Purines, Pyrimidines, and Imidazoles. Part 53.[1] Synthesis of Some 5-Halogeno-analogues of Metiamide and Cimetidine

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Ethyl 5-chloroimidazole-4-carboxylate has been prepared by diazotisation of ethyl 5-amino-1-(di-*O*-isopropylidene-α- or -α,β-D-mannofuranosyl)imidazole-4-carboxylate, reaction of the diazonium salt with copper(I) chloride and removal of the 1-substituent with hydrochloric acid, or by similar conversion of ethyl 5-amino-1-t-butylimidazole-4-carboxylate to ethyl 1-t-butyl-5-chloroimidazole 4-carboxylate, and removal of the t-butyl group with hydrogen bromide. Ethyl 5-fluoroimidazole-4-carboxylate has been prepared from ethyl 5-amino-1-t-butylimidazole-4-carboxylate by diazotisation and photolysis in the presence of tetrafluoroboric acid. Ethyl 5-chloroimidazole-4-carboxylate and ethyl 5-fluoroimidazole-4-carboxylate have been converted into the corresponding alcohols by reaction with lithium aluminium hydride. 5-Chloro-4-(hydroxymethyl)imidazole has also been prepared by electrolysis of 5-chloroimidazole-4-carboxylic acid at a mercury cathode. 5-Chloroimidazole has been converted into the 5-chloroimidazolyl analogues of metiamide and cimetidine by a sequence of reactions, and 5-fluoroimidazole has been similarly converted into the 5-fluoro-analogue of metiamide. The metiamide and cimetidine analogues were found to be histamine H_2-receptor antagonists.

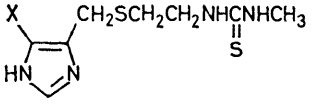
THE recently discovered histamine H_2-receptor antagonists metiamide (1a) and cimetidine (2a) [2-4] are potent inhibitors of gastric acid secretion and as such cimetidine is used in the treatment of peptic ulcers. Interest in analogues of metiamide and cimetidine has prompted us to examine synthetic routes to their 5-chloroimidazole (1b), (2b) and 5-fluoroimidazole analogues (1c) and (2c).

RESULTS AND DISCUSSION

Important intermediates required for the proposed synthesis of these compounds are the ethyl 5-halogenoimidazole-4-carboxylates (3a) and (3b). Attempts to prepare ethyl 5-chloroimidazole-4-carboxylate (3a) from ethyl 5-aminoimidazole-4-carboxylate [5] (4a) by diazotisation in the presence of cuprous chloride gave very low yields of (3a), presumably due to the formation of the stable diazo compound (5); stable diazo compounds of this type have been isolated by other workers.[6,7]

1-Substituted-5-aminoimidazoles however, form reactive diazonium salts.[8-10] We have accordingly investigated the preparation of imidazoles with readily removable protecting groups in the 1-position of the ring. In preliminary experiments the benzyl and *p*-methoxybenzyl aminoimidazole esters (4b) and (4c) respectively were prepared by reaction of the appropriate amine with the formimidate [8] (6) and converted into the corresponding 1-substituted-5-chloro- and -5-bromoimidazoles (3c—f) respectively by diazotisation in the presence of copper(I) halide. However, attempted removal of the benzyl or methoxybenzyl groups from (3c) or (3d) by hydrogenation resulted in the formation of mixtures of compounds, suggesting that hydrogenolysis of the halogens may also have occurred.

A novel acid-labile protecting group in this field would be a glycosyl group. Ethyl 5-amino-1-(2,3;5,6-di-*O*-isopropylidene-α- and -β-D-mannofuranosyl)imidazole-4-carboxylates (4d) are readily available [8] and the lipophilic 1-substituent could be expected to prove useful during the extraction of diazotisation reaction products. Initially the α-anomer of (4d) was converted into the 5-chloroimidazole nucleoside (3g) by diazotisation and reaction of the diazonium salt with copper(I) chloride, with concomitant loss of the 5,6-isopropylidene group, but this did not interfere with the isolation pro-



(1) a; X = Me
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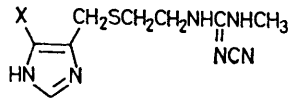
c; X = F



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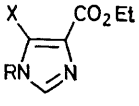
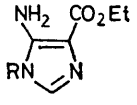


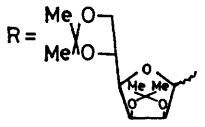
(3) a; R = H, X = Cl
b; R = H, X = F
c; R = CH_2Ph, X = Cl
d; R = 4-$MeOC_6H_4CH_2$, X = Cl
e; R = CH_2Ph, X = Br
f; R = 4-$MeOC_6H_4CH_2$, X = Br
g;

h; R = Bu^t, X = Cl

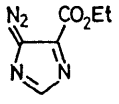


(4) a; R = H
b; R = CH_2Ph
c; R = 4-$MeOC_6H_4CH_2$

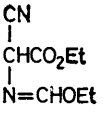
d;



e; R = Bu^t



(5)



(6)

cedure. The nucleoside (3g) was readily split with hot dilute hydrochloride acid to produce ethyl 5-chloroimidazole-4-carboxylate (3a). Similarly the α,β-mixture of nucleosides (4d) was converted into an analogous anomeric mixture corresponding to (3g), which was converted directly into the crystalline chloroimidazole (3a) by acid hydrolysis.

