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SYNTHESIS OF 3(*S*)-ACYLAMINO-1-[(PHENYL)(1H-TETRAZOL-5-YL)AMINO]-2-AZETIDINONES

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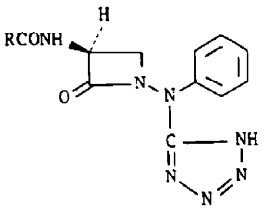
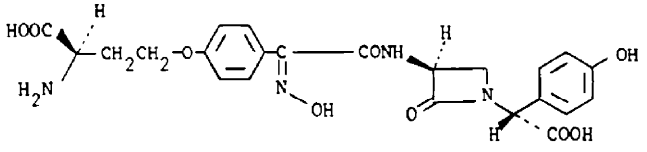
Abstract– 1-Phenyl-1-(1-benzyl-1H-tetrazol-5-yl)hydrazine has been synthesised from N^1-benzyloxycarbonyl-N^2-phenylhydrazide and benzyl isothiocyanate. Coupling with N-(benzyloxycarbonyl)-L-serine 3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl ester and cyclisation of the product, using triphenyl phosphine and dimethyl azodicarboxylate, gave a fully protected β-lactam. Hydrogenolytic deprotection and acylation gave the title compounds, which are related to Nocardicin A. Fast atom bombardment mass spectra showed $(M + H)^+$ peaks for all the β-lactams studied.

Our interest in the synthesis of the title compounds (I) arose from investigations of the properties of a new class of antibacterial agents, the phosphonopeptides.[1]



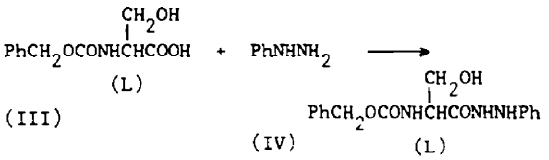
(I)



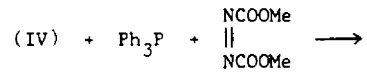
(II) Nocardicin A

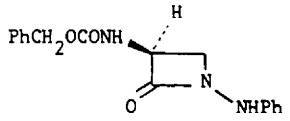
One compound, alafosfalin, L-alanyl-L-1-aminoethylphosphonic acid, exhibited antibacterial synergy, *in vitro* and *in vivo* when used in combination with ampicillin, mecillinam and cephalexin.[2] Another phosphonopeptide, L-norvalyl-L-1-aminoethylphosphonic acid, showed different antibacterial synergy in combination with Nocardicin A.† Total synthesis of simplified variants of Nocardicin A (II) was therefore initiated and our work in the tetrazole series (I) is reported herein.

Although N-benzyloxycarbonyl-L-serine (III) reacted with phenylhydrazine in the presence of N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) to give IV in 85% yield, further reaction with ethyl chloroformate was not selective. This appeared to rule out the possible selective reaction of IV with a 5-bromotetrazole as a route to I. However, IV could be cyclised to β-lactam V in 50% yield in a modified Mitsunobu reaction using triphenyl phosphine and dimethyl azodicarboxylate.[3] (The dimethyl ester was used so that the dimethyl hydrazodicarboxylate by-product could be washed out by water-solvent partition.) Unfortunately neither ethyl chloroformate nor cyanogen bromide reacted with V to substitute the nitrogen atom. Similarly, the anisyl analogue of V also failed to react with ethyl chloroformate.



(III) (IV) (L)

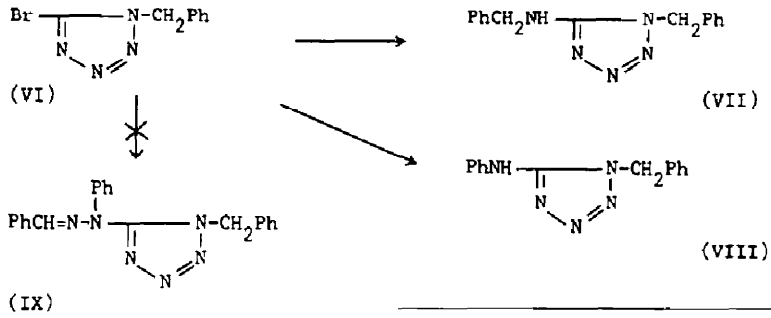




(V)

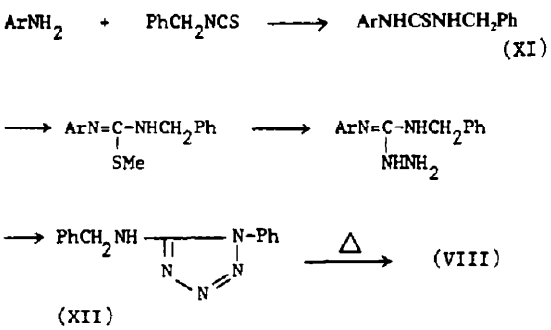
In an alternative approach, 1-benzyl-5-bromotetrazole (VI) was synthesised by a literature method. Compound VI reacted with benzylamine to give 1-benzyl-5-benzylaminotetrazole (VII) in 83% yield, but with aniline only 9% of VIII was obtained. There was no reaction between benzaldehyde phenylhydrazone and VI to give desired intermediate IX.

*Author to whom correspondence should be addressed.
†M. J. Hall, C. H. Hassall, W. J. Lloyd, D. Westmacott and P. Angehrn, submitted to *Antimicrobial Agents and Chemotherapy*.



(VI) (VII) (VIII) (IX)

Construction of the required 1-benzyl-5-phenylhydrazino tetrazole (X) from the 5-anilino-1-benzyltetrazole (VIII) was attempted as follows. Firstly, synthesis of VIII from aniline was accomplished in 77% overall yield from XI.

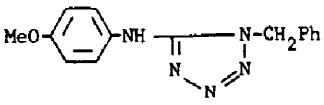


(XI) (XII)

Analogous synthesis from 4-anisidine gave 5-(4-methoxyphenyl)-amino-1-benzyl tetrazole (XIII) in 72% overall yield.

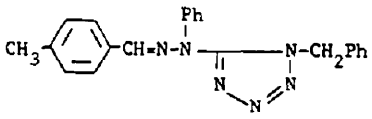
Attempted nitrosations of VIII gave only compounds nitrated in the aromatic ring, i.e. 5-(4-nitrophenyl)amino-1-benzyl tetrazole and 5-(2-nitrophenyl)amino-1-benzyl tetrazole. Nitrosation of XIII gave only 5-(4-methoxy-2-nitrophenyl)amino-1-benzyl tetrazole.

Modification of the above improved route to VIII finally led to the desired X as shown in Fig. 1.

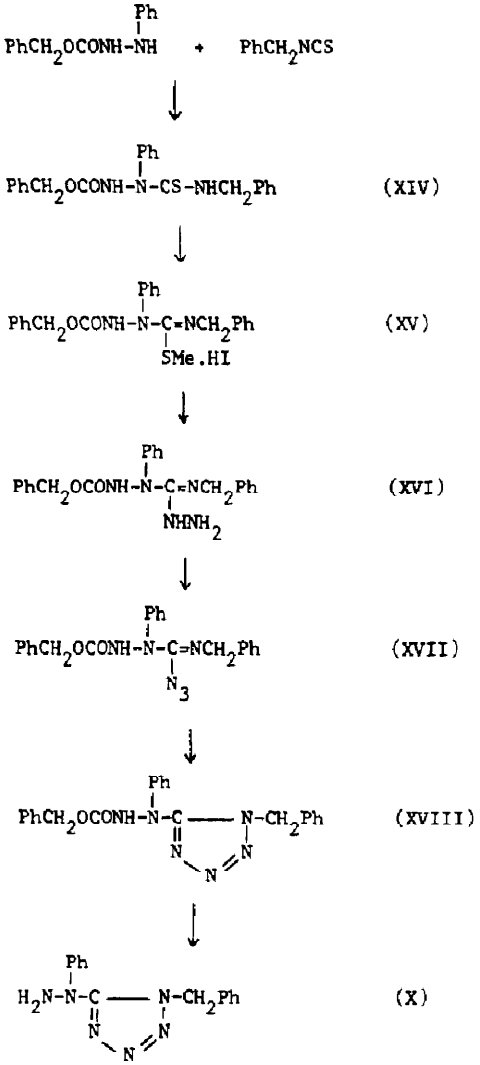


(XIII)

N¹-Benzyloxycarbonyl-N²-phenylhydrazide was reacted with benzyl isothiocyanate to give a near quantitative yield of XIV. Conversion to the methiodide XV (98%) and subsequent one-pot reactions XV→XVI→XXVII→XVIII gave 72% of XVIII overall. Deprotection of XVIII with HBr/AcOH gave 81% of X as the hydrobromide. The product X was further characterised with 4-tolualdehyde to give XIX.



