MODIFICATION OF SELDOMYCIN FACTOR 5 AT C-3′*

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(Received for publication February 13, 1978)

Attempted removal of the 3′-hydroxyl group of seldomycin factor 5 *via* displacement of a sulfonate ester has led to 3′-*epi*-seldomycin factor 5. Removal of the hydroxyl group has been effected by the BARTON procedure. The antibacterial activity of 3′-*epi*- and 3′-deoxyseldomycin factor 5 against various aminoglycoside-resistant strains is discussed.

Seldomycin factor 5 is the most active of a number of antibiotics elaborated by *Streptomyces hofuensis*. Structure **1** has been deduced[1] for this antibiotic and thus it is placed as a close relative of the kanamycin-gentamicin type of aminoglycoside. Structure activity relationships have been developed for this series particularly for the area of bacterial resistance mediated by enzymatic modification of the antibiotic. Resistance by virtue of *O*-phosphorylation can be overcome most successfully by deoxygenation, however a comparison of the antibacterial spectrum of tobramycin (3′-deoxykanamycin B) with that of kanamycin B shows that not only has deoxygenation at the 3′ position resulted in restored activity against 3′-*O*-phosphorylating resistant strains, it has also brought about a marked increase in activity against, the clinically important, *Pseudomonas aeruginosa*.

Seldomycin factor 5 has only two hydroxyl groups one of which is at C-3′ and is susceptible to 3′-*O*-phosphorylation by aminoglycoside resistant bacteria possessing this mechanism of resistance.[2] Accordingly removal of this hydroxyl group to form 3′-deoxyseldomycin factor 5 was an obvious goal of chemical efforts towards a more active derivative.

Discussion

Removal of hydroxyl groups is a well-trodden path in aminoglycoside chemistry and the 3′-hydroxyl group specifically has been removed to form 3′-deoxykanamycin[3] and 3′-deoxybutirosin B.[4] In each case a suitably *N* and *O* protected derivative of the parent antibiotic was sulfonylated at the 3′ position and the sulfonate ester was displaced by iodide ion. The iodide was then hydrogenolyzed over RANEY nickel to give the protected deoxy compound. Such a route was attempted with seldomycin factor 5. The carboethoxy group was chosen for *N*-protection and the per-*N*-carboethoxy derivative **2** was formed almost quantitatively. The 5 hydroxyl group as in other 4,6-di-*O*-substituted 2-deoxystreptamine antibiotics proved to be sterically hindered[3,5,6] and the desired 3′-*O*-mesylate (**3**) was formed in high yield by standard procedures. Displacement of the mesylate with sodium iodide in dimethylformamide led smoothly to a single product which did not have properties consistent with the expected 3′-iodide. Elemental analyses indicated that this compound contained

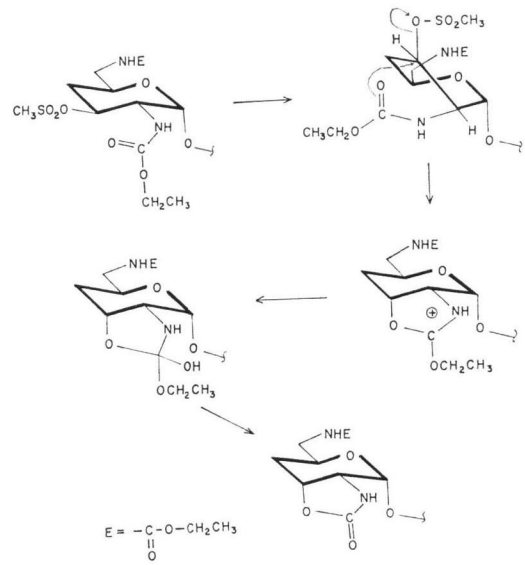
* This work was presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy, New York, Oct. 14, 1977.

