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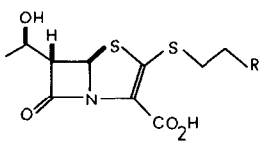
DESULPHURATIVE APPROACHES TO PENEM ANTIBIOTICS. IV. BROMINATION OF 3-METHYL-2-THIACEPHEMS, A NOVEL ENTRY IN THE SYNTHESIS OF POTENT ANTIMICROBIAL AGENTS

Ettore Perrone, Marco Alpegiani, Angelo Bedeschi, Franco Giudici, Maurizio Foglio and Giovanni Franceschi

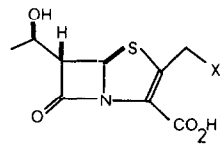
Chemical Research and Development, Farmitalia Carlo Erba, Via dei Gracchi 35, 20146 Milano, Italy

Abstract: The 3-methyl group in 2-thiacephem-4-carboxylates can be brominated in good yield, thus providing access to a series of highly active penem antibiotics.

At present, penems possessing outstanding antimicrobial activity can be allocated in two major classes, both characterized by an α-hydroxyethyl group in position 6 but differing in the 2-substituent, which can be either an alkylthio radical (leading compounds: Sch 29482[1], thiathienamycin[2]) or a functionalized methyl group (FCE 21420[3], FCE 22101[4]). Several strategies[5] are now available for the rapid derivation of a huge number of representatives of the first family, while for the second class, in an attempt to overcome the restrictiveness of the original Woodward route, heavy metal salts of 4-mercaptoazetidinone-phosphoranes[6] have been proposed as versatile intermediates. We wish here to describe how the functionalization of 3-methyl-2-thiacephem-4-carboxylates, whose synthesis and desulphurisation has been studied independently by us[7] and Hoechst's group[8], can provide a second, convenient answer to the problem.



Sch 29482, R = H
Thiathienamycin, R = NH_2



FCE 21420, X = $OCOCH_3$
FCE 22101, X = $OCONH_2$

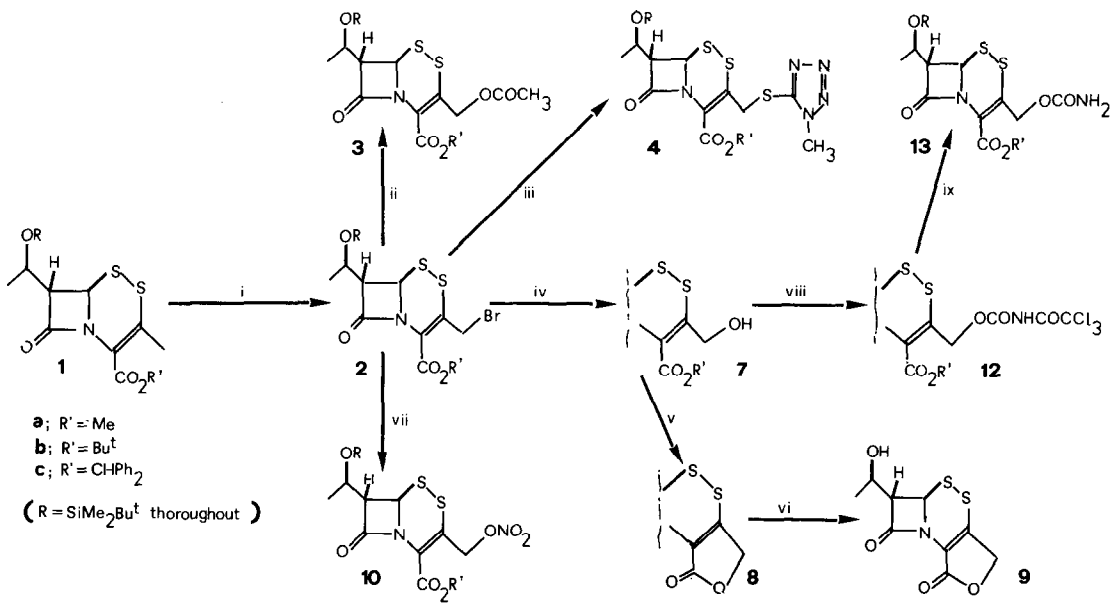
To this end, we had introduced[7] thiolsulphonates and sulphenimides as an alternative to benzothiazolyl azetidinyl disulphides in the synthesis of 2-thiacephems, since the former can undergo allylic[9] or electrochemical halogenation[10] on their isopropylidene moiety. However, our best hopes were surpassed by the finding that even the 2-thiacephem system is amenable to allylic bromination in good yields[11]; e.g., prolonged heating of 1a with NBS (1 mol. equiv., refluxing CCl_4, AIBN, propylene oxide) gave the 3-bromomethyl-2-thiacephem 2a as a syrup (85%); λ_{max} ($CHCl_3$) 282 (ε 7,323) and 336 nm (ε 3,120); ν_{max} (film) 1785, 1730 cm^{-1}; δ($CDCl_3$) 0.10 (6H, s), 0.89 (9H, s): 1.28 (3H, d), 3.23 (1H, dd, J = 2 and 3.5 Hz), 3.87 (3H, s), 4.30 (1H, m), 4.65 (2H, centre of ABq, J = 11.5 Hz, CH_2Br), and 4.76 ppm (1H, d, J = 2 Hz). Under these conditions NCS was ineffective.

