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Studies on Hypolipidemic Agents. III. Synthesis and Esterase-Inhibitory Activity of ω-Cycloalkyl-2-oxoalkyl Arenesulfonates

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Various ω-cycloalkyl-2-oxoalkyl arenesulfonates were synthesized and evaluated for esterase- and chymotrypsin-inhibitory activities and hypolipidemic activity. Among the tested compounds, 2-oxoalkyl arenesulfonates (**4**, **8** and **13**) having a cyclohexyl substituent at the terminus of the alkyl chain exhibited considerable esterase-inhibitory activity, and several compounds among **4** and **8** also exhibited potent hypolipidemic action. The structure–activity relationships of these compounds are discussed.

Keywords——alicyclic alkanoic acid; ω-cycloalkyl-2-oxoalkyl arenesulfonate; ω-oxyacycloalkyl-2-oxoalkyl arenesulfonate; α-diazoketone; α-hydroxyketone; esterase-inhibitory activity; chymotrypsin-inhibitory activity; hypolipidemic activity; structure–activity relationship

Treatment of hyperlipemia is currently considered to be important for the primary prevention of arteriosclerosis,[1,2] and drugs such as Lipocline,[3] Probucol[4] and their analogues have been clinically applied as hypolipidemic agents for this purpose. We have reported[5] that various 2-oxoalkyl arenesulfonates exhibited a selective esterase-inhibitory activity as well as a hypolipidemic effect, for which we postulated a novel action mechanism based on a decrease of uptake of triglycerides and cholesterol esters into the small intestinal mucosa owing to inhibition of the enzymes in the small intestinal lumen. This paper deals with syntheses, biological activities and structure–activity relationships of 2-oxoalkyl arenesulfonates having various cycloalkyl substituents on the oxoalkyl portion.

Synthesis

Two methods were applied to synthesize the 2-oxoalkyl arenesulfonates (**4**, **8** and **13**). The first one involves α-diazoketones (**2**, **7** and **12**) as intermediates (method A). The other involves α-hydroxyketones (**3** and **9**) as intermediates (method B). Some commercially unavailable cyclohexylalkanoic acids (**6**) were prepared by catalytic hydrogenation of the corresponding phenylalkanoic acids (**5**) in the presence of PtO_2 as a catalyst according to the procedure of Allinger and Freiberg.[6] Among the prepared carboxylic acids, **6d** and **6e** were produced as stereoisomeric mixtures of *trans* and *cis* isomers, and their ratio was estimated to be about 1:3 on the basis of the nuclear magnetic resonance (NMR) spectra. Because separation of the stereoisomers of **6d** and **6e** was difficult, they were used without separation in order to tentatively evaluate the activities. The intermediates, α-diazoketones (**2** and **7**), were prepared from the corresponding acyl halides by treatment with diazomethane, and the other intermediates, α-hydroxyketones (**3** and **9**), were prepared by chlorination of the diazoketones with hydrogen chloride followed by treatment with ethyl formate in methanolic potassium hydroxide according to the procedure of Levine and Walti.[7] Physical and spectral

TABLE I. Physical Data for **2**

$X\text{-}(CH_2)_nCOCHN_2$

2

Compd.[a] No.	X	n	MS (M^+)	^{1}H-NMR ($CDCl_3$) δ ppm
2a[b]		0	110	0.75—1.50 (4H, m), 2.00—2.35 (1H, br), 5.24 (1H, s)
2b		1	152	0.85—2.00 (9H, m), 2.30 (2H, s), 5.20 (1H, s)
2c[c]		0	152	1.00—2.00 (10H, m), 2.00—2.40 (1H, br), 5.22 (1H, s)
2d		1	166	0.70—2.10 (11H, m), 2.20 (2H, d, J=7.5 Hz), 5.21 (1H, s)
2e		2	180	0.60—2.00 (13H, m), 2.31 (2H, t, J=8 Hz), 5.23 (1H, s)
2j		3	194	0.60—2.10 (15H, m), 2.30 (2H, t, J=7.5 Hz), 5.20 (1H, s)
2g		0	140	1.70—2.60 (4H, m), 3.70—4.15 (2H, m), 4.20—4.60 (1H, m), 5.76 (1H, s)
2h		0	154	1.50—2.10 (4H, m), 2.20—2.70 (1H, m), 3.15—3.65 (2H, m), 3.70—4.20 (2H, m), 5.30 (1H, s)

a) All compounds were light yellowish oils, and yields of all compounds were nearly quantitative. *b*) Ref. 8. *c*) Ref. 9.

