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TOTAL SYNTHESIS OF THIA ANALOGUES OF CLAVULANIC ACID

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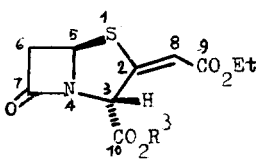
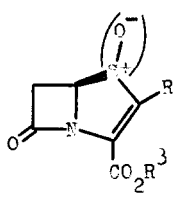
Non-classical β-lactam structures continue to draw the attention of numerous research groups. As a part of a continuing investigation into the synthesis of novel β-lactam compounds which might be either potential β-lactamase inhibitors or antibiotics, we wish to report the total synthesis of (±) thia-azabicycloheptane[1] 1 and (±) thia-azabicycloheptenes (penem) 2, formerly related to Beecham's clavulanic acid 3a[2a] and its analogues 3b-d[2a] and 4[2b,c].



1



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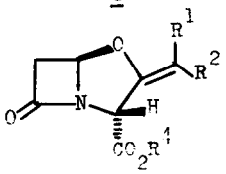
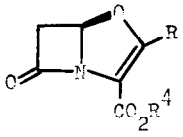
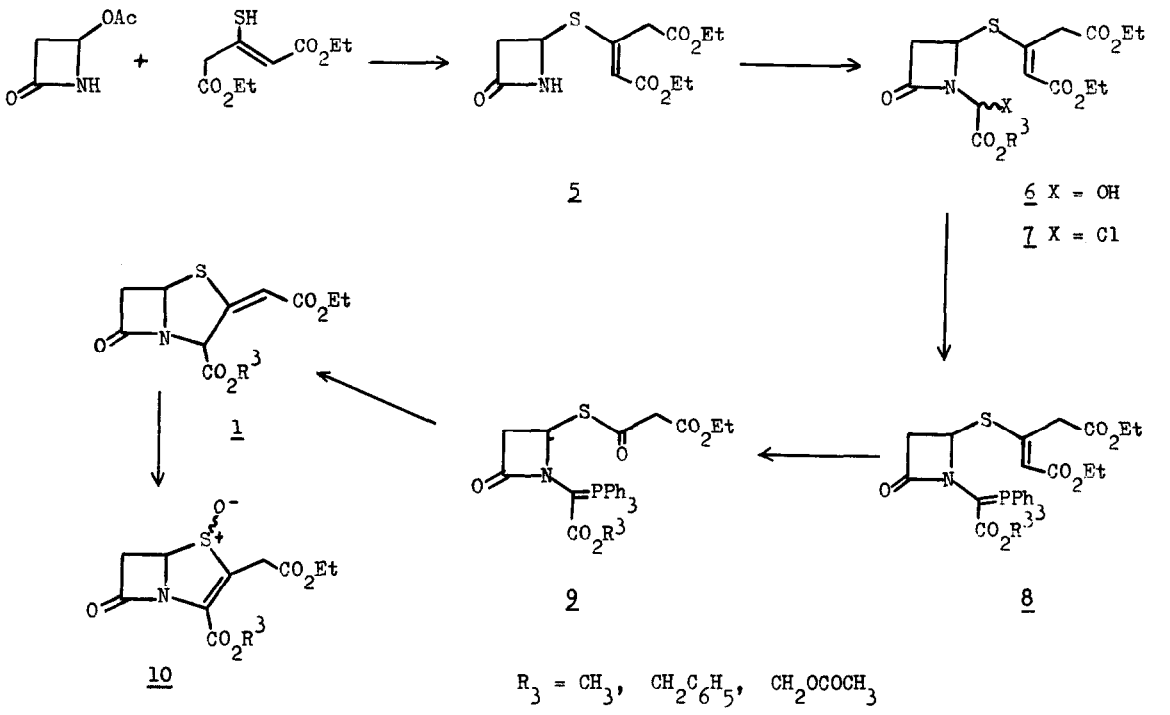


