CH_3CO_2H containing 2 g of 5% Pd/C was hydrogenated in a Parr apparatus for 48 h. The mixture was filtered, and solvent was removed at reduced pressure. The residue was triturated with ether, giving 4.81 g (88%) of **10** as a white powder: NMR ($CDCl_3$) δ 3.90–3.30 (m, 11 H, CH_2OCH_2, CH_2N, CHO), 3.20 (s, 9 H, $N(CH_3)_3$), 2.85 (s, 1 H, OH) 2.20–1.10 (m, 36 H, $(CH_2)_{16}$ $(CH_2)_2$), 0.90 (m, 3 H, terminal CH_3); IR (KBr) 3300 cm^{-1}; MS (FD) *m/z* 458 (M–Br). Anal. ($C_{28}H_{60}O_3NBr \cdot H_2O$) C, N, Br; H: calcd, 11.22; found, 10.70.

4-[2-(Acetyloxy)-3-(octadecyloxy)propoxy]-*N*,*N*,*N*-trimethyl-1-butanaminium Bromide (11). A mixture of acetic anhydride (5 mL) and **10** (0.5 g, 0.93 mmol) was refluxed under argon with stirring for 15 min. Excess acetic anhydride was removed at reduced pressure. Toluene was added and removed several times. Ether was added, and the mixture was cooled to 0 °C, giving 0.5 g (93%) of **11** as a white powder with no well-defined melting point: NMR ($CDCl_3$–CD_3OD) δ 5.10 (m, 1 H, C*H*OAc), 3.80–3.10 (m, 10 H, CH_2OCH_2, CH_2N), 3.15 (s, 9 H, $N(CH_3)_3$), 2.01 (s, 3 H, $COCH_3$), 1.85–1.08 (m, 36 H, $(CH_2)_{16}$, $(CH_2)_2$), 0.90 (m, 3 H, terminal CH_3); IR (KBr) 1730 cm^{-1}; MS (FD) *m/z* 500 (M – Br). Anal. ($C_{30}H_{62}BrNO_4 \cdot 1.25H_2O$) C, H, N, Br.

Acknowledgment. We thank Dr. L. Gehrlein and staff for microanalytical determinations, Dr. M. Siegel and G. O. Morton and staff for spectral data, R. A. Gabel for his assistance with the hypotension assay, and D. R. Nytko for her assistance with the platelet aggregation assay.

Synthesis and Hypolipidemic Activities of 5-Thienyl-4-oxazoleacetic Acid Derivatives[1]

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A series of 2,5-disubstituted 4-oxazoleacetic acid derivatives was synthesized and evaluated for hypolipidemic activity. Among them, those with a thienyl group at C-5 of the oxazole ring exerted highly potent hypolipidemic effects in rats. 2-(4-Fluorophenyl)-5-(3-thienyl)-4-oxazoleacetic acid (**88**) was the most potent derivative: it was about 2 times as active in normal SD male rats and about 4 times as active in hereditary hyperlipidemic rats (THLR/1) as clofibrate with an improved antiarterioschlerosis index (HDL-Cho/Total-Cho). In addition, it showed inhibition of platelet aggregation ex vivo.

In recent years, as the recognition of the role of hyperlipidemia as a risk factor for coronary heart diseases gained more momentum,[2] much attention has been paid to developing more satisfactory hypolipidemic agents such as an agent effective for Type IIa hyperlipidemia.

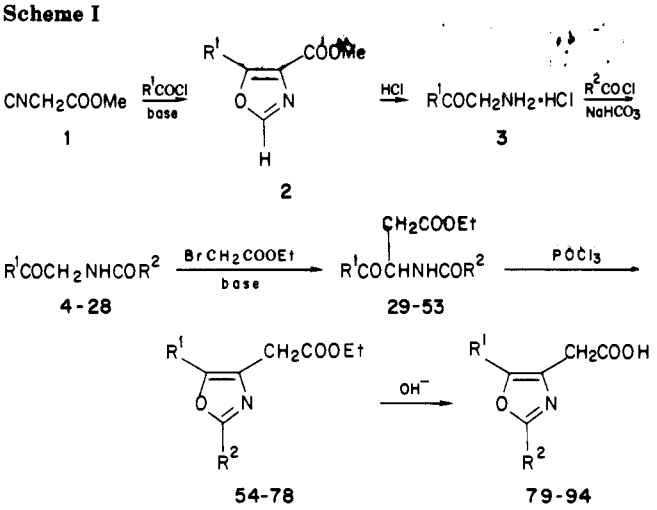
On the other hand, syntheses of biologically active compounds from amino acids continued to be of interest in our laboratory. Using methyl α-isocyanoacetate, which is a key reactive species of glycine, we have synthesized a number of heterocycles and amino acid derivatives.[3] In particular, we have systematically synthesized 5-aryl-4-oxazolecarboxylic acid derivatives having inhibitory activities on platelet aggregation,[4] and we found that some of them often showed hypolipidemic activities and did not exhibit marked toxicities.

In the present study, we synthesized more of the oxazole analogues and evaluated their hypolipidemic activities. From these compounds was found a series of 5-thienyl-4-oxazoleacetic acid derivatives that possess more potent hypocholesterolemic and hypotriglyceridemic activities than clofibrate [ethyl 2-(*p*-chlorophenoxy)isobutyrate].

Chemistry

A general synthetic method of 2,5-disubstituted 4-oxazoleacetic acid derivatives (**54–94**) is shown in Scheme I. The initial conversion of methyl α-isocyanoacetate (**1**) to α-amino ketones (**3**) was carried out as described in the previous reports:[5,6] the reaction of **1** with acyl halides under basic conditions followed by treatment with hydrochloric acid of the resulting oxazolecarboxylates (**2**)[7,8] afforded the α-amino ketone hydrochlorides (**3**) in good yields. After N-acylation of the α-amino ketone with a second acyl halide by the Schotten–Baumann reaction, an acetic acid moiety was selectively introduced to the active methylene group of the α-(*N*-acylamino) ketones (**4–28**) by base-as-

Scheme I



† Research Laboratory of Applied Biochemistry.
‡ Biological Research Laboratory.

(1) Synthesis of Amino Acids and Related Compounds. 29. This work was presented at the 104 Annual Meeting of the Pharmaceutical Society of Japan, Sendai, April 1984. Part 28: Seki, M.; Moriya, T.; Matsumoto, K. *Agric. Biol. Chem.* **1984**, *48*, 1251.
(2) Report of LRC-CPPT (Lipid Research Clinics Coronary Primary Prevention Trial), *J. Am. Med. Assoc.* **1984**, *251*, 351.
(3) Suzuki, M.; Moriya, T.; Matsumoto, K.; Miyoshi, M. *Synthesis* **1982**, 875.
(4) Ozaki, Y.; Maeda, S.; Iwasaki, T.; Matsumoto, K.; Odawara, A.; Sasaki, Y.; Morita, T. *Chem. Pharm. Bull.* **1983**, *31*, 4417.
(5) Suzuki, M.; Iwasaki, T.; Miyoshi, M.; Okumura, K.; Matsumoto, K. *J. Org. Chem.* **1973**, *38*, 3571.
(6) Maeda, S.; Suzuki, M.; Iwasaki, T.; Matsumoto, K.; Iwasawa, Y. *Chem. Pharm. Bull.* **1984**, *32*, 2536.
(7) Schöllkopf, U.; Schröder, R. *Angew. Chem.* **1971**, *83*, 358.

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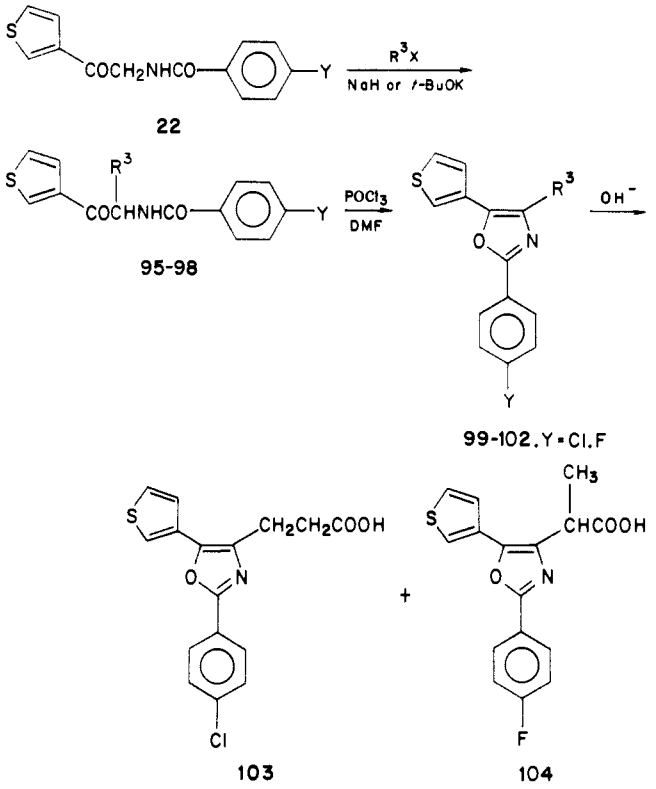
Scheme II



