Preparations of 5-Alkylmethylidene-3-carboxymethylrhodanine Derivatives and Their Aldose Reductase Inhibitory Activity

Yoshitaka OHISHI,*,[a] Teruo MUKAI,[a] Michiko NAGAHARA,[a] Motoyuki YAJIMA,[a] Norio KAJIKAWA,[a] Kazumoto MIYAHARA,[b] and Tsunehiro TAKANO[b]

Central Research Institute, Kaken Pharmaceutical Co., Ltd.,[a] 14, Minamikawara-machi Shinomiya, Yamashina-ku, Kyoto 607, Japan and Faculty of Pharmaceutical Science, Setsunan University,[b] 45-1, Nagaotoge-cho, Hirakata, Osaka 573-01, Japan. *Received December 25, 1989*

Reactions of 3-carboxymethylrhodanine (1) with aldehydes (2a—u) afforded stereoselectively the 5-monoalkylmethylidene-3-carboxymethylrhodanines (3a—u). The configuration of the 5-monoalkylmethylidene-3-carboxymethylrhodanine (3k) were examined by X-ray structure analysis and confirmed to be *Z*-configuration. The stereoselective reaction path was discussed. Several 5-dialkylmethylidene-3-carboxymethylrhodanines (15a—f) and alkylamino derivatives of 3-carboxymethylrhodanines (18a—o) were also prepared.

These products were evaluated for aldose reductase-inhibitory potency and half of them exhibited valuable inhibitory potency.

Keywords 5-monoalkylmethylidene-3-carboxymethylrhodanine; 5-dialkylmethylidene-3-carboxymethylrhodanine; 5-alkylaminomethylidene-3-carboxymethylrhodanine; stereoselectivity; configuration; X-ray structure analysis; aldose reductase; enzyme inhibitory potency

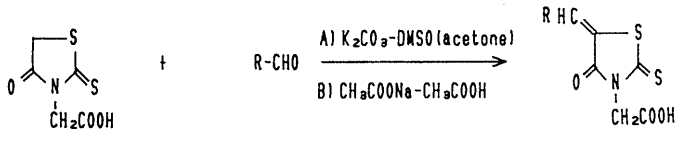
Several theories on the clinical mechanism of aldose reductase inhibitor for diabetic complications, such as those of sorbitol, *myo*-inositol and Na^+/K^+ adenosine triphosphatase (ATPase) have been proposed.[1] Some compounds with considerable inhibitory activity for aldose reductase (AR) are currently being studied for clinical use.[2] We recently reported that the benzo[*b*]furans substituted by the carboxymethylsulfamoyl group revealed potent inhibitory activity to AR.[3] We have also continuously researched other kinds of AR inhibitors.

In this paper, we describe preparations of the novel 3-carboxymethylrhodanine derivatives (**3a—u**, **15a—f**, **18a—o**), X-ray diffraction study for identification of their configuration, and the results of a screening test for inhibitory activity of the derivatives toward rat lens AR.[2a,4]

Chemistry The structure of 3-carboxymethylrhodanine (**1**) is, in part, similar to carboxymethylsulfamoyl group ($-SO_2NHCH_2COOH$) and **1** actually showed the moderate activity. Carboxymethylsulfamoyl group and **1** both have *N*-acetic acid group which is substituted by electron-withdrawing groups (sulfon; carbonyl and thiocarbonyl) on the amino group. Carboxy group and amino group of the carboxymethylsulfamoyl group bind toward the hydrophilic site of AR and the benzo[*b*]furan ring interacts with the hydrophobic site present on the enzyme.[3,5,6] We expected that the devised derivatives of 3-carboxymethylrhodanine would display considerable activity *in vitro* and *in vivo*.

Active methylene at 5-position of the rhodanine (**1**) was allowed to react smoothly with less hindered aldehydes in the presence of potassium carbonate to give the 5-monoalkylmethylidene derivatives. But hindered aldehydes, such as trimethylacetaldehyde, reacted with **1** in the presence of sodium acetate in acetic acid. The structure and physical constants of the 5-monoalkylmethylidene-3-carboxymethylrhodanine (**3a—u**) prepared from these reactions are shown in Chart 1 and Table I. To prepare other kinds of compounds, chloroacetaldehyde (**5**) was treated with 3-ethoxycarbonylmethylrhodanine (**4**)[7] in the presence of sodium hydrogen carbonate to give 5-(2-chloro-1-hydroxyethyl) derivative (**7**) in good yield but no 5-formylmethyl compound (**6**). Subsequently, compound (**7**) was converted to the 2-chloroethylidene derivative (**8**) by treatment with *p*-toluenesulfonic acid (Chart 2). The aldol-type compound **7** was probably obtained because the reaction of **4** with **5** was carried out at 0 °C while compounds (**3a—u**) were obtained from the reactions at about 100 °C. Compound **4** did not afford any products when treated with formaldehyde. The corresponding ester (**10**) and amides (**11—13**) of **3k** were also prepared in the usual manner to examine AR inhibitory activity (Chart 2).

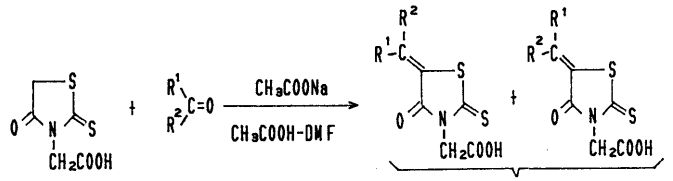
Only one kind of 5-methylidene proton was detected in proton nuclear magnetic resonance (^{1}H-NMR) spectra of all the 5-monoalkylmethylidene-3-carboxymethylrhodanines (**3a—u**). This shows that the reactions of **1** with the aldehydes (**2a—u**) proceeded stereoselectively. Chemical shifts of the 5-methylidene protons of these rhodanines (**3a—u**) were from 6.6 to 7.4 ppm. Especially, the 5-methylidene protons of the compounds (**3b—e**, **g**, **i—q**, **t**, **8**) lie in a narrow region from 6.9 to 7.0 ppm. Coupling constants of the protons are classified into three groups, namely $J=8.0$ Hz ($-CH_2C\underline{H}=C-S$), $J=9.8$ Hz, ($>CH-C\underline{H}=C-S$) and $J=12.0$ Hz ($=CH-C\underline{H}=C-S$) (Table I). Richerd and Clark reported the region of chemical shift of methylene protons of α-substituted methylenecamphors with the carbonyl group at the adjacent position. The chemical shifts of the protons on the same site as the carbonyl group are in a lower field than the shifts of the proton on the opposite site against the carbonyl group.[8] Attempts to obtain both stereoisomers by the reactions of **1** with several aldehydes were made under different conditions from those mentioned above [low temperature (−20——10 °C), change of the solvent (ether, tetrahydrofuran), change of the base (sodium hydride, butyllithium)] to presume the steric configuration of the compounds (**3a—u**), but only a single isomer (**3**) was detected. Fortunately, some of the 5-monoalkylmethylidene-3-carboxymethylrhodanines showed apparent effectiveness several *in vivo* screening tests, such as depression of sorbitol accumulation in sciatic nerve and lens and improvement of motor nerve conduction velocity of the tail in streptozotocin-induced diabetic rat.[9] Thus, to elucidate the molecular structure of the 5-monoalkylmethylidene-3-



1 2 3

	R	yield (%)	procedure
a	CH_3CH_2	69	A
b	$CH_3(CH_2)_2$	40	A
c	$CH_3(CH_2)_3$	69	A
d	$CH_3(CH_2)_4$	75	B
e	$CH_3(CH_2)_5$	43	A
f	$CH_3(CH_2)_9$	79	B
g	$CH_3(CH_3)CH$	66	A
h	$CH_3(CH_3)CHCH_2$	71	B
i	$(CH_3CH_2)_2CH$	35	B
j	$CH_3CH_2(CH_3)CH$	69	B
k	$(CH_3)_3C$	84	B
l	C_6H_{11}	77	B
m	$CH_2=CH$	67	A or B
n	$CH_3CH=CH$	67	A or B
o	$CH_3(CH_3)C=CH$	80	B
p	$CH_3(CH_2)_2CH=CH$	71	B
q	$CH_3CH=CHCH=CH$	73	B
r	$CH_3(CH_3)C=CH(CH_2)_2(CH_3)C=CH$	65	B
s	$CH_3[(CH_3)C=CH(CH_2)_2]_3(CH_3)C=CH$	54	B
t	$Cl(CH_2)_3$	76	A or B
u	$ClCH_2CH=CH$	85	A or B

