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Studies on Antidiabetic Agents. VII.[1] Synthesis and Hypoglycemic Activity of 4-Oxazoleacetic Acid Derivatives[2]

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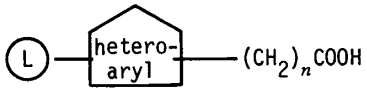
As part of a search for new antidiabetic agents, 4-oxazolealkanoic acid derivatives (III) were synthesized and tested for hypoglycemic activity in mice. 4-Oxazoleacetic acids (IIIb) bearing a styryl or a suitable aliphatic hydrocarbon moiety at the 2-position showed potent activity. The synthesis and structure–activity relationships of these compounds are presented.

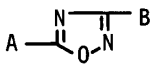
Keywords——oxazole; 4-oxazoleacetic acid; antidiabetic agent; hypoglycemic activity; structure–activity relationship

During the course of studies directed towards the synthesis of five-membered heteroaryl alkanoic acid derivatives (I) (Chart 1) as potential antidiabetic agents, we found that styryl-1,2,4-oxadiazolepropionic acids (II) had a hypoglycemic effect in mice.[3] However, these compounds were not selected as candidates for further development, because their activities were weak.

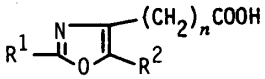
In an attempt to find more potent compounds, we switched our effort to oxazole derivatives, which correspond to the 2-deaza analogues of II. This paper describes the syntheses and activities of 2-substituted 4-oxazolealkanoic acid derivatives (III).



I (L = lipophilic group)



IIa: A = styryl, B = CH_2CH_2COOH
IIb: A = CH_2CH_2COOH, B = styryl



IIIa: $n=0$
IIIb: $n=1$
IIIc: $n=2$

Chart 1

Chemistry

The 4-oxazolecarboxylic acids (IIIa) were synthesized starting with α-amino-β-keto esters (IV) as shown in Chart 2. Cyclization of the *N*-acyl derivatives (V) was performed with phosphorus oxychloride. The cyclization of *N*-cinnamoyl-L-serine (VII) with polyphosphate ester (PPE),[4] followed by oxidation, gave VI wherein R^2 is hydrogen. Hydrolysis of VI afforded IIIa.

The carboxylic acids (IIIa) were reduced *via* the acid chlorides[5] with sodium borohydride to the alcohols (IX), which were then chlorinated to give the chloromethyloxazoles (X). The oxazole-acetic acids (IIIb) and the propionic acids (IIIc) were prepared from X by the usual processes (Chart 3).

Compound **16**,[6] a known compound, was synthesized for comparison by fusing cyclohexanecarboxamide (XIII) with ethyl 4-chloroacetoacetate (XIV) at 140—150 °C followed by hydrolysis (Chart 4).

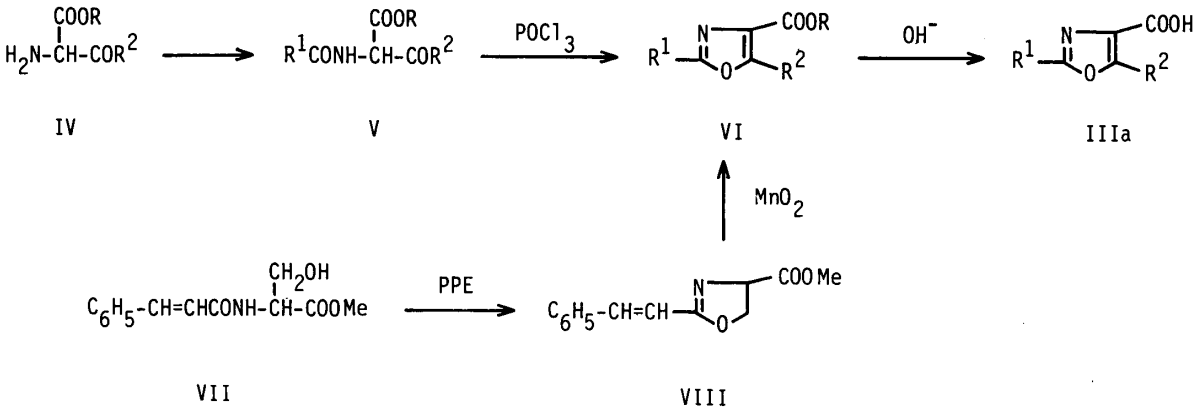


Chart 2

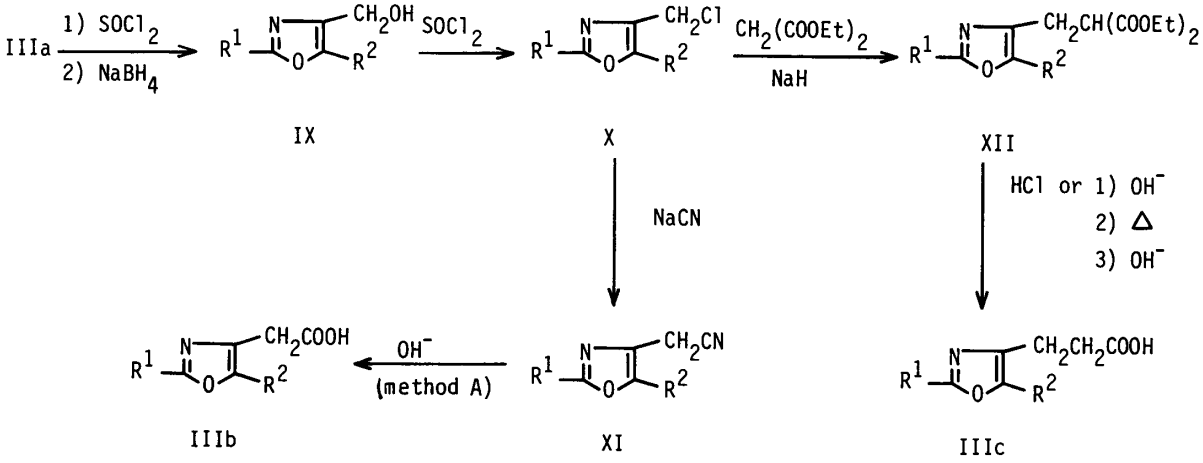


Chart 3

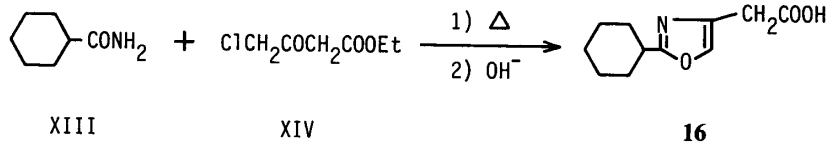
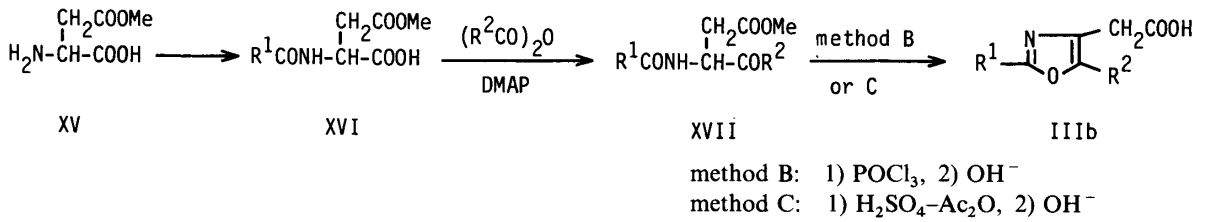