(XIX)

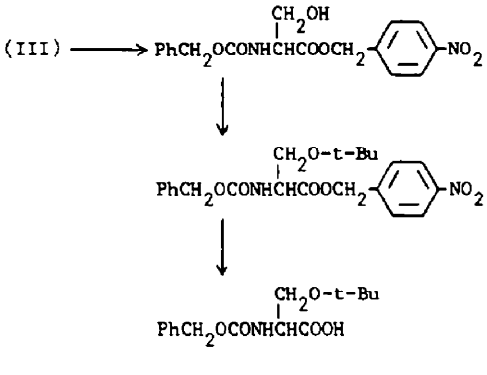


(XIV) (XV) (XVI) (XVII) (XVIII) (X)

Fig. 1. Synthesis of 1-phenyl-1-(1-benzyl-1H-tetrazol-5-yl)-hydrazine (X).

Attempts to acylate X with N-benzyloxycarbonyl-L-serine (III) and N-ethoxycarbonyl-2-ethoxy-1, 2-dihydroquinoline (EEDQ) or dicyclohexylcarbodiimide and hydroxybenztriazole failed due to poor reactivity of the amino group, and the amino acid derivative was lost in side reactions. The conventional approach to solve poor reactivity problems is to use

OH-protected serine to avoid side-reactions becoming predominant. The t-butyl ether was therefore prepared by the route III→XX→XXI→XXII.

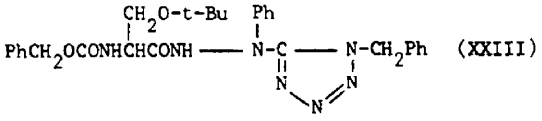


(XX)

(XXI)

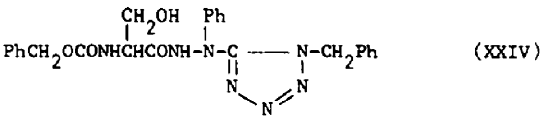
(XXII)

Condensation of XXII with X in the presence of carbonyl di-imidazole was slow at room temperature but more satisfactory at elevated temperatures. Thus XXIII was obtained in yields of 48% (7 days at 43°)



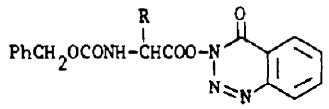
(XXIII)

and 65% (63 hr at 82°). The mixed anhydride of XXII with diethyl phosphate was formed by reaction of a salt with diethyl phosphorobromidate. This was more reactive and gave 51% of XXIII after 2 days at room temperature. Deprotection of XXIII with trifluoroacetic acid proceeded poorly, and only 25% of XXIV was obtained [XXII→XXIV only 16% overall].



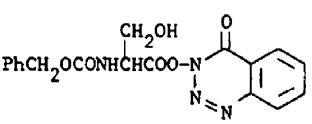
(XXIV)

Literature searches revealed that active esters of type XXV had been prepared[4] during studies on additives as racemisation inhibitors in dicyclohexylcarbodi-imide (DCC) condensation of CO and NH_2



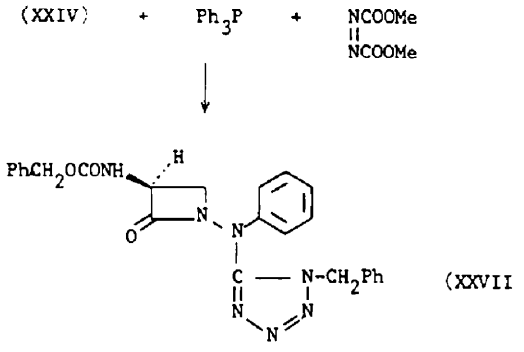
(XXV)

groups. They exhibited high C=O frequencies at 1810–1815 cm^{-1} and were said to be stable to OH groups. In fact, the serine derivative XXVI was described, though not examined in detail. The required heterocycle was readily prepared by the lit route[4] and was reacted with III and DCC to give XXVI in 89% yield, which had the previously reported properties.[4] Reaction of XXVI with X then gave XXIV in 60–70% yield after 24 hr at 42°.



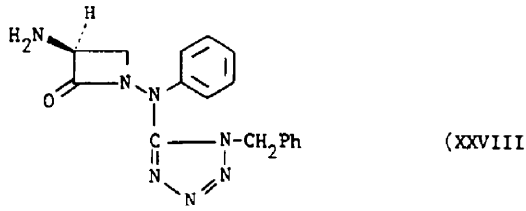
(XXVI)

Cyclisation of XXIV in the previously described adaptation (IV→V) of the Mitsunobu reaction[3] gave the fully protected β-lactam (XXVII). On catalytic



(XXVII)

hydrogenolysis, XXVII was rapidly O-debenzylated to XXVIII as expected. However, significant N-debenzylation to XXIX had also taken place before



(XXVIII)

all the XXVII had reacted. Coupling of this mixture with N-benzyloxycarbonyl-L-norvaline gave (mainly) a difficult to purify, fully protected, β-lactam. Acidification to pH 3 of the bicarbonate extract of this material gave, as a white solid, substantially pure XXX (Fig. 2). Overnight catalytic hydrogenation of XXVII in methanol, with fresh catalyst after 6 hr, gave fully deprotected β-lactam XXIX as the sole product. This material was then coupled with amino acid side chains by the free acid and active ester routes as shown in Fig. 2.

Attachment of a 2-aminothiazolyl side chain such as that found in cefotaxime and ceftriaxon to XXIX was achieved by the thiol ester route[5] as shown in Fig. 3. β-lactams (XXIX–XXXIII) and XXXV were all solids which could not be crystallised. The IR spectra showed characteristic β-lactam CO absorptions in the range 1770–1800 cm^{-1}. The ^1H NMR spectra also showed characteristic β-lactam resonances. In order to confirm the molecular formula, in some cases, mass spectral data was sought. Electron impact mass spectra were largely uninformative and no mole ions were seen. However, fast atom bombardment mass spectrometry[6,7] gave $(M+H)^+$ ions for all these β-lactams along with recognisable fragmentation patterns in most cases (e.g. Fig. 4). Accurate mass determinations of these ions led to confirmation of molecular compositions where needed.

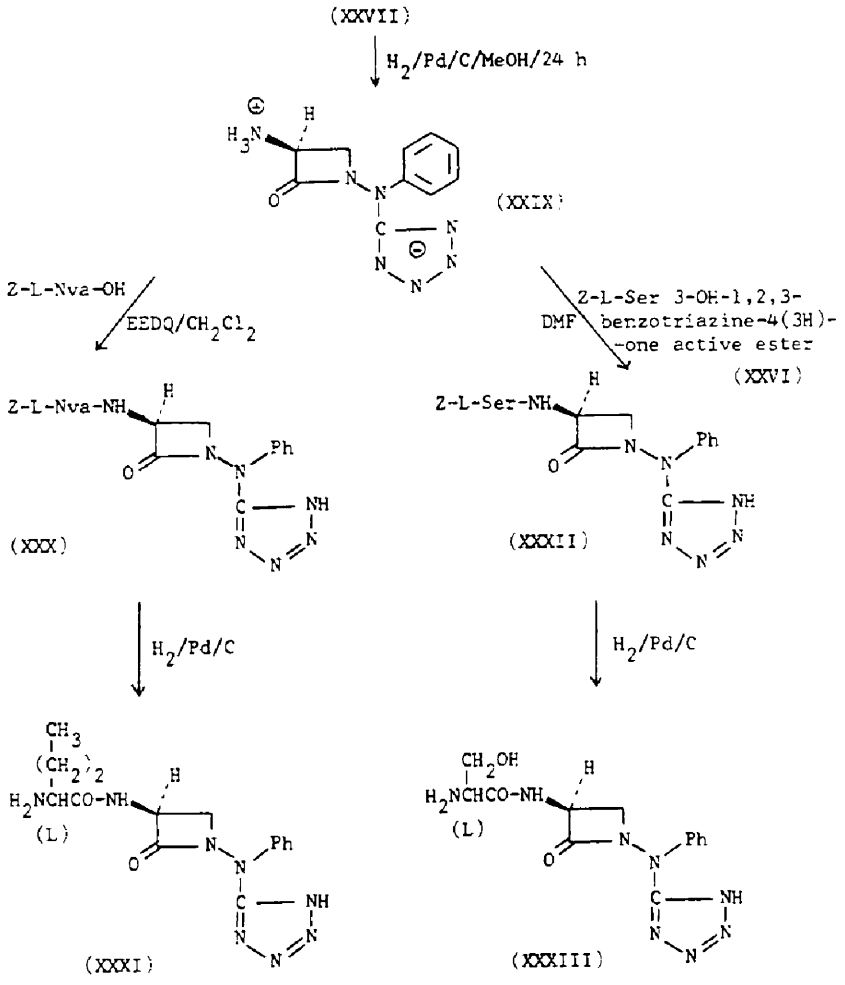


Fig. 2. Synthesis of 1-[(phenyl)-(1H-tetrazol-5-yl)]amino β-lactams with 3(S)-amino acid side chains.

