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Chemical Modifications of Erythromycin Antibiotics. 3.[1] Synthesis of 4″ and 11 Esters of Erythromycin A and B

Peter H. Jones,* Thomas J. Perun, Elizabeth K. Rowley, and Evelyn J. Baker

Experimental Therapy Division, Abbott Laboratories, North Chicago, Illinois 60064. *Received October 22, 1971*

A number of mono-, di-, and trisubstituted alkyl esters of the macrolide antibiotic erythromycins A and B were prepared by selective esterification and hydrolysis. This series of esters was valuable for determining antibacterial activities and absorption characteristics of substituted erythromycins wherein the aminoglycoside moiety remained unesterified. The compounds also provide useful protected intermediates for further chemical studies. The biological activities of the esters and a structure-activity analysis are discussed in the succeeding paper.

The structures of erythromycin A[2] and B[3] were determined by the Lilly group as macrocyclic lactones with two 6-deoxy sugars attached. Erythromycin A and B† (Figure 1) differ only by a tertiary hydroxyl group at C-12. Some of the additional common structural features include a second tertiary OH at C-6 and 3 secondary OH groups, one on each sugar and one at C-11 on the aglycone. Many papers have been written which discuss the esterification of the basic sugar, desosamine, at the 2′ position.[4] Esterification at this position is greatly enhanced by the neighboring Me_2N group which behaves as an intramolecular catalyst for the acylation. When taken orally these esters are well absorbed imparting high serum levels of the erythromycin ester.[4a,4d] These increased serum levels are caused by 2 factors: (1) the increased lipophilicity of the ester and (2) the decreased basicity of the amino group.[5] Recent work of Tardrew, *et al.*,[6] has shown that the 2′-esters are antimicrobially inactive and must first hydrolyze *in vivo* back to the parent erythromycin to be therapeutically effective. The Me_2N group again plays an important role by enhancing the rate of ester hydrolysis. Nevertheless the hydrolysis rate of the 2′-acetate or propionate ester is slow relative to the rate of excretion and a major portion of the antibiotic circulates as the inactive ester form.‡ Thus the observed higher blood levels of erythromycin esters are offset by the low availability of the active base.

When it became apparent that the 2′-esters were devoid of antibacterial activity, our attention turned to the esterification of the other 2 secondary OH groups. If the increased absorption was partly due to their increased lipophilicity, then esters of these groups might also exhibit enhanced serum levels. It was therefore our intention to synthesize erythromycin derivatives in which the 4″ and 11 positions were individually esterified and to study the effect of these substituents on the antibacterial activity and absorption.

Celmer had earlier described a parallel study with the related macrolide antibiotic oleandomycin in which he prepared mono-, di- and triesters and studied their antimicrobial activities and absorption characteristics.[7] Flynn, *et al.*, reported the synthesis of an erythromycin diacetate which was not further characterized.[5]

Recently a group from the Polish Academy of Sciences reported their work on the esterification of erythromycin with acetic and propionic anhydride.[8] Their work paralleled that part of our study which was devoted to the synthesis of the di- and triesters. However, our work was primarily directed toward the synthesis of monoesters at each of the secondary hydroxyl groups. This paper describes our results.

Synthesis. The methods of preparing the various esters of erythromycin A and B are outlined in Scheme I. The synthesis of the 4″ esters was straightforward using methods similar to those previously described.[5,8] The 2′- and 4″-OH groups were both acylated using the appropriate anhydride in pyridine followed by hydrolysis of the 2′ ester with MeOH to produce the 4″ ester. The 3′-dimethylamino group behaves as an intramolecular catalyst making possible the facile hydrolysis of the 2′ esters under neutral conditions in the presence of the 4″ ester. The 4″,11 diesters where both groups are the same were prepared by a prolonged acylation in pyridine to produce the 2′,4″,11 triester followed by a methanolic hydrolysis to the 4″,11 diester. In the case of a majority of the 4″,11 diesters the hydrolysis of the 4″ ester was too slow to permit the direct synthesis of the 11 ester by this procedure. Thus to prepare the 11 esters a new method of protecting the 4″ position had to be developed.

