β-Lactamase-Stable Penicillins. Synthesis and Structure–Activity Relationships of (*Z*)-Alkyloxyimino Penicillins; Selection of BRL 44154[1]

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A series of (*Z*)-2-alkyloxyimino-2-(2-aminothiazol-4-yl)acetamidopenicillins has been prepared. New methodology has been developed to prepare tertiary alkyl oximes. High stability to β-lactamases and potent antibacterial activity have been achieved against Gram-positive and certain Gram-negative organisms. Activity against methicillin-resistant *Staphylococcus aureus* was an unexpected finding. The cyclopentyl analogue **4f**, BRL 44154, has been selected for further study.

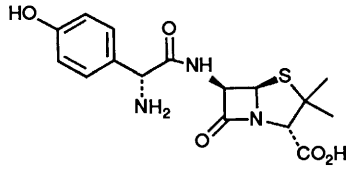
Over the last three decades penicillins have proved to be highly effective in the treatment of a wide range of antibacterial infections. They are, however, becoming increasingly susceptible to inactivation by β-lactamase enzymes produced by some organisms. The usefulness of amoxycillin **1** has been improved by combination with the β-lactamase inhibitor clavulanic acid. Good stability to staphylococcal β-lactamase has been achieved in the sterically hindered isoxazolyl penicillins,[2] *e.g.*, flucloxacillin, **2**, but while these have potent activity against Gram-positive organisms, activity against Gram-negative organisms is much reduced. The combination of a cephem nucleus and a 2-aminothiazol-4-yl-2-[(*Z*)-methoxyimino]acetamido side-chain found in the more recent generations of cephalosporins,[3] *e.g.*, cefotaxime, **3** leads to a combination of broad-spectrum activity and β-lactamase stability. However, activity against Gram-positive organisms is only moderate. Our objective in this study was to identify a penicillin with high activity against *Staphylococci*, in particular, and other pathogens commonly encountered in community-acquired infections; but with enhanced stability to bacterial β-lactamases.

The methoxyimine derivative **4a**[4] was not particularly active against *Staphylococci* and lacked the required stability to β-lactamase. We examined the effect of bulkier oxyimino substituents and this paper describes a series of 2-[(*Z*)-alkoxyimino]-2-(2-aminothiazol-4-yl)acetamido penicillins (Table 1). After the completion of our work Mandel and co-workers reported compounds **4b**, **4c**, **4f** and **4g**.[5]

Results and Discussion

Chemistry.—The synthesis of these penicillins is dependent upon the derivatisation of a free oxyimino substituent. It was found that cyclopentyl bromide reacted readily with the 2-aminothiazol-4-yloxime **8** or its *N*-trityl derivative **9**. In contrast the less reactive cyclohexyl to cyclooctyl halides only reacted efficiently with ethyl (*Z*)-2-hydroxyimino-3-oxobutyrate **5**.[6] Acid-catalysed bromination of ester **6** to bromo ester **7** followed by cyclisation with thiourea gave the aminothiazole esters **10**. Alkaline hydrolysis gave the acids **11** (Scheme 1). The (*E*)-isomers (typically <5%) were readily freed from the required (*Z*)-isomers by chromatography.

Reaction of cyclobutyl bromide with oxime **8** has been reported to give the cyclobutyl oxime **10e**;[7] but in our hands a mixture of isomers **10e**, **10s** and **10t** in the proportions 4:1:1 was obtained, which could not be separated efficiently by chromatography. This necessitated an alternative approach. The Mitsunobu condensation[8,9] between *N*-hydroxyphthalimide **16** and cyclobutanol gave compound **17** essentially free from isomers. Treatment of compound **17** with hydrazine hydrate gave *O*-cyclobutylhydroxylamine **18**, which was condensed with the protected glyoxylic acid **15** to give the cyclobutyl oxime **19** (Scheme 2). The chloroacetyl group was readily removed from the derived penicillin **20** by treatment with sodium *N*-methyldithiocarbamate.[10] A one-pot chloroacetylation of ethyl 2-aminothiazol-4-ylglyoxylate **13** in dimethylacetamide (DMA) in the absence of added base, followed by rapid alkaline



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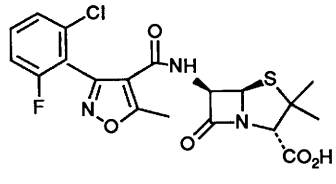

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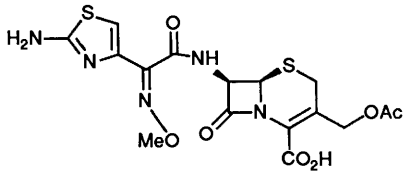

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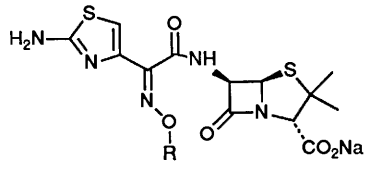

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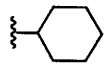
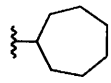
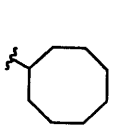
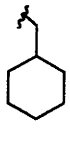
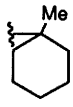
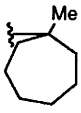
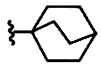
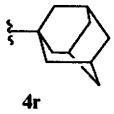
R defined in Table 1

Table 1 Comparative antibacterial activities, β-lactamase stability and serum binding of alkoxyiminopenicillins

R			Me	Et	Pr^i					
Compound	**1**	**2**	**4a**	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**	**4h**
Organism										
S. aureus Oxford	0.12	0.25	1.0	0.5	0.5	0.5	1.0	0.25	0.25	0.25
S. aureus MB9*	>64	1.0	8.0	8.0	2.0	4.0	2.0	0.5	0.5	0.25
S. aureus V573**	>64	>64	128	32	8.0	8.0	16	2.0	4.0	4.0
S. epidermidis PHLN20	>64	0.25	2.0	0.5	0.5	0.5	0.5	0.5	0.25	0.25
S. pneumoniae 1761	≤0.03	0.12	≤0.06	≤0.06	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03
H. influenzae NEMC1*	32	4.0	32	2.0	0.25	1.0	1.0	0.25	0.5	0.5
B. catarrhalis Ravasio*	8.0	8.0	32	2.0	2.0	8.0	2.0	0.5	0.5	0.25
E. coli NCTC 1048	4.0	>64	4.0	2.0	2.0	1.0	2.0	2.0	8.0	8.0
P. mirabilis C977	2.0	>64	2.0	1.0	4.0	2.0	2.0	4.0	16	16
Stability to β-lactamases ($t_{\frac{1}{2}}$/min)										
S. aureus MB9	<1	60	3.3	ND	35	7.7	27	86	93.5	94
H. Influenzae NEMC1	ND	ND	0.6	ND	ND	ND	ND	31	ND	ND
Human serum binding (%)	20	95	38	ND	62	35	58	60	66.5	84

R			Bu^t							
Compound	**4i**	**4j**	**4k**	**4l**	**4m**	**4n**	**4o**	**4p**	**4q**	**4r**
Organism										
S. aureus Oxford	0.25	0.25	0.25	0.5	0.5	0.5	0.5	0.25	0.25	0.25
S. aureus MB9*	0.5	16	0.5	4.0	1.0	1.0	0.5	0.5	0.25	0.5
S. aureus V573**	8.0	32	8.0	8.0	8.0	8.0	8.0	4.0	4.0	8.0
S. epidermidis PHLN20	0.25	1.0	0.25	0.5	0.5	0.25	0.25	0.12	0.12	≤0.03
S. pneumoniae 1761	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03	≤0.03
H. influenzae NEMC1*	0.5	4.0	0.25	1.0	0.5	0.5	0.5	1.0	1.0	2.0
B. catarrhalis Ravasio*	0.5	4.0	0.25	8.0	2.0	0.5	0.5	0.12	0.5	0.5
E. coli NCTC 1048	8.0	16	8.0	1.0	2.0	8.0	32	16	16	64
P. mirabilis C977	16	32	16	2.0	8.0	32	32	16	32	128
Stability to β-lactamases ($t_{\frac{1}{2}}$/min)										
S. aureus MB9	110	4.1	379	38	23	816	>900	ND	ND	476
H. Influenzae NEMC1	ND	ND	134	ND	ND	ND	ND	ND	ND	274
Human serum binding (%)	92	90	48	44	30	81	99	91	85	87

* β-Lactamase-producing strain. ** Methicillin-resistant strain. ND Not determined.

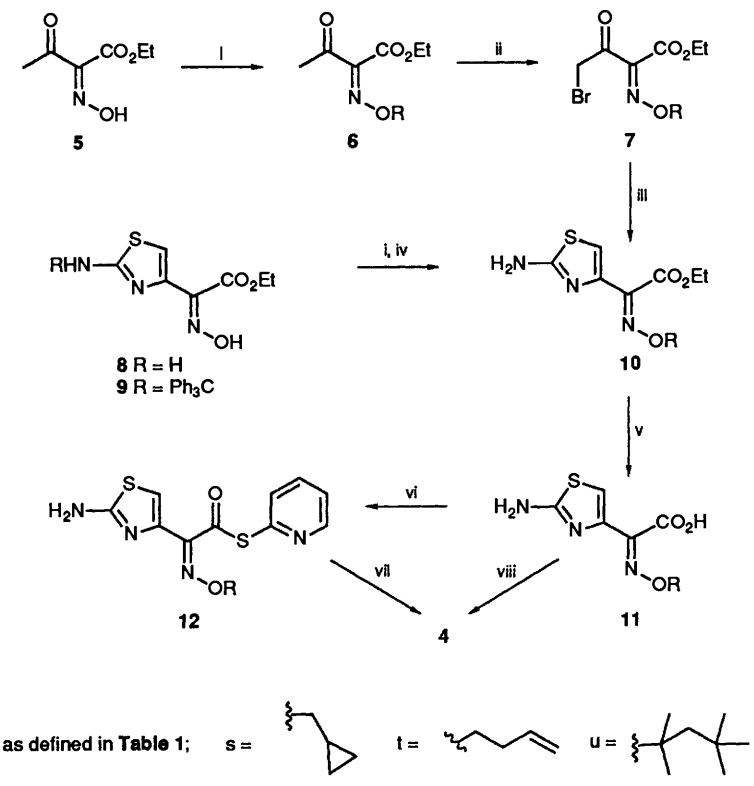
hydrolysis during extraction, obviated the need to isolate the ester **14**,[11] which was found to have irritant and sternutatory properties.

Apart from *O*-t-butyl oximes, readily available from condensation of carbonyl compounds with *O*-t-butylhydroxylamine,[12] and oximes derived from and related to dimethylacetic acid,[13] very little literature precedent could be found for the synthesis of *O*-tertiary alkyl oximes, so new methodology was developed.

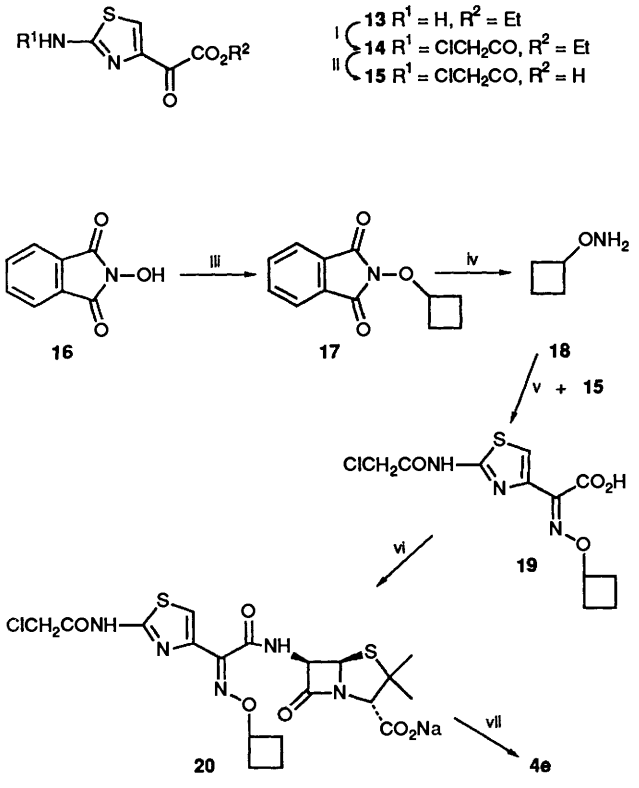
An old method [14] for the alkylation of aldoximes with methyl iodide utilised silver oxide, and so for initial investigation the use of a silver salt seemed to be appropriate. Therefore, reaction of the oxime **5** and t-butyl bromide in 1,4-dioxane with silver carbonate gave the desired *O*-t-butyl oxime **6k** in good yield. It was subsequently found that silver trifluoromethanesulphonate gave a more rapid reaction, as exemplified by the synthesis of the 1-methylcyclopentyl derivative **6n**.

