Synthesis of some 2,3-Benzo-1-oxaoctems

Anna Arnoldi, Lucio Merlini* and Leonardo Scaglioni

Istituto di Biochimica e di Chimica, Facoltà di Agraria, Università di Milano, Via Celoria, 2, I-20133 Milano, Italy

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The synthesis of some 8-hydroxy-2,3-benzo-1-oxaoctems is reported. The imide **7**, a potential β-lactamase inhibitor, was also synthesized.

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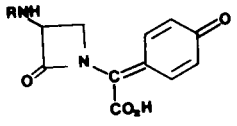
It has been suggested [1] that the active form of the antibiotic nocardicin *in vivo* may be the quinonoid compound **1**.



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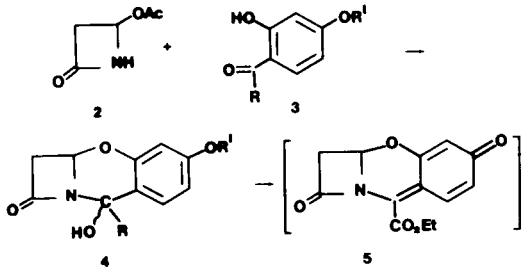
We report here on the synthesis of some new 2,3-benzo-1-oxaoctem compounds, prepared during an unsuccessful attempt to obtain cyclic oxa analogues of **1**.

The formation of a quinonemethide may be easily obtained by dehydration of a *p*-hydroxybenzyl alcohol. Therefore we set out a synthetic scheme towards **5** based on the known accessibility of 4-hydroxy-2,3-benzo-1-oxaoctems [2] from 4-acetoxyazetidin-2-one **2** and 2-hydroxybenzaldehydes or ketones **3** (Scheme 1).



2 **3** **4** **5**

a R,R' = H
b R = H, R' = CH_2Ph
c R = COOEt, R' = H
d R = COOEt, R' = CH_2Ph
e R = COOH, R' = H
f R,R' = $COOCH_2Ph$

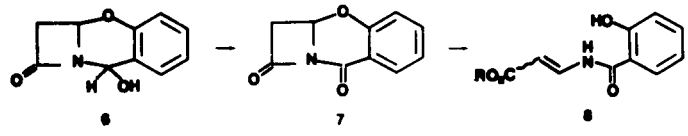
Scheme 1

In order to obtain a selective substitution onto **2**, the 2,4-dihydroxy derivatives **3** were protected in position 4. Thus 2,4-dihydroxybenzaldehyde **3a** was benzylated with benzyl bromide and sodium hydride in DMF to **3b**, then condensed in standard alkaline conditions [3] with **2** to give in moderate yield the protected β-lactam **4b**. Hydrogenolysis afforded in high yield the hydroxyderivative **4a**. This compound is formed as a sole isomer, but adding deuterium oxide to the chloroform solution the signals of H-8, H-2a and H-7 are doubled. We suppose that only one diastereoisomer is formed in the reaction [2], while equilibration is obtained with deuterium oxide through the open-chain compound.

Ethyl 2,4-dihydroxybenzoylformate **3c** was protected by treatment with benzyl bromide and potassium carbonate and condensed with **2** to give 40% of the ester **4d**. Hydrogenolysis afforded in high yield the hydroxy ester **4c**. These compounds were only models of the desired free acid **4e**. However it was apparent that due to the chemical sensitivity of this structure, a more easily deprotected ester was necessary. Alkaline hydrolysis of **3c** gave the corresponding acid **3e**, which was treated with benzyl chloroformate to give the benzyl ester **3f**, on its turn smoothly condensed with **2** to give **4f**. Good yields were obtained in this case only using stoichiometric amounts of calcium carbonate as a base instead of sodium hydroxide, to neutralize acetic acid. Unfortunately, repeated attempts to obtain the free acid **4e** by hydrogenolysis with palladium on charcoal as a catalyst, afforded a white solid which on filtration turned instantaneously into a red insoluble resin. Basic hydrolysis (potassium carbonate, THF, water) [4] gave only the ester **3f**. The instability of many β-lactam antibiotic carboxylic acids is well known.

Compounds **4a**, **4b**, **4c**, **4d** and **4f** were neither significantly active as antibiotics, when tested on a standard series of gram positive and gram negative bacteria, nor as β-lactamase inhibitors.