Chart 4

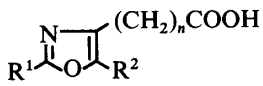
Among the compounds III synthesized, the acetic acid derivatives (IIIb) appeared to have the most potent hypoglycemic activities. Therefore, another convenient route to IIIb was investigated to make the variation of R^1 and R^2 easier. The process shown in Chart 5 was found to be very useful. The key step is the Dakin–West reaction[7] of *N*-acylaspartic acid *β*-ester (XVI) to give the acylamino keto esters (XVII). This transformation proceeded smoothly in the presence of 4-dimethylaminopyridine (DMAP). Cyclization of XVII was performed by using phosphorus oxychloride (method B) or sulfuric acid in acetic anhydride (method C), and the subsequent hydrolysis gave IIIb. Compound **29** was prepared by hydrogenation of **28**.



method B: 1) $POCl_3$, 2) OH^-
method C: 1) H_2SO_4–Ac_2O, 2) OH^-

Chart 5

TABLE I. Hypoglycemic Activities of 4-Oxazolealkanoic Acids (III)



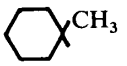
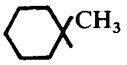
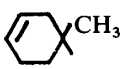
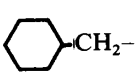
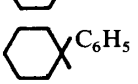
Compd. No.	R^1	R^2	n	Hypoglycemic activity (%)[a] Fasting	ITT (h) 1	ITT (h) 2
1[b]	$C_6H_5CH=CH-$	H	0	−12	−52[e]	−41
2	$C_6H_5CH=CH-$	H	1	−6	−17	−15
3[c]	$C_6H_5CH=CH-$	CH_3	0	0	−23	−21
4	$C_6H_5CH=CH-$	CH_3	1	−26[e]	−38[f]	−34[g]
5	$C_6H_5CH=CH-$	CH_3	2	−12	−20	−25
6	$C_6H_5CH=CH-$	C_2H_5	1	−6	−11	−17
7	$C_6H_5CH=CH-$	C_6H_{13}	1	−14	−4	−4
8	$C_6H_5CH=CH-$	C_6H_5	1	−9	−7	−5
9	4-Cl-$C_6H_4CH=CH-$	CH_3	1	−14	−15	−16
10	3-Cl-$C_6H_4CH=CH-$	CH_3	1	−32[e]	−29	−21[e]
11	2-Cl-$C_6H_4CH=CH-$	CH_3	1	−25	−51[g]	−30[g]
12	3-CF_3-$C_6H_4CH=CH-$	CH_3	1	−24	−40[g]	−25[g]
13	4-MeO-$C_6H_4CH=CH-$	CH_3	1	6	3	−4
14	C_6H_5	CH_3	1	−19	2	−8
15		CH_3	1	−22	−24[e]	−32[e]
16[d]		H	1	−25[e]	−12	−31[e]
17		CH_3	1	−47[h]	−49[h]	−53[g]
18		C_2H_5	1	−47[h]	−46[g]	−46[g]
19		C_3H_7	1	−39[g]	−28[f]	−27[e]
20		CH_3	1	−12	−12	3
21		CH_3	0	−32[f]	−13	−8
22 (AD-4610)		CH_3	1	−39[h]	−55[h]	−57[h]
23		CH_3	2	−10	−33[e]	−23
24		CH_3	1	−40[h]	−18	−36[f]
25		CH_3	1	−34[g]	−34[h]	−44[h]
26		CH_3	1	−11	−22[e]	−40[f]
27		CH_3	1	7	−8	−21
28	 (*endo*)	CH_3	1	−40[h]	−44[e]	−46[g]
29	 (*endo*)	CH_3	1	−32[g]	−44[e]	−56[g]
30	C_6H_{13}	CH_3	1	−3	13	0

TABLE I. continued

Compd. No.	R^1	R^2	n	Hypoglycemic activity (%)[a] Fasting	ITT (h) 1	ITT (h) 2
31	$C_3H_7-\overset{CH_3}{\underset{CH_3}{C}}-$	CH_3	1	−43[g]	−52[g]	−57[g]
32	$C_6H_5-\overset{CH_3}{\underset{CH_3}{C}}-$	CH_3	1	−6	0	−9

a) Student's *t*-test: *e*) $p<0.05$, *f*) $p<0.02$, *g*) $p<0.01$, *h*) $p<0.001$ *vs.* control; values without marks are not statistically significant. *b*) Methyl ester. *c*) Ethyl ester. *d*) See ref. 6.

The compounds prepared were evaluated for hypoglycemic effect in fasted mice followed by an insulin tolerance test to screen compounds that lower the fasting blood glucose level or stimulate the glycemic response to insulin. The biological data are shown in Table I.

Pharmacological Methods

Male ICR mice (7—9 weeks old, CLEA Japan) maintained on a laboratory chow, CE-2 (CLEA Japan), and water *ad libitum* were used. The test compounds, suspended in 5% gum arabic solution, were administered orally at a dose of 100 mg/kg. Then the mice were fasted for 20 h, and given a second dose (100 mg/kg) of the compounds. Blood samples were taken from the orbital vein 30 min later to determine the blood glucose levels by a glucose oxidase method.[8] The hypoglycemic effect (fasting) shown in Table I was calculated as a percentage change from the value of the control group which received the vehicle only.

The above mice were successively subjected to an insulin tolerance test (ITT). The mice received an i.p. insulin solution (Novo, regular) at a dose of 0.1 U/kg, and blood glucose levels were determined as above 1 and 2 h later. The decrease of blood glucose was calculated as a percentage change from the value of the control group treated with the vehicle and insulin only.

The data were analyzed by using Student's *t*-test.