Table 1. Carbon magnetic resonance spectra

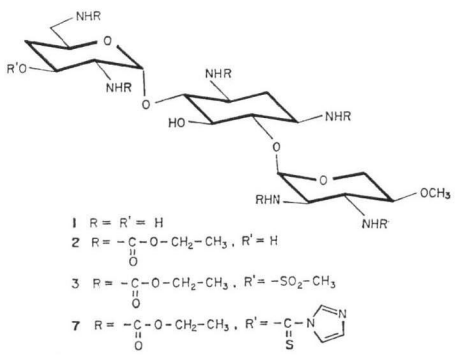
	1	2	3	4	5	6	7	8	9	10	11
C-1′	102.3	99.6	99.4	96.8	102.1	102.7	99.5	98.2	98.3	101.2	102.2
C-2′	57.7	57.6	59.6	51.2	51.6	51.9	54.2	50.6	50.8	50.4	50.8
C-3′	69.1	64.5	77.6	71.7	68.3	68.0	80.1	23.6	23.9	27.4	27.0
C-4′	36.9	37.0	38.0	27.2	35.3	35.5	31.9	27.3	27.8	28.4	28.4
C-5′	71.3	66.7	65.8	65.3	66.1	66.0	65.9	66.6	67.1	70.7	71.6
C-6′	45.7	44.4	43.8	44.0	45.6	45.6	43.8	44.5	45.0	45.9	45.9
C-1	51.1	50.6	50.7	50.9	48.1	51.0	50.4	50.6	50.2	47.9	51.2
C-2	36.5	34.9	35.1	34.6	18.2	36.6	34.9	34.9	34.7	18.2	36.7
C-3	50.1	49.9	49.8	49.5	45.6	50.0	49.7	49.7	50.2	45.9	50.3
C-4	88.1	82.4	82.7	81.9	76.2	88.8	82.7	82.1	82.4	77.5	88.2
C-5	75.1	74.7	74.6	74.8	70.8	75.1	74.3	74.8	74.9	71.8	75.2
C-6	87.0	79.6	79.6	78.8	80.1	87.0	79.5	79.6	81.8	80.2	87.2
C-1″	100.1	96.9	96.9	96.5	98.0	100.0	96.6	96.8	98.8	99.0	100.2
C-2″	56.2	54.4	54.4	54.3	55.5	56.2	54.2	54.4	64.5	55.5	56.3
C-3″	54.8	53.1	53.2	53.3	55.5	54.8	53.1	53.1	58.6	55.5	54.9
C-4″	80.3	76.3	76.3	76.4	80.1	80.3	76.2	76.2	73.1	79.3	80.3
C-5″	60.8	59.5	59.6	59.5	60.8	60.8	59.5	59.5	69.6	60.6	60.9
OCH_3	58.7	57.6	57.6	57.7	58.8	58.6	57.4	57.5	—	58.8	58.8
CH_3(Cbe)			14.4	14.4			14.2～14.3	14.4～14.6	14.5		
CH_2(Cbe)			59.6～59.9	59.5～59.8			59.4～59.9	59.5～59.8	59.7		
CO (Cbe)			155.5～156.5	155.7～156.6			155.4～156.4	155.5～156.5	155.7～156.5		
CO (other)				159.3	159.2					158.7	
CH_3-S			40.6								
C=S							183.2				
imidazole C's							118.1 130.7 136.6				
NCH_3									29.8		
CCH_3									22.2		

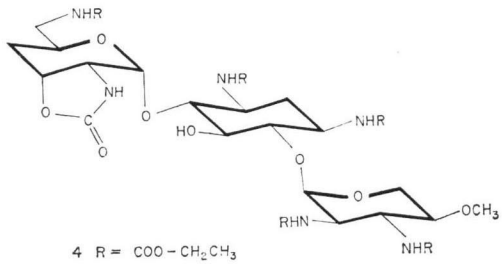
neither iodine nor sulfur and were consistent with the formula $C_{34}H_{56}N_6O_{18}$ indicating that in addition to the sulfonyl ester a further two carbon fragment had been lost from the starting material **3**. Comparison of the carbon-13 magnetic resonance spectrum of this compound with that of per-*N*-carboethoxyseldomycin factor 5 suggested that the only structural difference, between these compounds occurred in the hexose ring. A peak at 159.3 Hz in this spectrum (Table 1) indicated the presence of a carbonyl group of a different nature to those of the carboethoxy groups and this was confirmed by the presence of an absorption band at 1770 cm^{-1} in the infra-red spectrum of this compound. The same product was found to be formed simply by heating the mesylate in dimethylformamide without the addition of sodium iodide. It was also the product from an attempted preparation of the 3′-trifluoromethyl sulfonate from per-*N*-carboethoxyseldomycin factor 5. These observations were accommodated by formulation of the displacement product as 1,3,6′,2″,3″-penta-*N*-carboethoxy-3′-*epi*-seldomycin factor 5-2′-*N*-3′-*O*-carbamate (**4**). A postulated mechanism for the formation of this product is shown in Scheme 1. Here displacement of the sulfonate ester is the result of nucleophilic attack from the carbonyl of the 2′-*N*-protecting group. Subsequent hydrolytic loss of the elements of ethanol give the cyclic carbamate. Epimerization at C-3′ is a consequence of this mechanism. 2″-*epi*-Gentamicin C-1 was formed by a similar displacement from the 3″-*N*-acetyl derivative[6] however formation of an intermediate comparable to the carbamate obtained here is not possible with the *N*-acetate.

