Synthesis of Some New Isoxazolylacetic Acid Derivatives

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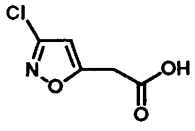
(3-Chloroisoxazol-5-yl)acetic acid **1**, a known acylating agent, useful for the synthesis of semi-synthetic cephalosporins was synthesized by a new route. Several α-substituted 3-chloroisoxazolylacetic acids **9a, b**; **10a, b** and **15**, potential acylating agents for semi-synthetic β-lactams, were also prepared. The (*E*)- and (*Z*)-3-chloro-α-methoxyiminoisoxazol-5-ylacetic acids **10a, b** were separated and their structures unambiguously determined by ^{1}H NMR spectroscopic and X-ray measurements.

Several semisynthetic penicillins [1] and cephalosporins [2] acylated with (3-chloroisoxazol-5-yl)acetic acid **1** have been found to be very efficient broad-spectrum antibiotics. We report here the synthesis of some α-substituted derivatives of isoxazolylacetic acid **1**, potential acylating agents for cephalosporins and 3-aminomonobactamic acid.



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The known compound, (3-chloroisoxazol-5-yl)acetic acid **1** [3] has been synthesized by a new route in our laboratory. The isoxazole ring is known to be attacked by both electrophiles and radicals at the 4-position. In spite of this, it was possible to selectively chlorinate the corresponding acid chloride **3** in the side chain with sulfuryl chloride in carbon tetrachloride in the presence of dibenzoyl peroxide. The crude product was treated with 40% aqueous sodium hydroxide. Subsequent acidification gave 3-[(*E*)-3-chloroisoxazol-5-yl]acrylic acid **4**. The acid **4** was converted into the (3-chloroisoxazol-5-yl)acetaldoxime **6** *via* a Curtius rearrangement of the corresponding acyl azide. The unsaturated isocyanate was hydrolysed to the enamine which reacted with hydroxylamine in aqueous solution as 3-chloroisoxazol-5-ylacetaldehyde. Compound **6** was dehydrated and the crude nitrile was hydrolysed to give the acid **1** (Scheme 1).

The acrylic acid **4** was converted by a known method [4] into the hydroxy ester **7**. After bromine addition and esterification, the 2,3-dibromo ester was successively treated with sodium methoxide and 20% hydrochloric acid to give 5-acetyl-3-chloroisoxazole. The crude α,α-dibromo-5-acetyl derivative gave, in an internal Cannizzaro reaction, the α-hydroxy-acid, which was treated with ethereal diazomethane to obtain the hydroxy ester **7**. Compound **7**, when stirred with manganese(IV) oxide in dichloromethane gave the α-oxo ester **8**. Treatment of compound **8** with *O*-methylhydroxylamine furnished a mixture of two diastereoisomers **9a** and **9b**, which were separated by column chromatography on silica gel. Hydrolysis of esters **9a** and **9b** to the corresponding acids **10a** and **10b** was carried out at 0 °C with aqueous potassium hydroxide.

The 4-H signal appears at lower fields in the ^{1}H NMR spectra of compounds **9a** and **10a**, than in those of **9b** and **10b** (Table 1), probably as a result of the deshielding effect of the proximate methoxy group, and suggests that **9a** and **10a** are the *E*-isomers. This stereochemical assignment was corroborated by the X-ray molecular structure determination of compound **10b**. A perspective view of the molecular structure computed from the atomic coordinates, listed in Table 2, is shown in Fig. 1.

