The Conformational Analysis of Derivatives of Erythromycin A. *X*-Ray Crystallographic and Nuclear Magnetic Resonance Spectroscopic Studies of (*E*)-11-*O*-(2-Dimethylaminoethoxy)methyl-9-deoxo-9-methoxyiminoerythromycin A

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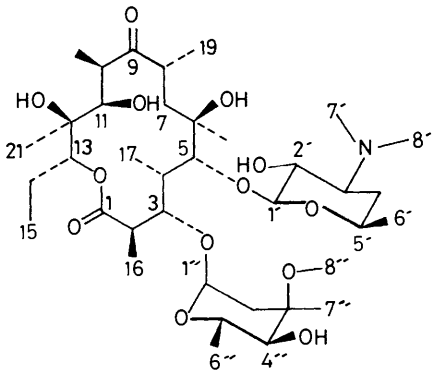
(*E*)-11-*O*-(2-Dimethylaminoethoxy)methyl-9-deoxo-9-methoxyiminoerythromycin A (**3**) has been synthesised from erythromycin A (**1**) and its crystal structure conformation compared with that of (**1**). The conformations of the two sugars and their orientation with respect to one another are the same in (**1**) and (**3**). The conformations of the aglycones are, however, markedly different. In comparison with (**1**), the main conformational changes in (**3**) appear to be a folding in the aglycone about the C-7 methylene and lactone ring oxygen, which moves the C-6 hydroxy and lactone carbonyl away from the substituents at C-9 and C-11, and an inward folding (towards C-11) of the C-3 to C-5 region and the attached sugars.

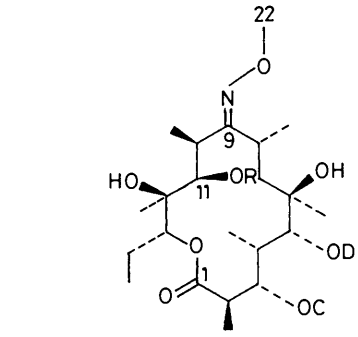
The conformation of (**3**) in $CDCl_3$ was investigated by measuring ^1H vicinal coupling constants, ^1H n.O.e.s, and ^{13}C spin–lattice relaxation times. These studies show that in solution (**3**) exists in a state of fast exchange between conformations of the C-3 to C-5 'folded out' and C-3 to C-5 'folded in' types. One of the simplest representations of this would be a rapid equilibrium between conformations similar to those found in the crystal structures of (**1**) and (**3**).

Erythromycin A (**1**)† is the best known and clinically the most useful member of the macrolide group of antibiotics. Because of its importance in antimicrobial chemotherapy, it is also the most studied of the 14-membered macrolides in terms of its behaviour and derivatisation.[1] Much of this work has, of course, been aimed at preparing semi-synthetic erythromycins in the

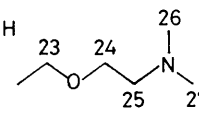


(**1**)

hope of finding new compounds with improved properties as chemotherapeutic agents. As part of one such programme of work, we prepared a series of 11-ether derivatives of (*E*)-9-deoxo-9-methoxyiminoerythromycin A (**2**),[2] and some of these showed improvements over erythromycin in terms of their



(**2**) R = H

(**3**) R =  , C = α-L-cladinosyl,

D = β-D-desosaminyl

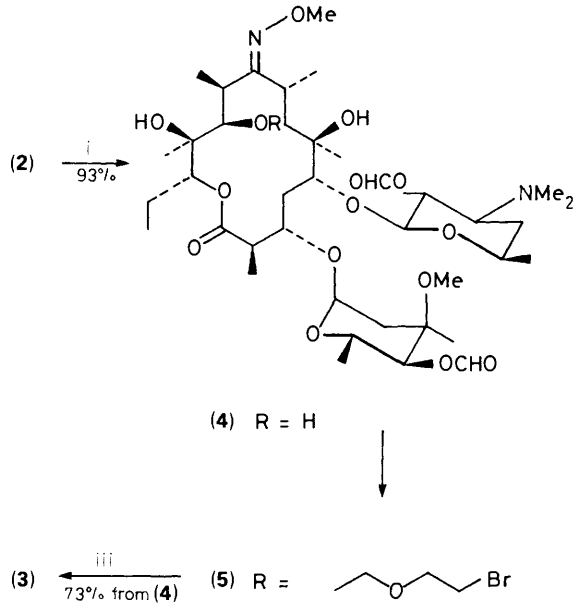
pharmacokinetic properties. In particular, the 11-(2-dimethylaminoethoxy)methyl ether (**3**) showed activity *in vitro* similar to that of erythromycin, but its oral absorption in rodents was markedly better than that of (**1**) and resulted in superior activity against experimental infections in mice.[3]‡ In view of its interesting biological properties, we decided to examine the conformation of the ether (**3**) using *X*-ray crystallography and n.m.r. spectroscopy. In this paper we present the results of these studies.

Results and Discussion

Synthesis.—The synthesis of the ether (**3**) is outlined in the Scheme. Starting with erythromycin (**1**), the 9-methoxyimino derivative (**2**) was prepared (70% yield) by reaction with *O*-methylhydroxylamine hydrochloride in pyridine. This was

† The erythromycin A molecule consists of a 14-membered lactone, termed erythronolide A, substituted by an amino sugar, D-desosamine, and a neutral sugar, L-cladinose.

‡ Unfortunately, recent oral studies in human volunteers using (**3**) resulted in blood levels inferior to those of (**1**). This otherwise interesting compound does not, therefore, appear to warrant further progression.



Scheme. *Reagents:* i, AcOCHO, 4-dimethylaminopyridine, CH_2Cl_2; ii, $BrCH_2CH_2OCH_2Cl$, 2,6-lutidine, *N,N*-dimethylformamide; iii, $HNMe_2$, *N,N*-dimethylformamide, 60 °C. The yields of each step are given.

converted into the diformate (**4**), and then the remaining secondary hydroxy was alkylated using 2-bromoethoxymethyl chloride and 2,6-lutidine to give the 11-ether (**5**). Finally, the formate protection groups were removed and the dimethylamino group was introduced into the ether side-chain by treating (**5**) with dimethylamine in hot *N,N*-dimethylformamide. This gave the ether (**3**), which was purified by crystallisation from ethyl acetate.

Crystal Structure.—The crystal structure of compound (**3**) is shown in Figure 1. Fractional atomic co-ordinates for the non-hydrogen atoms are given in Table 1, and bond lengths and bond angles are listed in Tables 2 and 3. The crystal structure confirms the *E* configuration for the 9-methoxyimino group.[4] Also, as with the crystal structures of other derivatives,[5] it shows that both sugar rings are in the chair conformation and that they adopt the same orientation with respect to one another as that found in erythromycin.[5a] The conformation of the aglycone, however, differs markedly from that of erythromycin (see the torsion angles in Table 4).

Comparing the crystal structures of other erythromycin derivatives, erythromycin A (**1**),[5a] megalomycin A (**6**),[5e] and the oxime ether (**7**)[5f] all have the same conformation for the 14-membered lactone. The two carbonate derivatives, (**8**)[5c] and (**9**),[5b] adopt a different conformation for the lactone ring, at least in part because of the 6,9-oxygen bridge in these derivatives. Yet another conformation for the lactone is shown by the erythromycylamine 9,11-cyclic derivative (**10**),[5d] and this conformation is very similar to that seen in the 11-ether (**3**). Some differences between the crystal structure conformation of erythromycin (**1**) and that of the 9,11-cyclic derivative (**10**), the so-called 'folded-out' and 'folded-in' conformations, have already been discussed.[6]

In order to examine more closely the differences between the aglycone conformations of erythromycin (**1**) and the 11-ether (**3**), we used molecular modelling[7] to construct erythronolide A in these two conformations. Erythronolide A in the erythromycin conformation was constructed from the crystal structure of erythromycin (**1**), and this was then subjected to CNDO[8] (charge calculation) and MM2[9] (energy minimisation) procedures. Erythronolide A in the conformation of the 11-ether (**3**) was similarly constructed starting with the crystal structure of (**3**). The steric energies[9] (6 and 37.6 kcal mol^{-1}) and the net repulsion energies[7] (589.3 and 662.7 kcal*) both indicate that the erythromycin conformation is the more stable.