A: K_2CO_3–DMSO (or acetone), B: CH_3COONa–CH_3COOH



1 14 15

		yield (%)
a	$R^1=R^2=CH_3$	64
b	$R^1=CH_3, R^2=CH_3CH_2$	65[a]
c	$R^1=R^2=CH_3CH_2$	59
d	$R^1=CH_3, R^2=CH_3(CH_3)CH$	34[a]
e	$R^1=R^2=CH_3CH_2CH_2$	42
f	$R^1=CH_3CH_2, R^2=CH_3CH_2CH_2$	46[a]
g	$R^1=R^2=CH_3(CH_3)CH$	0

a) a mixture of *E*- and *Z*-isomer

Chart 1

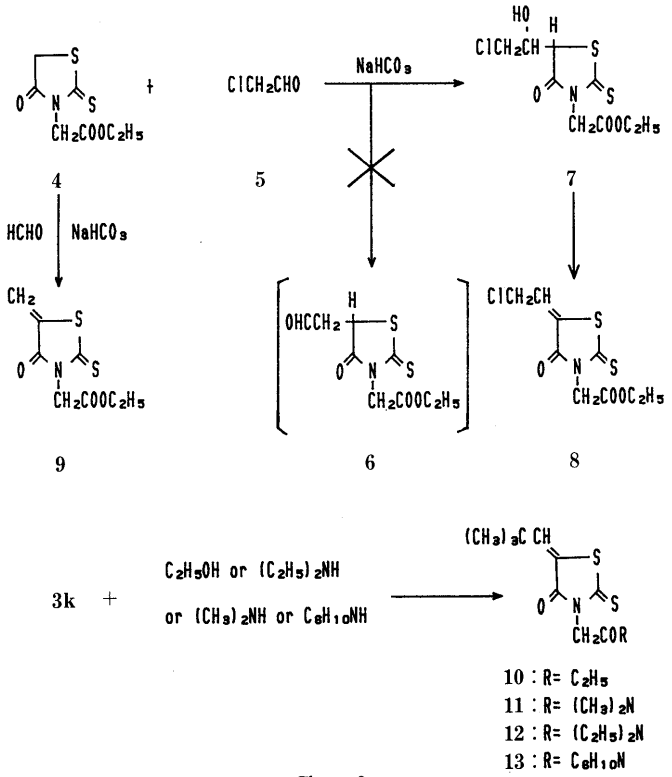


Chart 2

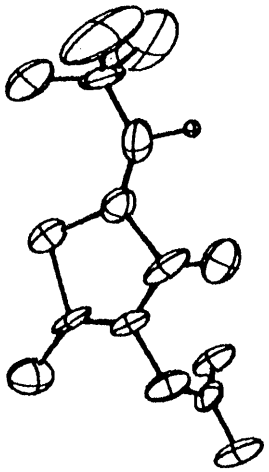


Fig. 1

carboxymethylrhodanine (**3a—u**), an X-ray structure analysis of the representative compound (**3k**) was carried out. Slow evaporation of an ethyl acetate solution of **3k** gave columnar colorless crystals, and *Z*-configuration was confirmed by the X-ray work as shown in Fig. 1.

Two kinds of reaction paths in the stereoselective reaction of **1** with pivalaldehyde are possible (Chart 3). Formations of two kinds of hydroxy ketone anion intermediates (A, C) are expected as first-formed products. In the two intermediates, steric interactions of A are minimized in formation of the compound (B), which may be convertible into the *E*-isomer (**3k'**) (path a); actually, however the *E*-isomer was never detected. The result suggests that the reaction of **1** with pivalaldehyde is not kinetically controlled aldol condensation. Under these reaction conditions, ready reversibility of the aldol condensation may lead to an equilibrium mixture of aldol products (B and D). The equilibrium between B and D may lie to the compound (D), probably because D changes easily to considerably thermodynamically stable **3k** (*Z*-form). The steric repulsion between the alkyl group in the methylidene group and carbonyl group of *E*-isomer (**3k'**) may be much larger than that of the *Z*-isomer considering the space-filling model (CPK precision molecular models). It is estimated that the reaction of **1** with pivalaldehyde may be thermodynamically controlled to produce **3k** exclusively (path b) (Chart 3). Dubois and Dubois discussed the reaction path of comparable aldol reactions of cyclopentanone with isobuthylaldehyde.[10] The 5-monoalkylmethylidene derivatives (**3a—j, l—u, 8**) are presumed to be *Z*-isomers on the

TABLE I. Physical Constants of 3-Carboxymethyl-5-monoalkylmethylidenerhodanines (**3a—u**) and of 3-Carboxymethyl-5-dialkylmethylidenerhodanines (**15a—f**)

Compd.	mp (°C)	^{1}H-NMR (ppm)	Formula	Analysis Calcd (Found) C	H	MS *m/z*	IR (cm^{-1})
3a	138—140	6.05 (3H, t, CH_3), 2.15 (2H, m, $CH_3C\underline{H}_2$), 4.38 (2H, s, NCH_2), 6.59 (1H, t, CH=)[e], 8.05 (1H, br s, COOH)[a]	$C_8H_9NO_3S_2$	41.54 (41.68	3.92 (3.99)	231 (M^+), 213, 185	3150, 1720
3b	145—147	0.98 (3H, t, CH_3), 1.30—1.98 (2H, m, $CH_3C\underline{H}_2$), 2.03—2.47 (2H, m, $C\underline{H}_2CH$=), 4.80 (2H, s, NCH_2), 7.02 (1H, t, CH=),[e] 7.43 (1H, br s, COOH)[b]	$C_9H_{11}NO_3S_2$	44.07 (44.32	4.52 4.40)	245 (M^+), 199	2460—2500, 1730, 1710
3c	157—159	0.93 (3H, t, CH_3), 1.48 (4H, m, $CH_3(C\underline{H}_2)_2$), 2.26 (2H, m, $C\underline{H}_2CH$=), 4.83 (2H, s, NCH_2), 7.03 (1H, t, CH=),[e] 9.51 (1H, s, COOH)[b]	$C_{10}H_{13}NO_3S_2$	46.31 (46.29	5.05 4.95)	259 (M^+), 241	3000, 1703
3d	136—140	0.84 (3H, t, CH_3), 1.05—1.70 (6H, m, $CH_3(C\underline{H}_2)_3$), 2.18 (2H, m, $C\underline{H}_2CH$=), 4.56 (2H, s, NCH_2), 6.98 (1H, t, CH=),[e] 8.70 (1H, s, COOH)[a]	$C_{11}H_{15}NO_3S_2$	48.33 (48.22	5.53 5.60)	273 (M^+), 227, 204	3430, 1715
3e	120—122	0.89 (3H, t, CH_3), 1.36 (8H, m, $CH_3(C\underline{H}_2)_4$), 2.28 (2H, m, $C\underline{H}_2CH$=), 4.85 (2H, s, NCH_2), 7.03 (1H, t, CH=),[e] 10.57 (1H, br s, COOH)[b]	$C_{12}H_{17}NO_3S_2$	50.15 (50.19	5.96 6.14)	287 (M^+), 204	3020, 1714
3f	61—63	0.82 (3H, d, CH_3), 1.20—1.79 (16H, m, $CH_3CH_2(C\underline{H}_2)_8$), 2.16 (2H, q, $CH_3C\underline{H}_2$), 4.49 (2H, s, NCH_2), 6.72 (1H, t, CH=),[e] 8.20 (1H, br s, COOH)[a]	$C_{16}H_{25}NO_3S_2$	55.95 (56.16	7.34 7.19)	329 (M^+), 204	2950, 1730
3g	152—155	1.15 (6H, d, $CH_3\times2$), 2.54 (1H, m, $C\underline{H}CH$=), 4.78 (2H, s, NCH_2), 6.86 (1H, d, CH=),[f] 9.27 (1H, br s, COOH)[c]	$C_9H_{11}NO_3S_2$	44.07 (43.80	4.52 4.43)	245 (M^+), 199	3170, 1708
3h	139—141	0.97 (6H, d, $CH_3\times2$), 1.69—2.27 (3H, m, $C\underline{H}C\underline{H}_2CH$=), 4.86 (2H, s, NCH_2), 7.68 (1H, t, CH=),[e] 10.24 (1H, s, COOH)[b]	$C_{10}H_{13}NO_3S_2$	46.31 (46.11	5.05 5.06)	259 (M^+), 149	3010, 1726
3i	106—108	0.90 (6H, t, $CH_3\times2$), 1.31—1.76 (5H, m, $(CH_3C\underline{H}_2)C\underline{H}$), 4.87 (2H, s, NCH_2), 6.87 (1H, d, CH=),[f] 10.49 (1H, s, COOH)[b]	$C_{11}H_{15}NO_3S_2$	48.33 (48.36	5.53 5.41)	273 (M^+), 149	3030, 1719
3j	153—155	0.90 (3H, t, $C\underline{H}_3CH_2$), 1.13 (3H, d, $C\underline{H}_3CH_2$), 1.54 (2H, m, $CH_3C\underline{H}_2$), 2.27 (1H, m, $C\underline{H}CH$=), 4.78 (2H, s, NCH_2), 6.84 (1H, d, CH=),[f] 9.36 (1H, br s, COOH)[c]	$C_{10}H_{13}NO_3S_2$	46.31 (46.01	5.05 4.75)	259 (M^+), 213	2170, 1707
3k	182—184	1.17 (9H, s, $C(CH_3)_3$), 4.69 (2H, s, NCH_2), 6.88 (1H, s, CH=), 9.81 (1H, br s, COOH)[a]	$C_{10}H_{13}NO_3S_2$	46.31 (46.50	5.05 5.21)	259 (M^+), 241, 213	3300—3100, 1730
3l	209—211	1.23—1.84 (10H, m, $(CH_2)_5$), 2.27 (1H, m, $C\underline{H}CH_2$=), 4.79 (2H, s, NCH_2), 6.88 (1H, d, CH=),[f] 8.22 (1H, br s, COOH)[c]	$C_{12}H_{15}NO_3S_2$	50.51 (50.21	5.30 5.46)	285 (M^+), 267, 204	2850, 1716
3m	144—146	4.39 (2H, s, NCH_2), 5.50 (1H, dd, one of H of $C\underline{H}_2$=CH), 5.69 (1H, dd, one of H of $C\underline{H}_2$=CH), 6.10 (1H, m, CH_2=$C\underline{H}$), 6.98 (1H, d, CH_2=CHC$\underline{H}$=), 8.52 (1H, br s, COOH)[a]	$C_8H_7NO_3S_2$	41.91 (41.76	3.08 2.88)	229 (M^+), 112	3430, 1735
3n	217—219	1.82 (3H, d, CH_3), 4.45 (2H, s, NCH_2), 6.05 (1H, dd, CH_3CH=C$\underline{H}$), 6.35 (1H, m, $CH_3C\underline{H}$=), 7.18 (1H, d, CH_3CH=CHC$\underline{H}$=), 8.03 (1H, br s, COOH)[a]	$C_9H_9NO_3S_2$	44.43 (44.35	3.73 3.83)	243 (M^+), 225, 197	3140, 1737, 1686
3o	209—211	1.88 (6H, s, $CH_3\times2$), 4.48 (2H, s, NCH_2), 5.82 (1H, d, $(CH_3)_2C$=C$\underline{H}$), 7.30 (1H, s, $(CH_3)_2C$=CHC$\underline{H}$=), 8.80 (1H, br s, COOH)[a]	$C_{10}H_{11}NO_3S_2$	46.67 (46.70	4.31 4.31)	257 (M^+), 239, 212	3220, 1737, 1697
3p	190—191	0.85 (3H, t, CH_3), 1.40 (2H, m, $CH_3C\underline{H}_2$), 2.14 (2H, m, $CH_3CH_2C\underline{H}_2$), 4.49 (2H, s, NCH_2), 5.98 (1H, dd, CH=CHC$\underline{H}$=), 6.36 (1H, m, C$\underline{H}$=CHCH=), 7.10 (1H, d, CH=CHC$\underline{H}$=), 9.10 (1H, br s, COOH)[a]	$C_{11}H_{13}NO_3S_2$	48.69 (48.44	4.83 5.03)	271 (M^+), 253, 225	3100, 1724
3q	116—117	1.17 (3H, d, CH_3), 4.40 (2H, s, NCH_2), 5.60—6.70 (4H, m, CH=CHCH–CH), 7.01 (1H, d, CH_3CH=CHCH=CHC$\underline{H}$=), 8.30 (1H, br s, COOH)[a]	$C_{11}H_{11}NO_3S_2$	49.05 (48.90	4.12 4.19)	269 (M^+), 251, 223	3050—3200, 1705
3r	89—101	1.55 (3H, br s, terminal CH_3), 1.58 (3H, br s, terminal CH_3), 1.85 (4H, m, CH_2CH_2), 1.92 (3H, s, CH_3), 4.58 (2H, s, NCH_2), 4.98 (1H, t, $(CH_3)_2C$=C$\underline{H}$), 5.95 (1H, d, C(CH_3)=C$\underline{H}$CH=), 7.44 (1H, d, C(CH_3)=CHC$\underline{H}$=)[a]	$C_{15}H_{19}NO_3S_2$	55.36 (55.50	5.89 5.95)	325 (M^+), 282, 257	3400
3s	37—39	1.48 (15H, br s, $CH_3\times5$), 1.87 (12H, m, $(CH_2CH_2)\times3$), 4.48 (2H, br s, NCH_2), 4.84 (3H, m, $(C(CH_3)$=C$\underline{H})\times3$), 5.76 (1H, d, C(CH_3)=C$\underline{H}$CH=), 7.30 (1H, d, C(CH_3)=CHC$\underline{H}$=), 7.99 (1H, br s, COOH)[a]	$C_{25}H_{35}NO_3S_2$	65.04 (65.31	7.64 7.80)	461 (M^+), 416, 257	3450, 1730, 1720
3t	157—159	1.90 (2H, m, $ClCH_2C\underline{H}_2$), 2.32 (2H, q, $C\underline{H}_2CH$=), 3.54 (2H, t, $ClC\underline{H}_2$), 4.51 (2H, s, NCH_2), 6.78 (1H, d, $CH_2C\underline{H}$=), 8.10 (1H, br s, COOH)[a]	$C_9H_{10}ClNO_3S_2$	38.64 (38.51	3.60 3.77)	279 (M^+), 261, 243	3180, 1734, 1635
3u	207—209	4.20 (2H, d, $ClCH_2$), 4.48 (2H, s, NCH_2), 6.30—6.54 (2H, m, CH=CH), 7.26 (1H, d, CH=CHC$\underline{H}$=), 8.03 (1H, br s, COOH)[a]	$C_9H_8ClNO_3S_2$	38.92 (38.69	2.90 2.83)	277 (M^+), 259, 243, 131	3150, 1739, 1677
15a	171—173	2.05 (3H, s, CH_3), 2.46 (3H, s, CH_3), 4.87 (2H, s, NCH_2), 8.18 (1H, s, COOH)[b]	$C_8H_9NO_3S_2$	41.55 (41.56	3.92 3.82)	231 (M^+), 213	2850, 1705

