Journal of Fluorine Chemistry, 30 (1986) 415–428

Received: June 25, 1985; accepted: September 14, 1985

THERMAL CONDENSATION OF IMIDAZOLE WITH TRIFLUOROACETALDEHYDE

SHOZO FUJII, YASUO MAKI, HIROSHI KIMOTO*

Government Industrial Research Institute, Nagoya;
Hirate-cho, Kita-ku, Nagoya 462 (Japan)

LOUIS A. COHEN

Laboratory of Chemistry, National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases, National Institute of Health; Bethesda, Maryland 20205 (U.S.A.)

SUMMARY

The title condensation occurred readily at reflux (100°C) with the methyl hemiacetal of trifluoroacetaldehyde and provided 37.3% of 4(5)-(1'-hydroxy-2',2',2'-trifluoroethyl)-imidazole as the major product, together with 8.8% of 2-(1'-hydroxy-2',2',2'-trifluoroethyl)imidazole, 7.2% of 2,4(5)-bis-(1'-hydroxy-2',2',2'-trifluoroethyl)imidazole and 0.4% of the 4,5-bis-product. (Trifluoroacetyl)imidazoles were prepared by oxidation of these condensation products. Nitration and bromination of the condensation products gave the corresponding nitro- and bromoimidazoles, respectively.

INTRODUCTION

The thermal condensation of suitably substituted imidazoles with formaldehyde is a well-known route to (hydroxymethyl)-imidazoles[1]. Although such condensations have also been achieved with a few other aliphatic and aromatic aldehydes[2], reaction with fluorine-containing aldehydes has not been reported. We investigated the condensation of imidazole with

0022-1139/86/$3.50

trifluoroacetaldehyde as an extension of our studies on the direct introduction of fluoroalkyl groups into heteroaromatic rings[3].

Imidazoles with strong electronegative substituents are of potential biological significance: e.g., 2-nitroimidazole (azomycin antibiotic): 2-fluorohistidine (antimalarial)[4]; 4-(trifluoromethyl)imidazole-TRH (cardioselective hormone)[5]. We were interested, therefore, in the development of routes to C-(trifluoroacetyl)imidazoles. In contrast to N-acetylation of imidazoles, C-acetylation is difficult by normal electrophilic mechanisms, and only one compound, N-methyl-2-trifluoroacetylimidazole, has been reported[6]. In the present work, direct condensation of imidazole with the methyl hemiacetal of trifluoroacetaldehyde provides secondary alcohol adducts at both the 2- and 4-positions; these products are oxidized to the trifluoroacetyl derivatives. Since nitro- and halo-(trifluoromethyl)imidazoles have been found to have pesticide activity[7], we also describe the nitration and bromination of the initial condensation products.

RESULTS AND DISCUSSION

Since free trifluoroacetaldehyde is a gas, its use in the condensation would require sealed tubes or autoclaves; however, trifluoroacetaldehyde methyl hemiacetal (TFAM) or ethyl hemiacetal (TFAE) provide the desired compounds by simple reflux. The products (Ia ~ IVa) were separated without difficulty by column chromatography (silica gel), and were characterized by elemental analyses, IR, mass and NMR spectra. Isolated yields and NMR data are given in Table. The condensation occurs preferentially at C-4 (or 5) of the imidazole ring. The two isomers of the monosubstituted product (Ia and IIa) are readily differentiated on the basis of their ^{1}H NMR spectra: the ring protons of the 4-isomer (Ia) show two well-separated singlets, whereas the ring protons at C-4 and C-5 of the 2-isomer (IIa) show only the one singlet expected for the tautomerically equivalent forms.

TABLE

Yields and NMR data for the products obtained by thermal condensation of imidazole with TFAM

Product	Yield (%)	^{1}H NMR (δ)[a]				^{19}F NMR (δ)[b]	
		H-2	H-4(5)	CH-2	CH-4(5)	CF_3-2	CF_3-4(5)
Ia	37.3	7.72	7.25		5.19[c]		- 0.79
IIa	8.8		7.03	5.24[c]		- 0.51	
IIIa	7.2		7.25	5.30[c]	5.12[c]	- 0.43	- 0.78
IVa	0.4	7.78			5.53[c]		- 0.73

