Synthesis of *O*-Vinyl Oximes and Derived Penicillins using Organoselenium Intermediates

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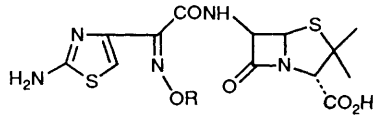
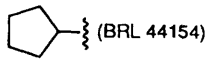
A synthetic scheme is described for the conversion of ethyl 2-hydroxyimino-3-oxobutyrate **3** into ethyl 2-(2-aminothiazol-4-yl)-2-vinyloxyiminoacetate **9** *via* ethyl 2-{[2-(2-nitrophenylselenyl)ethoxy]-imino}-3-oxobutyrate **5**. The analogous 2-(1-phenylvinyloxyimino) **22** and 2-(isopropenyloxyimino) **23** esters were obtained similarly from ethyl 2-hydroxyimino-3-oxobutyrate **3** or the corresponding methyl ester **25** by routes involving the epoxide-derived β-hydroxy selenides 2-(2-nitrophenylselenyl)-1-phenylethanol **14** and 1-(2-nitrophenylselenyl)propan-2-ol **15**. Subsequently ethyl 2-(2-amino-thiazol-4-yl)-2-vinyl- **9** and 2-(1-phenylvinyl)-oxyiminoacetate **22** were successfully converted into the corresponding 6β-(substituted acetamido)penicillin sodium salts **11** and **24**.

A recent publication from these laboratories[1] described the preparation of penicillins **1** and **2** which were distinguished by their broad-spectrum activity against Gram-positive and Gram-negative bacteria and good stability to β-lactamases. As part of the programme, we naturally investigated the synthesis of analogues of compounds **1** and **2** bearing other oxime substituents including, in the present instance, the rather rare *O*-vinyl oxime moiety. Despite the plethora of semi-synthetic β-lactams, especially cephalosporins, containing a [2-(alkyl-oximino)-2-(2-aminothiazol-4-yl)]acetamido side-chain,[2] very few examples have alluded to *O*-vinyl oximes either as final products or as intermediates.[3] Our route was designed to introduce the double bond at a late stage, in view of the possible instability of such systems to acidic or even aqueous conditions. Some preliminary experiments showed that the elimination of hydrogen halide from *O*-(2-halogenoethyl) oximes[4] could not be effected in the presence of a (2-aminothiazol-4-yl) substituent. The use of organoselenium intermediates which could release a vinyl oxime by a mild oxidation–elimination sequence, potentially at a late stage, appeared to offer an attractive solution.



1 R =  (BRL 44154)

2 R = Bu^t

The successful synthesis, illustrated for the unsubstituted vinyl system initially, is shown in Scheme 1. Alkylation of oxime **3**[5] with 2-bromoethanol was effected by using potassium carbonate as base in excellent yield; the resulting alcohol **4** showed no tendency towards lactonisation. Reaction of this product with *o*-nitrophenyl selenocyanate and tributylphosphine according to Grieco's procedure[6] afforded the nicely crystalline selenide **5** in high yield. Monobromination of this ketone [best effected by treatment with trimethylsilyl trifluoromethanesulphonate, then *N*-bromosuccinimide (NBS)] was followed, without purification, by closure to the aminothiazole **6** as the single *Z*-isomer shown (characteristic chemical shift of the ring 2-proton);[2] we believe that earlier intermediates in the sequence are also single *Z*-isomers.

Initially we planned to generate the *O*-vinyl oxime only at the very last step, and consequently ester **6** was hydrolysed to the amino acid **7** in high yield. This product was satisfactorily coupled to 6-aminopenicillanic acid (6-APA) by using a known mixed anhydride-type procedure[1,7] to give the penicillin **8**. However, we were disappointed to find that selective oxidation of this product at selenium could not be effected, a complex mixture of products resulting. Hence we returned to the ester **6**; this material could be oxidised by using 3-chloroperbenzoic acid (MCPBA), but Clive's procedure[8] using sodium periodate gave a significantly better yield. Elimination from the selenoxide to give the vinyl oxime was sluggish; it was known[9] that, when the selenoxide has a choice, it prefers to eliminate away from oxygen.* Here, however, we found that the desired vinyl oxime *was* produced where the selenoxide had no choice. It was possible to heat the mixture after oxidation was complete to accelerate elimination, but best of all was to isolate the selenoxide into an organic solvent and simply store it over a drying agent ($MgSO_4$) in the presence of triethylamine,[11] at ambient temperature. This gave an excellent yield of *O*-vinyl oxime **9**. A recent example of the synthesis of an *O*-vinyl *ether* by selenoxide elimination[12] is quite comparable. The crystalline ester **9** was easily obtained microanalytically pure and could be stored at ambient temperature for months with little decomposition.

On base hydrolysis of ester **9**, the acid **10** was obtained in good yield, and proved stable enough for isolation by extraction from aqueous solution at pH 2 and storage. In this case, coupling to 6-APA was best effected by an active-ester procedure[13] to give the penicillin **11** in fair yield.

The necessary intermediates for the synthesis of analogues of compound **11** were generated by the known selenide anion opening of epoxides.[9] Hence, reaction of (*RS*)-2-phenyloxirane **12** with 2-nitrophenyl selenocyanate and sodium borohydride afforded a separable 1:1 mixture of β-hydroxy selenides **14** and **16** in 86% yield. In this case, reaction of isomer **14** with oxime **3** was achieved by Mitsunobu-type etherification[14] [triphenylphosphine–di*methyl* azodicarboxylate (DMAD)], giving a satisfactory yield of oxime ether **17**. While our earlier work[1] had shown that this isomer, in which the bulky phenyl substituent was α- to the oxime, was more likely to give the important property of good β-lactamase stability in the final penicillin (*cf.* the biological activity of compound **11**, quoted later), a very

* This was true in all examples studied by Sharpless.[9] A more recent acyclic example[10] demonstrated ready oxidation of a β-hydroxy selenide to a ketone, however, by using excess of MCPBA in methanol.

