The Synthesis of 9-*epi*-Leucomycin A_3. The Revised Configurational Assignment of C-9 in Natural Leucomycin A_3

Summary: The configurational assignment of C-9 in leucomycin A_3 has been revised, based on spectral data obtained with 9-*epi*-leucomycin A_3 and the natural material, which were synthesized from niddamycin.

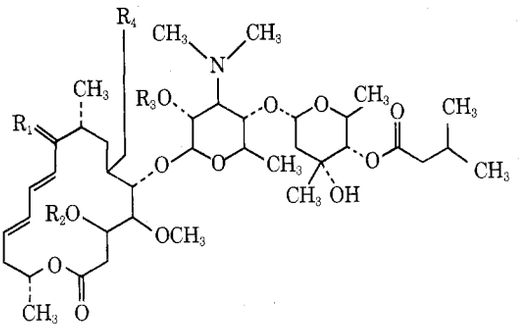
Sir: The absolute configuration of the lactone ring of the antibiotic leucomycin A_3, except for C-9, has been established by X-ray spectroscopy of an acid degradation product.[1] The absolute configuration at C-9 has been assigned independently by the application of the benzoate or Mills' rule to 3,5-dinitrobenzoate derivatives.[2] We now wish to report the synthesis and characterization of the two C-9 epimers of leucomycin A_3 and present spectral evidence which suggests the configuration at C-9 in the natural material is *R*, epimeric to the previous assignment.[3]

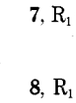
The initial synthetic step was the selective protection of the aldehyde group of niddamycin (1)[5,6] by acid-catalyzed dimethyl acetal formation. A methanol solution of **1** (0.085 *M*) and difluoroacetic acid (10 equiv) on standing for 66 hr at 25° gave 6b-niddamycin dimethyl acetal (**2**) in 50% yield: mp 208–211° (ethyl acetate–hexane); $[\alpha]^{25}D$ −39.3°.[7] Under these mild conditions, dimethyl acetal formation is found to proceed at a much faster rate than acid-catalyzed methanolysis of glycosidic bonds.[8] Next, the required 3-(*O*)-acetyl group was introduced by exhaustive acetylation of **2** with acetic anhydride–pyridine at 25° to give the diacetate **3** [mp 176–181° (ethyl acetate–hexane), $[\alpha]^{25}D$ −32.7°], followed by removal of the 2′-(*O*)-acetyl group by hydrolysis with $NaHCO_3$ in MeOH–H_2O to give 3-(*O*)-acetyl-6b-niddamycin dimethyl acetal (**4**): mp 202–208° (MeOH–H_2O); $[\alpha]^{25}D$ −10.5°; λ_{max}^{MeOH} 278 nm (ϵ 21,800).

Studies on the sodium borohydride reduction of **4** showed the ratios of C-9 epimeric alcohols obtained were markedly sensitive to the solvent employed. Thus, reduction of **4** in dioxane at 25° provided a 4:1 (epi:natural) mixture of isomers (tlc) from which the major product was isolated by column chromatography on silica gel [benzene–methanol (2%)] to give a 35% yield of pure 9-*epi*-leucomycin A_3 dimethyl acetal (**5**): amorphous; $[\alpha]^{25}D$ −36.2°; λ_{max}^{MeOH} 232 nm (ϵ 25,800). In contrast, reduction of **4** in methanol at 25° provided a 1:4 (epi:natural) mixture, which gave after chromatography (silica gel) a 57% yield of leucomycin A_3 dimethyl acetal (**6**): amorphous; $[\alpha]^{25}D$ −64.0°; λ_{max}^{MeOH} 232 nm (ϵ 28,200).

