Isoxazole–Oxazole Conversion by Beckmann Rearrangement

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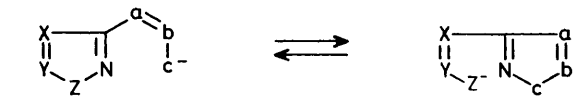
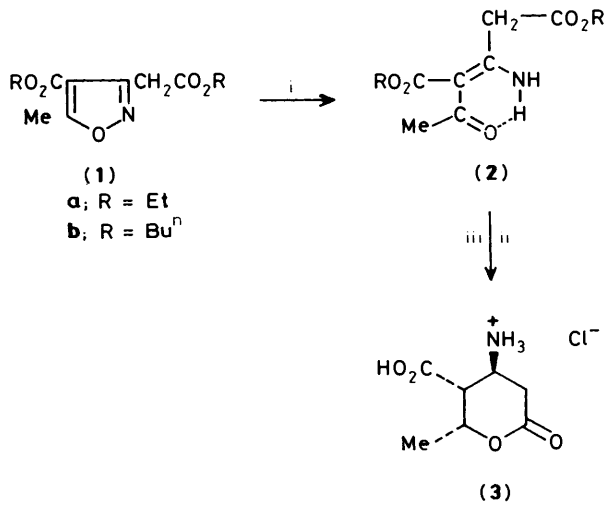
A novel base-catalysed isoxazole–oxazole ring transformation was realized in the conversion of ethyl 5-hydroxy-3-(5-methylisoxazol-4-yl)isoxazole-4-carboxylate into 4-cyano-5-methyloxazol-2-ylacetic acid. A new process was developed for the preparation of *t*-4-amino-*c*-2-methyl-6-oxotetrahydropyran-*r*-3-carboxylic acid hydrochloride, a starting material for the synthesis of thienamycin.

The so-called mononuclear heterocyclic rearrangement of five-membered heterocyclic compounds (Scheme 1) is well known.[1] We report here a case when the related Beckmann rearrangement was observed instead of the expected mononuclear heterocyclic rearrangement.



Scheme 1.

Diesters of 4-carboxy-5-methylisoxazol-3-ylacetic acid (**1**) were needed in order to synthesize *t*-4-amino-*c*-2-methyl-6-oxotetrahydropyran-*r*-3-carboxylic acid (**3**),[2] an important starting material for the synthesis of the antibiotic thienamycin in a novel way not based on 2-oxopropanedioic acid. The lactone (**3**) was to be obtained by the reduction of the diesters of the (*E*)-2-acetyl-3-aminopent-2-enedioic acids (**2**) formed in the catalytic reduction of the starting isoxazolyl diesters with sodium cyanotrihydroborate in acetic acid (Scheme 2).



Scheme 2. *Reagents and conditions:* i, H_2/Pd, EtOH, room temp.; ii, $NaBH_3CN$; iii, HCl, H_2O, reflux

Synthesis of the starting isoxazole derivative was attempted as shown in Scheme 3. The condensation of ethyl ethoxymethyleneacetoacetate (**4**), formed in the known reaction[3] of triethyl orthoformate, acetic anhydride, and ethyl acetoacetate with hydroxylamine, produced ethyl 5-methylisoazol-4-ylcarboxylate (**5**).[4] The acid (**6**) obtained by hydrolysis of the ester (**5**) was converted into the acid chloride (**7**) with thionyl chloride. Although the isoxazole derivatives (**5**)—(**7**) are sensitive to base (which removes 3-H), the acid chloride (**7**) gave the expected malonic ester derivative (**8**) with diethyl ethoxymagnesiomalonate[5] in high yield. Compound (**8**) was in turn converted into the bisisoxazole derivative (**9**) by refluxing, with hydroxylamine hydrochloride in ethanol.[6] Decarboxylation of the malonic acid derivative, formed from (**9**) with base by the known fragmentation of the isoxazole ring and a subsequent mononuclear heterocyclic rearrangement of the nitrile formed, was expected to yield ethyl of 4-cyano-5-methylisoxazol-3-ylacetate (**10**).