Results and Discussion

The hypoglycemic activities of the oxazole-4-acetic acid derivatives (IIIb) were more potent than those of the 4-carboxylic acids (IIIa) and the 4-propionic acids (IIIc) (**4** *vs.* **3**, **5**; **22** *vs.* **21**, **23**). A methyl group seemed to be the best substituent at the 5-position (**4** *vs.* **2**, **6**, **7**, **8**; **17** *vs.* **16**, **18**, **19**). Although compound **4** with a styryl group at the 2-position had hypoglycemic activity, introduction of substituents into its benzene ring did not improve the activity (**4** *vs.* **9**—**13**).

It is noteworthy that the 2-phenyl derivative (**14**) did not show significant activity, whereas the 2-cyclohexyl derivative (**17**) had a potent hypoglycemic effect. However, the 2-cyclopentyl derivative (**15**) was less potent than **17**, and the cycloheptyl derivative (**20**) had almost no activity. The cyclohexylmethyl derivative (**26**) was also less potent than **17**. On the other hand, the activity of **17** was retained after the introduction of a methyl group or a double bond into the cyclohexane ring (*e.g.* **22**, **24**, **25**), or even after the introduction of

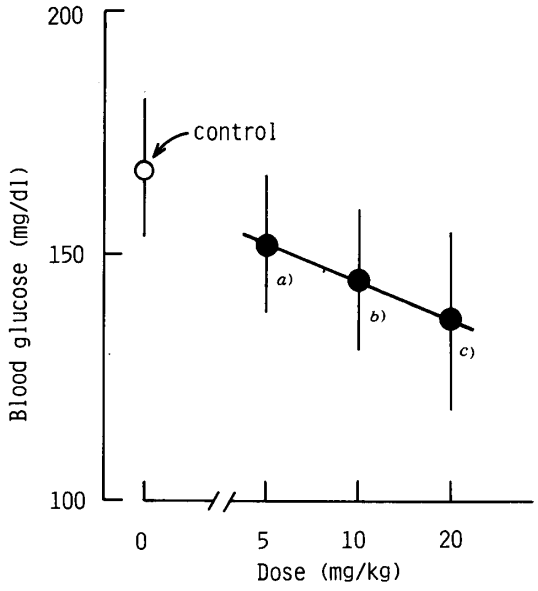


Fig. 1. Dose-Dependent Decrease of Blood Glucose in Fasted Yellow KK Mice after an Oral Administration of **22** (AD-4610)

After 20-h fasting, male yellow KK mice (10 weeks old) were orally administered **22** (AD-4610). Blood samples were taken 1 h after dosing. Each value represents the mean ± S.D. ($n=10$). *a*) $p<0.05$, *b*) $p<0.01$, *c*) $p<0.001$ *vs.* control.

a carbon bridge (*e.g.* **28**, **29**). Introduction of a phenyl group, however, resulted in complete loss of activity, as seen in **27**.

It should also be noted that compound **31** with a C_6-alkyl group branched at the α-position possesed potent activity, whereas compound **30** with a straight C_6-alkyl group did not show any activity. Compound **32** bearing a phenyl group on a branched alkyl group did not show any activity, as in the case of **27**.

Since the cycloalkyl group can be regarded as a sort of branched alkyl group, it is concluded that the α-branched structure of a 2-aliphatic hydrocarbon residue of suitable size appears to be a very important feature for hypoglycemic activity of the oxazoleacetic acids. Although the reason why the 2-styryl derivatives show activities similar to those of the cycloalkyl derivatives is uncertain, the two series may differ in their mode of action.

Compound **22** (AD-4610), one of the most interesting compounds in terms of activity and toxicity, also showed hypoglycemic activity in genetically obese and diabetic mice, yellow KK,[9] as shown in Fig. 1. Since yellow KK mice do not respond to sulfonylureas or biguanides, AD-4610 may be categorized into a hitherto unknown class of antidiabetic agent. Furthermore, this compound does not cause hypoglycemia or lactic acidosis, the main defect of sulfonylureas or biguanides, even at a high dose level in mice and rats. Therefore, AD-4610 is expected to be useful and safe drug for treating diabetes mellitus. Detailed pharmacological data including its mechanism of action will be reported elsewhere.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on a Hitachi IR-215 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM-390 spectrometer using tetramethylsilane as an internal standard. Chemical shifts are given in ppm and the following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, br = broad.

2-Acyl-2-acylaminoacetates (V)——A typical example is given to illustrate the general procedure.

Ethyl 2-Cinnamoylaminoacetoacetate: Triethylamine (8.3 ml) was added dropwise to a stirred, ice-cooled mixture of ethyl 2-aminoacetoacetate hydrochloride (5.43 g), cinnamoyl chloride (5.0 g) and $CHCl_3$ (90 ml). The whole was stirred with cooling for 20 min, washed with water and dried ($MgSO_4$). After removal of the solvent, the residue was treated with isopropyl ether to yield the title compound as crystals (6.1 g, 73.9%). Recrystallization from EtOH gave colorless needles, mp 113—114 °C. IR ν_{max}^{Nujol} cm^{-1}: 3240, 1755, 1730, 1655, 1620. NMR ($CDCl_3$) δ: 1.35 (3H, t, $J=7$ Hz), 2.43 (3H, s), 4.33 (2H, q, $J=7$ Hz), 5.45 (1H, d, $J=7$ Hz), 6.58 (1H, d, $J=16$ Hz), 7.00 (1H, br d), 7.45 (5H, m), 7.70 (1H, d, $J=16$ Hz). *Anal.* Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.55; H, 6.08; N, 5.01.

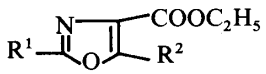
Table II. 2-Acyl-2-acylaminoacetates (V)

$$R^1CONH\text{–}\underset{\displaystyle COOR}{\underset{|}{CH}}\text{–}COR^2$$

R^1	R^2	R	Yield (%)	mp (°C)	Recrystn. solvent[a]	Formula[b]
$C_6H_5CH=CH-$	C_2H_5	CH_3	63.8	119—120	EtOH	$C_{15}H_{17}NO_4$
$C_6H_5CH=CH-$	C_6H_{13}	CH_3	90.3	85—86	IPE	$C_{19}H_{25}NO_4$
$C_6H_5CH=CH-$	C_6H_5	C_2H_5	64.6	125—126	EtOH	$C_{20}H_{19}NO_4$

a) IPE, isopropyl ether. *b*) All compounds were analyzed for C, H, and N. Analytical results obtained for these elements were within ±0.3% of the calculated values.