Another compound of this series, with a potentially highly reactive β-lactam ring, is the 4-oxo derivative **7**, where the electron withdrawing effect of the 4-oxo group should increase the carbonyl character of the β-lactam amide group (Scheme 2).



6 **7** **8**

a E, R = H
b Z, R = H
c E, R = CH_3
d Z, R = CH_3

Scheme 2

The desired compound was obtained by pyridinium chlorochromate oxidation [5] of the known 4-hydroxyderivative **6**.

Compound **7** is stable, with ν max (CO) = 1800 and 1690 cm^{-1}. Alkaline hydrolysis of **7** with stoichiometric sodium hydroxide in aqueous methanol gave the *E*-ester **8c** in mixture with a small amount of the *Z* isomer. This reaction was conducted also in an nmr tube adding sodium deuteroxide to the solution of **7** in DMSO-d_6, and the immediate formation of the *E*-acid **8a**, together with a small amount of the *Z*-isomer, was observed. The mechanism of the ring opening, due to the attack of nucleophilic ion onto the lactam group followed by elimination of the good leaving group phenoxide, is strongly reminiscent of the similar behaviour of clavulanic acid and other β-lactamase inhibitors, where the β-aminoacrylate group can become a trap for the enzyme [6]. Therefore compound **7** was tested for β-lactamase inhibitory activity, but did not appear to be active.

EXPERIMENTAL

Melting points are uncorrected. The ^{1}H-nmr spectra were recorded in deuteriochloroform, unless otherwise stated, with TMS as internal standard at 80 MHz on a Bruker WP-80 SY spectrometer or at 90 MHz on a Varian EM-390 spectrometer. Chemical shifts are expressed in ppm (δ). Mass spectra were obtained with a Finnigan 4021 spectrometer equipped with INCOS Data System at 70 eV. Column chromatographies were performed on silica gel Merck 60 (230-400 mesh).

4-Acetoxyazetidin-2-one **2** was obtained from vinyl acetate and chlorosulphonylisocyanate [3].

4-Benzyloxy-2-hydroxybenzaldehyde **3b** was obtained in 65% yield by benzylation of 2,4-dihydroxybenzaldehyde **3a** with benzyl bromide and sodium hydride in DMF, 80-82° (lit [7] mp 74-76°).

The ethyl ester **3c** was obtained in 98% yield by condensation of resorcinol with ethyl cyanoformate in anhydrous ethyl ether, mp 65-67° (lit [8] 65-66°).

2,4-Dihydroxybenzoylformic acid **3e** was obtained from the corresponding ethyl ester **3c** (90% yield) with sodium hydroxide in ethanol-water, mp 164-166° (ethanol), (lit [8] mp 161-163°).

Compound **6** was obtained in 40% yield from 2-hydroxybenzaldehyde and 4-acetoxyazetidin-2-one **2**, mp 130-132° (lit [9] 136-137°).

5-Benzyloxy-2,2a-dihydro-1*H*,8*H*-azeto[2,1-*b*][1,3]benzooxazin-1-on-8-ol (**4b**).

A mixture of the aldehyde **3b** (0.7 g, 3 mmoles) and 4-acetoxyazetidin-2-one **2** (0.4 g, 3 mmoles) in water (3 ml) and dioxane (5 ml) at 0° was added with 1*M* sodium hydroxide (3 ml). After 4 hours, the mixture was extracted with ethyl acetate (3 × 5 ml), the organic layer was washed with water and concentrated. Compound **4b** was obtained by column chromatography, 33% yield, mp 120-122°; ^{1}H-nmr (acetone-d_6): δ 2.93 (1H, d, J = 15, H-2), 3.42 (1H, dd, J = 15 and 3, H-2), 5.17 (2H, s, OCH_2Ph), 5.42 (1H, d, J = 3, H-2a), 5.67 (1H, s, H-8), 5.57 (OH), 6.63 (1H, d, J = 2, H-4), 6.80 (1H, dd, J = 6 and 2, H-6), 7.2-7.6 (6H).

Anal. Calcd. for $C_{17}H_{15}NO_4$: C, 68.67; H, 5.08; N, 4.71. Found: C, 68.79; H, 5.12; N, 4.69.

2,2a-Dihydro-1*H*,8*H*-azeto[2,1-*b*][1,3]benzoxazin-1-one-5,8-diol (**4a**).