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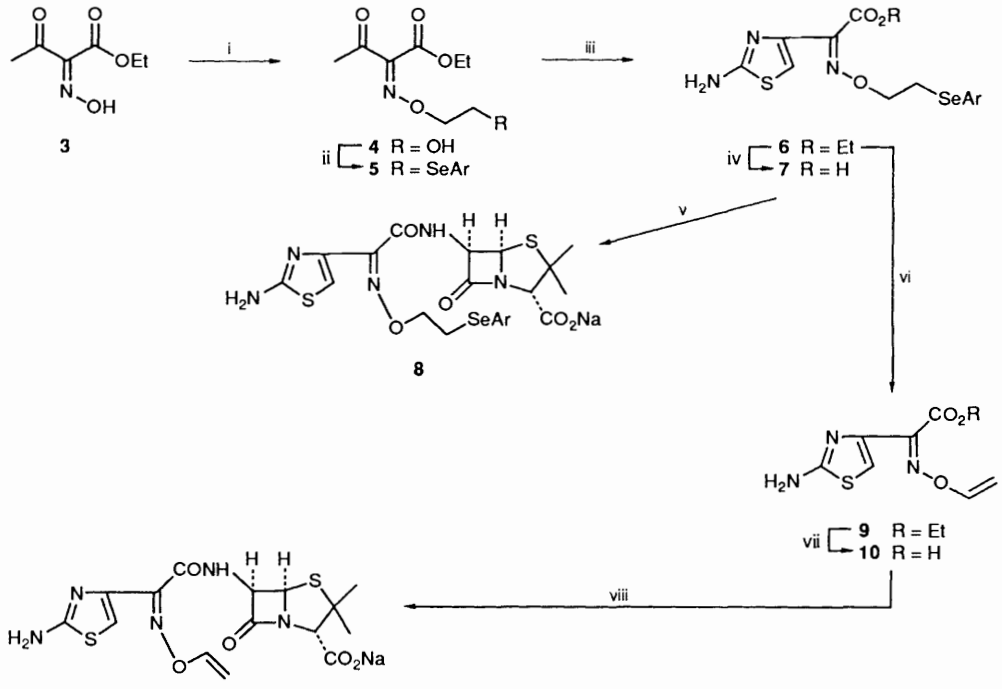
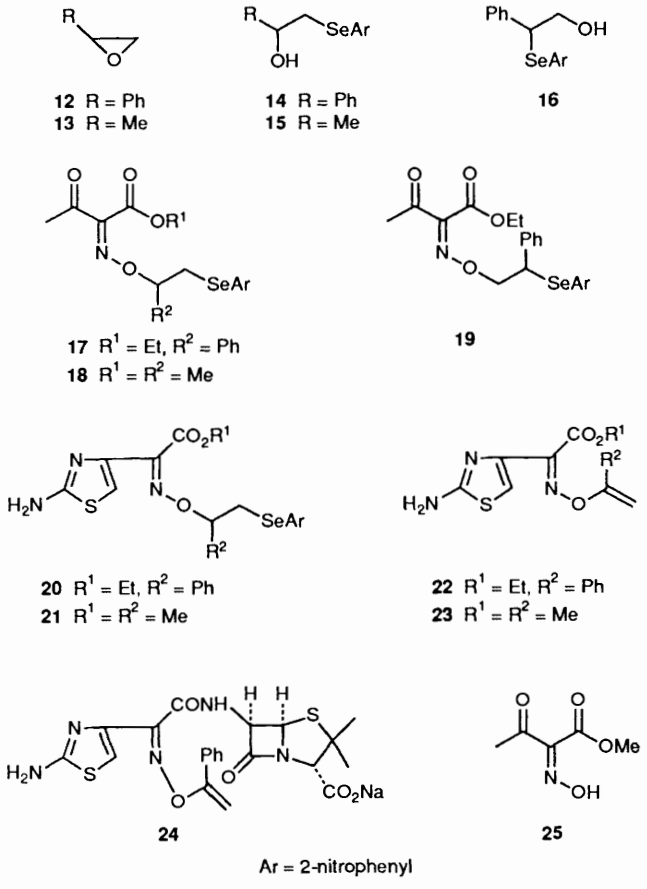


Scheme 1 Synthesis of an *O*-vinyloxyimino penicillin; Ar = 2-nitrophenyl. *Reagents and conditions*: i, $Br[CH_2]_2OH$, K_2CO_3, DMF, 91%; ii, ArSeCN, Bu_3P, THF, 86%; iii, $CF_3SO_3SiMe_3$, Et_3N; then NBS, then $(H_2N)_2C{=}S$, $PhNMe_2$, EtOH, 78%; iv, NaOH, aq. EtOH, 89%; v, $MeSO_2Cl$, Pr^i_2EtN, DMF; then 6-APA, CH_2Cl_2, Et_3N, 25%; vi, $NaIO_4$, aq. THF; isolate selenoxide; Et_3N, 87%; vii, NaOH, aq. MeOH, 83%; viii, *N*,*N*′-dicyclohexylcarbodiimide, 1-hydroxybenzotriazole; then 6-APA, Et_3N, 44%.

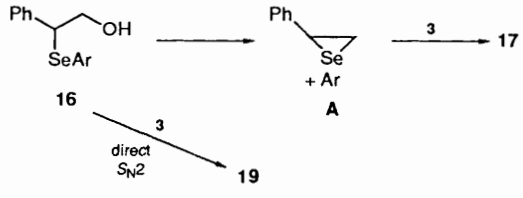


interesting result was nevertheless obtained in the Mitsunobu coupling of the isomeric β-hydroxy selenide **16** to oxime **3**. This afforded a roughly 2:1, chromatographically inseparable, mixture of the previous oxime ether **17** with the expected product **19**. Participation by selenium, assisted in this case by the phenyl substituent, may give rise to an episelenonium-type cationic species[11] as postulated in the well known reductive elimination of β-hydroxy selenides to give olefins.†

Bromination of intermediate **17** followed by closure to the aminothiazole **20**, then selenoxide formation and elimination, produced the desired ester **22** as in the unsubstituted series (Scheme 1). In this case, the product from base hydrolysis of ester **22** was of borderline stability and indeed could not be purified in the acid form. However, prompt coupling of this material to 6-APA as above gave a modest yield of the desired penicillin **24**, which had adequate aqueous stability as the sodium salt for antibacterial testing.

The selenide anion opening of (*RS*)-2-methyloxirane **13**, in contrast, gave the *single* regioisomer **15** in excellent yield (94%). This alcohol was progressed similarly, *viz*. by Mitsunobu condensation, this time on the methyl ester **25**, to give oxime ether **18**, bromination and thiourea treatment to give the aminothiazole **21**, and selenoxide formation–elimination to the

† It may be that the primary alcohol **16** reacts partly *via* direct S_N2 displacement and partly *via* a selenonium intermediate **A**:



In this case one has to postulate that **A** reacts very largely at the benzylic carbon (S_N1-like) giving only compound **17**; secondary alcohol **14** reacts only *via* **A**, giving compound **17**. I am grateful to Dr A. W. Taylor for suggesting this mechanism.

