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Chemical and Biochemical Studies on Carbohydrate Esters. II.[1] Antitumor Activity of Saturated Fatty Acids and Their Ester Derivatives against Ehrlich Ascites Carcinoma[2]

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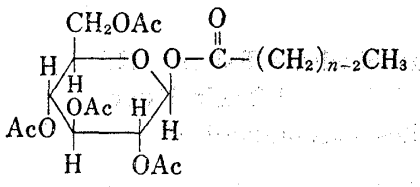
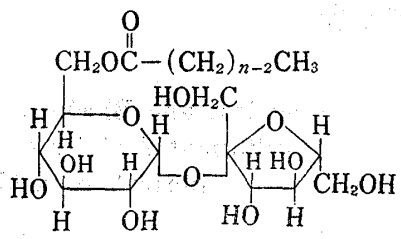
Antitumor activity of normal saturated monocarboxylic acids and their ester derivatives was examined with Ehrlich ascites carcinoma in mice. The samples used were a) a series of fatty acids ranging in carbon chain length from C_3 to C_{18}, that is, propionic, butyric, valeric, caproic, caprylic, pelargonic, capric, lauric, myristic, palmitic, and stearic acids, b) their methyl esters, c) 1-O-acyl-β-D-glucopyranose tetraacetates derived from these fatty acids, and d) the so-called "sucrose monoesters" of caprylic, lauric, and myristic acids. Each agent was administered to mice by intraperitoneal injection at the dose of 400 mg/kg/day ×5, and the effect was evaluated with total packed cell volume ratio on the 7th day after the tumor implantation. Among eleven fatty acids tested, lauric and myristic acids were highly effective, while others were either ineffective or toxic. On the other hand, the methyl esters corresponding to the antitumor inactive fatty acids with a carbon chain length of C_6 to C_{10} were found to possess significant effect. The most prominent activity was exhibited with methylcaprylate. All members of the group c proved to show negligible antitumor effect. In contrast, the sucrose monoesters, especially myristate, have been suggested to exert marked activity, although their strong toxicity could not be overlooked.

The present paper reports the results obtained when saturated normal monocarboxylic acids and their ester derivatives were tested for antitumor activity against Ehrlich ascites carcinoma in mice. The samples used in this study are divided into four groups: a) free fatty acids ranging in carbon chain length from C_3 to C_{18}, that is, propanoic (propionic), butanoic (butyric), pentanoic (valeric), hexanoic (caproic), octanoic (caprylic), nonanoic (pelargonic), decanoic (capric), dodecanoic (lauric), tetradecanoic (myristic), hexadecanoic (palmitic), and octadecanoic (stearic) acids, b) their methyl esters, c) a series of 1-O-acyl-β-D-glucopyranose tetraacetates (I—XI) (Chart 1) derived from these fatty acids, and d) the so-called "sucrose monoesters" of caprylic, lauric, and myristic acids. Preparation procedures and physical properties of the compounds belonging to the group c have been reported in our previous paper.[1] The sucrose monoesters were synthesized according to the method of Osipow,[5] namely by transesterification between sucrose and the methyl ester of an appropriate fatty acid in dimethylformamide using pottasium carbonate as an alkaline catalyst. Evaporation of the reaction mixture, followed by washing with *n*-hexane for complete removal of unreacted methyl ester of fatty acid, afforded the product called preparation A, which contained a variety of sucrose esters along with the catalyst added and a considerable amount of unesterified sucrose. By extracting the preparation A with acetone and then with butanol, a further

1) Part I: Y. Nishikawa, K. Yoshimoto, K. Michishita, and G. Kurono, *Chem. Pharm. Bull.* (Tokyo), **23**, 597 (1975).
2) This work was presented at the 94th Annual Meeting of the Pharmaceutical Society of Japan, Sendai, April, 1974.
3) The author to whom inquiries should be addressed.
4) Location: *a) 13–1 Takaramachi, Kanazawa, 920,* Japan; *b) 5–1–1 Tsukiji, Chuo-ku, Tokyo, 104, Japan.*
5) L. Osipow, F.D. Snell, W.C. York, and A. Finchler, *Ind. Eng. Chem.*, **48**, 1459 (1956).