Problems associated with this methodology were the use of expensive reagents and long reaction times, even with silver trifluoromethanesulphonate. With a view to scale-up, an alternative alkylation procedure was sought. We believed that the tertiary alcohol could be used to generate a carbonium ion which could be intercepted by the oxime to give the *O*-tertiary alkyl oxime. This avoided the need to form the bromo derivative from the alcohol. Thus the oxime **5** and t-butyl alcohol were treated with some Lewis acids in refluxing methylene dichloride containing molecular sieves. Boron trifluoride–diethyl ether was the most effective and gave a high yield of the oxime **6k**, obtained as a separable mixture of (*Z*)- and (*E*)-isomer together with compound **6u** in 10:1:1 proportions. This new methodology was applied to the synthesis of the 1-methylcyclobutyl analogue **6m**.

The 1-methylcyclopropyl oxime **61** was prepared starting from 2-bromopropionyl chloride **21** (Scheme 3); $LiAlH_4$ reduction to the alcohol, followed by protection as the t-butyldimethylsilyl ether gave compound **22**, which alkylated the ketooxime **5** to give ester **23**. Direct cleavage of the silyl ether with triphenylphosphine dibromide[15] yielded the 3-bromopropan-2-yl oxime **24**. Acetalisation to compound **26** followed by elimination formed the isopropenyl oxime **28**, which was cyclopropanated (Et_2Zn, CH_2I_2)[16] to give the desired cyclopropane **30**. Deprotection of the ketone [trifluoroacetic acid (TFA)–aq. tetrahydrofuran (THF)] gave the oxyimino



Scheme 1 *Reagents and conditions:* 1, See text; ii, Br_2, CCl_4, HBr–AcOH; iii, $(H_2N)_2CS$, $PhNMe_2$, EtOH; iv, (R = Ph_3C) aq. HCO_2H; v, aq. NaOH, EtOH; vi, 2,2′-dithiodipyridine, PPh_3, MeCN; vii, 6-APA, TMSCl, NEt_3, CH_2Cl_2; viii, $MeSO_2Cl$, Pr^i_2NEt, DMF; or Na^+ salt, $MeSO_2Cl$, DMF; then 6-APA, aq. NEt_3

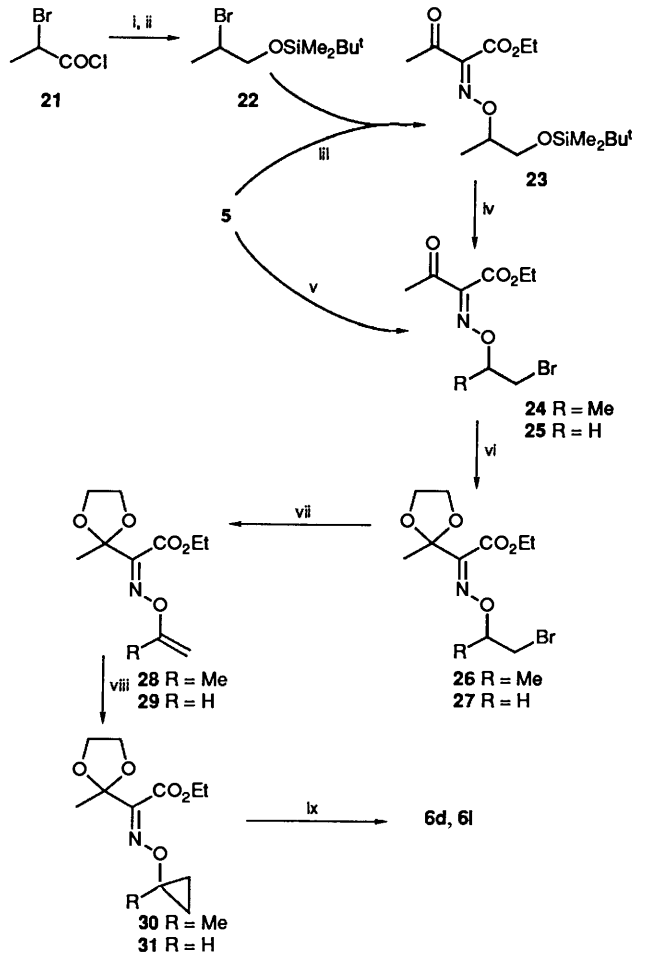


Scheme 2 *Reagents and conditions:* i, $ClCH_2COCl$, DMA; ii, aq. NaOH, EtOAc; iii, $CH_2CH_2CH_2CHOH$, PPh_3, DEAD, THF; iv, $N_2H_4{\cdot}H_2O$, MeOH, CH_2Cl_2; v, aq. THF, pH 5; vi, $MeSO_2Cl$, Pr^i_2NEt, DMF; then 6-APA, aq. NEt_3; vii, NaSC(S)NHMe, aq. THF

ketone **61**. The unsubstituted cyclopropane derivative[17] **6d** was prepared from ethylene dibromide using a parallel procedure.

6-Aminopenicillanic acid (6-APA) was acylated without the need for protection of the 2-aminothiazole group. Our initial method involved the preparation of the pyridyl thioesters **12** from the acids **11** and their subsequent reaction with the *N,O*-bis(trimethylsilyl) derivative of 6-APA. Latterly we found that activation of the acids **11**, or their sodium salts, as the mixed methanesulphonic anhydrides and subsequent reaction with 6-APA itself was more expedient (Scheme 1). The penicillin derivatives **4a–r** were isolated as their sodium salts.

Structure–Activity Relationships.—The *in vitro* activities of penicillins **4a–r** (Table 1) against a range of clinically important aerobic bacteria were determined as minimum inhibitory concentration (MIC) values by serial dilution in agar. The data for amoxycillin **1** and flucloxacillin **2** are included for comparison. In general, increasing the size of the alkyl group resulted in increased activity against the Gram-positive bacteria and the other common respiratory pathogens *Haemophilus influenzae* and *Branhamella catarrhalis*. Activity against other Gram-negative organisms *Escherichia coli* and *Proteus mirabilis*, was only moderate and the MICs in general increased with increasing lipophilicity of the substituent. Activity against the β-lactamase-producing organisms is significantly increased as the steric bulk is increased. This was confirmed by an increase in the half-lives of the penicillins against cell-free preparations of β-lactamases from *Staphylococcus aureus* MB9 and the Gram-negative *H. infuenzae* NEMC1. With the latter organism a secondary effect, presumed to be increasing lipophilicity, reduced activity, as the substituent became very large. Activity against the methicillin-resistant *S. aureus* V573 (MRSA) was an unexpected finding; this was most pronounced in the cyclopentyl and cyclohexyl examples **4f** and **4g**. This improved activity has been attributed to an increased affinity for the altered target site in the cell wall.[18] Introduction of a methylene group **4j** dramatically reduced the stability to β-lactamase. The corresponding (*E*)-isomers in all cases, although retaining



Scheme 3 *Reagents and conditions:* i, $LiAlH_4$, Et_2O, 0 °C; ii, Bu^tMe_2SiCl, Et_3N, DMAP, CH_2Cl_2; iii, K_2CO_3, DMSO; iv, $Ph_3P{\cdot}Br_2$, $CHCl_3$, reflux; v, $BrCH_2CH_2Br$, K_2CO_3, DMF; vi, $HOCH_2CH_2OH$, PTSA, C_6H_6, reflux; vii, $KOBu^t$, THF, DMSO; viii, Et_2Zn, CH_2I_2, cyclohexane, C_6H_6; ix, TFA, aq. THF

antibacterial activity, lost stability to β-lactamase. Greater binding to human serum protein was observed with increasing lipophilicity of the oxime substituent.

While the tertiary alkyl oximes showed the greatest stability to β-lactamases, the optimum compound for antibacterial activity as measured in terms of breadth of spectrum, degree of potency and activity against MRSA was the cyclopentyl oxime **4f** BRL 44154.

Experimental

M.p.s were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer 197 or 983 spectrophotometers. Proton NMR spectra were recorded on Varian EM 360 (60 MHz), Perkin-Elmer R32 (90 MHz) or Bruker AM 250 (250 MHz) spectrometers. Chemical shifts are quoted in ppm relative to tetramethylsilane as internal reference for solutions in $CDCl_3$ or $(CD_3)_2SO$ and external HOD set at δ 4.80 for solutions in D_2O. *J*-values are in Hz. Mass spectra, electron impact (EI), chemical ionisation (CI) using ammonia and fast-atom bombardment (FAB) using thioglycerol, were obtained on VG 7070F or VG ZAB 1F mass spectrometers. Microanalytical data were determined on a Carlo Erba 1106 elemental analyser. pH Determinations were made using a pH meter with a combination electrode. Organic extracts were dried over anhydrous magnesium sulphate, and evaporation refers to removal of solvents on a rotary evaporator under reduced pressure. Column chromatography was performed on Merck Silica gel 60 (9385) and (7729) using mixtures of ethyl acetate and hexane as eluents, columns were packed and eluted under pressure. Sodium salts of penicillins were purified on Mitsubishi Diaion HP20SS using mixtures of water and THF as eluents and HPLC monitoring. HPLC was performed on a Waters Associates system using a μ-Bondapak™ C_{18} column and eluting with mixtures of acetonitrile and 0.05 mol dm^{-3} sodium acetate in water at pH 5.0. Detection was at 240 nm with a Cecil Instruments CE 212 monitor. The penicillins, although pure by HPLC contain a small amount of water as freeze-dried solids. The methyl, ethyl and isopropyl oxyiminopenicillins **4a**,[4] **4b**[5] and **4c**[5] have been reported and were prepared using standard methodology.

Ethyl (Z)-2-*Hydroxyimino*-3-*oxybutyrate* **5**.[6]—A solution of sodium nitrite (187 g, 2.71 mol) in water (420 cm^3) was added dropwise to a mixture of ethyl acetoacetate (303 cm^3, 2.38 mol) and acetic acid (350 cm^3) with the temperature maintained below 0 °C. On completion of the addition the mixture was allowed to warm to room temperature during 1 h. Water (1500 cm^3) was added and the mixture was stirred for a further 1 h, then extracted with diethyl ether (3 × 400 cm^3). Water (800 cm^3) was added to the combined extracts and the mixture was neutralised by the addition of solid sodium hydrogen carbonate. The organic phase was washed successively with water and brine, dried and evaporated. The residual oil, which solidified on storage was washed with hexane and dried under reduced pressure over phosphorus pentaoxide to give ethyl (*Z*)-2-hydroxyimino-3-oxobutyrate **5** (342.9 g, 91%).

Alkylation of Ethyl 2-*Hydroxyimino*-3-*oxobutyrate* **5**.—*Ethyl* (Z)-2-*cyclohexyloxyimino*-3-*oxobutyrate* **6g**. Cyclohexyl bromide (55 g, 0.34 mol) was added to a mixture of oxime **5** (35.8 g, 0.225 mol), potassium carbonate (40.4, 0.293 mol) and dimethyl sulphoxide (DMSO) (30 cm^3). This mixture was stirred for 16 h at room temperature, then poured into water and extracted with ethyl acetate. The organic phase was washed successively with water and brine, dried and evaporated. The residue was purified by chromatography to give the product **6g** as an oil (34 g, 63%), ν_{max}(neat)/cm^{-1} 1745 and 1695; δ($CDCl_3$) 1.32 (3 H, t, *J* 7, *Me*CH_2), 1.3–2.0 (10 H, m, cyclohexyl CH_2), 2.37 (3 H, s, MeCO) and 4.33 (3 H, q + m, MeCH_2, CH); *m/z* (CI) 242 (MH^+).

