[Chem. Pharm. Bull. 34(8)3252—3266(1986)]

Studies on Hypolipidemic Agents. II.[1] Synthesis of 1-Arenesulfonyloxy-2-alkanone Derivatives as Potent Esterase Inhibitors and Hypolipidemic Agents

KAZUO OGAWA,*,[a] TADAFUMI TERADA,[a] YOSHIYUKI MURANAKA,[a] TOSHIHIRO HAMAKAWA,[a] SADAO HASHIMOTO,[a] and SETSURO FUJII[b]

Research Institute, Taiho Pharmaceutical Co., Ltd.,[a] Kawauchi-cho, Tokushima 771-01, Japan and Osaka University,[b] 3-2 Yamadaoka, Suita, Osaka 564, Japan

(Received January 16, 1986)

Many 2-oxoalkyl arenesulfonate derivatives having straight or branched alkyl chains of different lengths, 2-oxoalkyl bis-arenesulfonate derivatives, and alkyl arenesulfonate derivatives having a ketal moiety at the 2-position on the alkyl chain were synthesized, and their esterase-inhibitory activities, as well as hypolipidemic activities, were evaluated.

Among these compounds, 1-(2,4,6-trimethylbenzenesulfonyloxy)-2-dodecanone (III-1u), and 1-(2,3,4,6-tetramethylbenzenesulfonyloxy)-2-hexanone (III-1w), -2-octanone (III-1x) and -2-decanone (III-1y) exhibited potent esterase-inhibitory activities ($IC_{50} = 3 \times 10^{-10}$, 2×10^{-10}, 2×10^{-10} and 3×10^{-11} M, respectively). However, the sulfonate (XV) having a ketal moiety on the alkyl chain and the bis-sulfonate (XVI) exhibited low inhibitory activities toward esterase in comparison with III and XII. Most of the compounds III and some of the compounds XII exhibited potent hypolipidemic activities corresponding to more than 50% lipid-lowering effect (plasma triglyceride and cholesterol ester) *in vivo*. The structure–activity relationships of these compounds are discussed.

Keywords——benzenesulfonyloxyalkanone; benzenesulfonyloxyalkane; diazoketone; hydroxyketone; bromoketone; enzyme inhibition; esterase-inhibitory activity; esterase; chymotrypsin; hypolipidemic activity; structure–activity relationship

In the previous paper,[1] we reported the preparation of various 1-(substituted benzenesulfonyloxy)-2-pentanone derivatives possessing selective esterase-inhibitory activities and hypolipidemic character with a novel action mechanism; inhibition of esterase and lipase activities in the small intestinal lumen may be responsible for the decrease in the plasma lipid levels.

As a part of our continuing search for more effective hypolipidemic agents, we found that several 2-oxoalkyl arenesulfonates possessed potent esterase-inhibitory activity (greater than that of esterastin,[2] an esterase inhibitor), as well as potent hypolipidemic activity. In the present paper, we wish to report the preparations, biological activities and structure–activity relationships of various arenesulfonates having straight or branched 2-oxoalkyl chains of various lengths, some of which bear substituents (such as chlorine, acetoxy, hydroxy, alkoxy and alkoxycarbonyl) and some of which carry the carbonyl group at the 2-position in a ketal form.

Synthesis

2-Oxoalkyl arenesulfonate derivatives (III-1 and 2), which have straight or branched chains of different lengths, were prepared by three methods (A, B and C) as shown in Chart 1. Method A was mainly used for the preparations of most of the compounds (III-1 and 2) in Tables I and II.

Method A——Treatment of the alkanoyl chlorides (I) with diazomethane in ethereal

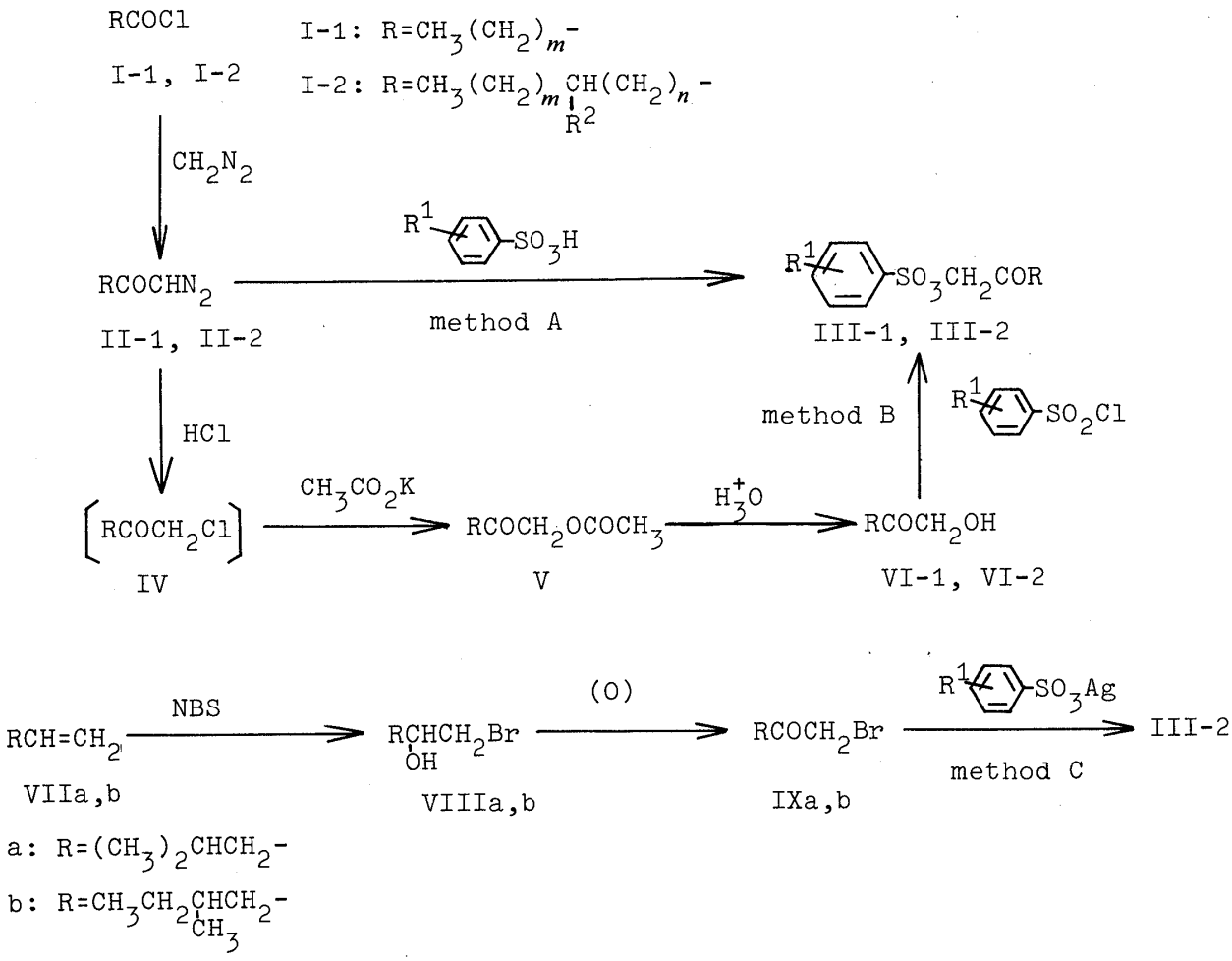


Chart 1

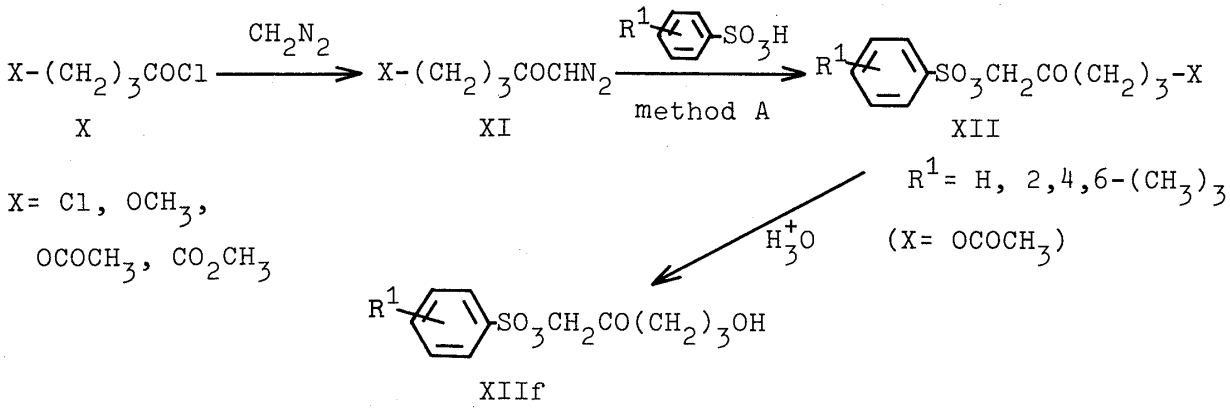
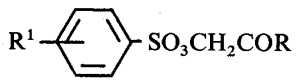


Chart 2

solution according to Haworth *et al.*[3] gave 1-diazo-2-alkanone derivatives (II) in good yields, and these were reacted with the corresponding arenesulfonic acids according to Crowther and Holt[4] to give the arenesulfonates (III-1 and 2) in fair yields.