Compound **4b** (200 mg) was hydrogenated in ethyl acetate (5 ml) in the presence of 50 mg 5% palladium on charcoal. The mixture was filtered and concentrated to give compound **4a** as a white solid, 85 mg, 60%, mp 190-194°; ^{1}H-nmr (acetone-d_6): δ 2.8-3.5 (2H, AB of ABX, H-2), 5.37 (1H, d, J = 3, H-2a), 5.70 (1H, s, H-8), 6.43 (1H, J = 2, H-4), 6.57 (1H, dd, J = 9 and 2, H-6), 7.33 (1H, d, J = 9, H-7).

Anal. Calcd. for $C_{10}H_9NO_4$: C, 57.97; H, 4.38; N, 6.76. Found: C, 57.71; H, 4.35; N, 6.71.

After treatment with deuterium oxide of a sample of **4a** in the nmr tube, a mixture of isomers was obtained. The new isomer has; ^{1}H-nmr: δ 5.58 (1H, d, J = 3, H-2a), 5.95 (1H, s, H-8), 7.47 (1H, d, J = 9, H-7).

Ethyl (4-Benzyloxy-2-hydroxyphenyl)-2-oxoacetate (**3d**).

A mixture of the ester **3c** (2.1 g, 10 mmoles), benzyl bromide (1.2 ml, 10 mmoles) and potassium carbonate (1.4 g, 10 mmoles) in acetone (20 ml) was refluxed for 10 hours. The mixture was diluted with water and extracted with ethyl acetate (3 × 20 ml). After evaporation of the solvent the oily benzyl ether **3d** was obtained by column chromatography in 13% yield; ^{1}H-nmr: δ 1.40 (3H, t, J = 7, CH_3), 4.43 (2H, d, J = 7, OCH_2), 5.12 (2H, s, OCH_2Ph), 6.57 (2H, H-5 and H-3), 7.40 (5H, Ph), 7.67 (1H, d, J = 7, H-6), 11.77 (1H, OH); ms: m/z (%) 300 (M^+, 30), 227 (100), 181 (16), 136 (11), 108 (23), 91 (84).

Anal. Calcd. for $C_{17}H_{16}O_5$: C, 67.99; H, 5.37. Found: C, 67.95; H, 5.39.

Ethyl 8-Benzyloxy-2,2a-dihydro-1*H*,8*H*-azeto[2,1-*b*][1,3]benzoxazin-1-one-8-carboxylate (**4d**).

A mixture of ester **3d** (350 mg) in dioxane (3 ml) and 4-acetoxyazetidin-2-one (150 mg) in water (3 ml) were stirred, while a solution of 10% sodium hydroxide was added in 2 hours. The mixture was then diluted with water and extracted with ethyl acetate. The β-lactam **4d** was obtained by column chromatography in 40% yield; ^{1}H-nmr: δ 1.13 (3H, t, J = 7, CH_3), 2.9-3.4 (2H, AB of ABX, H-2), 4.2 (2H, m, OCH_2), 5.03 (2H, s, OCH_2Ph), 5.30 (1H, d, J = 3, H-2a), 6.7 (2H), 7.1-7.7 (6H).

Anal. Calcd. for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.19; N, 3.79. Found: C, 65.21; H, 5.22; N, 3.66.

Ethyl 8-Hydroxy-2,2a-dihydro-1*H*,8*H*-azeto[2,1-*b*][1,3]benzoxazin-1-one-8-carboxylate (**4c**).

The benzyl ether **4d** (170 mg, 0.46 mmole) was treated with hydrogen in 10 ml of ethyl acetate in the presence of 70 mg of 10% palladium on charcoal. The mixture was eluted through a short column of silica gel. The β-lactam **4c** was obtained in 78% yield, mp 161-164° dec; ^{1}H-nmr (acetone-d_6): δ 1.10 (3H, t, J = 7, CH_3), 2.73 (1H, OH), 3.00 (1H, d, J = 15, H-2), 3.37 (1H, dd, J = 15 and 3, H-2), 4.10 (2H, m, CO_2CH_2), 5.30 (1H, d, J = 3, H-2a), 6.38 (1H, d, J = 2, H-4), 6.57 (1H, dd, J = 6 and 2, H-6), 7.27 (1H, d, J = 6, H-7).

Anal. Calcd. for $C_{13}H_{13}NO_6$: C, 55.91; H, 4.70; N, 5.02. Found: C, 55.75; H, 4.68; N, 4.00.

Benzyl 4-Benzyloxycarbonyloxy-2-hydroxybenzoylformate (**3f**).

