Synthesis and Antimicrobial Activity of Oxazolidin-2-ones and Related Heterocycles

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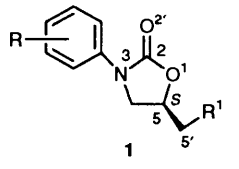
A series of 5-membered heterocycles, structurally related to the known antibacterial oxazolidin-2-ones **1**, have been prepared by modifying the model compound **1a** at the **1**-, **2**-, **2'**- and **3**-positions. The antibacterial activity of compound **1a** was strongly affected by these modifications to the heterocycle, although none of these resulted in an improvement in the microbiological activity. The physicochemical and antibacterial properties of the synthesized compounds are reported.

Five-membered heterocycles containing two or three hetero atoms form a broad class of compounds that include several successful drugs that act upon the central nervous system,[1] the gastrointestinal tract,[2] or act as cardiovascular,[3] anti-inflammatory[4] or as antitumour agents.[5]

A new class of synthetic antibacterial agents that possess a oxazolidin-2-one core structure **1** (Fig. 1) has been reported.[6,7,8]



1

(*S*)-**1a**: R = Ac, R' = AcNH

Fig. 1

Compound **1a**,[8] shown to be a promising antibacterial agent, was active *in vitro* against Gram-positive bacteria, but not against Gram-negative bacteria or fungi (Minimal inhibitory concentrations, MIC, Fig. 1). It was active *in vivo* either by intravenous and oral administration, showing no toxicity up to 1 g kg^{-1}. Its mechanism of action, disruption of bacterial protein synthesis, has yet to be elucidated in detail,[9,10,11] although preliminary studies on its potential clinical applications have been performed.[12,13]

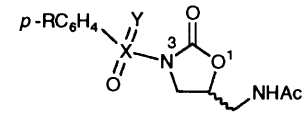
Structure–activity relationships, for modifications of the R and R' groups (Fig. 1), have been reported,[14,15] and we have attempted a similar study for modifications to atoms 1, 2, 2' and 3 in the heterocyclic ring (Fig. 1), in order to find new and more potent analogues of these antibacterial agents.

We designed several oxazolidinone-like structures and performed a theoretical analysis using molecular modelling. This approach allowed the selection of the most promising structures in terms of their predicted physicochemical properties.

The selected heterocycles (Fig. 2) were chosen in order to study how modifications of the oxazolidin-2-ones altered their physical properties (*e.g.* geometry, polarizability, stability, lipophilicity and their steric and electronic characteristics).

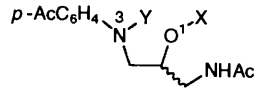
Compounds **2** were thought likely to have enhanced electron-withdrawing properties as a result of the *N*-substituent, a feature which appears to be important for biological activity.[14] The introduction of a group between the two rings should also influence the geometric properties of the molecules.

The open-chain compounds **3** should mimic the product of a possible enzyme-catalysed opening of the electron-deficient carbamate moiety through the action of a nucleophilic residue, such as lysine, cysteine, serine, *etc.*



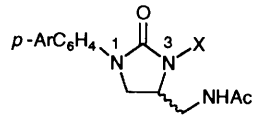
2

2a X = C, Y = absent, R = H
2b X = S, Y = O, R = Me



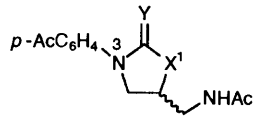
3

3a X = Y = H
3b X = Y = Ac
3c X = H = CHO



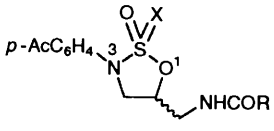
4

4a X = Bn, R = Ac
4b X = Me, R = Ac
4c X = H, R = CH(OH)Me



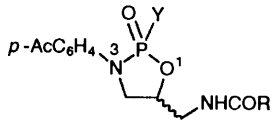
5, 6

5a X = S, Y = O
6a X = O, Y = S



7

7a X = absent, R = Me, *cis*
7b X = absent, R = Me, *trans*
7c X = O, R = Me
7d X = absent, R = Bu^t, *cis*
7e X = absent, R = Bu^t, *trans*



8

8a–b Y = MeO, R = Me
8c–d Y = MeO, R = OBu^t

Fig. 2

The 1-oxygen was replaced with a nitrogen, producing imidazolidin-2-ones **4** with increased stability towards basic hydrolysis, additional steric hindrance and with different lipophilic properties due to the various X groups employed.

The 1- and 2'-oxygen were replaced with sulfur, producing thiazolidin-2-ones **5** (X = S) and oxazolidine-2-thiones **6** (Y = S) with the introduction of a highly polarizable and bulky atom in this part of the molecule.

The 2-carbon was replaced either with sulfur or with phosphorus, producing 1,2,3-oxathiazolidin-2-ones or 2,2-diones **7** and 1,3,2-oxazaphospholidin-2-ones **8**. These mimic the tetrahedral structure of the transition state for the above mentioned nucleophilic attack.

Results and Discussion

Molecular Modelling.—Details of the software and hardware are reported in the Experimental section. The designed structures were built 'on screen' together with compound **1a**, and their minimum energy conformations after being computed were compared with their predicted physicochemical properties. The distances among the functional groups (Fig. 3, Table 1),

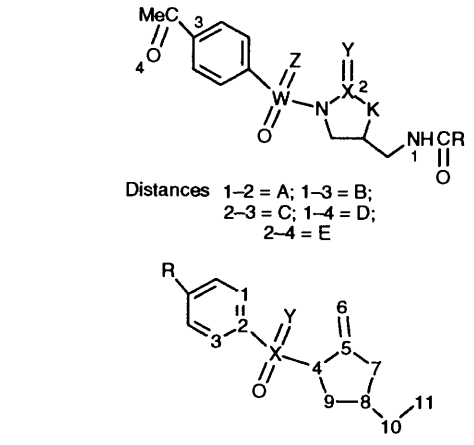


Fig. 3

the dihedral angles (Fig. 3, Table 2) and the partial charges on single atoms (Fig. 3, Table 3) were selected as important criteria for the compounds to be synthesized.