The cycloheptyl **6h** and cyclooctyl **6i** oximes were similarly prepared from oxime **5** and cycloheptyl bromide and cyclooctyl iodide, respectively:

Ethyl (Z)-2-*cycloheptyloxyimino*-3-*oxobutyrate* **6h**. This was an oil (80%) (Found: MH^+, 256.1547. $C_{13}H_{22}NO_4$ requires *m/z*, 256.1550); ν_{max}(neat)/cm^{-1} 1750 and 1690; δ($CDCl_3$) 1.31 (3 H, t, *J* 7, *Me*CH_2), 1.4–2.0 (12 H, m, CH_2), 2.35 (3 H, s, MeCO) and 4.32 (3 H, q + m, MeCH_2, CH).

Ethyl (Z)-2-*cyclooctyloxyimino*-3-*oxobutyrate* **6i**. This was an oil (69%); ν_{max}(neat)/cm^{-1} 1740 and 1695; δ($CDCl_3$) 1.31 (3 H, t, *J* 7, *Me*CH_2), 1.4–2.0 (14 H, m, CH_2), 2.38 (3 H, s, MeCO), 4.33 (2 H, q MeCH_2) and 4.4 (1 H, m, CH); *m/z* (CI) 270 (MH^+).

Preparation of Tertiary Alkyl Oximes using Silver Salts.—*Ethyl* (Z)-2-(*t-Butoxyimino*)-3-*oxobutyrate* **6k**. Ethyl (*Z*)-2-hydroxyimino-3-oxobutyrate **5** (4.77 g, 30 mmol) in 1,4-dioxane (15 cm^3) was treated with silver(I) carbonate (8.27 g, 33 mmol), followed by t-butyl bromide (3.37 cm^3, 4.11 g, 30 mmol). The mixture was stirred in the dark and further quantities of silver(I) carbonate (8.27 g) and (4.14 g), t-butyl bromide (6.74 cm^3) and (3.7 cm^3) and 1,4-dioxane (10 cm^3) and (10 cm^3) were added after 5 and 64 h, respectively. After 66.5 h more t-butyl bromide

($3.7\ cm^3$) was added and the mixture was stirred in the dark for a further 3.5 h. The mixture was filtered through Celite, and the filter cake was washed well with 1,4-dioxane. The filtrate and washings were combined and concentrated. Purification by chromatography gave the alkyl oxime **6k** (4.5 g, 70%) as an oil, $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1745, 1690, 1365, 1230, 1180, 1070 and 990; $\delta(CDCl_3)$ 1.36 (12 H, s, superimposed on t, Me_3C, $MeCH_2$), 2.40 (3 H, s, MeCO) and 4.33 (2 H, q, *J* 6.5, OCH_2Me); *m/z* (EI) 170.0813 ($M^+ - OCH_2CH_3$. $C_8H_{12}NO_3$ requires *m/z*, 170.0817); (CI, isobutane) 216 ($M H^+$).

Similarly prepared was ethyl (*Z*)-3-oxo-2-(tricyclo-[3.3.1.1^{3,7}]decan-1-yloxyimino)butyrate **6r** obtained as an oil (40%), ν_{max}(neat)/cm^{-1} 2830, 2750, 1745, 1730 and 1700; ν_{max}-$(CH_2Cl_2)/cm^{-1}$ 2820, 2750, 1735, 1700sh and 1680; $\delta(CDCl_3)$ 1.31 (3 H, t, *J* 7, $MeCH_2$), 1.67 (6 H, br s, 3 × CH_2), 1.94 (6 H, br s, 3 × CH_2), 2.21 (3 H, br s, 3 × CH), 2.35 (3 H, s, MeCO) and 4.30 (2 H, q, *J* 7, OCH_2Me).

Ethyl (Z)-2-(1-*Methylcyclopentyloxyimino*)-3-*oxobutyrate* **6n**.—Ethyl (*Z*)-2-hydroxyimino-3-oxobutyrate **5** (5.6 g, 35.2 mmol) and 1-methylcyclopentyl bromide (6.01 g, 36.8 mmol) in dry 1,4-dioxane ($30\ cm^3$) were stirred in the dark and treated with silver trifluoromethanesulphonate (9.45 g, 36.8 mmol), added portionwise during 3 h. The mixture was stirred for a further 40 h, filtered through Celite and the solvent was removed to leave an oil, to which toluene was added and removed. The residual oil was chromatographed to give the *O*-(1-methylcyclopentyl)oxime **6n** (4.45 g, 50%) as an oil, ν_{max}(neat)/cm^{-1} 2970, 1745, 1690, 1590, 1370, 1320, 1230, 1070 and 990; $\delta(CDCl_3)$ 1.31 (3 H, t, *J* 7, $MeCH_2$), 1.48 (3 H, s, Me), 1.1–2.2 (8 H, m, 8 × cyclopentyl CH), 2.35 (2 H, s, MeCO) and 4.30 (2 H, q, *J* 7, OCH_2Me).

Similarly prepared were the following: *ethyl* (Z)-2-(1-*methylcyclohexyloxyimino*)-3-*oxobutyrate* **6o** (69%) as an oil (Found: C, 61.2; H, 8.3; N, 5.6%; MH^+, 256.1537. $C_{13}H_{21}NO_4$ requires C, 61.15; H, 8.3; N, 5.5%; MH, 256.1549); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2945, 1740, 1685, 1370, 1320, 1235, 1060 and 1005; $\delta(CDCl_3)$ 1.35 (6 H, s superimposed on t, Me, $MeCH_2$), 1.4–2.0 (10 H, m, 10 × cyclohexyl CH), 2.37 (3 H, s, MeCO) and 4.55 (2 H, q, *J* 7, OCH_2Me).

Ethyl (*Z*)-2-(1-methylcycloheptyloxyimino)-3-oxobutyrate **6p** (65%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2930, 2850, 1740, 1685, 1595, 1370, 1320, 1230, 1070 and 1000; $\delta(CDCl_3)$ 1.33 (6 H, s superimposed on t, MeC, $MeCH_2$), 1.4–1.8 (10 H, m, 10 × cycloheptyl CH), 1.99 (2 H, dd, *J* ~ 13.5 and 7.5, 2 × cycloheptyl CH), 2.40 (3 H, s, MeCO) and 4.35 (2 H, q, *J* 7.1, OCH_2Me); *m/z* (CI) 270 (MH^+).

Ethyl (*Z*)-2-(bicyclo[2.2.2]octan-1-yloxyimino)-3-oxobutyrate **6q** (22%), $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 2950, 2925, 2860, 1735, 1685, 1370 and 1325; $\delta(CDCl_3)$ 1.3 (3 H, t, *J* 7, $MeCH_2$), 1.64 (s) and 1.75 (s) (together 13 H, 6 × CH_2, CH), 2.36 (3 H, s, MeCO) and 4.30 (2 H, q, *J* 7, OCH_2Me); *m/z* (CI) 298 (MH^+).

Preparation of Tertiary Alkyl Oximes using BF_3•Et_2O.—*Ethyl* (Z)-2-(*t-Butoxyimino*)-3-*oxobutyrate* **6k** (*Alternative Preparation*). Ethyl (*Z*)-2-hydroxyimino-3-oxobutyrate **5** (1.59 g, 10 mmol), t-butyl alcohol (0.925 g, 12.5 mmol) and 3Å molecular sieves (5 g) in dry methylene dichloride ($25\ cm^3$) under argon were stirred and treated with boron trifluoride–diethyl ether ($1.85\ cm^3$, 2.13 g, 1.5 mmol) and the mixture was heated under reflux for 3 h. The solvent was decanted off and the molecular sieves were washed well with methylene dichloride. The combined organic solutions were washed successively with water, dil. aq. sodium hydrogen carbonate, water and brine, and then dried. After removal of solvent the residue was chromatographed on silica gel to give the (*Z*)-oxime **6k** (1.16 g, 54%) together with ethyl (*E*)-2-(t-butoxyimino)-3-oxobutyrate (0.11 g, 5%), $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1720, 1365, 1320, 1220, 1180, 1090 and 985; $\delta(CDCl_3)$ 1.35 (12 H, s, superimposed on t, Me_3, $MeCH_2$), 2.36 (3 H, s, MeCO) and 4.30 (2 H, q, *J* 7, OCH_2Me); and *ethyl* 3-*oxo*-2-(1,1,3,3-*tetramethylbutoxyimino*)*butyrate* **6u** (0.104 g, 4%), $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 1740, 1685, 1370, 1315, 1235, 1070 and 1000; $\delta(CDCl_3)$ 0.98 (9 H, s, Me_3C), 1.31 (3 H, t, *J* 7, $MeCH_2$), 1.41 (6 H, s, Me_2C), 1.70 (2 H, s, CH_2), 2.39 (3 H, s, MeCO) and 4.30 (2 H, q, *J* 7, OCH_2Me), *m/z* (EI) (Found: MH^+, 272.1864. $C_{14}H_{26}NO_4$ requires *m/z*, 272.1862.

Similarly prepared was ethyl (*Z*)-2-(1-methylcyclohexyloxyimino)-3-oxobutyrate **6o** (73%) obtained as an oil, together with a 16:5 mixture of the (*E*)- and (*Z*)-isomer (14%).

Ethyl (Z)-2-(1-*Methylcyclobutyloxyimino*)-3-*oxobutyrate* **6m**.—Methyllithium (8 mmol) in diethyl ether was added dropwise to a solution of cyclobutanone (0.50 g, 7.1 mmol) in diethyl ether ($3\ cm^3$) at 0 °C. The mixture was stirred at room temperature for 1 h then quenched with saturated aq. ammonium chloride. The ethereal layer was washed with brine, dried and evaporated. The residual 1-methylcyclobutanol[19] was used without further purification.

Boron trifluoride–diethyl ether ($0.88\ cm^3$, 7.17 mmol) was added to a mixture of ethyl (*Z*)-2-hydroxyimino-3-oxobutyrate **5** (1.14 g, 7.17 mmol), the residual 1-methylcyclobutanol and 4 Å sieves (4 g) in methylene dichloride ($15\ cm^3$). The mixture was stirred under reflux for 24 h, then decanted into water. The organic phase was washed successively with saturated aq. sodium hydrogen carbonate, water and brine, dried and evaporated. The residue was purified by chromatography to give the title product **6m** (0.428 g, 26%) as an oil, ν_{max}(neat)/cm^{-1} 2970, 1740 and 1690; $\delta_H(CDCl_3)$ 1.34 (3 H, t, *J* 7.1, OCH_2Me), 1.49 (3 H, s, Me), 1.60–2.05 (4 H, m, 2 × CH_2), 2.3–2.5 (5 H, m, superimposed on s at δ 2.41, MeCO, CH_2) and 4.35 (2 H, q, *J* 7.2, OCH_2Me); δ_C(100 MHz; $CDCl_3$) 12.5 (C-3′), 14.1 (OCH_2Me), 23.9 (1′-Me), 25.1 (C-4), 33.4 (C-2′ and C-4′), 61.8 (OCH_2Me), 85.4 (C-1′), 150.2 (C-2), 161.6 (C-1) and 193.1 (C-3).

Preparation of Aminothiazoles **10**.—*Ethyl* (Z)-2-(2-*aminothiazol*-4-*yl*)-2-(*cyclohexyloxyimino*)*acetate* **10g**. A solution of bromine ($4.50\ cm^3$, 87 mmol) in carbon tetrachloride ($50\ cm^3$) was added dropwise to a mixture of oxime **6g** (20 g, 83 mmol), 45% hydrogen bromide in acetic acid ($1.0\ cm^3$) and carbon tetrachloride ($150\ cm^3$) during 1.5 h. After being stirred for a further 1 h the mixture was evaporated. The residual oil was dissolved in ethyl acetate, and the solution was washed successively with water and brine, dried and evaporated to give the bromo ketone **7g** as a pale yellow oil.

This oil was dissolved in ethanol ($250\ cm^3$), thiourea (6.06 g, 79.7 mmol) and *N*,*N*-dimethylaniline (9.64 g, 79.7 mmol) were added and the mixture was stirred at room temperature for 17 h. The solvent was evaporated off and the residue was partitioned between ethyl acetate and water. The organic phase was washed with brine, dried and evaporated. Chromatography and recrystallisation from cyclohexane gave the *title product* **10g** (17.0 g, 72%), m.p. 133–134 °C (Found: C, 52.7; H, 6.7; N, 14.1. $C_{13}H_{19}N_3O_3S$ requires C, 52.5; H, 6.4; N, 14.1%); $\nu_{max}(CHCl_3)/cm^{-1}$ 1730 and 1605; $\delta(CDCl_3)$ 1.34 (3 H, t, *J* 7, $MeCH_2$), 1.3–2.0 (10 H, m, CH_2), 4.3 (1 H, m, CH), 4.36 (2 H, q, $MeCH_2$), 5.4 (2 H, br s, NH_2) and 6.68 (1 H, s, thiazole 5-H).

