THE STRUCTURE OF EFROTOMYCIN

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The antibiotic efrotomycin (**I**), $C_{59}H_{88}N_2O_{20}$, was isolated from cultures of *Nocardia lactamdurans* as an amorphous yellow powder. Mass spectral and NMR analyses show that the compound is a glycoside of the known antibiotic aurodox (**II**), $C_{44}H_{62}N_2O_{12}$. Ozonolysis and hydrolysis of **I** produced the disaccharide **V**, 6-deoxy-4-*O*-(6-deoxy-2,4-di-*O*-methyl-α-L-mannopyranosyl)-3-*O*-methyl-β-D-allopyranose. This disaccharide is attached to the 4-hydroxyl group of the hexahydropyran substructure of aurodox *via* a β-linkage to C-1 of the allose.

The discovery of efrotomycin in cultures of *Nocardia lactamdurans* has been reported from our laboratories[1,2]. In the following we wish to communicate the data which define structure **I** of the antibiotic.

Preparative silica gel TLC in methylene chloride - methanol - concd ammonium hydroxide (80: 20: 2) gave a light yellow, slightly deliquescent, amorphous powder of Rf 0.2, whose UV absorption spectrum in methanol - 0.05 M phosphate buffer (pH 6.84) (20: 80) showed λ_{max} nm (log ε) 219 (4.78), 230 (4.77), 325 (4.57), analogous to, but of lower intensity than, those of aurodox, **II** (also known as antibiotic X5108[3] or goldinodox[4]). The ^{1}H NMR spectra of **I** (Fig. 1; 100 MHz, $CDCl_3$ showed the following distinctive signals in addition to those of aurodox: δ 1.21 (3H, d, J=6 Hz, CH_3CHO), 1.31 (3H, d, J=6 Hz, CH_3CHO), 3.45 (3H, s, CH_3O), 3.54 (3H, s, CH_3O), 3.58 (3H, s, CH_3O), 4.63 (1H, d, J=8 Hz, OCHO), 4.87 (1H, d, J=1.3 Hz, OCHO) and a complex envelope at δ 3.5

Fig. 1. 100 MHz ^{1}H NMR spectrum of efrotomycin ($CDCl_3$).

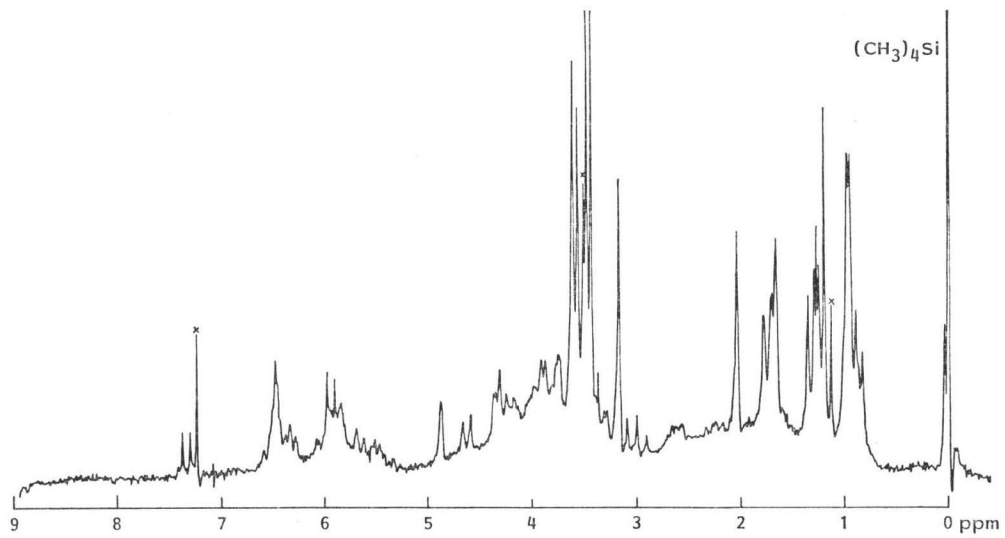
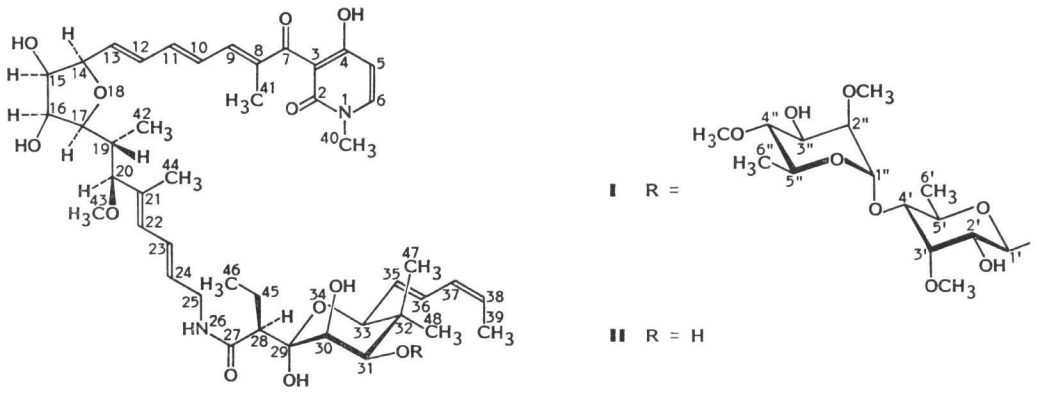