Compd. No.: I II III IV V VI VII VIII IX X XI
n : 3 4 5 6 8 9 10 12 14 16 18
Chart 1



Compd. No.: XII XIII XIV
n : 8 12 14
Chart 2

purified preparation, which was almost free from the catalyst and sucrose, was obtained and designated as preparation B. As revealed in our preliminary examination, preparation B is predominantly composed of isomers of monoesters, accompanying with small amounts of di- and poly-esters.[6] By application of column chromatography, a fraction, named preparation C, consisting solely of a mixture of monoesters was separated from the minor fractions of highly substituted derivatives. For antitumor assay of the sucrose monoesters, the preparations A, B, and C of different purity thus prepared from each fatty acid were employed. Among the sucrose monoesters produced, the major component has been determined as an isomer where the fatty acyl function is attached to the primary hydroxyl group at C_6 of the glucose moiety (XII, XIII, or XIV (Chart 2)).[6] In addition, presence of monoesters bearing the acyl group at either 1′ or 6′ position of the fructose unit, as well as of some unidentified positional isomers, albeit in trace amounts, was also found to be detectable.[6] Throughout the present work, the agents to be tested were administered to mice by intraperitoneal injection, and the antitumor effect was evaluated with total packed cell volume ratio (TPCV ratio; % T/C) on the 7th day after tumor implantation. Unless otherwise stated, 400 mg/kg/day × 5 was adopted as the standard dosage. Some samples which proved to exert marked activity at this dose were further subjected to the dose response assay.

Materials and Methods

Materials——All fatty acids and the methyl esters used in the present study were of the highest purity available commercially (Tokyo Kasei Kogyo Co., Ltd., and Wako Pure Chemical Industries, Ltd.). The purity of these chemicals was satisfactory from the gas chromatography, so they were used without further purification. As reported in our previous paper,[1] 1-O-acyl-β-D-glucopyranose tetraacetates (I—XI) were prepared by condensation of the silver salt of an appropriate fatty acid with α-acetobromoglucose (2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide). Synthesis of the sucrose monoesters of caprylic, lauric, and myristic acids (major products: XII, XIII, and XIV, respectively) was carried out according to the method of Osipow.[5] Well-dried sucrose (3 moles) was dissolved in dimethylformamide, and a methyl ester of fatty acid (1 mole) was added with K_2CO_3 (0.1 mole) as an alkaline catalyst. The reaction mixture was maintained at 90—95° under 80—100 mmHg pressure with stirring. After 6 to 9 hr, the solvent was distilled off *in vacuo* to give a solid mass, which was washed thoroughly with *n*-hexane for removal of the unreacted methyl ester of fatty acid and then dried over silica gel in a desiccator. A slightly brownish powder, preparation A, thus obtained was extracted first with acetone and then with *n*-BuOH by heating on a water-bath, and while hot, the undissolved materials (K_2CO_3 and recovered sucrose) were filtered off. The combined extracts were evaporated to dryness under reduced pressure to yield preparation B as a hygroscopic powder. The composition of preparation B was analysed by thin-layer chromatography (TLC), using the conditions developed by Kinoshita[7]: adsorbent, Silica Gel G; solvent system, $CHCl_3$: MeOH: AcOH: H_2O (79: 11: 8: 2). Each preparation B gave one large spot with low *Rf* value due to monoester isomers and several much smaller spots with higher *Rf* values which were attributable to di-, tri-, and poly-esters: *Rf* values of monocaprylate, monolaurate, and monomyristate were 0.09, 0.13, and 0.15, respectively. Thus the preparation B was column chromatographed over Silica Gel with the same solvent system as employed in TLC analysis, and the fraction

6) The results were presented at the 95th Annual Meeting of the Pharmaceutical Society of Japan, Mukogawa, April, 1975.
7) S. Kinoshita, "Thin-Layer Chromatography, II," (an extra issue (No. 64) of the *Kagaku No Ryoiki*), ed. by S. Hara, O. Tanaka, and S. Takitani, Nankodo, Co., Ltd., Tokyo, 1964, p. 79.

corresponding to monoesters was collected to furnish the preparation C as an almost colorless hygroscopic powder.