Method B——Treatment of the diazoketones (II-1 and 2) with dry hydrogen chloride in ethereal solution gave chloroketones (IV), which were reacted with potassium acetate to give 1-acetoxy-2-alkanones (V). These were subjected to acid hydrolysis to give the 1-hydroxy-2-alkanones (VI-1 and 2). A one-pot procedure could be used for the conversion of II to VI. The esterification of the 1-hydroxy-2-alkanones (VI-1 and 2) with the corresponding arenesulfonyl chloride in the presence of triethylamine in dichloromethane also gave arenesulfonates (III-1c,

TABLE I. Inhibitory Activities on Enzymes, and Hypolipidemic Effects of III-1 and 2



III-1, 2

III-1: $R = -(CH_2)_mCH_3$

III-2: $R = -(CH_2)_mCH(R^2)(CH_2)_nCH_3$

Compd. No.	R^1	R^2	m	n	Method[a]	Yield (%)	mp (°C)	Inhibitions		Reductions[d]	
								Esterase[b] IC_{50} (μM)	Chymotry.[c] (1×10^{-4} M)	Trigly.[e]	Chol.[f]
III-1a	H	—	3	—	A	61	Oil	0.1	54	98	67
III-1b	H	—	4	—	A	62	Oil	0.07	100	87	60
III-1c	H	—	5	—	A	70	Oil	0.07	96	88	62
					B	51					
III-1d	H	—	8	—	A	78	33—34	0.008	14	80	61
					B	43					
III-1e	H	—	10	—	A	71	34—35	0.062	53	—[h]	—
III-1f	4-CH_3	—	3	—	A	64	Oil	1.0	44	61	33
III-1g	4-CH_3	—	5	—	A	77	Oil	3.0	100	78	41
					B	47					
III-1h	4-CH_3	—	7	—	A	70	32—33	1.1	59	70[g]	43[g]
III-1i	4-CH_3	—	8	—	A	80	50—51	0.34	39	62[g]	—
					B	61					
III-1j	4-CH_3	—	9	—	A	67	47—48	2.7	44	64[g]	—
III-1k	4-OCH_3	—	3	—	A	70	40—41	24.0	23	87	72
III-1l	4-OCH_3	—	4	—	A	71	Oil	0.4	72	62	62
III-1m	4-OCH_3	—	6	—	A	69	42—43	0.2	91	62	62
III-1n	4-OCH_3	—	8	—	A	73	46—47	0.1	45	—	—
III-1o	4-OCH_3	—	10	—	A	60	52—53	3.0	17	58[g]	—
III-1p	2,4,6-$(CH_3)_3$	—	3	—	A	80	33—34	0.04	33	77	87
III-1q	2,4,6-$(CH_3)_3$	—	4	—	A	73	Oil	0.04	45	53	60
III-1r	2,4,6-$(CH_3)_3$	—	5	—	A	83	32—33	0.03	60	55	62
					B	60					
III-1s	2,4,6-$(CH_3)_3$	—	6	—	A	69	Oil	0.01	57	80	74
					B	52					

III-1t	2,4,6-$(CH_3)_3$	—	7	—	A	54	36—37	0.0006	72	56	61
III-1u	2,4,6-$(CH_3)_3$	—	9	—	A	87	35—36	0.0003	55	63[g]	—
III-1v	2,4,6-$(CH_3)_3$	—	10	—	A	68	48—49	0.12	46	60[g]	—
III-1w	2,3,4,6-$(CH_3)_4$	—	3	—	A	56	32—33	0.0002	12	68	71
III-1x	2,3,4,6-$(CH_3)_4$	—	5	—	A	61	42—43	0.0002	24	55	47
III-1y	2,3,4,6-$(CH_3)_4$	—	7	—	A	70	36—37	0.00003	26	70[g]	71[g]
III-1z	2,3,4,6-$(CH_3)_4$	—	8	—	A	63	29—30	0.04	—	—	—
III-2a	2,4,6-$(CH_3)_3$	CH_3	0	1	A	68	30—31	6.2	5	98	72
					B	53					
III-2b	2,4,6-$(CH_3)_3$	CH_3	0	2	A	70	50—51	1.8	13	84	79
					B	48					
III-2c	2,4,6-$(CH_3)_3$	CH_3	0	3	A	80	33—34	1.8	19	67	71
					B	59					
III-2d	2,4,6-$(CH_3)_3$	C_2H_5	0	3	A	74	33—34	2.0	23	—	—
III-2e	2,4,6-$(CH_3)_3$	n-C_3H_7	0	3	A	62	38—39	2.9	9	58	62
III-2f	2,4,6-$(CH_3)_3$	n-C_4H_9	0	3	A	54	45—46	3.0	22	67	66
III-2g	2,4,6-$(CH_3)_3$	CH_3	0	4	A	79	38—39	1.9	32	75	77
III-2h	2,4,6-$(CH_3)_3$	CH_3	1	0	B	53	36—37	0.1	7	81	67
					C	66					
III-2i	2,4,6-$(CH_3)_3$	CH_3	1	1	B	69	Oil	0.6	9	82	83
					C	50					
III-2j	2,4,6-$(CH_3)_3$	CH_3	1	2	A	57	Oil	0.4	17	74	70
III-2k	2,4,6-$(CH_3)_3$	CH_3	2	0	A	59	39—40	1.0	56	—	—
					B	48					
III-2l	2,4,6-$(CH_3)_3$	CH_3	2	1	A	69	Oil	0.1	42	49	51
III-2m	2,4,6-$(CH_3)_3$	CH_3	3	0	A	60	Oil	0.1	47	51	56
III-2n	2,4,6-$(CH_3)_3$	CH_3	6	0	A	84	Oil	0.1	3	—	—

a) See the experimental section. *b*) Methyl butyrate was used as a substrate. *c*) ATEE was used as a substrate. Expressed as percentage inhibition of chymotrypsin inhibitory activity at 1×10^{-4} M. *d*) Expressed as percentage deviation from the control value. Dose: 100 mg/kg, *p.o.* in rats. See the experimental section. *e*) Plasma triglyceride. *f*) Plasma total cholesterol. *g*) Dose: 200 mg/kg, *p.o.* in rats. *h*) Not tested.