Structure **2a** showed non-coplanarity between the two cycles (F and G, Table 2), while for structure **2b**, the phenyl ring and the chain nitrogen were significantly closer than in all the other computer-generated structures (B, Table 1); the charges of compounds **2** were strongly influenced by the groups between the two cycles (Table 3). The open-chain compounds **3** showed a considerable difference in their dihedral angles (C and D, Table 2) in the absence of geometrical constraints by a 5-membered ring. Structures **4** showed an increased electronegativity in positions δ2 and δ4 (Table 3) and the presence of sulfur in structures **5** and **6** greatly influenced their electronic properties (δ1, δ2 and δ4, Table 3) and geometry (F and G, Table 2). In structures **7** and **8** the introduction of tetrahedral heteroatoms (H and I, Table 2) also strongly affected the electronic properties of these molecules (δ1, δ2, δ3, δ4 and δ7, Table 3). The chemical synthesis and microbiological evaluation of this set of compounds, for which different chemical stabilities were predicted, should have allowed the determination of positive modifications of structure **1a** with respect to the antibacterial activity.

Synthesis.—The synthesis of compounds **2a** and **2b** is shown in Scheme 1. The amino diol **9**[16] was treated with triphosgene and sodium carbonate in water to produce the cyclic compound **10** that was subsequently protected with tosyl chloride and triethylamine (TEA) to give compound **11**. This compound, through its aza-anion generated *in situ* with BuLi, was treated,

Table 1

Compds.	Distances/Å[a] A	B	C	D	E
1a	4.71	8.35	5.27	10.18	7.64
2a	4.73	8.93	5.93	—	—
2b	4.54	5.16	5.58	—	—
3a	—	8.26	—	10.15	—
3b	4.87	8.16	5.19	10.83	7.55
3c	4.90	8.19	5.22	10.04	7.60
4a	4.76	8.35	5.27	10.16	7.65
4b	4.69	8.02	5.27	9.87	7.64
4c	4.72	8.23	5.26	10.28	7.32
5a	5.01	8.19	5.24	9.95	7.61
6a	4.71	8.35	5.25	10.22	7.62
7a	4.90	8.36	5.29	10.23	7.69
7b	4.02	8.56	5.29	10.76	6.68
7c	4.90	8.37	5.30	10.22	7.70
7d	4.90	8.35	5.29	10.22	7.69
7e	4.03	8.57	5.29	10.77	7.68
8a	4.96	8.32	5.36	10.11	7.75
8b	4.96	8.34	5.36	10.13	7.75
8c	4.96	8.31	5.36	10.10	7.75
8d	4.95	8.33	5.36	10.12	7.75

[a] See Fig. 3.

Table 2

Compds.	Dihedral angles[a] F	G	H	I	J	K
1a	13.3	15.1	2.9	14.5	61.4	−178.7
2a	120.3	85.5	3.9	11.3	62.5	−175.8
2b	7.6	−18.6	−3.0	−15.9	61.2	179.8
3a	−2.4	1.2	—	64.7	65.1	−174.6
3b	−39.0	−41.8	104.4	65.1	60.5	−169.3
3c	−19.4	−23.8	111.2	65.2	61.2	−177.3
4a	10.7	12.1	0.3	5.3	69.4	−174.4
4b	−12.3	−14.0	0.2	−8.1	66.0	−178.4
4c	−6.2	−7.7	5.1	1.6	65.1	179.7
5a	19.4	20.3	7.5	28.0	65.0	−174.9
6a	18.0	22.3	−0.6	19.2	61.9	−178.0
7a	4.1	10.6	34.7	31.0	63.3	−179.0
7b	4.0	10.6	35.9	25.6	67.0	−178.8
7c	2.1	13.1	38.2	27.7	63.4	−179.2
7d	4.0	10.6	34.7	31.0	62.9	−179.3
7e	4.0	10.6	32.5	27.5	67.2	−174.9
8a	1.1	1.6	14.8	19.0	58.9	177.7
8b	3.5	−0.6	7.9	21.5	59.1	178.1
8c	1.1	1.5	14.7	19.3	58.5	177.3
8d	3.5	−0.5	8.0	21.7	58.9	177.9

[a] See Fig. 3.

respectively, with benzoyl chloride or tosyl chloride to produce the intermediates **12a** and **12b**. These compounds were transformed, respectively, into compounds **2a** and **2b** through the displacement of the tosylate with sodium azide and the reaction with thioacetic acid (Scheme 1).

The synthesis of compounds **3a–c** is shown in Scheme 2. Compound **3a** was prepared from compound **1a**[8] *via* an aqueous basic hydrolysis, whilst compound **3b** was prepared by acetylation of compound **3a** and compound **3c** by a selective formylation of compound **3a** with compound **14**[17] (Scheme 2).

The synthesis of compounds **4a–c** is shown in Scheme 3. In analogy with the synthesis of the oxazolidinones,[8] where the key step was the condensation between an aromatic isocyanate and an optically active epoxide, substitution of the epoxide with the aziridines **17** (prepared from the commercially available

Table 3

Compound	Electronic properties[a]							
	δ1[b]	δ2[b]	δ3[b]	δ4[b]	δ5[b]	δ6[b]	δ7[b]	δ8[c]
1a	+0.456	−0.356	−0.392	−0.248	−0.300	−0.415	−0.372	4.248
2a	δ1: +0.462 C: +0.440 O: −0.238	−0.329	−0.499	−0.237	—	−0.415	−0.371	7.425
2b	δ1: +0.416 S: +1.648 O_1: −0.657 O_2: −0.617	−0.272	−0.629	−0.235	—	−0.416	−0.368	10.042
3a	—	—	−0.438	−0.305	−0.307	−0.414	−0.375	1.260
3b	+0.335	−0.357	−0.388	δ4: −0.308 C: +0.339 O: −0.353	−0.301	−0.411	−0.376	3.930
3c	+0.361	−0.359	−0.399	−0.306	−0.299	−0.416	−0.375	3.563
4a	+0.478	−0.425	−0.385	−0.429	−0.304	−0.413	−0.380	3.404
4b	+0.476	−0.421	−0.387	−0.438	−0.303	−0.413	−0.376	4.021
4c	+0.460	−0.431	−0.402	−0.402	−0.306	−0.414	−0.379	4.532
5a	+0.253	−0.326	−0.373	+0.126	−0.300	−0.415	−0.372	3.734
6a	+0.180	−0.168	−0.343	−0.211	−0.298	−0.415	−0.371	4.827
7a	+1.344	−0.730	−0.691	−0.481	−0.301	−0.416	−0.373	4.846
7b	+1.331	−0.728	−0.692	−0.484	−0.300	−0.403	−0.383	4.323
7c	+1.815	O_1: −0.677 O_2: −0.647	−0.694	−0.451	−0.298	−0.418	−0.364	6.992
7d	+1.345	−0.731	−0.692	−0.483	−0.302	−0.402	δ7: −0.429 O: −0.332	5.072
7e	+1.332	−0.727	−0.692	−0.483	−0.300	−0.387	δ7: −0.438 O: −0.329	4.378
8a	+1.286	δ2: −0.588 OMe: −0.456	−0.607	−0.432	−0.302	−0.416	−0.366	8.165
8b	+1.286	δ2: −0.589 OMe: −0.458	−0.608	−0.424	−0.302	−0.414	−0.378	4.378
8c	+1.287	δ2: −0.589 OMe: −0.454	−0.607	−0.434	−0.302	−0.399	δ7: −0.423 O: −0.333	7.128
8d	+1.286	δ2: −0.589 OMe: −0.458	−0.608	−0.425	−0.302	−0.397	δ7: −0.432 O: −0.332	4.378

[a] Calculated with MOPAC. [b] See Fig. 3, partial charges in electron units. [c] Dipole, Debye.

precursors **15** and **16**) produced the desired imidazolidin-2-one nucleus **19** (Scheme 3).