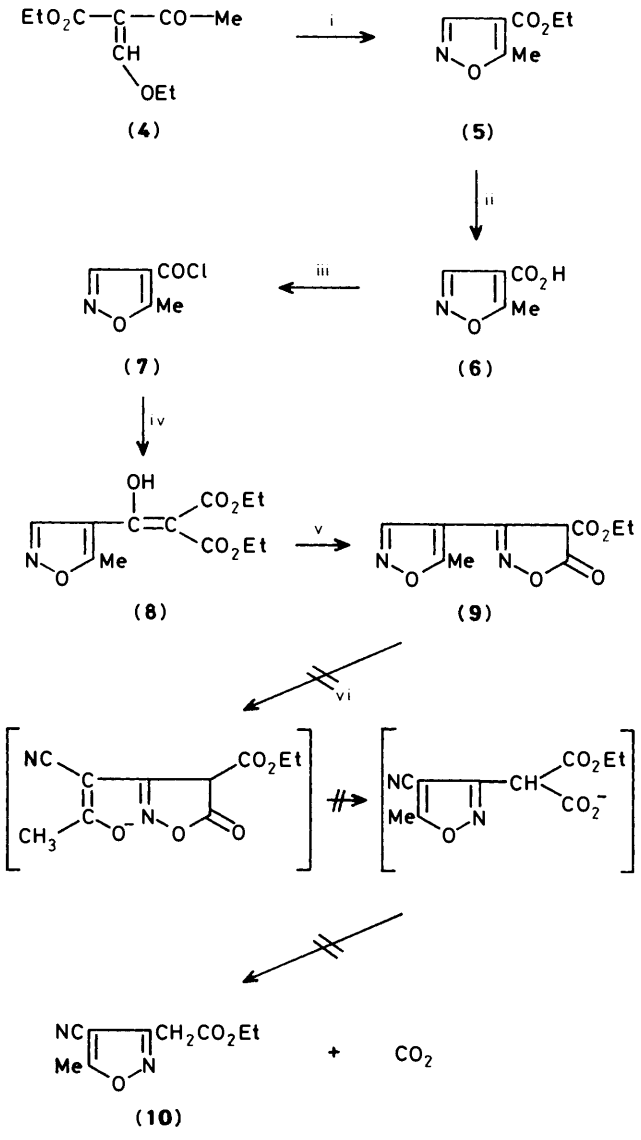
Indeed, on treatment with potassium t-butoxide in dimethylformamide, the ester (**9**) lost carbon dioxide in an exothermic reaction to give a product which could have been that expected on the basis of its i.r. and ^1H n.m.r. spectral and elemental analytical data. However on acidic ethanolysis it yielded diethyl malonate, and it could not be decomposed reductively by catalytic hydrogenation. The oxazole structure (**11**) was therefore considered more likely, and was confirmed by degradation to the known isoxazole (**14**).[7]

The carboxylic acid (**12**), formed by careful alkaline hydrolysis from (**11**), lost carbon dioxide on heating and was converted into 2,5-dimethyloxazole-4-carbonitrile (**13**). The structure (**13**) was confirmed by alkaline hydrolysis to the known carboxylic acid (**14**), identical with an authentic sample obtained from (**15**).[7]

The acid was also obtained directly when compound (**9**) was stirred in aqueous alkali, in an exothermic reaction concurrent with hydrolysis of the ester group. The formation of (**11**) from (**9**) can be rationalized in terms of Beckmann rearrangement instead of the expected mononuclear heterocyclic rearrangement following fragmentation of the isoxazole ring. The dominance of the Beckmann rearrangement can be explained by the formation of a stable mesomeric anion from (**9**) with base as a consequence of the presence of the 4-ethoxycarbonylisoxazol-5-one unit.

Evidence in favour of this concept was given by deethoxycarbonylation of (**9**) in acetic acid–sulphuric acid, producing the less acidic bisisoxazole derivative (**16**). On treatment with base, (**16**) yielded the expected isoxazolecarboxylic acid (**17**) in an exothermic reaction by a mononuclear heterocyclic rearrangement. The structure (**17**) was proved by the fact that catalytic reduction of the diester (**1**) of the dicarboxylic acid (**18**) obtained by acidic hydrolysis of (**17**) and successive esterification produced the diester (**2**) of the pentenedioic acid. Reductive cleavage of the dibutyl ester (**1b**) by catalytic hydrogenation followed by reduction with sodium tetrahydroborate in acetic acid yielded a product which in turn was converted by acid hydrolysis into a compound identical with the authentic lactone (**3**).[2,8]

Thus our original aim, *i.e.* a novel synthesis of the lactone (**3**), was also achieved.