TABLE II. Physical Data for III-1 and 2

Compd. No.	Formula	Analysis (%) Calcd (Found) C	H	^{1}H-NMR ($CDCl_3$) δ ppm
III-1a	$C_{12}H_{16}O_4S$	56.32 (56.35	6.29 6.50)	0.80 (3H, t), 1.00—1.65 (4H, m), 2.38 (2H, t), 4.47 (2H, s), 7.30—7.50 (3H, m), 7.65—7.72 (2H, m)
III-1b	$C_{13}H_{18}O_4S$	57.76 (57.44	6.71 6.56)	0.80 (3H, t), 1.00—1.75 (6H, m), 2.40 (2H, t), 4.48 (2H, s), 7.25—7.50 (3H, m), 7.65—7.80 (2H, m)
III-1c	$C_{14}H_{20}O_4S$	59.13 (59.01	7.09 7.15)	0.81 (3H, t), 1.00—1.67 (8H, m), 2.39 (2H, t), 4.49 (2H, s), 7.32—7.52 (3H, m), 7.64—7.72 (2H, m)
III-1d	$C_{17}H_{26}O_4S$	62.55 (62.40	8.03 7.85)	0.82 (3H, t), 1.00—1.70 (14H, m), 2.43 (2H, t), 4.49 (2H, s), 7.40—7.70 (3H, m), 7.80—8.00 (2H, m)
III-1e	$C_{19}H_{30}O_4S$	64.37 (64.24	8.53 8.75)	0.90 (3H, t), 1.02—1.90 (16H, m), 2.50 (2H, t), 4.48 (2H, s), 7.35—7.70 (3H, m), 7.70—8.00 (2H, m)
III-1f	$C_{13}H_{18}O_4S$	57.76 (57.65	6.71 6.78)	0.81 (3H, t), 1.00—1.68 (4H, m), 2.36 (2H, t), 2.37 (3H, s), 4.42 (2H, s), 7.18—7.32 (2H, m), 7.60—7.80 (2H, m)
III-1g	$C_{15}H_{22}O_4S$	60.38 (60.38	7.43 7.46)	0.79 (3H, t), 1.00—1.65 (8H, m), 2.35 (2H, t), 2.36 (3H, s), 4.43 (2H, s), 7.15—7.35 (2H, m), 7.60—7.82 (2H, m)
III-1h	$C_{17}H_{26}O_4S$	62.55 (62.75	8.03 8.33)	0.85 (3H, t), 1.00—1.78 (12H, m), 2.41 (2H, t), 2.43 (3H, s), 4.45 (2H, s), 7.15—7.35 (2H, m), 7.60—7.80 (2H, m)
III-1i	$C_{18}H_{28}O_4S$	63.50 (63.07	8.29 8.64)	0.87 (3H, t), 1.00—1.80 (14H, m), 2.41 (2H, t), 2.42 (3H, s), 4.45 (2H, s), 7.20—7.35 (2H, m), 7.65—7.80 (2H, m)
III-1j	$C_{19}H_{30}O_4S$	64.37 (64.40	8.53 8.80)	0.87 (3H, t), 1.00—1.70 (16H, m), 2.41 (2H, t), 2.41 (3H, s), 4.45 (2H, s), 7.18—7.35 (2H, m), 7.60—7.80 (2H, m)
III-1k	$C_{13}H_{18}O_5S$	54.53 (54.84	6.34 6.26)	0.82 (3H, t), 1.00—1.70 (4H, m), 2.42 (2H, t), 3.84 (3H, s), 4.44 (2H, s), 6.97 (2H, d), 7.80 (2H, d)
III-1l	$C_{14}H_{20}O_5S$	55.98 (55.57	6.71 6.82)	0.81 (3H, t), 1.00—1.70 (6H, m), 2.44 (2H, t), 3.85 (3H, s), 4.43 (2H, s), 6.95 (2H, d), 7.81 (2H, d)
III-1m	$C_{16}H_{24}O_5S$	58.51 (58.54	7.37 7.54)	0.80 (3H, t), 1.00—1.72 (10H, m), 2.42 (2H, t), 3.82 (3H, s), 4.42 (2H, s), 6.95 (2H, d), 7.79 (2H, d)
III-1n	$C_{18}H_{28}O_5S$	60.56 (60.42	7.92 7.90)	0.84 (3H, t), 1.00—1.80 (14H, m), 2.44 (2H, t), 3.84 (3H, s), 4.43 (2H, s), 6.95 (2H, d), 7.82 (2H, d)
III-1o	$C_{20}H_{32}O_5S$	62.47 (62.20	8.38 8.77)	0.84 (3H, t), 1.00—1.60 (18H, m), 2.44 (2H, t), 3.84 (3H, s), 4.44 (2H, s), 6.98 (2H, d), 7.82 (2H, d)
III-1p	$C_{15}H_{22}O_4S$	60.38 (60.53	7.43 7.38)	0.80 (3H, t), 1.05—1.70 (4H, m), 2.20 (3H, s), 2.40 (2H, t), 2.54 (6H, s), 4.38 (2H, s), 6.92 (2H, s)
III-1q	$C_{16}H_{24}O_4S$	61.51 (61.15	7.74 7.84)	0.80 (3H, t), 1.00—1.75 (6H, m), 2.21 (3H, s), 2.42 (2H, t), 2.54 (6H, s), 4.35 (2H, s), 6.90 (2H, s)
III-1r	$C_{17}H_{26}O_4S$	62.55 (62.43	8.03 7.98)	0.92 (3H, t), 1.00—1.66 (8H, m), 2.24 (3H, s), 2.54 (6H, s), 4.36 (2H, s), 6.88 (2H, s)
III-1s	$C_{18}H_{28}O_4S$	63.50 (63.64	8.29 8.50)	0.82 (3H, t), 1.00—1.78 (10H, m), 2.25 (3H, s), 2.46 (2H, t), 2.56 (6H, s), 4.38 (2H, s), 6.93 (2H, s)
III-1t	$C_{19}H_{30}O_4S$	64.37 (64.28	8.53 8.72)	0.82 (3H, t), 1.00—1.78 (12H, m), 2.24 (3H, s), 2.44 (2H, t), 2.52 (6H, s), 4.38 (2H, s), 6.92 (2H, s)
III-1u	$C_{21}H_{34}O_4S$	65.93 (65.99	8.97 9.28)	0.84 (3H, t), 1.00—1.78 (16H, m), 2.26 (3H, s), 2.40 (2H, t), 2.60 (6H, s), 4.38 (2H, s), 6.94 (2H, s)
III-1v	$C_{22}H_{36}O_4S$	66.63 (66.35	9.15 9.29)	0.84 (3H, t), 1.00—1.70 (18H, m), 2.26 (3H, s), 2.46 (2H, t), 2.60 (6H, s), 4.39 (2H, s), 6.93 (2H, s)
III-1w	$C_{16}H_{24}O_4S$	61.51 (61.32	7.74 7.87)	0.81 (3H, t), 1.00—1.74 (4H, m), 2.14 (3H, s), 2.24 (3H, s), 2.46 (2H, t), 2.53 (6H, s), 4.38 (2H, s), 6.91 (1H, s)
III-1x	$C_{18}H_{28}O_4S$	63.50 (63.44	8.29 8.57)	0.82 (3H, t), 1.00—1.80 (8H, m), 2.16 (3H, s), 2.26 (3H, s), 2.48 (2H, t), 2.56 (6H, s), 4.38 (2H, s), 6.94 (1H, s)
III-1y	$C_{20}H_{32}O_4S$	65.18 (65.19	8.75 8.96)	0.81 (3H, t), 1.00—1.70 (12H, m), 2.14 (3H, s), 2.24 (3H, s), 2.47 (2H, t), 2.54 (6H, s), 4.38 (2H, s), 6.93 (1H, s)
III-1z	$C_{21}H_{34}O_4S$	65.93 (65.84	8.95 9.13)	0.78 (3H, t), 1.10—1.82 (16H, m), 2.20 (3H, s), 2.30 (3H, s), 2.49 (2H, t), 2.60 (6H, s), 4.40 (2H, s), 6.90 (1H, s)

TABLE II. (continued)

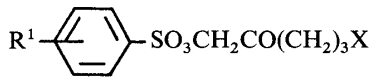
Compd. No.	Formula	Analysis (%) Calcd (Found) C	H	^{1}H-NMR ($CDCl_3$) δ ppm
III-2a	$C_{15}H_{22}O_4S$	60.38 (60.29	7.43 7.61)	0.82 (3H, t), 1.02 (3H, d), 1.20—1.90 (2H, m), 2.28 (3H, s), 2.46—2.80 (1H, m), 2.64 (6H, s), 4.50 (2H, s), 6.95 (2H, s)
III-2b	$C_{16}H_{24}O_4S$	61.51 (61.26	7.74 7.96)	0.70—1.70 (7H, m), 1.04 (3H, d), 2.30 (3H, s), 2.64 (6H, s), 2.60—2.88 (1H, m), 4.52 (2H, s), 7.00 (2H, s)
III-2c	$C_{17}H_{26}O_4S$	62.55 (62.48	8.03 8.34)	0.85 (3H, t), 1.05 (3H, d), 1.00—1.80 (6H, m), 2.29 (3H, s), 2.40—2.90 (1H, m), 2.64 (6H, s), 4.50 (2H, s), 6.99 (2H, s)
III-2d	$C_{18}H_{28}O_4S$	63.50 (63.60	8.29 8.60)	0.60—1.80 (14H, m), 2.22 (3H, s), 2.30—2.90 (1H, m), 2.58 (6H, s), 4.48 (2H, s), 6.94 (2H, s)
III-2e	$C_{19}H_{30}O_4S$	64.37 (64.10	8.53 8.63)	0.86 (6H, t), 1.00—1.80 (10H, m), 2.28 (3H, s), 2.40—2.80 (1H, br), 2.64 (6H, s), 4.50 (2H, s), 6.98 (2H, s)
III-2f	$C_{20}H_{32}O_4S$	65.18 (65.43	8.75 9.06)	0.84 (6H, t), 1.00—1.90 (12H, m), 2.28 (3H, s), 2.40—2.90 (1H, br), 2.64 (6H, s), 4.50 (2H, s), 6.98 (2H, s)
III-2g	$C_{18}H_{28}O_4S$	63.50 (63.50	8.29 8.66)	0.69—1.80 (14H, m), 2.30 (3H, s), 2.64 (6H, s), 2.40—2.85 (1H, m), 4.52 (2H, s), 7.00 (2H, s)
III-2h	$C_{15}H_{22}O_4S$	60.37 (60.52	7.43 7.47)	0.91 (6H, d), 2.22 (3H, s), 1.85—2.36 (3H, m), 2.54 (6H, s), 4.30 (2H, s), 6.84 (2H, s)
III-2i	$C_{16}H_{24}O_4S$	61.51 (61.31	7.74 7.87)	0.82 (3H, d), 0.83 (3H, t), 1.00—1.35 (2H, m), 1.60—2.00 (1H, m), 2.20 (3H, s), 2.30 (2H, d), 2.50 (6H, s), 4.30 (2H, s), 6.89 (2H, s)
III-2j	$C_{17}H_{26}O_4S$	62.55 (62.13	8.03 8.19)	0.70—1.00 (6H, m), 1.05—1.40 (4H, m), 1.80—2.20 (1H, m), 2.30 (3H, s), 2.65 (6H, s), 4.38 (2H, s), 6.99 (2H, s)
III-2k	$C_{16}H_{24}O_4S$	61.51 (62.00	7.74 7.98)	0.80 (6H, d), 1.22—1.60 (3H, m), 2.22 (3H, s), 2.56 (6H, s), 4.34 (2H, s), 6.89 (2H, s)
III-2l	$C_{17}H_{26}O_4S$	62.55 (62.80	8.03 8.17)	0.85 (3H, t), 0.87 (3H, d), 1.00—1.70 (5H, m), 2.30 (3H, s), 2.47 (2H, t), 2.64 (6H, s), 4.42 (2H, s), 7.00 (2H, s)
III-2m	$C_{17}H_{26}O_4S$	62.55 (62.31	8.03 8.05)	0.88 (6H, d), 1.00—1.78 (5H, m), 2.29 (3H, s), 2.46 (2H, t), 2.62 (6H, s), 4.39 (2H, s), 6.98 (2H, s)
III-2n	$C_{20}H_{32}O_4S$	65.18 (65.07	8.75 8.58)	0.75 (3H, d), 0.82 (3H, d), 1.00—1.80 (11H, m), 2.20—2.50 (2H, m), 2.59 (6H, s), 4.39 (2H, s), 6.93 (2H, s)

1d, 1g, 1i, 1r, 1s, III-2a—c, 2h, 2i and 2k).