Determination of Antitumor Activity——Female ddY mice weighing 23±2 g were used, and 0.05 ml (7×10^6 cells/mouse) of seven-day-old Ehrlich ascites carcinoma was inoculated intraperitoneally. For preparation of the uniform suspensions, N-saline with 0.2% Tween 80 was used as a vehicle, when the agents to be tested were free fatty acids, methyl esters, or 1-O-acyl-β-D-glucopyranose tetraacetates (I—XI), since all of them, except some lower fatty acids, were insoluble in water. The sucrose monoester preparations were readily soluble in water, and hence test samples of this group were dissolved in N-saline without containing the detergent. No significant difference could be observed in the tumor growth between the control mice treated with the saline containing Tween 80 and those which received the saline without containing it. Treatment was initiated 24 hr after tumor implantation, the test compounds being given by intraperitoneal injection once daily for 5 consecutive days at the standard dosage of 400 mg/kg/day ×5. The antitumor activity of the sample was evaluated with TPCV (TPCV (ml) = volumes of ascites (ml) × ascitocrit) ratio on the 7th day after the tumor implantation. Results were evaluated as follows:

Evaluation	##	#	+	−
TPCV ratio (% *T/C*)	0—10	11—40	41—65	66—100

Results

The antitumor activity of free fatty acids, their methyl esters, and 1-O-acyl-β-D-glucopyranose tetraacetates (I—XI) is shown in Tables I, II, and III, respectively.

Of eleven free fatty acids tested, lauric (C_{12}) and myristic (C_{14}) acids exerted remarkable antitumor effect, while others were completely or nearly ineffective; although the fatty acids of shorter chain length from C_3 to C_5 were, as expected, too toxic to be determined their TPCV ratios (Table I).

As can be seen in Table II, esterification of the fatty acids by a methyl group significantly altered the antitumor activity of the parent compounds. The strong effect of free lauric and myristic acids was almost completely prevented by methyl substitution. In contrast, marked activity was exhibited in the methyl esters which correspond to the antitumor ineffective fatty acids having carbon numbers from 6 to 10. It is of interest that there appears to be a strict relationship between the intensity of the antitumor activity of the methyl derivatives

Table I. Antitumor Activity of Free Fatty Acids

Compd.	TPCV ratio (% *T/C*)	Evaluation of activity	Body wt. change (g)		Deaths/Total	
			Treated	Control	Treated	Control
Propionic	highly toxic		n.d.[a]	−0.1	6/6	1/6
Butyric	highly toxic		n.d.	+1.3	6/6	1/6
Valeric	highly toxic		n.d.	+1.3	6/6	1/6
Caproic	83.8	−	−1.4	−0.7	2/6	0/6
Caprylic	125.0	−	+0.5	−0.7	2/6	0/6
Pelargonic	107.8	−	−1.8	+0.1	0/6	0/6
Capric	76.6	−	−1.5	+0.1	0/6	0/6
Lauric	0.5[b]	##	−3.1	+0.1	0/6	0/5
	6.1	##	−2.5	−0.8	1/6	0/6
Myristic	0.0	##	−1.4	−1.3	0/6	0/6
	12.1	#	−0.7	+0.2	0/6	0/6
Palmitic	44.6[b]	+	−2.2	+0.1	0/6	0/5
	51.9	+	−1.3	+0.1	0/6	0/6
	68.5	−	−0.8	+0.2	0/6	0/6
Stearic	90.0	−	−3.1	−1.3	1/6	0/6

a) n.d.=not determined
b) ddN Mice, instead of ddY strain, were used.

