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Studies on Hypolipidemic Agents. IV.[1] Syntheses and Biological Activities of *trans*- and *cis*-2-(4-Alkylcyclohexyl)-2-oxoethyl Arenesulfonates

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trans- and *cis*-2-Diazo-1-(4-alkylcyclohexyl)-1-ethanones were reacted with arenesulfonic acids to afford the corresponding 2-(4-alkylcyclohexyl)-2-oxoethyl arenesulfonates. The esterase-inhibitory activity and hypolipidemic effect of the arenesulfonates were examined, and it was found that in most cases, the *trans*-isomers were more active than the corresponding *cis*-isomers.

Stereoselective syntheses of several biologically potent *trans*-isomers (*trans*-**3**) were also developed.

Keywords——diazoketone; *trans*-arenesulfonate; *cis*-arenesulfonate; 4-alkylcyclohexyl methyl-ketone; α-bromoketone; α-hydroxyketone; esterase-inhibitory activity; chymotrypsin-inhibitory activity; hypolipidemic activity; structure–activity relationship

We have previously reported the synthesis and esterase-inhibitory activity as well as hypolipidemic effect of 2-oxoalkyl arenesulfonates.[1] In the preceding paper,[1c] we also found that stereoisomeric mixtures of several 2-(4-alkylcyclohexyl)-2-oxoethyl arenesulfonates possess considerable activities. In general, the pharmaceutical activities of stereoisomers are considerably different.[2,3] Thus, stereoselective synthesis or separation of the stereoisomers of arenesulfonates (**3**) is important for pharmaceutical evaluation. In this paper, we wish to report preparations and pharmaceutical evaluations of both stereoisomers of the arenesulfonates (**3**), as well as stereoselective synthesis of the *trans*-arenesulfonates (*trans*-**3**).

Chemistry

Catalytic hydrogenation of 4-isopropylbenzoic acid over platinum oxide catalyst afford-

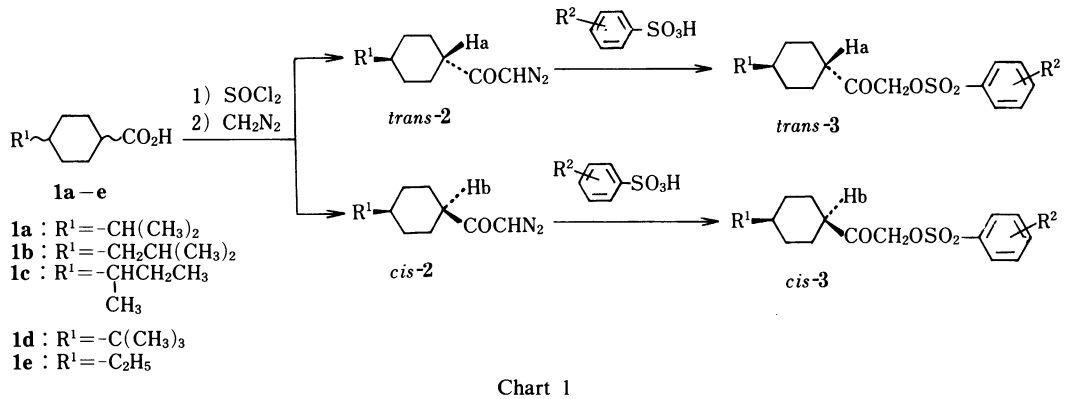
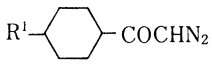


Chart 1

ed a stereoisomeric mixture of *trans*- and *cis*-4-isopropylcyclohexanecarboxylic acid (**1a**),[4] whose separation by distillation was difficult. However, the *cis*- and *trans*-isomers (ratio *ca.* 3:1) of 2-diazo-1-(4-isopropylcyclohexyl)-1-ethanone (**2b**),[4] which were obtained by treating a stereoisomeric mixture of 4-isopropylcyclohexane-carbonyl chloride with diazomethane, could be separated into *trans*- (*trans*-**2b**) and *cis*-isomers (*cis*-**2b**) by column chromatography.

