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2-AZACEPHEMS

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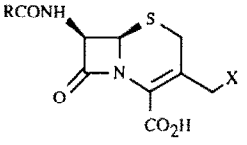
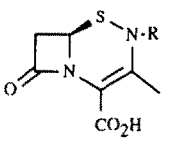
New heteroannelation methodology for the synthesis of 2-azacephems, and 7-acylamino-2-azacephems is described

2-Azacephems (2) and (3) represent new structural variants of the natural antibiotic skeleton (1). Related bicyclic systems (4) based upon the 1-aza-2-thiacephem structure are known,[1] as are the 1-carba-2-thiacephems (5)[2], the 1-carba-2-oxacephems (6)[3] and the 1-carba-2-azacephems (7)[4]. We therefore report our routes to targets (2) and (3).



(1)



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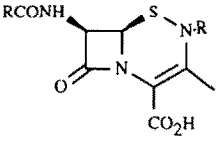

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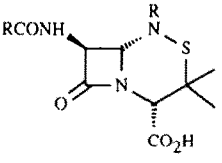

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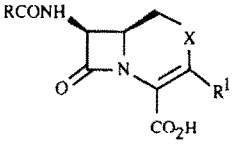
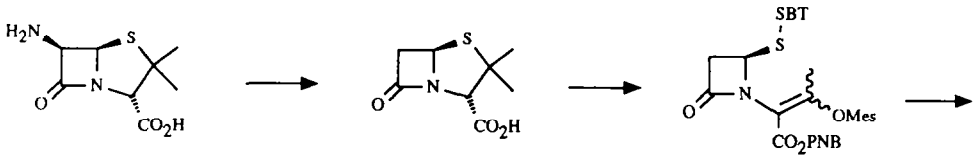


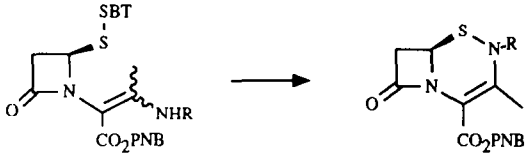
(5) X=S
(6) X=O
(7) X=NR^2

The penicillin nucleus (8) possesses the requisite stereochemistry at C(5) for transformation into the desacetamido β-lactam (2), and also the correct stereochemistry for elaboration into the 6β-acetamido β-lactam (3). Thus, (8) was converted by standard procedures into (9) and thence the butenoyl mesylate (10).[5] Treatment with amines gave, as a mixture of geometrical isomers, the enamines (11) and (12). In a novel heteroannelation method, (11) and (12) were cyclized by silver acetate,[6] giving the 2-azacephems (13) and (14).



(8) (9) (10)

