ACYL DERIVATIVES OF 16-MEMBERED MACROLIDES

II. ANTIBACTERIAL ACTIVITIES AND SERUM LEVELS OF 3''-*O*-ACYL DERIVATIVES OF LEUCOMYCIN

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3''-*O*-Acylation of leucomycin A_5 increased its *in vitro* antibacterial activity against sensitive microorganisms and also some resistant ones. An increased effect was particularly noted when an acetyl or propionyl group was introduced. On the contrary, acylation of the C-3 and C-9 hydroxyl groups reduced the antibacterial activity *in vitro*. Introduction of an acyl group at the C-3'' hydroxyl group increased the serum level of the compound. The increase in serum level from 3''-*O*-acylation is higher than that from 3-*O*-acylation. The serum level of the 3''-*O*-propionyl derivative of leucomycin A_5 was higher than that of the 3''-*O*-acetyl derivative. 3''-*O*-Propionylleucomycin A_5 (**5**) was the derivative that showed the highest antibacterial activity and yielded the highest serum level among the derivatives examined.

The leucomycins[1] are a 16-membered macrolide group of antibiotics showing potent activities against Gram-positive bacteria and mycoplasmas, and are composed of 10 components[2]. Many C-3, C-9 and C-2'-*O*-acyl derivatives of leucomycins have been synthesized. However, none of them exhibited activities higher than those of the natural 10 components *in vitro*[3].

This report describes the comparison of the antibacterial activities (MIC) and the serum levels in dogs and pigs among the derivatives where various acyl groups were introduced at the tertiary hydroxyl group at the C-3'' position in the leucomycins and midecamycins[4].

Materials and Methods

Materials

Acylation of the hydroxyl group at the C-3'' position of leucomycins A_1, A_3, A_4 and A_5, which have strong antibacterial activities, and midecamycin[5], was fundamentally performed by the method described in the previous report[4,6,7]. Fig. 1 shows the structure of the leucomycins and midecamycin** which were used as starting materials for the syntheses. The structures of the derivatives obtained are shown in Tables 1 and 2 along with their antimicrobial activity.

Antibacterial Activity

MIC (Minimum inhibitory concentration; μg/ml) was determined by the two-fold serial agar dilution method in heart infusion agar (Difco). One loopful of an overnight culture of the test organisms in trypticase soy broth (BBL) was streaked on assay plates containing varying concentrations of the test materials, and the plates were incubated at 37°C for 20 hours.

** Midecamycin was purchased from Meiji Seika Kaisha, Ltd. and its potency was corrected with the standard sample from National Institute of Health of Japan.

Table 1. Antimicrobial activity (MIC; μg/ml)

Test organisms (Inoculum size 10^8/ml)	No.	1	2	3	4	5	6
	R_3*	Ac	Ac	Ac	Ac	Pro	Pro
	R_4	Bu	Bu	Bu	Bu	Bu	Bu
	R_1	H	Ac	H	Ac	H	Ac
	R_2	H	H	Ac	Ac	H	H
Staph. aureus ATCC 6538 P		1.6	1.6	0.8	1.6	0.8	1.6
Staph. aureus MS 353		1.6	1.6	1.6	3.1	1.6	1.6
Staph. aureus MS 353 AO (Mac^r A)		>100	>100	>100	>100	>100	>100
Staph. aureus 0116 (Mac^r A)		>100	>100	>100	>100	>100	>100
Staph. aureus 0127 (Mac^r A)		>100	>100	>100	>100	>100	>100
Staph. epidermidis sp-al-1		0.8	1.6	0.8	1.6	0.4	0.8
Strept. pyogenes N.Y. 5		0.1	0.2	0.2	0.4	≦0.05	0.2
Strept. pyogenes 1022 (Mac^r)		25	>100	12.5	>100	>100	>100
Strept. faecalis 1501		0.8	1.6	1.6	6.3	0.8	1.6
Strept. agalactiae 1020		0.2	0.4	0.4	0.8	0.2	0.2
Micro. luteus ATCC 9341		≦0.05	≦0.05	0.1	0.1	≦0.05	≦0.05
Corynebact. diphtheriae P.W. 8		≦0.05	≦0.05	≦0.05	≦0.05	≦0.05	≦0.05
Bac. subtilis ATCC 6633		0.4	0.4	0.8	0.8	0.4	0.4
E. coli NIHJ-JC 2		>100	>100	>100	>100	>100	>100
Salm. enteritidis Gaertner		>100	>100	>100	>100	>100	>100
Shigella sonnei E 33		>100	>100	>100	>100	>100	>100