Table III. 4-Oxazolecarboxylates (VI)



R^1	R^2	Yield (%)	mp (°C)[a]	Formula[b]
$C_6H_5CH=CH-$	C_6H_5	90.9	81—82	$C_{20}H_{17}NO_3$
4-Cl–$C_6H_4CH=CH-$	CH_3	79.4[c]	105—106	$C_{15}H_{14}ClNO_3$
3-Cl–$C_6H_4CH=CH-$	CH_3	51.7[c]	116—117	$C_{15}H_{14}ClNO_3$
2-Cl–$C_6H_4CH=CH-$	CH_3	44.1[c]	99—100	$C_{15}H_{14}ClNO_3$
3-CF_3–$C_6H_4CH=CH-$	CH_3	76.5[c]	103—104	$C_{16}H_{14}F_3NO_3$
4-MeO–$C_6H_4CH=CH-$	CH_3	41.8[c]	116—117	$C_{16}H_{17}NO_4$

a) All compounds were recrystallized from EtOH. *b*) See footnote *b*, Table II. *c*) Overall yield based on IV.

Other compounds V in Table II were similarly prepared. Unlisted compounds were subjected to the next reaction without isolation.

4-Oxazolecarboxylates (VI)——Typical examples are given to illustrate the general procedure.

Ethyl 5-Methyl-2-styryl-4-oxazlecarboxylate (**3**): A stirred mixture of ethyl 2-cinnamoylaminoacetoacetate (5.7 g) and $POCl_3$ (40 ml) was heated at 100—110 °C for 30 min. After removal of the $POCl_3$, the residue was diluted with aq. $NaHCO_3$ and extracted with $CHCl_3$. The $CHCl_3$ layer was worked up and the residue was crystallized from hexane to yield the title compound (4.3 g, 80.7%). Recrystallization from EtOH gave light yellow prisms, mp 98—99 °C. IR ν_{max}^{Nujol} cm^{-1}: 1720, 1640. NMR ($CDCl_3$) δ: 1.43 (3H, t, J=7 Hz), 2.68 (3H, s), 4.50 (2H, q, J=7 Hz), 6.98 (1H, d, J=17 Hz), 7.50 (5H, m), 7.63 (1H, d, J=17 Hz). *Anal.* Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.81; H, 5.79; N, 5.37.

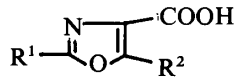
Other compounds VI, except methyl 2-styryl-4-oxazolecarboxylate (**1**), were similarly prepared and are listed in Table III. Unlisted oily compounds were isolated by column chromatography on silica gel and used without further purification.

Methyl 2-Styryl-4-oxazolecarboxylate (**1**): (1) A solution of cinnamoyl chloride (16.6 g) in AcOEt (30 ml) was added dropwise with ice-salt cooling to a mixture of L-serine methyl ester hydrochloride (15.50 g), water (100 ml), $NaHCO_3$ (21.8 g) and AcOEt (150 ml). The whole was stirred for 1.5 h with cooling and the AcOEt layer was separated. The aqueous layer was extracted with AcOEt and the combined AcOEt layer was worked up to yield *N*-cinnamoyl-L-serine methyl ester (VII) as crystals (21.74 g, 87.3%). Recrystallization from AcOEt gave colorless needles, mp 94—95 °C. IR ν_{max}^{Nujol} cm^{-1}: 3420, 3350, 1640, 1600. NMR ($CDCl_3$) δ: 3.72 (3H, s), 3.95 (2H, m), 4.73 (1H, m), 6.43 (1H, d, J=16 Hz), 7.22 (8H, m), 7.48 (1H, d, J=16 Hz). *Anal.* Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.53; H, 5.99; N, 5.60.

(2) A stirred mixture of VII (21.0 g), PPE[4] (84 g) and $CHCl_3$ (300 ml) was heated under reflux for 50 min. The solvent was removed and the residue was diluted with ice-water, neutralized with K_2CO_3, and extracted with Et_2O. The organic layer was worked up and the residue was chromatographed on silica gel (200 g) with hexane–acetone (8:2, v/v) to yield methyl 2-styryl-2-oxazoline-4-carboxylate (VIII) as an oil (14.8 g, 76.0%). NMR ($CDCl_3$) δ: 3.77 (3H, s), 4.55 (2H, s), 4.63 (3H, m), 6.37 (1H, d, J=16 Hz), 7.27 (6H, m).

(3) A stirred mixture of VIII (6.0 g), benzene (200 ml) and active MnO_2 (30 g) was heated under reflux for 20 min.

TABLE IV. 4-Oxazolecarboxylic Acids (IIIa)



R^1	R^2	Yield (%)	mp (°C)	Recrystn. solvent[a]	Formula[b]
$C_6H_5CH=CH-$	H	94.4	202—203	MeOH	$C_{12}H_9NO_3$
$C_6H_5CH=CH-$	C_2H_5	97.7[c]	143—144	EtOH	$C_{14}H_{13}NO_3$
$C_6H_5CH=CH-$	C_6H_{13}	97.4[c]	133—134	IPE	$C_{18}H_{21}NO_3$
$C_6H_5CH=CH-$	C_6H_5	92.2	229—230	EtOH	$C_{18}H_{13}NO_3$
4-Cl-$C_6H_4CH=CH-$	CH_3	89.8	244—245	Acetone	$C_{13}H_{10}ClNO_3$
3-Cl-$C_6H_4CH=CH-$	CH_3	98.4	213—214	Acetone	$C_{13}H_{10}ClNO_3$
2-Cl-$C_6H_4CH=CH-$	CH_3	96.3	223—224	Aq. AcOH	$C_{13}H_{10}ClNO_3$
3-CF_3-$C_6H_4CH=CH-$	CH_3	99.4	204—205	EtOH	$C_{14}H_{10}F_3NO_3$
4-MeO-$C_6H_4CH=CH-$	CH_3	88.9	205—206	MeOH	$C_{14}H_{13}NO_4$
	CH_3	54.9[d]	119—120	IPE	$C_{10}H_{13}NO_3$
	CH_3	40.7[d]	173—174	Aq. EtOH	$C_{11}H_{15}NO_3$
	CH_3	46.3[d]	147—148	AcOEt–hexane	$C_{17}H_{19}NO_3$

a) See footnote *a*, Table II. *b*) See footnote *b*, Table II. *c*) Overall yield based on V. *d*) Overall yield based on IV.

The MnO_2 was filtered off and the filtrate was concentrated to yield **1** as crystals (4.05 g, 68.1%). Recrystallization from MeOH gave colorless needles, mp 134—135 °C. NMR ($CDCl_3$) δ: 3.95 (3H, s), 6.95 (1H, d, J=16 Hz), 7.45 (5H, m), 7.70 (1H, d, J=16 Hz), 8.25 (1H, s). *Anal.* Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.40; H, 4.70; N, 6.41.