BT=2-benzothiazolyl



(11) R=Et
(12) R=Ph

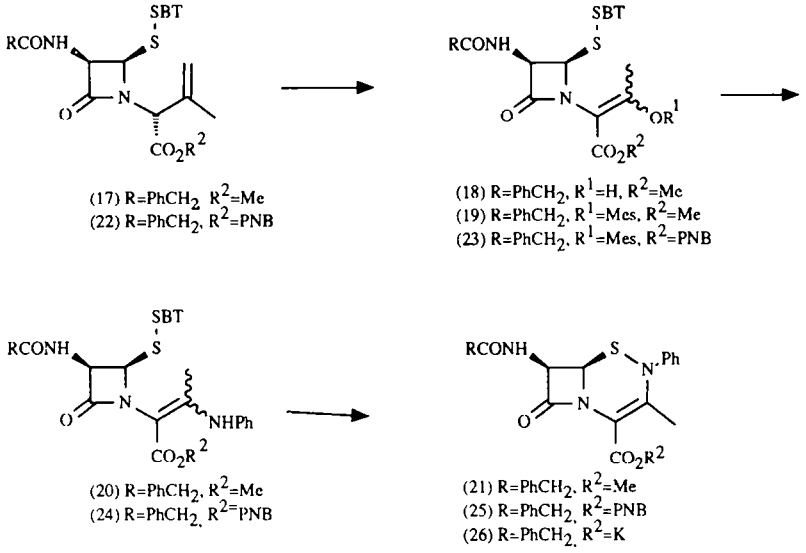
(13) R=Et
(14) R=Ph

In an interesting variation the disulphide (10) was treated with ethylamine and silver acetate, giving the sulphenamide (15). This was subsequently reacted with DABCO. Monitoring of the reaction of (15) by NMR spectroscopy indicated build-up of an intermediate, with probable allene structure (16) (singlet, δ5.68). This intermediate increased and then decayed with the simultaneous growth of absorptions due to formation of the 2-azacephem (13).

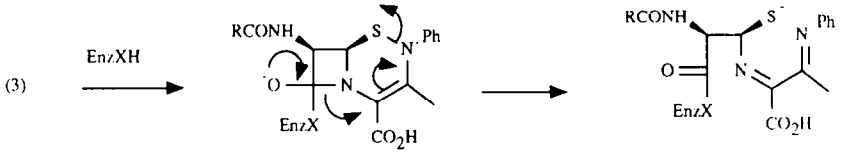
(15) (16)

The problem remaining to be addressed was the synthesis of target (3), which presented potential problems because of participation by the acylamino side-chain during the sequence of transformations.

Penicillin G, as its methyl ester, was taken by the Kamiya method[7] to the 2-mercaptobenzothiazole adduct (17). Ozonolysis gave the E- and Z- isomers (18), which



were converted to the mesylates (19). Aniline/triethylamine gave the enamines (20). Cyclization to (21) was only effected by finely divided silver acetate in scrupulously dry benzene under high dilution conditions. The more polar Z- isomer reacted much more rapidly, and equilibration of the remaining less polar E- isomer to the Z- isomer was very slow. The resultant methyl ester (21) was relatively unstable, and could not be deprotected. However, the p-nitrobenzoate ester (22) was progressed by a similar sequence via (23) and (24) to the 2-azacephem (25) which was deprotected (H_2-Pd/50psi/$KHCO_3$) to give the potassium salt of the target β-lactam (26).



The deprotected β-lactam exhibited weak antibacterial activity (MIC 12.5 μg/ml) against *Streptomyces pyogenes* and *Streptomyces faecium*, and also *Bacillus subtilis*. It can be postulated that this involves enzymic immobilization via (27) and thence ring-opened products derived from (28).

Acknowledgements

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Experimental

p-Nitrobenzyl-[4R-(2-benzthiazolyldithio)-2-oxo-1-azetidinyl] -3-ethylamino but-2-enoate (11).

A solution of 5.0 g of *p*-nitrobenzyl-[4R-(2-benzthiazolyldithio)-2-oxo-1-azetidin yl]-3-methylsulphonyloxy but-2-enoate (10) in 105 ml dry dichloromethane was cooled to -20° under an argon atmosphere, and to this was added 1.23 ml ethylamine. After stirring for one hour, the solution was filtered through Hyflo, evaporated *in vacuo* and chromatographed on silica gel eluting with hexane/ethyl acetate (1:1) 4.04 g (11) (88%) was obtained as a pale yellow solid; mp 149.5-150.5°; υ_{max} (film) 1770, 1660 cm^{-1}; δ ppm ($CDCl_3$) 1.23 (3H, t, J = 7.5Hz, CH_2CH_3), 2.11 (3H, S, CH_3), 2.90-3.73 (4H, m, CH_2CH_3, H-3), 5.22 (3H, m, CH_2Ph, H-4), 7.20-8.38 (8H, m, aromatics), 9.10 (1H. m, NH).