Table 1. Proton-decoupled ^{13}C NMR resonances of I, II and V*.

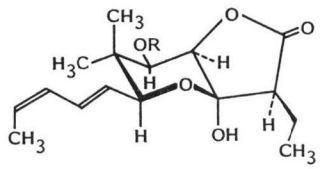
Efrotomycin (I)	Aurodox (II)	Disaccharide V	Efrotomycin (I)	Aurodox (II)	Disaccharide V
11.2	11.2		83.0		
12.2 (2)	12.3 (2)		84.4		83.8
13.7	13.7		84.6		84.4
13.9	13.9		84.8	84.9	
16.6	15.9		91.8	91.8	
18.2 (2)		18.1			95.4
		18.2	100.1		100.2
21.2	21.1		Obscured (2)	100.9	
24.5	24.6		103.7	Obscured	
36.6	36.7		112.1	111.9	
37.1	37.2		126.9	126.3	
39.6	39.9		127.7 (2)	127.6	
42.0	42.2		127.8	128.1 (2)	
52.2	52.4		129.5	129.3	
56.2	56.2		130.3 (2)	130.5 (4)	
59.2		59.2	130.7		
61.0		60.9	131.0		
62.1		62.0	133.5	133.6	
69.7 (2)		69.1	135.8 (2)	135.9	
		69.9		136.1	
70.5	71.3		139.2	140.4 (2)	
71.8		71.8	140.0		
73.1	73.9 (2)		142.0	142.1	
73.8		74.3	164.4	164.3	
74.8	74.9		171.9	172.9	
77.1	77.2		177.6	177.8	
81.7	81.5		187.2	187.2	
82.3 (2)		82.4			
		82.6			

* Spectra were recorded on a Varian HA 100 or CFT 20 spectrometer in CD_3OD with $(CH_3)_4Si$ at 0 ppm as internal standard.



to 4.5. The proton decoupled ^{13}C NMR spectrum of I (Table 1; CD_3OD, chemical shifts in ppm downfield from internal $(CH_3)_4Si$) also showed a close correlation with that of aurodox with additional signals at 18.2 (2C), 59.2, 61.0, 62.1, 69.7 (2C), 71.8, 73.8, 82.3 (2C), 84.4, 84.6, 100.1 and 103.7 ppm. FD mass spectra showed peaks up to *m/z* 1,167.4 ($C_{59}H_{88}N_2O_{20}\cdot Na^+$); *Anal* Calcd for $C_{59}H_{88}N_2O_{20}\cdot$

H_2O: C 60.91, H 7.80, N 2.41%, Found: C 61.00, H 7.70, N 2.41%. A mass spectral fragment of underivatized **II** at *m/z* 296, assigned to the previously described[5], thermally generated lactone **III**, was found at *m/z* 630 in the spectrum of underivatized **I**. The difference in elemental composition between these two fragments, $C_{15}H_{26}O_8$, is equal to the difference in elemental composition between **I** and **II**. The NMR data given above suggested a disaccharide substituent consisting of two 6-deoxyhexose subunits carrying one and two *O*-methyl groups, respectively. The complete interpretation of the 300 MHz NMR spectra of an efrotomycin derivative will be discussed later in this paper.