Method C——The reaction[5] of vinyl derivatives (VII) with *N*-bromosuccinimide in the presence of a catalytic amount of acetic acid in water gave the bromohydrins (VIII), which were subjected to oxidation with the acidic dichromate to give the 1-bromo-2-alkanones (IX). Treatment of IX with the appropriate silver arenesulfonates in acetonitrile gave the arenesulfonates (III-2h and 2i).

The overall yields of III by using methods B and C were lower than that of method A, which was mainly used for the preparation of arenesulfonates (III-1 and 2) (Table I). The arenesulfonates (XII) having substituents such as chlorine, acetoxy, hydroxy, methoxy and methoxycarbonyl on the terminal position of the alkyl chain were prepared by method A as shown in Chart 2 (Tables III and IV). The desired arenesulfonates (XII) were obtained in fair yields, and compound XIIh was subjected to deacetylation under acidic conditions to give 5-hydroxy-1-(2,4,6-trimethylbenzenesulfonyloxy)-2-pentanone (XIIf) in 30% yeild. Arenesulfonates (XV) having a ketal moiety at the 2-position of the alkyl chain were prepared by two methods (D and E) as shown in Chart 3 (Tables V and VII). 1-Acetoxy-2,2-ethylenedioxyoctane (XIII), which was obtained from the ketone (V),[6] was subjected to basic hydrolysis to give the 2,2-ethylenedioxy-1-hydroxyoctane (XIV). 2,2-Ethylenedioxy-1-(2,4,6-trimethylbenzenesulfonyloxy)octane (XVd) was prepared by the reaction of XIV with 2,4,6-

TABLE III. Inhibitory Activities on Enzymes, and Hypolipidemic Effect of XII



XII

Compd. No.	R^1	X	Yield (%)	mp (°C)	Inhibitions		Reduction[d]
					Esterase[b] IC_{50} (μM)	Chymotry.[c] (1×10^{-4} M)	Trigly.[e]
XIIa	H	Cl	81	39—40	0.8	47	—[f]
XIIb	H	OCH_3	72	Oil	2.4	3	—
XIIc	H	$OCOCH_3$	61	Oil	26	22	62
XIId	H	CO_2CH_3	70	Oil	6.8	65	78
XIIe	2,4,6-$(CH_3)_3$	Cl	82	34—35	9.4	—	—
XIIf	2,4,6-$(CH_3)_3$	OH	30[a]	54—55	320	28	—
XIIg	2,4,6-$(CH_3)_3$	OCH_3	68	Oil	1.5	10	—
XIIh	2,4,6-$(CH_3)_3$	$OCOCH_3$	63	63—64	120	6	—
XIIi	2,4,6-$(CH_3)_3$	CO_2CH_3	61	Oil	29	28	—

a) Yield from XIIh. *b*—*e*) See the corresponding footnote in Table I. *f*) Not tested.

TABLE IV. Physical Data for XII

Compd. No.	Formula	Analysis (%) Calcd (Found)		^{1}H-NMR ($CDCl_3$) δ ppm
		C	H	
XIIa	$C_{11}H_{13}ClO_4S$	47.74 (47.68)	4.74 5.03)	1.80—2.15 (2H, m), 2.63 (2H, t), 3.47 (2H, t), 4.49 (2H, s), 7.40—8.00 (5H, m)
XIIb	$C_{12}H_{16}O_5S$	52.93 (52.87	5.92 5.70)	1.60—2.05 (2H, m), 2.49 (2H, t), 3.10—3.40 (5H, m), 4.49 (2H, s), 7.40—8.00 (5H, m)
XIIc	$C_{13}H_{16}O_6S$	51.99 (51.87	5.37 5.17)	1.65—2.05 (2H, m), 1.91 (3H, s), 2.52 (2H, t), 3.97 (2H, t), 4.50 (2H, s), 7.35—7.98 (5H, m)
XIId	$C_{13}H_{16}O_6S$	51.99 (51.53	5.37 5.30)	1.60—2.05 (2H, m), 2.10—2.65 (4H, m), 3.56 (3H, s), 4.50 (2H, s), 7.40—7.98 (5H, m)
XIIe	$C_{14}H_{19}ClO_4S$	52.74 (52.43	6.01 5.93)	1.85—2.20 (2H, m), 2.30 (3H, s), 2.65 (6H, s), 2.70 (2H, t), 3.50 (2H, t), 4.42 (2H, s), 7.00 (2H, s)
XIIf	$C_{14}H_{20}O_5S$	55.98 (56.16	6.71 6.83)	1.65—2.10 (4H, m), 2.28 (3H, s), 2.20—2.42 (8H, m), 2.75 (1H, s), 3.90 (2H, s), 6.98 (2H, s)
XIIg	$C_{15}H_{22}O_5S$	57.30 (57.10	7.05 6.68)	1.70—2.10 (2H, m), 2.20—2.45 (5H, m), 2.45—2.70 (8H, m), 3.61 (3H, s), 4.39 (2H, s), 6.99 (2H, s)
XIIh	$C_{16}H_{22}O_6S$	56.12 (56.42	6.47 6.50)	1.70—2.05 (2H, m), 2.01 (3H, s), 2.28 (3H, s), 2.40—2.70 (2H, m), 2.63 (6H, s), 3.42 (3H, s), 4.01 (2H, t), 4.40 (2H, s), 7.00 (2H, s)
XIIi	$C_{16}H_{22}O_6S$	56.12 (56.46	6.47 6.31)	1.60—2.05 (2H, m), 2.30 (3H, s), 2.62 (6H, s), 2.65 (2H, t), 3.22 (3H, s), 3.30 (2H, t), 4.43 (2H, s), 7.00 (2H, s)

trimethylbenzenesulfonyl chloride in the presence of triethylamine in dichloromethane (method D). On the other hand, protection of the carbonyl group in compounds III with ethylene glycol or with orthoesters[7] in the presence of conc. sulfuric acid in alcohol also gave the arenesulfonates (XV) in fair yields (method E). The bis-arenesulfonates (XVI) were prepared by the reaction of the diazoketones (II) with the corresponding bis-arenesulfonic acids in good yields (method F) (Chart 4, Tables VI and VII).

