Ethano- and Etheno-bridged 2-Pyridyl Isoxazoles and Thiazoles, and Their Reduced Variants

M. M. Campbell,[a,*] N. D. P. Cosford,[a] D. R. Rae[b] and M. Sainsbury[a,*]
[a] *School of Chemistry, University of Bath, Claverton Down, Bath, BA2 7AY, UK*
[b] *Organon Laboratories Ltd., Newhouse, Lanarkshire, ML11 5SH, UK*

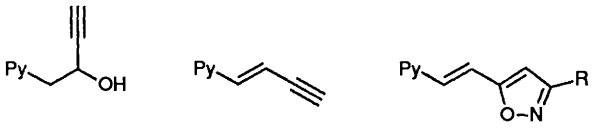
(*E*)-2-(2-Oxobut-3-enyl)pyridine **21**, (*E*)-2-(but-1-en-3-ynyl)pyridine **7** and (*E*)-2-(buta-1,3-dienyl)pyridine **15** are precursors for 2-pyridyl etheno-bridged isoxazoles and thiazoles, and a range of specifically reduced variants.

Thiazoloquinolines are known dopamine agonists which are of potential use in the treatment of schizophrenia and Parkinson's disease. For example, aminothiazoles **1**[1] and **2**[2] exhibit dopaminergic activity. The central ring is not always necessary, as shown by the activity of the aminothiazole **3**.[3] We have targeted a range of acyclic structural variants of **1–3**, including the pyridyl and tetrahydropyridyl systems of general structure **4** and **5**, where the heterocyclic moieties were aminothiazoles, isoxazoles and isoxazolines. The synthetic developments which emerged in this study are now described.

Nitrile oxide 1,3-dipolar cycloaddition to acetylenes is a general route to isoxazoles. Thus, 2-pyridylmethyllithium was added to propynal to give the alkynol **6** in 44% yield. Mesylation and elimination (DBU) gave the new pyridyl enyne **7** (99%) as the *E*-isomer. Reaction with benzonitrile oxide *in situ* gave the isoxazole **8** (43%) with the regioselectivity as shown. The alternative isoxazole **9** was not detected. [The 4-H resonance of this compound appeared at δ 6.65, as distinct from the regioisomer **9** in which the 5-H signal would have appeared at *ca.* δ 8.4,[4] being adjacent to oxygen.] Similarly obtained was the ethyl isoxazole-3-carboxylate **10** (44%). [Again, a singlet at δ_H 6.74 was commensurate with the resonance of isoxazole 4-H, and in the ^{13}C NMR spectrum a doublet at δ_C 103.1 was assigned to the resonance of C-4: in the regioisomer the corresponding oxazolyl carbon signal would have appeared at *ca.* δ_C 158.[5]] Thus, in each case reaction occurred only at the acetylenic part of the enyne, and only with the regioselectivity indicated. Hydrogenation of the alkene group in pyridylisoxazole **10** provided the ethano-bridged product **11** (R = CO_2Et) (85%).

To progress towards an amino functionality corresponding to those in the dopaminergic aminothiazoles **1–3**, the isoxazole **10** was converted in low yield (35%) into the hydrazide **12** and thence the acyl azide **13** (75%) and the *tert*-butyl carbamate **14** (57%).

The regioselectivity observed for the dipolar cycloaddition of the enyne **7** prompted a study of the 2-(dienyl)pyridine **15**.[6] Reaction with ethoxycarbonyl nitrile oxide gave isoxazoline **16** (65%) none of the regioisomer **17** being isolated. The proton chemical shifts were in accord with structure **16**, but more convincing evidence came from the ^{13}C NMR spectrum in which a triplet at δ_C 39.1 corresponded to the C-4 resonance and a doublet at δ_C 83.3 was assigned to the signal of C-5. Oxidation of the isoxazoline **16** with manganese dioxide gave the isoxazole **10** (67%), thus supporting the regiochemical assignments previously made. Reduction of **16** (H_2, Pd/C) gave the ethano-bridged pyridyl isoxazoline **18** (86%), without cleavage of the N–O bond.

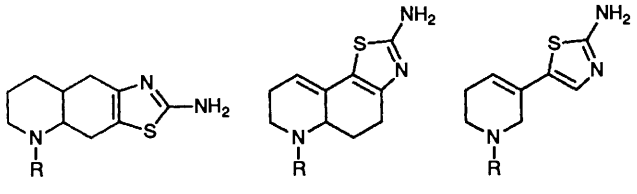


6 **7** **8** R=Ph; **10** R=CO_2Et; **12** R=$CONHNH_2$; **13** R=CON_3; **14** R=$NHCO_2Bu^t$

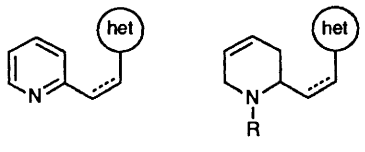
Py = 2-pyridyl

Related studies were performed in the pyridyl 2-aminothiazole series. The bromomethyl ketone **22** required for aminothiazole synthesis could not be obtained from the known enone **21**[6] by standard procedures including Br_2–HOAc, which work for closely related systems.[7] Instead, **23** was obtained by the reaction of the ylide **19**[8] with pyridine-2-carbaldehyde (67%). Reaction with thiourea[7] gave the 2-aminothiazole **24** (99%) as the hydrochloride salt which could be converted into the free base by treatment with EtOH–NH_3.

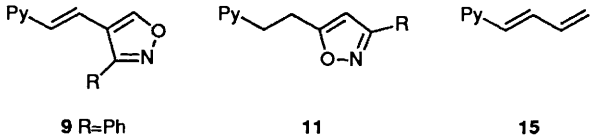
Elaboration of the amine **24** towards potential dopaminergic systems **5** was undertaken. Quaternization by iodomethane gave the *N*-methylpyridinium iodide **25** (69%), with no detectable reaction at the aminothiazole moiety. Reduction



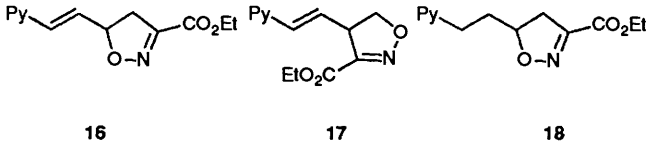
1 **2** **3**



4 **5**



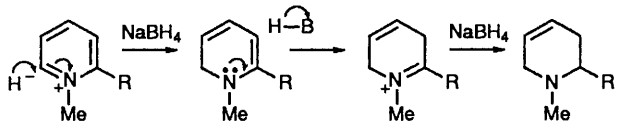
9 R=Ph **11** **15**



16 **17** **18**

Py = 2-pyridyl

(2 equiv. $NaBH_4$–MeOH) gave two tetrahydropyridine products, **26** (64%) and **27** (14%). Decoupling difference ^1H NMR experiments indicated the Δ^4-isomer as in **26** rather than the Δ^3-isomer. This was further established by COSY analysis of the ^2N-acetyl derivative **28**. The specificity of the hydride reduction, which probably proceeds as in Scheme 1, is in accord with previous studies.[9,10]

