SYNTHESIS OF SULFONAMIDE ANALOGS OF THE PYRROLO[1,4]BENZODIAZEPINE ANTIBIOTIC ABBEYMYCIN*

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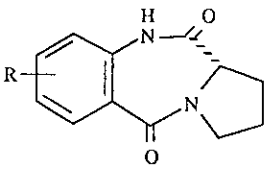
Abstract - Sulfonamide analogs of antitumor antibiotics of the pyrrolo-[1,4]benzodiazepine group were prepared from (S)-prolinol as carbinolamine ethers.

The pyrrolo[1,4]benzodiazepine group of antitumor antibiotics is of increasing interest from both the synthetic and the biological points of view.[1] Thus several methodologies have been followed[2-5] to synthesize compounds of this group, including in most cases a dilactam of type 1[2] or a N-*o*-nitrobenzoyl-2-formylpyrrolidine 2[3] as key intermediates. Reductive cyclization by catalytic hydrogenation of 2, leading to an imine 3, or its chemical equivalent (carbinolamine, carbinolamine ether) seems the most direct route but unfortunately suffers from limitations, according to Thurston and Langley.[3g] The main disadvantages of this method were the sequential reduction of the generated imine 3 to a secondary amine 4 or the incomplete reduction of the aromatic nitro group before the cyclization step.[3g] We showed that the use of Raney nickel catalysts in place of palladium catalysts provided a good improvement of this method which we successfully applied to the synthesis of the antitumor antibiotics neothramycins 5 and their related analogs.[3e,f] As an extension of our previous work in this field we investigated a synthesis of sulfonamide analogs of the antibiotic abbeymycin 6[6] and initially we chose deoxy-structure 7 as our target molecule.

*The authors wish to dedicate this work to the memory of the late Professor E. Lederer.

Thus (S)-prolinol was treated with *o*-nitrobenzenesulfonyl chloride under Schotten-Baumann conditions affording the N-*o*-nitrobenzenesulfonyl-2S-hydroxymethylpyrrolidine 8 in 93% yield. The oxidation of 8 with dimethyl sulfoxide and the complex SO_3-pyridine led to the aldehyde 9 (83%). The optical rotation of the alcohol 8 obtained by quantitative reduction of the aldehyde 9 using $NaBH_4$, indicated that some epimerization (7%) occurred at C-2 during the formation or isolation steps.



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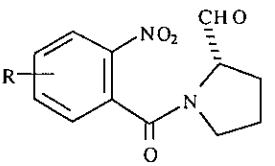

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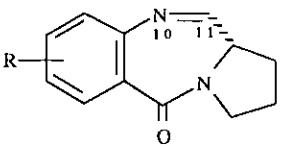

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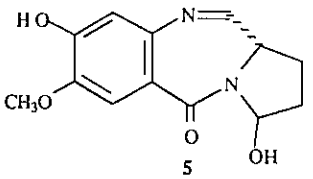

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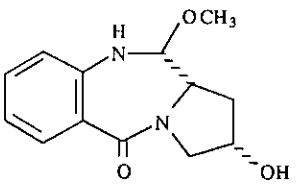

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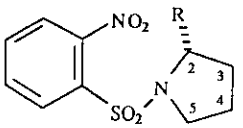
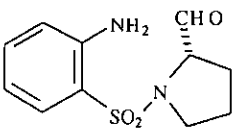


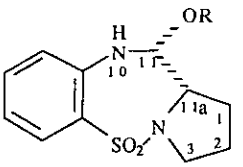
8 R = CH_2OH

9 R = CHO

10 R = CO_2CH_3



11



7 R = CH_3

12 R = CH_2CH_3

13 R = $CH(CH_3)CO_2CH_2CH_3$

Thus, optically pure 9 was prepared employing diisobutylaluminium hydride reduction of the corresponding N-*o*-nitrobenzenesulfonyl-2S-methoxycarbonylpyrrolidine 10.