Similarly prepared were: *Ethyl* (Z)-2-(2-*aminothiazol*-4-*yl*)-2-(*cyclopropyloxyimino*)*acetate* **10d** (76%), m.p. 163–166 °C (from EtOAc–hexane) (Found: C, 47.3; H, 5.1; N, 16.4. $C_{10}H_{13}N_3O_3S$ requires C, 47.05; H, 5.1; N, 16.5%); $\nu_{max}(CDCl_3)/cm^{-1}$ 1735, 1715 and 1605; $\delta(CDCl_3)$ 0.60–0.95 (4 H, m, CH_2), 1.35 (3 H, t, *J* 7, $MeCH_2$), 4.17 (1 H, m, CH), 4.37 (2 H, q, $MeCH_2$), 5.48 (2 H, br s, NH_2) and 6.72 (1 H, s, thiazole 5-H).

Ethyl (Z)-2-(2-*aminothiazol*-4-*yl*)-2-(*cycloheptyloxyimino*)-*acetate* **10h** (69%), m.p. 107–108 °C (from methylene dichloride–hexane) (Found: C, 54.2; H, 6.7; N, 13.3. $C_{14}H_{21}N_3O_3S$

requires C, 54.0; H, 6.8; N, 13.5%); ν_{max}(KBr)/cm^{-1} 1723 and 1611; δ($CDCl_3$) 1.33 (3 H, t, *J* 7, *Me*CH_2), 1.4–2.0 (12 H, m, CH_2), 4.35 (3 H, q + m, MeCH_2, CH), 5.60 (2 H, br s, NH_2) and 6.64 (1 H, s, thiazole 5-H).

Ethyl (Z)-2-(2-*aminothiazol*-4-*yl*)-2-(*cyclooctyloxyimino*)*acetate* **10i** (72%), m.p. 117–118 °C (from cyclohexane) (Found: C, 55.7; H, 7.2; N, 12.45. $C_{15}H_{23}N_3O_3S$ requires C, 55.4; H, 7.1; N, 12.9%); ν_{max}(KBr)/cm^{-1} 1718 and 1610; δ($CDCl_3$) 1.35 (3 H, t, *J* 7, *Me*CH_2), 1.4–2.0 (14 H, m, CH_2), 4.36 (3 H, q + m, MeCH_2, CH), 5.65 (2 H, br s, NH_2) and 6.66 (1 H, s, thiazole 5-H).

Ethyl (Z)-2-(2-*aminothiazol*-4-*yl*)-2-(*t-butoxyimino*)*acetate* **10k** (74%), m.p. 111–112 °C (from ethyl acetate–hexane) (Found: C, 49.0; H, 6.2; N, 15.5% M^+, 271.0994. $C_{11}H_{17}N_3O_3S$ requires C, 48.7; H, 6.3; N, 15.5%; M, 271.0991); ν_{max}(CH_2Cl_2)/cm^{-1} 3470, 3375, 1735, 1610 and 1430; δ($CDCl_3$) 1.33 (9 H, s, Me_3C), 1.35 (3 H, t, *Me*CH_2), 4.40 (2 H, q, *J* 7, OCH_2Me), 6.18 (2 H, s, NH_2) and 6.70 (1 H, s, thiazole, 5-H).

Ethyl (Z)-2-(2-*aminothiazol*-4-*yl*)-2-(1-*methylcyclopropyloxyimino*)*acetate* **10l** (51%), m.p. 102–103 °C (from cyclohexane–hexane) (Found: C, 49.1; H, 5.6; N, 15.35. $C_{11}H_{15}N_3O_3S$ requires C, 49.1; H, 5.6; N, 15.6%); ν_{max}(KBr)/cm^{-1} 1733, 1612 and 1535; δ($CDCl_3$) 0.58 (2 H, m, 2 × cyclopropyl CH), 1.00 (2 H, m, 2 × cyclopropyl CH), 1.35 (3 H, t, *J* 7.1, *Me*CH_2), 1.57 (3 H, s, MeC), 4.37 (2 H, q, *J* 7.1, MeCH_2), 5.70 (2 H, br s, NH_2) and 6.73 (1 H, s, thiazole 5-H).

Ethyl (Z)-2-(2-*aminothiazol*-4-*yl*)-2-(1-*methylcyclobutyloxyimino*)*acetate* **10m** (57%), m.p. 106–107 °C (from cyclohexane) (Found: C, 51.0; H, 5.9; N, 14.5. $C_{12}H_{17}N_3O_3S$ requires C, 50.9; H, 6.05; N, 14.8%); ν_{max}(KBr)/cm^{-1} 1734, 1614 and 1540; δ($CDCl_3$) 1.37 (3 H, t, *J* 7.1, OCH_2*Me*), 1.46 (3 H, s, Me), 1.6–2.0 (4 H, m, 2 × CH_2), 2.39 (2 H, m, CH_2), 4.40 (2 H, q, *J* 7.1, OCH_2Me), 5.70 (2 H, br s, NH_2) and 6.75 (1 H, s, thiazole 5-H).

Ethyl (Z)-2-(2-*aminothiazol*-4-*yl*)-2-(1-*methylcyclopentyloxyimino*)*acetate* **10n** (64%), m.p. 94–95 °C (from ethyl acetate–hexane) (Found: C, 52.8; H, 6.4; N, 14.1. $C_{13}H_{19}N_3O_3S$ requires C, 52.5; H, 6.4; N, 14.1%); ν_{max}(CH_2Cl_2)/cm^{-1} 3475, 3380, 2960, 1735, 1605, 1530, 1175 and 970; δ($CDCl_3$) 1.34 (3 H, t, *J* 7, *Me*CH_2), 1.45 (3 H, s, MeC), 1.0–2.2 (8 H, m, 8 × cyclopentyl CH), 4.31 (2 H, q, *J* 7, OCH_2Me), 5.95 (2 H, s, NH_2) and 6.62 (1 H, s, thiazole 5-H).

Ethyl (Z)-2-(2-*aminothiazol*-4-*yl*)-2-(1-*methylcyclohexyloxyimino*)*acetate* **10o** (71%), m.p. 125.5 °C (from cyclohexane–hexane) (Found: C, 54.2; H, 6.9; N, 13.25%; M^+, 311.1303. $C_{14}H_{21}N_3O_3S$ requires C, 54.0; H, 6.8; N, 13.5%; M, 311.1303); ν_{max}(CH_2Cl_2)/cm^{-1} 3470, 3380, 1735, 1605, 1530, 1375, 1240, 1045 and 975; δ($CDCl_3$) 1.0–2.0 (16 H, m, MeC, *Me*CH_2, 10 × cyclohexyl CH), 4.35 (2 H, q, *J* 7, OCH_2Me), 5.85 (2 H, br s, NH_2) and 6.67 (1 H, s, thiazole 5-H).

Ethyl (Z)-2-(2-*aminothiazol*-4-*yl*)-2-(1-*methylcycloheptyloxyimino*)*acetate* **10p** (73%), obtained as an oil (Found: M^+, 325.1468. $C_{15}H_{23}N_3O_3S$ requires M, 325.1460); ν_{max}(CH_2Cl_2)/cm^{-1} 3470, 3380, 3260, 3110, 2930, 1730, 1605, 1520, 1210, 1175 and 1030; δ($CDCl_3$) 1.35 (3 H, s, MeC), 1.1–1.20 (15 H, m, *Me*CH_2, 12 × cycloheptyl CH), 4.33 (2 H, q, *J* 7, OCH_2Me), 6.18 (2 H, s, NH_2) and 6.61 (1 H, s, thiazole 5-H).

Ethyl (Z)-2-(2-*aminothiazol*-4-*yl*)-2-(*bicyclo*[2.2.2]*octan*-1-*yloxyimino*)*acetate* **10q** (59%), m.p. 139–140 °C (from methylene dichloride–hexane) (Found: C, 56.1; H, 6.4; N, 12.8. $C_{15}H_{21}N_3O_3S$ requires C, 55.7; H, 6.55; N, 13.0%); ν_{max}(CH_2Cl_2)/cm^{-1} 3480, 3390, 2960, 2930, 2870, 1735 and 1605; δ($CDCl_3$) 1.35 (3 H, t, *J* 7.1, *Me*CH_2), 1.57 (1 H, m, CH), 1.6–1.9 (12 H, m, 6 × CH_2), 4.37 (2 H, q, *J* 7.1, OCH_2Me), 5.49 (2 H, br s, NH_2) and 6.73 (1 H, s, thiazole 5-H).

Ethyl (Z)-2-(2-*aminothiazol*-4-*yl*)-2-*tricyclo*[3.3.1.1^{3,7}]*decan*-1-*yloxyimino*)*acetate* **10r** (47%), m.p. 152–153 °C (from ethyl acetate–hexane) (Found: C, 58.7; H, 6.6; N, 11.9; M^+, 349.1461. $C_{17}H_{23}N_3O_3S$ requires C, 58.4; H, 6.6; N, 12.0%; M, 349.1460); ν_{max}(CH_2Cl_2)/cm^{-1} 2915, 2855, 1735, 1605, 1530, 1305, 1075, 1040 and 975; δ($CDCl_3$) 1.35 (3 H, t, *J* 7, *Me*CH_2), 1.65 (6 H, br s, 6 × adamantyl CH), 1.90 (6 H, br s, 6 × adamantyl CH), 2.16 (3 H, br s, 3 × adamantyl CH), 4.37 (2 H, q, *J* 7, OCH_2Me), 5.65 (2 H, br s, NH_2) and 6.71 (1 H, s, thiazole 5-H).

Alkylation of Ethyl (Z)-2-(2-*Aminothiazol*-4-*yl*)-2-(*hydroxyimino*)*acetate* **8**.—A solution of oxime **8*** (10 g, 46.5 mmol) in DMSO (100 cm^3) was treated with cyclopentyl bromide (10.4 g, 70 mmol) and anhydrous potassium carbonate (20.5 g, 148 mmol). The mixture was stirred at 50 °C for 20 h, then poured into stirred water (1000 cm^3). The precipitate was collected by filtration, washed with water and dried at 40 °C under reduced pressure to give ethyl (*Z*)-2-(2-aminothiazol-4-yl)-2-(cyclopentyloxyimino)acetate **10f** (10.7 g, 81%), m.p. 136–138 °C (from cyclohexane) (lit.,[20] 134–136 °C) (Found: C, 51.0; H, 6.2; N, 14.6. Calc. for $C_{12}H_{17}N_3O_3S$: C, 50.9; H, 6.05; N, 14.8%); ν_{max}($CHCl_3$)/cm^{-1} 1725, 1600 and 1525; δ($CDCl_3$) 1.33 (3 H, t, *J* 7, *Me*CH_2), 1.5–1.9 (8 H, m, cyclopentyl CH_2), 4.34 (2 H, q, MeCH_2), 4.81 (1 H, m, cyclopentyl CH), 5.65 (2 H, br s, NH_2) and 6.64 (1 H, s, thiazole 5-H).

Alkylation of Ethyl (Z)-2-*Hydroxyimino*-2-(2-*tritylaminothiazol*-4-*yl*)*acetate* **9** *and Detritylation Procedure*.—Cyclohexylmethyl bromide (2.21 g, 12.5 mmol) was added to a mixture of oxime **9*** (3.08 g, 6.7 mmol) and potassium carbonate (2.07 g, 15 mmol) in DMSO (15 cm^3). The mixture was stirred for 22 h, then partitioned between ethyl acetate and water. The organic phase was washed with water and brine, dried and evaporated. The residue was dissolved in a mixture of formic acid (30 cm^3) and water (6 cm^3). After being stirred for 3 h, the mixture was evaporated and the residue was chromatographed and crystallised from cyclohexane to give *ethyl* (Z)-2-(2-*aminothiazol*-4-*yl*)-2-(*cyclohexylmethoxyimino*)*acetate* **10j** (1.2 g, 62%), m.p. 107–107.5 °C (Found: C, 54.2; H, 6.6; N, 13.3. $C_{14}H_{21}N_3O_3S$ requires C, 54.0; H, 6.8; N, 13.5%); ν_{max}($CHCl_3$)/cm^{-1} 1730 and 1600; δ($CDCl_3$) 1.0–1.8 (11 H, m, CH_2, CH), 1.33 (3 H, t, *J* 7, *Me*CH_2), 3.97 (2 H, d, *J* 6, OCH_2CH), 4.35 (2 H, q, MeCH_2), 5.60 (2 H, br s, NH_2) and 6.63 (1 H, s, thiazole 5-H).