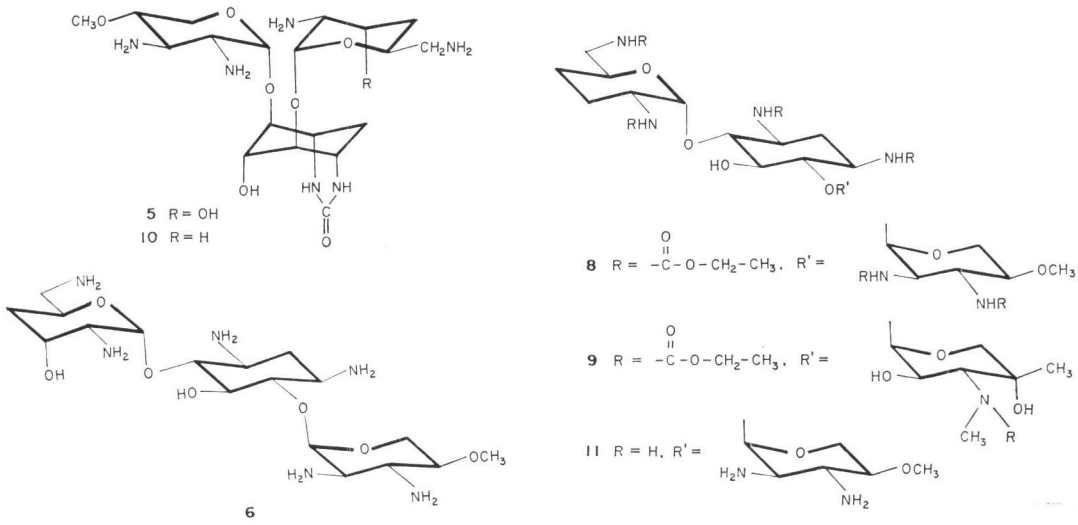
Scheme 1.



Attempts to obtain an iodide by displacement of a 3′-tosylate and of a 3′-brosylate were ineffective, nor was the course of the reaction altered by changes in solvent and nucleophile. Attempts were made to displace the 3′-mesylate with iodide in dimethylsulfoxide and in hexamethylphosphoric







triamide and by thioacetate in dimethylformamide. In every case the sole product detected was the carbamate **4**.

The difference between the displacement of a 3′-sulfonate ester of seldomycin factor 5 and that of similar derivatives of kanamycin A[3] and butirosin B[4] is interesting and must be ascribed to the influence of the 4′-hydroxyl group present in the last two examples and absent in the first. (The *N*-protecting groups used were the same for both seldomycin factor 5 and kanamycin A). It is possible that 4′-hydroxyl group provides a steric inhibition to attack of the carbonyl oxygen of the 2′-*N*-protecting group at C-3′ as envisaged in Scheme 1. An alternative explanation is that the iodide enters the 3′ position in the kanamycin A and butirosin B cases not by displacement of the sulfonate ester but by regiospecific opening of an intermediate epoxide. Such an epoxide would arise by internal displacement of the 3′-sulfonate by the 4′-hydroxyl group. This possibility probably occurred to the authors[3,4] who refrained from assigning a configuration to the 3′-iodo substituent which would be *epi* if it arose from a direct displacement mechanism and *normal* if it arose from epoxide ring-opening.

