Long-Chain Carboxylic Acids Containing Ether Linkage: III. The Antibacterial and Antifungal Activities of the Amine Salts of Some β-Alkoxypropionic Acids

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Abstract

Octylamine, dodecylamine, octadecylamine and triethanolamine salts of β-dodecyloxy- and β-tetradecyloxypropionic acids, without or with one and with two oxyethylene groups between the alkoxy group and the propionic acid group, were prepared and examined as the growth inhibiting agents against *Staphylococcus aureus* and *Penicillium*. Some of them were also tested against *Trichophyton asteroides, T. interdigitale, T. granulosus, Epidermophyton floccosum* and *Microsporum canis*. The effects of the alkyloxy, oxyethylene and amine groups on antibacterial and antifungal activities were determined. The dodecyl radical was more potent than the tetradecyloxy radical. The enhancing effect of the oxyethylene group was obscure in the amine salts. The most effective amine was dodecylamine and its salt of β-dodecyloxypropionic acid showed almost the same effectiveness as that of its mercury salt against *Trichophyton*. As for the soluble amine salts, it was confirmed that their surface activities had nothing to do with their antibacterial and fungicidal powers.

Introduction

It has been reported that the β-alkyloxypropionic acids, $RO(CH_2CH_2O)_nCH_2CH_2COOH$, their methyl esters (1), and heavy metal salts (2) were more active than the corresponding normal fatty acids against some microbes. Generally, β-dodecyloxypropionic acid grouping seemed to contribute antibacterial and antifungal activity.

In the present work some amine salts of β-dodecyl- and β-tetradecyloxypropionic acids were tested for their antibacterial and antifungal powers.

Since long-chain amine salts have known germicidal powers (3–5) it was of interest to prepare and examine microbiologically some amine salts of β-alkoxypropionic acids.

Experimental Procedures

Materials

β-Alkyloxypropionic acids were prepared by the cyanoethylation of the corresponding alcohols followed by hydrolysis, as stated in a previous report (1).

TABLE I
The Physical Properties of β-Tetradecyloxypropionic Acids ($C_{14}H_{29}-(OCH_2CH_2)_n-OCH_2CH_2COOH$) and Starting Alcohols[a]

β-Tetradecyloxypropionic Acid				Alcohol	
		Neutr. V.			
n	Mp, C	Found	Calculated	Bp, C/mmHg	n_D^{45}
0	58.5–60.0	185.7	196.0	129–31/2	1.4391
1	43.0– 4.5	161.5	169.8	149–50/1	1.4410
2	37.8– 9.0	144.9	149.8	163– 9/0.5	1.4431

[a] The physical characteristics of β-dodecyloxypropionic acids and starting alcohols have been previously reported (1).

The starting dodecyl and tetradecyl alcohols were purified carefully by fractional distillation in vacuo of commercially available alcohols and their purities were checked by gas liquid chromatography (GLC). The purities of alcohols were 99.3% and 97.8%, respectively, as measured by GLC. 2-Oxyethyl and 2-(2-oxyethyl) oxyethyl ethers were prepared in the conventional base-catalyzed procedure from the corresponding alcohols and ethylene oxides, and purified as described previously (1).

Triethanolamine, which was reagent grade, was reacted without distillation. Other amines were the highest grade of Kao Soap products; they were distilled right before the reaction with β-alkoxypropionic acids. Their purities varied from 97.5% to 100% as measured by GLC. The boiling point and refractive index of the β-tetradecyloxypropionic acids along with the corresponding starting alcohols are shown in Table I.

Preparation of Amine Salts

The amine salts of β-alkyloxypropionic acid were prepared by the solvent recrystallization method described by Mod, Magne and Skau (6) from β-alkyloxypropionic acid and freshly prepared fatty amine or triethanolamine. Almost all amine salts were obtained as white crystals with melting points as given in Table II, which also shows nitrogen analysis data. The octylamine salts of dodecyloxyethyloxyethyloxy- and tetradecyloxyethyloxyethyloxypropionic acids had rather high solubilities, and even though they were separated and recrystallized at temperatures under −30 C, they could not be obtained in the pure state.

