Chem. Pharm. Bull.
25(9)2292—2299(1977)

UDC 547.789.4.04 : 547.787.04

Syntheses of 2-Disubstituted-amino-4-arylthiazol-5-ylalkanoic Acids[1]

KENTARO HIRAI and HIROHIKO SUGIMOTO

Shionogi Research Laboratory, Shionogi and Co., Ltd.[2]

(Received January 17, 1977)

A novel method of synthesizing 2-disubstituted-amino-4-arylthiazol-5-ylalkanoic acids (3) was studied.

Dehydration of *S*-(α-benzoyl-β-ethoxycarbonyl)ethyl 1-piperidinethiocarbonate (**5a**) in the presence of aqueous perchloric acid–acetic anhydride yielded 4-ethoxycarbonylmethyl-5-phenyl-2-piperidino-1,3-oxathiolium perchlorate (**1a**). Nucleophilic reaction of ammonia with **1a** afforded 5-ethoxycarbonylmethyl-4-phenyl-2-piperidinothiazole (**2a**). Acid-catalyzed hydrolysis of **2a** gave **3a** as a hydrochloride. The acids (3) were also synthesized by the classical Hantzsch method.

These alkanoic acids were evaluated as antiinflammatory agents on carrageenin-induced abscess in rat.

Keywords——2-dialkylamino-4-arylthiazol-5-ylacetic acid; α-(2-dialkylamino-4-arylthiazol-5-yl)propionic acid; 2-dialkylamino-4-ethoxycarbonylmethyl-5-aryl-1,3-oxathiolium cation; Hantzsch synthesis; antiinflammatory activity

2-Disubstituted-amino-5-aryl-1,3-oxathiolium cation (**1**) reacts easily with nucleophiles and is a versatile intermediate for a variety of heterocyclic compounds. The reaction of **1** with ammonia gave the thiazole derivative (**2**) in good yield.[3] As an extention of this reaction, we attempted syntheses of 2-disubstituted-amino-4-arylthiazol-5-ylacetic or propionic acid derivatives (**3**) as potential antiinflammatory agents. Thiazolylacetic acids (2-yl,[4] 4-yl[5] and 5-yl[6]) constitute one category of nonsteroidal antiinflammatory agents and contain an acidic group. Recently, thiazolylacetic acids containing the 2-disubstituted-amino group were synthesized by condensation of α-substituted (halogen or SCN) carbonyl compounds with thiourea.[7]

Here we report a novel synthetic method of synthesizing the title compounds *via* 1,3-oxathiolium cation (**1**) and also *via* Hantzsch method.

Results and Discussion

The syntheses of thiazol-5-ylacetic acids are depicted in Chart 1. Friedel–Crafts reaction of substituted benzene with succinic anhydride in the presence of $AlCl_3$ gave β-benzoyl-pro-

---

[1] This paper forms Part XI in a series on the "Studies on Heterocyclic Cation Systems." Preceding paper, Part X: K. Hirai, H. Sugimoto, T. Ishiba, *Tetrahedron*, **33**, 1595 (1977); This work was presented at the 96th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, April 1976.

[2] Location: *Sagisu, Fukushima-ku, Osaka.*

[3] K. Hirai and T. Ishiba, *Chem. Commun.*, **1971**, 1318.

[4] K. Geward and U. Hain, *J. Prakt. Chem.*, **317**, 329 (1975); L. Farkas, E. Kasztreimer, F. Andrasi, J. Borsi, and I. Koczka, *Ger. Offen.*, 2453083 (1975) [*C.A.*, **83**, 114377*x* (1975)].

[5] I. Simiti, I. Schwartz, and M. Coman, *Rev. Roum. Biochem.*, **11**, 139 (1974); T. Lewis, *Ger. Offen.*, 2456822 (1975) [*C.A.*, **83**, 114382*v* (1975)]; R. Maeda and K. Hirose, *Japan Kokai.*, 69076 (1975) [*C.A.*, **84**, 17321*n* (1976)].

