REVISED STRUCTURE AND THE CHEMICAL TRANSFORMATIONS OF FR900148

NOBUYOSHI YASUDA and KAZUO SAKANE

New Drug Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., 2-1-6 Kashima, Yodogawa-ku, Osaka 532, Japan

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The structure of an antibiotic FR900148, which was isolated from Streptomyces xanthocidicus No. 301 in 1980, was reported as a pyrrolidine derivative as shown in Fig. 1.1,2 In 1984, CHAIET et al.3, isolated 4-amino-3-chloro-2-pentenedioic acid and they suggested that the structure 1 of FR900148 was questionable. This prompted us to reexamine the previous conclusions and has led us to conclude that the correct structure of FR900148 is represented by the open-chain acid (2).

FR900148 was reisolated from the same strain

Fig. 1. Previous structure of FR900148.

Fig. 2. Chemical modification of the free derivative (2) of FR900148.

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1 Present address: Process Research Labs., Merck Sharp & Dohme, P. O. Box 2000, Rahway, NJ 07065, U.S.A.
and its biological and physical data were exactly the same as in the previous isolation. In order to confirm the presence of a chlorine atom in the antibiotic, free acid derivative (2) was isolated from the fermented broth filtrate by successive column chromatography on activated carbon, DEAE-Sephadex, CM-Sephadex and Sephadex G15. The $^{13}$C NMR of 2 in D$_2$O showed 10 carbons (5 17.38 (q), 18.21 (q), 30.48 (d), 59.10 (d), 61.92 (d), 126.51 (d), 134.91 (s), 169.06 (s), 171.94 (s), and 172.66 (s)). FAB-MS data of the sodium salt of 2 showed strong signals at m/z 279 (M+H$^+$), 301 (M+Na$^+$), and 323 (M+2Na$^+$) and each signal displayed the usual one chlorine isotope pattern. FAB-MS data of 2 (free acid) showed signals at m/z 199 ((M+H$^+$) of 7), 235 ((M+H$^+$) - COO), 245 (M-Cl$^-$) and 279 (M$^+$), and two signals at 235 and 279 displayed the usual one chlorine isotope pattern. Titration of 2 showed pKa 1 = 2.00, pKa 2 = 3.37 and pKa 3 = 7.97. (In the previous report$^1$, the titration was reported as pKa 1 = 3.25 and pKa 2 = 7.90). Therefore, 2 must have two carboxylic acid moieties and one amino group. From these data and also elemental analysis of 2 (C$_{10}$H$_{15}$ClN$_2$O$_5$·2H$_2$O: Calcd: C 38.16, H 6.08, Cl 11.26, N 8.90, Found: C 37.87, H 5.08, Cl 10.79, N 9.23), the formula of 2 is established to be C$_{10}$H$_{15}$ClN$_2$O$_5$.

Then we reexamined the chemical transformations of 2$^2$. Hydrogenation$^2$ of 2 gave a dipeptide 3. Acid hydrolysis$^2$ of 3 gave l-Val and l-Glu, whose absolute stereochemistries were determined by chiral HPLC. FAB-MS and 2D-NMR data of the Boc derivative (4) of 3 clearly revealed that 4 was Boc-l-Val-l-Glu, which was converted into the corresponding dimethyl ester by treatment with diazomethane. The fact that no racemization had occurred during these reactions suggested that each corresponding carbon in 2 to the $\alpha$-carbons in l-Val and l-Glu should be an optically active secondary carbon. Treatment of 2 with diazomethane in MeOH$^2$ gave an oxazole compound 5, whose structure was confirmed by $^1$H NMR (CDCl$_3$) δ 0.94 (3H, d, J = 7 Hz), 0.98 (3H, d, J = 7 Hz), 2.16 (1H, m), 3.74 (3H, s), 3.91 (3H, s), and 4.13 (2H, s), $^{13}$C NMR (CDCl$_3$) δ 18.082 (q), 18.917 (q), 31.982 (t), 33.343 (d), 52.203 (q), 52.577 (q), 55.802 (d), 129.053 (s), 151.541 (s), 162.339 (s), 165.996 (s), and 168.040 (s), and UV ($\lambda$ = 213 nm, $\varepsilon$ = 1.10 × 10$^4$ in EtOH)$^4$.

$^1$H NMR of the acetylated compound 6$^2$ in THF-d$_8$ and THF-d$_8$-D$_2$O were very similar to that of 2. Two amide protons of 6 were assigned from a decoupling experiment as follows: δ 8.08 (1H, d, J = 7.92 Hz, D-Val-CONH$^-$) and 7.24 (1H, d, J = 7.90 Hz, AcNH-Val-). The fact that no racemization had occurred at only the amino moiety of the valine group. Interestingly, 2 spontaneously decarboxylated upon dissolution in DMSO-d$_6$ and gave the oxazolylactic acid derivative 7 ($^1$H NMR (DMSO-d$_6$) δ 0.84 (3H, d, J = 7 Hz), 0.99 (3H, d, J = 7 Hz), 2.27 (1H, m), 3.80 (2H, s), 4.32 (1H, d, J = 6 Hz), and 7.08 (1H, s); $^{13}$C NMR (DMSO-d$_6$) δ 17.18 (q), 18.54 (q), 30.78 (d), 31.21 (t), 53.03 (d), 124.56 (d), 147.27 (s), 158.96 (s), and 169.56 (s).

From these data and $^{13}$C-$^1$H shift collation by long-range coupling (COLOC) of 2, the structure of 2 and the chemical transformations were revised as shown in Fig. 2. We could not determine the geometry of the double bond, however, from Chaiet's data$^3$, we assumed that it is the Z form.

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References