Hydrolysis of the Ethyl Esters **10**.—(Z)-2-(2-*Aminothiazol*-4-*yl*)-2-(*cyclopentyloxyimino*)*acetic acid* **11f**. 1 mol dm^{-3} NaOH (14 cm^3) was added to a solution of ester **10f** (2.0 g, 7.06 mmol) in ethanol (30 cm^3)–water (15 cm^3). The mixture was stirred at room temperature for 16 h. The ethanol was evaporated off and the residual solution was diluted with water (25 cm^3), washed with ethyl acetate and acidified to pH 2.8 with 1 mol dm^{-3} HCl. The precipitate was collected by filtration, washed with cold water and dried at 40 °C under reduced pressure to give the title product **11f** (1.44 g, 80%), m.p. 174 °C (decomp.) (from water) [lit.,[20] 186 °C (decomp.)] (Found: C, 47.05; H, 5.2; N, 16.3. Calc. for $C_{10}H_{13}N_3O_3S$: C, 47.05; H, 5.1; N, 16.45%); ν_{max}(KBr)/cm^{-1} 1640; δ[$(CD_3)_2SO$] 1.7 (8 H, m, CH_2), 4.5 (2 H, br s, NH_2), 4.66 (1 H, m, CH), 6.79 (1 H, s, thiazole 5-H) and 7.2 (1 H, br s, CO_2H).

Similarly prepared were: (Z)-2-(2-*Aminothiazol*-4-*yl*)-2-(*t-butoxyimino*)*acetic acid* **11k** (713 mg, 29%), m.p. 164–166 °C (decomp.) (Found: C, 44.0; H, 5.4; N, 16.8%; M^+, 243.0682. $C_9H_{13}N_3O_3S$·0.25H_2O requires C, 43.6; H, 5.5; N, 17.0%; M, 243.0678); ν_{max}(KBr)/cm^{-1} 1628, 1448, 1386, 1363, 1262, 1192 and 992; δ[$(CD_3)_2SO$] 1.35 (9 H, s, Me_3C), 6.85 (1 H, s, thiazole 5-H) and 7.28 (3 H, br s, NH_2, CO_2H). Evaporation of the water washings gave a further quantity of the acid **11k** (1.03 g, 42%) (combined yield 71%).

(*Z*)-2-(2-Aminothiazol-4-yl)-2-(1-methylcyclopentyloxy-

* Purchased from Lonza Ltd, Basle.

imino)acetic acid **11n** (52%), m.p. 192–193 °C; ν_{max}(KBr)/cm^{-1} 3365, 2963, 1636, 1574, 1391 and 984; δ[$(CD_3)_2SO$] 1.37 (3 H, s, MeC), 1.54–1.61 (6 H, m, 6 × cyclopentyl CH), 1.80–1.95 (2 H, m, 2 × cyclopentyl CH), 6.81 (1 H, s, thiazole 5-H) and 7.27 (2 H, s, NH_2).

(*Z*)-2-(2-*Aminothiazol*-4-*yl*)-2-(1-*methylcyclohexyloxyimino*)*acetic acid* **11o** (69%), m.p. 203–204 °C (Found: M^+, 283.0991. $C_{12}H_{17}N_3O_3S$ requires M, 283.0991); ν_{max}(KBr)/cm^{-1} 1639, 1573, 1395, 987 and 972; δ[$(CD_3)_2$] 1.23 (3 H, s, Me), 1.31–1.51 (8 H, m, 8 × cyclohexyl CH), 1.78 (2 H, br d, *J* 12.6, 2 × cyclohexyl CH), 6.80 (1 H, s, thiazole 5-H) and 7.28 (2 H, br s, NH_2).

(*Z*)-2-(2-*Aminothiazol*-4-*yl*)-2-(1-*methylcycloheptyloxyimino*)*acetic acid* **11p** (66%), m.p. 173–179 °C (decomp.) (Found: C, 51.9; H, 6.3; N, 13.6. $C_{13}H_{19}N_3O_3S$·0.25H_2O requires C, 51.7; H, 6.5; N, 13.9%); ν_{max}(KBr)/cm^{-1} 1626; δ[$(CD_3)_2SO$] 1.26 (3 H, s, MeC), 1.27–2.0 (12 H, m, 12 × cycloheptyl CH), 6.79 (1 H, s, thiazole 5-H) and 7.27 (2 H, s, NH_2); *m*/*z* (CI) 298 (MH^+).

(*Z*)-2-(2-Aminothiazol-4-yl)-2-(bicyclo[2.2.2]octan-1-yloxyimino)acetic acid, **11q** (45%), ν_{max}(KBr)/cm^{-1} 1640, 1571, 1396 and 976; δ$(CD_3)_2SO$] 1.53 (1 H, br s, CH), 1.66 (12 H, br s, 6 × CH_2), 6.77 (1 H, thiazole 5-H) and 7.24 (2 H, s, NH_2); *m*/*z* (EI) 295 (M^+).

(*Z*)-2-(2-Aminothiazol-4-yl)-2-(tricyclo[3.3.1.1^{3,7}]decan-1-yloxyimino)acetic acid **11r**, m.p. 203–204 °C; ν_{max}(KBr)/cm^{-1} 1628, 1450, 1393, 1351, 1300 and 973; δ[$(CD_3)_2SO$] 1.73 (6 H, br s, 6 × adamantyl CH), 1.92 (6 H, br s, 6 × adamantyl CH), 2.23 (3 H, br s, 3 × adamantyl CH), 6.85 (1 H, s, thiazol 5-H) and 7.37 (2 H, br s, NH_2); *m*/*z* (EI) 277.1246 ($M^+ - CO_2$ requires *m*/*z*, 277.1249); *m*/*z* (FAB) 322 (MH^+), 344 (MNa^+), 643 [$(2M + H)^+$] and 665 [$(2M + Na)^+$].

Sodium (*Z*)-2-(2-*Aminothiazol*-4-*yl*)-2-(1-*methylcyclopropyloxyimino*)*acetate* **11l** Sodium Salt.—The ester **10l** (170 mg, 0.63 mmol) was hydrolysed in a similar way to that described above, but the aq. solution containing the sodium salt was concentrated, loaded onto HP20SS and eluted with water. Fractions containing the pure sodium salt were freeze-dried to give the title product (**11l** sodium salt) (138 mg, 78%); ν_{max}(KBr)/cm^{-1} 1616, 1531, 1401, 1255 and 956; δ(D_2O) 0.59 (2 H, m, 2 × cyclopropyl CH), 0.94 (2 H, m, 2 × cyclopropyl CH), 1.49 (3 H, s, MeC) and 6.83 (1 H, s, thiazole 5-H); *m*/*z* (FAB) 264 (MH^+) and 286 (MNa^+).

Similarly prepared was sodium (*Z*)-2-(2-aminothiazol-4-yl)-2-(1-methylcyclobutyloxyimino)acetate **11m** sodium salt (50%), ν_{max}(KBr)/cm^{-1} 1610, 1529, 1399, 1253, 1163 and 958; δ(D_2O) 1.42 (3 H, s, MeC), 1.50–1.85 (2 H, m, 2 × cyclobutyl CH), 1.85–2.0 (2 H, m, 2 × cyclobutyl CH), 2.20–2.35 (2 H, m, 2 × cyclobutyl CH) and 6.79 (1 H, s, thiazole 5-H); *m*/*z* (FAB) 278 (MH^+) and 300 (MNa^+).

Preparation of Thioesters **12**.—S-2-*Pyridyl* (Z)-2-(2-*aminothiazol*-4-*yl*)-2-(*cyclohexyloxyimino*)*thioacetate* **12g**. 2,2′-Dithiodipyridine (7.95 g, 36 mmol) was added to a solution of triphenylphosphine (9.46 g, 36 mmol) in acetonitrile (80 cm^3). After 15 min the mixture was cooled to 0 °C and acid **11g** (6.5 g, 24 mmol) was added. The mixture was allowed to warm to room temperature and was stirred for 4 h. The solvent was evaporated off and the residue was chromatographed to give the *title product* **12g** (7.4 g, 85%), m.p. 154–156 °C (from ethyl acetate–hexane) (Found: C, 52.9; H, 5.3; N, 15.3. $C_{16}H_{18}N_4O_2S_2$ requires C, 53.0; H, 5.0; N, 15.5%); ν_{max}(KBr)/cm^{-1} 1683, 1645 and 1537; δ($CDCl_3$) 1.3–2.0 (10 H, m, CH_2), 4.33 (1 H, m, CH), 5.69 (2 H, br s, NH_2), 6.82 (1 H, s, thiazole 5-H), 7.34 (1 H, m, pyridine-H), 7.76 (2 H, m, pyridine-H) and 8.66 (1 H, m, pyridine-H).

Similarly prepared were: S-2-*Pyridyl* (*Z*)-2-(2-*aminothiazol*-4-*yl*)-2-(*t-butoxyimino*)*thioacetate* **12k** (90%), m.p. 155–156 °C (from ethyl acetate–hexane) (Found: C, 50.0; H, 4.8; N, 16.8%; M^+, 336.0704. $C_{14}H_{16}N_4O_2S_2$ requires C, 50.0; H, 4.8; N, 16.65%; M, 336.0715); δ[($CDCl_3$) + $(CD_3)_2SO$] 1.31 (9 H, s, Me_3C), 6.74 (1 H, s, thiazole 5-H) and 6.8–8.7 (6 H, m, NH_2, 4 × pyridyl CH).

S-2-*Pyridyl* (Z)-2-(2-*aminothiazol*-4-*yl*)-2-(1-*methylcyclopentyloxyimino*)*thioacetate* **12n** (57%) (except that the reaction time was 20 min), m.p. 146–149 °C (from ethyl acetate) (Found: C, 52.9; H, 4.9; N, 15.5%; M^+, 362. $C_{16}H_{18}N_4O_2S_2$ requires C, 53.0; H, 5.0; N, 15.5%; M, 362); ν_{max}(KBr)/cm^{-1} 1697, 1649, 1624, 1573, 1539, 1421, 1207, 990 and 924; δ[$(CD_3)_2SO$] 1.39 (3 H, s, Me), 1.63 (6 H, m, 6 × cyclopentyl CH), 1.92 (2 H, m, 2 × cyclopentyl CH), 6.92 (1 H, s, thiazole 5-H), 7.71 (1 H, dd, *J* 7.8 and 0.8, pyridyl CH), 7.37 (2 H, s, NH_2), 7.50 (1 H, m, pyridyl CH), 7.96 (1 H, dt, *J* 1.9 and 7.7, pyridyl CH) and 8.64 (1 H, m, pyridyl CH).

S-2-*Pyridyl* (Z)-2-(2-*Aminothiazol*-4-*yl*)-2-(*1-methylcyclohexyloxyimino*)*thioacetate* **12o** (71%), m.p. 158 °C (from ethyl acetate–hexane) (Found: C, 54.4; H, 5.3; N, 14.9%; M^+, 376.1029. $C_{17}H_{20}N_4O_2S_2$ requires C, 54.2; H, 5.35; N, 14.9%; M, 376.1028); ν_{max}(KBr)/cm^{-1} 1694, 1652, 1623, 1538, 1419, 1059, 988, 936 and 918; δ[$(CD_3)_2SO$] 1.23 (3 H, s, Me), 1.48 (8 H, m, 8 × cyclohexyl CH), 1.84 (2 H, br d, *J* 12.8, 2 × cyclohexyl (CH), 6.91 (1 H, s, thiazole 5-H), 7.36 (2 H, s, NH_2), 7.50 (1 H, m, pyridyl CH), 7.71 (1 H, d, *J* 7.8, pyridyl CH), 7.96 (1 H, dt, *J* 1.8 and 7.7, pyridyl CH) and 8.64 (1 H, m, pyridyl CH).