The condensation of compounds **17** and **18**[18] was performed by a modification of the original experimental conditions,[8] then a single-step reduction and acetylation of the nitrile in compound **19** with Raney nickel and hydrogen (50 p.s.i.) in acetic anhydride–sodium acetate to give compounds **4a** and **4b**. Compound **4c** was obtained by *N*-debenzylation and reduction with Na–NH_3 of compound **4a** in anhydrous THF at −60 °C (Scheme 3). The concomitant carbonyl reduction to the alcohol did not affect the utility of compound **4c** since the corresponding oxazolidin-2-one retained a good antibacterial activity.

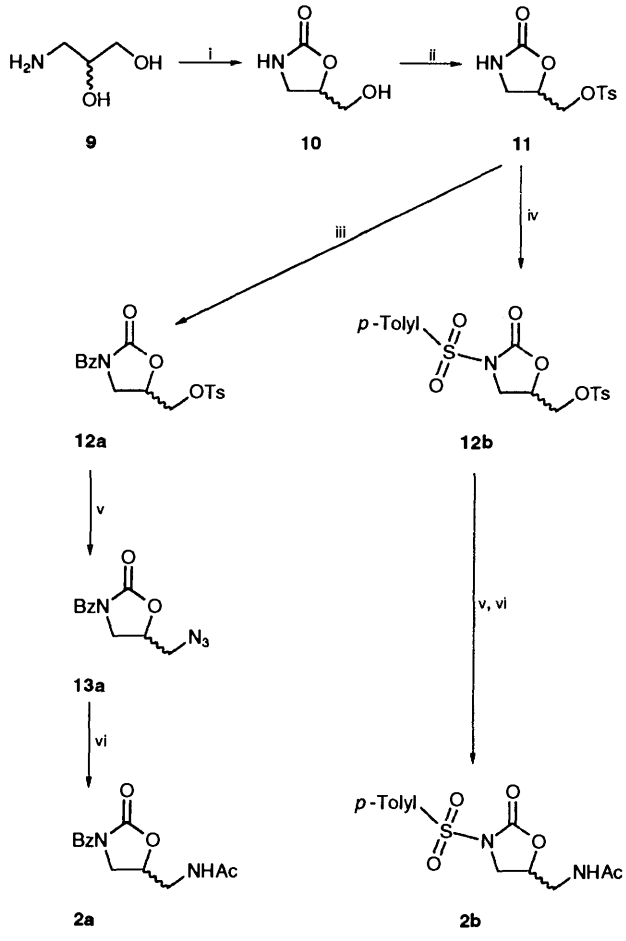
The synthetic strategy was also applied to the thiiranes to obtain **5a**, but it proved to be unsuccessful. The failure was probably due to the different chemical reactivity and stability of thiiranes when compared with aziridines and epoxides.

Reaction of compound **3a** with thiophosgene produced compound **6a** (Scheme 4), while condensation with sulfuryl chloride to obtain compound **7c** was unsuccessful, in accordance with the literature.[19] Compound **3a** was subjected to condensation with thionyl chloride and phosphorus oxychloride; the reaction was monitored by HPLC and new peaks, possibly corresponding to products **7a–b** and **8a–b**, were observed but could not be isolated because of their extreme lability in any work-up procedure. This was probably due to the reactivity of the acetamido function towards the sensitive heterocycle. Replacing the acetamide with a *tert*-butyl carbamate to give **22** (Scheme 4) and treatment with thionyl chloride gave the two geometrical isomers **7d** and **7e** and with phosphorus oxychloride the mixture **8c–d** after methanolic work-up. The determination of sulfur chirality and the assignment of a *trans* conformation to compound **7e** and a *cis* conformation to compound **7d** were made through the NMR chemical shifts and the coupling constants of the 5-proton (Fig. 1) accordingly to Deyrup *et al.*[19] Attempts to remove the Boc moiety, either in acidic (anhydrous TFA, 0 °C) or in neutral conditions (trimethylsilyl iodide, anhydrous methylene dichloride, 0 °C), produced only complex mixtures of open compounds; nevertheless, the Boc-substitution on the chain nitrogen of the oxazolidin-2-one antibacterials provided compounds with microbiological activity.

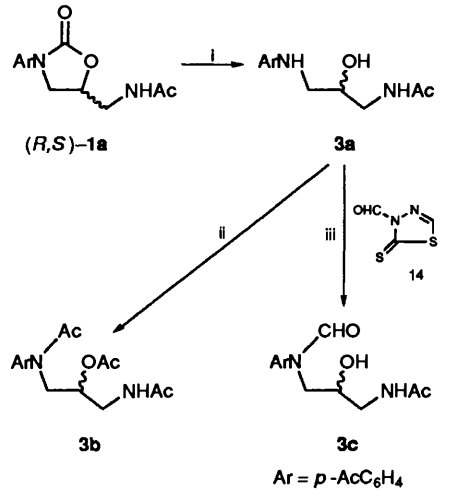
All the intermediates and the final compounds were analytically characterized by means of TLC, NMR, MS and IR techniques as reported in the Experimental section.

Microbiology.—The experimental techniques used to determine the minimum inhibitory concentrations (MIC) values of the synthesized compounds are reported in the Experimental section. The microbiological activity of compounds **1** was completely lost for the compounds modified in position **1**, **2** and **3** of the heterocyclic ring (MIC > 128). Only the oxazolidine-2-thione **6a** showed a reduced antibacterial activity (MIC = 64–128).

