

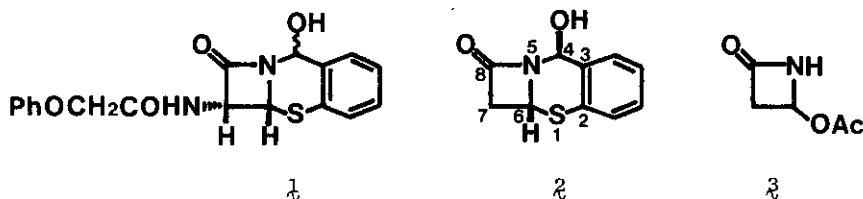
SYNTHESES OF SOME 2,3-BENZO-1-THIAOCTEMS

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Abstract — 2,3-Benzo-1-thiaoctems **2**, **9**, and **6** were synthesized from 4-acetoxiazetidin-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 C₇ position and their sulfoxides and sulfones.



A mixed solution of *o*-mercaptobenzyl alcohol⁴ (1.1 equiv) and sodium ethoxide (1.05 equiv) was added to a solution of 4-acetoxiazetidin-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'-dithiobisbenzaldehyde⁷ in 65% yield [(i) HOCH₂CH₂OH, TsOH, C₆H₆, reflux, (ii) LiAlH₄, Et₂O], with **3** gave **8**⁶ (85%). Oxidation of **5** with pyridinium chloro chromate⁸ (1.5 equiv, CH₂Cl₂, rt, 2 hrs) afforded 4-hydroxy-2,3-benzo-1-thiaoctem **9**^{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 **12**¹² (91%, mp 116-117°C) which was easily hydrolyzed (Me₂CO, H₂O, 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 **2**. Permanganate oxidation (KMnO₄, Me₂CO, H₂O, dil H₂SO₄, rt) of **2** 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 shifts¹⁹ (ASIS) of the C₄ and C₆ 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 C₆-H in compound **14** and no shift for C₆-H in compound **13** compared with that of **2** support the β-sulfoxide configuration for **13** and α-sulfoxide configuration for **14**. The upfield-shift (+0.21 ppm) for C₄-H in compound **13** shows that there is a *trans*-relationship between C₄-H and C₆-H in the series of compounds. Furthermore, the relatively large deshielding (-0.29 ppm in CDCl₃) for C₄-H in compound **14** compared with that in **2** indicates a *cis*-relationship between C₄-H and the sulfoxide group.²¹

Only sulfoxides **11** and **12** showed appreciable antibacterial activity.

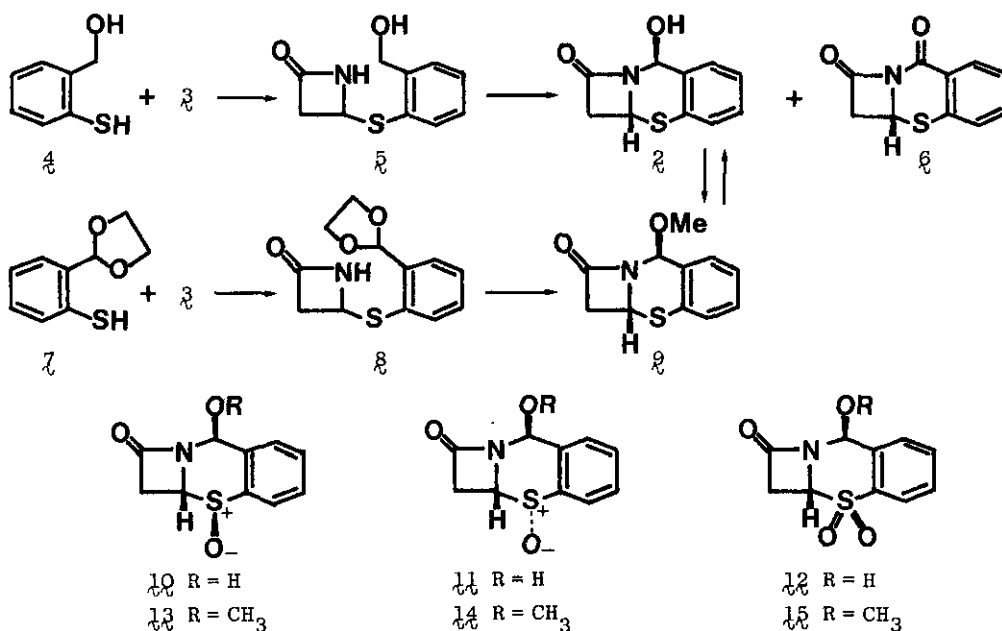


Table 1 Benzene-induced Solvent Shifts for Methyl Ethers^a

Compound	Solvent	C-7H α	C-7H β	C-6H	C-4H	OMe
9	CDCl ₃	3.05	3.57	4.90	5.58	3.55
	CDCl ₃ /C ₆ D 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 ₆ D 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 ₆ D 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. $\Delta = \delta(\text{CDCl}_3) - \delta(\text{CDCl}_3/\text{C}_6\text{D}_6)$. (b) 50% (V/V) C₆D₆ in CDCl₃.