Ac; $COCH_3$, Pro; $COCH_2CH_3$, Bu; $COCH_2CH_2CH_3$, *i*-Val; $COCH_2CH(CH_3)_2$

* See Fig. 1

Table 2. Antimicrobial activity (MIC; μg/ml)

Test organisms (Inoculum size 10^8/ml)	No.	15	16	17	18	19	20
	R_3	Bu	Bu	Bu	Bu	Bu	Bu
	R_4	Ac	Ac	Ac	Ac	Pro	Pro
	R_1	H	Ac	H	Ac	H	H
	R_2	H	H	Ac	Ac	H	Ac
Staph. aureus ATCC 6538 P		1.6	3.1	1.6	3.1	1.6	1.6
Staph. aureus MS 353		1.6	3.1	3.1	6.3	1.6	3.1
Staph. aureus MS 353 AO (Mac^r A)		>100	>100	>100	>100	>100	>100
Staph. aureus 0116 (Mac^r A)		>100	>100	>100	>100	>100	100
Staph. aureus 0127 (Mac^r A)		>100	>100	>100	>100	>100	>100
Staph. epidermidis sp-al-1		0.8	3.1	1.6	3.1	0.8	0.8
Strept. pyogenes N.Y. 5		0.1	0.4	0.2	0.8	0.2	0.2
Strept. pyogenes 1022 (Mac^r)		>100	>100	>100	>100	>100	>100
Strept. faecalis 1501		0.8	1.6	1.6	6.3	1.6	6.3
Strept. agalactiae 1020		0.2	0.8	0.4	0.8	0.2	1.6
Micro. luteus ATCC 9341		≦0.05	0.1	0.1	0.1	≦0.05	0.2
Corynebact. diphtheriae P.W. 8		≦0.05	0.1	0.1	0.1	≦0.05	≦0.05
Bac. subtilis ATCC 6633		0.4	0.8	0.8	1.6	0.4	1.6
E. coli NIHJ-JC 2		>100	>100	>100	>100	>100	>100
Salm. enteritidis Gaertner		>100	>100	>100	>100	>100	>100
Shigella sonnei E 33		>100	>100	>100	>100	>100	>100

of leucomycin derivatives.

7	8	9	10	11	12	13	14	LM-A_5	LM-A_3
Pro	Bu	Ac	Ac	Ac	Pro	Ac	Ac	H	H
Bu	Bu	*i*-Val	*i*-Val	*i*-Val	*i*-Val	Pro	Pro	Bu	*i*-Val
H	H	H	Ac	Ac	H	Pro	Pro	H	Ac
Ac	H	H	H	Ac	H	H	Ac	H	H
1.6	0.8	0.8	1.6	1.6	0.8	3.1	3.1	1.6	3.1
3.1	1.6	1.6	1.6	1.6	1.6	3.1	3.1	1.6	3.1
>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
>100	100	100	>100	>100	100	>100	>100	>100	>100
>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
1.6	0.8	0.8	1.6	1.6	0.8	3.1	1.6	1.6	3.1
0.4	0.2	0.1	0.1	0.2	0.1	0.4	0.2	0.1	0.2
>100	>100	100	>100	100	50	>100	>100	>100	>100
1.6	0.8	0.8	1.6	1.6		6.3	3.1	1.6	3.1
0.8	0.2	0.2	0.2	0.4	0.8	0.4	0.8	0.2	0.4
0.1	≦0.05	≦0.05	0.1	0.1	0.1	≦0.05	≦0.05	0.1	0.1
0.1	≦0.05	≦0.05	≦0.05	0.1	≦0.05	≦0.05	≦0.05	≦0.05	≦0.05
1.6	0.4	0.4	0.4	0.8	0.8	0.4	0.4	0.4	0.4
>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
>100	>100	>100	>100	>100	>100	>100	>100	>100	>100

of leucomycin derivatives.

