SYNTHESIS OF 6-FLUOROQUINOLONES SUBSTITUTED AT C-7 BY 1'-DEMETHYLLINCOMYCIN AND BY DIHYDROCONESSIMINE

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Abstract -- The boron-chelated carboxylic acid of 6,7-difluoroquinolone (8) was substituted at C-7 by the 2,3,4,7-tetra-Q-acetate of 1'-demethyllincomycin (4) and by dihydroconessimine (14). The resulting dechelated products did not reveal any antibacterial activity. A new efficient procedure for the preparation of the 2,3,4,7-tetra-Q-acetate of 1'-demethyllincomycin (4) is proposed.

Considerable efforts have been devoted during recent years towards the synthesis of new 6-fluoroquinolones as highly efficient antibacterial agents. Structure-activity relationship studies have shown that substitution of their aromatic ring at C-7 by specifically substituted pyrrolidine unit markedly enhance their in vitro antibacterial activity. These biological results prompted us to attempt the covalent association of a 6-fluoroquinolone (7) with two pyrrolidine containing substances: 2,3,4,7-tetra-Q-acetyl-1'-demethyllincomycin (4) and dihydroconessimine (14), readily available from naturally occurring lincomycin (1) and conessine derived 5,6-dihydroconessine (12), respectively.

RESULTS AND DISCUSSION

Lincomycin (1), a clinically important antibiotic exerts its antibacterial activity by the inhibition of protein synthesis at the ribosomal level. Improvement of lincomycin type activity of the target molecule (11) could not reasonably be expected on the basis of previous structure-activity relationship investigations within this family of compounds. However, it was of interest to test whether the appropriate association between lincomycin - with its unique pyrrolidine structure - and a 6-fluoroquinolone, via its C-7 site, would enhance the quinolone type antibacterial activity of the combined product. Quinolones are almost insoluble in water and the influence upon activity of the four hydroxyl groups of the lincomycin moiety was also thought worth to be investigated.

The microbial and chemical synthesis of 1'-demethyllincomycin (5) has been reported previously. However, all the procedures used furnished 5 only in moderate yields. We succeeded in preparing 2,3,4,7-tetra-Q-acetyl-1'-demethyllincomycin (4), from lincomycin base (1), in three steps with an overall yield of 47%.

Tetra-Q-acetylation of lincomycin base (1) was followed by 2,2,2-trichloroethyl chloroformate treatment furnishing 3 and then reductive removal of the carbamate group, using zinc/tetrahydrofuran/pH 4.2 phosphate
buffer, gave 4.

Although, conessine and its derivatives are not known for their antibacterial properties, we were interested to associate the tetrasubstituted pyrrolidine ring of dihydroconessimine (14) with the C-7 site of a 6-fluoroquinolone and evaluate the activity of the product thus generated.

In order to synthesize dihydroconessimine (14) from the selectively N-dimethylamino protected dihydroconessine (13), preparation of the corresponding 2,2,2-trichloroethyl carbamate was first attempted, as described above in the 1'-demethylation of lincomycin. However, the reaction afforded under various conditions pyrrolidine ring-opened unsaturated products. Therefore, for the preparation of dihydroconessimine (14) the method advocated by Picot and Lusinchi was adopted.

Aromatic substitution at C-7 of 7-chloro-6-fluoroquinolone (6) with C-2 cyclic pyrrolidine or piperidine nucleophiles gave disappointing results in our hands. However, such substitution reactions could be readily performed with virtually quantitative yields, when the boron-chelated derivative of carboxylic acids of 6,7-difluoroquinolones were used in dimethyl sulfoxide at room temperature, and in the presence of 1.5 equiv. of pyrrolidine (4) or (14) and also 1.5 equiv. of triethylamine. The boron-chelated compound (8) was prepared from carboxylic ester (7) with boron trifluoride etherate in diphenyl ether at 200 °C. This procedure allowed the preparation of 2 and 15 which after liberation of the free carboxylic acids, by reflux in the appropriate solvent system, gave 10 and 16, respectively. The water soluble deacetylated 11 could be directly obtained by base
treatment from 2. The structure of 10, 11 and 16 was unambiguously established by $^{13}$C nmr spectroscopy. Compounds (10, 11 and 16) were unfortunately devoided of any antibacterial activity.
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EXPERIMENTAL PART

General procedures. A Perkin-Elmer Model 141 MC polarimeter and 1-dm tubes were used for measurement of specific rotations. $^1$H Nmr spectra were recorded in chloroform-$d$, DMSO-$d_6$, MeOH-$d_4$ solutions at 200, 250 and 400 MHz. The $^{13}$C nmr spectra were measured in chloroform-$d$, DMSO-$d_6$, MeOH-$d_4$ solutions at 50.33 MHz with a Bruker WP-200 spectrometer or at 62.91 MHz with a Bruker WP-250 spectrometer. Chemical shifts are given in parts per million, and tetramethylsilane was the internal standard ($\delta$ 0.000). Microanalyses were performed by the Service Central de Microanalyse du CNRS. Silica gel 60 PF254 (Merck) activated at 120°C was the support for tlc and for column chromatography.