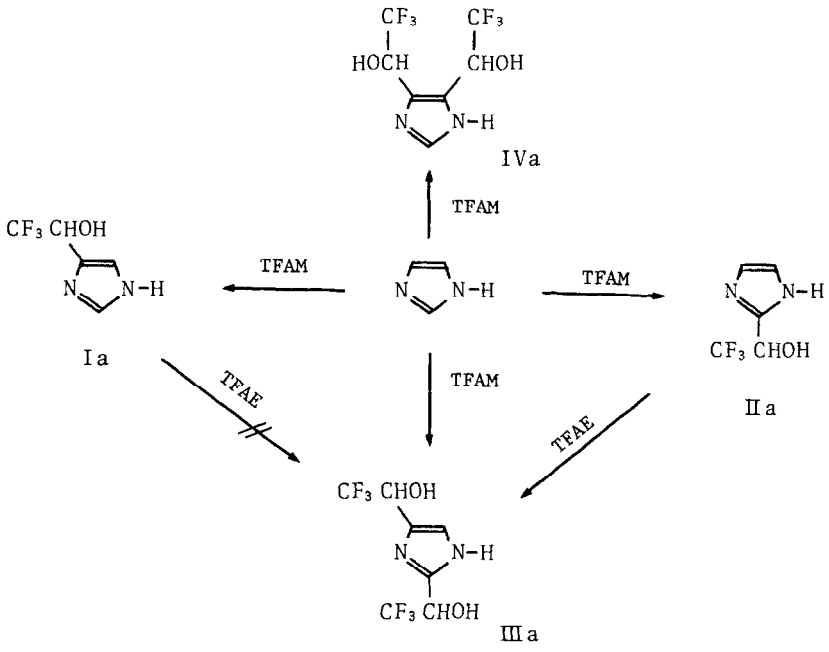
[a] ^{1}H NMR signals are singlets unless otherwise specified.

[b] All doublets, J = 7Hz. c) Quartets, J = 7Hz.

Despite the use of an excess of imidazole, a significant amount of the 2,4-bis-adduct (IIIa) and a small amount of the 4,5-bis-adduct (IVa) were also obtained. The bis isomers were identified in the basis of their ^{1}H and ^{19}F NMR spectra. The signal for the ring proton of IVa appears at lower field than that of IIIa. The imidazole-ring proton at C-2 usually appears at lower field than that at C-4 (or 5). The CH and CF_3 groups of the side chains of IIIa show two quartets and two doublets, respectively. The signals of the tautomerically equivalent side chains of IVa appear as one quartet and one doublet. The bis-products (IIIa and IVa) have two asymmetric carbons in each molecule and are obtained as mixtures of diastereoisomers; however, NMR signals for the diastereoisomers failed to resolve nor could the compounds be separated by chromatography. Compound IIIa crystallized from ether solution after several days; IVa was purified by chromatography but failed to crystallize.

The thermal condensation of IIa with excess TFAE gave IIIa in 46.7% yield and 30% of IIa was recovered. In contrast, Ia resisted further condensation with TFAE; most of Ia was recovered while small amounts of IIIa and IVa were detected by GLC and ^{19}F NMR. Apparently, the major bis-product (IIIa) is formed mainly from IIa by additional condensation with TFAM; however, the initial condensation at C-4 (or 5) is still

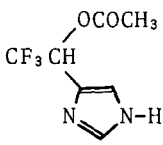
favored over that at C-2 since the yield of Ia is greater than the total yield of IIa and IIIa. This difference in the reactivities of Ia and IIa is puzzling and is being examined in greater detail. Studies on the thermal condensation of substituted imidazoles with TFAE are in progress, in order to evaluate directing and activating/deactivating effects of substituents.



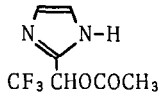
Neither acetaldehyde nor trichloroacetaldehyde parallel the results with trifluoroacetaldehyde. 4-Methylimidazole does condense with chloral at C-5 [8], while the thermal reaction between imidazole and chloral produces a black tar[9]. We found no reaction between imidazole and trichloroacetaldehyde ethyl hemiacetal at reflux. N-alkylimidazoles give no condensation products with aqueous or anhydrous acetaldehyde, or with chloral hydrate[2]. Current mechanistic studies may reveal the basis for these differences in reactivity.