Scheme 3. *Reagents and conditions:* i, NH_2OH·HCl, NaOAc; ii, HCl, H_2O, reflux; iii, $SOCl_2$; iv, $EtOMgCH(CO_2Et)_2$; v, NH_2OH·HCl, EtOH; vi, $KOBu^t$, Me_2NCHO

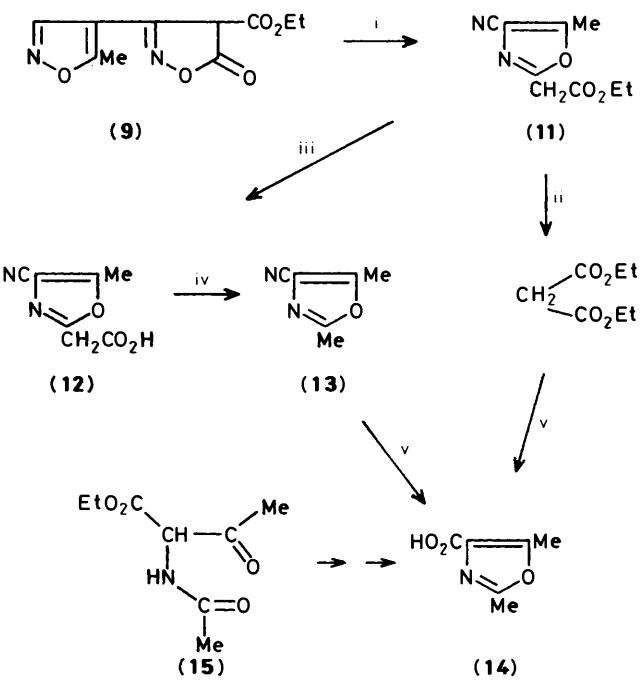
The conversion (**8**) ⟶ (**11**) constitutes a novel base-catalysed isoxazole–oxazole ring transformation, which takes its place beside the better known photochemical routes and those involving thermolysis *via* 2*H*-azirine derivatives.[9]

Experimental

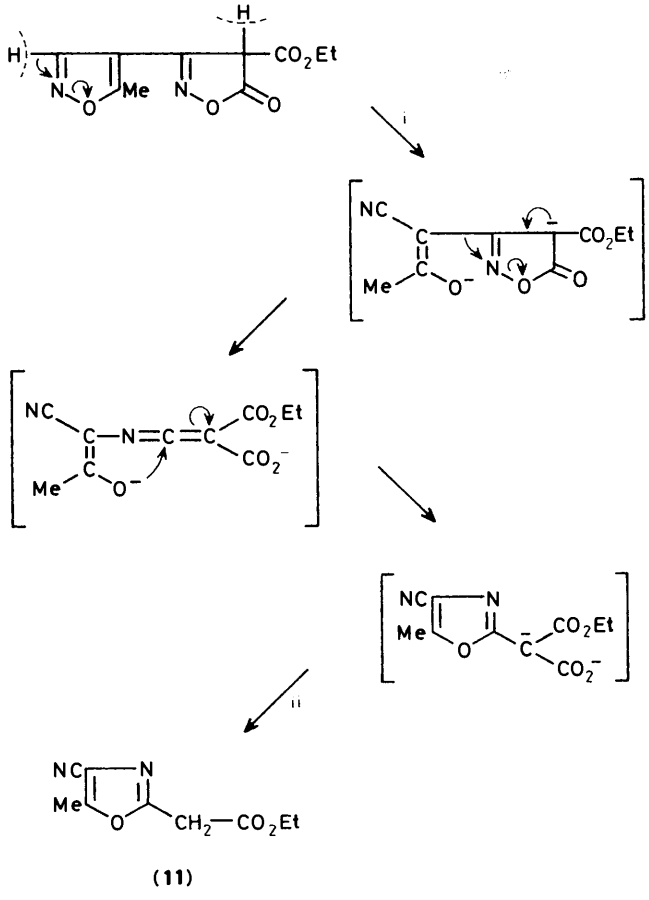
M.p.s were measured with a Koffler hot-stage apparatus. I.r. spectra were measured for KBr discs with a Spectromom 2000 spectrometer. ^1H N.m.r. spectra were recorded at 60 MHz, with a Perkin-Elmer R-20 spectrometer, with $SiMe_4$ as standard.

5-Methylisoxazole-4-carbonyl Chloride (**7**).—Intermediates were prepared on the basis of references 3 and 4.