Mild basic hydrolysis of **4** resulted in formation of the 1-*N*-3-*N*-ureide **5** in high yield. Production of such ureides has been reported for other 2-deoxystreptamine containing antibiotics.[7] The structure **5** is formulated to account for the infra-red spectral data on this compound which show a strong absorption band at 1630 wave numbers characteristic of a cyclic ureides.[7] Furthermore the CMR spectrum of **5** indicates the presence of only one carbonyl carbon at 159.2 ppm and exhibits large shifts for all of the carbons of the 2-deoxystreptamine ring which are well accommodated by structure **5** in which all of the ring substituents are locked into the normally sterically-unfavorable axial orientation (Table 1).

Drastic basic hydrolysis of either **4** or the ureide **5** leads to the preparation of 3′-*epi*-seldomycin factor 5(**6**) in high yield. The CMR spectrum of this derivative (Table 1) shows the expected near coincidence of each of the resonances assigned to the 2-deoxystreptamine and pentose rings with their position in the spectrum of seldomycin factor 5(**1**). Upfield shifts are exhibited for many of the carbons of the hexose sugar in comparison with their position in the spectrum of the parent and this is as expected for epimerization of a substituent from an equatorial to an axial orientation.

Table 2. Antibacterial activity of 3′-*epi*- and 3′-deoxy-seldomycin factor 5

Organism	Strain	Resistance mechanism	Minimum inhibitory concentrations (mcg/ml)			
			Seldomycin factor 5	3′-*epi*-Seldomycin factor 5	3′-Deoxy-seldomycin factor 5	Gentamicin C complex
Bacillus subtilis	U. of Ill. 10707	—	0.08	0.08	0.02	0.01
Staphylococcus aureus	ATCC 6358P	—	0.16	1.25	0.31	0.01
Streptococcus faecalis	ATCC 10541	—	>10	>10	>10	5.0
Enterobacter cloacae	ST-10	Unknown	>20	>20	>20	5.0
Escherichia coli	ATCC 26	—	0.31	1.25	0.24	0.06
	76-2	ANT 2″	2.5	1.25	0.16	5.0
	R_3	Unknown	>10	>10	5.0	1.25
	R_5	APH 3′-I	>20	2.5	0.16	0.08
	R_{12}	ANT-2″	0.31	1.25	0.16	1.25
	R_{16}	Unknown	2.5	0.31	0.04	0.01
	R_{17}	AAC 6′	0.31	2.5	0.31	0.01
	R_{18}	APH 3′-II ANT 2″	0.63	0.63	0.31	0.63
	R_{19}	ANT 3″ AAC 3-I	5.0	20	5.0	1.25
	R_{20}	APH 3′-I	>20	1.25	0.16	0.08
Klebsiella pneumoniae	ATCC 10031	—	0.08	0.47	0.08	0.04
	ATCC 8045	—	0.04	0.31	0.04	0.02
	KY 4261	ANT 2″	>20	0.63	0.16	5.0
	KY-4262	ANT 2″	2.5	1.25	0.16	2.5
	K-1296	Unknown	>20	1.25	0.08	0.08
Proteus mirabilis	Finland 9	—	0.63	1.25	0.31	0.04
	G 18867	Unknown	1.25	2.5	0.63	0.08
Proteus vulgaris	ATCC 6897	—	0.63	5.0	0.63	0.04
	U 953	Unknown	10	10	5.0	1.25
Providencia stuartii	ATCC 25825	—	1.25	20	2.5	0.31
	164	AAC 2′	20	>20	>20	5.0
Pseudomonas aeruginosa	BMH #1	—	10	10	2.5	0.47
	BMH #4	—	10	10	2.5	0.63
	BMH #6	—	10	10	2.5	0.63
	BMH #10	—	0.08	0.16	0.04	<0.01
	ATCC 10145	—	10	20	5.0	0.63
	KY-8510	AAC 6′	>20	>20	20	1.25
	KY-8511	AAC 3-I	>20	>20	>20	>20
	KY-8512	APH 3′-I, II	20	20	2.5	0.63
	KY-8516	AAC 6′	>20	>20	>20	1.25
	KY-8562	Unknown	>20	>20	>20	>20
	Z 444	AAC 6′	>20	>20	>20	>20
	Z 445	AAC 6′	>20	>20	>20	2.5
	PST-1	AAC 3-II	>20	>20	>20	>20
Serratia marcescens	ATCC 4003	—	0.31	1.25	0.16	0.16
	POE 1065	AAC 6′	>20	>20	>20	0.31

Formulation of **6** as 3′-*epi*-seldomycin factor 5 is further confirmed by its biological activity (see later).