S-2-Pyridyl (*Z*)-2-(2-Aminothiazol-4-yl)-2-(1-methylcycloheptyloxyimino)thioacetate **12p** (except that the reaction time was 20 min and the solvent used was methylene dichloride) (88%), an oil; ν_{max}(CH_2Cl_2)/cm^{-1} 3300, 3130, 2920, 1690, 1525, 1050, 985 and 925; δ($CDCl_3$) 1.36 (3 H, s, Me), 1.4–2.2 (12 H, m, 12 × cycloheptyl CH), 6.77 (1 H, s, thiazole 5-H), 6.98 (2 H, s, NH_2), 7.25 (1 H, m, pyridyl CH), 7.65 (2 H, br s, 2 × pyridyl CH) and 8.62 (1 H, m, pyridyl CH).

S-2-*Pyridyl* (Z)-2-(2-*aminothiazol*-4-*yl*)-2-(*tricyclo*[3.3.1.1^{3,7}]-*decan*-1-*yloxyimino*)*thioacetate* **12r** (87%), m.p. >300 °C (from acetonitrile) (Found: C, 57.8; H, 5.4; N, 12.9%; M^+, 414.1184. $C_{20}H_{22}N_4O_2S_2$ requires C, 57.9; H, 5.35; N, 13.5%; M^+, 414.1184); ν_{max}(Nujol)/cm^{-1} 3290, 3125, 1680, 1645, 1530, 1345, 1070, 990, 925 and 915; δ[$(CD_3)_2SO$] 1.61 (6 H, br s, 6 × adamantyl CH), 1.81 (6 H, br s, 6 × adamantyl CH), 2.15 (3 H, br s, 3 × adamantyl CH), 6.9 (1 H, s, thiazole 5-H), 7.36 (2 H, s, NH_2), 7.5 (1 H, m, pyridyl CH), 7.7 (1 H, d, *J* 7.8, pyridyl CH), 7.94 (1 H, m, pyridyl CH) and 8.64 (1 H, m, pyridyl CH).

Formation of Penicillins **4** *using the Thioester Coupling Procedure.—Sodium* 6β-[(Z)-2-(2-*aminothiazol*-4-*yl*)-2-(*cyclohexyloxyimino*)*acetamido*]*penicillanate* **4g**. To a solution of 6β-aminopenicillanic acid (3.29 g, 15.2 mmol) in methylene dichloride (70 cm^3) was added triethylamine (4.67 cm^3, 33.5 mmol) and trimethylsilyl chloride (4.25 cm^3, 33.5 mmol). The mixture was heated under reflux for 1 h, cooled to 0 °C, and the thioester **12g** (4.6 g, 12.7 mmol) was added. After the mixture had been stirred at room temperature for 26 h the solvent was evaporated off. The residue was partitioned between ethyl acetate and water, and the pH was adjusted to 7. Ethyl acetate was added to the aq. layer and the pH was adjusted to 2.8 (1 mol dm^{-3} HCl). This organic phase was washed successively with water and brine. Water was added to the organic phase and the pH was adjusted to 7 (1 mol dm^{-3} NaOH). The aq. phase was concentrated and chromatographed on HP20SS. Lyophilisation gave the title product **4g** (3.49 g, 56%); ν_{max}(KBr)/cm^{-1} 1766, 1662 and 1608; δ(D_2O) 1.3–1.9 (10 H, m, CH_2), 1.53 (3 H, s, 2-Me), 1.64 (3 H, s, 2-Me), 4.25 (2 H, s + m, 3-H, CH), 5.64 and 5.68 (2 H, d + d, *J* 4, 5- and 6-H) and 6.99 (1 H, s, thiazole 5-H); *m*/*z* (FAB) 512 (MNa^+) and 490 (MH^+).

The following penicillins were prepared from the esters **10h**,

10i and **10j**; yields are given for ester hydrolysis, thioester formation and penicillin coupling.

Sodium 6β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(cycloheptyloxyimino)acetamido]penicillanate **4h** (76, 21, 44%); ν_{max}(KBr)/cm^{-1} 1767, 1668 and 1610; δ(D_2O) 1.4–1.9 (12 H, m, CH_2), 1.51 (3 H, s, 2-Me), 1.62 (3 H, s, 2-Me), 4.23 (1 H, s, 3-H), 4.44 (1 H, m, CH), 5.62 and 5.65 (2 H, d + d, *J* 4, 5- and 6-H) and 6.96 (1 H, s, thiazole 5-H); *m/z* (FAB) 526 (MNa^+) and 504 (MH^+).

Sodium 6β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(cyclooctyloxyimino)acetamido]pencillanate **4i** (93, 94, 29%); ν_{max}(KBr)/cm^{-1} 1766, 1670 and 1608; δ(D_2O) 1.5–1.9 (14 H, m, CH_2), 1.50 (3 H, s, 2-Me), 1.60 (3 H, s, 2-Me), 4.19 (1 H, s, 3-H), 4.36 (1 H, m, CH), 5.59 and 5.63 (2 H, d + d, *J* 4, 5- and 6-H) and 6.90 (1 H, s, thiazole 5-H); *m/z* (FAB) 540 (MNa^+) and 518 (MH^+).

Sodium 6β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(cyclohexylmethoxyimino)acetamido]penicillanate **4j** (77, 70, 42%); ν_{max}(KBr)/cm^{-1} 1766, 1668 and 1608; δ(D_2O) 0.97 (2 H, m, CH_2), 1.20 (3 H, m, CH_2, CH), 1.51 (3 H, s, 2-Me), 1.62 (3 H, s, 2-Me), 1.68 (6 H, m, CH_2), 4.01 (2 H, m, OCH_2), 4.22 (1 H, s, 3-H), 5.61 and 5.64 (2 H, d + d, *J* 4, 5- and 6-H) and 6.97 (1 H, s, thiazole 5-H); *m/z* (FAB) 526 (MNa^+) and 504 (MH^+).

Similarly prepared from the thioesters were: sodium 6β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(t-butoxyimino)acetamido]penicillanate **4k** (447 mg, 32%) (the reaction was allowed to proceed for 44 h), ν_{max}(KBr)/cm^{-1} 1766, 1516, 1456, 1398, 1365 and 1323; δ(D_2O) 1.33 (9 H, s, Me_3C), 1.51 (3 H, s, 2-Me), 1.62 (3 H, s, 2-Me), 4.23 (1 H, s, 3-H), 5.62 (1 H, d, *J* 4.1, 5-H), 5.67 (1 H, d, *J* 4.0, 6-H) and 6.95 (1 H, s, thiazole 5-H); *m/z* (FAB) 464 (MH^+).

Sodium 6β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(1-methylcyclopentyloxyimino)acetamido]penicillanate **4n** (30%) (reaction time 70 h), λ_{max}(H_2O)/nm 290 (ε/dm^3 mol^{-1} cm^{-1} 7730) and 232 (12 580); ν_{max}(KBr)/cm^{-1} 1765, 1608, 1525, 1397 and 1323; δ(D_2O) 1.43 (3 H, s, Me), 1.51 (3 H, s, Me) 1.92 (9 H, s, superimposed on m, Me, 6 × cyclopentyl CH), 1.98 (2 H, m, 2 × cyclopentyl CH), 4.22 (1 H, s, 3-H), 5.62 (1 H, d, *J* 4.0, 5-H), 5.66 (1 H, d, *J* 4.0, 6-H) and 6.94 (1 H, s, thiazole 5-H); *m/z* (FAB) 512 (MNa^+).

Sodium 6β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(1-methylcyclohexyloxyimino)acetamido]penicillanate **4o** (32%) (reaction time 48 h), ν_{max}(KBr)/cm^{-1} 1766, 1662, 1608, 1515, 1398 and 1322; δ(D_2O) 1.28 (3 H, s, MeC), 1.41 (8 H, br m, 8 × cyclohexyl CH), 1.51 (3 H, s, Me), 1.61 (3 H, s, Me), 1.87 (2 H, m, 2 × cyclohexyl CH), 4.22 (1 H, s, 3-H), 5.62 (1 H, d, *J* 3.9, 5-H), 5.69 (1 H, d, *J* 4.0, 6-H) and 6.93 (1 H, s, thiazole 5-H); *m/z* (FAB) 504 (MH^+) and 526 (MNa^+).

Sodium 6β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(1-methylcycloheptyloxyimino)acetamido]penicillanate **4p** (37%) (reaction time 4 days), λ_{max}(EtOH)/nm 288 (ε/dm^3 mol^{-1} cm^{-1} 8050) and 232 (12 130); ν_{max}(KBr)/cm^{-1} 1766, 1675, 1609 and 1515; δ(D_2O) 1.32 (3 H, s, MeC), 1.52 (3 H, s, MeC), 1.62 (3 H, s, MeC), 1.3–1.7 (10 H, m, 10 × cycloheptyl CH), 1.85–2.05 (2 H, m, 2 × cycloheptyl CH), 4.22 (1 H, s, 3-H), 5.63 (1 H, d, *J* 4.1, 5-H), 5.68 (1 H, d, *J* 4.0, 6-H) and 6.93 (1 H, s, thiazole 5-H); *m/z* (FAB) 518 (MH^+) and 540 (MNa^+).

Sodium 6β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(tricyclo-[3.3.1.1^{3,7}]decan-1-yloxyimino)acetamido]penicillanate **4r** (32%) (reaction time 80 h), ν_{max}(KBr) 1766, 1685, 1608, 1515, 1351, 1397, 1070 and 964; δ(D_2O) 1.52 (3 H, s, MeC), 1.63 (9 H, br s, MeC, 6 × adamantyl CH), 1.90 (6 H, m, 6 × adamantyl CH), 2.17 (3 H, br s, 3 × adamantyl CH), 4.24 (1 H, s, 3-H), 5.63 (1 H, d, *J* 4, 5-H), 5.68 (1 H, d, *J* 4.1, 6-H) and 6.96 (1 H, s, thiazole 5-H); *m/z* (FAB) 542 (MH^+) and 564 (MNa^+).

Preparation of Penicillins via *the Mixed Sulphonic Acid Anhydride Route.—Sodium* 6β-[(Z)-2-(2-*aminothiazol*-4-*yl*)-2-(*cyclopentyloxyimino*)*acetamido*]*penicillanate* **4f**.—A solution of acid **11f** (5.0 g, 19.6 mmol) in dimethylformamide (DMF) (25 cm^3) was treated with *N*,*N*-diisopropylethylamine (3.9 cm^3, 22 mmol), then cooled to −50 °C. Methanesulphonyl chloride (1.75 cm^3, 22 mmol) was added and the solution was stirred at −50 °C for a further 1 h, then added to a preformed solution of 6β-aminopenicillanic acid (5.3 g, 24 mmol) and triethylamine (6.6 cm^3, 47 mmol) in water (20 cm^3) at 0 °C. After the mixture had been stirred for 10 min at 0 °C, ethyl acetate and water were added. The pH was adjusted to 2.8 with 1 mol dm^{-3} HCl. The organic phase was washed successively with water and brine. Water was added to the organic phase and the pH adjusted to 7 with 1 mol dm^{-3} NaOH; the aq. phase was then concentrated and chromatographed on HP20SS. Lyophilisation gave the title product **4f** (5.2 g, 56%), ν_{max}(KBr)/cm^{-1} 1764, 1662 and 1607; δ(D_2O) 1.52 (3 H, s, 2-Me), 1.63 (3 H, s, 2-Me), 1.6–1.8 (8 H, m, CH_2), 4.23 (1 H, s, 3-H), 4.80 (1 H, m, CH), 5.62 and 5.64 (2 H, d + d, *J* 4, 5- and 6-H) and 6.98 (1 H, s, thiazole 5-H); *m/z* (FAB) 498 (MNa^+) and 476 (MH^+).

Similarly prepared were: Sodium 6β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(cyclopropyloxyimino)acetamido]penicillanate **4d** (30%), ν_{max}(KBr)/cm^{-1} 1765 and 1610; δ(D_2O) 0.6–0.9 (4 H, m, CH_2), 1.50 (3 H, s, 2-Me), 1.60 (3 H, s, 2-Me), 4.13 (1 H, m, CH), 4.22 (1 H, s, 3-H), 5.60 (2 H, s, 5- and 6-H) and 7.04 (1 H, s, thiazole 5-H); *m/z* (FAB) 470 (MNa^+) and 448 (MH^+).