Table II. Antitumor Activity of Methyl Esters of Fatty Acids

Compd.	TPCV ratio (% T/C)	Evaluation of actiivty	Body wt. change (g)		Deaths/Total	
			Treated	Control	Treated	Control
Propionate	144.5	−	−3.2	−0.1	0/6	1/6
Butyrate	54.4	+	−3.1	+1.3	3/6	1/6
Valerate	52.0	+	−3.5	+1.3	4/6	1/6
Caproate	15.4	++	−2.1	−0.7	1/6	0/6
Caprylate	4.0	+++	−1.6	−0.7	2/6	0/6
	7.6	+++	−2.3	−0.6	0/6	0/6
Pelargonate	30.5	++	−0.9	+0.1	1/6	0/6
Caprate	34.4	++	+0.3	+0.1	0/6	0/6
Laurate	58.2	+	+1.1	−0.8	1/6	0/6
Myristate	103.7	−	−0.3	−1.3	0/6	0/6
Palmitate	99.4	−	−1.7	+0.1	2/6	0/6
Stearate	155.0	−	−0.6	−1.3	1/6	0/6

Table III. Antitumor Activity of 1-O-Acyl-β-D-glucopyranose Tetraacetates (Compounds I—XI)

Compd. No.	Acyl	TPCV ratio (% T/C)	Evaluation of activity	Body wt. change (g)		Deaths/Total	
				Treated	Control	Treated	Control
I	propionyl	178.2	−	−2.7	−0.1	1/6	1/6
II	butyryl	91.8	−	−1.2	+1.3	0/6	1/6
III	valeryl	107.0	−	−0.2	+1.3	0/6	1/6
IV	caproyl	121.3	−	+0.9	−0.7	0/6	0/6
V	capryloyl	139.0	−	+0.02	−0.7	0/6	0/6
VI	pelargonoyl	59.4	+	−3.1	−0.8	4/6	0/6
VII	caprinoyl	92.3	−	−3.2	−2.6	0/6	0/6
VIII	lauroyl	89.7	−	−2.6	−0.8	2/6	0/6
IX	myristoyl	144.0	−	−2.4	−1.3	0/6	0/6
X	palmitoyl	85.2	−	−3.2	−2.6	3/6	0/6
XI	stearoyl	100.9	−	−3.4	−1.3	0/6	0/6

and the number of carbon atoms contained in their molecules. The greatest activity, which was of found with methyl caprylate, an ester of C_8-acid, tended to decrease regressively with either increasing or decreasing chain length of the parent fatty acids.

On the other hand, all members of the series belonging to 1-O-acyl-β-D-glucopyranose tetraacetates (I—XI) were demonstrated, without exception, to possess negligible effect against the Ehrlich ascites tumor (Table III). It was conceivable that the ineffectiveness might be caused by the absence of free hydroxyl groups in the carbohydrate moiety of these compounds.

Accordingly, our investigation was next directed towards testing the antitumor activity of so-called sucrose monoesters of fatty acids. Application of this type of derivatives to the biological studies of fatty acids has recently been recommended by Arima, *et al.*, since they are water soluble and, therefore, can provide reproducible results without interferance from the sparing solubility of higher fatty acids.[8] On the basis of the data presented in Tables I

8) *a*) A. Kato, K. Ando, G. Tamura, and K. Arima, *Cancer Res.*, **31**, 501 (1971); *b*) A. Kato and K. Arima, *Biochem. Biophys. Res. Comm.*, **42**, 596 (1971); *c*) A. Kato, K. Ando, S. Suzuki, G. Tamura, and K. Arima, "Progress in Antimicrobial and Anticancer Chemotherapy, Proceedings of the 6th International Congress of Chemotherapy, Tokyo, Japan," Vol. II, ed. by H. Umezawa, University of Tokyo Press, Tokyo, 1970, p. 142.

and II, we chose caprylic, lauric, and myristic acids as the compounds to be combined with sucrose. From each fatty acid selected, sucrose monoester preparations A, B, and C, except preparation C of caprylate, were prepared according to the procedures described above. The three preparations were different in their monoester concentrations: A<B<C. The antitumor activity of the crude preparations A and B was tested at the standard dose of 400 mg/kg/day×5, while that of the purified preparation C was assayed under the less dosage of 250 mg/kg/day×5. Although frequent death prior to the evaluation of the activity was encountered in the mice treated with these preparations, it has been suggested from the results