Table 1 Minimum inhibitory concentrations (MICs) in μg cm^{-3} of penicillins against selected organisms. MICs were measured by serial dilution in nutrient agar against inocula of 1 × 10^6 colony-forming units per cm^3, following incubation at 37 °C for 18 h

	BRL 44154			
	11	**24**	**8**	**1**
Staphylococcus aureus Oxford	0.5	2.0	1.0	0.5
Staphylococcus aureus MB9[a]	16	4.0	8.0	1.0
Haemophilus influenzae Q1	0.25	1.0	1.0	0.06
Haemophilus influenzae NEMC1[a]	8	4.0	4.0	0.5

[a] β-Lactamase-producing strains.

O-vinyl derivative **23**. Attempted base hydrolysis of this ester, however, gave only decomposition.

Biological Results.—The antibacterial activity of penicillins **8**, **11** and **24** against pairs of β-lactamase-producing and non-β-lactamase-producing organisms is shown in Table 1, contrasted with that of BRL 44154 **1**. It will be seen that compound **11** maintained good intrinsic activity against non-β-lactamase-producing strains but was less stable to β-lactamases than was compound **1**. Analogue **24** was less active but more stable than compound **11**, while the intermediate penicillin **8** was only a little less stable than compound **24** against staphylococcal β-lactamase and was of moderate intrinsic activity.

Experimental

Abbreviations used for common solvents are DMF (*N,N*-dimethylformamide) and THF (tetrahydrofuran). Organic extracts were finally washed with saturated brine and dried over anhydrous magnesium sulphate prior to rotary evaporation at or below 30 °C under reduced pressure. Solids were dried *in vacuo* over P_2O_5. Solution pHs were measured with a Pye Unicam instrument using a glass electrode. M.p.s were determined using a Büchi oil-immersion apparatus or a Köfler hot-stage and are uncorrected. Unless otherwise noted, IR spectra were recorded for KBr discs in a Perkin-Elmer 457 instrument. ^{1}H NMR spectra were recorded on a Bruker WM250 instrument at 250 MHz unless otherwise stated, using an appropriate internal standard in the solvent quoted; all δ-values quoted are δ_H and coupling constants *J* are in Hz. Mass spectra were recorded using a VG 7070 instrument for the electron-impact mode (EI) or a VG ZAB instrument for the chemical ionisation mode (CI) or the fast-atom bombardment mode (FAB). Homogeneity of all products quoted was assessed by TLC on Merck silica gel 60 F_{254} plates, and by analytical HPLC on a Waters μBondapak™ C_{18} reversed-phase column where appropriate. Preparative chromatography was performed on Merck silica gel 7729 (finer than 230 mesh ASTM).

Ethyl 2-[(2-*Hydroxyethoxy*)*imino*]-3-*oxobutanoate* **4**.—Ethyl 2-hydroxyimino-3-oxobutanoate **3**[5] (3.98 g, 25 mmol) was dissolved in anhydrous DMF (20 cm^3) and the solution was stirred at ambient temperature with anhydrous potassium carbonate (3.8 g, 27.5 mmol) and 2-bromoethanol (3.55 cm^3, 6.25 g, 50 mmol). After 17 h, the mixture was poured into water and extracted with ethyl acetate (2 ×); the combined extracts were washed with water and evaporated to give a crude product (5.7 g), which was purified by column chromatography, applied in toluene solution and eluted with ethyl acetate–hexane (1:2, then 1:1). Appropriate fractions (TLC) were pooled and evaporated to give the *title alcohol* as an oil (4.60 g, 91%); ν_{max}(CHCl$_3$)/cm^{-1} 3500br, 1810, 1780, 1740br, vs, 1690 and 1600; δ(60 MHz; CDCl$_3$) 1.30 (3 H, t, *J* 7, *Me*CH$_2$O), 2.30 (3 H, s, MeCO), 2.60 (1 H, brs, D$_2$O exch, OH), 3.85 (2 H, m, sharpened on D$_2$O exch, C*H*$_2$OH) and 4.10–4.50 (4 H, 2m, 2 × CH$_2$O); *m/z* (CI; NH$_3$) MNH$_4^+$, 221 (45%) and MH$^+$, 204 (25). An *analytical sample* was obtained by double Kugelrohr distillation, bath temp. 230 °C at 2 mmHg, the distillate being slightly hygroscopic (Found: C, 47.3; H, 6.5; N, 6.55. $C_8H_{13}NO_5$ requires C, 47.3; H, 6.4; N, 6.9%).

Ethyl 2-({2-[(2-*Nitrophenyl*)*seleno*]*ethoxy*}*imino*)-3-*oxobutanoate* **5**.—2-Nitrophenyl selenocyanate (0.82 g, 3.6 mmol)[6] was added to a solution of the alcohol **4** (0.61 g, 3 mmol) in anhydrous THF (12 cm^3). The solution was cooled to 0 °C, stirred under argon, and treated with tributylphosphine (0.89 cm^3, 0.72 g, 3.6 mmol). The solution was allowed to regain ambient temperature, and after 0.25 h (when reaction appeared complete by TLC) it was evaporated to give a red oil (2.2 g). Chromatography (application in toluene and elution with ethyl acetate–hexane mixtures) afforded a yellow oil, which on brief trituration with hexane deposited fine yellow needles that were filtered off, washed with a little hexane, and dried to give the *selenide* **5** (1.00 g, 86%), m.p. 88–89 °C (from ethyl acetate–hexane) (Found: C, 43.2; H, 4.2; N, 7.2. $C_{14}H_{16}N_2O_6Se$ requires C, 43.4; H, 4.1; N, 7.2%); ν_{max}(CHCl$_3$)/cm^{-1} 1740, 1695, 1595, 1510 and 1335; δ(CDCl$_3$) 1.35 (3 H, t, *J* 7, *Me*CH$_2$O), 2.43 (3 H, s, MeCO), 3.27 (2 H, t, *J* 7, SeC*H*$_2$CH$_2$O), 4.36 (2 H, q, *J* 7, CH$_3$C*H*$_2$O), 4.58 (2 H, t, *J* 7, OC*H*$_2$CH$_2$Se), 7.25–7.60 (3 H, m, ArH) and 8.32 (1 H, m, ArH); *m/z* (EI) M$^+$, 388 (6%).

