Regioselectivity in the Lithiation of Methyl-substituted Thiazole- and Oxazole-Carboxylic Acids and Carboxamides: General Methods for the Elaboration of Trisubstituted Thiazoles and Oxazoles

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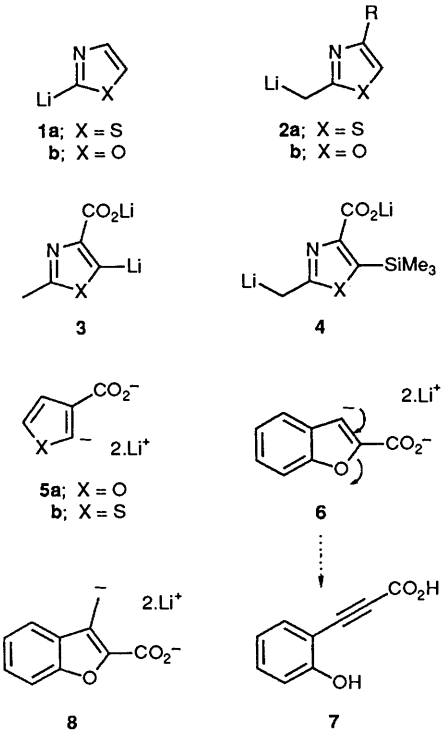
A number of anionic intermediates have been developed which are suitable for the elaboration of trisubstituted thiazoles and oxazoles. Thus, deprotonation of 2,4-dimethylthiazole-5-carboxylic acid **9** using either BuLi or LDA occurs regiospecifically at the 2-methyl site to give dianion **10** which has been condensed with a range of electrophiles leading to high yields of the homologues **11**. The chemistry of the corresponding oxazole **17** is essentially the same, leading to homologues **19** *via* dianion **18**. When the 2-position is substituted by a phenyl group, as in 4-methyl-2-phenylthiazole-5-carboxylic acid **23**, deprotonation of the 4-methyl group, although relatively more difficult, is possible to give dianion **24** and thence homologues **25**. Similar reactions of the corresponding oxazole **26a** appeared to be less useful. Deprotonations of the 2,5-dimethyl isomers **28a** and **31a** were not regiospecific but occurred in varying proportions at both sites under a variety of conditions. Again, substitution of the 2-position by a phenyl group allowed regiospecific deprotonation of the 5-methyl group in acids **33** and **36a**. The thiazole dianion **34** gave good yields of the expected derivatives **35** upon reactions with electrophiles. The regioselectivity problems associated with deprotonations of the 2,5-dimethylazole acids **28a** and **31a** were solved by conversion into the corresponding amides **37** and **40**, both of which underwent regiospecific deprotonation using BuLi leading to the monoanions **38** and **41** and thence to the homologues **39** and **42**.

In general, metallation of five-membered heteroaromatics by proton–lithium exchange occurs at a site α to a heteroatom.[1] As this effect is additive, it is not surprising that thiazole undergoes exclusive deprotonation at the 2-position when treated with an appropriate base, typically butyllithium.[2,3] The resulting lithio species **1a** reacts well with carbonyl compounds but homologations using other electrophiles are often less productive.[1,2] Also in line with this is the observation that when the 2-position of the thiazole nucleus is blocked, then metallation occurs selectively at the 5-position.[4] Access to the 4-position can be gained when the 2-position is blocked, but using halogen–rather than hydrogen–lithium exchange.[5] Oxazole undergoes deprotonation in exactly the same manner, selectively at the 2-position;[1,6,7] however, a crucial difference with the resulting lithio species **1b** is its instability with respect to ring opening, leading to a lithium α-isocyanatoethanoate species. The intermediate **1b** can be trapped efficiently using aryl aldehydes, aryl nitriles, various formylating agents and tin halides as the electrophiles but tends to give ring opened products when treated with alkyl halides, acyl halides and, perhaps surprisingly, chlorotrimethylsilane.[8] 2-Lithiooxazoles have also been acylated using pyridinecarboxamides.[9]

An alternative strategy in this type of metallation chemistry is to deprotonate a methyl or alkyl substituent attached to the heteroaromatic nucleus.[1] As expected, the heteroatoms play a directing role in such reactions although, in the case of thiazoles, it turns out that the kinetic acidities of the protons on a 2-methyl group and the 5-proton of the thiazole nucleus are quite similar. Hence, deprotonation of 2-methylthiazole occurs mainly at the 5-position but largely at the 2-methyl group in 2,4-dimethylthiazole.[2d,10] In contrast, a 4-phenyl substituent is able to direct metallation almost exclusively to the 5-position. These observations were made at low temperatures (−78 °C); at higher temperatures, transmetallation takes place to give the thermodynamically more stable 2-lithio species **2a**. Similarly, a 2-methyl group of an oxazole can be easily and selectively deprotonated and the resulting anions **2b** reacted with a wide range of electrophiles to provide generally excellent yields of the expected homologues, at least when the 5-position is blocked with respect to deprotonation.[11] A powerful directing group positioned at the 4-position is capable of directing such a reaction to the 5-position of an oxazole as in the treatment of 2-methyloxazole-4-carboxylic acid with butyllithium which results in the formation of dianion **3**.[12] Unfortunately, this species was found to react very poorly with a range of electrophiles and was not therefore synthetically useful. Oxazole-4-carboxylic acid was found to behave similarly. (This drawback has been rather neatly solved by deprotonation and homologation of an intermediate on the way to the oxazole nucleus using the Cornforth approach).[12] A second way to achieve deprotonation of the 2-methyl group in such systems is to first block the 5-position. One way in which this can be achieved is by silylation; subsequent treatment with a second equivalent of base then gives the alternative dianionic species **4**.[13]

We have shown that a β-carboxylate function is also capable of directing metallation specifically to an adjacent α-position in furans and thiophenes to give the synthetically useful dianions **5**.[14] Furthermore, a carboxylate residue is able to direct metallation to the 3-position of benzofuran-2-carboxylic acid but, unfortunately, the resulting dianionic species **6** undergoes rapid ring opening to give the acetylenic acid **7** before it can usefully be trapped by all but the most reactive of electrophiles.[15] A solution to this limitation was to deprotonate the 3-methyl analogue to give the homologous dianion **8** which is incapable of undergoing ring opening. This latter species reacted smoothly with a wide range of electrophiles and can thus be used to prepare a wide variety of 2,3-disubstituted benzofurans.[15b] In view of this finding and the synthetic limitations associated with the metallation chemistry of simple thiazole- and oxazole-carboxylic acids (*vide supra*), we have examined the behaviour of a variety of methylated homologues of these acids and some of their derived amides. This has led to the definition of a

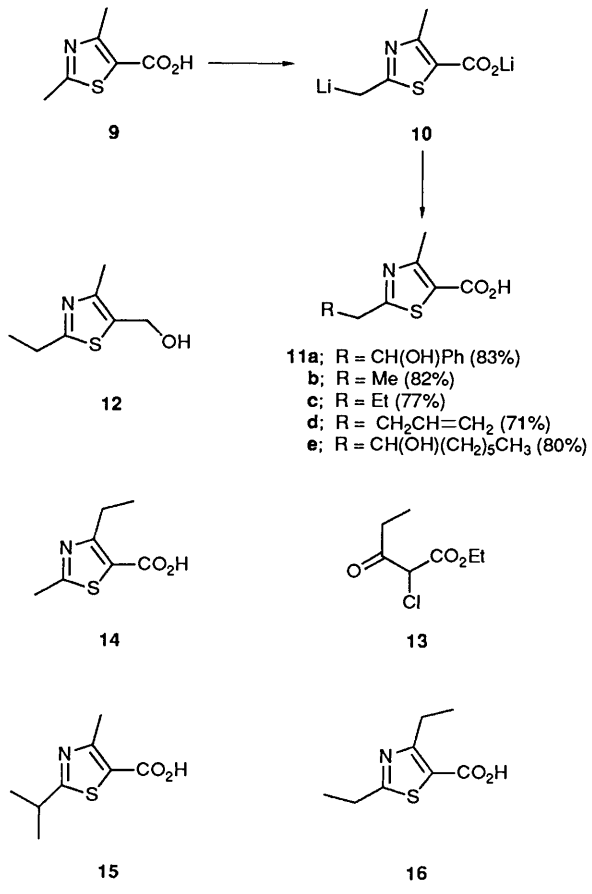


number of synthetically useful intermediates in this area which we describe in full herein.[16]

Results and Discussion

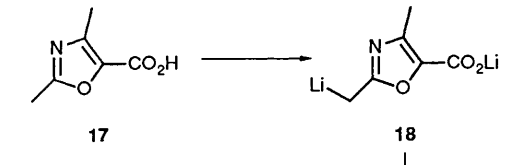
Our studies began with 2,4-dimethylthiazole-5-carboxylic acid **9**, which is readily prepared using the Hantzsch method of condensation between ethyl 2-chloroacetoacetate and thioacetamide followed by saponification of the resulting thiazole ester.[17] Treatment of this acid in tetrahydrofuran (THF) with either lithium diisopropylamide (LDA) or butyllithium (BuLi) at −78 °C resulted in the formation of a greenish brown suspension which was rapidly decolourised upon addition of either benzaldehyde or iodomethane. The resulting products were clearly single regioisomers according to ^{1}H NMR data and were established as the 2-substituted homologues **11**, formed *via* the dianion **10**, as follows. Firstly, attempts to lactonize the benzaldehyde adduct **11a** failed. Secondly, reduction of the methyl ester of product **11b** by lithium aluminium hydride led to an alcohol **12** which showed a clear NOE enhancement between the 4-methyl and the hydroxymethyl methylene groups. Finally, authentic 4-ethyl-2-methylthiazole-5-carboxylic acid **14**, the alternative product which would have resulting from deprotonation of the 4-methyl group and subsequent alkylation by iodomethane, was prepared by condensation of the chloro keto ester **13**[18] with thioacetamide using the Hantzsch method,[17] followed by saponification. This acid, m.p. 176–178 °C, was clearly distinguishable, especially by ^{1}H NMR data, from the metallation product **11b**, m.p. 157 °C. Both of these acids provided the expected dianions upon deprotonation. Thus, sequential treatment of the 2-ethyl acid **11b** with BuLi and iodomethane led to the 2-isopropyl derivative **15** while a similar sequence when applied to the 4-ethyl acid **14** gave the 2,4-diethyl derivative **16**.

As well as coupling efficiently with benzaldehyde and iodomethane, the dianion **10** also gave excellent yields of the expected products **11c–e** from reactions with iodoethane, allyl bromide and heptanal respectively. This correlates with the results obtained with the benzofuran species **8**[15b] and contrasts with the general chemistry of the related sp^2 centred intermediates **3** and **5** which do not couple efficiently with alkyl halides (with the exception of iodomethane) or allylic or benzylic halides.[12,14] Perhaps not surprisingly, dianion **10** appeared to be both the kinetically and thermodynamically preferred species; upon warming to 0 °C, transmetallation did not occur to an extent which could be detected by ^{1}H NMR spectroscopy. In addition, the species was stable with respect to protonation, presumably by the solvent, in marked contrast to the vinylic dianions **5**,[14] but similar to the relatively more nucleophilic but less basic sp^3 centred dianion **8**.[15b]



The metallation chemistry of 2,4-dimethyloxazole-5-carboxylic acid **17**[19] was found to be very similar to the foregoing thiazole species. The dianion **18** was generated exclusively when the acid **17** was treated with either LDA or BuLi in THF at temperatures between −78 °C and −10 °C. Condensations with aldehydes, both aliphatic and aromatic, were clean and efficient and the intermediate also condensed efficiently with benzophenone to give, in each case, the expected products **19a–e**. The regiospecificity of the deprotonation was proven by similar methods to those used in the foregoing thiazole example. Thus, sequential esterification using diazomethane and reduction of the 2-ethyl acid **19e** gave the alcohol **20** which exhibited NOE enhancements between the 4-methyl and 5-hydroxymethyl methylene groups. An authentic sample of the isomeric alcohol **22b** was prepared from methyl 2-acetyloxy-3-oxopentanoate **21**[20] by condensation with ammonium acetate[19] and reduction of the intermediate ester **22a**. The two alcohols **20** and **22b** were clearly distinguishable by both ^{1}H and ^{13}C NMR spectral data. No evidence was found for deprotonation at any other sites in acid **17**; the directing ability of the carboxylate function was therefore not sufficient to cause reaction at the 4-methyl group in preference to the 2-methyl site, even when BuLi was used as the base.[15b,21]

It seemed possible that deprotonation of a 4-methyl group in



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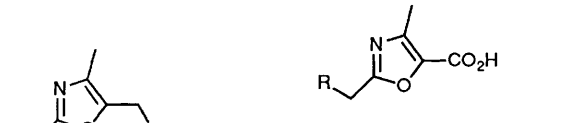

