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THE STRUCTURE OF A NEW ISOTETRACENONE ANTIBIOTIC, CAPOAMYCIN

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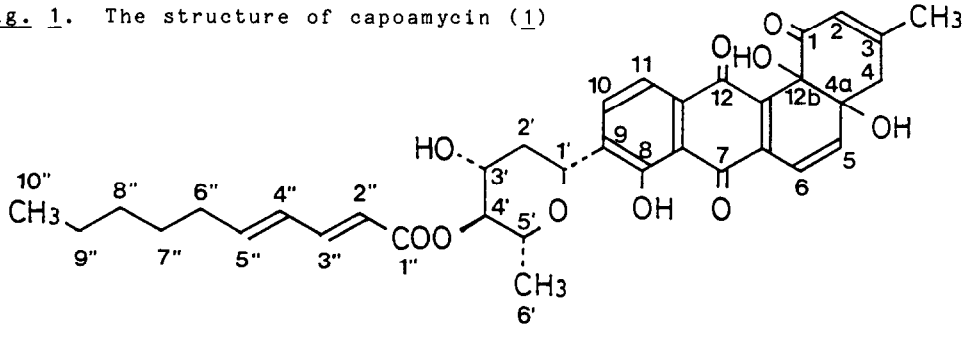
Summary: Based on ^{1}H and ^{13}C NMR spectral data and chemical degradation, the structure of capoamycin, a new isotetracenone antibiotic has been determined as shown in Fig. 1.

Capoamycin is a new antitumor antibiotic produced by Streptomyces capoamus No. 23-41, which belongs to the isotetracenone antibiotic group.[1] This substance induced differentiation of mouse myeloid leukemia cells (M1)[2] and prolonged the survival periods of mice bearing Ehrlich ascites carcinoma.

The physicochemical properties of capoamycin (1) are as follows: orange yellow powder, no definite m.p.; FAB-MS, m/z 724 (M + diethanolamine + H)$^{+}$; Anal. found, C 68.03, H 6.26, O 25.71, calcd. for $C_{35}H_{38}O_{10}$, C 67.95, H 6.19, O 25.86; $[\alpha]_D^{21}$ +209°(c 0.1, acetone); UV λ_{max}^{MeOH} nm ($E_{1cm}^{1\%}$), 235(704), 257(782), 305(139) and 442(100). The IR spectrum of 1 (KBr) showed the absorptions due to hydroxyl groups (3420 cm^{-1}), an unsaturated ester (1710 cm^{-1}), an unsaturated ketone in a 6-membered ring (1690 cm^{-1}), a non-chelated quinone (1670 cm^{-1}, sh) and a chelated quinone carbonyl group (1638 cm^{-1}).

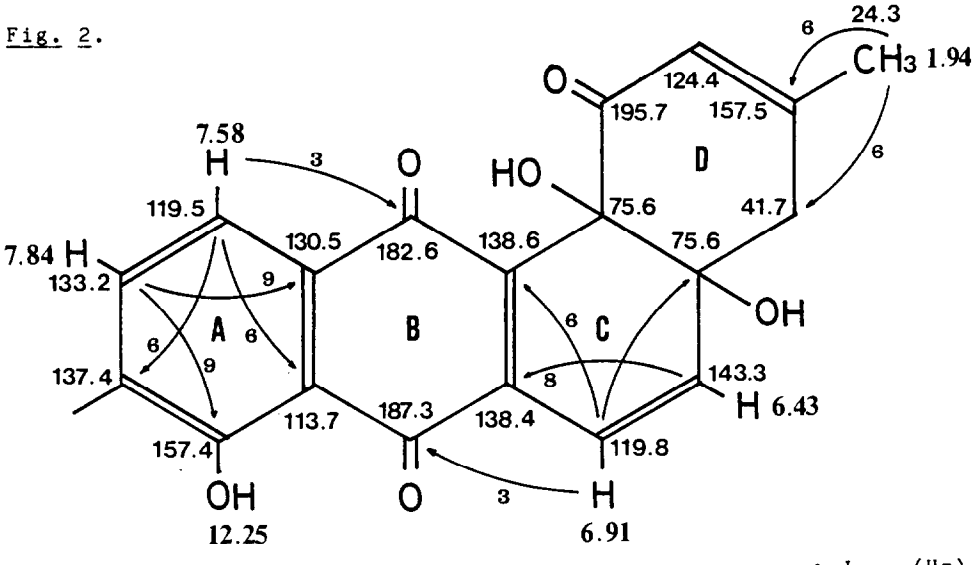
Fig. 1. The structure of capoamycin (1)



