Isoxazole Amino-acids as Glutamic Acid Agonists. Synthesis of Some Analogues and Homologues of Ibotenic Acid

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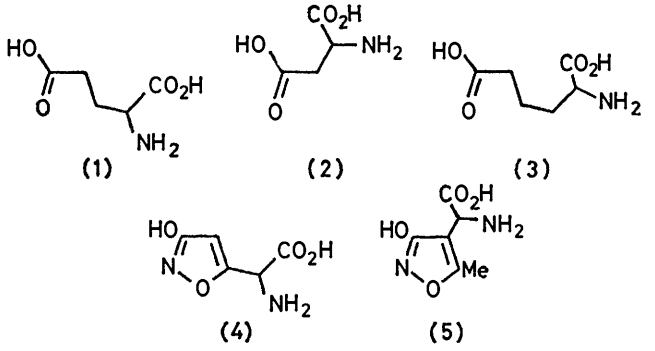
(*R,S*)-α-Amino-3-hydroxy-4-methylisoxazol-5-ylacetic acid (4-methylibotenic acid) (14) was prepared *via* amination of 3-methoxy-4-methylisoxazol-5-ylacetic acid (12) with *O*-mesitylenesulphonyloxyamine. (*R,S*)-α-Amino-3-hydroxyisoxazol-5-ylpropionic acid (homoibotenic acid) (17), (*R,S*)-α-amino-4-bromo-3-hydroxyisoxazol-5-ylpropionic acid (4-bromohomoibotenic acid) monohydrate (24), and (*R,S*)-α-amino-3-hydroxy-5-methylisoxazol-4-ylpropionic acid monohydrate (33) were all synthesized *via* alkylation of diethyl acetamidomalonate. An alternative synthesis of homoibotenic acid proceeded by addition of ammonia to (*E*)-3-methoxyisoxazol-5-ylpropenoic acid (16) with concurrent tin(IV)-induced cleavage of the methoxy-group. This ether cleavage under basic conditions appears to be of general utility for the deprotection of 3-methoxyisoxazoles.

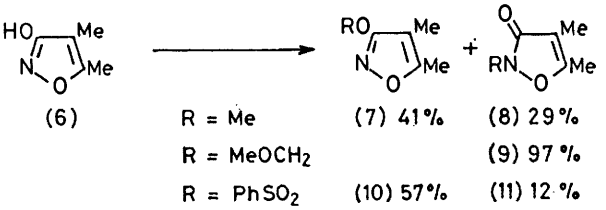
SUBSTANTIAL evidence supports the function of (*S*)-glutamic acid (Glu) (1) and (*S*)-aspartic acid (Asp) (2) as excitatory neurotransmitters in the mammalian central nervous system.[1] Ibotenic acid [(*R,S*)-α-amino-3-hydroxyisoxazol-5-ylacetic acid] (4), a naturally occurring amino-acid isolated from *Amanita muscaria*,[2] is a



conformationally restricted analogue of Glu with a similar, but more potent, excitatory action.[3] A large number of analogues of Glu and Asp have been prepared and neurophysiologically tested [4] in order to elucidate the properties of the putative Glu and Asp receptors. The excitatory action of Glu and Asp appears to be differentially antagonized by Glu diethyl ester [5,6] and (*R*)-α-aminoadipic acid [6,7] (3), but more selective antagonists, as well as agonists, are needed. We considered that structural manipulations of ibotenic acid, retaining the conformational restrictions imposed by the isoxazole ring, might lead to more potent and more selective agonists and antagonists. Therefore, the Asp analogue (5) was previously prepared,[8] and this paper reports the preparation of four new 3-hydroxyisoxazole amino-acids structurally analogous to Glu and α-aminoadipic acid. Part of the results have been presented in a preliminary communication.[9]

RESULTS AND DISCUSSION

O-Methylation is the most commonly used procedure for protection of 3-hydroxyisoxazoles in spite of a relatively low yield because of concomitant *N*-methylation. Moreover, the drastic deprotection conditions, usually reflux in concentrated solutions of hydrogen bromide, constitutes another disadvantage. Hence, we decided first to examine the methoxymethyl [10,11] and the benzenesulphonyl [11,12] groupings as potential 3-hydroxyisoxazole protecting groups for our synthetic sequences. Reaction of 3-hydroxy-4,5-dimethylisoxazole [13] (6) with dimethoxymethane [10] and benzenesulphonyl chloride,[12] as well as with diazomethane,[14] gave the yields of isolated products presented in Scheme 1. The sole product of methoxymethylation was identified as the *N*-alkylated derivative (9) by its u.v. absorption at 240 nm and lack of i.r. absorption between 1 500 and 1 600 cm^{-1} (ref. 15). However, treatment of the protected isoxazoles (7), (9), and (10) with butyl-lithium or lithium di-isopropylamide, with subsequent addition of carbon dioxide, caused decomposition of (9) and (10), whereas (7) was carboxylated to give 3-methoxy-4-methylisoxazol-5-ylacetic acid (12) as previously described.[16] Because the subsequent reactions in our



SCHEME 1

syntheses included steps involving strong bases, we therefore decided to revert to *O*-methylation as a means of protection.

A study [17] of the amination of α-lithiated carboxylic acids concluded that methoxyamine was the best aminating reagent. However, reaction of 3-methoxy-4-methylisoxazol-5-ylacetic acid (12) with lithium di-isopropylamide followed by methoxyamine under a variety of conditions only led to recovery of the starting material. *O*-Mesitylenesulphonyloxyamine [*O*-(2,4,6-trimethylphenylsulphonyl)hydroxylamine] is a relatively stable aminating reagent containing a better leaving group than that of methoxyamine; surprisingly, no

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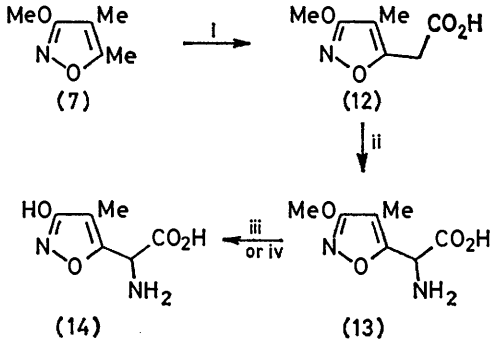
reactions of this reagent with α-lithiated carboxylic acids are mentioned in a recent review.[18] *O*-Mesitylenesulphonyloxyamine may explode when isolated in the dry state;[19] hence, we used a dried tetrahydrofuran solution of the moist [18] compound to convert the carboxylic acid (12) into the amino-acid (13) in *ca.* 20% yield (Scheme 2). No improvement in the yield was obtained by using recrystallized *O*-mesitylenesulphonyloxyamine. Subsequent deprotection, either by hydrogen bromide in glacial acetic acid or by tin(IV) chloride added to aqueous ammonia (see above), gave (*R,S*)-α-amino-3-hydroxy-4-methylisoxazol-5-ylacetic acid (4-methylibotenic acid) (14).