All of the secondary alcohols (Ia ~ IVa) underwent facile O-acetylation with acetic anhydride to provide the respective

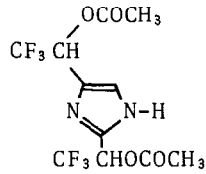
mono- and diacetates (Ib ~ IVb). O-acetylation facilitated chromatographic separation of products but the diastereoisomers of IIIb and IVb still could not be resolved; on the other hand, two ^{19}F NMR signals were observed for the CF_3 group at C-2 in IIIb.



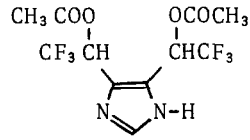
Ib



IIb

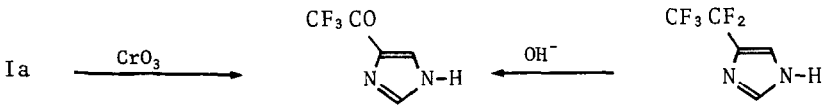


IIIb

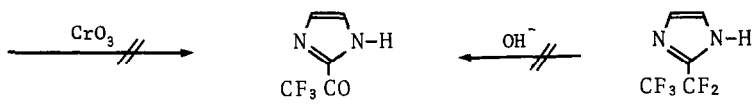


IVb

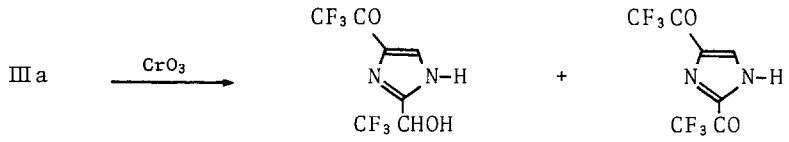
Oxidation of Ia with chromium trioxide in aqueous acid afforded 4(5)-(trifluoroacetyl)imidazole (V) in 59.1% yield. Surprisingly, IIa resisted oxidation and most of the material was recovered under the same reaction conditions. Extended heating with chromium trioxide resulted in loss of IIa and in isolation of a trace of 2-(trifluoroacetyl)imidazole (VI). Oxidation of IIIa gave the 4(5)-trifluoroacetyl derivative (VII) in 57.2% yield, together with 11.5% of the bis-trifluoroacetyl product (VIII). Thus, a practical route has been developed for 4(5)-(trifluoroacetyl)imidazoles but not for the 2-isomers. As an alternative, we examined the alkaline hydrolysis of (pentafluoroethyl)imidazoles[3b, 10]; while V was obtained in 78.9% yield, the yield of VI was negligible.



V



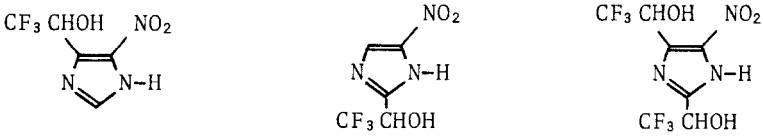
VI



VII VIII

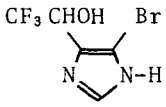
In the NMR spectrum of V, the signals of imidazole ring protons appear at δ 8.14 ppm for H-2 and δ 8.30 ppm for H-4 (or 5), which are assigned on the basis of proton-fluorine long range coupling (^5J = 1Hz). The assignment violates the rule that H-2 appears at lower field than H-4 (or 5). The large paramagnetic shift of H-4 (or 5) is probably due to anisotropic effect of the carbonyl group and electron withdrawing effect of trifluoroacetyl group.

Treatment of alcohols (Ia ~ IIIa) with a mixture of fuming nitric-sulfuric acids provided the corresponding 4(5)-nitro derivatives (IX ~ XI). While 4(5)-(hydroxymethyl)imidazoles are known to undergo oxidation with concentrated nitric acid [11], we found no oxidation to occur in the course of nitration Since it is well-established that nitration will always occur at a free 4 (or 5) position, successful nitration of IIIa supports its assignment as the 2,4-bis product.

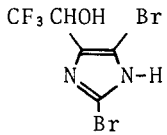


IX X XI

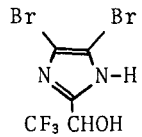
The bromination of Ia with excess bromine in acetic acid afforded XII (42.4%) and XIII (43.8%). Consistent with general experience in the halogenation of imidazoles, no mono 2-bromo derivative was detected. The greater ease of bromination at C-4 (or 5) [12] is also revealed by the fact that, under the same reaction conditions, IIa gave only XIV in 92.0% yield.