[6] K. Brown, D.P. Cater, J.F. Cavalla, D. Green, R.A. Newberry, and A.B. Wilson, *J. Med. Chem.*, **17**, 1177 (1974); A. Poittevim and V. Torelle, *Ger. Offen.*, 2605838 (1976) [*C.A.*, **85**, 143092*x* (1976)]; S.C. Bell and P.H. Wei, *J. Med. Chem.*, **19**, 524 (1976); E. Galinberti, S. Cerutti, A. Forlani, and G. D'Atri, *Arzneim.-Forsch.*, **26**, 392 (1976); M.F.A. Abdel-Lateef, D. Rusek, J. Cybulski, A. Mizerski, and Z. Eckstein, *Rocz. Chem.*, **50**, 323 (1976).

[7] E. Mangishi, A. Salimbeni, and G. Fregan, *Ger. Offen.*, 2365526 (1975) [*C.A.*, **83**, 179041*c* (1975)].

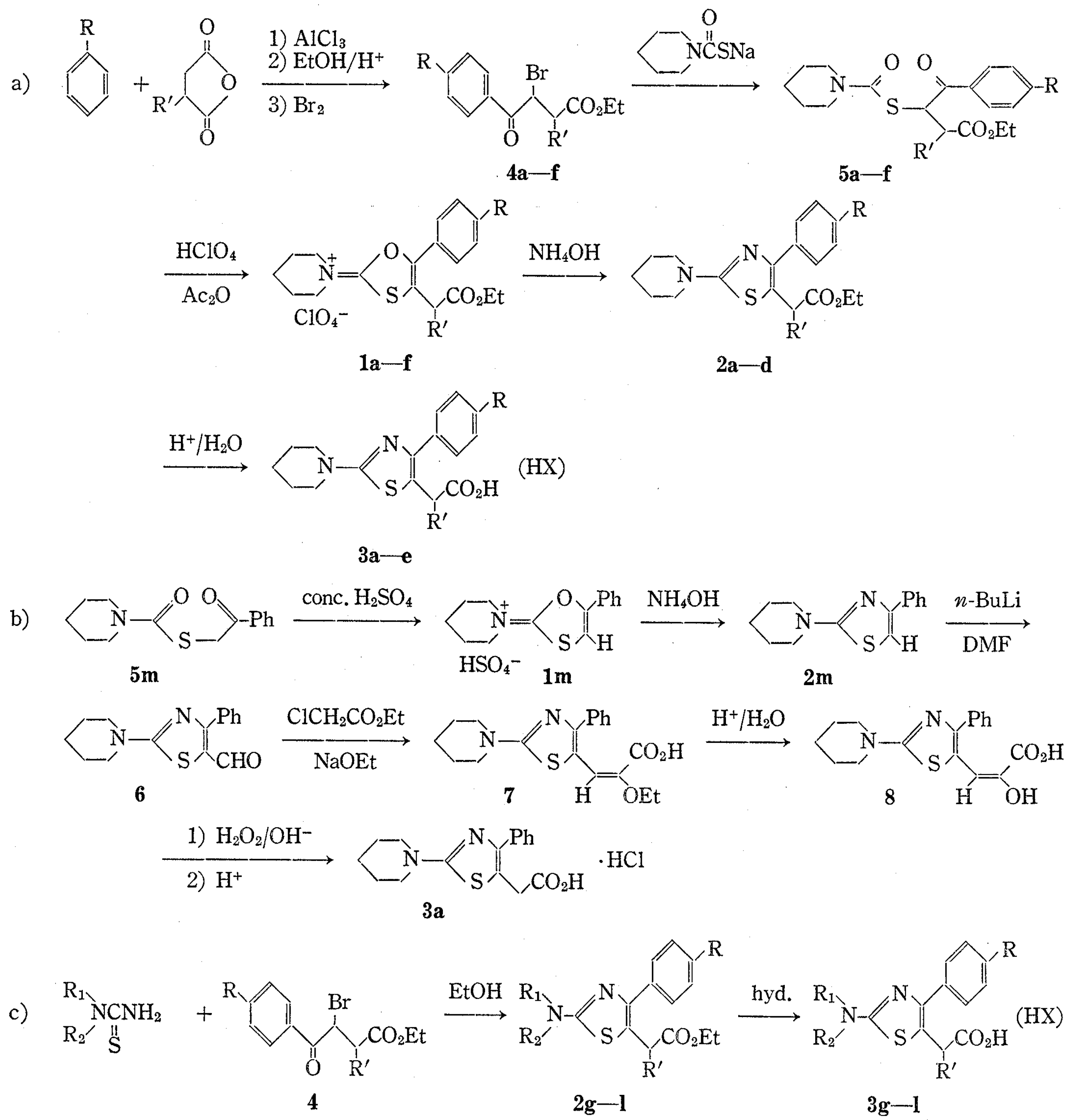


Chart 1. Several Methods of Synthesizing 2-Disubstituted-amino-4-arylthiazol-5-ylalkanoic acids (3). Common Suffices (a—l) were used through Chart 1 and Table I, II, III and IV.

pionic acid derivatives. Acid-catalyzed esterification with ethanol and subsequent bromination yielded α-bromoketo compounds (**4**). When methylsuccinic anhydride was used, acylation of benzene took place at the carbon which is remote from the methyl substituent.[8]

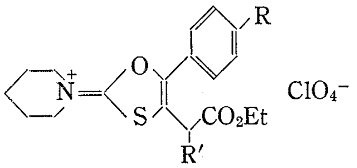
Reaction of **4** with S-sodium *N*,*N*-disubstituted-aminothiocarbonate in refluxing ethanol afforded the corresponding thiocarbonate ester (**5**), generally as an oil. We have reported the ring closure of *N*,*N*-disubstituted-aminothiocarbonate (phenacyl ester) in the presence of conc. H_2SO_4.