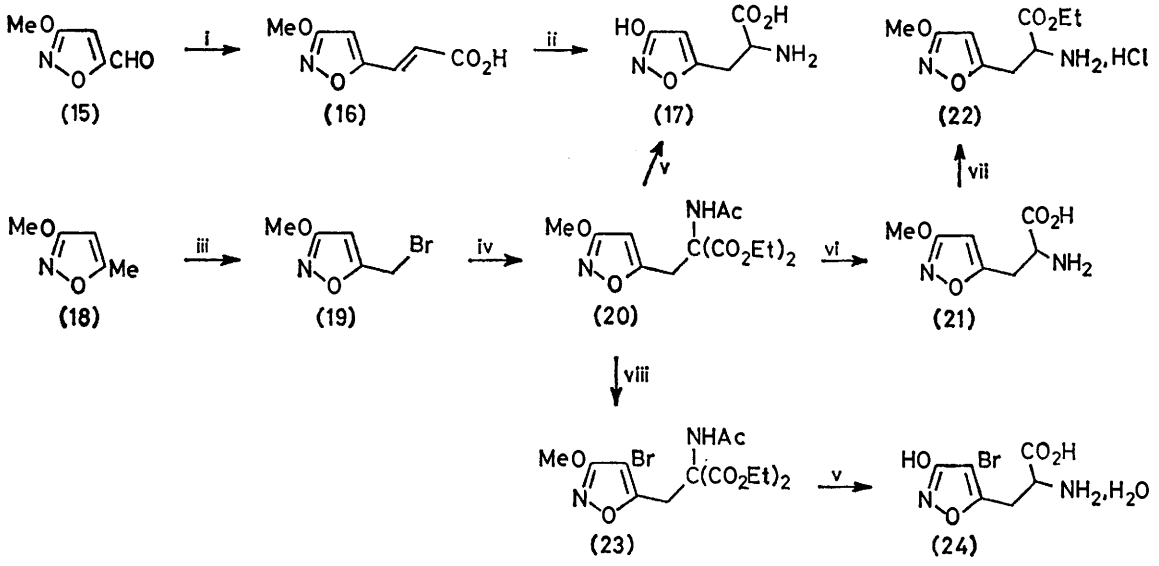
During the preparation of 3-methoxyisoxazol-5-ylpropionic acid (25) by a published procedure,[20] we observed the formation of a second constituent which on t.l.c. appeared slightly less polar and more u.v. absorbing. After esterification the two constituents were separated by column chromatography to yield the methyl esters of 3-methoxyisoxazol-5-ylpropionic acid and (*E*)-3-methoxyisoxazol-5-ylpropenoic acid, respectively. Hydrolysis afforded the corresponding carboxylic acids; and the structure of the propenoic acid (16) was confirmed by its independent synthesis by a Knoevenagel-type condensation of 3-methoxyisoxazole-5-carbaldehyde [21] (15) with malonic acid (Scheme 3).

worked up to give a *ca.* 25% yield of a pure amino-acid containing a 3-hydroxyisoxazole moiety, as evidenced from t.l.c. and i.r. and ^{1}H n.m.r. spectroscopy. The spectroscopic data did not allow an identification of the product as an α- or a β-amino-acid, the latter usually



SCHEME 2 i, BuLi, CO_2; ii, Pr^i_2NLi, *O*-mesitylenesulphonyloxyamine; iii, HBr–AcOH, Et_3N; iv, $SnCl_4$–NH_4OH

being obtained by this type of Michael addition. However, the product proved identical with the independently synthesized (*R,S*)-α-amino-3-hydroxyisoxazol-5-ylpropionic acid (homoibotenic acid) (17), showing that the isoxazole moiety, rather than the carboxylate group, directed the course of the nucleophilic addition, probably



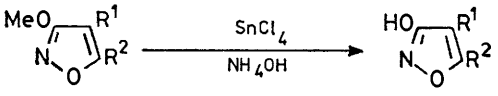
SCHEME 3 i, $CH_2(CO_2H)_2$; ii, $SnCl_4$–NH_4OH; iii, NBS; iv, AcNH·$CH(CO_2Et)_2$–NaOEt; v, HBr aq., Et_3N; vi, HCl aq., Et_3N; vii, HCl–EtOH; viii, Br_2 (neat)

Treatment of the propenoic acid (16) with concentrated aqueous ammonia for 3—4 days under pressure at 105 °C gave a brown reaction mixture, from which only a very small amount (1—2% yield) of a Ninhydrin-active product mixture could be obtained. Addition of tin(IV) chloride [22] to a solution of (16) in concentrated aqueous ammonia resulted in precipitation of tin(IV) oxide hydrate. Heating this mixture to 105 °C for 4—9 days gave an almost colourless reaction mixture, due to better stabilization of an intermediary α-carbanion. This is in accord with the recent finding [23] that reaction of lithiated 3-methoxyisoxazol-5-ylpropionic acid (25) with methyl iodide introduces a methyl group regiospecifically α to the isoxazole ring. Although (17) is obtained in relatively low yield, the addition reaction apparently proceeds with a high degree of regioselectivity. In no case could any β-amino-acid be isolated from the reaction mixture; the only detectable by-product,

present in small amounts, was identified as (*E*)-3-hydroxyisoxazol-5-ylpropenoic acid, the deprotected starting material. The best yield of (17) was obtained after addition of *ca.* 0.7 molar equivalents of tin(IV) chloride, but the isolated yield never exceeded 30%.

The observed methoxy-group cleavage under mildly basic conditions is a new reaction in isoxazole chemistry. To test the general validity of this reaction, 3-methoxyisoxazol-5-ylpropionic acid (25) was treated under similar conditions for 2 days to give 3-hydroxyisoxazol-5-ylpropionic acid (26) in 28% yield. This demethylation was neither effected by heating (25) with concentrated aqueous ammonia alone, nor by refluxing (25) with aqueous tin(IV) chloride. 5-Hydroxymethyl-3-methoxyisoxazole [24] (27), which could not be deprotected cleanly with hydrogen bromide in glacial acetic acid, gave, after heating with aqueous ammonia and tin(IV) chloride, a 36% yield of 3-hydroxy-5-hydroxymethylisoxazole (28). Demethylation of the amino-acid (13) by this procedure afforded, as mentioned earlier, 4-methylibotenic acid (14) in 12% yield. These reactions are summarized in Scheme 4, and we conclude that the procedure, despite its modest yields, constitutes a general reaction which may be especially useful for the deprotection of 3-methoxyisoxazoles containing additional acid-labile groups. The reactive species, requiring both ammonia and tin(IV) chloride, remains unidentified; by analogy with the Lewis acid-induced deprotection of phenols,[11] it may be assumed that the species in some way complexes with the 3-methoxyisoxazole moiety, furnishing protection against decomposition and facilitating cleavage of the methoxy-group.