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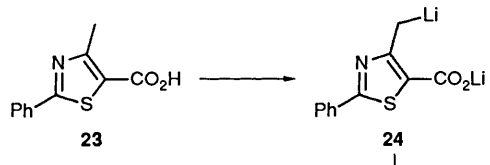
19a; R = CH(OH)Ph (87%)
b; R = C(OH)Ph$_2$ (78%)
c; R = CH(OH)(CH$_2$)$_5$CH$_3$ (80%)
d; R = CH(OH)*p*-MeOC$_6$H$_4$ (50%)
e; R = Me (87%)

21

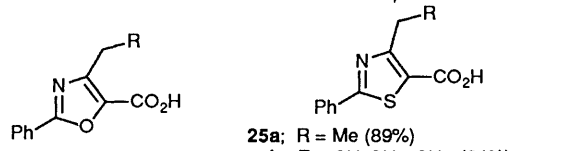
22a; R = CO$_2$Me
b; R = CH$_2$OH

these systems could be effected if the 2-position was blocked. To investigate this, we examined the behaviour of 4-methyl-2-phenylthiazole-5-carboxylic acid **23**, which can be very readily prepared by a Hantzsch-type condensation of thiobenzamide with ethyl 2-chloroacetoacetate[22] and hydrolysis. An alternative to deprotonation of the relatively inactivated 4-methyl group in this substrate could be *ortho*-metallation of the 2-phenyl ring, possibly assisted by the thiazole nitrogen atom.[1] However, in the event, treatment of acid **23** with 2 equivalents of LDA in THF at −18 °C resulted in exclusive formation of the dianion **24**, as addition of iodomethane led to an excellent isolated yield of the 4-ethyl homologue **25a**. There was no evidence from ^{1}H NMR analysis for methylation at any other site of acid **23**. In contrast to the foregoing metallations and probably because the 4-methyl group of acid **23** is less activated with respect to deprotonation, reaction with either LDA or BuLi at −78 °C resulted in only *ca.* 30% conversion into the dianion **24**; at temperatures above −50 °C, attempted deprotonation using BuLi appeared to result instead in nucleophilic attack of the base on the thiazole ring. In any event, little or no homologated thiazole or starting acid **23** was isolated after treatment of the reaction mixture with iodomethane. However, a brief trial indicated that the dianion **24** is synthetically useful. Once again, coupling with allyl bromide proved to be very efficient leading to homologue **25b** and the good yield of the hydroxy-acid **25c** from 1,2-epoxybutane indicates that the dianion **24** is rather nucleophilic. Although conversion into the acetophenone adduct **25d** was relatively inefficient, the reaction gave an excellent material balance, the remainder of the product consisting of unchanged starting acid **23**. This indicates that, at least in examples of relatively unreactive ketones, deprotonation of the electrophile by the dianionic species is a competing process.

The corresponding 4-methyloxazole-5-carboxylic acid **26a** proved to be much less easy to prepare. Oxidation[23] of ethyl 3-aminocrotonate using benzoyl peroxide gave ethyl 2-benzoyloxy-3-oxobutanoate which was converted into the desired oxazole by a modification of the Cornforth procedure[19] using ammonium benzoate followed by saponification of the resulting oxazole ester. Like the corresponding thiazole **23**, the oxazole acid **26a** was only deprotonated to an extent of *ca.* 30% by LDA or BuLi at −78 °C. At higher temperatures, deprotonation was still incomplete, the best result being obtained using LDA at



23 24

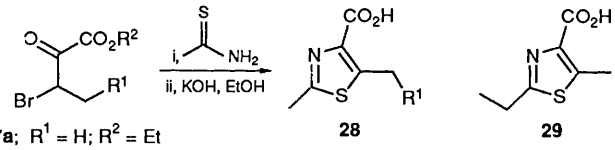


26a; R = H
b; R = Me

25a; R = Me (89%)
b; R = CH$_2$CH=CH$_2$ (84%)
c; R = CH$_2$CH(OH)CH$_2$CH$_3$ (66%)
d; R = PhC(OH)Me (50%)

−35 °C when addition of iodomethane resulted in a 68% conversion into the 4-ethyl derivative **26b**. At −15 °C, the yield of the homologated product was reduced to *ca.* 40% and significant amounts of unidentified decomposition products were formed. This, coupled with the relative difficulty in preparing the starting acid, led us to abandon this section of the study.

We then examined the possibility of effecting deprotonation of a 5-methyl group using a 4-carboxylate function as a directing group in both thiazoles and oxazoles. The required thiazole acid **28a** was relatively straightforward to prepare by a Hantzsch-type synthesis[17] in which thioacetamide was condensed with ethyl 3-bromo-2-oxobutanoate **27a**[24] to give the corresponding ethyl ester which was then saponified. The 5-ethyl derivative **28b** was also prepared as a reference sample, by condensation of thioacetamide with methyl 3-bromo-2-oxopentanoate **27b**, followed by saponification. Deprotonations of the thiazole acid **28a** were however not synthetically useful as little selectivity was observed between reaction at the 2- or 5-methyl substituents. Thus, sequential treatment of acid **28a** with LDA at −78 °C and iodomethane gave, in excellent yield, a 59:41 mixture of the 2- and 5-ethyl acids (**29** and **28b**) respectively. The ratio was determined from ^{1}H NMR data and by comparison with the spectral data displayed by the authentic 5-ethyl acid **28b**. At the higher temperature of −15 °C, the ratio changed to 67:33 in favour of the 2-ethyl derivative, possibly indicating a slight thermodynamic preference for deprotonation at this position. By contrast, deprotonation of acid **28a** using BuLi at −78 °C followed by quenching with iodomethane led to a 46:54 mixture of the 2- and 5-ethyl acids (**29** and **28b**); the slight preference for the 5-isomer was probably due to

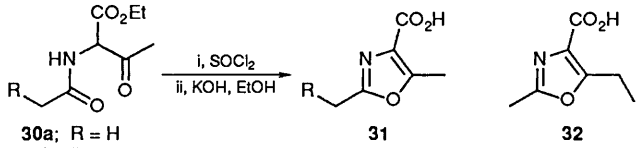


27a; R^1 = H; R^2 = Et
b; R^1 = R^2 = Me

28 29

some complexation between the carboxylate function and the base.[14,21] It is therefore clear that in the case of acid **28a**, the various activation factors affecting the two methyl groups are essentially equivalent. We wondered if the extra methyl substituent in acid **28b** would tip the balance in favour of deprotonation at the 2-methyl position. However, treatment of this acid with LDA and iodomethane at −78 °C gave a product ratio of 60:40 in favour of deprotonation of the 2-methyl group. (*cf.* 59:41 for the 2,5-dimethyl acid **28a**). The extra substituent therefore had essentially no effect on the regioselectivity of deprotonation.

Much the same pattern of reactivity was found with the corresponding 2,5-dimethyloxazole-4-carboxylic acid **31a**. This acid was obtained by cyclodehydration using thionyl chloride[25] of the 2-acetylamino keto-ester **30a**.[26] An authentic comparison sample of the 2-ethyl homologue **31b** was prepared using the same route but starting with the corresponding 2-propanoylamino derivative **30b**. Deprotonation of acid **31a** by LDA followed by quenching with iodomethane resulted in a 1:1 mixture of the two possible ethyl-substituted acids **31b** and **32**. Low temperature deprotonation using BuLi did improve this ratio to 7:3 in favour of the 5-ethyl homologue **32**, presumably

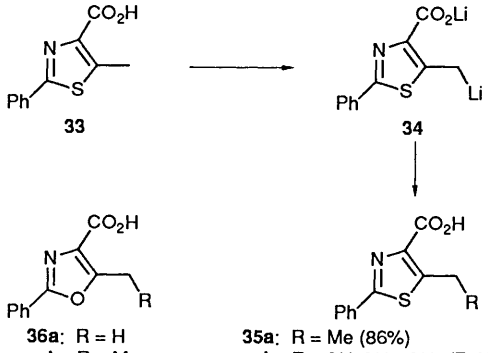


30a; R = H
b; R = Me

31 **32**

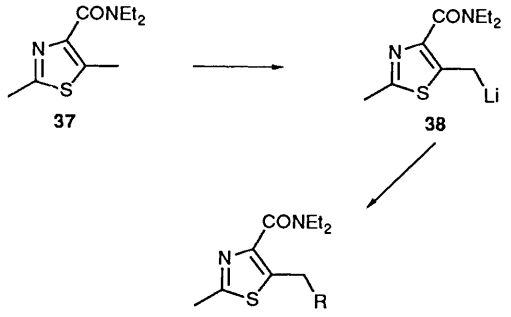
owing to some extra complexation between the carboxylate function and the base. However, this lack of regioselectivity renders the method of little synthetic value and it was therefore not studied further.

When the 2-position is blocked with respect to deprotonation, synthetically useful dianions can be obtained by regiospecific deprotonation of the 5-methyl group in such azole-4-carboxylic acids. The 2-phenylthiazole-4-carboxylic acid **33** was readily prepared by a Hantzsch-type condensation[17] between thiobenzamide and ethyl 3-bromo-2-oxobutanoate **27a**.[24] Deprotonation to give the dianion **34** occurred smoothly when a solution of the acid in THF was treated with BuLi at −78 °C;



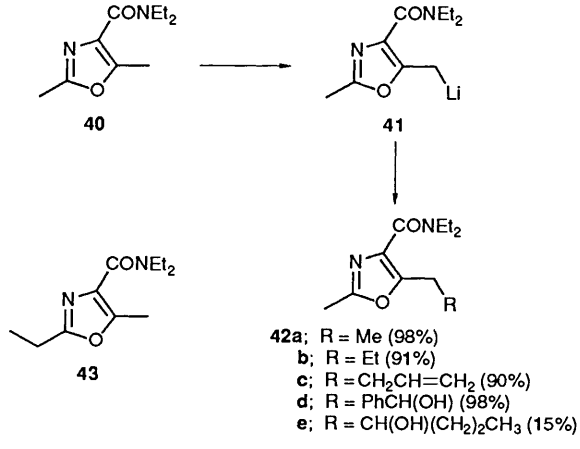
subsequent alkylations with both iodomethane and allyl bromide gave good isolated yields of the expected products **35a** and **35b**. The dianion **34** was also alkylated efficiently by epoxybutane, to give the hydroxy-acid **35c**, indicating that, in common with 4-methyl isomer **24**, this intermediate is a good nucleophile. No evidence for deprotonation at any other site in acid **33** was apparent from spectral data of the crude products **35**. The corresponding oxazole **36a** proved to be much more difficult to prepare, the method of Allan and Walter[27] being very variable and capricious in our hands. We therefore only investigated the possibility of dianion formation from this acid. This again was readily achieved by treatment with BuLi in THF at −78 °C as shown by the isolation of an excellent yield of the 5-ethyl homologue **36b** following the addition of iodomethane. In both cases, the ease of deprotonation relative to the corresponding 4-methyl isomers (**23** and **26a**) presumably reflects the closer proximity of the methyl groups to a heteroatom in the heterocyclic ring.

The viability of deprotonation of a 5-methyl group in such azole systems is somewhat diminished by the lack of regioselectivity in such reactions of the 2,5-dimethylazole-4-carboxylic acids (**28a** and **31a**) and presumably of homologous 2,5-alkyl derivatives (*cf.* metallation of **28b**). We therefore sought a more powerful directing group which, in combination with the more readily co-ordinating base BuLi, would perhaps tip the clearly delicate balance in favour of deprotonation at the 5-methyl site. As a good candidate for this appeared to be an amide function,[1,28] we prepared the two diethylamides **37** and **40** from the corresponding acids **28a** and **31a** using established methodology.[29,30] We were pleased to find that the tertiary amide group was indeed superior to the carboxylate residue in directing metallation to the adjacent 5-methyl site. Thus, treatment of the thiazole carboxamide **37** with BuLi at −78 °C in THF generated the red monoanion **38** which reacted



smoothly with a range of electrophiles to give the homologues **39** in excellent isolated yields. That the deprotonation was regiospecific in favour of the 5-methyl site was ascertained by comparison of the spectral data of the metallation-derived product **39a** with an authentic sample prepared from the corresponding acid **28b**. These were identical and, in addition, no isomers were evident in the ^{1}H NMR spectrum of the sample of the metallation product **39a**.

The metallation chemistry of the corresponding oxazole amide **40** turned out to be essentially the same. Once again, using BuLi as the base, this amide also gave a single anion **41** which subsequently reacted smoothly with a range of electrophiles to give generally excellent yields of the expected



homologues **42**. One exception was condensation with an aliphatic aldehyde which evidently proceeded preferentially *via* deprotonation of the electrophile rather than coupling, as a good yield of the starting amide was obtained along with a poor 15% yield of the desired product **42e**. Again, the regiospecificity

of the deprotonation was proven by comparison with an authentic compound, this time the 2-ethyl amide **43** derived from the acid **31b**. As in the case of the thiazole amide **37**, no trace of products arising from reaction at the alternative 2-methyl site in oxazole **40** could be detected by ^{1}H NMR spectroscopy.