[9] However, ester **5** did not cyclize under the conditions mentioned above. Ring closure was performed in acetic anhydride in the presence of perchloric acid at low temperature. Table I summarizes the physicochemical properties of the cations (**1**).

---

[8] E.R. Alexander and A. Mudrak, *J. Am. Chem. Soc.*, **72**, 3194 (1950).

[9] K. Hirai and T. Ishiba, *Chem. Pharm. Bull.* (Tokyo), **20**, 304 (1972).

Table I. Physicochemical Properties of Oxathiolium Cation (1)

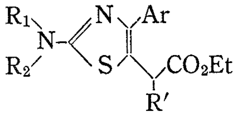


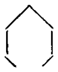
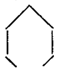
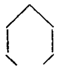
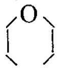
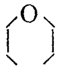
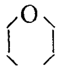
1	R′	R	dec. (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	S	Found C	H	N	S
a	H	H	110—111	65	$C_{18}H_{22}ClNO_7S\cdot H_2O$	48.05	5.38	3.11	7.13	48.23	5.38	2.85	6.64
b	H	Cl	155—156	*a*)	$C_{18}H_{21}Cl_2NO_7S$	46.36	4.54	3.00	6.88	46.15	4.42	3.17	6.69
d	H	OMe	174—176	86	$C_{19}H_{24}ClNO_8S$	49.40	5.24	3.03	6.94	49.04	5.49	3.03	6.74
e	Me	H	164—165	*a*)	$C_{19}H_{24}ClNO_7S$	51.18	5.42	3.14	7.19	51.38	5.47	3.47	7.10
f	Me	Cl	85—87	*a*)	$C_{19}H_{23}Cl_2NO_7S$	47.51	4.84	2.92	6.68	47.26	4.96	3.20	6.97

a) Not isolated except analytical sample.

