Tetrahedron Letters, Vol.31, No.24, pp 3509-3512, 1990
Printed in Great Britain

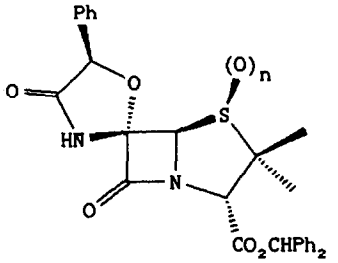
0040-4039/90 $3.00 + .00
Pergamon Press plc

REARRANGEMENT OF *unsym*-AZETIDINONE DISULPHIDES TO 2β-(THIO-SUBSTITUTED METHYL)PENAMS

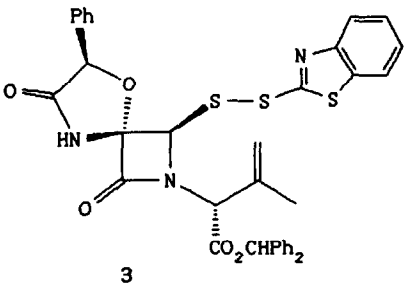
Marco Alpegiani, Franco Giudici, Ettore Perrone* and Daniela Borghi
Farmitalia Carlo Erba, via dei Gracchi 35, 20146 Milano, Italy

Summary: *Two azetidinyl benzothiazolyl disulphides, 3 and 8, were found to rearrange to 2β-(benzothiazolylthiomethyl)penams upon thermolysis in toluene. When an external acid catalyst was added, the reaction became general and could be used as a synthetic tool.*

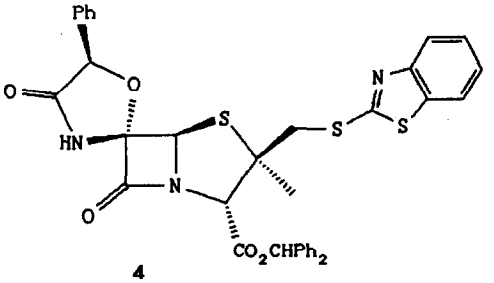
Unsymmetrical azetidinone disulphides have gained popularity in β-lactam chemistry after the work of Kamiya,[1] when 2-mercaptobenzothiazole (MBT) was found to be an efficient trapper of the penicillin-derived sulphenic acids. Among others, we became involved with "Kamiya disulphides" as intermediates for antibacterial penems.[2] Renewed interest in these compounds arose from their use in the synthesis of 2β-(heterocyclylthiomethyl)penam sulphones, recently described as new potent β-lactamase inhibitors.[3,4] This prompts us to report a capricious reaction observed on disulphides 3 and 8, whose rationalization provided a general method for preparing 2β-(benzothiazolylthiomethyl)penams.



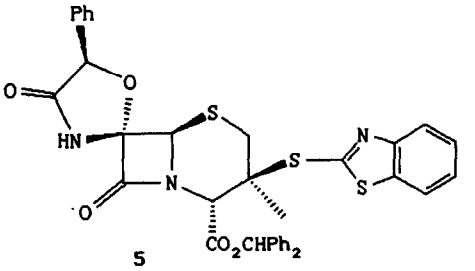
1 : n=0
2 : n=1



3



4

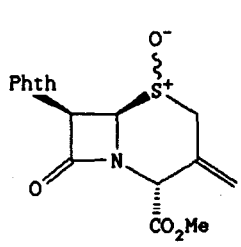


5

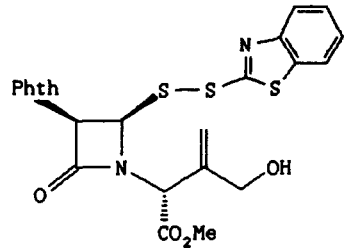
When the spirocyclic penam sulphoxide 2[5] was heated in toluene with MBT (1 mol equiv., 110°C, 4 h) a product isomeric with the expected disulphide 3 (elemental analysis, MS/FD) was generated in quantitative yield. Spectral data[6] were consistent with the 2β-(thio-substituted methyl)penam structure 4. In particular, a 2D heteronuclear correlation experiment (^{13}C-^{1}H) showed long-range coupling between benzothiazole C_2 and the CH_2S protons,

which is in accord with structure 4 but not with the cepham alternative 5. Stereochemistry at penam C_2 was denounced by the high-field resonance (δ 1.36 ppm) of the terminal methyl protons, indicative of their α-facial orientation.[7]