Table 1. Atom co-ordinates (× 10^4) with estimated standard deviations in parentheses for compound (**3**).

Atom	*x*	*y*	*z*
O(1)	5 329(4)	7 579(2)	9 095(2)
C(1)	4 694(4)	7 048(2)	9 035(2)
C(2)	4 808(4)	6 393(2)	9 374(2)
C(3)	5 730(4)	5 840(2)	9 101(1)
O(3)	6 986(2)	5 789(1)	9 359(1)
C(4)	5 107(4)	5 109(2)	9 083(1)
C(5)	5 958(4)	4 592(2)	8 758(1)
O(5)	6 012(2)	3 909(1)	9 009(1)
C(6)	5 497(4)	4 451(2)	8 187(1)
O(6)	6 465(3)	4 005(1)	7 940(1)
C(7)	5 497(4)	5 149(2)	7 880(1)
C(8)	5 820(5)	5 103(2)	7 282(1)
C(9)	5 758(4)	5 828(2)	7 027(2)
N(9)	6 640(4)	6 086(2)	6 726(2)
O(9)	7 744(4)	5 647(2)	6 668(2)
C(10)	4 511(4)	6 269(2)	7 090(2)
C(11)	4 655(4)	6 806(2)	7 539(2)
O(11)	5 495(3)	7 372(2)	7 386(1)
C(12)	3 349(4)	7 136(2)	7 736(2)
O(12)	2 879(3)	7 646(2)	7 367(1)
C(13)	3 596(4)	7 504(2)	8 263(2)
O(13)	3 830(3)	6 950(1)	8 649(1)
C(14)	2 458(5)	7 963(3)	8 442(2)
C(15)	2 640(7)	8 378(4)	8 887(3)
C(16)	5 230(5)	6 581(2)	9 930(2)
C(17)	7 932(4)	6 275(2)	9 169(2)
O(17)	8 436(3)	6 086(2)	8 682(1)
C(18)	9 004(4)	6 386(3)	9 581(2)
C(19)	10 080(4)	5 843(3)	9 590(2)
O(19)	9 621(3)	5 155(2)	9 763(1)
C(20)	10 524(4)	5 679(3)	9 030(2)
O(20)	6 352(2)	3 227(1)	10 006(1)
C(21)	9 342(4)	5 503(2)	8 690(2)
C(22)	9 072(7)	5 097(4)	10 281(2)
C(23)	11 242(5)	6 081(4)	9 932(2)
C(24)	9 690(6)	5 346(3)	8 125(2)
C(25)	7 261(4)	3 710(2)	9 207(1)
O(25)	8 066(3)	3 574(1)	8 763(1)
C(26)	7 069(4)	3 057(2)	9 545(1)
O(26)	11 481(3)	5 132(2)	9 014(1)
C(27)	8 423(4)	2 755(2)	9 695(1)
N(27)	8 441(3)	2 120(2)	10 026(1)
C(28)	9 223(4)	2 640(2)	9 192(2)
C(29)	9 357(4)	3 314(2)	8 886(2)
C(30)	10 076(5)	3 219(3)	8 362(2)
C(31)	7 501(5)	1 589(2)	9 844(2)
C(32)	8 283(5)	2 259(3)	10 585(2)
C(33)	4 160(4)	4 085(2)	8 181(2)
C(34)	4 901(7)	4 617(3)	6 971(2)
C(35)	8 672(8)	5 998(4)	6 325(3)
C(36)	4 106(6)	6 619(3)	6 573(2)
C(37)	2 245(4)	6 610(2)	7 782(2)
C(38)	6 824(5)	7 340(3)	7 543(3)
O(38)	6 937(4)	7 807(3)	7 956(2)
C(39)	8 172(8)	7 888(4)	8 130(3)
C(40)	8 347(8)	8 419(4)	8 520(3)
N(40)	8 318(6)	9 128(3)	8 387(2)
C(41)	8 293(10)	9 544(4)	8 849(3)
C(42)	9 426(9)	9 339(4)	8 073(3)
C(43)	4 830(4)	4 832(2)	9 635(2)

* 1 cal = 4.184 J.

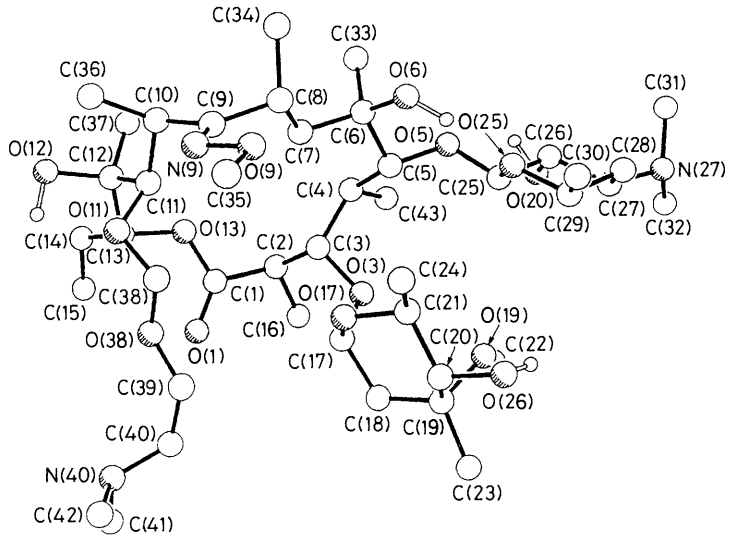


Figure 1. The molecular structure of (**3**) showing the crystallographic numbering scheme. There are intramolecular hydrogen bonds: O(6)···O(25) = 2.77, H···O = 1.80 Å, ∠O–H···O 170°; O(26)···O(19) = 2.68, H···O = 2.09 Å, ∠O–H···O 117°. There are intermolecular hydrogen bonds: O(12)···O(6′) = 2.78, H···O = 2.11 Å, ∠O–H···O = 124°; O(20)···N(27′) = 3.01, H···N = 2.10 Å, ∠O–H···N 155°.

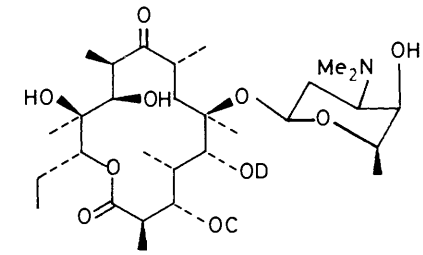
Table 2. Bond lengths/Å, with e.s.d.s in parentheses, for compounds (**3**).

O(1)–C(1)	1.206(5)	C(1)–C(2)	1.521(5)
C(1)–O(13)	1.326(5)	C(2)–C(3)	1.566(5)
C(2)–C(16)	1.520(6)	C(3)–O(3)	1.432(4)
C(3)–C(4)	1.528(5)	O(3)–C(17)	1.414(5)
C(4)–C(5)	1.545(5)	C(4)–C(43)	1.526(5)
C(5)–O(5)	1.449(4)	C(5)–C(6)	1.551(5)
O(5)–C(25)	1.409(4)	C(6)–O(6)	1.439(4)
C(6)–C(7)	1.541(5)	C(6)–C(33)	1.518(5)
C(7)–C(8)	1.558(5)	C(8)–C(9)	1.525(6)
C(8)–C(34)	1.531(7)	C(9)–N(9)	1.273(6)
C(9)–C(10)	1.521(6)	N(9)–O(9)	1.401(6)
O(9)–C(35)	1.444(9)	C(10)–C(11)	1.540(6)
C(10)–C(36)	1.529(6)	C(11)–O(11)	1.424(5)
C(11)–C(12)	1.543(6)	O(11)–C(38)	1.401(6)
C(12)–O(12)	1.431(5)	C(12)–C(13)	1.534(6)
C(12)–C(37)	1.502(6)	C(13)–O(13)	1.461(5)
C(13)–C(14)	1.513(7)	C(14)–C(15)	1.394(9)
C(17)–O(17)	1.389(5)	C(17)–C(18)	1.521(6)
O(17)–C(21)	1.438(5)	C(18)–C(19)	1.499(7)
C(19)–O(19)	1.456(6)	C(19)–C(20)	1.527(7)
C(19)–C(23)	1.530(7)	O(19)–C(22)	1.433(7)
C(20)–C(21)	1.511(6)	C(20)–O(26)	1.420(6)
O(20)–C(26)	1.415(4)	C(21)–C(24)	1.509(6)
C(25)–O(25)	1.416(4)	C(25)–C(26)	1.524(5)
O(25)–C(29)	1.428(5)	C(26)–C(27)	1.531(5)
C(27)–N(27)	1.473(5)	C(27)–C(28)	1.529(5)
N(27)–C(31)	1.462(6)	N(27)–C(32)	1.456(5)
C(28)–C(29)	1.506(6)	C(29)–C(30)	1.528(6)
C(38)–O(38)	1.380(8)	O(38)–C(39)	1.331(9)
C(39)–C(40)	1.428(11)	C(40)–N(40)	1.391(8)
N(40)–C(41)	1.417(9)	N(40)–C(42)	1.433(10)