The t-butyl group has also been found to be an equally useful acid-labile protecting group in this series. Thus reaction of the formimidate (6) with t-butylamine readily produced the aminoimidazole (4e) which was converted into the 5-chloro-derivative (3h), from which the t-butyl group was removed by treatment with a hot solution of hydrogen bromide in acetic acid to produce (3a).

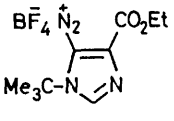
A sample of ethyl 5-fluoroimidazole-4-carboxylate (3b) was prepared by diazotisation of (4a) in tetrafluoroboric acid solution and photolysis of the intermediate diazonium salt, according to a published method.[7] However, the yields obtained were disappointingly low and purification of the dark product which is formed required extensive column chromatography. These difficulties prompted us to seek a more convenient synthesis of the fluoro-ester (3b).

Diazotisation of the t-butyl derivative (4e) at −20 °C in 50% tetrafluoroboric acid led to the formation in good yield of an insoluble precipitate of a diazonium tetrafluoroborate which still retained the t-butyl group (M^+ 223 corresponding to the ethyl 5-diazo-1-t-butylimidazolium ion). Irradiation of a fresh solution of the diazonium salt in tetrafluoroboric acid gave ethyl 5-fluoroimidazole-4-carboxylate (3b), readily isolated as a crystalline solid. The diazonium salt (7) presumably loses isobutene to produce (5) which captures a fluorine radical to afford (3b). The ability to separate the intermediate diazonium salt in this reaction sequence is of considerable practical value, and leads to much cleaner products which do not need column chromatography for purification.

It has been reported [7] that the fluoro-ester (3b) can be converted to the alcohol (8b) by reduction with lithium aluminium hydride. However, in our hands addition of (3b) to a stirred solution of lithium aluminium hydride in dry ether resulted in the recovery of starting material, and on one occasion of ethyl oxamate ($CO_2EtCONH_2$) which is a result of ring-cleavage. On the other hand, when lithium aluminium hydride was added portionwise to a stirred solution of the esters (3a) and (3b) the corresponding alcohols (8a) and (8b), respectively, were then obtained in modest yield. In both cases large excesses of the hydride were required, and even then it was not found possible to achieve a complete conversion of (3b) to (8b) and it was always possible to recover starting material by chromatography on silica gel. The chloro-alcohol (8a) was also prepared by electrolytic reduction [11] at a mercury cathode of the carboxylic acid (9a) prepared *in situ* by hydrolysis of the ester (3a) with 25% sulphuric acid. The yield of product was similar to that obtained using lithium aluminium hydride. An attempt to prepare the fluoro-acid (9b) by similar acid hydrolysis of the ester (3b) was unsuccessful. In addition alkaline hydrolysis of (3b) and electrolytic reduction of the product, presumably (9b), failed to produce the fluoro-alcohol (8b) but gave a product which from t.l.c. examination may have been the imidazolyl alcohol (8c).

The alcohols (8a) and (8b) with cysteamine in hot hydrochloric acid gave good yields of the thioethers (10a) and (10b) respectively, which with methyl isothiocyanate gave the chloro- (1b) and fluoro-imidazole (1c) analogues of metiamide (1a) respectively.

The chloroimidazole analogue (2b) of cimetidine (2a) was also prepared by reaction of (10a) with dimethyl *N*-cyanodithioimidocarbonate (11) to produce the *N*-cyano-*S*-methyl derivative (12), and reaction of this with alcoholic methylamine.



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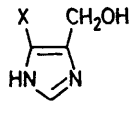

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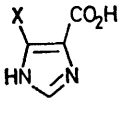
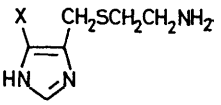
c; X = H



(9) a; X = Cl
b; X = F



(10) a; X = Cl
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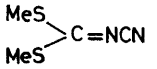

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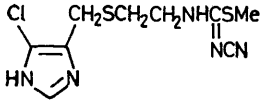

(12)

The metiamide and cimetidine analogues (1b), (1c), and (2b) were found to be active as H_2-receptor antagonists when tested [4] for inhibition of histamine-evoked tachycardia of the guinea-pig right atrium, and evoked contraction of the rat uterus *in vitro* and histamine-stimulated gastric acid secretion in the anaesthetised rat *in vivo*.