Although preliminary attempts to desulphurise this compound to a 2-bromomethyl penem synthon gave poor results[12], the unexpected stability of the 2-thiacephem disulphide moiety towards positive halogen sources offered us a convenient entry to novel functionalized representatives[13]. Thus, displacement of bromine from 2a with Bu_4NOAc and with sodium 1-methyl-1H-tetrazol-5-yl-mercaptide, gave, respectively, the acetoxymethyl and the tetrazolylthiomethyl derivatives: 3a (95%), λ_{max} ($CHCl_3$) 279 (ε 6,067) and 332 nm (ε 2,912); ν_{max} (film) 1790, 1740, 1720 sh cm^{-1}; δ($CDCl_3$) 0.10 (6H, s), 0.87 (9H, s), 1.26 (3H, d), 2.05 (3H, s), 3.12 (1H, dd, J = 2.5 and 4 Hz), 3.80 (3H, s), 4.33 (1H, m), 4.64 (1H, d, J = 2.5 Hz), and 4.9 ppm (2H, centre of ABq, J = 13 Hz, $\underline{CH_2}OAc$); 4a (85%); λ_{max} (EtOH) 281 (ε 5900) and 333 nm (ε 3085); ν_{max} (film) 1790, 1725 cm^{-1}; δ($CDCl_3$) 0.10 (6H, s), 0.89 (9H, s), 1.26 (3H, d), 3.15 (1H, dd, J = 2.2 and 3.5 Hz), 3.88 (3H, s), 3.92 (3H, s, NCH_3), 4.38 (1H, m), 4.46 (2H, centre of ABq, J = 14 Hz, CH_2S), and 4.68 ppm (1H, d, J = 2.2 Hz). Finally, triphenylphosphine-mediated ring contraction of these compounds (MeCN[14], -40° to 0°C) smoothly afforded the desired penems 5a and 5b (60 and 65%), accompanied by their 5S diastereomers 6a, 6b (35 and 30%)[15].