Sodium 6β-[(*Z*)-2-(2-chloroacetamidothiazol-4-yl)-2-(cyclobutyloxyimino)acetamido]penicillanate **20** (38%), ν_{max}(KBr)/cm^{-1} 1768, 1670 and 1603; δ(D_2O) 1.48–1.85 (2 H, m, CH_2), 1.49 (3 H, s, 2-Me), 1.60 (3 H, s, 2-Me), 2.01–2.29 (4 H, m, CH_2), 4.22 (1 H, s, 3-H), 4.35 (2 H, s, $ClCH_2$), 5.63 and 5.66 (2 H, d + d, *J* 4, 5- and 6-H) and 7.48 (1 H, s, thiazole 5-H); *m/z* (FAB) 560 (MNa^+) and 538 (MH^+).

Sodium 6β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(bicyclo[2.2.2]-octan-1-yloxyimino)acetamido]penicillanate **4q** (300 mg, 55%), ν_{max}(KBr)/cm^{-1} 1768, 1669, 1601 and 1517; δ(D_2O) 1.49 (3 H, s, 2-Me), 1.50 (1 H, br s, CH), 1.61 (3 H, s, 2-Me), 1.72 (12 H, br s, 12 × CH), 4.20 (1 H, s, 3-H), 5.59 (1 H, d, *J* 4.0, 5-H), 5.64 (1 H, d, *J* 4.0, 6-H) and 6.92 (1 H, s, thiazole 5-H); *m/z* (FAB) 516 (MH^+) and 538 (MNa^+).

Sodium 6β-[(Z)-2-(2-*Aminothiazol*-4-*yl*)-2-(1-*methylcyclopropyloxyimino*)*acetamido*]*penicillanate* **41**.—The sodium salt of the acid **11l** (0.13 g, 0.49 mmol) was suspended in dry DMF (2 cm^3), the mixture was cooled to −55 °C, methanesulphonyl chloride (0.043 cm^3, 64 mg, 0.55 mmol) was added, and the mixture was allowed to warm to −10 °C during 40 min. The resultant solution of the mixed sulphonic acid anhydride was then added to a solution of 6-APA (140 mg, 0.65 mmol) and triethylamine (0.15 cm^3, 108 mg, 1.08 mmol) in water (2 cm^3) at 0 °C. After being stirred for 10 min the mixture was diluted with water, its pH was adjusted to 7.0 (from 5.0), and the mixture was washed with ethyl acetate. The penicillin was then extracted into ethyl acetate at pH 2.8 (2 ×), the extracts were washed with brine, and the penicillin was then extracted into water at pH 7.0. The aq. solution was concentrated and chromatographed on HP20SS to give the penicillin **41** (0.141 g, 62%); ν_{max}(KBr)/cm^{-1} 1765, 1663, 1610 and 1528; δ(D_2O) 0.64 (2 H, m, 2 × cyclo-propyl CH), 0.97 (2 H, m, 2 × cyclopropyl CH), 1.50 (3 H, s, Me), 1.52 (3 H, s, Me), 1.60 (3 H, s, Me), 4.21 (1 H, s, 3-H), 5.59 and 5.62 (2 H d + d, *J* 4, 5- and 6-H) and 7.02 (1 H, s, thiazole 5-H); *m/z* (FAB) 484 (MNa^+) and 462 (MH^+).

Similarly prepared was: Sodium 6β-[(*Z*)-2-(2-aminothiazol-4-yl)-2-(1-methylcyclobutyloxyimino)acetamido]penicillanate **4m** (62%); ν_{max}(KBr)/cm^{-1} 1765, 1663 and 1609; δ(D_2O) 1.45 (3 H, s, Me), 1.51 (3 H, s, Me), 1.62 (3 H, s, Me), 1.6–2.0 (4 H, m, 4 × cyclobutyl CH), 2.30 (2 H, m, 2 × cyclobutyl CH), 4.23 (1 H, s, 3-H), 5.62 and 5.66 (2 H, d + d, *J* 4, 5- and 6-H) and 6.98 (1 H, s, thiazole 5-H); *m/z* (FAB) 498 (MNa^+), 476 (MH^+) and 454 [(M − Na + 2 H)$^+$].

Removal of the Chloroacetamido Protecting Group.—*Sodium* 6β-[(Z)-2-(2-*aminothiazol-4-yl*)-2-(*cyclobutyloxyimino*)*acetamido*]*penicillinate* **4e**. Sodium *N*-methyldithiocarbamate[21] (32 mg, 0.25 mmol) was added to a solution of the penicillin **20** (134 mg, 0.25 mmol) in water (2 cm^3)–THF (1 cm^3), and the mixture was stirred for 1.5 h. Water (5 cm^3) was added and the THF was evaporated off. The residual solution was chromatographed on HP20SS. Lyophilisation gave the title product **4e** (91 mg, 79%); ν_{max}(KBr)/cm^{-1} 1768, 1663 and 1603; δ(D_2O) 1.49 (3 H, s, 2-Me), 1.60 (3 H, s, 2-Me), 1.5–1.9 (2 H, m, CH_2), 2.0–2.35 (4 H, m, CH_2), 4.21 (1 H, s, 3-H), *ca.* 4.63 (1 H, m, CH, obscured by HOD), 5.61 and 5.63 (2 H, d + d, *J* 4, 5- and 6-H) and 6.99 (1 H, s, thiazole 5-H); *m/z* (FAB) 462 (MH^+) and 440 [$(M - Na + 2H)^+$].

Preparation of (Z)-2-(2-*Chloroacetamidothiazol-4-yl*)-2-(*cyclobutyloxyimino*)*acetic Acid* **19**.—N-*Cyclobutyloxyphthalimide* **17**. Cyclobutanol (2.52 g, 35 mmol), triphenylphosphine (13.8 g, 53 mmol) and *N*-hydroxyphthalimide **16** (6.85 g, 42 mmol) were dissolved in THF (200 cm^3) and treated dropwise with a solution of diethyl azodicarboxylate (DEAD) (8.27 cm^3, 53 mmol) in THF (10 cm^3). The mixture was stirred for 1.5 h and then evaporated. The residue was chromatographed and recrystallised from ethyl acetate–hexane to give the *title product* **17** (5.0 g, 66%), m.p. 95–96 °C (Found: C, 66.3; H, 5.1; N, 6.4. $C_{12}H_{11}NO_3$ requires C, 66.35; H, 5.1; N, 6.45%); ν_{max}(CH_2Cl_2)/cm^{-1} 1785 and 1730; δ($CDCl_3$) 1.5–2.4 (6 H, m, CH_2), 4.78 (1 H, quintet, *J* 7, CH) and 7.80 (4 H, m, Ph).

(2-*Chloroacetamidothiazol-4-yl*)*glyoxylic acid* **15**. A solution of ethyl (2-aminothiazol-4-yl)glyoxylate **13** (16.0 g, 80 mmol) in DMA (120 cm^3) was treated with chloroacetyl chloride (19.2 cm^3, 240 mmol) and stirred for 1 h. Ethyl acetate (400 cm^3) and water (200 cm^3) were added, followed by 0.5 mol dm^{-3} NaOH (400 cm^3). After separation the organic layer was shaken vigorously with 1 mol dm^{-3} NaOH (2 × 200 cm^3). Ethyl acetate was added to the combined 1 mol dm^{-3} NaOH extracts followed by addition of 5 mol dm^{-3} HCl (80 cm^3) and sodium chloride (100 g). The aq. layer was extracted with a further portion of ethyl acetate, and the combined extracts were dried and evaporated. The residue was triturated with diethyl ether, and the resulting solid was collected by filtration, washed with diethyl ether and dried to give the product **15** (13.6 g, 68%), m.p. 200–205 °C (decomp.) (from water) [lit.,[11] 205–210 °C (decomp.)] (Found: C, 33.9; H, 2.2; N, 11.1. Calc. for $C_7H_5ClN_2O_4S$: C, 33.8; H, 2.0; N, 11.3%); ν_{max}(KBr)/cm^{-1} 1720, 1705 and 1677; δ[$(CD_3)_2SO$] 4.42 (2 H, s, CH_2), 8.46 (1 H, s, thiazole 5-H) and 13.01 (2 H, s, NH and OH).

(Z)-2-(2-*Chloroacetamidothiazol-4-yl*)-2-(*cyclobutyloxyimino*)*acetic acid* **19**. A solution of *N*-cyclobutyloxyphthalimide **17** (4.95 g, 22.8 mmol) in methylene dichloride (100 cm^3) was treated with hydrazine hydrate (2.28 g, 45.6 mmol) in methanol (10 cm^3). After 1 h, 5 mol dm^{-3} ammonium hydroxide (100 cm^3) was added. The aq. phase was extracted with more methylene dichloride, and the combined organic phases were evaporated to leave cyclobutyloxyamine **18**.

The oxyamine **18** was taken up in THF (100 cm^3) and the solution was added to a solution of (2-chloroacetamidothiazol-4-yl)glyoxylic acid **15** (5.67 g, 22.8 mmol) in THF (100 cm^3)–water (100 cm^3). The pH of the mixture was maintained at 5.0 by the addition of 2.5 mol dm^{-3} NaOH. After 1.5 h the mixture was diluted with water (100 cm^3), the pH was adjusted to 7.0 and the THF was evaporated off. The residual aq. solution was washed with ethyl acetate. Further ethyl acetate was added and the pH was adjusted to 2.5 (1 mol dm^{-3} HCl). The aq. layer was extracted a further four times with ethyl acetate, and the combined extracts were dried and evaporated. Recrystallisation from ethyl acetate gave the *title product* **19** (5.8 g, 80%), m.p. 187 °C (decomp.) (Found: C, 41.7; H, 3.7; N, 13.1; Cl, 11.2; S, 9.85. $C_{11}H_{12}N_3ClO_4S$ requires C, 41.6; H, 3.8; N, 13.2; Cl, 11.2; S, 10.1%); ν_{max}(KBr)/cm^{-1} 1713, 1576 and 1543; δ($CDCl_3$–CD_3OD 2:1) 1.6–2.4 (6 H, m, CH_2), 4.27 (2 H, s, $ClCH_2CO$), 4.82 (1 H, quintet, *J* 7, CH) and 7.36 (1 H, s, thiazole 5-H).

Preparation of Ethyl (Z)-2-(1-*Methylcyclopropyloxyimino*)-3-*oxobutyrate* **61** *and Ethyl* (Z)-2-*Cyclopropyloxyimino*-3-*oxobutyrate*[17] **6d**.—2-*Bromo*-1-(*t-butyldimethylsiloxy*)*propane* **22**. A solution of 2-bromopropionyl chloride **21** (10 cm^3, 0.10 mol) in diethyl ether (30 cm^3) was added dropwise to a suspension of lithium aluminium hydride (3.8 g, 0.10 mol) in diethyl ether (250 cm^3) during 1 h at 0 °C. After being stirred for a further 0.5 h, the mixture was heated to reflux, cooled, and water (3.8 cm^3), 15% aq. NaOH (3.8 cm^3) and water (11.4 cm^3) were sequentially added. Filtration and evaporation gave a liquid, which was distilled to afford 2-bromopropyl alcohol (7.2 g, 52%), b.p. 73–75 °C at 30 mmHg (lit.,[22] 62.8–64.0 °C at 24 mmHg).

4-Dimethylaminopyridine (DMAP) (0.63 g, 5.1 mmol) was added to a mixture of 2-bromopropyl alcohol (7.1 g, 51 mmol), t-butyldimethylsilyl chloride (9.24 g, 61.3 mmol) and triethylamine (10.7 cm^3, 76.8 mmol) in methylene dichloride (100 cm^3) at 0 °C. After being stirred at room temperature for 18 h the mixture was washed successively with dil. HCl, saturated aq. $NaHCO_3$ and water, dried, and evaporated. The residue was distilled to give the title compound **22** (12.6 g, 97%), b.p. 102–106 °C at 25 mmHg; δ(CCl_4) 0.05 (6 H, s, $SiMe_2$), 0.87 (9 H, s, Me_3CSi), 1.63 (3 H, d, *J* 6.2, *Me*CH) and 3.7 (3 H, m, $CHCH_2$).