The desired deoxygenation of seldomycin factor 5 was effected in high yield by employing the method of BARTON and MCCOMBIE[8] which by virtue of its radical mechanism was particularly appealing following the unexpected course of the displacement type reactions above. The *N*-protecting group chosen was again the carboethoxy group and treatment of per-*N*-carboethoxyseldomycin factor 5 with N,N′-thiocarbonyldiimidazole in tetrahydrofuran/pyridine gave selectively the 3′-thiocarbonylimidazolide (**7**) in high yield. Reduction of **7** in dioxane with tributylstannane gave 3′-deoxy-per-*N*-carboethoxyseldomycin factor 5 (**8**) also in high yield. A comparison of the CMR spectrum of this derivative with that of per-*N*-carboethoxygentamicin C_{1a} (**9**) prepared by standard methods (Table 1) highlights the striking coincidence of resonances assigned to both the hexose and 2-deoxystreptamine rings.

Mild basic hydrolysis of **8** again led to a high yield of the ureide **10** which was cleaved with strong base to give the desired 3′-deoxyseldomycin factor 5 (**11**).

The antibacterial activity of seldomycin factor 5 (**1**), 3′-*epi*-seldomycin factor 5 (**6**), 3′-deoxyseldomycin factor 5 (**11**) and, for reference, gentamicin complex against a wide range of aminoglycoside sensitive and resistant strains is shown in Table 2. It should be pointed out that the conditions of the assay which gave these particular data are such as to lead to particularly low MIC values. Thus a strain with an MIC value of 1.25 against an antibiotic in this assay may be regarded as resistant. It can be seen that 3′-*epi*-seldomycin factor 5 is in general a rather weak antibiotic losing much of the activity of the parent against aminoglycoside-sensitive strains and in a few odd cases gaining activity over resistant strains. (see later). 3′-Deoxyseldomycin factor 5 is, on the other hand, quite a striking improvement over the parent. Not only has it increased in activity against 3′-*O*-phosphorylating aminoglycoside-resistant strains it shows a general increased activity against aminoglycoside-sensitive strains. Although this increase in activity does extend to *Pseudomonas aeruginosa* strains it is not the large difference that might have been expected from a comparison of the activities of tobramycin and kanamycin B shown in Table 3.

One observation from Table 2 is suprising; four strains, two *Escherichia coli* and two *Klebsiella*, owe their aminoglycoside resistance to the possession of the enzyme ANT 2″, *i.e.* they are capable of

Table 3. Antipseudomonal activities of kanamycin B and tobramycin

Pseudomonas aeruginosa strain	Minimum inhibitory concentration (mcg/ml)	
	Kanamycin B	Tobramycin
BMH #1	3.86	<0.03
BMH #4	7.7	0.07
BMH #10	0.12	<0.03
ATCC 10145	7.7	0.13
KY-8510	30.9	8.2
KY-8511	30.9	0.26
KY-8512	7.7	0.13
KY-8516	62.0	8.2
KY-8562	>62.0	66.0
PAR-13	15.5	4.1
PAR-14	62.0	16.4
PST-1	>62.0	66.0

adenylylating gentamicin at the 2″-hydroxyl group. Despite the fact that seldomycin factor 5 does not possess a 2″-hydroxyl group, three of the four strains may be considered resistant to this antibiotic and for each strain this resistance has been overcome by epimerization and to a much greater extent by deoxygenation at the 3′ position. This suggests that in seldomycin factor 5 the 3′-hydroxyl group is acting as a substrate for the enzyme ANT-2″. Confirmation of this somewhat surprising hypothesis must await enzymatic studies.

