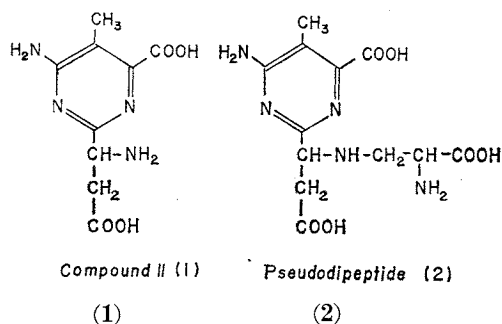


CHEMISTRY OF BLEOMYCIN. VII  
SYNTHESIS OF  $\beta$ -AMINO- $\beta$ -(4-AMINO-6-CARBOXY-5-METHYLPYRIMIDIN-2-YL)-PROPIONIC ACID, AN AMINE COMPONENT OF BLEOMYCIN

Sir :

The bleomycins comprise a group of related glycopeptide antitumor antibiotics. By total acid hydrolysis, bleomycin gave at least 6 amino acids and an amine which is specific for each bleomycin<sup>1,2</sup>. To one of the amino acids, designated compound II in the former report<sup>1</sup>, we assigned the structure  $\beta$ -amino- $\beta$ -(4-amino-6-carboxy-5-methylpyrimidin-2-yl)-propionic acid<sup>3</sup> (1). Compound II is

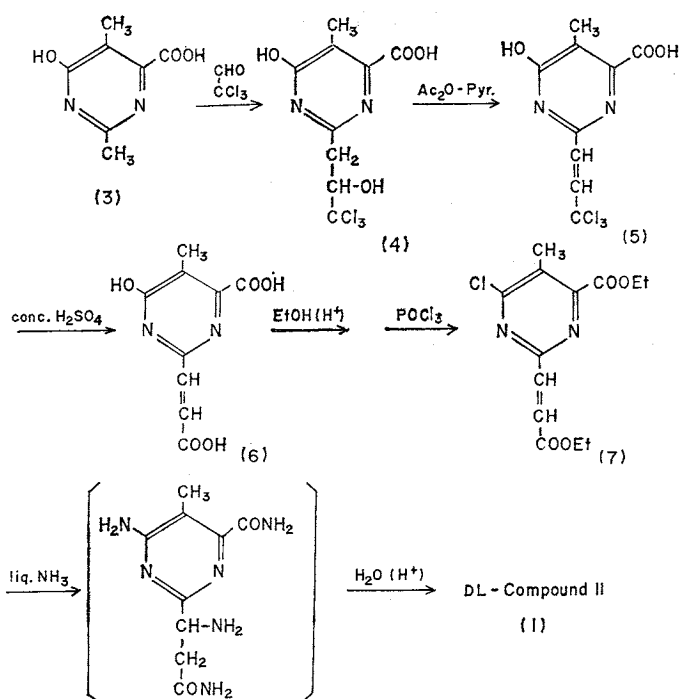


present as a part of a more complex fragment, termed pseudodipeptide<sup>4</sup> (2), in the bleomycin molecule. The pseudodipeptide was obtained by successive selective cleavages of bleomycin<sup>4</sup>. In the process of total acid hydrolysis, the pseudodipeptide moiety gave two amino acids, compound II and  $\beta$ -aminoalanine, by competitive  $\beta$ -elimination. In this communication, synthesis of compound II is described.

Compound II has now been obtained from 4-carboxy-2,5-dimethyl-6-hydroxypyrimidine<sup>5</sup> (3) via the following route.

4-Carboxy-2,5-dimethyl-6-hydroxypyrimidine (3) (m. p. 242°C) and chloral were reacted at 95°C for 44 hours in pyridine. The product (4) was obtained

in 90% yield, m. p. 193°C; NMR in DMSO (internal TMS reference):  $\delta$  2.09 (3H, singlet), 2.87, 3.30 and 4.72 (ABX-pattern,  $J_{AB} = 14.5$ ,  $J_{AX} = 9$ ,  $J_{BX} = 3$  Hz). It is obvious that the more reactive 2-methyl group was involved in this reaction<sup>5,6</sup>. Treatment of 4 with acetic anhydride and pyridine at room temperature yielded almost quantitatively the dehydration product (5), m. p. 177°C; NMR in DMSO:  $\delta$  2.16 (3H, singlet), 6.89 and 7.67 (trans-olefin,  $J = 15$  Hz). Compound 5 was converted to the corresponding  $\alpha,\beta$ -unsaturated acid (6) with 95%  $H_2SO_4$  at 70°C for 18 hours (94% yield), NMR in  $CD_3OD$ :  $\delta$  2.25 (3H, singlet), 7.08 and 7.32 (trans-olefin,  $J = 15$  Hz). Esterification of 6 with ethanol saturated with hydrogen chloride yielded the di-ethyl ester (gummy, 86% yield) which was refluxed in  $POCl_3$  for 30 minutes to yield 7 (gummy, 70% yield). Compound 7 gave a spot of  $R_f$  0.80 on silica gel thin-layer chromatography with ethyl acetate and methanol (1:1), while the starting di-ester had  $R_f$  0.62. Compound 7 was reacted with liquid ammonia in ethanol solution at 135°C for 18 hours. The product was without purification, hydrolyzed with 6 N HCl at 105°C for 18 hours. The final



product, compound II (1) was purified with sulfonic acid resin (Dowex 50) column chromatography (20% yield).

The behavior on thin-layer chromatography, paper electrophoresis and UV and NMR spectra were the same as natural II. The IR spectrum was different from natural II, because natural II is partially racemized while the synthetic material is completely racemic.

Since the pseudodipeptide has been derived from compound II and methyl acetamidoacrylate<sup>4)</sup>, the total synthesis of pseudodipeptide has been accomplished.

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