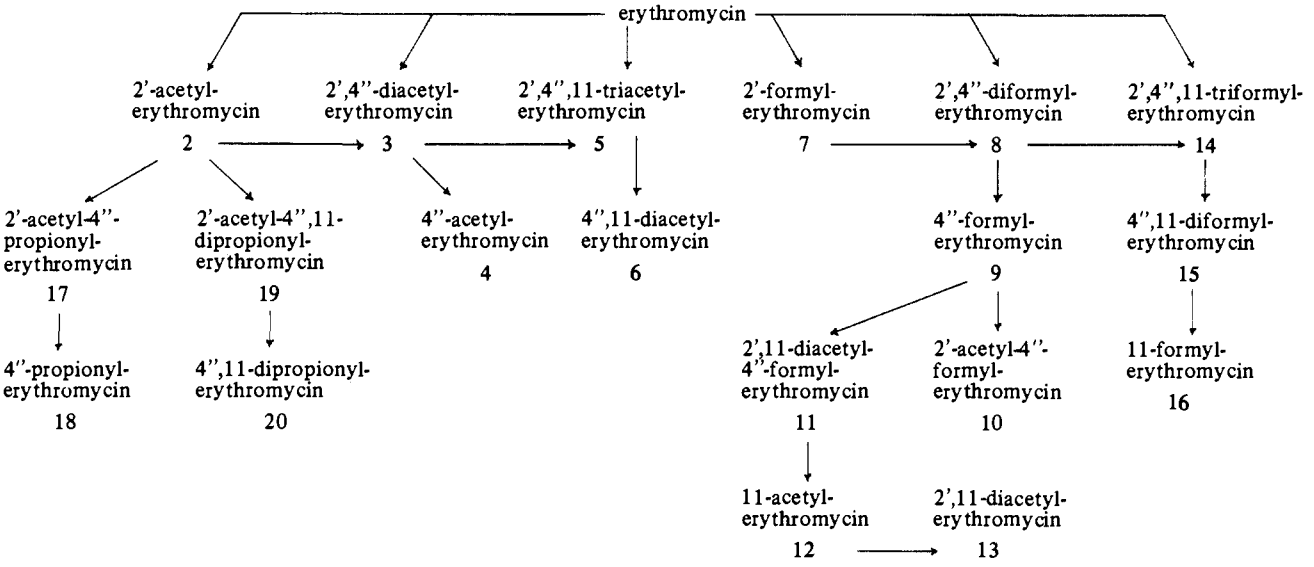
The major side reaction which occurs during the more drastic basic conditions necessary to remove a 4″-acyl group is the hydrolysis of the lactone group of the macrolide ring, a reaction first recognized by the Lilly group. This problem could be overcome by introducing a more base-labile ester at C-4″. Thus by the synthesis of the appropriate triester, a mild base treatment would produce the desired 11 ester. Our attention then was focused on esters of formic acid for it is well recognized that they are more base labile than the corresponding acetates.

The 2′-formates 7 were prepared by the usual method used for 2′ esters, whereby the antibiotic was treated with anhydride and an acid acceptor such as K_2CO_3. We used formic acetic anhydride as the formylating reagent since it is more stable than $(HCO)_2O$[9] and is known to produce formate rather than acetate esters.[10] The 2′-formates were found to be very unstable and in fact were converted to the

†The position numbering system shown in Figure 1 was chosen for this study. The compounds are numbered as shown in Scheme I. The letters A and B following the numbers indicates the erythromycin A or erythromycin B series, respectively.

‡Unpublished human blood level data, Abbott Laboratories.

Scheme 1. Synthesis of Erythromycin Esters



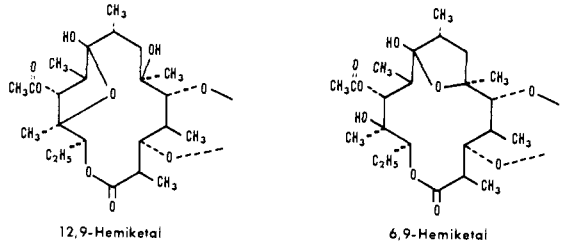


Figure 1. Structure of erythromycin A and B.

formic acid salt of the parent erythromycin by exposing the ester to room humidity for 1 day. The formate ester could be stored indefinitely under N_2. The 2',4''-diformates (8) were prepared by the usual pyridine method and the 4''-formates (9) by selective hydrolysis of the 2'-formate of 8. The conditions of hydrolysis had to be carefully adjusted so as not to remove both groups. The 24-hr MeOH method developed for removal of the 2'-acetates gave an equal mixture of 9 and erythromycin, **1**. A short acetone-aqueous bicarbonate treatment gave a clean 4''-formate. A more drastic hydrolysis using MeOH and bicarbonate cleanly removed both groups to give **1**. Extended treatment of **1** with formic acetic anhydride gave the triester **14** which on mild hydrolysis gave the 4'',11-diformate **15**. Treatment of **14** or **15** with MeOH for 6 days selectively removed the 2' and 4'' groups to produce the first 11 ester, 11-formyl-erythromycin B (**16B**). Treatment of **15B** and **16B** with MeOH and bicarbonate again produced the parent **1B**.