EXPERIMENTAL

Evaporations were carried out with a Büchi rotary evaporator, under water-pump vacuum with a flask temperature ≤40 °C unless stated otherwise. I.r. spectra were recorded with a Perkin-Elmer 157 spectrophotometer, n.m.r. spectra with a JEOL JNM-MH-100 spectrometer using $SiMe_4$ as internal standard, and mass spectra with an A.E.I. MS 902 spectrometer. Silica gel 0.05—0.20 mm, 325—70 mesh from Machery Nagel and Co., was used for column chromatography, and silica gel $60F_{254}$ 0.25-mm pre-

coated glass plates from Merck were used for t.l.c. with (A) $CHCl_3$–MeOH (9 : 1), or (B) EtAc–MeOH–aqueous NH_3 (*d* 0.88) (5 : 1 : 1) as development solvent systems. Imidazoles were detected on t.l.c. plates by the Pauly spray,[12] u.v. absorbance at 254 nm or, in the case of 5-aminoimidazoles, by the Bratton–Marshall [13] test.

Ethyl 2-Amino-2-cyanoacetate.—The following preparation is more convenient than those hitherto described. To aluminium foil (25 g, 1-cm squares) was added a solution of mercury(III) chloride (10.0 g) in water (1.0 l), the mixture swirled for 1 min, and then the turbid solution decanted off. The aluminium amalgam was washed successively with water (1.0 l), methanol (2 × 500 ml), and dry ether (2 × 500 ml), then suspended in dry ether (700 ml) and cooled to 0 °C. A solution of ethyl 2-hydroxyimino-2-cyanoacetate [14] (110 g) in dry ether (500 ml) was added with stirring to the ice-cooled mixture, followed by water (50 ml) at a rate (*ca.* 50 min) necessary to maintain gentle reflux; stirring was continued for an additional 0.5 h. The mixture was filtered through Celite and the residue extracted with ether (1.0 l). The combined filtrates were added to a solution of oxalic acid (30 g) in ethanol (200 ml) with rapid stirring. A white solid rapidly precipitated. The mixture was set aside at 4 °C for 1 h, and the product collected, washed with ether, and dried *in vacuo*. The *amine oxalate dihydrate* (54.2 g) crystallised from ethanol–ether as needles, m.p. 115 °C [Found: C, 37.5; H, 5.7; N, 14.8. $(C_5H_8N_2O_2)_2 \cdot (COOH)_2 \cdot 2H_2O$ requires C, 37.7; H, 5.8; N, 14.65%]; the amine is readily stored as the oxalate. A suspension of the oxalate dihydrate (10 g) in chloroform (100 ml) was shaken with a solution of sodium hydrogencarbonate (5.0 g) in water (50 ml). The chloroform layer was collected and the aqueous fraction extracted with chloroform (2 × 100 ml). The combined chloroform extracts were dried (Na_2SO_4), and the solution filtered and evaporated to give an oil (6.25 g); the free amino-ester was normally used immediately.

Ethyl 5-Aminoimidazole-4-carboxylate (4a).—To a solution of ethyl 2-amino-2-cyanoacetate (5.25 g) (from 10 g of the oxalate), chloroform (100 ml), and ethanol (75 ml) was added formamidine acetate (5.0 g) and the mixture refluxed for 2.5 h under nitrogen. The solution was evaporated and the residue in chloroform (150 ml) was rapidly extracted with water (50 ml). The aqueous fraction was extracted with chloroform (3 × 50 ml) and the combined chloroform extracts dried (Na_2SO_4), filtered, and evaporated to dryness. The imidazole (2.6 g) crystallised from ethyl acetate as needles, m.p. 181 °C (lit.,[5] m.p. 181 °C).

Ethyl 5-Amino-1-benzylimidazole-4-carboxylate (4b).—A solution of ethyl 2-amino-2-cyanoacetate (6.25 g) (from 10 g of oxalate) in acetonitrile (50 ml) and triethyl orthoformate (7.6 g) was refluxed for 35 min, then evaporated to give an oil. A solution of this in acetonitrile (50 ml) and benzylamine (5.35 g) was refluxed for 15 min then evaporated to dryness. A solution of the residue in chloroform (100 ml) was washed with 2M-sodium hydroxide (25 ml) and water (25 ml), dried (Na_2SO_4), and evaporated to a gum which soon crystallised when triturated with ethyl acetate. The *aminoimidazole* (4.56 g) separated from ethyl acetate as needles, m.p. 160 °C (decomp.) (Found: C, 63.3; H, 6.2; N, 16.65%; M^+, 245. $C_{13}H_{15}N_3O_2$ requires C, 63.65; H, 6.15; N, 17.15; *M*, 245); δ [$(CD_3)_2SO$] 5.12 (s, CH_2Ph), 5.96—6.2 (s, NH_2), and 7.24—7.36 (m, H-2 and Ph). The compound was readily diazotised and gave a red colour with the Bratton–Marshall reagents.