REFERENCES AND NOTES

1. Nomenclature follows that reported by A. K. Bose, *J. Heterocyclic Chem.*, 1976, 13, 93.
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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(CHCl₃) 3580, 3340 (OH), and 1760 cm⁻¹ (C=O); NMR(CDCl₃) 2.96 (1H, dd, J = 1.5 and 15 Hz, C₇ α -H), 3.47 (1H, dd, J = 4 and 15 Hz, C₇ β -H), 4.48 (1H, d, J = 5.5 Hz, OH), 4.88 (1H, dd, J = 1.5 and 4 Hz, C₆-H), 5.99 (1H, d, J = 5.5 Hz, C₄-H), 7.22 (3H, s, ArH), and 7.66 (1H, m, ArH).
11. IR(CHCl₃) 1817 and 1685 cm⁻¹ (C=O); NMR(CDCl₃) 3.32 (1H, dd, J = 3 and 16.5 Hz, C₇ α -H), 3.62 (1H, dd, J = 5 and 16.5 Hz, C₇ β -H), 5.45 (1H, dd, J = 3 and 5 Hz,

- C₆-H), and 7.10-8.20 (4H, m, ArH).
12. IR(CHCl₃) 1773 cm⁻¹ (C=O); NMR(CDCl₃) 3.05 (1H, dd, J = 1.5 and 15.5 Hz, C₇α-H), 3.55 (3H, s, OMe), 3.57 (1H, dd, J = 4 and 15.5 Hz, C₇β-H), 4.90 (1H, dd, J = 1.5 and 4 Hz, C₆-H), 5.58 (1H, s, C₄-H), and 7.08-7.60 (4H, m, ArH).
 13. IR(CHCl₃) 3580, 3280 (OH), 1770 (C=O), and 1065 cm⁻¹ (S+O); NMR(DMSO-d₆) 3.46 (1H, dd, J = 1.5 and 15.5 Hz, C₇α-H), 3.68 (1H, dd, J = 4 and 15.5 Hz, C₇β-H), 4.51 (1H, dd, J = 1.5 and 4 Hz, C₆-H), 5.85 (1H, d, J = 8.5 Hz, C₄-H), 7.19 (1H, d, J = 8.5 Hz, OH), and 7.48-7.84 (4H, m, ArH).
 14. IR(CHCl₃) 3580, 3350 (OH), 1763 (C=O), and 1070 cm⁻¹ (S+O); NMR(DMSO-d₆) 3.04 (1H, dd, J = 1.5 and 15.5 Hz, C₇α-H), 3.42 (1H, dd, J = 4.5 and 15.5 Hz, C₇β-H), 4.89 (1H, dd, J = 1.5 and 4.5 Hz, C₆-H), 5.97 (1H, d, J = 9 Hz, C₄-H), 7.16 (1H, d, J = 9 Hz, OH), and 7.40-7.92 (4H, m, ArH).
 15. IR(CHCl₃) 3580, 3280 (OH), 1778 (C=O), 1324, 1156, and 1130 cm⁻¹ (SO₂); NMR(DMSO-d₆) 3.38 (1H, dd, J = 1.5 and 15.5 Hz, C₇α-H), 3.64 (1H, dd, J = 4.5 and 15.5 Hz, C₇β-H), 5.25 (1H, dd, J = 1.5 and 4.5 Hz, C₆-H), 6.04 (1H, d, J = 8 Hz, C₄-H), 7.35 (1H, d, J = 8 Hz, OH), and 7.55-8.05 (4H, m, ArH).
 16. IR(CHCl₃) 1783 (C=O) and 1070 cm⁻¹ (S+O); NMR(CDCl₃) 3.50 (1H, dd, J = 1.5 and 15.5 Hz, C₇α-H), 3.66 (3H, s, OMe), 3.70 (1H, dd, J = 4 and 15.5 Hz, C₇β-H), 4.48 (1H, dd, J = 1.5 and 4 Hz, C₆-H), 5.61 (1H, s, C₄-H), and 7.50-8.00 (4H, m, ArH).
 17. IR(CHCl₃) 1783 (C=O) and 1080 cm⁻¹ (S+O); NMR(CDCl₃) 3.45 (2H, d, J = 3 Hz, C₇-H₂), 3.69 (3H, s, OMe), 4.66 (1H, t, J = 3 Hz, C₆-H), 5.87 (1H, s, C₄-H), and 7.40-7.95 (4H, m, ArH).
 18. IR(CHCl₃) 1790 (C=O), 1323, 1154, and 1129 cm⁻¹ (SO₂); NMR(CDCl₃) 3.53 (1H, dd, J = 4 and 16 Hz, C₇β-H), 3.62 (3H, s, OMe), 3.67 (1H, dd, J = 2 and 16 Hz, C₇α-H), 4.87 (1H, dd, J = 2 and 4 Hz, C₆-H), 5.73 (1H, s, C₄-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 Δ²-cephalosporin is reported by R. D. G. Cooper *et al.*²⁰

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