(6R)-2-Ethyl-3-methyl-4-(p-nitrobenzyloxycarbonyl)-2-azacephem (13)

To a solution of (11) 4.7 g in 3l of dry benzene under an argon atmosphere, was added 5 g of finely divided silver acetate. The vigorously stirred solution was refluxed until the reaction was shown by thin layer chromatography to be essentially complete. The suspension was filtered through Hyflo then evaporated *in vacuo*, and the residue was chromatographed on silica gel eluting with hexane/ethyl acetate (1:1) 1.46 g of (13) (50.6%) was obtained as a white crystalline solid; mp 110-122°; υ_{max} ($CHCl_3$) 1775, 1706 cm^{-1}; δ pm ($CDCl_3$) 1.77 (3H, t, J = $7H_2$, CH_2CH_3), 2.43 (3H, s, CH_3), 2.77 (1H, dd, Jab = 15.5Hz, Jax = 2Hz H-7), 3.13-3.87 (2H, m, CH_2CH_3), 3.80 (1H, dd, Jab = 15.5Hz, Jbx = 5Hz, H-7), 4.38 (1H, dd, Jax = 2Hz, Jbx = $5H_z$ H-6), 5.35 (2H, s, CH_2Ph) 7.43-8.37 (4H, m, aromatics); m/e found 363.0837; $C_{16}H_{17}N_3O_5S$ requires 363.0888.

p-Nitrobenzyl-[4R-(2-benzthiazolyldithio)-2-oxo-1-azetidinyl]-3-anilino but-2-enoate (12).

To a stirred solution of 2.274 g of *p*-nitrobenzyl-2-[4R-(2-benzthiazolyldithio)-2-oxo-1-azetidinyl]-3-methylsulphonyloxy but-2-enoate (10) in 60 ml dry dichloromethane was added 0.7 ml of purified aniline followed by a solution of 0.438 g of diazabicyclo-[2.2.2]-octane in 6 ml dry dichloromethane. After stirring for one hour the solution was evaporated *in vacuo* and chromatographed on silica gel, eluting with hexane/ethyl acetate (1:1), to give 1.59 g (70%) of (12); υ_{max} (film) 1765, 1664 cm^{-1}; δ ppm ($CDCl_3$) 2.13 (3H, S, CH_3) 3.10 (1H, dd, Jab = 16Hz Jax = 2.5Hz, H-3) 3.49 (1H, dd, - Jab = 16Hz, Jbx = 4.5 Hz,

H-3) 5.27 (3H, m, H-4, $PhCH_2$) 6.86-8.33 (13H, m, aromatics) 10.80 (1H, S, NH).

(6R)-3-Methyl-2-phenyl-4- (p-nitrobenzyloxycarbonyl)-2-azacephem (14).

To a vigorously stirred solution of 12 (1.59 g) in 1l dry benzene under an argon atmosphere was added 1.59 g of finely divided silver acetate. The solution was brought to reflux and stirring was continued until the reaction was shown by thin layer chromatography to be complete. The solution was then filtered through Hyflo and concentrated *in vacuo*. Chromatography on silica gel using hexane/ethyl acetate (1:1) as eluant afforded 0.76 g (62%) of (14) as a colorless foam; υ_{max} (film) 1782, 1715 cm^{-1}; δ ppm ($CDCl_3$) 2.20 (3H, s, CH_3), 2.83 (1H, dd, Jab = 16Hz, Jax = 2Hz, H-7) 3.80 (1H, dd, Jab = 16Hz, Jbx = 5Hz H-7), 4.50 (1H, dd, Jax = 5Hz, H-6), 5.37 (2H, S, $PhCH_2$), 6.90-8.42 (9H, m, aromatics); m/e Found 411.0880, $C_{20}H_{17}N_3O_5S$ requires 411.0888.

p-Nitrobenzyl 2-[4R-ethylsulphenamoyl-2-oxo-1-azetidinyl]-3-methylsulphonyloxy but-2-enoate (15)