Table IV. Antitumor Activity of Sucrose Monoester Preparations of Caprylic, Lauric, and Myristic Acids (Predominant Components; XII, XIII, and XIV, respectively)

Sample	Dose (mg/kg/day)	TPCV ratio (% T/C)	Evaluation of activity	Body wt. change (g)		Deaths/Total	
				Treated	Control	Treated	Control
Sucrose monocaprylate							
preparation A	400×5	75.2	−	−0.5	+0.5	0/6	1/6
preparation B	400×5	35.6	++	−0.7	+0.5	4/6	1/6
Sucrose monolaurate							
preparation A	400×5	34.0	++	−1.9	−0.9	1/6	0/6
preparation B	400×4[a]		toxic	−3.7	−0.9	6/6	0/6
preparation C	250×5	24.5	++	−3.7	−0.9	4/6	0/6
Sucrose monomyristate							
preparation A	400×5	47.0	+	−1.1	−0.9	1/6	0/6
preparation B	400×5	1.0	+++	−0.5	−0.9	2/6	0/6
preparation C	250×5	0.0	+++	−4.2	−0.6	5/6	0/6

a) All mice died prior to the fifth injection.

shown in Table IV that the sucrose monoesters, especially myristate, might be highly effective against Ehrlich ascites carcinoma. It is probable that the antitumor activity and the strong toxicity depend chiefly, if not entirely, upon the predominant component, XII, XIII, or XIV, among the sucrose esters produced. In order to elucidate the influence of the location and content of acyl function on both of these biological effects, further detailed studies are now under progress.

Finally, dose reponse assay was carried out using four samples, *i.e.*, lauric acid, myristic acid, methylcaprylate, and sucrose monomyristate (preparation B), which have been demonstrated to show prominent antitumor activity at the standard dosage. As summarized in Table V, it was generally observed that the TPCV ratios tended to increase progressively (a tendency to gradual decrease in the antitumor activity) with decreasing dose amounts administered. However, there appears to be considerable difference between the minimum effective doses of the free fatty acids and those of the two types of esters examined. In the case of the free fatty acids, daily doses less than 200 mg/kg resulted in complete ineffectiveness. On the other hand, the methyl ester and the sucrose monoester were both found to be effective even at the daily dose of 100 mg/kg. At this dosage, the sucrose monomyristate preparation showed the TPCV ratio whose value was approximately equal to that given by daily administration of free myristic acid at 300 mg/kg. This means that about 40 mg of the myristic acid moiety contained in 100 mg of the sucrose monoester can exert the antitumor activity corresponding to that resulted from 300 mg of the same acid in the free form. In addition, it might be noteworthy to mention that apparently no significant toxicity was evoked in the mice which received the sucrose monomyristate at or below 300 mg/kg/day.

Discussion

In the 1920's, antitumor activity of fatty acids was first reported by Nakahara.[9] He revealed the value of unsaturated fatty acids in increasing the resistance of mice to several forms of transplantable tumors. Subsequently, a number of papers concerning the *in vivo* and *in vitro* antitumor activities of fatty acids (either saturated or unsaturated) and related compounds have been published by various workers.[8,10–15] For example, Morgan, *et al.* have examined extensively the *in vitro* antitumor activity of a variety of fatty acids against three lines of ascitic tumor cells in mice (Ehrlich carcinoma, 6C3HED lymphosarcoma, and TA_3 mammary carcinoma).[11] Yamamoto and associates performed intensive investigations on the antitumor agent so-called OX, which is an unsaturated fatty acid fraction obtained from the liver of X-ray irradiated rabbit, and established its *in vivo* activity against the Brown-Pearce sarcoma of rabbit, Ehrlich ascites tumor in solid form, and several human carcinomas.[12] Since 1968, Arima and co-workers have developed a series of systematic studies on the *in vivo* and *in vitro* antitumor effects of various fatty acids and their ester derivatives, using the Ehrlich ascites tumor implanted in mice.[8,13]