The stability of the cations (**1**) thus obtained depended on the substituent of the phenyl group. The electron-donating group stabilized the 6π electronic cation. On the other hand, purification of the cation with the electron-withdrawing group was very difficult or unsuccessful. Treatment of cation **1** with ammonium hydroxide afforded 2-disubstituted-

Table II. Physicochemical Properties of Ethyl 2-Disubstituted-amino-4-arylthiazol-5-ylacetate (2)

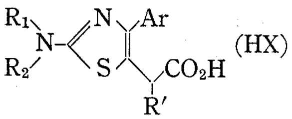


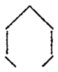
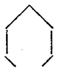
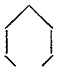
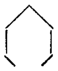
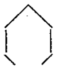
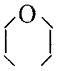
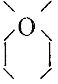
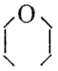
2	R_1	R_2	R′	Ar*a*)	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	S	Found C	H	N	S
a			H	Ph	oil	92	$C_{18}H_{22}N_2O_2S\cdot 2H_2O$	58.99	7.15	7.65	8.75	59.31	6.18	7.44	8.65
c			H	BrPh	71—72	54*b*)	$C_{18}H_{21}BrN_2O_2S$	52.82	5.17	6.84	7.83	52.55	5.23	7.25	7.85
d			H	MeOPh	58—59	98	$C_{19}H_{24}N_2O_3S$	63.31	6.71	7.77	8.09	63.19	6.78	7.73	9.24
g			H	ClPh	113—114	82*c*)	$C_{17}H_{19}ClN_2O_3S$	55.65	5.22	7.64	8.74	55.71	5.09	7.41	8.97
h			Me	ClPh	102—103	73	$C_{18}H_{21}ClN_2O_3S$	56.76	5.56	7.36	8.42	57.02	5.42	7.12	8.51
i	Me	H	H	ClPh	107—108	89	$C_{14}H_{15}ClN_2O_2\cdot HBr\cdot H_2O$	41.04	4.43	6.84	7.83	41.09	4.53	6.67	8.54
j	PhCO	H	H	BrPh	140—141	78	$C_{20}H_{17}BrN_2O_3S$	53.94	3.85	6.29	7.20	53.90	3.78	6.12	7.23
k	*p*-Cl-PhCO	H	H	BrPh	190—192	68	$C_{20}H_{16}BrClN_2O_3S$	50.02	3.37	5.85	6.68	50.25	3.58	5.77	6.64
l			H	2-thienyl	58—59	54	$C_{15}H_{18}N_2O_3S_2$	53.23	5.36	8.24	18.95	53.41	5.21	8.21	18.74

a) *p*-Substituted phenyl. *b*) From **5c**. *c*) Esters **2g**—**l** were synthesized by the Hantzsch method, others *via* oxathiolium cation.

amino-4-aryl-5-ethoxycarbonylmethylthiazole (**2**).[10] Subsequent acid-catalyzed hydrolysis of the ester moiety of **2** gave 2-disubstituted-amino-4-arylthiazol-5-ylacetic acid (**3**). Use of methylsuccinic anhydride gave α-thiazol-5-ylpropionic acid by the same procedure. The results for the ester (**2**) and the acid (**3**) are summarized inTables II and III, respectively.

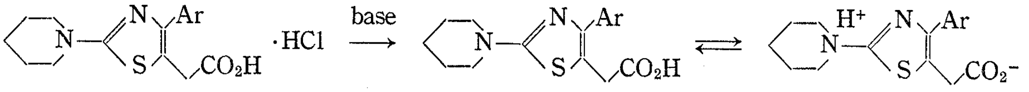
Table III. Physicochemical Properties of 2-Disubstituted-amino-4-arylthiazol-5-ylacetic Acid (**3**)