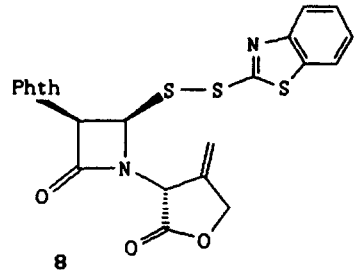
Along a different synthetic sequence, an aged sample (2 months) of 3-exomethylenecepham 6 (2:1 mixture of *S* and *R* oxides)[8] was found to produce, when reacted with MBT under the usual conditions, a mixture of disulphide-lactone 9[9] and an isomeric compound (48% and 16%, respectively, after flash-chromatography). Structure 10 was assigned easily on the basis of spectral properties[6], analogies with 4, and mechanistic inferences.[10]



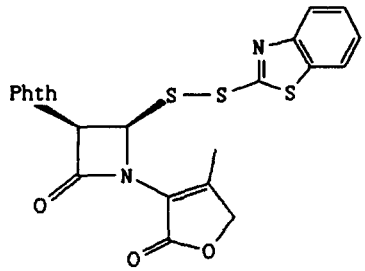
6



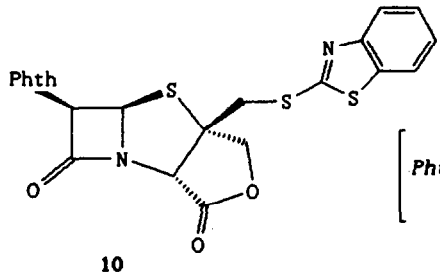
7



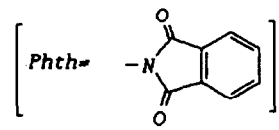
8



9



10

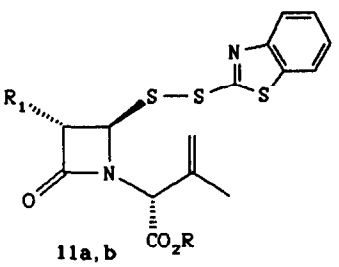


On re-examination, it was found that formation of benzothiazolylthiomethylpenams could be repressed in part (in the case of 4) or totally (in the case of 10) by using freshly recrystallized penam sulphoxide precursors. Thus, from 2 a 1:1 mixture of 3 and 4 was obtained, and the disulphide 3 prevailed under partial conversion conditions (refluxing benzene, 1 h). Pure 3 was isolated and shown to isomerize quantitatively to penam 4 in refluxing toluene. Identification of 8, the plausible precursor of 10, was less straightforward. Freshly recrystallized 6 on shorter reaction times gave mainly the carbinol 7,[2b] accompanied by variable amounts of butenolide 9 and of a compound whose ^1H nmr spectrum (taken in admixture with 7 and 9) was consistent with the unconjugated lactone structure 8. Unfortunately, this compound could never be isolated pure because of its extremely facile isomerization to 9 upon contact with SiO_2 or Fluorisil®