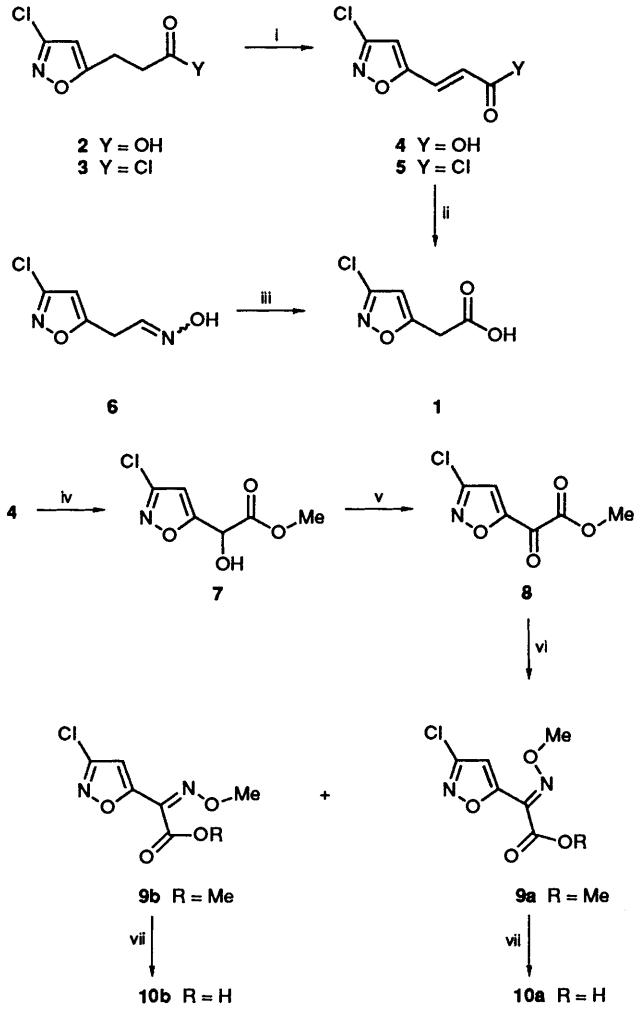
Table 1 Selected characteristic ^{1}H NMR spectroscopic data of compounds **9a, 9b, 10a** and **10b** in $CDCl_3$

Compound	δ_H 4-H	δ_H CH_3O-
9a	7.01	4.26
10a	7.09	4.31
9b	6.61	4.12
10b	6.83	4.25

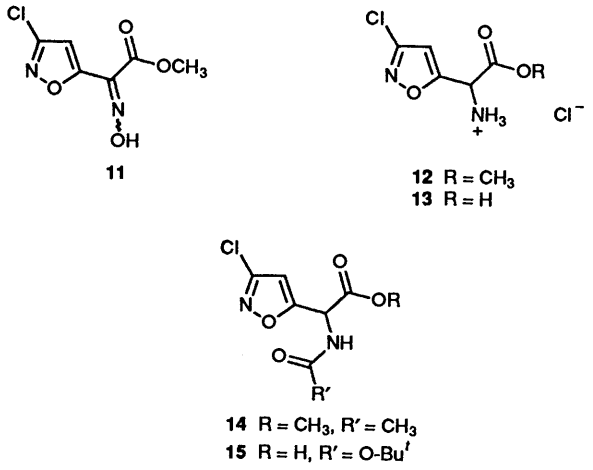
Table 2 Fractional atomic coordinates for the non-hydrogen atoms of compound **10b** with e.s.d's in parentheses

Atom	*x/a*	*y/b*	*z/c*
O(1)	0.213 6(2)	0.614 4(1)	0.549 3(1)
N(2)	0.262 0(2)	0.742 0(2)	0.400 7(2)
C(3)	0.334 0(2)	0.646 2(2)	0.280 4(2)
C(4)	0.338 4(3)	0.455 5(2)	0.341 1(2)
C(5)	0.259 8(2)	0.443 7(2)	0.508 8(2)
Cl(6)	0.406 00(8)	0.757 89(7)	0.076 49(7)
C(7)	0.221 2(2)	0.289 8(2)	0.648 4(2)
N(8)	0.144 0(2)	0.328 5(2)	0.796 6(2)
O(9)	0.107 1(2)	0.173 7(1)	0.915 7(1)
C(10)	0.041 9(4)	0.218 6(3)	1.083 2(3)
C(11)	0.275 4(2)	0.096 3(2)	0.610 2(2)
O(12)	0.185 9(2)	0.087 7(1)	0.484 8(1)
O(13)	0.386 1(2)	−0.027 2(2)	0.686 0(2)

Compound **11** was similarly synthesized using hydroxylamine instead of *O*-methylhydroxylamine. Catalytic reduction (H_2/10% Pd–C) of oxime **11** in ethanol saturated with hydrogen chloride provided the ester hydrochloride **12**. When the reduction was carried out with zinc–acetic acid, the main product was the 2-acetylamino ester **14**. Acid hydrolysis of compound **14** furnished the hydrochloride of the amino acid **13**, which, on subsequent treatment with di-(*tert*-butyl) oxydiformate (BOC_2O) in the presence of potassium carbonate, gave the protected amino acid **15** in a moderate yield. By applying our earlier method,[5] compound **15** was also prepared directly from



