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Studies of Hypolipidemic Agents. I. Syntheses and Hypolipidemic Activities of 1-Substituted 2-Alkanone Derivatives[1)]

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Many 1-substituted 2-alkanone derivatives were synthesized and their inhibitory activities toward pancreatic lipase and esterase were examined in order to obtain hypolipidemic agents. 1-Benzenesulfonyloxy-2-pentanone (VI-2a) and 1-(2,4,6-trimethylbenzenesulfonyloxy)-2-pentanone (VI-2q) exhibited not only potent and selective esterase inhibitions (IC_{50}: 9.0×10^{-7} M and 1.0×10^{-6} M, respectively), but also potent hypolipidemic action (90 and 92% reductions of plasma triglyceride, and 53 and 90% reductions of plasma total cholesterol, respectively). A novel working hypothesis is presented to account for the lowering of the plasma lipids level, *i.e.*, that inhibition of esterase and lipase activities in the small intestinal lumen may be responsible for the decrease in the plasma lipids level.

Keywords——1-chloro-2-alkanone; 1-substituted 2-pentanone; enzyme inhibition; lipase; esterase; chymotrypsin; plasmin; trypsin; hypolipidemic activity; structure–activity relationship

It is well-known that hyperlipemia is one of the predisposing factors for arteriosclerosis, and therefore, suppression of hyperlipemia has usually been attempted for the primary prevention of arteriosclerosis. Clofibrate,[2)] nicomol[3)] and cholestyramine[4)] have been used clinically as hypolipidemic agents; they act as inhibitors of cholesterol synthesis, of cholesterol absorption and of bile acid absorption, respectively. We are currently searching for hypolipidemic agents acting with a novel mechanism. This paper describes the syntheses of various 1-substituted ketones as pancreatic esterase-inhibiting agents and discusses their structure–activity relationship.

In general, triglycerides and cholesterol esters in food are hydrolyzed at their ester linkages in the small intestinal lumen, then the hydrolysis products (fatty acid, monoglycerides and free cholesterol) form micelles by binding with bile acid, and the micelles are absorbed into the intestinal mucosa.[5)] If pancreatic lipase and esterase in the small intestinal lumen were inhibited, the absorption of lipids (triglycerides and cholesterol esters) into the small intestinal mucosa should be considerably decreased, and therefore novel hypolipidemic agents may be found among inhibitors of these enzymes. This was our fundamental working hypothesis for the present research.

Little work has been done on esterase and lipase inhibitors,[6a,b)] but 1-chloro-3-(*N*-tosylamino)-4-phenyl-2-butanone (TPCK)[7)] and 7-amino-1-chloro-3-(*N*-tosylamino)-2-heptanone (TLCK)[8)] have been reported as chymotrypsin and trypsin inhibitors, respectively. Thus, we initially synthesized eight 1-chloro-2-alkanones (IIIa—h) by methods A and B (Chart 1). However, the compounds (IIId—f) showed little hypolipidemic activities *in vivo* despite having considerable esterase inhibitory activities *in vitro*.

It was found that the value of *n* ($n=1$—12) in III (Chart 1) did not greatly affect the

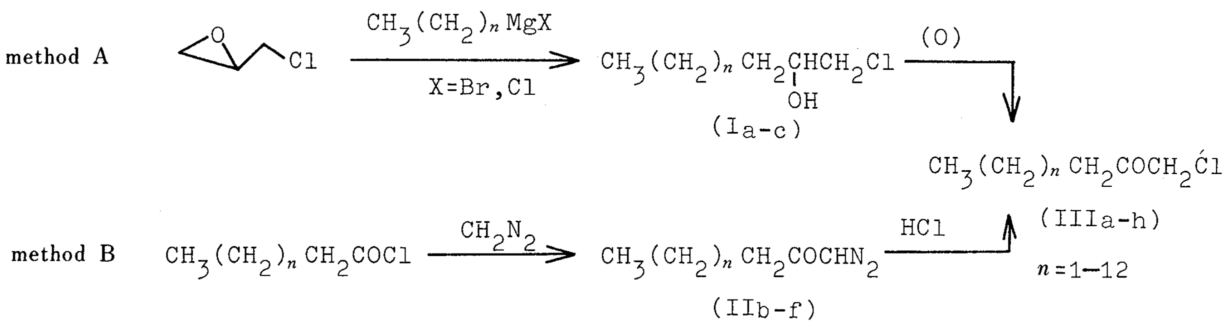

Chart 1

TABLE I. Inhibitory Activity on Esterase and Hypolipidemic Effect of III

$CH_3(CH_2)_nCH_2COCH_2Cl$
III

Compd. No.	n	Method[a]	Yield (%)	mp (°C) or (bp °C/mmHg)	Inhibitory activity IC_{50}[k] ($\times 10^{-6}$ M)	Percent decrease of triglyceride[l]
IIIa	1	A	36[b]	(65—70/26—27)[d]	520	—[m]
IIIb	3	B	91[c]	Oil[e]	16	—[m]
IIIc	4	A	36[b]	(100—105/20)[f]	13	—[m]
IIId	5	B	90[c]	Oil[g]	10	23
IIIe	7	A	43[b]	(115/6)[h]	5	20
IIIf	8	B	85[c]	30.5—31.5[i]	11	21
IIIg	10	B	63[c]	43—44[j]	—[m]	—[m]
IIIh	12	B	88[c]	50—51	—[m]	—[m]

a) See the experimental section. *b)* Yield from the corresponding alkyl halide. *c)* Yield from the corresponding alkanoic acid chloride. *d)* Lit.,[9a] bp 64—66 °C/26 mmHg. *e)* Purified by column chromatography and assigned by ^{1}H-NMR. Lit.,[10] bp 79—82 °C/8 mmHg. *f)* Lit.,[11] bp 92.8—93.5 °C/10 mmHg. *g)* Purified and assigned in the same manner as described for IIIb. Lit.,[11] bp 110—110.5 °C/10 mmHg. *h)* Lit.,[11] bp 136—138 °C/10 mmHg. *i)* Lit.,[11] bp 87—90 °C/0.05 mmHg. *j)* Lit.,[12] bp 126—128 °C/1 mmHg. *k)* Methyl butyrate was used as a substrate. *l)* Dose; 0.3 mmol/kg, *p.o.* in rats. See the experimental section. *m)* Not tested.