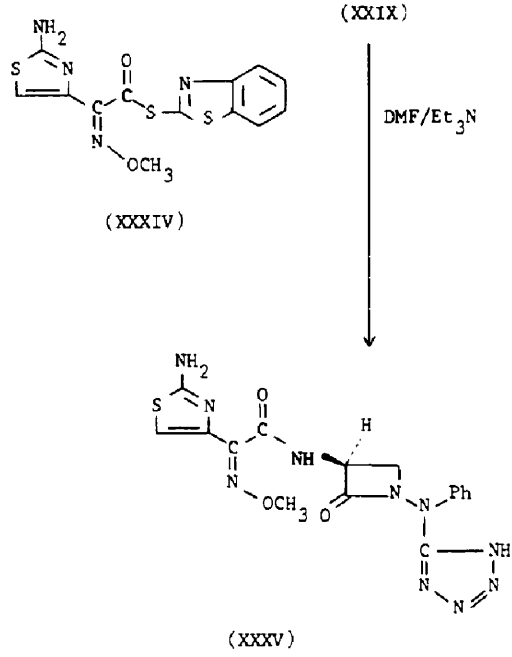


Fig. 3. Synthesis of a 1-[(phenyl)-(1H-tetrazol-5-yl)]amino β-lactam with a 3(S)-[(2-(2-aminothiazol-4-yl)-2-syn-methoximino)acetamido]sidechain.

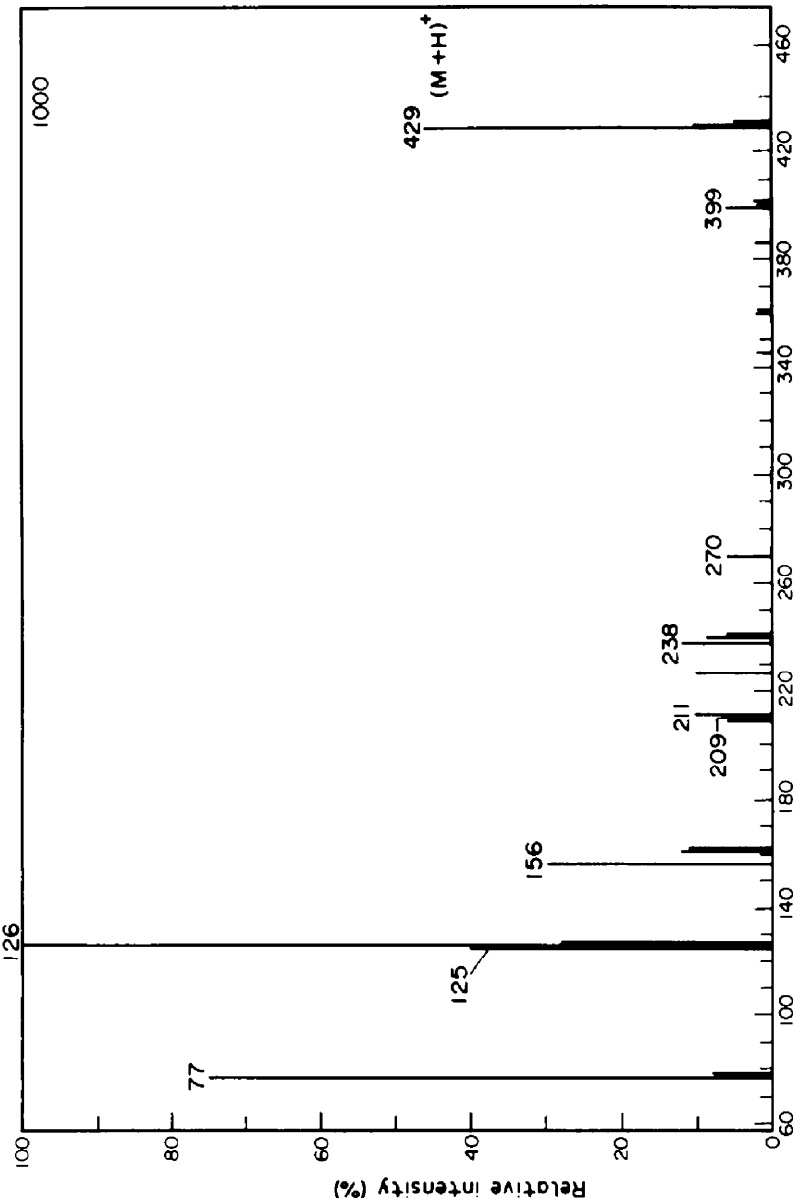


Fig. 4. Fast atom bombardment mass spectrum of (XXXV).

EXPERIMENTAL

NMR spectra were recorded on a Bruker WM 300 and on a Varian XL 100/15 spectrometer and chemical shifts (δ) are presented in ppm from internal TMS. Mass spectra were obtained using a Kratos MS 902 mass spectrometer in the normal electron impact mode or fitted with a Kratos Fast Atom Bombardment (FAB) source. Positive ion FABMS were recorded. Samples were mixed with glycerol on the probe tip from acetone, dimethylformamide or dimethyl sulphoxide solns. Source accelerating voltage 8 KV. Multiplier gain 10^3. IR spectra were determined on a Pye–Unicam SP 1000 spectrometer and elemental analyses were carried out on a Perkin–Elmer Model 240 instrument. TLC was carried out using glass-supported silica gel 60 plates. Optical rotations were measured on a Perkin–Elmer Model 141 polarimeter. M.ps were recorded on a Buchi melting point apparatus and are uncorrected.

N^1-Phenyl-N^2-(N-benzyloxycarbonyl)-L-seryl hydrazide (IV)

N-Benzyloxycarbonyl-L-serine (11.95 g, 50 mmol) was stirred as a suspension in CH_2Cl_2 (100 ml) at +5° as phenylhydrazine (5.6 g, 52 mmol) in CH_2Cl_2 (15 ml) was added dropwise. The mixture was cooled to −10° and was treated dropwise with a soln of EEDQ in CH_2Cl_2 (30 ml). Cooling was maintained for 1 hr when a clear soln was obtained. The mixture was then stirred at room temp overnight. The resulting yellow solid 14.0 g (85%), m.p. 168–170°, was filtered off and recrystallised from a mixture of MeOH (200 ml) and ether (250 ml) to give 11.8 g of pure IV, m.p. 171–172°. (Found: C, 61.9; H, 5.8; N, 12.6. $C_{17}H_{19}N_3O_4$ requires: C, 62.0; H, 5.8; N, 12.8%). δ ^{1}H (DMSO-d_6) 3.66 (2H, t, CH_2OH), 4.18 (1H, 2t, CH–CH), 4.79 (1H, t, NH), 5.05 (2H, s, $PhCH_2O$), 6.65–7.3 (10H, m, Ar), 7.45 (1H, s, NH), 9.62 (1H, s, NH). Resonances at 4.79, 7.45 were eliminated by CF_3COOH which reduced resonances at 3.66 and 4.18 to a doublet and triplet respectively.

Benzyl (2-oxo-1-anilino-3(S)-azetidinyl)carbamate (V)

Triphenyl phosphine (2.9 g, 11 mmol) was stirred in CH_2Cl_2 (50 ml) as dimethyl azodicarboxylate (1.6 g, 11 mmol) in CH_2Cl_2 (20 ml) was added dropwise. The resulting exothermic reaction raised the internal temp by 10°. Solid IV (3.3 g, 10 mmol) was added and the mixture was stirred overnight.