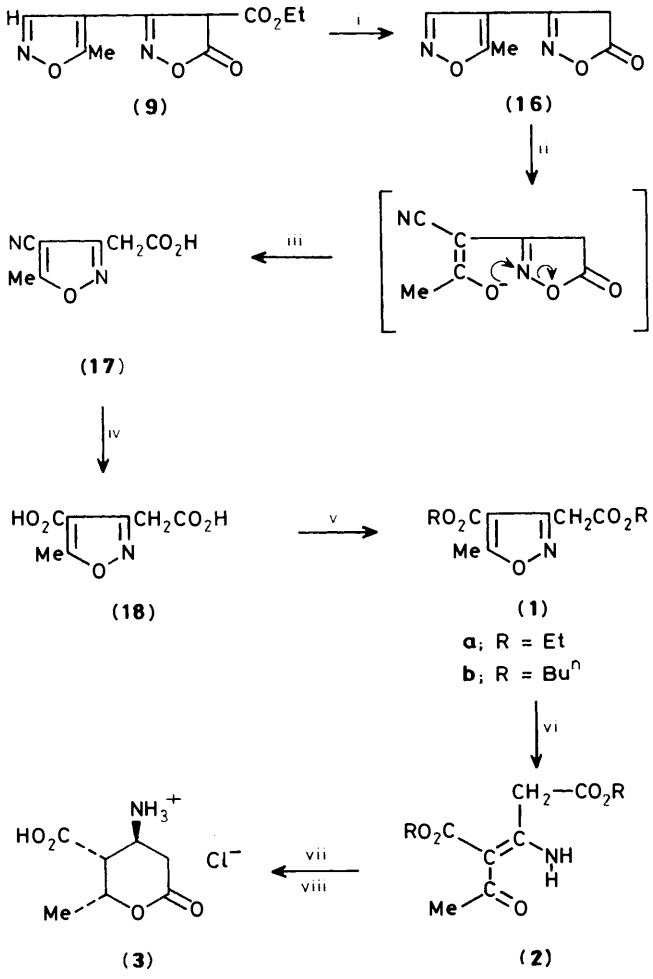
Triethyl orthoformate (580 ml, 3.67 mol), acetic anhydride (700 ml, 7.36 mol), and ethyl acetoacetate (466 ml, 3.67 mol) were heated to the boil, then kept under reflux for 40 min without heating, and then heated again to reflux for a further 20 min. The resulting mixture was distilled initially at atmospheric pressure up to 180 °C, then under reduced pressure to yield



Scheme 4. *Reagents and conditions:* i, $KOBu^t$, Me_2NCHO, $-CO_2$; ii, EtOH–H_2SO_4; iii, NaOH, H_2O; iv, 140—150 °C, $-CO_2$; v, NaOH, H_2O



Scheme 5. *Reagents and conditions:* i, $KOBu^t$, Me_2NCHO, $-2H^+$; ii, $-CO_2$, $+2H^+$



Scheme 6. *Reagents and conditions:* i, AcOH, H_2SO_4, $-CO_2$; ii, NaOH, H_2O or EtONa, EtOH, $-H^+$; iii, HCl, H_2O, $+H^+$; iv, HCl, H_2O, v, ROH, H_2SO_4; vi, H_2/Pd, room temp.; vii, $NaBH_3CN$, AcOH; viii, HCl, H_2O

ethyl ethoxymethyleneacetoacetate (**4**) (420—430 g), b.p. 140—150 °C at 14 mmHg, as a yellowish-red liquid.

Hydroxylamine hydrochloride (190 g, 2.7 mol) and sodium acetate trihydrate (370 g, 2.7 mol) in water (500 ml) were added to a solution of (**4**) in ethanol (500 ml). The mixture was stirred for 2 h with cooling (ice–water), then kept overnight at 0 °C and extracted with dichloromethane (1 200 ml). The extract was evaporated to dryness to give the isoxazolecarboxylic acid (**5**) (340—350 g).

The acid (**5**) was refluxed in acetic acid (300 ml), water (300 ml), and conc. HCl (300 ml) for 10 h, and the mixture was then evaporated to dryness. Acetone (500 ml) was added and evaporated off and the residue was dried *in vacuo* to afford 5-methylisoxazole-4-carboxylic acid (**6**) (260—270 g). Thionyl chloride (400 ml) was added and the mixture was stirred and heated to reflux for 3 h. Distillation under reduced pressure [in an oil-bath at 150 °C (max.) because of explosion hazard] yielded the acid chloride (**7**) (240—250 g, 44—47%), b.p. 78—79 °C at 14 mmHg, as a pungent liquid (Found: C, 41.2; H, 2.9; Cl, 24.2; N, 9.6. $C_5H_4ClNO_2$ requires C, 41.25; H, 2.8; Cl, 24.35; N, 9.7%); $\nu_{max.}$ 1 770 (CO) and 1 580 cm^{-1} (isoxazole).

Diethyl[Hydroxy-(5-methylisoxazol-4-yl)methylene]-malonate (**8**).—A solution of diethyl malonate (630 ml, 3.96 mol) in dry benzene (900 ml) and ethanol (220 ml) was added in portions to a mixture of Mg turnings (96 g, 4 g atom) (suitable for Grignard reactions), ethanol (30 ml), dry benzene (750 ml), and carbon tetrachloride (2 ml). Initially 50 ml of the solution was added and the mixture was stirred and heated cautiously until the exothermic dissolution of Mg started. The solution was then added at a rate which maintained boiling.

