Erythromycin Series. Part 11.[1] Ring Expansion of Erythromycin A Oxime by the Beckmann Rearrangement

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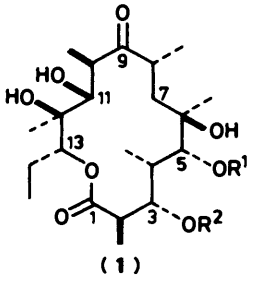
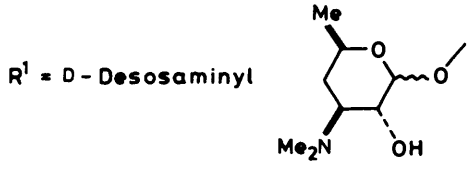
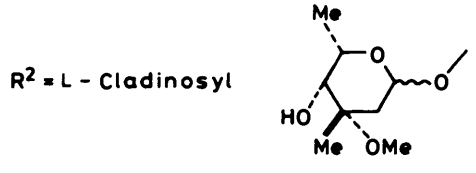
The synthesis of 10-dihydro-10-deoxo-11-azaerythromycin A (**11**) by the Beckmann rearrangement of erythromycin A oxime (**2**) and reduction of the imino ether so obtained (**5**) is described. The structure elucidation of the new ring-expanded semisynthetic erythromycins (**5**) and (**11**) has been established on the basis of their analytical and spectral data and acid-catalysed degradation into the aglycones (**7**) and (**13**), respectively. Finally, the complete structure of ring-expanded erythronolides (**7**) and (**13**) has been determined by *X*-ray crystallography.

Erythromycin A (**1**)[2–4] is a macrolide antibiotic characterized by a 14-membered lactone ring, erythronolide A,[5,6] with a 9-oxo group. In efforts to modify its biological and/or pharmacodynamic properties numerous derivatives of (**1**) have been prepared, including 9-imino derivatives.[7] Of the nucleophiles



(**1**)
Erythromycin A





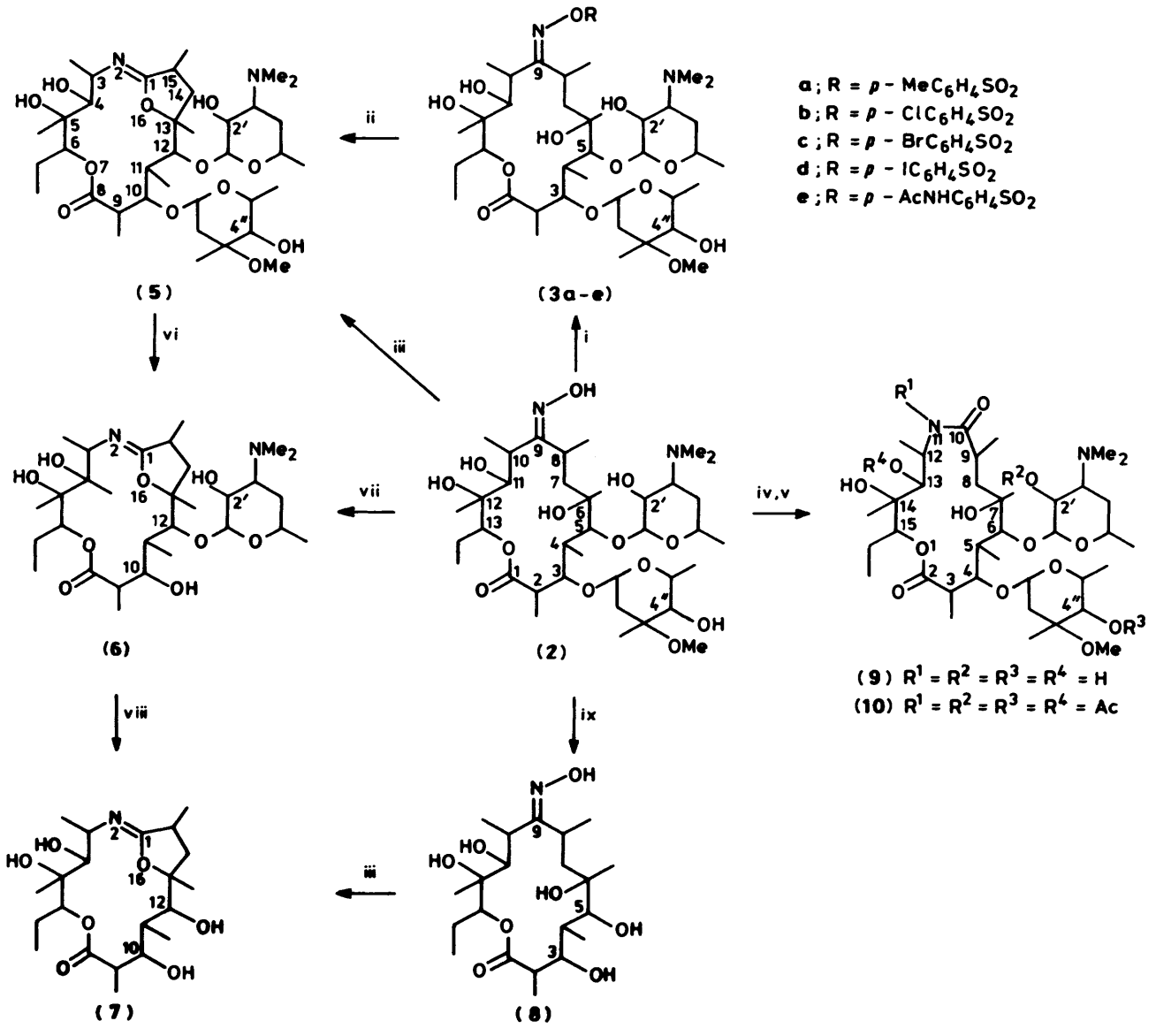
with low steric requirements which were allowed to react at the 9-carbonyl centre of (**1**), hydroxylamine was the most interesting[8,9] in that it yielded erythromycin A oxime, a substrate with potential for further modification of the aglycone ring. On the basis of its configurational analysis it was suggested that the *E*-isomer (**2**) predominated in the product.[7] To develop a method for the efficient introduction of the nitrogen atom into the 14-membered ring we studied the Beckmann rearrangement of 9-oxime (**2**) and conversion of the product (**5**) so obtained into a secondary amine (**11**).[10] Such erythromycin derivatives are the first of their kind in the literature.

Results and Discussion

It is well known that *O*-arylsulphonyloximes, especially *p*-tosyl compounds, are very suitable precursors in the Beckmann rearrangement of ketoximes.[11] By the reaction of the 9-oxime (**2**) with *para*-substituted arene sulphonyl chlorides in dry acetone in the presence of sodium hydrogen carbonate, a series of new erythromycin A 9-*O*-arylsulphonyloximes (**3a**—**e**) was prepared (Scheme 1).

The structure of these compounds was assigned from their spectroscopic properties. In particular, the i.r. spectrum of (**3a**) (Table 1) revealed new bands at 1 680 (C=N) and 1 600, 810, and 680 cm^{-1} (*p*-Ph). The ^1H n.m.r. spectrum displayed signals at δ 2.35 (s, 3 H, *p*-Me), 3.36 (s, 3 H, OMe), and 7.36 (q, 4 H, *p*-Ph). Apart from a typical chemical shift for dimethylamino protons of (**1**) (lit.,[12] 2.29 p.p.m.), (**3a**) showed a signal at δ 2.83 (s, 6 H) which corresponded to the *N*-methyl hydrogens of the protonated dimethylamine;[13] this indicated formation of the hydrochloric salt of (**3a**). Further characterization of (**3a**) was achieved by potentiometric titration which showed 4.07% (requires 3.77%) ionic bonded chlorine.