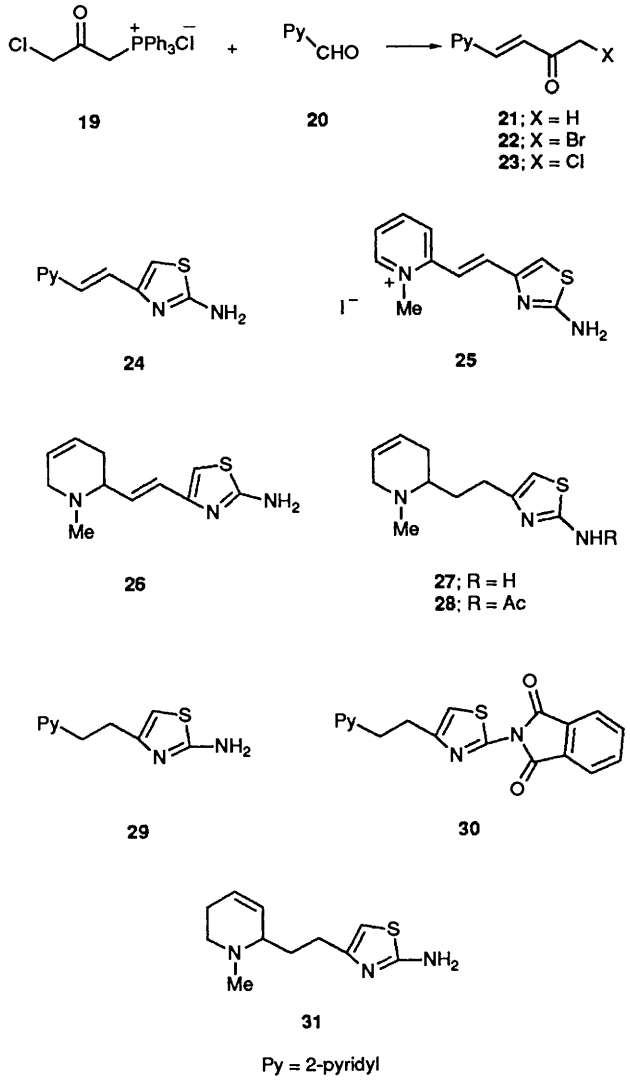


Scheme 1

Discrete reduction of the ethene unit in **24** was now addressed. The compound was resistant to catalytic hydrogenation with conventional heterogeneous catalysts such as Pd/C, Raney Ni and PtO_2, in contrast to the readily reduced isoxazole analogue **10**. Diimide–selenium,[11] however, effected the reduction to **29** (63%), as did sodium hydrogen telluride–MeOH (64%).[12–14]

In pursuit of a Δ^3-isomer **31** corresponding to the Δ^4-isomer **27** described above, the *N*-phthaloyl derivative **30** was quaternized and reduced, giving **27** and **31** in low yields. The C–H correlation spectrum, decoupling difference analysis and COSY data allowed unambiguous assignment of structure **31**.

The etheno-bridged tetrahydropyridine **26**, as its fumarate salt, displayed modest dopaminergic activity in biological screens.



Experimental

Petroleum refers to light petroleum b.p. 60–80 °C, it and all other solvents were distilled prior to use and where necessary dried and purified by standard methods.

Medium pressure (flash) column chromatography was used in general for the purification of reaction mixtures. Silica gel refers to Amicon 84072 silica gel (230–400 mesh), or Merck 9385 silica gel. Alumina refers to Aldrich 19.997–4 neutral alumina. In addition, preparative centrifugally accelerated thin layer radial chromatography was employed for some separations, using a model 2 Chromatotron. Thin layer chromatography (TLC) was performed on aluminium plates coated with Kieselgel 600 F_{254}. Electronic spectra were recorded in 95% ethanol solution with a Perkin Lambda 3 spectrometer, IR spectra were recorded using a Perkin-Elmer 938G instrument and NMR spectra were obtained with either JEOL GX FT 400 or 270 instruments, or with a Bruker AM 200 spectrometer. *J* Values are are given in Hz. Mass spectra were measured with a VG 7070E spectrometer linked to a 2000 data system.

2-(2-*Hydroxybut*-3-*ynyl*)*pyridine* **6**.—Diisopropylamine (0.9 cm^3, 6.4 mmol) was dissolved in dry tetrahydrofuran) (THF) (30 cm^3) under nitrogen and the solution was cooled to −10 °C for 10 min. Butyllithium (1.6 mol dm^{-3} solution in hexane; 3.7 cm^3) was then added slowly, and after a further 10 min 2-methylpyridine (0.5 cm^3, 5.4 mmol) was added. The mixture was stirred at room temperature for 1 h, and then cooled to −78 °C. A solution of propynal (0.3 cm^3, 5.4 mmol) in THF (5 cm^3) was added slowly dropwise to the stirred anion solution which changed colour from dark red to light brown. The mixture was allowed to warm to room temperature and after 20 min water was added (20 cm^3). Most of the THF was removed under reduced pressure and the organic phase was extracted with chloroform (3 × 20 cm^3). The combined organic extracts were washed with brine (2 × 15 cm^3), dried (Na_2SO_4) and concentrated to afford an oil. This was chromatographed on silica gel using 20–50% ethyl acetate in petroleum (60–80 °C) as the eluent to yield the *title compound* as an amorphous solid (350 mg, 44%); ν_{max}(Nujol)/cm^{-1} 3300 (alkyne CH), 3050br (OH), 2100w (C≡C), 1590 (C=C); δ_H(60 MHz, $CDCl_3$) 2.40 (1 H, d, $J_{2,4}$ 2, 4-H), 3.20 (2 H, d, $J_{1,2}$ 6, 1-H), 4.90 (1 H, td, $J_{1,2}$ 6, $J_{2,4}$ 2, 2-H), 5.60–5.80 (1 H, br s, OH), 7.30 (2 H, m, 3′-H, 5′-H), 7.65 (1 H, m, 4′-H), 8.45 (1 H, dm, $J_{5',6'}$ 5, 6′-H); *m/z* (isobutane CI) 148 (M − 1, 100%) and 130 (21, M − H_2O) (Found: C, 73.2; H, 6.3; N, 9.3. C_9H_9NO requires C, 73.45; H, 6.2; N, 9.5%).

(E)-2-(*But*-1-*en*-3-*ynyl*)*pyridine* **7**.—The alkynol **6** (30 mg, 0.2 mmol) was dissolved in dry dichloromethane (5 cm^3) under nitrogen and triethylamine (0.3 cm^3, 2 mmol) was added. The stirred solution was cooled to −5 °C and methanesulphonyl chloride (0.017 cm^3, 0.22 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperature after which it was heated under reflux for 0.5 h. Prior to the addition of DBU (1,8-diazabicyclo[5.4.0]undec-5-ene) (0.1 cm^3, 0.6 mmol) the reaction mixture was allowed to cool slightly, but afterwards it was heated for a further 1 h at reflux. The solvents were removed under reduced pressure and the crude product chromatographed on silica gel with ethyl acetate–petroleum (60–80 °C) (1:3) as the eluent. The *title compound* was thus obtained as an oil (26 mg, 99%), ν_{max}($CHCl_3$)/cm^{-1} 3300s (alkyne C–H); δ_H(270 MHz; $CDCl_3$) 3.15 (1 H, dd, $J_{1,4}$ 0.7, 4-H), 6.73 (1 H, dd, $J_{1,2}$ 16 $J_{2,4}$ 2.7, 2-H), 7.06 (1 H, d, $J_{1,2}$ 16, 1-H), 7.18 (1 H, ddd, $J_{4,5}$ 7.4, $J_{5,6}$ 4.7 $J_{3,5}$ 1.4, 5′-H), 7.23 (1 H, d, $J_{3,4}$ 7.4, 3′-H), 7.64 (1 H, td, $J_{3,4,5}$ 7.4, $J_{4,6}$ 2, 4′-H), 8.56 (1 H, d, $J_{5,6}$ 6′-H); δ_C(67.8 MHz; $CDCl_3$) 8.11 (d, 4-C), 82.5 (s, 3-C), 111.4 (d, 2-C), 122.3 (d, 5′-C), 123.2 (d, 3′-C), 136.6 (d, 4′-C), 141.8 (d, 1-C), 149.7 (d, 6′-C), 153.6 (s, 2′-C): *m/z* (low eV EI) 129 (M^+,

54%), 94 (52) (Found: M^+, 129.058, C_9H_7N requires *M*, 129.0577).