3	R_1	R_2	R′	Ar[a]	dec. (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	S	Found C	H	N	S
a			H	Ph	140—144	76	$C_{16}H_{18}N_2O_2S \cdot HCl$	56.71	5.65	8.27	9.46	57.20	6.30	7.99	9.19
b			H	ClPh	188—189	35[b]	$C_{16}H_{17}ClN_2O_2S \cdot HCl$	51.46	4.86	7.56	8.59	51.56	5.10	7.71	8.61
c			H	BrPh	206—209	81	$C_{16}H_{17}BrN_2O_2S \cdot HCl$	46.00	4.34	6.71	7.68	45.88	4.50	6.62	7.72
d			H	MeOPh	178—181	85	$C_{17}H_{20}N_2O_3S \cdot HCl \cdot 1/2H_2O$	54.03	5.87	7.41	8.48	53.87	5.84	7.41	8.34
e			Me	Ph	158—161	32[c]	$C_{17}H_{20}O_2N_2S$	64.53	6.37	8.87	10.13	64.31	6.47	8.59	10.13
g			H	ClPh	212—214	80	$C_{15}H_{15}ClN_2O_3S \cdot HCl$	48.52	4.34	7.55	8.64	48.12	4.25	7.62	8.65
h			Me	ClPh	194—196	82	$C_{16}H_{17}ClN_2O_3S$	54.46	4.86	7.94	9.09	54.72	4.83	8.10	9.28
i	Me	H	H	ClPh	216—220	71	$C_{12}H_{10}ClN_2O_2S \cdot HBr$	39.63	3.33	7.70	8.82	39.99	3.45	7.79	9.07
j	PhCO	H	H	BrPh	288	68	$C_{18}H_{13}BrN_2O_3S$	51.81	3.14	6.71	7.68	51.36	3.08	6.73	7.75
k	*p*-Cl-PhCO	H	H	BrPh	292	64	$C_{18}H_{12}BrClN_2O_3S$	47.86	2.68	6.20	7.10	47.28	2.66	6.34	7.25
l			H	2-thienyl	110—111	65	$C_{13}H_{14}N_2O_3S_2$	50.30	4.55	9.03	20.66	50.38	4.48	8.81	20.64

a) *p*-Substituted phenyl. *b*) From **5b**. *c*) From **5e**.

Acids (**3**) are generally salts due to the presence of a basic 2-dialkylamino group. Neutralization of the salt gave free acid (**3′**). The IR spectrum of the salt **3′c** showed a strong



3c **3c′**

and sharp carbonyl band at 1725 cm⁻¹, whereas the free acid (**3′c**) showed only a broad band at 1705 cm⁻¹; the UV spectrum exhibited a marked solvent effect. A saturated solution of **3′c** in EtOH and H_2O showed three absorption bands at about 240, 270, and 310 nm. Among them, the band at 270 nm changed little with solvent polarity. However, the other two bands exhibited a blue shift with increasing solvent polarity, *i.e.*, 238 and 310 nm in EtOH and 235

---

10) Transformation of heterocyclic conjugated systems containing oxygen atom into corresponding nitrogen analogs by the nucleophilic reaction of ammonia or amines has been well established.[11]

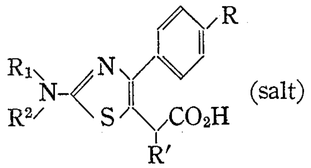
11) H.C. van der Plas, "Ring Transformations of Heterocycles," Vol. 1, Academic Press, New York, 1973, p. 377; *ibid.*, Vol. 2, p. 18, 196, and 208.

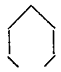
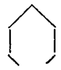
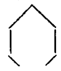
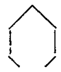
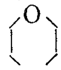
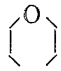
and 285 nm in H_2O. This kind of blue shift was also observed for iso-nicotinic acid.[12] These results indicate that free acid is an equilibrium mixture of the species shown above. Furthermore, free acid is less stable than the corresponding salt; the former changes into green-colored material on exposure to air.