Ethyl (Z)-2-{[1-(*t-Butyldimethylsiloxy*)*propan*-2-*yl*]*oxyimino*}-3-*oxobutyrate* **23**. A mixture of bromide **22** (1.76 g, 6.92 mmol), ethyl (*Z*)-2-hydroxyimino-3-oxobutyrate **5** (1.0 g, 6.29 mmol), potassium carbonate (1.13 g, 8.2 mmol) and DMSO (5 cm^3) was stirred at room temperature for 16 h, then partitioned between ethyl acetate and water. The organic phase was washed successively with water and brine, dried and evaporated. The residue was purified by chromatography to give the title compound **23** (1.07 g, 51%) as an oil, ν_{max}(neat)/cm^{-1} 2940, 1740 and 1695; δ($CDCl_3$) 0.05 (6 H, s, Me_2Si), 0.89 (9 H, s, Me_3CSi), 1.31 (3 H, d, *J* 6.3, *Me*CH), 1.32 (3 H, t, *J* 7, *Me*CH_2), 2.39 (3 H, s, MeCO), 3.73 (2 H, m, CH_2OSi), 4.33 (2 H, dq, MeCH_2) and 4.47 (1 H, m, CH); *m/z* (CI, isobutane) 332 (MH^+).

Ethyl (Z)-2-[(1-*bromopropan*-2-*yl*)*oxyimino*]-3-*oxobutyrate* **24**. Bromine (0.52 cm^3, 10.0 mmol) was added dropwise to a solution of triphenylphosphine (2.66 g, 10.1 mmol) in chloroform (30 cm^3) at 10 °C. To the resulting suspension of triphenylphosphine dibromide was added a solution of the silyl ether **23** (3.05 g, 9.21 mmol) in chloroform (10 cm^3). After 10 min at room temperature and 30 min at reflux, the solvent was evaporated off and the residue was chromatographed to give the title compound **24** (2.12 g, 82%) as an oil; ν_{max}(neat)/cm^{-1} 1740 and 1695; δ($CDCl_3$) 1.34 (3 H, t, *J* 7.1, *Me*CH_2), 1.46 (3 H, d, *J* 6.4, *Me*CH), 2.41 (3 H, s, MeCO), 3.53 (2 H, m, CH_2Br), 4.36 (2 H, q, MeCH_2) and 4.60 (1 H, m, CH); *m/z* (CI, isobutane) 282 and 280 (MH^+).

Ethyl (Z)-2-[(1-*bromopropan*-2-*yl*)*oxyimino*]-3,3-*ethylenedioxybutyrate* **26**. Oxime **24** (1.05 g, 3.75 mmol), ethylene glycol (1.9 g, 31 mmol), toluene-*p*-sulphonic acid (PTSA) monohydrate (0.12 g, 0.63 mmol) and benzene (20 cm^3) were heated under reflux with azeotropic removal of water. After four days the mixture was diluted with ethyl acetate, washed successively with water and brine, dried and evaporated. Purification by chromatography gave the acetal **26** (1.03 g, 85%) as an oil, ν_{max}(neat)/cm^{-1} 1735; δ($CDCl_3$) 1.34 (3 H, t, *J* 7, *Me*CH_2), 1.36 (3 H, d, *J* 6.4, MeCH), 1.66 (3 H, s, MeC) 3.43 and 3.53 (2 H, dd + dd, *J* 10.5, 6.3 and 4.4, CH_2Br), 4.02 (4 H, m, OCH_2CH_2O), 4.33 (2 H, q, MeCH_2) and 4.44 (1 H, m, CH); *m/z* (CI, isobutane) 326 and 324 (MH^+).

Ethyl (Z)-3,3-*Ethylenedioxy*-2-(*isopropenyloxyimino*)*butyrate*

28. A mixture of potassium t-butoxide (0.38 g, 3.39 mmol) in THF (25 cm^3) was added dropwise to a solution of the acetal **26** (1.0 g, 3.09 mmol) in DMSO (9 cm^3) at 0 °C. After being stirred at 0 °C for 10 min the mixture was poured into ice–water and extracted with ethyl acetate. The extract was washed successively with water and brine, dried and evaporated to give the *title product* **28** (0.714 g, 95%) as an oil (Found: M^+, 243.1107. $C_{11}H_{17}NO_5$ requires M, 243.1107); ν_{max}(neat)/cm^{-1} 1730 and 1650; δ($CDCl_3$) 1.35 (3 H, t, *J* 7.1, *Me*CH_2), 1.70 (3 H, s, MeC), 1.86 (3 H, d, *J* 0.9, *Me*C=CH_2), 4.03 (4 H, m, OCH_2CH_2O), 4.08 (1 H, m, C=CH), 4.36 (2 H, q, MeCH_2) and 4.60 (1 H, d, *J* 1.2, C=CH).

Ethyl (Z)-3,3-[*ethylenedioxy*-2-(1-*methylcyclopropyloxyimino*)*butyrate*] **30**. A solution of diethylzinc (0.603 cm^3, 5.88 mmol) in cyclohexane (1.9 cm^3) was added to a solution of the isopropenyl oxime **28** (0.714 g, 2.94 mmol) in benzene (15 cm^3), followed by a solution of methylene diiodide (0.51 cm^3, 6.33 mmol) in benzene (5 cm^3) during 15 min. After 1 h at room temperature the mixture was partitioned between ethyl acetate and water, and acidified with dil. HCl. The organic phase was washed successively with water and brine, dried and evaporated. Chromatography gave the oxime **30** (0.55 g, 73%) as an oil, ν_{max}(neat)/cm^{-1} 1730; δ($CDCl_3$) 0.53 (2 H, m, cyclopropyl CH), 0.92 (2 H, m, cyclopropyl CH), 1.30 (3 H, t, *J* 7.1, *Me*CH_2), 1.49 (3 H, s, 1′-Me), 1.65 (3 H, s, 3-Me), 4.00 (4 H, m, OCH_2CH_2O) and 4.29 (2 H, q, MeCH_2); *m*/*z* (CI, isobutane) 258 (MH^+).

Ethyl (Z)-2-(1-*methylcyclopropyloxyimino*)-3-*oxobutyrate* **61**. TFA (9 cm^3) was added to a solution of acetal **30** (0.55 g, 2.14 mmol) in THF (9 cm^3)–water (0.2 cm^3). The mixture was stirred for 16 h at room temperature; after evaporation the residue was dissolved in ethyl acetate and washed successively with saturated aq. sodium hydrogen carbonate, water and brine, dried and evaporated. Chromatography gave the oxime **61** (0.315 g, 69%) as an oil, ν_{max}(neat)/cm^{-1} 1745 and 1695; δ($CDCl_3$) 0.64 (2 H, m, cyclopropyl CH), 1.02 (2 H, m, cyclopropyl CH), 1.32 (3 H, t, *J* 7.1, *Me*CH_2), 1.58 (3 H, s, MeC), 2.42 (3 H, s, 3-Me) and 4.33 (2 H, q, MeCH_2).

Ethyl (Z)-2-(2-*bromoethoxyimino*)-3-*oxobutyrate* **25**. A mixture of oxime **5** (10 g, 62.9 mmol), DMF (140 cm^3), potassium carbonate (5.2 g, 37.7 mmol) and ethylene dibromide (40 cm^3, 464 mmol) was stirred at room temperature for 19 h, then poured into water and extracted with ethyl acetate. The extract was washed with brine, dried and evaporated. Chromatography gave the oxime **25** (12.5 g, 75%) as an oil (Found: M^+, 264.9963. $C_8H_{12}BrNO_4$ requires M, 264.9950); ν_{max}($CHCl_3$)/cm^{-1} 1740 and 1690; δ($CDCl_3$) 1.32 (3 H, t, *J* 7, *Me*CH_2), 2.38 (3 H, s, MeCO), 3.54 (2 H, t, *J* 7, OCH_2CH_2Br), 4.30 (2 H, t, OCH_2CH_2Br) and 4.48 (2 H, q, MeCH_2).

Ethyl (Z)-2-(2-*bromoethoxyimino*)-3,3-*ethylenedioxybutyrate* **27**. Oxime **25** (2.0 g, 7.5 mmol), ethylene glycol (1.5 cm^3, 26 mmol), PTSA monohydrate (0.143 g, 0.75 mmol) and benzene (20 cm^3) were heated under reflux with azeotropic removal of water. After 28 h the mixture was diluted with ethyl acetate, washed successively with water, saturated aq. sodium hydrogen carbonate and brine, dried and evaporated. Purification by chromatography gave the *acetal* **27** as an oil (2.0 g, 86%) (Found: MH^+, 310.0290. $C_{10}H_{17}BrNO_5$ requires *m*/*z*, 310.0290); ν_{max}($CHCl_3$)/cm^{-1} 1730; δ($CDCl_3$) 1.30 (3 H, t, *J* 7, *Me*CH_2), 1.61 (3 H, s, Me), 3.46 (2 H, t, *J* 7, CH_2CH_2Br), 3.97 (4 H, s, OCH_2CH_2O), 4.27 (2 H, q, MeCH_2) and 4.31 (2 H, t, OCH_2CH_2Br).

Ethyl (Z)-3,3-*ethylenedioxy*-2-*vinyloxyiminobutyrate* **29**. A mixture of potassium t-butoxide (0.61 g, 5.4 mmol) in THF (30 cm^3) was added dropwise to a solution of the acetal **27** (1.4 g, 4.5 mmol) in DMSO (10 cm^3) at 0 °C. The mixture was stirred at 0 °C for 15 min. Ice–water was added and the resulting mixture was extracted twice with diethyl ether. The combined extracts were washed successively with water and brine, dried and evaporated. Chromatography gave the unstable *vinyl oxime* **29** as an oil (0.706 g, 69%) (Found: MH^+, 230.1035. $C_{10}H_{16}NO_5$ requires *m*/*z*, 230.1028); ν_{max}($CHCl_3$)/cm^{-1} 1730, 1650, 1640 and 1620; δ($CDCl_3$) 1.33 (3 H, t, *J* 7, *Me*CH_2), 1.65 (3 H, s, Me), 3.99 (4 H, s, OCH_2CH_2O), 4.18 (1 H, dd, *J* 7 and 2, OCH=C*H cis*), 4.32 (2 H, q, MeCH_2), 4.56 (1 H, dd, *J* 14, OCH=C*H trans*) and 6.83 (1 H, dd, OC*H*=CH_2).

Ethyl (Z)-2-*cyclopropyloxyimino*-3-*oxobutyrate* **6d**. A solution of diethylzinc (0.41 cm^3, 4 mmol) in cyclohexane (1.3 cm^3, 4 mmol) was added to a solution of the vinyl oxime **29** (0.50 g, 2.2 mmol) in benzene (10 cm^3), followed by dropwise addition of a solution of methylene diiodide (0.35 cm^3, 4.4 mmol) in benzene (3 cm^3) during 15 min. The mixture was stirred for a further 15 min at room temperature, then at 50 °C for 22 h. The reaction mixture was poured onto water–cyclohexane, acidified with dil. HCl, and the separated organic phase was washed successively with saturated aq. sodium hydrogen carbonate and brine, dried and evaporated. Chromatography gave the cyclopropyl oxime **31**.

This compound was dissolved in a mixture of TFA (3 cm^3) and water (0.1 cm^3) and the solution was stirred for 3 h. After evaporation the residue was dissolved in diethyl ether and the solution was washed successively with saturated sodium hydrogen carbonate and brine, dried and evaporated. Chromatography gave the oxime **6d** as an oil (0.11 g, 25%) (Found: MH^+, 200.0921. $C_9H_{14}NO_4$ requires M, 200.0923); ν_{max}($CHCl_3$)/cm^{-1} 1730 and 1690; δ($CDCl_3$) 0.65–0.95 (4 H, m, CH_2), 1.32 (3 H, t, *J* 7, *Me*CH_2), 2.42 (3 H, s, Me), 4.2 (1 H, m, CH) and 4.33 (2 H, q, MeCH_2).

MIC.—MIC determinations were carried out by serial dilution using DST agar (Oxoid) with inoculum of 10^6 colony-forming units. MICs were determined after incubation at 37 °C for 18 h.

β-*Lactamase Stability Test*.—Compounds were made up to a final concentration of 100 μg cm^{-3} in 0.01 mol dm^{-3} phosphate buffer at pH 7 and the solutions were warmed to 37 °C before addition of a concentrated, cell-free enzyme preparation derived from *S. aureus* MB9, or *H. influenzae* NEMC1. Degradation of the compounds were monitored by HPLC and the results expressed as half-lives in Table 1.

Human Serum Binding.—Compounds were made up to a final concentration of 50 μg cm^{-3} in pooled human serum and left at room temperature for 15 min before being centrifuged in an Amicon Micropartition system. The ultrafiltrate was then assayed using a hole-in-plate bioassay.

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