The stereochemistry of the separated *trans*-isomer (*trans*-**2b**) and *cis*-isomer (*cis*-**2b**) was confirmed as follows. The proton nuclear magnetic resonance (^{1}H-NMR) spectra of *trans*-**2b** and *cis*-**2b** in $CDCl_3$ showed the signal of the methine proton (Ha and Hb) at the 1-position of the cyclohexane ring at δ 2.18 pm (1H, t, J=12 Hz) and δ 2.46 ppm (1H, m, $W_{1/2}$=13 Hz), respectively. The former signal can be assigned as the axial proton and the latter, the equatorial proton based on comparisons with the data reported by Jensen *et al.*[5] Although the signal of Ha overlapped partially with the signals of protons at other positions on the cyclohexane ring in the 100 MHz ^{1}H-NMR spectrum of *trans*-**2b**, it was clearly isolated in the 400 MHz ^{1}H-NMR spectrum at δ 2.16 ppm (1H, tt, J=3.5 and 12 Hz). Furthermore, there is no difference between the chemical shifts of the two methyls on the isopropyl group of *trans*-**2b** (δ 0.85 ppm, d, J=6.5 Hz) and those of *cis*-**2b** (δ 0.85 ppm, d, J=6.5 Hz). These results indicate that the isopropyl group in both *trans*-**2b** and *cis*-**2b** is equatorial. From the above spectral observations, *trans*-**2b** and *cis*-**2b** were clearly assigned as *trans*-isomer and *cis*-isomer, respectively. Stereoisomeric mixtures of other diazoketones (**2a** and **2c**—**e**), which were obtained from the corresponding acyl halides of **1b**—**e** by treatment with diazomethane, were also separated into the *trans*-isomer (*trans*-**2a** and *trans*-**2c**—**e**) and the *cis*-isomer (*cis*-**2a** and *cis*-**2c**—**e**) in the same manner as described for *trans*-**2b** and *cis*-**2b**. The structure of *trans*-**2a**, *trans*-**2c**—**e**, *cis*-**2a** and *cis*-**2c**—**e** were similarly confirmed. The physical data for *trans*-**2** and *cis*-**2** are listed in Table I.

TABLE I. Physical Data for *trans*-**2** and *cis*-**2**

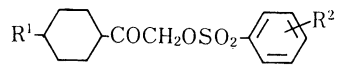


trans-**2**, *cis*-**2**

Compd.[a] No.	R^1	mp (°C)	MS (M^+)	^{1}H-NMR ($CDCl_3$) δ ppm
trans-**2a**	$-C_2H_5$	Oil	180	0.60—2.40 (14H, m), 2.18 (1H, t, J=12 Hz), 5.27 (1H, s)
cis-**2a**	$-C_2H_5$	Oil	180	0.60—2.04 (14H, m), 2.38 (1H, br m), 5.33 (1H, s)
trans-**2b**	$-CH(CH_3)_2$	34—35	194	0.85 (6H, d), 0.96—2.36 (10H, m), 2.18 (1H, t, J=12 Hz), 5.24 (1H, s)[b]
cis-**2b**	$-CH(CH_3)_2$	Oil	194	0.85 (6H, d), 0.95—2.15 (10H, m), 2.46 (1H, br m), 5.31 (1H, s)
trans-**2c**	$-\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}HCH_2CH_3$	Oil	208	0.60—2.35 (18H, m), 2.18 (1H, t, J=12 Hz), 5.24 (1H, s)
cis-**2c**	$-\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}HCH_2CH_3$	Oil	208	0.65—2.14 (18H, m), 2.40 (1H, br m), 5.33 (1H, s)
trans-**2d**	$-CH_2CH(CH_3)_2$	36—37	208	0.89 (6H, d), 0.70—2.38 (12H, m), 2.20 (1H, t, J=12 Hz), 5.27 (1H, s)
cis-**2d**	$-CH_2CH(CH_3)_2$	Oil	208	0.85 (6H, d), 1.00—2.04 (12H, m), 2.38 (1H, br m), 5.32 (1H, s)
trans-**2e**[c]	$-C(CH_3)_3$	58—59	208	0.84 (9H, s), 0.60—2.32 (9H, m), 2.18 (1H, t, J=12 Hz), 5.25 (1H, s)
cis-**2e**[c]	$-C(CH_3)_3$	32—33	208	0.82 (9H, s), 0.65—2.28 (9H, m), 2.38 (1H, br m), 5.36 (1H, s)

a) All compounds were light yellowish oils. All IR spectra of these compounds in $CHCl_3$ showed the presence of a diazo group and a carbonyl group at 2100 and 1630 cm^{-1}, respectively. *b*) ^{1}H-NMR (400 MHz) spectrum at 50 °C in $CDCl_3$: 0.86 (6H, d, J=6.8 Hz), 0.92—1.15 (3H, m), 1.30—1.65 (3H, m), 1.80 (2H, br d, J=11.2 Hz), 1.89 (2H, br d, J=11.2 Hz), 2.16 (1H, tt, J=3.5, 12 Hz), 5.20 (1H, s). *c*) Lit.,[6]: *trans*-isomer: mp 61.5—63 °C, *cis*-isomer: mp 34—36 °C.