Thiazol-5-ylacetic acid (**3**) was also obtained *via* stepwise carbon elongation from 2-piperidino-4-phenylthiazole (**2m**) as is shown in Chart 1, method b. The ring closure of S-phenacyl 1-piperidinethiocarbonate (**5m**) by conc. H_2SO_4 gave 5-phenyl-2-piperidino-1,3-oxathiolium hydrogen sulfate (**1m**). Treatment of **1m** with ammonium hydroxide yielded thiazole (**2m**). Formylation of **2m** was carried out by treatment with *n*-BuLi at −70° followed by addition of DMF. Condensation of the formyl group of 5-formyl-4-phenyl-2-piperidinothiazole (**6**) with ethyl chloroacetate in the presence of base gave the acrylic acid derivative (**7**).[13] In this reaction, no epoxy compound was obtained. Hydrolysis of **7** in the presence of acid afforded the keto acid (**8**). The NMR spectrum of **8** showed the preference of the enol form over the keto form, evidence by the olefinic proton at δ 6.50. Decarboxylation of **8** was carried out under the condition of H_2O_2–NaOH, but the yield of **3a** was not good.

To obtain the thiocarbonate ester (**5b**) from **5b′**, we tried C-alkylation in the presence of *n*-BuLi. However, we obtained the *O*-alkylated product (**9**) in 68% yield, which was confirmed from its spectral data.

TABLE IV. Antiinflammatory Activity of 2-Disubstituted-amino-4-arylthiazolylalkanoic Acids



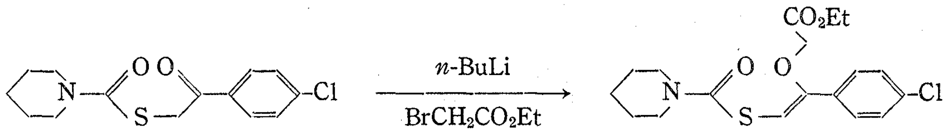
3	R_1	R_2	R′	R	Salt	% inhibition	mg/kg *p. o.*
i	Me	H	H	Cl	HBr	20	100
a			H	H	HCl	34	50
b			H	Cl	HCl	57	50
c			H	Br	HCl	52	50
d			H	OMe	HCl	26	50
e			Me	H		19	50
h			Me	Cl		52	50
g			H	Cl	HCl	74	50
						57	5
						38	2.5
j	PhCO	H	H	Br		16	50
Phenylbutazone						35	50

% inhibition of rat carrageenin abscess.

---

[12] H.P. Stephenson and H. Sponer, *J. Am. Chem. Soc.*, **79**, 2050 (1957).

[13] The limited spectral data do not clarify the ambiguity of whether the structure is the **7** or ethyl α-hydroxyacrylate derivative.



5b′ → 9

Finally, we studied the alternative classical Hantzsch method of preparing **3** using α-bromo keto compounds (**4**) (Chart 1, method c). Refluxing morpholinothiourea with **4** in ethanol gave thiazole (**2**) in good yield. Subsequent hydrolysis afforded **3**. The results are summarized in Tables II and III.

These alkanoic acids were evaluated as antiinflammatory agents on carrageenin–induced abscess in rat. Inhibition effects are summarized in Table IV together with that of phenylbutazone for comparison. The presence of a secondary amino group at the C-2 position of the thiazole ring resulted in reduction of the activity. Furthermore, replacement of R′ by Me instead of H lowered the activity slightly. Substitution of the electron-withdrawing group at the para position of the 4-phenyl ring enhanced the activity. Acid **3g** was the strongest among the acids investigated. It was about twenty times effective than phenylbutazone.

Experimental

Melting points are uncorrected. The UV spectra were measured with a Hitachi EPS-2 spectrophotometer, IR spectra in KBr with a JASCO DS-403G spectrometer, NMR spectra on a Varian A-60 instrument with TMS as an internal standard.

Synthesis of 3——A typical example is described for the synthesis of **3d**.

***S*-{*β*-Ethoxycarbonyl-*α*-(*p*-methoxybenzoyl)}ethyl 1-Piperidinethiocarbonate (5d)**——Friedel-Crafts reaction of anisole with succinic anhydride in the presence of $AlCl_3$ was described by Olah.[14] The obtained *β*-(*p*-methoxyphenyl)propionic acid (102.6 g) in 300 ml of ethanol, 50 ml of benzene and 5.0 ml of conc. H_2SO_4 were refluxed for 2.5 hr. The mixture was cooled, neutralized with saturated sodium bicarbonate solution, and concentrated to about one-third volume. The residue was extracted with benzene, washed with water, separated and dried over sodium sulfate. Removal of the solvent gave 105.0 g (90.2%) of ethyl *β*-(*p*-methoxyphenyl)propionate, mp 43—44° from EtOH.