activity except for $n=1$ (IIIa: low activity). Next we synthesized various 1-substituted 2-pentanone derivatives (Va—j) having about eleven carbon atoms, which was the number in the most effective compound (IIIe) among the III series (Table I), and we examined their esterase inhibitory activities *in vitro*. They all exhibited low activities. We thought that the reason for the lower activity of the V series *in vitro* as compared with the III series might be that the substitutents at the 1-position of the V series possessed low reactivity with the enzyme in comparison with the chlorine atom of the III series. Thus, we planned to introduce a sulfonyloxy group at the 1-position of 2-pentanone. Various 1-sulfonyloxy-2-pentanones (VI-1a—1e and VI-2a—2w) were synthesized, and their esterase inhibitory activities were examined, resulting in the finding that some of the compounds (VI-2a, 2c, 2d, 2m, 2n, 2q, and VI-2r) possessed selective esterase inhibitory activities, and two were potent hypolipidemic agents (VI-2a, 2q).

Synthesis

1-Chloro-2-alkanone derivatives (III) were prepared by two methods (A and B) as shown in Chart 1. Namely, the α-chlorohydrins (Ia—c) were obtained by treating epichlorohydrin with the corresponding alkylmagnesium halide, and they were oxidized to the α-chloroketones (IIIa, c, e) with acidic dichromate according to Elderfield *et al.*[9a,b] (method A). Other α-chloroketones (IIIb, d, f—h) were prepared by treating the diazoketones (IIb—f) with hydrogen chloride according to Haworth *et al.*[17] (method B) (Chart 1). The compounds

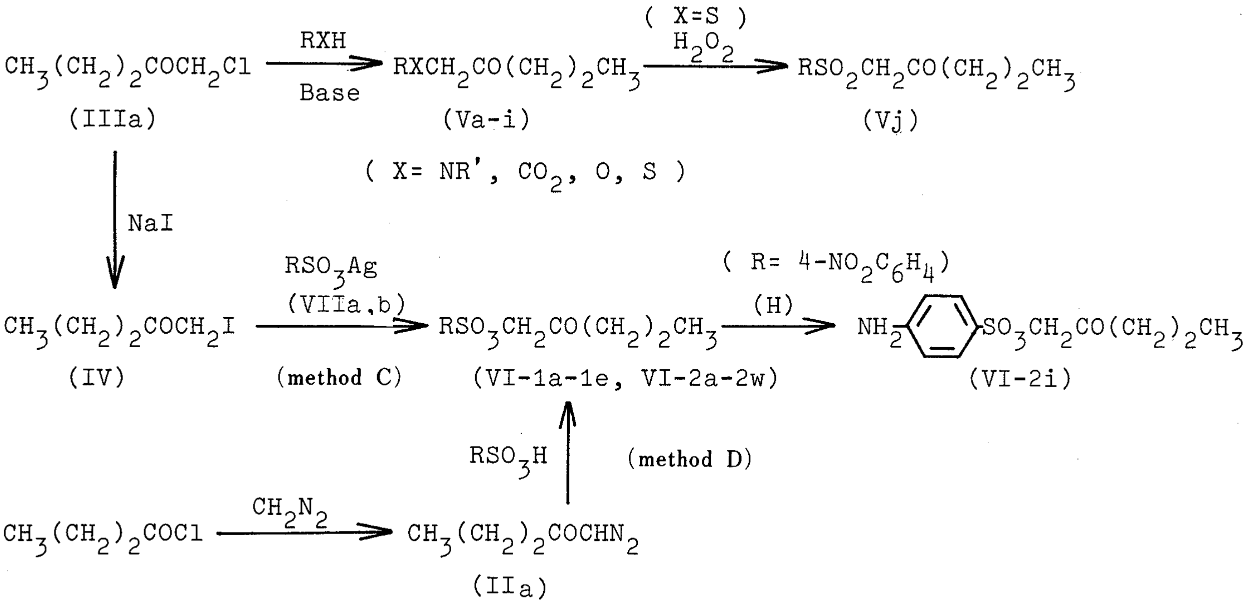

Chart 2

TABLE II. Inhibitory Activity on Esterase of V

$RXCH_2CO(CH_2)_2CH_3$
V

Compd. No.	RX	Yield (%)	mp (°C)	Formula	Inhibitory activity IC_{50}[f] ($\times 10^{-6}$ M)
Va	C_6H_5NH-	42	61—62[a]	$C_{11}H_{15}NO$	—[g]
Vb	Phthalimidyl-	52	86—87	$C_{13}H_{13}NO_3$	—[g]
Vc	$4-Cl-C_6H_4CO_2-$	58	48—49	$C_{12}H_{13}ClO_3$	—[g]
Vd	$4-CH_3O-C_6H_4CO_2-$	51	42—44	$C_{13}H_{16}O_4$	—[g]
Ve	C_6H_5O-	38	Oil[b]	$C_{11}H_{14}O_2$	21
Vf	$4-Cl-C_6H_4O-$	56	37—38	$C_{11}H_{13}ClO_2$	250
Vg	C_6H_5S-	57	25—26[c]	$C_{11}H_{14}OS$	70
Vh	$4-Cl-C_6H_4S-$	53	46—47[d]	$C_{11}H_{13}ClOS$	260
Vi	$4-CH_3-C_6H_4S-$	62	33—34	$C_{12}H_{16}OS$	160
Vj	$4-CH_3-C_6H_4SO_2-$	53	Oil[e]	$C_{12}H_{16}O_3S$	—[g]

a) Lit.,[13] mp 63—64 °C. b) Lit.,[14] bp 112 °C/4 mmHg. Purified by column chromatography and assigned by ^1H-NMR. c) This compound was reported by Kuwajima and Kurata (ref. 15), but detailed physical data were not given. d) Lit.,[16] bp 155—156 °C/3 mmHg. e) Purified and assigned by the same manner as Ve. f) Methyl butyrate was used as a substrate. g) $IC_{50} = > 1 \times 10^{-3}$ M.

