of hydrolysis of 4-(trifluoromethyl)-imidazole 45-fold [11] and, thus, the retardation effect in IVa is probably not electronic in nature. Perhaps the primary amino group, operating through a proximity effect, interferes with aquatosolvation of the departing fluoride ion in formation of the fulvene [4]. Preparative hydrolysis was performed with triethylamine (5% solution) as base, providing XIXa in 65.2% yield.




IIIa,c XVIIa,c XVIIIa,b

a) R = H, b) R = $COOCH_3$, c) R = COOH



IVa,c XIXa,b

a) R = H, b) R = $COOCH_3$, c) R = COOH

Hydrolysis of IIIc to XVIIc occurred with $k_{obsd}$ = 0.97 $min^{-1}$ ($t_{1/2}$ = 0.71 min, 30°C, 0.1N NaOH). The preparative scale conversion was performed with 4% ammonia solution, and the product was isolated as the N-trifluoroacetyl methyl ester (XVIIIb) in 42.1% yield. In the conversion of IVc to XIXb, several byproducts are formed, and purification has not been achieved.

In monocyclic imidazoles, the pentafluoroethyl group is 40~80 times as reactive to hydrolysis as the trifluoromethyl group. Such enhanced reactivity does not appear to extend to benzimidazoles, since neither 2-(trifluoromethyl)benzimidazole [12] nor 2-(pentafluoroethyl)benzimidazole is hydrolyzed by strong base at 30°C. We have previously offered an explanation for this lack of reactivity [4].

## EXPERIMENTAL

### Materials

α-N-(Trifluoroacetyl)histamine was prepared by trifluoroacetylation of histamine dihydrochloride [3]. Since the crude product contained acids, it was neutralized with triethylamine and was purified by elution from a column of silica gel with ethyl acetate. The slightly yellow crystals obtained were used without further purification.

α-N-(Trifluoroacetyl)-L-histidine methyl ester was prepared from L-histidine methyl ester hydrochloride [3] and was purified similarly. Compound V. mp 120~121°C [2],XII, mp 163~164°C [2], and 2-(pentafluoroethyl)benzimidazole, mp 213~214°C

[13] were prepared according to literature methods. Pentafluoroethyl iodide was obtained from PCR.

Analytical methods and instrumentation

UV spectra were recorded on a Hitachi Spectrophotometer Model 320. pH Values were measured on an Orion Research Model 801A digital pH meter. Other analytical methods and instrumentation have been described previously [5]. $^{1}H$ NMR spectra were recorded with TMS (for acetone-$d_6$) and TSP (for $D_2O$) as internal references; $^{19}F$ NMR spectra are reported with positive $\delta$ values downfield from the external reference, trifluoroacetic acid. The homogeneity and identity of each product were verified by NMR, MS, GC, and TLC.

Photopentafluoroethylation of α-N-(trifluoroacetyl)histamine

Pentafluoroethyl iodide was bubbled into a solution of α-N-(trifluoroacetyl)histamine (20.72g, 100 mmol) and triethylamine (5.06g, 50 mmol) in 50 ml of methanol until the weight had increased by 12.30g (50 mmol of pentafluoroethyl iodide). The solution was irradiated for 3 days at ambient temperature, using a 60W low pressure mercury lamp (Eikosya EL-J-60) with Vycor filter. The reaction mixture was analyzed directly by GC-MS (at 200°C, 3 mm x 3 m glass column packed with 1.5% OV-17 Chromosorb WAW DMCS 80~100 mesh); two products were found at retention times 1.8 min and 2.1 min in the ratio 41 : 59, together with unreacted α-N-(trifluoroacetyl)histamine at 3.7 min. The reaction mixture was evaporated to dryness under reduced pressure, the residual material was applied to a column of silica gel (360 ml), and the column was eluted with ethyl acetate - methanol 9 : 1. The three early fractions (100 ml each) were combined and which was rechromatographed on another silica gel column (180 ml), eluted with (a) ether - ethyl acetate 1 : 1, (b) ethyl acetate, and (c) ethyl acetate - methanol 9 : 1. There was obtained 3.06g (18.8% yield) of 2-(pentafluoroethyl)-αN-(trifluoroacetyl)histamine (nc) (Ia) as colorless needles recrystallized from ether - ethyl acetate: mp 141 ~ 142°C: Analysis; Found C, 33.34%; H, 2.21%; N, 12.98%: $C_9H_7F_8N_3O$ requires C, 33.24%; H, 2.17%; N, 12.92%: MS m/e 325 $M^{+}$,

