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THE REACTION OF (9-E)-9-DEOXO-9-HYDROXIMINOERYTHROMYCIN A WITH ALKALINE N-BROMOSUCCINIMIDE

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Abstract: (9-E)-9-Deoxo-9-hydroximinoerythromycin A (2) was reacted with N-bromosuccinimide in aqueous sodium bicarbonate to give 9-deoxo-11-deoxy-9,11-epoxy-9-nitroso-3'-des-N-methylerythromycin A (5) which was converted into 3'-des-N-methyl-9-deoxo-9-hydroximinoerythromycin A (7) with tri n-butyl tin hydride.

Erythromycin A (1) is still the most clinically important 14-membered macrolide antibiotic in use today. However a major disadvantage of (1) in the clinic is its instability to mild acid[1]. The hydroxy groups at C-6 and C-12 react with the ketone at C-9 to give products of reduced biological activity. Improved acid stability has been achieved by conversion of the ketone at C-9 to an oxime[2] (2) [or O-alkylated oxime[3] eg (3)] and to the 9(S)-amine[2b,4] (4) and many derivatives of these compounds have been prepared in the quest for improved chemotherapeutic agents.

During our search for novel analogues of the 9-oxime of erythromycin A (2), we investigated the reaction of (2) with N-bromosuccinimide (NBS) in aqueous sodium bicarbonate solution. Under these conditions, Iffland and Criner[5] have converted oximes into gem-bromonitroso compounds which were used as intermediates in the synthesis of nitro derivatives. Treatment of (2) in dimethoxyethane with 3 equivalents of NBS in aqueous $NaHCO_3$ solution (containing 3 equivalents of base) for 2hr at room temperature gave a 42% isolated yield (after chromatography) of a faint blue-white foam. This foam was stable at -20° for several months but was unstable overnight at room temperature in chloroform solution and had the following physical properties: ^1H and ^{13}C nmr spectra[6] - (Tables 1 and 2); mp 151-154° ($CHCl_3$); $[\alpha]_D20$ -35.8° (c = 1.0 w/v in $CHCl_3$); ν_{max} (CH_2Cl_2) 3425, 2980, 2945, 1735, 1633, 1460, 1380, 1165, 1125, 1090, 1055 and 950cm^{-1}; FAB-MS m/z (thioglycerol matrix) 733 (MH^+), accurately measured as 733.4500 ($C_{36}H_{65}N_2O_{13}$ requires 733.4487) using a reference of phosphoric acid in glycerol; E.I.-M.S. m/z 701

(M-31), 144 (100%). These ions were accurately measured; 701.4345 ($C_{36}H_{63}NO_2$ requires 701.4354) and 144.1023 ($C_7H_{14}NO_2$ requires 144.1024). The product was shown to be the nitroso oxetan (5) by a combination of 1-D and 2-D proton and ^{13}C nmr spectroscopy.[7] The proton spectrum was fully assigned from the COSY-45 (figure) and 1-D decoupling experiments which in combination with the spin-echo and DEPT-90 and -135 carbon-13 n.m.r spectra, and the $^{1}J_{C-H}$ correlation experiment, gave the complete proton and ^{13}C assignments (Table 1).

The main evidence for structure (5) was as follows: in the ^{13}C spectrum of (5) the signal for C-11 has shifted from δ71.0 in (2) to δ84.20 ppm, which implies that the hydroxyl group on C-11 has been alkylated. The signal for C-9 has also shifted from δ171.0 in (2) to δ130.80 ppm but is still that of a quaternary carbon. Oxidative N-demethylation of the tertiary amine at C-3' on the desosamine sugar has also occurred by a reaction similar to that described[8,9] for tertiary amines. Further evidence in support of this structure was obtained from mass spectrometry. FAB-MS gave a protonated molecular ion MH^+ 733 which was accurately measured and the molecular formula of $C_{36}H_{64}N_2O_{13}$ for (5) corresponds to a formal loss of CH_4 from the starting oxime (2). The E.I.-mass spectrum gave ions at m/z 701 (M-31) and 144 which were both accurately measured. The ion at m/z 701 corresponds to a loss of NO+H from (5) while (6) m/z 144 was derived from the N-desmethyl desosamine. The N-demethylation of the desosamine sugar gives rise to some characteristic shifts in the ^{13}C spectrum particularly for carbons C-2' to C-4' (Table 1).