To a solution of 0.329 g of (10) in 4 ml dry chloroform was added 0.094 g silver acetate, followed by 37μl ethylamine. When the reaction was shown by thin layer chromatography to be complete, the solution was filtered through Hyflo, evaporated *in vacuo*, and chromatographed on silica gel, eluting with ethyl acetate/hexane (1:1) 0.194 g (75% of the theoretical yield), of 4′-nitrobenzyl-2-[4R-ethylsulphenamoyl-2-oxo -1-azetidinyl]-3-methylsulphonyloxy crotonate was obtained, as a mixture of E- and Z- isomers, as a pale yellow syrup. Major isomer; δ ppm ($CDCl_3$) 1.07 (3H, t, J = 7.5Hz, CH_2CH_3), 2.65 (3H, S, CH_3), 2.90 (2H, q, J = 7.5Hz, CH_2CH_3) 3.03-3.43 (2H, m, H-3), 3.30 (3H, s, SO_2CH_3), 5.00 (1H, t, J = 4Hz H-4), 5.38 (2H, S, CH_2PNB) 7.43-8.47 (4H, m, aromatics). Minor isomer; 1.07 (3H, t, J = 7.5Hz, CH_2CH_3) 2.37 (3H, s, CH_3), 2.90 (2H, q, J = 7.5Hz, CH_2CH_3) 3.03-3.43 (2H, m, H-3), 3.23 (3H, s, SO_2CH_3), 5.03 (1H, t, J = 4Hz H-4), 5.38 (2H, s, CH_2Ph), 7.43-8.47 (4H, m, aromatics).

Methyl 2-[4R-(2-benzthiazolyldithio)-2-oxo-3R-phenylacetamido-1-azetidinyl]-3-hydroxybut-2-enoate (18)

Azetidin-2-one (17)[7] (12.1g) was ozonized at -78°C in dichloromethane. The ozonide was decomposed with dimethylsulphide, the solution evaporated *in vacuo*, and the product (18) isolated by column chromatography (ethyl acetate-petroleum ether 60-80) (8.62g, 71%) as a pale yellow foam; υ_{max} ($CHCl_3$) 3300, 1780, 1665 and 1615 cm^{-1}; δ ($CDCl_3$) 2.22 (s, 3H), 3.35 (s, 3H), 3.42 (s, 2H), 4.74 (dd, 1H, J_1 = 8Hz, J_2 = 5Hz), 5.19 (d, 1H, J = 5Hz), 7.1-7.6 (m, 10H), 18.8 (s, 1H); M (+ve FAB) 516.81 (M^+).

Methyl 2-[4R-(2-benzthiazolyldithio)-2-oxo-3R-phenylacetamido-1-azetidinyl]-3-methylsulphonyloxybut-2-enoates (19)

A solution of (18) (5.49g) in dichloromethane (150ml) was reacted with mesyl chloride (1.14 ml) and triethylamine (1.78 ml) under dry nitrogen at -15° for 18h. The reaction mixture was filtered through Celite, evaporated *in vacuo* and the mesylate isolated by column chromatography as above giving (19) (2.86g, 45%) as an oil (two geometrical isomers); υ_{max} ($CDCl_3$) 3380, 1785, 1740 and 1680cm^{-1}; δ ($CDCl_3$) 1.22 (s, C = CMe, minor isomer), 2.04 (s, C = CMe, major isomer), 2.59 (s, OMes, minor isomer), 3.28 (s, OMes, major isomer), 3.59 (s, 2H), 3.66 (s, CO_2Me, major isomer), 3.81 (s, CO_2Me, minor isomer), 5.12 (dd, 1H, J_1 = 8Hz, J_2 = 4.5Hz), 5.61 (d, 1H, J = 4.5Hz), 7.20-8.00 (m, 10H); M (+ FAB) 594.93 (M^+).

