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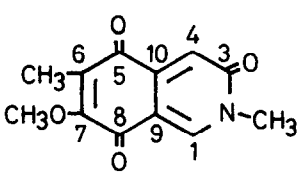
THE STRUCTURES OF NOVEL ANTIBIOTICS, SAFRAMYCIN B AND C

Tadashi Arai*
Department of Antibiotics, Research Institute for Chemobiodynamics,
Chiba University, Inohana, Chiba, Japan
Katsuhiro Takahashi
Chiba Cancer Center Research Institute, Nitona, Chiba, Japan
Akinori Kubo* and Shinsuke Nakahara
Meiji College of Pharmacy, Nozawa, Setagaya, Tokyo, Japan
Sadao Sato, Kimie Aiba and Chihiro Tamura*
Central Research Laboratories, Sankyo Co. Ltd.
Hiromachi, Shinagawa, Tokyo, Japan

The structure of saframycin C(3) has been established by an X-ray crystallographic analysis; this result allows the assignment of structure to the closely related saframycin B(2) by ^{13}C NMR spectroscopy.

We have described the isolation of a number of satellite antibiotics derived from streptothricin-producing strain of *Streptomyces lavendulae* No. 314.[1] One of the satellite antibiotics was designated mimosamycin and its structure was determined as 7-methoxy-2,6-dimethyl-3,5,8-trioxo-2,3,5,8-tetrahydroisoquinoline(1) by an X-ray crystallographic analysis[2] and its total synthesis.[3] We reported the isolation and biological



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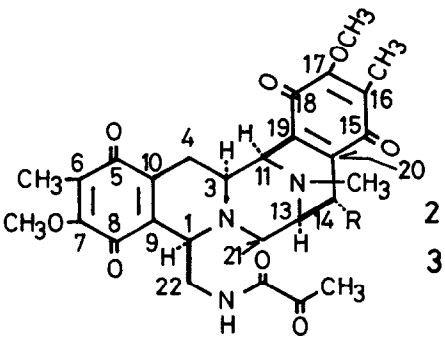

2 R = H
3 R = OCH_3

properties of novel antibiotics, saframycin A, B, C, D and E from the same strain.[4]

We wish to report here the structural elucidation of two major antibiotics, saframycin B(2) and C(3), possessing dimeric structures of mimosamycin(1).

Saframycin B and C were obtained from the basic fractions of the methylene chloride extract of the cultured broth and purified by silica gel and LH-20 Sephadex column chromatography.

The physical constants of saframycin B(2), orange yellow prisms, are as follows: mp 108-109°(ether); $[\alpha]_D$-54.4°(MeOH); $C_{28}H_{31}N_3O_8$; mass spectrum *m/e*(%):537(M^+,14),437(M-100,100),220(68),218(46); UV λ_{max}^{MeOH} nm(log ε):269 (4.35),368(3.13); CD(MeOH):275nm(Δε -14.8); IR $\nu_{max}^{CHCl_3}$ cm^{-1}:3430,1720,1690, 1660,1620. The ^1H NMR spectrum($CDCl_3$,100MHz) showed signals at δ1.90 (s),1.98(s),2.23(s),2.28(s),4.00(2xs) due to six methyl groups.

Its ^{13}C NMR spectrum($CDCl_3$) revealed the nature of the methyl groups [δ8.6(2xC-$\underline{C}H_3$),24.2(CO$\underline{C}H_3$),41.2(N-$\underline{C}H_3$),60.9(2xO$\underline{C}H_3$)] and showed six pairs of singlets at δ127-187 ascribed to the quaternary aromatic and carbonyl carbons. Comparisons of these ^{13}C NMR data with those of mimosamycin (1)[5](Table 1) and 3,6-dimethoxythymoquinone[6] revealed the presence of two 2-methyl-3-methoxy-*p*-benzoquinone moieties in 2.