4-Oxazolecarboxylic Acids (IIIa)——A typical example is given to illustrate the general procedure.

5-Methyl-2-(1-methylcyclohexyl)-4-oxazolecarboxylic Acid (**21**): A mixture of ethyl 5-methyl-2-(1-methylcyclohexyl)-4-oxazolecarboxylate (oil, 10.6 g), EtOH (45 ml) and 2 N NaOH (43 ml) was heated at 90 °C (bath) for 15 min and allowed to stand at room temperature for 30 min. After dilution with water, the mixture was adjusted to pH 2 with 2 N HCl and extracted with Et_2O. The Et_2O layer was worked up and the residue was crystallized from hexane to give **21** (8.0 g, 80.8%). Recyrstallization from hexane afforded colorless needles, mp 128—129 °C. NMR ($CDCl_3$) δ: 1.28 (3H, s), 1.47 (8H, br s), 2.17 (2H, br), 2.25 (3H, s). *Anal.* Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.55; H, 7.68; N, 6.24.

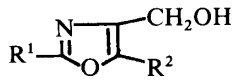
Other compounds IIIa listed in Table IV were similarly prepared. Unlisted oily compounds were used in the next reaction without further purification.

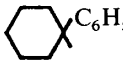
4-Hydroxymethyloxazoles (IX)——Typical examples are given to illustrate the general procedure.

4-Hydroxymethyl-5-methyl-2-styryloxazole: A solution of **3** (2.14 g) in a mixture of tetrahydrofuran (THF) (10 ml) and Et_2O (15 ml) was added dropwise to a stirred, and ice-cooled mixture of $LiAlH_4$ (0.34 g) and Et_2O (20 ml). The whole mixture was stirred with cooling for 1 h and treated cautiously with water (2 ml). The resultant white precipitate was filtered off and the filtrate was concentrated to give the title compound as crystals (1.28 g, 71.5%). Recrystallization from acetone afforded colorless prisms, mp 106—107 °C. IR ν_{max}^{Nujol} cm^{-1}: 3230, 1640. NMR ($CDCl_3$) δ: 2.37 (3H, s), 4.30 (1H, br d, exchanged with D_2O), 4.63 (2H, br), 6.92 (1H, d, J=17 Hz), 7.47 (6H, m). *Anal.* Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.46; H, 6.01; N, 6.22.

2-(2-Chlorostyryl)-4-hydroxymethyl-5-methyloxazole: A stirred mixture of 2-(2-chlorostyryl)-5-methyl-4-oxazolecarboxylic acid (4.8 g) and $SOCl_2$ (24 ml) was refluxed for 1 h. The $SOCl_2$ was removed and the residual crystals (acid chloride) were collected with isopropyl ether. A solution of the crystals in dimethoxyethane (DME) (20 ml) was then added dropwise to a stirred and ice-cooled suspension of $NaBH_4$ (1.4 g) in DME (30 ml). The mixture was stirred with cooling for 30 min and then treated with 2 N HCl at pH 2 under reflux for 30 min. After removal of the solvent, the residue was partitioned between AcOEt and aq. $NaHCO_3$. The organic layer was separated and worked up to give the title compound as crystals (3.9 g, 85.9%). Recrystallization from EtOH afforded colorless needles, mp 122—123 °C. NMR ($CDCl_3$) δ: 2.43 (3H, s), 4.25 (1H, br), 4.63 (2H, br), 6.92 (1H, d, J=17 Hz), 7.13—7.80 (4H, m), 7.93 (1H, d, J=17 Hz). *Anal.* Calcd for $C_{13}H_{12}ClNO_2$: C, 62.53; H, 4.84; N, 5.61. Found: C, 62.49; H, 4.64; N, 5.75.

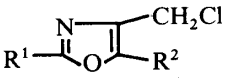
Table V. 4-Hydroxymethyloxazoles (IX)

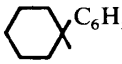


R^1	R^2	Yield (%)	mp (°C)	Recrystn. solvent[a]	Formula[b]
$C_6H_5CH=CH-$	H	87.3	93—94	IPE	$C_{12}H_{11}NO_2$
$C_6H_5CH=CH-$	C_2H_5	83.4	90—91	Et_2O	$C_{14}H_{15}NO_2$
$C_6H_5CH=CH-$	C_6H_{13}	63.2	44—45	Hexane	$C_{18}H_{23}NO_2$
$C_6H_5CH=CH-$	C_6H_5	71.3	135—136	EtOH	$C_{18}H_{15}NO_2$
4-Cl-$C_6H_4CH=CH-$	CH_3	88.4	129—130	EtOH	$C_{13}H_{12}ClNO_2$
3-Cl-$C_6H_4CH=CH-$	CH_3	83.3	147—148	EtOH	$C_{13}H_{12}ClNO_2$
3-CF_3-$C_6H_4CH=CH-$	CH_3	65.5	134—135	EtOH	$C_{14}H_{12}F_3NO_2$
4-MeO-$C_6H_4CH=CH-$	CH_3	80.3	100—101	AcOEt	$C_{14}H_{13}NO_3$
	CH_3	93.1	125—126	EtOH	$C_{17}H_{21}NO_2$

a) See footnote *a*, Table II. b) See footnote *b*, Table II.

Table VI. 4-Chloromethyloxazoles (X)



R^1	R^2	Yield (%)	mp (°C)	Recrystn. solvent[a]	Formula[b]
$C_6H_5CH=CH-$	C_6H_5	85.8	125—126	EtOH	$C_{18}H_{14}ClNO$
4-Cl-$C_6H_4CH=CH-$	CH_3	92.8	121—122	EtOH	$C_{13}H_{11}Cl_2NO$
3-Cl-$C_6H_4CH=CH-$	CH_3	90.7	86—87	IPE	$C_{13}H_{11}Cl_2NO$
2-Cl-$C_6H_4CH=CH-$	CH_3	99.7	109—110	Et_2O	$C_{13}H_{11}Cl_2NO$
3-CF_3-$C_6H_4CH=CH-$	CH_3	88.5	99—100	IPE	$C_{14}H_{11}ClF_3NO$
4-MeO-$C_6H_4CH=CH-$	CH_3	72.7	99—100	Et_2O	$C_{14}H_{14}ClNO_2$
	CH_3	99.2	88—89	IPE	$C_{17}H_{20}ClNO$

a) See footnote *a*, Table II. b) See footnote *b*, Table II.