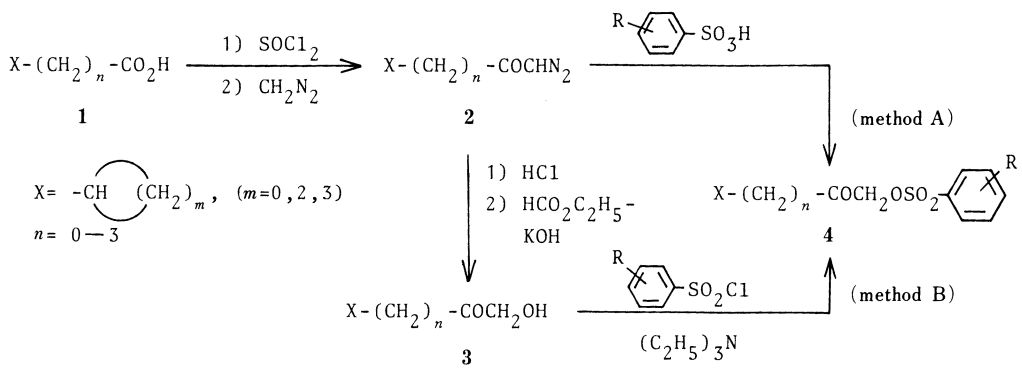


Chart 1

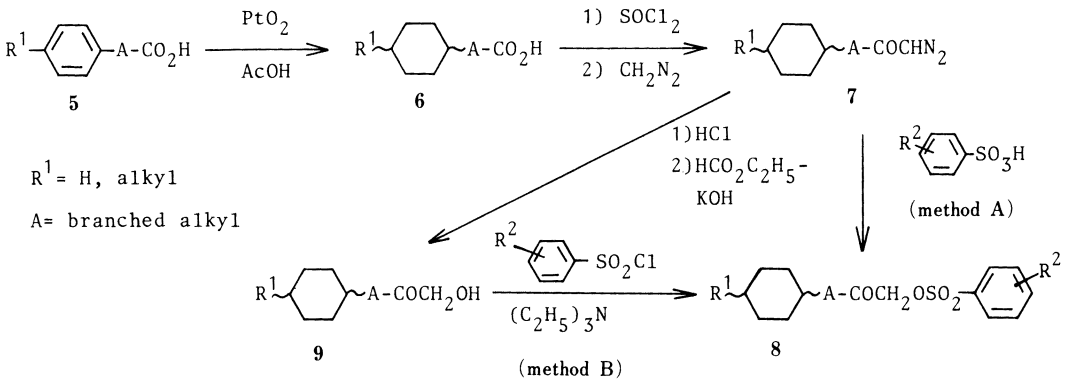
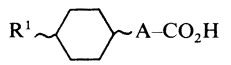


Chart 2

TABLE II. Physical Data for **3**, **6**, **7**, and **9**



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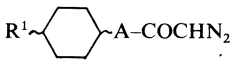

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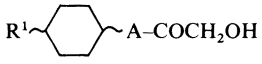


3 and **9**

Compd.[a] No.	R^1	A	bp °C/mmHg (mp °C)	MS (M^+)	^{1}H-NMR ($CDCl_3$) δ ppm
6a[b]	H	$-CH_2CH(CH_3)-$	129/1	170	0.70—1.90 (13H, m), 1.18 (3H, d, J=7 Hz), 2.35—2.70 (1H, m), 11.22 (1H, br)
6b	H	$-CH_2CH(C_2H_5)-$	135—136/1	184	0.96 (3H, t, J=7.5 Hz), 0.70—2.15 (15H, m), 2.20—2.65 (1H, m), 10.75 (1H, br)
6c	H	$-CH_2C(CH_3)_2-$	(68—69)	184	0.80—1.85 (13H, m), 1.19 (6H, s), 10.00 (1H, br)
6d[c]	$-C_2H_5$	—	120/1	156	0.89 (3H, t, J=7.5 Hz), 0.70—2.15 (11H, m), 2.15—2.65 (1H, m), 11.55 (1H, br)
6e[d]	$-CH(CH_3)_2$	—	131—134/1	170	0.88 (6H, d, J=8 Hz), 0.95—2.20 (10H, m), 2.20—2.70 (1H, m), 11.35 (1H, br)
7a	H	$-CH_2CH(CH_3)-$	Oil	194	0.65—1.85 (16H, m), 2.25—2.63 (1H, m), 5.22 (1H, s)
7b	H	$-CH_2CH(C_2H_5)-$	Oil	208	0.65—2.00 (18H, m), 2.10—2.50 (1H, m), 5.20 (1H, s)
7c	H	$-CH_2C(CH_3)_2-$	Oil	208	0.75—1.85 (13H, m), 1.12 (6H, s), 5.42 (1H, s)
7d	$-C_2H_5$	—	Oil	180	0.70—2.20 (14H, m), 2.20—2.43 (1H, s), 5.21, 5.28 (1H, s)
7e	$-CH(CH_3)_2$	—	Oil	194	0.86 (6H, s), 0.80—2.05 (10H, m), 2.05—2.50 (1H, m), 5.22, 5.30 (1H, s)
3a[e]	H	—	115—116/4	142	1.00—2.00 (10H, m), 2.10—2.55 (1H, m), 3.14 (1H, t, J=4 Hz), 4.26 (2H, d, J=4 Hz)
3b	H	$-CH_2CH_2-$	95—97/2	170	0.60—2.00 (13H, m), 2.40 (2H, t, J=8 Hz), 3.14 (1H, t, J=4 Hz), 4.20 (2H, d, J=4 Hz)
9a	H	$-CH_2CH(C_2H_5)-$	110/1	198	0.89 (3H, t, J=7.5 Hz), 0.70—2.00 (15H, m), 2.30—2.68 (1H, m), 3.18 (1H, br), 4.20 (2H, s)
9b	H	$-CH_2C(CH_3)_2-$	Oil[f]	198	0.70—1.80 (13H, m), 1.16 (6H, s), 3.26 (1H, t, J=4 Hz), 4.38 (2H, d, J=4 Hz)

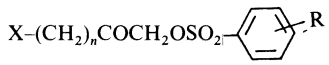
a) Compounds **6d**, **6e**, **7d** and **7e** are stereoisomeric mixtures. *b*) Ref. 10. *c*) Ref. 11. *d*) Ref. 12. *e*) Ref. 13. *f*) Purified by column chromatography on silica gel. Not distilled.

data for the obtained cyclohexylalkanoic acids (**6**), α-diazoketones (**2** and **7**) and α-hydroxyketones (**3** and **9**) are listed in Tables I and II.

