propylpropane →[27] allylcyclopropane; the NMR was identical with that reported.[28] The deuterated 1,5-hexadienes were made according to Sunko et al.;[5] the reduction step of the bis(dimethylamide) was done in THF, thus reducing the reaction time to only 2 h.

Acknowledgment. This work was supported by the Danish Natural Science Research Council. We thank Professor N. M. M. Nibbering and his staff (University of Amsterdam) for assistance with the FI measurements and Dr. J. K. Terlouw (University of Utrecht) for access to and help with the ZAB measurements.

Registry No. 1, 592-42-7; $1^{+\cdot}$, 74056-39-6.

(27) P. Veravagu, R. T. Arnold, and E. W. Eigenmann, *J. Am. Chem. Soc.*, **86**, 3072 (1964).
(28) R. Srinivasan, *J. Am. Chem. Soc.*, **83**, 4923 (1961).

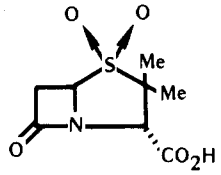
Efficient Preparation of 6,6-Dihalopenicillanic Acids. Synthesis of Penicillanic Acid *S,S*-Dioxide (Sulbactam)

R. A. Volkmann,* R. D Carroll, R. B. Drolet, M. L. Elliott, and B. S. Moore

Central Research, Pfizer Inc., Groton, Connecticut 06340

Received March 15, 1982

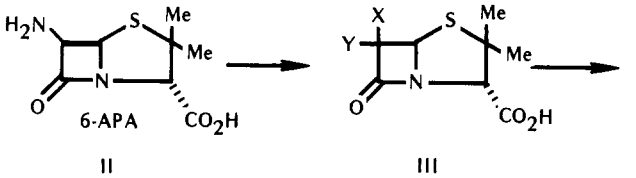
The discovery of novel β-lactam antibiotics[1] in recent years is largely responsible for the continued synthetic interest in the chemical manipulations of readily available β-lactam structures. The penicillin nucleus has, in fact, been utilized in the construction of nonclassical β-lactams such as the Woodward penems,[2] oxacephems,[3] and carbapenems.[4] In this paper we report a similar strategy in the synthesis of the novel β-lactamase inhibitor sulbactam I (CP-45,899).[5]



I

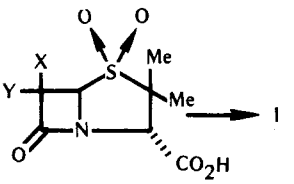
Key to an efficient synthesis of sulbactam is the development of technology for eliminating the 6-β-amido (amino) side chain of the penicillin framework. A solution to this problem was suggested by the work of Clayton,[6] who studied the diazotization/halogenation of 6-aminopenicillanic acid (II) in aqueous media. Accordingly, Clayton was able to generate 6,6-dibromopenicillanic acid (IIIa), a most useful β-lactam intermediate,[7] in approximately 34% yield and was able to convert this product via a reduction to penicillanic acid (IIIb). While this diazotization/halogenation procedure conceptually provided a solution to our problem, the low yield for this transformation was unacceptable for our purposes and similarly has plagued those who have used IIIa in β-lactam syntheses.

This diazotization reaction, in our hands, generated varying amounts of α-bromopenicillanic acid (IIIc) in addition to the desired 6,6-dibromopenicillanic acid (IIIa).[8] The inefficiency of this transformation, we thought, could be attributed to the presence of hydrogen bromide in the reaction media, which was intercepting the diazo intermediate to form IIIc, and also to the prolonged exposure of the desired dihalogenated product IIIa to strongly acidic conditions. We therefore reasoned that a high-yield conversion of 6-APA (II) to 6,6-dibromopenicillanic acid (IIIa)



6-APA II III

a) X, Y = Br
b) X, Y = H
c) X = H, Y = Br
d) X = Cl, Y = I
e) X = Br, Y = I



IV

might best be achieved if the diazo intermediate, once formed, were more effectively exposed to bromine. To this end, a two-phase diazotization/bromination reaction was designed to exploit the solubility of bromine and the 6-diazopenicillanic acid intermediate in organic solvents and the solubility of hydrogen bromide in water. Following this rationale, we added 6-APA (II) as a solid charge to a cooled methylene chloride/sulfuric acid mixture containing sodium nitrite and bromine, and it was converted exclusively to the desired 6,6-dibromopenicillanic acid (IIIa, ~80% yield). Other halogen atoms[9] were similarly introduced on the penicillin framework. For example, ICl and IBr addition generated IIId (53% yield) and IIIe (72% yield), respectively.

