SYNTHESES OF SOME 2,3-BENZO-1-THIAOCTEMS

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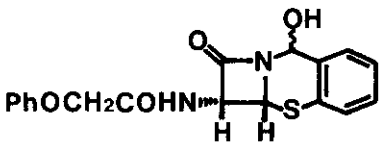
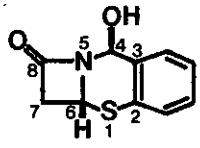
Abstract — 2,3-Benzo-1-thiaoctems 2, 9, and 6 were synthesized from 4-acetoxyazetidin-2-one (3). Oxidation of 2 and 9 afforded the corresponding sulfoxides and sulfones. The relative stereochemistries of the products were determined from nmr aromatic solvent induced shifts (ASIS).

In connection with our interest in the biological activity of synthetic 2,3-benzo-1-thiaoctem (1),[1,2] we previously synthesized some 2,3-benzo-1-oxaoctems.[3] Now we report the syntheses of 2,3-benzo-1-thiaoctems with no substituent at the C_7 position and their sulfoxides and sulfones.



1



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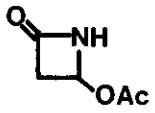


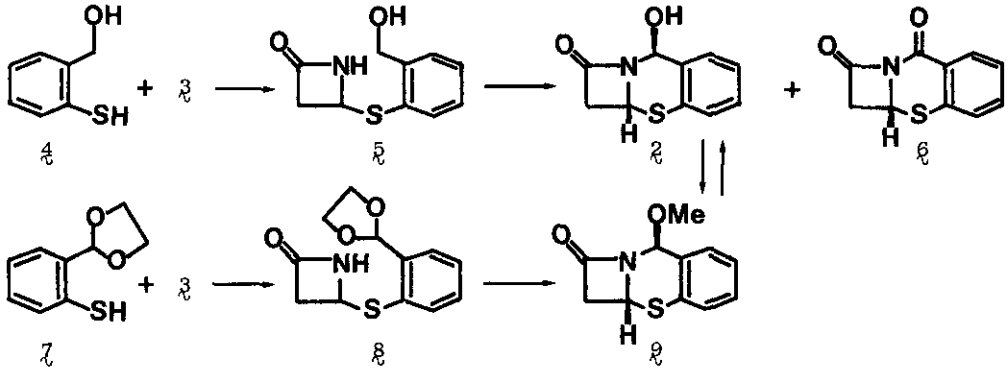
3

A mixed solution of *o*-mercaptobenzyl alcohol[4] (1.1 equiv) and sodium ethoxide (1.05 equiv) was added to a solution of 4-acetoxyazetidin-2-one (3)[5] (1 equiv) in water under ice cooling. After 2 hrs at 0°C, the solution was extracted with ethyl acetate and worked up in the usual way to give 4-(2-hydroxymethylthio) azetidin-2-one (5)[6] (70%) by chromatography. A similar reaction of thiophenol 7, which was obtained from 2,2'-dithiobisbenzaldehyde[7] in 65% yield [(i) $HOCH_2CH_2OH$, TsOH, C_6H_6, reflux, (ii) $LiAlH_4$, Et_2O], with 3 gave 8[6] (85%). Oxidation of 5 with pyridinium chloro chromate[8] (1.5 equiv, CH_2Cl_2, rt, 2 hrs) afforded 4-hydroxy-2,3-benzo-1-thiaoctem 2[9,10] (62%, mp 111-112°C) and 6[11] (20%, mp 180-181°C). Alternatively, methanolysis (MeOH, TsOH, 50°C, 3 hrs) of 8 gave methyl ether 9[12] (91%, mp 116-117°C) which was easily hydrolyzed (Me_2CO, H_2O, rt, 3 hrs) to 2 (65%). Methanolysis (MeOH, TsOH, rt, 3hrs) of compound 2 gave 9 (93%).

Oxidation of compound 2 with 2 equiv of *m*-chloroperbenzoic acid in chloroform for 10 hrs gave the two isomeric sulfoxides 10[13] (18%, mp 165-166°C, dec.) and 11[14] (65 %, mp 162-163°C, dec.). Of the two isomers, the former (the minor product) appeared less-polar on t.l.c. Treatment of 2 with 4 equiv of *m*-chloroperbenzoic acid for 24 hrs led to formation of the sulfone 12[15] (68%, mp 166-167°C, dec.). By use of the same procedure as that for 10 and 11, 13[16] (12%, mp 158-159°C) and 14[17] (71%, mp 136-137°C) were obtained from 9. Permanganate oxidation ($KMnO_4$, Me_2CO, H_2O, dil H_2SO_4, rt) of 9 gave sulfone 15[18] (92%, mp 161-162°C, dec.).