(Va—i) in Table II possessing an *n*-pentanoyl moiety were prepared by treating IIIa with the corresponding nucleophiles in the presence of an appropriate HCl scavenger. The sulfone (Vj) was prepared by oxidation of the sulfide (Vi) with an equimolar amount of hydrogen peroxide in acetic acid (Chart 2). The substituted arylsulfonates (VI-2b, 2q) in Table III were prepared by alkylation of the corresponding silver sulfonates (VIIa, b)[18] with 1-iodo-2-pentanone (IV), which was obtained by the treatment of IIIa with potassium iodide (method C). Other sulfonates (VI-1, VI-2) were prepared by treating 1-diazo-2-pentanone (IIa)[19] with the corresponding sulfonic acids according to the procedure of Crowther and Holt[20-22] (method D). The *p*-nitroarylsulfonate (VI-2h) was reduced with activated iron in benzene to give the *p*-amino compound (VI-2i).

TABLE III. Inhibitory Activity on Esterase of VI-1 and VI-2

$RSO_3CH_2CO(CH_2)_2CH_3$
VI-1, VI-2

Compd. No.	R	Yield[a] (%)	mp (°C)	Recryst. solv.[b]	Inhibitory activity IC_{50}[d] ($\times 10^{-6}$ M)
VI-1a	$C_6H_5CH_2$–	66	45—46	E–PE	37.0
VI-1b	C_2H_5–	53	Oil[c]		12.0
VI-1c	*cyclo*-C_6H_{11}–	68	Oil[c]		46.0
VI-1d	$C_2H_5(CH_2)_3$–	62	Oil[c]		260.0
VI-1e	β-Naphtyl-	46	40—41	E–PE	4.0
VI-2a	C_6H_5–	77	Oil[c]		0.9
VI-2b	4-CH_3–C_6H_4–	80	33—35	PE	5.2
VI-2c	2-CH_3–C_6H_4–	60	Oil[c]		1.7
VI-2d	4-Cl–C_6H_4–	81	Oil[c]		2.6
VI-2e	4-OH–C_6H_4–	70	85—87	Et	16.0
VI-2f	4-OC_2H_5–C_6H_4–	68	37—38	Et	46.0
VI-2g	4-O–*n*-C_4H_9–C_6H_4–	64	28—29	PE	70.0
VI-2h	4-NO_2–C_6H_4–	58	93—94	PE	76.0
VI-2i	4-NH_2–C_6H_4–	68	67—68	Et	80.0
VI-2j	3-CO_2H–C_6H_4–	60	107—108	E	350.0
VI-2k	4-$NHCOCH_3$–C_6H_4–	52	118—119	B	170.0
VI-2l	4-*n*–$C_{12}H_{25}$–C_6H_4–	61	Oil[c]		—[e]
VI-2m	2,4-$(CH_3)_2$–C_6H_3–	61	44—45	PE	1.3
VI-2n	2,5-$(CH_3)_2$–C_6H_3–	62	63—64	M–PE	0.3
VI-2o	2,5-$(Cl)_2$–C_6H_5	45	95—96	M	8.0
VI-2p	3-Cl,4-CH_3–C_6H_3–	64	Oil[c]		5.8
VI-2q	2,4,6-$(CH_3)_3$–C_6H_2–	94	57—58	Et–W	1.0
VI-2r	2,4,5-$(CH_3)_3$–C_6H_2–	44	60—61	PE	1.3
VI-2s	2,3,4-$(CH_3)_3$–C_6H_2–	50	55—56	Et–W	3.7
VI-2t	2,4,5-$(Cl)_3$–C_6H_2–	65	80—81	M–W	2.5
VI-2u	2,4,6-$(C_2H_5)_3$–C_6H_2–	40	Oil[c]		160.0
VI-2v	2,4,6-$\{CH(CH_3)_2\}_3$–C_6H_2–	49	29—30	M–W	—[e]
VI-2w	2,3,4,6-$(CH_3)_4$–C_6H–	60	49—50	PE	2.0

a) Yields of VI-2b and VI-2q are from 1-iodo-2-pentanone (IV), and that of VI-2i is from VI-2h. Yields of other compounds are those from 1-diazo-2-pentanone (IIa). *b*) E = ether, PE = petroleum ether, Et = ethanol, B = benzene, M = methanol, W = H_2O. *c*) Purified by column chromatography and assigned by ^1H-NMR. *d*) Methyl butyrate was used as a substrate. *e*) $IC_{50} \geqq 1 \times 10^{-3}$ M.

Enzyme Inhibitory Activity (*in Vitro* Experiments)

Methyl butyrate, *N*-acetyltyrosine ethyl ester (ATEE), N^{α}-tosylarginine methyl ester (TAME) and olive oil were used for the activity determinations of esterase,[23,24] chymotrypsin,[23,24] plasmin[23,24] and lipase,[25] respectively (Tables I—III and V).

Pharmacological Examinations (*in Vivo* Experiments)

Male Wistar rats (7 weeks old) were used, with five animals in each experimental group. A test compound (0.3 mmol) was mixed with 10 ml of olive oil containing cholesterol (15%), and the mixture was orally administered to the rats at the ratio of 10 ml per kg. Blood samples for the determination of the plasma triglyceride and the plasma total cholesterol were taken from the orbital vein at 2 and 8 h, respectively, after the administration. Concentrations of plasma triglyceride and plasma total cholesterol were analyzed by using commercially available analysis kits (Triglyceride-B-Test Wako[26] and Cholesterol-Test Wako[27]). Decreases of triglyceride and cholesterol were expressed as percentage decreases with respect to the control values obtained by using olive oil containing no test compound.