XII



XIII



XIV

EXPERIMENTAL

Materials

TFAM was obtained from PCR Inc. and TFAE from Central Glass Co., Ltd. The hemiacetals were distilled prior to use and showed less than 5% alcohols in the azeotropic mixtures (NMR).

Analytical methods and instrumentation

Melting points are uncorrected. ^{1}H NMR (90 MHz) spectra were recorded on a Hitachi R22 spectrometer with tetramethylsilane as internal reference. ^{19}F NMR (56.45 MHz) spectra were recorded on a Hitachi R20b spectrometer; positive δ values are downfield from the external reference, trifluoroacetic acid. All NMR spectra were measured in acetone-d_6 solution. IR spectral data were obtained from a Hitachi 285H grating spectrometer and mass spectral data from a Hitachi M-80 instrument (electron-impact ionization at 70eV). GC-MS data were recorded on a Shimadzu instrument (Model 7000); separation were performed at 150～180°C with helium carrier gas, using a glass column (3mm x 300cm) packed with 1.5% OV-17 Chromosorb WAW DMCS (80～100mesh). Elemental analyses were performed by the Takarazuka Research Center of Sumitomo Chemical Co., Ltd. The homogeneity and identity of each product were verified by NMR, IR, MS, GLC and TLC.

Thermal condensation of imidazole with TFAM

Imidazole (84.5g, 1.24mol) and TFAM (88.4g, 0.68mol) were placed in a 200ml flask and the mixture was heated at reflux under argon for 2 hours (oil bath, 150°C). With a rise in temperature, the mixture became homogeneous and the generated methanol refluxed. The reaction mixture was evaporated under

reduced pressure to remove methanol, the residual material was applied to a column (5 x 50cm) of silica gel (1000ml), and the column was eluted with (a) ether, (b) ether-ethyl acetate, 1:1, (c) ethyl acetate, and (d) 5% methanol in ethyl acetate. The impure fractions were rechromatographed on smaller silica gel column (200ml each). There were obtained 42.1g (37.3%) of 4(5)-(1'-hydroxy-2',2',2'-trifluoroethyl)imidazole (Ia) as colorless needles from ethyl acetate: mp. 133-5°C, Analysis: Found: C, 36.08; H, 2.91; N, 16.82%: $C_5H_5F_3N_2O$ requires C, 36.16; H, 3.03; N, 16.87%: MS m/e 166 (M^+), 97 (M^+- CF_3), 69; 9.9g (8.8%) of 2-(1'-hydroxy-2',2',2'-trifluoroethyl)imidazole (IIa) as colorless plates recrystallized from ethyl acetate: mp. 185-186°C (decomp.), Analysis: Found: C, 36.03; H, 2.80; N 17.02%: $C_5H_5F_3N_2O$ requires C, 36.16; H, 3.03; N, 16.87%: MS m/e 166 (M^+), 97 (M^+- CF_3), 69; 6.5g (7.2%) of 2,4-bis-(1'-hydroxy-2',2',2'-trifluoroethyl)imidazole (IIIa) as colorless clusters from ether: mp. 167-71°C, Analysis: Found: C, 31.88; H, 2.04; N, 10.88%: $C_7H_6F_6N_2O_2$ requires C, 31.83; H, 2.29; N, 10.61%: MS m/e 264 (M^+), 195 (M^+- CF_3), 177 (M^+- CF_3 - H_2O), 157; and 0.4g (0.4%) of 4,5-bis-(1'-hydroxy-2',2',2'-trifluoroethyl)imidazole (IVa) as a slightly yellow gum: MS m/e 264 (M^+), 195 (M^+- CF_3), 177 (M^+- CF_3 - H_2O), 157. The order of elution from the large silica gel column was IIIa, IIa, IVa, Ia, and imidazole.

Thermal condensation of Ia with TFAE

A mixture of Ia (0.83g, 5 mmol) and TFAE (0.79g, 5.5 mmol) was heated at reflux in an oil bath for 2 hours. The reaction mixture was analyzed directly by GLC. A small peak ($<5\%$) of overlapping IIIa and IVa was found, together with a large peak ($>95\%$) for Ia. ^{19}F NMR (acetone) showed two large doublet corresponding to Ia and TFAE, and very small signals for IIIa and IVa.