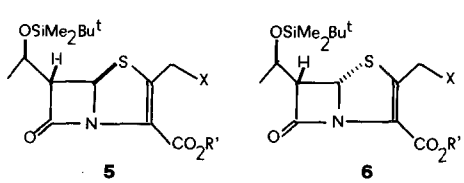
While the above sequence provided access to the acetoxy compound FCE 21420 and to a series of heterocyclylthio analogues currently under advanced investigation[16], every attempt to obtain 12a, a formal precursor of FCE 22101, was thwarted by spontaneous cyclization of the parent hydroxymethyl compound 7a into the lactone 8[17]; ν_{max} (film) 1800-1750 br cm^{-1}; δ($CDCl_3$) 0.06 (3H, s), 0.11 (3H, s), 0.90 (9H, s), 1.33 (3H, d), 3.33 (1H, dd, J = 2.5 and 4.5 Hz), 4.44 (1H, m), 4.62 (1H, d, J = 2.5 Hz) and 4.98 (2H, s, CH_2O). To overcome this problem two strategies were developed. According to the first, a 2-hydroxymethylpenem was prepared by unmasking the OH group after the ring-contraction step, taking advantage from the reluctancy of the penem ring system to form tricyclic lactones. The 2-thiacephem nitrate 10a was conveniently prepared from 2a and $AgNO_3$ (sat. acetone solution, 1 h, 0°C) and then desulphurised (PPh_3 in THF) into a 7:3 mixture of the trans and cis penem nitrates 5c, 6c, in turn easily reduced (Zn/HOAc in CH_2Cl_2) to the corresponding 2-hydroxymethylpenems 5d, 6d[18]. Alternatively, we argued that some control could be gained over the spontaneous lactonisation of 3-hydroxymethyl-2-thiacephem-4-carboxylates by the appropriate choice of the ester group; and, particularly, that tert-butyl and diphenylmethyl esters, two types of carboxy protecting groups otherwise popular in the ß-lactam area, could find here and for the first time the opportunity of being exploited for a penem synthesis. Tert-butyl and diphenylmethyl 3-methyl-2-thiacephem-4-carboxylates 1b,c were prepared from the corresponding 6,6-dibromopenicillanates along our general procedure[7]. First, their usefulness was checked by acid hydrolysis, thereby obtaining the fully deprotected synthon 11b (from 1b or 1c, neat TFA, 1 h r.t.) or the silylated derivative 11a (from 1c, 20% TFA in dichloromethane, 0°C, few min), immediate precursors of penem acids; e.g., sulphur extrusion from 11a gave 5e, 6e in variable amounts according to the solvent (1:4 isomer ratio in $CHCl_3$; 3:2 in acetone).

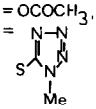
Secondly, 1b,c were brominated under the previously reported conditions, thus obtaining the bromomethyl-2-thiacephem esters 2b,c (60 and 65% yield, respectively), which could indeed be converted into the carbinols 7b,c, the first, owing to the bulkiness of the tert-butyl moiety, being stable enough to be isolated pure; λ_{max} ($CHCl_3$) 281 (ε 5230) and 335 nm (ε 2800); ν_{max} (film) 3450, 1785, 1712 cm^{-1}; δ($CDCl_3$) 0.1 (6H, s), 0.86 (9H, s), 1.25 (3H, d), 1.50 (9H, s, OC_4H_9), 3.13 (1H, dd, J = 2.5 and 4.5 Hz), 4.25 (2H, centre of ABq, J = 14 Hz, $\underline{CH_2}OH$), 4.37 (1H, m) and 4.60 ppm (1H, d, J = 2.5 Hz).

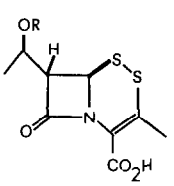
Conversion of 7b,c into the urethanes 12b,c (trichloroacetylisocyanate, CH_2Cl_2, -40°C to r.t.) and unmasking of the carbamoyloxy group in the former to give 13b (SiO_2/MeOH, several hours) formally completed this series of key manipulations inside the 2-thiacephem family, now to be considered a versatile source of the most promising penem antibiotics[19].