The relative stereochemistries of the products were determined by examination of the aromatic solvent induced shifts[19] (ASIS) of the C_4 and C_6 protons in the nmr of methyl ethers 13 and 14 (Table 1). It is well established that benzene solvates the positive end of a solute dipole and causes large upfield-shifts for protons located on the side of the molecule with which benzene associates.[20] Thus, the fact that there is a large upfield-shift (+0.31 ppm) for C_6-H in compound 14 and no shift for C_6-H *in compound 13 compared with that of 9 support the* β-sulfoxide configuration for 13 and α-sulfoxide configuration for 14. The upfield-shift (+0.21 ppm) for C_4-H in compound 13 shows that there is a *trans*-relationship between C_4-H and C_6-H in the series of compounds. Furthermore, the relatively large deshielding (-0.29 ppm in $CDCl_3$) for C_4-H in compound 14 compared with that in 9 indicates a *cis*-relationship between C_4-H and the sulfoxide group.[21]

Only sulfoxides 11 and 12 showed appreciable antibacterial activity.



10 R = H
13 R = CH_3

11 R = H
14 R = CH_3

12 R = H
15 R = CH_3

Table 1 Benzene-induced Solvent Shifts for Methyl Ethers[a]

Compound	Solvent	C-7Hα	C-7Hβ	C-6H	C-4H	OMe
9	$CDCl_3$	3.05	3.57	4.90	5.58	3.55
	$CDCl_3/C_6D_6$[b]	2.60	2.95	4.43	5.39	3.37
	Δ_9	+0.45	+0.62	+0.47	+0.19	+0.18
13	$CDCl_3$	3.50	3.70	4.48	5.61	3.66
	$CDCl_3/C_6D_6$[b]	2.99	2.99	4.01	5.21	3.45
	Δ_{13}	+0.51	+0.71	+0.47	+0.40	+0.21
	$\Delta_{13}-\Delta_9$	+0.06	+0.09	0.00	+0.21	+0.03
14	$CDCl_3$	3.45	3.45	4.66	5.87	3.69
	$CDCl_3/C_6D_6$[b]	3.12	2.79	3.88	5.68	3.51
	Δ_{14}	+0.33	+0.66	+0.78	+0.19	+0.18
	$\Delta_{14}-\Delta_9$	-0.12	+0.04	+0.31	0.00	0.00

(a) In parts per million in 3% (W/V) solution with TMS as an internal reference, measured on a JEOL PS-100. $\Delta = \delta(CDCl_3)-\delta(CDCl_3/C_6D_6)$. (b) 50% (V/V) C_6D_6 in $CDCl_3$.

REFERENCES AND NOTES

1. Nomenclature follows that reported by A. K. Bose, *J. Heterocyclic Chem.*, 1976, 13, 93.
2. J. C. Sheehan, H. C. Dalzell, J. M. Greenwood, and D. R. Ponzi, *J. Org. Chem.*, 1974, 39, 277.
3. M. Shibuya and S. Kubota, *Heterocycles*, 1979, 12, 947.
4. G. W. Stacy, F. W. Villaescusa, and T. E. Wollner, *J. Org. Chem.*, 1965, 30, 4074.
5. K. Clauss, D. Grimm, and G. Prossel, *Justus Liebigs Ann. Chem.*, 1974, 539.
6. Satisfactory spectroscopic data were obtained.
7. K. J. Brown and O. Meth-Cohn, *Tetrahedron Letters*, 1974, 4069.
8. E. J. Corey and J. W. Suggs, *Tetrahedron Letters*, 1975, 2647.
9. This and all other compounds synthesized were *dl*-mixtures, but only one enantiomer is depicted for convenience. Satisfactory analytical data were obtained for all crystalline compounds.
10. IR($CHCl_3$) 3580, 3340 (OH), and 1760 cm^{-1} (C=O); NMR($CDCl_3$) 2.96 (1H, dd, J = 1.5 and 15 Hz, C_7α-H, 3.47 (1H, dd, J = 4 and 15 Hz, C_7β-H), 4.48 (1H, d, J = 5.5 Hz, OH), 4.88 (1H, dd, J = 1.5 and 4 Hz, C_6-H), 5.99 (1H, d, J = 5.5 Hz, C_4-H), 7.22 (3H, s, ArH), and 7.66 (1H, m, ArH).
11. IR($CHCl_3$) 1817 and 1685 cm^{-1} (C=O); NMR($CDCl_3$) 3.32 (1H, dd, J = 3 and 16.5 Hz, C_7α-H), 3.62 (1H, dd, J = 5 and 16.5 Hz, C_7β-H), 5.45 (1H, dd, J = 3 and 5 Hz,

C_6-H), and 7.10-8.20 (4H, m, ArH).