Thermal condensation of IIa with TFAE

A mixture of IIa (0.50g, 3 mmol) and TFAE (0.50g, 3.5 mmol) was heated at reflux for 3 hours. After removal of ethanol and unchanged TFAE by evaporation, the residual material was resolved on 100ml of silica gel (elution with ether-dichloromethane, 1:1) There was obtained 0.37g (46.7%) of IIIa and 0.15g (30%) of IIa.

Acetylations of Ia ~ IVa

A solution of Ia (1.66g, 10 mmol) in acetic anhydride (20ml) was heated at reflux for 1 hour. The reaction mixture was evaporated to dryness in vacuo and the residual material was refluxed with methanol (20ml) for 0.5 hour. Following evaporation of solvent, the residual tar was passed through 100ml of silica gel (elution with ether and ethyl acetate) to give 4-(1'-acetoxy-2',2',2'-trifluoroethyl)imidazole (Ib, 1.59g, 81.2%) as colorless needles from ethyl acetate: mp. 134-5°C, Analysis: Found: C, 40.31; H, 3.28; N, 13.55%: $C_7H_7F_3N_2O_2$ requires C, 40.39; H, 3.39; N, 13.46%: IR (KBr) 1760 cm^{-1} (c=o): MS m/e 208 (M^+), 166 (M^+- CH_2CO), 165 (M^+- CH_3CO), 97 (M^+- CF_3 - CH_2CO): ^1H NMR δ 7.68 (s, 1, H-2), 7.35 (s, 1, H-5 or 4), 6.34 (q, 1, J = 7Hz, CH-4 or 5), 2.11 (s, 3, CH_3CO): ^{19}F NMR δ 1.60 (d, J = 7Hz, CF_3).

A similar procedure was used to obtain the following products:

2-(1'-Acetoxy-2',2',2'-trifluoroethyl)imidazole (IIb) : 74.9% yield: fine needles from acetone-ether: mp. 160-1°C: Analysis: Found: C, 40.37; H, 3.29; N, 13.40%: $C_7H_7F_3N_2O_2$ requires C, 40.39; H, 3.39; N, 13.46%: IR (KBr) 1765 cm^{-1} (c=o): MS m/e 208 (M^+), 166 (M^+- CH_2CO), 165 (M^+- CH_3CO), 129 (M^+- HF - CH_3CO_2), 97 (M^+- CF_3 - CH_2CO): ^1H NMR δ 7.15 (s, 2, H-4 and 5), 6.45 (q, 1, J = 7Hz, CH-2), 2.16 (s, 3, CH_3CO): ^{19}F NMR δ 1.95 (d, J = 7Hz, CF_3).

2,4(5)-Bis-(1'-acetoxy-2',2',2'-trifluoroethyl)imidazole (IIIb): 85.0% yield: pale yellow viscous oil: IR (neat film) 1762 cm^{-1} (c=o): MS m/e 348 (M^+), 305 (M^+- CH_3CO), 247, 246, 245, 295: ^1H NMR δ 7.28 (s, 1, H-5 or 4), 7.03 (q, 1, J = 7Hz, CH-2), 6.28 (q, 1, J = 7Hz, CH-4 or 5), 2.13 (s, 3, 2-CH_3CO), 2.10(s, 3, CH_3CO-4 or 5): ^{19}F NMR δ 3.72 and 3.76 (equal intensity of two d, J = 7Hz each, 2-CF_3 diastereoisomers), 1.82 (d, J = 7Hz, CF_3 4 or 5).

4,5-Bis-(1'-acetoxy-2',2',2'-trifluoroethyl)imidazole (IVb): colorless clusters from acetone: mp. 194-8°C: Analysis: Found: C, 37.85; H,2.81; N, 7.98%: $C_{11}H_{10}F_6N_2O_4$ requires C, 37.94; H 2.89; N, 8.05%: IR (KBr) 1765 cm^{-1} (c=o): MS m/e 348 (M^+), 305 (M^+- CH_3CO), 263, 247, 246, 245, 210, 195, 192, 177: ^1H NMR δ 7.80 (s, 1, H-2), 6.55 (q, 2, J = 7Hz, CH-4 and 5), 2.15 (s, 6,

CH_3CO-4 and 5): ^{19}F NMR δ 1.47 (d, J = 7Hz, CF_3-4 and 5). Acetate IVb was obtained from the acetylation of a mixture of Ia and IVa. The mixture (2.3g) was treated with acetic anhydride and the products were separated on 100ml of silica gel with ether-ethyl acetate as eluant; IVb (0.69g) was eluted with ether and Ib (1.9g) was eluted with ether-ethyl acetate (1:1).