The diazoketones (**2** and **7**) were converted to the corresponding arenesulfonates (**4a**—**u** and **8a**—**h**) in good yields by treatment with arenesulfonic acids according to the procedure of Crowther and Holt[14] (method A). Otherwise, the α-hydroxyketones (**3a**, **b** and **9a**, **b**) were esterified with various arenesulfonyl chlorides in the presence of triethylamine to afford the corresponding arenesulfonates (**4d**, **l**, **m** and **8d**, **f**) (method B).

3-Cyclohexyloxy-2-oxoalkyl arenesulfonates (**13**) were similarly obtained by method A starting from the corresponding carboxylic acids (**11**), which were prepared by catalytic hydrogenation of the corresponding 2-phenoxyalkanoic acids (**10**) in the presence of the Rh–Pt (3 : 1) as a catalyst. Physical, spectral, and biological data for the obtained 2-oxoalkyl

TABLE III. Enzyme-Inhibitory Activities of **4**



4

Compd. No.	X	*n*	R	Method[a]	Yield[b] (%)	mp (°C)	Inhibitions: Esterase[d] IC_{50} (μM)	Inhibitions: Chymotry.[e] (1×10^{-4} M)	Reduction[f]: Trigly.[g]
4a		0	4-OCH_3	A	37	Oil[c]	>1000	3	—[h]
4b		0	2,4,6-$(CH_3)_3$	A	41	82—83 (Et–W)[i]	>1000	14	—[h]
4c		1	4-CH_3	A	65	51—52 (M–W)	4.4	90	—[h]
4d		0	H	A B	61 67	Oil[c]	1.6	13	—[h]
4e		0	4-Cl	A	55	69—70 (PE–E)	1.5	32	—[h]
4f		0	4-OH	A	67	124—125 (M–W)	2.6	15	—[h]
4g		0	2,4,6-$(CH_3)_3$	A	68	95—96 (M–W)	0.9	10	—[h]
4h		1	4-CH_3	A	52	32—33 (PE–E)	3.5	98	—[h]
4i		1	4-OH	A	60	92—93 (Et–W)	0.8	—[h]	—[h]
4j		1	4-OC_2H_5	A	67	48—49 (PE)	5.9	97	55
4k		1	2,4,6-$(CH_3)_3$	A	68	37—38 (PE–E)	0.2	10	70
4l		2	H	A B	66 73	46—47 (M–W)	2.2	100	77
4m		2	4-CH_3	A B	69 77	73—74 (M–W)	3.1	100	—[h]
4n		2	4-OC_2H_5	A	54	44—45 (PE–E)	4.0	94	82
4o		2	4-NO_2	A	83	77—78 (PE–E)	7.4	98	—[h]
4p		3	4-OC_2H_5	A	72	40—41 (PE)	6.5	98	56
4q		0	4-CH_3	A	25	103—106 (M–W)	>1000	0	—[h]
4r		0	H	A	60	54—55 (E)	220	9	—[h]
4s		0	4-OH	A	51	154—155 (Et–W)	240	—[h]	—[h]

TABLE III. (continued)

Compd. No.	X	n	R	Method[a]	Yield[b] (%)	mp (°C)	Inhibitions: Esterase[d] IC_{50} (μM)	Inhibitions: Chymotry.[e] (1×10^{-4} M)	Reduction[f]: Trigly.[g]
4t		0	4-OC_2H_5	A	55	57—58 (Et–W)	350	—[h]	—[h]
4u		0	2,4,6-$(CH_3)_3$	A	64	64—65 (PE)	32	—[h]	—[h]

a) See the experimental section. *b*) Yield from the corresponding diazoketone (**2**) (method A) or α-ketoalcohol (**3**) (method B). *c*) Purified by column chromatography on silica gel. *d*) Methyl butyrate was used as a substrate. *e*) ATEE was used as a substrate. Expressed as percentage inhibition of chymotrypsin inhibitory activity at 1×10^{-4} M. *f*) Expressed as percentage deviation from the control value. Dose: 0.3 mmol/kg *p.o.* in rats. See the experimental section. *g*) Plasma triglyceride. *h*) Not tested. *i*) Recrystallization solvents: Et = ethanol, M = methanol, E = ethyl ether, PE = petroleum ether W = H_2O.

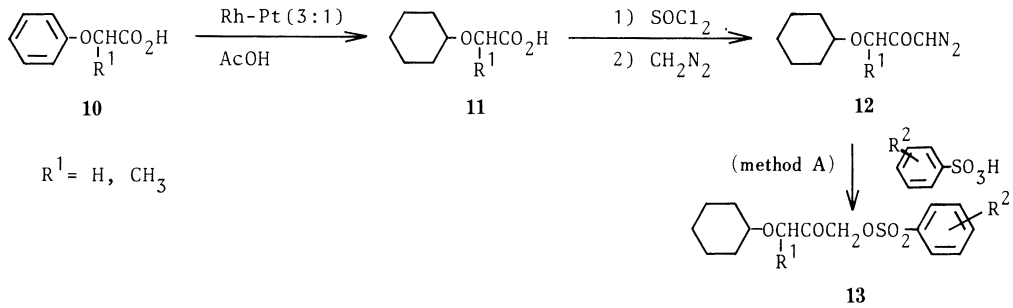


Chart 3

arenesulfonates (**4**, **8** and **13**) are listed in Tables III—VII.