Using these techniques of formation and hydrolysis of the 4''-formates, we could use this ester as a protecting group for the cladinose OH group and thereby prepare other 11 esters. By treating 9 with Ac_2O under conditions similar to the synthesis of the triacetates (**5**), the mixed triesters (**11**) were formed in good yield. A methanolic hydrolysis gave the 11-acetate (**12**). This procedure is quite general and can be applied to the synthesis of other 11-substituted erythromycins. A summary of the conditions of synthesis and hydrolysis of the acetates and formates is tabulated in Table I.

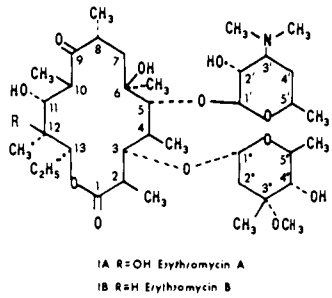
Evidence for the structures of the esters was provided by their ir and nmr spectra. When possible the structures were further verified by hydrolysis to the parent erythromycin. This technique, however, was not applicable with the 4'' or

Table 1. Physical and Chemical Properties of the Ester Moieties

Ester	Synthesis	Hydrolysis	Nmr chemical shift, ppm
2'-Acetate	Ac_2O-K_2CO_3; 25°; 2 hr	MeOH; 25°; 1 day	2.07
4''-Acetate	Ac_2O-pyridine; 25°; 3 days	Stable	2.11
11-Acetate	Ac_2O-pyridine; 25°; 10 days	Stable	2.05
2'-Formate	FAcO-K_2CO_3; 25°; 2 hr	Me_2CO-$NaHCO_3$; 25°; 2 hr	8.15
4''-Formate	FAcO-pyridine; 25°; 6 hr	MeOH; 25°; 6 days	8.20
11-Formate	FAcO-pyridine; 25°; 5 days	MeOH-$NaHCO_3$; 25°; 1 day	7.80

11 esters other than formate. The various acetate and formate moieties usually exhibited resonance absorptions in the nmr which were unique for both the type of ester and its position. These chemical shifts which are shown in Table I permit an easy identification of the various ester groups and their position. This technique is extremely valuable for the structural assignment of more complex erythromycins in which these ester moieties are used as protecting groups.

An examination of the ir carbonyl region of the ester derivatives gave further verification of their structure. Each ester showed an enhanced ester C=O absorption (1733 cm^{-1}). Since the lactone C=O of erythromycin also absorbs at this frequency, the number of ester groups can only be estimated by the relative intensities. The C-O stretching bond was observed at 1233-1238 cm^{-1} for the acetates and at 1163-1170 cm^{-1} for the formates. The derivatives which were not esterified at C-11 exhibited the normal erythromycin ketone C=O band at 1684-1690 cm^{-1}. This frequency is lower than that expected for an aliphatic ketone C=O which would be expected at 1725-1735 cm^{-1}. This shift of 35-40 wave numbers is presumably due to the H bonding of the C-9 ketone with the OH groups at C-11 and/or C-6. The conformation of the lactone ring of erythromycin proposed by Perun, *et al.*,[11] show that both of these OH groups are pseudoaxial and are close enough to the ketone to permit H bonding. When the 11-OH of erythromycin B is esterified, the ketone absorption shifts to the 1705-1708 cm^{-1} region indicating a decrease in H bonding. This result further verifies the presence of the 11-hydrox-



1A R=OH Erythromycin A

1B R=H Erythromycin B

Figure 2. Hemiketal structures of the 11-acetate.