To a suspension of 100 g of the above ester in 300 ml of ether was added 68 g of bromine dropwise at room temperature. The mixture was stirred for an additional 1 hr. Undissolved substance was removed by filtration and the filtrate was washed several times with saturated sodium bicarbonate solution, separated, dried and concentrated. The oily product (129 g of **4d**, 96.7%) was used without further purification for the next step.

A suspension of 31.5 g of **4d** and 15.3 g of S-sodium piperidinethiocarbonate[15] in 100 ml of ethanol was stirred for 30 min at room temperature. The mixture was separated by filtration, and the filtrate was concentrated. The residue was extracted with ethyl acetate. The organic phase was washed with water, separated, dried and concentrated *in vacuo*. The ester (**5d**, 35.6 g, 92.3%) was obtained as an oil. NMR ($CDCl_3$) δ: 1.17 (3H, t, Me), 1.58 (6H, broad s, piperidino), 2.53—3.27 (2H, m, CH_2), 3.48 (4H, broad s, piperidino), 3.85 (3H, s, OMe), 4.10 (2H, q, CH_2), 5.42—5.72 (1H, m, CH), 6.87—8.22 (4H, m, Ar). This was used for further reaction without any other purification.

4-Ethoxycarbonylmethyl-5-*p*-methoxyphenyl-2-piperidino-1,3-oxathiolium Perchlorate (1d)——A solution of 9.40 g of **5d** in 20 ml of acetic anhydride was cooled to 0° with dry ice. To this solution, 4.0 ml of 60% perchloric acid solution was added dropwise. The reaction was highly exothermic and efficient cooling and stirring were needed. The mixture was stirred for 1 hr at 0°. Excess ether was added and the precipitate was separated by filtration. Washing with ethanol yielded 9.84 g (86.0%) of **1d**, dec. 174—176°. NMR ($CDCl_3$) δ: 1.23 (3H, 5, Me), 1.77 (6H, broad s, piperidino), 3.85 (3H, s, OMe), 3.98 (4H, broad s, piperidino), 4.02 (2H, s, CH_2), 4.17 (2H, q, CH_2), 6.83—7.70 (4H, q, Ar). IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 1730, 1678, 1610, 1593, 1090.

Ethyl 4-*p*-Methoxyphenyl-2-piperidinothiazol-5-ylacetate (2d)——A solution of 7.8 g of **1d** in 100 ml of 28% ammonia solution was stirred for 1 hr at room temperature. Next, the mixture was extracted with chloroform, washed with water, separated and dried. Removal of the solvent under reduced pressure followed by recrystallization from petroleum ether gave 6.0 g (98%) of **2d**, mp 58—59°. NMR ($CDCl_3$) δ:

---

14) G.A. Olah, "Friedel-Crafts and Related Reactions," Interscience, New York, 1963, Vol. 3, Part, p. 36; L.F. Fieser and E.B. Hershberg, *J. Am. Chem. Soc.*, **58**, 2314 (1936).

15) K. Hirai, *Tetrahedron Lett.*, **1971**, 1137.

1.58 (3H, t, Me), 1.63 (6H, broad s, piperidino), 3.47 (4H, broad s, piperidino), 3.37 (2H, s, CH_2), 4.18 (2H, q, CH_2), 6.78—7.65 (4H, q, Ar).