Enzyme-Inhibitory Activity (*in Vitro* Experiments)

Methyl butyrate and *N*-acetyltyrosine ethyl ester (ATEE) were used as substrates for the activity determination of esterase[15] and chymotrypsin,[15] respectively (Tables III, V and VI).

Pharmacological Examination (*in Vivo* Experiment)

Male Wistar rats (7 weeks old) were used, with five animals in each experimental group. A test compound (0.3 mmol) was mixed with 5 ml of olive oil and the mixture was orally administered to rats at the dose of 0.3 mmol/kg. A blood sample for the determination of plasma triglyceride was taken from the orbital vein of the rats at 2 h after the administration. Plasma triglyceride was analyzed by using a commercially available analysis kit (Determiner TG-S Kyowa[16]). Decrease of triglyceride was expressed as the percentage deviation from the control value obtained by using olive oil containing no test compound.

Results and Discussion

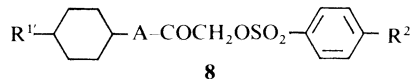
On the basis of the biological data from the *in vitro* and *in vivo* screening tests, the structure–activity relationships of the arenesulfonates may be summarized as follows. i) The biological data for the substituted arenesulfonates (**4**), which have various cycloalkyl or oxacycloalkyl substituents with various methylene chain lengths ($n=0$—3), are listed in Table III. The data indicate that the cyclopentyl (only one example, **4c**) and cyclohexyl

TABLE IV. Physical Data for **4**

Compd. No.	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR ($CDCl_3$) δ ppm
4a	$C_{12}H_{14}O_5S$	53.32 (53.37	5.22 5.13)		0.88—1.30 (4H, m), 1.90—2.30 (1H, m), 3.82 (3H, s), 4.60 (2H, s), 7.00 (2H, d, J=9 Hz), 7.84 (2H, d, J=9 Hz)
4b	$C_{14}H_{18}O_4S$	59.50 (59.57	6.43 6.73)		0.90—1.20 (4H, m), 2.00—2.40 (1H, m), 2.30 (3H, s), 2.65 (6H, s), 4.55 (2H, s), 7.00 (2H, s)
4c	$C_{15}H_{20}O_4S$	60.78 (60.71	6.80 6.90)		0.80—2.30 (9H, m), 2.43 (3H, s), 2.48 (2H, d, J=5 Hz), 4.46 (2H, s), 7.36 (2H, d, J=8 Hz), 7.84 (2H, d, J=8 Hz)
4d	$C_{14}H_{18}O_4S$	59.50 (59.65	6.43 6.27)		1.00—2.00 (10H, m), 2.00—2.70 (1H, br), 4.61 (2H, s), 7.44—8.05 (5H, m)
4e	$C_{14}H_{17}ClO_4S$	53.07 (53.04	5.40 5.44)		1.00—2.00 (10H, m), 2.20—2.65 (1H, m), 4.62 (2H, s), 7.50 (2H, d, J=8 Hz), 7.84 (2H, d, J=8 Hz)
4f	$C_{14}H_{18}O_5S$	56.36 (56.34	6.08 6.11)		1.00—1.90 (10H, m), 2.18—2.56 (1H, br), 3.28 (1H, s), 4.82 (2H, s), 6.90 (2H, d, J=9 Hz), 7.73 (2H, d, J=9 Hz)
4g	$C_{17}H_{24}O_4S$	63.24 (63.02	7.45 7.60)		1.00—2.00 (11H, m), 2.28 (3H, s), 2.60 (6H, s), 4.46 (2H, s), 6.98 (2H, s)
4h	$C_{16}H_{22}O_4S$	61.91 (61.93	7.14 7.13)		0.70—2.00 (11H, m), 2.29 (2H, d, J=6 Hz), 2.43 (3H, s), 4.44 (2H, s), 7.34 (2H, d, J=8 Hz), 7.82 (2H, d, J=8 Hz)
4i	$C_{15}H_{20}O_5S$	57.67 (57.75	6.45 6.53)		0.70—2.00 (11H, m), 2.33 (2H, d, J=6 Hz), 4.53 (2H, s), 6.93 (2H, d, J=9 Hz), 7.77 (2H, d, J=9 Hz)
4j	$C_{17}H_{24}O_5S$	59.97 (59.93	7.10 6.90)		0.70—2.15 (14H, m), 2.34 (2H, d, J=6 Hz), 4.10 (2H, q, J=6.5 Hz), 4.45 (2H, s), 6.98 (2H, d, J=8.5 Hz), 7.81 (2H, d, J=8.5 Hz)
4k	$C_{18}H_{26}O_4S$	63.88 (63.86	7.74 7.48)		0.80—2.00 (11H, m), 2.30 (3H, s), 2.34 (2H, d, J=6.5 Hz), 2.65 (6H, s), 4.40 (2H, s), 7.00 (2H, s)
4l	$C_{16}H_{22}O_4S$	61.90 (61.74	7.14 7.29)		0.60—1.85 (13H, m), 2.45 (2H, t, J=7 Hz), 4.50 (2H, s), 7.35—8.00 (5H, m)
4m	$C_{17}H_{24}O_4S$	62.93 (62.89	7.45 7.25)		0.80—2.30 (13H, m), 2.42 (2H, t, J=7 Hz), 2.46 (3H, s), 4.45 (2H, s), 7.34 (2H, d, J=8 Hz), 7.83 (2H, d, J=8 Hz)
4n	$C_{18}H_{26}O_5S$	60.99 (60.90	7.39 7.56)		0.60—1.85 (13H, m), 1.44 (3H, t, J=7 Hz), 2.44 (2H, t, J=7 Hz), 4.08 (2H, q, J=7 Hz), 4.45 (2H, s), 7.00 (2H, d, J=9 Hz), 7.85 (2H, d, J=9 Hz)
4o	$C_{16}H_{21}NO_6S$	54.07 (54.04	5.96 6.01	3.94 3.74)	0.70—1.85 (13H, m), 2.44 (2H, t, J=7.5 Hz), 4.66 (2H, s), 8.02 (2H, d, J=9 Hz), 8.32 (2H, d, J=9 Hz)
4p	$C_{19}H_{28}O_5S$	61.93 (61.94	7.65 7.62)		0.60—1.85 (18H, m), 2.44 (2H, t, J=7 Hz), 4.10 (2H, q, J=6.5 Hz), 4.46 (2H, s), 6.98 (2H, d, J=8.5 Hz), 7.81 (2H, d, J=8.5 Hz)
4q	$C_{13}H_{16}O_5S$	54.92 (55.03	5.67 6.00)		1.60—2.25 (4H, m), 2.42 (3H, m), 3.10—3.40 (2H, m), 4.03 (2H, q, J=18 Hz), 5.35—5.60 (1H, m), 7.32 (2H, d, J=8.5 Hz), 7.82 (2H, d, J=8.5 Hz)
4r	$C_{13}H_{16}O_5S$	54.92 (54.92	5.67 5.76)		1.50—1.80 (4H, m), 2.60—3.00 (1H, m), 3.20—3.60 (2H, m), 3.80—4.15 (2H, m), 4.62 (2H, s), 7.40—8.10 (5H, m)
4s	$C_{13}H_{16}O_6S$	51.99 (51.86	5.37 5.51)		1.50—1.90 (4H, m), 2.50—3.00 (1H, m), 3.20—3.60 (2H, m), 3.80—4.10 (2H, m), 4.54 (2H, s), 6.96 (2H, d, J=9 Hz), 7.72 (2H, d, J=9 Hz)
4t	$C_{15}H_{20}O_6S$	54.86 (54.57	6.13 6.24)		1.43 (3H, t, J=8 Hz), 1.50—2.00 (4H, m), 2.60—3.00 (1H, m), 3.20—3.55 (2H, m), 3.80—4.10 (2H, m), 4.06 (2H, q, J=8 Hz), 4.53 (2H, s), 7.00 (2H, d, J=9 Hz), 7.84 (2H, d, J=9 Hz)
4u	$C_{16}H_{22}O_5S$	58.87 (58.84	6.79 6.91)		1.50—1.85 (4H, m), 2.28 (3H, s), 2.60 (6H, s), 2.50—3.00 (1H, m), 3.20—3.60 (2H, m), 3.80—4.10 (2H, m), 4.50 (2H, s), 6.98 (2H, s)