yl 9-ketone H bond. In the 11-substituted erythromycin A series the ketone band is not observed. If the band were further shifted to 1720 cm^{-1}, it would disappear under the ester band. An alternate explanation is the one described by Banaszek, *et al.*,[8] who also prepared the triacetate of erythromycin A (5A). They proposed 2 valence tautomeric hemiacetal forms which involve the 12-OH or the 6-OH and 9-ketone. The loss of the n-π^* band at 288 mμ in the uv gives support to this hypothesis. The formation of the 12,9-hemiacetal structure (Figure 2) would require a conformational change, since in the proposed erythromycin conformation[11] the 12-OH is pseudoequatorial and it therefore must rotate 120° in order to react with the ketone. The nmr spectra of the 11 esters of erythromycin A indicate that no such conformational change has occurred. The formation of a 6,9-hemiacetal on the other hand does not require such a major conformational change and the use of molecular models shows that this structure is consistent with the nmr and uv spectra.§ The hemiacetal structures all contain a characteristic peak in the nmr spectrum at 90 Hz due to the singlet methyl at C-6. This peak was previously observed in the nmr spectrum of an erythronolide B derivative which in solution was in equilibrium with its hemiacetal structure.[12]

The *in vitro* and *in vivo* biological studies of these esters are reported in the following paper.[13]

Experimental Section

General Procedures. Melting points were detd in open capillary tubes using the Thomas-Hoover Uni-Melt and are corrected. Where analyses are indicated only by symbols of the elements, analytical results for those elements were within ±0.4% of the theoretical values. The formic acetic anhydride used in the formylations was prepared by the method of Muramatsu, *et al.*[9] All solvents were removed on a rotary evaporator at 30° under reduced pressure.

The course of the reactions and the purity of the products were detd by tlc on silica gel G plates activated at 100° for 2 hr. The spots were detected by spraying the plates with arsenomolybdate reagent[14] and heating for several min at 100°. The plates were developed using one of the following solvent systems: A, $CHCl_3$–MeOH, 95:5; B, C_6H_6–MeOH, 80:20; C, C_6H_6–MeOH, 70:30; D, CH_2Cl_2–C_6H_6–MeOH–$HCONH_2$, 80:20:20:2;[15] E, CCl_4–DMF, 14:1. Since the R_f values varied widely from plate to plate, they are not recorded. The inclusion of tlc and the system after the melting point of each new compd infers that the new compd was shown to be free of starting material and side products by a tlc analysis using the stated system.

The structures of the products were detd by ir, nmr, and, when possible, hydrolysis back to the parent erythromycin A or B. The ir spectra were obtained in $CHCl_3$ with a Perkin-Elmer Model 421 or 521 grating spectrophotometer. All new esters had lactone and ester C=O and ketone C=O frequencies which were consistent with the assigned structures. Some interesting correlations are discussed in the text. The nmr spectra [$CDCl_3$ (Me_4Si)] were recorded on a Varian A-60 instrument. The shifts in the region 7.5–8.3 ppm were corrected by adjusting the $CHCl_3$ peak to 7.30 ppm. The chemical shift of the protons of the formate and acetate groups are summarized in Table 1. The nmr spectra of all new esters had peaks which corresponded within 0.02 ppm to the values shown in Table 1.

To further demonstrate that degradation did not accompany the esterification, the final products were hydrolyzed by stirring in a MeOH–5% $NaHCO_3$ mixt for 1 day at 25°. After the usual Et_2O extn, the product was characterized by tlc and ir. By this procedure all the 2′ esters and the 4″- or 11-formates could be removed. Each new ester was characterized by this method.

2′,4″-Diacetylerythromycin A (3A). The diacetate (3A) was prepd by a procedure which was similar to that published by Banaszek, *et al.*,[8] whereby 3A was obtd in 71% yield, mp 135–139° (lit.[8] 135–140°), tlc system B. *Anal.* ($C_{41}H_{71}NO_{15}$) C, H, N, O.

4″-Acetylerythromycin A (4A). The diacetate 3A (5 g) was dissolved in 100 ml of MeOH and the hydrolysis followed by tlc (system B). After 2–3 days at 25° MeOH was removed to yield 4.5 g (95%) of the 4″-acetate 4A as a glass. Two crystns from $CHCl_3$–hexane yielded 3.2 g (68%) of 4A, mp 138–142° (lit.[8] 135–140°), tlc system B. *Anal.* ($C_{39}H_{69}NO_{14}$) C, H, N, O.