Surprisingly, Beckmann rearrangement of 9-*O*-arylsulphonyloximes (**3a**—**e**) carried out by a literature[14,15] method for related systems gave none of the expected lactam (**9**). Instead, it afforded the new compound (**5**) (erythromycin A imino ether) in 70—87% yield. This structure was confirmed by spectroscopic analysis. The i.r. spectrum of (**5**) showed strong absorption at 1 725 associated with the C-8 lactone carbonyl stretching and a new carbon–nitrogen (C=N) vibration at 1 705 cm^{-1}. The mass spectrum of (**5**) showed a peak at *m/z* 730, arising from loss of water from M^+ of the lactam (**9**) (Table 2) whilst the fragmentation pattern showed peaks at *m/z* 572 and 556, accounting for removal of cladinose with or without the glycosidic oxygen atom. The aglycone fragment devoid of both sugars gave rise to peaks at *m/z* 414 and 382. The fragments at *m/z* 174 and 158 indicated the presence of desosamine.[16] The ^{13}C n.m.r. spectrum displayed two singlets in a ^1H decoupling experiment (off-resonance decoupled: o.r.d.): at 178.8 [lit.,[17] 175.5 p.p.m. for (**1**)] arising from the C-8 lactone and at 163.9 p.p.m. for the imino C-1 carbon adjacent to the additional nitrogen atom of the aglycone ring. Comparison of the chemical shifts for the



Scheme 1. *Reagents:* i, *p*-substituted benzenesulphonyl chloride, dry Me_2CO, $NaHCO_3$; ii, CH_2Cl_2, 2M-HCl; iii, TsCl, Me_2CO–H_2O, $NaHCO_3$; iv, TsCl, Et_2O, pyridine; v, Ac_2O, pyridine; vi, 1% HCl in MeOH; vii, PCl_5, $CHCl_3$; viii, 2M-HCl, $CHCl_3$, reflux; ix, *cf.* Ref. 6

Table 1. Physical properties and analytical data of erythromycin A 9-*O*-arylsulphonyloximes (**3a—e**)

Compound (Formula)	Yield (%)	M.p. (°C)	$[\alpha]_D^{25}$ (°)[a]	$\nu_{max.}$/cm^{-1} [b]	Cl^- [c] Found (%) (Required)
(**3a**) ($C_{44}H_{74}N_2O_{15}S$·HCl)	84.5	137—138	−29.9	1 730 (C=O), 1 680 (C=N), 1 600, 810, 680 (*p*-Ph)	4.07 (3.77)
(**3b**) ($C_{43}H_{71}ClN_2O_{15}S$·HCl)	87.8	137—141	−23.7	1 730 (C=O), 1 680 (C=N), 1 580, 805, 645 (*p*-Ph)	3.85 (3.69)
(**3c**) ($C_{43}H_{71}BrN_2O_{15}S$·HCl)	90.6	146—148	−27.2	1 730 (C=O), 1 680 (C=N), 1 578, 740, 630 (*p*-Ph)	3.80 (3.53)
(**3d**) ($C_{43}H_{71}IN_2O_{15}S$·HCl)	85.6	143—151	−31.5	1 735 (C=O), 1 680 (C=N), 1 575, 1 000, 735 (*p*-Ph)	3.67 (3.37)
(**3e**) ($C_{45}H_{75}N_3O_{16}S$·HCl)	90.0	162—165	−49.3	1 730 (C=O), 1 680 (C=N), 1 595, 835, 715 (*p*-Ph), 1 530 (AcNH)	3.92 (3.61)

[a] c = 1 In methylene chloride. [b] I.r. spectra were taken in KBr. [c] Potentiometric titration using $AgNO_3$.

Table 2. The mass spectral fragmentation patterns of some new erythromycins with the expanded aglycone ring in comparison with erythromycin A oxime (2)

Fragment	m/z (%) (2)	(5)	(9)
M^+	748 (0.10)	730 (0.90)	748 (0.08)
M^+ – Me	733 (0.03)	715 (0.25)	
M^+ – H_2O	730 (0.03)	712 (0.13)	730 (0.12)
M^+ – EtCHO	690 (0.05)		689 (1.30)
M^+ – Me – EtCHO		657 (0.70)	675 (0.50)
M^+ – cladinose	590 (0.44)	572 (6.40)	590 (4.70)
M^+ – cladinose – O	574 (0.33)	556 (2.30)	574 (0.70)
M^+ – cladinose – desosamine	432 (0.65)	414 (3.60)	432 (1.90)
M^+ – cladinose – O – desosamine	416 (0.89)	398 (8.40)	416 (1.50)
M^+ – EtCHO – cladinose – desosamine		356 (1.90)	374 (0.80)
M^+ – EtCHO – cladinose – O – desosamine	358 (0.23)	340 (1.10)	358 (1.00)
$C_8H_{16}NO_3$(desosamine + O)	174 (2.12)	174 (17.0)	174 (3.40)
$C_8H_{16}NO_2$(desosamine)	158 (100)	158 (100)	158 (100)

corresponding atoms in compounds (5) and (2) (Table 3) showed that introduction of a nitrogen atom into the ring in the former compound resulted in an upfield shift of −6.6 p.p.m. for the 9-oxime carbon and a downfield shift of 27.4 p.p.m. for the C-10 signal. The downfield chemical shift of +12.2 p.p.m. for the C-6 signal of (2) compared with the corresponding C-13 chemical shift of (5) suggested the additional change in the aglycone structure, *e.g.* formation of an internal imino ether, similar to that described for 8,9-anhydroerythromycin A 6,9-hemiacetal.[18,19] Selective cleavage of cladinose from (5) with hydrogen chloride in methanol provided the 12-*O*-desosaminyl derivative (6). The same compound was also obtained by Beckmann rearrangement of the oxime (2) with phosphorus pentachloride. Further acid hydrolysis of (6) removed desosamine to give the aglycone (7). An identical product was obtained in an alternative synthesis from the oxime (2), proceeding *via* erythronolide A oxime (8), according to the method of LeMahieu *et al.*,[6] and subsequent Beckmann rearrangement of this.

The structure of the aglycone (7) was proved by *X*-ray structural analysis. The perspective view of the molecular structure is given in the Figure computed from the final atomic

Table 3. ^{13}C N.m.r. absorption of erythromycin A (1), erythromycin A oxime (2), and some new aza erythromycins (5), (7), (9), (11), and (13)

δ/p.p.m.[a–c] (1)[d]	(2)	(5)	(7)	(9)	(11)	(13)
175.5, s, C-1	175.1, s, C-1	178.1, s, C-8	175.1, s, C-8	179.6, s, C-2	178.5, s, C-2	176.8, s, C-2
44.8, d, C-2	44.5, d, C-2	43.3, d, C-9	43.2, d, C-9	43.1, d, C-3	45.3, d, C-3	43.8, d, C-3
80.0, d, C-3	79.4, d, C-3	76.1, d, C-10	76.9, d, C-10	78.0, d, C-4	78.1, d, C-4	80.4, d, C-4
39.4, d, C-4	38.9, d, C-4	42.6, d, C-11	35.4, d, C-11	39.7, d, C-5	42.1, d, C-5	34.7, d, C-5
83.6, d, C-5	82.3, d, C-5	79.0, d, C-12	79.8, d, C-12	81.3, d, C-6	83.4, d, C-6	83.7, d, C-6
74.8, s, C-6	75.0, s, C-6	87.7, s, C-13	85.6, s, C-13	86.0, s, C-7	73.7, s, C-7	73.5, s, C-7
38.5, t, C-7	37.7, t, C-7	37.1, t, C-14	36.3, t, C-14	38.0, t, C-8	42.2, t, C-8	39.8, t, C-8
44.8, d, C-8	32.5, d, C-8	35.1, d, C-15	34.4, d, C-15	34.2, d, C-9	29.9, d, C-9	29.2, d, C-9
221.1, s, C-9	170.5, s, C-9	163.7, s, C-1	161.5, s, C-1	174.6, s, C-10	57.3, t, C-10	56.8, t, C-10
38.2, d, C-10	25.2, d, C-10	52.3, d, C-3	52.5, d, C-3	47.9, d, C-12	56.7, d, C-12	58.3, d, C-12
68.7, d, C-11	70.9, d, C-11	72.6, d, C-4	71.9, d, C-4	78.8, d, C-13	73.2, d, C-13	74.1, d, C-13
74.8, s, C-12	74.1, s, C-12	74.9, s, C-5	74.6, s, C-5	74.0, s, C-14	73.8, s, C-14	73.4, s, C-14
77.0, d, C-13	76.5, d, C-13	77.1, d, C-6	78.6, d, C-6	76.1, d, C-15	77.2, d, C-15	77.4, d, C-15
18.5, 2-Me	16.5, 2-Me	16.0, 9-Me	16.4, 9-Me	18.0, 3-Me	15.0, 3-Me	16.1, 3-Me
9.1, 4-Me	9.1, 4-Me	9.2, 11-Me	7.1, 11-Me	11.0, 5-Me	9.2, 5-Me	7.3, 5-Me
26.8, 6-Me	26.9, 6-Me	23.7, 13-Me	26.4, 13-Me	25.1, 7-Me	27.4, 7-Me	26.0, 7-Me
16.2, 8-Me	14.4, 8-Me	13.5, 15-Me	14.4, 15-Me	12.2, 9-Me	14.0, 9-Me	13.7, 9-Me
12.0, 10-Me	18.6, 10-Me	18.2, 3-Me	18.2, 3-Me	19.0, 12-Me	21.9, 12-Me	21.1, 12-Me
16.0, 12-Me	16.1, 12-Me	17.4, 5-Me	16.9, 5-Me	15.2, 14-Me	16.2, 14-Me	15.8, 14-Me
21.3, 13-CH_2	20.9, 13-CH_2	21.4, 6-CH_2	21.1, 6-CH_2	22.2, 15-CH_2	21.1, 15-CH_2	20.8, 15-CH_2
10.5, 13-Me	10.6, 13-Me	11.1, 6-Me	10.8, 6-Me	11.1, 15-Me	11.2, 15-Me	10.8, 15-Me
103.1, d, C-1′	102.4, d, C-1′	102.6, d, C-1′		103.1, d, C-1′	103.9, d, C-1′	
70.9, d, C-2′	70.9, d, C-2′	70.5, d, C-2′		70.8, d, C-2′	70.9, d, C-2′	
65.3, d, C-3′	65.1, d, C-3′	65.5, d, C-3′		65.4, d, C-3′	65.5, d, C-3′	
28.7, t, C-4′	29.0, t, C-4′	28.4, t, C-4′		29.3, t, C-4′	28.8, t, C-4′	
68.8, d, C-5′	67.9, d, C-5′	68.7, d, C-5′		69.2, d, C-5′	68.7, d, C-5′	
21.3, 5′-Me	21.2, 5′-Me	21.3, 5′-Me		21.2, 5′-Me	21.4, 5′-Me	
40.3, 3′-NMe_2	40.2, 3′-NMe_2	40.3, 3′-NMe_2		40.4, 3′-NMe_2	40.3, 3′-NMe_2	
96.2, d, C-1″	96.1, d, C-1″	94.5, d, C-1″		95.0, d, C-1″	94.9, d, C-1″	
35.0, t, C-2″	35.2, t, C-2″	34.6, t, C-2″		35.2, t, C-2″	34.8, t, C-2″	
72.5, s, C-3″	72.7, s, C-3″	72.9, s, C-3″		72.8, s, C-3″	72.9, s, C-3″	
77.9, d, C-4″	77.8, d, C-4″	77.9, d, C-4″		77.9, d, C-4″	77.9, d, C-4″	
65.4, d, C-5″	65.3, d, C-5″	65.8, d, C-5″		65.6, d, C-5″	65.7, d, C-5″	
21.3, 3″-Me	21.4, 3″-Me	21.6, 3″-Me		21.6, 3″-Me	21.6, 3″-Me	
18.3, 5″-Me	18.6, 5″-Me	18.3, 5″-Me		18.5, 5″-Me	18.3, 5″-Me	
49.4, 3″-OMe	49.2, 3″-OMe	49.4, 3″-OMe		49.4, 3″-OMe	49.4, 3″-OMe	