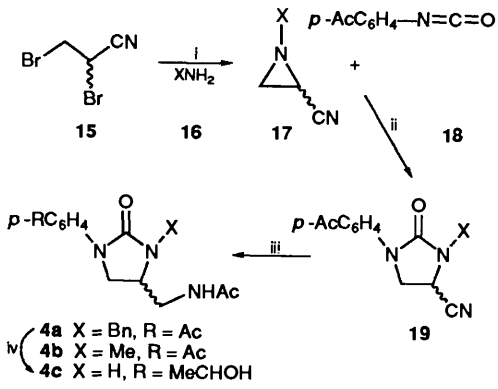
General Remarks.—It may be inferred that only the *S* enantiomer of antibacterial oxazolidin-2-ones is active (Fig. 1), while the *R* enantiomer is completely inactive;[14] this would have halved the biological activity of our racemates. Moreover, some of the groups introduced in the analogues are known to be 'not ideal' for microbiological activity[14,15] in the model



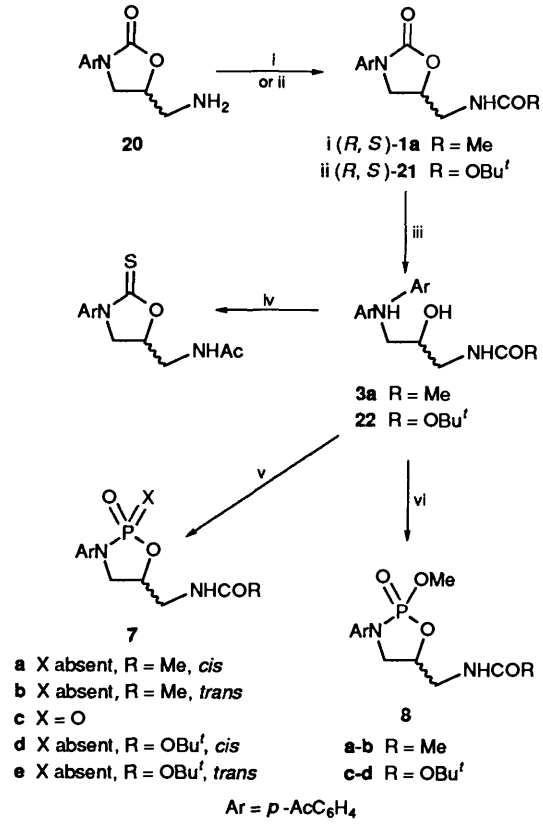
Scheme 1 *Reagents and conditions:* i, triphosgene, sodium carbonate, water; ii, TsCl, TEA, dichloromethane; iii, B_3Cl, BuLi, THF; iv, TsCl, BuLi, THF; v, sodium azide, DMF; vi, thioacetic acid



Scheme 2 *Reagents and conditions:* i, acetone–water 1:1, NaOH 1 mol dm^{-3}; ii, AcOH, DCC, methylene dichloride; iii, **14**, DMF



Scheme 3 *Reagents and conditions:* i, TEA, toluene; ii, LiBr, tributylphosphine oxide, xylene; iii, hydrogen, Raney nickel, acetic anhydride, sodium acetate; iv, THF, liq. ammonia, sodium



Scheme 4 *Reagents and conditions:* i, Ref. 8; ii, *tert*-butyl pyrocarbonate; iii, acetone–water (1:1), NaOH (1 mol dm^{-3}); iv, thiophosgene, TEA, CH_2Cl_2; v, thionyl/sulfonyl chloride, TEA, CH_2Cl_2; vi, phosphorus oxychloride, TEA, CH_2Cl_2

structure **1** (Fig. 1): examples are the carbamates in **7d**, **7e** and **8c–d** or the lack of substituents on the phenyl ring in **2a**. Nevertheless, the complete loss of biological activity for all the derivatives cannot be explained solely by these considerations.

We have clearly assessed the crucial importance of the cyclic carbamate moiety for the antibacterial activity. In future, positions 4 and 5 of the oxazolidinone ring (Fig. 1) could be modified by introduction of 4- and 5-disubstitution or 4-5 condensation and new ring formation, as recently reported in the literature.[20] This work supports all the generalisations derived from the results of earlier studies of structure–activity relationships.[14,15]

Experimental

The solvents and reagents were purified and dried by standard techniques.[21] Solvents were removed using a Buchi EL131 rotary evaporator at bath temperatures varying from room temp. to 50 °C. The reactions, the intermediates and the final compounds were analysed by direct phase TLC using Merck Kieselgel 60 F_{254} thin-layer plates with eluent mixtures including methylene dichloride, chloroform, methanol, acetone, ethyl acetate and

light petroleum (30–50 °C). IR spectra (Nujol, $CDCl_3$ solution) were recorded on a Perkin-Elmer 850 spectrometer and the values are reported in cm^{-1} (ν). $^1H(^{13}C)$ NMR spectra were recorded at 250 (62.5) MHz with a Bruker AM 250 and processed using an Aspect 3000 computer. The spectra were recorded at 37 °C in deuteriated chloroform or deuteriated DMSO. The chemical shifts (δ) are reported in ppm downfield from the internal reference, tetramethylsilane (TMS, δ 0.00). MS spectra were recorded on a TSQ700 Finnigan quadrupole instrument under electron impact (EI) conditions (70 eV, ion source temperature 180°). A Model 1106 Carlo Erba instrument was used for elemental analysis utilizing standard techniques. The molecular modelling studies were carried out on a Silicon Graphics 4D/340 workstation using the Biosym software packages DISCOVER and INSIGHTII. INSIGHTII was used to construct and visualize the molecules, while the energy calculations used the consistent valence force field of DISCOVER.

5-Hydroxymethyloxazolidin-2-one **10**.—A solution of the aminodiol **9** (12 g, 131.7 mmol) and sodium carbonate (48.46 g, 461.00 mmol) in water (200 cm^3) was stirred at room temp. whilst triphosgene [bis(trichloromethyl)carbonate] (13.02 g, 43.90 mmol) was added in several portions. After 4 h, the mixture was extracted with methylene dichloride (2 × 100 cm^3). The aqueous phase was then neutralized with 1 mol dm^{-3} hydrochloric acid and evaporated to dryness by the azeotropic removal of water with absolute ethanol. The solid residue was then suspended in absolute ethanol and the inorganic salts were filtered off. The filtrate was evaporated to give crude material (25 g). This was chromatographed on silica gel (R_f 0.35, MeOH–CH_2Cl_2 15:85), to yield the oxazolidinone **10** as a white solid (9.10 g, 60%), m.p. 71–72 °C; ν_{max}(Nujol)/cm^{-1} 3397, 3248 and 1734; δ_H([$^2H_6$]DMSO) 7.39 (1 H, br, NH), 5.09 (1 H, br, OH), 4.52 (1 H, m, 5-CH) and 3.17–3.57 (4 H, m, 4- and 5′-CH_2).

