Purines, Pyrimidines, and Imidazoles. Part 58.[1] Synthesis and Reactions of some Imidazole-2,4-dicarboxylic Acid Derivatives

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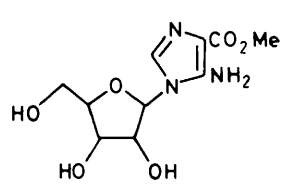
Diethyl 5-amino-1-(*p*-methoxybenzyl)imidazole-2,4-dicarboxylate (3b) has been prepared from ethyl 2-amino-2-cyanoacetate and ethyl 1-ethoxycarbonyformimidate hydrochloride or ethyl triethoxyacetate followed by reaction with *p*-methoxybenzylamine. The diester, with one equivalent of dilute sodium hydroxide solution, furnished ethyl 5-amino-1-(*p*-methoxybenzyl)imidazole-4-carboxylate (7a). Diazotisation of the diester (3b) and reaction of the diazonium salt with copper(I) chloride produced diethyl 5-chloro-1-(*p*-methoxybenzyl)imidazole-2,4-dicarboxylate (9a) which, with dilute alkali, gave ethyl 5-chloro-1-(*p*-methoxybenzyl)imidazole-4-carboxylate (7b). Diazotisation of the diester (3b) in the presence of hypophosphorous acid gave diethyl-1-(*p*-methoxybenzyl)imidazole-2,4-carboxylate (9b) which, when hydrogenated over palladium–charcoal, produced diethyl imidazole-2,4-dicarboxylate (9c). This with bromine (chlorine) gave diethyl 5-bromo(chloro)imidazole-2,4-dicarboxylate (9d and e). The chloro derivative (9a) was similarly hydrogenated using palladium–charcoal to produce diethyl 5-chloroimidazole-2,4-dicarboxylate (9e).

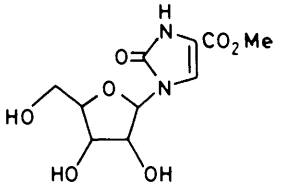
We have recently [2] described the synthesis of some 5-halogenoimidazole analogues of the histamine H_2-receptor antagonists metiamide and cimetidine which are potent inhibitors of gastric acid secretion. In these syntheses a halogen atom was conveniently introduced into the imidazole ring by replacement of the primary amino group of a 5-aminoimidazole derivative using Sandmeyer-type reactions. However, in certain reactions involving diazotisation of 5-aminoimidazole derivatives, the reactivity of the 2-position may present difficulties. Thus, an attempt [3] to convert the amino group of methyl 5-amino-1-(β-D-ribofuranosyl)imidazole-4-carboxylate (1) into an hydroxy group by diazotisation and treatment of the diazonium salt with a weak alkaline solution resulted in the formation of the ribosyl imidazol-2-one (2). We have been interested, therefore, in investigating the preparation of 5-aminoimidazole derivatives containing a readily removable blocking group in the 2-position. To this end we have examined the synthesis of appropriate 5-amino-2-ethoxycarbonylimidazoles.

We have earlier recorded [4] the novel formation of diethyl 5-aminoimidazole-2,4-dicarboxylate (3a) when ethyl 2-amino-2-cyanoacetate (4) was set aside at 35 °C but the low yield obtained (*ca.* 10%) made this reaction of limited preparative value. However, reaction of the amino ester (4) either with the imidate (5) derived from ethyl cyanoformate or with ethyl triethoxyacetate [5] gave the complex imidate (6) which reacted with *p*-methoxybenzylamine to produce the crystalline diethyl 5-amino-1-(*p*-methoxybenzyl)imidazole-2,4-dicarboxylate (3b). Treatment of this compound with one equivalent of hot 0.1M-sodium hydroxide during 30 min, followed by neutralisation with hydrochloric acid, gave an excellent (88%) yield of the monoester (7a). The structure of the latter compound was confirmed by elemental analysis, ^{1}H n.m.r. spectra, and by an unambiguous synthesis from the imidate (8) [4] and *p*-methoxybenzylamine. Under these conditions it is clear that hydrolysis occurs almost exclusively at the 2-ethoxycarbonyl group and its selective removal by mild alkaline treatment makes it a valuable group for protecting the 2-position in imidazoles of these types.