2′,4″,11-Triacetylerythromycin A (5A). Erythromycin A (5.0 g) was dissolved in 125 ml of pyridine and 20 ml of Ac_2O was added. After standing at 25° for 10 days, the soln was poured over ice and the pH adjusted to 9 with cold dil NaOH. The cloudy soln was extd with 2 portions of Et_2O and the combined exts were dried (Na_2SO_4) and evapd. The residue was dissolved in C_6H_6 and evapd to remove residual pyridine. The glassy solid obtd (5.4 g, 92%) was crystd from Me_2CO–hexane, mp 143–145° (lit.[8] mp 144–147°), tlc system B.

4″,11-Diacetylerythromycin A (6A). The diacetate was prepd from the triacetate 5A by the procedure for 4A. From 1.0 g of 5A was obtd 0.95 g (100%) of glassy solid which was crystd by slow evapn from Me_2CO–hexane, mp 140–145°. Tlc analysis (system E) showed a single component different from 5A.

2′-Formylerythromycin A (7A). In a soln of erythromycin A (36.7 g, 0.05 mole) dissolved in 1 l. of dry Et_2O was suspended 20 g of K_2CO_3. To this stirred suspension was slowly added (0.5 hr) 26.4 g (0.30 mole) of formic acetic anhydride. After 3 hr at 25° the mixt was poured over ice. The Et_2O layer was washed twice with cold, excess 5% $NaHCO_3$ and once with H_2O. After drying (Na_2SO_4), Et_2O was removed to yield 34 g (93%) of a glass which was crystd from EtOAc to yield 28 g (77%) of 7A, mp 151–154°, tlc systems B and D. *Anal.* ($C_{38}H_{67}NO_{14}$) C, H, N, O.

2′,4″-Diformylerythromycin A (8A). To a soln of 7.3 g (0.01 mole) of erythromycin A dissolved in 250 ml of Et_2O and 5 ml of pyridine was added at 0° formic acetic anhydride (16 ml, 0.18 mole). After stirring at 0° for 2 hr and 25° for 3 hr, the mixt was poured onto ice. The Et_2O layer was washed 3 times with cold, excess $NaHCO_3$ and once with H_2O. After drying (Na_2SO_4), Et_2O was removed to yield 7.5 g (95%) of the diformate 8A which was crystd from Et_2O, mp 128–132°, tlc systems B and A. *Anal.* ($C_{39}H_{67}NO_{15}$) C, H, N, O.

4″-Formylerythromycin A (9A). To a stirred soln of 7.9 g (0.01 mole) of the diformate 8A dissolved in 100 ml of Me_2CO was added 100 ml of 5% $NaHCO_3$. The reaction was monitored by tlc (system B and D). After 2 hr the Me_2CO was removed and the residue was extd with CH_2Cl_2. After a H_2O wash the CH_2Cl_2 layer was dried (Na_2SO_4) and concd. The product was crystd twice from Et_2O to yield 6.3 g (83%) of the formate ester 9A, mp 147–150°, tlc system B and D. *Anal.* ($C_{38}H_{67}NO_{14}$) C, H, N, O.

2′-Acetyl-4″-formylerythromycin A (10A). To a suspension of 3 g of K_2CO_3 in a soln of 7.6 g (0.01 mole) of the formate ester 9A dissolved in Me_2CO (100 ml) was added 2.1 ml (0.02 mole) of Ac_2O. After stirring at 25° for 4 hr, the mixt was poured over ice. The aqueous layer was extd with Et_2O, and the Et_2O layer washed twice with cold, excess 5% $NaHCO_3$ and once with H_2O. After drying (Na_2SO_4) the solvent was removed to yield 8.2 g of a glass. Two crystns from cyclohexane yielded the mixed ester 10A, mp 120–125°, tlc system A. *Anal.* ($C_{40}H_{69}NO_{15}$) C, H, N, O.

2′,11-Diacetyl-4″-formylerythromycin A (11A). The mixed ester 11A was prepd from 9A by the acetylation procedure described for 5A. From 3.0 g of 9A was obtd a glassy solid which was shown to be the desired product by nmr and tlc analysis (system B). This crude product was used directly in the prepn of the 11-acetate, 12A.

11-Acetylerythromycin A (12A). The monoacetate was prepd from crude 11A by the methanolysis procedure described for 4A except that the time was increased to 7 days. The material obtd was crystd from CH_2Cl_2–hexane yielding 1.8 g (55%), mp 138–140°, tlc system B. *Anal.* ($C_{39}H_{69}NO_{14}$) C, H, N.