(E)-3-*Phenyl*-5-[2-(2-*pyridyl*)*vinyl*]*isoxazole* **8**.—The enyne **7** (36 mg, 0.28 mmol) was dissolved in dry diethyl ether (20 cm^3) under nitrogen atmosphere and to this was added benzohydroximinoyl chloride (43 mg, 0.28 mmol). A solution of triethylamine (0.043 cm^3, 0.31 mmol) in dry diethyl ether (20 cm^3) was added dropwise to the stirred mixture at room temperature over 3 h. After this time water (15 cm^3) was introduced causing the precipitation of triethylamine hydrochloride. This was filtered off and the organic phase was separated. The aqueous layer was extracted twice with diethyl ether and the combined organic phases were dried (Na_2SO_4) and concentrated to yield an oil. This was chromatographed on silica gel using ethyl acetate–petroleum (60–80 °C) (1:3) as the eluent to yield the *title compound* **8** as a solid (30 mg, 43%), m.p. 98–100 °C; λ_{max}(EtOH)/nm (ε) 244 (16 115), 277sh (15 840), 312 (33 380), 325sh (14 200); δ_H(400 MHz; $CDCl_3$) 6.65 (1 H, s, 4-H), 7.25 (1 H, ddd, $J_{4,5}$ 8, $J_{5,6}$ 5, $J_{3,5}$ 1.5, 5″-H), 7.40 (1 H, d, $J_{3,4}$ 8, 3″-H), 7.42 (1 H, d, $J_{1,2}$ 16, 1′-H), 7.48 (3 H, m, 3, 4 and 5-H Ph), 7.63 (1 H, d, $J_{1,2}$ 16, 2′-H), 7.72 (1 H, td, $J_{3,4,5}$ 8, $J_{4,6}$ 2, 4″-H), 7.85 (2 H, m, 2 and 6 H Ph), 8.65 (1 H, dm, $J_{5,6}$ 5, 6″-H); *m/z* (low eV EI) 248 (M^+, 100%), 145 (30) (Found: M^+, 248.0944, $C_{16}N_{12}O$ requires *M*, 148.0949) (Found: C, 77.8; H, 4.7; N, 11.2, $C_{16}H_{12}N_2O$ requires C, 77.4; H, 4.9; N, 11.3%).

(E)-*Ethyl* 5-[2-(2-*Pyridyl*)*vinyl*]*isoxazole*-3-*carboxylate* **10**.—The enyne **7** (36 mg, 0.28 mmol) and ethyl chlorooximidoacetate (63 mg, 0.42 mmol) were dissolved in dry diethyl ether (20 cm^3) and the mixture stirred at room temperature under nitrogen. A solution of triethylamine (0.06 cm^3, 0.42 mmol) in dry diethyl ether (20 cm^3) was added dropwise over 1 h to the vigorously stirred reaction mixture, causing precipitation of triethylamine hydrochloride. After the mixture had been stirred for a further 0.5 h water (15 cm^3) was added and the organic layer was separated. The aqueous phase was extracted with diethyl ether (2 × 10 cm^3) and the combined organic extracts were dried (Na_2SO_4) and concentrated to afford an oil. This was chromatographed on silica gel with ethyl acetate–petroleum (60–80 °C) (1:3) as eluent to yield the *title compound* as a colourless crystalline solid (30 mg, 44%), m.p. 83–84 °C (ethanol); λ_{max}(EtOH)/nm (ε) 273sh (10 740) and 311 (24 670); ν_{max}($CHCl_3$)/cm^{-1} 1730s (C=O) and 1585 (C=C); δ_H(270 MHz; $CDCl_3$) 1.44 (3 H, t, *J* 6.75, $CO_2CH_2CH_3$), 4.46 (2 H, q, *J* 6.75, $CO_2CH_2CH_3$), 6.74 (1 H, s, 4-H), 7.25 (1 H, ddd, $J_{4,5}$ 8, $J_{5,6}$ 4.5, $J_{3,5}$ 1, 5″-H), 7.39 (1 H, d, $J_{3,4}$ 8, 3″-H), 7.41 (1 H, d, $J_{1,2}$ 16, 1′-H), 7.60 (1 H, d, $J_{1,2}$ 16, 2′-H), 7.72 (1 H, td, $J_{3,4,5}$ 8, $J_{4,6}$ 1.7, 4″-H) and 8.65 (1 H, dm, $J_{5,6}$ 4.5, 6″-H); δ_C(67.8 MHz; $CDCl_3$) 14.1 (q, $CO_2CH_2CH_3$) 62.1 (t, $CO_2CH_2CH_3$), 103.1 (d, 4-C), 115.8 (d, 1′-C), 123.6 (d, 5″-C), 123.9 (d, 3″-C), 134.4 (d, 2′-C), 136.8 (d, 4″-C), 149.9 (d, 6″-C), 153.0 (s, 2″-C), 156.7 (s, 5-C), 159.8 (s, 3-C) and 169.6 (s, CO_2Et); *m/z* (low eV EI) 244 (M^+. 100%), 171 (12, M − CO_2Et) and 145 (65) (Found: C, 64.2; H, 4.95; N, 11.4. $C_{13}H_{12}N_2O_3$ requires C, 63.9; H, 4.95; N, 11.5%).

Ethyl-5-[2-*pyridyl*)*ethyl*]*isoxazole*-3-*carboxylate* **11** (R = CO_2Et).—The isoxazole **10** (139 mg, 0.57 mmol) was dissolved in methanol (30 cm^3) and to this solution was added 10% palladium on charcoal (50 mg). The slurry was stirred under hydrogen gas (1 atm) at room temperature. After 1 h, TLC analysis showed the presence of a new compound with no unchanged starting material. The reaction mixture was diluted with ethyl acetate (50 cm^3) and filtered through Celite. The filtrate was concentrated under reduced pressure and the resultant oil was chromatographed on silica gel eluting with ethyl acetate–petroleum (60–80 °C) (1:1) to yield the *title compound* as a clear oil (119 mg, 85%) λ_{max}/nm (ε) 248 (6300), 253 (6420), 259 (6030) and 265sh (3800); ν_{max}($CHCl_3$)/cm^{-1} 2920 (CH) and 1720s (C=O); δ_H(270 MHz; $CDCl_3$) 1.41 (3 H, t, *J* 4.6, $CO_2CH_2CH_3$), 3.20 (2 H, t, $J_{1,2}$ 5, 1′-H), 3.32 (2 H, t, $J_{1,2}$ 5, 2′-H), 4.42 (2 H, q, *J* 4.6, $CO_2CH_2CH_3$), 6.40, (1 H, s, 4-H), 7.13 (1 H, d, $J_{3,4}$ 5, 3″-H), 7.16 (1 H, dd, $J_{4,5}$ 5, $J_{5,6}$ 3.5″-H), 7.60 (1 H, td, $J_{3,4,5}$ 5, $J_{4,6}$ 1.2, 4″-H) and 8.56 (1 H, dm, $J_{5,6}$ 3, 6″-H); δ_C(67.8 MHz; $CDCl_3$) 14.0 (q, $CO_2CH_2CH_3$), 26.0 (t, C-1′), 35.2 (t, C-2′), 61.9 (t, $CO_2CH_2CH_3$), 101.7 (d, C-4, 121.6 (d, C-5″, 122.8 (d, C-3″), 136.5 (d, C-4″), 149.3 (d, C-6″), 156.2 (s, C-5), 158.8 (s, C-3), 160.0 (s, C-2″) and 174.4 (s, $CO_2CH_2CH_3$); *m/z* (low eV EI) 246 (M^+, 35%), 173 (13, M − CO_2Et) and 147 (100) (Found: M^+, 246.0992. $C_{13}H_{14}N_2O_3$ requires: *M*, 246.1003).

