CHEMICAL MODIFICATION OF ANTHRACYCLINE ANTIBIOTICS. V SYNTHESIS OF 2-HYDROXYACLACINOMYCIN A BY CHEMICAL GLYCOSIDATION

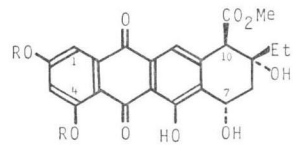
Sir:

A new anthracycline antibiotic, 2-hydroxyaclacinomycin A (**1**)[1], which has a potent antitumor activity against L1210 leukemia in mice, has been produced by microbial glycosidation of 2-hydroxyaklavinone (**2**)[2]. We have also reported[3] the chemical glycosidation of various anthracyclinones with a trisaccharide (**4**) obtained from aclacinomycin A[4,5]. In this paper, we will report on the synthesis of **1** by chemical glycosidation. The activities of **1** and its *O*-acetyl compounds in inhibiting the growth of cultured L1210 cells are also described.

The direct glycosidation of **2** with *O*-α-L-cinerulosyl-(1→4)-*O*-(3-*O*-acetyl-2-deoxy-α-L-fucosyl)-(1→4)-α,β-L-rhodosamine (**4**)[3] gave 3″-*O*-acetyl-2-hydroxyaclacinomycin A (**7**) (7% yield) and many side products. Therefore, the 2- and 4-hydroxyl groups of **2** were protected. Treatment of **2** (120 mg) with boroacetic anhydride[6] [$B(OH)_3$ (52 mg) - Ac_2O (0.51 ml)] in tetrahydrofuran (THF) for 30 minutes at room temperature, followed by addition of pyridine (0.027 ml) completed the selective acetylation, affording 2,4-di-*O*-acetyl-2-hydroxyaklavinone (**3**) in 87% yield. **3**: mp 113~115°C; $[\alpha]_D^{24}$ +90.7° (*c* 0.03, $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 260, 286, 417, 432 nm; ν_{max}^{KBr} 1780, 1735, 1680, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (t, CH_3, *J*=6 Hz), 1.50~2.35 (m, 2×CH_2), 2.35, 2.45 (s, 2×$COCH_3$), 3.48 (d, OH-7, *J*=3.5 Hz), 3.69 (s, $COOCH_3$), 3.88 (s, OH-9), 4.05 (s, H-10), 5.32 (bs, H-7, W_H=~8 Hz), 7.23 (d, H-3, *J*=2.5 Hz), 7.61 (s, H-11), 7.96 (d, H-1, *J*=2.5 Hz), 13.25 (s, OH-6).

Compound **3** was coupled with **4** by the following one-pot reaction. A CH_2Cl_2 solution of **3** (65 mg) was added to a solution of the bromo sugar from **4** (87 mg), prepared by reaction at −60°C with $(CF_3SO_2)_2O$ (0.042 ml) in the presence of *n*-Bu_4NBr (122 mg) and 2,4,6-collidine (0.075 ml) in CH_2Cl_2. After 2 hours at 23°C, the same amount of similar freshly prepared bromo sugar solution was again added at −60°C and the reaction kept for 2 hours at 23°C. The mixture was worked up and chromatographed on a silica gel column. The first eluate with $CHCl_3$ gave unreacted **3** (46% recovery); the second eluate with $CHCl_3$ - MeOH (80: 1) afforded 2,4,3″-tri-*O*-acetyl-2-hydroxyaclacinomycin A (**5**) in 30% yield and 4,3″-di-*O*-acetyl-2-hydroxyaclacinomycin A (**6**) in 5% yield. **5**: mp 137~140°C; $[\alpha]_D^{24}$ −113.3° (*c* 0.03, $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 259, 266, 418, 438 nm; ν_{max}^{KBr} 1780, 1730, 1675, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.08, 2.37, 2.49 (s, 3×$COCH_3$), 2.17 (s, $N(CH_3)_2$), 3.66 (s, $COOCH_3$), 4.95~5.55 (m, 3×anomeric-H, H-7, H-3″), 7.27 (d, H-3), 7.64 (s, H-11), 7.98 (d, H-1), 13.24 (s, OH-6); *Anal.* (calcd. for $C_{48}H_{59}NO_{19}\cdot 2.5H_2O$): C 57.71 (57.64), H 6.21 (6.11), N 1.40 (1.27). **6**: mp 167~171°C; $[\alpha]_D^{24}$ −110.5° (*c* 0.04, $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 270, 418, 440 nm; ν_{max}^{KBr} 1770, 1730, 1675, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.08, 2.37 (s, 2×$COCH_3$), 2.29 (s, $N(CH_3)_2$), 3.75 (s, $COOCH_3$), 4.95~5.55 (m, 3×anomeric-H, H-7, H-3″), 6.58 (d, H-3), 7.17 (d, H-1), 7.41 (s, H-11), 13.30 (s, OH-6). It was confirmed that the C-1′ anomeric position of **5** possessed the α-configuration based on ^1H NMR analysis (H-1′: δ 5.55, W_H=~6 Hz). The β-glycoside corresponding to **5** was not found in this reaction.