TABLE II. Inhibitory Activities on Enzymes, and Hypolipidemic Effect of *trans*-**3** and *cis*-**3**



trans-**3**, *cis*-**3**

Compd. No.	R^1	R^2	Yield[a] (%)	mp (°C)	Recryst.[b] solv.	Inhibitions: Esterase[c] IC_{50} (μM)	Inhibitions: Chymotry.[d] (1×10^{-4} M)	Reduction[e] Trigly.[f]
trans-**3a**	$-C_2H_5$	H	76	58—59	Et	0.0012	65	—[g]
cis-**3a**	$-C_2H_5$	H	65	39—40	E	0.02	16	—[g]
trans-**3b**	$-CH(CH_3)_2$	H	78	48—49	Et–W	0.065	62	90
cis-**3b**	$-CH(CH_3)_2$	H	84	42—43	E	0.7	16	60
trans-**3c**	$-CH(CH_3)_2$	4-OC_2H_5	69	80—81	Et	2.0	35	76
cis-**3c**	$-CH(CH_3)_2$	4-OC_2H_5	73	71—72	Et	11.0	14	50
trans-**3d**	$-CH(CH_3)_2$	2,4,6-$(CH_3)_3$	78	66—67	Et	0.13	—[g]	—[g]
cis-**3d**	$-CH(CH_3)_2$	2,4,6-$(CH_3)_3$	75	45—46	PE–E	1.2	—[g]	—[g]
trans-**3e**	$-CHCH_2CH_3$ (CH$_3$)	H	72	Oil[h]	—	0.15	19	76
cis-**3e**	$-CHCH_2CH_3$ (CH$_3$)	H	68	29—30	PE–E	0.56	13	61
trans-**3f**	$-CH_2CH(CH_3)_2$	H	77	50—51	Et–W	0.07	43	79
cis-**3f**	$-CH_2CH(CH_3)_2$	H	74	36—37	Et	0.4	30	57
trans-**3g**	$-C(CH_3)_3$	H	79	73—74	Et	4.6	0	72
cis-**3g**	$-C(CH_3)_3$	H	75	79—80	Et	4.6	0	52

a) Yields from the corresponding diazoketones *trans*-**2** or *cis*-**2**. *b*) Recrystallization solvents: Et = ethanol, E = diethyl ether, PE = petroleum ether, W = H_2O. *c*) Methyl butyrate was used as a substrate. *d*) ATEE was used as a substrate. The activity was expressed as percentage inhibition of chymotrypsin-inhibitory activity at 10^{-4} M. *e*) The activity was expressed as percentage deviation from the control value. Dose: 0.3 mmol/kg, *p.o.* in rats. See also the experimental section. *f*) Plasma triglyceride. *g*) Not tested. *h*) This compound was purified by column chromatography.

Treatment of the *trans*- (*trans*-**2**) and *cis*-diazoketones (*cis*-**2**) with arenesulfonic acids afforded the corresponding *trans*- (*trans*-**3**) and *cis*-arenesulfonates (*cis*-**3**) in fairly good yields, respectively.

Enzyme-Inhibitory Activity (*in Vitro* Experiments)

Methyl butyrate and *N*-acetyltyrosine ethyl ester (ATEE) were used as substrates for the determination of esterase[7] and chymotrypsin[7] activities, respectively (Table II).

Pharmacological Examination (*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 5 ml of olive oil and the mixture was orally administered to rats at the dose of 0.3 mmol per kg. Blood 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[8]). Decreases of the triglyceride were expressed as percentage values with respect to the control value obtained for animals given olive oil containing no test compound.

Results and Discussion

The physical and biological data for the *trans*- (*trans*-**3**) and *cis*-arenesulfonates (*cis*-**3**) are listed in Tables II and III. As shown in Table II, in most cases, except for *trans*-**3g** and *cis*-**3g**, the *trans*-isomers (*trans*-**3**) exhibited 4 to 20 times more potent esterase-inhibitory activity

