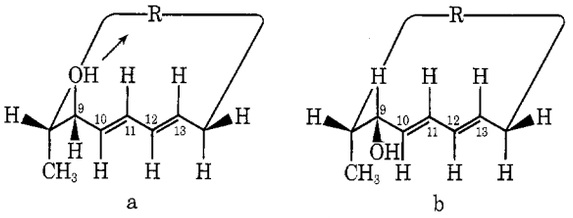

Figure 1. Projection view of the C-8 to C-14 portion of the lactone ring of (a) 9-*epi*-leucomycin A_3 (7) and (b) leucomycin A_3 (8) (R = remainder of lactone ring).

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*.

Acknowledgment. We wish to thank Dr. S. Omura, Kitasato University, Japan, for the gift of a sample of leucomycin A_3. We thank Ms. R. S. Stanaszek for help in obtaining ^1H nmr spectra, Mr. M. J. Kukla for ir spectra, and Dr. R. Hasbrouck and Mr. J. Leonard for tlc analyses.

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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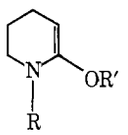
Received May 23, 1974

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.

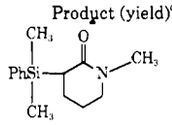
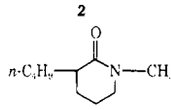
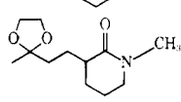
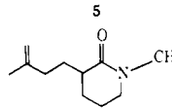
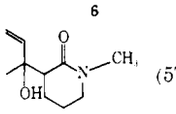
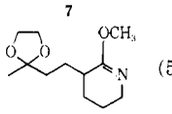
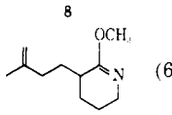
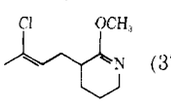
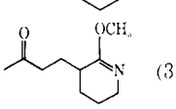
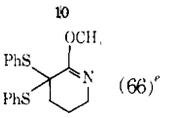
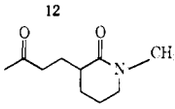
Sir: The direct alkylation of carboxylic acid derivatives has rapidly become a very useful method in organic synthesis.[1-5] More recently, this methodology has been extended to lactones.[3] For alkaloid synthesis, direct alkylation of lactams has great potential for developing molecular architecture. 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

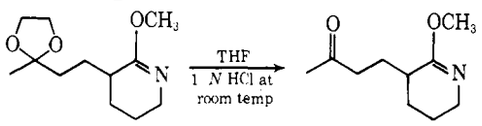
The enolate **1a** was generated by the treatment of 1-methyl-2-piperidone with lithium diisopropylamide or *N*-cyclohexyl-*N*-isopropylam ide in THF at −78°. After 15-min generation time, silylation with dimethylphenylchlorosilane produced a quantitative yield of the C-silylated product **2**[6] [ir 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.

Chart I
Reaction of Lactam Derivatives

Derivative	Electrophile	Product (yield)[a,b]	Time[c,d]	Temp, °C[c,d]
1a	$PhSi(CH_3)_2Cl$	 (100)	15 min 1 hr	0 −78
1a	C_4H_9I	 (78)	12 hr	−15
1a	 3	 (68)	8 hr	−15
1a	 4	 (72)	14 hr	−15
1a		 (57)	15 min	−78
1b	3	 (56)	4 hr	Room temp
1b	4	 (60)	3 hr 20 min	−78 22
1b		 (37)	2 hr 12 hr	−78 Room temp
1b		 (31)	5 min 20 min	−78 Room temp
1b	PhSSPh	 (66)[e]	3 min 30 min	−78 Room temp
1c		 (29)	22 hr	Room temp

[a] The yields are for isolated pure product except as otherwise noted. [b] See ref 6. [c] The enolate derivatives were normally generated at −78° for 2 hr. [d] Times and temperatures given represent variables after addition of electrophiles. [e] Mp 93–94°.

The metalated lactim **1b** offers a simple approach to α-substituted secondary lactams. Again metalation proceeds readily with lithium diisopropylamide (but not *n*-butyllithium[5]) at −78°. Alkylation of the less reactive **1b** with **3** or **4** requires room temperature to produce **8** [ir 1669 cm^{-1}; nmr δ 3.82 (4 H, s), 3.50 (3 H, s), and 1.20 (3 H, s)] and **9** [ir 1672 and 1655 cm^{-1}; nmr δ 4.63 (2 H, br s, 3.50 (3 H, s), and 1.70 (3 H, br s)], respectively (see Chart I), whereas alkylation of **1a** proceeded at −15° for comparable times. In contrast to **1a**, addition of methyl vinyl ketone to **1b** led to isolation of only the conjugate addition product **10** [ir 1724 and 1675 cm^{-1}; nmr δ 3.50 (3 H, s) and 2.05 (3 H, s)]. Comparison of the spectral properties of the product of hydrolysis of **8** to those of **10** confirmed the structure of the latter. This discrepancy in behavior can be rationalized by assuming that, with the less reactive lactim derivative, delocalization of charge in the transition state of addition becomes more important. In agreement with this concept, the ketene aminal **1c** only yielded the product of conjugate addition with methyl vinyl ketone, **11**[6] [ir 1721 and 1642 cm^{-1}; nmr δ 2.92 (3 H, s) and 2.10 (3 H, s)], albeit in low yield.



8 **10**

In an ancillary experiment, sulfenylation of 1b proceeded to produce the bissulfide **12**.[6] This reaction is indeed general for enolates of carboxylic acid derivatives and should become a useful entry into α-ketocarboxylic acid derivatives.[8]

Acknowledgment. We wish to thank the National Institutes of Health and the National Science Foundation for their generous support of our programs.

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Received May 17, 1974