CROATICA CHEMICA ACTA CCACAA **69** (2) 661–667 (1996)

ISSN-0011-1643
CCA-2332

Original Scientific Paper

Synthetic Approach to New Monocyclic β-Lactam Synthons*

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Received January 19, 1996; accepted March 5, 1996

New *cis* and *trans* β-lactam synthons **4** and **9** have been prepared as suitable precursors for novel monocyclic β-lactam species. A new simple method have been found for the generation of **4** and **9** by hydrolysis of the 2-sulphonic acid methyl ester group and cleavage of the 3-phenoxyacetamido side chain of **2** and **7**.

INTRODUCTION

To avoid β-lactam ring rupture and provide the β-lactam intermediates, 6-aminopenicillanic acid (6-APA), 3-aminonocardicinic acid (3-ANA), 3-aminomonobactamic acid (3-AMA), very specific chemical methods were developed for the cleavage of the amide bond in the side chain of penicillin, nocardicin and sulphazecin. A very efficient process, which utilised phosporus pentachloride, was developed for the cleavage of the amide side chain in naturally occurring penicillins to produce 6-APA.[1–3] Other chemical methods have also been found to cleave the amide side chain selectively from naturally occurring nocardicin and sulphazecin giving rise to 3-ANA and 3-AMA.[4,5]

We wish to report here a novel simple procedure useful for the cleavage of the phenoxyacetamido side chain of a 4-oxoazetidine-2-sulphonate, during which the monocyclic *cis* and *trans* β-lactam synthons 3-amino-4-oxoazetidine-2-sulphonic acid (3-AAA) were generated (Figure 1).

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* The authors dedicate this paper to Professor Vladimir Prelog for his 90th birthday.
† Deceased on March 12, 1995.

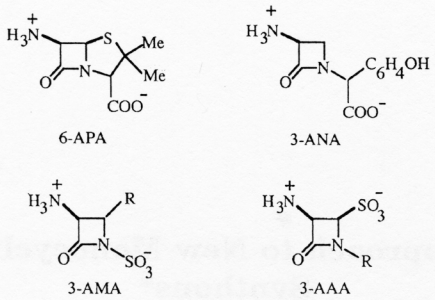


Figure 1.

RESULTS AND DISCUSSION

Recently, we have described the 4-oxoazetidine-2-sulphonic acid derivatives as novel monocyclic β-lactam structures.[6] Among them, 4-oxoazetidine-2-methylsulphonates were prepared and hydrolyzed to the corresponding 4-oxoazetidine-2-sulphonic acids under mild conditions.

Now, we have found that some of these compounds are suitable intermediates for the generation of 3-AAA analogs. Thus, the *(2R,3R)*-3-phenoxyacetamido-4-oxoazetidine-2-sulphonic acid methyl ester **2**, upon reaction with methanol, gave *(2R,3R)*-3-amino-4-oxoazetidine-2-sulphonic acid **4** and methyl phenoxyacetate **5**. Using the mixture acetone-ether a single crystal was prepared and the X-ray structure analysis confirmed the zwitter ionic structure **4** monohydrate (Figure 2).[7]