[a] ^{13}C N.m.r. spectra were taken with JOEL 90 Q spectrometer at 33.35 MHz. [b] Solvent: $CDCl_3$ or $(CD_3)_2SO$ [compounds (2) and (7)]. [c] s = singlet, d = doublet, t = triplet. [d] *Tetrahedron Lett.*, 1975, 2583.

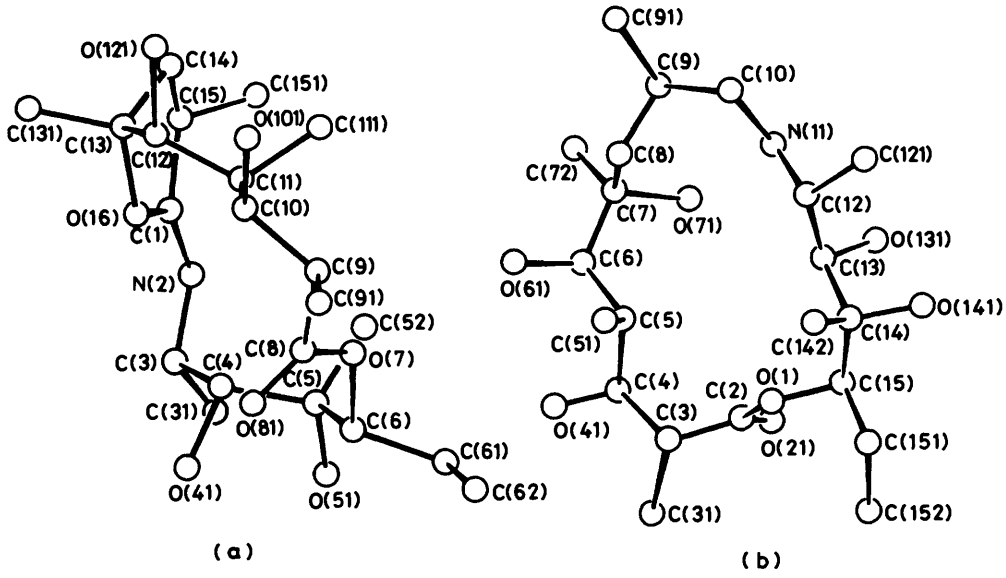


Figure. Perspective view of the structures of (a) aglycone (**7**), and (b) the cation of the HI salt of amine (**13**). Although the unit cell of (**7**) contains two crystallographically independent molecules since both have the same conformation only one is shown. Hydrogen atoms are omitted for clarity.

Table 4. Atomic positional parameters with estimated standard deviations for $C_{21}H_{37}NO_7 \cdot 1.5H_2O$

	Molecule (A)				Molecule (B)		
Atom	*x/a*	*y/b*	*z/c*	Atom	*x/a*	*y/b*	*z/c*
C(1)	0.145(1)	1.070(1)	0.216(2)	C(1)	−0.453(1)	0.469(1)	−0.803(2)
N(2)	0.112(1)	1.056(1)	0.072(1)	N(2)	−0.478(1)	0.446(1)	−0.935(1)
C(3)	0.000(1)	1.009(1)	−0.020(1)	C(3)	−0.405(1)	0.475(1)	−1.017(2)
C(4)	−0.023(1)	0.871(1)	−0.005(1)	C(4)	−0.378(1)	0.613(1)	−0.996(1)
C(5)	0.032(1)	0.760(1)	−0.085(1)	C(5)	−0.472(1)	0.703(1)	−1.064(1)
C(6)	−0.001(1)	0.628(2)	−0.064(2)	C(6)	−0.427(1)	0.842(1)	−1.031(2)
O(7)	0.057(1)	0.615(1)	0.097(1)	O(7)	−0.402(1)	0.893(1)	−0.870(1)
C(8)	−0.004(1)	0.612(1)	0.185(1)	C(8)	−0.298(1)	0.922(1)	−0.789(2)
C(9)	0.065(1)	0.584(1)	0.338(1)	C(9)	−0.282(1)	0.983(2)	−0.626(2)
C(10)	0.084(1)	0.711(1)	0.453(1)	C(10)	−0.253(1)	0.880(2)	−0.528(2)
C(11)	0.145(1)	0.809(1)	0.415(1)	C(11)	−0.345(1)	0.788(2)	−0.554(1)
C(12)	0.134(1)	0.942(1)	0.513(1)	C(12)	−0.300(1)	0.675(2)	−0.472(2)
C(13)	0.154(1)	1.065(1)	0.460(2)	C(13)	−0.357(1)	0.541(2)	−0.547(2)
C(14)	0.270(1)	1.087(2)	0.467(2)	C(14)	−0.473(2)	0.532(2)	−0.564(2)
C(15)	0.256(1)	1.126(2)	0.316(2)	C(15)	−0.521(1)	0.438(2)	−0.710(2)
O(16)	0.090(1)	1.040(1)	0.297(1)	O(16)	−0.356(1)	0.522(1)	−0.705(1)
C(31)	0.001(0)	0.994(0)	−0.169(0)	C(31)	−0.490(0)	0.443(0)	−1.161(0)
O(41)	−0.142(1)	0.848(1)	−0.079(1)	O(41)	−0.296(1)	0.623(1)	−1.063(1)
O(51)	−0.014(1)	0.762(1)	−0.241(1)	O(51)	−0.505(1)	0.664(1)	−1.227(1)
C(52)	0.158(1)	0.771(2)	−0.031(2)	C(52)	−0.575(1)	0.701(2)	−1.019(2)
C(61)	0.031(1)	0.509(2)	−0.159(2)	C(61)	−0.517(1)	0.937(2)	−1.110(2)
C(62)	−0.009(2)	0.385(2)	−0.138(2)	C(62)	−0.466(2)	1.066(2)	−1.091(3)
O(81)	−0.099(1)	0.633(1)	0.151(1)	O(81)	−0.222(1)	0.901(1)	−0.838(1)
C(91)	0.002(1)	0.487(2)	0.379(2)	C(91)	−0.195(2)	1.085(2)	−0.582(2)
O(101)	0.136(1)	0.692(1)	0.600(1)	O(101)	−0.211(1)	0.942(2)	−0.381(2)
C(111)	0.262(1)	0.765(2)	0.424(2)	C(111)	−0.435(3)	0.868(3)	−0.512(3)
O(121)	0.209(1)	0.952(1)	0.665(1)	O(121)	−0.316(1)	0.703(1)	−0.325(1)
C(131)	0.106(1)	1.184(2)	0.536(2)	C(131)	−0.283(2)	0.440(2)	−0.477(2)
C(151)	0.353(2)	1.094(2)	0.258(2)	C(151)	−0.647(2)	0.458(2)	−0.785(2)
O(1w)	0.226(1)	0.156(1)	0.904(1)				
O(2w)	0.324(1)	0.349(1)	0.827(1)				
O(3w)	0.299(1)	0.508(1)	0.619(1)				