TABLE III. Physical Data for *trans*-**3** and *cis*-**3**

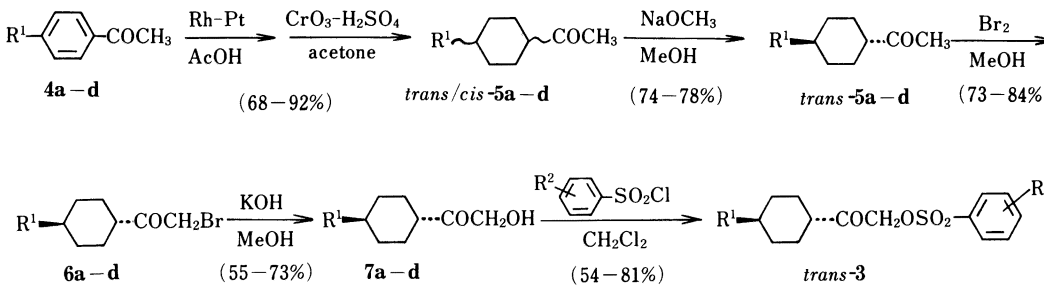
Compd. No.	Formula	Analysis (%) Calcd (Found) C	H	^{1}H-NMR ($CDCl_3$) δ ppm
trans-**3a**	$C_{16}H_{22}O_4S$	61.91 (61.87)	7.14 6.98)	0.87 (3H, t), 1.00—2.00 (11H, m), 2.46 (1H, tt, J=4, 12 Hz), 4.64 (2H, s), 7.40—7.82 (3H, m), 7.82—8.10 (2H, m)
cis-**3a**	$C_{16}H_{22}O_4S$	61.91 (62.17	7.14 7.22)	0.84 (3H, t), 1.00—2.00 (11H, m), 2.64 (1H, br m), 4.65 (2H, s), 7.40—7.80 (3H, m), 7.80—8.10 (2H, m)
trans-**3b**	$C_{17}H_{24}O_4S$	62.94 (62.78	7.46 7.39)	0.85 (6H, d), 0.94—2.00 (10H, m), 2.46 (1H, tt, J=4, 12 Hz), 4.63 (2H, s), 7.50—8.10 (5H, m)
cis-**3b**	$C_{17}H_{24}O_4S$	62.94 (62.76	7.46 7.51)	0.82 (6H, d), 0.94—2.10 (10H, m), 2.70 (1H, br m), 4.65 (2H, s), 7.50—8.10 (5H, m)
trans-**3c**	$C_{19}H_{28}O_5S$	61.93 (61.84	7.66 7.65)	0.86 (6H, d), 1.45 (3H, t), 0.95—2.00 (10H, m), 2.48 (1H, tt, J=4, 12 Hz), 4.11 (2H, q), 4.58 (2H, s), 6.99 (2H, d), 7.85 (2H, d)
cis-**3c**	$C_{19}H_{28}O_5S$	61.93 (61.92	7.66 7.77)	0.82 (6H, d), 1.45 (3H, t), 0.94—2.10 (10H, m), 2.72 (1H, br m), 4.11 (2H, q), 4.59 (2H, s), 6.99 (2H, d), 7.86 (2H, d)
trans-**3d**	$C_{20}H_{30}O_4S$	65.54 (65.48	8.25 8.34)	0.85 (6H, d), 0.95—2.04 (10H, m), 2.32 (3H, s), 2.50 (1H, tt, J=4, 12 Hz), 2.64 (6H, s), 4.54 (2H, s), 6.99 (2H, s)
cis-**3d**	$C_{20}H_{30}O_4S$	65.54 (65.20	8.25 8.20)	0.82 (6H, d), 0.95—2.10 (10H, m), 2.31 (3H, s), 2.64 (6H, s), 2.70 (1H, br m), 4.56 (2H, s), 6.98 (2H, s)
trans-**3e**	$C_{18}H_{26}O_4S$	63.88 (63.97	7.74 7.85)	0.70—2.10 (18H, m), 2.46 (1H, tt, J=4, 12 Hz), 4.63 (2H, s), 7.45—8.10 (5H, m)
cis-**3e**	$C_{18}H_{26}O_4S$	63.88 (63.68	7.74 8.05)	0.60—2.10 (18H, m), 2.68 (1H, br m), 4.65 (2H, s), 7.44—8.10 (5H, m)
trans-**3f**	$C_{18}H_{26}O_4S$	63.88 (64.20	7.74 7.97)	0.84 (6H, d), 0.64—2.00 (12H, m), 2.48 (1H, tt, J=4, 12 Hz), 4.64 (2H, s), 7.42—8.10 (5H, m)
cis-**3f**	$C_{18}H_{26}O_4S$	63.88 (63.89	7.74 7.98)	0.83 (6H, d), 0.95—2.00 (12H, m), 2.66 (1H, br m), 4.66 (2H, s), 7.45—8.10 (5H, m)
trans-**3g**	$C_{18}H_{26}O_4S$	63.88 (63.64	7.74 7.85)	0.84 (9H, s), 0.60—2.04 (9H, m), 2.44 (1H, tt, J=4, 12 Hz), 4.63 (2H, s), 7.50—8.08 (5H, m)
cis-**3g**	$C_{18}H_{26}O_4S$	63.88 (63.66	7.74 8.03)	0.79 (9H, s), 0.78—2.30 (9H, m), 2.70 (1H, br m), 4.66 (2H, s), 7.48—8.08 (5H, m)

than the *cis*-isomers (*cis*-**3**). On the other hand, alkyl substituents on the cyclohexane ring of *trans*-**3** increased the esterase-inhibitory activity in the following order: ethyl > isopropyl ≧ isobutyl > *sec*-butyl > *tert*-butyl. An ethoxy substituent on the benzene ring as in **3c** decreased the activity. Chymotrypsin-inhibitory activity of the *trans*-isomers (*trans*-**3**) was also more potent than that of the *cis*-isomers (*cis*-**3**). Further, in the tests of plasma triglyceride-reducing effect *in vivo*, the *trans*-isomers (*trans*-**3**) showed a more potent hypolipidemic action than the *cis*-isomers (*cis*-**3**).