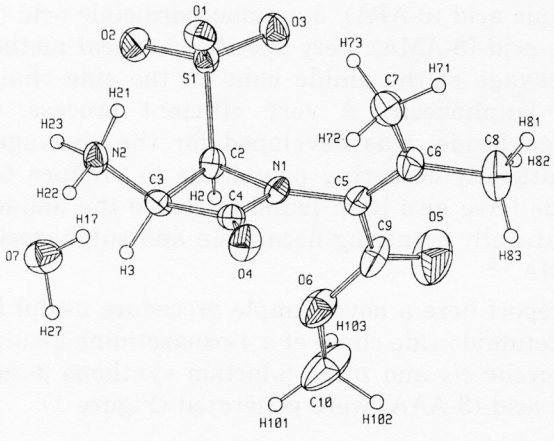
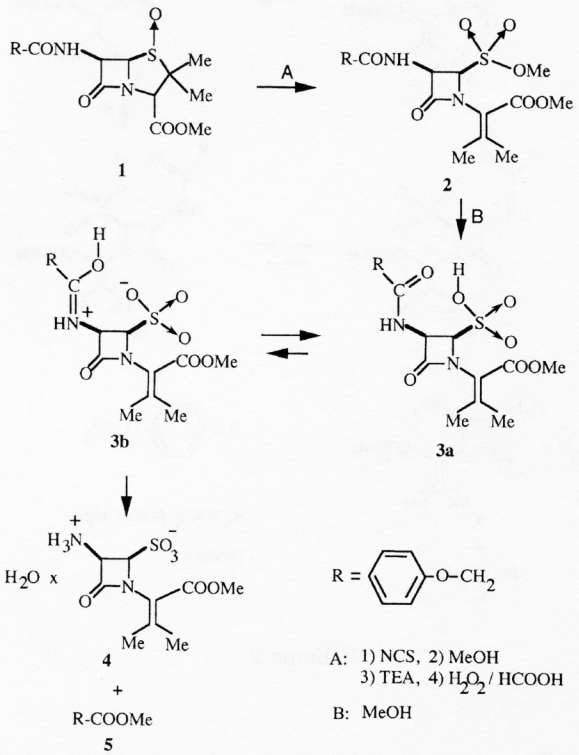


Figure 2. The ORTEP drawing of **4** as a zwitterion and crystalline water molecule (O7), with the thermal ellipsoids scaled at 30% probability level.

The mother liquor residue of compound **4** was fractionated by column chromatography on silica-gel and *(2R,3R)*-3-phenoxyacetamido-4-oxoazetidine-2-sulphonic acid **3a** was isolated. Generally, it was evident that this proccess includes the hydrolysis of the 2-sulphonic acid methyl ester group and the 3-phenoxyacetamido group of **2**. The formation of **3a** upon hydrolysis of **2** was evident to occur and the possible zwitter ionic imino tautomer **3b** seems to have been generated and alcoholyzed to give products **4** and **5**.

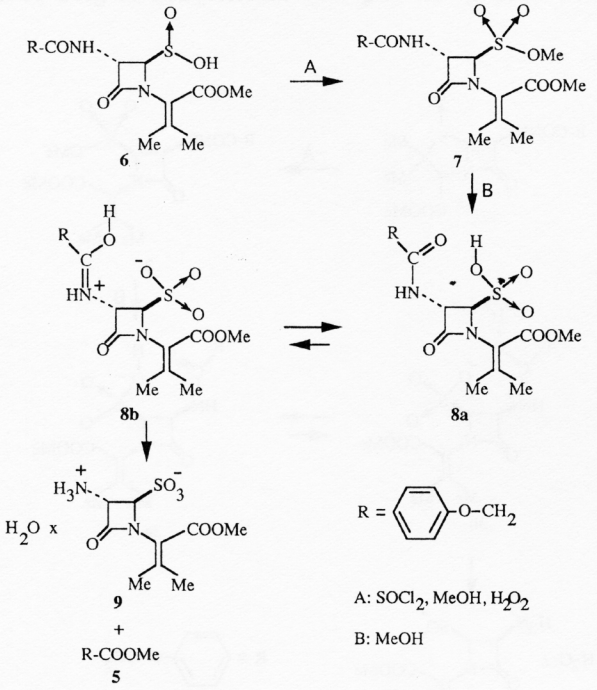


Scheme 1.

This has been supported in part by examination of the reactivity of the *(2R,3R)*-3-phenoxyacetamido-4-oxoazetidine-2-sulphonic acid **3a** by treating it under the same reaction conditions. Actually, after treating the sulphonic acid **3a** with methanol, we isolated compound **4** in 52% yield.

The reactivity of the epimeric *(2R,3S)*-3-phenoxyacetamido-4-oxoazetidine-2-sulphonic acid methyl ester **7** was also examined. Epimer **7** was prepared starting from the *(2R,3S)*-3-phenoxyacetamido-1-(1'-methyloxycar-

bonyl-2'-methyl-prop-1'-enyl)-4-oxoazetidine-2-sulphinic acid **6** using thionylchloride and methanol.[8,9] Compound **7** was transformed into the *(2R,3S)*-3-amino-4-oxoazetidine-2-sulphonic acid **9** in 51% yield by treatment with methanol (Scheme 2).