Despite a few limitations such as availability of the starting materials or incompatibility with a particular type of electrophile, the new anionic species identified in this work should be useful for the synthesis of a wide range of trisubstituted thiazoles and oxazoles.

Experimental

Melting points were determined on a Kofler hot-stage apparatus and are not corrected. UV spectra were recorded using ethanol solutions and a Philips TU8720 spectrophotometer. IR spectra were recorded using a Pye-Unicam SP3-100 instrument; unless otherwise stated, spectra of solid samples were obtained using KBr pellets whereas liquids were run as films. ^{1}H NMR spectra were measured at 90 MHz using a Perkin-Elmer R-32 instrument and dilute solutions in deuteriochloroform unless stated otherwise. Tetramethylsilane was used as the standard throughout. *J* Values are given in Hz. ^{13}C NMR spectra were recorded using a Bruker WP 80SY or a WM 250 instrument operating at 20.15 and 62.8 MHz respectively. Shifts are recorded in ppm from tetramethylsilane for deuteriochloroform solutions unless otherwise stated. Mass spectra and molecular weights were determined using a VG MM7070E or an AEI MS 902 spectrometer, both operating in the electron impact mode at 70 eV.

All glassware was oven-dried at 120 °C and cooled under an atmosphere of dry nitrogen or argon. All reactions were performed under a positive pressure of dry nitrogen or argon. Tetrahydrofuran was always freshly distilled from benzophenone ketyl. Ether throughout refers to diethyl ether; dry samples were obtained by distillation from lithium aluminium hydride. Benzene and toluene were dried over sodium wire. Diisopropylamine and diethylamine were dried by distillation from potassium hydroxide pellets and stored over freshly activated molecular sieves. Iodomethane was purified by distillation from phosphorus pentoxide. All other liquid electrophiles were distilled just prior to use; solid electrophiles were dried by high vacuum for at least 3 h. All organic solutions from work-ups were dried using anhydrous magnesium sulphate.

Generation of Dianion **10** *from* 2,4-*Dimethylthiazole*-5-*carboxylic Acid* **9**; *Typical Procedures*.—(i) *Using lithium diisopropylamide* (*LDA*). Butyllithium (1.6M solution in hexanes; 1.38 ml, 2.2 mmol) was added dropwise to a stirred solution of diisopropylamine (0.31 ml, 2.2 mmol) in dry THF (15 ml) maintained at −20 °C. After 0.25 h, the resulting solution of LDA was cooled to −78 °C (solid CO_2–acetone bath) and treated *via* syringe with a suspension of 2,4-dimethylthiazole-5-carboxylic acid **9**[17] (0.157 g, 1 mmol) in THF (15 ml). The resulting greenish brown suspension was stirred at this temperature for 10 min, before addition of the electrophile.

(ii) *Using butyllithium*. Butyllithium (1.6M solution in hexanes; 2.76 ml, 4.4 mmol) was added dropwise to a stirred solution of the acid **9**[17] (0.314 g, 2 mmol) in dry THF (30 ml) maintained at −78 °C (solid CO_2–acetone bath). After 0.5 h at this temperature, the resulting greenish brown mixture was treated with the electrophile.

2-(2-*Hydroxy*-2-*phenylethyl*)-4-*methylthiazole*-5-*carboxylic acid* **11a**. A suspension of dianion **10** (1.1 mmol) was prepared by procedure (i) and treated with benzaldehyde (0.4 ml, 3.9 mmol). The mixture was instantly decolourised and, after warming to ambient temperature, was poured into saturated aqueous ammonium chloride (50 ml). The separated aqueous layer was acidified to pH 4 using 2M hydrochloric acid and then extracted with ethyl acetate (2 × 25 ml). The combined organic extracts were washed with water (50 ml) and brine (50 ml) and then dried and evaporated. Crystallisation of the residue from chloroform gave the *hydroxy acid* **11a** (0.24 g, 83%) as a colourless powder, m.p. 230 °C (decomp.), ν_{max}/cm^{-1} 3560, 3100–2100, 1695, 1600 and 1580; δ_H[$(CD_3)_2CO$] 2.66 (3 H, s, 4-Me), 3.36 [2 H, d, *J* 7, CH_2CH(OH)], 5.17 [1 H, t, CH_2CH(OH)] and 7.27–7.67 (5 H, m, Ph); *m*/*z* 263 (M^+, 1%), 245 (22, M − H_2O) 244 (32), 158 (11), 157 (100), 107 (31), 105 (11), 79 (31) and 77 (27) (Found: C, 57.6; H, 5.1; N, 5.2. $C_{13}H_{13}NO_3S\cdot\frac{1}{2}H_2O$ requires C, 57.3; H, 5.2; N, 5.1%).

2-*Ethyl*-4-*methylthiazole*-5-*carboxylic acid* **11b**. Treatment of the dianion **10** (3 mmol) in THF (35 ml), generated using procedure (i), with iodomethane (0.5 ml, 8 mmol) followed by warming to ambient temperature and the foregoing work-up, which in this case included an additional wash with 1% aqueous sodium thiosulphate, gave the 2-*ethyl acid* **11b** (0.35 g, 68%), after crystallisation from benzene, as colourless needles, m.p. 157 °C; ν_{max}/cm^{-1} 3200–2100, 1710 and 1555; δ_H[$(CD_3)_2SO$] 1.32 (3 H, t, *J* 7, CH_2CH_3), 2.61 (3 H, s, 4-Me) and 2.96 (2 H, q, *J* 7, CH_2CH_3); *m*/*z* 171 (M^+, 100%), 170 (60), 116 (41), 71 (22) and 56 (9) (Found: C, 49.6; H, 5.6; N, 8.0. $C_7H_9NO_2S$ requires C, 49.1; H, 5.3; N, 8.2%).

In a second experiment, generation of the dianion **10** (2 mmol) using procedure (ii) followed by reaction with iodomethane (0.4 ml) gave the 2-ethyl acid **11b** (0.28 g, 82%) which was identical to the foregoing sample.

4-*Methyl*-2-*propylthiazole*-5-*carboxylic acid* **11c**. Using the general procedure (i), iodoethane (0.3 ml, 3.75 mmol) was added to a suspension of dianion **10** (1 mmol) in THF (30 ml). After warming to ambient temperature, the solvents were evaporated and the residue dissolved in water and acidified using concentrated hydrochloric acid. Extraction with ethyl acetate (2 × 30 ml) as usual then gave the 2-*propyl acid* **11c** (0.142 g, 77%) as a cream solid, m.p. 149–150 °C, λ_{max} 265 nm; ν_{max}/cm^{-1} 3200–2100, 1700 and 1530; δ_H[$(CD_3)_2SO$] 0.97 (3 H, t, *J* 7, CH_2CH_3), 1.72 (2 H, m, $CH_2CH_2CH_3$), 2.62 (3 H, s, 4-Me) and 2.92 (2 H, t, *J* 7, $CH_2CH_2CH_3$); *m*/*z* 185 (M^+, 14%), 184 (14), 170 (25) and 157 (100). (Found: C, 52.0; H, 6.1; N, 7.2. $C_8H_{11}NO_2S$ requires C, 51.9; H, 6.0; N, 7.6%).

2(*But*-3-*enyl*)-4-*methylthiazole*-5-*carboxylic acid* **11d**. A suspension of dianion **10** (1 mmol) prepared by method (i) was treated with allyl bromide (0.3 ml); the resulting pale yellow solution was left at −78 °C for 20 min and then warmed to ambient temperature over 1 h and the solvent evaporated. The residue was dissolved in water (30 ml), the solution acidified to pH 4 using concentrated hydrochloric acid then extracted with ethyl acetate (3 × 30 ml). The combined extracts were washed with water (50 ml) and brine (50 ml), then dried and evaporated to leave the *butenyl acid* **11d** (0.14 g, 71%) as a cream solid, m.p. 142 °C (decomp.), λ_{max} 263 nm; ν_{max}/cm^{-1} 3200–2100, 1700 and 1640; δ_H[$(CD)_3)_2SO$] 2.38–2.70 (2 H, m, CH_2CH:), 2.62 (3 H, s, 4-Me), 3.07 (2 H, t, *J* 7, CH_2CH_2), 5.05–5.30 (2 H, m, CH_2=CH) and 5.66–6.22 (1 H, m, CH=CH_2); *m*/*z* 197 (M^+, 100%), 196 (92), 182 (33), 157 (27) and 156 (65). (Found: C, 54.6; H, 5.6; N, 6.7. $C_9H_{11}NO_2S$ requires C, 54.8; H, 5.6; N, 7.1%).

2-(2-*Hydroxyoctyl*)-4-*methylthiazole*-5-*carboxylic acid* **11e**. A suspension of the dianion **10** (1 mmol) prepared by method (i) was treated with heptanal (0.3 ml, 2.2 mmol) and allowed to reach ambient temperature over 1 h; it was then poured into saturated aqueous ammonium chloride. The separated aqueous layer was acidified to pH 3 with 2M hydrochloric acid and extracted with ethyl acetate (3 × 10 ml). The combined organic extracts were washed with water (25 ml) and brine (25 ml), dried and evaporated. Crystallisation of the residue from ethyl acetate–light petroleum (b.p. 40–60 °C) gave the *hydroxy acid* **11e** (0.217 g, 80%) as a colourless powder, m.p. 226–230 °C, ν_{max}/cm^{-1} 3400–2100, 1695, 1600 and 1580; δ_H 0.85 (3 H, t, *J* 7,

8′-Me), 1.10–1.70 (10 H, m, 5 × CH_2), 2.74 (3 H, s, 4-Me), 3.14 (2 H, m, 1-CH_2) and 3.90–4.23 (1 H, br m, C*H*OH).

(*2-Ethyl-4-methylthiazol-5-yl*)*methanol* **12**. Methyl 2-ethyl-4-methylthiazole-5-carboxylate was prepared by methylation of the corresponding acid **11b** (*vide supra*) using an excess of ethereal diazomethane at ambient temperature for 1 h in the usual way, and was an oil which showed R_f 0.58 [ether–light petroleum (40–60); 1:1]; ν_{max}/cm^{-1} 2892, 2880, 1720, 1535 and 1270; δ_H 1.39 (3 H, t, *J* 7, CH_2CH_3), 2.74 (3 H, s, 4-Me), 3.02 (2 H, q, *J* 7, $CH_2CH_2CH_3$) and 3.90 (3 H, s, OMe) (Found: M^+, 185.0514. $C_8H_{11}NO_2S$ requires *M*, 185.0511).

Lithium aluminium hydride (0.08 g, 2.1 mmol) was added to a vigorously stirred solution of the foregoing ester (0.16 g, 0.86 mmol) in dry ether (20 ml) at 0 °C. Stirring was continued for 1.5 h after which 0.5M aqueous sodium hydroxide (1 ml) was added dropwise. The resulting mixture was filtered, the solid washed with ether and the filtrate dried and evaporated to give the *alcohol* **12** (0.12 g, 88%) as a colourless oil, ν_{max}/cm^{-1} 3500–3100, 2992, 2920, 1560 1025; δ_H(250) 1.33 (3 H, t, *J* 7.6, CH_2CH_3), 2.28 (3 H, 4-Me), 2.92 (2 H, q, *J* 7.6, CH_2CH_3) and 4.72 (2 H, s, CH_2OH); *m/z* 157 (M^+, 100%), 140 (19), 128 (46), 102 (14), 73 (11) and 51 (13) (Found: M^+, 157.0548. $C_7H_{11}NOS$ requires *M*, 157.0561).

In an NOE experiment, irradiation of the resonance at δ4.72 caused a 2.4% increase in the intensity of the signal at δ 2.28.

Ethyl 2-chloro-3-oxopentanoate **13**. Sulphuryl chloride (3.5 ml, 43.6 mmol) was added dropwise to ethyl 3-oxopentanoate (6.28 g, 43.6 mmol) which was stirred and cooled in ice.[18] The cooling bath was removed, the mixture stirred for 18 h and then for 3 h under water-pump vacuum. The residue was distilled through a Vigreux column to give the chloride **13** (4.62 g, 59%) as a colourless oil, b.p. 90–94 °C/11 mmHg (lit.,[18] b.p. 110–111 °C/21 mmHg); ν_{max}/cm^{-1} 2985, 1760–1730 and 1025; δ_H 1.14 (3 H, t, *J* 7, 5-Me), 1.33 (3 H, t, *J* 7, OCH_2CH_3), 2.79 (2 H, q, *J* 7, 4-CH_2), 4.34 (2 H, q, *J* 7, OCH_2) and 4.87 (1 H, s, 2-H). The material was used directly in the next step.