3 a $R^1 = CH_2OH$, $R^2 = H$ b $R^1 = H$, $R^2 = CH_2OH$
c $R^1 = H$, $R^2 = CO_2Me$ d $R^1 = CO_2Me$, $R^2 = H$



4

The synthetic route planned for the thiaclavulanoid 1 is presented in the Scheme. The reaction between the versatile 4-acetoxyazetidinone[3] and diethyl thioacetonedicarboxylate[4] ($NaHCO_3$, H_2O-Me_2CO, RT) led to the oily adduct 5[5] (93 % yield after filtration on silica gel) which was condensed with a suitable glyoxylate $CHOCOOR^3$ (Et_3N, THF, RT[6] or refluxing C_6H_6[7]) to give the diastereoisomeric carbinols 6[8] in 70-80 % yield after purification, depending on the nature of R^3. Subsequent chlorination of 6 ($SOCl_2$, pyridine, THF, -30-0°C) afforded the chlorides 7[9] (65-85 % yield after column chromatography) which were transformed into the ylid 8 (PPh_3, pyridine, THF, 25-50°C) in rather good yields[7]. Ozonolysis[10] of purified 8 (CH_2Cl_2, CF_3COOH, -20°C) followed by basic aqueous work up produced quantitatively the thioester 9 which was cyclised[7,10] into the thiaclavulanoid 1[11] (refluxing $C_6H_5CH_3$, 2-3 hrs, 75-82 % after purification).



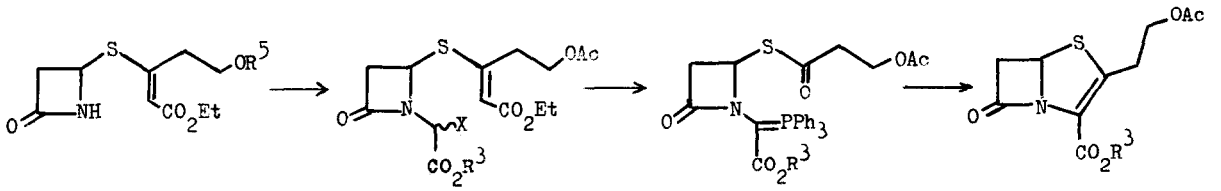
$R_3 = CH_3$, $CH_2C_6H_5$, CH_2OCOCH_3

The relative stereochemistry at C-3 and C-5 was assigned as identical to the one in natural penicillins on the basis of the low field (δ 5.53-5.55) chemical shift of the C-3 proton, according to NMR correlation studies performed by other authors[12] on similar systems. The geometry around the double bond in 1 was assumed as E on the basis of the very low chemical shift (δ 6.14-6.18) of the vinyl proton[2a,13a] and on the basis of the greater thermodynamic stability of this configuration with respect to the cross conjugated Z assembly as reported[2a] in the case of 3c and of the unstable 3d and as exemplified by the case of the E/Z 2-tetrahydrofurylidene and 2-thiolanylidene acetates[13a,b]. ^{13}C NMR correlation studies are under investigation and will be reported in the future.

Interestingly, but not surprisingly, the oxidation of 1 (m-CPBA, CH_2Cl_2, RT) afforded the novel penem sulfoxide 10[14], in a way reminescent of the Δ^2-Δ^3 isomerisation in the cephem series.

In a rather similar way, the penem 16, related to Woodward's penem[15], was synthesised from 4-acetoxyazetidinone and the ethyl ester of the 3-thio-5-hydroxy pentanoic acid[16] which were coupled as described before to give the adduct 11[17]. After acetylation of the alcoholic moiety (Ac_2O, Et_3N, CH_2Cl_2, RT), the resulting synthon 12 was transformed into the carbonylamides 13[18] and the chlorides 14[19], from which the ylid 15 was easily prepared. Cyclisation into penem 16[20] was accomplished in 65 % yield after purification by preparative TLC.

The synthesis of chiral 1 and 2, starting from penicillin, and their *in vitro* activities will be reported elsewhere[21].



11 R^5 = H
12 R^5 = Ac

13 X = OH
14 X = Cl

15

16

Aknowledgements are given to Dr (Mrs) M. Ballabio for physical chemical measurements and to Mr E. Sassi for technical assistance.

REFERENCES AND FOOTNOTES

1. Penicillin numbering.

2. (a) P.H. Bentley, P.D. Berry, G. Brooks, M.L. Gilpin, E. Hunt, and I.I. Zomaya, J.C.S. Chem. Comm., 1977, 748; (b) P.H. Bentley, G. Brooks, M.L. Gilpin, and E. Hunt, J.C.S. Chem. Comm., 1977, 905; (c) P.H. Bentley and E. Hunt, J.C.S. Chem. Comm., 1978, 518.

3. K. Klauss, D. Grimm, and G. Prossel, Justus Liebigs Ann. Chem., 1974, 539.

4. S.K. Mitra, J. Ind. Chem. Soc., 10, 71 (1933).

5. δ 1.27 (6H,t,J=7 Hz) 3.00 (1H,dq,J_1=16 Hz, J_2=2.5 Hz, J_4=1.5 Hz) 3.53 (1H,dq,J_1=16 Hz, J_3=5 Hz, J_4=1.5 Hz) 3.83 (2H,s) 4.17 (2H,q,J=7 Hz) 4.18 (2H,q,J=7 Hz) 5.13 (1H,dd,J_2=2.5 Hz, J_3=5 Hz) 5.78 (1H,s) 7.42 (1H,br); ν_{max} 3420, 1785, 1730, 1710, 1605, 1160 cm^{-1}.