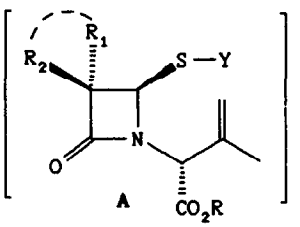
Formation of 2-(benzothiazolylthiomethyl)penams (2:1 mixture of β and α isomers) from Kamiya disulphides has one literature precedent.[11] The poor stereoselectivity and the reaction conditions suggested a radical mechanism. In our case, a different mechanism is operative. We ran reactions of 2 and 6 with MBT in the presence of catalytic amounts of AIBN, hydroquinone, pyridine, benzoic acid, *p*-toluenesulphonic acid (PTSA), but an increment of the benzothiazolylthiomethylpenam products was observed only with the acid catalysts. Isomerization of 3 to 4 (refluxing benzene) was markedly accelerated by traces of PTSA. From 6, the presence of this and other sulphonic and carboxylic acid catalysts suppressed the accumulation of disulphide-carbinol 7 at any time. The unconjugated lactone 8 was the main product, and its progressive conversion to 9 and 10 by further heating could be monitored.

From these observations we surmised that proper conditions could be found for the isomerization of any Kamiya disulphide to the corresponding 2β-(benzothiazolylthiomethyl)penam. Disulphides **11a** and **11b**[12] were selected as model substrates. Indeed such compounds, though stable in refluxing toluene, afforded penams **12a** (55%) and **12b** (53% at ca. 50% conversion) under PTSA catalysis. Sensitiveness of the products under the reaction conditions was the only apparent limitation. Pyridinium tosylate and *N*-tosylimidazole were milder but less effective agents, on balance inferior to PTSA.

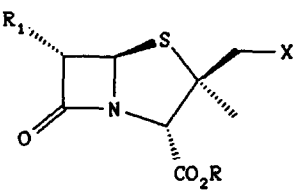
For comparison purposes, an authentic sample of **12a** was prepared from **11a** by reaction with copper(II) chloride and displacement of obtained chloromethylpenam[3,4] **13a** with MBT ($NaHCO_3$ aq. DMF). Compound **12a** obtained in this way could not be purified easily from accompanying by-products; its estimated overall yield did not exceed 27%. Thus, in practice, the preparation of **12a** by direct rearrangement of **11a** was not only more straightforward, but occurred with higher material balance. Mechanistically, both routes are presumably mediated by formation and nucleophilic opening of the fused thiiranium species **B**. In the literature procedure this process occurs *twice*, both in the synthesis and displacement of **13a**. One can predict that generation of species **B** from Kamiya disulphides in the absence of mercaptane scavengers (copper salts) is bound to afford benzothiazolylthio-substituted products directly. In particular, in the acid-catalysed rearrangement we propose that a mixed anhydride (**A**, Y= RSO_2O or RCOO) originates from disulphides **3**, **8**, **11** and the catalyst, with release of MBT, which, owing to its bulk (α face expulsion: stereoselective formation of of the *endo*-thiiranium **B**), accompanied by good nucleophilicity and poor nucleofugality (chemoselective, irreversible cleavage of **B**), makes the reaction evolve towards the kinetic products **4**, **10**, **12**.

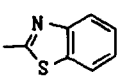


11a,b

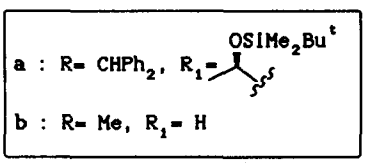


A



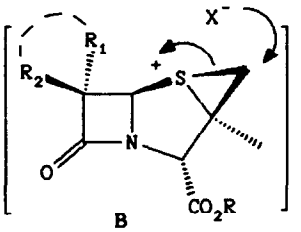
12a,b : X= 

13a : X= Cl



a : R= $CHPh_2$, R_1=

b : R= Me, R_1= H



B

Entropic factors favouring in species **A** addition of the sulphur atom to the terminal olefin could account for the difference of reactivitity observed among disulphides **3**, **8**, **11**. In the spirocyclic compound **3**, in particular, which rearranges to **4** even in the absence of catalysts, steric compression from the spirocycle might perhaps make the disulphide reactive enough to evolve to **B** directly.