Stereoselective Synthesis of *trans*-Isomers (*trans*-3)

Biological tests of the *trans*- (*trans*-**3**) and the *cis*-arenesulfonates (*cis*-**3**) showed that *trans*-**3** exhibited more potent esterase-inhibitory activity as well as greater hypolipidemic effect than *cis*-**3**. Thus, we devised a synthetic scheme for a facile synthesis of *trans*-**3**, which might be applicable to large-scale preparation (Chart 2).

Catalytic hydrogenation of 4-alkylacetophenones (**4**) over rhodium–platinum (3 : 1) was carried out at room temperature under a pressure of 50—60 atm in acetic acid to afford mixtures of the acetylcyclohexanes (**5**) and a small quantity of the cyclohexyl alcohols. The mixtures were subjected to Jones oxidation[9] to afford stereoisomeric mixtures (**5**). Equilibration of the stereoisomeric mixtures (**5**) by refluxing in methanol in the presence of sodium methoxide[10] proceeded successfully to give the *trans*-isomers (*trans*-**5**) in 74—78% yield. Bromination of the active methyl group of *trans*-**5** was performed according to the



4a–d (68–92%) *trans*/*cis*-**5a–d** (74–78%) *trans*-**5a–d** (73–84%)

6a–d (55–73%) **7a–d** (54–81%) *trans*-**3**

a : R^1=-$CH(CH_3)_2$ **b** : R^1=-$CH_2CH(CH_3)_2$ **c** : R^1=-$CHCH_2CH_3$ (CH_3) **d** : R^1=-$C(CH_3)_3$

Chart 2

TABLE IV. Conversion of 2-Bromo-1-(*trans*-4-isobutylcyclohexyl)-1-ethanone (**6b**) into 2-Hydroxy-1-(*trans*-4-isobutylcyclohexyl)-1-ethanone (**7b**)

Entry[a]	Substrate (**6b**) (mmol)	Solvent MeOH (ml)	Basic conditions	Temp. (°C)	Time (h)	Yield[b] (%)
1	9.6	20	KOH (1.1 eq)/H_2O (6 ml)	5	1	51
2	9.6	20	KOH (1.2 eq)/MeOH (25 ml)	5	1	58
3	30.8	60	NaOMe (1.3 eq)/MeOH (30 ml)	5	0.5	51
4	19.2	50	KOH (1.3 eq)/MeOH (15 ml)	10	1	66
5	19.2	50	*tert*-BuOK (1.2 eq)	20	2	52
6	19.2	50	HCO_2K (1.5 eq), NaI (0.1 eq)	40	16	63
7	19.2	50	HCO_2K (1.5 eq), NaI (0.5 eq)	40	16	26

a) In the cases of entries 1—4, a solution of the base was added dropwise to a solution of **6b** in MeOH. In the cases of entries 5—7, the base was added in one portion. *b*) Isolated yield, recrystallized from hexane–ether.

procedure of Bettahar *et al.*[11] to give the bromoacetylcyclohexanes (**6**) in 73—84% yield. Hydrolysis of 2-bromo-1-(*trans*-4-isobutylcyclohexyl)-1-ethanone (**6b**) into 2-hydroxyl-1-(*trans*-4-isobutylcyclohexyl)-1-ethanone (**7b**) under various basic conditions was examined as shown in Table IV in order to find optimum conditions. In this reaction, the yield was almost independent of the kind of bases (entries 1—6) and the reaction temperature (entries 1—5) except in the case of potassium formate as a base, which required a long reaction time at 40 °C (entry 6). Addition of a larger excess of sodium iodide than that used in entry 6 rather lowered the yield (entry 7). Thus, the conditions of entry 4 are recommended as a general method for the preparation of **7** starting from **6**.

Esterification of **7** into the *trans*-arenesulfonates (*trans*-**3**) was performed by the same method as described in the preceding paper.[1c] The properties of the products were identical with those of the *trans*-arenesulfonates (*trans*-**3**) obtained from the *trans*-diazoketones (*trans*-**2**). The synthetic route to *trans*-**3** starting from **4** seems to be suitable for large-scale operation.

Conclusion

We prepared the *trans*- (*trans*-**3**) and the *cis*-arenesulfonates (*cis*-**3**) from the pure *trans*- (*trans*-**2**) and the *cis*-diazoketones (*cis*-**2**), respectively, and their esterase-inhibitory activity and hypolipidemic effect were evaluated. The *trans*-isomers (*trans*-**3**) were synthesized in six steps starting from the acetophenone derivatives (**4**) and the synthetic route seems to be

suitable for large-scale operation. The biological activities of the *trans*-isomers (*trans*-**3**) were found to be more potent than those of the *cis*-isomers (*cis*-**3**). Among the effective *trans*-isomers (*trans*-**3**), we consider that *trans*-**3a**, *trans*-**3b** and *trans*-**3f** may be favorable as hypolipidemic agents, and these compounds are now undergoing pre-clinical studies.