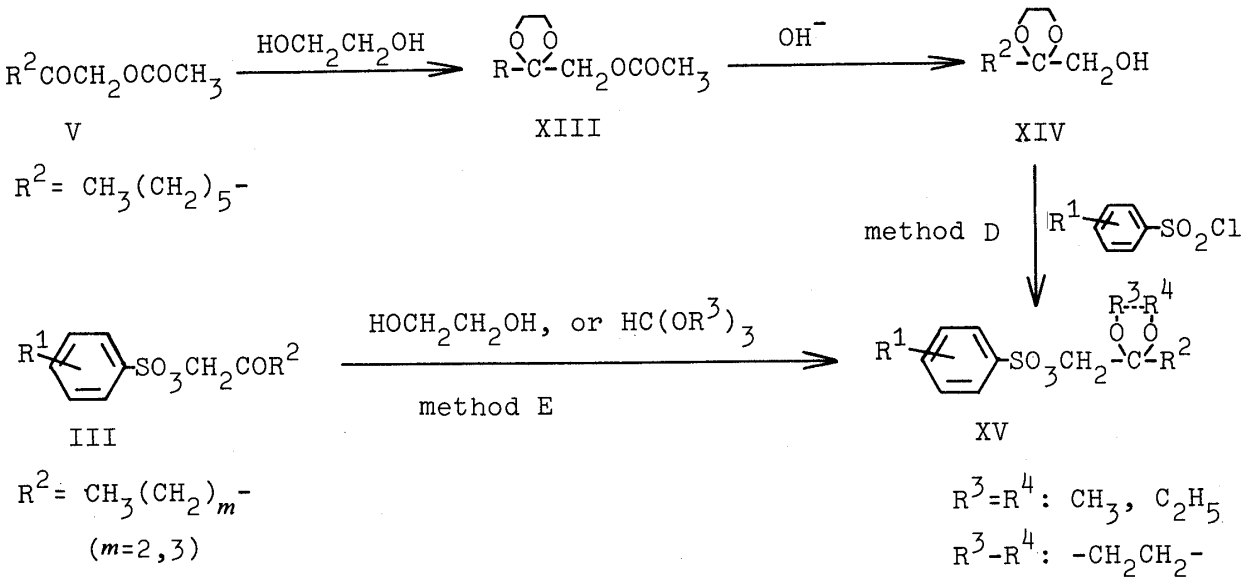


Chart 3

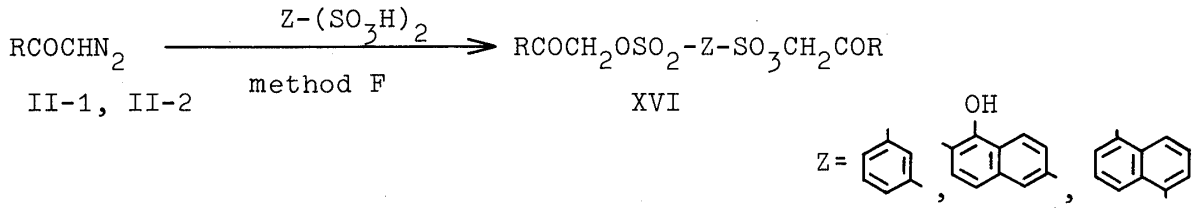
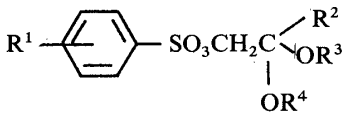


Chart 4

TABLE V. Inhibitory Activities on Enzymes of XV



XV

Compd. No.	R^1	R^2	R^3	R^4	Method[a]	Yield (%)	mp (°C)	Inhibitions: Esterase[b] IC_{50} (μM)	Inhibitions: Chymotry.[c] (1×10^{-4} M)
XVa	2,4,6-$(CH_3)_3$	$(CH_2)_2CH_3$	CH_3	CH_3	E	60	43—44	>1000	14
XVb	2,4,6-$(CH_3)_3$	$(CH_2)_2CH_3$	C_2H_5	C_2H_5	E	56	73—75	80	21
XVc	H	$(CH_2)_3CH_3$	$-CH_2CH_2-$		E	72	Oil	85	6
XVd	2,4,6-$(CH_3)_3$	$(CH_2)_5CH_3$	$-CH_2CH_2-$		D	88	Oil	50	25

a) See the experimental section. *b, c*) See the corresponding footnote in Table I.

Enzyme-Inhibitory Activity (*in Vitro* Experiments)

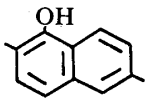
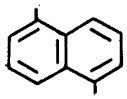
Methyl butyrate and *N*-acetyltyrosine ethyl ester (ATEE) were used as substrates for the activity determination of esterase[8] and chymotrypsin,[8] respectively (Tables I, III, V and VI).

Pharmacological Examinations (*in Vivo* Experiments)

Male Wistar rats (7 weeks old) were used, with five animals in each experimental group. A test compound (100 or 200 mg) was mixed with 10 ml of olive oil containing cholesterol

TABLE VI. Inhibitory Activity on Esterase of XVI

$RCOCH_2OSO_2$–Z–SO_3CH_2COR
XVI

Compd. No.	R	Z	Yield (%)	mp (°C)	Inhibition Esterase[a] IC_{50} (μM)
XVIa	$(CH_2)_2CH_3$		78	Oil	100
XVIb	$(CH_2)_4CH_3$		69	74—75	—[b]
XVIc	$(CH_2)_7CH_3$		71	141—143	150
XVId	$CH(CH_2)_3CH_3$ C_2H_5		77	123—124	—[b]

a) Methyl butyrate was used as a substrate. *b*) Not tested.

TABLE VII. Physical Data for XV and XVI

Compd. No.	Formula	Analysis (%) Calcd (Found) C	H	^{1}H-NMR ($CDCl_3$) δ ppm
XVa	$C_{16}H_{26}O_5S$	58.16 (58.59	7.93 8.15)	0.70—1.70 (7H, m), 2.29 (3H, s), 2.64 (6H, s), 3.08 (6H, s), 3.80 (2H, s), 6.90 (2H, s)
XVb	$C_{18}H_{30}O_5S$	60.30 (60.01	8.44 8.62)	0.75—1.75 (13H, m), 2.29 (3H, s), 2.62 (6H, s), 3.15—3.48 (4H, q), 3.81 (2H, s), 6.90 (2H, s)
XVc	$C_{14}H_{20}O_5S$	55.98 (55.93	6.71 6.91)	0.70—1.75 (9H, m), 3.87 (4H, s), 3.89 (2H, s), 7.35—7.92 (5H, m)
XVd	$C_{19}H_{30}O_5S$	61.59 (61.72	8.16 8.32)	0.70—1.80 (13H, m), 2.30 (3H, s), 2.64 (6H, s), 3.78 (2H, s), 3.88 (4H, s), 6.90 (2H, s)
XVIa	$C_{16}H_{22}O_8S_2$	47.75 (47.88	4.51 4.71)	0.75—1.00 (6H, m), 1.30—1.80 (4H, m), 2.20—2.50 (4H, m), 4.64 (4H, s), 7.60—7.85 (1H, m), 8.05—8.45 (3H, m)
XVIb	$C_{20}H_{30}O_8S_2$	51.93 (51.83	6.54 6.53)	0.88—1.75 (18H, m), 2.41 (4H, t), 4.66 (4H, s), 7.60—8.50 (3H, m)
XVIc	$C_{30}H_{44}O_9S_2$	58.80 (58.74	7.23 7.29)	[a] 0.70—1.70 (30H, m), 2.32 (4H, t), 4.82 (2H, s), 4.89 (2H, s), 7.31 (1H, d), 7.96 (1H, dd), 8.22—8.45 (2H, m), 8.77 (1H, d)
XVId	$C_{28}H_{40}O_8S_2$	59.13 (59.19	7.09 7.00)	0.65—1.75 (28H, m), 2.30—2.55 (2H, m), 4.60 (4H, s), 7.75 (3H, s), 8.32 (3H, s)

a) DMSO-d_6 was used as a solvent.

(15%), and the mixture was orally administered to rats at the dose of 10 ml per kg. Blood samples for the determination of plasma triglyceride and plasma total cholesterol were taken from the orbital vein of the rats at 2 and 8 h, respectively, after the administration. Plasma triglyceride and plasma total cholesterol were analyzed by using commercially available analysis kits (Triglyceride-B-Test Wako[9] and Cholesterol-Test Wako[10]). Decreases of triglyceride and cholesterol were expressed as percentages with respect to the control values

obtained by using olive oil containing no test compound.

Results and Discussion

The physical and biological data for the compounds (III, XII, XV and XVI) are listed in Tables I—VII. On the basis of the data obtained by *in vitro* and *in vivo* screening, the structure–activity relationships of arenesulfonates are considered to be as follows.

1) In the series of III-1. i) The esterase-inhibitory potencies of the compounds having trimethyl or tetramethyl substituents on the benzene ring were higher than those of the compounds having a monomethyl or monomethoxy group on the benzene ring. ii) On the other hand, chymotrypsin-inhibitory potencies decreased with increasing number of substituents on the benzene ring.

2) Regarding the alkyl chain of the sulfonate, the peak of esterase-inhibitory potency was obtained with the compounds having a carbon number of 10 to 12, *i.e.*, III-1d, 1i, 1n, 1u and 1y; $IC_{50} = 8 \times 10^{-9}$, 3.4×10^{-7}, 1×10^{-7}, 3×10^{-10} and 3×10^{-11} M, respectively. In particular, III-1y exhibited the highest potency among compounds hitherto reported by us. On the other hand, the peak of chymotrypsin-inhibitory potency was obtained at a slightly shorter carbon number (7 to 9) of the side chain than that for the esterase potency.

3) A 2,4,6-trimethylphenyl group was introduced into all the compounds of the series III-2 because of the effect of this group in the series III-1, as mentioned above. Several arenesulfonates (III-2) having a branched chain on the alkyl ester moiety were synthesized, but most of the compounds (III-2) showed much lower inhibitory activities toward esterase and chymotrypsin than III-1. Moreover, most of the compounds in the series of III-2 showed similar inhibitory potency toward esterase irrespective of the carbon chain length of the alkyl ester moiety.

4) In the series of XII. Several substituents were introduced at the terminal position of the alkyl chain. The order of inhibitory potency toward esterase was as follows: Cl > OCH_3 > CO_2CH_3 > $OCOCH_3$ > OH.

5) In the series of XV and XVI. Protection of the carbonyl group in the case of XV as well as introduction of two sulfonate functions (XVI) resulted in greatly reduced inhibitory activity. Therefore, a monosulfonate and a carbonyl group at the 2-position on the alkyl chain are required for enhancement of inhibitory activity toward esterase.