21	22	23	24	25	26	27	LM-A_5	LM-A_3
Bu	Bu	*i*-Val	*i*-Val	*i*-Val	Pro	Pro	H	H
Pro	Bu	Ac	Ac	Ac	Ac	Ac	Bu	*i*-Val
H	H	Ac	H	Ac	Pro	Pro	H	Ac
Pro	H	H	Ac	Ac	H	Ac	H	H
3.1	1.6	3.1	3.1	3.1	6.3	6.3	1.6	3.1
3.1	3.1	3.1	3.1	3.1	6.3	6.3	1.6	3.1
>100	>100	>50	>100	>100	>100	>100	>100	>100
>100	100	>50	>100	>100	>100	>100	>100	>100
>100	>100	>50	>100	>100	>100	>100	>100	>100
1.6	1.6	3.1	1.6	6.3	3.1	3.1	1.6	3.1
0.4	0.2	0.4	0.2	0.4	0.4	0.4	0.1	0.2
>100	>100	>50	>100	>100	>100	>100	>100	>100
6.3	3.1	1.6	3.1	3.1	6.3	3.1	1.6	3.1
1.6	1.6	0.8		1.6	0.8	0.8	0.2	0.4
0.2	0.1	0.1	0.2	0.2	0.1	0.1	0.1	0.1
0.1	≦0.05	0.1	0.1	0.4	0.1	0.1	≦0.05	≦0.05
1.6	0.8	0.8	0.8	3.1	1.6	1.6	0.4	0.4
>100	>100	>100	>100	>100	>100	>100	>100	>100
>100	>100	>100	>100	>100	>100	>100	>100	>100
>100	>100	>100	>100	>100	>100	>100	>100	>100

Table 3. Antimicrobial activity (MIC; μg/ml)

Test organisms (Inoculum size 10^6/ml)	No.	1	2	3	4	5	6
	R_3	Ac	Ac	Ac	Ac	Pro	Pro
	R_4	Bu	Bu	Bu	Bu	Bu	Bu
	R_1	H	Ac	H	Ac	H	Ac
	R_2	H	H	Ac	Ac	H	H
Staph. aureus ATCC 6538 P		0.2	0.4	0.4	0.8	0.2	0.2
Staph. aureus MS 353		0.4	0.8	0.8	0.8	0.4	0.4
Staph. aureus MS 353 AO (Mac^r A)		>100	>100	>100	>100	>100	>100
Staph. aureus 0116 (Mac^r A)		6.3	50	12.5	100	12.5	50
Staph. aureus 0127 (Mac^r A)		>100	>100	>100	>100	>100	>100
Staph. epidermidis sp-al-1		0.4	0.8	0.4	0.8	0.2	0.4
Strept. pyogenes N.Y. 5		≦0.05	≦0.05	≦0.05	0.1	≦0.05	≦0.05
Strept. pyogenes 1022 (Mac^r)		0.4	1.6	0.4	0.8	0.4	0.4
Strept. faecalis 1501		0.8	1.6	0.8	1.6	0.4	0.8
Strept. agalactiae 1020		0.2	0.4	0.4	0.4	0.2	0.2
Micro. luteus ATCC 9341		≦0.05	≦0.05	≦0.05	0.1	≦0.05	≦0.05
Corynebact. diphtheriae P.W. 8		≦0.05	≦0.05	≦0.05	≦0.05	≦0.05	≦0.05
Bac. subtilis ATCC 6633		0.4	0.8	0.4	0.4	0.2	0.2
E. coli NIHJ-JC 2		>100	>100	>100	>100	>100	>100
Salm. enteritidis Gaertner		>100	>100	>100	>100	>100	>100
Shigella sonnei E 33		>100	>100	>100	>100	>100	>100

Table 4. Antimicrobial activity (MIC; μg/ml)

Test organisms (Inoculum size 10^6/ml)	No.	15	16	17	18	19	20
	R_3	Bu	Bu	Bu	Bu	Bu	Bu
	R_4	Ac	Ac	Ac	Ac	Pro	Pro
	R_1	H	Ac	H	Ac	H	H
	R_2	H	H	Ac	Ac	H	Ac
Staph. aureus ATCC 6538 P		0.4	0.8	0.8	1.6	0.4	0.8
Staph. aureus MS 353		0.8	1.6	0.8	3.1	0.4	1.6
Staph. aureus MS 353 AO (Mac^r A)		25	25	25	>100	>100	>100
Staph. aureus 0116 (Mac^r A)		50	>100	50	>100	50	50
Staph. aureus 0127 (Mac^r A)		>100	>100	>100	>100	>100	>100
Staph. epidermidis sp-al-1		0.4	0.8	0.8	1.6	0.4	0.8
Strept. pyogenes N.Y. 5		0.1	0.2	0.1	0.2	≦0.05	0.1
Strept. pyogenes 1022 (Mac^r)		6.3	25	6.3	100	1.6	1.6
Strept. faecalis 1501		0.8	1.6	0.8	3.1	0.4	1.6
Strept. agalactiae 1020		0.2	0.8	0.4	0.8	0.2	0.8
Micro. luteus ATCC 9341		≦0.05	≦0.05	0.1	0.1	≦0.05	0.1
Corynebact. diphtheriae P.W. 8		≦0.05	≦0.05	≦0.05	0.1	≦0.05	≦0.05
Bac. subtilis ATCC 6633		0.4	0.8	0.8	0.8	0.2	0.8
E. coli NIHJ-JC 2		>100	>100	>100	>100	>100	>100
Salm. enteritidis Gaertner		>100	>100	>100	>100	>100	>100
Shigella sonnei E 33		>100	>100	>100	>100	>100	>100