212 $M^+ - CF_3CONH_2$, 200, 199, 152, 143, 126, 69: $^1H$ NMR (2% in acetone-$d_6$) δ 2.87 (t, 2, J = 7Hz, $CH_2$-β), 3.60 (t-d, 2, J = 7Hz and 6Hz, $CH_2$-α), 7.22 (s, 1, H-4), 8.52 (broad t, 1, J = 6Hz, NH-α); $^{19}F$ NMR δ 1.2 (s, 3, $COCF_3$-α), - 6.7 (t, 3, J = 3Hz, $CF_3$-2), - 35.3 (q, 2, J = 3Hz, $CF_2$-2) and 4.32g (26.6% yield) of 4-(pentafluoroethyl)-α-N-(trifluoroacetyl)histamine (nc) (IIa) as colorless grains recrystallized from ethyl acetate: mp 180 ~ 182°C: Analysis; Found C, 33.32%; H, 2.24%; N, 12.99%: $C_9H_7F_8N_3O$ requires C, 33.24%; H, 2.17%; N, 12.92%: MS m/e 325 $M^+$, 212 $M^+ - CF_3CONH_2$, 200, 199, 143, 131, 126, 69: $^1H$ NMR (5% in acetone-$d_6$) δ 3.09 (t, 2, J = 7Hz, $CH_2$-β), 3.63 (t-d, 2, J = 7Hz and 7Hz, $CH_2$-α), 7.73 (s, 1, H-2), 8.71 (broad t, 1, J = 7Hz, NH-α); $^{19}F$ NMR δ 1.3 (s, 3, $COCF_3$-α), - 7.1 (t, 3, J = 3Hz, $CF_3$-4), - 33.3 (q, 2, J = 3Hz, $CF_2$-4).

Photopentafluoroethylation of α-N-(trifluoroacetyl)-L-histidine methyl ester

To a solution of α-N-(trifluoroacetyl)-L-histidine methyl ester (26.52g, 100 mmol) and triethylamine (5.06g, 50 mmol) in methanol (30 ml), was added pentafluoroethyl iodide (12.30g, 50 mmol). The solution was irradiated (60W lamp) for 7 days at ambient temperature. The crude reaction mixture was directly analyzed by GC-MS; two products were found at retention times 2.6 min and 2.9 min in the ratio 45 : 55, together with unreacted α-N-(trifluoroacetyl)histidine methyl ester at 7.4 min. The reaction mixture was evaporated to dryness and the residualmaterial was fractionated on silica gel columns (ethyl acetate and ethyl acetate - methanol 9 : 1 as eluent). There was obtained 3.62g (18.9% yield) of 2-(pentafluoroethyl)-α-N-(trifluoroacetyl)histidine methyl ester (nc) (Ib) as colorless fine needles recrystallized from ether - ethyl acetate: mp 102 ~ 103°C: Analysis; Found C, 34.30%; H, 2.41%; N, 10.93%; $C_{11}H_9F_8N_3O_3$ requires C, 34.48%; H, 2.37%; N, 10.97%: MS m/e 383 $M^+$, 324 $M^+ - COOCH_3$, 270, 199, 69: $^1H$ NMR (2% in acetone-$d_6$) δ 3.21 (d, 2, J = 6Hz, $CH_2$-β), 3.67 (s, 3, $OCH_3$), 4.82 (t-d, 1, J = 6Hz and 6Hz, CH-α), 7.30 (s, 1, H-4), 8.78 (broad d, 1, J = 6Hz, NH-α); $^{19}F$ NMR δ 1.1 (s, 3, $COCF_3$-α), - 6.7 (t, 3, J = 3Hz, $CF_3$-2), - 35.4 (q, 2, J = 3Hz, $CF_2$-2) and 5.15g, (26.9% yield)