Scheme 2.

The mother liquor residue was chromatographed on silica-gel and *(2R,3S)*-3-phenoxyacetamido-4-oxoazetidine-2-sulphonic acid **8a** was separated in 35% yield. This suggests the generation of the *trans* imino tautomer intermediate **8b** and it's alcoholysis into the *trans* synthon **9**.

The generation of the *cis* imino tautomer intermediate **3b** seems to be faster than of the *trans* imino tautomer intermediate **8b.** The better yield of the *cis* product **4** in correlation with **9** is indicative and supports easier transformation of **3b** into **4**, then **8b** into **9**.

This simple method, with a minor rupture of the β-lactam ring in **2** and **7**, presents a new useful procedures for the generation of new *cis* and *trans* analogues of 3-AAA.

EXPERIMENTAL

Melting points (uncorrected): Fisher-Johns apparatus. IR spectra: Perkin Elmer 257G spectrometer. ^{1}H-NMR spectra: Varian XL-GEM 300 (300 MHz); chemical shifts δ were recorded in ppm downfield from $SiMe_4$. MS: Shimadzu GCMS-QP 1000 A instrument operating at 70 eV. T.l.c.: Merck Kieselgel HF_{254} plates; compounds were visualized under UV light or I_2 vapour adsorption. Column chromatography was performed on Merck Kieselgel 60 (70–230 mesh ASTM).

*(2R,3R)-3-Amino-1-(1'-methyloxycarbonyl-2'-methyl-prop-1'-enyl)-4-oxoazetidine-2-sulphonic Acid Monohydrate (**4**)*

a) *(2R,3R)*-3-Phenoxyacetamido-1-(1'-methyloxycarbonyl-2'-methyl-prop-1'-enyl)-4-oxoazetidine-2-sulphonic acid methyl ester (**2**)[6] (3.28 g, 7.7 mmol) was dissolved in 5 ml of methanol and stirred for 24 hours at room temperature. Methanol was evaporated under reduced pressure and a crude residue obtained. After adding 5 ml of acetone, aminosulphonic acid **4** crystallized by stirring to yield 1.80 g (78.9%); m.p. 225–236 °C (decomp.); R_f = 0.26 in CH_2Cl_2-MeOH (4 : 1); $[\alpha]_D$ = +2,1° (*c* = 1, H_2O); IR(KBr) ν_{max}/cm^{-1}: 3600–3460b, 1785vs, 1735s, 1670m, 1635m, 1535m, 1445m, 1395s, 1275s, 1225vs, 1195vs, 1035vs; ^{1}H-NMR (DMSO-d_6) δ/ppm: 2.05 and 2.20 [2s, 6H, $C(CH_3)_2$], 3.30 (bs, 2H, HOH), 3.72 (s, 3H, OCH_3), 4.70 and 4.80 (2d, *J* = 5.5 Hz, 2H, 2-H and 3-H), 8.65 (bs, 3H, $^+NH_3$); MS (70 eV), *m/z* (%): 278 (3) (M^+-H_2O), 182 (23.4), 154 (30.6), 129 (100);

Anal. Calcd. for $C_9H_{14}N_2O_6S \times H_2O$ (M_r = 296.28): C 36.60, H 5.12, N 9.49, S 10.86%; found C 36.75, H 5.15, N 9.65, S 10.75%.

b) *(2R,3R)*-3-Phenoxyacetamido-1-(1'-methyloxycarbonyl-2'-methyl-prop-1'-enyl)-4-oxoazetidine-2-sulphonic acid (**3a**) (0.38 g, 0.9 mmol) was dissolved in 10 ml of methanol and stirred for 14 hours at room temperature. Methanol was evaporated under reduced pressure to the crude residue and 10 ml of acetone was added and stirred for 30 minutes to give 0.08 g (32.0%) of white crystals; an additional 0.05 g (20.0%) of the same material was obtained from the mother liquor upon separation by column chromatography. The product was identical (m.p., R_f, IR, ^{1}H-NMR) to that described under procedure a).