Scheme 1 *Reagents and conditions:* i, 1, SO_2Cl_2, Bz_2O_2, CCl_4, reflux; 2, aq. NaOH, reflux; 3, AcOH; ii, 1, NaN_3, DMF, 0 °C, ether; 2, dioxane, reflux, 45 min; 3, AcOH, H_2SO_4, reflux 10 min; 4, $NH_2OH.HCl$, NaOAc; iii, 1, $SOCl_2$, ether, 0 °C; 2, AcOH–HBr, reflux; iv, see Ref. 4; 1, Br_2, AcOH, reflux; 2, MeOH, H_2SO_4, reflux; 3, MeOH, NaOMe, reflux; 4, 20% HCl, steam bath; 5, 2 mol Br_2, AcOH; 6, 10% NaOH, room temp.; 7, Ether, CH_2N_2; v, MnO_2, CH_2Cl_2, room temp.; vi, $MeONH_3$ Cl, NaOH, MeOH; vii, aq. KOH



the ester hydrochloride **12** with BOC_2O in the presence of excess of potassium hydroxide. Hydrolysis and *N*-acylation proceeded simultaneously.

The use of the isoxazolylacetic acids **9a**, **b**, **10a**, **b** and **15** as acylating agents for the synthesis of new monobactams will be published in the near future.

Table 3 Bond lengths (Å) and bond angles (°) for compound **10b** with e.s.d's in parentheses

Bond lengths

O(1)–N(2)	1.395(3)	C(7)–C(11)	1.514(3)
O(1)–C(5)	1.359(3)	N(8)–O(9)	1.377(2)
N(2)–C(3)	1.301(3)	O(9)–C(10)	1.428(3)
C(3)–C(4)	1.409(3)	C(11)–O(12)	1.316(3)
C(3)–Cl(6)	1.704(2)	C(11)–O(13)	1.193(3)
C(4)–C(5)	1.350(3)		
C(5)–C(7)	1.457(3)		
C(7)–N(8)	1.283(3)		

Bond angles

N(2)–O(1)–C(5)	108.2(3)
O(1)–N(2)–C(3)	105.7(4)
N(2)–C(3)–C(4)	112.5(4)
N(2)–C(3)–Cl(6)	119.2(3)
C(4)–C(3)–Cl(6)	128.4(3)
C(3)–C(4)–C(5)	103.8(4)
O(1)–C(5)–C(4)	109.9(4)
O(1)–C(5)–C(7)	116.6(3)
C(4)–C(5)–C(7)	133.5(4)
C(5)–C(7)–N(8)	117.1(4)
C(5)–C(7)–C(11)	118.3(3)
N(8)–C(7)–C(11)	124.5(4)
C(7)–N(8)–O(9)	111.8(3)
N(8)–O(9)–C(10)	109.9(4)
C(7)–C(11)–O(12)	110.8(3)
C(7)–C(11)–O(13)	122.6(4)
O(12)–C(11)–O(13)	126.6(4)

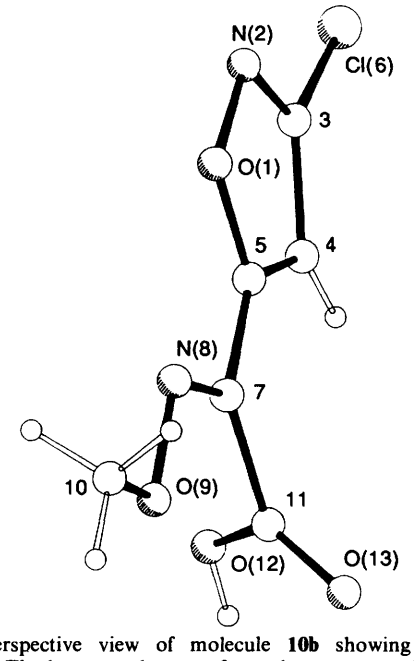


Fig. 1 Perspective view of molecule **10b** showing the atomic numbering. The bone numbers are for carbon atoms, unless indicated otherwise. H atoms are shown, but not labelled.