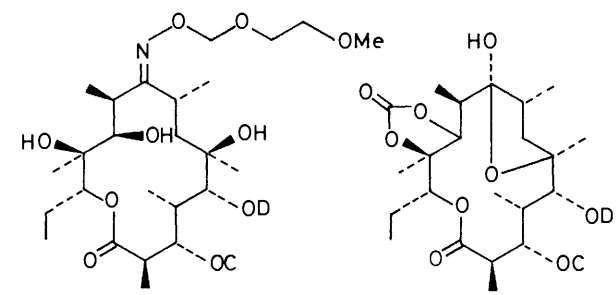
Drawings of the erythromycin and the 11-ether conformations are presented in Figure 2, and some interatomic distances [7] are listed in Table 5. In going from the erythromycin conformation of erythronolide A to the 11-ether conformation the following changes are noted.

(i) The C-7 methylene is twisted into an inside-ring position (*i.e.* both hydrogens positioned inside the macrolide ring).

(ii) The C-6 hydroxy is twisted from its inside-ring position

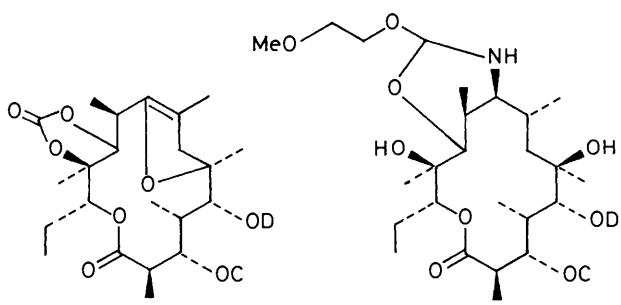


(**6**)



(**7**)

(**8**)



(**9**) (**10**)

Structures (**6**)–(**10**): C = α-L-cladinosyl; D = β-D-desosaminyl.

Table 3. Bond angles /°, with e.s.d.s in parentheses, for compound (**3**).

O(1)–C(1)–C(2)	125.0(4)	O(1)–C(1)–O(13)	124.1(4)
C(2)–C(1)–O(13)	110.8(3)	C(1)–C(2)–C(3)	110.1(3)
C(1)–C(2)–C(16)	110.9(3)	C(3)–C(2)–C(16)	113.9(3)
C(2)–C(3)–O(3)	111.6(3)	C(2)–C(3)–C(4)	112.4(3)
O(3)–C(3)–C(4)	108.5(3)	C(3)–O(3)–C(17)	113.3(3)
C(3)–C(4)–C(5)	111.6(3)	C(3)–C(4)–C(43)	111.1(3)
C(5)–C(4)–C(43)	112.0(3)	C(4)–C(5)–O(5)	110.8(3)
C(4)–C(5)–C(6)	116.4(3)	O(5)–C(5)–C(6)	105.7(2)
C(5)–O(5)–C(25)	115.6(3)	C(5)–C(6)–O(6)	107.9(3)
C(5)–C(6)–C(7)	109.1(3)	O(6)–C(6)–C(7)	106.7(3)
C(5)–C(6)–C(33)	110.8(3)	O(6)–C(6)–C(33)	109.2(3)
C(7)–C(6)–C(33)	113.0(3)	C(6)–C(7)–C(8)	116.6(3)
C(7)–C(8)–C(9)	110.9(3)	C(7)–C(8)–C(34)	114.3(4)
C(9)–C(8)–C(34)	107.5(3)	C(8)–C(9)–N(9)	125.2(4)
C(8)–C(9)–C(10)	119.2(4)	N(9)–C(9)–C(10)	115.4(4)
C(9)–N(9)–O(9)	112.9(4)	N(9)–O(9)–C(35)	107.7(4)
C(9)–C(10)–C(11)	111.5(3)	C(9)–C(10)–C(36)	111.8(4)
C(11)–C(10)–C(36)	111.9(4)	C(10)–C(11)–O(11)	110.8(3)
C(10)–C(11)–C(12)	115.5(3)	O(11)–C(11)–C(12)	106.9(3)
C(11)–O(11)–C(38)	117.4(4)	C(11)–C(12)–O(12)	110.2(3)
C(11)–C(12)–C(13)	109.3(3)	O(12)–C(12)–C(13)	108.5(3)
C(11)–C(12)–C(37)	112.8(3)	O(12)–C(12)–C(37)	104.9(3)
C(13)–C(12)–C(37)	110.9(4)	C(12)–C(13)–O(13)	106.6(3)
C(12)–C(13)–C(14)	113.8(4)	O(13)–C(13)–C(14)	109.7(4)
C(1)–O(13)–C(13)	120.2(3)	C(13)–C(14)–C(15)	118.1(5)
O(3)–C(17)–O(17)	112.6(3)	O(3)–C(17)–C(18)	109.5(4)
O(17)–C(17)–C(18)	113.0(3)	C(17)–O(17)–C(21)	114.8(3)
C(17)–C(18)–C(19)	115.5(4)	C(18)–C(19)–O(19)	113.2(4)
C(18)–C(19)–C(20)	109.8(4)	O(19)–C(19)–C(20)	101.2(4)
C(18)–C(19)–C(23)	111.1(4)	O(19)–C(19)–C(23)	109.8(4)
C(20)–C(19)–C(23)	111.5(4)	C(19)–O(19)–C(22)	118.1(4)
C(19)–C(20)–C(21)	110.3(4)	C(19)–C(20)–O(26)	112.0(4)
C(21)–C(20)–O(26)	110.9(4)	O(17)–C(21)–C(20)	109.8(4)
O(17)–C(21)–C(24)	106.6(4)	C(20)–C(21)–C(24)	113.9(4)
O(5)–C(25)–O(25)	106.1(3)	O(5)–C(25)–C(26)	107.8(3)
O(25)–C(25)–C(26)	112.0(3)	C(25)–O(25)–C(29)	114.3(3)
O(20)–C(26)–C(25)	110.3(3)	O(20)–C(26)–C(27)	109.6(3)
C(25)–C(26)–C(27)	109.5(3)	C(26)–C(27)–N(27)	117.5(3)
C(26)–C(27)–C(28)	108.5(3)	N(27)–C(27)–C(28)	110.8(3)
C(27)–N(27)–C(31)	112.2(3)	C(27)–N(27)–C(32)	114.1(3)
C(31)–N(27)–C(32)	111.4(4)	C(27)–C(28)–C(29)	111.0(3)
O(25)–C(29)–C(28)	109.0(3)	O(25)–C(29)–C(30)	106.4(3)
C(28)–C(29)–C(30)	113.1(4)	O(11)–C(38)–O(38)	105.6(4)
C(38)–O(38)–C(39)	113.9(5)	O(38)–C(39)–C(40)	115.5(7)
C(39)–C(40)–N(40)	120.9(6)	C(40)–N(40)–C(41)	109.9(5)
C(40)–N(40)–C(42)	113.0(6)	C(41)–N(40)–C(42)	108.7(6)

Table 4. Lactone ring torsion angles/° for the crystal structures of (**1**) and (**3**).