5-(Tosyloxymethyl)oxazolidin-2-one **11**.—A solution of the alcohol **10** (3 g, 25.60 mmol), toluene-*p*-sulfonyl chloride (5.86 g, 30.70 mmol) and triethylamine (4.63 cm^3, 33.30 mmol) in methylene dichloride (30 cm^3) was stirred at room temp. for 16 h. It was then diluted with methylene dichloride (200 cm^3), washed with water (100 cm^3), 1 mol dm^{-3} aqueous sodium hydrogen carbonate (2 × 100 cm^3) and finally water (3 × 100 cm^3), dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue on silica gel (R_f 0.39, MeOH–CH_2Cl_2 5:95) gave the pure tosylate **11** (5.72 g, 82%) as a white solid, m.p. 98–99 °C; ν_{max}($CHCl_3$)/cm^{-1} 3468, 1769, 1672 and 1559; δ_H($CDCl_3$) 7.79 (2 H, d, *J* 8.2, Ar), 7.36 (2 H, d, *J* 8.2, Ar), 5.48 (1 H, b, NH), 4.80 (1 H, m, 5-CH), 4.16 (2 H, d, *J* 4.5, 5′-CH_2), 3.68 (1 H, dt, *J* 2.1 and 8.4, 4-CH_2), 3.46 (1 H, ddd, *J* 2.1, 5.3 and 8.2, 4-CH_2) and 2.45 (3 H, s, Me).

3-Benzoyl-5-(tosyloxymethyl)oxazolidin-2-one **12a**.—A solution of compound **11** (5.55 g, 20.50 mmol) in anhydrous tetrahydrofuran (10 cm^3) was cooled to −78 °C under an argon atmosphere. A solution of butyllithium (1.6 mol dm^{-3} in hexanes; 14 cm^3, 22.40 mmol) was added dropwise and then the mixture was allowed to warm to −20 °C for 15 min. The reaction mixture was then recooled to −78 °C and a solution of benzoyl chloride (3.26 cm^3, 28.10 mmol) in anhydrous tetrahydrofuran (5 cm^3) was added to it dropwise. After a further 15 min at this temperature the mixture was allowed to warm to room temp. at which it was stirred for 1 h. It was then diluted with ethyl acetate (50 cm^3), washed twice with water (20 cm^3), dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product (9.10 g). This was purified by chromatography on silica gel (R_f 0.31, acetone–$CHCl_3$ 3:97) to yield the title compound **12a** as a white solid (5.16 g, 67%), m.p. 161–162 °C; ν_{max}($CHCl_3$)/cm^{-1} 1798, 1686, 1626 and 1599; δ_H($CDCl_3$) 7.81 (2 H, d, *J* 8.0, Ar), 7.55 (3 H, m, Ar), 7.39 (4 H, m, Ar), 4.83 (1 H, m, 5-CH), 4.33–4.25 (2 H, dq, *J* 3.5, 5′-CH_2), 4.27–4.21 (1 H, dd, *J* 7.8 and 11.4, 4-CH_2), 3.99 (1 H, dd, *J* 5.6 and 11.5, 4-CH_2) and 2.45 (3 H, s, Me).

5-Azidomethyl-3-benzoyloxazolidin-2-one **13a**.—A solution of the *N*-benzoylated tosylate **12a** (13.30 mmol) and sodium azide (960 mg, 14.70 mmol) in dimethylformamide (DMF) (100 cm^3) (previously dried over 4 Å molecular sieves) was heated to 60 °C for 1 h. The mixture was then diluted with water (750 cm^3) and the suspension was extracted with ethyl acetate (3 × 300 cm^3). The organic phase was then washed with water (4 × 300 cm^3), dried (Na_2SO_4) and concentrated under reduced pressure to give the crude product **13a** (3.28 g, 100%); this was used without purification for the following reaction (R_f 0.30, acetone–$CHCl_3$ 3:97); ν_{max}($CHCl_3$)/cm^{-1} 2114, 1794, 1686, 1626 and 1603; δ_H($CDCl_3$) 7.40–7.67 (5 H, m, Ar), 4.80 (1 H, m, 5-CH), 4.23 (1 H, dd, *J* 8.6 and 11.1, 4-CH_2), 4.00 (1 H, dd, *J* 6.2 and 11.1, 4-CH_2) and 3.57–3.80 (2 H, dq, 5′-CH_2).

N-(3-Benzoyl-2-oxooxazolidin-5-ylmethyl)acetamide **2a**.—A solution of the azide **13a** (3.2 g, 13.00 mmol) in thioacetic acid (10 cm^3) was stirred at room temp. under an argon atmosphere for 48 h. Evaporation of the excess of thioacetic acid gave the crude product (6.82 g) that was then purified by chromatography on silica gel (R_f 0.13, MeOH–CH_2Cl_2 3:97) to give the title acetamide **2a** as a yellow solid (1.87 g, 55%), m.p. 151–152 °C; ν_{max}($CHCl_3$)/cm^{-1} 3489, 1695 and 1610; *m/z* 262 (M^+, 5%), 218 (85), 191 (10) and 105 (100); δ_H($CDCl_3$) 7.40–7.65 (5 H, m, Ar), 6.04 (1 H, bt, NH), 4.79 (1 H, m, 5-CH), 4.18 (1 H, dd, *J* 8.3 and 11.2, 4-CH_2), 3.87 (1 H, dd, *J* 7.4 and 11.3, 4-CH_2), 3.75 (1 H, ddd, 5′-CH_2), 3.53 (1 H, dt, *J* 3.3, 6.5 and 14.5, 5′-CH_2) and 2.02 (3 H, s, Me) (Found: C, 59.4; H, 5.5; N, 10.6. Calc. for $C_{13}H_{14}N_2O_4$: C, 59.53%; H, 5.38; N, 10.68%).

N-[3-(4-Acetylanilino)-2-hydroxypropyl]acetamide **3a**.—A solution of compound **1a**[8] (2.03 g, 7.33 mmol) in 1 mol dm^{-3} sodium hydroxide–acetone (1:1; 100 cm^3) was stirred at room temp. for 2 h. The mixture was then neutralized with 1 mol dm^{-3} hydrochloric acid and concentrated under reduced pressure. The residue was taken up with absolute ethanol and the inorganic salts were filtered off. After concentration under reduced pressure, the residue (2.4 g) was chromatographed on silica gel (R_f 0.20, MeOH–$CHCl_3$ 2:98) to give the acetamide **3a** (1.04 g, 59%) as a brown solid, m.p. 132–134 °C; ν_{max}(Nujol)/cm^{-1} 3849, 1695 and 1610; *m/z* 250 (M^+, 27%), 232 (222), 148 (100) and 119 (15); δ_H([$^2H_6$]DMSO) 7.84 (1 H, bt, N*H*CO), 7.69 (2 H, d, *J* 8.6, Ar), 6.60 (2 H, d, *J* 8.6, Ar), 6.46 (1 H, bt, N*H*Ar), 5.02 (1 H, d, *J* 4.9, OH), 3.65 (1 H, m, 2-CH), 3.00–3.18 (4 H, m, 1- and 3-CH_2), 2.37 (3 H, s, *Me*COAr) and 1.82 (3 H, s, *Me*CONH) (Found: C, 62.2; H, 7.4; N, 11.1. Calc. for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; C, 11.19%).

