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AN EFFICIENT SYNTHESIS OF PENICILLANIC ACID S,S-DIOXIDE IN HIGH YIELD

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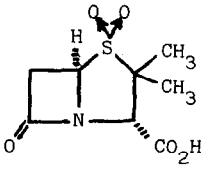
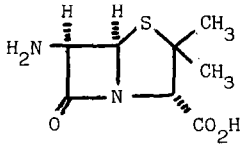
Summary: Diazotization/bromination of 6-aminopenicillanic acid S,S-dioxide (4) into 6,6-dibromopenicillanic acid S,S-dioxide (5a) in the presence of methanol and subsequent reduction of (5a) with magnesium/acid have resulted in a high yield synthesis of penicillanic acid S,S-dioxide (sulbactam).

Penicillanic acid S,S-dioxide (1) and its esters, which are readily hydrolyzable in vivo, act as valuable β-lactamase inhibitors enhancing the effectiveness of certain β-lactam antibiotics when used in combination to treat bacterial infections[1]. Volkmann and coworkers[2] have recently prepared penicillanic acid S,S-dioxide by diazotization/bromination of 6-aminopenicillanic acid (2) into 6,6-dibromopenicillanic acid (3) as the key step. The debromination of the corresponding 6,6-dibromosulfone (5a) into penicillanic acid S,S-dioxide has been performed catalytically (Pd/C).

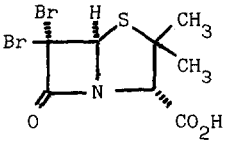


(1)

In continuation of our research on efficient synthesis of β-lactam antibiotics, we wish to report here a practical alternative to the preparation of penicillanic acid S,S-dioxide in high yield by using 6-aminopenicillanic acid S,S-dioxide[3] (4) as the starting material.



(2)



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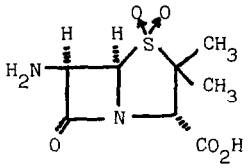

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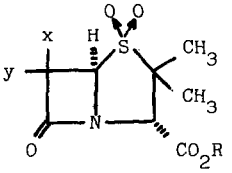

(5)

a) x,y= Br, R= H
b) y= H, x= Br, R= H
c) x,y= Br, R= CH_3
d) y= H, x= Br, R= CH_3
e) y= Br, x= OCH_3, R= H
f) y= Br, x= OCH_3, R= CH_3
g) y= H, x= OCH_3, R=CH_3

Diazotization/bromination of 6-aminopenicillanic acid S,S-dioxide (4) under the reaction conditions described by Clayton[4] or Volkmann et al[2] gives the corresponding dibromo-product (5a) in a low yield and of undesirable quality. Further variations of their reaction conditions fail to improve the yield of dibromopenicillanic acid S,S-dioxide (5a). We have found that diazotization/bromination of 6-aminopenicillanic acid S,S-dioxide (4) can be significantly influenced by carrying out the reaction in the presence of an alcohol. The diazotization/bromination procedure involves portionwise addition of sodium nitrite (29.7 mmol) to a cooled solution of 6-aminopenicillanic acid S,S-dioxide (4) (6.2 g., purity= 90%, 22.5 mmol), bromine (37.5 mmol), hydrobromic acid (7.1 ml; 64.0 mmol) and methanol (98.75 mmol) in dichloromethane (100 ml). The 6,6-dibromopenicillanic acid S,S-dioxide (5a), thus formed, can be isolated with high purity in about 90% yield. As shown in table A, the yield of (5a) is strongly dependent on the amount of methanol present in the reaction mixture. Diazotization/bromination of (4) when carried out in large excess of methanol (e.g. 82 Mol equiv.) has resulted in a mixture of 6,6-dibromopenicillanic acid S,S-dioxide (5a), 6α-bromopenicillanic acid S,S-dioxide (5b) and 6-bromo, 6α-methoxypenicillanic acid S,S-dioxide (5e)[5] in 13%, 26% and 41% yields respectively[6]. Replacement of methanol by other alcohols gives the dibromo-β-lactam (5a) (table B) in lower yield. We have made no attempt to elucidate the specific role of methanol in this reaction.

Table A. Effect of methanol on the yield of 6,6-dibromopenicillanic acid S,S-dioxide (5a).

CH_3OH (Mol equiv.)	Product (5a) Purity (%)[7]	Yield (%)[7]
0.00	98.8	53.1
0.11	97.2	57.2
0.44	94.9	62.3
1.10	99.4	80.1
2.19	99.1	82.2
3.29	98.5	88.9
4.39	99.1	89.9
6.58	92.6	86.7
88.22	13.1	8.7

Table B. Effect of other alcohols on diazotization/bromination of 6-aminopenicillanic acid S,S-dioxide (4).

Alcohol (4.389 Mol equiv.)	Product (5a) Purity (%)[7]	Yield (%)[7]
Ethanol	95.4	76.0
n-Butanol	93.0	74.0
Isopropanol	91.5	70.9
Isobutanol	92.5	68.5
1.2-Propanediol	91.5	74.8
Cyclohexanol	92.0	54.2

6,6-Dibromopenicillanic acid S,S-dioxide (5a), thus obtained, has been smoothly converted into penicillanic acid S,S-dioxide (1) by a new debromination method in which magnesium under acidic conditions has been employed as the reducing agent. In a typical procedure magnesium powder (3.8 g) is added portionwise to a cooled stirred solution of 6,6-dibromopenicillanic acid S,S-dioxide (5a) (6.0 g; purity= 97.4%; 14.9 mmol) in ethyl acetate (150 ml) and water (35 ml) while maintaining the pH at about 3.5 with 4 N hydrochloric acid. By carrying out this procedure, the reduction of (5a) into sulbactam (1) was effected in about 90% yield. The purity of sulbactam was more than 95%.

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References and notes.

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2. R.A. Volkmann, R.D. Carroll, R.B. Drolet, M.L. Elliott and B.S. Moore, J. Org. Chem., 47, 3344 (1982).

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4. J.P. Clayton, J. Chem. Soc., C 2123 (1969).

5. C-6α stereochemistry of $-OCH_3$ in (5e) has been assigned on the basis of two-dimensional NOE studies of the corresponding methyl ester (5f). Reduction of (5f) gave only 6α-methoxy β-lactam (5g).

6. 6,6-Dibromopenicillanic acid S,S-dioxide (5a) fails to react with methanol in the presence of hydrobromic acid in dichloromethane to produce (5b) and/or (5e).

7. Satisfactory spectroscopic data and mass spectrometric or elemental analysis have been obtained for new compounds. Purities of the β-lactam products have been determined through NMR spectroscopy by using an internal standard. Yields are reported for products directly isolated from the reaction mixture without purification and after determination of their purities.

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