The resulting mixture was washed with water (3 × 30 ml), dried over Na_2SO_4 and evaporated to give an oil (8.7 g) which was chromatographed on Kieselgel 60 (150 g). Elution with $CHCl_3$ initially and then 1% MeOH in $CHCl_3$ followed by 5% MeOH/$CHCl_3$ gave the product as an oil (2.7 g). Crystallisation from a mixture of benzene and petroleum ether, b.p. 40–60, gave 1.56 g (50%) of essentially pure product, m.p. 120–122°, ν_{max} ($CHCl_3$) 1773 and 1715 cm^{-1}. A 1.3 g sample of this material was further purified by recrystallisation from a mixture of EtOAc (15 ml), diethyl ether (45 ml) and petroleum ether, b.p. 40–60° (40 ml) to give 0.93 g of pure V, m.p. 124–125°, $[\alpha]_D^{28}$ −59.2° (c = 1%, MeOH). (Found: C, 65.5; H, 5.4; N, 13.4. $C_{17}H_{17}N_3O_3$ requires C, 65.6; H, 5.5; N, 13.5%.) δ ^{1}H ($CDCl_3$) 3.51 (1H, m, H-4), 3.70 (1H, t, H-4), 4.70 (1H, m, H-3), 5.08 (2H, s, $PhCH_2O$), 6.08 (1H, d, CONH), 6.5–7.4 (11H, m, 10Ar + NHPh).

5-Benzylamino-1-benzyltetrazole (VII)

Compound VI[8] (2.4 g, 10 mmol) and benzylamine (5.4 g, 50 mmol) were refluxed in acetonitrile (25 ml) for 50 hr. The solvent was evaporated and water (40 ml) was added to give a crystalline solid, 2.2 g (83%), m.p. 166–168°. Recrystallisation from EtOH (30 ml) gave 1.4 g of pure VII, m.p. 168–171°. (Found: C, 68.1; H, 5.7; N, 26.5. $C_{15}H_{15}N_5$ requires: C, 67.9; H, 5.7; N, 26.4%.) δ ^{1}H (DMSO-d_6) 4.54 (2H, d, $NHCH_2Ph$), 5.44 (2H, s, $PhCH_2N<$), 7.32 (10H, m, Ar), 7.6 (1H, t, $NHCH_2Ph$). The resonance at 7.6 was eliminated by D exchange and the 4.54 doublet collapsed to a singlet.

5-Anilino-1-benzyl tetrazole (VIII)

(a) *From 1-benzyl-5-bromotetrazole* (VI). Compound VI (2.4 g, 10 mmol) in aniline (4.65 g, 50 mmol) under argon was heated for 3.5 hr at 160°. The mixture was then partitioned between CH_2Cl_2 (50 ml) and water (50 ml). The organic layer was washed with N HCl (2 × 40 ml) and water (40 ml) then dried by filtration. The soln was evaporated and the residue was triturated with ether (100 ml). The ether was decanted and the residue was triturated with MeOH (5 ml) to give a solid, 0.23 g (9%), m.p. 182–4°; λ_{max} (MeOH) at 250 nm. δ ^{1}H (DMSO-d_6) 5.71 (2H, s, CH_2), 6.9–7.8 (10H, m, Ar), 9.4 (1H, s, NH). The resonance at 9.4 was eliminated by deuterium exchange.

(b) *From aniline and benzyl isothiocyanate.* Compound XI (48 g, 200 mmol)[9a,b] in acetone (200 ml) was stirred and MeI (13.7 ml, 220 mmol) was added. The mixture was refluxed for 4 hr. More MeI (6.85 ml, 110 mmol) was added and reflux was continued for 5 hr. The solvent was then evaporated and the residue was taken up in CH_2Cl_2 (200 ml) and water (200 ml). The mixture was cooled to 0° and a concentrated soln of K_2CO_3 (39 g, 280 mmol) in water (50 ml) was added. The K_2CO_3 aq was then extracted with CH_2Cl_2 (50 ml) and the combined organic extracts were dried and evaporated. The crude methyl thio compound (20 mmol) so obtained was stirred in EtOH (125 ml) and conc HCl (17.5 ml) was added, followed by hydrazine hydrate (10 g, 200 mmol). The mixture was refluxed for 5 hr, then evaporated *in vacuo*. Water was added to the residue and a small amount of oily by-product was removed by ether extraction. The aqueous layer was partially evaporated to remove ether and then diluted with water to 200 ml.

The aqueous soln of the hydrazide (200 mmol) so obtained was cooled in ice-salt and treated with conc HCl (19 ml, 220 mmol), followed by dropwise addition of a soln of $NaNO_2$ (14 g, 200 mmol) in water (25 ml). After 30 min at 0–5° further $NaNO_2$ (1 g) in water (4 ml) was added. The mixture then became KI/starch positive.

Anhyd K_2CO_3 (30 g, 220 mmol) was added portionwise when the temp rose to 10°. The mixture was stirred for 2 hr and the solid residue was ground up in a pestle and mortar then stirred for a further 2 hr with the supernatant. The resulting solid was filtered off and washed with water to give 43.4 g (86%) of XII. A sample of XII (3.3 g) was recrystallised from isopropanol (18 ml) to give 2.1 g of pure XII, m.p. 134–136°. (Found: C, 66.8; H, 5.2; N, 27.9. $C_{14}H_{13}N_5$ requires: C, 66.9; H, 5.2; N, 27.9%). λ_{max} (ϵ) 209 (14,200), 248 (6,830) nm; λ_{min} (ϵ) 234 (5,490) nm. δ ^{1}H ($CDCl_3$) 4.61 (2H, d, CH_2), 5.04 (1H, t, NH), 7.32 (5H, Ar), 7.50 (5H, Ar).

The XII so obtained (15.1 g, 60 mmol) was stirred in xylene (90 ml) and refluxed for 2 hr. The mixture was cooled and a solid was filtered off and washed with toluene and then with petroleum ether, b.p. 40–60°, to give 13.9 g (92%) of VIII, m.p. 187–190°. A mixed m.p. with VIII produced from 5-bromo-1-benzyl tetrazole by method (a) above showed no depression. A 2 g sample of VIII [route (b)] was recrystallised from EtOH (60 ml) to give 1.6 g of pure VIII, m.p. 188–190°. (Found: C, 66.7; H, 5.2; N, 27.8. $C_{14}H_{13}N_5$ requires: C, 66.9; H, 5.2; N, 27.9%). λ_{max} (ϵ) 208 (14,900), 246 (17,100) nm; λ_{min} (ϵ) 221 (4,050) nm. δ ^{1}H(DMSO-d_6) 5.68 (2H, s, CH_2), 7.0–7.8 (10H, m, Ar), 9.4 (1H, s, NH).

1-Phenyl-1-(1-benzyl-1H-tetrazol-5-yl)hydrazine (X)

Compound XVIII (2 g, 5.0 mmol) was stirred in 45% HBr/AcOH (10 ml) for 1.5 hr. Anhyd ether (60 ml) was added to precipitate a gum which solidified to give 1.1 g of the hydrobromide of X, m.p. 169–170° (dec). (Found: C, 48.3; H, 4.2; N, 23.9. $C_{14}H_{14}N_6 \cdot 0.7\,HBr$ requires: C, 48.4; H, 4.35; N, 24.2%.) δ ^{1}H(DMSO-d_6) 5.64 (2H, s, CH_2), 6.76 (3H(?), broad, NH_3), 7.05–7.42 (10H, m, Ar).

Using 20 g of XVIII there was similarly obtained 14.1 g (81%), m.p. 161–164° of this hydrobromide of X. A sample of this (10.7 g, 31 mmol) was stirred as a suspension in CH_2Cl_2 (100 ml) as K_2CO_3 (5 g, 36 mmol) in water (30 ml)

was added. Stirring was continued for 1 hr. Phases were separated and the organic layer was washed with water (3 × 50 ml), dried over Na_2SO_4 and evaporated. The solid residue was triturated with anhyd ether and filtered to give 7.3 g of X, m.p. 114–118°. Recrystallisation from EtOAc (45 ml) with charcoal treatment of the hot soln, gave 5.45 g of pure X, m.p. 116–118°. (Found: C, 62.9; H, 5.3; N, 31.6. $C_{14}H_{14}N_6$ requires: C, 63.1; H, 5.3; N, 31.6%). ν_{max} ($CHCl_3$) 1500, 1540 cm^{-1}; *m/e* 266 (M).