Antibacterial and Antifungal Study

Antibacterial and antifungal evaluations were carried out by a dilution method as described previously

TABLE II
Melting Points and Nitrogen Analysis Data of the Amine Salts of β-Alkoxypropionic Acids: $R-(OCH_2CH_2)_n-OCH_2CH_2COOH\cdot amine$

R	n	Amines	Mp, C	N Contents, %	
				Found	Calculated
$C_{12}H_{25}$	0	Octyl	44.0–5.5	3.57	3.61
	1		30.0–1.7	2.92	3.25
	2		.....	.....	2.94
$C_{14}H_{29}$	0		57.8–8.6	3.27	3.37
	1		43.4–4.9	2.94	2.85
	2		.....	.....	2.78
$C_{12}H_{25}$	0	Dodecyl	66.7–8.0	3.06	3.15
	1		48.3–9.1	2.89	2.87
	2		33.2–3.9	2.77	2.68
$C_{14}H_{29}$	0		67.5–8.1	2.94	2.97
	1		51.9–2.8	2.64	2.56
	2		37.2–8.2	2.49	2.50
$C_{12}H_{25}$	0	Octadecyl	82.0–2.6	2.70	2.65
	1		72.1–2.6	2.58	2.45
	2		57.8–8.3	2.27	2.27
$C_{14}H_{29}$	0		86.2–7.2	2.54	2.52
	1		73.5–4.4	2.38	2.22
	2		57.8–8.1	2.24	2.18
$C_{12}H_{25}$	0	Triethanol	59.0–9.7	3.28	3.44
	1		60.1–1.0	3.16	3.10
	2		43.5–4.2	2.78	2.83
$C_{14}H_{29}$	0		66.8–7.8	3.22	3.22
	1		65.5–6.4	2.91	2.92
	2		47.7–9.9	2.61	2.68

TABLE III

The Minimum Inhibitory Concentrations (γ/ml) of Amine Salts of β-Dodecyloxy-, and β-Tetradecyloxypropionic Acids for *Staphylococcus aureus* 209-p and *Penicillium* 408–701

Tested microbes	Amine	R / n	$C_{12}H_{25}$			$C_{14}H_{29}$			Lauric[a] acid
			0	1	2	0	1	2	
S[b]	Octyl		100	50	50	500	500	.....	500
P[c]	Octyl		100	50	100	10^3	10^3	.....	100
S	Dodecyl		10	50	50	50	50	50	10
P	Dodecyl		10	100	50	50	500	500	50
S	Octadecyl		500	100	100	10^3	10^3	500	100
P	Octadecyl		10^3	10^3	10^3	10^3	10^3	10^3	10^3
S	Triethanol		500	100	50	10^3	500	10^3	500
P	Triethanol		10^3	250	250	10^3	10^3	10^3	500

[a] For comparison.
[b] *Staphylococcus aureus* 209-P; Incubation period: 24 hr at 37 C.
[c] *Penicillium* 408–701; Incubation period: 48 hr at 27 C.

(1). Activities against *S. aureus* 209-P and *Penicillium* 408–701 are summarized in Table III and activities against *T. asteroides, T. interdigitale, T. granulosus, E. floccosum,* and *M. canis* in Table IV.

Surface Activity

Some of the amine salts were readily soluble in water, and some of them dissolved with difficulty. The soluble amine salts were examined from the point of view of their behavior as surface active agents. The surface tensions of aqueous solutions were measured with the Wilhelmy tensiometer at 23 ± 1 C. Results are shown in Figure 1 (octylamine salts) and Figure 2 (triethanolamine salts).