Experimental

All melting point were recorded with Yanagimoto micromelting point apparatus and are uncorrected. Spectral data were obtained as follows: infrared (IR) spectra with a Hitachi 260-50 spectrophotometer; mass spectra (MS) with a JEOL JMS-01G-2 spectrometer; ^{1}H-NMR spectra with JEOL JMN-FX 100 and Bruker WH-400 spectrometers (using tetramethylsilane as an internal standard). Chemical shifts of ^{1}H-NMR spectra are given in δ values (ppm).

Starting Materials——Stereoisomeric mixtures of the 4-alkylcyclohexanecarboxylic acids (**1a—e**) were prepared by catalytic hydrogenation of the corresponding 4-alkylbenzoic acids over platinum oxide according to the procedure described in the preceding paper.[1c] **1a**[4]: bp 133—134 °C/1 mmHg. **1b**: bp 128—130 °C/3 mmHg (lit.[12] bp 118—119 °C/0.8 mmHg). **1c**[13]: bp 173 °C/20 mmHg. MS *m/z*: 184 (M^+). ^{1}H-NMR ($CDCl_3$): 0.75—1.90 (18H, m), 2.00—2.75 (1H, m), 11.10 (1H, br). **1d**: mp 92—94 °C (lit.[14] mp 111 °C). MS *m/z*: 184 (M^+). ^{1}H-NMR ($CDCl_3$): 0.75—2.15 (18H, m), 2.20—2.75 (1H, m), 11.70 (1H, br). **1e**[4]: bp 120 °C/1 mmHg. The 4-alkylacetophenones (**4a—d**) were prepared from alkylbenzene and acetyl chloride by means of the Friedel–Crafts reaction according to the procedure of Allen.[15] **4a**: bp 94—96 °C/1 mmHg (lit.[15] bp 118 °C/13 mmHg). **4b**: bp 98—99 °C/2 mmHg (lit.[12] bp 110 °C/3 mmHg). **4c**: bp 98—101 °C/1 mmHg (lit.[16] bp 133—136 °C/2 mmHg). **4d**: bp 100—102 °C/2 mmHg (lit.[17] bp 134—135 °C/11 mmHg).

2-Diazo-1-(*trans*-4-ethylcyclohexyl)-1-ethanone (*trans*-2a) and 2-Diazo-1-(*cis*-4-ethylcyclohexyl)-1-ethanone (*cis*-2a)——Typical procedure for the syntheses of the stereoisomeric mixtures (**2a—e**) and for the separation into the *trans*-isomers (*trans*-**2a—e**) and the *cis*-isomers (*cis*-**2a—e**). A mixture of thionyl chloride (30 ml) and 4-ethylcyclohexanecarboxylic acid (**1e**)[4] (1.7 g) was stirred for 2 h under reflux, and then the reaction mixture was evaporated under reduced pressure. The residue (4-ethylcyclohexylcarbonyl 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 under reduced pressure to give **2a**[4] as a crude oil (stereoisomeric mixture, *cis* : *trans* = *ca.* 3 : 1). The crude oil (**2a**) (2.0 g) was chromatographed on a long silica gel column with chloroform as an eluent. From the first eluate, the *cis*-isomer (*cis*-**2a**) was obtained as a yellowish oily product. Yield, 1.0 g (51%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2100 (N_2), 1630 (CO). From the second eluate, the *trans*-isomers (*trans*-**2a**) was obtained as a yellowish oily product. Yield, 0.3 g (15%). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2100 (N_2), 1630 (CO). Similar procedures were used for the preparations of the other stereoisomeric mixtures (**2b—e**) and for the separations into the *trans*-isomers (*trans*-**2b—e**) and the *cis*-isomers (*cis*-**2b—e**). Other data are listed in Table I.

2-(*trans*-4-Ethylcyclohexyl)-2-oxoethyl Benzenesulfonate (*trans*-3a) and 2-(*cis*-4-Ethylcyclohexyl)-2-oxoethyl Benzenesulfonate (*cis*-3a)——Typical procedure for the syntheses of the *trans*-isomers (*trans*-**3a—g**) and the *cis*-isomers (*cis*-**3a—g**). Benzenesulfonic acid monohydrate (1.5 g) was added to an ethereal solution (50 ml) of the *trans*-diazoketone (*trans*-**2a**) (0.5 g) under ice-cooling. After being stirred for 1 h at room temperature, the reaction mixture was washed with water and dried over sodium sulfate. The ethereal layer was evaporated under reduced pressure. The crude product was purified by column chromatography on silica gel with chloroform as an eluent, followed by recrystallization from ethanol to give the *trans*-arenesulfonate (*trans*-**3a**). Yield, 0.65 g (76%). A similar procedure was used for the preparations of the *trans*- (*trans*-**3b—g**) and *cis*-arenesulfonates (*cis*-**3a—g**). Other data are listed in Tables II and III.