derivatives (**4h, j, l—p**) show potent esterase- and chymotrypsin-inhibitory activities, but the cyclopropyl (**4a, b**) and oxacycloalkyl derivatives (**4q—u**) are not effective. On the other hand, the arenesulfonates, **4d—g** and **4k** with $n=0$, show only esterase inhibition. The value of n and the substituent on the phenyl group have no significant effect on the esterase-inhibitory

TABLE V. Enzyme-Inhibitory Activities and Hypolipidemic Effect of **8**



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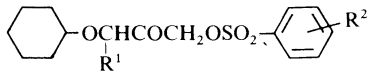
Compd. No.	R^1	A	R^2	Method[a]	Yield[b] (%)	mp (°C)	Inhibitions: Esterase[d] IC_{50} (μM)	Inhibitions: Chymotry.[e] (1×10^{-4} M)	Reduction[f]: Trigly.[g]
8a	H	$-CH_2CH(CH_3)-$	H	A	75	51–52 (Et–W)[i]	0.35	31	60
8b	H	$-CH_2CH(CH_3)-$	$-CH_3$	A	71	50–51 (E)	7.8	31	50
8c	H	$-CH_2CH(CH_3)-$	$-OCH_3$	A	78	33–34 (PE–E)	4.0	22	63
8d	H	$-CH_2CH(C_2H_5)-$	H	A	70	Oil[c]	4.7	24	80
				B	82				
8e	H	$-CH_2CH(C_2H_5)-$	$-OCH_3$	A	73	Oil[c]	[h]	[h]	52
		$-CH_2C(CH_3)-$							
8f	H		H	A	68	40–41	[h]	[h]	[h]
				B	83	(PE–E)			
8g[j]	$-C_2H_5$	—	H	A	75	Oil[c]	0.2	58	[h]
8h[j]	$-CH(CH_3)_2$	—	H	A	81	Oil[c]	0.4	23	87

a–*i*) See the corresponding footnotes in Table III. *j*) These compounds were stereoisomeric mixtures.