Ethyl 5-[2-(2-*Pyridyl*)*ethyl*-4,5-*dihydroisoxazole*-3-*carboxylate* **18**.—The isoxazoline **16** (200 mg) was dissolved in ethanol (20 cm^3) and to this solution was added 10% palladium on charcoal (20 mg). The suspension was stirred under hydrogen gas (1 atm) at room temperature. After 2 h, TLC analysis indicated complete conversion of starting material into a new compound of slightly lower R_F. The mixture was diluted with ethyl acetate (50 cm^3) and filtered through Celite. The solvents were removed under reduced pressure to afford an oil which was chromatographed on silica gel with ethyl acetate–petroleum (60–80 °C) (1:1) as the eluent to yield the *title compound* as a clear oil (172 mg, 86%); ν_{max}($CHCl_3$)/cm^{-1} 2930s (CH), 1710 (C=O) and 1690 (C=C); δ_H(270 MHz; $CDCl_3$) 1.36 (3 H, t, *J* 7.5, $CO_2CH_2CH_3$), 2.15 (2 H, m, 1′-H), 2.90 (2 H, m, 2′-H), 2.91 (1 H, dd, $J_{4,4(gem)}$ 18, $J_{4.5(vic)}$ 7.5, 4-H), 3.28 (1 H, dd, $J_{4,4(gem)}$ 18, $J_{4,5(vic)}$ 11.2, 4-H), 4.34 (2 H, q, *J* 7.5 Hz, $CO_2CH_2CH_3$), 4.85 (1 H, m, 5-H), 7.16 (1 H, ddd, $J_{4,5}$ 7.5, $J_{5,6}$ 5.2, $J_{3,5}$ 1.5, 5″-H), 7.20 (1 H, d, $J_{3,4}$ 7.5, 3″-H), 7.62 (1 H, td, $J_{3,4,5}$ 7.5, $J_{4,6}$ 2.3, 4″-H) and 8.53 (1 H, dm, $J_{5,6}$ 5.2, 6″-H); δ_C(67.8 MHz; $CDCl_3$) 13.9 (q, $CO_2CH_2CH_3$), 33.4 (t, C-1′), 34.6 (t, C-2′), 38.3 (t, C-4), 61.8 (t, $CO_2CH_2CH_3$), 83.1 (d, C-5), 121.3 (d, 5″-C), 122.9 (d, C-3″), 136.5 (d, C-4″), 149.1 (d, C-6″), 151.3 (s, C-3), 160.2 (s, C-2″) and 160.6 (s, $CO_2CH_2CH_3$): *m/z* (%) (isobutane CI) 249 (M − 1, 82%), 175 (25), 106 (54) and 93 (100) (Found: C, 62.6; H, 6.65; N, 11.4, $C_{13}H_{16}N_2O_3$ requires C, 62.9; H, 6.45; N, 11.3%).

2-(4-*Chlorobut*-1-*enyl*)*pyridine* **23**.—The ylide **19** (53.6 g, 152 mmol) and pyridine-2-carbaldehyde (14.4 cm^3, 151 mmol) were dissolved in dichloromethane (300 cm^3) and stirred at room temperature for 24 h. Analysis by TLC showed that the reaction had gone to completion and the solvents were removed under reduced pressure. Ethyl acetate was added to the amorphous mixture and this was heated to effect dissolution of the products. The solution was filtered and allowed to cool, resulting in crystallisation of triphenylphosphine oxide. This was collected and the filtrate concentrated and chromatographed on silica gel with ethyl acetate–petroleum (60–80 °C) (1:4) as eluent to yield the *title compound* as a solid (18.5 g, 67%), m.p. 48–49 °C; ν_{max}($CHCl_3$)/cm^{-1} 1675s (C=O) and 1615 (C=C); δ_H(270 MHz; $CDCl_3$) 4.35 (2 H, s, CH_2Cl), 7.32 (1 H, ddd, $J_{4',5'}$ 7.5, $J_{5',6'}$ 4.5, $J_{3',5'}$ 1, 5′-H), 7.43 (1 H, d, $J_{3,4}$ 16, 3-H), 7.48 (1 H, d, $J_{3',4'}$ 7.5, 3′-H), 7.70 (1 H, d, $J_{3,4}$ 16, 4-H), 7.76 (1 H, td, $J_{3',4',5'}$ 7.5, $J_{4',6'}$ 2, 4′-H) and 8.68 (1 H, dm, $J_{5',6'}$ 4.5, 6′-H); δ_C(67.8 MHz; $CDCl_3$) 47.7 (t, CH_2Cl), 124.7 (d, C-5′), 125.1 (d, C-3′), 125.2 (d, C-3), 136.8 (d, C-4′), 143.2 (d, C-4), 150.2 (d, C-6′), 152.3 (s, C-2′) and 191.2 (s, C=O); *m/z* (%) (isobutane CI) 184 [M + 1 (^{37}Cl), 100], 182 (M + 1 ^{35}Cl), 35) 148 (30) and 132 (80) (Found: M^+ (^{37}Cl), 183.0226. C_9H_8 $^{37}ClNO$ requires *M*, 183.0264).

(E)-3-*Hydrazinocarbonyl*-5-[2-(2-*pyridyl*)*vinyl*]*isoxazole* **12**.—The isoxazole ester **10** (125 mg, 0.51 mmol) and hydrazine hydrate (0.025 cm^3, 0.51 mmol) were dissolved in ethanol (3 cm^3). The mixture was heated under reflux for 2 h. A further 2

equiv. of hydrazine hydrate (0.05 cm^3, 1.02 mmol) were added and the mixture heated for another 2 h before it was allowed to cool. The solid which crystallised from the reaction mixture was collected and dried to yield the crude product (80 mg). This was pre-adsorbed onto silica gel and chromatographed with ethyl acetate as the eluent. The title compound was isolated as a colourless powder (40 mg, 35%), m.p. 145–155 °C (decomp.); ν_{max}(Nujol)/cm^{-1} 3315, 3240 (NH), 1670s (amide I) and 1630 (amide II); δ_H[270 MHz, $(CD_3)_2SO$] 4.69 (2 H, br s, NH_2), 7.07 and 7.15 [1 H, 2 s (4:1), 4-H], 7.38 (1 H, ddd, $J_{4,5}$ 7.5, $J_{5,6}$ 5.25, $J_{3,5}$ 1.5, 5″-H), 7.54 and 7.57 [1 H, 2 d (4:1), $J_{1,2}$ 16.5, 1′-H), 7.67 (1 H, d, $J_{3,4}$ 7.5, 3″-H), 7.87 (1 H, td, $J_{3,4,5}$ 7.5, $J_{4,6}$ 2.3, 4″-H), 8.65 (1 H, dm, $J_{5,6}$ 5.25, 6″-H) and 10.11 and 10.82 [1 H, 2 s, (4:1), CO_2NHNH_2]; δ_C 270 MHz $(CD_3)_2SO$] 102.6 (d, C-4), 115.9 (d, C-1′), 124.0 (d, C-5″), 124.1 (d, C-3″), 134.5 (d, C-2′), 137.3 (d, C-4″), 150.0 (d, C-6″), 153.0 (s, C-2″), 157.8 (s, C-5), 162.7 (s, C-3) and 168.8 (s, *C*ONHNH$_2$); *m/z* (70 eV EI) 230 (M^+, 100%), 199 (18, M − $NHNH_2$), 171 (15), 132 (30), 117 (16), 104 (20) and 78 (25).