A sample of X · HBr (0.26 g, 0.75 mmol) in EtOH (5 ml) was treated with NaOAc (0.10 g, 0.75 mmol) in water (1 ml). *p*-Tolualdehyde (0.18 g, 1.5 mmol) was added and the mixture was stirred overnight. The resulting solid was filtered off and washed successively with water, MeOH and ether to give 0.155 g, m.p. 123–5°. Recrystallisation of 0.1 g from a mixture of EtOAc (2 ml), ether (3 ml) and petroleum ether, b.p. 40–60° (3 ml) gave 0.047 g of the derivative XIX of X. (Found: C, 71.2; H, 5.5; N, 22.6. $C_{22}H_{20}N_6$ requires: C, 71.7; H, 5.5; N, 22.8%.) δ ^1H ($CDCl_3$) 2.34 (3H, s, CH_3), 5.88 (2H, s, CH_2), 7.0–7.54 (11H, Ar + CH).

5-(4-Methoxyphenyl)amino-1-benzyl tetrazole (XIII)

Anisidine (25 g, 200 mmol) in MeOH (125 ml) was treated with benzyl isothiocyanate (31 g, 200 mmol) and the mixture was stood for 24 hr. The resulting solid was filtered off to give 45 g (83%) of product, m.p. 113–114°. Recrystallisation of a 4 g sample from MeOH (20 ml) gave 3.2 g of N^1-benzyl-N^2-(4-methoxyphenyl)-thiourea, m.p. 110–112°. (Found: C, 66.1; H, 5.8; N, 10.2. $C_{15}H_{16}N_2OS$ requires: C, 66.15; H, 5.9; N, 10.3%). δ ^1H ($CDCl_3$) 3.80 (3H, s, OCH_3), 4.88 (2H, d, $PhCH_2$), 6.16 (1H, broad, $PhCH_2\underline{NH}$), 6.80–7.40 (9H, m, Ar), 8.08 (1H, s, NHAr).

This thiourea (41 g, 150 mmol) was treated with MeI (18.6 ml), as for the preparation of VIII above, to give 61 g (98%) of the corresponding methyl thio compound. This material (61 g) was further treated with hydrazine, $NaNO_2$, HCl and K_2CO_3, as for VIII above, to obtain 35 g (83%) of 5-benzylamino-1-p-methoxyphenyl tetrazole, m.p. 155–157°. Recrystallisation of a 4.5 g sample from EtOH (60 ml) gave 3.9 g, m.p. 158–159° of the pure product. (Found: C, 63.8; H, 5.5; N, 24.9. $C_{15}H_{15}N_5O$ requires: C, 64.0; H, 5.4; N, 24.9%) λ_{max} (ϵ) 206 (17,000), 232 (12,000), 245 (inflexion) (10,400); λ_{min} (ϵ) 220 (10,000) nm. δ ^1H (DMSO-d_6) 3.88 (3H, s, OCH_3), 4.53 (2H, d, $PhCH_2$), 7.06–7.64 (10H, m, Ar + NH).

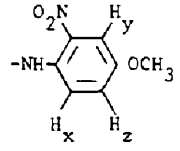
Thermal rearrangement of this 5-benzylamino-1-p-methoxyphenyl tetrazole (2 g, 7.1 mmol) in decalin at 160° for 3 hr gave 1.6 g of product, m.p. 179–180°. (Repetition with 70 g gave 92% yield.) Recrystallisation from EtOH gave 0.6 g of pure XIII, m.p. 181–182°. (Found: C, 64.0; H, 5.5; N, 24.9. $C_{15}H_{15}N_5O$ requires: C, 64.0; H, 5.4; N, 24.9%). λ_{max} (ϵ) 207 (19,100), 248 (17,200), 293 (inflexion) (2,400) nm; λ_{min} (ϵ) 221 (4,500) nm. δ ^1H (DMSO-d_6) 3.77 (3H, s, OCH_3), 5.63 (2H, s, CH_2Ph), 6.85–7.65 (9H, m, Ar), 9.19 (1H, s, NH).

Nitrosation of VIII *and* XIII

Compound VIII (2.5 g, 10 mmol) and $NaNO_2$ (2.5 g, 36 mmol) were stirred in water (25 ml) at 0° as 10% HCl (25 ml) was added dropwise over 20 min, following the method of Butler *et al.*[10] Addition of CH_2Cl_2 (30 ml) led to crystallisation of a high melting product, 0.7 g, m.p. 239–242° (dec). (Found: C, 57.3; H, 4.3; N, 28.0. $C_{14}H_{12}N_6O_2$ requires: C, 56.8; H, 4.1; N, 28.4%.) *M/e* 296 supported formation of the nitro compound. ^1H NMR identified the *para* isomer, i.e. 5-(4-nitrophenyl)amino-1-benzyl tetrazole. δ ^1H (DMSO-d_6) 5.69 (2H, s, $PhCH_2$), 7.28–7.47 (5H, m, Ph), 8.10 (4H, q, AA^1BB^1, NHC_6H_4–NO_2-p), 10.20 (1H, s, NH). The resonance at 10.20 was eliminated by CF_3COOD exchange.

Chromatography on Kiesel 60 of the CH_2Cl_2 extract gave 0.39 g of a low melting product, m.p. 136–138°. *M/e* 296 (M for nitro compound.) ^1H NMR ($CDCl_3$) identified the *ortho* isomer, i.e. as 5-(2-nitrophenyl-amino-1-benzyl tetrazole. δ ^1H ($CDCl_3$) 5.61 (2H, s, CH_2Ph), 7.0–7.8 (3H, m, 3 characteristic ortho protons) 7.38–7.50 (5H, m, Ph), 8.30 (1H, dd, ortho to NO_2), 10.22 (1H, s, NH). The resonance at 10.22 was eliminated by CF_3COOD exchange.

Compound XIII (2.8 g, 10 mmol) was nitrosated with iso-amyl nitrite (2 ml, 15 mmol) in glacial AcOH following the method of Tobin *et al.*[11] Work up as above gave 1 g of pure 5-(4-methoxy-2-nitrophenyl)amino-1-benzyl tetrazole. (Found: C, 55.0; H, 4.4; N, 25.6. $C_{15}H_{14}N_6O_3$ requires: C, 55.2; H, 4.3; N, 25.75%.) ^1H NMR showed that the exchangeable proton remained. δ ^1H ($CDCl_3$) 3.84 (3H, s, OMe), 5.49 (2H, s, $PhCH_2$), 7.18 (1H, dd, H_z), 7.34 (5H, m, Ph), 7.56 (1H, d, H_y), 8.69 (1H, d, H_x), 9.99 (1H, s, NH). The resonance at 9.99 was eliminated by CF_3COOD exchange.



4-Benzyl-1-benzyloxycarbonyl-2-phenyl-thiosemicarbazide XIV

Phenylhydrazine (19.7 ml, 200 mmol) in dry ether (200 ml) was treated at 0°, dropwise, with benzyloxychloroformate (14.2 ml, 100 mmol) during 20 min, keeping the internal temp below +10°. The resulting solid was filtered off and the filtrate was refrigerated overnight to give 2.3 g of N^1-benzyloxycarbonyl-N^2-phenylhydrazide. (Found: C, 69.5; H, 6.0; N, 11.7. $C_{14}H_{16}N_2O_2$ requires: C, 69.4; H, 5.8; N, 11.6%.) ^1H NMR showed one exchangeable proton. δ ^1H ($CDCl_3$) 5.16 (2H, s, CH_2Ph), 5.79 (1H, s), 6.65–7.41 (11H, m, Ph + $N\underline{H}Ph$). The resonance at 5.79 was eliminated by CF_3COOD exchange.

N^1-Benzyloxycarbonyl-N^2-phenylhydrazide (19.4 g, 80 mmol) and benzyl isothiocyanate[12] (15 g, 100 mmol) were stirred in refluxing toluene (200 ml) for 24 hr. The solvent was evaporated and the solid residue was triturated with ether and filtered off to give 12.7 g (40%) of XIV, m.p. 152–155°. (Found: C, 67.4; H, 5.4; N, 10.8. $C_{22}H_{21}N_3O_2S$ requires: C, 67.5; H, 5.4; N, 10.7%.) δ ^1H ($CDCl_3$) 4.84 (2H, d, $NH\underline{CH_2}Ph$), 5.16 (2H, s, $PhCH_2O$), 6.67 (1H, broad, $NHCH_2Ph$), 7.19–7.51 (15H, m, 3 × Ph), 8.38 (1H, s, –NH–N<). The resonance at 8.38 was eliminated by deuterium exchange.