1-(4-Isobutylcyclohexyl)-1-ethanone (5b)——Typical procedure for the syntheses of **5a—d**. Hydrogenation of 4-isobutylacetophenone (**4b**) (40.0 g) in AcOH (70 ml) was carried out in the presence of a catalytic amount of rhodium–platinium (1.5 g) under a pressure of 50 atm at room temperature (about 4 h). The reaction mixture was evaporated under reduced pressure to give a crude mixture of the acetylcyclohexane (**5b**) and the cyclohexyl alcohol. Jones reagent (120 ml) (consisting of CrO_3; 31 g, conc. H_2SO_4; 27 ml and water) was added dropwise to a solution of the mixture in acetone (100 ml) under ice-cooling. The whole was stirred for 5 h at room temperature, then water (200 ml) was added and the separated material was extracted with ether (200 ml × 2). The ethereal layer was washed with water (50 ml), dried over sodium sulfate, and evaporated under reduced pressure to give **5b** as a crude oily product, which was purified by distillation. Yield, 32.0 g (77%). bp 120—130 °C/24 mmHg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1695 (CO). MS *m/z*: 182 (M^+). ^{1}H-NMR ($CDCl_3$): 0.83, 0.86 (6H, d, J = 6.5 Hz), 0.75—2.65 (13H, m), 2.15, 2.16 (3H, s). A similar procedure was used for the syntheses of **5a**, **5c** and **5d**. **5a**: Yield, 77%. bp 105—115 °C/18 mmHg. (lit.[18] bp 59—60 °C/0.8 mmHg). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1695 (CO). MS *m/z*: 168 (M^+). ^{1}H-NMR ($CDCl_3$): 0.84, 0.86 (6H, d, J = 6.5 Hz), 0.80—2.60 (11H, m), 2.13, 2.14 (3H, s). **5c**: Yield, 68%. bp 110—125 °C/18 mmHg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700 (CO). MS *m/z*: 182 (M^+). **5d**: Yield, 92%. bp 125—130 °C/24 mmHg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700 (CO). MS *m/z*: 182 (M^+).

***trans*-1-(4-Isobutylcyclohexyl)-1-ethanone (*trans*-5b)**——Typical procedure for the syntheses of *trans*-**5a—d**. A

solution of sodium methoxide (9.9 g) in MeOH (350 ml) was added to the ketone (**5b**) (32.0 g). After being stirred for 4 h under refluxing, the reaction mixture was evaporated under reduced pressure, water (100 ml) was added and the mixture was extracted with benzene (200 ml). The benzene layer was washed with water, dried over sodium sulfate and evaporated under reduced pressure to give *trans*-**5b** as a crude oily product, which was purified by distillation. Yield, 25.0 g (78%). bp 125—128 °C/22 mmHg. ^{1}H-NMR ($CDCl_3$): 0.86 (6H, d, J=6.5 Hz), 0.78—2.45 (13H, m), 2.11 (3H, s). A similar procedure was used for the syntheses of *trans*-**5a**, *trans*-**5c** and *trans*-**5d**. *trans*-**5a**: Yield, 75%. bp 109—113 °C/19 mmHg. ^{1}H-NMR ($CDCl_3$): 0.86 (6H, d, J=6.5 Hz), 0.60—2.50 (11H, m), 2.13 (3H, s). *trans*-**5c**: Yield, 76%. bp 127—130 °C/18 mmHg. ^{1}H-NMR ($CDCl_3$): 0.60—2.10 (18H, m), 2.10—2.50 (1H, br), 2.13 (3H, s). *trans*-**5d**[19]: Yield, 74%. bp 127—131 °C/22 mmHg. ^{1}H-NMR ($CDCl_3$): 0.85 (9H, s), 0.70—2.45 (10H, m), 2.11 (3H, s).