Ethyl 2-(2-*Aminothiazol*-4-*yl*)-2-[(Z)-{2-[(2-*nitrophenyl*)*seleno*]*ethoxy*}*imino*]*acetate* **6**.—A solution of the selenide **5** (1.05 g, 2.71 mmol) in dichloromethane (10 cm^3) was stirred at ambient temperature and treated sequentially with trimethylsilyl trifluoromethanesulphonate (0.75 cm^3, 0.86 g, 3.9 mmol) and triethylamine (0.55 cm^3). After 0.5 h, NBS (0.69 g, 3.9 mmol) was added in one portion and the mixture was stirred for a further 0.5 h. The solution was diluted with ethyl acetate (40 cm^3), washed successively with dil. aq. sodium hydrogen carbonate, dil. aq. sodium thiosulphate, and water, and evaporated to give a crude bromo ketone (1.33 g), which was sufficiently pure to use directly; NMR analysis showed loss of the signal at δ 2.43 (3 H, s) in compound **5** and the appearance of a new signal at δ 4.40 (2 H, s).

This product was suspended in ethanol (16 cm^3) and the mixture was stirred at ambient temperature with *N,N*-dimethylaniline (0.35 cm^3) and thiourea (0.26 g, 3.42 mmol). After 2 h, the solution was concentrated to low volume, diluted with ethyl acetate, and washed with water (2 ×). Following evaporation, the residue (1.17 g) was chromatographed, and elution with ethyl acetate–hexane mixtures (30–100% ethyl acetate) afforded, after pooling and evaporation of appropriate fractions, the *aminothiazole* **6** as a yellow solid (0.93 g, 78%), m.p. 138–139 °C (from ethyl acetate–hexane) (Found: C, 40.7; H, 3.4; N, 12.4; S, 7.2%. $C_{15}H_{16}N_4O_5SSe$ requires C, 40.6; H, 3.6; N, 12.6; S, 7.2%); ν_{max}/cm^{-1} 3430, 1726, 1613, 1590, 1504, 1437, 1408 and 1332; δ(CDCl$_3$) 1.39 (3 H, t, *J* 7, *Me*CH$_2$O), 3.26 (2 H, t, *J* 7, OCH$_2$C*H*$_2$Se), 4.42 (2 H, q, *J* 7, MeC*H*$_2$O), 4.54 (2 H, t, *J* 7, OC*H*$_2$CH$_2$Se), 5.36 (2 H, br s, D$_2$O exch, NH$_2$), 6.76 (1 H, s, 5-H), 7.33 and 7.58 (3 H, 2 m, ArH) and 8.30 (1 H, approx. dd, ArH); *m/z* (EI) M$^+$, 444 (5%).

2-(2-*Aminothiazol*-4-*yl*)-2-[(Z)-{2-[(2-*nitrophenyl*)*seleno*]*ethoxy*}*imino*]*acetic Acid* **7**.—A solution of the ester **6** (0.22 g, 0.50 mmol) in THF (1 cm^3)–ethanol (1 cm^3) was stirred at ambient temperature with 1 mol dm^{-3} aq. sodium hydroxide (1.5 cm^3). After 2 h further THF (0.5 cm^3) was added to improve solubility; after 19 h, when no ester could be detected by TLC, the solution was evaporated to dryness, the residue was redissolved in water (10 cm^3), and the solution was washed with

ethyl acetate (2 ×). The aq. phase was separated, then acidified to pH 3 with 2 mol dm^{-3} hydrochloric acid and cooled to complete precipitation. The yellow solid was filtered off, washed successively with a little cold water and then with diethyl ether, and dried to give the *amino acid* **17** (0.185 g, 89%), m.p. 166–168 °C (with darkening) (Found: C, 36.8; H, 2.8; N, 13.3; S, 7.4. $C_{13}H_{12}N_4O_5SSe \cdot 0.5\ H_2O$ requires C, 36.8; H, 3.1; N, 13.2; S, 7.5%); ν_{max}/cm^{-1} 3600–2100br, 1647, 1605sh, 1590, 1565, 1506 and 1330; $\delta[(CD_3)_2SO]$ 3.32 (2 H, t, *J* 7, OCH_2CH_2Se), 4.37 (2 H, t, *J* 7, OCH_2CH_2Se), 6.93 (1 H, s, 5-H), 7.28 (2 H, br s, D_2O exch, NH_2), 7.49 and 7.80 (3 H, 2 m, ArH), 8.30 (1 H, approx. dd, ArH) and 14.5 (1 H, br s, D_2O exch, CO_2H); *m/z* (positive FAB; glycerol) MH^+, 417 (27%).

Sodium 6β-{2-(2-*Aminothiazol*-4-*yl*)-2-[(Z)-{2-[(2-*nitrophenyl*)*seleno*]*ethoxy*}*imino*]*acetamido*}*penicillanate* **8**.—A solution of the rigorously dried amino acid **7** (0.108 g, 0.26 mmol) in DMF (0.5 cm^3) was stirred at −60 °C under argon and treated with ethyl(diisopropyl)amine (0.045 cm^3, 0.036 g, 0.28 mmol), then with methanesulphonyl chloride (0.025 cm^3, 0.037 g, 0.32 mmol).[7] The mixture was stirred for 1 h and the temperature was allowed to rise to −30 °C: meanwhile 6-APA (0.065 g, 0.30 mmol) was dissolved by being stirred in dichloromethane (1 cm^3) containing triethylamine (0.1 cm^3). The two solutions were combined, allowed to regain ambient temperature, and stirred for 0.5 h, then poured into water and washed with diethyl ether (2 ×). The aq. phase was separated, acidified to pH 2 with 2 mol dm^{-3} hydrochloric acid, and extracted with ethyl acetate (2 ×). The combined organic extracts were washed with water (2 ×) and evaporated to give a yellow solid, which was dissolved in THF (10 cm^3) and diluted with ethyl acetate (10 cm^3); water was added and the pH adjusted to 7 by using dil. aq. sodium hydrogen carbonate. The aq. phase was separated, the organic phase was again washed with water, and the combined aq. extracts were concentrated and lyophilised to give a crude product (0.145 g). Purification was effected by chromatography on HP20SS resin ('Diaion'), eluted with THF–water mixtures, to give, after pooling and lyophilisation of appropriate fractions, the title penicillin **8** as a fluffy yellow solid (0.041 g, 25%); ν_{max}/cm^{-1} 1768, 1669, 1611, 1565w, 1511 and 1332; $\delta(D_2O)$ 1.41 and 1.51 (6 H, 2 s, Me_2C), 3.33 (2 H, t, *J* 6, OCH_2CH_2Se), 4.16 (1 H, s, 3-H), 4.52 (2 H, t, *J* 6, OCH_2CH_2Se), 5.46 (2 H, ABq, *J* 4, 5- + 6-H), 6.97 (1 H, s, thiazole 5-H) and 7.38, 7.66 and 8.27 (4 H, 3m, ArH); *m/z* (positive FAB; thioglycerol) MH^+, 637 (base peak) and 615 (MH^+, free acid, 45%).