TABLE I. (continued)

Compd.	mp (°C)	^{1}H-NMR (ppm)	Formula	Analysis Calcd (Found) C	Analysis Calcd (Found) H	MS *m/z*	IR (cm^{-1})
15b[d]	140—146	1.16 (3H, t, C<u>H</u>$_3$CH$_2$), 2.02 (1.5H, s, CH$_3$C=), 2.27 (1H, q, CH$_3$C<u>H</u>$_2$), 2.43 (1.5H, s, CH$_3$C=), 2.92 (1H, q, CH$_3$C<u>H</u>$_2$), 4.83 (2H, s, NCH$_2$), 10.34 (1H, s, COOH)[b]	$C_9H_{11}NO_3S_2$	44.07 (44.32)	4.52 4.59)	245 (M^+), 227, 199	3030, 1730
15c	163—165	1.14 (3H, t, CH$_3$), 1.17 (3H, t, CH$_3$), 2.28 (2H, q, CH$_3$C<u>H</u>$_2$), 2.92 (2H, q, CH$_3$C<u>H</u>$_2$), 4.88 (2H, s, NCH$_2$), 10.01 (1H, s, COOH)[b]	$C_{10}H_{13}NO_3S_2$	46.31 (46.21)	5.05 4.94)	259 (M^+), 241, 213	3010, 1740
15d[d]	143—148	1.08 (3H, d, (C<u>H</u>$_3$)$_2$CH), 1.13 (3H, d, (C<u>H</u>$_3$)$_2$CH), 1.93 (1.5H, s, CH$_3$C=), 2.17—2.72 (0.5H, m, (CH$_3$)C<u>H</u>), 2.34 (1.5H, s, CH$_3$C=), 4.45 (0.5H, m, (CH$_3$)$_2$C<u>H</u>), 4.87 (2H, s, NCH$_2$), 10.67 (1H, s, COOH)[b]	$C_{10}H_{13}NO_3S_2$	46.31 (46.56)	5.05 5.09)	259 (M^+), 241, 213	3040, 1731
15e	127—130	0.99 (6H, t, CH$_3$ × 2), 1.51 (4H, m, CH$_3$C<u>H</u>$_2$ × 2), 2.10—2.42 (2H, m, CH$_3$CH$_2$C<u>H</u>$_2$), 2.71—2.98 (2H, m, CH$_3$CH$_2$C<u>H</u>$_2$), 4.83 (2H, s, NCH$_2$), 10.27 (1H, s, COOH)[b]	$C_{12}H_{17}NO_3S_2$	50.15 (50.24)	5.96 5.94)	287 (M^+), 269, 241	3050, 1730
15f[d]		0.88—1.28 (6H, m, CH$_3$ × 2), 1.59 (2H, m, CH$_2$), 2.14—2.48 (2H, m, CH$_2$), 2.15—3.10 (2H, m, CH$_2$), 4.85 (2H, s, NCH$_2$), 10.27 (1H, br s, COOH)[b]	$C_{11}H_{15}NO_3S_2$	48.33 (48.49)	5.53 5.62)	273 (M^+), 255, 227	3040, 1732

a) In DMSO-d_6. *b*) In $CDCl_3$. *c*) In acetone-d_6. *d*) A mixture of *E*- and *Z*-isomer. *e*) J=8.0 Hz. *f*) J=9.8 Hz. *g*) J=12.0 Hz.