Diazotisation of the diester (3b) and treatment of the diazonium chloride with copper(I) chloride furnished the 5-chloroimidazole diester (9a), alkaline hydrolysis of which at room temperature during 1 h then produced, in a similar way as before, the 5-chloroimidazole monoester (7b) in excellent (82%) yield. The structure of this compound was confirmed by its identity with the product obtained [2] by reaction of copper(I) chloride with the diazonium salt derived from the monoamino monoester (7a).



(1)

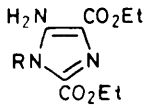


(2)

Diazotisation of the diester (3b) in the presence of hypophosphorous acid gave the 5-hydro diester (9b), hydrogenation of which in the presence of palladium–charcoal produced diethyl imidazole-2,4-dicarboxylate (9c). Bromination or chlorination of compound (9c) with bromine (or chlorine) in chloroform containing triethylamine readily produced the 5-bromo(chloro)imidazole diesters (9d) and (9e), respectively. The 5-chloroimidazole (9e) was also obtained by hydrogenation of the *p*-methoxybenzyl derivative (9a) over palladium–charcoal. The ease of removal of the *p*-methoxybenzyl group from the diester derivatives (9a) and (9b) by hydrogenation contrasts with the difficulties experienced [2] during attempts to remove either a benzyl or a *p*-methoxybenzyl group from the chloroimidazole monoesters (7b) or (7c), respectively, when mixtures of products were obtained, leading us to suggest that in these examples removal of the halogen atom had also occurred to some extent.

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 (Machery Nagel and Co.) was used for column chromatography, and

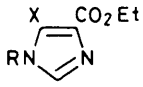


(3) a; R = H
b; R = *p*-methoxybenzyl

$NCCH(NH_2)CO_2Et$
(4)

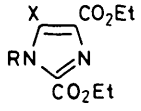
$Cl^- H_2\overset{+}{N}{=}C(OEt)CO_2Et$
(5)

$NCCH[N{=}C(OEt)CO_2Et]CO_2Et$
(6)



(7) a; R = *p*-methoxybenzyl, X = NH_2
b; R = *p*-methoxybenzyl, X = Cl
c; R = benzyl, X = Cl

$NCCH(N{=}CHOEt)CO_2Et$
(8)



(9) a; R = *p*-methoxybenzyl, X = Cl
b; R = *p*-methoxybenzyl, X = H
c; R = X = H
d; R = H, X = Br
e; R = H, X = Cl

silica gel $60F_{254}$ (0.25 mm) precoated glass plates from Merck were used for t.l.c. with (A) $CHCl_3$–MeOH (9 : 1), or (B) EtOAc–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,[6] u.v. absorbance at 254 nm, or, in the case of 5-aminoimidazoles, by the Bratton–Marshall test.[7] Light petroleum refers to that fraction boiling in the range 40—60 °C.

Ethyl 1-*Ethoxycarbonylformimidate Hydrochloride* (5).—Hydrogen chloride gas was passed into an ice-cooled mixture of ethanol (4.6 g, 0.1 mol) and ethyl cyanoformate (9.9 g, 0.1 mol) in anhydrous diethyl ether (50 ml) until an increase in weight of 4.0 g was attained. The mixture was set aside in an unstoppered flask until crystallisation was complete (2 h). Care is necessary since the ether may boil due to the heat of crystallisation. The *formimidate hydrochloride* (12.5 g, 66%) m.p. 104 °C was collected by filtration, washed with diethyl ether, and dried *in vacuo* (Found: C, 39.5; H, 6.75; Cl, 26.6; N, 7.6. $C_6H_{12}ClNO_3$ requires C, 39.65; H, 6.65; Cl, 26.45; N, 7.7%).