Table IV. Physical Data for VI-1 and VI-2

Compd. No.	MS (M$^+$)	Formula	Analysis (%) Calcd (Found)			^{1}H-NMR (CDCl$_3$) δ ppm
			C	H	N	
VI-1a	256	$C_{12}H_{16}O_4S$	56.23 (56.21	6.29 6.36)		0.87 (3H, t), 1.32—1.80 (2H, m), 2.30 (2H, t), 4.50 (2H, s), 7.34 (5H, s)
VI-1b	194	$C_7H_{14}O_4S$	43.28 (42.80	7.26 6.94)		0.92 (3H, t), 1.44 (3H, t), 1.32—1.85 (2H, m), 2.42 (2H, t), 3.22 (2H, q), 4.70 (2H, s)
VI-1c	248	$C_{11}H_{20}O_4S$	53.20 (52.88	8.12 8.04)		0.89 (3H, t), 1.10—2.50 (12H, m), 2.41 (2H, t), 3.00—3.35 (1H, m), 4.67 (2H, s)
VI-1d	252	$C_{10}H_{20}O_5S$	47.60 (47.24	7.99 7.87)		0.94 (3H, t), 1.18 (3H, t), 1.40—1.85 (2H, m), 2.00—2.23 (2H, m), 2.45 (2H, t), 3.25—3.62 (6H, m), 4.71 (2H, s)
VI-1e	292	$C_{15}H_{16}O_4S$	61.63 (61.73	5.52 5.72)		0.82 (3H, t), 1.35—1.98 (2H, m), 2.42 (2H, t), 4.49 (2H, s), 7.50—8.50 (6H, m), 8.40 (1H, s)
VI-2a	242	$C_{11}H_{14}O_4S$	54.53 (54.41	5.82 5.77)		0.87 (3H, t), 1.32—1.80 (2H, m), 2.42 (2H, t), 4.49 (2H, s), 7.35—8.00 (5H, m)
VI-2b	256	$C_{12}H_{16}O_4S$	56.23 (56.35	6.29 6.10)		0.84 (3H, t), 1.30—1.80 (2H, m), 2.41 (3H, s), 2.42 (2H, t), 4.43 (2H, s), 7.31 (2H, d), 7.78 (2H, d)
VI-2c	256	$C_{12}H_{16}O_4S$	56.23 (56.49	6.29 6.45)		0.90 (3H, t), 1.40—1.80 (2H, m), 2.46 (2H, t), 2.68 (3H, s), 4.49 (2H, s), 7.20—7.70 (3H, m), 7.92 (1H, d)
VI-2d	276	$C_{11}H_{13}ClO_4S$	47.74 (47.85	4.74 4.80)		0.83 (3H, t), 1.32—1.85 (2H, m), 2.38 (2H, t), 4.50 (2H, s), 7.60—8.10 (4H, m)
VI-2e	258	$C_{11}H_{14}O_5S$	51.15 (51.30	5.46 5.25)		0.82 (3H, t), 1.33—1.66 (2H, m), 2.40 (2H, t), 4.45 (2H, s), 6.82 (2H, d), 7.65 (2H, d)
VI-2f	286	$C_{13}H_{18}O_5S$	54.52 (54.61	6.33 6.49)		0.84 (3H, t), 1.37 (3H, t), 1.30—1.78 (2H, m), 2.38 (2H, t), 4.20 (2H, q), 4.42 (2H, s), 6.91 (2H, d), 7.70 (2H, d)
VI-2g	314	$C_{15}H_{22}O_5S$	57.30 (57.15	7.05 7.10)		0.84 (3H, t), 0.92 (3H, t), 1.20—1.90 (6H, m), 2.41 (2H, t), 4.00 (2H, t), 4.43 (2H, s), 6.95 (2H, d), 7.80 (2H, d)
VI-2h	287	$C_{11}H_{13}NO_6S$	45.99 (46.01	4.56 4.66	4.88 4.85)	0.87 (3H, t), 1.35—1.75 (2H, m), 2.39 (2H, t), 4.66 (2H, s), 8.20 (2H, d), 8.38 (2H, d)
VI-2i	257	$C_{11}H_{15}NO_4S$	51.35 (51.54	5.88 5.81	5.44 5.32)	0.90 (3H, t), 1.34—1.78 (2H, m), 2.45 (2H, t), 4.20—4.40 (2H, d), 4.40 (2H, s), 6.64 (2H, d), 7.60 (2H, d)
VI-2j	286	$C_{12}H_{14}O_6S$	50.34 (50.16	4.93 4.89)		0.87 (3H, t), 1.32—1.80 (2H, m), 2.32 (2H, t), 4.48 (2H, s), 7.43—7.70 (1H, t), 7.95—8.55 (3H, m), 10.20—10.55 (1H, b)
VI-2k	299	$C_{13}H_{17}NO_5S$	52.16 (52.12	5.72 6.03	4.68 4.81)	0.74 (3H, t), 1.28—1.70 (2H, m), 2.03 (3H, s), 2.31 (2H, t), 4.71 (2H, s), 7.75 (4H, s), 10.20—10.40 (1H, b)
VI-2l	410	$C_{23}H_{38}O_4S$	67.28 (67.01	9.33 9.31)		0.50—1.80 (30H, m), 2.40 (2H, t), 4.42 (2H, s), 7.22—7.82 (4H, m)
VI-2m	270	$C_{13}H_{18}O_4S$	57.75 (57.55	6.71 7.02)		0.82 (3H, t), 1.32—1.80 (2H, m), 2.30 (3H, s), 2.40 (2H, t), 2.56 (3H, s), 4.40 (2H, s), 6.94—7.20 (2H, m), 7.76 (1H, d)
VI-2n	270	$C_{13}H_{18}O_4S$	57.75 (57.44	6.71 6.81)		0.84 (3H, t), 1.33—1.82 (2H, m), 2.31 (3H, s), 2.42 (2H, t), 2.58 (3H, s), 4.40 (2H, s), 7.20—7.30 (2H, m), 7.70 (1H, s)
VI-2o	310	$C_{11}H_{12}Cl_2O_4S$	42.45 (42.45	3.89 3.81)		0.88 (3H, t), 1.36—1.80 (2H, m), 2.44 (2H, t), 4.60 (2H, s), 7.40 (2H, m), 7.90 (1H, m)
VI-2p	290	$C_{12}H_{15}ClO_4S$	49.57 (49.31	5.20 5.18)		0.84 (3H, t), 1.30—1.80 (2H, m), 2.39 (2H, t), 2.40 (3H, s), 4.45 (2H, s), 7.20—7.78 (3H, m)
VI-2q	284	$C_{14}H_{20}O_4S$	59.13 (58.95	7.09 7.37)		0.89 (3H, t), 1.35—1.80 (2H, m), 2.30 (3H, s), 2.48 (2H, t), 2.60 (6H, s), 4.36 (2H, s), 6.89 (2H, s)
VI-2r	284	$C_{14}H_{20}O_4S$	59.13 (59.22	7.09 7.50)		0.89 (3H, t), 1.36—1.82 (2H, m), 2.26 (6H, s), 2.49 (2H, t), 2.58 (3H, s), 4.43 (2H, s), 7.13 (1H, s), 7.70 (1H, s)
VI-2s	284	$C_{14}H_{20}O_4S$	59.13 (59.08	7.09 7.31)		0.88 (3H, t), 1.32—1.82 (2H, m), 2.22 (3H, s), 2.32 (3H, s), 2.46 (2H, t), 2.58 (3H, s), 4.42 (2H, s), 7.12 (1H, d), 7.73 (1H, d)
VI-2t	344	$C_{11}H_{11}Cl_3O_4S$	38.23 (38.17	3.28 3.25)		0.89 (3H, t), 1.35—1.82 (2H, m), 2.26 (6H, s), 2.49 (2H, t), 2.58 (3H, s), 4.43 (2H, s), 7.13 (1H, s), 7.70 (1H, s)
VI-2u	326	$C_{17}H_{26}O_4S$	62.55 (62.49	8.03 7.96)		0.90 (3H, t), 1.24 (3H, t), 1.26 (6H, t), 2.51 (2H, t), 2.64 (2H, q), 3.07 (4H, q), 4.45 (2H, s), 7.05 (2H, s)
VI-2v	368	$C_{20}H_{32}O_4S$	65.18 (65.10	8.75 8.80)		0.88 (3H, t), 1.22 (12H, d), 1.24 (6H, d), 1.36—1.80 (2H, m), 2.32—2.60 (3H, m), 4.43 (2H, s), 7.36 (1H, s), 7.78 (1H, s)
VI-2w	298	$C_{15}H_{22}O_4S$	60.38 (60.50	7.43 7.58)		0.85 (3H, t), 1.35—1.77 (2H, m), 2.16 (3H, s), 2.44 (3H, s), 2.45 (2H, t), 2.55 (6H, s), 4.38 (2H, s), 6.94 (1H, s)