TABLE IV

The Minimum Inhibitory Concentration (γ/ml) of Amine Salts of β-Dodecyloxypropionic Acid for *Trichophyton, Epidermophyton* and *Microsporum*[a]

Amine	*T. asteroides*	*T. interdigitale*	*T. granulosus*	*E. floccosum*	*M. canis*
Octyl	12.5	12.5	12.5	12.5	12.5
Dodecyl	6.25	6.25	6.25	6.25	6.25
Octadecyl	6.25	6.25	6.25	6.25	6.25
Triethanol	12.5	25.0	25.0	12.5	12.5

[a] Incubation period: 7 days at 27 C.

Results and Discussion

From Table III, it can be seen that the β-dodecyloxypropionic acid series was more active than β-tetradecyloxypropionic acid against *Staphylococcus* and *Penicillium.* The relationship of the enhancement of the inhibiting activity of these amine salts to the increase in the number of oxyethylene groups was not clear. Only the triethanol amine salts of β-dodecyloxypropionic acid tended to exhibit an enhancing effect, as previously noted with the acids and their methyl esters with increase in number of oxyethylene groups. The activities of salts also varied with the kinds of amines. The optimum in vitro activity was shown in the dodecylamine salts. The greatest inhibiting power against some *Trichophyton, Epidermophyton* and *Microsporum* was shown by the dodecylamine and octylamine salts (Table IV). And, it is worth noting, that dodecyl- and octylamine salts