In conclusion, a direct rearrangement of Kamiya disulphides to 2β-(benzothiazolylthiomethyl)penams has been found. Since heteroaromatic thiols other than MBT cleave penicillin sulphoxides to *unsym*-azetidinone disulphides,[1,13,14] we expect the reaction to be useful for preparing new 2β-(heterocyclylthiomethyl)penam derivatives.

REFERENCES AND NOTES

1. T. Kamiya, T. Teraji, Y. Saito, M. Hashimoto, O. Nakaguchi and T. Oku, *Tetrahedron Lett.*, 1973, 3001.
2. a) M. Alpegiani, A. Bedeschi, M. Foglio, F. Giudici and E. Perrone, *Tetrahedron Lett.*, 1983, 24, 1627; b) M. Alpegiani, A. Bedeschi, E. Perrone and G. Franceschi, *Tetrahedron Lett.*, 1984, 25, 4167; c) M. Alpegiani, A. Bedeschi, E. Perrone and G. Franceschi, *Tetrahedron Lett.*, 1984, 25, 4171.
3. H. Tanaka, M. Tanaka, A. Nakai, S. Yamada, N. Ishida, T. Otani and S. Torii, *J. Antibiotics*, 1988, 41, 579.
4. R. Singh, M.P. Singh and R.G. Micetich, *Heterocycles*, 1989, 29, 947.
5. This compound was prepared by MCPBA oxidation of 1, itself obtained from the mandelamido penicillin precursor under the Koppel-Koehler 6α-methoxylation conditions (LiOMe/*t*-BuOCl, THF -70°C, 55% overall). Alternatively, 2 could be prepared from the mandelamidopenam 1β-oxide under the same conditions. Details on this chemistry have lost interest after the publication of two papers on closely related compounds. See: G.A. Koppel and R.E. Koehler, *Tetrahedron Lett.*, 1973, 1943; P.G. Sammes, S. Smith and B.C. Ross, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2117; G. Burton and F.P. Harrington, *J. Chem. Soc., Perkin Trans. 1*, 1987, 635.
6. Full data of key-compounds: 4: m.p. 92°C (from Et_2O); $[\alpha]_D$ +153° (0.1% $CHCl_3$); MS/FD 679 m/z; anal. C,H,N,S agree with $C_{36}H_{29}N_3O_5S_3$; ν_{max}($CHCl_3$) 1790 (β-lactam CO), 1740 cm^{-1} (ester and oxazolidine CO); ^1H nmr δ($CDCl_3$) 1.36(3H,s,CH_3), 3.58 and 3.92(2H,each d,J=13.8 Hz,CH_2S), 4.99 (1H,s,H_3), 5.54(1H,s,CH spiro), 5.75(1H,s,H_5), 7.00(1H,s,$OCHPh_2$), 7.38(12H, Ar), 7.72 and 8.20(2H,each d,J=7.9Hz,BTZ), 8.89(1H,s,NHCO); ^{13}C nmr δ($CDCl_3$) 23.60(CH_3), 48.06(CH_2S), 67.33(C_3), 69.83(C_2), 77.26(C_5), 79.04(OCH), 79.74(oxazolidine C_5), 102.31 (C_6), 120.81, 122.50, 125.13, 126.18, 126.53, 127.11, 127.57, 128.72, 128.98, 134.93, 135.03, 138.70, 138.76, 152.17(Ar), 165.74(COO), 165.97(BTZ C_2), 171.09(β-lactam CO), 171.21(oxazolidine CO);