TABLE VI. Enzyme-Inhibitory Activities of [13]



13

Compd. No.	R^1	R^2	Yield[a] (%)	mp[b] (°C)	Inhibitions: Esterase[c] IC_{50} (μM)	Inhibitions: Chymotry.[d] (1×10^{-4} M)
13a	H	H	64	Oil	18.0	52
13b	H	4-CH_3	73	Oil	7.8	51
13c	H	4-OCH_3	68	Oil	4.6	50
13d	CH_3	H	78	Oil	34.0	14
13e	CH_3	4-CH_3	70	Oil	29.0	8
13f	CH_3	2,4,6-$(CH_3)_3$	85	Oil	6.2	20

a) Yield from the corresponding diazoketone (**12**) (method A). *b*) Purified by column chromatography on silica gel. *c*) Methyl butyrate was used as a substrate. *d*) ATEE was used as a substrate. Expressed as percentage inhibition of chymotrypsin-inhibitory activity at 1×10^{-4} M.

activity, but the compounds with $n=1$, 2 and 3 in Table III are more effective as chymotrypsin inhibitors than the compounds with $n=0$. ii) The data in Table V indicate that alkyl substituents on the side chain or on the cyclohexane ring of the arenesulfonates (**8**) do not have any appreciable effect on the esterase inhibition, but tend to cause a considerable

TABLE VII. Physical Data for **8** and **13**

Compd. No.	Formula	Analysis (%) Calcd (Found) C	H	^{1}H-NMR ($CDCl_3$) δ ppm
8a	$C_{17}H_{24}O_4S$	62.94 (63.04	7.46 7.55)	0.70—1.80 (16H, m), 2.60—2.90 (1H, m), 4.61 (2H, s), 7.40—8.00 (5H, m)
8b	$C_{18}H_{26}O_4S$	63.88 (63.94	7.74 7.91)	0.75—1.80 (16H, m), 2.44 (3H, s), 2.60—2.95 (1H, m), 4.59 (2H, s), 7.30 (2H, d, J=8.5 Hz), 7.78 (2H, d, J=8.5 Hz)
8c	$C_{18}H_{26}O_5S$	60.99 (60.85	7.39 7.62)	0.70—1.85 (16H, m), 2.60—2.92 (1H, m), 3.88 (3H, s), 4.56 (2H, s), 6.97 (2H, d, J=9 Hz), 7.81 (2H, d, J=9 Hz)
8d	$C_{18}H_{26}O_4S$	63.88 (63.52	7.74 7.86)	0.60—1.90 (18H, m), 2.40—2.80 (1H, m), 4.58 (2H, s), 7.35—8.05 (5H, m)
8e	$C_{19}H_{28}O_5S$	61.93 (62.33	7.66 7.72)	0.65—1.85 (18H, m), 2.42—2.82 (1H, m), 3.88 (3H, s), 4.53 (2H, s), 6.98 (2H, d, J=8.5 Hz), 7.84 (2H, d, J=8.5 Hz)
8f	$C_{18}H_{26}O_4S$	63.88 (63.99	7.74 7.89)	0.70—1.80 (13H, m), 1.10 (6H, s), 4.90 (2H, s), 7.40—7.80 (3H, m), 7.90—8.10 (2H, m)
8g	$C_{16}H_{22}O_4S$	61.91 (61.80	7.14 7.30)	0.60—2.00 (14H, m), 2.20—2.70 (1H, m), 4.62 (2H, s), 7.35—8.00 (5H, m)
8h	$C_{17}H_{24}O_4S$	62.93 (63.17	7.46 7.66)	0.70—2.10 (16H, m), 2.50—2.70 (1H, m), 4.61, 4.63 (2H, s), 7.35—8.00 (5H, m)
13a	$C_{15}H_{20}O_5S$	57.67 (57.38	6.45 6.75)	0.90—2.12 (10H, m), 3.10—3.45 (1H, br), 4.18 (3H, s), 4.91 (2H, s), 7.48—8.14 (5H, m)
13b	$C_{16}H_{22}O_5S$	58.88 (58.70	6.79 6.85)	0.90—2.08 (10H, m), 2.47 (3H, s), 3.05—3.44 (1H, br), 4.18 (2H, s), 4.86 (2H, s), 7.39 (2H, d, J=8 Hz), 7.86 (2H, d, J=8 Hz)
13c	$C_{16}H_{22}O_6S$	56.12 (56.33	6.48 6.41)	1.00—2.02 (10H, m), 3.10—3.40 (1H, br), 3.91 (3H, s), 4.18 (2H, s), 4.84 (2H, s), 7.05 (2H, d, J=9 Hz), 7.92 (2H, d, J=9 Hz)
13d	$C_{16}H_{22}O_5S$	58.88 (58.90	6.79 6.49)	0.85—2.08 (10H, m), 1.28 (3H, d, J=7 Hz), 3.10—3.48 (1H, br), 4.07 (1H, q, J=7 Hz), 5.02 (2H, s), 7.46—8.12 (5H, m)
13e	$C_{17}H_{24}O_5S$	59.98 (59.67	7.11 7.31)	0.90—2.10 (10H, m), 1.28 (3H, d, J=7 Hz), 2.46 (3H, s), 3.10—3.50 (1H, br), 4.07 (1H, q, J=7 Hz), 4.99 (2H, s), 7.37 (2H, d, J=8 Hz), 7.86 (2H, d, J=8 Hz)
13f	$C_{19}H_{28}O_5S$	61.93 (62.35	7.66 8.07)	0.90—2.08 (10H, m), 1.27 (3H, d, J=7 Hz), 2.32 (3H, s), 2.66 (6H, s). 3.10—3.54 (1H, br), 4.06 (1H, q, J=7 Hz), 4.95 (2H, s), 7.00 (2H, s)

decrease of the chymotrypsin-inhibitory activity in comparison with that of **4** (*i.e.* **4h, j, l—p**). iii) The data in Table VI indicate that a 3-cyclohexyloxy substituent (**13a—f**) has a moderate effect on both the esterase- and the chymotrypsin-inhibitory activities, which do not exceed the values for **4c, h, j, l—o** and **4p** as regards the chymotrypsin-inhibitory activity or those of **4e, g, i, k** and **8a, g, h** as regards the esterase-inhibitory activity. A branch ($R^1=CH_3$) on the alkyl moiety decreases the chymotrypsin-inhibitory action. iv) Hypolipidemic evaluations of **4j—l, n, p** and **8a—h** were carried out (Tables III and V). Among the tested compounds, the arenesulfonates (**4k, l, n** and **8d, h**) afforded good results (70%, 77%, 82%, 80% and 87% reductions of the triglyceride in plasma, respectively), though the *in vitro* chymotrypsin-inhibitory activities of **4k, 8d** and **8h** (but not **4l** or **4n**) are considerably lower. This result indicates that the chymotrypsin-inhibitory action is not directly related to the reduction of the triglyceride in plasma.