4-Ethyl-2-methylthiazole-5-carboxylic acid **14**.—A mixture of the foregoing chloro-keto ester **13** (4.62 g, 23.6 mmol) and thioacetamide (1.77 g, 23.6 mmol) in ethanol (100 ml) was heated under reflux for 7 h[17] and then cooled and diluted with dichloromethane (300 ml). The precipitate was filtered off and the filtrate washed successively with saturated aqueous sodium hydrogen carbonate (100 ml) and brine (100 ml), then dried and evaporated to leave the *ethyl 4-ethyl-2-methylthiazole-5-carboxylate* (4.32 g, 92%), ν_{max}/cm^{-1} 2990, 2930, 1710 and 1525; δ_H 1.30 (3 H, t, *J* 7, 4-CH_2CH_3 (1.38 (3 H, t, *J* 7, OCH_2CH_3), 2.72 (3 H, 2-Me), 3.16 (2 H, q, *J* 7, 4-CH_2CH_3) and 4.38 (2 H, q, *J* 7, OCH_2CH_3); *m/z* 199 (M^+, 69%), 181 (13), 170 (100), 158 (13), 154 (31), 131 (18), 119 (15), 85 (24), 69 (60 and 57 (14) (Found: M^+, 199.0658. $C_9H_{13}NO_2S$ requires *M*, 199.0667).

The foregoing ester (3.04 g, 15.3 mmol) was stirred with potassium hydroxide (2.14 g, 38.2 mmol) in ethanol (100 ml) and water (10 ml) at ambient temperature for 48 h. The resulting solution was evaporated to dryness, the residue dissolved in water and then acidified to pH 3 using 2M hydrochloric acid. The resulting precipitate was filtered off and dried *in vacuo* to give the *acid* **14** (1.53 g, 58%) as a colourless powder, m.p. 176–178 °C; λ_{max} 259 nm; ν_{max}/cm^{-1} 3100–2200, 1695 and 1532; δ_H[$(CD_3)_2SO$] 1.22 (3 H, t, *J* 7, CH_2CH_3), 2.67 (3 H, s, 2-Me) and 3.05 (2 H, q, *J* 7, CH_2CH_3); *m/z* 171 (M^+, 100%), 162 (11), 156 (7, 130 (66), 126 (14), 87 (12), 85 (54), 71 (12) and 59 (13) (Found: C, 48.6; H, 5.2; N, 7.9. $C_7H_9NO_2S$ requires C, 49.1; H, 5.3; N, 8.2%).

2-Isopropyl-4-methylthiazole-5-carboxylic acid **15**. Butyllithium (1.6M solution in hexanes; 1.38 ml, 2.2 mmol) was added dropwise to a well stirred solution of 2-ethyl-4-methylthiazole-5-carboxylic acid **11b** (0.171 g, 1 mmol) in THF (10 ml) at −78 °C. A greenish-brown colouration developed; after 0.5 h at −78 °C, iodomethane (0.3 ml) was added dropwise. The mixture rapidly clarified and lightened in colour. After a further 0.5 h at −78 °C, the cooling bath was removed and, after 0.25 h, the mixture was evaporated. The residue was dissolved in water (15 ml) and the resulting solution acidified using 2M hydrochloric acid then extracted with ethyl acetate (2 × 20 ml). The combined extracts were washed with water (20 ml) and brine (20 ml) and then dried and evaporated. Crystallisation of the pale yellow solid residue from benzene gave the *acid* **15** (0.113 g, 61%) as a colourless powder, m.p. 157–158 °C; ν_{max}/cm^{-1} 3200–2100, 1690 and 1532; δ_H[$(CD_3)_2SO$] 1.33 [6 H, d, *J* 6.8, $CH(CH_3)_2$], 2.59 (3 H, s, 4-Me) and 3.05–3.45 [1 H, m, $CH(CH_3)_2$]; *m/z* 185 (M^+, 48%), 170 (100) and 96 (11) (Found: C, 51.6; H, 6.1; N, 7.4. $C_8H_{11}NO_2S$ requires C, 51.9; H, 6.0; N, 7.6%).

2,4-Diethylthiazole-5-carboxylic acid **16**. Using the foregoing procedure, sequential treatment of *4-ethyl-2-methylthiazole-5-carboxylic acid* **14** (0.342 g, 2 mmol) in THF (16 ml) with butyllithium (4.4 mmol) and iodomethane (0.5 ml) gave the *acid* **16** (0.35 g, 95%) which crystallised from benzene as colourless needles, m.p. 121–122 °C, ν_{max}/cm^{-1} 3200–2200, 1692 and 1530; δ_H 1.32 (3 H, t, *J* 7, CH_2CH_3), 1.42 (3 H, t, *J* 7, CH_2CH_3) and 2.96–3.32 (4 H, m); *m/z* 185 (M^+, 100%), 140 (14), 130 (61) and 85 (40) (Found: C, 52.2; H, 6.2; N, 7.4. $C_8H_{11}NO_2S$ requires C, 51.9; H, 6.0; N, 7.6%).

Stability of Dianion **10**.—The dianion **10** (3 mmol) in THF (50 ml) was generated at −78 °C as described above. Aliquots (7 ml) were withdrawn and immediately quenched with benzaldehyde (0.1 ml) as the temperature of the reaction mixture was raised to 0 °C over 1.5 h. After work-up as described above, analysis of the products by ^1H NMR spectroscopy showed essentially quantitative conversion into the hydroxy acid **11a** throughout this range of temperatures. There was no evidence of metallation at other sites or protonation of the dianion.

Generation and Reactions of Dianion **18** *from 2,4-Dimethyloxazole-5-carboxylic Acid* **17**: *General Procedures*.—(i) *Using lithium diisopropylamide*. An ice-cold solution of LDA (2.2 mmol) in THF (6 ml) was added dropwise to a suspension of 2,4-dimethyloxazole-5-carboxylic acid **17**[19] (0.141 g, 1 mmol) in THF (4 ml) at −78 °C to give a yellow–orange fluorescent solution which was maintained at this temperature for 0.5 h before addition of the electrophile, neat if a liquid or dissolved in a minimum amount of THF if a solid. The resulting mixture was warmed slowly to ambient temperature over 1 h, then diluted with saturated aqueous ammonium chloride (3 ml). The separated aqueous layer was diluted with water (2 ml), acidified with 2M hydrochloric acid and extracted with ethyl acetate (3 × 5 ml). The combined extracts were dried and evaporated and the residue further purified by crystallisation.

(ii) *Using butyllithium*. Butyllithium (1.6M solution in hexanes; 2.75 ml, 4.4 mmol) was added dropwise to a stirred suspension of 2,4-dimethyloxazole-5-carboxylic acid **17** (0.282 g, 2 mmol) in THF (25 ml) maintained at −78 °C. After 0.5 h, the electrophile was added, the mixture warmed to ambient temperature over 1 h, concentrated to *ca.* 10 ml then worked up, all as described above.

2-(2-Hydroxy-2-phenylethyl)-4-methyloxazole-5-carboxylic acid **19a**. By the general procedure (i), reaction between acid **17** (0.98 mmol) and benzaldehyde (0.3 ml, 3 mmol) afforded the *hydroxy acid* **19a** (0.21 g, 87%), which crystallised from chloroform as a powder, m.p. 230–232 °C, ν_{max}/cm^{-1} 3400–2300, 3340, 1705, 1640 and 1575; δ_H[$(CD_3)_2SO$] 2.36 (3 H, s, 4-Me), 3.07 [2 H, d, *J* 7, $CH(OH)CH_2$], 5.07 [1 H, t, *J* 7, $CH(OH)CH_2$], 5.40–5.75 (1.5 H, br s, OH) and 7.25–7.55 (5 H, m, Ph); *m/z* 247 (M^+, <1%), 142 (10), 141 (100), 107 (66), 97 (9), 79 (50), 77 (28)

and 67 (18) (Found: C, 60.6; H, 5.3; N, 5.5. $C_{13}H_{13}NO_4 \cdot \frac{1}{2}H_2O$ requires C, 60.9; H, 5.5; N, 5.5%).

In a second experiment, generation and reaction of the dianion **18** (1 mmol) with benzaldehyde was carried out using procedure (i) but at −30 °C throughout. The product **19a** (0.20 g, 81%) was identical with the foregoing sample.

2-(2-*Hydroxy*-2,2-*diphenylethyl*)-4-*methyloxazole*-5-*carboxylic acid* **19b**. Using procedure (i), reaction between acid **17** (0.14 g, 0.99 mmol) and benzophenone (0.195 g, 1.07 mmol) gave the *hydroxy acid* **19b** (0.244 g, 76%) which crystallised from chloroform as a colourless powder, m.p. 230 °C; ν_{max}/cm^{-1} 3440, 3500–2200, 1715, 1640 and 1555; δ_H 2.37 (3 H, s, 4-Me), 4.77 (2 H, s) and 7.24–7.65 (10 H, m, 2 × Ph); *m/z* 323 (M^+, 11%), 204 (7), 184 (11), 183 (80), 141 (50), 105 (100) and 77 (47) (Found: C, 69.1; H, 5.6; N, 4.0. $C_{19}H_{17}NO_4 \cdot \frac{1}{2}H_2O$ requires C, 68.7; H, 5.5; N, 4.2%).

By general procedure (ii), reaction between acid **17** (0.282 g, 2 mmol) and benzophenone (0.4 g) gave the same *hydroxy acid* **19b** (0.51 g, 79%) which was identical with the foregoing material.

2(2-*Hydroxyoctyl*)-4-*methyloxazole*-5-*carboxylic acid* **19c**. By general procedure (i), condensation of acid **17** (0.141 g, 1 mmol) with heptanal (0.3 ml, 2 mmol) gave the *hydroxy acid* **19c** (0.205 g, 80%) as a colourless powder, m.p. 126–127; ν_{max}/cm^{-1} 3500, 2940, 2850, 2800–2100, 1710 and 1630; $\delta_H(CD_3OD)$ 0.70–1.00 (3 H, t, *J ca.* 7, Me), 1.10–1.70 (10 H, m), 2.45 (3 H, s, 4-Me), 2.95 [2 H, d, *J* 7, CH(OH)CH_2] and 4.00–4.20 [1 H, br m, C*H*(OH)CH_2]; *m/z* 255 (M^+, <1%), 170 (8), 142 (6), 141 (100) and 55 (10) (Found: M^+, 255.1474. $C_{13}H_{21}NO_4$ requires *M*, 255.1471).

The foregoing experiment was repeated but with formation and trapping of the dianion **18** at −10 °C; the same product was obtained in 83% yield.

Methyl 2-[2-*hydroxy*-2-(4-*methoxyphenyl*)*ethyl*]-4-*methyloxazole*-5-*carboxylate*. By procedure (i), condensation of acid **17** (1 mmol) with 4-methoxybenzaldehyde gave a 1 : 1 mixture of the desired product **19d** and starting material. Esterification of this mixture by treatment with excess ethereal diazolmethane for 0.5 h at 0 °C followed by evaporation and column chromatography of the residue using silica gel eluted with 40% ethyl acetate in light petroleum (b.p. 60–80 °C) gave the *ester* (R_F 0.13) which crystallised from toluene as colourless prisms, m.p. 114–115 °C, ν_{max}/cm^{-1} ($CHCl_3$) 3700, 3050, 1730 and 1620; δ_H 2.45 (3 H, s, 4-Me), 3.17 [2 H, d, *J* 7, CH(OH)CH_2], 3.87 (3 H, s, OMe), 3.97 (3 H, s, CO_2Me), 5.29 [1 H, t, *J* 7, C*H*(OH)CH_2], 7.02 (2 H, d, *J* 9) and 7.47 (2 H, d, *J* 9); *m/z* 291 (M^+, <1%), 273 (24), 272 (26), 155 (91), 145 (15), 137 (100), 136 (10), 135 (19), 109 (13) and 55 (10) (Found: C, 61.8; H, 6.1; N, 5.0. $C_{15}H_{17}NO_5$ requires C, 61.8; H, 5.9; N, 4.8%).

2-*Ethyl*-4-*methyloxazole*-5-*carboxylic acid* **19e**. Using procedure (i), but with addition of a suspension of the acid **17** (1 mmol) in THF (2 ml) to the LDA solution [2.2 mmol in THF (8 ml)] and using iodomethane as the electrophile led to the 2-*ethyl acid* **19e** (0.135 g, 87%) which crystallised as colourless needles from ethyl acetate, m.p. 222 °C, ν_{max}/cm^{-1} 3100–2200, 1710, 1630 and 1560; $\delta_H[(CD_3)_2SO]$ 1.22 (3 H, t, *J* 7, CH_2CH_3), 2.38 (3 H, s, 4-Me) and 2.86 (2 H, q, *J* 7, CH_2CH_3); *m/z* 155 (M^+, 100%), 141 (19), 110 (56), 100 (43), 82 (20), 68 (14), 56 (21), 51 (19) and 42 (85) (Found: M^+, 155.0546. $C_7H_9NO_3$ requires *M*, 155.0582).