Ethyl 5-Amino-1-(p-methoxybenzyl)imidazole-4-carboxylate (4c).—This was prepared in the same way as the benzyl derivative, yield 5.54 g, and formed needles from ethyl acetate, m.p. 193 °C (Found: C, 60.45; H, 6.35; N, 14.7%; M^+, 275. $C_{14}H_{17}N_3O_3$ requires C, 61.1; H, 6.2; N, 15.25%; *M*, 275); δ [$(CD_3)_2SO$] 3.6 (s, OMe), 5.12 (s, CH_2Ph), 5.86 (s, NH_2), and 6.72—7.12 (m, H-2 and Ph).

Ethyl 5-Amino-1-t-butylimidazole-4-carboxylate (4e).—This was prepared as above in similar yield, and crystallised from ethyl acetate as needles, m.p. 136 °C (Found: C, 57.0; H, 8.1; N, 20.0%; M^+, 211. $C_{10}H_{17}N_3O_2$ requires C, 56.85; H, 8.1; N, 19.9%; *M*, 211); δ [$(CD_3)_2SO$] 1.56 (s, Me_3C).

Ethyl 5-Chloro-1-(p-methoxybenzyl)imidazole-4-carboxylate (3d).—To a rapidly stirred solution of ethyl 5-amino-1-(*p*-methoxybenzyl)imidazole-4-carboxylate (8.25 g) in 6M-hydrochloric acid (300 ml) at −25 °C was added a solution of sodium nitrite (10.35 g) in water (30 ml) at a rate necessary to maintain a temperature of −22 to −25 °C. The addition required 5 min, and after an additional 5 min a mixture of freshly prepared copper(I) chloride (25 g) in 6M-hydrochloric acid (30 ml) was added portionwise with stirring, at a rate required to maintain a temperature of −25 °C. The solution was stirred at −25 °C for 2 h or until evolution of nitrogen had ceased. The dark mixture was cooled in ice and adjusted to pH 6.5—7 by the dropwise addition of a solution of sodium hydroxide (80 g) in water (100 ml). The solution was stirred for 5 min with ethyl acetate (600 ml) and Celite (30 g) then filtered and the organic layer collected. The aqueous fraction was extracted with ethyl acetate (3 × 250 ml) and the combined ethyl acetate fractions washed with saturated sodium hydrogencarbonate solution (100 ml) and water (100 ml), dried (Na_2SO_4), filtered, and evaporated to give a gum, which rapidly crystallised on addition of ethyl acetate. The *imidazole* (3.5 g) was recrystallised from ethyl acetate as needles, m.p. 106 °C (Found: C, 57.1; H, 5.1; N, 9.25%; M^+ 294, 296. $C_{14}H_{15}ClN_2O_3$ requires C, 57.05; H, 5.15; N, 9.5%; *M*, 294.5); δ [$(CD_3)_2SO$] 3.79 (s, OMe), 5.05 (s, CH_2Ph), and 7.46 (s, H-2).

Ethyl 1-Benzyl-5-chloroimidazole-4-carboxylate (3c).—The compound was prepared as in the preceding experiment in similar yield. The *imidazole* crystallised from ether as needles, m.p. 45 °C (Found: C, 59.15; H, 5.0; N, 10.5; Cl, 13.1%; M^+, 264, 266. $C_{13}H_{13}ClN_2O_2$ requires C, 59.0; H, 4.95; N, 10.6; Cl, 13.4%; *M*, 264.5). An attempt to debenzylate the compound by hydrogenation over palladium led to the formation of a mixture of several compounds (t.l.c. examination), suggesting that the halogen was being removed.

Ethyl 5-Bromo-1-(p-methoxybenzyl)imidazole-4-carboxylate (3f).—This was prepared in the same manner as the chloro-derivative using 48% hydrobromic acid as solvent and freshly prepared copper(I) bromide (21.8 g) in hydrobromic acid (30 ml). The *imidazole* (20%) crystallised from ethyl acetate as needles, m.p. 113 °C (Found: C, 49.55; H, 4.5; N, 8.35%; *M*, 338, 340. $C_{14}H_{15}BrN_2O_3$ requires C, 49.55; H, 4.5; N, 8.25%; *M*, 339). δ [$(CD_3)_2SO$] 3.68 (s, OMe) and 7.36 (s, H-2).

Ethyl 1-Benzyl-5-bromoimidazole-4-carboxylate (3e).—This was prepared as in the preceding experiment. The product (20%) was purified by chromatography on silica gel eluting with chlcroform–methanol (97 : 3). The *imidazole hemihydrate* crystallised from ether as needles, m.p. 80 °C (Found: C, 49.15; H, 4.15; N, 8.55%; *M*, 308, 310. $C_{13}H_{13}BrN_2O_3 \cdot 0.5H_2O$ requires C, 49.05; H, 4.4; N, 8.8%; *M*, 309).