Diethyl 5-*Amino*-1-(p-*methoxybenzyl*)*imidazole*-2,4-*dicarboxylate* (3b).—(*a*) A solution of ethyl 2-amino-2-cyanoacetate (3.84 g, 0.03 mol) (from 6.0 g of the oxalate)[8] in dry acetonitrile (100 ml) was treated with finely powdered ethyl 1-ethoxycarbonylformimidate hydrochloride (5) (5.87 g, 0.03 mol). The suspension was agitated for 1 h with exclusion of moisture and was then filtered and added to *p*-methoxybenzylamine (4.14 g, 0.03 mol). The reaction mixture was cooled, filtered from precipitated *N*,*N*′-di-(*p*-methoxybenzyl)-oxamide, and evaporated to dryness to give a red gum which was dissolved in chloroform (100 ml) and the solution was rapidly extracted with 2M-sodium hydroxide (30 ml) followed by water (50 ml). The chloroform solution was dried (Na_2SO_4), filtered, and evaporated to dryness to give a gum which was dissolved in ethyl acetate–diethyl ether (1 : 1) and the solution set aside at 4 °C for 20 h. The crystalline product was dissolved in boiling ethyl acetate (25 ml), the filtered solution was cooled to 0 °C, and then treated with light petroleum to incipient turbidity and set aside at 4 °C until crystallisation was complete. The *imidazole diester* (3b) (4.15 g, 41%) was recrystallised from ethyl acetate–light petroleum as needles, m.p. 141 °C [Found: C, 58.4; H, 6.1; N, 12.0; *m*/*z* 347 (M^+) and 274. $C_{17}H_{21}N_3O_5$ requires C, 58.75; H, 6.1; N, 12.1%; *M*, 347, (*M* − CO_2Et), 274]; δ[$(CD_3)_2SO$] 1.08—1.36 (m, CH_2CH_3), 4.0—4.32 (m, CH_2CH_3), 3.2 (s, OCH_3), 5.38 (s, CH_2Ar), 6.44 (NH_2, s), and 6.68—7.08 (C_6H_4).

(*b*) (With Victor Postoyalko). A solution of ethyl 2-amino-2-cyanoacetate (6.25 g) (from 10 g of the oxalate) and ethyl triethoxyacetate (11 g) in acetonitrile (50 ml) was refluxed for 35 min with exclusion of water vapour, then evaporated to dryness to give a straw-coloured oil. This was kept at 80 °C *in vacuo* for 30 min, then was dissolved in acetonitrile (50 ml) containing *p*-methoxybenzylamine (6.9 g) and the mixture was boiled under reflux for 1 h then evaporated to dryness to give a gum. This was triturated with cold diethyl ether (3 × 25 ml). The resultant gum was worked up as in (*a*) above to give the imidazole diester (3b) (5.2 g, 30%), m.p. and mixed m.p. 142 °C.

Ethyl 5-*Amino*-1-(p-*methoxybenzyl*)*imidazole*-4-*carboxylate* (7a).—A solution of diethyl 5-amino-1-(*p*-methoxybenzyl)-imidazole-2,4-dicarboxylate (3b) (0.10 g, 0.000 29 mol) in 0.1M-sodium hydroxide (2.9 ml, 0.000 29 mol) was boiled under reflux for 0.5 h, cooled, and added to 0.1M-hydrochloric acid (5.8 ml, 0.000 58 mol). The solution was heated briefly to 70 °C to allow complete decarboxylation and was then cooled and treated with saturated aqueous sodium hydrogen carbonate until evolution of carbon dioxide had ceased, then was extracted with ethyl acetate (3 × 20 ml). The combined extracts were dried (Na_2SO_4), filtered, and evaporated to dryness, to give a gum which solidified after repeated re-evaporation with ethyl acetate. The solid (0.07 g, 88%), m.p. and mixed m.p. 193 °C, was identical (t.l.c., i.r.) with an authentic sample[2] of ethyl 5-amino-1-(*p*-methoxybenzyl)-imidazole-4-carboxylate (7a).

Diethyl 5-*Chloro*-1-(p-*methoxybenzyl*)*imidazole*-2,4-*dicarboxylate* (9a).—To a rapidly stirred solution of diethyl 5-amino-1-(*p*-methoxybenzyl)imidazole-2,4-dicarboxylate (3b) (10.41 g, 0.03 mol) in 6M-hydrochloric acid (300 ml) cooled to −25 °C was added a solution of sodium nitrite (10.35 g, 0.15 mol) 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 solution of freshly prepared copper(I) chloride (25.0 g, 0.15 mol) in 6M-hydrochloric acid (30 ml) was added portionwise to the stirred mixture at a rate required to maintain a temperature of −25 °C. The solution was then stirred at −25 °C for an additional 2 h or until evolution of nitrogen had ceased. The dark mixture was cooled in ice, accurately adjusted to pH 6.57 by the dropwise addition of a solution of sodium hydroxide (80 g) in water (100 ml), then added to a stirred mixture of ethyl acetate (600 ml) and Celite (30 g). The mixture was stirred for another 5 min, then filtered and the organic layer was separated. The aqueous fraction was extracted with ethyl acetate (3 × 250 ml) and the combined ethyl acetate fractions were washed in turn with saturated aqueous sodium hydrogen carbonate (100 ml) and water (100 ml), dried (Na_2SO_4), filtered, and evaporated to dryness to give a gum. The product was purified on a column