2-Bromo-1-(*trans*-4-isobutylcyclohexyl)-1-ethanone (6b)——Typical procedure for the syntheses of **6a—d**. Bromine (14.0 g) was added in one portion to a solution of *trans*-**5b** (15.0 g) in MeOH (250 ml) at room temperature. After being stirred for 4 h, the reaction mixture was evaporated under reduced pressure. Water (20 ml) and benzene (100 ml) were added to the residue. The benzene layer was washed with water, dried over sodium sulfate and evaporated under reduced pressure to give **6b** as a crude oily product, which was purified by distillation. Yield, 18.0 g (84%). bp 124—127 °C/1.5 mmHg. ^{1}H-NMR ($CDCl_3$): 0.70—2.10 (18H, m), 2.46—2.86 (1H, br), 3.97 (2H, s). *Anal.* Calcd for $C_{12}H_{21}BrO$: C, 54.97; H, 8.07. Found: C, 55.35; H, 8.32. A similar procedure was used for the syntheses of **6a**, **6c** and **6d**. **6a**: Yield, 73%. bp 113—115 °C/2 mmHg. ^{1}H-NMR ($CDCl_3$): 0.75—2.15 (16H, m), 2.40—2.85 (1H, br), 3.95 (2H, s). *Anal.* Calcd for $C_{11}H_{19}BrO$: C, 53.45; H, 7.46. Found: C, 53.47; H, 7.75. **6c**: Yield, 75%. bp 130—133 °C/2 mmHg. ^{1}H-NMR ($CDCl_3$): 0.60—2.20 (18H, m), 2.44—2.84 (1H, br), 3.96 (2H, s). *Anal.* Calcd for $C_{12}H_{21}BrO$: C, 54.97; H, 8.07. Found: C, 54.59; H, 7.89. **6d**[9]: Yield, 81%. bp 117—119 °C/1 mmHg. ^{1}H-NMR ($CDCl_3$): 0.50—2.16 (18H, m), 2.44—2.82 (1H, br), 3.97 (2H, s). *Anal.* Calcd for $C_{12}H_{21}BrO$: C, 54.97; H, 8.07. Found: C, 54.90; H, 8.12.

2-Hydroxy-1-(*trans*-4-isobutylcyclohexyl)-1-ethanone (7b)——Typical procedure for the syntheses of **7a—d**. The reaction conditions of entry 4 in Table IV were used for the synthesis of **7b**. A solution of KOH (5.0 g) in MeOH (50 ml) was added dropwise to a solution of **6b** (18.0 g) in MeOH (180 ml) below 10 °C. After being stirred for 1 h at the same temperature, the reaction mixture was concentrated to about 50 ml under reduced pressure. Water (30 ml) was added and the mixture was extracted with ether (100 ml × 2). The ethereal layer was washed with water, dried over sodium sulfate and evaporated under reduced pressure to give **7b** as a crude oily product, which was recrystallized from hexane–ether. Yield, 9.3 g (68%). mp 69—70 °C. ^{1}H-NMR ($CDCl_3$): 0.86 (6H, d, J=6.6 Hz), 0.80—2.10 (12H, m), 2.34 (1H, tt, J=4, 12 Hz), 3.15 (1H, t, J=5 Hz), 4.30 (2H, d, J=5 Hz). *Anal.* Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.47; H, 11.30. Compound **7b** was also obtained by hydrolysis of **6b** under various basic conditions as shown in Table IV (entries 1—7). Reaction conditions and data are listed in Table IV. A similar procedure was used for the syntheses of **7a**, **7c** and **7d**. **7a**: Yield, 70%. mp 43—44 °C. ^{1}H-NMR ($CDCl_3$): 0.88 (6H, d, J=6.5 Hz), 0.70—2.10 (10H, m), 2.34 (1H, tt, J=4, 12 Hz), 3.16 (1H, t, J=4.5 Hz), 4.30 (2H, d, J=4.5 Hz). *Anal.* Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.51; H, 10.92. **7c**: Yield, 55%. bp 117—123 °C/2 mmHg. ^{1}H-NMR ($CDCl_3$): 0.85 (6H, d, J=6.5 Hz), 0.60—2.00 (12H, m), 2. 32 (1H, tt, J=4, 12 Hz), 3.16 (1H, t, J=4.5 Hz), 4.30 (2H, d, J=4.5 Hz). **7d**: Yield, 73%. mp 64—65.5 °C. ^{1}H-NMR ($CDCl_3$): 0.85 (9H, s), 0.70—2.10 (9H, m), 2.32 (1H, tt, J=4, 12 Hz), 3.16 (1H, t, J=4.5 Hz), 4.30 (2H, d, J=4.5 Hz). *Anal.* Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.54; H, 11.45.

2-(*trans*-4-Isobutylcyclohexyl)-2-oxoethyl Benzenesulfonate (*trans*-3f)——Typical procedure for the syntheses of *trans*-**3b**, *trans*-**3e**, *trans*-**3f** and *trans*-**3g** from **7a—d**; Triethylamine (11 ml) was added dropwise to a solution of benzenesulfonyl chloride (12.0 g) and **7b** (15.0 g) in dichloromethane (20 ml) at 0—5 °C. After being stirred for 2 h, the reaction mixture was extracted with ether (200 ml) and washed with 1 N HCl (50 ml × 2). The ethereal layer was dried over sodium sulfate and evaporated under reduced pressure. The residue was recrystallized from aqueous ethanol to give white crystals. The product was identical with *trans*-**3f**, which was obtained from the *trans*-diazoketone (*trans*-**2d**). Yield, 20.7 g (81%). A similar procedure was used for the syntheses of *trans*-**3b**, *trans*-**3e** and *trans*-**3g** in 60%, 54% and 73% yields, respectively.

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

Pharmacology——The triglyceride level in plasma was measured by the same method as described in the preceding paper.[1c]

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