6,6-Dibromopenicillanic acid (IIIa), once formed, need not be isolated and could be converted in high yield (~90%) to the corresponding sulfone IVa by a potassium permanganate oxidation.[10] Finally, 6,6-dibromo-

(1) A. G. Brown, *J. Antimicrob. Chemother.*, **7**, 15 (1981).
(2) (a) I. Ernest, J. Gosteli, C. W. Greengrass, W. Holick, D. E. Jackman, H. R. Pfaendler, and R. B. Woodward, *J. Am. Chem. Soc.*, **100**, 8214 (1978). (b) I. Ernest, J. Gosteli, and R. B. Woodward, *ibid.*, **101** 6301 (1979). (c) T. Hayashi, A. Yoshida, N. Takeda, S. Oida, S. Sugawara, and E. Ohki, *Chem. Pharm. Bull.*, **29**, 3158 (1981).
(3) (a) S. Uyeo, I. Kikkawa, Y. Hamashima, H. Ona, Y. Nishitani, K. Okada, T. Kubota, K. Ishikura, Y. Ide, K. Nakano, and W. Nagata, *J. Am. Chem. Soc.*, **101** 4403 (1979). (b) M. Yoshioka, T. Tsuji, S. Uyeo, S. Yamamoto, T. Aoki, Y. Nishitani, S. Mori, H. Satoh, Y. Hamada, H. Ishitobi, and W. Nagata, *Tetrahedron Lett.*, **351** (1980).
(4) (a) H. Onoue, M. Narisada, S. Uyeo, H. Matsumura, K. Okada, T. Yano, and W. Nagata, *Tetrahedron Lett.*, 3867 (1979). (b) S. Karady, J. S. Amato, R. A. Reamer, and L. M. Weinstock, *J. Am. Chem. Soc.*, **103**, 6765 (1981).
(5) (a) A. R. English, J. A. Retsema, A. E. Girard, J. E. Lynch, and W. E. Barth, *Antimicrob. Agents Chemother.*, **14**, 414 (1978). (b) D. G. Brenner and J. R. Knowles, *Biochemistry*, **20**, 3680 (1981).
(6) J. P. Clayton, *J. Chem. Soc. C* 2123 (1969).
(7) (a) F. DiNinno, T. R. Beattie, and B. G. Christensen, *J. Org. Chem.*, **42**, 2960 (1977). (b) J. A. Aimetti and M. S. Kellogg, *Tetrahedron Lett.*, 3805 (1979). (c) J. A. Aimetti, E. S. Hamanaka, D. A. Johnson, and M. S. Kellogg, *ibid.*, 4631 (1979). (d) M. J. Loosemore, R. F. Pratt, *J. Org. Chem.*, **43**, 3611 (1978). (e) V. M. Girijavallabhan, A. K. Ganguly, S. M. McCombie, P. Pinto, and R. Rizvi, *Tetrahedron, Lett.*, 3485 (1981). (f) A. Yoshida, T. Hayashi, N. Takeda, S. Oida, and E. Ohki, *Chem. Pharm. Bull.*, **29**, 2899 (1981).
(8) Clayton[6] also reported the concomitant formation of the α and β sulfoxides of IIIa when the brominations were conducted without external cooling.
(9) This technology did not appear useful for the preparation of 6,6-diiodopenicillanic acid, which was obtained in low yield (~15%), and of 6,6-dichloropenicillanic acid.
(10) D. A. Johnson, C. A. Panetta, and D. E. Copper, *J. Org. Chem.*, 28, 1927 (1963).

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penicillanic acid S,S-dioxide (IVa) could be smoothly converted to sulbactam I (80–90% yield) by a catalytic hydrogenation (5% Pd/C). A two-phase (ethyl acetate/aqueous sodium bicarbonate) system was employed to minimize the exposure of product to hydrogen bromide. With this procedure sulbactam I is produced in ca.. 54–65% overall yield from 6-APA (II).

Experimental Section

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were recorded by using Perkin-Elmer Model 21 and Model 727B spectrometers. NMR spectra were obtained with a Varian XL-100 spectrometer with Me_4Si as an internal standard. Mass spectra were taken with an AEI MS-30 mass spectrometer. Microanalyses were performed by the Pfizer Analytical Department.