Using procedure (ii), the same reaction led to an identical product in 90% yield on a 2 mmol scale.

(2-*Ethyl*-4-*methyloxazol*-5-*yl*)*methanol* **20**. The foregoing acid **19e** was esterified using ethereal diazomethane in the usual way to give *methyl* 2-*ethyl*-4-*methyloxazole*-5-*carboxylate* as an oil ν_{max}/cm^{-1} 2985, 2950, 1720, 1615, 1555 and 1150; δ_H 1.36 (3 H, t, *J* 7, CH_2CH_3), 2.44 (3 H, s, 4-Me), 2.81 (2 H, q, *J* 7, CH_2CH_3) and 3.90 (3 H, OMe).

Lithium aluminium hydride (0.05 g) was added to a stirred solution of the foregoing ester (0.036 g) in dry ether (20 ml) at 0 °C. After 0.5 h, aqueous 0.5M sodium hydroxide (1 ml) was added, the resulting mixture filtered and the filtrate dried and evaporated to provide the *alcohol* **30** (0.018 g, 60%) as a colourless oil, ν_{max}/cm^{-1} 3500–3100, 1595 and 1020; δ_H(250) 1.24 (3 H, t, *J* 7.6, CH_2CH_3), 2.05 (3 H, s, 4-Me), 2.66 (2 H, q, *J* 7.6, CH_2CH_3) and 4.51 (2 H, s, CH_2OH); δ_H 11.1 (2 × Me), 21.6 (CH_2), 53.9 (CH_2), 133.1 (C), 145.0 (C) and 164.9 (C); *m/z* 141 (M^+, 59%), 140 (32), 124 (74), 112 (47), 110 (49), 85 (34), 82 (100), 57 (48) and 56 (51) (Found: M^+, 141.0767. $C_7H_{11}NO_2$ requires *M*, 141.0790).

(4-*Ethyl*-2-*methyloxazol*-5-*yl*)*methanol* **22b**. According to the procedure of Dimroth and Schweizer,[20] oxidation of methyl 3-oxopentanoate (20 ml, Aldrich) with lead(IV) acetate (60 g) in benzene (100 ml) gave *methyl* 2-*acetoxy*-3-*oxopentanoate* **21** (13.1 g, 44%), b.p. 89–91 °C at 1.5 mmHg; ν_{max}/cm^{-1} 2992, 2950 and 1660–1610; δ_H 1.11 (3 H, t, *J* 7, CH_2CH_3), 2.25 [3 H, s, C(O)Me], 2.74 (2 H, q, *J* 7, CH_2CH_3), 3.86 (3 H, s, OMe) and 5.60 (1 H, s, CHOAc); *m/z* 188 (M^+, 2%), 157 (7), 132 (43), 98 (48), 57 (100) and 43 (90) (Found: C, 50.8; H, 6.8. $C_8H_{12}O_5$ requires C, 51.1; H, 6.4%).

Using the procedure of Cornforth and Cornforth,[19] condensation of the foregoing acetoxyester **21** (13.1 g) with ammonium acetate (24.76 g) in acetic acid (75 ml) at reflux for 2 h gave *methyl* 4-*ethyl*-2-*methyloxazole*-5-*carboxylate* **22a** (7.29 g) as a pale brown oil, pure according to ^1H NMR spectroscopy; ν_{max}/cm^{-1} 2995, 1735, 1640, 1570 and 1160; δ_H 1.23 (3 H, t, *J* 7, CH_2CH_3), 2.51 (3 H, s, 2-Me), 2.84 (2 H, q, *J* 7, CH_2CH_3) and 3.90 (3 H, s, OMe); *m/z* 169 (M^+, 100%), 154 (9), 138 (20), 128 (95), 113 (48), 110 (43), 82 (26) and 69 (71). (Found: M^+, 169.0749. $C_8H_{11}NO_3$ requires *M*, 169.0739). The sample was reduced without further purification.

Lithium aluminium hydride (0.36 g) was added to a stirred solution of the foregoing ester **22a** (1.17 g) in dry ether (50 ml) at 0 °C. After 2.5 h, aqueous 0.5M aqueous sodium hydroxide (2 ml) was added dropwise and the resulting precipitate filtered off and washed with ether (30 ml). The filtrate was washed with brine (50 ml) then dried and evaporated to leave the *alcohol* **22b** (0.67 g, 69%) as a colourless oil, ν_{max}/cm^{-1} 3500–3100, 2585, 2570, 1585 and 1030; δ_H 1.19 (3 H, t, *J* 7, CH_2CH_3), 2.41 (3 H, s, 2-Me), 2.49 (2 H, q, *J* 7, CH_2CH_3) and 4.60 (2 H, s, CH_2OH); δ_C 13.75 (2 × Me), 18.95 (4-CH_2), 53.5 (5-CH_2), 138.6 (C), 145.1 (C) and 160.7 (C); *m/z* 141 (M^+, 100%), 140 (22), 126 (20), 124 (45), 110 (40), 99 (41), 69 (24), 43 (37) and 42 (43) (Found: M^+, 141.0796. $C_7H_{11}NO_2$ requires *M*, 141.0790).

4-*Ethyl*-2-*phenylthiazole*-5-*carboxylic acid* **25a**. A solution of 4-methyl-2-phenylthiazole-5-carboxylic acid **23**[22] (0.22 g, 1 mmol) in THF (13 ml) was added dropwise *via* a syringe to a stirred solution of LDA (2.2 mmol) in THF (6 ml) maintained at −25 °C. The resulting dark magenta solution was warmed to −18 °C over 0.25 h then treated with iodomethane (0.25 ml). After the solution had warmed to ambient temperature, the solvents were evaporated, the residue was dissolved in water (20 ml) and the resulting solution acidified to pH 3 using 2M hydrochloric acid. The precipitate was filtered off, washed with water and crystallised from benzene to give the 4-*ethyl acid* **25a** (0.208 g, 89%) as a pale yellow powder, m.p. 197–198 °C; ν_{max}/cm^{-1} 3200–2100, 1670 and 1510; $\delta_H[(CD_3)_2SO]$ 1.27 (3 H, t, *J* 7.4, CH_2CH_3), 3.12 (2 H, q, *J* 7.4, CH_2CH_3), 7.49–7.62 (3 H, m) and 7.94–8.05 (2 H, m); *m/z* 233 (M^+, 100%), 188 (14), 130 (29), 104 (37), 85 (26), 84 (32) and 77 (15) (Found: C, 62.3; H, 4.8; N, 6.1. C_{12} $H_{11}NO_2S$ requires C, 61.8; H, 4.8; N, 6.0%).

4-(*But*-3-*enyl*)-2-*phenylthiazole*-5-*carboxylic acid* **25b**. A solution of LDA (16.9 mmol) in THF (50 ml) cooled to −30 °C was added dropwise *via* a cannula over 20 min to a stirred solution of the acid **23**[22] (1.68 g, 7.67 mmol) in THF (180 ml)

maintained at −30 °C. The resulting purple solution was stirred for 5 min after which allyl bromide (3 ml, 34 mmol) was added in one portion. The cooling bath was removed, the solution stirred overnight and then evaporated, and the residue dissolved in water (50 ml). The resulting solution was adicified to pH 3 using 2M hydrochloric acid and extracted with ethyl acetate (2 × 100 ml). Evaporation of the dried extracts and crystallisation of the residue from toluene gave the *butenyl acid* **25b** (1.66 g, 84%) as a light brown powder, m.p. 171–173 °C; ν_{max}/cm^{-1} 3430, 3200–2200, 1670 and 1520; $\delta_H[(CD_3)_2SO]$ 2.25–2.70 (2 H, m, CH_2CH_2CH=), 3.24 (2 H, t, *J* 7, CH_2CH_2CH=), 4.92–5.14 (2 H, m), 5.67–6.14 (1 H, m), 7.45–7.60 (3 H, m) and 7.91–8.00 (2 H, m); *m/z* 259 (M^+, 26%), 258 (100), 219 (30), 214 (11), 121 (13), 104 (38), 77 (15) and 69 (11) (Found: C, 64.6; H, 4.9; N, 5.4. $C_{14}H_{13}NO_2S$ requires C, 64.8; H, 5.1; N, 5.4%).

4-(3-*Hydroxypentyl*)-2-*phenylthiazole*-5-*carboxylic acid* **25c**. Following the foregoing procedure, sequential treatment of the acid **23** (2.00 g, 9.13 mmol) in THF (180 ml) with LDA (20 mmol) in THF (50 ml) and 1,2-epoxybutane (3.8 ml, 44 mmol) gave the *hydroxy acid* **25c** (1.75 g, 66%) as a cream microcrystalline solid, m.p. 137–138 °C (decomp.); ν_{max}/cm^{-1} 3350, 2960, 2930, 2870, 3400–2200, 1665 and 1540; $\delta_H[(CD_3)_2SO]$ 0.90 (3 H, t, *J* 7, CH_2CH_3), 1.42 (2 H, m), 1.60–1.97 (2 H, m), 3.06–3.65 (3 H, m), 7.42–7.60 (3 H, m) and 7.87–8.08 (2 H, m); *m/z* 291 (M^+, 3%), 273 (8), 262 (31), 233 (17), 232 (40), 220 (14), 219 (100), 216 (10), 188 (42), 175 (18), 121 (15), 104 (48), 84 (14), 77 (19) and 70 (15) (Found: C, 62.1; H, 5.7; N, 4.8. $C_{15}H_{17}NO_3S$ requires C, 61.8; H, 5.9; N, 4.8%).

Methyl 4-(2-*hydroxy*-2-*phenylpropyl*)-2-*phenylthiazole*-5-*carboxylate*. Following the procedure in the foregoing condensation, reaction between acid **23** (2.02 g, 9.22 mmol), LDA (20 mmol) and acetophenone led to a product (2.10 g) which was a 1:1 mixture of acid **23** and the desired product **25d** according to ^1H NMR analysis. The mixture was esterified using ethereal diazomethane in the usual way and the resulting esters separated by chromatography over silica gel eluted with 20% ethyl acetate in light petroleum (b.p. 60–80 °C) to give the *ester* as colourless plates, m.p. 123 °C; ν_{max}/cm^{-1} 3400–3300, 1720, 1610 and 1540; δ_H 1.63 (3 H, s, Me), 3.62 [1 H, d, *J* 15, $CH_ACH_BC(OH)$], 3.89 (3 H, s, OMe), 4.02 [1 H, d, *J* 15, $CH_ACH_BC(OH)$], 5.66 (1 H, OH), 7.06–7.71 (8 H, m) and 7.86–8.00 (2 H, m); *m/z* 335 ($M^+ - H_2O$, 15%), 276 (9), 233 (100), 201 (15), 175 (19), 121 (11), 104 (18) and 77 (13) (Found: C, 68.0; H, 5.7; N, 3.9. $C_{20}H_{19}NO_3S$ requires C, 68.0; H, 5.4; N, 4.0%).

4-*Methyl*-2-*phenyloxazole*-5-*carboxylic acid* **26a**. Using a modification of the Cornforth procedure,[19] a mixture of ethyl 2-benzoyloxy-3-oxobutanoate[23] (11.98 g, 48 mmol) [prepared from ethyl 3-aminocrotonate (Aldrich) and benzoyl peroxide] and ammonium benzoate (30.0 g, 216 mmol) in acetic acid (60 ml) was refluxed for 3 h then cooled, diluted with water (200 ml) and neutralised using solid sodium hydrogencarbonate. The resulting mixture was extracted with ether (2 × 300 ml) and the combined extracts washed with water (2 × 200 ml) and brine (200 ml) then dried and evaporated. The residue, 35 g of a brown solid, was found to contain a substantial quantity of benzoic acid and so was dissolved in ether (300 ml) and the resulting solution washed successively with saturated aqueous sodium hydrogen carbonate (200 ml), 2M aqueous sodium hydroxide (200 ml), water (200 ml) and brine (200 ml). Evaporation of the dried organic phase and distillation of the residue (Kugelrohr) gave ethyl 4-methyl-2-phenyloxazole-5-carboxylate (3.56 g, 32%) as a pale yellow oil, b.p. 220 °C (oven temp.) at 6 mmHg, which subsequently crystallised as cream needles, m.p. 42 °C (lit.,[23] m.p. 45–46 °C); ν_{max}/cm^{-1} ($CHCl_3$) 1710; δ_H 1.39 (3 H, t, *J* 7.1, OCH_2CH_3), 2.51 (3 H, s, 4-Me), 4.38 (2 H, q, *J* 7.1, OCH_2CH_3), 7.35–7.52 (3 H, m) and 8.02–8.14 (2 H, m); *m/z* 231 (M^+, 100%), 203 (24), 159 (21), 158 (22), 130 (55), 104 (48) and 77 (22).