2,3,4,7-Tetra-$Q$-acetyl-1'-[2,2,2-trichloroethoxycarbonyl]-1'-demethyllincomycin (3). To a solution of 2 (2.0 g, 3.48 mmol) in dry toluene (40 ml) was added potassium carbonate (0.24 g, 1.74 mmol) and the mixture was stirred at reflux for 15 min. Then, 2,2,2-trichloroethyl chloroformate (1.25 ml, 9.26 mmol) was added dropwise and the reflux maintained for 48 h. The mixture was poured into ice-water saturated with NaHC03, extracted with CH2Cl2 and the organic layer dried over Na2S04 and concentrated. The residue was chromatographed affording pure syrupy 3 (1.65 g, 64%); $[\alpha]_D +93^{\circ}$ (c 1.0, CHC13), mass spectrum: m/z 736 (M+ + H), $^1$H nmr (250 MHz, CDC13) $\delta$ 7.26 (d, lH, $J_{NH} = 10.5$ Hz, NH), 5.63 (d, lH, $J_{1,2} = 6$ Hz, H-I), 5.24 (m, 2H, $H_{2,4}$), 5.05 (m, 2H, $H_{3,7}$), 5.00 and 4.74 (2d, 2H, $J_{gem} = 13.5$ Hz, NCO2CH2CCl3), 4.57 (dt, 1H, $J_{NH,6} = J_{6,7} = 10.5$ Hz, $J_{6,7} = 3$ Hz, H-6), 4.35 (d, 1H, J2',3' = 9 Hz, H-2'), 4.23 (d, 1H, $J_{5.6} = 10.5$ Hz, H-5), 3.77 (m, lH, H-5'b), 3.02 (m, 1H, H-5'b), 2.49-2.25 (m, 2H, H-3'a and H-4'), 2.20-1.92 (m, 15H, 4 x OAc + SMe), 1.54 (m, 1H, H-3'b), 1.45-1.21 [m, 7H, $\alpha$CH2(Pr) + $\beta$CH2(Pr) + Me-8], 0.95 [m, 3H, $\gamma$Me(Pr)]; $^{13}$C nmr (62.91 MHz, CDC13) $\delta$ 170.5-169.9 (CONH + 4 x OAc), 154.9 (NCO2CH2CCl3), 95.6 (NCO2CH2CCl3), 84.8 (C-1), 75.4 (NCO2CH2CCl3), 70.7 (C-3), 68.5-67.0 (C-2,4,5,7), 60.2 (C-2'), 52.5 (C-5'), 49.5 (C-6), 37.5 (C-4'), 35.2 (NCH2(Pr)), 33.8 (C-3'), 21.2 [NCH2(Pr)], 21.1-20.7 (4 x OAc), 14.8 (C-8), 14.1 [NMe(Pr)], 13.7 (SMe). Anal. Calcd for C28H41N2O12C13S: C, 45.69; H, 5.61; N, 3.80. Found: C, 45.77; H, 5.61; N, 3.52.