Compound 9 was reduced with an excess of Raney-Ni at room temperature under the conditions which led to the imine 3 (R = H) starting from the aldehyde 2 (75% in a one step process). This reaction gave a compound (78%) that we were unable to characterize satisfactorily owing to its facile decomposition. However, spectral evidence was sufficient to identify this labile compound as species 11 : the ir (ν cm^{-1}: 1730) and ^1H nmr spectra (δ CHO : 9.67 ppm) of 11

confirmed the presence of a formyl group; its mass spectrum exhibited a peak $M^{+\cdot}$ at m/z 254 and a base peak at m/z 156 consistent with the presence of an aminobenzenesulfonyl group.

Isolation of the aminoaldehyde 11 is worthy of note as far as the related intermediate, N-o-nitrobenzoyl-2-formylpyrrolidine 2 gave rise spontaneously to the pyrrolo[1,4]benzodiazepines of type 3, under exactly the same conditions.

Compound 11 was slowly transformed at room temperature in a dichloromethane solution containing a low percentage (0.2%) of ethanol as stabilizer, into the more stable ethoxy derivative 12 ($M^{+\cdot}$ at m/z 282 in ms). ^{13}C Nmr spectrum of 12 showed a methine signal at 87.4 ppm, a chemical shift characteristic of the aminoacetal carbon C-11*, as in anthramycin[8] or tomaymycin.[9] In the ^{1}H nmr spectrum of 12, decoupling experiments allowed an interpretation of each signal as shown in Table , and the coupling constant $J_{11,11a} \leq 3$ Hz agreed with the configuration at C-11 indicated in formula 11.[10]

Table : ^{1}H Nmr of 7 and 12 (400 MHz, $CDCl_3$)

H	H-C-1 H-C-2	H_a-C-3	H_b-C-3	H-C-6	H-C-7 H-C-8	H-C-9	H-N-10	H-C-11	H-C-11_a	CH_2O	CH_3
δ_{ppm}/TMS	2.09	3.05	3.48	7.82	7.32	6.81	4.42	5.07	4.12	3.48	1.08
12	1.90				6.99					3.68	
7	2.13	3.11	3.56	7.83	7.35	6.86	4.55	4.91	4.18		3.39
	1.93				7.01						

This cyclization step was probably favoured by the acidity of the solvent. The same results were indeed obtained with 11 in pure dichloromethane containing methanol (0.4%) and trifluoroacetic acid (0.002%), leading to the methoxy derivative 7. Using an optically pure alcohol, (S)-ethyl lactate, only one diastereoisomer of structure 13 was detected in ^{1}H nmr spectrum, thus indicating no epimerization at the asymmetric center of 11 occurred during the reaction.

Further syntheses of structural analogs of pyrrolo[1,4]benzodiazepine antibiotics are in progress to study the biological activity of these new compounds.

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* The numbering employed is consistent with other antitumor antibiotics of the pyrrolo[1,4]-benzodiazepine group.

EXPERIMENTAL

Melting points were measured with a Kofler apparatus and are corrected. Optical rotations ($CHCl_3$) were measured on a Perkin-Elmer 241 polarimeter. Ir spectra ($CHCl_3$, ν cm^{-1}) were recorded on a Perkin-Elmer 297 spectrophotometer and uv spectra [CH_3OH, λ_{max} (nm, (ε)] on a λ 5 Perkin-Elmer spectrophotometer. ^1H Nmr spectra were obtained in $CDCl_3$ on a Bruker WM400 or WP200SY spectrometer with tetramethylsilane as the internal reference; coupling constants, J, are given in hertz; s, d, t and m indicate singlet, doublet, triplet and multiplet, respectively. ^{13}C Nmr spectra ($CDCl_3$, δ = 0 ppm, TMS) were recorded on a Bruker WP200SY spectrometer. Mass spectra were measured on a MS50. Preparative tlc was performed with Kieselgel HF 254 + 366 Merck.