Reagents= i, NBS/AIBN; ii, Bu_4NOAc; iii, MMTZ sodium salt; iv, Ag_2O or $AgClO_4$/wet acetone, or Cu_2O/DMSO/water; v, spontaneous (for 7a and 7c); vi, TFA; vii, $AgNO_3$/dry acetone; viii, $Cl_3CCONCO$; ix, SiO_2/MeOH



a; X = $OCOCH_3$, R' = Me
b; X =  R' = Me
c; X = ONO_2, R' = Me
d; X = OH, R' = Me
e; X = R' = H



11a, R = $SiMe_2Bu^t$
11b, R = H

References and Notes

1) A.K. Ganguly, V.M. Girijavallabhan, S.W. McCombie, P. Pinto, R. Rizvi, P.D. Jeffrey, and S. Lin, J. Antimicrob. Chemother., 1982, 9 (Suppl. C), 1.

2) T. Hayashi, A. Yoshida, N. Takeda, S. Oida and S. Sugawara, Chem. Pharm. Bull., 1981, 29, 3158.

3) A. Sanfilippo, C. Della Bruna, D. Jabes, E. Morvillo, G. Schioppacassi, G. Franceschi, F. Arcamone, C. Battistini, M. Foglio, and F. Zarini, J. Antibiot., 1982, 35, 1248.

4) C. Della Bruna, D. Jabes, A. Sanfilippo, G. Schioppacassi, F. Arcamone, M. Foglio and G. Franceschi, "FCE 22101, a new broad-spectrum penem derivative" - presented at the XXII Interscience Conference on Antimicrobial Agents and Chemotherapy, 4-6 October 1982, Miami Beach (abstract No. 216).

5) These methods include: chemical manipulation of the side chain (S. Oida, A. Yoshida, T. Hajashi, N. Takeda, and E. Ohki, Chem. Pharm. Bull., 1980, 28, 3258), cyclization of chloro-dithiane or dithiolane azetidinones (T. Tanaka, T. Hashimoto, K. Iino, Y. Sugimura, and T. Miyadera, Tetrahedron Lett., 1982, 23, 1075), alkylation of 2-thioxopenams (T. Tanaka, T. Hashimoto, K. Iino, Y. Sugimura and T. Miyadera, J. Chem. Soc., Chem. Commun., 1982, 714), and displacement of 2-alkylsulphinylpenems with thiols (F. Di Ninno, D.A. Muthard, R.W. Ratcliffe, and B.G. Christensen, Tetrahedron Lett., 1982, 23, 3535).

6) A. Longo, P. Lombardi, C. Gandolfi, and G. Franceschi, Tetrahedron Lett., 1981, 22, 355; A. Martel, P. Dextraze, J.P. Daris, R. Saintonge, P. Lapointe, T.T. Conway, I. Monkovic, G. Kavadias, Y. Ueda, P. Elie, S. Patil, G. Caron, J.L. Douglas, M. Menard, and B. Belleau, Can. J. Chem. , 1982, 60, 942.

7) E. Perrone, M. Alpegiani, A. Bedeschi, M. Foglio, and G. Franceschi, Tetrahedron Letters, in press.

8) A. Henderson, G. Johnson, K.W. Moore, and B.C. Ross, J. Chem. Soc., Chem. Commun., 1982, 809.

9) J. Verweji, and H.S. Tan, "Fifth International Congress on Heterocyclic Chemistry", 13 August 1975, Ljubljana.

10) S. Torii, H. Tanaka, N. Saitoh, T. Siroi, M. Sasaoka, and J. Nokami, Tetrahedron Lett., 1982, 23, 2187.

11) Similar reaction cannot be carried out conveniently on Δ_3 cephems and 1-oxa-1-dethiacephems.

12) This compound is too unstable to be isolated pure, but in further experiments we were able to achieve a one-pot conversion of 2a into 5b,6b (1:1 diastereomeric mixture) (PPh_3, $CDCl_3$, -30°C; then MMTZ sodium salt, THF/$CDCl_3$, -30°C, several hours).

13) An ab initio approach to each different substition had been used beforehand (R.B. Woodward, Ger. Offen. 2,153,554; Chem. Abstr., 1972, 77, 126700)

14) A pronounced solvent effect was observed on the stereochemical outcome of these desulphurisations.