Other compounds IX listed in Table V were similarly prepared by reducing the acid chlorides of IIIa with $NaBH_4$. Unlisted oily compounds were isolated by column chromatography on silica gel and used in the next reaction without further purification.

4-Chloromethyloxazoles (X)——A typical example is given to illustrate the general procedure.

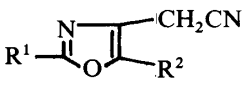
4-Chloromethyl-5-methyl-2-styryloxazole: A mixture of 4-hydroxymethyl-5-methyl-2-styryloxazole (1.0 g) and $SOCl_2$ (3 ml) was allowed to stand at room temperature for 30 min. After removal of the $SOCl_2$, the residue was partitioned between AcOEt and aq. $NaHCO_3$. The organic layer was separated and worked up to yield the title compound as crystals (0.98 g, 90.7%). Recrystallization from Et_2O afforded light yellow plates, mp 108—109 °C IR ν_{max}^{Nujol} cm^{-1}: 1637. NMR ($CDCl_3$) δ: 2.37 (3H, s), 4.45 (2H, s), 6.75 (1H, d, J=17 Hz), 7.33 (6H, m). *Anal.* Calcd for $C_{13}H_{12}ClNO$: C, 66.81; H, 5.18; N, 5.99. Found: C, 67.07; H, 5.16; N, 6.08.

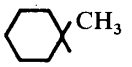
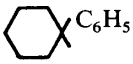
Other compounds X listed in Table VI were similarly prepared. Unlisted oily compounds were used in the next reaction without further purification.

4-Oxazoleacetonitriles (XI)——A typical example is given to illustrate the general procedure.

5-Methyl-2-styryl-4-oxazoleacetonitrile: A solution of 4-chloromethyl-5-methyl-2-styryloxazole (2.33 g) in dimethylsulfoxide (DMSO) (15 ml) was added dropwise to a stirred solution of NaCN (0.95 g) in DMSO (15 ml). The mixture was stirred for 1.5 h and diluted with ice-water. The resulting precipitate was filtered off to yield the title compound (2.10 g, 93.8%). Recrystallization from isopropyl ether gave colorless prisms, mp 72—73 °C. IR ν_{max}^{Nujol} cm^{-1}: 2230, 1640. NMR ($CDCl_3$) δ: 2.38 (3H, s), 3.57 (2H, s), 6.75 (1H, d, J=16 Hz), 7.35 (6H, m). *Anal.* Calcd

TABLE VII. 4-Oxazoleacetonitriles (XI)



R^1	R^2	Yield (%)	mp (°C)	Recrystn. solvent[a]	Formula[b]
$C_6H_5CH=CH-$	H	42.4[c]	106—107	EtOH	$C_{13}H_{10}N_2O$
4-Cl-$C_6H_4CH=CH-$	CH_3	98.4	124—125	EtOH	$C_{14}H_{11}ClN_2O$
3-Cl-$C_6H_4CH=CH-$	CH_3	96.9	119—120	EtOH	$C_{14}H_{11}ClN_2O$
2-Cl-$C_6H_4CH=CH-$	CH_3	96.9	89—90	EtOH	$C_{14}H_{11}ClN_2O$
3-CF_3-$C_6H_4CH=CH-$	CH_3	95.9	107—108	EtOH	$C_{15}H_{11}F_3N_2O$
4-MeO-$C_6H_4CH=CH-$	CH_3	94.8	103—104	EtOH	$C_{15}H_{14}N_2O_2$
	CH_3	73.7[d]	57—58	IPE	$C_{13}H_{18}N_2O$
	CH_3	93.1	125—126	EtOH	$C_{17}H_{21}NO_2$

a) See footnote *a*, Table II. *b*) See footnote *b*, Table II. *c*) Overall yield based on IX. *d*) Overall yield based on IIIa.

for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 74.82; H, 5.18; N, 12.27.

Other compounds XI listed in Table VII were prepared similarly. Unlisted oily compounds were isolated by extraction with AcOEt and used in the next reaction without purification.

Methyl 3-Acyl-3-acylaminopropionates (XVII)——A typical example is given to illustrate the general procedure.

Methyl 3-(1-Methylcyclohexylcarbonyl)amino-4-oxovalerate: (1) 1-Methylcyclohexylcarbonyl chloride (32.0 g) was added dropwise to a stirred, cooled (ice-salt) mixture of L-aspartic acid β-methyl ester hydrochloride (XV·HCl) (36.7 g), CH_2Cl_2 (370 ml) and triethylamine (100.8 ml). The mixture was stirred with cooling for 1 h and 2 N HCl (130 ml) was added thereto. The CH_2Cl_2 layer was separated and worked up. The residue was crystallized from isopropyl ether to give colorless prisms (48.0 g, 88.4%), mp 88—89 °C. IR ν_{max}^{Nujol} cm^{-1}: 3375, 1745, 1725, 1630. NMR ($CDCl_3$) δ: 1.15 (3H, s), 1.43 (8H, br), 1.92 (2H, br), 2.21 (3H, s), 2.71 (1H, dd, J=16.5, 4.5 Hz), 2.98 (1H, dd, J=16.5, 4.5 Hz), 3.67 (3H, s), 4.75 (1H, m), 6.95 (1H, br d, J=7.5 Hz, exchanged with D_2O). *Anal.* Calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.63; H, 7.72; N, 5.41.

(2) A stirred mixture of *N*-(1-methylcyclohexylcarbonyl)-L-aspartic acid β-methyl ester (48.0 g), Ac_2O (106 ml), pyridine (88 ml) and DMAP (1.06 g) was heated at 90 °C (bath) for 2 h. Water (100 ml) was added thereto at the same temperature and the whole was heated for another 15 min. After cooling, the mixture was diluted with water and extracted with AcOEt. The AcOEt layer was washed with dil. HCl, water, aq. $NaHCO_3$ and water, and then dried ($MgSO_4$). The solvent was removed to yield the title compound as crystals (45.0 g, 94.5%). An aliquot was recrystallized from isopropyl ether to give colorless needles, mp 54—55 °C. IR ν_{max}^{Nujol} cm^{-1}: 3320, 1740, 1620. NMR ($CDCl_3$) δ: 1.15 (3H, s), 1.42 (8H, br), 1.88 (2H, br), 2.20 (3H, s), 2.87 (2H, m), 3.63 (3H, s), 4.68 (1H, m). *Anal.* Calcd for $C_{14}H_{23}NO_4$: C, 62.43; H, 8.61; N, 5.20. Found: C, 62.63; H, 8.33, N, 5.35.

Other compounds XVII listed in Table VIII were prepared similarly. In general, the intermediates (XVI) were converted to XVII without purification.