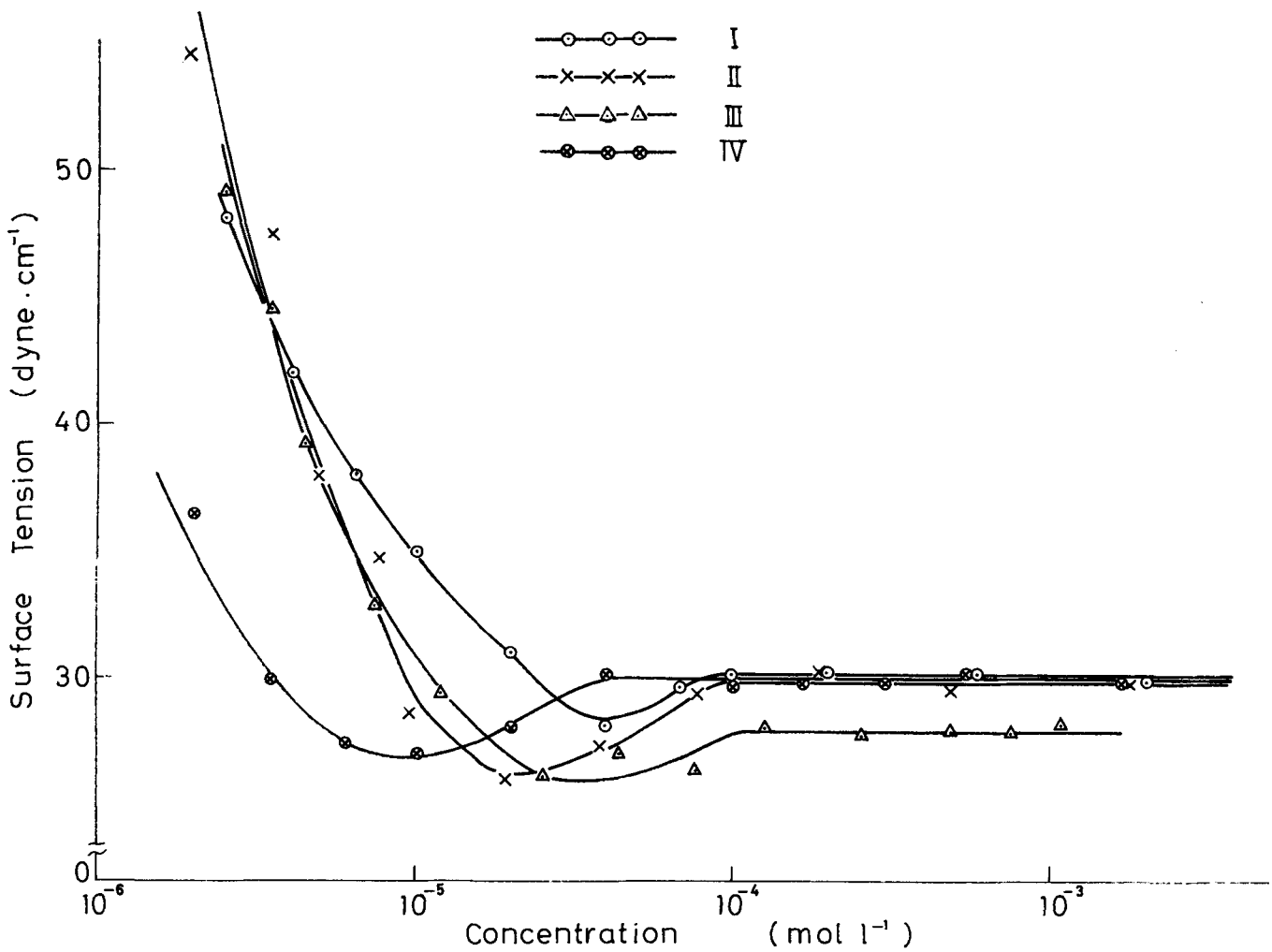

FIG. 1. Surface tension—concentration curves of the aqueous solutions of octylamine salts of β-dodecyloxy- and tetradecyloxypropionic acids. I: $C_{12}H_{25}OCH_2CH_2CO_2H \cdot C_8H_{17}NH_2$; II: $C_{12}H_{25}(OCH_2CH_2)_2COOH \cdot C_8H_{17}NH_2$; III: $C_{14}H_{29}OCH_2CH_2CO_2H \cdot C_8H_{17}NH_2$; IV: $C_{14}H_{29}(OCH_2CH_2)_2COOH \cdot C_8H_{17}NH_2$.