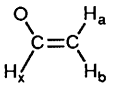
Ethyl 2-(2-*Aminothiazol*-4-*yl*)-2-[(Z)-*vinyloxyimino*]*acetate* **9**.—A solution of the ester **6** (0.600 g, 1.35 mmol) in THF (30 cm^3) was stirred at ambient temperature and treated with aq. sodium metaperiodate (0.863 g, 4.05 mmol in 15 cm^3). Further water was added at intervals to maintain a clear solution; after 5 h, when no starting ester was visible by TLC, the solution was diluted with ethyl acetate and washed with half-saturated aq. sodium hydrogen carbonate. The organic phase was separated, the aq. phase was washed with further ethyl acetate, and the total organic extract was stored over anhydrous magnesium sulphate in the presence of triethylamine (0.3 cm^3)[11] at ambient temperature. After 19 h the drying agent was filtered off, then the filtrate was evaporated and the residue was redissolved in 5% methanol–chloroform, then chromatographed and eluted with ethyl acetate–hexane mixtures. Pooling and evaporation of appropriate fractions gave the *vinyl oxime* **9** as a pale yellow solid (0.296 g, 89%), m.p. 108.5–109.5 °C (from ethyl acetate–hexane) (Found: C, 44.85; H, 4.4; N, 17.0; S, 13.2%; M^+, 241.0524. $C_9H_{11}N_3O_3S$ requires C, 44.8; H, 4.6; N, 17.4; S, 13.3%; M, 241.0519); ν_{max}/cm^{-1} 3447, 3269, 1716, 1639, 1616 and 1544; $\delta(CDCl_3)$ 1.40 (3 H, t, *J* 7, $MeCH_2O$), 4.24 (1 H, dd, *J* 6.5 and 2, vinyl H_b),* 4.45 (2 H, q, *J* 7, $MeCH_2O$), 4.66 (1 H, dd, *J* 14 and 2, vinyl H_a), 5.40 (2 H, br s, D_2O exch, NH_2), 6.84 (1 H, s, 5-H) and 7.00 (1 H, dd, *J* 14 and 6.5, vinyl H_x). This substance could be stored for some months at ambient temperature with only slight degradation.

2-(2-*Aminothiazol*-4-*yl*)-2-[(Z)-*vinyloxyimino*]*acetic Acid* **10**.—A solution of the ester **9** (0.153 g, 0.64 mmol) in THF–ethanol (1:1; 2.5 cm^3) was treated with 1 mol dm^{-3} aq. sodium hydroxide (1.90 cm^3) and stirred at ambient temperature for 16 h. Water (10 cm^3) was added, then the solution was washed with ethyl acetate (2 ×). The aq. phase was saturated with sodium chloride, acidified to pH 2.5 with 2 mol dm^{-3} hydrochloric acid, and extracted with THF (5 × 20 cm^3). The combined extracts were stirred for 0.5 h with anhydrous magnesium sulphate, then the drying agent was filtered off, the filtrate was evaporated to dryness, and the residue was triturated with water (3 cm^3) to deposit a solid. After being cooled to complete precipitation, the solid was filtered off, washed with a little cold water, and dried to give the *title acid* **10** (0.112 g, 83%, in two crops), m.p. >230 °C (from ethanol–methanol–water) (Found: C, 36.4; H, 3.8; N, 17.9; S, 14.1; M^+, 213.0203. $C_7H_7N_3O_3S \cdot H_2O$ requires C, 36.4; H, 3.9; N, 18.2; S, 13.9%; M, 213.0208); ν_{max}/cm^{-1} 3259br, 1635, 1611, 1570sh, and 1458; $\delta[(CD_3)_2SO]$ 4.25 (1 H, dd, *J* 6.7 and 1.7, vinyl H_b),* 4.61 (1 H, dd, *J* 14 and 1.7, vinyl H_a), 6.95 (1 H, dd, *J* 14 and 6.7, vinyl H_x), 7.05 (1 H, s, 5-H) and 7.35 (2 H, br s, D_2O exch, NH_2).

Sodium 6β-{2-(2-*Aminothiazol*-4-*yl*)-2-[(Z)-*vinyloxyimino*]-*acetamido*}*penicillanate* **11**.—A solution of the acid **10** (0.055 g, 0.26 mmol) and 1-hydroxybenzotriazole[13] monohydrate (0.050 g, 0.33 mmol) in DMF (1 cm^3) was stirred at 0 °C and *N*,*N*′-dicyclohexylcarbodiimide (0.055 g, 0.27 mmol) was added; TLC analysis after 0.5 h showed no starting acid. Meanwhile 6-APA (0.070 g, 0.32 mmol) was solubilised in dichloromethane–triethylamine as described for the preparation of compound **8**. The solutions were combined, and then were stirred at ambient temperature for 4 h. The mixture was filtered, the precipitate was washed with a little DMF, and the combined filtrate and washings were worked up to afford a sodium salt as described under compound **8**. The crude yellow lyophilised product (0.165 g) was purified by HP20SS chromatography by using 0–4% THF in water; appropriate fractions (HPLC) were pooled, concentrated, and lyophilised to give the title penicillin **11** (0.049 g, 44%); ν_{max}/cm^{-1} 1768, 1665, 1636, 1610 and 1532; $\delta(D_2O)$ 1.50 and 1.59 (6 H, 2 s, Me_2C), 4.23 (1 H, s, 3-H), 4.33 (1 H, dd, *J* 6.5 and 2, vinyl H_b), 4.74 (1 H, dd, *J* 14 and 2, vinyl H_a), 5.63 (2 H, s, 5- + 6-H), 6.94 (1 H, dd, *J* 14 and 6.5, vinyl H_x) and 7.14 (1 H, s, thiazole 5-H); *m/z* (positive FAB; glycerol) MH^+, 434 (8%) and MNa^+, 456 (4).