III: R=H
IV: R=$C_{15}H_{27}O_8$ (as for **I**)

The lactone disaccharide degradation product **IV** was obtained by dissolving efrotomycin in glacial acetic acid at 60°C for 24 hours, IR ν_{max} ($CHCl_3$) cm^{-1} 1776; UV nm (log ε) 231 (4.42) and 264 (sh, 4.17); EI-MS relative intensity (%) *m/z* 612 (1.6, M−H_2O), 598 (0.5), 594 (0.7), 580 (0.6), 512 (2.3), 494 (1.7), 485 (1.7), 467 (2.5), 452 (6), 407 (6), 335.1681 (12, $C_{15}H_{27}O_8$, calcd 335.1706), 307 (35), 297 (8), 296 (9), 279 (35), 271 (8), 261 (17), 247 (14), 189 (49), 183 (29), 178 (46), 175 (100), 169 (35), 157 (58), 143 (29), 135 (31), 131 (81), 115 (38), 111 (47) and 101 (88); *Anal* Calcd for $C_{31}H_{50}O_{13}\cdot 0.5H_2O$: C 58.20, H 8.04%, Found: C 58.27, H 8.45%.

Hydrolysis of efrotomycin with dilute aqueous hydrochloric acid produced a complex mixture of products, one of which gave a characteristic carbohydrate color reaction with vanillin-sulfuric acid and was identified as **V**. The purification of **V** was greatly simplified by prior ozonolysis of the antibiotic in ethyl acetate at −20°C followed by treatment with hydrogen peroxide and hydrolysis in dilute acetic acid. It crystallized from 2-propanol, mp 149~151°C; $[\alpha]_D^{25}$ −30.2° (*c* 1.0, CH_3OH); *Anal* Calcd for $C_{15}H_{28}O_9$: C 51.13, H 8.01%, Found: C 51.41, H 8.18%; ^1H NMR (CD_3OD) δ 1.41 (3H, d, *J*=6.2 Hz, CH_3CHO), 1.48 (3H, d, *J*=6.3 Hz, CH_3CHO), 3.45 (3H, s, CH_3O), 3.53 (3H, s, CH_3O), 3.58 (3H, s, CH_3O), 3.03 (1H, dd, *J*=9.2, 9 Hz, CHO), 3.23 (1H, m, CHO), 3.33 (1H, m, CHO), 3.41 (1H, m, CHO), 3.58 (1H, m, CHO), 3.73 (3H, m, 3CHO), 4.75 (1H, d, *J*=8 Hz, OCHO), 4.86 (1H, d, *J*=2.4 Hz, OCHO); ^{13}C NMR (CD_3OD) see Table 1; EI-MS see Table 2. Reaction of **V** with acetic anhydride in pyridine gave the triacetyl derivative **VI**, mp 141~142°C; $[\alpha]_D^{25}$ −60° (*c* 1.0, $CHCl_3$); *Anal* Calcd for $C_{21}H_{34}O_{12}$: C 52.71, H 7.16%, Found: C 52.15, H 7.00%; EI-MS see Table 2; ^1H NMR ($CDCl_3$) see Table 3. The mass spectral and NMR data establish the structure

Table 2. Mass spectral characteristics of **V** and its derivatives*.

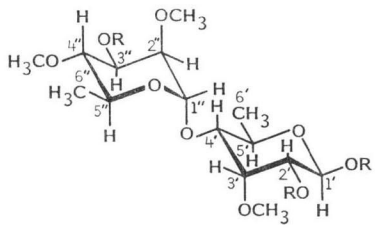
R=H	R=$COCH_3$	R=$Si(CH_3)_3$	R=$Si(CD_3)_3$	Assignment
	478 (vw)	568 (vw)	595 (vw)	M^+
		553	577	$M-CH_3/CD_3$
		521	545	$M-(CH_3OH+CH_3/CD_3)$
335 (w)	419 (w)	479 (w)		M−OR
248 (w)	374 (w)	464 (s)	491 (s)	$[C_6H_8O(OCH_3)(OR)_2OC_3H_2O(OR)]^+$
247 (s)	331 (m)	391 (s)	409 (s)	$[C_6H_8O(OCH_3)_2(OR)OC_3H_3(OR)]^+$
175 (s)	217 (s)	247 (s)	256 (s)	$[C_6H_8O(OCH_3)_2OR]^+$
157 (s)	157 (s)	157 (s)	157 (s)	$[C_6H_8O(OCH_3)_2]^+$
101 (s)	101 (s)	101 (s)	101 (s)	$[C_3H_3(OCH_3)_2]^+$