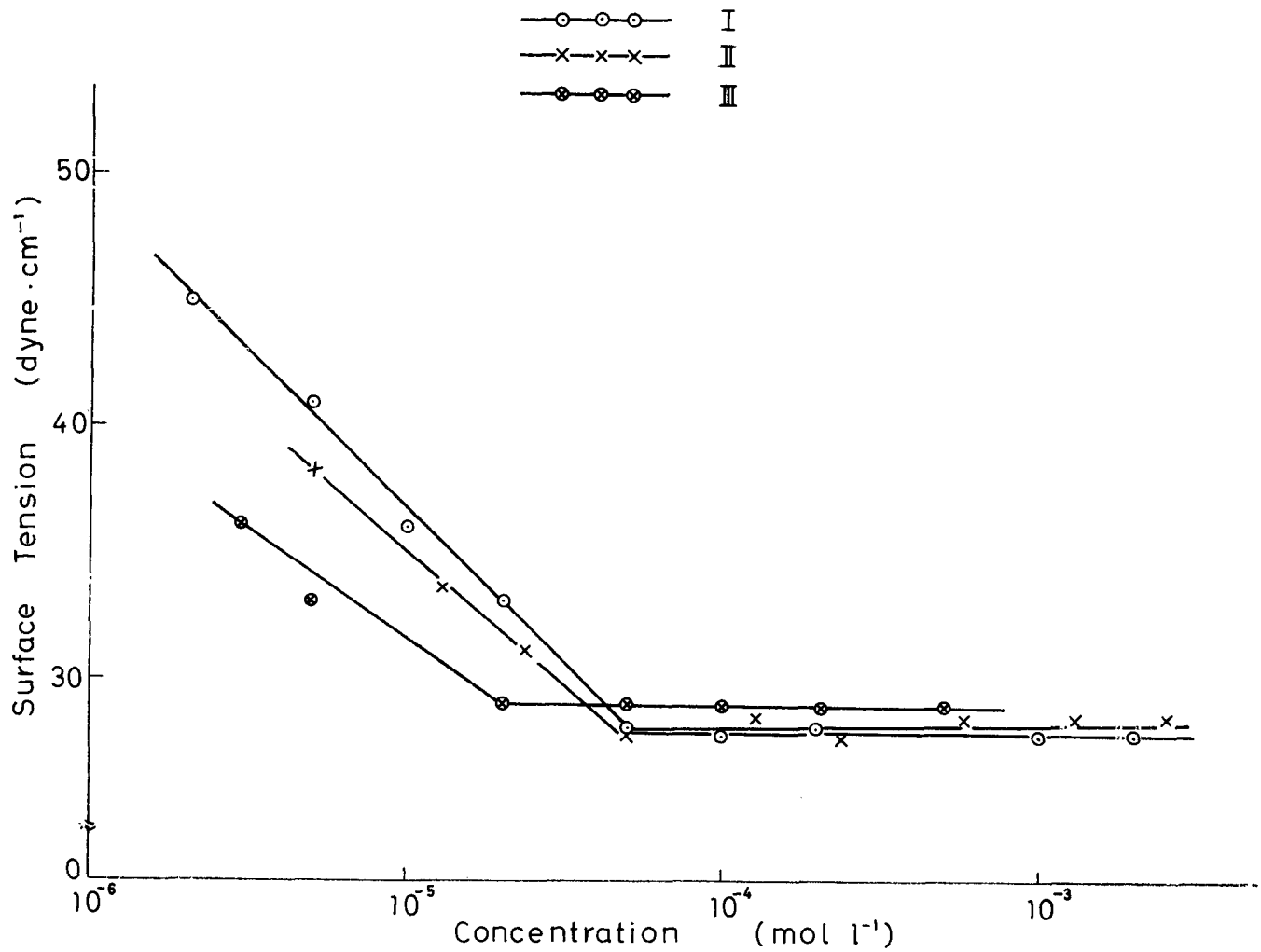

FIG. 2. Surface tension—concentration curves of the aqueous six solutions of triethanolamine salts of β-dodecyloxy- and tetradecyloxy-propionic acids. I: $C_{12}H_{25}OCH_2CH_2CO_2H \cdot (HOCH_2CH_2)_3N$; II: $C_{12}H_{25}(OCH_2CH_2)_2CO_2H \cdot (HOCH_2CH_2)_3N$; III: $C_{14}H_{29}(OCH_2CH_2)_2CO_2H \cdot (HOCH_2CH_2)_3N$.

have almost the same effectiveness as the mercury salt against the tested microbes.

As shown in the surface tension-concentration curves on the aqueous solution of these soluble salts, the breaking points were obtained at about 10^{-4} mole/liter, and it was deviated to the lower concentration as the number of oxyethylene groups in the same series. β-Tetradecyloxypropionic acid salts were less surface active than the corresponding salts of β-dodecyloxypropionic acids. Moreover, it was found that the surface activities of these amine salts were not directly related to their biological activities.

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REFERENCES

1. Abe, Y., Lipids *1*, 141–145 (1966).
2. Abe, Y., and T. Sakurada, Specialities (London), *2*, 11–12 (1966).
3. Schwartz, A. M., and J. W. Perry, "Surface Active Agents," Vol. 1, Interscience Publishers, Inc., New York, 1949, p. 153; A. M. Schwartz, J. W. Perry and J. Berch, "Surface Active Agents," Vol. 2, 1958, p. 240.
4. Coan, S. B., and D. Papa, J. Am. Chem. Soc. *77*, 2402–2404 (1955).
5. Shimo, M., M. Kono, E. Fukuzumi, H. Kato, H. Yamaguchi and Y. Kidokoro, Shokuhin Eiseigaku Zassi *7*, 55–59 (1966).
6. Mod, R. R., F. C. Magne and E. L. Skau, JAOCS *36*, 616–619 (1959).

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