(RS)-2-[(2-*Nitrophenyl*)*seleno*]-1-*phenylethanol* **14** *and* (*RS*)-2-[(2-*nitrophenyl*)*seleno*]-2-*phenylethanol* **16**.—A solution of 2-nitrophenyl selenocyanate (0.91 g, 4.0 mmol) in THF (5 cm^3)–ethanol (15 cm^3) was stirred under argon at 0 °C and sodium borohydride (0.16 g, 4.4 mmol) was added (**CARE**! HCN evolved). After 0.5 h the solid had largely dissolved to give a dark red solution; (*RS*)-2-phenyloxirane **12** (0.6 g, 5.0 mmol) was added, then the mixture was allowed to regain ambient temperature and stirred for 16 h. 2 Mol dm^{-3} hydrochloric acid (3 cm^3) was added (the solution lightened in colour noticeably),

* Denoting the vinyl group as



then ethyl acetate was added and the solution was washed successively with saturated aq. sodium hydrogen carbonate and water. Evaporation gave a yellow solid (1.6 g), which was carefully chromatographed and eluted with ethyl acetate–hexane mixtures. The less polar product, after pooling and evaporation of appropriate fractions, then trituration with hexane, filtration, washing with a little hexane, and drying, afforded the *secondary alcohol* **14** (0.56 g, 43%) as a yellow solid, m.p. 70–71 °C (Found: C, 52.1; H, 3.9; N, 4.4%; M, 323.0064. $C_{14}H_{13}NO_3Se$ requires C, 52.2; H, 4.0; N, 4.3%; M, 323.0061); ν_{max}(Nujol)/cm^{-1} 3250, 1590, 1565, 1505, 1325 and 1300; δ($CDCl_3$) 2.44 (1 H, br s, D_2O exch, OH), 3.31 (2 H, dd, *J* 6.5 and 1, $SeCH_2CHOH$), 5.02 (1 H, approx. t, *J* 6.2, $OCHCH_2$), 7.25–7.65 (8 H, m, ArH) and 8.28 (1 H, dd, *J* 8.2 and 1.3, ArH). Further elution of the column gave a more polar product; pooling and evaporation of appropriate fractions, trituration with hexane, *etc.* as for compound **14** afforded the isomeric *primary alcohol* **16** (0.55 g, 43%), m.p. 84–86 °C (Found: C, 52.1; H, 3.9; N, 4.4%; M^+, 323.0061); ν_{max}(Nujol)/cm^{-1} 3520, 1585, 1565, 1500, 1330 and 1300; δ($CDCl_3$) 1.84 (1 H, br s, D_2O exch, OH), 4.14 (2 H, m, $CHCH_2OH$; AB of ABX), 4.66 (1 H, dd, $SeCHCH_2$; X of ABX), 7.25–7.55 (8 H, m, ArH) and 7.70 (1 H, dd, *J* 8.2 and 1.2, ArH).

Ethyl 2-[(Z)-{(1RS)-2-[(2-*Nitrophenyl*)*seleno*]-1-*phenyl ethoxy*}*imino*]-3-*oxobutanoate* **17**.—A solution of the oxime **3** (0.24 g, 1.50 mmol), triphenylphosphine (0.43 g, 1.65 mmol) and the secondary alcohol **14** (0.53 g, 1.65 mmol) in anhydrous toluene (5 cm^3) was stirred under argon at 0 °C and DMAD (0.22 cm^3, 0.24 g, 1.65 mmol) was added dropwise. The mixture was stirred for 16 h and was then allowed to regain ambient temperature, then it was heated at 70 °C for 2 h, when TLC indicated complete reaction. The yellow solution was diluted with ethyl acetate, washed with water (3 ×), and evaporated to give a crude product (1.27 g). Chromatography (application in toluene and elution with up to 20% ethyl acetate in hexane) afforded, on pooling and evaporation of appropriate fractions, the *title compound* **17** as a yellow foam (0.22 g, 32%) (Found: M, 464.0482. $C_{20}H_{20}N_2O_6Se$ requires M, 464.0487); δ($CDCl_3$) 1.35 (3 H, t, *J* 7, $MeCH_2O$), 2.34 (3 H, s, MeCO), 3.34 (1 H, dd, *J* 12.5 and 6.3, $CHCHHSe$), 3.55 (1 H, dd, *J* 12.5 and 7.5, $CHCHHSe$; AB of ABX), 4.37 (2 H, q, *J* 7, $MeCH_2O$), 5.58 (1 H, dd, *J* 7.1 and 6.6, $OCHCH_2Se$; X of ABX), 7.30–7.55 (8 H, m, ArH) and 8.33 (1 H, d, ArH).

Mitsunobu Coupling of Alcohol **16**.—A solution of oxime **3** (0.24 g, 1.5 mmol), triphenylphosphine (0.43 g, 1.65 mmol), and the primary alcohol **16** (0.53 g, 1.65 mmol) in toluene (5 cm^3) was allowed to react with DMAD (0.22 cm^3, 0.24 g, 1.65 mmol) as described for the preparation of compound **17**, but for 65 h at ambient temperature and with no heating. Work-up and chromatography as for compound **17** afforded an apparently homogeneous product (TLC in different ethyl acetate–hexane mixtures) as a yellow foam (0.442 g, 64%); NMR spectroscopy revealed this to be a mixture of compound **17** and *ethyl* 2-[(Z)-{(2*RS*)-[2-(2-*nitrophenyl*)-2-*phenylseleno*]*ethoxy*}*imino*]-3-*oxobutanoate* **19**, which showed distinctive signals at δ($CDCl_3$) 1.18 (3 H, t, *J* 7, $MeCH_2O$), 2.33 (3 H, s, MeCO), 4.23 (2 H, q, *J* 7, $MeCH_2O$), 4.65–4.90 [3 H, m, $OCH_2CH(Ph)Se$]; ArH similar to compound **17**, extra signals at δ 7.70 (approx. d) and 8.37 (dd); ratio **17**:**19** ≅ 5:3; mass spectral data as for its isomer **17**.