N-[2-Acetoxy-3-(4,N-diacetylanilino)propyl]acetamide **3b**.—Acetic acid (1.86 cm^3, 32.60 mmol) and dicyclohexylcarbodiimide (DCC) (3.9 g, 18.90 mmol) were added at room temp. to a stirred solution of the acetamide **3a** (680 mg, 2.70 mmol) in methylene dichloride (20 cm^3). After 16 h the solid was filtered off and the filtrate was concentrated to give an oily residue. This was chromatographed on silica gel (R_f 0.35, MeOH–CH_2Cl_2 1:99) to produce the acetamide **3b** (545 mg, 60%) as a yellow oil; ν_{max}($CDCl_3$)/cm^{-1} 3453, 1726, 1673 and 1601; *m/z* 292 (M^+, 2%), 250 (15) and 148 (100); δ_H($CDCl_3$) 8.03 (2 H, d, *J* 8.5, Ar), 7.81 (2 H, d, *J* 8.5, Ar), 6.05 (1 H, b, NH), 4.97 (1 H, m, 2-CH), 3.90–4.02 (1 H, dq, *J* 5.2, 3-CH_2), 3.68–3.75 (1 H, m, 3-CH_2), 3.45 (2 H, m, 1-CH_2, 2.49 (3 H, s, MeCOAr) and 2.08, 2.06 and 2.02 (9 H, s, other Me) (Found: C,

61.4; H, 7.0; N, 9.4. Calc. for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.58%).

N-[3-(4-*Acetyl*-N-*formylanilino*)-2-*hydroxypropyl*]*acetamide* **3c**.—A stirred solution of the acetamide **3a** (1 g, 4 mmol) in DMF (30 cm^3) was cooled to 0 °C under a nitrogen atmosphere. The formylating reagent **14**[17] (3.53 g, 22.00 mmol) was then added and the mixture was stirred at 0 °C for a further 16 h. The solution was then poured into water (400 cm^3), filtered and the filtrate extracted with ethyl acetate (3 × 300 cm^3). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure to give a brown oil. This was chromatographed on silica gel (R_f 0.28, MeOH–CH_2Cl_2 5:95) to give the acetamide **3c** (465 mg, 42%) as a yellow solid; *m/z* 278 (M^+, 0.2%), 250 (20) and 148 (100); δ_H($CDCl_3$) 8.50 (1 H, s, CHO), 8.01 (2 H, d, *J* 8.5, Ar), 7.84 (2 H, d, *J* 8.5, Ar), 6.20 (1 H, b, NH), 4.27 (1 H, m, 2-CH), 4.02–4.18 (2 H, dq, *J* 3.9 and 8.6, 3-CH_2), 3.50 (2 H, m, 1-CH_2), 2.60 (3 H, s, *Me*COAr), 2.47 (1 H, d, *J* 8.1, OH) and 2.02 (3 H, s, *Me*CONH) (Found: C, 60.3; H, 6.6; N, 9.9. Calc. for $C_{14}H_{18}N_2O_4$: C, 60.62; H, 6.52; N, 10.07%).

1-*Benzylaziridine*-2-*carbonitrile* **17a**.—A solution of the carbonitrile **15** (2.34 cm^3, 23.49 mmol) in toluene (16 cm^3) was cooled to −10 °C with an external ice–salt bath. A solution of benzylamine **16a** (2.57 cm^3, 23.49 mmol) and triethylamine (6.54 cm^3, 46.98 mmol) in toluene (24 cm^3) was then added dropwise to it over 15 min. The stirred solution was then heated at 80 °C for 3 h and then at room temp. overnight. The reaction mixture was filtered to remove the inorganic salts and the filtrate was dried (Na_2SO_4), and concentrated under reduced pressure. The oily residue (4.00 g) was chromatographed on silica gel (R_f 0.38, EtOAc–light petroleum 20:80) to give the benzylated aziridine **17a** (2.60 g, 70%); δ_H($CDCl_3$) 7.35 (5 H, Ar), 3.62–3.89 (1 H, dd, *J* 6.1 and 7.2, 2-CH), 3.52 (2 H, s, CH_2Ar), 2.32 (1 H, dd, *J* 3.1 and 7.1, 3-CH_2) and 2.04 (1 H, dd, *J* 3.1 and 6.2, 3-CH_2).

[1-(4-*Acetylphenyl*)-3-(*benzyl*)-2-*oxo*-4-*imidazolidine*-4-*carbonitrile* **19a**.—A solution of lithium bromide (137 mg, 1.58 mmol) and tributylphosphine oxide (345 mg, 1.58 mmol) in xylene (50 cm^3) was azeotropically refluxed with a Dean–Stark apparatus for 1 h. A solution of the aziridine **17a** (2.50 g, 15.80 mmol) and the isocyanate **18**[18] (5.09 g, 31.60 mmol) in anhydrous xylene (16 cm^3) was then added dropwise while the mixture was kept at a gentle reflux. The resulting mixture was then refluxed for 4 h and, after cooling, was filtered to remove the inorganic salts and then concentrated at 45 °C under reduced pressure. The residue was chromatographed on silica gel (R_f 0.25, $CHCl_3$) to give the title compound **19a** (3.40 g, 67%) as a white solid, m.p. 130–132 °C; δ_H([$^2H_6$]DMSO) 8.01 (2 H, d, *J* 7.1, Ar), 7.78 (2 H, d, *J* 7.1, Ar), 7.35 (5 H, m, Ar), 5.64 (1 H, dd, *J* 3.3 and 8.5, 4-CH), 4.47 (2 H, q, CH_2Ar), 3.70 (2 H, m, 5-CH_2) and 2.55 (3 H, s, Me).