Torsion angle	(**1**)	(**3**)
O–C(1)–C(2)–C(3)	115.9	79.9
C(1)–C(2)–C(3)–C(4)	−61.2	−130.8
C(2)–C(3)–C(4)–C(5)	164.8	173.6
C(3)–C(4)–C(5)–C(6)	−116.1	−100.1
C(4)–C(5)–C(6)–C(7)	−68.5	60.1
C(5)–C(6)–C(7)–C(8)	175.0	148.0
C(6)–C(7)–C(8)–C(9)	−77.0	178.9
C(7)–C(8)–C(9)–C(10)	−60.8	−53.9
C(8)–C(9)–C(10)–C(11)	122.0	97.2
C(9)–C(10)–C(11)–C(12)	−173.3	−164.0
C(10)–C(11)–C(12)–C(13)	167.8	165.6
C(11)–C(12)–C(13)–O	−68.6	−70.1
C(12)–C(13)–O–C(1)	107.3	144.6
C(13)–O–C(1)–C(2)	171.3	−177.9

to an outside-ring position, which brings it closer to the C-5 hydroxy; the C-6 methyl (Me-18) moves closer to the C-4 and C-8 methyls.

Table 5. Interatomic distances/Å in erythronolide A.

	Erythromycin conformation	11-Ether (**3**) conformation
C(2)Me–C(4)Me	4.55	3.43
C(4)Me–C(6)Me	5.06	4.02
C(6)Me–C(8)Me	4.41	3.33
C(1)O–C(9)O	5.55	6.76
C(1)O–C(11)O	3.45	4.37
C(3)O–C(5)O	3.71	3.81
C(5)O–C(6)O	3.67	2.77
C(6)O–C(9)O	3.22	4.98
C(6)O–C(11)O	3.68	6.63
C(9)O–C(11)O	2.90	3.17
C(11)O–C(12)O	2.34	2.69

(iii) The C-4 methyl (Me-17) moves to a more outside-ring position; this takes it away from the position now occupied by the C-6 methyl, but forces it closer to the C-2 methyl. The C-4 methyl is thus pushed into a more sterically congested environment.

(iv) The C-5 hydroxy moves to a more outside-ring position; this is accompanied by similar movement of the C-3 hydroxy such that the separation of these groups remains almost unchanged. Both hydroxy groups are moved away from the position now occupied by the C-4 methyl. This reorganisation in the C-3 to C-5 region results in the hydrogens on C-3 and C-5 being moved to more inside-ring positions, while the hydrogen on C-4 moves to a more outside-ring position. This 'folding-in' of C-3 and C-5 has also been described in comparing the crystal structures of (**10**) and (**1**).[6] In (**3**), these changes are associated with large torsion angle changes (Table 4) about the C(2)–C(3) and C(5)–C(6) bonds.

(v) Rotation of the lactone group moves the ring oxygen inside the ring while the carbonyl moves to an outside-ring position.

(vi) Small changes in the C-9 to C-12 region result in the C-11 hydroxy being further away from the C-9 carbonyl and the C-12 hydroxy. Changes elsewhere in the molecule also result in the C-11 hydroxy being further away from the C-1 carbonyl and the C-6 hydroxy.

In terms of gross conformation the overall effect of the above changes is a general folding of the molecule which moves the oxygens on C-1 and C-6 away from those on C-9 and C-11. This can be seen most clearly in the space-filled drawings in Figure 3. This folding of the molecule takes place primarily about the C-7 methylene and lactone ring oxygen as these groups move to positions more inside the macrocycle (Figure 2). It is perhaps noteworthy that these are the only unsubstituted groups in the lactone ring. This folding of the molecule is also accompanied by some major conformational changes in the C-3 to C-6 region, whereas the C-8 to C-13 region remains virtually unchanged.

Comparing the intact macrolide (**3**) with erythromycin (**1**) (Figure 4), the folding of the aglycone about the C-7 methylene and lactone ring oxygen reduces steric congestion, from the lactone carbonyl and C-6 hydroxy, on the additional substituents at C-9 and C-11. This is partially off-set, however, by the inward folding of C-3 and C-5 which carries the two sugars in towards the C-9 to C-11 region. As noted earlier, despite the changes at C-3 and C-5, the orientations of the two sugars with respect to one another and to the lactone ring remain virtually the same in (**3**) as in (**1**).

^{1}H *and* ^{13}C *N.M.R. Spectral Assignments.*—The 400 MHz ^{1}H and 100 MHz ^{13}C n.m.r. spectra of the ether (**3**) in $CDCl_3$ were assigned using a variety of 1D and 2D n.m.r. experiments similar to those previously described.[6,10] Figure 5 shows a contour plot

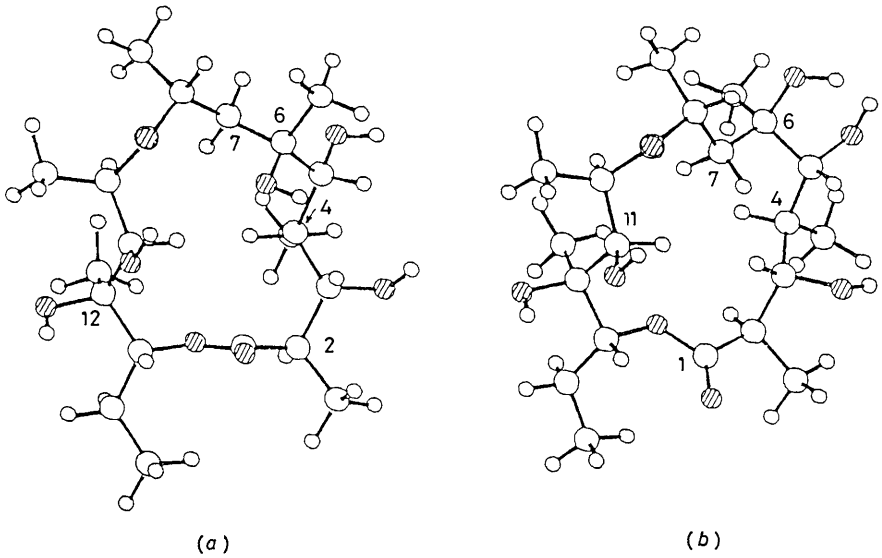


Figure 2. Erythronolide A modelled in the (*a*) erythromycin A conformation and (*b*) the 11-ether (**3**) conformation. Oxygen atoms are shaded.

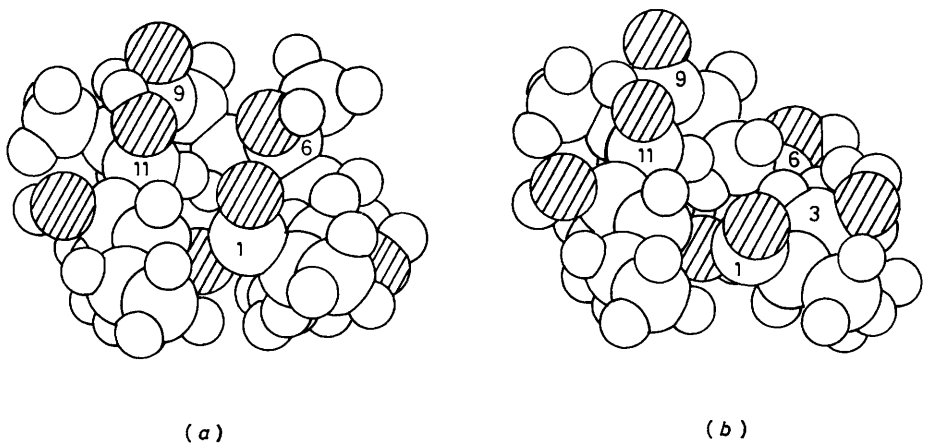


Figure 3. Space-filled drawings of erythronolide A modelled in the (*a*) erythromycin A conformation and (*b*) the 11-ether (**3**) conformation. Oxygen atoms are shaded.