2′-Acetylerythromycin B (2B). Erythromycin B (1B) (7.2 g, 0.01 mole) was acetylated as described for 10A. Two crystns from

§ R. S. Egan, unpublished results.

Me_2CO yielded 5.7 g (75%) of the acetate 2B, mp 125–130°, tlc system B and A. *Anal.* ($C_{39}H_{69}NO_{13}$) C, H, N, O.

2',4''-Diacetylerythromycin B (3B). To a soln of erythromycin B (5.0 g) in pyridine (125 ml) was added 5 ml of Ac_2O. After 3 days at 25° the reaction mixt was poured onto ice. The pH was adjusted to 9 with dil NaOH and the cold soln extd with 2 portions of Et_2O. The combined Et_2O exts were dried (Na_2SO_4) and evapd. The residue was dissolved in C_6H_6 and the soln evapd to remove residual pyridine. The glassy solid obtd was crystd from Et_2O yielding 1.5 g of the diacetate 3B, mp 220–225°. A second crop, 1.4 g, mp 212–216°, was recrystd from CH_2Cl_2–hexane to give 1.3 g, mp 220–224°, tlc system D, total yield 50%. *Anal.* ($C_{41}H_{71}NO_{14}$) C, H, N, O.

4''-Acetylerythromycin B (4B). The acetate 4B was prepd from the diacetate 3B as described for 4A. From 1.3 g of 3B was obtd 0.75 g (61%) of 4B crystd from Me_2CO, mp 125–130°, tlc system D. *Anal.* ($C_{39}H_{69}NO_{13}$) C, H, N, O.

2',4'',11-Triacetylerythromycin B (5B). The prepn was carried out according to the procedure as described for 5A. From 5.0 g of erythromycin B was obtd a glassy solid which was crystd from Et_2O to yield 3.9 g (66%) of the triacetate 5B, mp 191–193°, tlc system B. *Anal.* ($C_{43}H_{73}NO_{15}$) C, H, N, O.

4'',11-Diacetylerythromycin B (6B) was prepd from the triacetate 5B as described for 4A. From 1.0 g of 5B was obtd 0.95 g (100%) of 6B as a glassy solid which resisted crystn, tlc system B. *Anal.* ($C_{41}H_{71}NO_{14}$) C, H, N, O.

2'-Formylerythromycin B (7B) was prepd from erythromycin B as described for 7A. From 7.2 g of 1B was obtd 4.0 g (54%) of 7B crystd from Et_2O–hexane, mp 135–137°, tlc system E. *Anal.* ($C_{38}H_{67}NO_{13}$) C, H, N, O.

2',4''-Diformylerythromycin B (8B) was prepd from erythromycin B as described for 8A. From 7.2 g of 1B was obtd 6.1 g (79%) of 8B crystd from Et_2O–hexane, mp 145–148°, tlc system E. *Anal.* ($C_{39}H_{67}NO_{14}$) C, H, N, O.

2',4'',11-Triformylerythromycin B (14B). To a suspension of 12 g (0.017 mole) of erythromycin B in Et_2O (450 ml) and pyridine (17 ml) at 0° was slowly added 5.3 ml (0.6 mole) of formic acetic anhydride. After stirring for 3 hr at 0° and 5 days at 25°, the soln was again cooled to 0° and filtered under N_2 to yield 2.0 g of the triester 14B, mp 201–209°. One recrystn (CH_2Cl_2–hexane) yielded 1.8 g (12%) of 14B, as the CH_2Cl_2 solvate, mp 221–222°, tlc system E. Attempts to remove CH_2Cl_2 from the crystals by ordinary drying methods were not successful. *Anal.* ($C_{40}H_{67}NO_{15}\cdot CH_2Cl_2$) C, H, N, Cl.

The filtrate from the first filtration was poured into cold, excess 5% $NaHCO_3$. The Et_2O layer was washed twice with cold, excess 5% $NaHCO_3$, dried (Na_2SO_4), and evapd to yield 11.3 g of a glass which by tlc (system E) and nmr analyses contd only 75% of the triformate 14B and 25% of the diformate 8B. This mixt was used to prepare 15B.