Finally, the acetal protecting groups were removed by acid hydrolysis in 50% acetonitrile–water. Treatment of an 0.075 *M* solution of **5** with 2.5 equiv of difluoroacetic acid at 25° for 4 hr gave 9-*epi*-leucomycin A_3 (**7**) in quantitative yield: amorphous; $[\alpha]^{25}D$ −38.7°; λ_{max}^{MeOH} 232 nm (ϵ 26,600). Under identical conditions **6** required 24 hr for complete hydrolysis, giving after chromatography a 50% yield of leucomycin A_3 (**8**): mp 125–127° (benzene); $[\alpha]^{25}D$ −69.1°; λ_{max}^{MeOH} 231 nm (ϵ 28,100).[9] Similarly, hydrolysis of **4** gave carbomycin B (**9**): mp 193–200° (prisms, acetone–water); $[\alpha]^{25}D$ −37° (*c* 1.00, $CHCl_3$); λ_{max}^{MeOH} 278 nm (ϵ 23,200).[10]

Proton nmr and high dilution differential ir spectral data were employed to establish the configurations at C-9 in **5**–**8**. Since the C-9 and double-bond region of the molecule had not been defined by the X-ray structure, these proton resonances were of particular interest. The coupling constants of $J_{10,11}$ and $J_{12,13}$ = 15 Hz indicate that the double bonds are trans[11] and the value of $J_{11,12}$ = 10 Hz that the diene systems are in a nearly planar *S* (trans) conformation.[12] In the natural series (**6** and **8**) $J_{9,10}$ = 9.0 Hz, indicating that H-9 lies nearly in the plane of the diene system.[13] In the epi series (**5** and **7**), however, H-9 forms an appreciable angle with this plane as shown by the values of $J_{9,10}$ = 4.0 Hz[13] and the 4-bond allylic coupling $J_{9,11}$ = 1.8 Hz.[14] In both epimers and their derivatives, coupling between H-8 and H-9 is small ($J_{8,9}$ = 3–4 Hz), indicating a dihedral angle of $\phi \simeq 60°$ between these protons. Anticipating that the plane of the diene system is approximately perpendicular to the general plane of the lactone ring,[1,15] the nmr data are consistent with the configurational assignments as shown in Figure 1.



1, R_1 = O; R_2 = R_3 = H; R_4 = CHO
2, R_1 = O; R_2 = R_3 = H; R_4 = $CH(OCH_3)_2$
3, R_1 = O; R_2 = R_3 = Ac; R_4 = $CH(OCH_3)_2$
4, R_1 = O; R_2 = Ac; R_3 = H; R_4 = $CH(OCH_3)_2$
5, R_1 =  ; R_2 = Ac; R_3 = H; R_4 = $CH(OCH_3)_2$
6, R_1 =  ; R_2 = Ac; R_3 = H; R_4 = $CH(OCH_3)_2$
7, R_1 =  ; R_2 = Ac; R_3 = H; R_4 = CHO
8, R_1 =  ; R_2 = Ac; R_3 = H; R_4 = CHO
9, R_1 = O; R_2 = Ac; R_3 = H; R_4 = CHO

Evidence that these assignments are correct was obtained from ir spectral studies. Corey–Pauling–Koltun (CPK) molecular models of the C-9 leucomycin A_3 epimers were constructed to fit the observed lactone ring coupling constants and X-ray structure. These models reveal the 9-hydroxyl group of the *S* epimer **7** is in close proximity (~3.2 Å) to the 3-(*O*)-acetyl carbonyl oxygen and should form an intramolecular hydrogen bond. Furthermore, in **5** (the dimethyl acetal derivative) a second hydrogen bond accepting site (an OMe group) is available. However, the CPK model of the *R* epimer **8** shows the 9-hydroxyl group to be 5 Å or greater from any potential intramolecular hydrogen bonding site. This situation is not changed by any reasonable conformation reorganization of the model.