TABLE II. Fractional Atomic Coordinates (× 10^4) and Anisotropic Thermal Parameters (× 10^3)

Atom	*x*	*y*	*z*	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
S1	839 (5)	9101 (6)	372 (8)	47 (3)	68 (4)	42 (3)	13 (3)	14 (2)	11 (3)
S2	−1433 (6)	10003 (7)	1407 (11)	65 (4)	99 (5)	66 (4)	41 (4)	4 (3)	15 (3)
O4	201 (18)	7025 (17)	4971 (24)	103 (13)	104 (12)	51 (9)	45 (11)	30 (9)	41 (9)
O12(1)	−2858 (12)	6377 (13)	2692 (20)	40 (8)	66 (9)	37 (7)	−1 (7)	16 (6)	−11 (6)
O12(2)	−3745 (14)	7023 (16)	5777 (22)	55 (10)	97 (12)	48 (9)	23 (9)	29 (8)	−2 (8)
N3	−583 (14)	8513 (16)	3575 (23)	25 (8)	61 (10)	38 (9)	9 (8)	14 (7)	3 (8)
C2	−506 (18)	9227 (19)	1984 (31)	24 (10)	47 (12)	44 (11)	−9 (9)	22 (9)	−13 (9)
C4	204 (20)	7740 (21)	3752 (32)	43 (13)	64 (14)	40 (12)	−12 (11)	24 (10)	−19 (10)
C5	1241 (21)	8062 (20)	1894 (33)	61 (14)	47 (12)	46 (12)	13 (11)	20 (11)	5 (10)
C6	2213 (24)	7523 (23)	1673 (40)	69 (16)	69 (16)	88 (18)	24 (13)	16 (14)	49 (14)
C7	3252 (21)	7656 (25)	95 (38)	36 (13)	105 (19)	76 (16)	37 (13)	32 (12)	28 (14)
C8	4579 (29)	8121 (58)	1581 (67)	43 (19)	430 (76)	156 (34)	68 (31)	21 (21)	156 (44)
C9	3802 (49)	8998 (49)	−405 (88)	231 (48)	238 (47)	310 (59)	164 (42)	239 (48)	210 (46)
C10	3034 (54)	6229 (35)	−1186 (82)	290 (61)	91 (26)	245 (50)	50 (32)	197 (50)	−13 (29)
C11	−1686 (21)	8293 (23)	5089 (31)	52 (13)	88 (16)	29 (11)	24 (12)	14 (10)	2 (10)
C12	−2786 (18)	7133 (20)	4368 (33)	22 (10)	60 (13)	70 (14)	11 (10)	16 (10)	38 (11)
S1′	556 (5)	12051 (6)	−3111 (8)	47 (3)	76 (4)	46 (3)	20 (3)	18 (3)	17 (3)
S2′	2825 (6)	11109 (7)	−4137 (10)	72 (4)	86 (4)	69 (4)	43 (4)	7 (3)	9 (3)
O4′	1243 (17)	14082 (16)	−7746 (25)	96 (13)	85 (11)	70 (10)	47 (10)	42 (10)	32 (9)
O12(1)′	4356 (15)	14824 (15)	−5447 (24)	63 (10)	76 (10)	65 (10)	13 (9)	33 (8)	−22 (8)
O12(2)′	5104 (14)	14199 (16)	−8752 (21)	45 (9)	91 (11)	45 (9)	0 (8)	29 (7)	−7 (7)
N3′	2020 (16)	12666 (16)	−6351 (28)	44 (10)	47 (10)	65 (11)	15 (8)	11 (9)	7 (8)
C2′	1862 (21)	11926 (22)	−4606 (31)	56 (13)	77 (14)	34 (11)	39 (12)	−8 (10)	9 (10)
C4′	1081 (20)	13331 (19)	−6346 (32)	47 (13)	46 (12)	55 (13)	12 (10)	5 (10)	14 (10)
C5′	179 (19)	13117 (20)	−4686 (29)	34 (11)	66 (14)	35 (11)	7 (10)	7 (9)	11 (10)
C6′	−692 (20)	13688 (22)	−4576 (31)	44 (13)	84 (16)	35 (11)	37 (12)	15 (10)	−13 (11)
C7′	−1904 (26)	13537 (27)	−3028 (39)	89 (19)	107 (20)	65 (15)	63 (17)	44 (14)	41 (14)
C8′	−1260 (35)	14872 (35)	−1144 (51)	131 (29)	146 (29)	87 (21)	55 (24)	48 (21)	−26 (20)
C9′	−2935 (34)	13780 (48)	−4013 (63)	101 (27)	297 (53)	163 (35)	133 (33)	64 (25)	135 (37)
C10′	−1979 (29)	12479 (34)	−1448 (48)	96 (22)	173 (30)	97 (20)	82 (22)	72 (18)	86 (21)
C11′	2989 (18)	12698 (20)	−8029 (34)	26 (11)	52 (13)	62 (14)	−7 (10)	23 (10)	2 (11)
C12′	4222 (21)	13997 (22)	−7254 (36)	48 (13)	72 (15)	61 (14)	23 (12)	−4 (11)	2 (12)

The anisotropic thermal parameters are expressed in the form: $\exp -2\pi(U_{11}h^2a^{*2} + \cdots + 2U_{23}klb^*c^*)$. The standard deviation for the last digit is given in parentheses.

basis of the X-ray study of **3k** and of the chemical shift region of their methylidene protons.

Compound **1** was treated with several ketones (**14a—g**) in the presence of sodium acetate in a mixture of acetic acid and dimethylformamide (DMF) to afford the corresponding 5-dialkylmethylidene derivatives (**15a—f**). A mixture of the two geometrical stereoisomers (**15b, d, f**) (ratio, *ca.* 1 : 1) was obtained on the basis of the ^{1}H-NMR spectra when unsymmetic ketones (**14b, d, f**) were treated with **1** (Chart 1). Physical data of **15a—e** are shown in Table I. It was assumed that these reactions proceeded similarly to the path in the reactions of **1** with aldehydes. In this series, compound

1 did not react with several bulky ketones such as **15g**.

More hydrophilic and polar 5-aminomethylidene derivatives (**18a—o**) were also prepared to test the inhibitory activity. Compound **1** was treated with triethyl orthoformate in acetic anhydride to give 5-ethoxymethylidene-3-carboxymethylrhodanine (**16**). Subsequently, compound **16** was treated with several alkylamines (**17a—o**) in the presence of triethylamine in ethanol to afford the corresponding 5-alkylaminomethylidene-3-carboxymethylrhodanine (**18a—o**) (Chart 4); their physical data are shown in Table V.[11] It is noteworthy that all of the products (**16**, **18a—o**) were also obtained as single stereoisomers, respectively.

AR-Inhibitory Activity All of the rhodanine derivatives prepared were tested for their ability to inhibit AR obtained from rat lens. The inhibition IC_{50} values are shown in Table VI. Most of the compounds have considerable activity (IC_{50} value: 10^{-7}—10^{-8} M).

In series 1, nine compounds are effective potent inhibitiors (**3b, c, e, k, l, n, p—r**), with an IC_{50} of 10^{-8} M. The propyl derivative (**3b**) is the most active compound in this study, and the *n*-pentyl derivative (**3d**) is about 10 times less active.

TABLE III. Bond Lengths and Their Standard Deviations (Å)

S1–C2	1.79 (1)	S1′–C2′	1.71 (2)
O4–C4	1.17 (3)	O4′–C4′	1.26 (3)
N3–C2	1.34 (3)	N3′–C2′	1.43 (3)
C4–C5	1.60 (3)	C4′–C5′	1.41 (3)
C7–C8	1.59 (7)	C7′–C8′	1.62 (5)
C11–C12	1.40 (3)	C11′–C12′	1.57 (3)
S2′–C2′	1.64 (3)	S2–C2	1.59 (2)
O12(2)′–C12′	1.32 (3)	O12(2)–C12	1.34 (3)
N3′–C11′	1.47 (3)	N3–C11	1.49 (3)
C6′–C7′	1.60 (4)	C6–C7	1.47 (4)
C7′–C10′	1.62 (5)	C7–C10	1.54 (7)
S1–C5	1.75 (2)	S1′–C5′	1.78 (2)
O12(1)–C12	1.18 (3)	O12(1)′–C12′	1.27 (3)
N3–C4	1.40 (3)	N3′–C4′	1.43 (3)
C5–C6	1.36 (4)	C5′–C6′	1.29 (3)
C7–C9	1.46 (6)	C7′–C9′	1.40 (6)

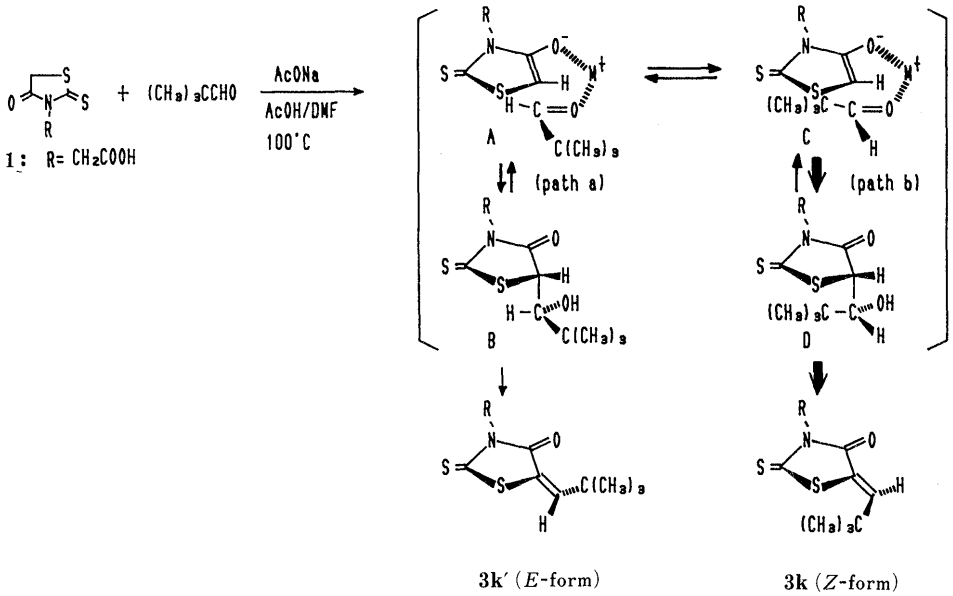
The standard deviation for the last digit is given in parentheses.