When this reaction was repeated (160 mmol scale) using methyl cyclohexane as solvent two crops of 81% and 9% of XIV were obtained. This was as expected due to displacement of the equilibrium by choice of a poorer solvent for the product, compared to starting material.

4-Benzyl-1-benzyloxycarbonyl-S-methyl-isothiosemicarbazide hydrogen iodide (XV)

The thiosemicarbazide, XIV (98 g, 250 mmol) was suspended in acetone (700 ml) and treated with MeI (50 ml, 800 mmol). The mixture was stirred and refluxed for 5 hr and stirred for a further 12 hr. More MeI (20 ml, 320 mmol) was added and the mixture was stirred at reflux for a further 3 hr. On cooling the mixture was filtered to give 125 g (94%) of pure XV. [Concentration of the filtrate gave a further 5.6 g (4%).] (Found: C, 51.6; H, 4.5; N, 7.9. $C_{23}H_{23}N_3O_2S.HI$ requires: C, 51.8; H, 4.5; N, 7.9%.) *M/e* 405 (M-HI). δ ^1H (DMSO-d_6) 2.27 (3H, s, SCH_3), 4.80 (2H, s, $=NCH_2Ph$), 5.18 (2H, s, $PhCH_2O$), 7.28–7.56 (15H, m, 3 × Ph), 9.24 (1H, s, NHN).

Benzyl 3-(1-benzyl-1H-tetrazol-5-yl)-3-phenylcarbazate (XVIII)

The XV (43 g, 80 mmol), prepared above, was stirred in a mixture of water (160 ml) and CH_2Cl_2 (240 ml) and cooled to 2° as Na_2CO_3 (16 g, 150 mmol) in water (60 ml) was

added rapidly. After 0.5 hr the phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 40 ml). The combined solvent extracts were washed with water (50 ml), dried, evaporated and re-evaporated with EtOH (2 × 40 ml). The residual oil was taken up in EtOH (240 ml) and stirred as conc HCl (6.9 ml) was added and stirring was continued overnight. A NaOCl trap was attached to the reaction vessel and hydrazine hydrate (4 ml, 80 mmol) was added. The mixture was then refluxed for 5 hr with evolution of methyl mercaptan, then stirred at room temp overnight. Volatiles were then evaporated to give XVI.

The crude XVI so prepared was re-dissolved in a mixture of EtOH (160 ml) and water (130 ml). The soln was stirred at +1° as conc HCl (8 ml) was added dropwise. This was followed by cautious addition of $NaNO_2$ (8.5 g, 120 mmol) in water (20 ml), keeping the internal temp below +3°. The mixture was stirred for a further 0.5 hr when a positive response to starch iodide paper was seen, but XVII, was not isolated.

The solution of XVII so produced was treated at once with K_2CO_3 (12.2 g, 88 mmol) which caused a red gum to be precipitated. After 3 hr the gum had solidified and was filtered off and washed with water. The solid was taken up in CH_2Cl_2 (160 ml) which was washed with water (3 × 50 ml). The organic phase was dried by filtration and evaporated. The residual oil was re-evaporated with toluene then taken up in anhyd ether and refrigerated.

The product crystallised out slowly over 3 days to give 22.7 g (71%) of XVIII, m.p. 105–107°. (Found: C, 65.7; H, 5.2; N, 20.7. $C_{22}H_{20}N_6O_2$ requires: C, 66.0; H, 5.0; N, 21.0%.) *M/e* 400 (M). δ ^{1}H ($CDCl_3$) 5.08 (2H, s, NCH_2Ph), 5.29 (2H, s, $PhCH_2O$), 6.77–7.38 (15H, m, 3 × Ph), 8.43 (1H, s, NH).

Benzyl [L-1-[3-(1-*benzyl*-1H-*tetrazol*-5-*yl*)-3-*phenylcarbazoyl*]-2-*t*-*butoxyethyl]carbamate* (XXIII)

Compound XXII[13] was liberated from its dicyclohexylamine salt (10.2 g, 21.5 mmol) by dissolving in CH_2Cl_2 followed by extraction with NaOH aq then liberation of the free acid with HCl. To the free XXII so obtained was added 1,2-dichloroethane (100 ml). The soln was stirred as 1,1'-carbonyldi-imidazole (3.95 g, 24.4 mmol) was added in one portion. The mixture was refluxed for 0.5 hr cooled briefly and treated with X (5.3 g, 20 mmol) when a clear soln was obtained. The mixture was then refluxed for 63 hr, when some gum had been precipitated.

The supernatant was decanted from the gum and diluted with CH_2Cl_2 (100 ml). The soln was washed with water (50 ml), cold 0.5N HCl (3 × 50 ml), water, 15% $KHCO_3$ (3 × 50 ml) and finally with water. The organic phase was dried over Na_2SO_4 and evaporated to give 13.5 g of oil. This was dissolved in a mixture of EtOAc (12 ml), CH_2Cl_2 (6 ml) and petroleum ether, b.p. 40–60° (12 ml) and chromatographed on Kieselgel 60 (180 g). Elution was monitored by TLC to give a product fraction which was triturated with ether to give XXIII as a solid, 7.1 g (65%), m.p. 132–134°. (Found: C, 63.9; H, 6.3; N, 18.0. $C_{29}H_{33}N_7O_4$ requires: C, 64.1; H, 6.1; N, 18.0%.) δ ^{1}H ($CDCl_3$) 1.15 (9H, s, CMe_3), 3.46 (1H, dd, CH_2OBu-t), 3.82 (1H, dd, CH_2OBu-t), 4.35 (1H, m, NHCHCO), 5.10 (2H, s, $PhCH_2O$), 5.39 (2H, s, $PhCH_2O$), 5.73 (1H, d, NHCH), 6.70–7.36 (15H, m, 3 × Ph), 9.32 (H, s, NHN).

Benzyl [L-1-[3-(1-*benzyl*-1H-*tetrazol*-5-*yl*)-3-*phenylcarbazoyl*]-2-*hydroxyethyl]carbamate* (XXIV)

(a) *Deprotection of* XXIII. The ether XXIII (1.4 g, 2.5 mmol) was stirred in trifluoroacetic acid (12 ml, 160 mmol) at room temp for 6 hr. Volatiles were evaporated *in vacuo* and the residual oil was taken up in CH_2Cl_2 (25 ml). Et_3N (2 ml) was added and the soln was washed with water (10 ml) then 15% $KHCO_3$ aq and again with water (2 × 10 ml). The organic phase was dried over Na_2SO_4 and evaporated to give 1.2 g of yellow gum.

When this experiment was repeated with XXIII (1.1 g, 2 mmol and trifluoracetic acid (8 ml, 10 mmol) but in CH_2Cl_2 (50 ml) and in the presence of anisole 4 ml) for 48 hr there was obtained 1.25 g of a similar quality gum. These products were combined in a mixture of EtOAc (2 parts), CH_2Cl_2 (1 part) and petroleum ether, b.p. 40–60° (2 parts) and chromatographed on Kieselgel 60 (50 g). The crude gummy product 1.7 g (R_f 0.1) was triturated with anhyd ether to give two crops of solid, 0.67 g, m.p. 105–150° and 0.12 g, m.p. 90–115°. These crops were combined in EtOAc (25 ml) and the cloudy soln was charcoaled, filtered and treated with petroleum ether, b.p. 40–60° (25 ml). After refrigeration overnight there was obtained 0.55 g (25%) of XXIV, m.p. 99–105°. (Found: C, 61.2; H, 5.2; N, 19.9. $C_{25}H_{25}N_7O_4$ requires: C, 61.6; H, 5.2; N, 20.1%). *M/e* 487 (M); ν_{max} ($CHCl_3$) 1715 cm^{-1}. δ ^{1}H NMR ($CDCl_3$) 3.69 (1H, m, CH_2OH), 3.92 (1H, m, CH_2OH), 4.34 (2H, m, NHCH and CH_2OH), 5.02 (2H, s, $PhCH_2N$), 5.14 (2H, s, $PhCH_2O$), 6.01 (1H, m, NHCH), 6.80–7.30 (15H, m, 3 × Ph), 9.93 (1H, s, NHN). The resonance at 9.93 was eliminated by CF_3COOD. The integral of the resonances at 4.34 was halved by CF_3COOD and the seryl protons sharpened to 8 lines.