A solution of the foregoing ester (3.0 g) and potassium hydroxide (1.12 g) in ethanol (90 ml) and water (10 ml) was stirred at ambient temperature for 48 h then evaporated. The residue was dissolved in water (100 ml) and the resulting solution washed with ether (2 × 100 ml). The separated aqueous phase was acidified to pH 3 using concentrated hydrochloric acid then extracted with ethyl acetate (2 × 100 ml). Evaporation of the dried organic extracts gave the oxazole acid **26a** (1.58 g, 60%) which crystallised from aqueous ethanol as a colourless powder, m.p. 240 °C (lit.,[31] 237–239 °C); ν_{max}/cm^{-1} 3200–2200, 1718 and 1605; $\delta_H[(CD_3)_2SO]$ 2.51 (3 H, s, 4-Me), 7.50–7.72 (3 H, m) and 8.00–8.22 (2 H, m); *m/z* 203 (M^+, 100%), 159 (14), 158 (17), 130 (73), 104 (67), 89 (11) and 77 (25). (Found: C, 64.9; H, 4.6; N, 7.1. Calc. for $C_{11}H_9NO_3$: C, 65.0; H, 4.5; N, 6.9%).

Deprotonation of 4-*Methyl*-2-*phenyloxazole*-5-*Acid* **26a**.—A solution of the acid **26a** (0.203 g, 1 mmol) in THF (6 ml) was added *via* syringe to a well stirred solution of LDA (2.2 mmol) in THF (8 ml) maintained at −78 °C. The resulting reddish-purple mixture was stirred at this temperature for 1 h then iodomethane (0.3 ml) was added. After warming to ambient temperature, the solvent was evaporated and the residue dissolved in water (25 ml) which was then acidified to pH 3 using 2M hydrochloric acid and extracted with ethyl acetate (3 × 10 ml). Evaporation of the dried extracts gave a solid residue (0.190 g) estimated by ^1H NMR analysis to be a 7:3 mixture of the starting acid **26a** and the desired product **26b**. The latter showed $\delta_H[(CD_3)_2SO]$ 1.24 (3 H, t, *J* 7, CH_2CH_3), 2.88 (2 H, q, *J* 7, CH_2CH_3), 7.53–7.66 (3 H, m) and 7.96–8.10 (2 H, m).

A similar reaction using 0.45 mmol of acid **26a** in which the metallation was carried out for 20 min at −35 °C gave a product (0.10 g) estimated by ^1H NMR spectroscopy to be a 68:18:14 mixture of the desired 2-ethyl derivative **26b**, the starting acid **26a** and an unidentified by-product. Repetition of this experiment but at −15 °C gave a product mixture (0.08 g) consisting of *ca.* 39:44:17 proportions of the 2-ethyl derivative **26b**, an unidentified impurity and starting material **26a** respectively.

2,5-*Dimethylthiazole*-4-*carboxylic acid* **28a**. A solution of ethyl 3-bromo-2-oxobutanoate **27a**[24] (5.57 g, 27 mmol) (*vide infra*) and thioacetamide (2.20 g, 27 mmol) in ethanol (50 ml) was refluxed for 3 h. The cooled solution was concentrated to *ca.* 10 ml, diluted with dichloromethane and filtered. The filtrate was washed with aqueous sodium hydrogen carbonate (2 × 150 ml) and brine (150 ml) then dried and evaporated to leave crude *ethyl* 2,5-*dimethylthiazole*-4-*carboxylate* (3.25 g) as a pale orange oil which was homogeneous by TLC and which showed ν_{max}/cm^{-1} 2985, 1710 and 1510; δ_H 1.42 (3 H, t, *J* 7, OCH_2CH_3), 2.68 (3 H, s, Me), 2.73 (3 H, s, Me) and 4.43 (2 H, q, *J* 7, OCH_2CH_3); *m/z* 185 (M^+, 52%), 140 (62), 139 (100) and 113 (23) (Found: M^+, 185.0496. $C_8H_{11}NO_2S$ requires *M*, 185.0510).

Saponification of the crude ester (3.25 g) as described below during the preparation of the oxazole acid **31b**, gave the *acid* **28a** which crystallised from benzene as a pale solid (1.58 g, 57%), m.p. 179–180 °C; ν_{max}/cm^{-1} 3300–2100, 1690, 1500 and 1185; $\delta_H[(CD_3)_2SO]$ 2.63 (3 H, s) and 2.69 (3 H, s); *m/z* 157 (M^+, 21%), 140 (11), 139 (93) and 59 (100) (Found: C, 45.9; H, 4.6; N, 9.2. $C_6H_7NO_2S$ requires C, 45.9; H, 4.5; N, 8.9%).

5-*Ethyl*-2-*methylthiazole*-4-*carboxylic acid* **28b**. Methyl 2-oxopentanoate (b.p. 60–62 °C at 12 mmHg) was prepared from the commercial ketoacid using ethereal diazomethane. Dropwise addition of bromine (1.4 ml, 27.4 mmol) in chloroform (5 ml)[24] to a stirred warm (*ca.* 40 °C) solution of this ester (3.52 g, 27.1 mmol) in chloroform (5 ml) followed by stirring under water-pump vacuum for 2 h and fractional distillation gave *methyl* 3-*bromo*-2-*oxopentanoate* **27b** (3.75 g, 66%) as a pale oil,

b.p. 88–90 °C at 18 mmHg; ν_{max}/cm^{-1} 2980, 1730, 1255 and 1060; δ_H 1.08 (3 H, t, *J* 7, CH_2CH_3), 1.92–2.28 (2 H, m, CH_2CHBr), 3.93 (3 H, s, OMe) and 4.89–5.05 (1 H, m, CH_2-$CHBr$); *m/z* 210 (M^+, 3%), 208 (M^+, 3), 149 (72), 121 (86), 70 (100) and 56 (61) (Found: M^+, 209.9722 and 207.9746. $C_6H_9BrO_3$ requires *M*, 209.9715 and 207.9735). A solution of thioacetamide (1.35 g, 18 mmol) and the foregoing bromoketo ester **27b** (3.75 g, 18 mmol) in ethanol (40 ml) was refluxed for 16 h then cooled and poured into dichloromethane (250 ml). After filtration, the filtrate was worked up as described above to give a crude mixture (*ca.* 1:1) of methyl and ethyl 5-ethyl-2-methylthiazole-4-carboxylates (2.67 g). This mixture was saponified as described above (**31b**) to give the *acid* **28b** which crystallised from toluene as an off-white powder (1.23 g), m.p. 122–125 °C; ν_{max}/cm^{-1} 3300–2100, 1695 and 1495; δ_H 1.34 (3 H, t, *J* 7, CH_2CH_3), 2.76 (3 H, s) and 3.29 (2 H, q, *J* 7, CH_2CH_3); *m/z* 171 (M^+, 16%), 153 (100), 125 (42) and 59 (67) (Found: C, 49.4; H, 5.5; N, 8.2. $C_7H_9NO_2S$ requires C, 49.1; H, 5.3; N, 8.2%).

Deprotonations of 2,5-*Dimethylthiazole*-4-*carboxylic Acid* **28a**.—(i) *By butyllithium.* In exactly the same way and on the same scale as described in (i) below for oxazole acid **31a**, deprotonation of acid **28a** and reaction with iodomethane gave a 46:54 mixture, according to ^{1}H NMR spectroscopy, of 2-ethyl-5-methylthiazole-4-carboxylic acid **29** [δ_H 1.32 (3 H, t, *J* 7, CH_2CH_3), 2.79 (3 H, s, 5-Me) and 3.03 (2 H, q, *J* 7, CH_2CH_3)] and 5-ethyl-2-methylthiazole-4-carboxylic acid **28b**, identified by comparison with the authentic sample prepared as described above. The mixture showed *m/z* 171 (M^+, 18%), 167 (20), 153 (100), 152 (14), 139 (11), 125 (42), 73 (39), 59 (26) and 57 (9).

(ii) *Using LDA.* As described in (ii) below for acid **31a**, deprotonation of acid **28a** (1 mmol) using LDA at −78 °C gave a 59:41 mixture (0.148 g, 86%) of the 2-ethyl- and 5-ethyl-acids **29** and **28b** respectively. Repetition of the foregoing reaction at −15 °C throughout gave a similar product (0.12 g) as a 67:33 mixture of the 2-ethyl- and 5-ethyl-acids **29** and **28b**.

Deprotonation of 5-*Ethyl*-2-*methylthiazole*-4-*carboxylic Acid* **28b**.—Following procedure (i) given below for the corresponding oxazole **31a**, sequential treatment of the acid **28b** (1 mmol) with butyllithium (2.2 mmol) and iodomethane gave a yellow solid (0.162 g) which was, according to ^{1}H NMR analysis, a 43:29:28 mixture of 2,5-diethylthiazole-4-carboxylic acid (43%) [δ_H 1.34 (3 H, t, *J* 7, CH_2CH_3), 1.38 (3 H, t, *J* 7, CH_2CH_3), 3.06 (2 H, q, *J* 7, CH_2CH_3) and 3.30 (2 H, q, *J* 7, CH_2CH_3)], starting acid **28b** (29%) and 2-methyl-5-(1-methylethyl)thiazole-4-carboxylic acid (28%) [δ_H 1.34 (6 H, d, *J* 7, $CH(CH_3)_2$), 2.75 (3 H, s) and 4.28 (1 H, m].

2-*Ethyl*-5-*methyloxazole*-4-*carboxylic acid* **31b**. According to the general method of Treibs and Sutter,[25] thionyl chloride (11.9 ml) was added dropwise to an ice-cold, stirred solution of ethyl *N*-propionyl-2-aminoacetoacetate **30b** (29.31 g)[26] in dry benzene (15 ml). The mixture was then warmed to *ca.* 30 °C, stirred for a further 10 min then for 0.5 h under water-pump vacuum. The dark residue was partitioned between water (100 ml) and ether (100 ml). Solid potassium carbonate was added cautiously to the two-phase mixture until the aqueous phase was slightly alkaline. The separated organic layer was washed with water (100 ml) and brine (100 ml) and then dried and evaporated. Distillation of the residue (Kugelrohr) gave *ethyl* 2-*ethyl*-5-*methyloxazole*-4-*carboxylate* (15.37 g, 57%) as a clear oil, b.p. 200 °C (oven temp.)/14 mmHg; ν_{max}/cm^{-1} 2995 and 1725; δ_H 1.33 (3 H, t, *J* 7, 2-CH_2CH_3), 1.37 (3 H, t, *J* 7, OCH_2CH_3), 2.58 (3 H, s, 5-Me), 2.78 (2 H, q, *J* 7, 2-CH_2CH_3) and 4.36 (2 H, q, *J* 7, OCH_2CH_3); *m/z* 183 (M^+, 29%), 138 (31), 137 (56), 99 (15), 57 (100) and 43 (19). (Found: M^+, 183.0881. $C_9H_{13}NO_3$ requires *M*, 183.0895).

A mixture of the foregoing ester (14.7 g) and potassium hydroxide (9.0 g) in ethanol (200 ml) was stirred at ambient temperature for 48 h and then evaporated. The residue in water (300 ml) was washed with ether (200 ml) and then acidified to pH 3 using concentrated hydrochloric acid and extracted with ethyl acetate (2 × 200 ml). The combined extracts were washed with brine (200 ml) then dried and evaporated and the residue crystallised from benzene to give the *acid* **31b** (8.44 g, 68%) as a pale yellow powder, m.p. 146 °C (subl.) ν_{max}/cm^{-1} 3200–2200, 1705, 1630, 1586 and 1215; δ_H 1.23 (3 H, t, *J* 7, CH_2CH_3), 2.62 (3 H, s, 5-Me) and 2.79 (2 H, q, *J* 7, CH_2CH_3); *m/z* 155 (M^+, 46%), 137 (32), 99 (18) and 57 (100) (Found: C, 54.2; H, 5.9; N, 9.1. $C_7H_9NO_3$ requires C, 54.2; H, 5.9; N, 9.0%).

