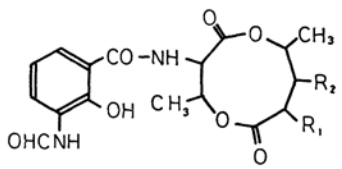
The Total Synthesis of Dehexyl-deisovaleryloxy-antimycin A_1

Mitsuhiro KINOSHITA and Sumio UMEZAWA

Department of Applied Chemistry, Faculty of Engineeering, Keio University, Koganei-shi, Tokyo

(Received January 23, 1969)

Antimycin A is a complex of at least four closely related antifungal antibiotics (A_1—A_4) produced by *Streptomyces* spp., and the structures of antimycin A_1 (Ib) and A_3 (Ic) were elucidated by van Tamelen *et al.*,[1] Birch *et al.*,[2] Yonehara *et al.*,[3] and Harada *et al.*[4] The most striking characteristic of the structure of antimycin A is its dilactone ring linked *via* an amide bond to 3-formamidosalicylic acid.



Ia Ib Ic

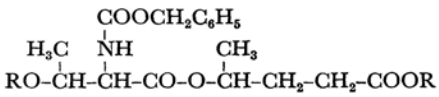
R_1: H n-C_6H_{13} n-C_4H_9

R_2: H i-C_4H_9COO i-C_4H_9COO

We wish to record the total synthesis of dehexyl-deisovaleryloxy-antimycin A_1 (Ia) which differs from natural antimycin A in that the acyloxy and alkyl substituents of the dilactone ring are replaced by hydrogen atoms.

N-Benzyloxycarbonyl-*O*-*t*-butyl-L-threonine[5] was condensed with *t*-butyl γ-hydroxyvalerate[6] using *N*,*N*′-dicyclohexylcarbodiimide (DCCI) in pyridine to afford *t*-butyl γ-(*N*-benzyloxycarbonyl-*O*-*t*-butyl-L-threonyloxy)valerate (II): $[\alpha]_D^{19}$ −4° (*c* 2, ethanol); yield 42%.

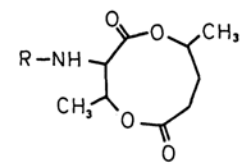
Treatment of II with trifluoroacetic acid gave γ-(*N*-benzyloxycarbonyl-L-threonyloxy)valeric acid



II III

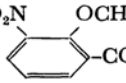
R: *t*-C_4H_9 H

(III): $[\alpha]_D^{21}$ −16° (*c* 2, ethanol); yield 85.5%. The hydroxycarboxylic acid (III) was cyclized with trifluoroacetic anhydride in benzene (concentration of III in benzene: 4×10^{-2}M) at 75°C for 16 hr to afford colorless crystals of *N*-benzyloxycarbonyl-4-amino-1,5-dimethyl-3,7-dioxo-2,6-dioxacyclononane (IV): mp 105—107°C; $[\alpha]_D^{21}$ +14° (*c* 2, ethanol); MW 335.140 (MS); ν_{max}^{KBr} 3320, 1745, 1693 and 1539 cm^{-1}; yield 32.5%.



IV V

R_1: $C_6H_5CH_2OCO$ O_2N $OCH_2C_6H_5$



The benzyloxycarbonyl group was removed and the resulting free amino dilactone was *N*-acylated with *O*-benzyl-3-nitrosalicylic acid *N*-hydroxysuccinimide ester to yield *N*-(*O*-benzyl-3′-nitrosalicyloyl)-4-amino-1,5-dimethyl-3,7-dioxo-2,6-dioxacyclononane (V): mp 188—189.5°C; $[\alpha]_D^{22}$ +20° (*c* 2, tetrahydrofuran); ν_{max}^{KBr}, 3200, 1743, 1645 and 1532 cm^{-1}; yield 72.4%. Hydrogenation of V over palladium black in methanol, followed by *N*-formylation with 98% formic acid and DCCI afforded dehexyl-deisovaleryloxy-antimycin A_1 (Ia): mp 154—155°C; $[\alpha]_D^{19}$ +70° (*c* 1, chloroform); λ_{max}^{MeOH} 226 (log ε 4.62), 320 mμ (log ε 3.93); $\nu_{max}^{CHCl_3}$ 3435, 1747, 1706, 1647, 1614, and 1531 cm^{-1}; yield 56%. The synthetic product Ia completely inhibited the growth of *Piricularia oryzae* in a concentration of 0.39 mcg/ml by dilution method using bouillon.

1) F. M. Strong, J. P. Dickie, M. F. Loomans, E. E. van Tamelen and R. S. Dewey, *J. Am. Chem. Soc.*, **82**, 1513 (1960); E. E. van Tamelen, J. P. Dickie, M. F. Loomans, R. S. Dewey and F. M. Strong, *ibid.*, **83**, 1639 (1961).

2) A. J. Birch, D. W. Cameron, Y. Harada and R. W. Rickards, *J. Chem. Soc.*, **1961**, 889.

3) H. Yonehara and S. Takeuchi, *J. Antibiotics*, **11A**, 122, 254 (1958).

4) K. Uzu, H. Kato, K. Kumabe and Y. Harada, *ibid.*, **14A**, 209 (1961).

5) E. Schröder, *Ann.*, **670**, 127 (1963).

6) *t*-Butyl γ-hydroxyvalerate was prepared from *t*-butyl levulinate by hydrogenation with Raney Ni.