95, 99. $R^3 = CH_2CH_3$; **96, 100.** $R^3 = CH_2CH{=}CH_2$:
97, 101. $R^3 = CH_2CH_2COOEt$; **98, 102.** $R^3 = CH(CH_3)COOEt$

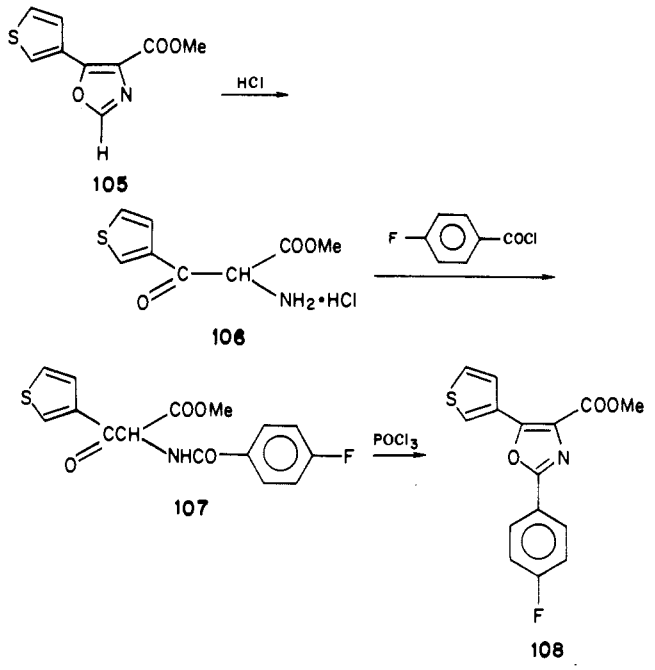
sisted condensation. The reaction proceeded under mild reaction conditions without competitive side reactions, such as N-substitution. Dehydrative cyclization of the β-(*N*-acylamino)-γ-keto esters (**29–53**) was performed to obtain the desired oxazoleacetates with use of phosphoryl chloride with heating in an inert solvent[9] or with use of the Vilsmeier–Haack reagent at low temperature. Saponification of the ethyl oxazoleacetates (**54–78**) afforded the corresponding acids (**79–94**). In these procedures, various substituents at C-2 and C-5 of the oxazole ring were arbitrarily introduced by selecting appropriate acylating agents in the first and third stages of the reaction (Scheme I).

Compounds **99–102** having an alkyl or propionic acid moiety at C-4 on the oxazole ring were similarly synthesized by alkylation of [*N*-(4-fluorobenzoyl)amino]methyl 3-thienyl ketone (**22**) with corresponding alkyl or (alkoxycarbonyl)alkyl halides followed by dehydrative cyclization (Scheme II). Compounds **103** and **104** were prepared by saponification of the corresponding ethyl 4-oxazolepropionates (**101** and **102**).

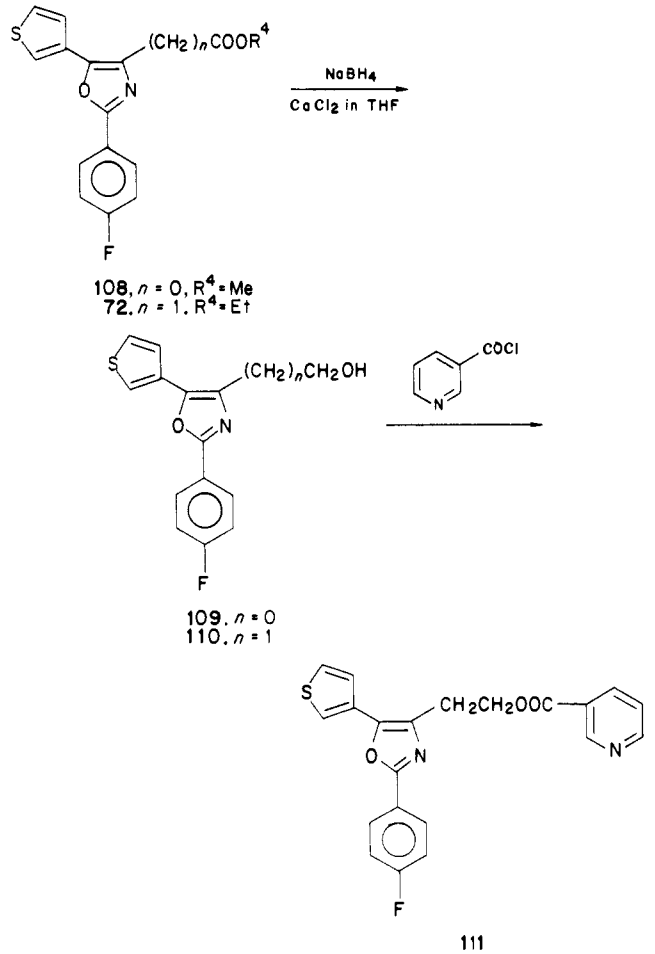
Methyl 2-(4-fluorophenyl)-5-(3-thienyl)-4-oxazolecarboxylate (**108**) was prepared by the reaction sequence shown in Scheme III. Compound **105** was converted to the α-amino-β-keto ester hydrochloride (**106**) by hydrochloric acid cleavage under mild conditions according to the method described in previous report.[6] Acylation of **106** afforded the α-(*N*-acylamino) β-keto ester (**107**) and successive cyclization gave the desired oxazole compound (**108**).

4-(ω-Hydroxyalkyl)oxazole derivatives (**109** and **110**) were prepared by reduction of the corresponding esters

Scheme III



Scheme IV

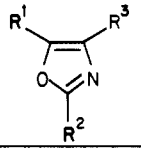


(**108** and **72**) with calcium borohydride. The nicotinoyl ester (**111**) was obtained by the reaction of **110** with nicotinoyl chloride (Scheme IV).

The 4-[(nicotinoyloxy)methyl]oxazole derivative (**114**) was synthesized via an alternative route as shown in Scheme V. The *N*-acylamino ketone (**22**) was converted to the hydroxymethyl derivative (**112**). After esterification

(8) Suzuki, M.; Iwasaki, T.; Matsumoto, K.; Okumura, K. *Synth. Commun.* **1972**, *2*, 237.
(9) Turchi, I. J.; Dewar, M. J. S. *Chem. Rev.* **1975**, 4.

Table I. Hypolipidemic Activities of 5-Aryloxazole Derivatives (140, 141, 54–64, and 79–82)



compd no.	R^1	R^2	R^3	yield,[a] %	mp, °C	IR,[b] cm^{-1} ν(C=O)	IR,[b] cm^{-1} ν(C=N)	formula[c]	reduction,[d] % Cho	reduction,[d] % TG
140[e]	Ph	H	COOH	90	163–164	1710	1600	$C_{10}H_7NO_3$	2	11
141[f]	Ph	Ph	COOEt						9	-30
54	Ph	Ph	CH_2COOEt	90	98–99	1730	1610	$C_{19}H_{17}NO_3$	13	6
55	Ph	4-FPh	CH_2COOEt	94	123–124	1730	1600	$C_{19}H_{16}FNO_3$	3	-4
56	Ph	4-ClPh	CH_2COOEt	88	131–132	1730	1600	$C_{19}H_{16}ClNO_3$	7	-12
57	Ph	4-BrPh	CH_2COOEt	93	142–143	1720	1600	$C_{19}H_{16}BrNO_3$	10	-7
58	Ph	4-MePh	CH_2COOEt	93	116–117	1730	1610	$C_{20}H_{19}NO_3$	5	-18
59	Ph	4-MeOPh	CH_2COOEt	91	106–107	1730	1610	$C_{20}H_{19}NO_4$	0	15
60	Ph	3,4,5-$(MeO)_3$Ph	CH_2COOEt	76	93–94	1725	1590	$C_{22}H_{23}NO_6$	0	-19
61	4-FPh	4-FPh	CH_2COOEt	90	133–134	1730	1510	$C_{19}H_{15}F_2NO_3$	7	39
62	4-FPh	4-ClPh	CH_2COOEt	74	141–142	1725	1510	$C_{19}H_{15}ClFNO_3$	22	3
63	4-FPh	4-BrPh	CH_2COOEt	76	128–131	1725	1510	$C_{19}H_{15}BrFNO_3$	12	-5
64	4-FPh	3-thienyl	CH_2COOEt	67	102–103	1735	1590	$C_{17}H_{14}FNO_3S$	11	15
79	Ph	Ph	CH_2COOH	85	181–182	1725	1610	$C_{17}H_{13}NO_3$	6	20
80	Ph	4-ClPh	CH_2COOH	94	208–209	1740	1600	$C_{17}H_{12}ClNO_3$	6	14
81	Ph	4-BrPh	CH_2COOH	91	217–218	1735	1600	$C_{17}H_{12}BrNO_3$	4	-14
82	4-FPh	3-thienyl	CH_2COOH	85	210–211	1720	1590	$C_{15}H_{10}FNO_3S$	13	31
CPIB[g]									15	16