Oxidation of Ia

To a solution of Ia (1.66g, 10 mmol) in 20% sulfuric acid (20ml) was added small portions of chromium trioxide (total of 2.0g, 20 mmol), and the mixture was heated at reflux for 0.5 hour. The solution was cooled in ice, was neutralized with saturated $NaHCO_3$ and was extracted with 5 x100ml of ethyl acetate. The combined extracts were dried (Na_2SO_4) and evaporated to give colorless crystals. Recrystallization from acetone gave 0,97g (59.1%) of 4(5)-(trifluoroacetyl)imidazole (V) as colorless needles: mp. 175-7°C: Analysis: Found: C, 36.47; H, 1.60; N, 17.13%: $C_5H_3F_3N_2O$ 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), 68, 67: ^1H NMR δ 8.14 (s, 1, H-2), 8.30 (q, 1, J = 1Hz, H-5 or 4): ^{19}F NMR δ 3.35 (d, J = 1Hz, CF_3).

Oxidation of IIa

A solution of IIa (0.83g, 5 mmol) and CrO_3 (1.0g, 10 mmol) in 20% sulfuric acid (10ml) was heated at reflux for 10 hours. The solution was worked up as above to give a colorless gum which was chromatographed on 100ml of silica gel. Elution with ether-ethyl acetate gave 0.05g of crude 2-(trifluoroacetyl)-imidazole (VI) as a colorless amorphous solid: IR (KBr) 1710cm^{-1} (c=o): MS m/e 164 (M^+), 95 (M^+- CF_3), 69, 68, 67: ^1H NMR δ 7.54 (s, H-4 and 5): ^{19}F NMR δ 4.40 (s, CF_3). Further elution of the column gave 0.4g of IIa .

Oxidation of IIIa

A solution of IIIa (1.32g, 5 mmol) and CrO_3 (2.0g, 20 mmol) in 20% sulfuric acid (20ml) was heated at reflux for 5 hours. The solution was worked up as for Ia to give a colorless gum which was chromatographed on 100ml of silica gel. Elution with

ether gave 0.75g (57.2%) of 2-(1'-hydroxy-2',2',2'-trifluoroethyl)-4(5)-(trifluoroacetyl)imidazole (VII) as colorless grains from chloroform-ether: mp. 157-9°C: Analysis: Found: C, 32.04; H, 1.46; N, 10.66%: $C_7H_4F_6N_2O_2$ requires C, 32.08; H, 1.54; N, 10.69%: IR (KBr) 1710 cm^{-1} (c=o): MS m/e 262 (M^+), 193 (M^+- CF_3), 175 (M^+- CF_3 -H_2O), 123, 121: ^1H NMR δ 8.19 (q, 1, J = 1Hz, H-5 or 4), 5.43 (q, 1, J = 7Hz, CH-2): ^{19}F NMR δ - 0.43 (d, 3, J = 7Hz, CF_3-2), 3.29 (d, 3, J = 1Hz, CF_3CO-4 or 5). Further elution gave 0.15g (11.5%) of 2,4(5)-bis-(trifluoroacetyl)-imidazole (VIII) as colorless needles from ether-chloroform: mp. 82-4°C: Analysis: Found: C, 31.73; H, 1.94; N, 10.37%: $C_7H_2F_6N_2O_2$ requires C, 32.33; H, 0.78; N, 10.77%: IR (KBr) 1715 cm^{-1} (c=o): MS m/e 260 (M^+), 191 (M^+- CF_3), 121 (M^+- CF_3 - CHF_3): ^1H NMR δ 8.22 (q, J = 1Hz, H-5 or 4): ^{19}F NMR δ 3.37 (s, 3, CF_3CO-2), 3.36 (d, 3, J = 1Hz, CF_3CO-4 or 5).

Alkaline hydrolysis of (pentafluoroethyl)imidazoles

A solution of 4-(pentafluoroethyl)imidazole[3b] (372mg, 2 mmol) in 50ml of 1N sodium hydroxide was left for 24 hours at ambient temperature and the solution was then neutralized to pH 6 with concentrated hydrochloric acid. The solution was evaporated to dryness in vacuo and the residual material was extracted with 3 x 20ml of ethyl acetate. The combined extracts were passed through a column of 30ml of silica gel, and the column was eluted with an additional 100ml of ethyl acetate. Evaporation of the eluates gave a powder, which was recrystallized from ethyl acetate to give V (259mg, 78.9%) as colorless needles: mp. 174-6°C.