12. IR($CHCl_3$) 1773 cm^{-1} (C=O); NMR($CDCl_3$) 3.05 (1H, dd, J = 1.5 and 15.5 Hz, $C_7\alpha$-H), 3.55 (3H, s, OMe), 3.57 (1H, dd, J = 4 and 15.5 Hz, $C_7\beta$-H), 4.90 (1H, dd, J = 1.5 and 4 Hz, C_6-H), 5.58 (1H, s, C_4-H), and 7.08-7.60 (4H, m, ArH).
13. IR($CHCl_3$) 3580, 3280 (OH), 1770 (C=O), and 1065 cm^{-1} (S→O); NMR(DMSO-d_6) 3.46 (1H, dd, J = 1.5 and 15.5 Hz, $C_7\alpha$-H), 3.68 (1H, dd, J = 4 and 15.5 Hz, $C_7\beta$-H), 4.51 (1H, dd, J = 1.5 and 4 Hz, C_6-H), 5.85 (1H, d, J = 8.5 Hz, C_4-H), 7.19 (1H, d, J = 8.5 Hz, OH), and 7.48-7.84 (4H, m, ArH).
14. IR($CHCl_3$) 3580, 3350 (OH), 1763 (C=O), and 1070 cm^{-1} (S→O); NMR(DMSO-d_6) 3.04 (1H, dd, J = 1.5 and 15.5 Hz, $C_7\alpha$-H), 3.42 (1H, dd, J = 4.5 and 15.5 Hz, $C_7\beta$-H), 4.89 (1H, dd, J = 1.5 and 4.5 Hz, C_6-H), 5.97 (1H, d, J = 9 Hz, C_4-H), 7.16 (1H, d, J = 9 Hz, OH), and 7.40-7.92 (4H, m, ArH).
15. IR($CHCl_3$) 3580, 3280 (OH), 1778 (C=O), 1324, 1156, and 1130 cm^{-1} (SO_2); NMR (DMSO-d_6) 3.38 (1H, dd, J = 1.5 and 15.5 Hz, $C_7\alpha$-H), 3.64 (1H, dd, J = 4.5 and 15.5 Hz, $C_7\beta$-H), 5.25 (1H, dd, J = 1.5 and 4.5 Hz, C_6-H), 6.04 (1H, d, J = 8 Hz, C_4-H), 7.35 (1H, d, J = 8 Hz, OH), and 7.55-8.05 (4H, m, ArH).
16. IR($CHCl_3$) 1783 (C=O) and 1070 cm^{-1} (S→O); NMR($CDCl_3$) 3.50 (1H, dd, J = 1.5 and 15.5 Hz, $C_7\alpha$-H), 3.66 (3H, s, OMe), 3.70 (1H, dd, J = 4 and 15.5 Hz, $C_7\beta$-H), 4.48 (1H, dd, J = 1.5 and 4 Hz, C_6-H), 5.61 (1H, s, C_4-H), and 7.50-8.00 (4H, m, ArH).
17. IR($CHCl_3$) 1783 (C=O) and 1080 cm^{-1} (S→O); NMR($CDCl_3$) 3.45 (2H, d, J = 3 Hz, C_7-H_2), 3.69 (3H, s, OMe), 4.66 (1H, t, J = 3 Hz, C_6-H), 5.87 (1H, s, C_4-H), and 7.40-7.95 (4H, m, ArH).
18. IR($CHCl_3$) 1790 (C=O), 1323, 1154, and 1129 cm^{-1} (SO_2); NMR($CDCl_3$) 3.53 (1H, dd, J = 4 and 16 Hz, $C_7\beta$-H), 3.62 (3H, s, OMe), 3.67 (1H, dd, J = 2 and 16 Hz, $C_7\alpha$-H), 4.87 (1H, dd, J = 2 and 4 Hz, C_6-H), 5.73 (1H, s, C_4-H), and 7.40-8.15 (4H, m, ArH).
19. J. E. G. Kemp, D. Ellis, and M. D. Closier, *Tetrahedron Letters*, 1979, 3781, and references cited therein.
20. R. D. G. Cooper, P. V. Demarco, C. F. Murphy, and L. A. Spangle, *J. Chem. Soc. (C)*, 1970, 340, and references cited therein.
21. A similar deshielding effect in a sulfoxide of a Δ^2-cephalosporin is reported by R. D. G. Cooper *et al.*[20]

Received, 15th August, 1980