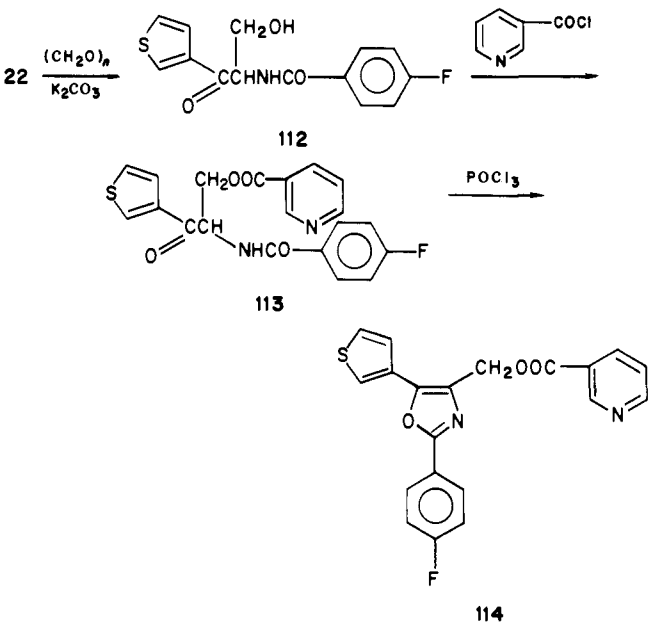
[a] Yields of esters were based on the acylamino keto esters of the cyclization reaction which is shown in Scheme I and those of acids were based on the corresponding ethyl oxazoleacetates. [b] Measured as a Nujol mull. [c] All compounds were analyzed for C, H, N, Br, Cl, F, and S and the results were within 0.4% of theory. [d] Biological results are from single experiments. [e] Prepared by saponification of methyl 5-phenyl-4-oxazolecarboxylate. [f] Prepared by Korte's method.[15] [g] Clofibrate.

of **112** with nicotinoyl chloride, successive dehydration afforded the desired oxazole compound (**114**).

Preparation of higher alkyl esters (**118–131**) of the 5-thienyl-2-(4-halophenyl)-4-oxazoleacetic acids (**87–89**) was performed by the following four methods as shown in Scheme VI: (A) conversion of the oxazoleacetic acids (**87–89**) to the acid chlorides (**115–117**) with thionyl chloride followed by reaction with an alcohol, (B) a reaction sequence similar to A using oxalyl chloride for preparation of the acid chlorides (**115–117**), (C) direct condensation of the acids (**88, 89**) with an alcohol using 1-methyl-2-chloropyridinium iodide (MCPI) as a condensation reagent, and (D) direct alkylation of **88** with an alkyl halide in the presence of base. The monoglyceride derivative (**133**) was synthesized by acidolysis of the dimethyl ketal (**132**) which was prepared from **89** and 2,3-(dimethylmethylenedioxy)propanol by method C.

The oxazoleacetamide analogues (**134–136**) were synthesized by amination of acid chlorides (**115–117**). The other *N*-alkyl amide congeners (**137–139**) were prepared from acid **88** and the corresponding amines with use of dicyclohexylcarbodiimide (DCC) as dehydrative agent (Scheme VII).

Scheme V



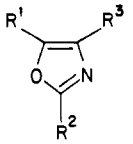
Biological Results and Discussion

Hypolipidemic activities of the test compounds were evaluated with normal SD male rats by determining percent decreases in serum cholesterol and triglyceride after 7-day dosing at 0.05% in the diet in comparison to control animals. Clofibrate, used as positive control drug, reduced serum cholesterol and triglyceride by 15% and 16%, respectively, under the same conditions.

5-Phenyl-4-oxazolecarboxylic acid (**140**), which was prepared during the course of the study of antiplatelet agents,[4] slightly reduced serum triglyceride, whereas the ethyl 2,5-diphenyl-4-oxazolecarboxylate (**141**)[4] rather increased the serum lipid levels.

Interestingly, elongation of the carboxylic substituent at the 4-position of the oxazole compound (**141**) to an acetic acid moiety (compound **54**) caused depression of serum cholesterol by 13%. Accordingly, we investigated in detail 2,5-diaryl-4-oxazoleacetic acid derivatives. As shown in Table I, some derivatives exhibited moderate activities, but there was none that substantially and simultaneously decreased both cholesterol and triglyceride. Surprisingly, two compounds (**64, 82**) having a thienyl substituent at the 2-position on the 4-oxazoleacetate skeleton showed potencies comparable to that of clofibrate. Therefore, introduction of the thienyl group in place of the aryl group at the 5-position to the oxazole ring was achieved. As a result, highly potent compounds that were superior to clofibrate in reducing both cholesterol and triglyceride were obtained as shown in Table II. Furthermore, there was an obvious relationship between the substituent of the

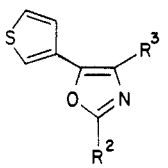
Table II. Hypolipidemic Activities of 2-Aryl-5-thienyl-4-oxazoleacetates (65–78) and the Acids (83–94)

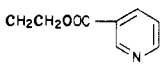
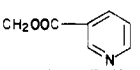


compd no.	R^1	R^2	R^3	yield,[a] %	mp, °C	IR,[b] cm^{-1} ν(C=O)	IR,[b] cm^{-1} ν(N=C)	formula[c]	reduction,[d] % Cho	reduction,[d] % TG
65	2-thienyl	Ph	CH_2COOEt	79	82–83	1725	1618	$C_{17}H_{15}NO_3S$	11	7
66	2-thienyl	4-FPh	CH_2COOEt	74	116–117	1720	1620	$C_{17}H_{14}FNO_3S$	17	31
67	2-thienyl	4-ClPh	CH_2COOEt	83	119–120	1730	1620	$C_{17}H_{14}ClNO_3S$	15	-10
68	2-thienyl	4-MePh	CH_2COOEt	70	125–126	1730	1618	$C_{18}H_{17}NO_3S$	9	-14
69	5-Br-2-thienyl	4-ClPh	CH_2COOEt	48	148–150	1730	1615	$C_{17}H_{13}BrClNO_3S$	0	20
70	5-Me-2-thienyl	4-ClPh	CH_2COOEt	95	123–125	1730	1620	$C_{18}H_{16}ClNO_3S$	4	39
71	3-thienyl	Ph	CH_2COOEt	79	90–91	1720	1620	$C_{17}H_{15}NO_3S$	15	41
72	3-thienyl	4-FPh	CH_2COOEt	85	112–113	1730	1620	$C_{17}H_{14}FNO_3S$	19	41
73	3-thienyl	4-ClPh	CH_2COOEt	78	127–128	1730	1630	$C_{17}H_{14}ClNO_3S$	16	47
74	3-thienyl	3-ClPh	CH_2COOEt	73	128–130	1730	1630	$C_{17}H_{14}ClNO_3S$	8	61
75	3-thienyl	2-ClPh	CH_2COOEt	68	73–75	1725	1620	$C_{17}H_{14}ClNO_3S$	-5	15
76	3-thienyl	4-MePh	CH_2COOEt	94	102–103	1725	1630	$C_{18}H_{17}NO_3S$	5	4
77	3-thienyl	4-MeOPh	CH_2COOEt	84	96–97	1735	1610	$C_{18}H_{17}NO_4S$	4	0
78	3-thienyl	3,4-Cl_2Ph	CH_2COOEt	77	127–128	1730	1630	$C_{17}H_{13}Cl_2NO_3S$	14	17
83	2-thienyl	Ph	CH_2COOH	95	187–190	1725	1615	$C_{15}H_{11}NO_3S$	-4	28
84	2-thienyl	4-FPh	CH_2COOH	91	208–209	1720	1066	$C_{15}H_{10}FNO_3S$	17	27
85	2-thienyl	4-ClPh	CH_2COOH	80	214–215	1720	1615	$C_{15}H_{10}ClNO_3S$	16	38
86	5-Me-2-thienyl	4-ClPh	CH_2COOH	72	186–187	1700	1615	$C_{16}H_{12}ClNO_3S$	9	-4
87	3-thienyl	Ph	CH_2COOH	88	187–188	1725	1630	$C_{15}H_{11}NO_3S$	15	41
88	3-thienyl	4-FPh	CH_2COOH	89	207–209	1720	1630	$C_{15}H_{10}FNO_3S$	23	39
89	3-thienyl	4-ClPh	CH_2COOH	89	218–219	1715	1625	$C_{15}H_{10}ClNO_3S$	16	43
90	3-thienyl	3-ClPh	CH_2COOH	93	194–197	1710	1630	$C_{15}H_{10}ClNO_3S$	7	38
91	3-thienyl	2-ClPh	CH_2COOH	89	163–165	1728	1630	$C_{15}H_{10}ClNO_3S$	1	22
92	3-thienyl	4-MePh	CH_2COOH	79	191–192	1710	1628	$C_{16}H_{13}NO_3S$	9	14
93	3-thienyl	4-MeOPh	CH_2COOH	60	198–199	1720	1590	$C_{16}H_{13}NO_4S$	3	26
94	3-thienyl	3,4-Cl_2Ph	CH_2COOH	87	233–234	1720	1620	$C_{15}H_9Cl_2NO_3S$	9	34

[a–d] Same as the footnotes in Table I.