TABLE V. Inhibitory Activities on Various Enzymes and Hypolipidemic Effect of VI-2

Compd. No.	Percent inhibition					Percent decrease	
	Lipase[a] $(1\times10^{-3}\,\mathrm{M})$[e]	Esterase[b] $(1\times10^{-4}\,\mathrm{M})$[e]	Chymotrypsin[c] $(1\times10^{-4}\,\mathrm{M})$[e]	Trypsin[d] $(1\times10^{-4}\,\mathrm{M})$[e]	Plasmin[d] $(1\times10^{-4}\,\mathrm{M})$[e]	Triglyceride[f]	Cholesterol[f]
VI-2a	—[g]	89	8	0	0	90	53
VI-2b	50	87	3	0	0	64	31
VI-2d	100	80	14	0	0	82	56
VI-2q	—[g]	90	13	0	0	92	90
Nicomol	—[g]	—[g]	—[g]	—[g]	—[g]	61[h]	—[g]

a) Olive oil was used as a substrate. *b*) Methyl butyrate was used as a substrate. *c*) ATEE was used as a substrate. *d*) TAME was used as a substrate. *e*) Molar concentration of the compound. *f*) Dose; 0.3 mmol/kg, *p.o.* in rats. See the experimental section. *g*) Not tested. *h*) Dose; 400 mg/kg, *p.o.* in rats.

Results and Discussion

The physical and biological data of the compounds (III, V, and VI) are listed in Tables I—V. Among 1-chloro-2-alkanone derivatives (III), considerable esterase inhibitory activities $\{IC_{50} \leqq 10^{-5}\,\mathrm{M}$; maximum value $= 5 \times 10^{-6}\,\mathrm{M}$ (IIIe)$\}$ were obtained in the *in vitro* tests with IIIb—f, but IIIa was not effective. The plasma triglyceride-reducing effect *in vivo* of IIIe was also examined, but no significant reduction of lipids levels was obtained. We presumed that IIIe might be rapidly absorbed or decomposed in the digestive organs before reaching the small intestinal lumen. As can be seen in Table II, the esterase inhibitory effects *in vitro* of the amino compounds (Va, b), the esters (Vc, d), the ethers (Ve, f), the thio-ethers (Vg—i) and the sulfone (Vj) did not exceed those of III, but two sulfonates (VI-1 and VI-2) showed more potent inhibitory activities ($IC_{50} = >10^{-6}$ to $10^{-7}\,\mathrm{M}$) than III, as shown in Table III. Some of these compounds (VI-2a, 2b, 2d and VI-2q) were also examined for reducing effects *in vivo* on plasma triglyceride and total cholesterol at a dose of 0.3 mmol/kg (oral administration), and considerable reductions of triglyceride uptake (64—92%) and of cholesterol uptake (31—90%) were found. In particular, VI-2q exhibited a potent and long-lasting hypolipidemic activity[28] than might be clinically useful.