(b) *Coupling of X and XXVI.* Active ester XXVI (5.3 g, 14 mmol) and X (3.3 g, 12.5 mmol) were stirred in CH_2Cl_2 (75 ml) for 3 hr then refluxed for 21 hr (internal temp 40°). Further XXVI (0.48 g, 1.2 mmol) was added and reflux was continued for 3 hr. The solid by-product was filtered off and the filtrate was washed with water (50 ml), 0.5N HCl (3 × 50 ml), water (50 ml), 15% $KHCO_3$aq (3 × 30 ml) and water (50 ml). The organic phase was dried over Na_2SO_4 and evaporated. The residual oil was re-evaporated twice with toluene and then triturated with anhyd ether to give 4.9 g (72%) of substantially pure XXIV (TLC compared to (a) above), m.p. 66–74°C. IR ($CHCl_3$) as for (a) above. Repeating this experiment on a 5 mmol scale gave 1.4 g, m.p. 70–80° and 0.5 g, m.p. 68–80, total 1.9 g (79%) of similar quality XXIV.

Benzyl [1-[(1-*benzyl*-1H-*tetrazol*-5-*yl*)-(*phenyl*)*amino*]-2-*oxo*-3(S)-*azetidinyl]carbamate* (XXVII)

Triphenyl phosphine (1.4 g, 5.5 mmol) was stirred in CH_2Cl_2 (25 ml) as dimethyl azodicarboxylate (0.81 g, 5.5 mmol) in CH_2Cl_2 (10 ml) was added rapidly dropwise. The XXIV (2.4 g, 5 mmol), prepared by method (b) above was then added and the soln was stirred for 48 hr at room temp. The mixture was washed with water (3 × 20 ml), dried over Na_2SO_4 and evaporated to give 4.6 g of oil. This oil was chromatographed on Kieselgel 60 (150 g) in a mixture of EtOAc (1 part) and petroleum ether, b.p. 40–60° (1 part) and then re-chromatographed on Kieselgel 60 (60 g) in the same solvent. (Yield 1.7 g, 74%). A narrow fraction of colourless oil, 0.19 g was almost free of similar R_f contaminant and was substantially pure XXVII m.p. 65–70°C. (Found: C, 64.4; H, 5.4; N, 19.2. $C_{25}H_{23}N_7O_3$ requires: C, 64.0; H, 4.9; N, 20.9%). *M/e* (FAB) 470 $(M+H)^+$, *m/e* 470·1927 ($C_{25}H_{24}N_7O_3$ = 470·1940, 4%), *m/e* (FAB) 508 $(M+K)^+$, *m/e* 508·1440 ($C_{25}H_{23}N_7O_3K$ = 508·1499), *m/e* (FAB) 91 $(PhCH_2)^+$, 100%. ν_{max} 1795 cm^{-1} (β-lactam) and 1730 cm^{-1}. δ ^{1}H NMR ($CDCl_3$) 3.68 (1H, dd, J = 3.0, 4.8Hz, H-4), 3.93 (1H, t (dd), J = 5.6Hz, H-4), 4.60 (1H, m, H-3), 5.09 (2H, s, OCH_2Ph), 5.32 (2H, s, NCH_2Ph), 5.52 (1H, d, J = 8.0Hz, NH), 6.81–7.38 (15H, m, 3 × Ph).

3(S)-*Amino*-1-[(*phenyl*)(1H-*tetrazol*-5-*yl*)*amino*]-2-*azetidinone* (XXIX)

The β-lactam XXVII (0.23 g, 0.5 mmol) was hydrogenated in MeOH (10 ml) in the presence of 10% Pd–C catalyst (20 mg) in a flask fitted with a soda lime trap. A plot of H_2 uptake with time showed an inflexion at 2 hr, presumably largely due to initial formation of XXVIII. After 5 hr a TLC on silica gel in 5% MeOH/$CHCl_3$ showed no XXVII (R_f 0.7), some XXVIII (?) (R_f 0.3) and mostly XXIX at the origin. Fresh catalyst (20 mg) was added and

hydrogenation was continued overnight. Catalyst was removed and the filtrate was evaporated to give 0.11 g of XXIX as a yellow oil which showed a single spot (R_f 0.45) on a silica gel TLC plate developed with n-BuOH (12); AcOH (3); H_2O (5). Crystallisation from a mixture of acetone (5 ml) and ether (25 ml), with concentration of liquors, gave two crops of XXIX, 0.020 g, m.p. > 75° and 0.015 g. m.p. > 95° as hygroscopic solids (TLC of mother liquors showed extensive decomposition). ν_{max} (KBr disc) 1780 cm^{-1} (β-lactam); *M/e* (FAB) 246 $(M+H)^+$ (12%); 77(Ph)$^+$ (100%) δ ^{1}H NMR (CD_3OD) 3.72 (1H, dd, J = 2.4, 4.8 Hz, H-4), 3.98 (1H, t (dd), J = 5.6 Hz, H-4), 4.43 (1H, m, H-3), 7.02–7.41 (5H, m, Ph).

Benzyl[1(S-[[2-*oxo*-1-[(*phenyl*)(1H-*tetrazol*-5-*yl*)*amino*]-3(S)-*azetidinyl*]*carbamoyl*]*butyl*]*carbamate* (XXX)

A sample of XXVII (0.5 g, 1 mmol) was hydrogenated as above for 5 hr to give a mixture of XXVIII and XXIX. Catalyst was removed and the filtrate was evaporated. The resulting product was stirred as a slurry in CH_2Cl_2 (10 ml) and N-benzyloxycarbonyl-L-norvaline (0.25 g, 1 mmol) was added. N-ethoxycarbonyl-2-ethoxy-1,2-dihydroisoquinoline (0.30 g, 1.2 mmol) in CH_2Cl_2 (2 ml) was added at 10° and the mixture was stirred for 72 hr at room temp. The soln was washed with water (10 ml) then with 15% $KHCO_3$ aq (3 × 5 ml) and again with water (10 ml). All the aqueous extracts were back washed with CH_2Cl_2. The combined CH_2Cl_2 extracts were evaporated to give 0.5 g of gum which contained β-lactam (ν_{max} 1790 cm^{-1}) (β-lactam NMR). The combined aqueous and bicarbonate extracts were acidified to pH 3 with 2N HCl to give 0.060 g of XXX, m.p. 95–110° (dec). (Found: C, 57.5; H, 5.5; N, 23.1. $C_{23}H_{26}N_8O_4$ requires: C, 57.7; H, 5.5; N, 23.4%); *m/e* (FAB) 479 $(M+H)^+$ (2.5%); 91 $(PhCH_2)^+$ (100%). ν_{max} ($CHCl_3$) 1800 cm^{-1} (β-lactam). $[\alpha]_D^{20}$ − 30.2° (c = 0.5%, MeOH). δ ^{1}H NMR ($CDCl_3$) 0.91 (3H, t, CH_3), 1.34 (2H, m, CH_2CH_3), 1.77 (2H, m, $CHCH_2$), 3.83 (1H, t (dd), J = 5.6 Hz, H-4), 4.02 (1H, m, H-4), 4.27 (1H, m, $CHCH_2$), 4.48 (1H, m, H-3), 5.08 (2H, s, OCH_2Ph), 5.36 (1H, d, J = 7.6 Hz, CHCONH), 7.20–7.65 (10H, m, 2 × Ph), 7.80 (1H, d, J = 7.0 Hz, OCONHC).

2(S)-*Amino*-N-[2-*oxo*-1-[(*phenyl*)(1H-*tetrazol*-5-*yl*)*amino*]-3(S)-*azetidinyl*]*pentanamide* (XXXI)