of 4-(pentafluoroethyl)-α-N-(trifluoroacetyl)histidine methyl ester (nc) (IIb) as colorless grains recrystallized from ethyl acetate: mp 125∼129°C: Analysis; Found C, 34.36%; H, 2.34%; N, 11.06%: $C_{11}H_9F_8N_3O_3$ requires C, 34.48%; H, 2.37%; N, 10.97%: MS m/e 383 $M^+$, 324 $M^+$ - $COOCH_3$, 270, 199, 69: $^1H$ NMR (3% in acetone-$d_6$) δ 3.39 (d, 2, J = 8Hz, $CH_2$-β), 3.68 (s, 3, $OCH_3$-α), 4.84 (t-d, 1, J = 8Hz and 6Hz, CH-α), 7.71 (s, 1, H-2), 8.84 (broad d, 1, J = 6Hz, NH-α); $^{19}F$ NMR δ 1.3 (s, 3, $COCF_3$-α), - 6.9 (t, 3, J = 3Hz, $CF_3$-4), - 33.0 (q, 2, J = 3Hz, $CF_3$-4).

Acid hydrolysis of Ia

A suspension of Ia (325 mg, 1.0 mmol) in 3N hydrochloric acid (30 ml) was maintained at 70°C for 3 hours. The solution was evaporated to dryness and the residual material was crystallized from ethanol. There was obtained 289 mg (95.7% yield) of 2-(pentafluoroethyl)histamine dihydrochloride (nc) (IIIa) as colorless needles: mp 211∼212°C (dec): Analysis; Found C, 27.67%; H, 3.23%; N, 13.98%; $C_7H_{10}Cl_2F_5N_3$ requires C. 27.83%; H, 3.34%; N, 13.91%: MS m/e 230 $M^+$(free histamine) + H, 200 $M^+$ + H - $CH_2NH_2$, 131 $M^+$+ H - $CH_2NH_2$ - $CF_3$,130: $^1H$ NMR (5% in $D_2O$) δ 3.0∼3.5 (m, 4, $CH_2$-$CH_2$), 7.71 (s, 1, H-4); $^{19}F$ NMR δ - 5.6 (t, 3, J = 3Hz, $CF_3$-2), - 37.0 (q, 2, J = 3Hz, $CF_2$-2).

The acid hydrolyses of IIa, Ib, and IIb were performed by essentially the same procedure, and the following compounds were obtained:

4-(Pentafluoroethyl)histamine dihydrochloride (nc) (IVa) : yield 94.0%: colorless needles recrystallized from ethanol: mp 219∼220°C: Analysis; Found C, 27.65%; H, 3.37%; N, 14.14%: $C_7H_{10}Cl_2F_5N_3$ requires C, 27.83%; H, 3.34%; N, 13.91%: MS m/e 230 $M^+$ (free histamine) + H, 200 $M^+$ + H - $CH_2NH_2$, 181, 131 $M^+$ + H - $CH_2NH_2$- $CF_3$, 130: $^1H$ NMR (5% in $D_2O$) δ 3.31 (broad s, 4, $CH_2$-$CH_2$), 8.73 (s, 1, H-2); $^{19}F$ NMR δ - 6.5 (t, 3, J = 3Hz, $CF_3$-4), - 34.7 (q, 2, J = 3Hz, $CF_2$-4).