Table III. Hypolipidemic Activities of 2-(4-Halophenyl)-5-(3-thienyl)oxazole Derivatives (99–114)



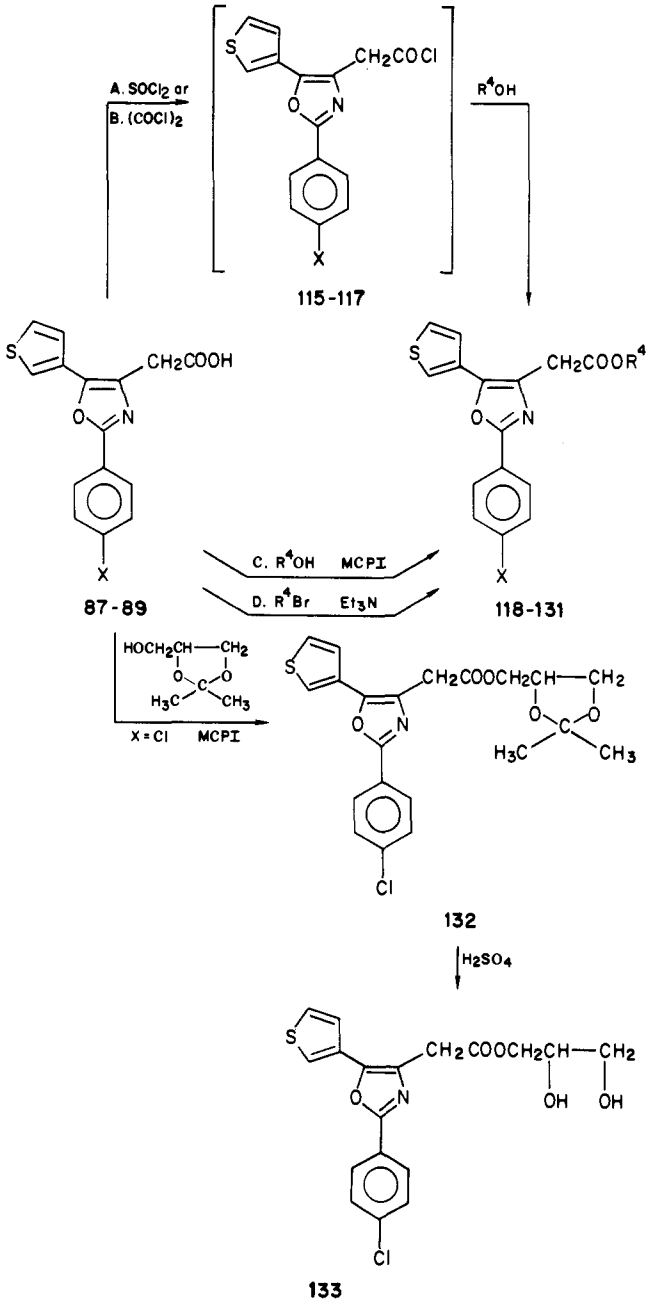
compd no.	R^2	R^3	yield,[a] %	mp, °C	IR,[b] cm^{-1}		formula[c]	reduction,[d] % Cho	reduction,[d] % TG
99	4-FPh	CH_2CH_3	77	49–50	1615	1605	$C_{15}H_{12}FNOS$	-4	20
100	4-FPh	$CH_2CH{=}CH_2$	85	49–50	1640	1620	$C_{16}H_{12}FNOS$	-2	3
101	4-ClPh	CH_2CH_2COOEt	79	57–58	1740	1625	$C_{18}H_{16}ClNO_3S$	0	34
102	4-FPh	$CH(CH_3)COOEt$	83	109–110	1738	1615	$C_{18}H_{16}FNO_3S$	6	19
103	4-ClPh	CH_2CH_2COOH	91	184–185	1742		$C_{16}H_{12}ClNO_3S$	5	51
104	4-FPh	$CH(CH_3)COOH$	74	169–170	1710		$C_{16}H_{12}FNO_3S$	6	40
108	4-FPh	COOMe	69	140–141	1710	1610	$C_{15}H_{10}FNO_3S$	5	16
109	4-FPh	CH_2OH	94	136–137	1615		$C_{14}H_{10}FNO_2S$	-10	-34
110	4-FPh	CH_2CH_2OH	93	109–110	1610		$C_{15}H_{12}FNO_2S$	4	1
111	4-FPh		71	107–108	1715	1592	$C_{21}H_{15}FN_2O_3S$	-2	3
114	4-FPh		63	119–121	1730	1610	$C_{20}H_{13}FN_2O_3S$	0	17

[a–d] Same as the footnotes in Table I.

phenyl group at C-2 of the oxazole ring and activity: i.e., substitution with electron-withdrawing groups such as halogen, was more favorable than with electron-donating groups in 5-(3-thienyl)oxazole series (for example, compare compounds **72**, **73**, and **78** with **76** and **77**) and the para substitution of the ring was optimal (for example, compare compound **73** with **74** and **75** and also **89** with **90** and **91** in Table II). On the other hand, introduction of either an electronegative or positive substituent to the thienyl group reduced the cholesterol suppression activity appreciably (see compounds **69**, **70**, and **86** in Table II). Furthermore, congeners having a 3-thienyl group on C-5 exhibited somewhat higher activities than those having a 2-thienyl group.

To determine an optimal substituent on C-4 of the oxazole ring, hypolipidemic activities among the analogues of 2-(4-halophenyl)-5-(3-thienyl)oxazoles, which seem to be the most favorable combination on C-2 and C-5, were

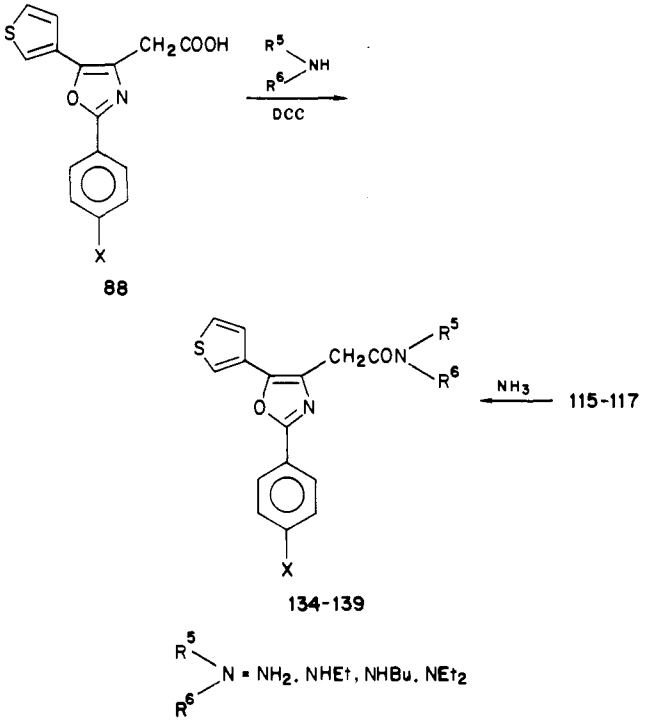
Scheme VI



115. X = H. **116.** X = F. **117.** X = Cl

investigated (Table III). Among the C-4 substituents bearing a carboxyl group, an acetic acid group exerted the most favorable effect reducing both cholesterol and triglyceride markedly. Both α- and β-propionic acid groups, the homo analogs (**101–104**) of the acetic acid derivatives (**72**, **73**, **88**, and **89**), also had high hypotriglyceridemic activities but no or only slight hypocholesterolemic activities. The derivative having a methoxycarbonyl group directly on the oxazole ring (**108**) was the least active among the carboxyl group series in analogy with the foregoing 2,5-diaryloxazole derivatives (Table I). Compounds **99** and **100** with an alkyl or allyl group on C-4 showed some hypercholesterolemic activity. Nicotinic acid is known as a hypolipidemic agent. However, the (nicotinoyloxy)alkyl derivatives (**111** and **114**) were ineffective. From these results, it was concluded that the acetic acid moiety on C-4 was necessary for high activity. Then, a more detailed study of 2-(4-halophenyl)-5-(3-thienyl)-4-oxazoleacetic acid derivatives, i.e., congeners of esters and amides, was undertaken. (Table IV).

Scheme VII



All of the normal alkyl esters containing up to 18 carbon atoms, i.e., the stearyl ester (**131**) and the primary monoglyceride (**133**), were as potent as the free acids (**87–89**), whereas introduction of a branched alkyl ester group, such as isopropyl ester (**122**, **126**), resulted in slightly less hypocholesterolemic activity than clofibrate as shown in Table IV. The amides (**134–136**) showed somewhat decreased hypotriglyceridemic activity compared with their hypocholesterolemic activity. Introduction of an alkyl substituent to the nitrogen atom of the amide group of **135** resulted in significant decrease of hypocholesterolemic activity. Furthermore, disubstitution of the amide nitrogen with alkyl groups was detrimental to both activities. Judging from these results and the observation that the main detectable metabolite of the ethyl oxazoleacetate (**72**) in plasma after oral administration in rats was the corresponding free acid (**88**), these esters (and possibly amides) may be converted to the original free acid as the active principle in the body.