co-ordinates given in Table 4. In the structure there are two crystallographically independent molecules, (A) and (B), and three water molecules. The gross structure comprises a 15-membered ring with the furanoic ring significantly out of the plane of the rest of the molecule. The torsion angles C(11)–C(12)–C(13)–C(14) and C(3)–N(2)–C(1)–C(15) are −69 and −176°, and −64 and −178° in the molecules (A) and (B), respectively. The majority of the interatomic distances and

Table 5. Bond lengths (Å) and bond angles (°) with estimated standard deviations for $C_{21}H_{37}O_7N{\cdot}1.5H_2O$

	Molecule (A)	Molecule (B)		Molecule (A)	Molecule (B)
C(1)–N(2)	1.29(2)	1.18(2)	C(8)–O(81)	1.18(2)	1.22(2)
C(1)–C(15)	1.52(2)	1.54(3)	C(9)–C(10)	1.54(1)	1.53(3)
C(1)–O(16)	1.31(2)	1.37(2)	C(9)–C(91)	1.54(3)	1.51(3)
N(2)–C(3)	1.48(2)	1.50(2)	C(10)–C(11)	1.52(2)	1.52(3)
C(3)–C(4)	1.56(2)	1.49(2)	C(10)–O(101)	1.40(1)	1.38(2)
C(3)–C(31)	1.42(1)	1.45(1)	C(11)–C(12)	1.56(1)	1.54(3)
C(4)–C(5)	1.54(2)	1.54(2)	C(11)–C(111)	1.53(2)	1.51(4)
C(4)–O(41)	1.48(2)	1.43(2)	C(12)–C(13)	1.56(2)	1.57(3)
C(5)–C(6)	1.56(3)	1.56(2)	C(12)–O(121)	1.45(1)	1.47(2)
C(5)–O(51)	1.43(1)	1.46(1)	C(13)–C(14)	1.51(2)	1.46(3)
C(5)–C(52)	1.54(2)	1.54(2)	C(13)–O(16)	1.49(2)	1.50(2)
C(6)–O(7)	1.51(2)	1.47(2)	C(13)–C(131)	1.53(2)	1.49(3)
C(6)–C(61)	1.52(3)	1.58(2)	C(14)–C(15)	1.54(3)	1.52(2)
O(7)–C(8)	1.34(2)	1.33(2)	C(15)–C(151)	1.53(3)	1.56(3)
C(8)–C(9)	1.52(1)	1.53(3)	C(61)–C(62)	1.52(3)	1.51(3)
N(2)–C(1)–C(15)	123(1)	126(1)	C(8)–C(9)–C(91)	108(1)	106(2)
N(2)–C(1)–O(16)	126(1)	126(1)	C(10)–C(9)–C(91)	111(1)	114(2)
C(15)–C(1)–O(16)	110(1)	108(1)	C(9)–C(10)–C(11)	112(1)	115(2)
C(1)–N(2)–C(3)	121(1)	123(1)	C(9)–C(10)–O(101)	113(1)	108(2)
N(2)–C(3)–C(4)	114(1)	116(1)	C(11)–C(10)–O(101)	111(1)	113(2)
N(2)–C(3)–C(31)	103(1)	92(1)	C(10)–C(11)–C(12)	108(1)	110(1)
C(4)–C(3)–C(31)	104(1)	107(1)	C(10)–C(11)–C(111)	112(1)	107(2)
C(3)–C(4)–C(5)	116(1)	117(1)	C(12)–C(11)–C(111)	116(1)	117(2)
C(3)–C(4)–O(41)	107(1)	109(1)	C(11)–C(12)–C(13)	118(1)	117(1)
C(5)–C(4)–O(41)	105(1)	106(1)	C(11)–C(12)–O(121)	111(1)	109(1)
C(4)–C(5)–C(6)	110(1)	109(1)	C(13)–C(12)–O(121)	105(1)	104(1)
C(4)–C(5)–O(51)	106(1)	107(1)	C(12)–C(13)–C(14)	117(1)	117(2)
C(4)–C(5)–C(52)	113(1)	116(1)	C(12)–C(13)–O(16)	103(1)	104(1)
C(6)–C(5)–O(51)	106(1)	105(1)	C(12)–C(13)–C(131)	111(1)	108(2)
C(6)–C(5)–C(52)	110(1)	112(1)	C(14)–C(13)–O(16)	105(1)	104(2)
O(51)–C(5)–C(52)	111(1)	108(1)	C(14)–C(13)–C(131)	112(1)	116(2)
C(5)–C(6)–O(7)	108(1)	108(1)	O(16)–C(13)–C(131)	109(1)	106(2)
C(5)–C(6)–C(61)	116(1)	112(1)	C(13)–C(14)–C(15)	104(1)	105(2)
O(7)–C(6)–C(61)	106(1)	104(1)	C(1)–C(15)–C(14)	103(1)	101(2)
C(6)–O(7)–C(8)	119(1)	118(1)	C(1)–C(15)–C(151)	118(2)	113(2)
O(7)–C(8)–C(9)	112(1)	114(1)	C(14)–C(15)–C(151)	116(2)	113(2)
O(7)–C(8)–O(81)	125(1)	124(1)	C(1)–O(16)–C(13)	112(1)	110(1)
C(9)–C(8)–O(81)	123(1)	123(1)	C(6)–C(61)–C(62)	113(2)	110(2)
C(8)–C(9)–C(10)	109(1)	111(1)			

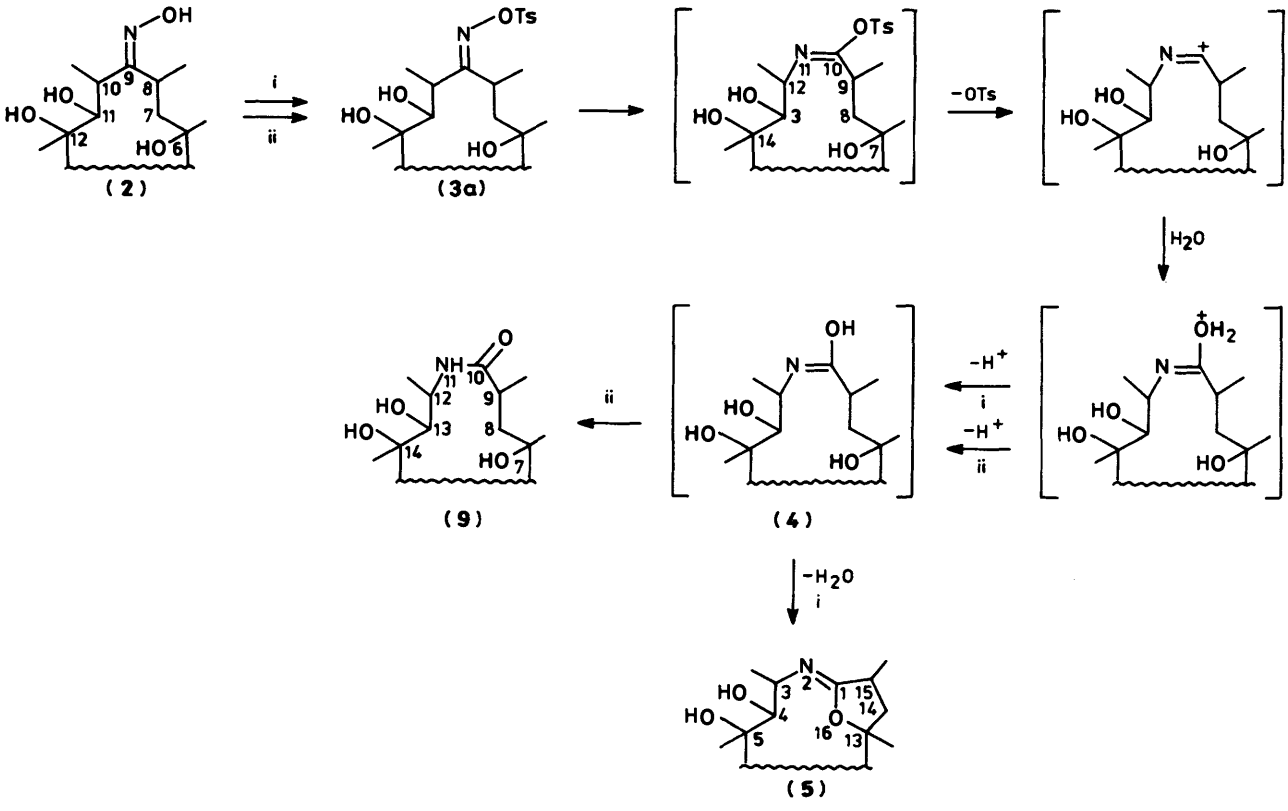
angles in the molecules (A) and (B) (Table 5) agree well with each other as well as with the known values found in the literature.[20,21]