2-(Pentafluoroethyl)histidine hydrochloride (nc) (IIIc): Crystallization of the salt could not be effected, and an amorphous powder was obtained in almost quantitative yield. MS m/e 229 $M^+$(free histidine) + H - $CO_2H$,200 $M^+$+ H - $NH_2CHCO_2H$, 131 $M^+$ + H - $NH_2CHCO_2H$ - $CF_3$ : $^1H$ NMR (5% in $D_2O$) δ 3.69 (d, 2,J = 7Hz,

$CH_2$-β), 4.66 (t, 1, J = 7Hz, CH-α), 7.92 (s, 1, H-4); $^{19}$F NMR δ - 5.1 (t, 3, J = 3Hz, $CF_3$-2), - 36.9 (q, 2, J = 3Hz, $CF_2$-2).

4-(Pentafluoroethyl)histidine hydrochloride (nc) (IVc): Crystallization of the salt could not be effected, and an amorphous powder was obtained in almost quantitative yield. MS m/e 229 $M^+$(free histidine) + H - $CO_2H$, 200 $M^+$+ H - $NH_2CHCO_2H$, 131 $M^+$ + H - $NH_2CHCO_2H$ - $CF_3$: $^1$H NMR (5% in $D_2O$) δ 3.68 (d, 2, J = 8Hz, $CH_2$-β), 4.57 (t, 1, J = 8Hz, CH-α), 9.12 (s, 1, H-2); $^{19}$F NMR δ - 5.9 (t, 3, J = 3Hz, $CF_3$-4), - 34.4 (q, 2, J = 3Hz, $CF_2$-4).

Alkaline hydrolysis of V in 0.2N NaOH

A solution of V (930 mg, 5.0 mmol) in 0.2N sodium hydroxide solution (100 ml) was left for 2 hours at ambient temperature and the solution was neutralized to pH 6 with 3N hydrochloric acid. The solution was evaporated to dryness in vacuo and the solid residue was extracted with three 30 ml portions of methanol. The combined extracts were evaporated to dryness and the residual material (colored tar) was purified by passage through a column of silica gel (100 ml) eluted with ethyl acetate. Evaporation of the combined eluates gave a colorless powder, which was recrystallized from ethyl acetate - ether to give 380 mg (46.3% yield) of 2-(trifluoroacetyl)imidazole (nc) (VII): as colorless needles: mp 188 ~ 189°C: Analysis; Found C, 36.43%; H, 2.02%; N, 17.11%; $C_5H_3F_3N_2O$ requires C, 36.60%; H, 1.84%; N, 17.07%: IR (KBr) 1710 $cm^{-1}$ (C=O): MS m/e 164 $M^+$, 95 $M^+$ - $CF_3$, 69, 68, 67: $^1$H NMR (5% in acetone-$d_6$) δ 7.52 (s, H-4,5); $^{19}$F NMR δ 4.48 (s, $CF_3CO$).

Alkaline hydrolysis of V in 4% aqueous ammonia

A suspension of V (930 mg, 5.0 mmol) in 4% aqueous ammonia (50 ml) was stirred at ambient temperature for 2 h: solution was complete in 0.5h. The solution was evaporated to dryness under reduced pressure, and the residual material was applied to a column of silica gel (100 ml). The column was eluted with ethyl acetate and the combined eluates were evaporated. Recrystallization of the residue from ethyl acetate - ether gave 790 mg (96.3% yield) of VII as colorless needles (mp 188 ~ 189°C).