This suggests that the affinity with the enzyme is closely related to the length of the normal carbon chain at the 5-position. It appears that the linear cabon-chain derivatives (**3b, c**) are more active than the corresponding branch carbon chain compounds (**3g, h, j**): for example, the *n*-propyl compound (**3b**) is 10 times as potent as the isopropyl compound (**3g**). Among compounds (**3g, j**) with the branched carbon chain, the inhibitory activity is almost equal. But, **3k** with the *tert*-butyl group is more active than the other branched carbon compounds (**3g—j**); several characteristically efficient potencies were found by *in vivo* screenings of the *tert*-butyl derivative (**3k**) as mentioned above. The pentene (**3p**) and the pentadiene derivative (**3q**) showed effective potency among the unsaturated compounds (**3m—s**).

TABLE IV. Bond Angles and Their Standard Deviations (°)

C2–S1–C5	94 (1)	C2–N3–C4	124 (2)
C2–N3–C11	121 (2)	C4–N3–C11	114 (2)
S1–C2–S2	123 (1)	S1–C2–N3	107 (1)
S2–C2–N3	130 (2)	O4–C4–N3	131 (2)
O4–C4–C5	124 (2)	N3–C4–C5	105 (2)
S1–C5–C4	107 (2)	S1–C5–C6	131 (2)
C4–C5–C6	121 (2)	C5–C6–C7	130 (2)
C6–C7–C8	105 (3)	C6–C7–C9	113 (3)
C6–C7–C10	106 (3)	C8–C7–C9	83 (3)
C8–C7–C10	107 (4)	C9–C7–C10	135 (4)
N3–C11–C12	115 (2)	O12(1)–C12–O12(2)	125 (2)
O12(1)–C12–C11	124 (2)	O12(2)–C12–C11	111 (2)
C2′–S1′–C5′	95 (1)	C2′–N3′–C4′	113 (2)
C2′–N3′–C11′	124 (2)	C4′–N3′–C11′	123 (2)
S1′–C2′–S2′	126 (1)	S1′–C2′–N3′	110 (2)
S2′–C2′–N3′	124 (2)	O4′–C4′–N3′	115 (2)
O4′–C4′–C5′	130 (2)	N3′–C4′–C5′	115 (2)
S1′–C5′–C4′	108 (2)	S1′–C5′–C6′	134 (2)
C4′–C5′–C6′	118 (2)	C5′–C6′–C7′	130 (2)
C6′–C7′–C8′	100 (3)	C6′–C7′–C9′	112 (3)
C6′–C7′–C10′	111 (2)	C8′–C7′–C9′	104 (3)
C8′–C7′–C10′	96 (2)	C9′–C7′–C10′	130 (3)
N3′–C11′–C12′	107 (2)	O12(1)′–C12′–O12(2)′	122 (2)
O12(1)′–C12′–C11′	125 (2)	O12(2)′–C12′–C11′	112 (2)

The standard deviation for the last digit is given in parentheses.



3k′ (*E*-form) 3k (*Z*-form)

Chart 3

TABLE V. Physical Constants of 5-Alkylaminomethylidenerhodanines (**18a—o**)

Compd.	mp (°C)	^{1}H-NMR (ppm) (in DMSO-d_6)	Formula	Analysis Calcd (Found) C	Analysis Calcd (Found) H	MS m/z	IR (cm^{-1})
18a	247—249	2.85 (3H, d, CH_3), 4.30 (2H, s, CH_2COOH), 7.25 (1H, d, CH=), 7.82—7.90 (1H, m, NH), 8.51 (1H, br s, COOH)	$C_7H_8N_2O_3S_2$	36.20 (36.39)	3.47 (3.72)	232 (M^+), 188	3300—2850, 2700—2450, 1730
18b	202—204	3.00 (6H, s, $N(CH_3)_2$), 4.30 (2H, s, CH_2COOH), 7.30 (1H, s, CH=), 8.15 (1H, br s, COOH)	$C_8H_{10}N_2O_3S_2$	39.01 (38.96)	4.09 (4.28)	246 (M^+)	3250—2800, 2650—2400, 1730
18c	172—173	2.95 (2H, t, CH_2OH), 3.21—3.70 (6H, m, $NHCH_2CH_2OH$ and $HOCH_2CH_2NH_2$), 4.25 (2H, s, CH_2COOH), 7.40 (1H, br s, CH=), 7.91 (5H, br s, NH_2, NH and 2×OH), 8.13 (1H, br s, COOH)	$C_8H_{10}N_2O_4S_2 \cdot NH_2CH_2CH_2 \cdot OH$	37.14 (36.92)	5.30 (5.46)	n.d.	3400—2800, 2600—2400, 1700
18d	170—172	3.75 (2H, dd, $=CHCH_2NH$), 4.23 (2H, s, CH_2COOH), 5.00 (2H, d, $CH_2=CHCl_2$), 5.43—5.70 (1H, m, $CH_2=CHCH_2$), 7.30 (1H, d, $NHCH=$), 7.83—7.90 (1H, m, NH), 8.50 (1H, br s, COOH)	$C_9H_{10}N_2O_3S_2$	41.85 (41.78)	3.90 (3.38)	285 (M^+)	3300—2850, 2600—2400, 1730
18e	174—176	0.90 (6H, d, CH_3×2), 1.40—1.85 (1H, m, $CH_3(CH_3)CH$), 2.95 (2H, dd, $CHCH_2NH$), 4.23 (2H, s, CH_2COOH), 7.20 (1H, d, $NHCH=$), 7.90—8.03 (1H, m, NH), 8.51 (1H, br s, COOH)	$C_{10}H_{14}N_2O_3S_2$	43.78 (43.57)	5.14 (4.97)	247 (M^+), 230	3300—2850, 2650—2450, 1720
18f	243—245	0.85 (3H, t, CH_3), 1.10—1.62 (8H, m, CH_2×4), 3.31—3.29 (2H, m, CH_2NH), 4.23 (2H, s, CH_2COOH), 7.31 (1H, d, $NCH=$), 7.83—8.17 (1H, br s, NH), 8.70 (1H, br s, COOH)	$C_{12}H_{18}N_2O_3S_2$	47.66 (47.52)	6.00 (5.79)	302 (M^+)	3300—2850, 2600—2400, 1710
18g	240—242	3.58 (3H, s, CH_3O), 4.40 (2H, s, CH_2COOH), 6.21—6.97 (4H, m, phenyl protons), 7.65 (1H, d, $NHCH=$), 8.36 (1H, br s, COOH), 9.83 (1H, d, NH)	$C_{13}H_{12}N_2O_4S_2$	48.14 (48.35)	3.73 (3.72)	324 (M^+)	3350—2800, 2700—2500, 1740, 1680
18h	244—246	3.60 (3H, s, CH_3O), 4.36 (2H, s, CH_2COOH), 6.50—7.10 (4H, m, phenyl protons), 7.55 (1H, d, $NHCH=$), 8.71 (1H, br s, COOH), 9.58 (1H, d, NH)	$C_{13}H_{12}N_2O_4S_2$	48.14 (47.99)	3.73 (3.73)	324 (M^+)	3300—2850, 2700—2450, 1720, 1675
18i	253—255	4.40 (2H, s, CH_2COOH), 6.68—7.15 (4H, m, phenyl protons), 7.70 (1H, d, $NHCH=$), 8.10 (1H, br s, COOH), 9.92 (1H, d, NH)	$C_{12}H_9ClN_2O_3S_2$	43.84 (43.63)	2.76 (2.70)	328 (M^+), 284	3350—2850, 2650—2350, 1720, 1670
18j	264—266	4.38 (2H, s, CH_2COOH), 6.85 (2H, d, benzene protons), 7.10 (2H, d, benzene protones), 7.65 (1H, d, CH=), 9.90 (1H, br s, NH)	$C_{12}H_9BrN_2O_3S_2$	38.62 (38.57)	2.43 (2.38)	375 (M^++2), 373 (M^+)	3350—2850, 2600—2350, 1730, 1670
18k	261—263	2.30 (3H, s, CH_3), 4.40 (2H, s, CH_2COOH), 6.60—7.20 (4H, m, phenyl protons), 7.70 (1H, d, $NHCH=$), 8.52 (1H, br s, COOH), 9.90 (1H, d, NH)	$C_{13}H_{12}N_2O_3S_2$	50.63 (50.64)	3.92 (3.98)	308 (M^+)	3350—2850, 2650—2400, 1740, 1680
18l	293—295	3.30—3.55 (8H, m, CH_2×4), 4.30 (2H, s, CH_2COOH), 7.30 (1H, s, NCH=), 8.71 (1H, br s, COOH)	$C_{10}H_{12}N_2O_4S_2$	41.66 (41.91)	4.19 (4.38)	288 (M^+), 244	3150—2850, 2650—2400, 1720, 1665
18m	250—252	2.33 (3H, s, CH_3), 2.40—2.81 (4H, m, $CH_2N(CH_3)CH_2$), 3.41—3.83 (4H, m, $CH_2N(CH=)CH_2$), 4.30 (2H, s, CH_2COOH), 7.40 (1H, s, CH=), 8.12 (1H, br s, COOH)	$C_{11}H_{15}N_3O_3S_2$	43.84 (43.63)	5.02 (5.14)	301 (M^+)	3350—2850, 2700—2300, 1720, 1670
18n	244—246	1.71—2.15 (2H, m, $NCH_2CH_2CH_2N$), 2.33 (3H, s, CH_3), 2.45—2.80 (4H, m, $CH_2N(CH_3)CH_2$), 3.40—3.77 (4H, m, $CH_2N(CH=)CH_2$), 4.35 (2H, s, CH_2COOH), 7.45 (1H, s, CH=), 8.12 (1H, br s, COOH)	$C_{12}H_{17}N_3O_3S_2$	45.70 (45.55)	5.43 (5.15)	315 (M^+)	3850—3350, 2700—2300, 1725, 1670
18o	248—250	4.40 (2H, s, CH_2COOH), 6.95—7.40 (9H, m, phenyl protons), 7.55 (1H, d, CH=), 8.37 (1H, br s, COOH), 9.80 (1H, d, NH)	$C_{18}H_{14}N_2O_3S_2$	58.36 (58.29)	3.81 (3.77)	370 (M^+)	3300—2850, 2650—2350, 1735, 1660