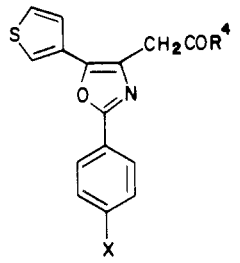
The most active compound among the compounds tested was 2-(4-fluorophenyl)-5-(3-thienyl)-4-oxazoleacetic acid (**88**). It reduced serum cholesterol and triglyceride by 23% and 39%, respectively, and improved the antiarterioschlerosis index (HDL-Cho/Total-Cho) by 76% after a week of dosing at 50 mg % in the diet in normal SD male rats. Furthermore, compound **88** was more effective for THLR/1 rats, which are the model of hereditary hyperlipidemia developed in our laboratory.[9] Namely, a dose of 5 mg % in the diet suppressed the serum cholesterol and triglyceride levels by 26% and 28%, respectively, the activity being about 4 times more than that of clofibrate.

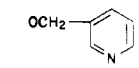
The oral LD_{50} of compound **88** in rats was above 2000 mg/kg. After 2 weeks of dosing at 480 mg % in the diet, there were no significant changes in body weight or in the weight of major organs nor was there any significant increase in the liver weight unlike clofibrate. Moreover, the drug inhibited platelet aggregation ex vivo in SD male rats by 93 ± 6% after dosing at 50 mg % in the diet for 1 week.

Experimental Section

Hypolipidemic Activity. Male Sprague–Dawley rats (4 weeks of age) were purchased from Nihon CLEA Co., Tokyo, and

Table IV. Hypolipidemic Activities of 2-Aryl-5-(3-thienyl)-4-oxazoleacetic Acid Derivatives (118–139)



compd no.	X	R^4	method	yield,[a] %	mp, °C	IR,[b] cm^{-1} ν(NH)	IR,[b] cm^{-1} ν(C=O)	formula[c]	reduction,[d] % Cho	reduction,[d] % TG
118	H	OBu	A	34	71–72		1725	$C_{19}H_{19}NO_3S$	15	21
119	H	OPen	A	40	61–62		1725	$C_{20}H_{21}NO_3S$	20	30
120	Cl	OMe	A	89	127–128		1740	$C_{16}H_{12}ClNO_3S$	14	29
121	Cl	$OCH_2CH{=}CH_2$	A	46	114–116		1720	$C_{18}H_{14}ClNO_3S$	11	39
122	Cl	O-*i*-Pro	B	55	118–119		1725	$C_{18}H_{16}ClNO_3S$	9	29
123	Cl	OBu	C	69	79–81		1730	$C_{19}H_{18}ClNO_3S$	22	17
124	Cl	OPen	A	49	86–87		1730	$C_{20}H_{20}ClNO_3S$	19	45
125	Cl		C	69	113–115		1730	$C_{21}H_{15}ClN_2O_3S$	13	3
126	F	O-*i*-Pro	C	74	108–110		1730	$C_{18}H_{16}FNO_3S$	8	27
127	F	OBu	B	44	81–82		1730	$C_{19}H_{18}FNO_3S$	20	19
128	F	OPen	B	53	78–80		1730	$C_{20}H_{20}FNO_3S$	13	20
129	F	O-*n*-C_8H_{17}	D	75	62–63		1730	$C_{23}H_{26}FNO_3S$	12	13
130	F	O-*n*-$C_{12}H_{25}$	D	86	70–71		1730	$C_{27}H_{31}FNO_3S$	18	34
131	F	O-*n*-$C_{18}H_{37}$	C	82	84–86		1730	$C_{33}H_{46}FNO_3S$	18	26
133	Cl	$OCH_2CH(OH)CH_2OH$	E***[e]	91	133–134		1735	$C_{18}H_{16}ClNO_5S$	15	43
134	H	NH_2	A	53	160–163*	3400	1655	$C_{15}H_{12}N_2O_2S$	20	3
135	F	NH_2	A	60	206–207*	3460	1670	$C_{15}H_{11}FN_2O_2S$	19	13
136	Cl	NH_2	A	70	203–205*	3350	1675	$C_{15}H_{11}ClN_2O_2S$	16	12
137	F	NHEt	F***	70	186–189	3300	1640	$C_{17}H_{15}FN_2O_2S$	-5	23
138	F	NHBu	F***	42	162–164	3300	1620	$C_{19}H_{19}FN_2O_2S$	-8	13
139	F	NEt_2	F***	61	84–86		1650	$C_{19}H_{19}FN_2O_2S$	-2	2

[a–d] Same as footnotes in Table I. [e] (*) Decomposed. (**) Hydrolysis of the acetonide 132, which was prepared by method C; yield 83%, mp 81–83 °C. (***) Direct condensation of the acid 88 with alkylamines using DCC.

maintained on commercial laboratory chow (Nihon CLEA CE-2 pellets) for at least 1 week before use. Grouping of rats (five rats per group), blood sampling, and calculation of the hypolipidemic effect were performed as described previously.[11] Test compounds were mixed with Nihon CLEA CE-2 powder in a mortar and administered ad libitum to experimental groups generally for a period of 7 days. The concentration of a test compound in the diet is 50 mg/100 g (mg %). This is found to be approximately equal to the dose expressed as (milligrams/kilogram of body weight)/day calculated from the amount of daily food consumption. Control rats were fed CE-2 powder. After the experimental period, total serum cholesterol and triglyceride were determined by the methods of Zak et al.[12] and Van Handel et al.,[13] respectively. The hypolipidemic activity of test compound is expressed in the tables as percent depressions of serum cholesterol and triglyceride compared to the mean lipid levels of the control group after the experimental period. The average mean levels of serum cholesterol and triglyceride of the control group in 25 experiments were 84 ± 1 and 79 ± 3 mg/100 mL, respectively.

Inhibitory Activity on Blood Platelet Aggregation. Platelet aggregation was determined by the method described elsewhere[14] with use of SD male rats.

Chemistry. Melting points were measured by the use of Yamato melting point apparatus and are uncorrected. The IR spectra were obtained on a Shimadzu IR-27G infrared spectrophotometer. The ^1H NMR spectra were recorded on a Hitachi Perkin-Elmer R-20A high-resolution NMR spectrometer with tetramethylsilane as an internal standard. The mass spectra were taken on a Hitachi RMU-6M spectrometer at an ionizing potential of 30 eV. Column chromatography was carried out on silica gel (Kiesel gel 60, 0.063–0.200 mm, E. Merck).

Materials. Methyl α-isocyanoacetate (1) was prepared according to the reported method.[5] Methyl 5-substituted oxazole-4-carboxylates were prepared by the reaction of 1 with acyl halides in the presence of Et_3N or *t*-BuOK by methods similar to those described by Schöllkopf et al.[7] and the authors.[8] Physicochemical properties of the new 4-oxazolecarboxylate, methyl 5-(5-bromo-2-thienyl)oxazole-4-carboxylate (**2**), are as follows: mp 165–167 °C; IR (Nujol) 3140, 1690, 1600 cm^{-1}.

α-Amino ketone hydrochlorides were prepared by acid hydrolysis of the 4-oxazolecarboxylates according to our previous report.[5] The newly prepared compound, aminomethyl 5-bromo-2-thienyl ketone hydrochloride (**3**), was characterized by the following spectral data: mp 225–227 °C dec; IR (Nujol) 1650, 1600, 1578 cm^{-1}; NMR (Me_2SO-d_6) δ 4.49 (2 H, s), 7.48 and 7.99 (1 H each, d, J = 5 Hz), 8.68 (3 H, br).

The 5-methyl-2-thienyl analogues of the 4-oxazolecarboxylate (**2**) and the corresponding α-amino ketone (**3**) were also prepared similarly and used for the preparation of ethyl 3-(4-chlorobenzamido)-4-(5-methyl-2-thienyl)-4-oxobutyrate (**45**) without purification.

Typical Procedure for Preparation of (*N*-Acylamino)methyl Aryl Ketones (4–28). [*N*-(4-Fluorobenzoyl)amino]methyl 3-Thienyl Ketone (22). To a suspension of aminomethyl 3-thienyl ketone hydrochloride (95 g, 0.54 mol) in EtOAc (900 mL) and H_2O (500 mL) was added $NaHCO_3$ (118 g, 1.4 mol) at 0 °C. Then, 4-fluorobenzoyl chloride (87 g, 0.55 mol)

(10) Fujinami, F.; Mori, T.; Takashima, K.; Ohshima, S., Japanese Association for Laboratory Animal Science 18th Meeting, Kobe, 1984, abstract A-65.
(11) Takashima, K.; Izumi, K.; Iwai, H.; Takeyama, S. *Atherosclerosis* **1973**, *17*, 491.
(12) Zak, B.; Dickenman, R. C.; White, E. G.; Burnett, H.; Cherney, P. J. *Am. J. Clin. Pathol.* **1954**, *24*, 1307.
(13) Van Handel, E.; Zilversmit, D. B. *J. Lab. Clin. Med.* **1957**, *50*, 152.
(14) Shinjo, A.; Sasaki, Y.; Inamasu, M.; Morita. T. *Thromb. Res.* **1978**, *13*, 941.
(15) Korte, F.; Storiko, K. *Chem. Ber.* **1960**, *93*, 1033.