The independent synthesis of homoibotenic acid (17) started with *N*-bromosuccinimide (NBS) bromination of 3-methoxy-5-methylisoxazole (18) (Scheme 3). This



(25) R^1,R^2 = H, $CH_2CH_2CO_2H$ (26)
(13) R^1,R^2 = Me, $CHNH_2CO_2H$ (14)
(27) R^1,R^2 = H, CH_2OH (28)

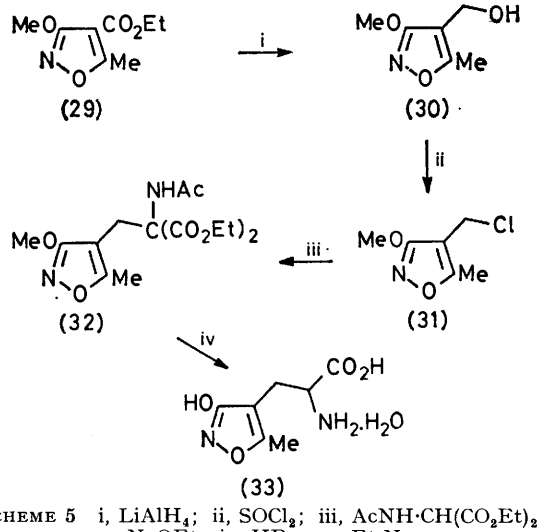
SCHEME 4

preparation requires several additions of NBS (freshly recrystallized to avoid bromination in the 4-position) to give an adequate yield of the bromomethylisoxazole (19), previously prepared [25] by treatment of (27) with phosphorus tribromide. Reaction of (19) with diethyl acetamidomalonate under basic conditions yielded the isoxazole (20). Heating of (20) with 48% aqueous hydrogen bromide at 140 °C for between 15 and 20 min afforded homoibotenic acid (17) in *ca.* 60% yield after triethylamine neutralization. Shorter deprotection times led to incomplete hydrolysis of the amide bond, and longer periods caused decomposition of the isoxazole ring.

Hydrolysis of the protected isoxazole (20) with 1M-hydrochloric acid furnished the methoxyisoxazole amino-acid (21), esterification of which gave ethyl (*R,S*)-α-amino-3-methoxyisoxazol-5-ylpropionate hydrochloride (22), an isoxazole homologue of Glu diethyl ester.

Halogenation of 3,5-disubstituted isoxazoles has been reported [26] to give 4-halogenoisoxazoles. However, reflux of (20) with bromine in tetrachloromethane failed to give any conversion within 24 h as evidenced by ^1H n.m.r. spectroscopy. In contrast, (20) dissolved in neat bromine was quantitatively converted into the 4-bromoisoxazole (23) within 6 h at room temperature. Deprotection of (23) with 48% aqueous hydrogen bromide, as described above, afforded (*R,S*)-α-amino-4-bromo-3-hydroxyisoxazol-5-ylpropionic acid (4-bromohomoibotenic acid), isolated as the monohydrate (24).

Reduction of ethyl 3-methoxy-5-methylisoxazole-4-carboxylate [16] (29) by lithium aluminium hydride yielded (Scheme 5) the hydroxymethylisoxazole (30),



SCHEME 5 i, $LiAlH_4$; ii, $SOCl_2$; iii, $AcNH{\cdot}CH(CO_2Et)_2$–NaOEt; iv, HBr, aq., Et_3N

which was converted into the chloromethylisoxazole (31) by reaction with neat thionyl chloride. Alkylation of diethyl acetamidomalonate by (31) yielded the protected derivative (32), which after deprotection by 48% aqueous hydrogen bromide and triethylamine treatment gave (*R,S*)-α-amino-3-hydroxy-5-methylisoxazol-4-ylpropionic acid monohydrate (33). The structure of (33) has been confirmed by *X*-ray crystallography.[27]

In neurophysiological studies 4-bromohomoibotenic acid and especially (*R,S*)-α-amino-3-hydroxy-5-methylisoxazol-4-ylpropionic acid proved to be very potent and specific Glu agonists. The details of these studies will be reported elsewhere.[28]

EXPERIMENTAL

Melting points, determined in capillary tubes, are uncorrected. Elemental analyses on new compounds were performed by Mr. P. Hansen at Chemical Laboratory II, University of Copenhagen. I.r. and u.v. spectra were recorded on a Perkin-Elmer grating i.r. spectrophotometer model 247 and a Perkin-Elmer u.v.–visible spectrophotometer model 402, respectively. I.r. bands, listed as $\nu_{max.}$,

were recorded from KBr discs or liquid films. ^{1}H N.m.r. spectra were recorded on a JEOL JMN-C-60HL instrument or, at 90 MHz, on a Bruker HXE-90 instrument (FT mode). Chemical shifts are expressed as δ values using $SiMe_4$ or DSS as internal standard, unless otherwise noted. A Waters PrepLC/System 500 instrument was used for preparative high-pressure liquid chromatography (h.p.l.c.). T.l.c. and gravity column chromatography were performed on silica F_{254} plates (Merck) and silica gel (Woelm, 0.063—0.200 mm), respectively. Evaporations were performed at temperatures below 50 °C, using a vacuum rotary evaporator connected to a water aspirator.

3-Methoxy-4,5-dimethylisoxazole (7) *and 2,4,5-Trimethylisoxazol-3-one* (8).—Diazomethane [29] methylation of 3-hydroxy-4,5-dimethylisoxazole [13] (6) yielded after evaporation a dark oil which was subjected to preparative h.p.l.c. on silica columns. Elution with hexane–ethyl acetate (8 : 1) gave the *O*-methylated product (7) in 41% yield; m.p. 32—33 °C after recrystallization from light petroleum (lit.,[14] m.p. 35—37 °C). Subsequent elution of the column with ethyl acetate furnished the *N*-methylated product (8) in 29% yield, a portion of which was ball tube distilled at 0.4 mmHg (oven temperature 100 °C) (lit.,[14] b.p. 130 °C at 15 mmHg).