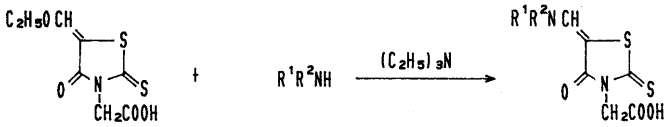
n.d.: not detect.

In series 2, all of the compounds (**15a—f**) showed moderate activity. This leads us to assume that a substitution in the neighboring the carbonyl group of the rhodanine ring does not contribute to increase of the inhibitory potency.[12]

In series 3, five of the arylaminomethylidene derivatives (**18g—k**) showed effective inhibition potency, with an IC_{50} of 10^{-8} M. Especially, **18g** and **18i** displayed a potency comparable to that of **3b**. It seems that hydrophilic and polar amino groups are not suitable for this type AR inhibitor.

In series 4, the ester (**10**) and the amides (**11—13**) are completely inactive. This makes clear it that presence of the carboxyl group is essential for the appearance of inhibitory activity of rhodanine derivatives.

A suitable bulky and lipophilic substituent at 5-position of 3-carboxymethylrhodanine (**1**) increases the inhibitory potency. On 3-carboxymethylrhodanine derivatives the carboxy group at the 3-position may interact with a complimentary binding site present on the enzyme, such as a guanidino group, and appreprate bulky and lipophilic groups at the 5-position may interact with a secondary lipopholic site present on the enzyme.[1k,5] Similar effect of the substituents was found earlier on effective inhibitory active benzo[*b*]furan derivatives.[3] Here, we can state that



16 17 18

		yield (%)
a	R^1=H, R^2=CH_3	47
b	R^1=R^2=CH_3	73
c	R^1=H, R^2=$HOCH_2CH_2$	53
d	R^1=H, R^2=CH_2=$CHCH_2$	53
e	R^1=H, R^2=$(CH_3)_2CHCH_2$	64
f	R^1=H, R^2=$CH_3(CH_2)_4CH_2$	60
g	R^1=H, R^2=*m*-$(CH_3O)C_6H_4$	69
h	R^1=H, R^2=*o*-$(CH_3O)C_6H_4$	63
i	R^1=H, R^2=*m*-$(Cl)C_6H_4$	73
j	R^1=H, R^2=*p*-$(Br)C_6H_4$	44
k	R^1=H, R^2=*m*-$(CH_3)C_6H_4$	74
l	R^1=$CH_2CH_2OCH_2CH_2$= R^2	67
m	R^1=$CH_2CH_2N(CH_3)CH_2CH_2$= R^2	70
n	R^1=$CH_2CH_2N(CH_3)CH_2CH_2CH_2$= R^2	80
o	R^1=H, R^2=*p*-$(C_6H_5)C_6H_4$	72

Chart 4

TABLE VI. Aldose Reductase-Inhibitory Activity

Series	Compd.	IC_{50} ($\times 10^{-7}$ M)	Series	Compd.	IC_{50} ($\times 10^{-7}$ M)
1	**3a**	2.0	2	**15c**	1.5
	3b	0.17		**15d**	4.8
	3c	0.80		**15e**	1.5
	3d	1.3		**15f**	2.5
	3e	0.48	3	**18a**	13
	3f	3.0		**18b**	6.5
	3g	1.7		**18c**	7.0
	3h	1.9		**18d**	3.0
	3i	1.2		**18e**	6.0
	3j	1.0		**18f**	2.8
	3k	0.71		**18g**	0.26
	3l	0.75		**18h**	0.50
	3m	7.5		**18i**	0.23
	3n	0.70		**18j**	0.50
	30	1.0		**18k**	0.36
	3p	0.4		**18l**	3.4
	3q	0.46		**18m**	2.0
	3r	0.75		**18n**	13
	3s	6.5		**18o**	1.5
	3t	1.4	4	**10**	$>10^{-5}$ M
	3u	1.3		**11**	$>10^{-5}$ M
2	**15a**	3.5		**12**	$>10^{-5}$ M
	15b	2.1		**13**	$>10^{-5}$ M
				Sorbinil	2.0

the AR inhibitors generally include at least a carboxy group and a suitable lipophilic group in the molecule.

Experimental

All melting points were measured with a Thomas Hoover capillary melting point apparatus, and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded with JEOL PS-100 and Varian XL-300 (75 MHz) spectrometers. Chemical shifts are given in δ values with tetramethylsilane (TMS) as an internal standard and the following abbreviations are used: s, singlet; d, doublet; dd, double of doublets; br s, broad singlet; br d, broad doublet. Low-resolution mass spectra (MS) were obtained with a Hitachi M-52 instrument. Infrared (IR) spectra were recorded with a Shimadzu IR-17G spectrometer. All the data for X-ray structural analysis were recorded with a Rigaku AFC-5 FOS four-cycle diffractometer.

3-Carboxymethyl-5-propylidenerhodanine (3a) General Procedure A: A mixture of **1** (4.0 g, 0.021 mol) and K_2CO_3 (3.5 g, 0.025 mol) in dry dimethyl sulfoxide (DMSO) (50 ml) was stirred at 25 °C for 30 min, then propioaldehyde (1.5 g, 0.025 mol) was added dropwise at 25 °C. The mixture was stirred at 75 °C for 1.5 h and then filtrated. The filtrate was poured into ice-water and acidified with 3 N HCl (120 ml). The aqueous solution was extracted with ether. The ether layer was washed with water and dried over Na_2SO_4. Removal of the ether gave a yellow solid which was recrystallized from ethyl acetate and benzene (7 : 2) to give **3a** as pale yellow prisms (3.5 g, 69%). Physical data, see Table I. Compounds **3b**, **3c**, **3e**, **3g**, **3m**, **3n**, **3t**, and **3u** were obtained by the same procedure as described for **3a**; the physical data are shown in Table I and the yields in Chart 1.

3-Carboxymethyl-5-(2,2-dimethylpropylidene)rhodanine (3k) General Procedure B: A mixture of **1** (4.0 g, 0.021 mol) and sodium acetate (4.3 g, 0.053 mol) in acetic acid (30 ml) was stirred at 30 °C for 0.5 h. Pivalaldehyde (2.1 g, 0.024 mol) was added dropwise to the mixture at 25 °C and the mixture was stirred at 100—105 °C for 3.5 h. The black reaction mixture was concentrated off under reduced pressure. The residual mixture was poured into water to form yellow precipitate which, in turn, was extracted with ethyl acetate and the extract was then washed with water and dried over Na_2SO_4. Removal of the solvent gave crude prisms. These were recrystallized from ethyl acetate and ethanol (3 : 1) to give **3k** as pale yellow prisms (4.6 g, 84%). ^{13}C-NMR (10% solution in $CDCl_3$) δ: 28.9 ($CH_3 \times 3$), 35.0 ($(CH_3)\underline{C}$), 44.3 (NCH_2), 121.9 ($CH=\underline{C}$–S), 149.4 ($\underline{C}H=C$–S), 166.9 (C=O or COOH), 171.8 (C=O or COOH), 193.7 (C=S). Physical data, see Table I. Compounds **3d**, **3f**, **3h—j**, and **3l—u** were obtained by the same procedure as described for **3k**, and the physical data and yields are shown in Table I and Chart 1, respectively.