Deprotonations of 2,5-*Dimethyloxazole*-4-*carboxylic Acid* **31a**.—(i) *By butyllithium.* Butyllithium (1.6M solution in hexanes; 1.38 ml, 2.2 mmol) was added dropwise to a stirred suspension of 2,5-dimethyloxazole-4-carboxylic acid **31a**[25,26] (0.141 g, 1 mmol) in THF (18 ml) maintained at −78 °C. The resulting green solution was stirred for 0.25 h and then treated with iodomethane (0.3 ml) and, after a further 0.25 h, allowed to warm slowly to ambient temperature when it was poured into water (20 ml). The resulting solution was washed with ether (20 ml) and then acidified to pH 3 (2M HCl) and extracted with ethyl acetate (2 × 20 ml). The combined extracts were washed with brine, dried and evaporated to give a cream solid (0.11 g, 71%) adjudged by ^{1}H NMR spectroscopy to be a 3:7 mixture of 2-ethyl-5-methyloxazole-4-carboxylic acid **31b**, identified by comparison with the authentic sample prepared as described above and 5-ethyl-2-methyloxazole-4-carboxylic acid **32**, δ_H 1.29 (3 H, t, *J* 7, CH_2CH_3), 2.52 (3 H, s, 5-Me) and 3.01 (2 H, q, *J* 7, CH_2CH_3).

(ii) *Using LDA.* A suspension of the acid **31a** (1 mmol) in THF (15 ml) was added to a stirred solution of LDA (2.2 mmol) in THF (10 ml) at −78 °C. After 0.5 h, iodomethane (0.3 ml) was added and the reaction completed as described in (i) to give a 1:1 mixture (0.13 g, 84%) of the acids **31b** and **32**.

5-*Methyl*-2-*phenylthiazole*-4-*carboxylic acid* **33**. A mixture of thiobenzamide (5.25 g, 38 mmol) and ethyl 3-bromo-2-oxobutanoate **27a**[24] (8.00 g, 38.3 mmol) in ethanol (100 ml) was heated under reflux for 12 h. The cooled mixture was poured into ether (200 ml) and the resulting solution washed with saturated aqueous sodium hydrogencarbonate (150 ml), water (150 ml) and brine (150 ml) and then dried and evaporated. Crystallisation of the residue from petroleum gave the *ethyl* 5-*methyl*-2-*phenylthiazole*-4-*carboxylate* (9.15 g, 97%) as colourless needles, m.p. 59–61 °C; λ_{max} 291 nm; ν_{max}/cm^{-1} (CCl_4) 1710; δ_H 1.44 (3 H, t, *J* 7, OCH_2CH_3), 2.78 (3 H, s, 5-Me), 4.46 (2 H, q, *J* 7, OCH_2CH_3), 7.38–7.56 (3 H, m) and 7.90–8.05 (2 H, m); *m/z* 247 (M^+, 73%), 201 (58), 173 (33) and 121 (100) (Found: C, 63.2; H, 5.5; N, 5.7. $C_{13}H_{13}NO_2S$ requires C, 63.1; H, 5.3; N, 5.7%).

The foregoing ester (7.90 g) was added to a solution of potassium hydroxide (4.48 g) in ethanol (200 ml) and water (20 ml). After *ca.* 2 min, the mixture solidified. Water (100 ml) was then added and the resulting solution stirred at ambient temperature for 48 h. Work-up as described for acid **26a** then gave the *acid* **33** as a colourless powder (5.66 g, 81%) after crystallisation from chloroform, m.p. 187–188 °C; ν_{max}/cm^{-1} 3200–2300 and 1665; δ_H[$(CD_3)_2SO$] 2.78 (3 H, s, 5-Me), 7.50–7.60 (3 H, m) and 7.92–8.04 (2 H, m); *m/z* 219 (M^+, 66%), 201 (55), 173 (36), 121 (100) and 105 (43) (Found: C, 60.3; H, 4.2; N, 6.4. $C_{11}H_9NO_2S$ requires C, 60.3; H, 4.1; N, 6.4%).

5-*Ethyl*-2-*phenylthiazole*-4-*carboxylic acid* **35a**. Using the procedure given below for the corresponding oxazole **36b**, reaction between acid **33** (0.219 g, 1 mmol), and butyllithium gave a deep magenta solution containing dianion **34**; subsequent addition of iodomethane (0.3 ml) gave the 5-*ethyl acid* **35a** which crystallised from benzene as a colourless powder (0.20 g,

86%), m.p. 159 °C; ν_{max}/cm^{-1} 3200–2100, 1680 and 1510; δ_H-[$(CD_3)_2SO$] 1.33 (3 H, t, *J* 7, CH_2CH_3), 3.29 (2 H, q, *J* 7, CH_2CH_3), 7.45–7.70 (3 H, m) and 7.90–8.14 (2 H, m); *m/z* 233 (M^+, 20%), 215 (36), 187 (30), 121 (100), 105 (13) and 77 (18) (Found: C, 61.5; H, 4.7; N, 6.0. $C_{12}H_{11}NO_2S$ requires C, 61.8; H, 4.7; N, 6.0%).

5-(*But*-3-*enyl*)-2-*phenylthiazole*-4-*carboxylic acid* **35b**. In the same way as described in the foregoing example, alkylation of acid **33** (1 mmol) using allyl bromide (0.3 ml) gave the *acid* **35b** as an off-white powder (0.194 g, 75%) from benzene, m.p. 176–178 °C; ν_{max}/cm^{-1} 3100–2400, 1680 and 1520; δ_H 2.37–2.68 (2 H, m, CH_2CH_2CH=), 3.44 (2 H, t, *J* 7, CH_2CH_2CH=), 4.98–5.28 (2 H, m, CH=CH_2), 5.65–6.15 (1 H, m, C*H*=CH_2), 7.34–7.62 (3 H, m) and 7.78–8.05 (2 H, m); *m/z* 259 (M^+, 8%), 241 (10), 219 (52), 218 (72), 215 (22), 173 (13), 122 (12), 121 (100), 105 (42), 104 (20) and 77 (37) (Found: M^+, 259.0664. $C_{14}H_{13}NO_2S$ requires *M*, 259.0667).

5-(3-*Hydroxypentyl*)-2-*phenylthiazole*-5-*carboxylic acid* **35c**. In the same way, condensation of the acid **33** (1 mmol) with 1,2-epoxybutane (0.19 ml) gave a mixture (0.222 g) of the desired product **35c** and starting material in a ratio of 60:40. The hydroxy acid showed δ_H 1.00 (3 H, t, *J* 7, CH_2CH_3), 1.57 (2 H, m), 1.81–2.16 (2 H, m), 3.36–3.86 (3 H, m), 7.40–7.63 (3 H, m) and 7.86–8.11 (2 H, m).

5-*Ethyl*-2-*phenyloxazole*-4-*carboxylic acid* **36b**. Butyllithium (1.6M solution in hexanes; 1.4 ml, 2.24 mmol) was added dropwise *via* syringe to a stirred solution of the acid **36a** (0.197 g, 0.97 mmol) in THF at −78 °C. The resulting magenta solution was stirred for 0.5 h at this temperature after which iodomethane (0.3 ml) was added. After warming to ambient temperature over 1 h, the now pale brown solution was worked-up as usual to give the *acid* **36b** which crystallised from aqueous ethanol as colourless needles (0.177 g, 84%), m.p. 135–137 °C, ν_{max}/cm^{-1} 3600–2200, 1670, 1620 and 1580; δ_H[$(CD_3)_2SO$] 1.28 (3 H, t, *J* 7, CH_2CH_3), 3.09 (2 H, q, *J* 7, CH_2CH_3), 7.38–7.68 (3 H, m) and 7.84–8.07 (2 H, m); *m/z* 121 (100%), 105 (94), 77 (97) and 51 (29) (Found: C, 65.8; H, 5.2; N, 6.2. $C_{12}H_{11}NO_3$ requires C, 66.3; H, 5.1; N, 6.4%).

N,N-*Diethyl*-2,5-*dimethylthiazole*-4-*carboxamide* **37**. By the same method as for the preparation of the corresponding oxazole amide **40** (below),[29,30] except that toluene was used as the solvent throughout, 2,5-dimethylthiazole-4-carboxylic acid **28a** (7.52 g, 47.9 mmol) was converted into the *amide* **37** (4.28 g, 42%), a pale-yellow oil, b.p. 130–132 °C (oven temp.)/1 mmHg, which crystallised on cooling into colourless plates, m.p. 53–54 °C; ν_{max}/cm^{-1} ($CHCl_3$) 2990, 2930 and 1630; δ_H 1.13 (3 H, br t, *J* 7, NCH_2CH_3), 1.25 (3 H, br t, *J* 7, NCH_2CH_3), 2.50 (3 H, s, 5-Me), 2.67 (3 H, s, 2-Me), 3.39 (2 H, br q, *J* 7, NCH_2CH_3) and 3.58 (2 H, br q, *J* 7, NCH_2CH_3); *m/z* 212 (M^+, 14%), 145 (6), 141 (16), 140 (62), 113 (33), 101 (7), 83 (6), 72 (100) and 64 (4) (Found: M^+, 212.0965. $C_{10}H_{16}N_2OS$ requires *M*, 212.0983) (Found: C, 56.8; H, 7.6; N, 13.0. $C_{10}H_{16}N_2OS$ requires C, 56.6; H, 7.6; N, 13.2%).

N,N,5-*Triethyl*-2-*methylthiazole*-4-*carboxamide* **39a**. Similarly, the acid **28b** (3.8 g, 22 mmol) was converted into the *amide* **39a** (2.20 g, 44%) as an oil, b.p. 130–135 °C (oven temp.)/1 mmHg; ν_{max}/cm^{-1} 2985, 2950, 2890, 1628 and 1500; δ_H 1.18 (3 H, br t, *J* 7, NCH_2CH_3), 1.23 (3 H, br t, *J* 7, NCH_2CH_3), 1.26 (3 H, t, *J* 7, 5-CH_2CH_3), 2.64 (3 H, s, 2-Me), 2.98 (2 H, q, *J* 7, 5-CH_2CH_3) 3.34 (2 H, br q, *J* 7, NCH_2CH_3) and 3.55 (2 H, br q, *J* 7, NCH_2CH_3); *m/z* 226 (M^+, 26%), 155 (21), 154 (72), 153 (19), 127 (36), 126 (26), 125 (15), 113 (11), 85 (14), 73 (11), 72 (100) and 56 (11) (Found: M^+, 226.1140. $C_{11}H_{18}N_2OS$ requires *M*, 226.1140).

Deprotonations of N,N-*Diethyl*-2,5-*dimethylthiazole*-4-*carboxamide* **37**.—These were carried out as described below for the oxazole amide **40** except that generation of the orange-red anion **38** was carried out over 25 min and reactions with electrophiles were carried out at −78 °C for 2 h prior to evaporation and work-up.

N,N,5-*Triethyl*-2-*methylthiazole*-4-*carboxamide* **39a**. By the general procedure, reaction between the amide **37** (0.344 mmol) and iodomethane (0.1 ml) gave the 5-*ethyl derivative* **39a** (0.076 g, 97%) which was identical according to ^{1}H NMR, IR, MS and TLC with an authentic sample prepared as described above from the corresponding acid **28b**.

N,N-*Diethyl*-2-*methyl*-5-*propylthiazole*-4-*carboxamide* **39b**. By the general procedure, reaction between the amide **37** (0.184 mmol) and iodoethane (0.12 ml) gave the 5-*propyl derivative* **39b** (0.043 g, 98%) as an oil; ν_{max}/cm^{-1} 2985, 2945, 28 98 and 1625; δ_H 0.98 [3 H, t, *J* 7, $(CH_2)_2CH_3$], 1.27 (6 H, br t, *J ca.* 7, 2 × NCH_2CH_3), 1.71 (2 H, m, 5-$CH_2CH_2CH_3$), 2.70 (3 H, s, 2-Me), 2.89 (2 H, t, *J* 7, 5-$CH_2CH_2CH_3$) 3.40 (2 H, q, *J* 7, NCH_2CH_3) and 3.62 (2 H, q, *J* 7, NCH_2CH_3); *m/z* 240 (M^+, 22%), 168 (31), 152 (14), 113 (33), 97v (4), 72 (100) and 65 (5) (Found: M^+ 240.1306. $C_{12}H_{20}N_2OS$ requires *M*, 240.1296).

5-(*But*-3-*enyl*)-N,N-*diethyl*-2-*methylthiazole*-4-*carboxamide* **39c**. By the general procedure, alkylation of the amide **37** (0.344 mmol) with allyl bromide (0.15 ml) gave the 5-*butenyl derivative* **39c** (0.083 g, 96%) as an oil, b.p. 125 °C (oven temp.)/0.7 mmHg; ν_{max}/cm^{-1} 3090, 2990, 2950, 2890 and 1624; δ_H 1.15 (3 H, br t, *J* 7, NCH_2CH_3), 1.20 (3 H, br t, *J* 7, NCH_2CH_3), 2.36 (2 H, br q, *J ca.* 7, CH_2CH=), 2.63 (3 H, s, 2-Me), 2.98 (2 H, t, *J* 7, CH_2CH_2CH=), 3.33 (2 H, br q, *J* 7, NCH_2CH_3), 3.54 (2 H, br 9, *J* 7, NCH_2CH_3), 5.00 (1 H, br dd, *J* 10 and 2, CH=CH_ACH_B), 5.05 (1 H, br dd, *J* 17 and 2, CH=CH_ACH_B) and 6.02 (1 H, ddt, *J* 17, 10 and 7, C*H*=CH_2); *m/z* 252 (M^+, 23%), 223 (2), 211 (3), 180 (12), 166 (5), 152 (19), 140 (9), 111 (7) and 72 (100) (Found: M^+, 252.1284. $C_{13}H_{20}N_2OS$ requires *M*, 252.1296).