N-{[1-(4-*Acetylphenyl*)-3-*benzyl*-2-*oxoimidazolidin*-4-*yl*]-*methyl*}*acetamide* **4a**.—Raney nickel (W2; 1 g, aqueous suspension) was filtered, washed twice with absolute ethanol and twice with acetic anhydride. It was then added to a solution of the cyanide **19a** (3.60 g, 11.27 mmol) and sodium acetate (1.35 g, 16.51 mmol) in acetic anhydride (50 cm^3). The resulting suspension was hydrogenated for 8 h in a Parr bottle under a hydrogen pressure of 50 p.s.i. The mixture was then filtered to remove the catalyst and the filtrate was concentrated under reduced pressure. The residue was then chromatographed on silica gel (R_f 0.21, MeOH–CH_2Cl_2 2:98) to give the acetamide **4a** (2.70 g, 66%) as a yellow solid, m.p. 52–53 °C; ν_{max}(Nujol)/cm^{-1} 3198, 1666 and 1599; *m/z* 365 (M^+, 0.4%), 306 (30), 293 (35) and 91 (100); δ_H($CDCl_3$) 7.96 (2 H, d, *J* 8.9, Ar), 7.79 (2 H, d, *J* 8.9, Ar), 7.35 (5 H, m, Ar), 5.60 (1 H, bt, NH), 4.54 (1 H, m, 4-CH), 4.45 (2 H, q, CH_2Ar), 3.75 (1 H, m, 5-CH_2), 3.48 (1 H, t, *J* 9.2, 5-CH_2), 3.18 (2 H, m, 4′-CH_2), 2.56 (3 H, s, *Me*COAr) and 1.87 (3 H, s, *Me*CONH) (Found: C, 68.9; H, 6.5; N, 11.4. Calc. for $C_{21}H_{23}N_3O_3$: C, 69.02; H, 6.34; N, 11.50%).

({1-[4-(1-*Hydroxyethyl*)*phenyl*]-2-*oxoimidazolidin*-4-*yl*}-*methyl*)*acetamide* **4c**.—A solution of compound **4a** (2.60 g, 7.11 mmol) in anhydrous tetrahydrofuran (15 cm^3) was cooled to −60 °C under an argon atmosphere and then treated with liquid ammonia (120 cm^3). To this solution, sodium (1.48 g, 64.40 mmol) was added in several portions to create a persistent deep blue solution. After 30 min, ammonium chloride was added until the blue colour disappeared, after which the ammonia was allowed to evaporate. The residue was taken up with methylene dichloride–ethanol 1:1 and filtered to eliminate the inorganic salts, after which it was concentrated under reduced pressure. The resulting dark solid was chromatographed on silica gel (R_f 0.20, MeOH–CH_2Cl_2 10:90) to give the deprotected acetamide **4c** (558 mg, 49%) as a white solid, m.p. 57–58 °C; *m/z* 277 (M^+, 30%), 260 (85), 218 (75), 205 (100) and 188 (70); δ_H([$^2H_6$]DMSO) 8.28 (1 H, bt, NHCON), 7.52 (2 H, d, *J* 8.6, Ar), 7.25 (2 H, d, *J* 8.6, Ar), 6.78 (1 H, b, N*H*COMe), 5.02 (1 H, d, *J* 4.3, OH), 4.66 (1 H, dt, *J* 4.4 and 6.4, CHO*H*), 4.33 (1 H, m, 4-CH), 3.43 (2 H, m, 4′-CH_2), 3.15 (1 H, dd, *J* 3.8 and 9.1, 5-CH_2), 2.90 (1 H, m, 5-CH_2), 1.79 (3 H, s, MeCO) and 1.30 (3 H, d, *J* 6.4, MeC*H*) (Found: C, 60.5; H, 7.0; N, 15.1. Calc. for $C_{14}H_{19}N_3O_3$: C, 60.63; H, 6.91; N, 15.15%).

N-{[3-(4-*Acetylphenyl*)-2-*thioxooxazolidin*-5-*yl*]*methyl*}-*acetamide* **6a**.—A solution of the acetamide **3a** (1.00 g, 4.00 mmol) and triethylamine (2 cm^3, 14.36 mmol) in anhydrous methylene dichloride (20 cm^3) was cooled to −5 °C under an argon atmosphere. A solution of thiophosgene (398 mm^3, 5.15 mmol) in anhydrous methylene dichloride (5 cm^3) was then added dropwise to it and the mixture was stirred at −5 °C for a further 30 min. The mixture was then allowed to warm to room temp. and was stirred for a further 4 h. An equimolecular amount of thiophosgene was then added and the resultant solution was stirred for a further 3 h. The reaction was then quenched with methanol and concentrated under reduced pressure to give the residue as a dark oil (1.04 g). This was chromatographed on silica gel (R_f 0.30, MeOH–CH_2Cl_2 5:95) to give the oxazolidinethione **6a** (580 mg, 50%) also as a dark oil; ν_{max}($CHCl_3$)/cm^{-1} 3448, 1683 and 1605; *m/z* 292 (M^+, 15%), 233 (100), 218 (50) and 148 (45); δ_H($CDCl_3$) 8.05 (2 H, d, *J* 8.7, Ar), 7.77 (2 H, d, *J* 8.7, Ar), 6.10 (1 H, bt, NH), 5.00 (1 H, m, 5-CH), 4.27 (1 H, t, *J* 9.5, 4-CH_2), 4.14 (1 H, dd, *J* 8.0 and 9.5, 4-CH_2), 3.73 (2 H, dd, *J* 4.4 and 6.3, 5′-CH_2), 2.62 (3 H, s, *Me*COAr) and 2.05 (3 H, s, *Me*CONH) (Found: C, 57.3; H, 5.6; N, 9.5; S, 10.7. Calc. for $C_{14}H_{16}N_2O_3S$: C, 57.52; H, 5.52; N, 9.58; S, 10.97%).

tert-*Butyl* N{[3-(4-*Acetylphenyl*)-2-*oxooxazolidin*-5-*yl*]-*methyl*}*carbamate* **21**.—A solution of compound **20**[8] (2.7 g, 10.00 mmol) and triethylamine (3.06 cm^3, 22.00 mmol) in DMF (20 cm^3) was stirred at room temp. for 10 min. Di-*tert*-butyl pyrocarbonate (3.57 g, 12 mmol) was added in several portions and the solution was stirred at room temp. for a further 2 h. The mixture was then poured into water (200 cm^3), neutralized with 1 mol dm^{-3} hydrochloric acid and filtered to give, after washing (water, 3 × 50 cm^3) and drying (40 °C, P_2O_5 *in vacuo*), the carbamate **21** (2.60 g, 78%) as a white solid, m.p. 154–155 °C (R_f 0.48, MeOH–$CHCl_3$ 2:98); δ_H([$^2H_6$]DMSO) 7.98 (2 H, d, *J* 8.8, Ar), 7.66 (2 H, d, *J* 8.8, Ar), 7.14 (1 H, br, NH), 4.73 (1 H, m, 5-CH), 4.17 (1 H, t, *J* 9.1, 4-CH_2), 3.86 (1 H, dd, *J* 6.0 and 9.2, 4-CH_2), 3.20 (2 H, t, *J* 5.6, 5′-CH_2), 2.54 (3 H, s, Me) and 1.35 (9 H, s, Bu^t).