Methyl 2-[4R-(2-benzthiazolyldithο)-2-oxo-3R-phenylacetamido-1-azetidinyl]-3-phenylaminobut-2-enoate (20)

A solution of mesylate (19) (1.0g) in dichloromethane (10ml) was stirred at 0°C under nitrogen. Phenylamine (0.16ml, 1 equiv.) and triethylamine (0.24ml, 1 equiv.) were added and stirring was continued for 1 hr. The reaction mixture was evaporated *in vacuo* and purified by chromatography on silica using 60% ethyl acetate/60-80 petrol as eluant, yielding 0.35g (35%) of the enamine (20, mixture of geometrical isomers) as a pale yellow foam, υmax ($CHCl_3$ soln.) 3290, 1771, 1674, 1602, 1580 cm^{-1} δ ($CDCl_3$) 1.23 (s, C =CMe, minor isomer), 2.41 (s, C = CMe, major isomer), 3.47 (s, 2H), 3.61 (s, CO_2Me, major isomer), 3.66 (s, CO_2Me, minor isomer), 4.59 (dd, 1H, J_1 = 7Hz, J_2=5Hz) 5.44 (d, 1H, J=5Hz), 6.92-7.32 (m, 9H), 8.83 (d, 1H, J=7Hz). m/e (+ ve FAB) 592.05 (M^+).

Methyl 2-phenyl-7β-phenylacetamido-2-azadesacetoxycephalosporanate (21)

The enamine (20) (0.3g) was stirred vigorously in benzene (distilled, 200ml) and finely divided silver acetate (0.3g) was added in one portion. The reaction mixture was heated under reflux for 1hr, then filtered through Celite and evaporated *in vacuo*. Chromatography on silica using 50% ethyl acetate/60-80 petrol as eluant gave 28mg (13%) of the 2-aza-1-thiacephem (21) as a cream coloured solid; υ_{max} (nujol) 3340, 1787, 1720, 1690 cm^{-1}; δ ($CDCl_3$) 2.12 (s, 3H), 3.51 (s, 2H), 3.79 (s, 3H), 4.76 (d, 1H, J = 5Hz), 5.89 (m, 2H), 6.82-7.37 (m, 10H); m/e (high res. EI) 423.1245 (M^+).

p-Nitrobenyl 2-[4R-(2-benzthiazolyldithio)-2-oxo-3R-phenylacetam ido-1-azetidinyl]-3-methylbut-3-enoate (22)

Penicillin G sulphoxide PNB ester (25.0g) was treated with 2-mercaptobenzothiazole

(8.6g,) in toluene (500ml) under reflux for 1.5 hr. The reaction mixture was cooled, evaporated *in vacuo*, and recrystallised from ethyl acetate, yielding 23.86g (73%) of the dithioazetidinone (22) as pale yellow crystals; υ_{max} (nujol) 3270, 1790, 1755, 1660 cm^{-1}; δ ($CDCl_3$) 1.95 (s, 3H), 3.71 (s, 2H), 5.04 (s, 2H), 5.14 (s, 1H), 5.18 (d, 1H, J = 3Hz), 5.31 (s, 1H), 5.43 (dd, 1H, J_1 = 3Hz, J_2 = 11Hz), 7.2-8.3 (m, 14H); m/e (70eV EI) 332 (no molecular ion observed with +ve or -ve FAB).

A solution of azetidin-2-one (22) (12.0g) in dichloromethane (350ml) was treated with ozonised oxygen at -78°C for 2.5hr. The ozonide was reduced using dimethyl sulphide. The reaction mixture was evaporated *in vacuo*, and purified by column chromatography on silica using 60% ethyl acetate/60-80 petrol as eluant, giving 8.55g (71%) of the enol (71%) as a pale yellow foam. υ_{max} ($CHCl_3$ soln.) 3430, 3310, 1760, 1735, 1670 cm^{-1} δ ($CDCl_3$) 2.30 (s, 3H), 3.52 (s, 2H), 5.05 (d, 1H, J = 4Hz), 5.20 (s, 2H), 5.30 (dd, 1H, J_1 = 4Hz, J_2 = 9Hz), 6.8-7.9 (m, 13H), 11.8 (s, 1H); m/z (70eV EI) 359 (corresponding to the fragment $[PhCH_2CONHCH{=}CHS\text{-}SBT]^+$). No molecular ion obtained with +ve or -ve FAB.