2-Methoxymethyl-4,5-dimethylisoxazol-3-one (9).—To 3-hydroxy-4,5-dimethylisoxazole [13] (6) (2.26 g, 20 mmol) dissolved in dichloromethane (40 ml) were added dimethoxymethane (10 ml, 8.6 g, 113 mmol) and toluene-*p*-sulphonic acid hydrate (20 mg). The reaction mixture was flushed with nitrogen and refluxed with condensation through a Soxhlet extractor containing molecular sieves (type 3A; 15 g). New portions of toluene-*p*-sulphonic acid hydrate (20 mg) were added again after 19 h and after 43 h reflux. After a total of 44 h reflux the reaction mixture was cooled, triethylamine (0.2 ml) added, and the whole washed with 1M-sodium hydroxide (2 × 20 ml), and dried (Na_2SO_4). Evaporation furnished 3.0 g (97%) of pale yellow oil (essentially pure on t.l.c. and n.m.r.), which was ball tube distilled at 0.3 mmHg (oven temperature 125—130 °C) to give 2.8 g (90%) of the *N-alkylated product* (9); $\nu_{max.}$ 2 940, 1 690, 1 650, 1 420, 1 365, 1 220, 1 090, and 940 cm^{-1}; $\lambda_{max.}$ (cyclohexane) 240 nm (ε 6 700); δ (CCl_4) 1.76 (s, 3 H), 2.22 (s, 3H), 3.36 (s, 3 H), and 5.06 (s, 2 H) (Found: C, 53.5; H, 7.2; N, 8.85. $C_7H_{11}NO_3$ requires C, 53.5; H, 7.05; N, 8.9%).

4,5-Dimethyl-3-(phenylsulphonyloxy)isoxazole (10) *and 4,5-Dimethyl-2-(phenylsulphonyl)isoxazol-3-one* (11).—3-Hydroxy-4,5-dimethylisoxazole [13] (6) (1.13 g, 10 mmol) and triethylamine (1.11 g, 11 mmol) were dissolved in toluene (10 ml) and benzenesulphonyl chloride (1.77 g, 10 mmol) added. The resulting suspension was refluxed for 1 h, cooled, and water (10 ml) added. The organic phase was separated, washed with water (20 ml), and dried (Na_2SO_4). After evaporation the residue was column chromatographed on silica (*ca.* 100 g). Elution with toluene–ethyl acetate (8 : 1) containing 1% added formic acid gave 1.45 g (57%) of *O*-substituted derivative (pure on t.l.c.). Recrystallization first from ether–light petroleum then from light petroleum yielded 1.14 g (45%) of *product* (10) with m.p. 35—36 °C; $\nu_{max.}$ 1 655w, 1 590w, 1 460, 1 400, 1 210, 1 100m, 840, and 760 cm^{-1}; δ ($CDCl_3$) 1.84 (s, 3 H), 2.25 (s, 3 H), 7.48—7.70 (m, 3 H), and 7.88—8.06 (m, 2 H) (Found: C, 52.3; H, 4.45; N, 5.55; S, 12.85. $C_{11}H_{11}NO_4S$ requires C, 52.15; H, 4.4; N, 5.55; S, 12.65%). Further elution of the column with toluene–ethyl acetate (2 : 1) with 1% added formic acid gave 0.30 g (12%) of *N*-substituted derivative (pure on t.l.c.). Recrystallization from ether yielded 0.24 g (9%) of *product* (11) with m.p. 125—126 °C; $\nu_{max.}$ 1 730, 1 670, 1 460m, 1 400, 1 210, 1 085, 800, and 760 cm^{-1}; δ ($CDCl_3$) 1.76 (s, 3 H), 2.11 (s, 3 H), 7.48—7.71 (m, 3 H), and 7.86—8.03 (m, 2 H) (Found: C, 52.3; H, 4.45; N, 5.6; S, 12.65. $C_{11}H_{11}NO_4S$ requires C, 52.15; H, 4.4; N, 5.55; S, 12.65%).

Attempted Carboxylation of Compounds (9) *and* (10).—(*a*) To 2-methoxymethyl-4,5-dimethylisoxazol-3-one (9) (1.6 g, 10 mmol) dissolved in dry tetrahydrofuran (30 ml) was added a 1.73M-butyl-lithium solution in hexane (8 ml; 14 mmol) under a nitrogen blanket at −78 °C. After being stirred for 75 min at −78 °C the reaction mixture was poured into carbon dioxide (*ca.* 200 g) in ether (100 ml). The carbon dioxide evaporated overnight, and the resulting suspension was extracted with 2M-sodium hydroxide (3 × 15 ml). The combined aqueous phase was acidified with hydrochloric acid and continuously extracted with ether overnight. The ether phase was dried ($MgSO_4$) and evaporated to give a yellow oil (0.27 g). The n.m.r. and t.l.c. results of this and of the aqueous phase showed complex mixtures with very little carboxylic acid present.

(*b*) 4,5-Dimethyl-3-(phenylsulphonyloxy)isoxazole (10) (506 mg, 2 mmol) was subjected to essentially the same procedure, but using lithium di-isopropylamide as base. After work-up the dried ether extract was evaporated to give a solid white residue (202 mg) shown by n.m.r. and t.l.c. to be 3-hydroxy-4,5-dimethylisoxazole contaminated with several impurities. One of these was isolated by suspending the residue in ethyl acetate, removing a small amount of insoluble material by filtration, and evaporating the filtrate. After digestion with ether, the insoluble residue (31 mg) was recrystallized from ethyl acetate–light petroleum to yield material (18 mg, 4%) with m.p. 178—182 °C. From t.l.c. [yellow colour with iron(III) chloride spray] and the analytical and spectroscopic data this material is tentatively identified as *3-hydroxy-4-methyl-5-(phenylsulphonylmethyl)-isoxazole*; $\nu_{max.}$ 1 660m, 1 550, 1 520m, 1 325, 1 310, 1 155, 1 135, and 1 085 cm^{-1}; δ ([$^2H_6$]acetone) 1.63 (s, 3 H), 4.60 (s, 2 H), 7.5—7.9 (m, 5 H), and 8.63br (s, 1 H) (Found: C, 52.35; H, 4.5; N, 5.6; S, 12.3. $C_{11}H_{11}NO_4S$ requires C, 52.15; H, 4.4; N, 5.55; S, 12.65%).