The following structure-activity relationships for esterase inhibitory activity in the series of sulfonates (VI) were found. i) The arylsulfonates (VI-2a, 2c, 2d, 2m, 2n ,2q and VI-2r) possess more potent activities than the alkyl- and aralkylsulfonates. ii) Among the substituted arylsulfonates, hydrophobic substituents such as hydroxyl (VI-2e), amino (VI-2i), carboxyl (VI-2j) and acetoamino (VI-2k) tend to decrease the inhibitory activity. iii) On the other hand, several small substituents such as methyl (VI-2b, 2c, 2m, 2n, 2q and VI-2w), chloro (VI-2d, 2o and 2t) and hydrogen (VI-2a) tended to increase the inhibitory activity, but relatively bulky lipophilic substituents such as *n*-butoxy (VI-2g), *n*-dodecyl (VI-2l), triethyl (VI-2u), triisopropyl (VI-2v) decreased it.

As shown in Table V, it is noteworthy that some compounds (VI-2a, 2b, 2d and VI-2q) exhibited selective inhibition of esterase and lipase but did not inhibit chymotrypsin, trypsin and plasmin; they exhibited more potent effects than the clinically used drug nicomol[3] as regards plasma triglyceride reduction *in vivo*.

Conclusion

As part of a search for novel hypolipidemic agents, we prepared a series of 1-substituted 2-alkanone derivatives and evaluated their inhibitory activities against enzymes (pancreatic esterase and lipase) secreted in the small intestinal lumen, as well as their hypolipidemic effects. Two compounds (VI-2a and VI-2q) exhibited not only potent and selective inhibitory activities against esterase and lipase, but also potent hypolipidemic activities.

Our investigations are continuing on the series of 2-oxo-alkyl-substituted benzenesulfonates, with the aim of finding even more potent hypolipidemic agents.

Experimental

All melting points were recorded with a Yanagimoto micromelting point apparatus and are uncorrected. Spectral data were obtained as follows: MS with a JEOL LMS-01G-2 spectrometer; proton nuclear magnetic resonance (^{1}H-NMR) with a JEOL JMN-FX 100 spectrometer (using tetramethyl silane as an internal standard). Chemical shifts are given in δ values (ppm) and the abbreviations of signal patterns are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Elemental analyses were carried out with a Yanagimoto C H N Corder MT-2 analyzer.

Starting Materials——Cyclohexylsulfonic acid[29] was prepared by the hydrolysis of cyclohexylsulfonyl chloride[30] which was obtained from the oxidation of cyclohexylthiuronium bromide with chlorine. Ethoxypropylsulfonic acid was prepared by the treatment of propanesultone with sodium ethoxide according to Helberger *et al.*[31] 2-Methylbenzenesulfonic acid[32] was prepared by the hydrolysis of 2-methylbenzenesulfonamide with 6 N HCl. 4-Ethoxybenzenesulfonic acid[33] and 4-*n*-butoxybenzenesulfonic acid[33] were prepared by the hydrolyses of 4-ethoxy- and 4-*n*-butoxybenzenesulfonyl chloride, which were obtained from the reactions of 4-ethoxy- and 4-*n*-butoxybenzene with chlorosulfonic acid, respectively, according to Morgan and Cretcher.[34] 4-Acetoaminobenzenesulfonic acid[35] was prepared by the reaction of acetoanilide with chlorosulfonic acid according to Morales' procedure.[35] 2,4,5-Trimethylbenzenesulfonic acid,[36] 2,3,4-trimethylbenzenesulfonic acid,[37] 2,3,4,6-tetramethylbenzenesulfonic acid,[38] 2,4,6-triethylbenzenesulfonic acid[39] and 2,4,6-tri-isopropylbenzenesulfonic acid[40] were prepared by treatments of the corresponding aromatic hydrocarbons with conc. H_2SO_4 according to Smith and Cass.[36] All sulfonic acids prepared were used without purification in the syntheses of VI. Other starting materials were all commercial products.

1-Chloro-2-alkanones (III)——Method A: 1-Chloro-2-pentanol (Ia), bp 75—78 °C/24 mmMg (lit.,[9b] bp 80 °C/28 mmHg) was prepared by the reaction of ethylmagnesium bromide with epichlorohydrin according to Elderfield *et al.*[9b] and it was oxidized with sodium dichromate–sulfonic acid according to Elderfield and Ressler[9a] to give 1-chloro-2-pentanone (IIIa), bp 65—70 °C/26—27 mmHg (lit.,[9a] bp 64—66 °C/26 mmHg). 1-Chloro-2-octanone (IIIc), bp 100—105 °C/20 mmHg (lit.,[11] bp 92.8—93.5 °C/10 mmHg), and 1-chloro-2-undecanone (IIIe), bp 115 °C/6 mmHg (lit.,[11] bp 136—138 °C/10 mmHg) were prepared *via* 1-chloro-2-octanol (Ib)[11] and 1-chloro-2-undecanol (Ic),[11] which were obtained by the reactions of *n*-pentylmagnesium bromide and *n*-octylmagnesium bromide respectively, with epichlorohydrin, according to the method used for the preparation of IIIa.

Method B: *n*-Hexanoyl chloride (1.4 g) was added dropwise to an ethereal solution (100 ml) of diazomethane (from 7.0 g of nitrosomethylurea) under stirring with ice-cooling according to Haworth *et al.*[17] The diazoketone was not isolated, but was converted directly to the chloromethyl ketone by saturating the ethereal solution with anhydrous hydrogen chloride over a period of 1 h. The reaction mixture was evaporated under reduced pressure, the residue was chromatographed on a silica gel column with chloroform, and the eluate was evaporated to give an oily product (IIIb). Yield 1.4 g (91%) (lit.,[10] bp 79—82 °C/8 mmHg). MS *m/e*: 148 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.84 (3H, t), 1.10—1.75 (6H, m), 2.50 (2H, t), 4.00 (2H, s). The other compounds (IIId, IIIf—h) were prepared from the corresponding alkanoic acid chlorides by the same procedure as used for the preparation of IIIb. Data are listed in Table I. (IIIh): 53—54 °C. MS *m/e*: 274 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t), 1.22 (20H, s), 1.40—1.80 (4H, m), 2.56 (2H, t), 4.00 (2H, s). *Anal.* Calcd for $C_{16}H_{13}ClO$: C, 69.91; H, 11.37. Found: C, 70.13; H, 11.69.