N,N-*Diethyl*-5-(2-*hydroxy*-2-*phenylethyl*)-2-*methylthiazole*-4-*carboxamide* **39d**. By the general procedure, reaction between the amide **37** (1 mmol) and benzaldehyde followed by chromatography over silica gel eluted with 30% ethyl acetate in light petroleum gave the *hydroxy amide* **39d** as an oil (0.283 g, 89%) which was pure according to TLC; ν_{max}/cm^{-1} 3500–3200, 3050, 2985, 2890 and 1630; δ_H 1.27 (6 H, br t, *J* 7, 2 × NCH_2CH_3), 2.68 (3 H, s, 2-Me), 3.27–4.78 [6 H, m, 2 × NCH_2CH_3 and $CH_2CH(OH)$], 5.10 [1 H, m, C*H*(OH)] and 7.30–7.80 (5 H, m, Ph).

N,N-*Diethyl*-5-(2-*hydroxy*-2-*phenylpropyl*)-2-*methylthiazole*-4-*carboxamide* **39e**. By the general procedure, reaction between the amide **37** (0.247 mmol) and acetophenone gave, after column chromatography over silica gel eluted with 40% ethyl acetate in light petroleum, the *hydroxy amide* **39e** (0.075 g, 92%) as a colourless oil which crystallised with time to give colourless plates, m.p. 89–91 °C; ν_{max}/cm^{-1} ($CHCl_3$) 3500–3200, 3010, 2990 and 1620; δ_H 1.14 (3 H, t, *J* 7, NCH_2CH_3), 1.24 (3 H, br t, *J* 7, NCH_2CH_3), 1.44 (3 H, s, Me), 2.51 (3 H, s, 2-Me), 3.65 [6 H, m, 2 × NCH_2CH_3 and $CH_2C(OH)$] and 7.13–7.54 (5 H, m, Ph); *m/z* 314 ($M^+ - H_2O$, 10%), 242 (12), 212 (52), 162 (8), 141 (28), 113 (15), 105 (8), 72 (100) and 59 (17) (Found: C, 65.2; H, 7.0; N, 8.4. $C_{18}H_{24}N_2O_2S$ requires C, 65.0; H, 7.3; N, 8.4%).

N,N-*Diethyl*-2,5-*dimethyloxazole*-4-*carboxamide* **40**.—A mixture of 2,5-dimethyloxazole-4-carboxylic acid **31a**[25] (6.82 g, 48.3 mmol) and thionyl chloride (6.0 ml, 82.3 mmol) was heated under reflux for 0.5 h.[30] The resulting thick, pink paste was suspended in dry benzene (20 ml) and refluxing continued for 2 h. The resulting suspension was left at ambient temperature overnight and then added dropwise to a stirred solution of dry diethylamine (20 ml) in benzene (50 ml), cooled to 0 °C.[30] After 6 h, the mixture was washed with water (100 ml), 2M hydrochloric acid (2 × 100 ml) and saturated aqueous sodium hydrogen carbonate (100 ml) and then dried and evaporated.

Distillation of the brown residue (Kugelrohr) gave the *amide* **40** (3.02 g, 32%) as a pale yellow oil, b.p. 110 °C b.p. 110 °C (oven temp.)/1 mmHg; ν_{max}/cm^{-1} 2890, 2940 and 1628; δ_H 1.20 (6 H, t, *J* 7, 2 × NCH_2CH_3), 2.38 (3 H, s, 2-Me), 2.48 (3 H, s, 5-Me) and 3.26–3.86 (4 H, br, 2 × NCH_2CH_3); *m/z* 196 (M^+, 44%), 125 (23), 124 (100), 97 (27), 82 (20), 72 (78) and 54 (14) (Found: M^+, 196.1177. $C_{10}H_{16}N_2O_2$ requires *M*, 196.1211).

N,N,2-*Triethyl*-5-*methyloxazole*-4-*carboxamide* **43**.—Similarly, acid **31b** (5.42 (g, 31.7 mmol) was converted into the *amide* 43 (2.53 g, 38%) as an oil, b.p. 110–115 °C (oven temp.)/1 mmHg; ν_{max}/cm^{-1} ($CHCl_3$) 3000 and 1640; δ_H 1.20 (6 H, t, *J* 7, 2 × NCH_2CH_3), 1.29 (3 H, t, *J* 7, 2-CH_2CH_3), 2.48 (3 H, s, 5-Me), 2.71 (2 H, q, *J* 7, CH_2CH_3) and 3.28–3.77 (4 H, br, 2 × NCH_2CH_3); *m/z* 210 (M^+, 25%), 139 (18), 138 (89), 111 (30), 100 (18), 96 (10), 72 (100), 68 (10), 57 (11) and 56 (11) (Found: M^+, 210.1368. $C_{11}H_{18}N_2O_2$ requires *M*, 210.1368).

Deprotonation of N,N-*Diethyl*-2,5-*dimethyloxazole*-4-*carboxamide* **40**: *General Procedure*.—Butyllithium (*ca.* 1.6M solution in hexanes; 1.1 equiv.) was added dropwise over 5 min to a stirred solution of the amide **40** (1 equiv.) in THF (12 ml $mmol^{-1}$) maintained at below −70 °C using a solid CO_2–acetone bath. The resulting yellow solution containing the monoanion **41** was stirred at this temperature for 0.5 h before the addition of a slight excess of an electrophile. The mixture was then allowed to warm to ambient temperature over 1 h and evaporated. The residue was dissolved in ethyl acetate (20 ml $mmol^{-1}$) and added to 0.5M hydrochloric acid (20 ml $mmol^{-1}$). The separated aqueous phase was extracted with ethyl acetate (2 × 5 ml $mmol^{-1}$) and the combined organic phases washed with water (2 × 20 ml $mmol^{-1}$) and brine (2 × 20 ml $mmol^{-1}$) and then dried and evaporated. Final purification was either by distillation or short column chromatography.

N,N,5-*Triethyl*-2-*methyloxazole*-4-*carboxamide* **42a**. By the general procedure, reaction between the amide **40** (2 mmol) and iodomethane finally at ambient temperature for 24 h followed by dissolution of the evaporated reaction mixture in ether (30 ml), washing with brine (30 ml), drying and evaporating and finally Kugelrohr distillation gave the 5-*ethyl amide* **42a** as a pale yellow oil (0.41 g, 98%), b.p. 110 °C (oven temp.)/1 mmHg; ν_{max}/cm^{-1} 2990, 2930 and 1630; δ_H 1.20 (6 H, t, *J* 2 × NCH_2CH_3), 1.23 (3 H, t, *J* 7, 5-CH_2CH_3), 2.40 (3 H, s, 2-Me), 2.89 (2 H, q, *J* 7, 5-CH_2CH_3) and 3.38–3.80 (4 H, br, 2 × NCH_2CH_3); *m/z* 210 (M^+, 51%), 195 (3), 167 (4), 139 (14), 138 (100), 137 (21), 111 (24), 72 (46), 69 (10) and 54 (14). (Found: M^+, 210.1369. $C_{11}H_{18}N_2O_2$ requires *M*, 210.1368) (Found: C, 62.5; H, 8.8; N, 13.3. $C_{11}H_{18}N_2O_2$ requires C, 62.8; H, 8.6; N, 13.3%).

N,N,-*Diethyl*-2-*methyl*-5-*propyloxazole*-4-*carboxamide* **42b**. By the general procedure, alkylation of the amide **40** (1.17 mmol) with iodoethane at −78 °C for 2.5 h prior to warming to ambient temperature gave the 5-*propyl derivative* **40**, b.p. 125 °C (oven temp.)/1 mmHg, as an oil (0.211 g, 91%); ν_{max}/cm^{-1} 2985, 2950, 2890 and 1628; δ_H 0.95 (3 H, t, *J* 7, 5-CH_2CH_3), 1.21 (6 H, t, *J* 7, 2 × NCH_2CH_3), 1.67 (2 H, m, 5-CH_2CH_3), 2.44 (3 H, s, 2-Me), 2.79 (2 H, t, *J* 7, 5-$CH_2CH_2CH_3$) and 3.42–3.82 (4 H, br, 2 × NCH_2CH_3); *m/z* 224 (M^+, 29%), 209 (6), 181 (4), 152 (70), 136 (8), 110 (5), 97 (28), 82 (20), 72 (100) and 51 (15) (Found: C, 64.0; H, 8.8; N, 12.7%; M^+, 224.1512. $C_{12}H_{20}N_2O_2$ requires C, 64.2; H, 9.0; N, 12.5%; *M*, 224.1525).

5-(*But*-3-*enyl*)-N,N-*diethyl*-2-*methyloxazole*-4-*carboxamide* **42c**. By the general procedure, reaction between the amide **40** (1.19 mmol) and allyl bromide gave the 5-*butenyl amide* **42c** (0.254 g, 90%) after Kugelrohr distillation, b.p. 125 °C (oven temp.)/0.8 mmHg, as a pale yellow oil; ν_{max}/cm^{-1} 3090, 2990, 2950, 2890 and 1625; δ_H 1.19 (6 H, t, *J* 7, 2 × NCH_2CH_3), 2.40 (3 H, s, 2-Me), 2.25–2.56 (2 H, m, CH_2CH_2CH=), 3.00 (2 H, t, *J* 7, CH_2CH_2CH=), 3.39–3.79 (4 H, br, 2 × NCH_2CH_3), 4.89–5.19 (2 H, m, $CH=CH_2$) and 5.63–6.01 (1 H, m, $CH=CH_2$); *m/z* 236 (M^+, 35%), 221 (8), 164 (25), 163 (23), 136 (18), 122 (31), 72 (100) and 55 (15) (Found: C, 65.8; H, 8.8; N, 12.0%; M^+, 236.1526). $C_{13}H_{20}N_2O_2$ requires C, 66.1; H, 8.5; N, 11.9%; *M*, 236.1533).

N,N-*Diethyl*-5-(2-*hydroxy*-2-*phenylethyl*)-2-*methyloxazole*-4-*carboxamide* **42d**. By the general procedure on a 0.61 mmol scale, condensation of the amide **40** with benzaldehyde gave the *amide* **42d** (0.191 g, 98%) after chromatography on silica gel eluted with 40% ethyl acetate in light petroleum as a pale yellow oil which was pure according to TLC and ^1H NMR analysis and which showed ν_{max}/cm^{-1} 3500–3200, 2990, 2950, 2890, 1620 and 1490; δ_H 1.20 (6 H, t, *J* 7, 2 × NCH_2CH_3), 2.33 (3 H, s, 2-Me), 3.15 (1 H, m, 1′-CH_ACH_B), 3.21 (1 H, m, 1′-CH_ACH_B), 3.47 (2 H, q, *J* 7, NCH_2CH_3), 3.70 (2 H, q, *J* 7, NCH_2CH_3), 4.93 [1 H, dd, *J* 8 and 4, CH(OH)], 5.65 (1 H, br, OH) and 7.13–7.48 (5 H, m, Ph); *m/z* 196 (100%), 125 (30), 124 (24), 105 (11), 97 (13) and 72 (88).

N,N-*Diethyl*-5-(2-*hydroxypentyl*)-2-*methyloxazole*-4-*carboxamide* **42e**. By the general procedure, condensation of the amide **40** (1.17 mmol) with butanal followed by column chromatography over silica gel eluted with 30% ethyl acetate in light petroleum gave unchanged starting material **40** (0.177 g, 77%) followed by the *hydroxy amide* **42e** (0.047 g, 15%) as an oil; ν_{max}/cm^{-1} 3500–3200, 2970, 2940, 2880 and 1620; δ_H 0.94 (3 H, br t, *J ca.* 7, $CH_2CH_2CH_3$), 1.20 (6 H, t, *J* 7, 2 × NCH_2CH_3), 1.36–1.64 (4 H, m), 2.40 (3 H, s, 2-Me), 2.98 [2 H, d, *J* 6, $CH_2CH(OH)$], 3.29–3.96 [5 H, br m, CH(OH) and 2 × NCH_2CH_3] and 4.64 (1 H, OH); *m/z* 268 (M^+, <1%), 250 (3), 225 (20), 196 (76), 178 (11), 124 (28), 111 (9), 97 (29), 72 (100), 54 (16) and 43 (28) (Found: M^+, 268.1779. $C_{14}H_{24}N_2O_3$ requires *M*, 268.1787).

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