Experimental

General Experimental

T.l.c. and column chromatography were performed with silica gel (Merck). Mass spectra were obtained on an A.E.I. MS-902 spectrometer at 50 eV using the direct insertion probe. P.m.r. spectra were measured on a Varian Associates HA-100 in D_2O with external TMS reference and are reported corrected (−0.42 ppm) to the commonly applied internal TSP scale. C.m.r. spectra were measured on a Varian Associates XL-100-15/TT-100 spectrometer system in D_2O with dioxane as internal reference (67.4 ppm) or in DMSO with TMS as internal reference. Chemical shifts are reported in ppm downfield from TMS. Assignments are given in Table 1 and have been made by analogy with like compounds. In compounds containing free amino groups (**5**, **6**, **10** and **11**), these are supported by CMR titrations from pH 2 to 10. The assignment of the 18.2 ppm resonance to C-2 in **10** was confirmed by an ORSFD experiment. Ir spectra were determined with KBr pellets using a Perkin Elmer Model 521 grating spectrometer. RAMAN spectra were measured on a Carey Model 83 spectrometer equipped with an Argon-ion laser. Optical rotations were determined with 2% solutions in water with a Hilger and Watts Polarimeter.

Microanalytical results are reported for those products which could be prepared free of solvent and carbonates formed by atmospheric exposure.

Antibacterial activity (minimum inhibitory concentrations) were determined by the agar dilution method on "B.B.L. Streptomycin Assay Agar with Yeast Extract" at pH ~7.5 incubated at 32°C for 18 hours.

Per-*N*-ethoxycarbonylseldomycin Factor 5 (**2**)

Seldomycin factor 5 free base (10.12 g, 22.4 millimole) and sodium carbonate (30 g, 0.28 mole) were dissolved in 200 ml of distilled water and the solution was cooled in an ice bath. A mixture of ethyl chloroformate (30 ml, 34.05 g, 0.31 mole) and acetone (50 ml) were added dropwise under stirring and the resulting mixture was warmed to room temperature and allowed to stand for two hours. The precipitated product was removed by filtration, washed twice with 200 ml portions of water and dried *in vacuo* to yield 16.8 g (85%) per-*N*-ethoxycarbonylseldomycin factor 5 (**2**).

IR 1710, 3340 cm^{-1}

Anal. Calcd. for $C_{36}H_{62}N_6O_{19}$: C, 48.97; H, 7.08; N, 9.52
Found: C, 48.98; H, 7.12; N, 9.48

Pre-*N*-ethoxycarbonyl-3′-methanesulfonylseldomycin Factor 5 (**3**)

To a cooled stirred solution of per-*N*-ethoxycarbonylseldomycin factor 5 (**2**) (5 g, 5.68 millimole) in anhydrous pyridine (120 ml) methanesulfonyl chloride (1.3 ml, 1.92 g, 16.8 millimole) was added. The mixture was allowed to stand at room temperature overnight and solvent was removed under reduced pressure. The residue was chromatographed over silica gel to yield 4.0 g (73%) of **3**.

IR 1150, 1710, 3340 cm^{-1}. RAMAN spectrum strong 1170 cm^{-1} band confirms presence of SO_3 ester.

Anal. Calcd. for $C_{37}H_{64}N_6O_{21}S$: C, 46.24; H, 6.71; N, 8.75; S, 3.34
Found: C, 45.85; H, 6.81; N, 8.56; S, 3.70

1,3,6′,2″,3″-Penta-*N*-ethoxycarbonyl-3′-*epi*-seldomycin Factor 5-2′-*N*-3′-*O*-Carbamate (**4**)

Per-*N*-ethoxycarbonyl-3′-methanesulfonylseldomycin factor 5 (**3**) (3.5 g, 3.64 millimole) was dissolved in anhydrous dimethylformamide (100 ml) and heated at 90°C overnight. Removal of the

solvent under reduced pressure and chromatography of the residue over silica gel gave 1.6 g (52%) of **4**.

IR 1710, 1770, 3340 cm^{-1}

Anal. Calcd. for $C_{34}H_{56}N_6O_{18}$: C, 48.0 ; H, 6.75; N, 10.04
Found: C, 47.59; H, 6.73; N, 9.70

3′-*epi*-Seldomycin Factor 5-1-*N*-3-*N*-Ureide (**5**)

1,3,6′,2″,3″-Penta-*N*-ethoxycarbonyl-3′-*epi*-seldomycin factor 5-2′-*N*-3′-*O*-carbamate (**4**) (2.35 g, 2.8 millimole) was dissolved in 250 ml of 1.9 N methanolic sodium hydroxide and heated under reflux overnight. The mixture was adjusted to pH 7 with 10 N sulfuric acid and the solvent was removed under reduced pressure. The residue was extracted with two 100 ml portions of $CHCl_3$ - MeOH-conc.NH_4OH (1: 2: 1, v;v;v) and the extract was chromatographed over silica gel to yield 1.0 g (75%) of **5**.