Experimental

M.p.s were measured on a hot-stage melting point apparatus and are uncorrected. IR spectra were obtained with a Specord 75 (Zeiss, GDR) instrument. ^1H NMR spectra were recorded on a Perkin-Elmer 12 (60 MHz) and JEOL FX-100 (100 MHz) spectrometers, with $SiMe_4$ as internal reference in $CDCl_3$, unless otherwise stated. Column and the thin layer chroma-

tography was carried out on Merck Kieselgel 60 (0.063–0.2) and Merck Kieselgel 60 F_{254}, and Alufolien, respectively. For preparative TLC Merck PSC-ready plates (Kieselgel 60 F_{254}, 20 × 20 cm, 2 mm) were used, unless otherwise indicated.

3-(3-*Chloroisoxazol-5-yl*)*propionyl Chloride* **3**.—(3-Chloroisoxazol-5-yl)propionic acid[6] (17.56 g, 0.1 mol) was stirred overnight in thionyl chloride (20 cm^3). The excess of thionyl chloride was removed and the residue was distilled from an oil bath heated at not above 160 °C to obtain *compound* **3** (19.09 g, 98%), b.p. 90–92 °C (0.2 mmHg) (Found: C, 37.0; 2.7; Cl, 36.4; N, 7.2. $C_6H_5Cl_2NO_2$ requires C, 37.1; H, 2.6; Cl, 36.55; N, 7.2%); ν_{max}(film)/cm^{-1} 3100 and 1770 (CO); δ_H(60 MHz) 3.0–3.65 (4 H, m, CH_2CH_2) and 6.17 (1 H, s, isoxazole-4-H).

(E)-3-(3-*Chloroisoxazol-5-yl*)*acrylic Acid* **4**.—A mixture of the acid chloride **3** (97.0 g, 0.5 mol), sulfuryl chloride (100 cm^3), carbon tetrachloride (400 cm^3), and dibenzoyl peroxide (1.0 g) was refluxed for 10 h. Then the same amounts of sulfuryl chloride and dibenzoyl peroxide were added to the mixture and it was refluxed for 10 h more. The solution was evaporated and poured into a cold solution of sodium hydroxide (80.0 g, 2.0 mol) in water (300 cm^3). The mixture was diluted with water (600 cm^3) and heated to reflux temperature. The solution was cooled to room temperature and extracted with ether (2 × 500 cm^3). The ethereal solutions were discarded. The aqueous layer was acidified to pH 2. The crude product was filtered off and crystallised from a 2:1 mixture of water–acetic acid to furnish compound **4** (71.0 g, 88.8%), m.p. 200–201 °C (lit.,[7] 190 °C) (Found: C, 41.4; H, 2.4; Cl, 20.6; N, 8.0. Calc. for $C_6H_4ClNO_3$; C, 41.5; H, 2.3; Cl 20.4; N, 8.1%); ν_{max}(KBr)/cm^{-1} 3400–2700 (OH), 1680 (CO) and 1560; δ_H[60 MHz; $(CD_3)_2SO$] 6.35 (1 H, d, *J* 18, –CH=), 7.0 (1 H, s, isoxazole-4-H) and 7.25 (1 H, d, *J* 18, –CH=).

(E)-3-(3-*Chloroisoxazol-5-yl*)*acryloyl Chloride* **5**.—A mixture of the acrylic acid **4** (19.0 g, 0.11 mol), thionyl chloride (14 cm^3), pyridine (1 cm^3) and benzene (75 cm^3) was stirred for 45 min in an oil bath at 110 °C. The solution was evaporated and the residue was crystallised from hexane to give the *compound* **5** (18.0 g, 85%), m.p. 74 °C (Found: Cl, 36.7; N, 7.45. $C_6H_3ClNO_2$ requires Cl, 36.9; N, 7.3%); ν_{max}(KBr)/cm^{-1} 1730 (CO) and 1540; δ_H(60 MHz) 6.50 (1 H, s, isoxazole-4-H), 6.69 (1 H, d, *J* 16, –CH=) and 7.42 (1 H, d, *J* 16, –CH=).