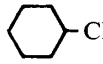
4-Oxazoleacetic Acids (IIIb)——Typical examples are given to illustrate the general procedure.

2-Cyclohexyl-4-oxazoleacetic Acid (**16**): A mixture of cyclohexanecarboxamide (XIII, 8.89 g) and ethyl 4-chloroacetoacetate (XIV, 11.4 g) was heated at 140—150 °C for 2 h. The mixture was diluted with water, neutralized with aq. $NaHCO_3$, and extracted with AcOEt. The AcOEt layer was worked up and the oily residue was briefly purified by column chromatography on silica gel (200 g) with hexane–acetone (50 : 2, v/v) to give ethyl 2-cyclohexyl-4-oxazoleacetate as an oil (3.5 g). This oil was then dissolved in EtOH (30 ml) and treated with 2 N NaOH (25 ml) at room temperature for 20 min. The mixture was diluted with water and washed with Et_2O. The aqueous layer was made acid with 2 N HCl and extracted with AcOEt. The AcOEt layer was worked up to give **16** as crystals (2.40 g). Recrystallization from isopropyl ether afforded colorless prisms (1.96 g, 18.2%), mp 113—114 °C (lit.[5] mp 114—116 °C). IR ν_{max}^{Nujol} cm^{-1}: 1730. NMR ($CDCl_3$) δ: 1.05—2.23 (10H, m), 2.57—3.00 (1H,m), 3.63 (2H, s), 7.50 (1H, s), 9.82 (1H, s). *Anal.* Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.15; H, 7.18; N, 6.56.

5-Methyl-2-styryl-4-oxazoleacetic Acid (**4**): Method A. A stirred mixture of 5-methyl-2-styryl-4-oxazoleacetonitrile (1.8 g), EtOH (25 ml) and 2 N NaOH (20 ml) was heated under reflux for 3 h. The mixture was concentrated, diluted with water and acidified with AcOH to yield **4** as crystals (1.75 g, 89.7%). Recrystallization from acetone gave needles (1.40 g, 71.8%), mp 182—183 °C. IR ν_{max}^{Nujol} cm^{-1}: 1730, 1640. NMR ($CDCl_3$ + DMSO-d_6) δ: 2.35

TABLE VIII. 3-Acyl-3-acylaminopropionates (XVII)

$$R^1CONH\text{–}\underset{\displaystyle CH_2COOCH_3}{\underset{|}{CH}}\text{–}COR^2$$

R^1	R^2	Yield[a] (%)	mp (°C)	Recrystn. solvent[b]	Formula[c]
$C_6H_5CH=CH-$	CH_3	41.8	82—83	Et_2O	$C_{15}H_{17}NO_4$
	CH_3	44.6	87—88	IPE	$C_{13}H_{21}NO_4$
	C_2H_5	39.5	99—100	Hexane	$C_{14}H_{23}NO_4$
	C_3H_7	36.4	82—83	IPE	$C_{15}H_{25}NO_4$
	CH_3	75.6	64—65	IPE	$C_{14}H_{23}NO_4$
	CH_3	64.4	69—70	Et_2O	$C_{13}H_{19}NO_4$
 CH_2-	CH_3	63.7	75—76	IPE	$C_{14}H_{23}NO_4$
C_6H_{13}	CH_3	75.2	63—64	IPE	$C_{13}H_{23}NO_4$

a) Overall yield based on L-aspartic acid β-methyl ester (XV). *b*) See footnote *a*, Table II. *c*) See footnote *b*, Table II.

(3H, s), 3.52 (2H, s), 6.93 (1H, d, $J=17$ Hz), 7.50 (5H, m), 7.78 (1H, d, $J=17$ Hz). *Anal.* Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.10; H, 5.40; N, 5.69.

This compound **4** was also obtained by method B in 77.3% yield.

5-Methyl-2-(1-methylcylohexyl)-4-oxazoleacetic Acid (**22**): Method B. (1) A mixture of methyl 3-(1-methylcyclohexylcarbonyl)amino-4-oxovalerate (45.0 g), toluene (250 ml) and $POCl_3$ (50 ml) was heated under reflux for 5 h. After removal of the solvent, the residue was diluted with water, neutralized with K_2CO_3 and extracted with Et_2O. The solvent was removed and the residue was distilled to yield methyl 5-methyl-2-(1-methylcyclohexyl)-4-oxazoleacetate as an oil (30.5 g, 72.6%), bp 110—113 °C (0.2 mm Hg). IR ν_{max}^{neat} cm^{-1}: 1740, 1650. NMR ($CDCl_3$) δ: 1.22 (3H, s), 1.42 (8H, br), 2.12 (2H, br), 2.22 (3H, s), 3.45 (2H, s), 3.65 (3H, s).

(2) A mixture of 64.3 g of the methyl ester obtained above, EtOH (100 ml) and 2 N NaOH (170 ml) was stirred at room temperature for 30 min. After dilution with water, the mixture was adjusted to pH 2 with HCl and extracted with Et_2O. The Et_2O layer was washed with water, dried ($MgSO_4$) and treated with morpholine (23 ml) to yield the morpholine salt of **22** as crystals (75 g). Recrystallization from acetone gave colorless needles (66 g), mp 109—110 °C. This salt was dissolved in water (200 ml), cooled, and treated with 6 N HCl with vigorous stirring to give **22** as crystals (44.9 g, 74.0%). Recrystallization from hexane afforded colorless prisms (43.0 g, 70.8%), mp 67—68 °C. IR ν_{max}^{Nujol} cm^{-1}: 1725. NMR ($CDCl_3$) δ: 1.23 (3H, s). 1.43 (8H, br), 2.08 (2H, br), 3.50 (2H, s), 10.43 (1H, s). *Anal.* Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.86; H, 7.85; N, 5.86.

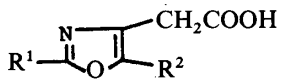
Method C. Only the method of cyclization is different from method B——Concentrated H_2SO_4 (18.7 ml) was added dropwise to a stirred suspension of methyl 3-(1-methylcyclohexylcarbonyl)amino-4-oxovalerate (94.3 g) in Ac_2O (250 ml). The mixture was then heated at 90 °C (bath) for 30 min and concentrated *in vacuo*. The residue was diluted with water (400 ml), neutralized with $NaHCO_3$, and extracted with AcOEt. The extract was worked up and the residue was distilled to yield **22** methyl ester (82.0 g, 93.2%), bp 120—127 °C (1.0 mm Hg). This sample was identical with that obtained in method B-(1).

Compound **22** was also obtained by method A in 76.5% yield.