2,4-Dihydroxybenzoylformic acid (1 g, 5.5 mmoles) **3e** in anhydrous THF (80 ml) was added dropwise with triethylamine (1.52 ml, 11 mmoles). A large amount of precipitate was formed. A solution of benzyl chloroformate (1.44 ml, 1.1 mmoles) in THF (5 ml) was added and the mixture was stirred for 1 hour. The solvent was evaporated. The residue was diluted with water and extracted with ethyl acetate. Compound **3f** was obtained by column chromatography, 70% yield, oily; ^{1}H-nmr: δ 5.25 (2H, s, OCH_2Ph), 5.98 (2H, s, OCH_2Ph), 6.74 (1H, dd, J = 9 and 2, H-5), 6.89 (1H, d, J = 2, H-3), 7.38 (10 H), 7.65 (1H, d, J = 9, H-6).

Anal. Calcd. for $C_{23}H_{18}O_7$: C, 67.97; H, 4.46. Found: C, 67.72; H, 4.44.

Benzyl 8-Benzyloxycarbonyl-2,2a-dihydro-1*H*,8*H*-azeto[2,1-*b*][1,3]benzoxazin-1-one-8-carboxylate (**4f**).

A mixture of the ester **3f** (1.1 g, 3 mmoles) in dioxane (15 ml) and 4-acetoxyazetidin-2-one (550 mg, 4.2 mmoles) in water (5 ml) were treated under stirring with sodium carbonate (320 mg, 3 mmoles) in water (2 ml). After 1 hour, the mixture was diluted with water and extracted with water and extracted with ethyl acetate. The yellow oil thus obtained was purified by column chromatography to give the β-lactam **4c**, 800 mg, 61% yield, mp 93-95°; ^{1}H-nmr: δ 3.05 (1H, dd, J = 17 and 1, H-2), 3.35 (1H, dd, J = 17 and 3, H-2), 5.13 (2H, AB, CO_2CH_2-), 5.24 (2H, s, OCH_2Ph), 5.30 (1H, dd, J = 3 and 1, H-2a), 6.8-7.5 (13H).

Anal. Calcd. for $C_{26}H_{21}NO_8$: C, 65.68; H, 4.45; N, 2.95. Found: C, 65.77; H, 4.48, N, 2.39.

2,2a-Dihydro-1*H*,8*H*-azeto[2,1-*b*]-1,3-benzoxazine-1,8-dione (**7**).

A mixture of the alcohol **6** (400 mg, 2.09 mmole) and pyridine chlorochromate (500 mg, 2.30 mmoles) was stirred for 15 minutes in dichloromethane (10 ml). The solution became very dark. Ethyl ether (20 ml) was added and the precipitate filtered. The organic solvents were evaporated and the residue purified by column chromatography. The white solid obtained was washed with ethyl ether, 300 mg, 75% yield, mp 165-167°; ir (nujol): cm^{-1} 1800, 1690, 1610, 1330, 860, 760; ^{1}H-nmr: δ 2.8-3.8 (2H, AB of ABX, CH_2), 5.74 (1H, X of ABX, CH), 6.9-8.1 (4H).

Anal. Calcd. for $C_{10}H_7NO_3$: C, 63.49; H, 3.73; N, 7.41. Found: C, 63.33; H, 3.80; N, 7.32.

When a solution of **7** (17.5 mg) in 0.4 ml of dimethylsulfoxide-d_6 and 0.1 ml of water in an nmr tube was added with 0.1 ml of 1*M* sodium hydroxide, the solution became immediately yellow, and the nmr spectrum showed the complete disappearance of the starting material, and signals corresponding to the salt of the acid **8a**, δ 5.54 (d, J = 14, H-3), 6.2-6.7 (2H, H-3′ and H-5′), 7.0-7.4 (H-4′), 7.80 (d, J = 14, H-2), 7.70 (dd, J = 8 and 2), plus *ca* 10% of the isomer **8b**, δ 5.03 (d, J = 8).

A similar reaction was carried out in aqueous methanol, and the complete conversion into the methyl ester **8c** was apparent from the nmr spectrum of the crude products; (acetone-d_6): δ 3.69 (3H, s, OCH_3), 5.84 (d, J = 14, H-3), 6.8-7.1 (H-3′ and H-5′), 7.4-7.6 (H-4′), 7.70 (dd, H-6′), 8.20 (d, J = 14, H-2), together with some **8d**, δ 5.26 (d, J = 8, H-3).

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