(E/Z)-(3-*Chloroisoxazol-5-yl*)*acetaldehyde Oxime* **6**.—Sodium azide (6.6 g, 0.1 mol) was added in small portions to a cold (0 °C) solution of the acryloyl chloride **5** (17.0 g; 88.6 mmol) in dry DMF (40 cm^3) during a 30 min period. The mixture was stirred for 1 h at 0 °C and poured into ice (100 g)–water (300 cm^3). The crude azide was filtered off, washed with cold water (2 × 50 cm^3) and dissolved in ether (500 cm^3). After drying ($CaCl_2$), the solution was evaporated under reduced pressure with the temperature of the bath maintained at 40 °C. The residue was heated at reflux for 45 min in dry dioxane (150 cm^3). This solution was added dropwise to a hot mixture of acetic acid (150 cm^3), water (150 cm^3) and sulfuric acid (150 cm^3). The mixture was refluxed for 10 min. Hydroxyammonium chloride (30 g, 0.43 mol) and sodium acetate (90 g, 1.1 mol) were then added to the cooled solution and the mixture was stirred for 3 h, diluted with water (600 cm^3) and extracted with ether (3 × 250 cm^3). The combined organic layers were washed with water (3 × 250 cm^3), dried ($CaCl_2$), treated with charcoal and filtered. The filtrate was evaporated and pentane (150 cm^3) was added to the residue. The pentane was distilled off and the residue was crystallised from a mixture of CH_2Cl_2–pentane (1:4) to give *compound* **6** (9.4 g, 66%), m.p. 71–72 °C (Found: Cl, 22.6; N, 17.1. $C_5H_5ClN_2O_2$ requires Cl, 22.1; N, 17.45%); ν_{max}(KBr)/cm^{-1} 3600–3000 and 1600; δ_H(100 MHz; $CDCl_3$ + D_2O) 3.7 (d, *J* 8.35, CH_2), 3.9 (d, *J* 6.66, CH_2) 6.15 (1 H, s, isoxazole-4-H), 6.95 (t, *J* 6.66, N=CH) and 7.55 (t, *J* 8.35, N=CH).

(3-*Chloroisoxazol-5-yl*)*acetic Acid* **1**.—Thionyl chloride (7.8 cm^3, 0.1 mol) was added to a solution of the oxime **6** (6.5 g, 40.5 mmol) in dry ether (40 cm^3) at 0 °C during 5 min. The mixture was allowed to warm to room temperature, and it was stirred for 30 min. The solution was evaporated, and dry benzene (60 cm^3) and pentane (60 cm^3) were successively distilled off from the residue under reduced pressure. The crude nitrile was hydrolysed by refluxing it in a mixture of acetic acid (15 cm^3) and 48% hydrogen bromide (15 cm^3) for 1.5 h. The solution was poured into ice (40 g)–water (80 cm^3). The undissolved material was filtered off and the filtrate extracted with ether (3 × 75 cm^3). The combined organic extracts were washed with brine (20 cm^3), dried ($MgSO_4$) and evaporated. The residue was crystallized from a mixture of benzene–hexane (1:2) to obtain compound **1** (4.3 g, 66%); m.p. 90–92 °C (Found: Cl, 2.85; N, 8.9. Calc. for $C_5H_4ClNO_3$ Cl, 21.95; N, 8.8%); ν_{max}/cm^{-1} 3500–2400br (OH) and 1700 (CO); δ_H(60 MHz) 3.9 (2 H, s, CH_2), 6.35 (1 H, s, isoxazole-4-H) and 10.25 (1 H, br s, CO_2H).

Methyl α-(3-*Chloroisoxazol-5-yl*)-α-*oxoacetate* **8**.—Methyl α-(3-chloroisoxazol-5-yl)-α-hydroxyacetate[4] **7** (7.18 g, 37.5 mmol) was dissolved in CH_2Cl_2 (65 cm^3) and stirred with 4.7 g of activated manganese(IV) oxide until all the starting material had reacted. The reaction was monitored by TLC (benzene–acetone, 7:3) [Further 1–1.5 g of manganese(IV) oxide was added when necessary.] The mixture was filtered, the inorganic material was washed with CH_2Cl_2 (2 × 15 cm^3), and the combined organic filtrates were evaporated. The residue was recrystallized from benzene–hexane to give *compound* **8** (6.1 g, 85.5%), m.p. 63 °C (Found: C, 37.9; H, 2.4; Cl, 19.1; N, 7.1. $C_6H_4ClNO_4$ requires C, 38.0; H, 2.1; Cl, 18.7; N, 7.4%); ν_{max}(KBr)/cm^{-1} 1740, 1700 (CO's), 1220 and 1020 (C–O–C); δ_H(60 MHz) 3.9 (3 H, s, OCH_3) and 7.10 (1 H, s, 4-H).