6) The order of inhibitory potency toward esterase *in vitro* was as follows: III-1 > III-2 $\geqq$XII > XV=XVI. The plasma triglyceride-reducing and cholesterol-reducing effects of III and XII were examined. Most of III-1 and 2 and some of XII caused significant reductions of lipid levels. In particular, III-1a—1d, 1p, 1s, 2a, 2b and 2g—2j showed potent hypolipidemic actions (74 to 98% reductions of plasma triglyceride and 60 to 87% reductions of plasma total cholesterol *in vivo*). However, we could not find any clear relationship between the esterase-inhibitory activity *in vitro* and the hypolipidemic effects *in vivo*. This might be because of insufficient incorporation of the highly lipophilic compounds into micelles containing bile acid and lipids in the intestinal lumen (*i.e.*, III-1t, 1u, 1x and 1y).

Conclusion

We prepared a series of 1-(substituted benzenesulfonyloxy)-2-alkanone derivatives and related compounds with the aim of finding more potent hypolipidemic agents, and evaluated their inhibitory activities toward enzymes in the small intestinal lumen (esterase and chymotrypsin) as well as their hypolipidemic effects. Many compounds of the series III-1 and 2 exhibited not only potent and moderate inhibitory activities toward esterase and toward chymotrypsin, respectively, but also potent hypolipidemic effects *in vivo*. In particular, 1-

(2,3,4,6-tetramethylbenzenesulfonyloxy)-2-decanone (III-1y) exhibited a more potent inhibitory activity toward esterase ($IC_{50} = 3 \times 10^{-11}$ M) than esterastin[2] ($IC_{50} = 2 \times 10^{-10}$ M). On the other hand, clear relationships between the inhibitory activity toward esterase *in vitro* and hypolipidemic effects *in vivo* in series III-1 and 2 were not apparent. Further researches are necessary in order to establish the structure–activity relationships.

Experimental

All melting points were recorded with a Yanagimoto micromelting point apparatus and are uncorrected. Spectral data were obtained as follows: mass spectrum (MS) with a JEOL LMS-01G-2 spectrometer; proton nuclear magnetic resonance (^{1}H-NMR) with a JEOL JMN-FX 100 spectrometer (using tetramethylsilane as an internal standard). Chemical shifts of ^{1}H-NMR spectra 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.

1-Diazo-2-hexanone (II-1a). Typical Procedure——*n*-Pentanoyl chloride (I-1a) (1.2 g) was added dropwise to an ethereal solution (100 ml) of diazomethane (from 7.0 g of nitrosomethylurea) under stirring and ice-cooling according

TABLE VIII. Physical Data for II-1 and 2

$CH_3(CH_2)_mCOCHN_2$ (II-1), $CH_3(CH_2)_mCH(R_2)(CH_2)_nCOCHN_2$ (II-2)

Compd.[a] No.	R^2	m	n	MS (M^+)	^{1}H-NMR ($CDCl_3$) δ ppm
II-1a[11]	—	3	—	126	0.92 (3H, t), 1.10—1.80 (4H, m), 2.29 (2H, t), 5.22 (1H, s)
II-1b[12]	—	4	—	140	0.90 (3H, t), 1.05—1.80 (6H, m), 2.29 (2H, t), 5.26 (1H, s)
II-1c[13]	—	5	—	154	0.83 (3H, t), 1.00—1.85 (8H, m), 2.28 (2H, t), 5.18 (1H, s)
II-1d[14]	—	6	—	168	0.85 (3H, t), 1.05—1.90 (10H, m), 2.30 (2H, t), 5.15 (1H, s)
II-1e[15]	—	7	—	182	0.87 (3H, t), 1.15—1.85 (12H, m), 2.31 (2H, t), 5.20 (1H, s)
II-1f[16]	—	8	—	196	0.89 (3H, t), 1.30 (10H, s), 1.45—1.75 (4H, m), 2.30 (2H, t), 5.21 (1H, s)
II-1g	—	9	—	210	0.82 (3H, t), 1.21 (12H, m), 1.40—1.75 (4H, m), 2.32 (2H, t), 5.12 (1H, s)
II-1h[17]	—	10	—	224	0.84 (3H, t), 1.20 (14H, m), 1.44—1.80 (4H, m), 2.30 (2H, t), 5.18 (1H, s)
II-2a[18]	CH_3	0	1	126	0.88 (3H, t), 1.12 (3H, d), 1.15—1.85 (2H, m), 1.95—2.40 (1H, m), 5.20 (1H, s)
II-2b	CH_3	0	2	140	0.90 (3H, t), 1.10 (3H, d), 1.05—1.80 (4H, m), 2.20—2.45 (1H, m), 5.21 (1H, s)
II-2c	CH_3	0	3	154	0.89 (3H, t), 1.10 (3H, d), 1.00—1.75 (6H, m), 2.15—2.50 (1H, m), 5.20 (1H, s)
II-2d	C_2H_5	0	3	168	0.89 (3H, t), 1.05—1.90 (8H, m), 2.00—2.35 (1H, m), 5.19 (1H, s)
II-2e	n-C_3H_7	0	3	182	0.70—1.00 (6H, m), 1.00—1.85 (10H, m), 2.05—2.40 (1H, m), 5.18 (1H, s)
II-2f	n-C_4H_9	0	3	196	0.89 (3H, t), 1.00—1.80 (12H, m), 2.00—2.40 (1H, m), 5.20 (1H, s)
II-2g	CH_3	0	4	168	0.88 (3H, t), 1.08 (3H, d), 1.05—1.80 (8H, m), 2.20—2.50 (1H, m), 5.19 (1H, s)
II-2h[19]	CH_3	1	0	126	0.88 (6H, d), 1.80—2.20 (3H, m), 5.19 (1H, s)
II-2i[20]	CH_3	1	1	140	0.65—1.50 (8H, m), 1.70—2.18 (1H, m), 2.20 (2H, t), 5.16 (1H, s)
II-2j	CH_3	1	2	154	0.65—1.00 (6H, m), 1.10—1.55 (4H, m), 1.70—2.10 (1H, m), 2.18 (2H, t), 5.19 (1H, s)
II-2k	CH_3	2	0	140	0.88 (6H, d), 1.10—1.80 (3H, m), 2.25 (2H, t), 5.18 (1H, s)
II-2l	CH_3	2	1	154	0.70—2.00 (11H, m), 2.30 (2H, t), 5.12 (1H, s)
II-2m	CH_3	3	0	154	0.89 (6H, d), 1.00—1.80 (5H, m), 2.28 (2H, t), 5.20 (1H, s)
II-2n	CH_3	6	0	196	0.65—1.80 (17H, m), 2.05—2.45 (2H, m), 5.18 (1H, s)

a) All compounds except II-1g, mp 78—79 °C, and II-1h, mp 43—44 °C (lit.,[19] mp 44—44.5 °C), were light yellowish oils, and the yields of all compounds were quantitative.

to Haworth *et al.*[3] After being stirred for 1 h, the reaction mixture was evaporated to dryness under reduced pressure to give II-1a quantitatively as a light yellowish oil. The other compounds (II-1b—1h and 2a—2n) were similarly prepared from the corresponding alkanoyl chlorides (I) and diazomethane. Data are listed in Table VIII.

1-Acetoxy-2-octanone (V)[6]——An ethereal solution (20 ml) containing diazoketone (II-1c) (1.5 g) was added dropwise to a saturated ethereal solution (100 ml) of anhydrous hydrogen chloride under stirring and ice-cooling. After being stirred for 0.5 h, the reaction mixture was evaporated to dryness under reduced pressure to give 1-chloro-2-octanone (IV).[21] The crude product (IV) was added to an 80% ethanol solution (50 ml) of potassium acetate (1.2 g). 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 water. The chloroform layer was dried over sodium sulfate and evaporated under reduced pressure to give V as a crude oil, which was purified by distillation. Yield 1.2 g (65%), bp 92—95 °C/1 mmHg (lit.,[6] bp 98—104 °C/5 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t), 1.27 (6H, s), 1.40—1.80 (2H, m), 2.15 (3H, s), 2.28 (2H, t), 4.60 (2H, s).

1-Hydroxy-3-methyl-2-pentanone (VI-2a). Typical Procedure——Dry hydrogen chloride was passed into an ethereal solution (100 ml) of 1-diazo-3-methyl-2-pentanone (II-2a)[18] (5.0 g) under stirring and ice-cooling. After being stirred for 0.5 h, the reaction mixture was worked up in the same manner as used for the preparation of V. The crude product was added to an 80% ethanol solution (100 ml) of potassium acetate (4.7 g). After being refluxed for 8 h, the reaction mixture was worked up in the same manner as used for the preparation of V. The residue was dissolved in a mixture of methanol (30 ml) and 6 N HCl (40 ml). After being stirred at 40—50 °C for 5 h, the reaction mixture was concentrated to about 20 ml under reduced pressure, then extracted with ether (100 ml). The ether layer was washed with water, dried over sodium sulfate and evaporated under reduced pressure to give VI as a crude oil, which was purified by distillation. Yield 3.0 g (65%). bp 68 °C/19 mmHg. Other data are listed in Table IX. Compounds VI-1a—1c and 2b—2f were similarly prepared from the corresponding 1-diazo-2-alkanones (II). Compounds VI-2b, 2c, 2e and 2f were purified by silica gel column chromatography with chloroform. Data are listed in Table IX.