(E)-*Azidocarbonyl*-5-[2-(2-*pyridyl*)*vinyl*]*isoxazole* **13**.—The hydrazide **12** (500 mg, 2.2 mmol) was dissolved in 2 mol dm^{-3} HCl (20 cm^3) with stirring at − 5 °C. Diethyl ether (20 cm^3) was added first and then solution of sodium nitrite (152 mg, 2.2 mmol) in water (5 cm^3) was dripped into the vigorously stirred mixture, the temperature being kept < 5 °C during the addition. The mixture was stirred for 5 min, after which time TLC analysis indicated a complete conversion into the new compound. Sodium carbonate was added until the solution was just basic to litmus and the diethyl ether layer was separated. The aqueous phase was extracted several times with diethyl ether and the combined organic phases were washed with brine, dried ($MgSO_4$) and evaporated to yield the azide **20** (R = CON_3) as a solid (398 mg, 75%); ν_{max}($CHCl_3$)/cm^{-1} 2160s (N_3), 1700s (C=O) and 1585 (C=C); δ_H(60 MHz; $CDCl_3$) 6.80 (1 H, s, 4-H), 7.20–8.00 (5 H, m, 1′-H and 2′-H, 3″-, 4″- and 5′-H) and 8.75 (1 H, dm, $J_{5,6}$ 5, 6″-H); *m/z* (low eV EI) 241 (M^+, 100%), 213 (51, M − N_2), 158 (38), 145 (21) and 117 (36).

(E)-tert-*Butylcarbamoyl*-5-[2-(2-*pyridyl*)*vinyl*]*isoxazole* **14**.—The azide **13** (338 mg, 1.4 mmol) was dissolved in *tert*-butyl alcohol (20 cm^3) and this was heated under reflux for 1 h. After cooling, the reaction mixture was evaporated under reduced pressure. The resulting solid was chromatographed on silica gel with ethyl acetate–petroleum (60–80 °C) (1:3) as eluent to yield the carbamate **14** as a colourless crystalline solid (228 mg, 57%), m.p. 180–182 °C; λ_{max}(EtOH)/nm (ε) 241 (15 830), 264sh (19 610), 269 (20 230), 311 (25 930), 325sh (11 960); ν_{max}($CHCl_3$)/cm^{-1} 3400 (N–H), 1730s (C=O) and 1590s (C=C); δ_H(270 MHz, $CDCl_3$) 1.54 [9 H, s, $CO_2C(CH_3)_3$], 6.86 (1 H, br s, 4-H), 7.22–7.24 (1 H, br s, NH), 7.23 (2 H, ddd, $J_{4,5}$ 8, $J_{5,6}$ 4, 5 $J_{3,5}$ 1.1, 5″-H), 7.33 (1 H, d, $J_{1,2}$ 16, 1′-H), 7.35 (1 H, d, $J_{3,4}$ 8, 3″-H), 7.50 (1 H, d, $J_{1,2}$ 16, 2′-H), 7.70 (1 H, td, $J_{3,4,5}$ 8, $J_{4,6}$ 2, 4″-H) and 8.64 (1 H, dm, $J_{5,6}$ 4.5, 6″-H); δ_C(67.8 MHz; $CDCl_3$) 28.2 [q, $CO_2C(CH_3)_3$], 81.9 [s, $CO_2C(CH_3)_3$], 96.5 (d, C-4), 116.9 (d, C-1′), 123.3 (d, C-5″), 123.7 (d, C-3″), 133.4 (d, C-2′), 136.8 (d, C-4″), 149.9 (d, C-6″), 151.8 (s, C-5), 153.5 (s, C-2″), 158.8 (s, C-3) and 167.9 [s, $CO_2C(CH_3)_3$]; *m/z* (low eV EI) (%) 287 (M^+, 100), 231 [45, M − C + $C(CH_3)_2$] and 187 [58, M − $CO_2C(CH_3)_3$] (Found: C, 62.5; H, 5.9; N, 14.8. $C_{15}H_{17}N_3O_3$ requires C, 62.7; H, 5.95; N, 14.6%).

2-(*Buta*-1,3-*dienyl*)*pyridine* **15**.—2-(2-Hydroxybut-3-enyl)pyridine[15] (10 g, 67 mmol) was dissolved in dry dichloromethane (250 cm^3) and the solution stirred under nitrogen. Triethylamine (17 cm^3, 122 mmol) was added and the mixture was cooled to 0 °C prior to the addition of methanesulphonyl chloride (5.2 cm^3, 67 mmol). Cooling was discontinued and the mixture was heated under reflux for 2 h. A further 2 equiv. of triethylamine (17 cm^3, 122 mmol) were added and heating was continued until TLC analysis indicated that none of the starting alcohol remained. After cooling, the mixture was filtered to remove insoluble material and the solvents were removed under reduced pressure. The crude oil was chromatographed on silica gel with ethyl acetate–petroleum (60–80 °C) (1:3) as the eluent to afford the diene **15** as an oil (6.35 g, 72%); δ_H(270 MHz, $CDCl_3$) 5.27 (1 H, d, J_{cis} 9.8, 4-H), 5.45 (1 H, d, J_{trans} 16.5, 4-H), 6.55 (2 H, m, 2-H, 3-H), 7.08 (1 H, dd, $J_{4,5}$ 7.5, $J_{5,6}$ 4, 5, 5′-H), 7.25 (1 H, m, 1-H), 7.58 (1 H, td, $J_{3,4,5}$ 7.5, $J_{4,6}$ 1.5, 4′-H), 8.54 (1 H, d, $J_{5,6}$ 6′-H); *m/z* (isobutane CI) 132 (M + 1, 100%).[16]

(E)-*Ethyl* 5-[2-(2-*Pyridyl*)*vinyl*]-4,5-*dihydroisoxazole*-3-*carboxylate* **16**.—The diene **15** (2.3 g, 17.6 mmol) and ethyl chlorooximidoacetate (4 g, 26.4 mmol) were dissolved in dry diethyl ether (100 cm^3) under nitrogen. A solution of triethylamine (3.68 cm^3, 26.4 mmol) in dry diethyl ether (50 cm^3) was added dropwise over 0.5 h to the vigorously stirred reaction mixture causing precipitation of triethylamine hydrochloride. Stirring was continued for a further 1 h after which water (30 cm^3) was added and the organic layer separated. The aqueous phase was washed twice with diethyl ether and the combined organic fractions were dried ($MgSO_4$) and concentrated to an oil. This was chromatographed on silica gel with ethyl acetate–petroleum (60–80 °C) (1:4) as eluent to afford the *title compound* as an oil (2.83 g, 65%); ν_{max}($CHCl_3$)/cm^{-1} 2900 (C–H), 1720s (C=O) and 1590 (C=C); δ_H(270 MHz; $CDCl_3$) 1.36 (3 H, t, *J* 6.8, $CO_2CH_2CH_3$), 3.17 (1 H, dd, $J_{4.4(gem)}$ 17.1, $J_{4,5(vic)}$ 11.4, 4-H), 3.46 (1 H, dd, $J_{4.4(gem)}$ 17.1, $J_{4,5(vic)}$ 8.6, 4-H), 4.35 (2 H, q, *J* 6.8, $CO_2CH_2CH_3$), 5.46 (1 H, m, 5-H), 6.73 (1 H, d, $J_{1,2}$ 16, 1′-H), 6.80 (1 H, d, $J_{1,2}$ 16, 2′-H), 7.18 (1 H, ddd, $J_{4,5}$ 8, $J_{5,6}$ 5, $J_{3,5}$ 1.1, 5″-H), 7.29 (1 H, d, $J_{3,4}$ 8, 3″-H), 7.66 (1 H, td, $J_{3,4,5}$ 8, $J_{4,6}$ 2.3, 4″-H) and 8.56 (1 H, d, $J_{5,6}$ 5, 6″-H); δ_C(67.8 MHz; $CDCl_3$) 13.9 (q, $CO_2CH_2CH_3$), 39.1 (t, C-4), 61.9 (t, $CO_2CH_2CH_3$), 83.3 (d, C-5), 122.3 (d, C-5″), 122.7 (d, C-3″), 129.9 (d, C-1′), 132.4 (d, C-2′), 136.6 (d, C-4″), 149.3 (d, C-6′), 151.0 (s, C-3), 153.7 (s, C-2″) and 160.2 (s, $CO_2CH_2CH_3$): *m/z* (low eV EI) 246 (M^+, 100%), 299 (50), 216 (42) (Found: M^+, 246.0995. $C_{13}H_{14}N_2O_3$ requires: *M*, 246.1003).