Conclusion

We prepared a series of the ω-cycloalkyl-2-oxoalkyl arenesulfonate derivatives and related compounds in order to find effective hypolipidemic agents. The potencies of the esterase-inhibitory activity of the present arenesulfonates (**4, 8** and **13**) were somewhat lower

than those of the previously reported 2-oxoalkyl arenesulfonates[5b] with no cycloalkyl substituent, but in *in vivo* examinations of the series of the arenesulfonates, **4** and **8** showed more potent hypolipidemic action (**4n** and **8d**, **h**; 82%, 80% and 87% reductions of the triglyceride in plasma, respectively) than previously reported compounds. Our search for more favorable hypolipidemic agents is continuing on the basis of the present results. Unfortunately, in the present studies, the favored compounds (**8g**, **h**) were both tested as stereoisomeric mixtures, and separation of the stereoisomers would be desirable in order to investigate the biological activities in more detail. Recently, we have found a more potent hypolipidemic agent among the separated stereoisomers of analogues of **8g** and **8h**. Further investigations on the stereochemistry and structure–activity relationships of the arenesulfonates (**8g**, **h** and their analogues) will be reported in a forthcoming paper.

Experimental

All melting points were recorded with a Yanagimoto micromelting point apparatus and are uncorrected. Spectral data were obtained as follows: mass spectra (MS) with a JEOL 01G-2 spectrometer; proton nuclear magnetic resonance (^{1}H-NMR) spectra 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).

2-Cyclopropyl-1-diazo-2-ethanone (2a) (Typical Procedure)——A mixture of thionyl chloride (20 ml) and cyclopropanecarboxylic acid (**1a**) (1.5 g) was stirred for 5 h under reflux and then the reaction mixture was evaporated under reduced pressure. The residue (cyclopropionyl chloride) was added dropwise to an ethereal solution (100 ml) of diazomethane (obtained from 7.0 g of nitrosomethylurea) under stirring with ice-cooling. After being stirred for 1 h, the reaction mixture was evaporated to dryness under reduced pressure to give **2a**[8] quantitatively as a light yellowish oil. Other compounds (**2b**—**h**) were similarly prepared. Other data are listed in Table I.

4-Cyclohexyl-1-hydroxy-2-butanone (3b) (Typical Procedure)——Dry hydrogen chloride was passed into an ethereal solution (200 ml) of **2e** (12.0 g) until saturation under stirring with ice-cooling. After being stirred for 0.5 h, the reaction mixture was evaporated under reduced pressure to give 1-chloro-4-cyclohexyl-2-butanone, which was added to a solution of ethyl formate (6.4 g) and potassium hydroxide (4.9 g) in 80% aqueous ethanol (100 ml). After being refluxed for 4 h, the reaction mixture was evaporated under reduced pressure. The residue was extracted with chloroform (100 ml) and the organic layer was washed with water. The chloroform layer was dried over sodium sulfate and evaporated under reduced pressure to give **3b** as a crude oil, which was purified by distillation. Yield, 5.0 g (44%). 2-Cyclohexyl-1-hydroxy-2-ethanone (**3a**)[13] was similarly prepared from 2-cyclohexyl-1-diazo-2-ethanone (**2c**).[9] Yield, 4.0 g (48%). Other data are listed in Table II.

2-Cyclopropyl-2-oxoethyl 4-Methoxybenzenesulfonate (4a) (Typical Procedure)——Method A: The title compound (**4a**) was prepared from **2a** (1.1 g) and 4-methoxybenzenesulfonic acid (3.8 g) in the same manner as described in the previous paper.[5] Yield, 1.0 g (37%). Compounds **4b**—**u** were similarly prepared from the diazoketones (**2a**—**h**) and the corresponding arenesulfonic acids. Other data are listed in Tables III and IV.

2-Cyclohexyl-2-oxoethyl Benzenesulfonate (4d) (Typical Procedure)——Method B: Triethylamine (3.5 ml) was added dropwise to a stirred solution of benzenesulfonyl chloride (3.4 g) and **3a** (2.8 g) in dichloromethane (10 ml) at 0—5 °C. after being stirred for 3 h, the reaction mixture was extracted with chloroform (100 ml) and the organic layer was washed with 1 N HCl (20 ml × 2). The chloroform layer was dried over sodium sulfate and evaporated under reduced pressure. The residue was chromatographed on a silica gel column with chloroform as an eluent and the eluate was evaporated under reduced pressure to give an oily product, which was identical with **4d** obtained by method A in terms of the ^{1}H-NMR spectrum. Yield, 3.8 g (67%). Compounds **4l** and **4m** were similarly prepared from the α-hydroxyketone (**3b**) and arenesulfonyl chloride. Other data are listed in Table III.