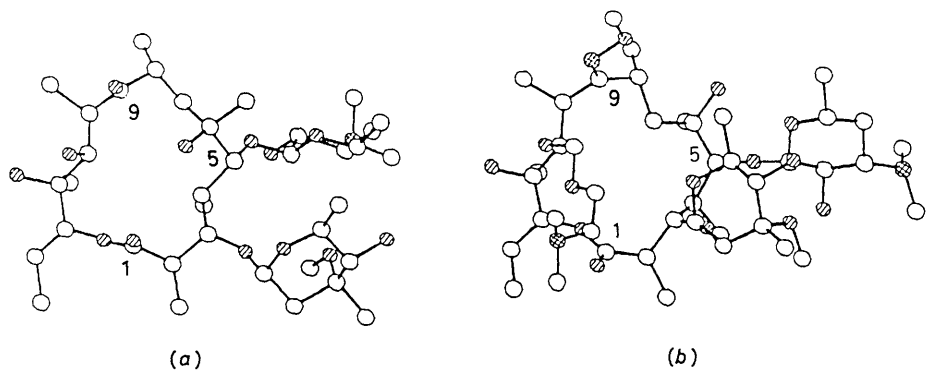


Figure 4. Crystals structures of (*a*) erythromycin A and (*b*) the 11-ether (**3**). Hydrogens have been omitted for clarity. Oxygen atoms are shaded and nitrogen atoms are cross-hatched.

of the 2D ^{1}H COSY-45 n.m.r. spectrum of (**3**). It was found convenient to run the experiments at a slightly elevated temperature (310 K) since this considerably sharpened some of the ^{13}C resonances, particularly those due to C-3, C-4, C-7, C-9, and C-18. All signals were unambiguously assigned and the results are summarised in Table 6. Table 6 also lists the ^{13}C NT_1 values for the protonated carbons (N = no. of protons on carbon; T_1 = carbon-13 spin–lattice relaxation time).

Solution-state Conformational Analysis of Ether (**3**) in $CDCl_3$.—Previously described n.m.r. results from these laboratories have shown that erythromycin A (**1**)[10] and some

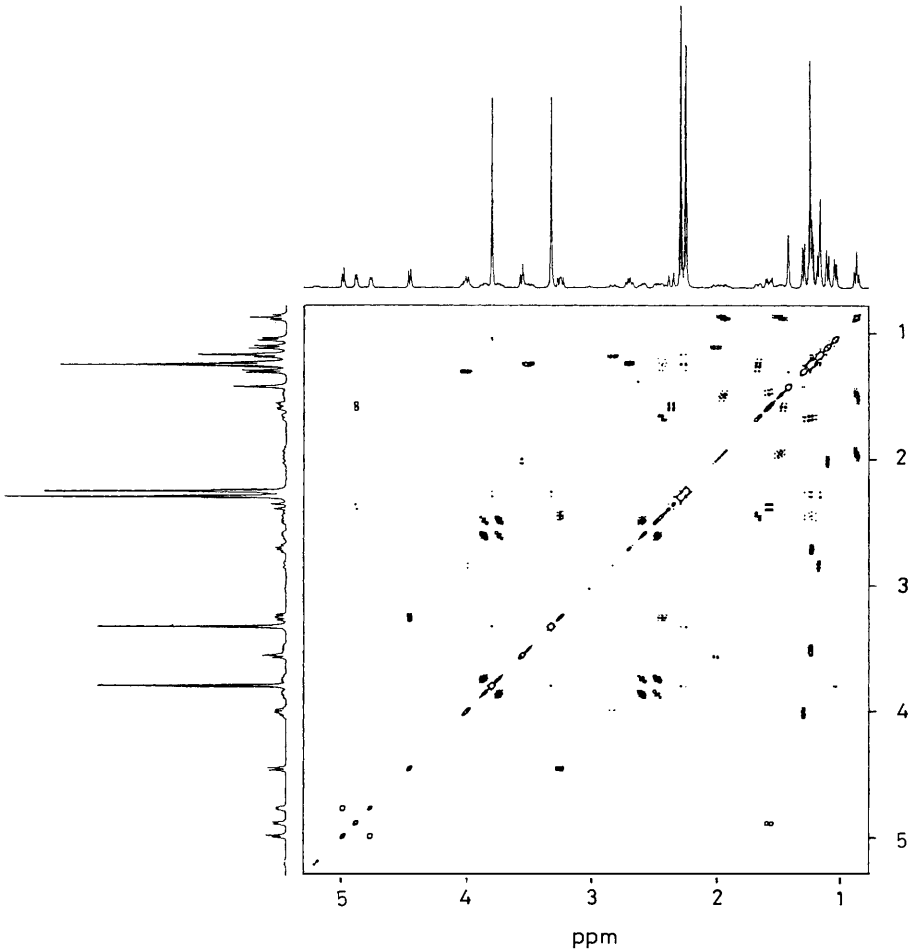


Figure 5. Contour plot of the 400 MHz 2D ^{1}H COSY-45 n.m.r. spectrum of (**3**) in $CDCl_3$–Me_4Si at 310 K.

of its C(9)-reduced derivatives[6] exist in $CDCl_3$ with their lactone rings in two main conformations (termed **A** and **B**) in varying proportions and in fast exchange. Conformation **A**[10] is based on the crystal structure of erythromycin (**1**)[5a] and is characterised, amongst other things, by having the C-3 to C-5 portion of the macrocycle 'folded out'. Conformation **B**[6] is based on the crystal structure of the erythromycylamine derivative (**10**)[5d] and has the C-3 to C-5 region 'folded in' towards the C-9 to C-11 region. The crystal structure conformation of (**3**) is also of the 'folded in' type, but differs from conformation **B** in the C-6 to C-9 region. This conformation will be referred to as **B**′.

In analysing the solution-state conformation of (**3**), we started by looking at the two sugar moieties. The $^3J_{HH}$ values for the sugar protons showed that both sugar rings adopt the same chair conformations as in (**1**).[10] Furthermore, the ^{1}H n.O.e.s[14] involving these protons indicated that each sugar also has the same orientation with respect to the rest of the molecule as it has in (**1**).[10] This is also in agreement with what was seen in comparing the solid-state conformations of (**1**) and (**3**). To gain some insight into the relative motional freedoms of the sugar rings, we compared the averaged ^{13}C NT_1 values[15] for the ring carbons of the desosamine, cladinose, and erythronolide moieties. This showed that the desosamine ring (average ^{13}C NT_1 = 0.40 ± 0.03 s) had greater motional freedom than the cladinose unit (0.37 ± 0.03 s) with respect to the aglycone (0.36 ± 0.02 s). This is the same order that was found for erythromycin[10] (0.46, 0.41, and 0.38 s), but the differences are less marked, suggesting that in (**3**) the sugars have less freedom with respect to the lactone than in (**1**).

We now turned to the solution-state conformation of the aglycone. The vicinal coupling constants for the lactone ring protons in (**1**) and (**3**) are compared in Table 7. It is evident that (**3**) adopts a different conformation for its lactone ring to that shown by (**1**). However, as was found previously for erythromycin[10] and some of its derivatives,[6] the change in $^3J_{HH}$ values with change in temperature suggests that (**3**) does not exist in $CDCl_3$ in a single, stable conformation.* This was further emphasised when, for example, $^3J_{2,3}$ was found to be 6.6 Hz for (**3**) in CD_3OD compared with 7.8 Hz in $CDCl_3$.