The 400 MHz ^1H NMR spectrum[3] of 1 in $CDCl_3$ revealed the following signals: δ 12.25 (s, exchangeable, 8-OH), 7.84 (d, J=7.6 Hz, 10-H), 7.58 (d, J=7.6, 11-H), 6.91 (d, J=10.0, 6-H), 6.43 (d, J=10.0, 5-H), 6.22 (br.s, 2-H), 2.76 (d, J=18.8, 4-Ha), 2.51 (d, J=18.8, 4-Hb) and 1.94 (3H, s, 3-CH_3) ascribed to a modified benz[a]anthraquinone chromophore which is characteristic to the isotetracenone antibiotics; δ 4.87 (dd, J=11.2, 1.6, 1'-H), 4.64 (dd, J=9.4, 9.0, 4'-H), 3.97 (ddd, J=11.0, 9.0, 5.3, 3'-H), 3.66 (dq, J=9.4, 6.0, 5'-H), 2.57 (ddd, J=11.3, 5.3, 1.6, 2'-Heq), 1.51 (ddd, J=11.3, 11.2, 11.1, 2'-Hax) and 1.30 (3H, d, J=6.0, 6'-H) assignable to a β-olivoside moiety; δ 7.33 (m, 3"-H), 6.19 (2H, m, 4"-H and 5"-H), 5.87 (d, J=15.4, 2"-H), 2.19 (2H, dt, J=5.4, 7.1, 6"-H_2), 1.44 (2H, tt, J=7.3, 7.1, 7"-H_2), 1.31 (4H, m, 8"-H_2 and 9"-H_2) and 0.90 (3H, t, J=7.4, 10"-H_3) due to a 2,4-decadienoic acid side chain.

Based on {^{13}C- ^1H} selective proton decoupling experiments[3] of 1 at 100 MHz, the following signals have been assigned (see Fig. 1): δ 78.8 (d, C-4'), 74.3 (d, C-5'), 71.5 (d, C-3'), 71.2 (d, C-1'), 40.1 (t, C-2') and 18.4 (q, C-6') due to the olivose residue; 167.7 (s, C-1"), 146.5 (d, C-3"), 145.8 (d, C-5"), 127.9 (d, C-4"), 117.9 (d, C-2"), 33.2 (t, C-6"), 31.6 (t, C-8"), 28.6 (t, C-7"), 22.7 (t, C-9") and 14.3 (q, C-10") due to the 2,4-decadienoic acid moiety. Long range selective proton decoupling (LSPD) experiments established the tetracyclic structure and the ^{13}C chemical shift assignments of the chromophore moiety as shown in Fig.2. The linkage of C and D rings was proved by observing nuclear Overhauser effect between 4-H_2 and 5-H. Thus, the structure of the chromophore was established to be 4a,12b-dihydro-4a,8,12b-trihydroxy-3-methyl-benz[a]anthracene-1,7,12(4H)-trione.

Fig. 2.

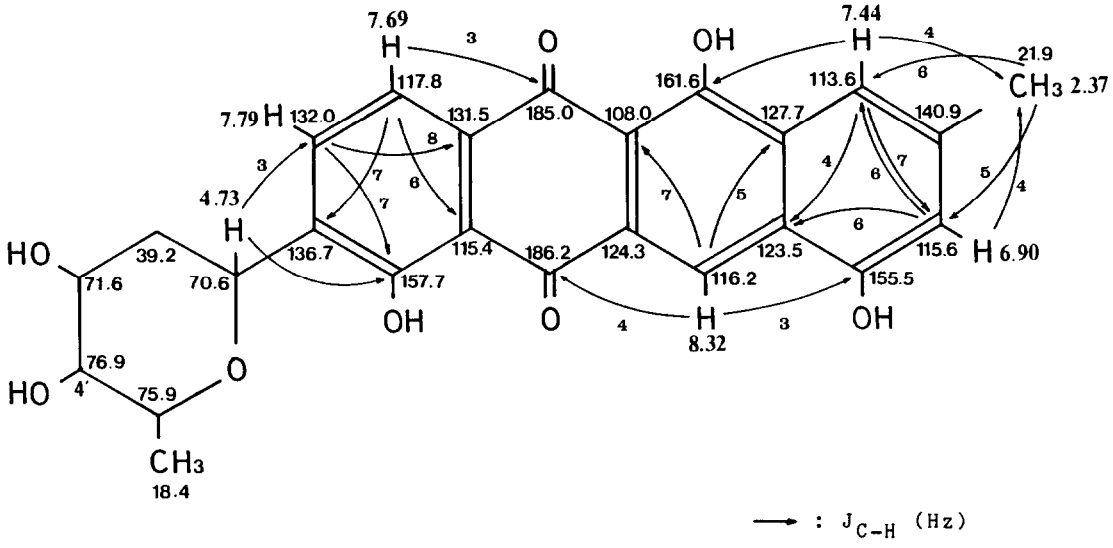


The long range coupling between 10-H and 1'-H indicates that the olivose residue is connected to C-9 position with a C-glycosidic linkage.