Oxidation of the Dihydroisoxazole **16** *to the Isoxazole* **10**.—The dihydroisoxazole **16** (1 g, 4 mmol) was dissolved in dry benzene (25 cm^3, distilled from CaH_2) and to the solution was added a slurry of active manganese dioxide (5 g) in a small volume of the same solvent. The mixture was heated under reflux and stirred for 2 h, and the water formed was removed by the use of a Dean–Stark trap. At the end of this time TLC analysis indicated a complete conversion into the product and the slurry was filtered through Celite. The filtrate was washed with dichloromethane and the combined filtrates were concentrated to afford an oil. This was chromatographed on silica gel with ethyl acetate–petroleum (60–80 °C) (1:3) as eluent to yield the isoxazole **10** as a colourless crystalline solid (660 mg, 67%) identical in all respects to the compound obtained previously.

(E)-2-*Amino*-4-[2-(2-*pyridyl*)*vinyl*]*thiazole* **24**.—The chloro ketone **23** (18.33 g, 101 mmol) and thiourea (7.7 g, 101 mmol) were dissolved in *p*-dioxane (40 cm^3) and ethanol (60 cm^3). The mixture was heated just to reflux temperature for 2 h after which it was allowed to cool and filtered to yield the *title compound* as the *hydrochloride salt*. This crystallised from ethanol as pale yellow prisms (24 g, 99%), m.p. 198–200 °C; λ_{max}(EtOH)/nm (ε) 257 (23 900) and 328 (20 830); ν_{max}(Nujol)/cm^{-1} 3260br (H_2O) and 3100 (NH), 2680br (N^+ − H); δ_H[270 MHz; $(CD_3)_2SO$] 7.10 (1 H, s, 5-H), 7.33 (1 H, d, $J_{1,2}$ 15.75, 1′-H), 7.62 (1 H, convergent dd, $J_{4,5}$ 8.25 $J_{5,6}$ 5.25, 5″-H),

7.70 (1 H, d, $J_{1,2}$ 15.75, 2′-H), 7.80–8.60 (2 H, br s, NH_2), 8.02 (1 H, d, $J_{3,4}$ 8.25, 3″-H), 8.23 (1 H, td, $J_{3,4,5}$ 8.25, $J_{4,6}$ 1.5, 4″-H) and 8.66 (1 H, dm, $J_{5,6}$ 5.25, 6″-H) (Found: C, 47.3; H, 4.3; Cl, 15.35; N, 16.55; S, 12.5. $C_{10}H_{10}ClN_3S$·0.5H_2O requires C, 47.6; H, 4.4; Cl, 15.45; N, 16.65; S, 12.7%).

The free amine was released from the salt as follows. The thiazolamine hydrochloride (7.5 g, 31 mmol) was stirred in 10% solution of ammonia in ethanol (25 cm^3) for 2 h. The free amine was collected by filtration, washed with ethanol and chromatographed on silica gel with 1% triethylamine in ethyl acetate as eluent to yield the *pure compound* as a pale yellow solid (6 g, 95%), m.p. 175–177 °C; λ_{max}(EtOH)/nm (ε) 257 (17 440) and 329 (16 180); ν_{max}(Nujol)/cm^{-1} 3250 and 3100 (N–H), 1650 and 1620 cm^{-1}; δ_H[270 MHz; $(CD_3)_2SO$] 6.77 (1 H, s, 5′-H), 7.10 (1 H, d, $J_{1,2}$ 16, 1′-H), 7.11 (2 H, br s, NH_2), 7.21 (1 H, ddd, $J_{4,5}$ 7.9, $J_{5,6}$ 4.5, $J_{3,5}$ 1.1, 5″-H), 7.37 (1 H, d, $J_{1,2}$ 16, 2′-H), 7.47 (1 H, d, $J_{3,4}$ 7.9, 3″-H), 7.74 (1 H, td, $J_{3,4,5}$ 7.9, $J_{4,6}$ 1.9, 4″-H) and 8.53 (1 H, dm, $J_{5,6}$ 4.5, 6″-H); δ_H[67.8 MHz; $(CD_3)_2SO$] 108.8 (d, C-5), 122.3 (d, C-5″), 122.4 (d, C-3″), 126.1 (d, C-1′), 128.2 (d, C-2′), 136.9 (d, C-4″), 149.4 (d, C-6″), 149.6 (s, C-4), 155.4 (s, C-2″) and 168.3 (s, C-2); *m/z* (%) (low eV EI) 203 (M^+, 100) and 202 (45) (Found: C, 59.2; H, 4.4; N, 20.7. $C_{10}H_9N_3S$ requires C, 59.1; H, 4.5; N, 20.7%).

(E)-2-*Amino*-4-[2-(1,2,3,6-*tetrahydro*-1-*methyl*-2-*pyridyl*)-*vinyl*]*thiazole* **26** *and* 2-*Amino*-4-[2-(1,2,3,6-*tetrahydro*-1-*methyl*-2-*pyridyl*)*ethyl*]*thiazole* **27**.—(*i*) The thiazolamine **24** (5.5 g, 27 mmol) was slurried in acetonitrile (100 cm^3) and heated to reflux temperature to effect dissolution. Iodomethane was added in five portions (*ca.* 2 cm^3 each) during the period of reflux (*ca.* 10 h). After this time the precipitated yellow solid was collected and chromatographed on alumina with propan-2-ol–ethyl acetate (1:3) as eluent to yield (E)-2-[2-(2-*aminothiazol*-4-*yl*)*vinyl*]-1-*methylpyridinium iodide* **25** as a yellow crystalline solid (6.5 g, 69%), m.p. 233–235 °C (from methanol); λ_{max}(EtOH)/nm (ε) 268 (8660), 285sh (6900) and 390 (6560); ν_{max}(Nujol)/cm^{-1} 3277 and 3137 (NH) and 1610 (C=C); δ_H[270 MHz; $(CD_3)_2SO$] 4.28 (3 H, s, CH_3), 7.19 (1 H, s, 5-H), 7.25 (1 H, d, $J_{1,2}$ 15.5, 1′-H), 7.30–7.50 (2 H, br s, NH_2), 7.71 (1 H, d, $J_{1,2}$ 15.5 Hz, 2′-H), 7.86 (1 H, m, 5″-H), 8.45 (2 H, m, 3″-H, 4″-H) and 8.93 (1 H, d, $J_{5,6}$ 6, 6″-H); δ_C[67.8 MHz; $(CD_3)_2SO$] 45.7 (q, CH_3), 115.6 (d, C-5), 116.7 (d, C-1′), 134.5 (d, C-5″), 124.6 (d, C-3″), 135.5 (d, C-2′), 144.1 (d, C-6″), 145.9 (d, C-4″), 148.1 (s, C-2″), (s, C-4) and 168.6 (s, C-2) (Found: C, 37.9; H, 3.45; N, 12.1. $C_{11}H_{12}IN_3S$ requires C, 38.3; H, 3.5; N, 12.2%).