(R,S)-α-*Amino-3-methoxy-4-methylisoxazol-5-ylacetic Acid* (13).—To di-isopropylamine (485 mg, 4.8 mmol) in dry tetrahydrofuran (3 ml) cooled to −10 °C under a nitrogen blanket was added a 1.52M-butyl-lithium solution in hexane (3.1 ml; 4.8 mmol); the mixture was then stirred for 15 min at −10 °C. 3-Methoxy-4-methylisoxazol-5-ylacetic acid [16] (12) (342 mg, 2 mmol) dissolved in tetrahydrofuran (1 ml) was added, and the resulting suspension stirred at −10 °C for 15 min. Addition of hexamethylphosphoric triamide (0.9 ml) gave a clear yellow solution which was stirred at −5 °C for 30 min. A dried ($MgSO_4$) solution of *O*-mesitylenesulphonyloxyamine [18,*] (645 mg, 3 mmol) in tetrahydrofuran (*ca.* 5 ml) was added, and after 3 h at 0 °C the reaction was terminated by addition of water (1 ml). Evaporation to 1—2 ml, addition of water (5 ml), and extraction with

* **CAUTION** In the preparation [18] of *O*-mesitylenesulphonyloxyamine, the product was precipitated by water and semi-dried by maintaining suction on the filter for *ca.* 1 h. In one of our preparations the 2.5 g product, which had been dried by suction for *ca.* 1½ h, was weighed and transferred to a preparation vial. After standing on the bench for *ca.* 30 min the vial was picked up, whereby the contents exploded, completely destroying the glass vial and causing some personal injury (see also ref. 19).

chloroform (4 × 5 ml) gave an aqueous phase which was neutralized to pH *ca.* 5 and evaporated to *ca.* 1.5 ml in order to induce crystallization. After addition of 0.3 ml of ethanol–water (1 : 1) the mixture was set aside at 5 °C overnight to give the product (80 mg) (pure on t.l.c.). Recrystallization from water–ethanol (5 : 2) yielded *amino-acid* (13) (72 mg, 19%), m.p. 197—198 °C (decomp.); $\nu_{max.}$ 2 950br, 1 655, 1 620, 1 590, 1 535, 1 380, and 1 350 cm^{-1}; δ (90 MHz, D_2O, CH_3CN = 2.02 added as internal standard) 1.87 (s, 3 H), 3.93 (s, 3 H), and 4.94 (s, 1 H) (Found: C, 44.9; H, 5.7; N, 15.0. $C_7H_{10}N_2O_4$ requires C, 45.15; H, 5.4; N, 15.05%).

In an earlier experiment the reaction mixture at the stage immediately before addition of *O*-mesitylenesulphonyloxyamine was quenched with deuterium oxide. Work-up gave the *α-monodeuteriated* starting material (12) in 70% yield with m.p. 97—99 °C; δ ($CDCl_3$) 1.83 (s, 3 H), 3.62 (s, 1 H), 3.91 (s, 3 H), and 9.3 (s, 1 H).

Essentially the same amination procedure, but using methoxyamine [30] instead of *O*-mesitylenesulphonyloxyamine, only led to the recovery of (12) in 50—60% yield.

(R,S)-α-*Amino*-3-*hydroxy*-4-*methylisoxazol*-5-*ylacetic Acid* (4-*Methylibotenic Acid*) (14).—(a) *By hydrogen bromide.* The amino-acid (13) (37 mg, 0.2 mmol) in 43% hydrogen bromide in glacial acetic acid (2 ml) was heated in a spring-closed flask to 110 °C for 6 min. After evaporation and drying *in vacuo* (over KOH) the residue was dissolved in water (0.3 ml) and triethylamine in ethanol added to give a pH of *ca.* 5; slow precipitation of the deprotected amino-acid then occurred. Filtration and drying yielded analytically pure 4-*methylibotenic acid* (24 mg, 70%), m.p. 191—193 °C (decomp.); $\nu_{max.}$ 2 970br, 1 650, 1 620, 1 585, 1 560, 1 525, and 1 350 cm^{-1}; δ (90 MHz, D_2O, CH_3CN = 2.02 added as internal standard) 1.86 (s, 3 H) and 4.92 (s, 1 H) (Found: C, 41.5; H, 4.85; N, 15.95. $C_6H_8N_2O_4$ requires C, 41.85; H, 4.7; N, 16.25%).

(b) *By tin*(IV) *chloride and aqueous ammonia.* To a solution of compound (13) (27 mg, 0.15 mmol) in concentrated aqueous ammonia (10 ml) was added tin(IV) chloride pentahydrate (21 mg, 0.06 mmol); tin(IV) oxide hydrate precipitated. The reaction mixture was placed in a sealed steel cylinder at 105 °C for 2—3 days and then cooled and filtered. The filtrate was evaporated, dissolved in water, and re-evaporated; this was repeated several times. The residue was dissolved in water (*ca.* 0.3 ml) and neutralized with 0.1M-hydrochloric acid. Evaporation to *ca.* 0.2 ml caused initial crystallization; addition then of ethanol (0.2 ml), filtration, and drying yielded (14) (3 mg, 12%), identical (i.r.) to 4-methylibotenic acid prepared above.

3-*Methoxyisoxazol*-5-*ylpropionic Acid* (25) *and* (E)-3-*Methoxyisoxazol*-5-*ylpropenoic Acid* (16).—2-(β-Nitrovinyl)-furan was converted *via* 3-bromoisoxazol-5-ylpropionic acid [31] into 3-methoxyisoxazol-5-ylpropionic acid and esterified by methanolic hydrogen chloride according to described procedures.[20] The isolated product had m.p. 54—58 °C, and t.l.c. showed the presence of two components. Column chromatography on silica with dichloromethane–ethyl acetate (19 : 1) as eluant gave the two constituents (pure on t.l.c.) in the ratio 8 : 1. The main component had m.p. 56—58 °C after recrystallization (light petroleum) and was identified as methyl 3-methoxyisoxazol-5-ylpropionate (lit.,[20] m.p. 56—57 °C). The minor constituent had m.p. 101—104 °C after recrystallization (light petroleum) and was assigned the structure *methyl* (E)-3-*methoxyisoxazol*-5-*ylpropenoate*; $\nu_{max.}$ 1 710, 1 645m, 1 605, 1 515, 1 445, 1 415, 1 330, 1 225, 1 180, and 985 cm^{-1}; δ [CCl_4–$CDCl_3$ (1 : 1)] 3.77 (s, 3 H), 3.96 (s, 3 H), 6.00 (s, 1 H), 6.49 (d, 1 H, *J* 17 Hz), and 7.34 (d, 1 H, *J* 17 Hz) (Found: C, 52.4; H, 5.05; N, 7.65. $C_8H_9NO_4$ requires C, 52.45; H, 4.95; N, 7.65%).

Hydrolyses * of the two pure methyl esters by methanolic potassium hydroxide yielded after acidification 3-methoxyisoxazol-5-ylpropionic acid (25) with m.p. 108—110 °C (lit.,[20] m.p. 100 °C) and (*E*)-3-methoxyisoxazol-5-ylpropenoic acid, identical (i.r.) to the propenoic acid (16) prepared below.