Alkaline methanolysis of V

Compound V (372 mg, 2.0 mmol) was dissolved in a solution of potassium hydroxide (1.12g, 20 mmol) in methanol (10 ml), and the mixture was left at ambient temperature for 24 hours. The solution was neutralized by addition of dry-ice (5g) in small portions, and was evaporated to dryness. The residual material was extracted three times with ethyl acetate (30 ml each). The combined extracts were evaporated to give a colorless powder which was recrystallized from ethyl acetate. There was obtained 395 mg (94.0% yield) of 2-(2',2',2'-trifluoro-1',1'-dimethoxyethyl)-imidazole (nc) (VII) as colorless needles: mp 190 ~ 192°C: Analysis; Found C, 40.01%; H, 4.53%; N, 13.32%; $C_7H_9F_3N_2O_2$ requires C, 40.01%; H, 4.32%; N, 13.33%: MS m/e 210 $M^+$, 180, 179 $M^+ - CH_3O$, 165, 141 $M^+ - CF_3$, 109, 95: $^1H$ NMR (3% in acetone-$d_6$) $\delta$ 3.39 (q, 6, J = 1Hz, $CH_3O$), 7.16 (s, 2, H-4,5); $^{19}F$ NMR $\delta$ 0.03 (m, J = 1Hz, $CF_3$).

Alkaline hydrolysis of XII in 4% aqueous ammonia

Compound XII (930 mg, 5.0 mmol) was hydrolyzed similarly to the method used for V, and 4-(trifluoroacetyl)imidazole (XIII, 810 mg, 98.7% yield) was obtained as colorless needles: mp 175 ~ 176°C (lit. 175 ~ 177°C [6]).

Alkaline methanolysis of XII

By use of a procedure similar to that used for V, XII (372 mg, 2.0 mmol) gave 414 mg (98.5% yield) of 4-(2',2',2'-trifluoro-1',1'-dimethoxyethyl)imidazole (nc) (XVI) as colorless prisms recrystallized from ethyl acetate: mp 180 ~ 181°C: Analysis; Found C, 39.95%; H, 4.62%; N, 13.17%; $C_7H_9F_3N_2O_2$ requires C, 40.01%; H, 4.32%; N, 13.33%: MS m/e 210 $M^+$, 179 $M^+ - CH_3O$, 141 $M^+ - CF_3$, 109, 95: $^1H$ NMR (3% in acetone-$d_6$) $\delta$ 3.34 (q, 6, J = 1Hz, $CH_3O$), 7.27 (d, 1, J = 1Hz, H-5), 7.72 (d, 1, J = 1Hz, H-2); $^{19}F$ NMR $\delta$ 0.02 (m, J = 1Hz, $CF_3$).

Alkaline hydrolysis of IIIa

A solution of IIIa (604 mg, 2.0 mmol) in 4% aqueous ammonia (50 ml) was left for 2 hours at ambient temperature. The solution was evaporated to dryness, the residual material was

added to trifluoroacetic anhydride (20 ml), and the mixture was heated at reflux for 1 hour. After recovery of excess trifluoroacetic anhydride, the residue was dissolved in methanol (100 ml), and heated at reflux for 0.5h. The solution was evaporated and the residual material was purified by passage through a silica gel column (100 ml, eluted with ether - dichloromethane 1 : 1). There was obtained 460 mg (75.9% yield) of 2,α-N-bis-(trifluoroacetyl)histamine (nc) (XVIIIa) as colorless needles recrystallized from ether - dichloromethane: mp 151∼153°C: Analysis; Found C, 35.71%; H, 2.48%; N, 14.75%; $C_9H_7F_6N_3O_2$ requires C, 35.66%; H, 2.33%; N, 13.86%: MS m/e 303 $M^+$, 234 $M^+ - CF_3$, 206 $M^+ - CF_3CO$, 190 $M^+ - NH_2COCF_3$, 178, 177 $M^+ - CH_2NHCOCF_3$, 126, 121, 108, 107: $^1H$ NMR (5% in acetone-$d_6$) δ 3.05 (t-d, 2, J = 7Hz and 7Hz, $CH_2$-α), 3.64 (t, 2, J = 7Hz, $CH_2$-β), 7.41 (s, 1, H-4), 8.8 (broad d, 1, J = 7Hz, NH-α); $^{19}F$ NMR δ 1.92 (s, 3, $CF_3CO$-α), 4.64 (s, 3, $CF_3CO$-2).