(*ii*) The pyridinium salt from the previous reaction (6.53 g) was slurried in ethanol (100 cm^3) and to the stirred, cooled (0 °C) mixture was added sodium borohydride (1.58 g, 42 mmol) in portions. This resulted in effervescence and after a few minutes a homogeneous solution was formed. The cooling bath was removed and the reddish solution stirred at room temperature for 0.5 h. Acetone (10 cm^3) was added to quench any unchanged sodium borohydride and the solvents were removed under reduced pressure. Ethyl acetate (30 cm^3) and 2 mol dm^{-3} aqueous HCl (20 cm^3) were added to the amorphous solid and the aqueous phase was made slightly basic with sodium carbonate. The organic layer was separated and the aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated to afford an oil. This was chromatographed on silica gel eluting with 1% triethylamine in methanol–dichloromethane (1:19) to yield the *title compound* **26** as a colourless solid (55%), m.p. 172 °C (from ethanol); λ_{max}(EtOH)/nm (ε) 220 (28 110) and 268 (14 490); ν_{max}(KBr)/cm^{-1} 3307vs and 3123vs (NH, H_2O), 2798 (CH), 1649vs (C=C) and 1544vs (C=C); δ_H(270 MHz; $CDCl_3$) 2.25 (2 H, m, 3″-H), 2.32 (3 H, s, CH_3), 2.94 (1 H, dm, $J_{6,6(gem)}$ 17, 6″-H), 3.02 (1 H, ddm, $J_{2,3(vic)}$ 14, $J_{2,3(vic)}$ 6.5, 2″-H), 3.25 (1 H, dm, $J_{6,6(gem)}$ 17, 6″-H), 5.38 or 5.95 (2 H, br s, NH_2), 5.69 (1 H, dm, $J_{4,5(cis)}$ 12, 5″-H), 6.25 (1 H, d, $J_{1,2}$ 16, 2′-H), 6.31 (1 H, s, 5-H), 6.34 (1 H, d, $J_{1,2}$ 16, 1′-H); δ_C(67.8 MHz; $CDCl_3$) 32.3 (t, 3″-C), 42.9 (q, CH_3), 53.0 (t, 6″-C), 62.0 (d, 2″-C), 104.9 (d, 5-C), 123.7 (d, 1′-C), 124.5 (d, 4″-C), 125.0 (d, 5″-C), 131.1 (d, 2′-C), 149.0 (s, 4-C), 167.8 (s, 2-C); *m/z* (low eV EI) 221 (M^+, 83%), 220 (31) and 94 (100) (Found: C, 57.35; H, 7.0; N, 18.3. $C_{11}H_{15}N_3S$·0.5H_2O requires 57.4; H, 6.95; N, 18.3%).

A more polar compound isolated as an oil proved to be the *title compound* **27** (96 mg, 2.3%); ν_{max}($CHCl_3$)/cm^{-1} 3481 and 3386 (NH) and 1604s (C=C); δ_H(270 MHz; $CDCl_3$) 1.65 (1 H, m, 2′-H), 1.95 (1 H, m, 3″-H), 2.02 (1 H, m, 2′-H), 2.20 (1 H, dm, $J_{3,3(gem)}$ 17, 3″-H, 2.35 (3 H, s, CH_3), 2.55 (3 H, m, 1′-H and 2″-H), 3.00 (1 H, dm, $J_{6,6(gem)}$ 17, 6″-H), 3.16 (1 H, dm, $J_{6,6(gem)}$ 17, 6″-H), 5.25 (2 H, br s, NH_2), 5.63 (1 H, dm, $J_{4,5(cis)}$ 11, 5″-H), 5.73 (1 H, dm, $J_{4,5(cis)}$ 11, 4″-H) and 6.10 (1 H, s, 5-H); δ_C(67.8 MHz; $CDCl_3$) 28.1 (t, 2′-C), 28.8 (t, 3″-C), 29.6 (t, 1′-C), 40.5 (q, CH_3), 53.1 (t, 6″-C), 57.5 (d, 2″-C), 101.7 (d, 5-C), 124.5 (d, 4″-C), 124.6 (d, 5″-C), 152.7 (s, 4-C) and 168.1 (s, 2-C); *m/z* (low eV EI) 223 (M^+, 15%), 97 (76) and 96 (100) (Found: M^+, 223.1122. $C_{11}H_{17}N_3S$ requires *M*, 223.1142).

2-*Acetamido*-4-[2-(1,2,3,6-*tetrahydro*-1-*methyl*-2-*pyridyl*)-*ethyl*]*thiazole* **28**.—The amine **27** (159 mg) and acetic anhydride (0.1 cm^3) were heated at reflux in acetonitrile (10 cm^3) for 2 h. Triethylamine (1 cm^3) was then added and the mixture allowed to cool to room temperature. The solvent and excess of reagents were then removed and the residue chromatographed on silica eluting with 1% ammonia in acetone–ethanol–chloroform (5:8:98). The title compound was isolated as a colourless oil (170 mg, 90%); ν_{max}($CHCl_3$)/cm^{-1} 3410 (NH) and 1680; δ_H(270 MHz; $CDCl_3$) 1.70 (1 H, m, 2′-H), 2.05 (3 H, m, 3″-H, 2′-H, NH), 2.25 (4 H, m, 3″-H, $NHCOCH_3$), 2.40 (3 H, s, NCH_3), 2.70 (3 H, m, 1′-H and 2″-H), 3.17 (1 H, dm, $J_{6,6(gem)}$ 18, 6″-H), 3.28 (1 H, dm, $J_{6,6(gem)}$ 18, 6″-H), 5.63 (1 H, dm, $J_{4,5(cis)}$ 10.5, 5″-H), 5.76 (1 H, dm, $J_{4,5(cis)}$ 10.5, 4″-H) and 6.53 (1 H, s, 5-H) COSY analysis: Observed δ_H (assignment) 5.76, 5.63 (4-H″, 5-H″)-cross peaks 3.28, 3.17, 2.25, 2.05 (6-H″, 6-H, 3-H″, 3-H″ respectively; δ_H 2.70 (1-H′, 2-H″)-cross peaks 2.25, 2.05, 1.70 (3-H″, 3-H″, 2-H′, 2-H′ respectively).

2-*Amino*-4-[2-(2-*pyridyl*)*ethyl*]*thiazole* **29**.—The thiazolamine **24** (27 g, 133 mmol) was dissolved in ethanol (350 cm^3) under nitrogen and in this solution was slurried tellurium powder (42.4 g, 332 mmol). The stirred mixture was cooled to 0 °C and sodium borohydride (25.15 g, 665 mmol) was added carefully in small portions. A highly exothermic reaction occurred which was controlled by use of an ice-bath. Once the reaction had subsided the mixture was heated gently under reflux for *ca.* 6 h until TLC analysis indicated complete conversion of starting compound into product. The mixture was allowed to cool and filtered through Celite, washing with ethanol. The solvent was removed under reduced pressure to afford a solid which was chromatographed on silica gel with 1% triethylamine in ethyl acetate–petroleum (b.p. 60–80 °C) (1:2) as the eluent to yield the title compound **29** as a colourless solid (17.3 g, 63.5%); m.p. 121 °C [EtOAc–petroleum (b.p. 60–80 °C)]; λ_{max}(EtOH)/nm (ε) 256 (11 400), 260 (11 520) and 266sh (8815); ν_{max}(KBr)/cm^{-1} 3293 and 3100 (NH); δ_H(270 MHz; $CDCl_3$) 2.95 (2 H, m, 1′-H), 3.10 (2 H, m, 2′-H), 5.50 (2 H, br s, NH_2), 6.04 (1 H, s, 5-H), 7.10 (1 H, m, 5″-H), 7.13 (1 H, d, $J_{3,4}$ 7.9, 3″-H), 7.57 (1 H, td, $J_{3,4,5}$ 7.9, 1.7, 4″-H) and 8.54 (1 H, dm, $J_{5,6}$ 5, 6″-H); δ_C(67.8 MHz; $CDCl_3$) 31.5 (t, C-1′), 37.3 (t, C-2′), 102.5 (d, C-5), 121.0 (d, C-5″), 122.8 (d, C-3″), 136.2 (d, C-4″), 149.2 (d, C-6″), 152.0 (s, C-4), 161.1 (s, C-2″) and 167.7 (s, C-2); *m/z* (%) (low eV EI) 205 (M^+, 100), 172 (7) and 130 (38) (Found: C, 58.7; H, 5.4; N, 20.55. $C_{10}H_{11}N_3S$ requires C, 58.5; H, 5.4; N, 20.5%).