Hydrolysis of 1 with 0.1 N NaOH at room temperature for 30 min gave a rearranged chromophore with a C-olivoside (2) [$C_{25}H_{22}O_8$; FAB-MS, m/z 451 $(M+H)^+$] and a 2,4-decadienoic acid (3) [$C_{10}H_{16}O_2$; EI-MS, m/z 182 (M^+, methyl ester)].

The ^1H and ^{13}C NMR spectra in DMSO-d_6 revealed that the compound 2 consists of a tetracene-quinone chromophore and an olivose moiety. Based on LSPD experiments, the structure of 2 was elucidated as shown in Fig. 3. Such a rearrangement as involved in the conversion of 1 with the modified benz[a]anthraquinone into the tetracene-quinone derivative (2) was reported in case of aquayamycin[6], an isotetracenone antibiotic.

Fig. 3. The structure of 2



The compound 3 was determined to be (E,E)-2,4-decadienoic acid[4] by the ^1H NMR spectral data in pyridine-d_5. The geometrical configurations were elucidated by the coupling constants of olefinic protons ($J_{2-H,3-H}$=15.4Hz, $J_{4-H,5-H}$=15.0 Hz).

Treatment of 1 with 0.1 N HCl at 100°C for 10 min yielded a rearranged product (4) [$C_{35}H_{36}O_9$; FAB-MS, m/z 601 $(M+H)^+$]. Comparison of the ^{13}C NMR spectrum[5] of 4 with those of 2 and 3 indicates that the compound 4 consists of 2 and 3. Since the acylation shift was observed on 4'-H (δ 2.90 → 4.67), the structure of 4 was determined to be a 4'-O-[(E,E)-2,4-decadienoyl] derivative of 2.

Thus, it is concluded that the structure of capoamycin (1) is as shown in

Fig. 1 with the uncertainty about the stereochemistry of the ring juncture between C and D and the absolute configuration.

Acknowledgement

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References and footnotes

1) Y. Hayakawa, T. Iwakiri, K. Imamura, H. Seto and N. Ōtake, J. Antibiotics, in press.

2) Y. Ichikawa, J. Cell. Physiol., 74, 234 (1969).

3) ^{1}H and ^{13}C spectra were obtained on a JEOL GX-400 spectrometer operating at 400 MHz and 100 MHz, respectively. Chemical shifts are given in ppm using TMS as internal standard.

4) ^{13}C NMR spectral data of 3 in $CDCl_3$ are as follows: δ 171.4 (C-1), 147.2 (C-3), 145.9 (C-5), 128.0 (C-4), 117.8 (C-2), 33.0 (C-6), 31.6 (C-8), 28.6 (C-7), 22.7 (C-9) and 14.3 (C-10).

5) ^{13}C NMR spectral data of 4 in $CDCl_3$-CD_3OD are as follows: δ 187.5(C-7), 186.3 (C-12), 167.3 (C-1"), 162.3 (C-1), 158.3 (C-8), 155.3 (C-5), 146.0 (C-3"), 145.5 (C-5"), 141.3 (C-3), 136.3 (C-9), 132.7 (C-10), 132.5 (C-11a), 128.7 (C-1a), 127.7 (C-4"), 125.4 (C-6a), 124.7 (C-5a), 118.5 (C-11), 117.9 (C-2"), 117.5 (C-6), 116.4 (C-7a), 116.0 (C-4), 115.5 (C-2), 108.9 (C-12a), 78.3 (C-4'), 74.4 (C-5'), 71.3 (C-1' and C-3'), 39.9 (C-2'), 33.1 (C-6"), 31.4 (C-8"), 28.4 (C-7"), 22.6 (C-9"), 22.3 (3-CH_3), 18.2 (C-6') and 14.0(C-10").

6) M. Sezaki, S. Kondo, K. Maeda, H. Umezawa and M. Ohno, Tetrahedron, 26, 5171 (1970).

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