(E)-3-*Methoxyisoxazol*-5-*ylpropenoic Acid* (16).—3-Methoxyisoxazole-5-carbaldehyde [21] (15) (126 mg, 1.0 mmol) and malonic acid (113 mg, 1.1 mmol) in pyridine (*ca.* 2 ml) were placed in a 80—90 °C warm oil bath overnight. After evaporation the solid residue was dissolved in acetone (*ca.* 10 ml), treated with carbon, and evaporated. Recrystallization from water afforded product (16) (89 mg, 53%). Subsequent recrystallization from ethanol yielded an analytical sample with m.p. 201—202 °C; $\nu_{max.}$ 3 110—2 550 (several bands), 1 675, 1 600, 1 510, 1 415, 1 280, 1 040, and 985 cm^{-1}; δ [$(CD_3)_2SO$–$CDCl_3$ (1 : 1)] 3.93 (s, 3 H), 6.46 (s, 1 H), 6.49 (d, 1 H, *J* 17 Hz), 7.38 (d, 1 H, *J* 17 Hz), and 9.1br (s, no integral) (Found: C, 49.7; H, 4.3; N, 8.3. $C_7H_7NO_4$ requires C, 49.7; H, 4.15; N, 8.3%).

(R,S)-α-*Amino*-3-*hydroxyisoxazol*-5-*ylpropionic Acid* (*Homoibotenic Acid*) (17).—(a) *From compound* (16). (*E*)-3-methoxyisoxazol-5-ylpropenoic acid (16) (36 mg, 0.21 mmol) was dissolved in concentrated aqueous ammonia (10 ml) saturated at 0 °C with gaseous ammonia. A solution of tin(IV) chloride pentahydrate (54 mg, 0.15 mmol) in water (0.5 ml) was added and tin(IV) oxide hydrate precipitated. The reaction flask was placed in a sealed steel cylinder at 105 °C for 4—9 days. After cooling, the weakly coloured reaction mixture was filtered and evaporated, then twice dissolved in water and re-evaporated. The crystalline residue, showing essentially only one ninhydrin-active (green) spot on t.l.c., was dissolved in water and evaporated until crystals appeared; ethanol was then added. Recrystallization of the precipitate from water yielded product (17) (9 mg, 25%) with an i.r. spectrum identical to that of homoibotenic acid prepared from compound (20); δ (90 MHz, D_2O) 3.29 (d, 2 H), 4.06 (t, 1 H), and 5.96 (s, 1 H). The mother-liquors contained only small amounts of amino-acid as evidenced by t.l.c. and n.m.r. spectroscopy. Extensive washing of the precipitated tin(IV) oxide hydrate failed to furnish additional product.

Despite several attempts we never isolated any β-amino-acid from the reaction mixtures. The only other product obtained, in low yield, was identified as (E)-3-*hydroxy-isoxazol*-5-*ylpropenoic acid*, showing no sharp m.p. but a gradual decomposition above 200 °C; $\nu_{max.}$ 3 100—2 600 (several bands), 1 695, 1 660, 1 590, 1 525, 1 425, 1 315, 1 295, 980, and 805 cm^{-1}; δ (ammonium salt, D_2O) 6.14 (s, 1 H), 6.47 (d, 1 H, *J* 17 Hz), and 7.08 (d, 1 H, *J* 17 Hz) (Found: C, 46.35; H, 3.4; N, 9.0. $C_6H_5NO_4$ requires C, 46.45; H, 3.25; N, 9.05%).

(b) *From compound* (20). Diethyl acetamido-(3-methoxyisoxazol-5-ylmethyl)malonate (20) (60 mg, 0.18 mmol) dissolved in 48% aqueous hydrobromic acid (*ca.* 6 ml) was refluxed under a nitrogen blanket on a 140 °C warm oil-bath for 15—20 min. The solution was rapidly cooled and evaporated, then twice dissolved in water and re-evaporated.

* Performed by Dr. A. L. N. Larsen.

After drying *in vacuo* (over KOH and P_2O_5) the crude hydrobromide was dissolved in ethanol (4 ml) and neutralized with triethylamine (30 μl) to precipitate the free amino-acid. Recrystallization from water afforded homoibotenic acid (18 mg, 58%), m.p. 255 °C (decomp.); $\nu_{max.}$ 3 000br, 1 640, 1 615, 1 540—1 480 (several bands), 1 345, and 785 cm^{-1} (Found: C, 41.65; H, 4.8; N, 16.2. $C_6H_8N_2O_4$ requires C, 41.85; H, 4.7; N, 16.25%).

The crude hydrobromide on recrystallization from isopropyl alcohol–ether gave *homoibotenic acid hydrobromide* (51%), m.p. 205 °C; $\nu_{max.}$ 2 900br, 1 705, 1 630m, 1 520m, 1 475, and 1 270m; δ (D_2O, CH_3CN = 2.02 added as internal standard) 3.39 (d, 2 H), 4.44 (t, 1 H), and 6.01 (s, 1 H) (Found: C, 28.35; H, 3.75; Br, 31.4; N, 10.9. $C_6H_9BrN_2O_4$ requires C, 28.5; H, 3.6; Br, 31.6; N, 11.05%).

5-Bromomethyl-3-methoxyisoxazole (19).—To 3-methoxy-5-methylisoxazole (18), prepared by diazomethane methylation of 3-hydroxy-5-methylisoxazole [32] (2.25 g, 20 mmol) dissolved in tetrachloromethane (50 ml) were added benzoyl peroxide (20 mg) and NBS (3.56 g, 20 mmol), freshly recrystallized from water. The mixture was refluxed for 4 h, and then further benzoyl peroxide (10 mg) and NBS (3.56 g, 20 mmol) were added and reflux continued overnight. Since after cooling and filtration the n.m.r. spectrum indicated only *ca.* 60% conversion, additional benzoyl peroxide (20 mg) and NBS (3.56 g, 20 mmol) were added. The reaction mixture was refluxed for a further 6 h, and then cooled, filtered, and evaporated to give the crude product (3.9 g). Part of this (2.3 g) was column chromatographed on silica (*ca.* 100 g) with dichloromethane–light petroleum (1 : 1) as eluant to yield compound (19) (1.16 g, 51%) (pure by n.m.r.), b.p. 118—123 °C/15 mmHg (lit.,[25] b.p. 102—104 °C/12 mmHg); $\nu_{max.}$ 2 950m, 1 620, 1 520, 1 450, 1 415, and 1 030 cm^{-1}; δ (CCl_4) 3.87 (s, 3 H), 4.23 (s, 2 H), and 5.80 (s, 1 H).

Diethyl Acetamido-(3-methoxyisoxazol-5-ylmethyl)malonate (20).—Diethyl acetamidomalonate (650 mg, 3 mmol) was added to a solution of sodium ethoxide (from 69 mg of sodium; 3 mmol) in ethanol (5 ml) and stirred for 10 min at room temperature. 5-Bromomethyl-3-methoxyisoxazole (19) (576 mg, 3 mmol) in ethanol (2 ml) was added and refluxed for 4½ h. The resulting suspension was evaporated, diluted with water (10 ml), and extracted with chloroform (5 × 10 ml). The organic phase was dried ($MgSO_4$), evaporated, and recrystallized from water to give the product (20) (0.53 g), m.p. 113—114 °C. The mother-liquor from the recrystallization upon evaporation to small volume deposited a second crop of crystals (0.10 g), m.p. 113—114 °C (combined yield 64%); $\nu_{max.}$ 1 740, 1 640, 1 520, 1 415, 1 305, and 1 200 cm^{-1}; δ ($CDCl_3$) 1.28 (t, 6 H), 2.02 (s, 3 H), 3.78 (s, 2 H), 3.95 (s, 3 H), 4.29 (q, 4 H), 5.65 (s, 1 H), and 6.79br (s, 1 H) (Found: C, 51.05; H, 6.3; N, 8.4. $C_{14}H_{20}N_2O_7$ requires C, 51.2; H, 6.15; N, 8.55%).