6. J. Finkelstein, K.G. Holden, and C.D. Perchonock, Tetrahedron Lett., 1978, 1620, ref. 9.

7. For similar transformations see, inter alia, R. Scartazzini, H. Peter, H. Bickel, K. Heusler, and R.B. Woodward, Helv. Chim. Acta, 55, 408 (1972).

8. In the case of R^3=CH_3 the two carbinols are easily separated by fractional crystallisation : δ 1.26 (6H,t,J=7 Hz) 3.07 (1H,dd,J_1=15 Hz, J_2=3 Hz) 3.53 (1H,dd,J_1=15 Hz, J_3=5 Hz) 3.91 (3H, s) 4.17 (2H,q,J=7 Hz) 4.21 (2H,q,J=7 Hz) 5.29 (2H,d+dd,J_2=3 Hz, J_3=5 Hz) 5.97 (1H,s); δ 1.27 (6H,t,J=7 Hz) 3.14 (1H,dd,J_1=15 Hz, J_2= 3 Hz) 3.59 (1H,dd,J_1=15 Hz, J_3=5 Hz) 3.82 (3H,s) 4.12 (2H,q,J=7 Hz) 4.13 (2H,q,J=7 Hz) 4.48 (1H,d,J=6 Hz) 5.27 (1H,dd,J_2=3 Hz, J_3=5 Hz). R^3=$CH_2C_6H_5$ δ 1.27 (6H,t,J=7 Hz) 2.87, 3.14 and 4.00 (2H,m) 3.77 and 3.80 (2H,s) 4.15 (4H,q,J=7 Hz) 4.53 (1H,d,J=8 Hz) 5.24 (4H,m) 5.83 (1H,s) 7.35 (5H,s); ν_{max} 3530, 1780, 1750, 1710, 1600 cm^{-1}. R^3= CH_2OCOCH_3 δ 1.28 (6H,t,J=7 Hz) 2.18 (3H,s) 3.10 and 3.60 (2H,m) 3.85 and 3.90 (1H,s) 4.18 and 4.21 (4H,2q,J=7 Hz) 5.28 and 5.52 (2H,m) 5.86 and 5.90 (2H,s) 5.98 (1H,s).

9. R^3=CH_3 δ 1.28 (6H,t,J=7 Hz) 3.20 (1H,dd) 3.67 (1H,dd) 3.87 (3H,s) 4.18 (4H,q,J=7 Hz) 5.37 and 5.62 (1H,dd) 5.88 (1H,s) 6.12 and 6.20 (1H,s). R^3=$CH_2C_6H_5$ δ 1.28 (6H,s,J=7 Hz) 3.12 (1H,dd) 3.65 (1H,dd) 3.80 (2H,s) 4.18 (4H,q,J=7 Hz) 5.24 and 5.28 (2H,s) 5.53 (1H,m) 5.82 (1H,s) 6.12

and 6.18 (1H,s) 7.33 (5H,s); ν_{max} 1790, 1750, 1710, 1600 cm^{-1}. $\underline{R^3=CH_2OCOCH_3}$ δ 1.30 (6H,t, J=7 Hz) 2.03 and 2.05 (3H,s) 3.03, 3.32 and 3.60 (2H,m) 3.85 and 3.87 (2H,s) 4.17 and 4.19 (4H,q,J=7 Hz) 5.35 and 5.56 (1H,q) 5.85, 5.89 and 5.91 (2H+1H,s) 6.08 and 6.15 (1H,s).

10. R.B. Woodward in: Recent Advances in the Chemistry of β-lactam Antibiotics, Ed. J. Elks, Chemical Society Special Publication No. 28, 1977, pag. 174.

