Synthesis of Antimycic Acid Methyl Ester Methyl Ether

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The structure of antimycic acid was shown to be *N*-(3-aminosalicyloyl)-L-threonine by Strong and co-workers[1,2]. Dembro and Okumura have been trying to synthesize this acid without success[3].

Recently, the synthesis of both L- and DL-antimycic acid methyl ester methyl ether (VIb) has been achieved by us by the following process.

3-Nitrosalicylic acid methyl ether (I), m. p. 195~196°C[4], was prepared by hydrolysis with sodium hydroxide after methylation of 3-nitrosalicylic acid with diazomethane. I was refluxed with thionyl chloride to give the chloride (II) which was condensed with DL-threonine to obtain *N*-(3-nitro-2-methoxybenzoyl)-DL-threonine (IIIa) in 89% yield, m. p. 144.5~145.5°C. (*Anal.* Found: N, 9.38. Calcd. for $C_{12}H_{14}O_7N_2$: N, 9.39%). Prolonged methylation of IIIa with diazomethane gave 87% yield of methyl ester of IIIa, m.p. 92.5~93.5°C. (*Anal.* Found: N, 9.17. Calcd. for $C_{13}H_{16}O_7N_2$: N, 8.98%). IIIa was boild with in acetic anhydride to give 85% yield of *N*-(-3-nitro-2-methoxybenzoyl)-aminocrotonic azlactone (IV), m. p. 175~176°C. (*Anal.* Found: N, 10.70. Calcd. for $C_{12}H_{10}O_5N_2$: N, 10.68%). IIIa was catalyticaly reduced in methanol solution with palladium-carbon to obtaln *N*-(3-amino-2-methoxybenzoyl)-DL-threonine (Va), in 98% yield, m. p. 163~164°C. (*Anal.* Found: N, 10.53. Calcd. for $C_{12}H_{16}O_5N_2$: N, 10.45%). Prolonged methylation of this product with diazomethane gave *N*-(3-amino-2-methoxybenzoyl)-DL-threonine methyl ester (VIa), in 60% yield, m. p. 128.5~129.5°C. (*Anal.* Found: N, 9.92. Calcd. for $C_{13}H_{18}O_5N_2$: N, 9.93%), which was also prepared by catalytic reduction of the methyl ester of IIIa with palladium-carbon in methanol in 91% yield.

II was condensed with L-threonine to obtain the oily *N*-(3-nitro-2-methoxybenzoyl)-L-threonine (IIIb), which gave *N*-(3-amino-2-methoxybenzoyl)-L-threonine, (antimycic acid methyl ether) (Vb) by prolonged catalytic reduction in methanol with palladium-carbon, in 83% yield, m. p. 123.5~124.5°C, $[\alpha]_D^{28°}+14°$ (c 1.82, alcohol). (*Anal.* Found: N, 10.28. Calcd. for $C_{12}H_{16}O_5N_2$: N, 10.45%). Vb was methylated in methanol with diazomethane to obtain 78% yield of *N*-(3-amino-2-methoxybenzoyl)-L-threonine methyl ester, (Antimycic acid methyl ester methyl ether) (VIb) m. p. 155~156°C, $[\alpha]_D^{28°}+10°$ (c 2.05, alcohol). (*Anal.* Found: C, 55.27; H, 6.54; N, 10.09. Calcd. for $C_{13}H_{18}O_5N_2$: C, 55.32; H, 6.43; N, 9.93%).

A sample of antimycic acid methyl ester methyl ether, m. p. 155~156°C, obtained by methylation of natural antimycic acid in methanol with diazomethane, showed no depression of m. p. when mixed with VIb, and neither the infrared nor the ultraviolet spectra showed any significant difference between the two substances. Va or Vb was boiled in acetic anhydride with pyridine to give respectively 84% or 78% yield of *N*-(3-acetamino-2-methoxybenzoyl)-aminocrotonic azlactone (VII), m. p. 136.5 ~ 137.5°C. (*Anal.* Found: N, 10.45. Calcd. for $C_{14}H_{14}N_4O_2$: N, 10.22%), which gave by prolonged hydrolysis with 0.08 N sodium hydroxide 73% yield of *N*-(3-acetamino-2-methoxybenzoyl)-aminocrotonic acid (VIII), m. p. 195.5~196.5°C. (*Anal.* Found: N, 9.66. Calcd. for $C_{14}H_{16}O_5N_2$: N, 9.59%), as described previously for antimycic acid itself by Strong[1,2].

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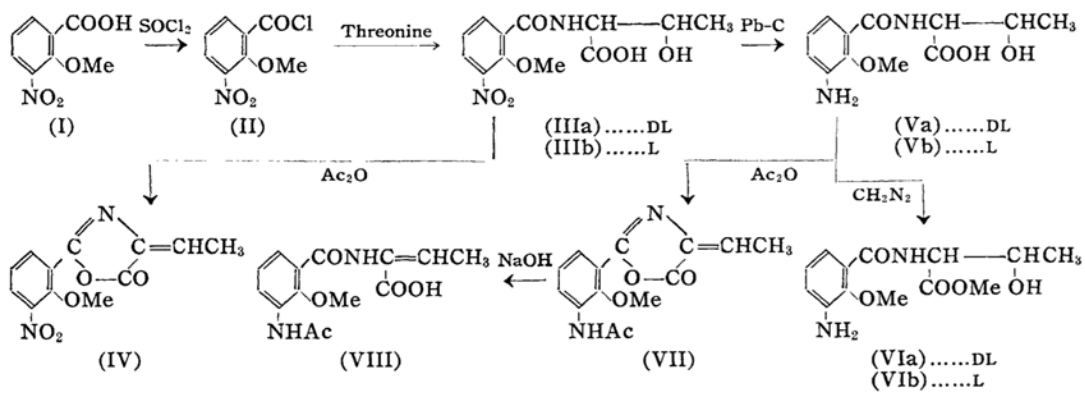

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1) G. M. Tener, F. M. Bumpus, B. R. Dunshee and F. M. Strong, *J. Am. Chem. Soc.*, **75**, 1100 (1953).

2) G. M. Tener, E. E. van Tamelen and F. M. Strong, ibid., **75**, 3623 (1953).

3) Unpublished work at Wisconsine University.

4) J. F. Simpnsen and M. G. Rau, *J. Chem. Soc.*, **111**, 220 (1917).

5) Eastman Organic Chemica[s.