Table IX. Physical Data for VI-1 and 2

$CH_3(CH_2)_mCOCH_2OH$ (VI-1), $CH_3(CH_2)_m\overset{\displaystyle R^2}{\underset{|}{C}}H(CH_2)_nCOCH_2OH$ (VI-2)

Compd. No.	R^2	m	n	Yield[a] (%)	bp (°C/mmHg)	^{1}H-NMR ($CDCl_3$) δ ppm
VI-1a[6]	—	5	—	50	118—121/23	0.89 (3H, t), 1.10—1.90 (8H, m), 2.38 (2H, t), 3.10 (1H, t), 4.20 (2H, d)
VI-1b[22]	—	6	—	55	128/28	0.89 (3H, t), 1.10—1.85 (8H, m), 2.38 (2H, t), 3.28 (1H, br), 4.20 (2H, s)
VI-1c[23]	—	8	—	37	47—49[b]	0.85 (3H, t), 1.24 (12H, s), 1.35—1.80 (2H, m), 2.35 (2H, t), 3.08 (1H, t), 4.20 (2H, d)
VI-2a	CH_3	0	1	65	68/19	0.89 (3H, t), 1.13 (3H, d), 1.13—1.90 (2H, m), 2.20—2.70 (1H, m), 3.22 (1H, br), 4.32 (2H, d)
VI-2b	CH_3	0	2	70	Oil[c]	0.90 (3H, t), 1.12 (3H, d), 1.20—1.85 (4H, m), 2.30—2.80 (1H, m), 3.10 (1H, t), 4.24 (2H, d)
VI-2c	C_2H_5	0	3	73	Oil[c]	0.88 (3H, t), 1.00—1.85 (8H, m), 2.15—2.50 (1H, m), 3.15 (1H, br), 4.20 (2H, s)
VI-2d[24]	CH_3	1	0	55	62—64/14	0.98 (6H, d), 1.90—2.40 (3H, m), 3.46 (1H, br), 4.19 (2H, s)
VI-2e	CH_3	1	1	78	Oil[c]	0.65—1.50 (8H, m), 1.70—2.20 (1H, m), 2.28 (2H, t), 3.28 (1H, br), 4.16 (2H, s)
VI-2f[24]	CH_3	2	0	67	Oil[c]	0.92 (6H, d), 1.25—1.70 (3H, m), 2.38 (2H, t), 3.14 (1H, t), 4.21 (2H, d)

a) Yield from the diazoketones (II). *b*) Melting point. *c*) Purified by column chromatography over silica gel.

1-Bromo-4-methyl-2-pentanol (VIIIa)——The title compound (VIIIa) was prepared by treating 4-methyl-1-pentene (VIIa) (25.0 g) with *N*-bromosuccinimide (53.0 g) in the presence of a catalytic amount of acetic acid (2—3 drops) in water (100 ml) according to Forgó and Büchi.[5] The obtained crude oil was purified by distillation to give VIIIa. Yield 27.2 g (50%), bp 75—76 °C/20 mmHg. MS *m/e*: 180 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.96 (6H, d), 1.10—2.00 (3H, m), 2.56 (1H, s), 3.25—3.50 (1H, m), 3.65—4.00 (2H, m). 1-Bromo-4-methyl-2-hexanol (VIIIb) was similarly prepared from 4-methyl-1-hexene (VIIb) (5.0 g). Yield 7.0 g (70%), bp 79 °C/4 mmHg. MS *m/e*: 194 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.65—1.10 (6H, m), 1.10—1.85 (5H, m), 2.60 (1H, s), 3.30—3.50 (1H, m), 3.60—4.00 (2H, m).

1-Bromo-4-methyl-2-pentanone (IXa)[25]——The title compound (IXa) was prepared by the oxidation of 1-bromo-4-methyl-2-pentanol (VIIIa) (27.0 g) with sodium dichromate–sulfuric acid according to Elderfield and Ressler.[26] Yield 12.0 g (41%), bp 89—91 °C/40 mmHg. ^{1}H-NMR ($CDCl_3$) δ: 0.80 (6H, d), 1.90—2.25 (1H, m), 2.52 (2H, d), 3.84 (2H, s). 1-Bromo-4-methyl-2-hexanone (IXb) was similarly prepared from 1-bromo-4-methyl-2-hexanol (VIIIb) (7.0 g). Yield 3.5 g (50%), bp 85 °C/15 mmHg. MS *m/e*: 192 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.70—1.10 (6H, m), 1.10—1.55 (2H, m), 1.75—2.15 (1H, m), 2.51 (2H, t), 3.88 (2H, s).

1-Benzenesulfonyloxy-2-hexanone (III-1a). Typical Procedure (Method A)——The title compound (III-1a) was prepared from II-1a (1.3 g) and benzenesulfonic acid monohydrate (3.5 g) in ethereal solution, in the same manner as described in the previous paper.[1] Yield 1.6 g (61%). Other data are listed in Tables I and II. Compounds III-1b—1z, 2a—2g and 2j—2n were similarly prepared from the corresponding sulfonic acids with diazoketones (II-1 and 2). Data are listed in Tables I and II.

1-Benzenesulfonyloxy-2-octanone (III-1c). Typical Procedure (Method B)——Triethylamine (1.7 ml) was added dropwise to a solution consisting of benzenesulfonyl chloride (1.7 g), VI-1a[6] (1.5 g) and dichloromethane (5 ml) under stirring at 0—5 °C. After being stirred for 2 h, the reaction mixture was extracted with chloroform (50 ml) and washed with 1 N HCl (20 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 an oily product. This product was identical with III-1c obtained by method A. Yield 1.5 g (51%). Compounds III-1d, 1g, 1i, 1r, 1s, 2a—2c and 2h—2k were similarly prepared from the corresponding alcohol (VI) and arenesulfonyl chloride. All of these compounds were identical with the compounds obtained by method A. Yields and other data are listed in Table I.

4-Methyl-1-(2,4,6-trimethylbenzenesulfonyloxy)-2-pentanone (III-2h). Typical Procedure (Method C)——Silver 2,4,6-trimethylbenzenesulfonate (25.5 g) was added to a solution of IXa (11.4 g) in acetonitrile (150 ml). After being stirred for 30 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 (200 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 the desired product. This product was identical with III-2h obtained by method A. Yield 12.5 g (66%). Compound III-2i was similarly prepared from silver 2,4,6-trimethylbenzenesulfonate and IXb. This compound was identical with III-2i obtained by method A. Yields and other data are listed in Table I.

5-Chloro-1-diazo-2-pentanone (XIa)——The title compound (XIa) was prepared by treatment of 5-chlorobutyroyl chloride (2.0 g) with diazomethane (1.5 eq) in ethereal solution in the same manner as used for the preparation of II-1a. The yield was quantitative. Other data are listed in Table X. Compounds XIb—e were similarly prepared from the corresponding acid chlorides (X) and diazomethane. Data are listed in Table X.

TABLE X. Physical Data for XI

$X-(CH_2)_3COCHN_2$ (XI)

Compd.[a] No.	X	MS (M^+)	^{1}H-NMR ($CDCl_3$) δ ppm
XIa[27]	Cl	146	1.90—2.25 (2H, m), 2.25 (2H, t), 3.56 (2H, t), 5.28 (1H, s)
XIb[28]	OCH_3	142	1.75—2.10 (2H, m), 2.15—2.50 (4H, m), 3.65 (3H, s), 5.28 (1H, s)
XIc	$OCOCH_3$	170	1.80—2.10 (2H, m), 2.02 (3H, s), 2.20—2.50 (2H, m), 4.04 (2H, t), 5.22 (1H, s)
XId[29]	CO_2CH_3	170	1.70—2.24 (4H, m), 2.40 (2H, t), 3.28 (3H, s), 5.30 (1H, s)

a) All compounds were light yellowish oils, and the yields were quantitative.

1-Benzenesulfonyloxy-5-chloro-2-pentanone (XIIa). Typical Procedure——The title compound (XIIa) was prepared from XIa (1.5 g) and benzenesulfonic acid monohydrate (2.3 g) in ethereal solution (30 ml) in the same manner as used for the preparation of III-1a by method A. Yield 2.3 g (81%). Other data are listed in Tables III and IV. Compounds XIIb—e, g—i were similarly prepared from diazoketones (XIb—d) and the corresponding arenesulfonic acids. Data are listed in Tables III and IV.

1-Benzenesulfonyloxy-5-hydroxy-2-pentanone (XIIf)——Compound XIIh (1.0 g) was added to a solution consisting of MeOH (3 ml), tetrahydrofuran (3 ml) and 15% HCl (6 ml). After being stirred for 50 h at room temperature, the reaction mixture was concentrated to about 5 ml 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 with chloroform and the eluate was evaporated to give XIIf. Yield 0.26 g (30%). Other data are listed in Tables III and IV.