Similar treatment of 2-(pentafluoroethyl)imidazole[3b] gave neither VI nor the unchanged starting material.

Nitrations of Ia~IIIa

To a solution of Ia (1.66g, 10 mmol) in 15ml of concentrated sulfuric acid was added 15ml of fuming nitric acid (d = 1.50) and the mixture was heated at reflux for 8 hours. The solution was cooled and poured into ice-water , was then neutralized with 20% aqueous sodium hydroxide and was extracted with 3 x 100ml of ethyl acetate. The combined extracts were dried (Na_2SO_4) and evaporated. The residual material was recrystal-

lized from ethyl acetate to give 1.26g (59.7%) of 5(4)-nitro-4(5)-(1'-hydroxy-2',2',2'-trifluoroethyl)imidazole (IX) as colorless needles: mp. 223-4°C (decomp.): Analysis: Found: C, 28.33; H, 1.76; N, 20.14%: $C_5H_4F_3N_3O_3$ requires C, 28.45; H, 1.91; N, 19.91%: IR (KBr) 1526 cm^{-1} (NO_2): MS m/e 211 (M^+), 194 (M^+- OH), 142 (M^+- CF_3), 69: ^1H NMR δ 8.18 (s, 1, H-2), 5.42 (q, 1, J = 7Hz, CH-4 or 5): ^{19}F NMR δ - 0.74 (d, J = 7Hz, CF_3).

Similar procedures were used for all nitrations, with variation only in the reaction time. Nitration of IIa for 0.5 hour gave 4(5)-nitro-2-(1'-hydroxy-2',2',2'-trifluoroethyl)-imidazole (X, 44.5% yield) as colorless grains from chloroform: mp. 201-3°C: Analysis: Found: C, 28.44; H, 1.82; N, 19.97%: $C_5H_4F_3N_3O_3$ requires C, 28.45; H, 1.91; N, 19.91%: IR (KBr) 1520 cm^{-1} (NO_2): MS m/e 211 (M^+), 142 (M^+- CF_3), 96 (M^+- CF_3 - NO_2): ^1H NMR δ 7.83 (s, 1, H-4 or 5), 6.12 (q, 1, J = 6Hz, CH-2): ^{19}F NMR δ - 0.38 (d, J = 6Hz, CF_3).

Compound IIIa was heated for 12 hours to give 5(4)-nitro-2,4-bis-(1'-hydroxy-2',2',2'-trifluoroethyl)imidazole (XI, 62.8% yield) as a colorless amorphous solid: Analysis: Found: C, 27.41; H, 2.13; N, 13.24%: $C_7H_5F_6N_3O_4$ requires C, 27.20; H, 1.63; N, 13.59%: IR (KBr) 1525 cm^{-1} (NO_2): MS m/e 309 (M^+), 291 (M^+- H_2O), 240 (M^+- CF_3), 222, 69: ^1H NMR δ 6.12 (q, 1, J = 7Hz, CH-2), 5.41 (q, 1, J = 7Hz, CH-4 or 5): ^{19}F NMR δ 0.05 and - 0.01 (equal intensity of two d, J = 7Hz each, diastereoisomers of CF_3), - 0.23 and - 0.35 (equal intensity of two d, J = 7Hz each, diastereoisomers of 4-CF_3).

Bromination of Ia

To a solution of Ia (0.83g, 5 mmol) in 20ml of acetic acid was added a solution of bromine (3.2g, 20 mmol) in 10ml of chloroform, and the mixture was heated at reflux for 8 hours. The reaction mixture was poured into a solution of $NaHSO_3$ containing ice, the pH was adjusted to 5∼6 with 20% aqueous NaOH and the mixture was extracted with 3 × 50ml of ethyl acetate. The combined extracts were washed with brine and dried (Na_2SO_4). Evaporation of the solvent gave a colorless oil; GLC indicated two products which were separated on 100ml of silica gel with ether as eluant. There were obtained 0.52g (42.4%) of 5(4)-bromo-4(5)-(1'-hydroxy-2',2',2'-trifluoroethyl)-