Table V. *N*-(Acylamino)methyl Aryl Ketones (4–28) ($R^1COCH_2NHCOR^2$)

compd no.	R^1	R^2	yield,[a] %	mp, °C	IR,[b] cm^{-1} ν(NH)	IR,[b] cm^{-1} ν(C=O) ketone	IR,[b] cm^{-1} ν(C=O) amide
4	Ph	Ph	90	124–125	3350	1690	1630
5	Ph	4-F-Ph	80	138–139	3380	1695	1600
6	Ph	4-ClPh	100	144–148	3350	1690	1630
7	Ph	4-BrPh	99	142–143	3350	1690	1630
8	Ph	4-MePh	100	109–110	3370	1690	1630
9	Ph	4-MeOPh	95	133–134	3330	1670	1630
10	Ph	3,4,5-$(MeO)_3$Ph	86	112–113	3300	1690	1625
11	4-FPh	4-FPh	97	153–155	3370	1690	1640
12	4-FPh	4-ClPh	94	179–181	3360	1685	1640
13	4-FPh	4-BrPh	98	183–184	3380	1685	1640
14	4-FPh	3-thienyl	80	185–188	3370	1690	1630
15	2-thienyl	Ph	93	146–147	3420	1660	1600
16	2-thienyl	4-FPh	94	147–148	3400	1660	1650
17	2-thienyl	4-ClPh	97	157–159	3320	1670	1640
18	2-thienyl	4-MePh	97	125–126	3320	1675	1640
19	5-Br-2-thienyl	4-ClPh	93	188–192	3400	1655	1640
20	5-Me-2-thienyl	4-ClPh	90	156–158	3400	1655	1640
21	3-thienyl	Ph	95	118–119	3300	1690	1640
23	3-thienyl	4-ClPh	100	160–161	3350	1680	1635
24	3-thienyl	3-ClPh	93	137–140	3300	1700	1645
25	3-thienyl	2-ClPh	96	111–112	3250	1680	1640
26	3-thienyl	4-MePh	69	143–144	3250	1680	1640
27	3-thienyl	4-MeOPh	91	154–155	3300	1680	1630
28	3-thienyl	3,4-Cl_2Ph	96	153–154	3370	1680	1640

[a,b] Same as the footnotes in Table I.

was added dropwise to the mixture with vigorous stirring and the stirring was kept at room temperature overnight. Precipitates separated out from the reaction mixture were gathered as the first crop of 22 (80 g, 57%). The organic layer of the filtrate was washed with H_2O, dried over $MgSO_4$, and then concentrated. The residue was crystallized from EtOAc as the second crop of 22 (57 g, 40%): mp 140–141 °C; IR (Nujol) 3160, 1680, 1640, 1600 cm^{-1}; NMR (Me_2SO-d_6) δ 4.66 (2 H, d, J = 6 Hz, collapsed to a singlet on D_2O exchange), 7.11–8.18 (6 H, m), 8.58–8.70 (1 H, m), 8.87 (1 H, br t, J = 6 Hz, D_2O exchangeable); MS, m/z 263 (M^+).

Similarly, other (*N*-acylamino)methyl aryl ketones (**4–28**) were prepared and the yields and physicochemical data are summarized in Table V.

Typical Procedure for Introduction of Alkyl and (Ethoxycarbonyl)alkyl Groups to the (*N*-Acylamino)methyl Aryl Ketones (4–28). Ethyl 3-[[(4-Fluorobenzoyl)amino]methyl]-4-(3-thienyl)-4-oxobutyrate (47). To a solution of [*N*-(4-fluorobenzoyl)amino]methyl 3-thienyl ketone (**22**; 65.0 g, 0.24 mol) in *N*,*N*-dimethylformamide (DMF, 350 mL) was added portionwise 50% sodium hydride on paraffin (14.2 g, 0.30 mol) at −40 to −50 °C with stirring. After 15 min, ethyl bromoacetate (45.3 g, 0.27 mol) was added to the reaction mixture at the same temperature and then the temperature was gradually raised to 0 °C for 30 min. When the reaction was over, the reaction mixture was quenched with acetic acid (6 mL). The mixture was poured into H_2O (700 mL) and extracted with EtOAc (500 mL × 2). The extract was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and then concentrated in vacuo. The residue was crystallized from EtOH to give colorless prisms of 47 (57.0 g, 66%): mp 75–77 °C; IR (Nujol) 3350, 1730, 1660 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (3 H, t, J = 7 Hz), 2.89 (2 H, d, J = 5 Hz), 4.15 (2 H, q, J = 7 Hz), 5.5–6.1 (1 H, m), 6.9–8.0 (7 H, m), 8.3–8.4 (1 H, m); MS, m/z 349 (M^+).

In a similar manner, introduction of alkyl and (ethoxycarbonyl)alkyl groups to (*N*-acylamino)methyl aryl ketones (**4–28**) was carried out to afford the corresponding (*N*-acylamino)alkyl aryl ketones (**95** and **96**), 3-(acylamino)-4-oxobutyrates (**29–46**, **48–53**, and **98**) and 4-(acylamino)-5-oxopentanoate (**97**). The yields and the physicochemical properties are listed in Tables VI and VII.

Typical Procedure for Cyclization of α-(*N*-Acylamino) Ketones to the Corresponding Oxazoles (54–77 and 99–102). Ethyl 2-(4-Fluorophenyl)-5-(3-thienyl)-4-oxazoleacetate (72). Phosphoryl chloride (24.6 g, 0.16 mol) was added dropwise to a solution of **72** (40 g, 0.126 mol) in DMF (150 mL) at below 0 °C. After stirring for 8 h at ambient temperature (20–25 °C), the reaction mixture was poured into a mixture of EtOAc (500 mL) and ice–water (500 mL) and then neutralized with $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was crystallized from EtOH to afford colorless needles of the ester (**72**; 32.4 g, 86%): mp 112–113 °C; IR (Nujol) 1730, 1620, 1495 cm^{-1}; NMR ($CDCl_3$) δ 1.27 (3 H, t, J = 7 Hz), 3.78 (2 H, s), 4.20 (2 H, q, J = 7 Hz), 7.0–7.7 (5 H, m), 7.8–8.2 (2 H, m); MS, m/z 331 (M^+).

The yields and physicochemical data of the other oxazoles (**54–71** and **73–78**) and 4-oxazolepropionates (**101** and **102**), synthesized in a similar manner, are shown in Tables I–III.

Typical Procedure for Saponification of the 4-Oxazoleacetates (54, 56, 57, 64–67, and 70–78). 2-(4-Fluorophenyl)-5-(3-thienyl)-4-oxazoleacetic Acid (88). To a solution of the ethyl ester **72** (27.4 g, 0.083 mol) in MeOH (700 mL) were added KOH (10.9 g, 0.19 mol) and H_2O (100 mL), and the reaction mixture was stirred at room temperature for a day. The reaction mixture was concentrated under reduced pressure and to the residue was added H_2O. After acidification of the aqueous mixture with concentrated HCl to pH 2, the mixture was extracted with EtOAc (500 mL × 2). The extract was washed with H_2O, dried, and then concentrated. The residue was crystallized from EtOH to afford colorless needles of **88** (22.3 g, 89%): mp 207–209 °C; IR (Nujol) 1725, 1630 cm^{-1}; NMR (Me_2SO-d_6) δ 3.80 (2 H, s,) 7.0–8.3 (7 H, m); MS, m/z 303 (M^+).

In a similar way, other ethyl 4-oxazoleacetates (**54**, **56**, **57**, **64–67**, **70**, **71**, and **73–78**) were hydrolyzed to the corresponding free acids (**79–94**, **103**, and **104**). The yields and physicochemical data are listed in Tables I–III.

Typical Procedure for Preparation of Esters 118–132. Pentyl 2-(4-Chlorophenyl)-5-(3-thienyl)-4-oxazoleacetate (124). Method A. Thionyl chloride (3.0 g, 0.025 mol) was added to a suspension of 2-(4-chlorophenyl)-5-(3-thienyl)-4-oxazoleacetic acid (**89**; 2.10 g, 0.0066 mol) in $CHCl_3$. After stirring at room temperature overnight, the reaction mixture was concentrated in vacuo and reacted with pentanol (30 mL) at the ambient temperature for 4 h. The excess pentanol was removed under reduced pressure and the residue was shaken with EtOAc and saturated aqueous $NaHCO_3$. The EtOAc extract was dried over anhydrous $MgSO_4$ and concentrated in vacuo and then the remainder was crystallized from EtOH to afford **124** (1.26 g, 49%): mp 86–87 °C; IR (Nujol) 1730, 1625 cm^{-1}; NMR ($CDCl_3$) δ 0.85 (3 H, t, J = 6 Hz), 1.03–1.98 (6 H, m), 3.78 (2 H, s), 4.12 (2 H, t, J = 6 Hz), 7.2–8.02 (7 H, m); MS, m/z 389 (M^+).