tert-*Butyl* N-[3-(4-*Acetylanilino*)-2-*hydroxypropyl*]*carbamate* **22**.—A solution of the oxazolidinone carbamate **21** (2.45 g, 7.33 mmol) in acetone–1 mol dm^{-3} sodium hydroxide (1:1; 100 cm^3) was treated as previously described for compound **3a** to produce the title compound **22** (1.76 g, 78%) as a white solid, m.p. 103–105 °C (R_f 0.22, MeOH–$CHCl_3$ 2:98); δ_H([$^2H_6$]DMSO) 7.69 (2 H, d, *J* 8.7, Ar), 6.65 (1 H, b, NH), 6.60 (2 H, d, *J* 8.7, Ar), 6.39 (1 H, bt, NH), 4.87 (1 H, d, *J* 3.3, OH), 3.67 (1 H, m, 2-CH), 2.93–3.21 (4 H, m, 1- and 3-CH_2), 2.39 (3 H, s, Me) and 1.38 (9 H, s, Bu^t).

tert-*Butyl* cis-N-{[3-(4-*Acetylphenyl*)-2,2-*dioxo*-2λ^4-1,2,3-*oxathiazolidin*-5-*yl*]*methyl*}*carbamate* **7d** *and trans*-**7e**.—A solution of compound **22** (500 mg, 1.62 mmol) and triethylamine (540 mm^3, 3.89 mmol) in anhydrous methylene dichloride (20 cm^3) was cooled to −5 °C under an argon atmosphere and a solution of thionyl chloride (129 mm^3, 1.78 mmol) in anhydrous methylene dichloride (5 cm^3) was then added dropwise to it. The resultant mixture was then stirred for 1 h at the same temperature. After warming to room temp., the solution was concentrated under reduced pressure to give a dark oily residue (1.05 g). This was chromatographed on silica gel to yield compound **7d** (129 mg, 22%) as a white solid, m.p. 126–128 °C, and compound **7e** (134 mg, 23%) as a white foam, m.p. 117–118 °C. **7d**: (R_f 0.33, acetone–CH_2Cl_2 2:98); ν_{max}($CHCl_3$)/cm^{-1} 3458, 1711, 1676 and 1610; δ_H($CDCl_3$) 7.95 (2 H, d, *J* 8.8, Ar), 7.05 (2 H, d, *J* 8.8, Ar), 5.46 (1 H, b, NH), 4.91 (1 H, m, 5-CH), 3.95 (1 H, dd, *J* 6.2 and 8.8, 4-CH_2), 3.66 (2 H, bt, 5′-CH_2), 3.54 (1 H, t, *J* 9.0, 4-CH_2), 2.56 (3 H, s, Me) and 1.44 (9 H, s, Bu^t). **7e**: (R_f 0.41, acetone–CH_2Cl_2 2:98); ν_{max}($CHCl_3$)/cm^{-1} 3454, 1707, 1678 and 1603; δ_H($CDCl_3$) 7.94 (2 H, d, *J* 8.7, Ar), 7.06 (2 H, d, *J* 8.7, Ar), 5.29 (1 H, b, NH), 5.13 (1 H, m, 5-CH), 3.84 (2 H, ddd, *J* 4.5, 7.0 and 9.9, 4-CH_2), 3.69 (2 H, m, 5′-CH_2), 2.55 (3 H, s, Me) and 1.41 (9 H, s, Bu^t); *m*/*z* (mixt. **7d**–**7e**) 354 (M^+, 0.3%), 298 (0.3), 290 (0.7), 234 (65) and 148 (100) [Found: (mixt. **7d**–**7e**): C, 54.1; H, 6.4; N, 7.8; S, 8.9. Calc. for $C_{16}H_{22}N_2O_5S$: C, 54.22; H, 6.26; N, 7.90; S, 9.05%).

tert-*Butyl* N-{[3-(4-*Acetylphenyl*)-2-*methoxy*-2-*oxo*-2λ^5-1,3,2-*oxazaphospholidin*-5-*yl*]*methyl*}*carbamate* **8c**–**d**.—The title compounds were prepared as for the sulfoxides **7d**–**e**, except for the substitution of phosphoryl oxychloride (163 mm^3, 1.78 mmol) for thionyl chloride, to give compounds **8c**–**d** (204 mg, 34%) as an oil (R_f 0.37, acetone–CH_2Cl_2 2:98); ν_{max}($CHCl_3$)/cm^{-1} 3456, 1713, 1678 and 1605; *m*/*z* 384 (M^+, 0.4%), 328 (0.7), 290 (5), 234 (60) and 148 (100); δ_H($CDCl_3$) 7.95 (2 H, d, *J* 8.7, Ar), 7.15 (2 H, d, *J* 8.7, Ar), 4.95 (1 H, b, NH), 4.81 (1 H, m, 5-CH), 3.89 (1 H, m, 4-CH_2), 3.83 (3 H, d, MeO), 3.62 (2 H, m, 5′-CH_2), 3.46 (1 H, m, 4-CH_2), 2.57 (3 H, s, MeCO) and 1.44 (9 H, s, Bu^t) (Found: C, 53.0; H, 6.7; N, 7.2. Calc. for $C_{17}H_{25}N_2O_6P$: C, 53.12; H, 6.56; N, 7.29%).

Microbiology.—Minimal inhibitory concentrations were determined using the microbroth dilution method. The media used were: Todd–Hewitt broth (Difco) for streptococci; Iso-Sensitest broth (Oxoid) for staphylococci, *Enterococcus faecalis*, *E. coli*, *P. vulgaris* and *P. aeruginosa*; GC base broth (Difco) + 1% v/v BBL Isovitalex for *N. gonorrhoeae*; brain–heart infusion broth (Difco) + 1% v/v Difco supplement C for *H. influenzae*. The inoculum was about 10^4 cfu cm^{-3}. Incubation was at 37 °C in 5% CO_2 for 48 h for *N. gonorrhoeae* and *H. influenzae*, in air for 18–24 h for other species.

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