15) We made no effort to separate these diastereomeric mixtures. Selected ir (ν_{max} C=O, film unless otherwise stated) and nmr data (δ_{ppm} relative to β-lactam protons, $CDCl_3$ unless otherwise stated) for new compounds are as follows: 1b: 1780, 1720 cm^{-1}; δ3.02 (dd, 2.5 and 5Hz) and 4.53 (d, 2.5Hz); 1c: 1775, 1720 cm^{-1}; δ3.08 (dd, 3 and 5Hz), 4.60 (d, 3Hz); 2b: 1787, 1720 cm^{-1}; δ3.18 (dd, 2.5 and 4.5Hz), 4.71 (d, 2.5Hz); 2c: 1778, 1728 cm^{-1}; δ3.10 (dd, 3 and 4.5 Hz). 4.65 (d, 3Hz); 5a and 6a: 1790, 1745, 1710 cm^{-1}; δ(CD_3CN) 3.80 (dd, 2.0 and 4.0Hz), 5.63 (d, 2.0Hz), and 3.93 (dd, 4.0 and 9.0Hz), 5.71 (d, 4.0Hz); 5b and 6b: 1780, 1710; δ3.68 (dd, 1.8 and 4Hz), 5.54 (d, 1.8Hz), and 3.80 (dd, 4.2 and 4.0Hz), 5.60 (d, 4.2Hz); 5c and 6c: 1790, 1710 cm^{-1}; δ 3.92 (dd, 1.5 and 4Hz), 5.60 (d, 1.5Hz), and 3.90 (dd), 5.67 (d, 4.2Hz); 5d and 6d: 1785, 1710 cm^{-1}; δ3.70 (dd, 1.8 and 4.5Hz), 5.57 (d, 1.8Hz), and 3.82 (dd, 4.0 and 9.5Hz), 5.64 (d, 4.0Hz); 5e and 6e: 1785 and 1685 cm^{-1}; δ3.66 (dd, 2.0 and 5.5Hz), 5.51 (d, 2.0Hz), and 3.77 (dd, 4.0 and 10.5Hz), 5.59 (d, 4.0Hz); 9: 1780, 1750 cm^{-1}; δ3.52 (dd, 4.5 and 2.5Hz), 4.79 (d, 2.5Hz); 10a: 1790, 1730 cm^{-1}; δ 3.18 (dd, 2.5 and 5.5Hz), 4.73 (d, 2.5Hz); 11a: 1765 and 1705 cm^{-1} (nujol); δ3.02 (dd, 2.5 and 5.5Hz), 4.57 (d, 2.5Hz); 11b: 1775, 1700 cm^{-1} (KBr); δ(acetone-d_6) 3.35 (dd), 4.74 (d, 2.0Hz); 12b: 1790 and 1725 br cm^{-1}; δ (CD_3CN) 3.40 (dd, 3 and 4 Hz), 4.80 (d, 3Hz); 13b: 1785, 1740 sh, 1720 cm^{-1}; δ3.1 (dd, 3 and 5Hz), 4.75 (d, 3Hz).

16) Detailed synthesis and structure-activity relationship in this class of compounds will be reported in due time.

17) Desilylation of this material (neat TFA, 45 min, r.t.) afforded the free-hydroxyethyl lactone 9, tested as an antibacterial (active at 16 and 32 γ/ml on Streptococci and Staphilococci, respect.) and a β-lactamase inhibitor (no activity).

18) 2-Hydroxymethylpenems had been previously obtained in our laboratories from another route and exploited for the synthesis of acyloxy, carbamoyloxy and heterocyclylthio derivatives; details will be published elsewhere.

19) 2-Thiacephems have recently been shown to be potential precursors of the 2-alkylthiopenem family of antibiotics as well: N.J. Daniels, G. Johnson, B.C. Ross, and M.A. Yeomans, J. Chem. Soc., Chem. Commun., 1982, 1119.

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