All three water molecules [$H_2O(1w)$, $H_2O(2w)$, and $H_2O(3w)$], apart of being hydrogen bonded to each other at 2.80(2) and 2.79(2) Å participate also in the hydrogen bonding to OH groups and N atoms from three different [one (**B**) and two (A)] aglycone molecules. These hydrogen bonds between N(2A)···O(1w), N(2B)···O(2w), O(51B)···O(3w), and O(101A)···O(3w) amount to 2.90(2), 2.90(2), 2.91(2), and 2.75(2) Å, respectively.

Beckmann rearrangement of erythromycin A oxime (**2**) with toluene-*p*-sulphonyl chloride (*p*-TsCl) gave in aqueous acetone the imino ether (**5**) (71.8% yield), identical with that obtained by the rearrangement of esters (**3a**—**e**). However, the rearrangement of (**2**) with *p*-TsCl in pyridine seems to give the erythromycin A lactam (**9**). Examination of the ^{13}C n.m.r. spectrum of (**9**) showed a singlet lactam carbonyl at 174.6 p.p.m. (o.r.d.). The mass spectrum showed the molecular ion peak at *m/z* 748, which together with the fragmentation pattern correspond to the structure of the lactam (**9**). To give some further chemical evidence for the structural assignment of the lactam, (**9**) was acetylated with an excess of acetic anhydride in pyridine (72 h, 25 °C), since it is known that the 2′-, 4″-, and 11-hydroxyl groups of erythromycin are acylated under these conditions.[22,23] Acetylation of the lactam (**9**) produced a new product (**10**) which had four acetyl signals in its ^1H n.m.r. spectrum and a molecular ion at *m/z* 916. The ^{13}C n.m.r. showed in the carbonyl region six singlets (o.r.d.). Apart from the signals at 179.3 (C=O, lactone) and 174.7 p.p.m. (C=O, lactam), compound (**10**) exhibited four new signals at 171.9, 170.5, 169.9, and 169.2 p.p.m.; these indicated that besides *O*-acylation at C-2′, C-4″, and C-13, *N*-acylation had also occurred at the 11-position.

To explain the formation of the imino ether (**5**) and lactam (**9**) in the Beckmann rearrangement of erythromycin A oxime (**2**), the mechanism outlined in Scheme 2 is suggested. Beckmann rearrangement generally involves conversion of the oxime hydroxy group into a better leaving group, followed by rearrangement and tautomerization.[24,25] Thus it was established that the lactim (**4**) may undergo two types of transformation depending on the solvent used: namely, izomerization (path ii) to yield the expected lactam (**9**), or elimination of water from the 7- and 10-hydroxyl groups (path i) to yield the unusual lactim ether (**5**). This result probably arises from the greater stability of (**4**) in aqueous acetone than in pyridine. Consequently, the rate of conversion of (**4**) into the lactam (**9**) is slowed. Since structure (**4**) is sterically well disposed for internal ether formation,[18] it is reasonable to suppose, that the elimination of water from (**4**) to give (**5**) will compete successfully with the izomerization of (**4**) into (**9**). In contrast, pyridine will favour rapid tautomerization of (**4**) into (**9**).

In order to prepare amino derivatives of the new macrocyclic



Scheme 2. *Reagents:* i, *p*-TsCl, Me_2CO–H_2O; ii, *p*-TsCl, pyridine

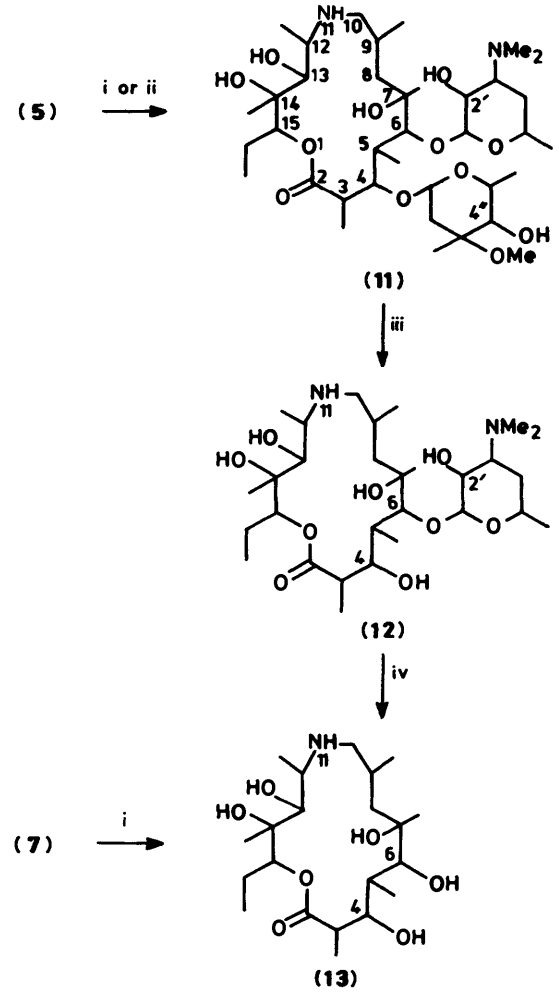
structure, the imino ethers (**5**) and (**7**) were subjected to reduction (see Scheme 3). Catalytic hydrogenation of the imino ether (**5**) in glacial acetic acid using platinum(IV) oxide gave in high yield (79.6%) compound (**11**); the i.r. spectrum of (**11**) lacked the imino band at 1 705 cm^{-1}, as well as a 1-imino carbon singlet (o.r.d.) at 163.9 p.p.m. in its ^{13}C n.m.r. spectrum. This spectrum also showed a new triplet at 57.3 p.p.m. suggesting the presence of a secondary amino group in the new 15-membered aglycone ring. The mass spectrum gave additional support to the structure proposed. An identical product, *i.e.* the 10-dihydro-10-deoxo-11-azaerythromycin A (**11**), was obtained by chemical reduction of the imino ether (**5**) with metal hydrides, *e.g.* sodium borohydride in methanol.

Glycosidic cleavage of (**11**) removed smoothly both sugars and yielded 10-dihydro-10-deoxo-11-azaerythronolide A (**13**) which exhibited the expected molecular ion at *m/z* 419 in the mass spectrum. The p*K* value of 8.3 (66% DMF) was consistent with the presence of the amino group in the ring. The same product (**13**) was obtained by the catalytic hydrogenation of the aglycone (**7**) with platinum(IV) oxide in glacial acetic acid. The final evidence for the structure of the amine (**13**) came from an *X*-ray analysis, but since it was impossible to obtain suitable crystals of amine (**13**) itself, its HI crystalline salt was prepared by treating the parent compound (**13**) with hydrogen iodide in dry acetone.