2,3,4,7-Tetra-$Q$-acetyl-1'-demethyllincomycin (4). To a solution of 3 (1.44 g, 1.95 mmol) in tetrahydrofuran (70 ml) was added activated zinc (1.9 g, 29 mmol) and a buffer solution (14 ml) of Na2HPO4 (95 : 5) whose pH was adjusted to 4.2. The reaction mixture was vigorously stirred at room temperature for 4 h. After filtration and washing of the metal with tetrahydrofuran, addition of a saturated solution of NaHCO3 and extraction with ethyl acetate, the organic layer was dried over MgSO4 and evaporated. The residue was chromatographed affording pure syrupy 4 (0.88 g, 80%); $[\alpha]_D +130^{\circ}$ (c 1.0, CHCl3), mass spectrum: m/z 561 (M+ + H), $^1$H nmr (200 MHz, CDC13) $\delta$ 8.01 (d, 1H, $J_{NH,6} = 11.5$ Hz, NH), 5.65 (d, 1H, J1,2 = 5.7 Hz, H-
The united organic layers were dried over sodium sulfate and concentration furnished after crystallization pure to 167.4 mg (169 mg, 99%); mp 154-155 °C, [α]D -4.0° (c 1.0, CHCl3), mass spectrum: m/z 816 (M+ + Na). 1H nmr (250 MHz, CDC13) δ 8.42 (s, 1H, H-2), 7.84 (d, 1H, J5,F = 14.2 Hz, H-5), 7.06 (d, 1H, JNH,6" = 10.5 Hz, CONH), 6.49 (d, 1H, J8,F = 6.7 Hz, H-8), 5.58 (d, 1H, J1",2" = 5.2 Hz, H-1"), 5.32 (d, 1H, J3",4" = 2.6 Hz, H-2"), 5.23 (dd, 1H, J2",3" = 10.8 Hz, J1",2" = 5.6 Hz, H-2"), 5.03 (dd, 1H, J2",3" = 10.8 Hz, J3",4" = 3.0 Hz, H-3"), 4.83 (m, 1H, H-7"), 4.55 (m, 2H, H-2', 6"), 4.26 (m, 3H, CH2Et), 3.88 (m, 1H, H-5'a), 3.01 (m, 1H, H-5'b), 2.33 (m, 2H, H-3'a, 4'), 2.16-1.82 (m, 16H, 4 x OAc, SMe, H-3'b), 1.53 (t, 3H, J11,12 = 6.8 Hz, Me(Pr)], 1.44 (m, 4H, αCH2(Pr), βCH2(Pr)], 1.12 (d, 3H, J7",g = 6.8 Hz, Me-8"), 0.94 (m, 3H, JMe(Pr)); 13C nmr (62.91 MHz, CDC13) δ 176.3 (C-4), 172.7 (CONH), 170.8-170.0 (4 x OAc), 167.4 (C-13), 150.3 (d, J6,F = 247.5 Hz, C-6), 146.6 (C-2), 142.0 (d, J7,F = 11.5 Hz, C-7), 137.5 (C-9), 117.4 (d, J10,F = 7.2 Hz, C-10), 112.2 (d, J5,F = 23.3 Hz, C-5), 107.5 (C-3), 100.0 (C-8), 84.9 (C-1"), 72.0
(C-7”), 68.7, 2 x 67.8, 67.2 (4C, C-2”, 3”, 4”, 5”), 66.0 (d, J2’,F = 7.2 Hz, C-2’), 56.8 (C-5”), 49.7 (C-6”), 49.6 [C-H2(Et)], 37.3 (C-3”), 36.4 (C-4”), 35.1 [αCH2(Pr)], 21.6-20.6 [4 x OAc + βCH2(Pr)], 16.2 (C-8”), 14.3-13.7 [Me(Al), SMe, γMe(Pr)]. Anal. Calcd for C37H48N3O3S: C, 55.97; H, 6.09; N, 5.29. Found: C, 56.03; H, 6.11; N, 5.11.

Compound (11). A solution of 2 (135 mg, 0.16 mmol) in a mixture of 1N sodium hydroxide (960 µl) in ethanol to which absolute ethanol (1 ml) was added was refluxed for 45 min. After cooling, neutralization with 1N HCl in ethanol, the precipitate was collected, filtered and dissolved in ethanol. After concentration and purification on sephadex LH-20, crystalline 11 (92 mg, 92%) was obtained; mp 224 °C, [α]D +9.8° (c 0.91, MeOH), mass spectrum: m/z 648 (M+ + Na), 1H nmr (200 MHz, MeOH-d4) δ 8.46 (s, 1H, H-2), 7.81 (d, 1H, J5,F = 14.2 Hz, H-5), 6.64 (d, 1H, Jg,F = 6.5 Hz, H-8), 5.27 (d, 1H, J1”,2” = 5.1 Hz, H-1”), 4.66-3.56 [m, 10H], 2.26-2.30 (m, 2H, H-3’a, 4’), 2.06 (s, 3H, SMe), 1.92 (m, 1H, H-3b’), 1.47 [m, 7H, α, β CH2(Pr), Me(Et)], 1.16 (d, 3H, J7-, γ” = 6.8 Hz, Me-8”), 1.00 [m, 3H, γMe(Pr)]; 13C nmr (62.91 MHz, MeOH-d4) δ 176.7 and 176.4 (C-4 and CONH), 172.8 (C-13), 150.7 (d, J6,F = 248.9 Hz, C-6), 148.7 (C-2), 141.3 (d, J7,F = 11.8 Hz, C-7), 138.5 (C-9), 120.8 (C-10), 117.3 (C-3), 116.5 (d, J5,F = 22.3 Hz, C-5), 100.8 (C-8), 89.3 (C-1”), 71.8-68.5 (C-2”, 3”, 4”, 5”, 7”), 67.0 (d, J2’,F = 8.8 Hz, C-2’), 58.4 (C-6”), 57.4 (C-5”), 38.9 (C-3”), 36.5 (C-4’), 36.0 [αCH2(Pr)], 22.7 [βCH2(Pr)], 20.9 (C-8”), 14.6 and 13.0 [Me(Et), SMe, γMe(Pr)]. Anal. Calcd for C29H40N3O9FS: C, 55.66; H, 6.44; N, 6.71. Found: C, 55.72; H, 6.57; N, 6.53.