* Letters in brackets after mass numbers indicate peak intensities: vw=very weak, w=weak, m=medium, s=strong (≥25% of base peak).

Table 3. ^{1}H NMR data for disaccharide triacetate **VI***.

C-6′ and 6″ CH_3	1.26 (3H, d, J=6.5) and 1.32 (3H, d, J=6.2)
CH_3CO	2.07 (3H, s), 2.09 (3H, s) and 2.13 (3H, s)
C-4″H	3.22 (1H, t, J=9.0)
C-4′H	3.34 (1H, dd, J=9.8, 2.5)
CH_3O	3.43 (3H, s), 3.54 (3H, s) and 3.57 (3H, s)
C-2″H	3.61 (1H, dd, J=2.5, 3.1)
C-5″H	3.76 (1H, dq, J=9.4, 6.5)
C-3′H	3.88 (1H, t, J=2.5)
C-5′H	4.05 (1H, dq, J=9.4, 6.5)
C-2′H	4.74 (1H, dd, J=8.8, 2.4)
C-1″H	4.81 (1H, d, J=2.5)
C-3″H	5.08 (1H, dd, J=8.8, 3.1)
C-1′H	5.07 (1H, d, J=8.3)

* Spectra were recorded in $CDCl_3$ solution; chemical shifts are given in ppm relative to internal tetramethylsilane; coupling constants are given in Hz.



V: R=H
VI: R=$COCH_3$

and relative configuration of the carbohydrate as the disaccharide **V**, 6-deoxy-4-*O*-(6-deoxy-2,4-di-*O*-methyl-α-L-mannopyranosyl)-3-*O*-methyl-β-D-allopyranose. The orientation of C-1″H of the rhamnosyl moiety was assigned on the basis of the $^3J^g$ couplings of 2.4 and 2.5 in **V** and **VI** respectively. These are in agreement with the reported range of 2~3.5 for the case of an electron withdrawing group antiperiplanar in a gauche proton-proton coupling in carbohydrates, and above 0.8~2.0 Hz for the case where both protons are antiperiplanar to electron withdrawing substituents[6]. The value of 1.3 in efrotomycin itself is low and is not understood. Relatively low couplings 1.1 and 1.8 Hz are reported for the α and β forms of rhamnose itself[7]. Recent unpublished ^{13}C NMR spectra taken on a Varian XL 400 instrument in our laboratories further support the configuration favored by the derivatives.

Cleavage of the disaccharide **V** with 40% sulfuric acid gave 2,4-di-*O*-methyl-L-rhamnopyranose as a syrup; $[\alpha]_D^{25}$ +5.6° (*c* 0.8, H_2O): reported a) hygroscopic solid, mp 91~93°C, $[\alpha]_D^{20}$ +10.6° (H_2O)[8]; b) syrup, $[\alpha]_D$ −17° (*c* 0.3)[9]; c) mp 82°C, $[\alpha]_D^{18}$ −19° (*c* 1.0, H_2O)[10]. Better definition was obtained for the 1-*N*-phenylamino derivative; mp 142~144°C, $[\alpha]_D^{25}$ +106° (*c* 1.0, C_2H_5OH) falling to +14° in nine days; reported a) mp 141~142.5°C, $[\alpha]_D^{18}$ +136° falling to + 4° (*c* 0.5, C_2H_5OH)[8]; b) mp 141~142°C, $[\alpha]_D$ +110° falling to + 7° (*c* 0.4, C_2H_5OH)[10]; c) mp 141~142.5°C, $[\alpha]_D^{18}$ +128.5° falling to +5.6° (*c* 0.4, C_2H_5OH)[11]. The 2,4-dinitrophenylhydrazone was also obtained, mp 169~171°C, $[\alpha]_D^{25}$ +30.1° (*c* 0.18, dioxane); reported: mp 164~165°C, $[\alpha]_D^{23}$ +39° (*c* 1.0, dioxane)[9]. A second product of the hydrolysis of **V** was identified as 6-deoxy-3-*O*-methyl-D-allopyranose, mp 123~124°C, $[\alpha]_D^{25}$ +4.5° (*c* 1.0, H_2O); reported: mp 122~123°C, $[\alpha]_D^{30}$ +9° (*c* 1.0)[12] and mp 119~121°C, $[\alpha]_D$ +3.8° (*c* 1.0, H_2O)[13]. The correlations establish the absolute configuration of **V** as shown.