Alkaline hydrolysis of IVa

A solution of IVa (906 mg, 3.0 mmol) in 5% aqueous triethylamine (40 ml) was left at ambient temperature for 1 hour. The solution was extracted with six 50 ml portions of ethyl acetate. The combined extracts were dried over sodium sulfate and were evaporated to dryness. The residual material was purified by passage through a column of silica gel (100 ml, eluted with ether - ethyl acetate 1 :1) to give 370 mg (65.2% yield) of 4-(trifluoromethyl)-6,7-dihydro-1H-imidazo[4,5-c]-pyridine (nc) (XIXa) as colorless needles recrystallized from ethyl acetate: mp 189∼191°C: Analysis; Found C, 44.43%; H, 3.22%; N, 22.44%; $C_7H_6N_3F_3$ requires C, 44.45%; H, 3.20%; N, 22.22%: MS m/e 189 $M^+$, 188 $M^+ - H$, 168 $M^+ - H_2F$, 161: $^1H$ NMR (3% in acetone-$d_6$) δ 2.89 (t, 2, J = 9Hz, $CH_2$-7), 3.98 (t-q, 2, J = 9Hz and 2Hz, $CH_2$-6), 7.72 (s, 1, H-2); $^{19}F$ NMR δ 7.0 (t, J = 2Hz, $CF_3$-4).

Alkaline hydrolysis of IIIc

A solution of IIIc (1.55 g, 5.0 mmol) in 4% aqueous ammonia (100 ml) was left at ambient temperature for 2 hours, and was evaporated to dryness. The residual material was suspended in

methanol (200 ml) and dry hydrogen chloride was bubbled into the suspension until saturation. The reaction mixture was heated at reflux for 1 hour, and was evaporated to dryness. The residual material was added to trifluoroacetic anhydride (30 ml) and was heated at reflux for 2 hours. After recovery of excess trifluoroacetic anhydride by distillation, the residue was dissolved in methanol (100 ml) and was refluxed for 1 hour. The solution was evaporated to dryness and the residual material was purified by passage through a silica gel column (100 ml, eluted with ether - dichloromethane 1 : 1). There was obtained 760 mg (42.1% yield) of 2,α-N-bis(trifluoro-acetyl)-L-histidine methyl ester (nc)(XVIIIb) as a colored gum: MS m/e 361 $M^+$, 302 $M^+$ - $COOCH_3$, 248 $M^+$ - $NH_2COCF_3$, 232, 217, 205, 177, 107, 106, 69: $^1H$ NMR (5% in acetone-$d_6$) δ 3.31 (d, 2, J = 6Hz, $CH_2$-β), 3.63 (s, 3, $CH_3O$), 4.99 (t-d, 1, J = 6Hz and 5Hz,CH-α), 7.44 (s, 1, H-4); $^{19}F$ NMR δ 1.8 (s, 3, $CF_3CO$-α), 4.6 (s, 3, $CF_3CO$-2).

Alkaline hydrolysis of IVc

A solution of IVc (619 mg, 2.0 mmol) in 5% aqueous triethylamine (30 ml) was left at ambient temperature for 2 hours. The solution was evaporated to dryness, the residual material was suspended in methanol (100 ml) and dry hydrogen chloride was added until saturation. The reaction mixture was refluxed for 1h, was evaporated to dryness and the residue was dissolved in water (3 ml). The solution was neutralized with aqueous ammonia, and was extracted with three portions of ethyl acetate (30 ml each). The combined extracts were evaporated to dryness and the residual material was purified by passage through a column of silica gel (100 ml, eluted with ethyl acetate). There was obtained a mixture of three products which have not yet been separated.

Kinetics

Rates of consumption of V (230 nm), IIIa (240 nm), and IIIc (230 nm), and formation of XIII (297 nm) and XIXa (312 nm) were followed by UV spectroscopy at the wavelengths shown in each parentheses. The rate constants ( $k_{obsd}$ ) were calculated on

the basis of 10 or more data points and were consistent with first-order kinetics (correlation coefficients $> 0.999$).

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