Structure of Ericamycin Having a 2-Azahexaphene Ring System

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An anti-staphylococcal antibiotic, ericamycin was found in the culture of *Streptomyces varius* n. sp. by a Meiji group in 1966.[1] In the 30 years since the first isolation of this antibiotic, no attempt has been made to elucidate the structure. In this paper, the structure determination by the MS, NMR and CD spectral studies are presented.

General Methods

UV spectra were recorded on a Hitachi U-3210 spectrophotometer. MS spectra were measured on Jeol JMS-SX102 (FAB mode) and on Jeol JMS-700 (FAB-HR-MS) mass spectrometers. NMR spectra in DMSO-d_6 at 60°C were taken on a Jeol JNM-LA400 spectrometer. ^{1}H NMR spectra were recorded at 400 MHz using TMS ($\delta=0$) as an internal standard, ^{13}C NMR spectra at 100 MHz using DMSO-d_6 ($\delta=39.5$) as an internal standard and ^{15}N NMR spectra at 40.6 MHz using $NH_4{}^{15}NO_3$ ($\delta=0$) as an external standard. CD curves in MeOH were recorded with a JASCO J-720W spectropolarimeter.

Results and Discussion

Ericamycin which was isolated from the streptomyces culture as the deep red crystals,[1] showed UV λ_{max}^{MeOH} nm (ε) 249 (39,508), 323 (15,800), 345 (13,129), 364 (12,435), 487 (14,451); $\lambda_{max}^{0.1\,N\,HCl\text{-}MeOH}$ nm (ε) 249 (45,125), 323

Fig. 1. Summary of HMBC and NOESY data for ericamycin.

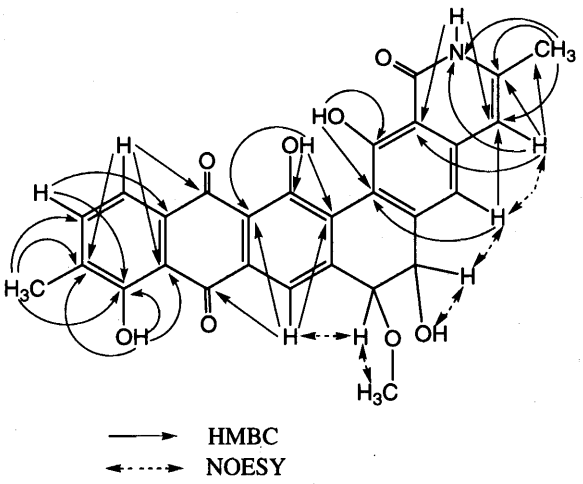
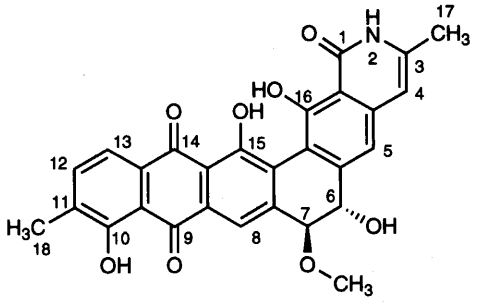


Table 1. ^{1}H and ^{13}C NMR data in DMSO-d_6 at 60°C.

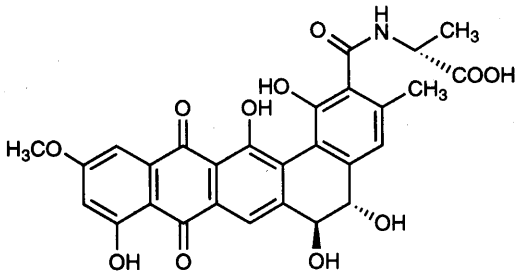
Position	^{13}C (δ)	^{1}H (δ) (J, Hz)	Position	^{13}C (δ)	^{1}H (δ) (J, Hz)
1	166.5 s		10-OH		12.92 s
2		11.73 s	11	134.6 s	
3	139.4 s		12	137.1 d	7.68 br d (7.8)
4	105.1 d	6.50 s	13	118.5 d	7.70 br d (7.8)
4a	139.8 s		13a	130.6 s	
5	110.7 d	7.19 s	14	187.4 s	
5a	145.7[a] s		14a	115.1 s	
6	71.2 d	4.54 br d (8.5)	15	158.8 s	
6-OH		5.90 br	15-OH		13.37 s
7	81.5 d	4.23 br d (8.5)	15a	126.5 s	
7-OCH_3	59.0 q	3.65 br s	15b	110.7 s	
7a	145.9[a] s		16	158.2 s	
8	115.1 d	7.89 s	16-OH		13.95 s
8a	130.6 s		16a	109.3 s	
9	187.2 s		17	18.3 q	2.29 s
9a	114.7 s		18	15.3 q	2.31 s
10	159.9 s				

[a] Exchangeable.

Fig. 2. Structures of ericamycin and benanomicinone.



Ericamycin



Benanomicinone

(18,513), 346 (14,825), 364 (13,940), 484 (16,682); $\lambda_{max}^{0.1\,N\,NaOH\text{-}MeOH}$ nm (ε) 209 (79,017), 253 (50,359), 324 (14,556), 360 (12,345), 520 (19,411); FAB-MS (pos.) *m/z* 500 $(M+H)^+$; FAB-HR-MS (pos.) *m/z* 500.1359 $(M+H)^+$, calcd for $C_{28}H_{22}NO_8$, 500.1346.

By the extensive NMR analyses including HMBC, HMQC and NOESY experiments (Fig. 1), the structure of ericamycin was elucidated, and all the proton and carbon signals were assigned as shown in Table 1. In addition, an HMQC correlation between ^{15}N (δ −217.8) and NH proton (δ 11.73) was observed. Although the broad proton signals were observed on the K-region of the polycyclic system, coupling constants (J=8.5 Hz) of pseudodiaxial protons were shown at 6-H and 7-H.

In the CD curve of ericamycin in MeOH, a negative Cotton effect at 262 nm ($\Delta\varepsilon$ = −33.7) and a positive Cotton effect at 242 nm ($\Delta\varepsilon$ = +27.2) showed that the substituted anthraquinone and isoquinolone rings had counterclockwise helicity.[2~6] Therefore, the conformation having 6*S*,7*S*-pseudodiaxial protons was suggested, as similar to that of benanomicin A.[6]

Finally the absolute structure of ericamycin was elucidated to be (6*S*,7*S*)-6,7-dihydro-6,10,15,16-tetrahydroxy-7-methoxy-3,11-dimethyl-2*H*-2-azahexaphene-1,9,14-trione, closely resembled that of benanomicinone (Fig. 2), the aglycon of benanomicin A. Several bioactive dihydrobenzo[*a*]naphthacenequinone compounds were isolated from *Actinomycetes* cultures; KS-619-1 inhibiting phosphodiesterase,[7] SF2446 with strong anti-staphylococcal activity,[8] benanomicins[6,9] and pradimicins[5,10] with antifungal and antiviral activities, bequinostatins inhibiting glutathione *S*-transferase,[11] WS79089 inhibiting endothelin converting enzyme,[12] and benaphthamycin with limited antibacterial activity.[13] Albofungin and related xanthone-isoquinolone antibiotics also showed interesting activities.[14,15] Ericamycin is a promising lead for studies on the structure-activity relationships of dihydrobenzo[*a*]naphthacenequinone compounds.

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