1-Anilino-2-pentanone (Va)——DBU (1,8-diazabicyclo[5.4.0]-7-undecene) (1.5 g) was added dropwise to an ethereal solution (20 ml) of aniline (0.9 g) with 1-chloro-2-pentanone (IIIa) (1.3 g) under stirring with ice-cooling. After being stirred for 12 h, the reaction mixture was poured into cold water and extracted with ether (50 ml). The ether layer was dried over sodium sulfate and evaporated to dryness under reduced pressure. The residue was chromatographed on a silica gel column with chloroform, and the eluate was evaporated to give Va as white crystals. Yield 0.8 g (42%), mp 61—62 °C (petroleum ether) (lit.,[13] mp 63—64 °C).

1-Phthalimidyl-2-pentanone (Vd)——Phthalimide (1.5 g), IIIa (1.2 g) and K_2CO_3 (0.8 g) were added to a 90% ethanol solution (50 ml). After being refluxed for 6 h, the reaction mixture was evaporated under reduced pressure. The residue was extracted with ether (50 ml) and dried over sodium sulfate, then evaporated to dryness under reduced pressure. The crude product was recrystallized from ethanol to give Vb as white needles. Yield 1.2 g (52%). mp 86—87 °C. MS *m/e*: 231 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t), 1.50—1.80 (2H, m), 2.49 (2H, t), 4.44 (2H, s), 7.55—7.90 (4H, m). *Anal.* Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.37; H, 5.75; N, 6.14.

1-(4-Chlorobenzoyloxy)-2-pentanone (Vc) and 1-(4-Methoxybenzoyloxy)-2-pentanone (Vd)——4-Chlorobenzoic acid (1.6 g), IIIa (1.3 g) and K_2CO_3 (0.8 g) were added to a 90% ethanol solution (30 ml). After being refluxed for 8 h, the reaction mixture was evaporated to dryness under reduced pressure. The residue was extracted with chloroform (50 ml) and washed with 1 N $NaHCO_3$ (10 ml). The chloroform layer was dried over sodium sulfate and evaporated to dryness under reduced pressure. The residue was chromatographed on a silica gel column with chloroform, and the eluate was evaporated to give Vc as white crystals. Yield 1.5 g (58%). mp 48—49 °C (petroleum ether). MS *m/e*: 240 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t), 1.35—1.80 (2H, m), 2.36 (2H, t), 4.78 (2H, s), 7.28 (2H, d), 7.88 (2H, d). *Anal.* Calcd for $C_{12}H_{13}ClO_3$: C, 59.88; H, 5.44. Found: C, 59.59; H, 5.35.

Compound Vd was prepared from 4-methoxybenzoic acid (1.5 g) and IIIa (1.3 g) in the same manner as used for the preparation of Vc. Yield 1.3 g (51%). Oily product. MS *m/e*: 236 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t), 1.38—1.80 (2H, m), 2.39 (2H, t), 3.78 (3H, s), 4.74 (2H, s), 6.80 (2H, d), 7.90 (2H, d).

1-Phenoxy-2-pentanone (Ve) and 1-(4-Chlorophenoxy)-2-pentanone (Vf)——Compound Ve was prepared from phenol (1.4 g) and IIIa (1.8 g) in the same manner as used for the preparation of Vc. Yield 1.0 g (38%). Oily product (lit.,[14] 112 °C/4 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, t), 1.35—1.80 (2H, m), 2.45 (2H, t), 4.40 (2H, s), 6.60—7.95 (3H, m), 7.00—7.25 (2H, m). Compound Vf was prepared from 4-chlorophenol (3.8 g) and IIIa (3.8 g) in the same manner as used for the preparation of Vc. Yield 3.5 g (56%). mp 37—38 °C (petroleum ether). MS *m/e*: 200 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t), 1.45—1.90 (2H, m), 2.52 (2H, t), 4.48 (2H, s), 6.74 (2H, d), 7.20 (2H, d).

1-Phenylthio-2-pentanone (Vg), 1-(4-Chlorophenylthio)-2-pentanone (Vh) and 1-(4-Methylphenylthio)-2-pentanone (Vi)——Thiophenol (1.1 g), IIIa (1.3 g) and NaOH (0.2 g) were added to a 90% ethanol solution (50 ml). After being refluxed for 6 h, the reaction mixture was treated in the same manner as used for the preparation of Vc to give Vg. Yield 1.2 g (57%). Oily product. MS *m/e*: 194 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, t), 1.30—1.75 (2H, m), 2.44 (2H, t), 3.52 (2H, s), 7.00—7.30 (5H, m). Compound Vh was prepared from 4-chlorothiophenol (1.5 g) and IIIa (1.2 g) in the same manner as used for the preparation of Vg. Yield 1.2 g (53%). mp 46—47 °C (petroleum ether) (lit.,[16] 155—156 °C/3 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 0.82 (3H, t), 1.30—1.75 (2H, m), 2.45 (2H, t), 3.51 (2H, s), 7.08 (4H, s). *Anal.* Calcd for $C_{11}H_{13}ClOS$: C, 57.76; H, 5.73. Found: C, 57.63; H, 6.13. Compound Vi was prepared from 4-methylthiophenol (1.3 g) and IIIa (1.3 g) in the same manner as used for the preparation of Vg. Yield 1.4 g (62%). mp 33—34 °C (petroleum ether). MS *m/e*: 208 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, t), 1.30—1.70 (2H, m), 2.20 (3H, s), 2.44 (2H, t), 3.98 (2H, s), 6.80—7.20 (4H, m). *Anal.* Calcd for $C_{12}H_{16}OS$: C, 69.19; H, 7.74. Found: C, 69.19; H, 8.07.