Ethyl 5-Chloro-1-(2,3-O-isopropylidene-α-D-mannofuranosyl)imidazole-4-carboxylate (3g).—To a cooled (−25 °C) solution of ethyl 5-amino-1-(2,3;5,6-di-*O*-isopropylidene-α-D-mannofuranosyl)imidazole-4-carboxylate (2 g) in 6M-hydrochloric acid (50 ml) was added a saturated solution of sodium nitrite (1.73 g) in water, dropwise with maintenance of temperature at −25 ± 5 °C. The addition required 5 min, after which copper(I) chloride (2.5 g) in 10M-hydrochloric acid (5 ml) was added portionwise with stirring, keeping the temperature at −25 ± 5 °C until nitrogen evolution had ceased. The cooled solution was adjusted to pH 7 with 10M-sodium hydroxide, stirred with ethyl acetate and Celite (10 g), and filtered. The aqueous phase was washed with ethyl acetate (3 × 50 ml). The organic phases were combined, washed with saturated sodium hydrogencarbonate (100 ml) and water (100 ml), dried (Na_2SO_4), and evaporated to dryness. The residue was purified by chromatography on silica gel using chloroform–methanol (9 : 1) as the elution solvent. The *chloroimidazole* (0.5 g) was obtained as a solid foam, homogeneous on t.l.c. (Found: C, 47.65; H, 5.85; N, 7.8%; *M*, 376, 378. $C_{15}H_{21}ClN_2O_7$ requires C, 47.8; H, 5.65; N, 7.45%; *M*, *M*, 376.5); δ ($CDCl_3$) 5.8 (s, H-1′) and 7.6 (s, H-2). A similar reaction using ethyl 5-amino-1-(2,3,5; 6-di-*O*-isopropylidene-α,β-D-mannofuranosyl)imidazole-4-carboxylate (anomeric mixture) gave a foam, δ 5.6 (d, H-1′, β-form) and 5.8 (s, H-1′, α-form); integration of the signals suggested that the anomers were present in roughly equal amounts.

Ethyl 5-chloroimidazole-4-carboxylate (3a).—(*a*) A solution of ethyl 5-chloro-1-(2,3-*O*-isopropylidene-α-D-mannofuranosyl)imidazole-4-carboxylate (0.38 g) in 0.1M-hydrochloric acid (20 ml) was set aside at 100 °C for 1 h, then cooled and neutralised with 2M-sodium hydroxide (1 ml) and extracted with ethyl acetate (3 × 25 ml). The combined ethyl acetate fractions were dried (Na_2SO_4), filtered, and evaporated to a solid. The *chloro-imidazole* (1.72 g) crystallised from ethyl acetate as needles, m.p. 178 °C (Found: C, 41.15; H, 3.8; N, 15.85; Cl, 20.1%; M^+, 174, 176. $C_6H_7ClN_2O_2$ requires C, 41.25; H, 4.05; N, 16.05; Cl, 20.3%; *M*, 174.5); δ [$(CD_3)_2SO$] 7.82 (s, H-2).

Similar reaction of crude ethyl 5-chloro-1-(2,3-*O*-isopropylidene-α,β-D-mannofuranosyl)imidazole-4-carboxylate prior to purification by column chromatography gave an almost quantitative yield of ethyl 5-chloroimidazole-4-carboxylate.

(*b*) To a rapidly stirred solution of ethyl 5-amino-1-t-butylimidazole-4-carboxylate (6.33 g) in 6M-hydrochloric acid (300 ml) cooled to −25 °C was added a solution of sodium nitrite (10.35 g) in water (30 ml) at a rate necessary to maintain a temperature of −25 ± 5 °C. The addition required 5 min and after a further 5 min a mixture of freshly prepared copper(I) chloride (15.0 g) in 6M-hydrochloric acid (30 ml) was added portionwise with stirring, so as to maintain a temperature of −25 ± 5 °C. The solution was stirred at −25 °C for 2 h or until evolution of nitrogen had ceased. The dark mixture was cooled in ice, adjusted to pH 6.5—7.0 with 10M-sodium hydroxide, and then added with stirring to ethyl acetate (600 ml) and Celite (30 g), filtered and the organic phase collected. The aqueous layer was extracted with ethyl acetate (3 × 150 ml) and the combined extracts washed with saturated sodium hydrogencarbonate solution (2 × 100 ml) and water (100 ml), dried (Na_2SO_4), and evaporated to a residue of *ethyl 5-chloro-1-t-butylimidazole-4-carboxylate* (2.8 g) (Found: M^+, 230, 232. $C_{10}H_{15}N_2O_2Cl$ requires *M*, 230.5). The compound was homogeneous on t.l.c. but did not crystallise.