Compound (15). To a solution of 8 (176 mg, 0.58 mmol) and dihydroconessamine 14 (301 mg, 0.87 mmol) in DMSO (7 ml), was added triethylamine (123 µl, 0.87 mmol). The mixture was stirred overnight at room temperature and then concentrated. The residue was dissolved in CH2Cl2 and the organic layer washed with water, dried and concentrated. Flash chromatography of the residue (CH2Cl2 : MeOH : NH4OH 8 : 1 : 0.5%) gave pure syrup 15 (358 mg, 98%), [α]D =-169.1° (c 1.1, CHCl3), mass spectrum: m/z 648 (M+ + Na). Anal. Calcd for C35H47N3O3~F: C, 56.03; H, 6.11; N, 5.29. Found: C, 56.03; H, 6.11; N, 5.11.

Compound (16). In a mixture (1 : 1) of CHCl3 and H2O (4 ml) was dissolved 15 (150 mg, 0.24 mmol). After refluxing it for 22 h, cooling, extraction with CH2Cl2, the organic layer was dried over sodium sulfate and evaporated. Flash chromatography (CH2Cl2 : MeOH : NH4OH 8 : 2 : 0.5%) gave 16 (97 mg, 70%) and starting material 15 (40 mg). A sample of 16 was crystallized from acetone-heptane: mp 130 °C, [α]D -95.2° (c 1.05, CHCl3), mass spectrum: m/z 600 (M+ + Na), 1H nmr (300 MHz, CDCl3) δ 8.62 (s, 1H, H-2), 8.00 (d, 1H, J5,F = 13.2 Hz, H-5), 6.53 (d, 1H, Jg,F = 6.8 Hz, H-8), 4.28 [m, 2H, CH2(Al)], 4.08 (m, 1H, H–20’), 3.63 (m, 1H, H-18’a), 3.07 (m, 1H, H-18’b), 2.40 [m, 7H, N(Me)2 + H-3’], 2.18 (m, 1H, H-17’), 1.60 [t, 3H, J11,12 = 7.1 Hz, Me(Et)], 1.25 (d, 3H, J20’,21’ = 7 Hz, Me-21’), 0.76 (s, 3H, Me-19’); 13C nmr (62.91 MHz, CDCl3) δ 176.5 (C-4’), 167.5 (C-13), 152.1 (d, J6,F = 249.8 Hz, C-6), 146.6 (C-2), 143.7 (d, J7,F = 12.3 Hz, C-7), 137.4 (C-9), 117.5 (C-10), 112.0 (d, J5,F = 22.6 Hz, C-5), 107.6 (C-3), 100.7 (C-8), 64.2 (C-3’), 55.9 (C-18’), 55.7 (C-20’), 53.7 (C-9’, 14’), 53.1 (C-17’), 52.3 (C-13’), 49.5 [CH2(Al)], 45.3 (C-5’),

HETEROCCYCLCS, Vol. 41, No. 2, 1995
40.9 [N(Me)2], 38.1 (C-8'), 37.4 (C-1'), 35.6 (C-10'), 34.1 (C-16'), 32.0 (C-7'), 30.6 (C-4'), 28.4 (C-6'), 24.5, 23.7, 23.0 (C-2', 12', 15'), 21.8 (C-11'), 15.1 (C-21'), 14.4 [Me(Et)], 12.3 (C-19'). Anal. Calcd for C35H48N3O3F: C, 72.75; H, 8.37; N, 7.27. Found: C, 72.79; H, 8.41; N, 7.18.

REFERENCES


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