

NOTES

STUDIES ON SIOMYCIN. IV
ACYL DERIVATIVES OF
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For the purpose of X-ray analysis on the structure of crystalline siomycin A¹⁻⁴), monoiodoacetyl derivative of the antibiotic was prepared *via* monochloroacetyl siomycin A. To investigate the nature of hydroxyl groups in siomycin A, tetraacetyl derivative was also made. These acyl derivatives obtained were more soluble in many organic solvents than the original antibiotic, but less biological activities were found.

Acetyl siomycin A: Five hundred milligrams of siomycin A (0.3 mmoles) were dissolved in 1.5 ml of pyridine, and into the

solution 2.82 ml of acetic anhydride (30 mmoles) were added. After standing at 25°C for 22 hours, the mixture was filtered and dried completely in CaCl₂ desiccator. Crude yield 420 mg. The crude materials were purified by a silica gel column (12×200 mm) using a mixture of chloroform and methanol (9:1). The purified acetyl siomycin A was further recrystallized from a mixed solvent of chloroform and benzene (44:56). Yield 275 mg. Analyses of this derivative show the tetraacetyl compound.

Chloroacetyl siomycin A: Siomycin A (2.0 g, 1.2 mmoles) was dissolved in a mixture of 40 ml of chloroform and 2 ml of pyridine. Into the mixture 2.04 g of monochloroacetic anhydride (12 mmoles) was added. After standing at 23°C for 48 hours, the mixture was evaporated to dryness and dried *in vacuo*. The excess reagent and monochloroacetic acid were removed off by washing with ether. Crystallized from chloroform-ethanol (1:1). Yield 1.78 g. The partial crude material of chloroacetyl siomycin A was purified by a silica gel column chromatography with a mixed solvent of

Table 1. Some properties of acyl derivatives of siomycin A

	Tetraacetyl siomycin A	Monochloroacetyl siomycin A	Monoiodoacetyl siomycin A
Appearance	slightly yellow crystalline	colorless crystalline	colorless crystalline
m. p.	240°C dec.	230°C dec.	210°C dec.
Elementary analysis (%)	C 52.29 H 5.45 N 13.95 S 8.32 Ac 18.97	C 50.41 H 5.09 N 13.62 S 8.97 Cl 2.59 Ac 10.72	C 48.52 H 4.92 N 12.63 S 8.87 I 5.02
Estimated formula	C ₈₄ H ₁₀₄ O ₂₄ N ₁₉ S ₅	C ₇₆ H ₉₁ O ₂₂ N ₁₈ S ₅ Cl	C ₇₆ H ₉₂ O ₂₃ N ₁₇ S ₅ I
[α] _D ²³ (c 1, dioxane)	-132.1	-102.2	-92.4
Solubility	Soluble in dioxane, ethanol, methanol, acetone, chloroform, dichloromethane.	More soluble in many organic solvent such as acetone and methanol than siomycin A.	
	Insoluble in water, ether, <i>n</i> -hexane, benzene.		But less soluble than monochloroacetyl derivative.
Antibacterial activity (siomycin A=100)	0.0	2.2	1.0

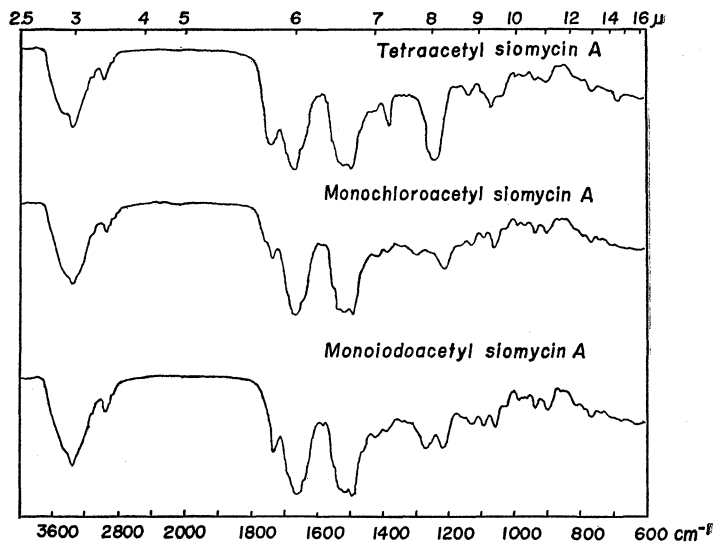
chloroform and methanol (9:1). Obtained fractions were combined, evaporated and recrystallized from diluted dioxane. Main product, (Cl content, 2.35~2.62%) was monochloroacetyl siomycin A. Minor product, (Cl content, 4.66%) would be di-(chloroacetyl)-siomycin A. From the chlorine content molecular weights of the antibiotics were estimated to be 1,741 and 1,713, respectively. Chloroacetylation of siomycin A by use of chloroacetyl chloride failed because many by-products were found on thin layer chromatogram.

Monoiodoacetyl siomycin A: Monochloroacetyl siomycin A was converted to monoiodoacetyl derivative by potassium iodide in a mixture of chloroform and methanol (1:1). One gram of monochloroacetyl siomycin A (0.52 mmoles) was dissolved in 80 ml of the mixture of chloroform and methanol. Into the solution, 10 ml of KI solution (KI, 860 mg, 5.2 mmoles in methanol) was added and stood at 65°C for 18 hours. After cooling the mixture was evaporated and washed with water to remove KI and KCl. Purification was performed by a silica gel column chromatography (12×500 mm) with a mixed solvent of chloroform and methanol (9:1). Yield, pure substance, 995 mg; partial purified material, 48 mg. This derivative was recrystallized from diluted dioxane. Crystallization in dimethylformamide-methanol gave big tetragonal crystals. Molecular weight of the derivative was measured to be 1,189 by the osmotic method.

Some properties of the three acyl derivatives of siomycin A were shown in Table 1. These are more soluble in many organic solvents than the original antibiotic, but almost no activity was found against *Bacillus subtilis*.

Fig. 1 shows infrared spectra of the acetyl-, chloroacetyl- and iodoacetyl derivatives of the antibiotic. These spectra,

Fig. 1. Infrared absorption spectra of tetraacetyl-, monochloroacetyl- and monoiodoacetyl derivatives of siomycin A by the KBr method.



especially that of the acetyl siomycin A indicate that the antibiotic was acylated by the individual acylating agent.

Bromoacetylation of siomycin A by use of monobromoacetic anhydride or bromoacetyl bromide was not proceeded under any conditions. Finally, succinyl siomycin A was also made by the direction of BODANSZKY and FRIED⁵⁾, but the preparation obtained was not homogeneous and no biological activity was found.

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