A solution of the gum (2.8 g) in 48% hydrogen bromide in acetic acid (25 ml) was refluxed for 1 h or until t.l.c. (system A) indicated disappearance of starting material, then evaporated to dryness and re-evaporated with toluene. The residue with ether gave a solid which was collected, dissolved in water (50 ml), and the solution added to one of sodium hydrogencarbonate (5 g) in water (50 ml). The solution was extracted with ethyl acetate (5 × 50 ml) and the combined extracts dried (Na_2SO_4), and evaporated to a solid (1.52 g), homogeneous on t.l.c. (system A), and identical (i.r.) to a sample of ethyl 5-chloroimidazole-4-carboxylate prepared as in (*a*).

(5-Chloroimidazol-4-yl)methanol (8a).—To a solution of ethyl 5-chloroimidazole-4-carboxylate (1.5 g) in dry ether, stirred rapidly at room temperature, was added lithium aluminium hydride (5.5 g) in aliquots of 0.5 g. The solution was monitored by t.l.c. (system B, Pauly reagent) after neutralisation with methanol until the ester had disappeared. Excess of lithium aluminium hydride was removed by the careful addition of water (15 ml) at 0 °C. Stirring was continued for a further 15 min and the mixture then filtered through Celite. The residual solid was slurried in methanol and treated with methanolic hydrogen chloride until neutral to litmus paper. After filtration the solid residue was extracted with hot methanol (3 × 50 ml) and the combined filtrates evaporated to a sticky solid which was dried by repeated evaporations with propan-1-ol. The solid was extracted with hot propan-2-ol (3 × 5 ml) and the combined extracts evaporated to a gum. The *chloro-alcohol* (0.35 g) crystallised from water as needles, m.p. 174 °C, which retained water. (Found: C, 35.4; H, 3.75; N, 20.60; Cl, 26.3%; M^+, 132, 134. $C_4H_5ClN_2O{\cdot}0.2H_2O$ requires C, 32.25; H, 3.95; N, 20.55; C, 26.1%; *M*, 132.5); δ [$(CD_3)_2SO$] 7.4 (s, H-2) and 4.35 (s, CH_2). The *imidazole picrate* precipitated from an aqueous solution, m.p. 193 °C (Found: C, 32.95; H, 2.15; N, 19.1; $C_{10}H_8ClN_5O_8$ requires C, 33.2; H, 2.25; N, 19.35%).

(*b*) A solution of ethyl 5-chloroimidazole-4-carboxylate (4.0 g) in aqueous sulphuric acid (25%, 60 ml) was refluxed until t.l.c. of a neutralised sample indicated that the hydrolysis was complete (6 h). The solution was placed in the cathode section of an electrolysis cell containing a mercury cathode. Dilute sulphuric acid (25%, 60 ml) was placed into the anode section. A platinised tungsten wire anode was used and a current of 1.84 A, equivalent to a current density of 0.15 A cm^{-2} at the cathode, was passed through the cell. The equilibrium temperature of the cathodic reaction mixture, attained after 1 h, was 53 °C. After 10 h, t.l.c. examination of a neutralised sample of the reaction mixture (system B) indicated that only a trace of the carboxylic acid remained, and that a substantial amount of the alcohol had been produced (R_F 0.6, orange colour with Pauly spray). The cathodic solution was removed from the cell and neutralised with solid potassium carbonate. The mixture was filtered and the filtrate evaporated to a paste which was repeatedly extracted with hot propan-2-ol until an extract gave a negative Pauly test; the combined extracts were evaporated to dryness. The chloro-alcohol (0.88 g) crystallised from water as needles, m.p. 171 °C, identical (i.r., t.l.c.) with material prepared as in (*a*).

2-[(5-Chloroimidazol-4-yl)methylthio]ethylamine (10a).—A solution of (5-chloroimidazol-4-yl)methanol (0.45 g) in 10M-hydrochloric (10 ml) containing cysteamine hydrochloride

(0.41 g) was refluxed for 17 h, then evaporated to dryness and repeatedly re-evaporated with propan-1-ol to a gum which solidified when treated with hot propan-2-ol. The *imidazole dihydrochloride hemihydrate* (0.79 g) crystallised from ethanol was needles, m.p. 202 °C (Found: C, 26.3; H, 4.75; N, 15.25; Cl, 39.50. $C_6H_{10}ClN_3S\cdot 2HCl\cdot 0.5H_2O$ requires C, 26.3; H, 4.8; N, 15.35; Cl, 38.95%); δ (D_2O) 2.75—3.5 (m, NCH_2CH_2), 3.95 (s, CH_2), and 5.95 (s, H-2). The compound gave an orange colour with the Pauly reagent.