imidazole (XII) as colorless grains from chloroform: mp. 186-8°C: Analysis: Found: C, 24.46; H, 1.58; N, 11.41%: $C_5H_4BrF_3N_2O$ requires C, 24.51; H, 1.65; N, 11.43%: MS m/e 246 and 244 (M^+), 177 and 175 (M^+- CF_3), 147 (M^+- HBr - OH), 122, 120, 95, 69: ^1H NMR δ 7.79 (s, 1, H-2), 5.35 (q, 1, J = 7Hz, CH-4 or 5): ^{19}F NMR δ - 0.68 (d, J = 7Hz, CF_3), and 0.71g (43.8%) of 2,5(4)-dibromo-4(5)-(1'-hydroxy-2',2',2'-trifluoroethyl)imidazole (XIII) as colorless plates from chloroform: mp. 164-6°C: Analysis: Found: C, 18.41; H, 0.82; N, 8.53%: $C_5H_3Br_2F_3N_2O$ requires C, 18.54; H, 0.93; N, 8.65%: MS m/e 326, 324, and 322 (M^+), 257, 255, and 253 (M^+- CF_3), 227 and 225 (M^+- HBr - OH), 175, 173, 69: ^1H NMR δ 5.28 (q, J = 7Hz, CH-4 or 5): ^{19}F NMR δ - 0.62 (d, J = 7Hz, CF_3).

Bromination of IIa

To a solution of IIa (0.83g, 5 mmol) in 20ml of acetic acid was added a solution of bromine (3.2g, 20 mmol) in 10ml of chloroform and the mixture was heated at reflux for 3 hours. The reaction mixture was worked up as above to give a crystalline residue after ethyl acetate extraction. Recrystallization from chloroform gave 1.49g (92.0%) of 4,5-dibromo-2-(1'-hydroxy-2',2',2'-trifluoroethyl)imidazole (XIV)as colorless needles: mp. 199-204°C: Analysis: Found: C, 18.73; H, 0.78; N, 8.71%: $C_5H_3Br_2F_3N_2O$ requires C, 18.54; H, 0.93; N, 8.65%: MS m/e 326, 324, and 322 (M^+), 257, 255, and 253 (M^+- CF_3), 202, 200, 198, 120, 118, 69: ^1H NMR δ 5.25 (q, J = 7Hz, CH-2): ^{19}F NMR δ - 0.47 (d, J = 7Hz, CF_3).

All the products synthesized in this work are new compounds.

REFERENCES

1 a) K. Hofmann,'Imidazole and Its Derivatives,' Interscience, New York, 1953, p. 99; b) E. S. Schipper and A. R. Day in 'Heterocyclic Compounds', R. C. Elderfield, Ed., Wiley, New York, Vol. 5, 1957, p. 208.

2 A. M. Roe, J. Chem. Soc., (1963) 2195.

3 a) Y. Maki, U. S. Patent, 4,172,946 (1979); Chem. Abstr., 92 (1980) 6416: b) H. Kimoto, S. Fujii and L. A. Cohen, J. Org. Chem., 47 (1982) 2867: c) ibid., 49 (1984) 1060.

4 R. J. Howard, A. T. Andrutis, J. H. Leech, W. Y. Ellis, L. A. Cohen and K. L. Kirk, Biochem. Pharmacol, in press.
5 G. Feuerstein, D. Lozovsky, L. A. Cohen, V. M. Labroo, K. L. Kirk, I. J. Kopin and A. I. Faden, Neuropeptides, 4 (1984) 303.
6 E. Regel and K. H. Buechel, Liebigs Ann. Chem., (1977) 145.
7 a) F. Seng, K. Sasse, G. Beck, L. Eue and R. R. Schmidt, German Patent 2,646,142 (1978); Chem. Abstr., 89 (1978) 24310: b) C. Swithenbank and T. T. Fujimoto, U. S. Patent 4,314,844 (1982); Chem. Abstr., 96 (1982) 181287: c) H. Kimoto, S. Fujii, H. Muramatsu, N. Hirata, H. Ooshio and K. Kamoshita, Japanese Patent Applications 59-232187 and 59-232188.
8 O. Gerngross, Ber., 45 (1912) 509.
9 L. A. Cohen, unpublished work.
10 a) H. Kimoto and L. A. Cohen, J. Org. Chem., 44 (1979) 2902; b) ibid., 45 (1980) 3831.
11 Reference 1a, p. 55.
12 F. L. Pyman, J. Chem. Soc., 97 (1910) 1814.