For evaluation of the *in vivo* antitumor activity of test compounds, the latter workers observed, principally, the life-span up to 30 days. Other conditions (tumor, mouse strain, route, dose, and vehicle) employed by them were, however, similar to those adopted in our present experiments. When compared their findings with our present observations, coincidental tendency could be found in many respects. In fact, the following results have been indicated by Arima, *et al.*: 1) Among the monocarboxylic acids ranging from C_{10} to C_{18}, compounds with 12 to 15 carbon atoms are effective, but others are ineffective.[13c] 2) Among the methyl esters of saturated fatty acids with even carbon numbers between 12 and 18, methyl laurate is an only example possessing the antitumor activity.[8c] 3) The sucrose monoesters of capric, lauric, myristic, and palmitic acids[16] are all active in inhibiting the tumor growth and elongating the life-span.[8a,c]

9) *a*) W. Nakahara, *J. Exptl. Med.*, **35**, 493 (1922); *b*) *Idem*, *ibid.*, **40**, 363 (1924); *c*) *Idem*, *ibid.*, **41**, 347 (1925); *d*) *Idem*, Gann, **19**, 1 (1925).

10) *a*) R. Bierich, *Leeuwenhoek-Vereeniging*, **i**, 14 (1922); *b*) J. Lecloux, *Compd. rend. Soc. de Biol. Med.*, **93**, 832 (1925); *c*) A.M. Begg, and H.A.A. Aitken, *Brit. J. Exptl. Pathol.*, **13**, 479 (1932); *d*) C. Hoffman, T.R. Schweitzer, and G. Dalby, *Food Research*, **4**, 539 (1939); *e*) J.G. Moloney, *J. Natl. Cancer Inst.*, **18**, 515 (1957); *f*) B. Sokoloff, M. Toyomizu, C.C. Saelhof, B. MacConnell, and F. Zbar, *Growth*, **22**, 215 (1958); *g*) L.R. Bennet and F.E. Connon, *J. Natl. Cancer Inst.*, **19**, 999 (1957); *h*) M.E. Hodes, C.G. Palmer, and A.E. Warren, *Exptl. Cell Research*, **21**, 164 (1960); *i*) M.E. Hodes, C.G. Palmer, and D. Livengood, *ibid.*, **24**, 298 (1961); *j*) S.M. Kupchan, I. Ognyanov, and J.L. Moniot, *Bioorg. Chem.*, **1**, 13 (1971); *k*) J.P.S. Sarin, H.S. Garg, N.M. Khanna, and M.M. Dhar, *Phytochem.*, **12**, 2461 (1973); *l*) M. Hatano and Y. Kurata, "Cell Membranes of Tumor Cells," ed. by H. Terayama, Nankodo Co. Ltd., Tokyo, 1969, p. 226.

11) *a*) G.F. Townsend, J.P. Morgan, and B. Hazlett, *Nature*, **183**, 1270 (1959); *b*) S. Tolnai and J.F. Morgan, *Canad. J. Biochem. and Physiol.*, **40**, 869, 1367 (1962); *c*) *Idem*, *ibid.*, **44**, 979 (1966).

12) *a*) M. Yamamoto, K. Utsumi, and S. Seno, *Acta Med. Okayama*, **17**, 129 (1963); *b*) T. Ofuji, *ibid.*, **18**, 55 (1964); *c*) S. Seno and M. Yamamoto, *ibid.*, **19**, 59 (1965); *d*) M. Yamamoto, T. Shiwaku, K. Aono, T. Tanabe, N. Katsumata, and Y. Hada, *Okayama Igaku Zasshi*, **75**, 695 (1963).

13) *a*) G. Tamura, A. Kato, K. Ando, K. Kodama, S. Suzuki, K. Suzuki, and K. Arima, *J. Antibiotics*, **21**, 688 (1968); *b*) A. Kato, K. Ando, S. Suzuki, G. Tamura, and K. Arima, *ibid.*, **22**, 83 (1969); *c*) K. Ando, A. Kato, S. Suzuki, G. Tamura, and K. Arima, "Progress in Antimicrobial and Anticancer Chemotherapy, Proceedings of the 6th International Congress of Chemotherapy, "Vol. II, ed. by H. Umezawa, University of Tokyo Press, Tokyo, 1970, p. 136. *cf.*) K. Ando, K. Kodama, A. Kato, G. Tamura, and K. Arima, *Cancer Res.*, **32**, 125 (1972).