The structure of the amine (**13**) consists of $C_{21}H_{42}O_7N^+$ cations and I^- anions. A perspective view of the molecular structure is shown in the Figure obtained from the final atomic parameters given in Table 6. A general feature of the molecule is here again the 15-membered ring with bond lengths and angles similar to those found in the structure of the aglycone (**7**) and to the data known from previously published analogous structures.[20,21] All relevant bond lengths and angles are given

Table 6. Atomic positional parameters with estimated standard deviations for $C_{21}H_{42}INO_7$

Atom	*x/a*	*y/b*	*z/c*
I	0.136 1(1)	0.242 0(2)	0.151 7(2)
O(1)	0.038(1)	0.315(2)	0.592(1)
C(2)	0.026(1)	0.236(4)	0.495(2)
C(3)	0.025(1)	0.084(3)	0.486(3)
C(4)	0.075(1)	0.021(2)	0.461(2)
C(5)	0.127(1)	0.069(2)	0.516(2)
C(6)	0.175(1)	0.007(3)	0.449(2)
C(7)	0.225(1)	0.105(2)	0.444(2)
C(8)	0.251(1)	0.124(2)	0.558(3)
C(9)	0.295(1)	0.240(3)	0.564(3)
C(10)	0.278(1)	0.377(2)	0.626(2)
N(11)	0.230(1)	0.432(3)	0.570(2)
C(12)	0.188(1)	0.479(3)	0.651(3)
C(13)	0.134(1)	0.491(3)	0.586(2)
C(14)	0.088(1)	0.518(3)	0.661(3)
C(15)	0.037(1)	0.478(2)	0.593(2)
O(21)	0.020(1)	0.305(2)	0.405(2)
C(31)	−0.024(1)	0.029(2)	0.455(3)
O(41)	0.071(1)	−0.128(2)	0.473(2)
C(51)	0.130(1)	0.013(3)	0.650(2)
O(61)	0.192(1)	−0.133(2)	0.486(2)
O(71)	0.206(1)	0.246(2)	0.410(1)
C(72)	0.263(1)	0.053(3)	0.360(3)
C(91)	0.344(1)	0.184(3)	0.627(3)
C(121)	0.203(1)	0.623(4)	0.718(3)
O(131)	0.140(1)	0.601(2)	0.508(2)
O(141)	0.081(1)	0.660(3)	0.686(2)
C(142)	0.088(1)	0.438(4)	0.774(2)
C(151)	−0.015(2)	0.503(6)	0.650(10)
C(152)	−0.065(1)	0.466(4)	0.576(3)



Scheme 3. *Reagents:* i, PtO_2, HOAc; ii, $NaBH_4$, MeOH; iii, *cf.* Ref. 26; iv, 6M-HCl, $CHCl_3$

in Table 7. There are no additional interactions between the aglycone rings except van der Waals contacts.

Experimental

All m.p.s were determined with a Fisher-Johns apparatus and are uncorrected. I.r. spectra (KBr pellets or $CHCl_3$) were taken on a Perkin-Elmer 257 G spectrometer. ^1H N.m.r. spectra were determined with a Varian A-60 spectrometer (solvents: $CDCl_3$, $(CD_3)_2SO$, CD_5N; $SiMe_4$ as internal reference). ^{13}C N.m.r. spectra were recorded with JOEL 90 Q spectrometer (with $SiMe_4$ as internal standard) and electron impact mass spectra with a CEC 21-110 C spectrometer at 70 eV. Characteristic frequencies only are reported; the spectra recorded were otherwise in agreement with the structure given.

T.l.c. was performed on Merck silica gel 60 F_{254} plates; the plates were initially examined under u.v. light and then detected with a mixture (3:100, w/v) of phenol–[ethanol–sulphuric acid (95:5, v/v)] The following solvent systems were used: (A) 40:55:5 C_6H_6–$CHCl_3$–MeOH (saturated with NH_3 vapour); (B) 4:1:5 BuOH–HOAc–H_2O (upper layer); (C) 7:3 $CHCl_3$–MeOH; (D) 3:1 DMF–MeOH. The homogeneity of all compounds was tested by t.l.c. and their analytical data are listed in Table 8. Merck silica gel 60 (70—230 mesh) was used for column chromatography. Solutions in organic solvents were dried over anhydrous potassium carbonate.

Table 7. Bond lengths (Å) and bond angles (°) with estimated standard deviations for $C_{21}H_{42}INO_7$

O(1)–C(2)	1.41(4)	C(8)–C(9)	1.56(4)
O(1)–C(15)	1.45(3)	C(9)–C(10)	1.56(4)
C(2)–C(3)	1.44(5)	C(9)–C(91)	1.55(4)
C(2)–O(21)	1.26(4)	C(10)–N(11)	1.50(4)
C(3)–C(4)	1.44(4)	N(11)–C(12)	1.50(4)
C(3)–C(31)	1.40(4)	C(12)–C(13)	1.57(4)
C(4)–C(5)	1.52(3)	C(12)–C(121)	1.64(5)
C(4)–O(41)	1.43(3)	C(13)–C(14)	1.49(4)
C(5)–C(6)	1.57(3)	C(13)–O(131)	1.41(3)
C(5)–C(51)	1.69(4)	C(14)–C(15)	1.60(4)
C(6)–C(7)	1.59(3)	C(14)–O(141)	1.40(4)
C(6)–O(61)	1.47(3)	C(14)–C(142)	1.55(5)
C(7)–C(8)	1.52(4)	C(15)–C(151)	1.52(8)
C(7)–O(71)	1.48(3)	C(151)–C(152)	1.58(9)
C(7)–C(72)	1.47(4)		

C(2)–O(1)–C(15)	123(2)	C(7)–C(8)–C(9)	115(2)
O(1)–C(2)–C(3)	126(3)	C(8)–C(9)–C(10)	115(2)
O(1)–C(2)–O(21)	116(3)	C(8)–C(9)–C(91)	111(2)
O(21)–C(2)–C(3)	117(3)	C(91)–C(9)–C(10)	105(2)
C(2)–C(3)–C(4)	115(2)	C(9)–C(10)–N(11)	107(2)
C(2)–C(3)–C(31)	114(2)	C(10)–N(11)–C(12)	114(2)
C(31)–C(3)–C(4)	125(3)	N(11)–C(12)–C(13)	109(2)
C(3)–C(4)–C(5)	123(2)	N(11)–C(12)–C(121)	113(2)
C(3)–C(4)–O(41)	109(2)	C(121)–C(12)–C(13)	113(2)
O(41)–C(4)–C(5)	108(2)	C(12)–C(13)–C(14)	114(2)
C(4)–C(5)–C(6)	109(2)	C(12)–C(13)–O(131)	107(2)
C(4)–C(5)–C(51)	111(2)	O(131)–C(13)–C(14)	111(2)
C(51)–C(5)–C(6)	109(2)	C(13)–C(14)–C(15)	106(3)
C(5)–C(6)–C(7)	115(2)	C(13)–C(14)–O(141)	113(2)
C(5)–C(6)–O(61)	115(2)	C(13)–C(14)–C(142)	116(3)
O(61)–C(6)–C(7)	107(2)	O(141)–C(14)–C(15)	107(2)
C(6)–C(7)–C(8)	113(2)	O(141)–C(14)–C(142)	107(3)
C(6)–C(7)–O(71)	106(2)	C(142)–C(14)–C(15)	108(2)
C(6)–C(7)–C(72)	110(2)	C(14)–C(15)–O(1)	107(2)
O(71)–C(7)–C(8)	106(2)	C(14)–C(15)–C(151)	114(4)
O(71)–C(7)–C(72)	109(2)	C(151)–C(15)–O(1)	104(3)
C(72)–C(7)–C(8)	112(2)	C(15)–C(151)–C(152)	113(7)

O-Arylsulphonyloximes (**3a**—**e**): *General Procedure.*—Sodium hydrogen carbonate (1.65 g, 1.9 mmol) was added to a stirred solution of the oxime (**2**) (3.0 g, 4 mmol) in dry acetone (90 ml) after which the corresponding *para*-substituted benzenesulphonyl chloride (9.5 mmol) dissolved in dry acetone (60 ml) was added dropwise, during 1 h at 0—5 °C. The mixture was stirred for further 3 h after which the precipitate was filtered off and the filtrate evaporated under reduced pressure. The residue was suspended in dry ether and filtered to give *O*-arylsulphonyloxyoximes (**3a**—**e**) (Table 1).

Erythromycin A Imino Ether (**5**).—*By the Beckmann rearrangement of erythromycin A* 9-O-p-*tolylsulphonyloxime* (**3a**). Water (50 ml) was added to a solution of the oxime tosylate (**3a**) (3.4 g, 3.8 mmol) in dichloromethane (50 ml) and the reaction mixture acidified with 2M-hydrochloric acid to pH 6. After the mixture had been stirred at room temperature for 15 min, the layers were separated and the aqueous layer extracted with dichloromethane (2 × 50 ml). The extraction was repeated at pH 6.5 (2 × 50 ml) and 8 (4 × 50 ml) and the extracts dried. Evaporation under reduced pressure of the extract collected at pH 8 gave the imino ether (**5**) (2.15 g, 78.3%), m.p. 128—131 °C; $[\alpha]_D^{20}$ −54.63 (*c* 1 in CH_2Cl_2); *m/z* 730 (M^+); $\nu_{max.}$($CHCl_3$) 1 725 (lactone CO) and 1 705 cm^{-1} (OC=N): δ_C($CDCl_3$) 178.1 (s, lactone CO), 163.9 (s, OC=N), and 52.6 p.p.m. (d, C-3).