Table VI. Ethyl 3-(Acylamino)-4-oxobutyrates (29–53)

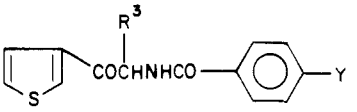
CH_2COOEt

$R^1COCHNHCOR^2$

compd no.	R^1	R^2	yield,[a] %	mp, °C	IR,[b] cm^{-1} ν(NH)	IR,[b] cm^{-1} ν(C=O) ester	ketone	amide	NMR,[c] δ COCH (m)	NMR,[c] δ CH_2COO (d, J = Hz)
29	Ph	Ph	71	85–87	3240	1730	1685	1640	5.8–6.2	2.95 (5.5)
30	Ph	4-FPh	81	97–98	3230	1735	1685	1635	5.7–6.2	2.95 (s)
31	Ph	4-ClPh	95	85–87	3300	1730	1690	1630	5.7–6.2	2.95 (5)
32	PH	4-BrPh	72	108–109	3240	1735	1690	1630	5.8–6.2	2.97 (5)
33	Ph	4-MePh	79	109–110	3230	1735	1685	1630	5.7–6.2	2.97 (5)
34	Ph	4-MeOPh	45	108–110	3320	1730	1690	1630	5.4–6.1	2.5–3.4 (m)
35	Ph	3,4,5-$(MeO)_3$Ph	87	158–159	3270	1730	1685	1620	5.7–6.2	2.95 (5)
36	4-FPh	4-FPh	77	153–155	3300	1740	1680	1640	5.7–6.2	2.91 (5)
37	4-FPh	4-ClPh	73	179–181	3350	1715	1680	1640	5.7–6.2	2.91 (5)
38	4-FPh	4-BrPh	76	183–184	3330	1740	1680	1640	5.7–6.2	2.5–3.4 (m)
39	4-FPh	3-thienyl	60	126–127	3300	1730	1690	1630	5.7–6.1	2.91 (7)
40	2-thienyl	Ph	63	75–76	3280	1735	1655	1635	5.5–6.1	2.9 (5.5)
41	2-thienyl	4-FPh	92	syrup	3300	1740	1660	1605	5.7–6.2	2.95 (6)
42	2-thienyl	4-ClPh	66	112–113	3320	1740	1660	1630	5.7–6.2	2.93 (6)
43	2-thienyl	4-MePh	85	99–100	3240	1740	1665	1630	5.7–6.2	2.95 (5.5)
44	5-Br-2-thienyl	4-ClPh	65	90–91	3320	1735	1665	1640	5.7–6.2	2.95 (6)
45	5-Me-2-thienyl	4-ClPh	44	102–104	3340	1740	1655	1640	5.7–6.2	2.94 (6)
46	3-thienyl	Ph	68	62–63	3320	1740	1685	1640	5.7–6.0	2.93 (6)
48	3-thienyl	4-ClPh	71	106–108	3300	1735	1680	1630	5.5–6.0	2.6–3.2 (m)
49	3-thienyl	3-ClPh	63	63–65	3250	1730	1680	1640	5.6–6.0	2.90 (6)
50	3-thienyl	2-ClPh	97	syrup	3300	1730	1680	1645	5.8–6.0	2.95 (6)
51	3-thienyl	4-MePh	70	95–96	3300	1720	1675	1640	5.4–5.8*	2.90 (8)
52	3-thienyl	4-MeOPh	34	74–79	3300	1725	1670	1630	5.7–5.9*	2.9 (6)
53	3-thienyl	3,4-Cl_2Ph	88	syrup	3310	1730	1660	1630	5.5–5.9	2.88 (6)

[a,b] Same as the footnotes in Table I. [c] Measured in Me_2SO-d_6.

Table VII. α-(*N*-Acylamino)alkyl 3-Thienyl Ketones (95–98)



compd no.	R^3	Y	yield,[a] %	mp, °C	IR,[b] cm^{-1} ν(NH)	IR,[b] cm^{-1} ν(C=O) ester	ketone	amide
95	CH_2CH_3	F	77	105–107	3340	1675	1647	
96	$CH_2CH{=}CH_2$	F	86	172–175	3250	1675	1630	
97	CH_2CH_2COOEt	Cl	66	88–89	3340	1715	1693	1640
98	$CH(CH_3)COOEt$	F	58	132–133	3200	1722	1680	1640

[a,b] Same as the footnotes in Table I.

Isopropyl 2-(4-Chlorophenyl)-5-(3-thienyl)-4-oxazoleacetate (122). Method B. The oxazoleacetic acid **89** (2.60 g, 0.008 mol) was added to an aqueous 50% MeOH solution of KOH (0.54 g, 20 mL). After stirring for 3 h at room temperature, the solution was evaporated to dryness under reduced pressure and the residue was treated with oxalyl chloride (6.40 g, 0.050 mol) overnight. The excess oxalyl chloride was removed in vacuo from the reaction mixture and then *i*-PrOH was added to the remaining acid chloride. The solution was stirred for 5 h, concentrated in vacuo, and then diluted with EtOAc. The EtOAc solution was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and then concentrated. The residue was crystallized from EtOH to afford the desired ester (**122**; 1.62 g, 55%): mp 118–119 °C; IR (Nujol) 1725, 1630 cm^{-1}; NMR ($CDCl_3$) δ 1.24 (6 H, d, J = 6 Hz), 3.73 (2 H, s), 5.03 (1 H, m), 7.13–8.08 (7 H, m); MS, *m/z* 361 (M^+).

Isopropyl 2-(4-Fluorophenyl)-5-(3-thienyl)-4-oxazoleacetate (126). Method C. To a solution of the 4-oxazoleacetic acid **88** (1.00 g, 0.0033 mol) and MCPI (0.93 g, 0.0037 mol) in *i*-PrOH (0.20 g, 0.0033 mol) and THF (40 mL) was added dropwise Et_3N (0.66 g, 0.0066 mol), and the whole was stirred at room temperature for 18 h. After dilution of the reaction mixture with H_2O, THF was evaporated in vacuo, followed by extraction of the residue with EtOAc. The extract was washed successively with aqueous 20% citric acid, aqueous $NaHCO_3$, H_2O, and brine. The solution was evaporated and the residue was crystallized from EtOH to give colorless needles of **126** (0.85 g, 74%): mp 108–110 °C; IR (Nujol) 1730, 1630, 1605 cm^{-1}; NMR ($CDCl_3$) δ 1.29 (6 H, d, J = 6 Hz), 3.85 (2 H, s), 4.9–5.4 (1 H, m), 7.0–8.3 (7 H, m); MS, *m/z* 345 (M^+).

Octyl 2-(4-Fluorophenyl)-5-(3-thienyl)-4-oxazoleacetate (129). Method D. A solution of the oxazoleacetic acid **88** (1.50 g, 0.005 mol), octyl bromide (1.00 g, 0.006 mol), and Et_3N (1.00 g, 0.01 mol) in DMF (5.0 mL) was stirred at 60–70 °C for 5 h. The reaction mixture was poured into H_2O and extracted with Et_2O/EtOAc (1:1 mixture). The extract was washed with H_2O and concentrated in vacuo. The residue was triturated with *i*-Pr_2O to form a solid which was recrystallized from EtOH to afford colorless needles of **129** (1.50 g, 75%): mp 76–77 °C; IR (Nujol) 1730 cm^{-1}; NMR ($CDCl_3$) δ 0.7–2.0 (13 H, m), 3.80 (2 H, s), 4.16 (2 H, t, J = 6 Hz), 7.0–8.2 (7 H, m); MS, *m/z* 401 (M^+).

Similarly, other esters were obtained. The method, yields, and the physicochemical data are shown in Table IV.

Typical Procedure for Preparation of 4-Oxazoleacetamides (137–139). *N*-Ethyl-2-(4-fluorophenyl)-5-(3-thienyl)-4-oxazoleacetamide (137). To a suspension of the acetic acid **88** (1.50 g, 0.005 mol), ethylamine hydrochloride (0.54 g, 0.0065 mol), and Et_3N (1.00 g, 0.01 mol) in THF (20 mL) was added DCC (1.22 g, 0.006 mol) at −5 °C, and the mixture was stirred at room temperature for 15 h. Acetic acid (0.6 mL, 0.01 mol) was added to the mixture, and the precipitates formed were filtered off. The filtrate was washed with dilute HCl and then aqueous $NaHCO_3$, followed by concentration in vacuo. The residue was chroma-

tographed on SiO_2 gel column using a mixed solvent $CHCl_3$/EtOAc (20:1) as an eluent. The separated amide (**137**) was crystallized from i-Pr_2O to afford colorless fine crystals (1.10 g, 70%): mp 186–189 °C; IR (Nujol) 3300, 1640 cm^{-1}; NMR ($CDCl_3$) δ 1.11 (3 H, t, J = 7 Hz), 3.25 (2 H, m), 3.63 (2 H, s), 7.0–8.3 (7 H, m); MS, m/z 330 (M^+).