*(2R,3R)-3-Phenoxyacetamido-1-(1'-methyloxycarbonyl-2'-methyl-prop-1'-enyl)-4-oxo-azetidine-2-sulphonic Acid (**3a**)*

a) After isolation of the aminosulphonic acid **4**, as was noted in experiment 4a), the mother liquor residue was chromatographed on silica gel using methylene chloride/methanol (4 : 1) as eluant and 0.47 g (19.6%) of sulphonic acid **3a** with R_f = 0.58 (CH_2Cl_2/MeOH = 4 : 1) was isolated; the obtained product was identical (R_f, IR, ^{1}H-NMR) to that described in the literature.[6]

b) The aminosulphonic acid **4** (0.20 g, 0.7 mmol) was suspended in 4 ml of methylene chloride and *N,O*-bis-trimethylsilyl urea (0.12 g, 0.7 mmol) was added at –10 °C. The reaction mixture was stirred at –10 °C for 1 hour, and 2 hours at 40 °C. To the cooled (–10 °C) suspension, (0.11 g, 0.7 mmol) of phenoxyacetic acid chloride in 2 ml of methylene chloride was added and the reaction was mixture stirred at –10 °C for 1 hour, and 8 hours at room temperature. Thereafter, 5 ml of water was added at 0 °C, stirred for 30 minutes, the oganic layer was separated and evaporated

to give 0.39 g of a foamy product. After purification by column chromatography in CH_2Cl_2-MeOH (4 : 1), the sulphonic acid **3a**, 0.1 g (33.7%), was separated; the product was identical (R_f, IR, ^{1}H-NMR) to that described in the literature.[6]

*(2R,3S)-3-Phenoxyacetamido-1-(1'-methyloxycarbonyl-2'-methyl-prop-1'-enyl)-4-oxoazetidine-2-sulphonic Acid Methyl Ester (**7**)*

(2R,3S)-3-Phenoxyacetamido-1-(1'-methyloxycarbonyl-2'-methyl-prop-1'-enyl)-4-oxoazetidine-2-sulphinic acid **6** [8] (5.00 g, 12.8 mmol) was dissolved in $SOCl_2$ (20 ml) and the solution was stirred for 2 hours at 25 °C. The excess of $SOCl_2$ was evaporated under reduced pressure. Methanol (25 ml) was added under cooling to keep the temperature at 25 °C, stirred for 1 hour and evaporated. The residue was dissolved in methylene chloride (50 ml) and formic acid (6 ml); 30% aqueous solution of H_2O_2 (15 ml) was added and the reaction mixture was stirred for 10 hours at 20 °C, whereafter water (100 ml) and methylene chloride (50 ml) were added. The organic layer was separated, washed with saturated aqueous sodium hydrogen carbonate, dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by silica-gel chromatography in methylene chloride-ethylacetate (5 : 3) gave 2.37 g (43%) **7** as a foam; R_f = 0.80 in CH_2Cl_2-EtOAc (5 : 3); $[a]_D$ = +29° (*c* = 1, CH_2Cl_2); IR(film) ν_{max}/cm^{-1}: 3350bs, 1785vs, 1725sh, 1685s, 1600m, 1520m, 1490m, 1435m, 1360vs, 1295m, 1225bs, 1175m, 1060m, 970vs, 790m, 755m, 690m; ^{1}H-NMR ($CDCl_3$) δ/ppm: 2.06 and 2.27 [2s, 6H, $C(CH_3)_2$], 3.81 and 3.94 (2s, 6H, $2OCH_3$), 4.55 (s, 2H, OCH_2), 5.27 (dd, 1H, *J* = 2.5 and 8.0 Hz, 3-H), 5.50 (d, 1H, *J* = 2.5 Hz, 2-H), 6.90–7.36 (m, 5H, OC_6H_5), 7.51 (d, 1H, *J* = 8.0 Hz, CONH);

Anal. Calcd. for $C_{18}H_{22}N_2O_8S$ (M_r = 426.44): C 50.69, H 5.20, N 6.57%; found C 50.65, H 5.38, N 6.48%.