Compound XXVII (0.235 g, 0.5 mmol) was hydrogenated as described for the preparation of XXIX above. The product (0.5 mmol) was dissolved in dry DMF (5 ml), cooled to 0° and treated with Et_3N (0.7 ml, 0.5 mmol). N-Benzyloxycarbonyl-L-norvaline (0.13 g, 0.5 mmol) was added, followed by N-ethoxycarbonyl-2-ethoxy-1, 2-dihydroisoquinoline (0.15 g, 0.5 mmol) in dry DMF (5 ml). The mixture was stirred at 0° for 2 hr then overnight at room temp, when very little XXIX remained. The mixture was evaporated and the residue was partitioned between 15% $KHCO_3$ aq (20 ml) and CH_2Cl_2 (20 ml). The organic phase was washed with water (20 ml) and the aqueous extracts were back extracted with CH_2Cl_2 (20 ml). The combined aqueous and bicarbonate extracts were concentrated and re-evaporated with water (2 × 10 ml). The aqueous residue was cooled to 0° and acidified to pH 3 to give 0.095 g of XXX as a gum. Extraction of the combined CH_2Cl_2 extracts with 15% $KHCO_3$aq followed by acidification to pH 3 gave a further 0.075 g of XXX. These fractions of XXX were combined in MeOH (15 ml) and hydrogenated with 10% Pd–C charcoal catalyst (50 mg) at room temp for 17 hr. Catalyst was filtered off and the filtrate was evaporated and re-evaporated with EtOAc to give a solid (0.090 g). This was triturated with EtOAc and filtered off. Attempted crystallisation in a mixture of MeOH (5 ml) and EtOAc (10 ml) removed, as a ppt, some L-norvaline impurity. The filtrate was evaporated (50 mg) and triturated with water to give the pure (TLC) product XXXI as a gum (0.015 g) (leaving a supernatant which was contaminated with norvaline). ν_{max} ($CHCl_3$) 1803 cm^{-1}; *m/e* (FAB) 345 $(M+H)^+$ (6%); 72 $(C_4H_{10}N)^+$ (100%) 72 (100%). δ ^{1}H ($CDCl_3$) 0.93 (3H, t, CH_3), 1.2–1.7 (4H, m, CH_2), 3.61 (1H, dd, J = 4.0, 7.0 Hz, H-4), 3.98 (1H, m, H-4), 4.15 (1H, m, $CHCH_2$), 4.44 (1H, dd, J = 2.8, 5.6 Hz, H-3), 7.20–7.77 (5H, m, Ph).

Benzyl [2-*hydroxy*-1(S)-[[2-*oxo*-1-[(*phenyl*)(1H-*tetrazol*-5-*yl*)*amino*]-3(S)-*azetidinyl*]*carbamoyl*]*ethyl*]*carbamate* (XXXII)

Compound XXVII (0.235 g, 0.5 mmol) was hydrogenated to give XXIX as described above. The product (0.5 mmol) was taken up in DMF (10 ml) and cooled to −5°. Et_3N (0.050 g, 0.5 mmol) was added followed by active ester XXVI (0.19 g, 0.5 mmol). The mixture was stirred for 2 hr at −5° then overnight at room temp when all the XXIX had been consumed [TLC, silica gel, n-BuOH (12); AcOH (3); H_2O (5)]. The mixture was evaporated and the residue was partitioned between water (50 ml) and CH_2Cl_2 (25 ml) and the aqueous phase was further extracted with CH_2Cl_2 (25 ml). The combined organic phase was extracted with 10% $KHCO_3$ aq (2 × 25 ml) and washed with water (50 ml). The combined bicarbonate and aqueous extracts were concentrated to about 25 ml, cooled to 0° and acidified to pH 3 with 2N HCl to give a ppt. This was filtered off, washed with water and dried to give 0.11 g of solid. The filtrate was extracted with CH_2Cl_2 which was dried and evaporated to give a further 0.13 g of solid. These solids were combined (0.24 g) and partitioned between water (50 ml) and CH_2Cl_2 (50 ml). The organic phase was further extracted with water (2 × 50 ml) and was then dried over Na_2SO_4 and evaporated to give 0.2 g of gum. This was taken up in EtOAc (5 ml), diethyl ether (50 ml) and petroleum ether b.p. 40–60° (20 ml) were added and the soln was refrigerated overnight. The resulting ppt was filtered off to give, as a hygroscopic solid, substantially pure (*ca* 95% by TLC) (XXXII), 0.025 g, m.p. *ca* 115° (dec). (Found: C, 53.0; H, 4.6; N, 23.4. $C_{21}H_{22}N_8O_5$ requires: C, 54.0; H, 4.75; N, 24.0%.) *M/e* (FAB) 467 $(M+H)^+$, 10%; 91 $(PhCH_2)^+$, 100%; *m/e* (FAB) 505 $(M+K)^+$ *m/e* 505·1380 ($C_{21}H_{22}N_8O_5K$ = 505·1349). ν_{max} (KBr disc) 1794 cm^{-1}. δ ^{1}H NMR ($CDCl_3$) 3.5–4.6 (resonances not resolved even after treatment with chelex resin), 5.07 (2H, s, $PhCH_2O$), 7.20–7.65 (10H, m, 2 × Ph).

2(S)-*Amino*-3-*hydroxy*-N-[2-*oxo*-1-[(*phenyl*)(1H-*tetrazol*-5-*yl*)*amino*]-3-(S)-*azetidinyl*]*propionamide* (XXXIII)

Compound XXXII (0.070 g, 0.15 mmol) was taken up in a mixture of MeOH (25 ml) and water (5 ml) and hydrogenated with 10% Pd–C catalyst (20 mg). Hydrogenolysis was complete after 4 hr (TLC). Catalyst was filtered off and the filtrate was evaporated to give 0.040 g of an oil. This oil was taken up in MeOH (5 ml) and filtered. EtOAc (50 ml) was added to give a white ppt of XXXIII, 0.007 g, m.p. *ca* 160° (dec). ν_{max} (KBr) 1772 cm^{-1} (β-lactam); *m/e* (FAB) 333 $(M+H)^+$, *m/e* 333.1392 ($C_{13}H_{17}N_8O_3$ = 333.1423, 100%). δ ^{1}H (D_2O) (300 MHz) 3.88 (1H, d, J = *ca* 2.5 Hz, J = *ca* 5.0 Hz, H-4), 3.98 (2H, d, J = *ca* 5.0 Hz, CH_2OH), 4.12 (2H, m, 5 lines, H-4 and H_2NCHCO), 5.13 (1H, dd, H-3), 7.26–7.52 (5H, m, Ph).

3(S)-[2-(2-*Amino*-4-*thiazolyl*)-2-(*methoxyimino*)*acetamido*]-1-[(*phenyl*)(1H-*tetrazol*-5-*yl*)*amino*]-2-*azetidinone* (XXXV)

Compound XXVII (0.47 g, 1 mmol) was hydrogenated to give XXIX as above. The product (1 mmol) was stirred in dry DMF (10 ml) at −5° as Et_3N (0.14 ml, 1 mmol) was added. The ester XXXIV[5] (0.35 g, 1 mmol) was added at −5° to give a yellow soln. The mixture was allowed to come to room temp over 3 hr and was then stirred overnight. The mixture was evaporated to give a gum which was partitioned between CH_2Cl_2 (20 ml) and 15% $KHCO_3$ aq (10 ml). The organic phase was extracted with a further 2 × 5 ml of 15% $KHCO_3$ aq. All $KHCO_3$ phases were back extracted with CH_2Cl_2 (2 × 10 ml). The $KHCO_3$ extracts were combined, concentrated and re-evaporated three times with water. An aqueous soln of the residue was acidified to pH 3 with HCl to give a white solid ppt. This was filtered off,

washed with water and dried to give 0.16 g (Crop 1) of XXXV, m.p. *ca* 225–235° (dec); ν_{max} (KBr disc) 1786 cm^{-1}; $[\alpha]_D^{20}$ − 10.9° (*c* = 0.2%, MeOH). Concentration of the filtrate gave a further 0.090 g of XXXV, m.p. 217–235° (dec). Attempts to further purify XXXV by recrystallisation, preparation of dicyclohexylamine salt, or a Na salt, all failed. A sample of XXXV (50 mg) was slurried overnight with a mixture of water (5 ml) and EtOH (0.05 ml). EtOH (0.2 ml) was added and the mixture was stirred for a further 3 hr and filtered to give 0.030 g of XXXV, m.p. *ca* 235° (dec). (Found: C, 45.5; H, 4.2; N, 30.7. $C_{16}H_{16}N_{10}O_3S$ requires: C, 44.9; H, 3.8; N, 32.7%.) *m/e* (FAB) 429 $(M+H)^+$, *m/e* 429.1179, ($C_{16}H_{17}N_{10}O_3S$ = 429.1206, 64%), *m/e* (FAB) 126 ($C_4H_4N_3S$), *m/e* 126.0130, ($C_4H_4N_3S$ = 126.0126, 100%). ν_{max} (KBr disc) 1782 cm^{-1} (β-lactam); $[\alpha]_D^{20}$ − 12.5° (c = 0.2%, MeOH). δ ^{1}H NMR (CD_3OD) *ca* 3.95 (1H, m, H-4), 3.98 (3H, s, OCH_3), 4.12 (1H, t (dd), J = 5.5 Hz, H-4), 5.08 (1H, dd, J = 3.0, 5.6 Hz, H-3), 6.88 (1H, s, thiazolyl ring), 7.20–7.70 (5H, m, Ph).

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