2-(4-Fluorophenyl)-5-(3-thienyl)-4-oxazoleacetamide (**135**). To a suspension of oxazoleacetic acid **88** (1.5 g, 0.005 mol) in toluene (30 mL) was added $SOCl_2$ (5 mL, 0.07 mol) at 5 °C and the mixture was stirred overnight at room temperature. After concentration in vacuo, the residue was dissolved in toluene (50 mL). Ammonia gas was passed through the solution for 1 h. The reaction mixture was concentrated and the residue was crystallized from EtOAc (10 mL) to afford colorless fine crystals of **135** (0.90 g, 60%): mp 206–207 °C; IR (Nujol) 3460, 3180, 1670, 1630 cm^{-1}; NMR (Me_2SO-d_6) δ 3.61 (2 H, s), 6.8–8.3 (9 H, m, among them 2 H were D_2O exchangeable); MS, m/z 302 (M^+).

In a similar manner, analogous amides **134** and **136** were obtained. The yields and physicochemical data are listed in Table IV.

2,3-Dihydroxypropyl 2-(4-Chlorophenyl)-5-(3-thienyl)-4-oxazoleacetate (**133**). To a solution of 2,2-dimethyl-1,3-dioxolanylmethyl 2-(4-chlorophenyl)-5-(3-thienyl)-4-oxazoleacetate (**132**; 1.70 g, 0.004 mol) in EtOAc/MeOH (1:1 mixture, 10 mL) was added 10% H_2SO_4 (10 mL) and the mixture was stirred at room temperature for 7 h. After evaporation of the solvent in vacuo, the residue was partitioned between EtOAc and H_2O. After successive washing with aqueous $NaHCO_3$, H_2O, and brine, the organic layer was dried and then concentrated. The residue was crystallized from acetone to afford colorless fine crystals of **133** (1.4 g, 91%): mp 133–134 °C; IR (Nujol) 3400, 1735, 1630 cm^{-1}; NMR (Me_2SO-d_6) δ 3.25–4.40 (5 H, m), 3.98 (2 H, s), 4.68 (1 H, t, J = 6 Hz, D_2O exchangeable), 4.96 (1 H, d, J = 5 Hz, D_2O exchangeable), 7.7–8.3 (7 H, m); MS, m/z 393 (M^+).

Methyl 2-(4-Fluorophenyl)-5-(3-thienyl)-4-oxazolecarboxylate (**108**). A mixture of methyl 2-(4-fluorobenzamido)-3-(3-thienyl)-3-oxopropionate (**107**; 3.37 g, 0.01 mol), phosphoryl chloride (3.06 g, 0.02 mol), and $CHCl_3$ (20 mL) was refluxed for 10 h. To the brown solution was added ice–water and the mixture was neutralized by addition of Na_2CO_3. After the organic layer was dried over $MgSO_4$, it was concentrated in vacuo and chromatographed on SiO_2 gel using $CHCl_3$ as an eluent to yield **108** (2.10 g, 69%): mp 140–141 °C; IR (Nujol) 1710, 1610, 1590 cm^{-1}; NMR ($CDCl_3$) δ 4.00 (3 H, s), 6.0–8.3 (6 H, m), 8.5–8.6 (1 H, m); MS, m/z 303 (M^+).

2-(4-Fluorophenyl)-4-(hydroxymethyl)-5-(3-thienyl)oxazole (**109**). A suspension of **108** (1.0 g, 0.0033 mol), $NaBH_4$ (0.5 g, 0.013 mol), and $CaCl_2$ (1.1 g, 0.01 mol) in THF (30 mL) was stirred at room temperature overnight. After evaporation of the solvent in vacuo, the residue was treated with EtOAc and dilute HCl. The organic layer was washed with H_2O and concentrated in vacuo to dryness. The residue was crystallized from Et_2O to afford colorless fine crystals of **109** (0.85 g 94%): mp 136–137 °C; IR (Nujol) 3170, 3250, 3110, 1685, 1615, 1600 cm^{-1}; NMR (Me_2SO-d_6) δ 4.55 (2 H, d, J = 6 Hz), 5.30 (1 H, t, J = 6 Hz), 7.2–8.2 (7 H, m); MS, m/z 275 (M^+).

In a similar manner, **72** (3.35 g 0.01 mol) was reduced by the $NaBH_4$–$CaCl_2$ complex in THF to afford 2-(4-fluorophenyl)-4-(2-hydroxyethyl)-5-(3-thienyl)oxazole (**110**; 2.69 g, 93%), which was crystallized from MeOH: mp 109–110 °C; IR (Nujol) 3320, 1628, 1610 cm^{-1}; NMR ($CDCl_3$) δ 2.95 (2 H, t, J = 6 Hz), 3.44 (1 H, m), 4.01 (2 H, t, J = 6 Hz), 6.9–7.5 (5 H, m), 7.8–8.1 (2 H, m); MS, m/z 289 (M^+).

2-(4-Fluorophenyl)-4-[2-(nicotinoyloxy)ethyl]-5-(3-thienyl)oxazole (**111**). To a solution of **109** (1.34 g, 0.0046 mol) and Et_3N (1.87 g, 0.018 mol) in THF (20 mL) was added portionwise nicotinoyl chloride hydrochloride (1.64 g, 1.17 mol) at 5–10 °C with stirring. The stirring was continued at 5–10 °C for 1 h and then at room temperature overnight. The reaction mixture was concentrated in vacuo and partitioned between EtOAc and aqueous $NaHCO_3$. The organic layer was washed with brine and then concentrated in vacuo. The residue was crystallized from MeOH as colorless prisms of **111** (1.39 g, 71%): mp 107–108 °C; IR (Nujol) 1715, 1592 cm^{-1}; NMR ($CDCl_3$) δ 3.25 (2 H, t, J = 6 Hz), 4.22 (2 H, t, J = 6 Hz), 6.95–7.6 (5 H, m), 7.85–8.25 (5 H, m), 8.71 (1 H, dd, J = 2 and 5 Hz); MS, m/z 394 (M^+).

2-(4-Fluorobenzamido)-3-(3-thienyl)-3-oxopropanol (**112**). A mixture of **22** (5.26 g, 0.02 mol), aqueous 38% formaldehyde (4.80 g, 0.06 mol), Et_3N (14 mL, 0.1 mol), THF (50 mL), and DMF (50 mL) was stirred at room temperature for 5 h. After evaporation of THF in vacuo, the remainder was diluted with H_2O and extracted with EtOAc. The organic layer was concentrated and the residue was solidified with i-Pr_2O. The precipitates were crystallized from EtOH to afford colorless prisms of **112** (3.5 g, 60%): mp 137–138 °C; IR (Nujol) 3250, 3200, 1675, 1625, 1600 cm^{-1}; NMR (Me_2SO-d_6) δ 3.90 (2 H, dd, J = 6 Hz each, collapsed to doublet on D_2O exchange), 5.00 (1 H, t, J = 6 Hz, D_2O exchangeable), 5.2–5.6 (1 H, dt, J = 6 Hz each, collapsed to triplet on D_2O exchange), 7.05–7.5 (4 H, m), 7.8–8.2 (2 H, m), 8.5–8.8 (2 H, m, among them 1 H was D_2O exchangeable); MS, m/z 239 (M^+).

2-(4-Fluorobenzamido)-3-(3-thienyl)-3-oxopropyl Nicotinate (**113**). To a solution of **112** (3.50 g, 0.012 mol) in THF (50 mL) and Et_3N (3.60 g, 0.036 mol) was added nicotinoyl chloride hydrochloride (3.2 g, 0.018 mol) at 0–5 °C. After stirring at room temperature overnight, the solvent was evaporated and the residue was partitioned between H_2O and EtOAc. The EtOAc layer was concentrated and the residue was crystallized from MeOH to afford **113** (3.20 g, 67%) as colorless prisms: mp 170–171 °C; IR (Nujol) 3280, 1720, 1690, 1655, 1600 cm^{-1}; NMR (Me_2SO-d_6) δ 4.35 (2 H, d, J = 6 Hz), 5.6–6.0 (1 H, m), 7.1–8.3 (7 H, m), 8.5–9.4 (4 H, m); MS, m/z 362 (M^+).

2-(4-Fluorophenyl)-4-[(nicotinoyloxy)methyl]-5-(3-thienyl)oxazole (**114**). Phosphoryl chloride (1.37 g, 0.009 mol) was added to a solution of **113** (3.00 g, 0.0075 mol) in DMF (100 mL) at 8–10 °C with stirring. The mixture was stirred at 10–15 °C for 6 h, poured into ice-water, and then extracted with EtOAc. The extract was concentrated and the residue was triturated with i-Pr_2O to precipitate fine crystals. The crystals were recrystallized from a mixed solvent of EtOH and i-Pr_2O to yield **114** (1.80 g, 63%): mp 119–121 °C; IR (Nujol) 3100, 1730, 1650, 1610, 1590 cm^{-1}; NMR (Me_2SO-d_6) δ 5.56 (2 H, s), 7.2–7.9 (5 H, m), 8.0–8.5 (4 H, m), 8.8–8.9 (1 H, m), 9.0–9.2 (1 H, m); MS, m/z 380 (M^+).

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