The reaction mixture was refluxed for a further 4 h then 800 ml of the solvent was evaporated off at atmospheric pressure. Dry dioxane (600 ml) was added and the mixture was cooled to 35 °C. The 5-methyl-4-carbonyl chloride (**7**) (275 g, 1.89 mol) was added with stirring and cooling (ice–water) at a rate which maintained the internal temperature between 35 and 45 °C, and the mixture was stirred for a further 30 min without cooling. It was then poured into a mixture of conc. HCl (600 ml), ice (1 000 g), and water (1 500 ml), the benzene phase was separated, and the aqueous layer was extracted with benzene (1 500 ml). The combined benzene extracts were washed successively with conc. HCl (150 ml) in water (600 ml), and water (1 600 ml), filtered, and evaporated, then the excess of malonic ester was distilled off (oil-bath at 120—140 °C); b.p. 70—80 °C at 0.8 mmHg. The remaining oil crystallized on cooling to give *compound* (**8**) (506 g, 99%), m.p. 56 °C (from ether–hexane) (Found: C, 53.4; H, 5.5; N, 5.0. $C_{12}H_{15}NO_6$ requires C, 53.5; H, 5.6; N, 5.2%); $\nu_{max.}$ 3 300—2 500br (OH), 1 750 (CO), 1 680 (CO), and 1 580 cm^{-1} (isoxazole); $\delta_H(CDCl_3)$ 1.30 (3 H, t, OCH_2CH_3), 2.70 (3 H, s, Me), 4.25 (2 H, q, OCH_2CH_3), 4.90 (1 H, s, 3′-H), and 8.50 (1 H, s, OH).

Ethyl 5-Hydroxy-3-(5-methylisoxazol-4-yl)isoxazol-4-ylcarboxylate (**9**).—The ester (**8**) (506 g crude product, 1.88 mol) was refluxed with hydroxylamine hydrochloride (160 g, 2.30 mol) in ethanol (1 000 ml) for 3 h. The mixture obtained was evaporated to dryness. The residue was treated with hot dichloromethane (2 000 ml), the suspension was filtered hot and the solid was washed with hot dichloromethane again (2 000 ml). The combined filtrates were washed with water (800 ml), and evaporated to dryness. The solid residue was triturated with ether (400 ml) and kept at 0 °C overnight. The suspension was filtered, and the solid was washed with ether (200 ml) and dried in air to give the *ester* (**9**) (273 g, 62%), m.p. 153—154 °C (from ethyl acetate) (Found: C, 50.4; H, 5.5; N, 5.05. $C_{10}H_{10}N_2O_5$: requires C, 50.5; H, 5.6; N, 5.2%); $\nu_{max.}$ 3 100—2 500br (OH or NH), 1 760sh (CO), and 1 730 (CO) cm^{-1}; $\delta_H(CDCl_3)$ 1.10 (3 H, t, OCH_2CH_3), 2.40 (3 H, s, Me), 4.05 (2 H, q, OCH_2), 8.60 (1 H, s, 3′-H), and 11.00 (1 H, s, OH or NH).

Ethyl 4-Cyano-5-methyloxazol-2-ylacetate (**11**).—Potassium t-butoxide (135 g, 1 200 mmol) was added to a stirred and cooled solution of the ester (**9**) (215 g, 903 mmol) in dimethylformamide (500 ml) at a rate which maintained the temperature under 40—45 °C (10 min). A precipitate separated. The mixture obtained was stirred at 120—130 °C for 30 min, then poured into a mixture of water (500 ml) and ice (1 000 g), acidified by careful addition of conc. HCl (150 ml) (gas evolution!) and extracted with ether (2 400 ml). The extract was washed with water (1 600 ml), dried ($CaCl_2$), and evaporated. Distillation of the residue (144.5 g, 82%) afforded the *ester* (**11**) (91 g, 52%), b.p. 118—120 °C at 0.3 mmHg (Found: C, 55.9; H, 5.2; N, 14.7. $C_9H_{10}N_2O_3$ requires C, 55.7; H, 5.2; N, 14.4%); $\nu_{max.}$ 2 250 (CN), 1 750 (CO), and 1 605 and 1 580 cm^{-1} (oxazole); $\delta_H(CDCl_3)$ 1.05 (3 H, t, OCH_2CH_3), 2.15 (3 H, s, Me), 3.25 (2 H, s, CH_2), and 3.85 (2 H, q, OCH_2CH_3).