As in the earlier studies,[6,10] the main armament in the arsenal of n.m.r. techniques for investigating macrolide conformation was the ^{1}H n.O.e.[14] Thus, in 'folded out' conformations, such as **A** 11-H is much closer to 4-H than to 3-H, whereas in 'folded in' conformations, such as **B** and **B**′, the opposite applies. Some inter-proton distances for the crystal structure of (**1**) ('folded out') and for the crystal structures of (**3**) and (**10**) ('folded in') are given in Table 8. Experimentally, therefore, 'folded out' conformations are expected to show a significant n.O.e. between 11-H and 4-H, but not between 11-H and 3-H.[6] For 'folded in' conformations the converse is expected. Similarly, the 'folded in' conformations **B** and **B**′, which are characterised by differences in the C-6 to C-9 region, should be distinguishable. In conformation **B**, 8-H occupies an inside-ring position, which brings it close (<3 Å) to 3-H, 5-H, and 11-H, and therefore for this conformation (but not for **A** and **B**′) n.O.e.s should be seen

* It is characteristic of a molecule which exists in a single, stable conformation in solution that the vicinal coupling constants remain invariant with respect to solvent and temperature changes.

Table 6. ^1H and ^{13}C n.m.r. chemical shifts (in ppm) and ^{13}C NT_1 values (N = no. of protons on carbon; T_1 = spin–lattice relaxation time in s) for (**3**) in $CDCl_3$–Me_4Si at 310 K.

Position	δ_H	δ_C	^{13}C NT_1 [a]
1	—	175.8	—
2	2.84	44.4	0.37
3	3.98	79.2	0.36
4	2.01	40.4	—[b]
5	3.57	83.8	0.35
6	—	75.0	—
7	1.56, 1.47	38.4	0.36
8	3.85	26.6	0.37
9	—	168.1	—
10	2.70	33.4	0.35
11	3.54	80.7	0.34
12	—	75.3	—
13	5.20	78.0	0.35
14	1.95, 1.47	22.0	0.57
15	0.87	11.2	3.40
16	1.17	15.1	0.91
17	1.10	9.3	1.36
18	1.42	25.8	1.83
19	1.04	18.9	1.55
20	1.23	15.1	1.64
21	1.16	17.8	1.13
22	3.79	61.0	3.20
23	4.99, 4.77	99.4	0.54
24	3.85, 3.73	67.3	0.85
25	2.60, 2.47	59.4	0.87
26, 27	2.28	45.2	2.30
1′	4.45	102.7	0.41
2′	3.24	70.8	0.39
3′	2.43	65.5	0.39
4′	1.67, 1.25	28.9	0.41
5′	3.48	69.0	0.42
6′	1.23	21.4	2.30
7′, 8′	2.29	40.4	1.65
1″	4.88	96.0	0.34
2″	2.37, 1.57	34.9	—[b]
3″	—	72.8	—
4″	3.03	77.8	0.39
5″	4.03	65.7	0.39
6″	1.30	18.2	1.93
7″	1.24	21.6	2.09
8″	3.31	49.5	3.39

[a] Average error is ±0.05 s. [b] Resonance was too broad for accurate measurement.

Table 7. Vicinal coupling constants $^3J_{HH}$/Hz for (**1**) and (**3**) in $CDCl_3$.

^3J	(**1**) at 292 K	(**3**) at 295 K	(**3**) at 310 K
$^3J_{2,3}$	9.3	7.8	7.3
$^3J_{3,4}$	1.4	1.9	1.8
$^3J_{4,5}$	7.7	7.3	7.0
$^3J_{7e,8}$	2.3	4.0	5.2
$^3J_{7a,8}$	11.3	9.6	8.7
$^3J_{10,11}$	1.4	*ca.* 1.5	*ca.* 1.5
$^3J_{13,14e}$	2.3	2.8	*ca.* 3
$^3J_{13,14a}$	11.0	10.1	*ca.* 10

between 8-H and 3-H, 5-H, and 11-H.[6] In conformation **B**′, the inside-ring position of the C-7 methylene means that both 7-protons are close to 11-H, and for this conformation n.O.e.s should be observed between 11-H and both of the C-7 protons [for **A** and **B** n.O.e.s are expected between 11-H and 7(*pro-S*)-H,* only].

For compound (**3**), irradiation of 11-H resulted in enhancements of both 3-H (1.0%) and 4-H (1.5%), indicating the presence of both 'folded out' and 'folded in' conformations. The observation of n.O.e. [18]5 and n.O.e. [18]8 also suggested the presence of the 'folded out' conformation **A**.[10] In addition, the observation of n.O.e. [18]4, n.O.e. [18]19, n.O.e. [11]7(*pro-R*), and n.O.e. [11]7(*pro-S*) suggested that the 'folded in' conformation **B**′ is also present, whereas no n.O.e. [8]3, n.O.e. [8]5, or n.O.e [8]11 were observed, indicating that conformation **B** is not significantly involved.[6] A complete matrix of ^1H n.O.e.s for compound (**3**) is given in Table 9. The evidence so far therefore points to (**3**) existing in solution as a mixture of 'folded out' and 'folded in' conformations. One simple description of this would be a fast exchange between conformations **A** and **B**′. The absence of conformation **B** should be noted, and suggests that in (**3**) there is less conformational flexibility in the C-6 to C-9 region than in the corresponding regions in (9*S*)-9-hydroxy-9-deoxoerythromycin A and (9*S*)-erythromycylamine A.†

The ^{13}C NT_1 values for the aglycone methyl groups are also consistent with the above conclusions. In conformation **A**,[10] the rotation of Me-16 is subject to much greater steric hindrance than that of Me-17, and, for example, in (**1**) this results in a very short NT_1 for Me-16 (0.78 s) compared with Me-17 (1.80 s).[10] In conformations **B**[6] and **B**′, the 'folding in' of the C-3 to C-5 region greatly eases the steric hindrance on Me-16, but forces Me-17 into a more hindered environment. Calculated rotational energy barriers[6] suggest that in 'folded in' conformations Me-17 is more hindered to rotation than is Me-16. For (**3**) the ^{13}C NT_1 values were 0.91 s for Me-16 and 1.36 s for Me-17. These are much closer together than expected for a pure **A** conformation,[6] but have not yet crossed over as would be expected[11] for pure **B** or **B**′.

Finally, ^{13}C NT_1 measurements also provided some information on the conformation of the 11-ether side-chain. The NT_1 values (Table 6) increases along the side-chain in the order C-11 < C-23 < C-24 ≈ C-25, indicating segmental motion in this group and the absence of any strong interaction between the side-chain and the rest of the molecule.

Conclusions

The crystal structure of the 11-ether (**3**) reveals a new solid-state conformation for an erythromycin-type molecule. Compared with erythromycin (**1**) itself, this new conformation is most simply described as resulting from a folding in the lactone ring about the C-7 methylene group and lactone ring oxygen together with an inward folding (towards C-11) of C-3 and C-5 and their attached sugar groups, and is similar in some respects to the previously described[5d] solid-state conformation of (9*S*)-9-*N*,11-*O*-[2-(2-methoxyethoxy)ethylidene]erythromycylamine A (**10**). In (**3**), this folding of the lactone ring moves the C-1 to C-6 region of the macrocycle away from the substituents on C-9 and C-11.

The solution-state conformation of (**3**) has been probed using ^1H and ^{13}C n.m.r. techniques. As in previous work,[6,10] the combined use of ^1H n.O.e. and ^{13}C T_1 experiments has proved to be a powerful tool in this type of investigation. In $CDCl_3$, (**3**)

* The previous[6,10] distinction between C-7 protons as 7_{eq}-H and 7_{ax}-H is potentially confusing. It should be noted that, because of conformational changes in the C-6 to C-9 region, 7_{ax}-H in conformation **A** and 7_{eq}-H in conformation **B** are both 7-*pro-S*.

† The conformational equilibria for (9*S*)-9-hydroxy-9-deoxoerythromycin A and (9*S*)-erythromycylamine A were previously described[6] as involving conformations **A** and **B** with additional flexibility in the C-6 to C-9 region. In particular, for erythromycylamine n.O.e.s were observed from 11-H to both C-7 protons, and in the light of the results for (**3**) this would imply that conformation **B**′ may also be involved in the conformational equilbrium for this compound.

Table 8. Interproton distances/Å for the crystal structures of (**1**), (**3**), and (**10**).