N-*o*-Nitrobenzenesulfonyl-2S-hydroxymethylpyrrolidine 8

To a solution of (S)-prolinol (1.52 g, 15 mmol) in dichloromethane (30 ml) was added a solution of sodium carbonate (3.18 g, 30 mmol) in water (30 ml). To the stirred mixture under nitrogen at 18°C was added a solution of *o*-nitrobenzenesulfonyl chloride (3.54 g, 16 mmol) in dry dichloromethane (20 ml). After being stirred at room temperature for 30 min, the reaction medium was extracted with dichloromethane, the organic layers were washed with an aqueous solution of sodium carbonate (10%) and the usual workup afforded the compound 8 which was purified by filtration on silica gel (hexane-ethyl acetate, 4-6) and crystallization (CH_2Cl_2): (3.99 g, 93%): mp = 88°C; $[\alpha]_D$ = -79° (c = 1.0); $C_{11}H_{14}N_2O_5S$ Calcd : C: 46.15, H: 4.93, N: 9.79. Found : C: 46.11, H: 4.94, N: 9.98; ir = 3550, 3300, 1540, 1365, 1160. ^1H Nmr (400 MHz): 8.09 (m, 1H, J = 8 and J < 2, aromatic H), 7.76 (m, 2H, aromatic H), 7.63 (m, 1H, J = 8 and J < 2, aromatic H), 4.01 (m, 1H, H-C-2), 3.69 (2dd, 2H, J = 12 and J = 4.5, CH_2-O), 3.49 (m, 2H, H-C-5), 2.35 (OH), 1.96 and 1.80 (2m, 4H, H-C-3 and H-C-4). ^{13}C Nmr: 148.1 and 130.9 (C-2' and C-1'), 133.8, 131.6, 130.4 and 123.7 (aromatic C-H), 64.5 (C-6), 61.5 (C-2), 49.3 (C-5), 28.3 and 24.0 (C-3 and C-4). Ms (m/z): 256, 255, 186, (100%), 170.

N-*o*-Nitrobenzenesulfonyl-2S-formylpyrrolidine 9 from 8

To a solution of alcohol 8 (2.86 g, 10 mmol) in DMSO (13.4 ml) was added under argon triethylamine (10.86 ml) and a solution of sulfur trioxide-pyridine (5.66 g) in DMSO (28.3 ml). After being stirred at room temperature until the reaction was complete, the mixture was diluted with ethyl acetate and washed with an aqueous solution of sodium carbonate (10%) and brine. The crude product obtained after usual treatment was chromatographied on silica gel (hexane-ethyl acetate, 1-1) to give the aldehyde 9 (2.36 g, 83%): $[\alpha]_D$ = -117° (c = 1.9).

$NaBH_4$ reduction of 9

$NaBH_4$ (11.4 mg, 0.30 mmol) was added under nitrogen to a solution of the aldehyde 9 obtained from 8 (42.6 mg, 0.15 mmol) in methanol (4.5 ml) at 0°C. The mixture was stirred for 5 min, diluted with water and extracted with dichloromethane to give the alcohol 8 (41.2 mg, 96%): $[\alpha]_D$ = -67° (c = 0.8).