Phthaloyl Derivative **30**. The thiazolamine **29** (12 g, 58.5

mmol) and phthalic anhydride (9.6 g, 65 mmol) were dissolved in chloroform (300 cm^3) and the solution was heated under reflux for *ca.* 5 h. The solvents then were removed under reduced pressure and the resultant oil was chromatographed on silica gel eluting with 1% triethylamine in ethyl acetate–petroleum (b.p. 60–80 °C) (1:3) to yield the phthalimide as an off-white solid (10 g, 51%), m.p. 134 °C (ethanol); $\nu_{max}(CHCl_3)/cm^{-1}$ 1790 and 1720s (CO); δ_H(270 MHz; $CDCl_3$) 3.27 (4 H, m, 1′-H, 2′-H), 6.90 (1 H, s, 5-H), 7.11 (1 H, ddd, $J_{4,5}$ 8, $J_{5,6}$ 5, $J_{3,5}$ 1, 5″-H), 7.16 (1 H, d, $J_{3,4}$ 8, 3″-H), 7.57 (1 H, td, $J_{3,4,5}$ 8, $J_{4,6}$ 2, 4″-H), 7.82 (2 H, dd, $J_{\beta,\gamma}$ 5.5, $J_{\beta,\gamma}$ 3 Hz, $_{\gamma,\gamma'}$-H), 7.98 (2 H, dd, $J_{\beta,\gamma}$ 5, 5 $J_{\beta,\gamma}$ 3, β,β′-H) and 8.55 (1 H, d, $J_{5,6}$ 5, 6″-H); δ_C(67.8 MHz; $CDCl_3$) 31.3 (t, C-1′), 37.1 (t, C-2′), 112.8 (d, C-5), 121.0 (d, C-5″), 122.9 (d, C-3″), 124.1 (d, β,β″-C), 131.0 (s, α,α′-C), 134.9 (d, γ,γ′-C), 136.2 (d, C-4″), 149.0 (d, C-6″), 150.9 (s, C-4), 153.6 (s, C-2), 160.6 (s, C-2″) and 164.6 (s, C=C); *m/z* (%) (isobutane CI) 336 (M + 1, 90) and 246 (30) (Found: C, 64.1; H, 3.8; N, 12.4. $C_{18}H_{13}N_3O_2S$ requires C, 64.45; H, 3.9; N, 12.5%).

2-Amino-4-[2-(1,2,3,6-tetrahydro-1-methyl-2-pyridyl)ethyl]-thiazole **27** *and 2-Amino-4-[2-(1,2,5,6-tetrahydro-1-methyl-2-pyridyl)ethyl]thiazole* **31**.—Phthalimide **30** (150 mg, 0.6 mmol) was dissolved in acetonitrile (10 cm^3) and this solution was heated to reflux with stirring. Iodomethane (*ca.* 2 cm^3) was added to the solution in small portions, and heating was continued for 3 h. On cooling, the product crystallised out and the solvent was removed under reduced pressure. The resulting solid was recrystallised from ethanol–methanol to yield the corresponding N^2-methiodide as a yellowish solid (160 mg, 75%), m.p. 205–207 °C; δ_H[270 MHz; $(CD_3)_2SO$] 3.32 (2 H, t, $J_{1,2}$, 1′-H), 3.55 (2 H, t, $J_{1,2}$ 7, 2′-H), 4.35 (3 H, s, CH_3), 7.55 (1 H, s, 5-H), 7.99 (5 H, m, 5″-H, phthalimide-H), 8.08 (1 H, d, $J_{3,4}$ 8, 3″-H), 8.51 (1 H, t, $J_{3,4,5}$ 8, 4′-H) and 9.03 (1 H, d, $J_{5,6}$ 6, 6″-H); δ_H[67.8 MHz; $(CD_3)_2SO$] 28.3 (t, C-1′), 31.2 (t, C-2′), 45.6 (q, CH_3), 115.4 (d, C-5), 124.0 (d, β,β-C), 125.4 (d, C-5″), 128.2 (d, C-3″), 131.0 (s, α,α′-C), 135.4′ (d, γ,γ′-C), 145.0 (d, C-6″), 146.5 (d, C-4′), 150.6 (s, 4-C), 151.5″ (s, C-2), 157.6 (s, C-2″) and 165.0 (s, C=O) (Found: C, 47.7; H, 3.3; N, 8.8. $C_{19}H_{16}IN_3O_2S$ requires C, 47.8; H, 3.4; N, 8.8%).

(*ii*) The methiodide (12.4 g, 26 mmol) was dissolved in ethanol (100 cm^3) and the stirred solution was cooled to 0 °C. Sodium borohydride (2.27 g, 60 mmol) was added and the reaction mixture was allowed to warm to room temperature over 1 h. The solvents were removed under reduced pressure and the residue was successively acidified (2 mol dm^{-3} HCl), basified (Na_2CO_3–NaOH solution) and finally extracted with ethyl acetate. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated. Analysis by TLC indicated however that the organic extract contained no products. The aqueous phase was therefore mixed with propan-2-ol and concentrated under reduced pressure to afford an oil. This was chromatographed on silica gel with 1% ammonia in methanol–chloroform (1:9) to yield the title compound **27** and **31** as a 3:1 mixture (1 g, 17%). Using preparative centrifugally accelerated thin layer radical chromatography, **31** was isolated in the pure state as an oil (294 mg, 5%); $\nu_{max}(CHCl_3)/cm^{-1}$ 3477 and 3407 (NH) and 1600 (C=C); δ_H(270 MHz; $CDCl_3$) 1.87 (2 H, m, 2′-H), 2.00 (1 H, dm, $J_{5,5(gem)}$ 16.5, 5″-H), 2.27 (1 H, m, 5′-H), 2.36 (3 H, s, CH_3), 2.43 (1 H, m, 6″-H), 2.52 (1 H, dd, *J* 10, 1′-H), 2.62 (1 H, dd, *J* 10, *J* 6, 1′-H), 2.72 (1 H, m, 2″-H), 2.87 (1 H, ddd, $J_{6,6}$ 12, $J_{5,6}$ 5, $J_{5,6}$ 4, 6″-H), 5.12–5.22 (2 H, br s, NH_2), 5.58 (1 H, dm, J_{cis} 10, 3″-H), 5.80 (1 H, dm, J_{cis} 10, 4″-H) and 6.09 (1 H, s, 5-H); δ_C(67.8 MHz; $CDCl_3$) 24.9 (t, C-2′), 27.0 (t, C-5″), 31.7 (t, C-1′), 43.0 (q, CH_3), 51.3 (t, C-6″), 61.3 (d, C-2″), 101.9 (d, C-5), 125.4 (d, C-4″), 129.2 (d, C-3″), 152.5 (s, C-4) and 168.2 (s, C-2); *m/z* (%) (isobutane CI) 224 (M + 1, 100), 223 (59), 222 (25), 109 (25) and 96 (82) (Found: M^+, 223.1136. $C_{11}H_{17}N_3S$ requires *M*, 223.1142). COSY analysis: Observed δ_H (assignment) 3.12, 3.00 (6″-H, 6″-H)-cross peaks (assignments) 2.30, 1.95 (3″-H, 3″-H); 2.93 (2″-H)-cross peaks 2.30, 2.05, 1.95, 1.76 (3″-H, 2′-H, 3″-H, 2′-H respectively); 2.71 (1′-H)-cross peaks 2.05, 1.76 (2′-H, 2′-H); 2.30 (3″-H)-cross peak 1.95 (3″-H); 2.05 (2′-H)-cross peak 1.76 (2′-H).

Compound **27** was also isolated pure (706 mg, 12%) and shown to have spectral data identical with those previously recorded.

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