IR 1380, 1490, 1630 cm^{-1}

Anal. Calcd. for $C_{19}H_{36}N_6O_8 \cdot 2H_2SO_4 \cdot H_2O$: C, 33.04; H, 6.13; N, 12.17
Found: C, 33.44; H, 6.30; N, 11.87

PMR spectrum: (at pH 10) 1.60～2.10 m, CH_2 at C-4′ and H-2e (3H); 2.28～2.58 m, H-2a (1H); 2.63～2.96 m CHN (5H) is shifted downfield to below δ 3.2 on acidification to pH 5; 2.96～3.30 m H-1 and H-3 (2H). 3.30～4.50 m CHO including 3.48 s, OCH_3 (total 11H); 5.01 d (J=4 Hz) and 5.28 d (J=5.5 Hz) H-1′ and H-1″ (each 1H).

3′-*epi*-Seldomycin Factor 5

(a) 1,3,6′,2″,3″-Penta-*N*-ethoxycarbonyl seldomycin factor 5-2′-*N*-3′-*O*-carbamate (2.35 g, 2.8 millimole) was dissolved in 50% methanolic KOH (100 ml, 6 N) and heated in a sealed tube at 135°C for 16 hours. The reaction mixture was adjusted to pH 7 with 10 N H_2SO_4 and the mixture taken to dryness under reduced pressure. The residue was extracted with 2×100 ml portions of $CHCl_3$ - MeOH - NH_4OH (1: 2: 1, v; v; v) and the extract was chromatographed over silica gel to yield 1.2 g (95%) of 3′-*epi*-seldomycin factor 5 (**6**).

(b) 3′-*epi*-Seldomycin factor 5-1-*N*-3-*N*-ureide (200 mg, 0.42 millimole) was dissolved in 50% methanolic KOH (15 ml, 6 N) and heated in a sealed tube at 135°C for 16 hours. Work up of the reaction mixture as outlined above gave 111 mg (59%) of 3′-*epi*-seldomycin factor 5 (**6**), $[\alpha]_D^{24}+81°$, M^+ *m/e* 450.2795. Calcd. for $C_{18}H_{38}N_6O_7$ *m/e* 450.2802 PMR spectrum: 1.05～2.15 m, CH_2 (4H); 2.60～3.1 m, CHN (7H); 3.1～4.3 m, (including 3.50 s OCH_3) CHO (total 11H); 5.06 d, (1H) and 5.20 d, (1H), C-1′ H and C-1″ H.

Per-*N*-ethoxycarbonylseldomycin Factor 5-3′-thiocarbonylimidazolide (**7**)

A solution of per-*N*-ethoxycarbonylseldomycin factor 5 (**1**) (15 g, 16.98 millimole) in anhydrous pyridine (250 ml) was diluted with tetrahydrofuran (500 ml) and treated with N,N′-thiocarbonyl diimidazole (6 g, 33.7 millimole). The reaction mixture was heated under reflux and after 4 hours additional N,N′-thiocarbonyldiimidazole (4 g, 22.4 millimole) was added. The mixture was heated under reflux overnight and the solvent was removed *in vacuo*. Chromatography of the residue on a column of silica gel gave 16.4 g (97%) per-*N*-ethoxycarbonylseldomycin factor 5-3′-thiocarbonyl-imidazolide (**7**).