6,6-Dibromopenicillanic Acid (IIIa). To a 2-L three-necked, round-bottomed flask equipped with a paddle stirrer and thermometer and containing methylene chloride (500 mL) cooled to about 5 °C were added bromine (119.9 g, 38.5 mL, 0.75 mol), 2.5 N sulfuric acid (200 mL), and sodium nitrite (34.5 g, 0.50 mol). Some foaming was observed upon addition of the sodium nitrite, but there was no exotherm. 6-APA (54.0 g, 0.25 mol) was added portionwise over a period of 30 min. The pot temperature was maintained at 4–10 °C. The resultant dark red solution was stirred at 5 °C for 30 min. A solution of 1 M sodium bisulfite (410 mL) was added dropwise at 5–15 °C over a period of 20 min until the bromine color was discharged, forming a light yellow solution. The organic layer was separated and the aqueous layer extracted with methylene chloride (2 × 150 mL). The combined organic extract was washed with brine (2 × 200 mL) and used in the second step of the process.

The organic extract can be concentrated to afford, in 80% yield, 6,6-dibromopenicillanic acid (IIIa): mp 144–146 °C; IR (KBr) ν_{max} 2600–3700, 1799, 1775 cm^{-1}; NMR ($CDCl_3/Me_2SO$) δ 1.60 (3 H, s, CH_3), 1.70 (3 H, s, CH_3), 4.57 (1 H, s, 3-H), 5.92 (1 H, s, 5-H). IIIa is more stable as its sodium salt: mp 205 °C; $[\alpha]^{20}_D$ +210° (c 0.01, pH 5 buffer); IR (KBr) ν_{max} 2600–3700, 1779, 1712 cm^{-1}; NMR ($CDCl_3/D_2O$) δ 1.47 (3 H, s, CH_3), 1.58 (3 H, s, CH_3), 4.35 (1 H, s, 3-H), 5.83 (1 H, s, 5-H). Anal. Calcd for $C_8H_8NO_3Br_2Na$: C, 25.22; H, 2.12; N, 3.68; S, 8.42. Found: C, 24.97; H, 2.48; N, 3.65; S, 8.24.

In a similar fashion, IIId [mp 148–152 °C; 58% yield; IR (KBr) ν_{max} 2500–3570, 1779, 1712 cm^{-1}; NMR ($CDCl_3/Me_2SO$) δ 1.50 (3 H, s, CH_3), 1.67 (3 H, s, CH_3), 4.50 (1 H, s, 3-H), 5.43 (1 H, s, 5-H)] and IIIe [mp 145–147 °C; 72% yield; IR (KBr) ν_{max} 2500–3571, 1786, 1718 cm^{-1}; NMR ($CDCl_3/Me_2SO$) 1.53 (3 H, s, CH_3), 1.67 (3 H, s, CH_3), 4.46 (1 H, s, 3-H), 5.57 (1 H, s, 5-H)] were prepared.

6,6-Dibromopenicillanic Acid S,S-Dioxide (IVa). To a 4-L beaker equipped with a mechanical stirrer and containing the methylene chloride solution from step I (~800 mL) was added water (300 mL) followed by the dropwise addition over a period of 30 min of 3 N sodium hydroxide (105 mL) until the pH stabilized at 7.0. The aqueous layer was separated, and the organic layer was again extracted with water (1 × 200 mL). To the combined aqueous layers which were placed in a 2-L, three-necked, round-bottomed flask equipped with a mechanical stirrer and cooled to −5 °C was added a premixed solution containing potassium permanganate (59.25 g, 0.38 mol), 85% phosphoric acid (18 mL, 0.31 mol), and water (600 mL) over a period of 50 min until the oxidation was complete as indicated by the persistence of the dark purple permanganate color (550 mL). The pH of this solution stabilized at 6.2. Following the addition, ethyl acetate (500 mL) was added, and the pH of the purple solution was lowered to 1.23 with 6 N hydrochloric acid (150 mL). To this biphasic solution was added dropwise a 1 M sodium bisulfite solution (250 mL) over a period of 10–15 min as the temperature was kept below 10 °C, and the pH was maintained at 1.25–1.35 by using 6 N hydrochloric acid (60 mL). The aqueous layer was then saturated with sodium chloride, and the two phases were separated. The aqueous solution was reextracted with additional ethyl acetate (2 × 150 mL), and the combined organic extracts were washed with brine (2 × 200 mL), dried over magnesium sulfate, filtered, and carried into the hydrogenation step. The desired product, 6,6-dibromopenicillanic acid S,S-dioxide (IVa, mp 201 °C dec) can be isolated at this stage (~72% yield from 6-APA): $[\alpha]^{20}_D$ +204.5° (c 0.01, pH 5 buffer); IR (KBr) ν_{max} 2700–3250, 1812, 1743, 1462, 1337 cm^{-1}; NMR ($CDCl_3/Me_2SO$), 1.49 (3 H, s, CH_3), 1.63 (3 H, s, CH_3), 4.49 (1 H, s, 3-H), 5.41 (1 H, s, 5-H). Anal. Calcd for $C_8H_9NO_5Br_2S$: C, 24.57; H, 2.32; N, 3.58; Br, 40.87. Found: C, 24.70; H, 2.39; N, 3.61; Br, 40.66.