3-Cyclohexyl-2-methylpropionic Acid (6a) (Typical Procedure)——A mixture of 2-methyl-3-phenylpropionic acid (**5a**)[17] (25.0 g) and PtO_2 (1.0 g) in acetic acid (150 ml) was hydrogenated under a pressure of 50 atm for 4 h at room temperature. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The oily residue was purified by distillation to give **6a**. Yield, 23.0 g (89%). bp 129 °C/1 mmHg (lit.,[10] bp 178—179 °C/2 mmHg). Compounds **6b**—**e** were similarly prepared from the corresponding arylcarboxylic acids (**5b**—**e**). Other data are listed in Table II.

3-Cyclohexylmethyl-1-diazo-2-butanone (7a) (Typical Procedure)——The title compound (**7a**) was prepared from **6a** (2.0 g) in the same manner as described for **2a**. Compounds **7b**—**e** were similarly prepared from the corresponding carboxylic acids (**6b**—**e**). Other data are listed in Table II.

3-Cyclohexylmethyl-1-hydroxy-2-pentanone (9a) (Typical Procedure)——The title compound (**9a**) was prepared from **7b** (2.0 g) in the same manner as described for **3b**. Yield, 1.4 g (74%). Compound **9b** was similarly prepared from the corresponding diazoketone (**7c**) (1.5 g). The crude product was purified by column chromatography on silica gel

with chloroform as an eluent to give **9b** as an oil. Yield, 0.8 g (56%). Other data are listed in Table II.

3-Cyclohexylmethyl-2-oxobutyl Benzenesulfonate (8a) (Typical Procedure)——Method A: The title compound (**8a**) was prepared from **7a** (2.0 g) and benzenesulfonic acid (3.5 g) in an ethereal solution (100 ml) in the same manner as described for **4a** (method A). Yield, 2.5 g (75%). Compounds **8b**—**h** were similarly prepared from the diazoketones (**7a**—**e**) and the corresponding arenesulfonic acids. Other data are listed in Tables V and VI.

3-Cyclohexylmethyl-2-oxopentyl Benzenesulfonate (8d) (Typical Procedure)——Method B: The title compound (**8d**) was prepared from **9a** (1.5 g) and benzenesulfonyl chloride (1.3 g) in dichloromethane (3 ml) in the same manner as described for **4d** (method B). The product was identical with **8d** obtained by method A, in terms of the ^{1}H-NMR spectrum. Yield, 2.1 g (82%). The compound (**8f**) was similarly prepared from the α-hydroxyketone (**9b**) and the corresponding arenesulfonyl chloride. Other data are listed in Table V.

Cyclohexyloxyacetic Acid (11a)——The title compound (**11a**) was prepared by hydrogenation of phenoxyacetic acid (**10a**) (25.0 g) in the presence of Rh–Pt (3 : 1, 1.5 g) as a catalyst in acetic acid (150 ml) under a pressure of 50 atm for 3 h at room temperature. The reaction mixture was worked-up in the same manner as described for **6a**. The oily residue was purified by distillation to give **11a**. Yield, 21.0 g (81%). bp 110—113 °C/2 mmHg (lit.,[18] bp 155—159 °C/20 mmHg). MS *m/z*: 158 (M^+). 2-Cyclohexyloxypropionic acid (**11b**) was similarly prepared from 2-phenoxypropionic acid (**10b**) (25.0 g). Yield, 22.0 g (85%). bp 120—123 °C/2 mmHg (lit.,[19] bp 117—119 °C/1.5 mmHg). MS *m/z*: 172 (M^+).

3-Cyclohexyloxy-1-diazo-2-propanone (12a) (Typical Procedure)——The title compound (**12a**) was quantitatively prepared starting from **11a** (3.0 g) in the same manner as described for **2a**. MS *m/z*: 182 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.80—2.15 (10H, m), 3.14—3.50 (1H, br), 4.04 (2H, s), 5.80 (1H, s). 3-Cyclohexyloxy-1-diazo-2-butanone (**12b**, oil). Yield, nearly quantitative. MS *m/z*: 196 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.90—2.15 (13H, m), 3.10—3.50 (1H, br), 4.02 (1H, q, J=7 Hz), 5.80 (1H, s).

3-Cyclohexyloxy-2-oxopropyl Benzenesulfonate (13a) (Typical Procedure)——The title compound (**13a**) was prepared from **12a** (2.0 g) and benzenesulfonic acid (3.5 g) in an ethereal solution (80 ml) in the same manner as described for **4a** (method A). Yield, 2.2 g (64%). Compounds **13b**—**f** were similarly prepared from the diazoketones (**12a**, **b**) and the corresponding arenesulfonic acids. Other 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.[5]

Pharmacology——Male Wistar rats weighing 200—220 g (7 weeks old) were used for the experiment. They were allocated to experimental groups of five animals. A test compound (0.3 mmol) was dissolved in olive oil (5 ml) and orally administered to the rats at the dose of 0.3 mmol/kg through a stomach tube. Blood samples were taken from the orbital vein under ether anesthesia at 2 h after administration. The samples were centrifuged at 3000 rpm at 5 °C to obtain the plasma. The triglyceride level in plasma was measured by using the Determiner TG-S Kyowa[16] (available from Kyowa Medex Co., Ltd., Japan). The control groups received only olive oil in the same manner, and the normal groups received no treatment. The plasma triglyceride levels of the control and normal groups were measured in the same manner. The percent reduction of the plasma triglyceride was calculated as follows:

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

A: plasma triglyceride level of the control group

B: that of the normal group

C: that of the group treated with the test compound

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