3-Ethoxycarbonylmethyl-5-(2-chloroethylidene)rhodanine (8) $NaHCO_3$ (1.0 g, 0.006 mol) was added to a mixture of 3-ethoxycarbonylmethylrhodanine (**4**) (0.5 g, 0.0023 mol), ethyl ether (10 ml) and water (10 ml) at 0 °C with vigorous stirring. Chloroacetaldehyde (**5**) (40% aqueous solution, 0.58 ml, 0.003 mol) was added to the mixture at 0 °C and the solution was stirred vigorously for 3 h at 0 °C. Ether was added to the solution and the ether layer was washed with 3% HCl and water. Removal of the ether left an oily residue which was purified by preparative thin layer chromatography (TLC) on SiO_2 (benzene : ether = 3 : 2) to afford pale yellow oil (3-ethoxycarbonylmethyl-5-(2-chloro-1-hydroxyethyl)rhodanine) (**7**) (0.48 g, 71%). *Rf* 0.62 (TLC, SiO_2, benzene : ether = 3 : 1). ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, t, J=7.4 Hz, CH_3), 3.00 (1H, br s, OH), 3.67—3.90 (2H, m, $C\underline{H}(OH)C\underline{H}$), 4.27 (2H, q, J=7.4 Hz, $C\underline{H}_2CH_3$), 4.78 (2H, s, NCH_2), 4.65—4.82 (2H, m, $ClCH_2$). MS *m/z*: 297 (M^+), 279, 244.

The hydroxy compound (**7**) was treated with *p*-toluenesulfonic acid (1.0 g) in benzene (90 ml) at 83 °C for 8 h. Water was separated as the benzene azeotrope. The reaction mixture was dried up to give **8** as pale yellow powder. The powder was purified by column chromatography on SiO_2 (ethyl acetate : hexane = 1 : 4). The compound **8** was obtained as colorless prism (1.8 g, 64%). mp 74—76 °C (from ethyl acetate). ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7 Hz, CH_3), 4.12 (2H, d, J=7.6 Hz, $ClCH_2$), 4.17 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.77 (2H, s, NCH_2), 7.00 (1H, t, J=7.6 Hz, CH=). IR ν_{max}^{KBr} cm^{-1}: 1750, 1730. MS *m/z*: 279 (M^+), 244, 234. *Anal.* Calcd for $C_9H_{10}ClNO_3S_2$: C, 38.64; H, 3.60. Found: C, 38.53; H, 3.75.

3-Ethoxycarbomethyl-5-(2,2-dimethylpropylidene)rhodanine (10) A mixture of **3k** (1.0 g, 0.0039 mol), ethanol (0.5 ml), benzene (20 ml) and *p*-toluenesulfonic acid (0.1 g) was refluxed with stirring for 4 h. The mixture was concentrated to give an oily residue. An ether solution of the residue was washed with aqueous $NaHCO_3$ solution and water, and dried over Na_2SO_4. Removal of ether gave **10** as yellow oil which was purified by distillation (0.92 g, 83%). bp 213—216 °C (0.1 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 1.22 (9H, s, $(CH_3)_3C$), 1.28 (3H, t, J=7.0 Hz, $C\underline{H}_3CH_2$), 4.24 (2H, q, J=7.0 Hz, $CH_3C\underline{H}_2$), 4.87 (2H, s, CH_2CO), 7.09 (1H, s, CH=). IR ν_{max}^{film} cm^{-1}: 1750, 1722. MS *m/z*: 287 (M^+), 241, 213. *Anal.* Calcd for $C_{12}H_{17}NO_3S_2$: C, 50.15; H, 5.96. Found: C, 50.15; H, 6.12.

3-Dimethylaminocarbonylmethyl-5-(2,2-dimethylpropylidene)rhodanine (11) A mixture of **3k** (3.0 g, 0.012 mol) and thionyl chloride (25 ml) was stirred at 45 °C for 0.5 h. Removal of thionyl chloride under reduced pressure gave crude acid chloride of **3k**. Dichloromethane (10 ml) solution of acid chloride of **3k** (2 g, 0.0072 mol) was added to a mixture of dimethylamine-hydrochloride (0.65 g, 0.008 mol), triethylamine (1.6 g, 0.016 mol) in dichloromethane (10 ml) at 0 °C and the reaction mixture was stirred at 2 °C for 1 h. It was then poured into water and extracted with ethyl acetate; the extract was washed with water and dried over Na_2SO_4. Removal of ethyl acetate gave crude **11** as pale yellow needles. The needles was recrystallized from dichloromethane to give pale yellow needles (1.2 g, 30%). mp 109—110.5 °C (from dichloromethane : cyclohexane (1 : 1)). ^{1}H-NMR ($CDCl_3$) δ: 1.23 (9H, s, $(CH_3)_3C$), 2.99 (3H, s,

$N(C\underline{H}_3)(CH_3)$), 3.11 (3H, s, $N(CH_3)(C\underline{H}_3)$), 4.88 (2H, s, CH_2CO). IR ν_{max}^{KBr} cm^{-1}: 1721, 1664. MS *m/z*: 286 (M^+), 241. *Anal.* Calcd for $C_{12}H_{18}N_2O_2S_2$: C, 50.32; H, 6.33. Found: C, 50.37; H, 6.55.

3-Diethylaminocarbonylmethyl-5-(2,2-dimethylpropylidene)rhodanine (12) A reaction of acid chloride of **3k** (2 g, 0.0072 mol) with diethylamine (0.063 g, 0.0086 mol) was carried out exactly according to the procedure for the preparation of **11**. The 3-diethylamino compound **12** was obtained as colorless oil (0.51 g, 23%), bp 260—262 °C (0.1 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 1.12 (3H, t, J=7.4 Hz, $C\underline{H}_3CH_2$), 1.22 (9H, s, $(CH_3)_3C$), 1.31 (3H, t, J=7.4 Hz, $C\underline{H}_3CH_2$), 3.40 (4H, q, J=7.4 Hz, $CH_3C\underline{H}_2\times 2$), 4.90 (2H, s, CH_2CO), 7.06 (1H, s, CH=). IR ν_{max}^{film} cm^{-1}: 1725, 1660. MS *m/z*: 314 (M^+), 299, 281. *Anal.* Calcd for $C_{14}H_{22}N_2O_2S_2$: C, 53.47; H, 7.05. Found: C, 53.60; H, 7.27.

3-(1-Piperidinecarbonylmethyl)-5-(2,2-dimethylpropylidene)rhodanine (13) A reaction of acid chloride of **3k** (2 g, 0.0072 mol) with piperidine (0.74 g, 0.0090 mol) was carried out according to the procedure for the preparation of **11**. The 3-(1-piperidinecarbonylmethyl) derivative (**13**) was obtained as colorless plates (1.8 g, 77%). mp 156—157.5 °C (from 1,2-dichloroethane–cyclohexane (1 : 1)). ^{1}H-NMR ($CDCl_3$) δ: 1.23 (9H, s, $(CH_3)_3C$), 1.52—1.69 (6H, m, $N\text{–}CH_2(C\underline{H}_2)_3$), 3.39—3.59 (4H, m, $CH_2\text{–}N\text{–}CH_2$), 4.87 (2H, s, CH_2CO), 7.07 (1H, s, CH=). IR ν_{max}^{KBr} cm^{-1}: 1721, 1648. MS *m/z*: 326 (M^+), 293. *Anal.* Calcd for $C_{15}H_{22}N_2O_2S_2$: C, 55.19; H, 6.79. Found: C, 54.99; H, 6.77.

X-Ray Structure Analysis A single crystal of **3k** (from AcOEt), $C_{10}H_{13}NO_3S_2$, was subjected to the X-ray analysis. The crystal data were as follows: size *ca.* 0.3×0.6×0.9 mm; triclinic; space group $P\bar{1}$ (z=2); cell dimensions a=10.823 (5), b=10.806 (5), c=6.188 (3) Å, α=100.51 (4), β=89.45 (4), γ=110.06 (3), V=667.3 (6) Å^3. The 1471 unique intensities were collected by 2θ–ω scan method within the limit $2\theta \leqq 100°$ on a Rigaku AFC-5 FOS four-circle diffractometer using graphite monochromated Cu-$K\alpha$ (λ=1.5418 Å) radiation. All the non-hydrogen atomic positions were revealed by a direct method (MULTAN[13]). The positions of hydrogen atoms except for those of carboxy and methyl groups were generated computationally on the basis of stereochemical and geometrical considerations. The block-diagonal least-squares refinements for the 1442 observed reflections ($F_o \leqq 2\sigma F_o$) with anisotropic thermal factors for non-hydrogen atoms and isotropic thermal factors for hydrogen atoms converged to the final R value of 0.089 (UNICS III[14]).[15] No absorption correction was performed.

An ORTEP[16] drawing of the structure (less hydrogen atoms) is shown in Fig. 1. The fractional atomic coordinates, bond lengths and bond angles are listed in Tables II—IV, respectively

Abnormal bond lengths and angles around the side chains (C7–C10 and C7′–C10′) are considered to be due to disordered atomic arrangement in the crystal.

3-Carboxymethyl-5-(isopropylidene)rhodanine (15a) General Procedure for **15b—f**: Acetone (45.5 g, 0.78 mol) was added to a mixture of **1** (30 g, 0.16 mol) and sodium acetate 39 g (0.48 mol) in acetic acid (30 ml) and DMF (150 ml) by portions at 80 °C under vigorous stirring. After the mixture was stirred at 95 °C for 3 h, the reaction mixture was poured into chilled 2 N HCl (290 ml) and extracted with ether. The extract was washed with water, dried over Na_2SO_4 and concentrated under reduced pressure to yield a pale yellow powder. The powder was recrystallized from 1,2-dichloroethane to afford **15a** as pale yellow prisms (23.1 g, 64%). Physical data, see Table I. Compounds **15b—f** were obtained by the same procedure as described for **15a**, and the physical data are shown in Table I and the yields in Chart 1.