(R,S)-α-*Amino-3-methoxyisoxazol-5-ylpropionic Acid* (21).—Diethyl acetamido-(3-methoxyisoxazol-5-ylmethyl)-malonate (20) (130 mg, 0.40 mmol) suspended in 1M-hydrochloric acid (10 ml) was refluxed for 7 h. The resulting solution was evaporated and dried *in vacuo* (over KOH and P_2O_5). The solid residue was dissolved in ethanol (*ca.* 3 ml) and neutralized with triethylamine (55 μl). The precipitated amino-acid was recrystallized from water–ethanol (1 : 3) to yield the *product* (21) (63 mg, 85%), m.p. 233 °C (decomp.); $\nu_{max.}$ 3 000br, 1 625, 1 590, 1 525, 1 415, and 1 325 cm^{-1}; δ (hydrochloride salt, D_2O, CH_3CN = 2.02 added as internal standard) 3.40 (d, 2 H), 3.90 (s, 3 H), 4.38 (t, 1 H), and 6.04 (s, 1 H) (Found: C, 45.1; H, 5.35; N, 15.05. $C_7H_{10}N_2O_4$ requires C, 45.15; H, 5.4; N, 15.05%).

Ethyl (R,S)-α-*Amino-3-methoxyisoxazol-5-ylpropionate Hydrochloride* (22).—Esterification of (*R,S*)-α-amino-3-methoxyisoxazol-5-ylpropionic acid (21) with 5% hydrogen chloride in ethanol, prepared by adding acetyl chloride to ethanol at 0 °C, gave after evaporation and three recrystallizations from ethanol–ether the *ester hydrochloride* (22) (59%), m.p. 139—140 °C; $\nu_{max.}$ 2 970br, 1 745, 1 630, 1 530, 1 470, 1 420, and 1 245 cm^{-1}; δ ($CDCl_3$) 1.24 (t, *ca.* 3 H), 3.3—3.6 (m, 2 H), 3.84 (s, 3 H), 4.18 (q, 2 H), 4.2—4.7 (m, 1 H), 5.97 (s, 1 H), and 7.4br (s, no integral) (Found: C, 42.7; H, 6.2; Cl, 14.25; N, 11.0. $C_9H_{15}ClN_2O_4$ requires C, 43.1; H, 6.05; Cl, 14.15; N, 11.2%).

Diethyl Acetamido-(4-bromo-3-methoxyisoxazol-5-ylmethyl)-malonate (23).—Diethyl acetamido-(3-methoxyisoxazol-5-ylmethyl)malonate (20) (45 mg, 0.14 mmol) was dissolved in bromine (neat, 2 ml). After 6 h at room temperature the bromine was removed by a stream of nitrogen, and the residue twice dissolved in chloroform and evaporated. The residue was recrystallized from water to yield the 4-bromoisoazole (23) (38 mg), m.p. 98—99 °C. The mother-liquor upon evaporation to small volume deposited a second crop of crystals (11 mg), m.p. 98—99 °C (combined yield 88%); $\nu_{max.}$ 1 750, 1 640, 1 540, 1 215, and 1 200 cm^{-1}; δ ($CDCl_3$) 1.28 (t, 6 H), 1.99 (s, 3 H), 3.75 (s, 2 H), 3.95 (s, 3 H), 4.24 (q, 4 H), and 6.67br (s, 1 H) (Found: C, 41.35; H, 4.85; Br, 19.8; N, 6.95. $C_{14}H_{19}BrN_2O_7$ requires C, 41.3; H, 4.7; Br, 19.6; N, 6.9%).

In contrast, compound (20) (46 mg, 0.14 mmol) dissolved in tetrachloromethane (3 ml), when treated with bromine (15 μl, 0.3 mmol) and refluxed for 24 h, showed only unchanged starting material (n.m.r.) after evaporation.

(R,S)-α-*Amino-4-bromo-3-hydroxyisoxazol-5-ylpropionic Acid* (*4-Bromohomoibotenic Acid*) *Monohydrate* (24).—Deprotection of diethyl acetamido-(4-bromo-3-methoxyisoxazol-5-ylmethyl)malonate (23) with 48% aqueous hydrogen bromide, as described in the preparation of (17), gave, after neutralization with triethylamine, 4-bromohomoibotenic acid monohydrate, m.p. 207 °C (decomp.) in 45% yield after recrystallization from water; $\nu_{max.}$ 2 930br, 1 620br, 1 530br, 1 405m, 1 365, and 1 345 cm^{-1}; δ (hydrobromide salt, D_2O, CH_3CN = 2.02 added as internal standard) 3.36 (d, 2 H) and 4.44 (t, 1 H) (Found: C, 26.85; H, 3.4; Br, 29.6; N, 10.35. $C_6H_9BrN_2O_5$ requires C, 26.8; H, 3.35; Br, 29.7; N, 10.4%).

3-Hydroxyisoxazol-5-ylpropionic Acid (26).—Demethylation of 3-methoxyisoxazol-5-ylpropionic acid (25) (0.5 g, 2.9 mmol) with concentrated aqueous ammonia (10 ml) and tin(IV) chloride pentahydrate (50 mg, 0.14 mmol) was performed as described in the preparation of compound (14). Acidification with 4M-hydrochloric acid precipitated 0.34 g of material which after several recrystallizations from methanol–dichloromethane and from acetone yielded a total of 131 mg (28%) of the *hydroxyisoxazole* (26), m.p. 187—189 °C; $\nu_{max.}$ 3 030—2 540 (several bands), 1 700, 1 620, 1 535, 1 440, 1 240, 1 200, and 800 cm^{-1}; δ [$(CD_3)_2SO$] 2.6—2.8 (m, *ca.* 4 H) and 5.72 (s, 1 H); acidic protons not visible (Found: C, 45.7; H, 4.5; N, 8.95. $C_6H_7NO_4$ requires C, 45.85; H, 4.5; N, 8.9%).

An attempted deprotection of (25) with concentrated aqueous ammonia [without addition of tin(IV) chloride] at 115 °C for 20 h yielded a complex, dark-brown reaction mixture containing (t.l.c.) very little, if any, (25) and (26). Reflux of (25) in aqueous tin(IV) chloride, showing gradual

precipitation of tin(IV) oxide hydrate, gave no deprotection within 16 h.