Saframycin C(3), orange red needles; mp 143-146°(ether); $[\alpha]_D$-20.8° (MeOH); $C_{29}H_{33}N_3O_9$, gave the following spectral data: mass spectrum *m/e* (%):567(M^+,2),537(M-30,2),467(M-100,20),437(20),220(26),218(100); UV λ_{max}^{MeOH} nm(log ε):266.5(4.32),368(3.19); CD(MeOH):273nm(Δε -28.3); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400,1720,1685,1655,1615. The ^1H NMR spectrum($CDCl_3$) showed signals at δ1.86(s),2.00(s),2.38(s),2.44(s),3.46(s),3.96(2xs) due to seven methyl groups. Its ^{13}C NMR spectrum($CDCl_3$) revealed the nature of the all methyl groups[δ8.7,9.0(2xC-$\underline{C}H_3$),24.3(CO$\underline{C}H_3$),42.3(N-$\underline{C}H_3$),59.3,60.9 and 61.0 (3xO$\underline{C}H_3$)]. Further features included the presence of the characteristic six pairs of singlets at δ127-187, which were almost identical to those of 2. These spectral data indicated that 3 had the same carbon skeleton as 2 and an additional methoxy group(δ59.3) which should be located at the

Table 1 ^{13}C Chemical Shifts(δ) of Mimosamycin(1), Saframycin B(2) and C(3) in $CDCl_3$[7]

Carbon No.	1	Carbon No.	2	3
5	183.5	5 or 15	185.7 or 187.0	185.5 or 186.6
6	133.6	6 or 16	127.7 or 129.2	127.9 or 130.7
7	159.5	7 or 17	155.5 or 156.1	155.4 or 156.1
8	177.3	8 or 18	181.3 or 182.8	181.3 or 183.2
9	111.3	9 or 19	136.3 or 136.6	136.6 or 136.6
10	138.9	10 or 20	141.6 or 142.8	141.5 or 141.6
6-CH_3	9.7	6 or 16 -CH_3	8.6 or 8.6	8.7 or 9.0
7-OCH_3	61.3	7 or 17 -OCH_3	60.9 or 60.9	60.9 or 61.0
N-CH_3	38.5	N-CH_3	41.2	42.3
		1 or 11	52.2 or 54.8	55.2 or 55.7
		3 or 13	56.9 or 57.4	57.6 or 58.0
		4	25.6(t)	25.5(t)
		14	22.7(t)	71.9(d)
		14-OCH_3		59.3
		21	58.7(t)	55.7(t)
		22	40.4(t)	40.7(t)
		NHCO	160.1	160.2
		$COCH_3$	24.2, 196.5	24.3, 196.5

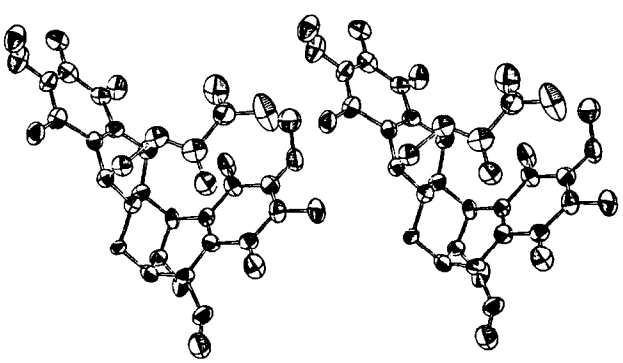

Figure 1. Stereoprojection of Saframycin C(3)

methylene carbon(δ22.7) adjacent to the one of *p*-quinone moieties in 2.

The complete structure and stereochemistry of 3 was established by an X-ray crystallographic study of its hydrobromide, orange prisms(acetone), mp >280°, $C_{29}H_{33}N_3O_9 \cdot HBr \cdot H_2O$. The crystals were found to have monoclinic space group $P2_1$. Cell dimensions measured on a Rigaku four circle diffractometer were; a= 11.819(3) b= 19.644(5) c= 7.650(3) Å, β= 114.7°.

A total of 2014 independent reflections accessible with CuKα radiation below 2θ= 128° were collected on the diffractometer. The structure was solved by heavy atom technique and the block diagonal least-squares refinement reduced the R factor to the final value of 0.085. The hetero atoms were assigned by means of chemical information, temperature factors of each atoms and their bond lengths and angles. Figure 1 shows the stereoscopic view of this salt which refers to the conformational feature of 3.

Saframycin B and C therefore have the structures depicted in 2 and 3 or their antipodes.

References and Notes

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7) Natural-abundance ^1H noise decoupled(PND) and off-resonance ^{13}C FT NMR spectra were recorded on a Jeol FX-60 and FX-100 FT NMR spectrometer. TMS served as an internal reference(δ0).

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