Other compounds IIIb listed in Table IX were prepared by method A or B. In general, the methyl esters of IIIb prepared by method B were subjected to hydrolysis without purification.

5-Methyl-2-(*endo*-2-norbornyl)-4-oxazoleacetic Acid (**29**): A mixture of 5-methyl-2-(*endo*-5-norbornen-2-yl)-4-oxazoleacetic acid (**28**, 1.0 g), AcOEt (15 ml) and 10% Pd/C (50% wet, 0.2 g) was hydrogenated at atmospheric pressure. The catalyst was filtered off and the filtrate was concentrated. The residue was recrystallized from isopropyl ether to give **29** as colorless needles (0.75 g, 74.3%), mp 108—109 °C. IR ν_{max}^{Nujol} cm^{-1}: 1723. NMR ($CDCl_3$) δ: 1.43 (7H, m), 1.83 (2H, m), 2.23 (3H, s), 2.60 (1H, br), 3.17 (1H, m), 3.53 (2H, s). *Anal.* Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 65.97; H, 7.06; N, 5.64.

Table IX. 4-Oxazoleacetic Acids (IIIb)



Compd.[a] No.	Method	Yield (%)	mp (°C)	Recrystn. solvent[b]	Formula[c]
2	A	73.2	179—180	EtOH	$C_{13}H_{11}NO_3$
6	A	58.8[d]	164—165	Et_2O	$C_{15}H_{15}NO_3$
7	A	70.3[d]	107—108	IPE	$C_{19}H_{23}NO_3$
8	A	84.5[e]	197—198	Et_2O	$C_{19}H_{15}NO_3$
9	A	83.7	157—158	AcOEt	$C_{14}H_{12}ClNO_3$
10	A	93.2	214—215	MeOH–CH_2Cl_2	$C_{14}H_{12}ClNO_3$
11	A	93.2	148—149	AcOEt	$C_{14}H_{12}ClNO_3$
12	A	80.3	157—158	Et_2O	$C_{15}H_{12}F_3NO_3$
13	A	84.6	164—165	Et_2O	$C_{15}H_{15}NO_4$
14	B	31.4[f]	126—127	Aq. EtOH	$C_{12}H_{11}NO_3$
15	A	20.8[g]	83—84	IPE	$C_{11}H_{15}NO_3$
17	A	14.5[g]	104—105	IPE	$C_{12}H_{17}NO_3$
	B	69.3			
18	B	92.8	101—102	Hexane	$C_{13}H_{19}NO_3$
19	B	96.2	110—111	Hexane	$C_{14}H_{21}NO_3$
20	B	81.0	84—85	IPE	$C_{13}H_{19}NO_3$
24	B	90.0	86—87	IPE	$C_{12}H_{15}NO_3$
25	A	22.8[h]	144—145	EtOH	$C_{13}H_{17}NO_3$
	B	47.5			
26	B	88.7	104—105	Et_2O	$C_{13}H_{19}NO_3$
27	A	95.3	146—147	EtOH	$C_{18}H_{21}NO_3$
28	B	21.6[f]	112—113	IPE	$C_{13}H_{15}NO_3$
30	B	45.7	38—39	Hexane	$C_{12}H_{19}NO_3$
31	B	78.1	97—98	IPE	$C_{12}H_{19}NO_3$
32	B	18.1[h]	94—95	IPE	$C_{15}H_{17}NO_3$

a) For R^1 and R^2, see Table I. *b*) See footnote *a*, Table II. *c*) See footnote *b*, Table II. *d*) Overall yield based on IX. *e*) Overall yield based on X. *f*) Overall yield based on XV. *g*) Overall yield based on IIIa. *h*) Overall yield based on IV.

4-Oxazolepropionic Acids (IIIc)——5-Methyl-2-styryl-4-oxazolepropionic Acid (**5**): A solution of diethyl malonate (2.4 g) in *N*,*N*-dimethylformamide (DMF) (20 ml) was treated with 60% NaH (0.4 g) at room temperature for 15 min. A solution of 4-chloromethyl-5-methyl-2-styryloxazole (2.33 g) in DMF (10 ml) was then added dropwise thereto with stirring. The mixture was stirred for 3 h, diluted with ice-water, and extracted with AcOEt. The AcOEt layer was worked up and the residue was dissolved in a mixture of AcOH (50 ml) and 6 N HCl (20 ml). The mixture was heated under reflux for 3.5 h, concentrated, and made alkaline with aq. NaOH. After being washed with Et_2O, the aqueous layer was made acid with AcOH and extracted with CH_2Cl_2. The CH_2Cl_2 layer was worked up to give **5** as crystals. Recrystallization from acetone yielded colorless needles (1.75 g, 68.1%), mp 147—148 °C. IR ν_{max}^{Nujol} cm^{-1}: 1718, 1643. NMR ($CDCl_3$) δ: 2.32 (3H, s), 2.67 (4H, m), 6.82 (1H, d, J=17 Hz), 7.42 (6H, m). *Anal.* Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.16; H, 5.69; N, 5.29.

5-Methyl-2-(1-methylcyclohexyl)-4-oxazolepropionic Acid (**23**): A solution of diethyl malonate (3.2 g) in DMF (20 ml) was treated with 60% NaH (0.44 g) at room temperature for 10 min. A solution of 4-chloromethyl-2-(1-methylcyclohexyl)-5-methyloxazole [prepared from the corresponding hydroxymethyl derivative (2.1 g)] in DMF (10 ml) was then added dropwise thereto with stirring. The mixture was stirred at room temperature for 1.5 h, diluted with water and extracted with Et_2O.

The Et_2O layer was worked up and the residue was dissolved in a mixture of EtOH (20 ml) and 2 N NaOH (20 ml). The mixture was stirred at room temperature for 1 h, diluted with water, and washed with Et_2O. The aqueous layer was adjusted to pH 2 with 2 N HCl and extracted with Et_2O. The Et_2O extract was worked up and the residue was heated in pyridine (20 ml) at reflux for 5 h. After removal of the solvent, the residue was dissolved in EtOH (10 ml) and treated with 2 N NaOH (10 ml) at room temperature for 1 h. The mixture was diluted with water, adjusted to pH 2 with 2 N HCl and extracted with Et_2O. The Et_2O layer was worked up and the residue

was crystallized from hexane to yield **23** as crystals (1.12 g, 44.6%). Recrystallization from hexane gave needles (1.0 g, 39.8%), mp 71—72 °C. NMR ($CDCl_3$) δ: 1.23 (3H, s), 1.43 (8H, br s), 2.12 (2H, br), 2.22 (3H, s), 2.70 (4H, s). *Anal.* Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 66.91; H, 8.37; N, 5.42.

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References and Notes

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