   10: m.p. 114°C dec. (from Et_2O); $[\alpha]_D$ +131° (0.1% $CHCl_3$); MS/FD 509 m/z; anal. C,H,N agree with $C_{23}H_{15}N_3O_5S_3$; ν_{max}(KBr) 1800, 1775, 1710 cm^{-1}; ^1H nmr δ (DMSO-d_6) 4.28 and 4.53(2H,each d,J=13.0Hz,CH_2S), 4.55 and 4.75(2H,each d,J=10.3Hz,CH_2O), 5.52(1H,d,J=4.0Hz, H_5), 5.71(1H,s,H_3), 6.03(1H,d,J=4.0Hz,H_6), 7.3-7.5(2H,m,BTZ), 7.9-8.0(6H,m,Ar); ^{13}C nmr δ (DMSO-d_6) 40.73(CH_2S), 66.77(C_3,C_5), 72.85(C_2), 74.81(CH_2O), 121.22, 121,87, 122.42, 123.65, 124.29, 124.79, 125.49, 126.46, 130.81, 135.07, 135.10, 152.24(Ar), 165.15(BTZ C_2), 166.34(2x Phth CO), 168.74, 170.79(lactone and β-lactam CO).
   Selected ^1H nmr ($CDCl_3$) data of other products: 1: 1.28(α-Me), 1.50(β-Me), 4.60(H_3), 5.42 (oxazolidine CH), 5.85(H_5); 2: 0.87, 1.61, 4.70, 5.03, 5.31; 3: 1.86(3H,s,Me), 5.06, 5.08, 5.19(each 1H,s,H_3 and $=CH_2$), 5.50, 5.55(each 1H,s,H_5 and oxazolidine CH); 8: 5.02(2H,m, CH_2O), 5.45, 5.57(2H,each m,$=CH_2$), 5.67, 5.89(each 1H,d,J=4.8Hz,H_5 and H_6), 5.98(1H,m,H_3) 9: 2.34(3H,s,Me), 4.56, 4.74(2H,each d,J=18.6Hz,CH_2O), 5.90, 6.25(each 1H,d,J=5.0Hz,H_5, H_6); 12a: 1.54(3H,s,Me), 3.40(1H,dd,J=1.9 and 5.2Hz,H_6), 3.90(2H,ABq,J=13.8Hz,CH_2S), 4.93 (1H,s,H_3), 5.35(1H,d,J=1.9Hz,H_5); 12b: 1.57(3H,s,Me), 3.16(1H,dd,J=1.8 and 15.9Hz,$H_{6\beta}$), 3.57(1H,dd,J=4.0 and 15.9Hz,$H_{6\alpha}$), 3.78(3H,s,OMe), 3.86, 4.04(2H,each d,J=13.8Hz,CH_2S), 4.84(1H,s,H_3), 5.34(1H,dd,J=1.8 and 4.0Hz,H_5); 13a: 1.30(3H,s,Me), 3.28(1H,dd,J=1.4 and 5.2Hz,H_6), 3.54(2H,s,CH_2Cl), 5.10(1H,s,H_3), 5.29(1H,d,J=1.4Hz,H_5).
7. S. Kukolja, N.D. Jones, M.O. Chaney, T.K. Elzey, M.R. Gleissner, J.W. Paschal and D.E. Dorman, *J. Org. Chem.*, 1975, 40, 2388.
8. S. Kukolja, R.S. Lammert, M.R.B. Gleissner and A.I. Ellis, *J. Am. Chem. Soc.*, 1976, 98, 5040.
9. H. Yanagisawa and A. Ando, *Tetrahedron Lett.*, 1982, 23, 3379.
10. There is a single literature precedent of a fused penam lactone, isolated as one of a "plethora of products" after peracid oxidation of a thiazoline-azetidinone in the presence of TFA: R.D.G. Cooper, *J. Am. Chem. Soc.*, 1972, 94, 1018.
11. Y. Maki and M. Sako, *J. Chem. Soc., Chem. Commun.*, 1978, 836.
12. I. Ernest, J. Gosteli and R.B. Woodward, *J. Am. Chem. Soc.*, 1979, 101, 6301.
13. R.G. Micetich, S.N. Maiti, M. Tanaka, T. Yamazaki and K. Ogawa, *Heterocycles*, 1985, 23, 325.
14. R.G. Micetich, S.N. Maiti, M.P. Singh, N. Tanaka, T. Yamazaki and K. Ogawa, *Tetrahedron Lett.*, 1985, 26, 5611.

(Received in UK 20 April 1990)