IR 1380, 1710, 3340 cm^{-1}

Anal. Calcd. for $C_{40}H_{64}N_8O_{19}S$: C, 48.38; H, 6.50; N, 11.29; S, 3.22
Found: C, 48.34; H, 6.63; N, 11.11; S, 3.17

3′-Deoxy-per-*N*-ethoxycarbonylseldomycin Factor 5 (**8**)

A solution of per-*N*-ethoxycarbonylseldomycin factor 5-3′-thiocarbonylimidazolide (**7**) (12.5 g, 12.58 millimole) in anhydrous dioxane (750 ml) was added dropwise to a refluxing mixture of tri-*n*-butylstannane (14.0 g, 12.7 ml, 48 millimole) in anhydrous dioxane (1200 ml) in a nitrogen atmosphere. After 2½ hours the solvent was removed under reduced pressure and the residue was chromatographed over a column of silica gel to yield 9.8 g (90%) of 3′-deoxy-per-*N*-ethoxycarbonylseldomycin factor 5 (**8**).

Anal. Calcd. for $C_{36}H_{62}N_6O_{18}$: C, 49.88; H, 7.21; N, 9.69
Found: C, 49.60; H, 7.30; N, 9.45

3′-Deoxyseldomycin Factor 5-1-*N*-3-*N*-Ureide (**10**)

3′-Deoxy-per-*N*-ethoxycarbonylseldomycin factor 5 (**8**) (4.7 g, 5.42 millimole) was dissolved in methanolic sodium hydroxide (1.9 N, 450 ml) and heated under reflux overnight. The mixture was adjusted to pH 7 with sulfuric acid (10 N) and the solvent removed under reduced pressure. The residue,was extracted with two portions (*ca.* 100 ml) of $CHCl_3$ - MeOH - NH_4OH (1: 2: 1, v; v; v) and the extract was chromatographed over silica gel to yield 2.2 g (88%) of 3′-deoxyseldomycin factor 5-1-*N*-3-*N*-ureide (**10**).

PMR spectrum: (at pH 10) 1.30~2.0 m, CH_2 at C-3′ and C-4′ and H-2e (5H); 2.35~2.60 m H-2a (1H); 2.60~2.90 CHN (5H) moves downfield to below δ 3.50 on acidification to pH 5.5; 3.0~3.37 m, H-1 and H-3 (2H); 3.40~4.10 m, CHO including 3.47 s OCH_3 (total 10H); 4.92 overlapping doublets H-1′ and H-1″ (2H).

3′-Deoxyseldomycin Factor 5 (**11**)

3′-Deoxy-per-*N*-ethoxycarbonylseldomycin factor 5 (**8**) (4.7 g, 5.42 millimole) was dissolved in 50% methanolic KOH (100 ml, 6 N) and heated in a sealed tube at 135°C for 16 hours. The reaction mixture was adjusted to pH 7 with sulfuric acid (10 N) and the solvent was removed under reduced pressure. The residue was extracted with two portions (100 ml each) of $CHCl_3$ - MeOH - conc.NH_4OH (1: 2: 1, v; v; v) and the extract was chromatographed over silica gel to yield 2.3 g (98%) of 3′-deoxyseldomycin factor 5.

PMR spectrum: 1.05~2.15 m, CH_2 at C-2, C-3′, C-4′ (total 6H); 2.60~3.2 m, CH-N (total 7H); 3.2~4.1 m, (including 3.49 s OCH_3) CHO (total 10H); 5.04 d, (1H) and 5.25 d, (1H) C-1′ H and C-1″ H.

M^+ *m/e* 434.2841

Calcd. for $C_{18}H_{38}N_6O_6$ 434.2853

The sulfate salt of **11** was prepared by treating a methanolic solution of the free base with 1 N methanolic sulfuric acid. The precipitated product was removed by filtration and dried *in vacuo* to yield a quantitative recovery of the sulfate salt. $[\alpha]_D^{24}$ +97°.

Anal. Calcd. for $C_{18}H_{38}N_6O_6 \cdot 3H_2SO_4 \cdot 4H_2O$: C, 26.99; H, 6.54; N, 10.49
Found: C, 27.09; H, 6.23; N, 10.34

Acknowledgements

The authors are grateful to their colleagues, Drs. J. S. TADANIER and R. S. EGAN and to Professors PETER BEAK of the University of Illinois, STEPHEN HANESSIAN of the University of Montreal and LESTER MITSCHER of the University of Kansas for their helpful discussions and advice. We also wish to acknowledge discussions with Messrs. H. MATSUSHIMA and Y. MORI[9] of the Kyowa Hakko Tokyo Research Laboratory during their similar but independent pursuit of the same goal.

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