Proton pairs	(1)	(3)	(10)
11-H, 3-H	3.7	2.5	2.2
11-H, 4-H	2.2	3.8	3.2
11-H, 7(*pro-S*)-H	2.6	2.2	2.2
11-H, 7(*pro-R*)-H	4.2	2.3	3.6
8-H, 3-H	5.9	4.4	2.2
8-H, 5-H	4.9	3.8	2.2
8-H, 11-H	4.1	3.8	2.4

exists in both C-3 to C-5 'folded out' and C-3 to C-5 'folded in' conformations, which are in fast exchange. One simple representation of this, which is fully consistent with the n.m.r. results, is a rapid exchange between a conformation (**B'**) similar to that shown by the crystal structure of (**3**) and a conformation (**A**) similar to that shown by the crystal structure of (**1**). The previously described[6] conformation **B** is not present to any significant extent, and it therefore appears that (**3**) has less conformational flexibility in the C-6 to C-9 region than was found[6] for (9*S*)-9-hydroxy-9-deoxoerythromycin A and (9*S*)-erythromycylamine A.

Both the crystal structure and n.m.r. studies show that the sugar moieties in (**3**) have the same conformations and the same orientations as in (**1**).

Experimental

M.p.s were determined using a Kofler hot-stage apparatus. Except where stated otherwise, i.r. spectra and specific rotations were recorded for solutions in chloroform. ^{1}H n.m.r. spectra were recorded at 400 MHz and ^{13}C n.m.r. spectra were recorded at 100 MHz on a Bruker AM400 n.m.r. spectrometer for solutions in $CDCl_3$ with $SiMe_4$ as an internal standard. Fast atom bombardment mass spectra were obtained using a VG ZAB 1F mass spectrometer operating at 6 kV accelerating voltage with Xe atoms as the collision beam accelerated to 8 kV, and using 3-nitrobenzyl alcohol as the matrix. Solutions were dried using magnesium sulphate and solvents were removed by evaporation under reduced pressure using a rotary evaporator with bath temperature below 30 °C.

(E)-9-*Deoxo*-9-*methoxyiminoerythromycin A* (**2**).—Erythromycin A (**1**) (10 g) in pyridine (15 cm^3) at 5 °C was treated with *O*-methylhydroxylamine hydrochloride (2.3 g) and the mixture was kept at 5 °C for 120 h, and then stirred at room temperature for 24 h. The mixture was evaporated to low volume, poured into 10% aqueous potassium carbonate (50 cm^3), and extracted with chloroform (3 × 50 cm^3). The combined extracts were dried and the solvent was removed to give a white solid. Crystallisation from acetone–water gave the methoxyimine (**2**) as colourless prisms (7.3 g), m.p. 128–129 °C; $[\alpha]_D^{21}$ −71.8° (*c* 1.0); $\nu_{max.}$ 3 425 and 1 725 cm^{-1}; δ_H 5.11 (1 H, dd, *J* 2.1 and 11.2 Hz, 13-H), 4.92 (1 H, d, *J* 4.4 Hz, 1″-H), 4.44 (1 H, d, *J* 7.2 Hz, 1′-H), 3.82 (3 H, s, CH_3ON=), 3.68 (1 H, s, 11-H), 3.32 (3 H, s, Me-8″), 3.25 (1 H, dd, *J* 7.1 and 9.95 Hz, 2′-H), 3.03 (1 H, br, 4″-H), and 2.35 (6 H, s, Me-7′ and Me-8′); δ_C 175.3 (C-1), 171.5 (C-9), 103.0 (C-1′), 96.3 (C-1″), 78.0 (C-4″), 72.7 (C-3″), 71.0 (C-2′), 70.5 (C-11), 65.5 (C-3′ and C-5″), 61.7 (CH_3ON=), 49.5 (C-8″), and 40.3 (C-7′ and C-8′) (Found: C, 59.5; H, 9.1; N, 3.5. $C_{38}H_{70}N_2O_{13}$ requires C, 59.8; H, 9.2; N, 3.7%).

(E)-2′-O-4″-O-*Diformyl*-9-*deoxo*-9-*methoxyiminoerythromycin A* (**4**).—The methoxyimine (**2**) (1.0 g) in dichloromethane (7 cm^3) at 0 °C was treated with acetic formic anhydride (1.0 cm^3) and 4-*N*,*N*-dimethylaminopyridine (10 mg). The solution was warmed to room temperature and kept for 5 h. The solution was diluted with ethyl acetate (100 cm^3) and was washed with saturated aqueous sodium hydrogen carbonate (2 × 50 cm^3) and saturated aqueous sodium chloride (50 cm^3). The solution was dried and the solvent removed to give a white foam. Crystallisation from di-isopropyl ether gave the diformate (**4**) as colourless crystals (0.99 g), m.p. 189–191 °C; $[\alpha]_D^{20}$ −62.2 (*c* 1.0); $\nu_{max.}$ 3 510, 3 420, and 1 720 cm^{-1}; δ_H 8.20 (1 H, s, OCHO), 8.14 (1 H, s, OCHO), 5.12 (1 H, dd, *J* 2.1 and 11 Hz, 13-H), 4.98 (1 H, d, *J* 4.7 Hz, 1″-H), 4.77 (1 H, dd, *J* 9.1 and 9.6 Hz, 2′-H), 4.66 (1 H, d, *J* 7.4 Hz, 4″-H), 3.82 (3 H, s, CH_3ON=), 3.63 (1 H, s, 11-H), 3.33 (3 H, s, Me-8″), and 2.30 (6 H, s, Me-7′ and Me-8′); δ_C 175.1 (C-1), 171.5 (C-9), 160.8 (OCHO), 160.4 (OCHO), 99.6 (C-1′), 96.1 (C-1″), 78.3 (C-4″), 72.6 (C-3″), 71.7 (C-2′), 70.6 (C-11), 62.8 and 62.7 (C-3′ and C-5″), 61.8 (CH_3ON=), 49.5 (C-8″), and 40.3 (C-7′ and C-8′) (Found: C, 59.0; H, 8.7; N, 3.3. $C_{40}H_{70}N_2O_{15}$ requires C, 58.7; H, 8.6; N, 3.4%).