Ethyl 2-(2-*Aminothiazol*-4-*yl*)-2-(Z)-[{(1RS)-2-[(2-*nitrophenyl*)*seleno*]-1-*phenylethoxy*}*imino*]*acetate* **20**.—A solution of the selenide **17** (0.220 g, 0.475 mmol) in dichloromethane (2 cm^3) was treated sequentially with trimethylsilyl trifluoromethanesulphonate and triethylamine, then with NBS as described above for compound **5**. The reaction was completed and the mixture was worked up as described under the preparation of compound **6**, the intermediate product (0.256 g) showing δ(60 MHz; $CDCl_3$), *inter alia*, 4.2 (2 H, s) and loss of the δ 2.34 signal in compound **17**. This product was dissolved in ethanol (2.5 cm^3) and the solution was stirred at ambient temperature with *N*,*N*-dimethylaniline (0.072 cm^3) and thiourea (0.43 g, 0.57 mmol). After 1.5 h, the solution was worked up as for compound **6**, to give, after chromatography, the *title compound* **20** as a pale yellow solid (0.179 g, 73%), m.p. 172–174 °C (Found: C, 48.6; H, 3.8; N, 10.6; S, 6.0, M, 520.0322. $C_{21}H_{20}N_4O_5SSe$ requires C, 48.6; H, 3.9; N, 10.8; S, 6.2%; M, 520.0320); ν_{max}/cm^{-1} 3443, 3243w, 1728, 1611, 1591, 1565, 1535, 1508, 1452w and 1328; δ($CDCl_3$) 1.41 (3 H, t, *J* 7, $MeCH_2O$), 3.30 and 3.46 (2 H, 2 dd, $OCHCH_2Se$; AB of ABX), 4.34 (2 H, 2q, *J* 7, $MeCH_2O$), 5.44 (2 H, br s, NH_2), 5.54 (1 H, approx. t, $OCHCH_2Se$; X of ABX), 6.65 (1 H, s, 5-H), 7.25–7.55 (8 H, m ArH) and 8.27 (1 H, approx. d, *J* 7.8, ArH).

Ethyl 2-(2-*Aminothiazol*-4-*yl*)-2-[(Z)-1-*phenylvinyloxyimino*]*acetate* **22**.—The aminothiazole **20** (0.152 g, 0.29 mmol) was suspended in THF–ethanol (1:1; 4 cm^3) and treated with aq. sodium metaperiodate (0.069 g, 0.32 mmol in 2.5 cm^3). Then, equal amounts of the same oxidant were added after the mixture had been stored at ambient temperature for 2.5 and 18 h, then the solution was heated for 1.5 h at 60 °C, when no starting material or intermediate selenoxide could be seen by TLC. Work-up as for compound **9**, with no filtration needed, afforded a crude product (0.099 g) which, after chromatography, eluting with ethyl acetate–hexane (1:3, then 1:2), afforded the *vinyl oxime* **22** (0.042 g, 45%) as a semi-solid (Found: M, 317.0827. $C_{15}H_{15}N_3O_7S$ requires M, 317.0834); δ($CDCl_3$) 1.37 (3 H, t, *J* 7, $MeCH_2O$), 4.45 (2 H, q, *J* 7, $MeCH_2O$), 4.93 and 5.09 (2 H, dd, *J* 2, geminal vinyl Hs), 5.45 (2 H, br s, D_2O exch, NH_2), 6.97 (1 H, s, 5-H), 7.30–7.45 (3 H, m, ArH) and 7.57 (2 H, m, ArH); *m*/*z* (EI) M^+, 317 (9%) and $(M - CO_2Et)^+$, 244 (67).

Sodium 6β-{2-(2-*Aminothiazol*-4-*yl*)-2-[(Z)-1-*phenylvinyloxyimino*]*acetamido*}*penicillanate* **24**.—A solution of the ester **22** (0.039 g, 0.123 mmol) in THF–ethanol (1:1; 1 cm^3) was treated with 1 mol dm^{-3} aq. sodium hydroxide (0.37 cm^3) and was then stirred at ambient temperature for 48 h. The dark solution was diluted with water and washed with ethyl acetate (2 ×), then the aq. phase was saturated with sodium chloride, acidified to pH 2 with 2 mol dm^{-3} hydrochloric acid, and extracted with THF. The organic phase was separated, stirred with anhydrous magnesium sulphate for 0.5 h, then evaporated to dryness; azeotropic distillation of the residue with toluene (3 × 5 cm^3), and finally drying *in vacuo*, gave a product (0.029 g) homogeneous on TLC [ethyl acetate–propan-2-ol–water (5:3:1)].

This material, which was too unstable for NMR analysis in [$^2H_6$]dimethyl sulphoxide, was promptly coupled by dissolution with 1-hydroxybenzotriazole monohydrate (0.020 g, 0.12 mmol) in anhydrous DMF (0.5 cm^3); the solution was then cooled to 0 °C and stirred with *N*,*N*′-dicyclohexylcarbodiimide (0.022 g, 0.12 mmol) for 1 h, while allowing the mixture to regain ambient temperature. Meanwhile 6-APA (0.027 g, 0.12 mmol) was solubilised in dichloromethane–triethylamine as described for the preparation of compound **8**. The two solutions were combined and stirred at ambient temperature for 4.25 h, then filtered, and the precipitate was washed with THF. The combined filtrate and washings were worked up for a sodium salt as described for the preparation of compound **8**. The crude lyophilised product (0.038 g) was purified as for the penicillin **11** but with elution with up to 20% THF in water to give after

pooling, concentration, and lyophilisation of appropriate fractions (HPLC), the title penicillin **24** (0.010 g, 21%); $\delta(D_2O)$ 1.41 and 1.49 [6 H, 2 s, Me_2C], 4.19 (1 H, s, 3-H), 5.04 (2 H, m, vinylic Hs), 5.58 and 5.67 (2 H, dd, 5- + 6-H), 7.22 (1 H, s, thiazole 5-H), 7.43 (3 H, m, ArH) and 7.61 (2 H, m, ArH); *m/z* (positive FAB; glycerol–thioglycerol) MH^+, 510 (9%) and MH^+ (free acid), 488 (10). This material, as the sodium salt, was sufficiently stable in aq. solution for antibacterial testing.