14) J. Leither, I. Wodinsky, A.R. Bourke, and M.A. Schneiderman, *Cancer Res.* (Cancer Chemotherapy Screening Data VII), **20**, 539 (1960).

15) R. Kojima, *Nippon Saikingaku Zasshi*, **26**, 533 (1971). *cf.*) T. Suzuki, K. Tanaka, I. Matsubara, and S. Kinoshita, *Agric. Biol. Chem.*, **33**, 1619 (1969).

16) The sucrose monoester specimens used by Arima, *et al.* correspond, probably, to those designated as preparation A in the present paper.

Table V. Dose Response Assay of Fatty Acids and Ester Derivatives[a)]

Compd.	Dose (mg/kg/day)	TPCV ratio (% T/C)	Evaluation of activity	Body wt. change (g)		Deaths/Total	
				Treated	Control	Treated	Control
Lauric acid							
	300×5[a,b)]	10.7	##	−1.6	+0.7	0/6	1/6
	200×5[b,c)]	81.9	−	−1.6	+0.7	1/6	1/6
	100×5[b)]	122.0	−	+0.1	+1.3	0/6	0/6
	30×5[b)]	120.0	−	+0.1	+1.3	0/6	0/6
Myristic acid							
	500×5[b)]	4.6	##	−1.6	+0.1	0/6	0/5
	300×5	35.0	##	−0.1	−0.6	0/6	0/6
	300×5	58.4	+	−1.8	−0.8	0/6	0/6
	200×5	76.6	−	−4.0	−0.8	1/6	0/6
	100×5	133.6	−	−2.5	−0.8	0/6	0/6
Methyl caprylate							
	300×5	8.3	##	−1.9	−0.6	1/6	0/6
	200×5	12.1	##	−0.5	−0.6	0/6	0/6
	100×5	31.8	##	−1.6	−0.6	2/6	0/6
Sucrose monomyristate (preparation B)							
	300×5[c)]	13.8	##	−2.4	−1.4	0/6	0/6
	200×5[c)]	31.9	##	−2.0	−1.4	0/6	0/6
	100×5[c)]	36.2	##	−2.8	−1.4	1/6	0/6

a) For the data resulted from the standard dosage of 400 mg/kg/day, see Tables I, II, and IV.
b) ddN Mice, instead of ddY strain, were used.
c) The test sample was suspended in N-saline without containing Tween 80.

In the present assay, Ehrlich ascites carcinoma was used as a sole tumor, and no attempt was made to reveal the antitumor-spectra of the test compounds. But it has been demonstrated by Leither that methyl caproate, pelargonic acid, capric acid, lauric acid, methyl laurate, myristic acid, methyl myristate, and palmitic acid are all ineffective against the solid form sarcoma 180, adenocarcinoma Ca-755, and ascites form of L-1210.[14)] Some additional interesting informations on the antitumor activities of fatty acids and carbohydrate esters against the solid form tumors are also available. As reported by Arima, the fatty acid mixture consisting of oleic and linoleic acids, when administered subcutaneously, can inhibit the growth of Ehrlich solid tumor.[13c)] Kojima has evidenced that the fatty acid-trehalose ester derived from Arthrobacter exerts a strong inhibiting activity upon sarcoma 180 solid tumor in mice, in spite of its weak anti-Ehrlich ascites tumor effect.[15)]

Although the exact mechanism involved in the antitumor activity of fatty acids and related compounds is still unknown, Arima has suggested that they act as a detergent on the tumor cell membrane, and subsequently alter or destroy it.[13c)] More recently, he has also indicated that the antitumor action of sucrose monoesters cannot be explained only by their physical attack of the tumor cells.[8a)]

Through the present experiments, we have observed some interesting relationships between chemical structure and antitumor activity of saturated fatty acids and their derivatives. In an attempt to furnish additional data, extended investigation is now under way using a variety of unsaturated fatty acids.

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