*(2R,3S)-3-Amino-1-(1'-methyloxycarbonyl-2'-methyl-prop-1'-enyl)-4-oxoazetidine-2-sulfonic Acid Monohydrate (**9**)*

(2*R*,3*S*)-3-Phenoxyacetamido-1-(1'-methyloxycarbonyl-2-methyl-prop-1'-enyl)-4-oxoazetidine-2-sulfonic acid methyl ester (**7**) (300 mg; 0.7 mmol) was stirred at room temperature in methanol for 10 hours and evaporated in vacuo. The solid was dissolved in acetone (15ml) and compound **9** was crystallized by stirring to yield 106 mg (51.1%); m.p. 260–263 °C; $[a]_D$ = –64,5° (*c* = 0.9, H_2O); H_2O (GC) = 7.3%; IR (KBr) ν_{max}/cm^{-1}: 3470m, 3400–2500bs, 1795vs, 1685vs, 1622m, 1500s, 1440m, 1398m, 1370m, 1325s, 1315s, 1255m, 1240m, 1220m, 1195s, 1135m, 1042s, 970m, 785m; ^{1}H-NMR (DMSO-d_6) δ/ppm: 1.93 and 2.17 [2s, 6H, $C(CH_3)_2$], 3.42 (bs, 2H, HOH), 3.71 (s, 3H, OCH_3), 4.38 and 4.64 (2d, *J* = 2.2 Hz, 2-H and 3-H), 9.04 (bs, 3H, $^+NH_3$).

*(2R,3S)-3-Phenoxyacetamido-1-(1'-methyloxycarbonyl-2'-methyl-prop-1'-enyl)-4-oxoazetidine-2-sulfonic Acid (**8a**)*

a) (2*R*,3*S*)-3-Phenoxyacetamido-1-(1'-methyloxycarbonyl-2-methyl-prop-1'-enyl)-4-oxoazetidine-2-sulfonic acid methyl ester (**7**) (500 mg, 1.17mmol) was dissolved in a mixture of acetone (6 ml) and water (4 ml) and stirred was 25 hours at 20 °C. The reaction mixture was evaporated in vacuo and the product was fractionated by silica-gel column chromatography using methylene chloride-methanol (4 : 1) as eluant; 420 mg (83.8%) of sulphonic acid **8a** was separated; $[\alpha]_D$ = +30,1° (*c* = 0.5, MeOH); H_2O (GC) = 6.6%; IR(KBr) ν_{max}/cm^{-1}: 3700–3120bs, 1770vs, 1670bs, 1600m, 1540m,

1490m, 1435m, 1390m, 1365m, 1305m, 1235vs, 1175sh, 1082m, 1045s, 755m, 690m; ^{1}H-NMR (DMSO-d_6) δ/ppm: 1.90 and 2.13 [2s, 6H, $C(CH_3)_2$], 3.67 (s, 3H, OCH_3), 4.55 (s, 2H, OCH_2), 4.73 (d, 1H, J = 2.6 Hz, 2-H), 4.92 (dd, 1H, J = 2.6 and 8.5 Hz, 3-H), 6.96–7.35 (m, 5H, OC_6H_5), 8.99 (d, 1H, J = 8.5 Hz, CONH).

b) The mother liquor residue, obtained after isolation of compound **9**, was fractionated by silica-gel column chromatography using methylene chloride-methanol (4 : 1) as eluant to give 115 mg (38.2%) of **8a**, identical (IR, ^{1}H-NMR) to those described above.

Acknowledgement. – The autors would like to express their gratitude to Mrs I. Horvatiček for technical assistance. We thank D. Sc. J. J. Herak, M. Sc. I. Lukić and M. Sc. M. Tomić for their valuable suggestions in preparing this manuscript. We also thank Prof. D. Sc. B. Kojić-Prodić for the preparation of the ORTEP drawing of **4**. This work was supported by the Ministry of Science and Technology of the Republic of Croatia.

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SAŽETAK

Sinteza novih monocikličkih β-laktamskih sintona

Zorica Mandić i Miće Kovačević

Novi *cis*- i *trans*-betalaktamski sintoni **4** i **9** priređeni su kao pogodni prekursori za nove monocikličke betalaktamske spojeve. Nađena je nova jednostavna metoda za generiranje spojeva **4** i **9** transformacijom metil-estera *(2R,3R)*- i *(2R,3S)*-3-fenoksiacetamido-4-oksoazetidin-2-sulfonskih kiselina **2** i **7**.