of silica gel using chloroform–methanol (99 : 1) as eluant. Evaporation of the major u.v.-absorbing fraction gave a gum which crystallised when dissolved in a little diethyl ether and set aside at 4 °C. The *chloroimidazole* (9a) (3.74 g) was recrystallised from ethyl acetate as needles, m.p. 82 °C (Found: C, 55.65; H, 5.3; Cl, 9.85; N, 7.60; M^+, 366, 368. $C_{17}H_{19}ClN_2O_5$ requires C, 55.65; H, 5.2; Cl, 9.7; N, 7.65%, *M*, 366.5); δ[$(CD_3)_2SO$] 1.39 (m, CH_3CH_2), 4.43 (m, CH_3CH_2), 3.78 (s, OCH_3), 5.7 (s, CH_2Ar), and 6.85—7.17 (m, C_6H_4).

Ethyl 5-Chloro-1-(p-methoxybenzyl)imidazole-4-carboxylate (7b).—A solution of diethyl 5-chloro-1-(*p*-methoxybenzyl)-imidazole-2,4-dicarboxylate (9a) (0.36 g, 0.001 mol) in ethanol (5 ml) and 0.1M-sodium hydroxide (10 ml) was set aside at room temperature for 1 h; 0.1M-hydrochloric acid (10 ml) was then added and the solvent was evaporated off to give a solid which was extracted with hot propan-2-ol (3 × 25 ml). The combined extracts were evaporated to dryness to give a gum which was dissolved in aqueous acetic acid (75% v/v; 50 ml) and the solution was boiled under reflux for 1 h, then evaporated to dryness to give a gum which soon crystallised. Ethyl 5-chloro-1-(*p*-methoxybenzyl)imidazole-4-carboxylate (7b) (0.24 g, 82%) was recrystallised from ethyl acetate as needles, m.p. and mixed m.p. 106 °C, identical (i.r., t.l.c.) with an authentic sample.[2]

Diethyl 1-(p-Methoxybenzyl)imidazole-2,4-dicarboxylate (9b).—To a well stirred solution of diethyl 5-amino-1-(*p*-methoxybenzyl)imidazole-2,4-dicarboxylate (3b) (3.0 g, 0.008 mol) in 50% hypophosphorous acid (60 ml) cooled to −20 °C was added dropwise a solution of sodium nitrite (0.79 g, 0.01 mol) in water (5 ml) at a rate necessary to maintain a temperature of less than −20 °C. The addition required 5 min and the reaction mixture was then stirred at −20 °C for an additional 2 h or until evolution of nitrogen had ceased. To the well cooled, rapidly stirred mixture was added dropwise a solution of 6M-sodium hydroxide. Care was taken to maintain a temperature of less than −20 °C to prevent hydrolysis of the 2-ethoxycarbonyl group. The solution was neutralised to pH 7, allowed to achieve room temperature, and added to a mixture of ethyl acetate (100 ml) and Celite (5 g); the complex mixture was stirred for 5 min, filtered, and the organic fraction was collected. The aqueous fraction was extracted with ethyl acetate (3 × 75 ml) and the combined ethyl acetate fractions were dried (Na_2SO_4), filtered, and evaporated to dryness to give a gum which was dissolved in ethyl acetate and set aside at 4 °C overnight to give a crystalline product. The *imidazole diester* (9b) (1.62 g) was recrystallised from ethyl acetate as needles, m.p. 172 °C (Found: C, 61.55; H, 6.35; N, 8.35; M^+, 332. $C_{17}H_{20}N_2O_5$ requires C, 61.45; H, 6.05; N, 8.45%; *M*, 332).