Table 8. Analytical data for the new ring-expanded erythromycins

Compound (Formula)	Yield (%)	M.p. (°C)	M^+ (m/z)	R_F	Found (%) (Required) C	H	N
(5) ($C_{37}H_{66}N_2O_{12}$)	78.3	128—131	730	0.782 (D) 0.205 (B)	60.3 (60.8)	9.2 (9.1)	3.5 (3.8)
(6) ($C_{29}H_{52}N_2O_9$)	89.9	109—115	572	0.164 (B)	60.4 (60.8)	9.5 (9.2)	4.7 (4.9)
(7) ($C_{21}H_{37}NO_7$)	55.6	164—168	415	0.412 (B)	60.3 (60.7)	9.2 (9.0)	3.4 (3.4)
(9) ($C_{37}H_{68}N_2O_{13}$)	63.0	83—86	748	0.121 (D)	59.0 (59.3)	9.5 (9.2)	3.6 (3.7)
(11) ($C_{37}H_{70}N_2O_{12}$)	79.6	113—116	734	0.219 (B)	60.1 (60.5)	9.9 (9.6)	3.7 (3.8)
(13) ($C_{21}H_{41}NO_7$)	51.8	193—196	419	0.466 (B)	59.9 (60.1)	9.6 (9.9)	3.6 (3.3)

By the Beckmann rearrangement of erythromycin A oxime (**2**). Toluene-*p*-sulphonyl chloride (4.9 g, 26 mmol) in acetone (42 ml) and sodium hydrogen carbonate (4.4 g, 52 mmol) in water (147 ml) were added dropwise over 2 h to a stirred solution of erythromycin A oxime (**2**) (9.6 g, 13 mmol) in acetone (120 ml) at 0—5 °C.

After the reaction mixture had been stirred for a further 2 h at this temperature, the acetone was evaporated under reduced pressure. Gradient extraction at pH 5.5, 6, and 8 with dichloromethane gave at pH 8 the imino ether (**5**) (7.6 g), identical with the product (**5**) obtained by the Beckmann rearrangement of (**3a**). The residue at pH 6 after evaporation of solvent was re-extracted (at pH 5.5, 6, and 8) to give additional (0.6 g) (**5**) (overall yield 86.5%).

12-O-*Desosaminylerythromycin A Imino Ether* (**6**).—(*a*) The imino ether (**5**) (10 g, 13.6 mmol) in methanol (500 ml) containing 1% hydrogen chloride was left for 2 days at ambient temperature. After neutralisation with sodium hydrogen carbonate the solvent was evaporated. Chloroform (250 ml) was added to the residue, washed with 3M-hydrochloric acid and then with water.

The combined HCl extract was made basic (pH 10) with 3M-sodium hydroxide and then extracted with chloroform (3 × 70 ml); the combined chloroform extracts were washed with saturated aqueous sodium hydrogen carbonate and dried. Evaporation of chloroform to dryness afforded 12-*O*-desosaminylerythromycin A imino ether (**6**) (7.1 g, 89.9%), m.p. 109—115 °C; $[\alpha]_D^{20}$ 58.71 (*c* 1 in CH_2Cl_2); *m/z* 572 (M^+); $\nu_{max.}$ 1 735 (lactone CO) and 1 705 cm^{-1} (OC=N); $\delta_H(CDCl_3)$ 2.23 (s, 6 H, NMe_2).

(*b*) Phosphorus pentachloride (1.1 g, 5.3 mmol) was added in portions to a stirred solution of the oxime (**2**) (1.3 g, 1.7 mmol) in chloroform (50 ml) after which the mixture was heated under reflux for 2 h and then poured into ice–water. The resulting solution was made alkaline by addition of 2M-aqueous sodium hydroxide to pH 10 and stirred for a further 3 h at ambient temperature. The layers were separated, and the aqueous layer was extracted with chloroform (3 × 30 ml) and dried.

The solvent was removed under reduced pressure to afford the crude product (1.02 g), which was recrystallized from chloroform–light petroleum (b.p. 40—60 °C) to yield the pure ether (**6**), m.p. 113—116 °C, identical with the sample prepared according to the method (*a*).

Erythronolide A Imino Ether (**7**).—(*a*) A mixture of 12-*O*-desosaminylerythronolide A imino ether (**6**) (1.0 g, 1.7 mmol), 2M-hydrochloric acid (20 ml) and chloroform (10 ml) was heated under reflux for 72 h. The mixture was cooled at room temperature, the layers were separated, and the aqueous layer was extracted with chloroform (2 × 5 ml). The pH of the aqueous solution was adjusted with 2M-aqueous sodium hydroxide to 9.0 and again extracted with chloroform (3 × 10 ml). The combined chloroform extract at pH 9.0 was dried and evaporated. T.l.c. revealed in a $CHCl_3$–MeOH (7:3) system a major spot moving much faster than (**6**) and several impurities. The analytical sample, m.p. 164—168 °C, was prepared by two recrystallisations from hot acetone solution; $[\alpha]_D^{20}$ 64.8 (*c* 1 in Me_2CO); *m/z* 415 (M^+); $\nu_{max.}$(Nujol) 1 712 (lactone CO) and 1 697 cm^{-1} (OC=N); $\delta_C[(CD_3)_2SO]$ 175.1 (s, lactone CO), 161.5 (s, OC=N), and 52.6 p.p.m. (d, C-3).

(*b*) Erythronolide A oxime (**8**) (5 g, 11.6 mmol), prepared by the procedure of LeMahieu *et al.*,[6] underwent the Beckmann rearrangement according to the procedure described for (**5**) to yield erythronolide A imino ether (**7**) (2.63 g, 55.6%), identical with that obtained according to method (*a*).

Erythromycin A Lactam (**9**).—Toluene-*p*-sulphonyl chloride (0.384 g, 2 mmol) in ether (10 ml) was added dropwise at 0—5 °C during 30 min to a stirred solution of the erythromycin A oxime (**2**) (0.748 g, 1 mmol) in dry pyridine and the mixture stirred at this temperature for a further 2 h. The solvent was removed under reduced pressure and water (50 ml) and chloroform (30 ml) were added to the oil residue; the pH was adjusted to 5.5 with 20% aqueous sodium hydroxide and the mixture extracted with chloroform (2 × 20 ml). The extraction was repeated at pH 6 and 8.3 and the extracts were dried. Evaporation of the solvent at pH 8.3 gave the erythromycin A lactam (**9**) (0.471 g, 63%), m.p. 83—86 °C; $[\alpha]_D^{20}$ −44.0 (*c* 1 in CH_2Cl_2); *m/z* 748 (M^+); $\nu_{max.}(CHCl_3)$ 1 725 (lactone CO), 1 760 (amide CO), and 1 580 cm^{-1} (amide NC=O); $\delta_C(CDCl_3)$ 179.6 (s, lactone CO), 174.6 (s, lactam CO), and 48.8 p.p.m. (d, C-12).

2′,4″,13-*N*-*Tetra-acetylerythromycin A Lactam* (**10**).—The erythromycin A lactam (**9**) (3.0 g, 4 mmol) and acetic anhydride (10 ml) in pyridine (40 ml) was left at 25 °C for 3 days. The reaction mixture was then poured into ice–water (200 ml), the pH adjusted to 8.5 with 2M-aqueous sodium hydroxide and

extracted with chloroform. The organic layer was washed with water, dried, and evaporated to dryness to give the crude product (3.08 g). Column chromatography on silica gel with chloroform–methanol (9:1) as eluant, afforded the title compound (**10**) (1.45 g, 39.5%), m.p. 101—105 °C; $[\alpha]_D^{20}$ −39.0 (*c* 1 in CH_2Cl_2); *m/z* 916 (M^+); $\nu_{max.}$($CHCl_3$) 1 730 (ester and lactone CO), 1 655 (amide CO), and 1 515 cm^{-1} (amide NC=O); δ_H($CDCl_3$) 3.27 (s, 3 H, OMe), 2.25 (s, 6 H, NMe_2), 2.10 (s, 3 H, 4″-Ac), 2.06 (s, 3 H, 2′-Ac), 2.03 (s, 3 H, 13-Ac), and 1.92 (s, 3 H, *N*-Ac); δ_C($CDCl_3$) 179.3 (s, lactone), 174.7 (s, lactam), 170.5, 169.9, and 169.2 (3 s, *O*-Ac), 171.9 (s, *N*-Ac), and 45.5 p.p.m. (d, C-12).