Methyl α-(3-*Chloroisoxazol-5-yl*)-α-*methoxyiminoacetate* **9**.—*O*-Methylhydroxylamine hydrochloride (0.97 g, 11.6 mmol), solid NaOH (0.47 g, 11.6 mmol) and dry $MgSO_4$ (2.78 g) were successively added to a stirred solution of compound **8** (2.0 g, 10.6 mmol) in methanol (20 cm^3) at 0 °C. The mixture was stirred until no starting material could be detected by TLC (about 20 h) (benzene–ether–acetone, 5:1:0.1). The suspension was evaporated, the residue was extracted by hot ether (3 × 35 cm^3) and the combined ethereal solutions were evaporated. The crude mixture of the diastereoisomers **9a** and **9b** were separated by column chromatography (200 g, heptane–ether, 8:2) to obtain:

(a) (E)-*Isomer* **9a** (0.8 g, 34.7%), m.p. 71 °C (from ether–hexane), R_f 0.38, benzene–ether–acetone (5:1:0.1) (phosphomolybdic acid) (Found: C, 37.8; H, 3.1; Cl, 15.8; N, 12.4. $C_7H_7ClN_2O_4$ requires C, 38.05; H, 3.2; Cl, 16.2; N, 12.7%); ν_{max}(KBr)/cm^{-1} 1740 (CO), 1210, 1080 and 1025; δ_H(100 MHz) 3.96 (3 H, s, CO_2CH_3), 4.26 (3 H, s, N–OCH_3) and 7.01 (3 H, s, 4-H).

(b) (Z)-*Isomer* **9b** (0.6 g, 26%) oil, R_f 0.61, benzene–ether–acetone (5:1:0.1), (phosphomolybdic acid) (Found: C, 38.4; H, 2.9; Cl, 16.7; N, 12.5. $C_7H_7ClN_2O_4$ requires C, 38.05; 3.2; Cl, 6.2; N, 12.7%); ν_{max}(film)/cm^{-1} 1740 (CO), 1240 and 1040br; δ_H(100 MHz) 3.95 (3 H, s, CO_2CH_3), 4.12 (3 H, s, N–OCH_3) and 6.61 (1 H, s, 4-H).

(E)-α-(3-*Chloroisoxazol-5-yl*)-α-*methoxyiminoacetic Acid*-**10a**.—The (*E*)-ester **9a** (0.7 g, 3.2 mmol) was stirred in aqueous KOH (4 cm^3, 0.36 g, 6.4 mmol) at 0 °C until the starting material was completely dissolved. The solution was acidified to pH 2,

extracted with ether (6 × 20 cm^3), dried ($MgSO_4$) and the extract was evaporated to give *compound* **10a** (0.44 g, 67.2%), m.p. 132 °C (benzene), R_f 0.1 (acetone–acetic acid, 10:0.5) (Found: C, 35.1; H, 2.5; Cl, 16.9; N, 13.3. $C_6H_5ClN_2O_4$ requires C, 35.2; H, 2.5; Cl, 17.3; N, 13.7%); ν_{max}(KBr)/cm^{-1} 1705 (CO), 1210, 1065 and 1025; δ_H(100 MHz) 4.31 (3 H, s, N–OCH_3) and 7.09 (1 H, s, 4-H).

(*Z*)-α-(3-*Chloroisoxazol-5-yl*)-α-*methoxyimonoacetic Acid* **10b**.—The (*Z*)-acid **10b** (0.44 g, 67.2%) was prepared as described for the (*E*)-acid **10a**, starting from the (*Z*)-ester **9b** (0.7 g, 3.2 mmol); m.p. 123 °C (from benzene), R_f 0.2 (acetone–acetic acid, 10:0.5) (Found: C, 34.5; H, 2.2; Cl, 17.4; N, 13.9. $C_6H_5ClN_2O_4$ requires C, 35.2; H, 2.5; Cl, 17.3; N, 13.7%); ν_{max}(KBr)/cm^{-1} 1730br (CO), 1180 and 1030; δ_H(100 MHz) 4.25 (3 H, s, N–OCH_3), 6.83 (1 H, s, 4-H) and 8.39 (1 H, br s, CO_2H).