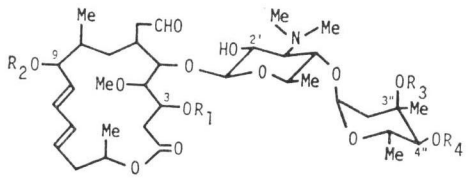
of leucomycin derivatives.

7	8	9	10	11	12	13	14	LM-A_5	LM-A_3
Pro	Bu	Ac	Ac	Ac	Pro	Ac	Ac	H	H
Bu	Bu	*i*-Val	*i*-Val	*i*-Val	*i*-Val	Pro	Pro	Bu	*i*-Val
H	H	H	Ac	Ac	H	Pro	Pro	H	Ac
Ac	H	H	H	Ac	H	H	Ac	H	H
0.4	0.4	0.4	0.4	0.8	0.4	0.4	0.4	0.4	0.4
0.8	0.4	0.4	0.8	0.8	0.8	0.8	0.8	0.8	0.8
>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
50	50	12.5	12.5	12.5	25	>100	>100	>100	>100
>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
0.4	0.4	0.4	0.4	0.8	0.4	0.8	0.8	0.8	0.8
0.1	≦0.05	0.1	0.1	0.2	0.1	0.1	0.1	0.1	0.2
0.8	0.8	0.8	0.8	0.8	0.8	3.1	3.1	>100	>100
0.8	0.8	0.8	1.6	1.6	0.8	1.6	1.6	1.6	3.1
0.4	0.2	0.2	0.2	0.8	0.4	0.4	0.4	0.2	0.4
0.1	≦0.05	≦0.05	≦0.05	≦0.05	≦0.05	≦0.05	≦0.05	≦0.05	≦0.05
≦0.05	≦0.05	≦0.05	≦0.05	≦0.05	≦0.05	≦0.05	≦0.05	≦0.05	≦0.05
0.8	0.2	0.4	0.4	0.8	0.4	0.4	0.4	0.4	0.4
>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
>100	>100	>100	>100	>100	>100	>100	>100	>100	>100
>100	>100	>100	>100	>100	>100	>100	>100	>100	>100

of leucomycin derivatives.

21	22	23	24	25	26	27	LM-A_5	LM-A_3
Bu	Bu	*i*-Val	*i*-Val	*i*-Val	Pro	Pro	H	H
Pro	Bu	Ac	Ac	Ac	Ac	Ac	Bu	*i*-Val
H	H	Ac	H	Ac	Pro	Pro	H	Ac
Pro	H	H	Ac	Ac	H	Ac	H	H
0.8	0.8	0.8	1.6	1.6	0.8	0.8	0.4	0.4
1.6	0.8	1.6	1.6	3.1	1.6	1.6	0.8	0.8
>100	>100	12.5	>100	>100	>100	>100	>100	>100
>100	50	>50	>100	>100	>100	>100	>100	>100
>100	>100	>50	>100	>100	>100	>100	>100	>100
0.8	0.8	1.6	0.8	3.1	1.6	1.6	0.8	0.8
0.2	0.1	0.2	0.2	0.2	0.2	0.1	0.1	0.2
6.3	6.3	6.3	100	100	50	12.5	>100	>100
1.6	1.6	1.6	1.6	3.1	3.1	1.6	1.6	3.1
0.8	0.4	0.4	0.4	0.8	0.8	0.4	0.2	0.4
0.1	≦0.05	≦0.05	0.1	0.2	≦0.05	≦0.05	≦0.05	≦0.05
≦0.05	≦0.05	≦0.05	≦0.05	≦0.05	≦0.05	≦0.05	≦0.05	≦0.05
0.8	0.4	0.8	0.8	3.1	0.8	0.4	0.4	0.4
>100	>100	>100	>100	>100	>100	>100	>100	>100
>100	>100	>100	>100	>100	>100	>100	>100	>100
>100	>100	>100	>100	>100	>100	>100	>100	>100