3-Hydroxy-5-hydroxymethylisoxazole (28).—Deprotection of 5-hydroxymethyl-3-methoxyisoxazole [24] (27) by tin(IV) chloride (1 molar equiv.) in concentrated aqueous ammonia was performed as described in the preparation of compound (14). After removal of the precipitated tin(IV) oxide hydrate the filtrate was extracted with ether. The aqueous phase was evaporated to *ca.* half volume, acidified by 4M-hydrochloric acid, and extracted with ethyl acetate. After drying (Na_2SO_4) the organic phase was evaporated and twice recrystallized from ethyl acetate–dichloromethane to give the *product* (28) (36%), m.p. 80—82 °C; $\nu_{max.}$ 3 400—2 650 (several bands), 1 630, 1 530, 1 345, 1 070, and 785 cm^{-1}; δ [$(CD_3)_2SO$–$CDCl_3$ (1 : 8)] 4.60 (s, 2 H), 5.92 (s, 1 H), and 7.10 (s, 2 H) (Found: C, 41.5; H, 4.4; N, 12.0. $C_4H_5NO_3$ requires C, 41.75; H, 4.4; N, 12.15%).

4-Hydroxymethyl-3-methoxy-5-methylisoxazole (30).—To ethyl 3-methoxy-5-methylisoxazole-4-carboxylate [16] (29) (1.29 g, 7.0 mmol) in dry ether (50 ml) was added lithium aluminium hydride (398 mg, 10.5 mmol). The mixture was stirred for 6 h at room temperature and then 4M-hydrochloric acid (7 ml) was slowly added. The phases were separated and the aqueous phase extracted with ether (3 × 50 ml). The combined, dried (Na_2SO_4) ether phase was evaporated and recrystallized from cyclohexane to yield the *product* (30) (0.75 g, 75%), m.p. 68—70 °C. Subsequent recrystallization from ether–light petroleum afforded an analytical sample, m.p. 71—72 °C; $\nu_{max.}$ 3 260, 1 660, 1 525, 1 480, 1 420, 1 280, and 1 010 cm^{-1}; δ ($CDCl_3$) 2.31 (s, 3 H), 2.64br (s, 1 H), 3.92 (s, 3 H), and 4.33 (s, 2 H) (Found: C, 50.6; H, 6.2; N, 9.7. $C_6H_9NO_3$ requires C, 50.35; H, 6.35; N, 9.8%).

4-Chloromethyl-3-methoxy-5-methylisoxazole (31).—To 4-hydroxymethyl-3-methoxy-5-methylisoxazole (30) (286 mg, 2.0 mmol) was added cold thionyl chloride (1 ml); a violent reaction occurred. The resulting solution was refluxed for 25 min and then evaporated. The residue was suspended in water (5 ml) and extracted with ether (4 × 5 ml). The combined ether phase was washed with 0.2M-sodium hydrogencarbonate (5 ml), followed by saturated aqueous sodium chloride (5 ml), and then dried (Na_2SO_4). The evaporated residue was dissolved in dichloromethane (6 ml) and filtered slowly through silica (*ca.* 1 g) which was then washed with dichloromethane (10 ml). The filtrate was evaporated to give the colourless crude *product* (31) (0.26 g, 80%). An analytical sample was ball tube distilled at 15 mmHg (oven temperature 140—200 °C); $\nu_{max.}$ 2 960m, 1 655, 1 535, 1 480, 1 420, 1 225, 1 075, and 725 cm^{-1}; δ ($CDCl_3$) 2.35 (s, 3 H), 3.97 (s, 3 H), and 4.27 (s, 2 H) (Found: C, 44.5; H, 5.05; Cl, 22.05; N, 8.65. $C_6H_8ClNO_2$ requires C, 44.6; H, 5.0; Cl, 21.95; N, 8.65%).

Diethyl Acetamido-(3-methoxy-5-methylisoxazol-4-ylmethyl)malonate (32).—This was prepared analogously to (20) from crude (31). Recrystallization first from ether–light petroleum then from water gave the *product* (32) (45%), m.p. 98—99 °C; $\nu_{max.}$ 1 745, 1 640, 1 525, 1 305, and 1 215 cm^{-1}; δ ($CDCl_3$) 1.27 (t, 6 H), 1.98 (s, 3 H), 2.16 (s, 3 H), 3.30 (s, 2 H), 3.85 (s, 3 H), 4.18 (q, 4 H), and 6.65br (s, 1 H) (Found: C, 52.8; H, 6.45; N, 8.05. $C_{15}H_{22}N_2O_7$ requires C, 52.65; H, 6.5; N, 8.2%).

(R,S)-α-Amino-3-hydroxy-5-methylisoxazol-4-ylpropionic Acid Monohydrate (33) *and Hydrobromide.*—Deprotection of (32) by 48% aqueous hydrogen bromide, as described in the preparation of (17), yielded the crude hydrobromide, dried *in vacuo* (over KOH and P_2O_5). Two recrystallizations from isopropyl alcohol–ether gave the *hydrobromide* (80%), m.p. 206—209 °C (decomp.). Recrystallization from isopropyl alcohol gave an analytical sample, m.p. 218—220 °C (decomp.); $\nu_{max.}$ 3 000br, 1 740, 1 660m, 1 535, 1 500, 1 255m, and 1 215 cm^{-1}; δ (D_2O, CH_3CN = 2.02 added as internal standard) 2.25 (s, 3 H), 2.95 (d, 2 H), and 4.25 (t, 1 H) (Found: C, 31.6; H, 4.05; Br, 29.8; N, 10.4. $C_7H_{11}BrN_2O_4$ requires C, 31.5; H, 4.15; Br, 29.9; N, 10.5%).

Neutralization of the hydrobromide in ethanol with triethylamine precipitated the free amino-acid which was recrystallized from water to give the *monohydrate* (33) (86%), m.p. 252 °C (decomp.); $\nu_{max.}$ 3 550—2 450 (several bands), 1 655, 1 625, 1 585, 1 535, 1 515, 1 400, 1 335, and 1 255 cm^{-1} (Found: C, 41.2; H, 5.95; N, 13.7. $C_7H_{12}N_2O_5$ requires C, 41.2; H, 5.9; N, 13.7%).

We express our thanks to Professor A. Kjær for discussion of the manuscript, to Dr. S. Jacobsen for recording the 90-MHz n.m.r. spectra, and to Mr. J. S. Johansen for excellent technical assistance. The loan of a PrepLC/System 500 instrument from Waters Ass., Denmark, and financial support from the Danish Medical Research Council are gratefully acknowledged.

[9/1669 *Received*, 22*nd October*, 1979]

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