4''-Formylerythromycin B (9B) was prepd from 8B as described for 9A. From 7.7 g (0.01 mole) of 8B was obtd 6.1 g (82%) of 9B crystd from Et_2O, mp 135–140°, tlc system E. *Anal.* ($C_{38}H_{67}NO_{13}$) C, H, N, O.

2'-Acetyl-4''-formylerythromycin B (10B) was prepd from the formate 9B as described for 10A, crystd from CH_2Cl_2–hexane as the CH_2Cl_2 solvate, mp 155–157°, tlc system E. The CH_2Cl_2 could not be removed from the crystals by ordinary drying methods and the analysis was done on the solvate as well as on the crude glass obtd from the extn. *Anal.* ($C_{40}H_{69}NO_{14}\cdot CH_2Cl_2$) C, H, N, Cl; ($C_{40}H_{69}NO_{14}$) C, H, N, O.

4'',11-Diformylerythromycin B (15B). The mixt of 75% triformate 14B and 25% diformate 8B obtd from the prepn of 14B was hydrolyzed as described for 9A. From 11.0 g of the mixt was obtd 10 g of a glass which upon fractional crystn from Et_2O yielded 2.0 g (18%) of the formate ester 9B, mp 134–139°, and 6.5 g (59%) of the diformate ester 15B, mp 204–206°, tlc system E. *Anal.* ($C_{39}H_{67}NO_{14}$) C, H, N, O.

2',11-Diacetyl-4''-formylerythromycin B (11B) was prepd by acetylation of the formate 9B as described for 5A. From 5.0 g of 9B was obtd 3.9 g (70%) of 11B crystd from Et_2O–hexane, mp 125–128°, tlc system E. *Anal.* ($C_{42}H_{71}NO_{15}$) C, H, N, O.

11-Acetylerythromycin B (12B) was prepd by hydrolysis of 11B as described for 12A. From 2.9 g of 11B was obtd 2.3 g (87%) of the acetate 12B crystd from MeOH–H_2O, mp 100–105°, tlc system E. *Anal.* ($C_{39}H_{69}NO_{13}$) C, H, N, O.

11-Formylerythromycin B (16B). A soln of 6.2 g of the diformate 15B in 600 ml of MeOH was stirred at 25° and the hydrolysis followed by tlc (system E). After 6 days the reaction was complete and the MeOH removed. The cryst residue was recrystd from EtOAc to yield 5.0 g (83%) of the formate ester 16B, mp 130–140°, tlc system E. *Anal.* ($C_{38}H_{67}NO_{13}$) C, H, N, O.

2',11-Diacetylerythromycin B (13B) was prepd by acetylation of the acetate 12B as described for 10A. From 2.2 g of 12B was obtd 1.9 g (82%) of 13B as a glass which could not be crystd but slow evapn from Et_2O–hexane gave a colorless powder, mp 105–110°. tlc system B. *Anal.* ($C_{41}H_{71}NO_{14}$) C, H, N, O.

2'-Acetyl-4''-propionylerythromycin B (17B) and 2'-Acetyl-4'',11-dipropionylerythromycin B (19B). The acetate 2B was esterified to a mixt of the diester 17B and the triester 19B as described for 5A substituting propionic anhydride for Ac_2O. From 1.0 g of 2B was obtd 1.05 g of a pale yellow glass which contd 2 new components (tlc, system B). Crystn from Et_2O–hexane gave 0.35 g of 17B, mp 225–230°, tlc system B. *Anal.* ($C_{42}H_{73}NO_{14}$) C, H, N, O. The filtrate was evapd to yield 19B (0.6 g) as a glass which was shown by tlc (system B) to contain only a trace of 17B. The glass could not be crystd and was used directly in the prepn of 20B. *Anal.* ($C_{45}H_{77}NO_{15}$) C, H, N, O.

4''-Propionylerythromycin B (18B) was prepd by hydrolysis of the mixed ester 17B as described for 4A. From 0.35 g of 17B was obtd 18B, crystd from Et_2O–hexane, mp 170–175°, tlc system B. *Anal.* ($C_{41}H_{71}NO_{14}$) C, H, N, O.

4'',11-Dipropionylerythromycin B (20B) was prepd by hydrolysis of 19B as described for 4A. From 0.30 g of 19B was obtd 20B as a glass which could not be crystd, tlc system B. *Anal.* ($C_{43}H_{75}NO_{14}$) C, H, N, O.

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