N-*o*-Nitrobenzenesulfonyl-2S-formylpyrrolidine 9 from 10

- Preparation of the methyl ester 10

Oxalyl chloride (0.9 ml, 10 mmol) and one drop of dimethylformamide were added under argon to a suspension of N-*o*-nitrobenzenesulfonyl-2S-pyrrolidine carboxylic acid[11] (2.5 g, 8.3 mmol) in dry toluene (22 ml) at room temperature. The reaction medium was stirred for 3 h before addition of dry methanol (22 ml). After additional stirring for 1 h, the solvents were evaporated under vacuum. A solution of the residue in ethyl acetate (100 ml) was washed twice with a saturated aqueous solution of sodium bicarbonate and with brine. The crude product obtained after usual treatment (2.8 g) was chromatographied on silica gel (pentane-ether, 1-3) to give compound 10: mp = 108°C (ether); $[\alpha]_D$ = -98° (c = 0.45), $C_{12}H_{14}N_2O_6S$ Calcd : C: 45.86, H: 4.49, N: 8.92. Found : C: 45.72, H: 4.62, N: 9.07; ir: 3300, 2900, 1740; uv: 208 (14000), 224 (13500), 277 (3300). ^1H Nmr (80 MHz): 8.03 (m, 1H, aromatic H), 7.60 (m, 3H, aromatic H), 4,50 (m, 1H, H-C-2), 3.67 (s, 3H, CO_2CH_3), 3.50 (m, 2H, H-C-5), 2.00 (m, 4H, H-C-3 and H-C-4). ^{13}C Nmr: 172.0 (CO), 147.9 and 132.3 (C-2' and C-1'), 133.7, 131.7, 130.6 and 123.9 (aromatic C-H), 60.7 (C-2), 52.1 (CH_3), 48.3 (C-5), 30.7 and 24.3 (C-3 and C-4). Ms (m/z): 314 ($M^{+\cdot}$), 255, 186 (100%).

Reduction of 10

A solution of DIBAH (17 ml solution 1.2M in toluene, 20.4 mmol) was added dropwise under argon to a solution of the ester 10 (3.2 g, 10.19 mmol) in dry toluene (80 ml) at -70°C. After being stirred at -70°C for 40 min, methanol (30 ml) was added slowly and the reaction mixture was heated at 0°C before addition of aqueous hydrochloric acid (5%, 30 ml). The organic solvents were evaporated under vacuum and the product was extracted with ethyl acetate (4 x 200 ml). After usual workup, the residue (3.9 g) was purified by chromatography on silica gel (pentane-ether, 1-3) to afford the starting material (1.2 g, 38%), $[\alpha]_D$ = -100° (c = 0.25), and the aldehyde 9 (1.62 g, 56%): $[\alpha]_D$ = -135° (c = 1.3); $C_{11}H_{12}N_2O_5S$ Calcd : C: 46.48, H: 4.26, N: 9.86. Found : C: 46.61, H: 4.39, N: 9.74; ir: 1725, 1540, 1360, 1160. ^1H Nmr (400 MHz): 9.63 (d, 1H, J ≃ 1.5, CHO); 8.07 (m, 1H, J = 8 and J < 2, aromatic H), 7.74 (m, 2H, aromatic H), 7.65 (m, 1H, J = 8 and J < 2, aromatic H), 4.38 (m, 1H, H-C-2), 3.64 (m, 1H, H_b-C-5), 3.54 (m, 1H, H_a-C-5), 2.16 and 1.93 (2m, 4H, H-C-3 and H-C-4).

^{13}C Nmr: 199.0 (CHO), 148.2 and 131.0 (C-2' and C-1'), 134.2, 131.9, 130.8 and 124.1 (aromatic C-H), 66.8 (C-2), 49.0 (C-5), 27.4 and 24.4 (C-3 and C-4). Ms (m/z): 285, 255, 186 (100%).

This aldehyde was reduced as above with $NaBH_4$ to give the alcohol 8 [92%, $[\alpha]_D$ = -78° (c = 0.2)].

Reduction of 9

An excess of Raney-Ni (as a slurry in water) was added at room temperature to a stirred solution of the aldehyde 9 (0.568 g, 2.0 mmol) in 22 ml of a mixture of ethyl acetate and methanol (85-15). The reaction medium was stirred for 25 min and the catalyst was eliminated by filtration and washed with the same mixture of solvents. The crude product obtained by evaporation of the solvents under vacuum at 20°C was rapidly chromatographied on silica gel (hexane-ether, 1-4) to afford 11 (396 mg, 78%): ir: 3475, 3375, 2950, 1730, 1600; uv: 206 (15250), 252 (5600), 311 (2500). ^1H Nmr (200 MHz): 9.67 (1H, CHO), 7.9-6.7 (m, 4H, aromatic H), 4.17 (m, 1H, H-C-2), 3.45 (m, 2H, H-C-5), the compound was unstable in $CDCl_3$. Ms (m/z): 254 ($M^{+\cdot}$), 225, 156 (100%), 92.