Treatment of (5) at 50° for 16hr with 2.5 equivalents of $^{n}Bu_3SnH$ and a catalytic amount of AIBN in benzene, gave a 62% yield of the N-demethylated oxime (7) which was identical to a sample prepared by hydrogenation of (9)[10] with 10% Pd-C. Reaction of (5) with $^{n}Bu_3SnH$ and AIBN in the presence of methyl acrylate (using ether as solvent) to trap out any intermediate, gave only (8) (53% yield).

There are several examples[11] of cyclic derivatives of erythromycin A involving carbons at C-9 and C-11, including 6,9; 9,11-acetals[12] but this is the first oxetan of this type to be described. Compound (5) has been treated with $^{n}Bn_3SnH$ and the alcohol at C-11 and the oxime at C-9 have been regenerated.

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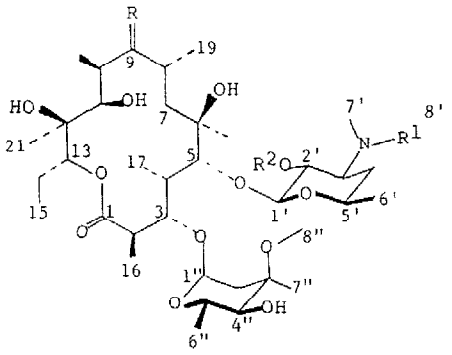
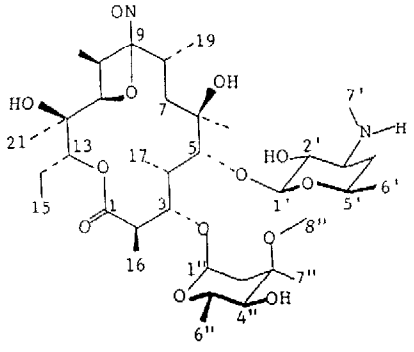
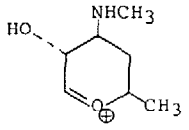


(1) R = O $R^1 = CH_3$ $R^2 = H$
(2) R = N.OH $R^1 = CH_3$ $R^2 = H$
(3) R = N.OCH_3 $R^1 = CH_3$ $R^2 = H$
(4) R = (S)-NH_2, H $R^1 = CH_3$ $R^2 = H$
(7) R = N.OH $R^1 = R^2 = H$
(8) R = N.OH $R^1 = {}^{22}CH_2.CH_2CO_2{}^{25}CH_3$ $R^2 = H$
(9) R = N.OH $R^1 = R^2 = CO_2CH_2Ph$



(5)



(6) m/z 144

Table 1: ^1H and ^{13}C NMR data[6] for compounds (5), (7) and (8)