1-Acetoxy-2,2-ethylenedioxyoctane (XIII)——A solution consisting of ethylene glycol (5.0 g), V (8.0 g) and benzene (100 ml) was refluxed for 16 h in the presence of a catalytic amount of *p*-toluenesulfonic acid, and the reaction mixture was washed with water. The benzene layer was dried over sodium sulfate and evaporated under reduced pressure to give XIII as a crude oil, which was purified by distillation. Yield 6.0 g (61%), bp 107—108 °C/1 mmHg. MS *m/e*: 230 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.90 (3H, t), 1.30 (8H, s), 1.40—1.90 (2H, m), 2.08 (3H, s), 3.96 (4H, s), 3.98 (2H, s).

2,2-Ethylenedioxy-1-hydroxyoctane (XIV)——Compound XIII (5.0 g) was added to a solution of MeOH (20 ml) and 1 N NaOH (23 ml). After being stirred for 0.5 h at room temperature, the reaction mixture was diluted with water (50 ml) and extracted with ether (100 ml). The ether layer was dried over sodium sulfate and evaporated under reduced pressure to give XIV as a crude oil, which was purified by distillation. Yield 3.0 g (73%), bp 95—97 °C/1 mmHg. MS *m/e*: 188 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.88 (3H, t), 1.28 (8H, s), 1.35—1.80 (2H, m), 2.08 (1H, t), 3.46 (2H, d), 3.97 (4H, s).

2,2-Ethylenedioxy-1-(2,4,6-trimethylbenzenesulfonyloxy)octane (XVd) (Method D)——Triethylamine (1.8 ml) was added dropwise to a solution consisting of 2,4,6-trimethylbenzenesulfonyl chloride (2.2 g), XIV (1.9 g) and dichloromethane (5 ml) under stirring at 0—5 °C. After being stirred for 3 h at the same temperature, the reaction mixture was worked up in the same manner as used for the preparation of III-1c by method B. The crude product was chromatographed on a silica gel column with chloroform, and the eluate was evaporated to give XVd as an oily material. Yield 3.3 g (88%). Other data are listed in Tables V and VII.

2,2-Dimethoxy-1-(2,4,6-trimethylbenzenesulfonyloxy)pentane (XVa) (Method E)——A solution consisting of 1-(2,4,6-trimethylbenzenesulfonyloxy)-2-pentanone[30] (5.0 g), methyl orthoformate (2.0 g) and dried methanol (20 ml) was stirred for 3 h at 70—80 °C in the presence of a catalytic amount of conc. H_2SO_4 (2 drops). The reaction mixture was diluted with water (100 ml) and extracted with ether (100 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 XVa as white crystals. Yield 3.5 g (60%). Other data are listed in Tables V and VII. Compound XVb was similarly prepared from 1-(2,4,6-trimethylbenzenesulfonyloxy)-2-pentanone[30] (2.0 g) and ethyl orthoformate (1.2 g). Yield 1.4 g (56%). Compound XVc was prepared by refluxing a solution consisting of III-1a (1.0 g), ethylene glycol (0.30 g) and benzene (30 ml) in the presence of a catalytic amount of *p*-toluenesulfonic acid. The reaction mixture was worked up in the same manner as used for the preparation of XIII. The crude product was chromatographed on a silica gel column with chloroform and the eluate was evaporated to give XVc. Yield 0.83 g (71%). Data are listed in Tables V and VII.

Bis-[1-(1,3-benzenedisulfonyloxy)-2-heptanone] (XVIb). Typical Procedure (Method F)——The title compound (XVIb) was prepared from 1,3-benzenedisulfonic acid (2.8 g) and II-1a (1.4 g) in the same manner as used for the preparation of III-1a by method A. The crude product was recrystallized from petroleum ether to give XVIb as white crystals. Yield 3.0 g (69%), mp 74—75 °C. Other data are listed in Tables VI and VII. Compounds XVIa, c and d were similarly prepared from the corresponding diazoketones (II) and arenedisulfonic acids. Data are listed in Tables VI and VII.

Enzyme-Inhibitory Activities——The inhibitory activities toward esterase and chymotrypsin were determined by the methods described in the previous paper.[1]

Pharmacology——The triglyceride and total cholesterol levels in plasma were measured at the dosage of 100 or 200 mg/kg in the same manner as described in the previous paper.[1]

Acknowledgment The authors wish to thank Professor M. Okamoto and Associate Professor S. Ohta of Kyoto Pharmaceutical University for their valuable advice.

References and Notes

1) Part I: K. Ogawa, T. Terada, T. Muranaka, T. Hamakawa, S. Hashimoto, and S. Fujii, *Chem. Pharm. Bull.*, **34**, 1118 (1986).
2) *a*) H. Umezawa, T. Aoyagi, T. Hazato, K. Uotani, F. Kojima, M. Hamada, and T. Takeuchi, *J. Antibiot.*, **31**, 639 (1978); *b*) S. Kondo, K. Uotani, M. Miyamoto, T. Hazato, H. Naganawa, T. Aoyagi, and H. Umezawa, *ibid.*, **31**, 801 (1978).
3) R. D. Haworth, H. K. Pindred, and P. R. Jefferies, *J. Chem. Soc.*, **1954**, 3617.
4) A. L. Crowther and G. Holt, *J. Chem. Soc.*, **1963**, 2818.
5) U. I. Forgó and J. Büchi, *Pharm. Acta Helv.*, **45**, 227 (1970).
6) W. J. Hickinbottom and D. R. Hogg, *J. Chem. Soc.*, **1954**, 4200.
7) E. C. Taylor and C. S. Chiang, *Synthesis*, **1977**, 467.
8) *a*) M. Muramatu and S. Fujii, *J. Biochem.* (Tokyo), **64**, 807 (1968); *b*) M. Muramatu, T. Onishi, S. Makino, Y. Hayakumo, and S. Fujii, *ibid.*, **58**, 214 (1965); *c*) S. Hestrin, *J. Biol. Chem.*, **180**, 249 (1949).
9) In the measurement of plasma triglyceride concentration, Fletcher's procedure was used with some modification. M. J. Fletcher, *Clin. Chim. Acta*, **22**, 393 (1968).

10) In the measurement of plasma total cholesterol concentration, Rosenthal's procedure was used with some modification. H. L. Rosenthal, *J. Lab. and Clin. Med.*, **50**, 318 (1957).
11) A. L. Fridman, N. A. Kolobov, and V. V. Zalesov, *Zh. Vses. Khim. O-va.*, **21**, 116 (1976).
12) S. A. Mathin and P. G. Sammes, *J. Chem. Soc., Perkin Trans. 1*, **1972**, 2623.
13) Joko Yakuhin Kogyo Co., Ltd., Japan Kokai, 75116465 [*Chem. Abstr.*, **84**, 73742*w* (1976)].
14) C. Grundmann, *Ann. Chem.*, **536**, 29 (1938).
15) L. T. Scott and M. A. Minton, *J. Org. Chem.*, **42**, 3757 (1977).
16) G. Cardillo, M. Orena, G. Porzi, and S. Sandri, *J. Org. Chem.*, **46**, 2439 (1981).
17) S. W. Pelletier, Z. Djarmati, S. D. Lajsic, I. V. Micovic, and D. T. C. Yang, *Tetrahedron*, **31**, 1659 (1975).
18) L. Lardicci, C. Battistini, and R. Menicagli, *J. Chem. Soc., Perkin Trans. 1*, **1974**, 344.
19) D. S. Tarbell and J. A. Price, *J. Org. Chem.*, **22**, 245 (1957).
20) I. G. Vasi and N. T. Nanavati, *J. Inst. Chem.*, **48**, 198 (1976).
21) F. Püshel and C. Kaiser, *Chem. Ber.*, **97**, 2903 (1964).
22) A. Wissner, *J. Org. Chem.*, **44**, 4617 (1979).
23) G. Cardillo, *J. Org. Chem.*, **46**, 2439 (1981).
24) T. Cuvigny, G. Valette, M. Larcheveque, and H. Normant, *J. Organomet. Chem.*, **155**, 147 (1978).
25) U. H. Lindberg, G. Bexell, J. Pedersen, and S. Ross, *Acta Pharm. Suecica.*, **7**, 423 (1970).
26) R. C. Elderfield and C. Ressler, *J. Am. Chem. Soc.*, **72**, 4059 (1950).
27) N. F. Woolsey and M. H. Khalil, *J. Org. Chem.*, **40**, 3521 (1975).
28) H. Garpio, E. Galeazzi, R. Greenhous, A. Guzmán, E. Velarde, Y. Antonio, F. Franco, A. Leon, V. Pérez, R. Salas, and D. Valdés, *Can. J. Chem.*, **60**, 2295 (1982).
29) J. Rokach, J. Adams, and R. Perry, *Tetrahedron Lett.*, **24**, 5158 (1983).
30) This compound was reported in the previous paper (ref. 1).