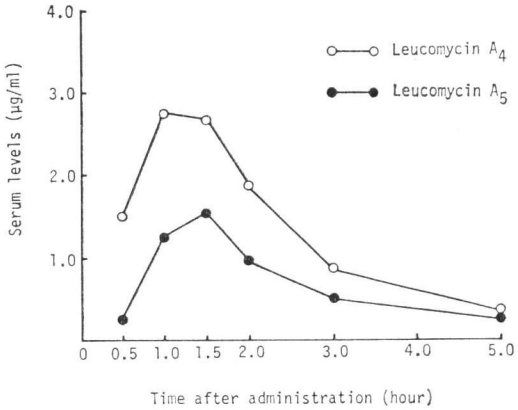
Fig. 1. Structure of leucomycins and midecamycin.



	R_1	R_4
Leucomycin A_1 (LM-A_1)	H	$COCH_2CH(CH_3)_2$
〃 A_3 (LM-A_3)	$COCH_3$	$COCH_2CH(CH_3)_2$
〃 A_4 (LM-A_4)	$COCH_3$	$CO(CH_2)_2CH_3$
〃 A_5 (LM-A_5)	H	$CO(CH_2)_2CH_3$
〃 U (LM-U)	$COCH_3$	H
〃 V (LM-V)	H	H
Midecamycin (MDM)	$COCH_2CH_3$	$COCH_2CH_3$
4″-Depropionyl-midecamycin (SF-837 M_1)	$COCH_2CH_3$	H

$R_2=R_3=H$

Fig. 2. Apparent serum levels* as antimicrobial activity of leucomycin A_4 and leucomycin A_5 in dogs (beagle) after oral administration (50 mg/kg).



* The mean value in 6 dogs is indicated.

Serum Levels in Beagle Dogs and Pigs

A single dose of 50 mg/kg was given orally to beagle dogs (10.0±1.0 kg), while a single dose of 30 mg/kg was given orally to pigs (16±2.0 kg). Blood samples were withdrawn from the antebrachium median vein (dog) or the jugular vein (pig) at the indicated times, and centrifuged at 3,000×*g* for 10 minutes to obtain serum. Antibiotic concentrations in the serum were bioassayed by the paper disk method using *Micrococcus luteus* ATCC 9341 as test microorganism.

Results and Discussion

Antibacterial Activity of 3-*O*-, 9-*O*-, 3″-*O*- and 4″-*O*-Acyl Derivatives of Leucomycins and Midecamycin

Tables 1 to 4 show the MICs of the derivatives prepared by introducing various acyl groups into hydroxyl groups at the C-3, C-9, C-3″ and C-4″ positions of leucomycins and midecamycin. The test organisms used were 13 Gram-positive bacteria and 3 Gram-negative bacteria, including macrolide-resistant strains, *Staphylococcus aureus* MS 353 AO, *Staphylococcus aureus* 0116, *Staphylococcus aureus* 0127 and *Streptococcus pyogenes* 1022.

3″-*O*-Acylations increase the antibacterial activity not only against sensitive bacterial strains but against some of the resistant strains; the increase of antibacterial activity by 3″-*O*-acylation depends on the length of the acyl groups introduced and on the 4″-*O*-acyl group. In leucomycin A_5, in which a butyryl group is attached to the 4″-hydroxyl group, the activity is increased when an acetyl or propionyl group is introduced at the 3″-hydroxyl group (compounds **1** and **5**), while the activity is rather depressed when a butyryl group is so attached. When using leucomycin A_1 as a starting material in which an *iso*-valeryl group is attached to the 4″-hydroxyl group, the 3″-*O*-acetyl derivative (compound **9**) is slightly more active *in vitro*, as compared with leucomycin A_5, while the 3″-*O*-propionyl derivative (compound **12**) remains almost the same. Thus, the increase of the antibacterial activities caused by the acylation of the 3″-hydroxyl group is larger in leucomycin A_5 than in leucomycin A_1. Among the derivatives shown in Table 1, 3″-*O*-propionylleucomycin A_5 (**5**) has the strongest anti-