The γ-lactone degradation products **III** and **IV** of aurodox and efrotomycin, respectively, are readily formed by mild acid hydrolysis, or thermally in the mass spectrometer, strongly suggesting that the disaccharide is linked to the C-31-hydroxyl group. The coupling constant of 8~8.5 Hz, observed for **II**, which must be assigned to C-1′H of the allose moiety attached to the aglycone, established the β-configuration for this linkage. The identity of the aglycone of efrotomycin with aurodox[14,15,16] is assumed on the basis of very similar ^{13}C NMR spectra of the two compounds (see Table 1).

Examination of the ^{1}H NMR characteristics of 4-pivaloylefrotomycin at 300 MHz made it possible

Table 4. Efrotomycin pivalate assignments ($CDCl_3$).

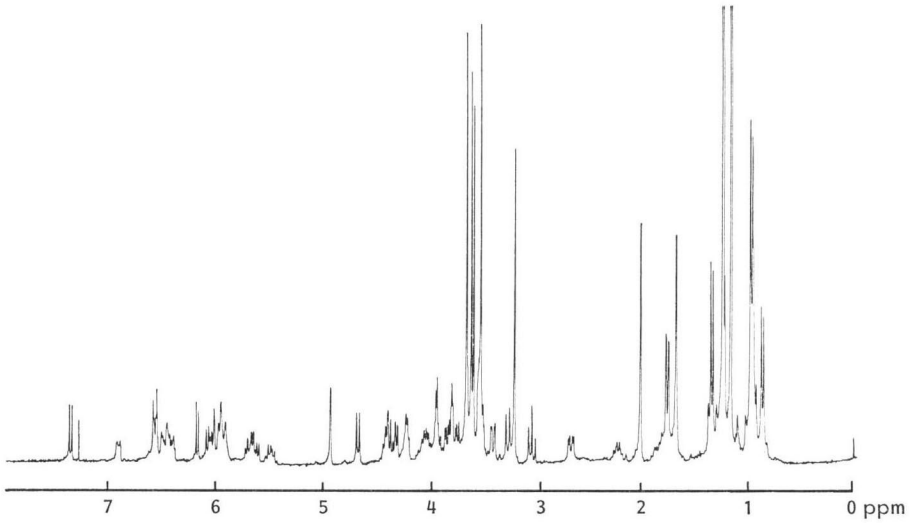
H	δ	J	H	δ	J
1″	4.91 d	1.0~1.5	4″(OCH_3)	3.50[a]	
2″	~3.50 dd	~1	2″(OCH_3)	(3.58 s or	
		3.5		3.63 s)[a]	
3″	3.82 dd	9.5	3′ (OCH_3)	(3.58 s or	
		3.5		3.63 s)[a]	
4″	3.02 t	9.0	25	4.02 m	
5″	3.73 dd	8.9	24	5.67 dt	15.0
		6.5			6.0
4′	3.39 dd	9.7	23	6.45 dd	12.0
		2.0			12.0
3′	3.77 t	2.0~2.5	22	5.92 d	12.0
2′	~3.52 dd	8.0	44	1.66 s	
		~2	19	2.22 d[b]	9.0
1′	4.65 d	8.0			6.5
5′	3.91 dd	9.5	20	3.25 d	9.0
		6.5	17	3.49 dd	6.5
30	3.91 d, 3.63 d	3.5			3.5
31			16	4.20 t	3.5
33	4.29 d	6.2	15	4.39 dt	~3.5
28	2.66 dd	11.0			6.5
		4.0	14	4.35 t	6.5
45	~1.75 m		13	6.04 dd	15.0
35	5.62 dd	14.7			6.5
		6.0	12	~6.45	15.0
36	~6.45 dd	15.0			12.0
		12.0	11	6.56 m	
37	6.00 t	12.0	10	6.56 m	
38	5.46 dq	11.0	9	6.90 m	
		7.0	5	6.16 t	8.0
39	1.75 dd	7.0	6	7.36 d	8.0
		~1.5	43	3.18[a]s	
46	0.95 t	6.5	42	0.86 d	6.5
47, 48	0.95, 0.97		41	1.99 s	
6	1.33 d	6.5	40	3.56[a]s	
6″	1.22 d	6.5	26	5.96	