10-*Dihydro*-10-*deoxo*-11-*azaerythromycin A* (**11**).—(*a*) Imino ether (**5**) (6.0 g, 8 mmol) was catalytically hydrogenated in acetic acid (60 ml) over PtO_2 (0.125 g) under hydrogen (70 atm) at room temperature for 2 h. The catalyst and solvent were removed and the residual oil was dissolved in water (160 ml) and extracted with dichloromethane at pH 6.0, 6.5, and 8.3. The extract at pH 8.3 was dried and evaporated to dryness under reduced pressure to give the title compound (**11**) (4.8 g, 79.6%), m.p. 113—116 °C; $[\alpha]_D^{20}$ −33.91 (*c* 1 in CH_2Cl_2); *m/z* 734 (M^+): $\nu_{max.}$ 1 725 (lactone CO) and 1 640 cm^{-1} (NH); δ_C($CDCl_3$) 178.5 (s, lactone), 57.3 (t, C-10), and 56.7 p.p.m. (d, C-12).

(*b*) To a stirred solution of the imino ether (**5**) (12 g, 16 mmol) in absolute methanol (300 ml) sodium borohydride (12 g, 0.316 mol) was added in portions at 4 °C over 4 h, and then left at ambient temperature for 24 h. Carbon dioxide was bubbled through the mixture until precipitation was completed after which the precipitate was filtered off, the filtrate evaporated to dryness, and the residue redissolved in chloroform (100 ml). Water was added and the mixture then acidified to pH 2.5 with 2M-hydrochloride acid; it was then stirred for 15 min, after which the pH was adjusted to 6 by addition of 20% aqueous sodium hydroxide and extracted with chloroform. The extraction was repeated at pH 6.5 and 8.3. Evaporation of the dried chloroform extract at pH 8.3 left a solid which as a supension in dry ether was stirred for 2 h whilst cooled with ice; the mixture was then filtered and the filtrate evaporated to afford the title compound (**11**) pure (7.3 g, 60.5%); it was identical with that obtained according to the method (*a*).

10-*Dihydro*-10-*deoxo*-11-*azaerythronolide A* (**13**).—(*a*) A mixture of 6-*O*-desosaminyl-10-dihydro-10-deoxo-11-azaerythronolide A (**12**) (9.3 g, 16.1 mmol) [prepared from (**11**) by a standard procedure],[26] 6M-hydrochloric acid (150 ml) and chloroform (75 ml) was heated under reflux for 70 h. The pH of the reaction mixture was adjusted with 20% aqueous sodium hydroxide to 5.0, after which the aqueous layer was separated and extracted with chloroform (2 × 30 ml). The extractions with chloroform were repeated at pH 7.5 (3 × 30 ml), and pH 9.0 (3 × 50 ml). The combined extracts at pH 9.0 were dried and evaporated to yield a colourless residue (5.96 g) which on crystallization from ether gave (**13**) (3.5 g, 51.8%), m.p. 193—196 °C; *m/z* 419 (M^+); $\nu_{max.}$ 1 710 (lactone CO) and 1 630 cm^{-1} (NH); δ_C($CDCl_3$) 176.9 (s, lactone), 56.8 (t, C-10), and 58.3 p.p.m. (d, C-12).

(*b*) The erythronolide imino ether (**7**) (0.350 g, 0.84 mmol) was catalytically hydrogenated in acetic acid (10 ml) over PtO_2 (0.0135 g) under hydrogen (40 atm) at room temperature for 10 h. The catalyst and the solvent were removed and the residual oil was dissolved in water (10 ml) and extracted with chloroform at pH 5.0 (3 × 2.5 ml), pH 7.5 (3 × 2.5 ml), and pH 9.0 (3 × 3.0 ml). The combined extracts at pH 9.0 were dried and evaporated to dryness under reduced pressure to give the title compound (**13**), identical with that obtained according to the method (*a*).

Hydroiodide of 10-*Dihydro*-10-*deoxo*-11-*azaerythronolide A*.—Hydroiodic acid (0.316 ml) was added dropwise to a stirred solution of 10-dihydro-10-deoxo-11-azaerythronolide A (**13**) (1 g, 2.4 mmol) in dry acetone (60 ml). After the mixture had been stirred at 25 °C for 15 min the solvent was removed under reduced pressure and the residue was dissolved in acetone (reflux); the solution was then filtered and left overnight at ambient temperature to give crystals suitable for *X*-ray analysis, m.p. 225—228 °C.

Crystal Structure of (**7**).—*Crystal data.* $C_{21}H_{37}NO_7 \cdot 1.5H_2O$ M_r = 885.11 Triclinic, *a* = 12.928(6), *b* = 10.601(5), *c* = 9.645(5) Å^3, α = 101.49(5), β = 109.57(4), γ = 85.85(6)°, *V* = 1 221 Å, space group *P*1, *Z* = 2, D_c = 1.204 g cm^{-3}, *F*(000) = 482, μ (Mo-K_α) = 0.99 cm^{-1}.

Data were collected on a Philips PW1100 automatic diffractometer using graphite monochromated Mo-K_α radiation (λ = 0.7107), ω—2θ scan in the range 2° > θ > 30° with scan width 1.60°, scan speed 0.04° s^{-1}. Three standard reflections were monitored every 2 h and showed no significant deviation. 5 095 Unique reflections were recorded but owing to the very poor quality of crystals only 2 948 [$I > 10\sigma(I)$] were used in the refinement. The data were corrected for Lorentz and polarization effects but not for absorption. The structure was solved by MULTAN[27] and refined initially with isotropic and at the later stage with anisotropic temperature factors for the atoms belonging to the basic ring and with isotropic temperature factors for terminal atoms. The refinement converged at *R* = 0.122 (R_w = 0.171). The function minimized was $\Sigma_w([F_o] - [F_c])^2$ with $w = 1/\sigma^2(F_o)$. The refinement of the positional and temperature parameters of the methyl atom C(31) in both (A) and (B) molecules was unsatisfactory so that they were located in a difference Fourier map and included in the calculations at the fixed positions. The isotropic temperature factors for O(101) and C(111) in the molecule (B) were also not refined in the final cycles. Hydrogen atoms were located either in a difference Fourier synthesis or generated from assumed geometries. The hydrogen atom positions were not refined. Atomic scattering factors were taken from ref. 28. Calculations were made on the UNIVAC 1110 computer of the University Computing Centre in Zagreb with the system of programs XRAY 76[29] and locally written programs for data reduction and CSK program for chemical connectivity relationship.

Crystal Structure of (**13**).—*Crystal data.* $C_{21}H_{42}INO_7$, M_r = 547.57, Orthorhombic, *a* = 25.304(10), *b* = 9.494(4), *c* = 11.924(5) Å, *V* = 2 864.6 Å^3, space group $P2_12_12_1$, *Z* = 4, D_c = 1.268 g cm^{-3}, *F*(000) = 1 136, μ (Mo-K_α) = 10.55 cm^{-1}.

Three-dimensional data were collected on the same diffractometer as for the aglycone (**7**), using Mo-K_α radiation (λ = 0.7107 Å), ω − 2θ scan technique in the range 3 > θ > 30°, scan width 1.20 °C and scan speed 0.04° s^{-1}. 3 595 Reflections were considered observed [$I > 3\sigma(I)$] and included in the structure determination and refinement. The data were corrected for Lorentz and polarization effects but not for absorption. The structure was solved by means of the three-dimensional Fourier synthesis based upon the iodine atom co-ordinates obtained from Patterson synthesis. The co-ordinates of all non-hydrogen atoms were refined by the least-squares method using anisotropic temperature factors up to an *R* index of 0.14 (R_w = 0.20). Unit weights were allotted to all observations. Hydrogen atoms were located either in a difference Fourier map or at calculated positions since they were all bonded to carbon or oxygen of well defined geometry. They were not refined. Calculations were performed in the same manner and on the same computer as for the structure of aglycone (**7**) using the set of programs SYST75.[30]

Hydrogen atom co-ordinates and anisotropic temperature

factors for both compounds (**7**) and (**13**) are available as a Supplementary Publication [SUP No. 56631 (12 pp.)]* Structure factor tables are available on request from the Editorial office.

* For details of the Supplementary Publication scheme see Instructions for Authors (1986), *J. Chem. Soc., Perkin Trans. 1*, 1986, Issue 1.

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Received 16*th October* 1985; *Paper* 5/1797