11. $\underline{R^3=CH_3}$ ν_{max} 1795, 1755, 1700, 1600 cm^{-1}. $\underline{R^3=CH_2C_6H_5}$ δ 1.28 (3H,s,J=7 Hz) 3.20 (1H,dd,J_1=16 Hz, J_2=2 Hz) 3.70 (1H,dd,J_1=16 Hz, J_3=4 Hz) 4.22 (2H,q,J=7 Hz) 5.20 (2H,s) 5.36 (1H,dd,J_3=4 Hz, J_2=2 Hz) 5.53 (1H,d,J=1.2 Hz) 6.14 (1H,d,J=1.2 Hz) 7.37 (5H,s); ν_{max} 1795 cm^{-1}. $\underline{R^3=CH_2OCOCH_3}$ m.p. 112-113°C; δ 1.32 (3H,s,J=7 Hz) 2.30 (3H,s) 3.23 (1H,dd,J_1=16 Hz, J_2=2 Hz) 3.82 (1H,dd,J_1=16 Hz, J_3=4 Hz) 4.26 (2H,q,J=7 Hz) 5.42 (1H,dd,J_3=4 Hz, J_2=2 Hz) 5.55 (1H,d,J=1.2 Hz) 5.82 (2H,s) 6.18 (1H,d,J=1.2 Hz); ^{13}C NMR ppm 14.58 and 61.09 (CH_3CH_2) 20.39, 169.68 and 80.86 (CH_3COOCH_2) 49.12 (C-6) 64.50 (C-5) 66.92 (C-3) 110.63 (C-8) 161.90 (C-2) 166.51 (C-9) 171.87 (C-7 and C-10); λ 283 nm.

12. R.G. Alexander and R. Southgate, J.C.S. Chem.Comm. 1977, 405.

13. (a) T.A. Bryson, J. Org. Chem. 38, 3428 (1973); (b) S.A. Krueger and T.A. Bryson, J. Org. Chem., 39, 3167 (1974).

14. $\underline{R^3=CH_2OCOCH_3}$ 1.28 and 1.30 (3H,t,J=7 Hz) 2.14 (3H,s) 3.30-4.00 (2H,m) 3.75 and 4.43 (2H,d, J=19 Hz) 4.17 (2H,q,J=7 Hz) 4.89 and 4.98 (1H,dd) 5.90 (2H,s); ν_{max} 1810, 1760, 1730 cm^{-1}; λ 294 nm.

15. R.B. Woodward, Acta Pharm. Suec., 14 Suppl., 23 (1977).

16. Simply obtained from the reduction of the thioacetondicarboxylate with $LiAlH_4$.

17. δ 1.32 (3H,t,J=7 Hz) 2.97 (2H+1H,br t,J=6Hz) 3.07 (1H,m,J_1=16 Hz) 3.50 (1H,dd,J_1=16 Hz, J_3=5 Hz) 3.85 (2H,t,J=6 Hz) 4.17 (2H,q,J=7 Hz) 5.07 (1H,dd,J_3=5 Hz, J_2=2.5 Hz) 5.63 (1H,s) 7.17 (1H,br).

18. $\underline{R^3=CH_3}$ δ 1.27 (3H,t) 2.01 (3H,s) 3.01 and 3.44 (4H,m) 3.83 and 3.87 (3H,s) 4.15 (4H,m) 5.21 (2H,m) 5.71 and 5.73 (1H,s). $\underline{R^3=CH_2OCOCH_3}$ δ 1.22 (3H,t) 1.98 (3H,s) 2.08 (3H,s) 2.80-3.80 (4 H,m) 4.10 (2H,q) 4.25 (2H,t) 5.10-5.80 (5H,m).

19. $\underline{R^3=CH_3}$ δ 1.28 (3H,t) 2.05 (3H,s) 3.16 and 3.60 (4H,m) 3.82 and 3.87 (3H,s) 4.17 (2H,t) 4.28 (2H,t) 5.32 and 5.55 (1H,dd) 5.68 (1H,s) 6.08 and 6.13 (1H,s).

20. $\underline{R^3=CH_3}$ δ 2.04 (3H,s) 3.21 (2H,t,J=6 Hz) 3.46 (1H,dd,J_1=16 Hz, J_2= 2 Hz) 3.77 (1H,dd,J_1=16 Hz, J_3=4 Hz) 3.83 (3H,s) 4.09 (2H,t,J=6 Hz) 5.64 (1H,dd,J_2=2 Hz, J_3=4 Hz); ν_{max} 1795, 1740, 1710 cm^{-1}; λ 263, 317 nm. $\underline{R^3=CH_2OCOCH_3}$ δ 2.08 (3H,s) 2.14 (3H,s) 3.20 (2H,t,J=6.5 Hz) 4.30 (2H,t, J=6.5 Hz) 3.52 (1H,dd,J_1=16 Hz) 3.82 (1H,dd,J_3=4 Hz, J_1=16 Hz) 5.67 (1H,dd,J_3=4 Hz, J_2=2 Hz) 5.88 (2H,s); ν_{max} 1800, 1770, 1740 cm^{-1}; λ 263, 323 nm.

21. M. Foglio, G. Franceschi, C. Scarafile, and F. Arcamone, to be communicated.

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