Preparation of the compound 7

A solution of trifluoroacetic acid (0.15 µl) in a mixture of dry dichloromethane-methanol [99.6-0.4 (1.0 ml)] was added under argon at room temperature to a solution of 11 (101.6 mg, 0.4 mmol) in the same solvents (6.56 ml). After 1.5 h the solvents were evaporated under vacuum at 20°C and the compound 7 was purified by preparative tlc (hexane-ether, 3-7): 80 mg (75%): $[\alpha]_D$ = + 37° (c = 0.56); ir: 3360, 1600, 1320; uv: 207 (30000), 249 (10000), 302 (4000); ^1H Nmr (cf. Table). Ms (m/z): 268 ($M^{+\cdot}$), 236, 220, 205, 135, 120.

Preparation of the ethoxy derivative 12

The compound 11 (50.7 mg, 0.2 mmol) was treated in the conditions used for the preparation of 7 with dry ethanol in place of dry methanol. After stirring for 4 h at room temperature, the product obtained by evaporation of the solvents was purified by preparative tlc (hexane-ether, 1-4) and afforded 12 (36.5 mg, 65%): $[\alpha]_D$ = + 51° (c = 0.38); ir: 3360, 1595, 1325, 1160; uv: 209 (15700), 247 (6000), 299 (2000). ^1H Nmr (400 MHz) (cf. Table); ^{13}C Nmr: 132.8, 128.9, 120.9 and 120.7 (aromatic C-H), 87.4 (C-11), 65.0 (CH_2-O), 63.1 (C-11a), 49.3 (C-3), 26.7 and 24.4 (C-1 and C-2), 15.0 (CH_3). Ms (m/z): 282 ($M^{+\cdot}$), 236, 224, 189, 149, 131, 120, 70.

Preparation of 13

A solution of the compound 11 (108 mg, 0.42 mmol) in dry dichloromethane (9 ml) containing trifluoroacetic acid (0.32 µl) was added under argon at room temperature to (S)-ethyl lactate

(198 mg, 1.68 mmol). The mixture was stirred for 6.5 h and the solvents were evaporated under vacuum. The crude product was chromatographied on silica gel (hexane-ether, 1-1) to afford unreacted 11 (39 mg, 33%) and 13 (52 mg, 35%): $[\alpha]_D$ = + 49° (c = 0.6); ir: 3360, 1730, 1600, 1325, 1160, 1135, 1100; uv: 211(18400), 246(8000), 297(2900); ^{1}H Nmr (400 MHz): 7.75 (d, 1H, J = 8, aromatic H), 7.26 (dd,1H, J = 8, aromatic H), 6.89 (dd, 1H, J = 8, aromatic H), 6.73 (d, 1H, J = 8, aromatic H), 5.52 (d, 1H, J = 3.1, H-C-11), 5.48 (exchanged with D_2O, NH), 4.19 (m, 3H, $CH_3\underline{CH_2}O$ and CH-O), 4.12 (m, 1H, H-C-11a), 3.50 (m, 1H, H_b-C-3), 3.00 (m, 1H, H_a-C-3), 2.36, 2.12, 2.02 and 1.93 (4 m, 4H, H-C-1 and H-C-2), 1.43 (d, 3H, J = 6.8, $\underline{CH_3}$-CH), 1.28 (t, 3H, J = 7.0, $\underline{CH_3}$-CH_2O). Ms (m/z): 354, 221, 205, 189.

Unreacted 11 (30.5 mg, 0.12 mmol) was treated with (S)-ethyl lactate, under the same conditions to give 13 whose optical rotation was the same as above.

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