Carbon	5		7		8		Carbon	5		7		8	
No.	^{13}C	^1H	^{13}C	^1H	^{13}C	^1H	No.	^{13}C	^1H	^{13}C	^1H	^{13}C	^1H
1	177.07	-	175.33	-	175.81	-	22					49.36	2.89 2.71
2	46.28	2.62	44.79	2.89	44.79	2.89	23					33.49	2.48
3	77.79	4.58	80.29	3.93	80.28	4.04	24					173.08	-
4	43.57	1.95	38.87	2.03	39.00	2.00	25					51.76	3.68
5	82.83	3.59	84.83	3.53	83.53	3.60							
6	74.04*	-	74.29*	-	74.50*	-	1'	103.16	4.32	102.83	4.40	103.18	4.42
7	37.92	1.85 1.53	37.60	1.53	37.79	1.62 1.57	2'	74.24	3.18	73.75	3.28	70.92	3.24
8	27.66	2.92	25.43	3.79	25.47	3.81	3'	60.39	2.53	60.03	2.55	65.72	2.51
9	130.80	-	170.92	-	171.13	-	4'	37.04	1.96 1.12	36.35	1.92 1.25	30.22	1.65 1.27
10	42.11	3.23	32.61	2.67	32.68	2.72	5'	68.89	3.53	68.67	3.57	68.76	3.49
11	84.20	4.33	71.10	3.74	70.97	3.71	6'	21.17	1.23	21.06	1.23	21.42	1.23
12	75.11*	-	74.94*	-	75.35*	-	$NHCH_3$	32.80	2.42	32.38	2.41	36.51	2.28
13	78.94	4.95	77.21	5.08	77.33	5.09							
14	21.68	1.89 1.54	21.11	1.93 1.49	21.04	1.93 1.48	1"	95.65	5.01	96.27	4.92	96.40	4.91
15	10.56	0.87	10.64	0.83	10.67	0.86	2"	34.84	2.35 1.56	35.09	2.36 1.57	35.16	2.35 1.58
16	15.81	1.22	16.21	1.18	16.26	1.19	3"	72.92	-	72.81	-	72.73	-
17	9.57	1.08	9.63	1.06	9.23	1.13	4"	78.01	3.02	78.05	3.01	78.14	3.00
18	28.20	1.45	26.90	1.51	27.03	1.51	5"	65.43	4.03	65.37	4.06	65.52	4.04
19	18.27	1.19	18.71	1.03	18.71	1.08	6"	18.46	1.31	18.47	1.29	18.61	1.30
20	12.90	1.25	14.71	1.19	14.43	1.21	7"	21.61	1.26	21.49	1.24	21.53	1.25
21	17.86	1.35	16.41	1.15	16.37	1.16	OCH_3	49.56	3.32	49.44	3.30	49.52	3.31

* may be reversed

Figure: The 400MHz 2D ^1H COSY-45 NMR spectrum of (5) in $CDCl_3$ beneath the corresponding 1D ^1H NMR spectrum

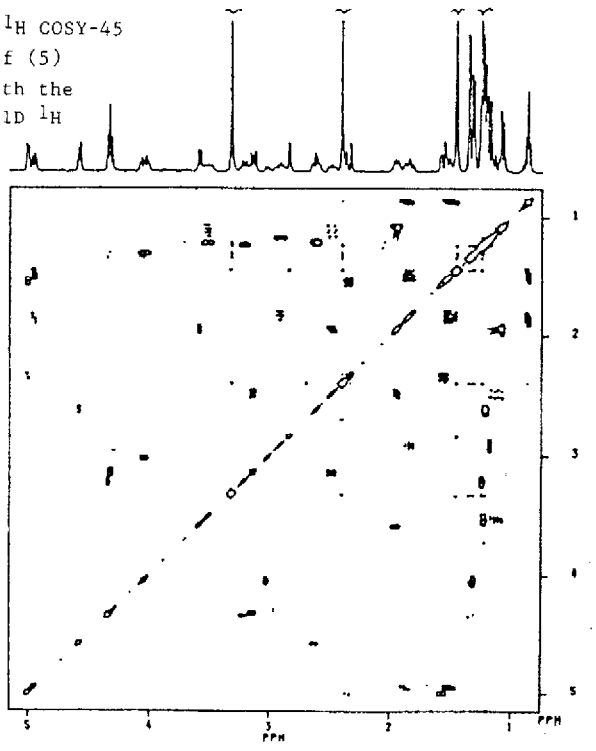


Table 2: Some vicinal proton-proton coupling constants

Coupling System	$^3J_{H,H}$ (Hz)		
	5	7	8
16-2	7.20	7.1	7.0
2-3	4.90	9.5	9.3
3-4	⩽0.5	<0.5	<0.5
4-5	8.60	6.6	7.4
4-17	7.25	7.4	7.4
7ax-8	11.40	~9.5	10.5
7eq-8	⩽1.00	~4.0	2.9
8-19	7.10	7.0	6.9
10-11	6.30	<0.5	1.2
10-20	~6.30	7.1	7.1
13-14eq	2.85	2.0	2.5
13-14ax	10.25	10.9	10.7
14-15	7.40	7.2	7.3

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