Methyl α-(3-*Chloroisoxazol-5-yl*)-α-*hydroxyiminoacetate* **11**.—A mixture of the oxo ester **8** (6.3 g, 33.2 mmol), hydroxylamine hydrochloride (6.93 g, 99.7 mmol) and dry methanol (120 cm^3) was refluxed for 15 h, and then evaporated to dryness. The residue was taken up in saturated aqueous NaCl (10 cm^3), extracted with ether (4 × 100 cm^3), dried ($MgSO_4$), and evaporated. The crude product was crystallized from benzene to give *compound* **11** (5.30 g, 77.9%), m.p. 114–114.5 °C (Found: C, 35.5; H, 2.6; Cl, 17.7; N, 13.9. $C_6H_5ClN_2O_4$ requires C, 35.2; H, 2.5; Cl, 17.3; N, 13.7%); ν_{max}/cm^{-1} 1730 (CO), 1240 and 1050; δ_H(100 MHz) 3.99 (3 H, s, CO_2CH_3), 7.15 (1 H, s, 4-H) and 10.5 (1 H, vbs, OH).

Methyl α-*Amino*-α-(3-*chloroisoxazol-5-yl*)*acetate Hydrochloride* **12**.—The α-hydroxyimino ester **11** (7.5 g, 36.7 mmol) was dissolved in dry ethanol saturated with HCl (75 cm^3) and hydrogenated in the presence of 10% Pd–C catalyst (1.5 g) at room temperature (12 h). The catalyst was removed by filtration, and the filtrate was evaporated. The residue on rubbing with dry ether gave the *ester·HCl* **12** (7.0 g, 84%), m.p. 157–158 °C (from methanol–ether) (Found: C, 31.9; H, 3.7; Cl 31.6; N, 12.0. $C_6H_8Cl_2N_2O_3$ requires C, 31.7; H, 3.55; Cl, 31.2; N, 12.3%); ν_{max}(KBr)/cm^{-1} 3300–2500 (NH_3), 1750 (CO), 1260 and 1080; δ_H[$(CD_3)_2SO$; 60 MHz] 3.78 (3 H, s, CO_2CH_3), 5.87 (1 H, s, α-H), 7.2 (1 H, s, 4-H) and 8.7–10.5 (3 H, vbr, NH_3).

α-*Amino*-α-(3-*chloroisoxazol-5-yl*)*acetic Acid Hydrochloride* **13**.—(a) The ester hydrochloride **12** (227 mg, 1.0 mmol) was stirred in 1:1 aqueous HCl (3 cm^3) at 60–70 °C for 6 h. The solution was evaporated. The residue, on rubbing with dry ether, gave *compound* **13** (201 mg, 94.4%), m.p. 130–140 °C (decomp.) (Found: C, 28.5; H, 2.9; Cl, 32.9; N, 13.4. $C_5H_6Cl_2N_2O_3$ requires C, 28.2; H, 2.8; Cl, 33.3; N, 13.2%); ν_{max}/cm^{-1} 3300–2500 and 2100–1940 (NH_3) and 1745 (CO); δ_H[$(CD_3)_2SO$, 60 MHz] 5.6 (1 H, s, α-H), 7.10 (1 H, s, 4-H) and 8.6 (vbr s, NH_3 + CO_2H + H_2O).

(b) The acid hydrochloride **13** (92%) was similarly prepared, by stirring at 80 °C, starting with compound **14**; the product proved completely identical (IR, NMR, m.p.) with the sample prepared as described under (a).

Methyl α-*Acetylamino*-α-(3-*chloroisoxazol-5-yl*)*acetate* **14**.—Zinc dust (2.32 g, 35.4 mmol) was added in small portions to a refluxing mixture of the α-hydroxyimino ester **11** (5.8 g, 28.4 mmol) and acetic acid (80 cm^3) during a 6 h period. After cooling, the mixture was poured onto 100 g of crushed ice and extracted with ether (4 × 50 cm^3). The combined ethereal solutions were washed with 5% $NaHCO_3$, dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography (69 g; $CHCl_3$–ether, 10:1) to obtain *compound* **14** (2.1 g, 32%), m.p. 123 °C (Found: C, 41.6; H, 3.8; Cl, 15.6; N, 11.8. $C_8H_9N_2O_4$ requires C, 41.3; H, 3.9; Cl, 15.2; N, 12.0%); ν_{max}/cm^{-1} 3300 (NH), 1750 and 1650 (CO s); δ_H(100 MHz), 2.09 (3 H, s, CH_3CO), 3.83 (3 H, s, CO_2CH_3), 5.88 (1 H, d, $J_{NH,\alpha}$ 7, α-H), 6.39 (1 H, s, 4-H) and 6.63 (1 H, d, $J_{\alpha,NH}$ 7, NH).