[a] Preferred assignments, [b] apparent quintet.

to assign virtually all non-labile proton resonances as shown in Table 4 and Fig. 2 with the help of double irradiation experiments and solvent changes.

Although the *N*-methyl and the four methoxyl signals have not been identified with certainty, distinctive chemical shifts, relaxation behavior and solvent effects provided the basis for preferred assignments. The unique, high field methyl peak at δ 3.18 is associated with the 43-OCH_3 (β to the tetrahydrofuran ring) because the nearby 20-H and 42-CH_3 resonances were displaced significantly upfield from their normal positions. It is thus reasonable to infer that the long-range shielding source responsible for shifting the 42-CH_3 and 20-H would also affect the neighboring methoxyl. Several partially relaxed spectra provided useful information in revealing that the methyl peaks at 3.50 and 3.56 have distinctly longer relaxation times than the remaining three members of the group. Since longer relaxation times correlate with increased mobility, these signals were best assigned to the two methyls least subject to motional restriction, namely the pyridone *N*-methyl and the 4″-methoxyl.

Fig. 2. 300 MHz ^1H NMR spectrum of efrotomycin pivalate ($CDCl_3$).



Supportive evidence for this view was indicated by the uncommonly long relaxation times for the proximate H-4″ and the pyridone nuclear protons relative to the other sugar and vinyl protons, respectively. The large 0.8 ppm upfield displacement in benzene solution of the peak, which in chloroform is observed at δ 3.56, is a strong argument for associating it with the pyridone *N*-methyl group. It corresponds closely to the 0.70 ppm upfield shift which we observed for *N*-methyl-5-chloropyridone in benzene as compared to chloroform solution, and is furthermore consistent with analogous chemical shift changes, which have been reported for *N*-methyl lactams[17]. The 0.4 ppm upfield shift of the signal at δ 3.50 would be unusually small for the *N*-methyl group; the signal is therefore better assigned to the 4″-methoxyl group.

An attempt to identify the remaining two methoxyl signals at δ 3.58 and 3.63 *via* NOE experiments proved fruitless. Double irradiation at either frequency failed to affect the nearby H-1″, H-4″ or H-1′ signals.

In addition to H-4″, the 4″-OCH_3 and NCH_3 groups, other proton types characterized by long relaxation times and hence relatively high mobility are H-3″, H-5″, H-36 and the 39-methyl protons. Conversely, the 43-methoxyl group being close to a shielding moiety and, by implication, in a crowded environment restricting its mobility, has the shortest relaxation time of the set of methoxyls. The two methyls, at C-32 not surprisingly, also exhibit short relaxation times. It should be noted that all of these qualitative inferences on the dynamics are easily rationalized in terms of the molecular geometry.

Except for the amide NH signal at δ 5.96, the active hydrogens appear as broad, featureless peaks in chloroform, acetone and benzene, which make them unusable for identification.

In conclusion, efrotomycin is described as the 31-(6-deoxy-4-*O*-(6-deoxy-2,4-di-*O*-methyl-α-L-mannopyranosyl)-3-*O*-methyl-β-D-allopyranosyl) derivative of aurodox and the only glycosylated representative of this structural type of antibiotics. Recent publication of a synthesis of efrotomycin is in support of these findings[18,19].

Besides aurodox, its *N*-demethyl analog mocimycin[20] (probably identical with kirromycin[21] and

azdimycin[22], dihydromocimycin[23], heneicomycin[24], factumycin[25], kirrothricin[26], A73A[27] and L-681,217[28] (lacking a pyridone moiety) have been described.

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