Ethanolysis of the Ester (**11**) *in Sulphuric Acid.*—The ester (**11**) (3 g, 15.4 mmol) was refluxed with ethanol (15 ml) and conc. H_2SO_4 (4 ml) for 8 h. The solution was poured on ice (40 g) and extracted with ether (30 ml). The extract washed with water (40 ml), dried ($CaCl_2$), and evaporated to dryness. Distillation of

the residual oil (1.9 g, 77%) yielded a liquid (1.5 g, 61%), b.p. 198—200 °C, identical with authentic diethyl malonate on the basis of its i.r. and ^{1}H n.m.r. spectra.

4-*Cyano*-5-*methyloxazol*-2-*ylacetic Acid* (**12**).—(*a*) The ester (**9**) (20 g, 84 mmol) was added to a stirred solution of sodium hydroxide (10 g, 250 mmol) in water (100 ml) cooled to 30 °C. Initially a precipitate separated, which then dissolved while the temperature rose to about 65 °C. The mixture was stirred for 5 min, cooled to 40 °C, then acidified by cautious addition of conc. HCl (15 ml) (gas evolution!), cooled again, and extracted with ether (150 ml). The extract was washed with water (60 ml), dried ($CaCl_2$), and evaporated to dryness. The remaining oil crystallized at room temperature to give compound (**12**) (3 g, 43%), m.p. 107 °C (from toluene) (Found: C, 50.8; H, 3.7; N, 17.1. $C_7H_6N_2O_3$ requires C, 50.6; H, 3.6; N, 16.7%); $\nu_{max.}$ 3 200—2 400br (OH), 2 240 (CN), 1 720 (CO), and 1 605 and 1 590 cm^{-1} (oxazole); δ_H($CDCl_3$) 2.50 (3 H, s, Me), 3.90 (2 H, s, CH_2), and 10.60 (1 H, br s, CO_2H).

(*b*) The ester (**11**) (5 g, 25.6 mmol) was added to a stirred solution of sodium hydroxide (5 g, 125 mmol) in water (650 ml). The mixture was stirred for 5 min at 65—70 °C, then cooled and extracted with ether (150 ml). The extract was washed with water (60 ml), dried ($CaCl_2$), and evaporated to dryness. The remaining oil crystallized on cooling to give a product (2.2 g, 51%), m.p. 107 °C, (from toluene), identical with that obtained as described in (*a*), on the basis of m.p., mixed m.p., and i.r. and ^{1}H n.m.r. spectra.

2,5-*Dimethyloxazole*-4-*carbonitrile* (**13**).—The acid (**12**) (10 g, 60.2 mmol) was stirred for 10 min at 140—150 °C. When evolution of CO_2 ceased, the vessel was cooled. Distillation of the oil obtained yielded the *oxazole* (**13**) (7 g, 95%), b.p. 84—85 °C at 18 mmHg (Found: C, 58.8; H, 4.9; N, 22.8. $C_6H_6N_2O$ requires C, 59.0; H, 4.95; N, 22.95%); $\nu_{max.}$ 2 230 (CN) and 1 605 and 1 585 cm^{-1} (oxazole); δ_H($CDCl_3$) 2.35 (3 H, s, Me) and 2.40 (3 H, s, Me).

2,5-*Dimethyloxazole*-4-*carboxylic Acid* (**14**).—Compound (**13**) (3.5 g, 28.6 mmol) was refluxed with a solution of sodium hydroxide (4 g, 100 mmol) in water (25 ml) for 2 h, with stirring. Initially a precipitate separated, which gradually dissolved. The mixture was cooled and acidified with conc. HCl (12 ml). The precipitate which separated was filtered off, washed with water (30 ml), and recrystallized from methanol (50 ml) to give the *acid* (**14**) (2 g, 50%), m.p. 236—237 °C (decomp.), identical with the product obtained as described in ref. 7 on the basis of m.p., mixed m.p., and i.r. and ^{1}H n.m.r. spectra (Found: C, 51.3; H, 4.9; N, 9.8. Calc. for $C_6H_7NO_3$: C, 51.1; H, 5.0; N, 9.9%); $\nu_{max.}$ 3 150—2 400br (OH), 1 690 (CO), and 1 610 and 1 585 cm^{-1} (oxazole); δ_H(CF_3CO_2H) 2.40 (3 H, s, Me) and 2.50 (3 H, s, Me).