α-tert-*Butoxycarbonylamino*-α-(3-*chloroisoxazol-5-yl*)*acetic Acid* **15**.—(a) A solution of KOH (5.2 g, 93 mmol) in water (30 cm^3), di-*tert*-butyl oxydiformate (8.0 g, 46.2 mmol) and *tert*-butyl alcohol (3 cm^3) were added to a solution of the ester hydrochloride **12** (7.0 g, 30.8 mmol) in water (30 cm^3) and the mixture was stirred at ambient temperature for 8 h. The solution was cooled to 0 °C, acidified with 2 mol dm^{-3} HCl to pH 2 and extracted with ethyl acetate (4 × 50 cm^3). The combined organic layers were dried ($MgSO_4$) and evaporated to dryness. The residue was crystallized from benzene to furnish *compound* **15** (5.12 g, 60.2%), m.p. 136–137 °C (Found: C, 43.6; H, 4.3; Cl, 12.8; N, 10.35. $C_{10}H_{13}ClN_2O_5$ requires C, 43.4; H, 4.7; Cl, 12.8; N, 10.15%); ν_{max}(KBr)/cm^{-1} 3300 (NH), 1745, 1730 and 1650 (CO s); δ_H[$(CD_3)_2SO$; 100 MHz] 1.40 (9 H, s, 3 × CH_3), 5.47 (1 H, d, $J_{NH,\alpha}$ 8.5, α-H), 6.8 (1 H, s, 4-H) and 7.97 (1 H, d, $J_{\alpha,NH}$ 8.5, α-H); δ_C[$(CD_3)_2SO$; 25 MHz)] 28.29 (CH_3), 51.08 (α-C), 79.39 [$OC(CH_3)_3$], 104.11 (C-4), 153.84 and 155.27 (C-3 and C-5), 168.55 (CO) and 171.21 (CO).

(b) The title compound **15** (39%) was similarly prepared starting from compound **13**; the product was completely identical (IR, NMR, m.p.) with the sample prepared as described under (a).

Crystal Structure Determination of **10b**.—*Crystal data.* $C_6H_5ClN_2O_4$, M = 204.6, Triclinic, a = 7.377(1), b = 7.618(1), c = 7.972(1) Å, α = 76.00(1), β = 79.65(1), γ = 75.02(1)°, V = 416.64(12) A^3 (by least squares refinement of diffractometer angles for 25 automatically centred reflections) [35 < θ < 30°, λ = 1.5418 Å], space group $P\bar{1}$ (No. 2). Z = 2, $F000$ = 208, D_x = 1.63 gcm^{-3}. Colourless crystals of approx. size of 0.25 × 0.40 × 0.40 mm, μ(Cu–Kα) = 40.52 cm^{-1}.

Data collection and processing. CAD4 diffractometer, $\omega/2\theta$ mode with ω scan width = 0.50 + 0.14 tanθ, ω scan speed 1–20 deg min^{-1}, graphite monochromated Cu–Kα radiaton; 1720 unique reflections measured (1.5 ≤ θ ≤ 75°, $-hk - l$). Three intensity check reflections measured every hour, the intensity variations indicated no crystal decay.

Structure analysis and refinement. Direct methods (all non-hydrogen atoms). Full matrix least squares with all non-hydrogen atoms anisotropic and hydrogens in calculated positions (except the OH hydrogen atom, which was located in a difference map), their isotropic B(Å^2) fixed at the equivalent isotropic B + 1 of the heavy atom to which they are bonded. The weighting scheme $w = 1/\sigma^2(F_o) + 0.040F_o^2]$, with $\sigma(F_o)$ from counting statistics. Final R and R_w values are 0.060, 0.095 for 1575 observed $F^2 > 3.0\sigma(F^2)$.

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