Diethyl Imidazole-2,4-dicarboxylate (9c).—Catalytic hydrogenation of diethyl 1-(*p*-methoxybenzyl)imidazole-2,4-dicarboxylate (9b) (0.10 g, 0.003 mol) at atmospheric pressure in ethyl acetate using Pd–C as catalyst gave, after 4 h, a single product. The clarified reaction mixture was evaporated to dryness to give a white solid which was washed with diethyl ether–ethyl acetate (1 : 1) and dried *in vacuo*. The *diester* (9c) was recrystallised from ethyl acetate as needles, m.p. 166 °C (Found: C, 50.8; H, 5.85; N, 13.1%; M^+, 212. $C_9H_{12}N_2O_4$ requires C, 50.95; H, 5.7; N, 13.2%; *M*, 212); δ[$(CD_3)_2SO$] 1.3 (t, CH_3CH_2), 1.32 (t, CH_3CH_2), 4.36 (q, CH_3CH_2), 4.38 (9, CH_3CH_2), and 7.97 [s, 5(4)-H].

Diethyl 5-Bromoimidazole-2,4-dicarboxylate (9d).—To a cold solution of diethyl imidazole-2,4-dicarboxylate (9c) (0.25 g, 0.0012 mol) in chloroform (5 ml) was added triethylamine (0.12 g, 0.0012 mol), then (dropwise) a solution of bromine in chloroform (10% bromine v/v) until the solution was permanently brown. The solvent was evaporated off to give a gum, t.l.c. examination (system A) of which showed the presence of a single u.v.-absorbing spot (R_F 0.7) in addition to some unchanged starting material (R_F 0.6). A solution of the gum in ethyl acetate was treated with diethyl ether and the precipitated triethylamine hydrobromide was removed. The filtrate was evaporated to dryness to give a gum which was applied to a silica-gel column. Elution with chloroform–methanol (1 : 1) followed by evaporation of the major u.v.-active fraction afforded a gum which was dissolved in a little diethyl ether and set aside at 4 °C when it crystallised. The *bromoimidazole* (9d) (0.18 g) was recrystallised from diethyl ether as needles, m.p. 142 °C (Found: C, 37.2; H, 3.85; N, 9.35; M^+, 290, 292. $C_9H_{11}BrN_2O_4$ requires C, 37.1; H, 3.8; N, 9.6%; *M*, 291). Starting material (9c) (0.1 g) was also recovered from the column eluate.

Diethyl 5-Chloroimidazole-2,4-dicarboxylate (9e).—(*a*) To a stirred, ice-cooled solution of diethyl imidazole-2,4-dicarboxylate (9c) (0.25 g, 0.00012 mol) in chloroform (5 ml) and triethylamine (9c) (0.12 g, 0.0012 mol) was added, in aliquots, a solution of chlorine in chloroform (prepared by saturating chloroform with chlorine gas at 0 °C). After each addition the composition of the reaction was examined by t.l.c. (system A). The starting material (R_F 0.6) slowly disappeared as the product (R_F 0.7) was formed. Addition of chlorine was discontinued when successive addition did not appear to change the composition of the reaction mixture. The solvent was removed by evaporation to leave a gum which was dissolved in ethyl acetate and treated with diethyl ether to precipitate triethylamine hydrochloride. Filtration followed by evaporation of the solvent afforded a gum which was applied to a silica-gel column. Elution with chloroform–methanol (1 : 1) afforded the major u.v.-active fraction which was evaporated to dryness, to give a gum. Addition of diethyl ether prompted crystallisation. The *chloroimidazole* (9e) (0.19 g) was recrystallised from diethyl ether as needles, m.p. 166 °C (Found: C, 43.85; H, 4.55; N, 11.20; M^+, 246, 248. $C_9H_{11}ClN_2O_4$ requires C, 43.8; H, 4.50; N, 11.35%; *M*, 246.5). Starting material (9c) (0.06 g) was also recovered from the column eluate.

(*b*) Hydrogenation of diethyl 5-chloro-1-(*p*-methoxybenzyl)-imidazole-2,4-dicarboxylate (9a) (0.1 g) in ethyl acetate over a palladium–charcoal catalyst was complete after 4 h. The clarified reaction mixture was evaporated to dryness to give a white solid (0.06 g), m.p. and mixed m.p. 166 °C, identical with an authentic sample of diethyl 5-chloroimidazole-2,4-dicarboxylate (9e) (i.r., t.l.c.).

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