3-(5-*Methylisoxazol*-4-*yl*)*isoxazol*-5(4H)-*one* (**16**).—The ester (**9**) (278 g crude product, 1.167 mol) was refluxed with acetic acid (1 200 ml; 99.5%) and conc. H_2SO_4 (25 mol) for 15 min. The mixture was cooled, sodium acetate (75 g, 915 mmol) was added, and the mixture was evaporated to dryness at 80 °C. Water (300 ml) was added and the mixture was extracted with dichloromethane (1 800 ml). The extract was washed with water (300 ml) and evaporated to dryness. The residue was recrystallized from Pr^{i}OH (300 ml) to give (**9**) (175 g, 90%), m.p. 95—96 °C (Found: C, 50.7; H, 3.7; N, 17.0. $C_7H_6N_2O_3$ requires C, 50.6; H, 3.6; N, 16.85%); $\nu_{max.}$ 1 800 and 1 780sh (CO) and 1 620 and 1 580 cm^{-1} (isoxazole); δ_H($CDCl_3$) 2.65 (3 H, s, Me), 3.70 (2 H, s, CH_2), and 8.30 (1 H, s, 3′-H).

4-*Cyano*-5-*methylisoxazol*-3-*ylacetic Acid* (**17**).—(*a*) A solution of sodium hydroxide (75 g, 1.875 mol) in water (500 ml) was cooled to 25 °C and compound (**16**) (130 g, 782 mmol) was added in one portion with stirring. The mixture was stirred for 2 min while the temperature rose to 70—75 °C, then cooled immediately to 30 °C, acidified with conc. HCl (210 ml) and extracted with dichloromethane (1 200 ml) (after cooling). The extract was evaporated to dryness to give a residual oil which crystallized on cooling to yield the *acid* (**17**) (122 g, 94%), m.p. 90—91 °C (from benzene) (Found: C, 50.85; H, 3.6; N, 16.9; $C_7H_6N_2O_3$ requires C, 50.6; H, 3.6; N, 16.85%); $\nu_{max.}$ 3 200—2 400br (OH), 2 280sh (CN), 1 740 (CO), and 1 590 cm^{-1} (isoxazole); δ_H($CDCl_3$) 2.60 (3 H, s, Me) and 4.00 (2 H, s, CH_2).

(*b*) Compound (**16**) (10 g, 60.1 mmol) was added to a stirred solution of sodium ethoxide (5.44 g, 80 mmol) in ethanol (50 ml) at 25 °C. An exothermic reaction took place. The mixture was stirred for 10 min then cooled. The precipitate which separated was filtered off, washed with ethanol (20 ml), and dissolved in water (30 ml). The solution was acidified with conc HCl (10 ml) and extracted with ether (90 ml). The extract was washed with water (30 ml), dried ($CaCl_2$), and evaporated to dryness. The residue (6 g, 60%), m.p. 90—91 °C (from benzene) was identical with the product obtained as described in (*a*) on the basis of m.p., mixed m.p., and i.r. and ^{1}H n.m.r. spectra.

4-*Carboxy*-5-*methylisoxazol*-4-*ylacetic Acid* (**18**).—The acid (**17**) (122 g crude product, 734 mmol) was refluxed with conc. HCl and water (225 ml each) for 3 h. The mixture obtained was cooled, and the precipitate which separated was filtered off, washed with cold water (100 ml), and dried in air at 100 °C to give the *acid* (**18**) (124 g, 91%), m.p. 230—231 °C (from water) (Found: C, 45.5; H, 3.6; N, 7.6. $C_7H_7NO_5$ requires C, 45.4; H, 3.8; N, 7.6%); $\nu_{max.}$ 3 400—2 500br (OH), 1 740sh (CO), 1 700 (CO), and 1 610 cm^{-1} (isoxazole); δ_H[$(CD_3)_2SO$] 2.40 (3 H, s, Me) and 3.55 (2 H, s, CH_2).

*Ethyl*4-*Ethoxycarbonyl*-5-*methylisoxazol*-3-*ylacetate* (**19a**).—The acid (**18**) (150 g, 810 mmol) was refluxed with ethanol (1 000 ml) and conc. H_2SO_4 (250 ml) for 10 h. The mixture obtained was poured into ice–water (3 000 g) and extracted with dichloromethane (1 800 ml). The extract was washed with water (1 300 ml) and evaporated to dryness. Distillation of the residue (160 g, 82%) under reduced pressure gave the *ester* (**19a**) (141 g, 72%), b.p. 130—132 °C at 0.4 mmHg, as a yellow oil which crystallized on cooling; m.p. 21 °C (Found: C, 54.6; H, 6.0; N, 5.6. $C_{11}H_{15}NO_5$ requires C, 54.7; H, 6.2; N, 5.8%); $\nu_{max.}$ 1 750 (CO), 1 730 (CO), and 1 615w cm^{-1} (isoxazole); δ_H($CDCl_3$) 1.25 (3 H, t, OCH_2CH_3), 1.30 (3 H, t, OCH_2CH_3), 2.60 (3 H, s, Me), 3.85 (2 H, s, CH_2), 4.15 (2 H, q, OCH_2CH_3), and 4.25 (2 H, q, OCH_2CH_3).