N-{2-[(5-*Chloroimidazol*-4-*yl*)*methylthio*]*ethyl*}-N′-*methylthiourea* (1b).—To a solution of 2-[5-chloroimidazol-4-yl)-methylthio]ethylamine dihydrochloride (0.8 g) in ethanol (10 ml) was added sodium ethoxide (0.42) in ethanol (10 ml). The solution was filtered, methyl isothiocyanate (0.15 g) was added, and the solution refluxed for 0.5 h. Evaporation gave a gum was crystallised when treated with a little acetonitrile. The *imidazolyl-thiourea* (0.4 g) recrystallised from acetonitrile as needles, m.p. 137 °C (Found: C, 36.25; H, 4.9; N, 21.15; Cl, 13.4; S, 24.20. $C_8H_{13}ClN_4S_2$ requires C, 36.3; H, 4.95; N, 21.15; Cl, 13.4; S, 24.2%); δ [$(CD_3)_2$-SO] 2.63—3.57 (m, CH_2CH_2), 3.72 (s, CH_3), and 7.51 (s, H-2). The compound gave a bright yellow colour with the Pauly reagent.

1-{2-[(5-*Chloroimidazol*-4-*yl*)*methylthio*]*ethyl*}-3-*cyano*-2-*methylisothiourea* (12).—To a solution of the dihydrochloride hemihydrate of (10a) (0.75 g) in propan-2-ol (1.5 ml) and water (5 ml) was added compound (11) (0.66 g). The mixture was warmed to ensure complete solution and potassium carbonate (0.82 g) was added. The mixture was stirred at room temperature for 17 h, when a weak u.v. absorbing spot (R_F 0.55) (system B) had been replaced by a strong u.v. absorbing spot (R_F 0.06). The solution was boiled briefly then evaporated to dryness. The solid residue was repeatedly re-evaporated with propan-1-ol and the residue extracted with hot propan-2-ol (2 × 50 ml). The extract was evaporated to dryness and the residue triturated with ether to give a solid which was collected and washed with ether. The *imidazolyl-isothiourea* (0.78 g) was recrystallised from acetonitrile as needles, m.p. 150 °C (Found: C, 37.4; H, 4.2; N, 25.0; Cl, 11.7. $C_9H_{12}ClN_5O_2$ requires C, 37.30; H, 4.2; N, 24.15; Cl, 12.25%). The compound gave an orange colour with the Pauly reagent.

1-{2-[(5-*Chloroimidazol*-4-*yl*)*methylthio*]*ethyl*}-2-*cyano*-3-*methylguanidine* (2b).—Compound (12) (0.70 g) was stirred in alcoholic methylamine (33%, 2 ml) for 2 h. The solution was evaporated to a gum, which solidified on addition of ether. The *imidazolyl-guanidine* (0.56 g) crystallised from acetonitrile as needles, m.p. 161 °C (Found: C, 39.7; H, 4.90; N, 30.85; S, 11.65; Cl, 12.7. $C_9H_{13}ClN_6S$ requires C, 39.65; H, 4.80; N, 30.8; S, 11.75; Cl, 13.00%); δ [$(CD_3)_2SO$] 2.5 (m, CH_2CH_2S), 2.71 (d, NH*Me*), 3.32 (m, NCH_2CH_2S), 3.73 (s, CH_3), and 6.9 (m, N*H*CN*H*).

Ethyl-5-*fluoroimidazole*-4-*carboxylate* (3b).—(*a*) To a solution of ethyl 5-amino-1-t-butylimidazole-4-carboxylate (3.14 g) in 50% tetrafluoroboric acid (150 ml), cooled to −25° ± 5 °C, was added slowly with stirring a solution of sodium nitrite (5.2 g) in the minimum of water. After 10 min the solid diazonium fluoroborate precipitate was collected, washed with a little water and ethanol, and redissolved in 50% tetrafluoroboric acid (150 ml). The solution was irradiated with a 150-W Hanovia mercury-arc u.v. lamp until evolution of nitrogen gas had ceased (72 h), cooled to 0 °C, adjusted to pH 7 with 6M-sodium hydroxide solution, then extracted with ethyl acetate (3 × 150 ml); the combined extracts were then washed with saturated sodium hydrogencarbonate solution (3 × 100 ml) and water (2 × 200 ml), dried (Na_2SO_4) and evaporated to give the fluoroimidazole as a solid (0.85 g), m.p. 145 °C (lit.,[7] 148 °C) (Found: C, 45.85; H, 4.6; N, 17.75. Calc. for $C_6H_7FN_2O_2$ C, 45.55; H, 4.45; N, 17.7%). The product was identical (i.r., mixed m.p.) with a sample of ethyl 5-fluoroimidazole-4-carboxylate prepared by the method of Cohen *et al.*[7]

(*b*) To a cooled (0 °C) solution of ethyl 5-aminoimidazole-4-carboxylate (5.0 g) in 50% aqueous tetrafluoroboric acid (125 ml) was added sodium nitrite (2.8 g) in water (20 ml) with maintenance of temperature at ⩽5 °C. The solution was irradiated with a 150-W Hanovia mercury-arc u.v. lamp until evolution of nitrogen ceased (72 h), cooled to 0 °C, and adjusted to pH 7 with 6M-sodium hydroxide. The solution was extracted with ethyl acetate (3 × 50 ml) and the combined extracts dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was chromatographed on a silica gel column by elution with chloroform–methanol (95 : 5). The major fraction active in the Pauly test was separated as a solid (0.5 g), m.p. 145 °C, identical with material prepared as in (*a*).