1-(4-Methylbenzenesulfonyl)-2-pentanone (Vj)——A 30% solution of hydrogen peroxide (6 ml) was added dropwise to a solution of Vi (1.3 g) in acetic acid (20 ml) under stirring at room temperature. After being stirred at 70 °C for 2 h, the reaction mixture was concentrated to about 5 ml and poured into cold water, then extracted with chloroform (50 ml). The chloroform layer was washed with 1 N $NaHCO_3$ and dried over sodium sulfate, then evaporated to dryness under reduced pressure. The residue was chromatographed on a silica gel column with chloroform, and the eluate was evaporated to give Vj as an oily product. Yield 0.8 g (53%). MS *m/e*: 240 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, t), 1.30—1.80 (2H, m), 2.40 (3H, s), 2.60 (2H, t), 4.10 (2H, s), 7.26 (2H, d), 7.65 (2H, d).

1-Diazo-2-pentanone (IIa)[19]——Compound IIa was prepared from *n*-butyryl chloride (1.7 g) with diazomethane (from 10 g of nitrosomethylurea) according to Haworth *et al.*[17] The crude product was chromatographed on a silica gel column with chloroform, and the eluate was evaporated to give IIa as a light yellowish oily product. Yield 1.7 g (95%). MS *m/e*: 112 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t), 1.32—1.80 (2H, m), 2.22 (2H, t), 5.18 (2H, s).

1-Benzenesulfonyloxy-2-pentanone (VI-2a)——Typical Procedure (Method C): Benzenesulfonic acid (2.3 g) was added in several portions to a solution of IIa (1.2 g) in ether (50 ml) under stirring with ice-cooling. The mixture was stirred until the evolution of nitrogen ceased at room temperature, then washed with water. The ether layer was dried over sodium sulfate and evaporated to dryness under reduced pressure. The residue was chromatographed on a silica gel column with chloroform, and the eluate was evaporated to give VI-2a as an oily product. Yield 2.0 g (77%). Other data are listed in Tables III and IV. Other Compounds (VI-1a, 1e, VI-2c—2h, VI-2j—2p and VI-2r—2w) were prepared from the corresponding sulfonic acid with diazoketone (IIa) in the same manner as used for the preparation of VI-2a. The data are listed in Tables III and IV.

1-(2,4,6-Trimethylbenzenesulfonyloxy)-2-pentanone (VI-2q)——Typical Procedure (Method D): Potassium iodide (8.0 g) was added to a solution of IIIa (6.0 g) in acetone (100 ml). After being stirred for 5 h at room temperature, the reaction mixture was filtered. The filtrate was evaporated under reduced pressure. The residual oil was extracted with ether (100 ml) and dried over sodium sulfate. The ether layer was evaporated under reduced pressure and the residual oil was distilled under reduced pressure to give 1-iodo-2-pentanone (IV). Yield 6.0 g (54%). bp 96—98 °C/25 mmHg. MS *m/e*: 222 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t), 1.65 (2H, q), 2.70 (2H, t), 3.80 (2H, s). Silver 2,4,6-trimethylbenzenesulfonate (0.7 g) was added to a solution of IV (0.4 g) in acetonitrile (30 ml). After being stirred for 40 h at room temperature, the reaction mixture was filtered and the filtrate was evaporated to dryness under reduced pressure. The residue was extracted with ether (30 ml) and dried over sodium sulfate. The ether layer was evaporated to dryness under reduced pressure, the residue was chromatographed on a silica gel column with chloroform, and the eluate was evaporated to give VI-2q as white crystals. Yield 0.5 g (94%). Compound VI-2b was prepared from silver *p*-toluenesulfonate with iodoketone (IV) in the same manner as used for the preparation of VI-2q. The data are listed in Tables III and IV.

1-(4-Aminobenzenesulfonyloxy)-2-pentanone (VI-2i)——Activated iron (40 g) was added to a solution of VI-2h

(4.0 g) in benzene (300 ml) under reflux with vigorous stirring. During the refluxing, water (1 ml) was added to the reaction mixture several times. After being refluxed for 5 h, the reaction mixture was filtered and the filtrate was evaporated to dryness under reduced pressure. The residue was chromatographed on a silica gel column with chloroform, and the eluate was evaporated to give VI-2i as white crystals. Yield 2.6 g (68%). The data are listed in Tables III and IV.

Enzyme-Inhibitory Activities——The inhibitory activities toward esterase, chymotrypsin, and trypsin and plasmin were determined by using methyl butyrate, ATEE and TAME, respectively, as the substrates, according to Muramatu *et al.*[23a,b] and Hestrin.[24] The inhibitory activity against lipase was determined by using olive oil as the substrate according to Mier's procedure.[25] The results are listed in Tables I—III and V, in which the inhibitory activities are expressed as IC_{50} for esterase, namely, the molar concentration at which a compound inhibits 50% of the activity of the enzyme toward the substrate. The potencies against lipase, chymotrypsin, trypsin and plasmin of the compounds (VI-2a, 2b, 2d and VI-2q) in Table V are expressed as percent inhibition at the concentration of 1×10^{-3} M for the lipase, and 1×10^{-4} M for other enzymes.

Pharmacology——Male Wistar rats, weighing 200—220 g (7 weeks old) were used for the present experiment. They were allocated to experimental groups of five animals. A test compound (0.3 mmol) was dissolved in olive oil (10 ml) containing 15% cholesterol and was orally administered to the rats at the dose of 10 ml per kg *via* a stomach tube. Blood samples for triglyceride at 2 h and for total cholesterol at 8 h after administration were taken from the orbital vein under ether anesthesia. The obtained blood samples were separated by centrifugation at 3000 rpm at 5 °C to give the plasma. The triglyceride and total cholesterol levels in plasma were measured by using Triglyceride-B Test Wako[26] and Cholesterol-Test Wako[27] (available from Wako Pure Chemical Industry Ltd., Japan), respectively. The control groups received only the olive oil containing cholesterol in the same manner, and the normal groups received no treatment. The plasma triglyceride and total cholesterol levels of the control and normal groups were measured in the same manner as used for the treated group. The percent reductions of the plasma triglyceride and total cholesterol were calculated as follows;

$$\text{reduction } (\%) = \frac{A-C}{A-B} \times 100$$

A: Plasma triglyceride level (or plasma total cholesterol) of the control group.
B: Those of the normal group.
C: Those of the group treated with the test compound.

The results are listed in Tables I and V.

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