Butyl (4-*Butoxycarbonyl*-5-*methylisoxazol*-3-*yl*)*acetate* (**19b**).—The acid (**18**) (100 g crude product, 540 mmol) was refluxed with benzene (1 000 ml), butan-1-ol (400 ml), and conc. H_2SO_4 (100 ml) for 10 h in a flask equipped with a water separator. The mixture was poured into ice–water (1 500 g) and the benzene phase was separated. The aqueous phase was extracted with benzene (1 500 ml), and the combined benzene phases were washed with water (1 000 ml), filtered and evaporated to dryness. The residual oil (160 g) was distilled to give the *ester* (**19b**) (100 g, 62%), b.p. 130—132 °C at 0.1 mmHg (Found: C, 60.6; H, 7.7; N, 4.6. $C_{15}H_{23}NO_5$ requires C, 60.6; H, 7.8; N, 4.7%); $\nu_{max.}$ 1 730 and 1 750sh (CO) and 1 605w cm^{-1} (isoxazole); δ_H($CDCl_3$) 0.90—1.05 (6 H, m, CH_2CH_3), 1.15—1.90 (8 H, m, $CH_2CH_2CH_2CH_3$), 2.65 (3 H, s, Me), 3.85 (2 H, s, CH_2), and 4.15 (4 H, q, $OCH_2CH_2CH_2CH_3$).

Diethyl (E)-2-*Acetyl*-3-*aminopentene*-2-*dioate* (**20a**).—The ester (**19a**) (91.3 g, 379 mmol) was hydrogenated at room temperature and 1 atm in ethanol (800 ml) in the presence of

10% palladium–carbon (4 g). After uptake of 1 equiv. of hydrogen, the catalyst was filtered off and washed with ethanol and the filtrate was evaporated to dryness. The remaining oil crystallized on cooling to give *compound* (**20a**) (91.2 g, 98%), m.p. 41—42 °C (from ether–hexane) (Found: C, 54.45; H, 7.1; N, 5.6. $C_{11}H_{17}NO_5$ requires C, 54.3; H, 7.05; N, 5.75%); $\nu_{max.}$ 3 300—2 700br (NH), 1 740 (CO), 1 720 (CO), and 1 700 (CO) cm^{-1}; $\delta_H(CDCl_3)$ 1.25 (3 H, t, OCH_2CH_3), 1.30 (3 H, t, OCH_2CH_3), 2.28 (3 H, s, CH_3), 3.55 (2 H, s, CH_2), 4.12 (2 H, q, OCH_2CH_3), and 4.18 (2 H, q, OCH_2CH_3).

t-4-*Amino*-c-2-*methyl*-6-*oxotetrahydropyran*-r-3-*carboxylic Acid Hydrochloride* (**3**).—The ester (**19b**) (10 g crude product, 33.6 mmol) was hydrogenated at 35—40 °C (1 atm) in glacial acetic acid (75 ml) in the presence of 10% palladium–carbon (1 g). After uptake of 1 equiv. of hydrogen, the catalyst was filtered off and sodium tetrahydroborate (10 g, *ca.* 260 mmol) was added to the filtrate with stirring and cooling (ice–water), at a rate which maintained the internal temperature at 15—20 °C (1 h). Acetic acid (30 ml) was then added. The mixture was stirred for a further 1 h with cooling (water), then kept overnight and evaporated to dryness. The residue was taken up in ether (50 ml) and (cautiously) aqueous sodium hydrogen carbonate (150 ml; 5%) and solid sodium hydrogen carbonate were added successively to the stirred mixture. The mixture obtained was filtered, and the aqueous layer was separated and extracted with ether (200 ml). The combined etheral phases were washed successively with water, aqueous sodium hydrogen carbonate; and water again, dried ($MgSO_4$), and evaporated to dryness. The residual oil (7.8 g) was refluxed with conc. HCl (30 ml) for 3 h. The mixture obtained was cooled, washed with ether (75 ml), and evaporated to dryness. The resulting oil was dissolved hot in conc. HCl (7 ml) and the solution was kept at 0 °C for 2 days. The white crystalline precipitate which separated was filtered off, washed successively with cold conc. HCl (2 ml), acetonitrile (5 ml), and ether (5 ml), and dried in air to give a product (2 g, 30%), m.p. 150—152 °C, identical with authentic material obtained as described in ref. 2 on the basis of m.p., mixed m.p., and i.r. and ^1H n.m.r. spectral data.

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