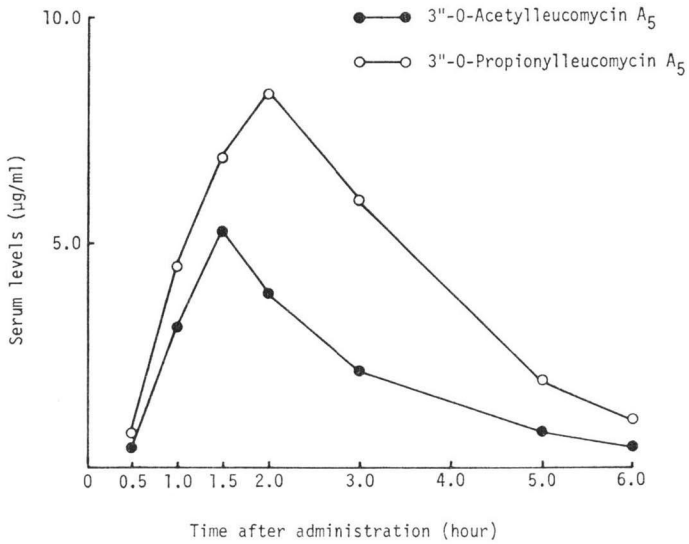
bacterial activity.

In 3''-*O*-acyl derivatives, the antibacterial activity is depressed by additional 3-*O*- and/or 9-*O*-acylations, as is consistent with the results reported by ŌMURA *et al.*[3]

Serum Levels of 3''-*O*-Acetylleucomycin A_5 (**1**) and 3''-*O*-Propionylleucomycin A_5 (**5**)

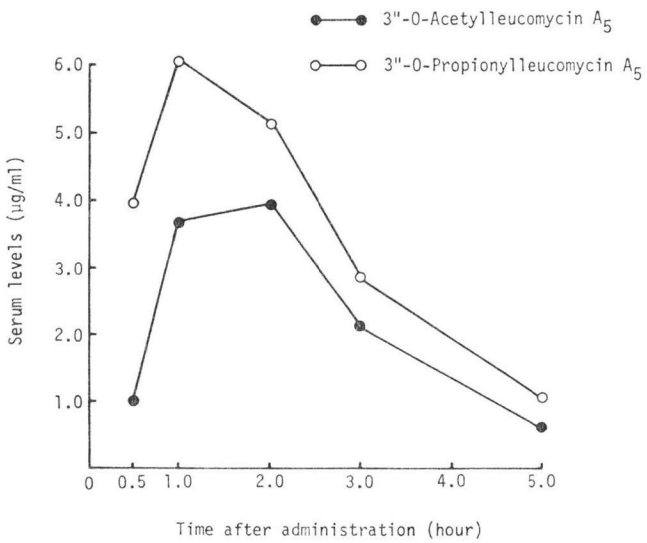
It has been reported that the serum levels of orally given 3-*O*-acyl leucomycins were generally higher

Fig. 3. Apparent serum levels* as antimicrobial activity of 3''-*O*-acetylleucomycin A_5 (**1**) and 3''-*O*-propionylleucomycin A_5 (**5**) in dogs (beagle) after oral administration (50 mg/kg).



* The mean value in 6 dogs is indicated.

Fig. 4. Apparent serum levels* as antimicrobial activity of 3''-*O*-acetylleucomycin A_5 (**1**) and 3''-*O*-propionylleucomycin A_5 (**5**) in pigs after oral administration (30 mg/kg).



* The mean value in 7 pigs is indicated.

than those of 3-hydroxyl leucomycins[2]. In the present experiments, the serum level of leucomycin A_4 (3-*O*-acetyl) was higher in dogs than that of leucomycin A_5 (3-hydroxyl) (Fig. 2). The serum levels of 3''-*O*-acetylleucomycin A_5 (**1**) and 3''-*O*-propionylleucomycin A_5 (**5**), which showed the highest *in vitro* antibacterial activity among the derivatives examined, were determined using dogs and pigs as test animals (Figs. 3 and 4). Drug absorption in these animals is rather close to that in human beings. In dogs, the serum level was higher in compounds **1** and **5** than in leucomycin A_4. Thus, the serum level was more elevated after acylation of the 3''-hydroxyl group than by that of the 3-hydroxyl group. In both dogs and pigs, the serum level of compound **5** was higher than that of compound **1**.

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