(2RS)-1-[(2-*Nitrophenyl*)*seleno*]*propan-2-ol* **15**.—2-Nitrophenyl selenocyanate (1.12 g, 4.93 mmol) was suspended in THF–ethanol (1:3; 20 cm^3) and the solution was stirred under argon at 0 °C while sodium borohydride (0.20 g, 5.5 mmol) was added (**CARE**! HCN evolved). After 0.5 h, the dark red solution was cooled to −30 °C and a solution of (*RS*)-2-methyloxirane **13** (0.44 cm^3, 0.36 g, 6.25 mmol) in THF (5 cm^3) was added dropwise. The mixture was allowed to regain ambient temperature, then was stirred for 16 h and worked up as for the preparation of compounds **14** and **16** to give a crude product (1.24 g). Brief chromatography, with elution with ethyl acetate–hexane mixtures, afforded homogeneous material (TLC) (1.20 g, 94%); trituration with hexane containing a few drops of diethyl ether deposited fine yellow crystals which were filtered off, washed with a little cold hexane, and dried to give the *title alcohol* **15** (1.11 g, 87%), m.p. 36–37 °C (Found: C, 41.5; H, 4.2; N, 5.4. $C_9H_{11}NO_3Se$ requires C, 41.5; H, 4.2; N, 5.4%); ν_{max}(Nujol)/cm^{-1} 3300br, 1595, 1565, 1505, 1330 and 1305; $\delta(CDCl_3)$ 1.41 (3 H, d, *J* 6, *Me*CH), 1.82 (1 H, br s, D_2O exch, OH), 3.08 (2 H, 8 lines, OCHCH_2Se, AB of ABX), 4.11 [1 H, m, simplified on D_2O exch, MeC*H*(OH)CH_2], 7.30–7.65 (3 H, m, ArH) and 8.29 (1 H, dd, *J* 8.3 and 1.3, ArH).

Methyl 2-[(Z)-{(1RS)-1-*Methyl*-2-[(2-*nitrophenyl*)*seleno*]*ethoxy*}*imino*]-3-*oxobutanoate* **18**. A solution of methyl 2-hydroxyimino-3-oxobutanoate **25*** (0.44 g, 3 mmol), triphenylphosphine (0.86 g, 3.3 mmol) and the alcohol **15** (0.86 g, 3.3 mmol) in anhydrous toluene (10 cm^3) was stirred under argon at 0 °C and DMAD (0.41 cm^3, 0.45 g, 3.3 mmol) was added dropwise. The yellow solution was subsequently heated at 70 °C for 3 h and was worked up as for the preparation of compound **17**. Chromatography, eluting with ethyl acetate–hexane mixtures, afforded the *title compound* **18** as a yellow foam (0.373 g, 32%) (Found: M, 388.0184. $C_{14}H_{16}N_2O_6$ requires M, 388.0174); ν_{max}(Nujol)/cm^{-1} 1745, 1695, 1595, 1515 and 1335; $\delta(CDCl_3)$ 1.54 (3 H, d, *J* 6, *Me*CHO), 2.45 (3 H, s, MeCO), 3.04 (1 H, dd, *J* 12.5 and 7.4, OCHC*H*HSe), 3.37 (1 H, dd, *J* 12.5 and 5.5, OCHCH*H*Se), 3.87 (3 H, s, MeO), 4.71 (1 H, m, MeC*H*CH_2), 7.30–7.65 (3 H, m, ArH) and 8.32 (1 H, dd, *J* 8.3 and 1.2, ArH). The NMR also showed *ca.* 7% contamination by starting oxime **25**, but this material was easily removed in the next step.

Methyl 2-(2-*Aminothiazol*-4-*yl*)-2-[(Z)-{(1RS)-1-*methyl*-2-[(2-*nitrophenyl*)*seleno*]*ethoxy*}*imino*]*acetate* **21**.—A solution of the selenide **18** (0.38 g, 0.98 mmol) in dichloromethane (4 cm^3) was α-brominated as described for compounds **5** and **17**. The reaction was completed and the reaction mixture was worked up as described for compound **6**; the intermediate bromo product (0.45 g) showed δ(60 MHz; $CDCl_3$) 4.35 (2 H, s), and loss of the signal at δ 2.45 (3 H, s), in the spectrum of compound **18**.

A solution of this product in ethanol (6 cm^3) was treated at ambient temperature with thiourea (0.095 g, 1.25 mmol) and *N*,*N*-dimethylaniline (0.14 cm^3). After 2 h the reaction mixture was worked up and the crude product was chromatographed as described for the preparation of compound **6**; evaporation of appropriate fractions afforded the *title compound* **21** (0.321 g, 74%) as a solid, m.p. 166–168 °C (from ethyl acetate–hexane) (Found: C, 41.0; H, 3.6; N, 12.4; S, 6.9. $C_{15}H_{16}N_4O_5SSe$ requires C, 40.6; H, 3.6; N, 12.6; S, 7.2%); ν_{max}/cm^{-1} 3456, 1725, 1616, 1589, 1564, 1532, 1498 and 1331; $\delta(CDCl_3)$ 1.48 (3 H, d, *J* 6, *Me*CH), 3.07 and 3.35 (2 H, 2 dd, OCHCH_2Se; AB of ABX), 3.92 (3 H, s, MeO), 4.70 (1 H, m, CHO), 5.29 (2 H, br s, D_2O exch, NH_2), 6.79 (1 H, s, 5-H), 7.25–7.70 (3 H, m, ArH) and 8.29 (1 H, dd, ArH); *m/z* (EI) M^+, 444 (5%).

Methyl 2-(2-*Aminothiazol*-4-*yl*)-2-[(Z)-*isopropenyloxyimino*]*acetate* **23**.—A solution of the aminothiazole **21** (0.222 g, 0.5 mmol) in THF (10 cm^3) was treated at ambient temperature with aq. sodium metaperiodate (0.321 g, 1.5 mmol, 5 cm^3). After being stirred for 9.5 h, the solution was diluted with ethyl acetate, washed successively with half-saturated aq. sodium hydrogen carbonate (2 ×) and water, and set aside at ambient temperature over anhydrous magnesium sulphate. After a further 72 h, when no intermediate selenoxide was visible by TLC, the solution was filtered, and the filtrate was evaporated to give a crude product (0.166 g). Chromatography, eluting with ethyl acetate–hexane mixtures, afforded, on evaporation of appropriate fractions, the O-*vinyl oxime* **23** (0.043 g, 36%) as a semi-solid (Found: M^+, 241.0526. $C_9H_{11}N_3O_3S$ requires M, 241.0519); ν_{max}/cm^1 3444, 3418, 1737, 1694w, 1653, 1624, 1587 and 1540; $\delta(CDCl_3)$ 1.91 (3 H, s, MeC=C), 3.95 (3 H, s, MeO), 4.14 and 4.68 (2 H, ABq, *J* 1, C=CH_2), 5.41 (2 H, br s, D_2O exch, NH_2) and 6.94 (1 H, s, 5-H).

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* In view of the very slow hydrolysis of ethyl ester **22** it was felt advisable to work through with a methyl ester in this series.