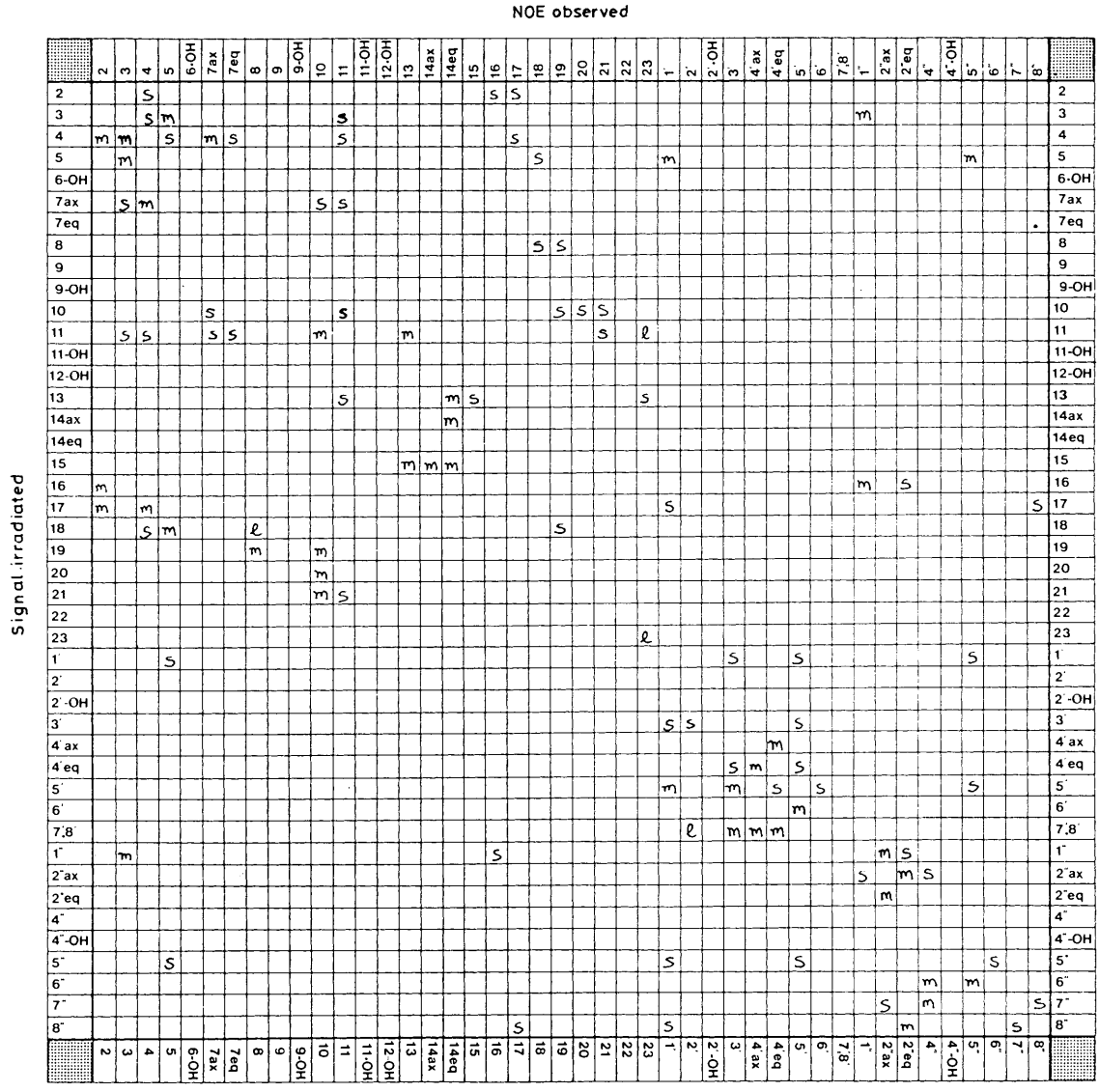
2-*Bromoethoxymethyl Chloride*.—2-Bromoethanol (12.5 g) in dichloromethane (100 cm^3) was treated with paraformaldehyde (3.0 g) and the mixture was cooled to 0 °C. Hydrogen chloride was passed into the mixture, which was kept at 0 °C, until all of the paraformaldehyde had dissolved (1 h). The solution was warmed to room temperature and kept for 2 h. The solution was dried and a stream of dry nitrogen was bubbled through the solution to remove excess hydrogen chloride. The solvent was removed to give a yellow oil, which was distilled to give 2-bromoethoxymethyl chloride as a colourless oil (11.3 g), b.p. 67 °C at 10 mmHg; ν_{max}(film) 2 960, 1 460, 1 420, 1 320, 1 280, 1 120, and 650 cm^{-1}; δ_H 3.52 (2 H, t, *J* 6 Hz), 4.01 (2 H, t, *J* 6 Hz), and 5.53 (2 H, s) (Found: C, 20.75; H, 3.5; Br, 46.1; Cl, 20.4. C_3H_6BrClO requires C, 20.8; H, 3.5; Br, 46.1; Cl, 20.4%).

(E)-11-O-(2-*Dimethylaminoethoxy*)*methyl*-9-*deoxo*-9-*methoxyiminoerythromycin A* (**3**).—The diformate (**4**) (0.99 g) in dry *N*,*N*-dimethylformamide (10 cm^3) was treated with 2,6-lutidine (1.89 cm^3) and 2-bromoethoxymethyl chloride (1.7 g) and the mixture was stirred for 6 h. The mixture was cooled to 0 °C and dimethylamine was passed into the solution until the weight had increased by 3.2 g. The reaction vessel was stoppered and heated at 60 °C (bath) for 1 h. Nitrogen was bubbled through the solution to remove excess dimethylamine, and the solution was then poured into acetate buffer (0.4 mol dm^{-3}, pH 4.8, 30 cm^3). The aqueous solution was washed with ethyl acetate (3 × 50 cm^3), and the pH was then adjusted to 11 by adding solid potassium carbonate. The mixture was extracted with ethyl acetate (3 × 50 cm^3), and the combined extracts were dried. The solvent was removed to give a yellow oil. The oil was dissolved in toluene (50 cm^3) and again the solvent was removed. The resulting residue was chromatographed on Merck silica gel 60 using 1:7:91 0.880 ammonia–methanol–chloroform to give the product as a white foam. Crystallisation from ethyl acetate gave the 11-ether (**3**) as colourless crystals (763 mg), m.p. 216–218 °C; $[\alpha]_D^{20}$ −69.5° (*c* 1.0); ν_{max} 3 500 br and 1 732 cm^{-1}; FAB-MS *m*/*z* 864 (MH^+) (Found: C, 60.0; H, 9.2; N, 4.8. $C_{43}H_{81}N_3O_{14}$ requires C, 59.8; H, 9.45; N, 4.9%).

Crystal Data.—Compound (**3**) $C_{43}H_{81}N_3O_{14}$, M = 864.1, orthorhombic, a = 10.093(2), b = 19.026(4), c = 25.454(7) Å, U = 4 888 Å^3, space group $P2_12_12_1$, Z = 4, D_c = 1.17 g m^{-3}, Cu radiation, λ = 1.541 78 Å. μ(Cu-K_α) = 7 cm^{-1}, F(000) = 1 888, approximate crystal dimensions 0.40 × 0.25 × 0.15 mm.

Data Collection and Processing.—3 699 independent reflections were measured ($2\theta < 116°$), of which 3 314 had $|F_o| > 3\delta(|F_o|)$ and were considered to be observed. Data were measured on a Nicolet R3m diffractometer with Cu-K_α

Table 9. ^{1}H N.O.e.s for (**3**) in $CDCl_3$.[a]



[a] S = small (0–2%), m = medium (2–5%), and l = large (> 5%) effect. The only side-chain n.O.e.s investigated were those involving the protons on C-23. The 23-H signal irradiated was that at δ 4.99; the n.O.e.s observed were for the 23-H absorbing at δ 4.77.

radiation (graphite monochromator) using ω-scans. Data corrected for Lorentz and polarisation factors; no absorption correction was applied.

Structure Analysis and Refinement.—The structure was solved by direct methods and the non-hydrogen atoms were refined anisotropically. The positions of the OH hydrogen atoms were determined from a ΔF map and refined isotropically. The other hydrogen atom positions were idealised (C–H = 0.96 Å), assigned isotropic thermal parameters [$U(H) = 1.2U_{eq}(c)$] and allowed to ride on their parent carbon atoms. The methyl groups were refined as rigid bodies. Refinement was by block-cascade, full-matrix least-squares and converged to give $R = 0.050$, $R_w = 0.056$ ($w^{-1} = \sigma^2(F) + 0.000\,83F^2$). The maximum and minimum residual electron densities in the final ΔF map were 0.35 and −0.23 e Å^{-3} respectively. Computations were carried out on an Eclipse S140 computer using the SHELXTL program system.[12]

Fractional atomic co-ordinates for the non-hydrogen atoms are given in Table 1. Tables 2 and 3 list the bond lengths and bond angles respectively. The fractional co-ordinates of the hydrogen atoms and their isotropic thermal parameters, and the anisotropic thermal parameters for the non-hydrogen atoms have been deposited at the Cambridge Crystallographic Data Centre.*

N.M.R.—All ^{1}H and ^{13}C n.m.r. experiments were conducted using standard pulse sequences on a Bruker AM400 n.m.r. spectrometer fitted with a 5 mm ^{1}H/^{13}C dual probe. A sample concentration of 200 mg cm^{-3} in $CDCl_3$ was used. Experiments

* For details of the CCDC deposition scheme, see section 5.6.3 of 'Instructions for Authors,' (1989), in the January issue.

were conducted at a slightly elevated temperature (310 K) in order to improve spectral resolution. The ^1H n.O.e. data were acquired using a modification of the method of Hall and Sanders.[13] The ^{13}C T_1 experiments used an inversion-recovery pulse sequence, the T_1 values being obtained as previously described.[6]

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