High dilution differential ir spectra of the epimeric alco-

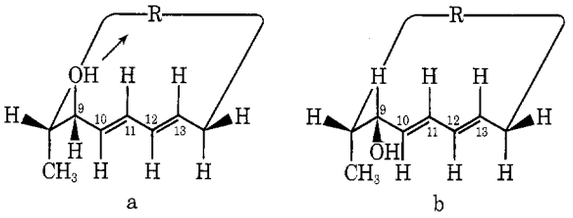


Figure 1. Projection view of the C-8 to C-14 portion of the lactone ring of (a) 9-*epi*-leucomycin A_3 (7) and (b) leucomycin A_3 (8) (R = remainder of lactone ring).

hols, employing the ketones **4** or **9** in the reference beam, were obtained for the hydroxyl region. The spectral data obtained at 2×10^{-3} *M* in CCl_4 were exactly reproduced at tenfold dilution, showing the intramolecular nature of the H-bonding patterns observed. The 9-epi derivative **7** showed bands at 3618 and 3550 cm^{-1} while the corresponding dimethyl acetal derivative **5** showed bands at 3618, 3535, and 3482 cm^{-1} providing clear evidence of intramolecular hydrogen bonding of the C-9 hydroxyl to oxygen electron pair donors. However, in agreement with results reported by Omura,[15] the C-9 hydroxyl groups of leucomycin A_3 [and the dimethyl acetal derivative (**6**)] show single strong hydroxyl bands at 3618 cm^{-1}. Therefore, we conclude that the configuration at C-9 of leucomycin A_3 is *R*, as shown in Figure 1b, which is epimeric to the previous assignment.

The configuration at C-9 in spiramycin has been shown to be the same as leucomycin A_3 by chemical interrelation[16] and should also be revised. The recently reported value of $J_{9,10}$ = 9.0 Hz for maridomycin II[17] suggests that the configuration at C-9 of this antibiotic is also *R*.

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Supplementary Material Available. Tables of nmr and ir spectral data will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-2474.

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(3) Application of the "sequence rule" [4] to the structure of natural leucomycin A_3 as shown in ref 2b gives *S* for the configuration at C-9. This result was confirmed in private communication with Kurt L. Loening, Nomenclature Director, Chemical Abstracts Service.
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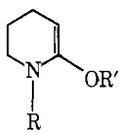
New Synthetic Reactions. Alkylation of Lactam Derivatives

Summary: Alkylation of the enolate equivalent of 1-methyl-2-piperidone (**1a**) and2-methoxy-3,4,5,6-tetrahyd ropyridine (**1b**) gave only substitution at carbon; with methyl vinyl ketone, **1a** gave carbonyl addition but **1b** gave conjugate addition.

Sir: The direct alkylation of carboxylic acid derivatives has rapidly become a very useful method in organic synthesis.[1-5] More recently, this methodology has been extended to lactones.[3] For alkaloid synthesis, direct alkylation of lactams has great potential for developing molecular architecture. We want to report a study comparing the reactivity of various lactam derivatives **1a–c,** which is, in many respects, in marked contrast to the behavior of lactone enolates.



1a, R = CH_3; R′ = Li
b, R = Li; R′ = CH_3
c, R = R′ = CH_3

The enolate **1a** was generated by the treatment of 1-methyl-2-piperidone with lithium diisopropylamide or *N*-cyclohexyl-*N*-isopropylam ide in THF at −78°. After 15-min generation time, silylation with dimethylphenylchlorosilane produced a quantitative yield of the C-silylated product **2**[6] [ir 1626 cm^{-1}; nmr δ 2.40 (3 H, s) and 0.10 (6 H, s); see Chart I]. "O" rather than "C" silylation normally predominates with ester enolates.[7] The higher bond energy of the amide carbonyl group rationalizes the opposite regioselectivity observed here. In contrast to lactone enolates, the unactivated alkylating agents **3** and **4** react smoothly in THF to produce **5**[6] [ir 1635 cm^{-1}; nmr δ 3.96 (4 H, s) and 2.83 (3 H, s)] and **6**[6] [ir 1639 cm^{-1}; nmr δ 4.67 (2 H, br s), 2.84 (2 H, s), and 1.72 (3 H, br s)], respectively. It is interesting to note that methyl vinyl ketone reacts highly regioselectively by carbonyl addition to produce **7**[6] [ir 3378 and 1616 cm^{-1}; nmr δ 5.5 (3 H, ABC), 2.82 (3 H, s), and 1.15 (3 H, s)] with no detectable amount of conjugate addition.