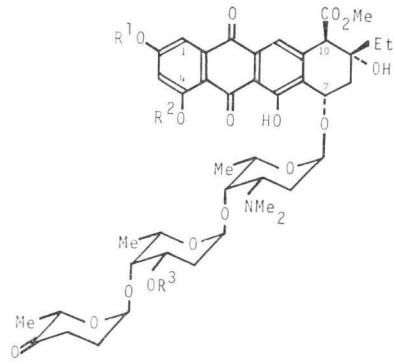
Fig. 1.



2 R=H
3 R=COMe

Brief treatment of **5** with methanolic sodium methoxide (0.1 N, 4 equivalents) in THF for 20 minutes at 0°C gave 3″-*O*-acetyl-2-hydroxyaclacinomycin A (**7**) in 74% yield, after purification. **7**: mp 169~170°C; $[\alpha]_D^{24}$ −42° (*c* 0.04, $CHCl_3$); $\lambda_{max}^{CHCl_3}$ 270, 287, 442 nm; ν_{max}^{KBr} 1735, 1675, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.08 (s, $COCH_3$), 2.22 (s, $N(CH_3)_2$), 3.73 (s, $COOCH_3$), 4.95~5.60 (m, 3×anomeric-H, H-7, H-3″), 6.28 (d, H-3), 6.77 (d, H-1), 7.43 (s, H-11), 11.92, 12.64 (br, OH-4 and -6). Furthermore, similar methanolysis of **5** for 2 hours at room temperature under a N_2 atmosphere furnished 2-hydroxyaclacinomycin A (**1**) in 65% yield: mp 166~167°C; $[\alpha]_D^{24}$ +43.2° (*c* 0.04, MeOH); $\lambda_{max}^{90\%MeOH}$ 222, 256, 295, 450 nm; ν_{max}^{KBr} 1735, 1675, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.30 (s, $N(CH_3)_2$), 3.72 (s, $COOCH_3$), 4.95~5.60 (m, 3×anomeric-H, H-7), 6.37 (d, H-3),

Table 1. Inhibitory effects of **1** and its acetates against L1210 leukemia cells.



Compound	R^1	R^2	R^3	IC_{50} (μg/ml)		
				Growth (day 2)	DNA synthesis	RNA synthesis
5	Ac	Ac	Ac	0.08	3.5	0.49
6	H	Ac	Ac	0.05	4.5	1.0
7	H	H	Ac	0.07	2.5	0.32
1	H	H	H	0.03	1.4	0.20
Biosynthetic **1**				0.03	1.1	0.18

6.83 (d, H-1), 7.37 (s, H-11). These physical and spectroscopic data were essentially identical with those[1] of **1** obtained by biotransformation. Thus, the preparation of **1** by regio- and stereoselective glycosidation was accomplished.

The effects of **1** and its synthetic intermediates (*O*-acetyl compounds) against cultured L1210 leukemia cells were examined by a previously described method[3]. As shown in Table 1, chemically synthetic **1** was biologically identical to material of microbial origin. *O*-Acetyl compounds **5**, **6** and **7** showed lower activities than **1** against the growth of L1210 cells and nucleic acid synthesis. In all cases, RNA synthesis was more strongly inhibited than DNA synthesis.

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References

1) OKI, T.; A. YOSHIMOTO, Y. MATSUZAWA, T. TAKEUCHI & H. UMEZAWA: New anthracycline antibiotic, 2-hydroxyaclacinomycin A. J. Antibiotics 34: 916~918, 1981
2) MATSUZAWA, Y.; A. YOSHIMOTO, N. SHIBAMOTO, H. TOBE, T. OKI, H. NAGANAWA, T. TAKEUCHI & H. UMEZAWA: New anthracycline metabolites from mutant strains of *Streptomyces galilaeus* MA144-M1. II. Structure of 2-hydroxyaklavinone and new aklavinone glycosides. J. Antibiotics 34: 959~964, 1981
3) TANAKA, H.; T. YOSHIOKA, Y. SHIMAUCHI, Y. MATSUSHITA, Y. MATSUZAWA, T. OKI & T. ISHIKURA: Chemical modification of anthracycline antibiotics. IV. Synthesis of new anthracyclines with trisaccharide. J. Antibiotics 35: 312~320, 1982
4) OKI, T.; Y. MATSUZAWA, A. YOSHIMOTO, K. NUMATA, I. KITAMURA, S. HORI, A. TAKAMATSU, H. UMEZAWA, M. ISHIZUKA, H. NAGANAWA, H. SUDA, M. HAMADA & T. TAKEUCHI: New antitumor antibiotics, aclacinomycins A and B.

J. Antibiotics 28: 830~834, 1975

5) OKI, T.; I. KITAMURA, Y. MATSUZAWA, N. SHIBAMOTO, T. OGASAWARA, A. YOSHIMOTO, T. INUI, H. NAGANAWA, T. TAKEUCHI & H. UMEZAWA: Antitumor anthracycline antibiotics, aclacinomycin A and analogues. II. Structural determination. J. Antibiotics 32: 801~819, 1979

6) FIESER, L. F. & M. FIESER: Reagent for Organic Synthesis. Vol. 1, pp. 63~64, John Wiley & Sons, Inc., New York, London, 1967