3-Carboxymethyl-5-ethoxymethylidenerhodanine (16) A mixture of **1** (36 g, 0.19 mol) and ethyl orthoformate (33.6 g, 0.23 mol) in acetic anhydride (250 ml) was stirred at 130 °C for 2.5 h. The mixture was concentrated under reduced pressure to afford a yellow colored solid. The solid was recrystallized from ethyl acetate to give **16** as pale yellow needles (33 g, 72%). mp 192—193 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz, CH_3), 4.15 (2H, q, J=7.7 Hz, $C\underline{H}_2CH_3$), 4.40 (2H, s, $C\underline{H}_2COOH$), 7.60 (1H, s, CH=). MS *m/z*: 247 (M^+), 291. IR ν_{max}^{KBr} cm^{-1}: 3100—2900, 2600—2400, 1730, 1680. *Anal.* Calcd for $C_8H_9NO_3S_2$: C, 48.23; H, 4.55. Found: C, 48.21; H, 4.63.

3-Carboxymethyl-5-methylaminomethylidenerhodanine (18a) General Procedure for **18b, 18e, 18f,** and **18l**: Triethylamine (2.3 g, 0.023 mol) was added to a solution of methylamine hydrochloride (1.6 g, 0.023 mol) in ethanol (7.5 ml). The solution was added dropwise to a solution of **16** (2.5 g, 0.012 mol) in ethanol (20 ml) at 25 °C. The reaction mixture was stirred for 2 h at 60 °C. The mixture was concentrated under reduced pressure to afford methylamine salt of **18a** as brown powder (2.3 g). The salt was dissolved in 45 ml of water. pH of the aqueous solution was adjusted to exactly 6.0 with 1 N HCl. The compound **18a** was precipitated from the aqueous solution. The precipitate is recrystallized from methanol and ethyl acetate (5 : 3) to afford **18a** as pale yellow plates (1.3 g, 47%). Physical data, see Table V. Compounds **18b, 18e, 18f,** and **18l** were obtained by the same procedure as described for **18a**, and their physical data and yields are shown in Table V and Chart 4, respectively.

3-Carboxymethyl-5-hydroxymethylaminomethylidenerhodaninethanolamine Salt (18c) General Procedure for **18d, 18g, 18k,** and **18m—o**: Monoethanolamine (1.5 g, 0.031 mol) was added to a solution of **16** (3.7 g, 0.016 mol) in ethanol (25 ml). The reaction mixture was stirred for 3 h at 65 °C. Upon cooling to 3 °C, the product **18c** crystallized from methanol and ether (7 : 3) to give **18c** as pale yellow prisms (2.6 g 53.1%). Physical data, see Table V. Free compounds **18d, 18g—k,** and **18m—o** were obtained by the same procedure as described for **18c**, and their physical data and yields are shown in Table V and Chart 4, respectively.

Enzyme Inhibitory Activity Aldose reductase activity was measured by the method of Hoyman and Kinoshita.[17] Assays were performed at 30 °C in 0.1 M sodium phosphate buffer (pH 6.2) containing 1.5 mM DL-glyceraldehyde, 0.25 mM reduced nicotinamide adenine diphosphate (NADPH) and an appropriate amount of enzyme (supernatant of homogenates of rat lens) in a total volume of 1.5 ml. The effect of an inhibitor on the enzyme activity was determined by adding 15 μl of dimethylsulfoxide solution of a test compound to the reaction mixture. The concentration of the inhibitor giving 50% inhibition of enzyme activity (IC_{50}) was estimated from the least-squares regression line in the plot of the logarithm of inhibition concentration *versus* remaining activity.

Acknowledgement The authors wish to thank Associated Professor Shunsaku Ohta of Kyoto Pharmaceutical University for his valuable advice.

References and Notes

1) *a*) D. Dvornik, N. Simard-Duquesne, M. Krami, K. Sestanj, K. H. Gabbay, J. H. Kinoshita, S. D. Varma and L. O. Merola, *Science*, **182**, 1146 (1973); *b*) C. A. Lipinski and N. J. Hutson, *Ann. Rep. Med. Chem.*, **19**, 169 (1984); *c*) P. F. Kador, J. H. Kinoshita and N. E. Sharpless, *J. Med. Chem.*, **28**, 841 (1985); *d*) J. H. Kinoshita, P. F. Kedor and M. Datiles, *J. Am. Med. Assoc.*, **1983**, 246, 257; *e*) M. Brown and A. Cerami, *Ann. Rev. Biochem.*, **1981**, 50, 385; *f*) W. F. Williams and J. D. Odom, *Science*, **1986**, 233, 223; *g*) D. A. Greene and S. A. Lattimer, *Diabetes*, **33**, 712 (1984); *h*) D. A. Greene, S. A. Lattimer and S. A. Sima, *A.A.F. New Eng. J. Med.*, **1987**, 316, 599; *i*) J. DeRuiter, R. F. Bone and C. A. Mayfield, *J. Med. Chem.*, **32**, 145 (1989); *j*) J. Butera, J. Bagli, W. Doubleday, L. Humber, A. Treasurywala, D. Loughney, K. Sestanj, J. Mallen and J. Sredy, *ibid.*, **32**, 727 (1989); *k*) J. DeRuiter, B. E. Swearingen, Vinay Wondrekar and C. A. Mayfield, *ibid.*, **32**, 1033 (1989); *l*) J. P. Rizzi, R. C. Schnur, N. J. Hutson, K. G. Kraus and P. R. Kelbaugh, *ibid.*, **32**, 1208 (1989).

2) *a*) T. Tadeo, S. Satoghi and K. Masamori, European Patent 045165 [*Chem. Abstr.*, **96**, 217830*n* (1982)]; T. Tadeo, K. Masamori and A. Akio, European Patent 047109 [*Chem. Abstr.*, **97**, 23781*x* (1982)]; *b*) K. Stribling, D. J. Mirrlees and D. C. N. Earl, *Diabetologia*, **1983**, 25, 196; *c*) K. Sestanj, N. A. Abraham, F. Bellini and A. Treasurywala, Canadian Patent 1147739 [*Chem. Abstr.*, **100**, 7158*z* (1983)].

3) Y. Ohishi, T. Mukai, M. Nagahara, M. Yajima and N. Kajikawa, *Chem. Pharm. Bull.*, **37**, 2398 (1989).

4) Y. Ohishi, M. Nagahara, Y. Takehisa, M. Yajima, S. Kurokawa, N. Kajikawa, A. Itoh and K. Nogimori, European Patent 0143461 [*Chem. Abstr.*, **103**, 196070*k* (1985)].

5) C. A. Mayfield and J. DeRuiter, *J. Med. Chem.*, **30**, 1595 (1987); J. DeRuiter, A. N. Brubaker, M. A. Garner, J. M. Barksdale and C. A. Mayfield, *J. Pharm. Sci.*, **76**, 149 (1987).

6) P. E. Kador, J. D. Goosey, N. E. Sharpless, J. Kolish and D. D. Miller, *Eur. J. Med. Chem.*, **16**, 293 (1981).

7) The ester (**4**) was obtained by refluxing the carboxy compound (**1**) in the presence of *p*-toluenosulfonic acid in ethanol and benzene. mp 58—60 °C (from ethanol–water (4 : 1)). ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, t, J=7.2 Hz, CH_3), 4.07 (2H, s, $COCH_2S$), 4.23 (2H, q, J=7.2 Hz, $C\underline{H}_2CH_3$), 4.72 (2H, s, NCH_2).

8) J. C. Richerd and R. Clark, *Can. J. Chem.*, **42**, 2073 (1964).

9) These data will be published and discussed elsewhere.

10) J. E. Dubois and M. Dubois, *Tetrahedron Lett.*, **43**, 4215 (1967); M. Stiles, R. R. Winkler, Y. Chang and L. Traynor, *J. Am. Chem. Soc.*, **86**, 3337 (1964); H. E. Zimmerman and M. D. Traxler, *ibid.*, **79**, 1920 (1957).

11) E. B. Knott, *J. Chem. Soc.*, **1954**, 1482.
12) The IC_{50} values of the mixture of stereoisomers were determined in the compounds (**15b, d, f**).
13) P. Main, M. M. Woolfson and G. Germain, "A Computer Programme for the Automatic Solution of Crystal Structures," Univ. of York, York, England and Univ. de Louvain, Leuven, Belgium, 1971.
14) T. Sakurai and K. Kobayasi, *Rika Gaku Kenkyusho Hokoku*, **55**, 69 (1979).
15) All the calculations were performed on a computer TOSBAC DS-600.
16) C. K. Johnson, ORTEP, Oak Ridge National Laboratory Report ORNL, Oak Ridge, Tenn., U.S.A., 1965.
17) S. Hoyman and J. H. Kinoshita, *J. Biol. Chem.*, **240**, 877 (1965).