(5-*Fluoroimidazol*-4-*yl*)*methanol* (8b).—To a rapidly stirred solution of ethyl 5-fluoroimidazole-4-carboxylate (3.5 g) in dry ether (250 ml) at 0 °C was added lithium aluminium hydride (5.5 g) in aliquots of 0.5 g until the composition of the reaction mixture was unchanged (t.l.c. examination). A small amount of starting material remained and appeared to be resistant to reaction. The ice-cooled solution was treated cautiously with water (15 ml) followed by methanol pre-saturated with carbon dioxide (50 ml). The mixture was stirred at room temperature for 10 min, boiled briefly, and filtered through Celite. The residue was extracted with CO_2-saturated methanol (3 × 100 ml) and the combined extracts were evaporated to a sticky solid. Extraction of the solid with ethanol (3 × 50 ml), followed by filtration and evaporation of the combined extracts, afforded a gum (3.0 g), t.l.c. of which (system B, Pauly spray) showed the presence of one major component (R_F 0.55), a lower-running substance, and some starting material.

A solution of the gum in chloroform (80 ml) and methanolic ammonia (2 ml) was applied to a silica gel column. The two major Pauly-active fractions were collected after elution with chloroform–methanolic ammonia (95 : 5). Unreacted ethyl 5-fluoroimidazole-4-carboxylate (0.8 g) was collected as the higher-running fraction, and (5-fluoroimidazol-4-yl)-methanol (0.85 g) was collected as the lower-running fraction. Further silica gel chromatography using chloroform–methanol was necessary to remove a low-running impurity from the alcohol. A pure sample of (5-fluoroimidazol-4-yl)methanol (0.8 g) was finally obtained, m.p. 137 °C (lit.,[7] 138 °C). When the above reduction was carried out according to published instructions [7] sublimination of the crude reaction product gave a crystalline solid identical (i.r.) with ethyl oxamate, m.p. 115 °C (Found: C, 40.65; H, 5.95; N, 11.95%; *M*, 117. Calc. for $C_4H_7O_3$: C, 41.0; H, 6.05; N, 11.95%; *M*, 117).

2-[(5-*Fluoroimidazol*-4-*yl*)*methylthio*]*ethylamine* (10b).—A mixture of (5-fluoroimidazol-4-yl)methanol (0.58 g) and cysteamine hydrochloride (0.56 g) was boiled under reflux for 17 h. Evaporation of the solvent followed by repeated evaporation with propan-1-ol afforded a gum which solidified on addition of hot propan-2-ol. The *imidazole hydrochloride hydrate* (0.91 g) when washed with ether had m.p.

166 °C (Found: C, 27.1; H, 4.9; N, 17.1. $C_6H_{10}FN_3S \cdot 2HCl \cdot H_2O$ requires C, 27.05; H, 5.30; N, 15.8); δ (D_2O) 2.81 (m, NCH_2CH_2), 3.21 (m, NCH_2CH_2), 3.88 (s, CH_2), and 8.04 (d, H-2).

N-{2[(5-*Fluoroimidazol*-4-*yl*)*methylthio*]*ethyl*}-N′-*methylthiourea* (1c).—A solution of the dihydrochloride monohydrate of (10b) (0.95 g) in water (10 ml) containing potassium hydrogencarbonate (0.78 g) in water (10 ml) was evaporated to dryness and the residue dried by repeated evaporation with propan-1-ol. The residue was extracted with propan-2-ol (3 × 20 ml) and the combined extracts evaporated to give a gum, which was dissolved in propan-2-ol (15 ml) and treated with methyl isothiocyanate (0.24 g). The mixture was refluxed for 5 min, then evaporated to a gum which crystallised on addition of a little acetonitrile. The *fluoroimidazolyl-thiourea* (0.54 g) separated from acetonitrile as needles, m.p. 126 °C (Found: C, 38.65; H, 5.2; N, 22.45; S, 25.6. $C_8H_{13}FN_4S_2$ requires C, 38.70, H, 5.3; N, 22.6; S, 25.8%); δ [$(CD_3)_2SO$] 2.57 (m, NCH_2CH_2), 2.77 (d, NH*Me*), 3.46 (m, NCH_2CH_2), 3.69 (s, CH_2), 7.21 (m, H-2), and 7.43 (m, *H*NCN*H*).

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