Sulbactam (I). In a 2-L Parr bottle were combined the ethyl acetate extract from step 2 containing 6,6-dibromopenicillanic acid S,S-dioxide (IVa, 705 mL), a saturated sodium bicarbonate solution (705 mL), and 5% Pd/C catalyst (50% water wet, 8.88 g). Some foaming occurred. The mixture was placed on a Parr shaker, purged with nitrogen, and hydrogenated under ~50 psi pressure for 1.25 h. The mixture was then purged with nitrogen and filtered through a Celite pad. After the filtrate was cooled to ~5 °C, the pH was adjusted to 1.2 with 6 N hydrochloric acid (77 mL). The aqueous layer was saturated with brine, the layers were separated, and the resultant aqueous layer was reextracted with ethyl acetate (3 × 200 mL). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated in vacuo to afford 33.5 g (57.5%) of crude product as a light yellow solid. Sulbactam was obtained in pure form by dissolving the crude product in ethyl acetate (600 mL), heating (~35 °) the solution with Darco, filtering, and concentrating this solution in vacuo to yield a white solid which was slurried in hexane (200 mL) and filtered to give 31.0 g (54%) of sulbactam: mp 170 °C dec; $[\alpha]^{20}_D$ +251° (c = 0.01, pH 5.0 buffer); IR (KBr) ν_{max} 2500–3636, 1786, 1754 cm^{-1}; NMR (Me_2SO) 1.37 (3 H, s, CH_3), 1.48 (3 H, s, CH_3), 3.23 (1 H, dd, J = 1.7, 16.4 Hz, 6β-H), 3.64 (1 H, dd, J = 4.4, 16.4 Hz, 6α-H), 4.26 (1 H, s, 3-H), 5.13 (1 H, dd, J = 1.7, 4.4 Hz, 5-H). Anal. Calcd for $C_8H_{11}NO_5S$: C, 41.20; H, 4.76; N, 6.00; S, 13.75. Found: C, 41.43; H, 4.72; N, 6.05; S, 13.76.

Acknowledgment. We are grateful to Dr. I. M. Goldman for helpful discussions.

Registry No. I, 68373-14-8; II, 551-16-6; IIIa, 24158-88-1; IIId, 76517-06-1; IIIe, 76517-24-3; IVa, 76646-91-8; IIIa Na, 76454-48-3.

Nitration of 2-Alkoxytoluenes: Formation of Biphenyl Derivatives

M. Mehdi Nafissi-V,* David P. Koharski, and Mohindar S. Puar

Research Division, Schering Corporation, Bloomfield, New Jersey 07003

Andrew T. McPhail*

Paul M. Gross Chemical Laboratory, Duke University, Durham, North Carolina 27706

Received January 21, 1981

In the nitration of aromatic compounds, a number of side reactions have been uncovered, thereby leading to an increase in the utility of this reaction for functionalization.[1] We here report on a coupling reaction which occurs when 2-alkoxytoluenes are nitrated. Although nitration of 2-alkoxytoluenes has been reported, the formation of biphenyl derivatives has not been claimed previously. Thus, Staedel[2] reported the preparation of mononitro- and dinitro-2-ethoxytoluenes by nitration of 2-ethoxytoluene in concentrated nitric acid. Nitration of 2-methylanisole in aqueous nitric–sulfuric acid afforded a mixture of 4- and 6-nitro-2-methylanisole as well as the corresponding phenolic byproducts.[3]

(1) H. Suzuki, *Synthesis*, 217 (1977); M. Shinoda and H. Suzuki, *J. Chem. Soc., Chem. Commun.*, 479 (1977).
(2) W. Staedel, *Justus Liebigs Ann. Chem.*, **217**, 153 (1883).

0022-3263/82/1947-3345$01.25/0