A solution of the above enol (1.75g) in dichloromethane (150ml) was treated with mesyl chloride (0.21ml, 1 equiv.) and triethylamine (0.38ml, 1 equiv.) under nitrogen at -15°C for 18 hr. The reaction mixture was filtered through Celite, evaporated *in vacuo*., and used in the next step without further purification. A solution of the crude mesylate in dichloromethane (100ml) was stirred at O°C under nitrogen. Phenylamine (0.25ml) and triethylamine (0.38ml) were added and stirring was continued for 1 hr. The reaction mixture was evaporated *in vacuo* and purified by chromatography on silica using 50% ethyl acetate/60-80 petrol as eluant, yielding 0.61g (32%) of the above enamine as a pale yellow foam. The product was shown to be a mixture of geometrical isomers (24) ; υ_{max} ($CHCl_3$ soln) 3420, 3290, 1770, 1730 1670 cm^{-1} δ (60 MHz, $CDCl_3$, major isomer) 2.38 (s, 3H), 3.51 (s, 2H), 4.78 (dd, 1H, J_1 = 9Hz, J_2 = 5Hz), 4.94 (s, 2H), 5.02 (bs, 1H), 5.38 (d, 1H, J = 5Hz), 6.64-7.99 (m, 18H), 9.1 (bs, 1H). The resonance at 5.02 ppm was removed by deuterium exchange. m/z (70eV EI) 544 (M^+ - HSBT). No molecular ion with either +ve or -ve FAB.

Preparation of 4-Nitrobenzyl
2-phenyl-7β-phenylacetamido-2-aza-desacetoxyacephalosporanate (25)

Disulphide (24) (358mg) was dissolved in dry benzene (11) and stirred vigorously under nitrogen. Finely divided silver acetate (400mg) was added, and reaction mixture was heated under reflux for 30 min, filtered through Celite and evaporated *in vacuo*. The product was recrystallised from ethyl acetate to give 56mg of the 2-aza-1-thiacephen (25) (21%) as a cream coloured solid; υ_{max} (nujol) 3270, 1785, 1710, 1660 cm^{-1}; δ (60MHz d6DMSO) 2.09 (s, 3H), 3.44 (s, 2H), 4.89 (d, 1H, J = 7Hz), 5.28 (s, 2H), 5.85 (dd, 1H, J_1 = 7Hz, J_2 = 9Hz),

6.86-8.17 (m, 14H), 8.82 (d, 1H, J = 9Hz); m/z 70ev E.I. - no molecular ion, but peaks at m/e 512, 410, 392; corresponding to loss of S, $PhCH_2CONH$, and $OCH_2C_6H_4NO_2$.

Potassium 2-phenyl-7β-phenylacetamido-2-aza-desacetoxyacephalosporanate (26)

Potassium hydrogen carbonate (28mg, 1 equiv.) and 10% palladium on carbon (302mg) were added to a suspension of the 2-azacephem (25) (150mg) in ethyl acetate (5ml) and water (5ml). The mixture was treated with hydrogen at 50 psi in a Paar hydrogenator for 1.5 hr. The reaction mixture was filtered through Celite,the aqueous layer was separated, washed with ethyl acetate (2x5ml), and evaporated *in vacuo* to give 25mg of the 2-azacephem (294) (21%) as a white solid, m.p. 187°C; υ_{max} (nujol) 3280, 1785, 1710, 1660 cm^{-1} δ (D_2O, 250MHz) 1.63 (s, 3H), 4.81 (q, 2H), 5.33 (d, 1H, J = 4.5Hz), 5.96 (d, 1H, J = 4.5Hz), 7.0-7.4 (m, 10H). m/e (-ve FAB) m/z 365 ($M^+ - CO_2$).

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