4-*p*-Methoxyphenyl-2-piperidinothiazol-5-ylacetic Acid Hydrochloride (**3d**)——A solution of 6.2 g of **2d** in 40 ml of conc. hydrochloric acid was refluxed for 2 hr. The mixture was cooled to room temperature and neutralized with saturated sodium bicarbonate solution of pH 2—3, then extracted with chloroform. The organic layer was separated, dried and concentrated. The residual oily product was triturated with acetone to give 5.5 g (85%) of **3d**. The analytical sample was recrystallized from acetone, mp 171—181°. NMR ($CDCl_3$) δ: 1.65 (6H, broad s, piperidino), 3.71 (2H, s, CH_2), 3.75 (4H, broad s, piperidino), 3.83 (3H, s, OMe), 6.97—7.58 (4H, q, Ar). IR ν_{max}^{KBr} cm^{-1}: 1730, 1610.

Acids **3a**—**e** were synthesized by the same procedure and the results are summarized in Tables II and III.

4-*p*-Bromophenyl-2-piperidino-thiazol-5-ylacetic Acid (**3c′**)——A suspension of 200 mg of **3c** [hydrochloride, NMR (d_6-DMSO) δ: 1.65 (6H, broad s, piperidino), 3.62 (4H, broad s, piperidino), 3.73 (2H, s, CH_2), 7.37—7.65 (4H, q, Ar)] in 40 ml of saturated sodium bicarbonate solution was stirred for 1 hr at 50—60°. The mixture became a clear solution, then was extracted with chloroform, separated and dried. Removal of the solvent *in vacuo* followed by recrystallization from CH_2Cl_2–hexane afforded 95 mg (45%) of **3c′**, mp 98—101°. *Anal.* Calcd. for $C_{16}H_{17}BrN_2O_2S \cdot H_2O$: C, 48.13; H, 4.80; Br, 20.01; N, 7.02; S, 8.03. Found: C, 47.80; H, 4.40; Br, 19.72; N, 6.84; S, 7.94. NMR (d_6-DMSO) δ: 1.57 (6H, broad s, piperidino), 3.37 (4H, broad s, piperidino), 3.52 (2H, s, CH_2), 7.55 (4H, s, Ar).

5-Formyl-4-phenyl-2-piperidinothiazole (**6**)——To a cooled (−70°) solution of 3.9 g of **2m** in 15 ml of THF was added 18 ml of 15% *n*-BuLi hexane solution, and the mixture was stirred for 1 hr. Then 4.0 ml of DMF in 5.0 ml of THF was added dropwise to obtain a red solution. The mixture was stirred for an additional 1 hr, being allowed to warm to room temperature. It was then poured into excess dilute hydrochloric acid solution. This was neutralized with saturated sodium bicarbonate solution and concentrated. The residual oil was triturated with ethanol to give the crude product. Recrystallization from methanol afforded 3.2 g (72%) of **6**, mp 93—94°. *Anal.* Calcd. for $C_{15}H_{16}N_2OS$: C, 66.15; H, 5.92; N, 10.29; S, 11.77. Found: C, 66.35; H, 6.06; N, 10.06; S, 11.76. NMR ($CDCl_3$) δ: 1.72 (6H, broad s, piperidino), 3.68 (4H, broad s, piperidino), 7.35—7.88 (5H, m, Ph), 9.75 (1H, s, CHO). IR ν_{max}^{KBr} cm^{-1}: 1640.

α-Ethoxy-β-(2-piperidino-4-phenylthiazol-5-yl)acrylic Acid (**7**)——A solution of 200 mg of **6** in 4.0 ml of THF was cooled to 3° with external dry ice cooling. To this, freshly prepared sodium ethoxide solution (100 mg of sodium in 5.0 ml of ethanol) was added. The yellow suspension was stirred for 2 hr at room temperature. The mixture was separated by filtration. To the filtrate, 1.0 ml of AcOH and excess of water were added and the mixture was extracted with methylene chloride. The organic layer was dried and concentrated. The residue was separated by column chromatography on silica gel with an ether as an eluant. Recrystallization from methanol gave 90 mg (34%) of **7**, mp 135—137°. *Anal.* Calcd. for $C_{19}H_{22}N_2O_3$: C, 63.66; H, 6.19; N, 7.81; S, 8.94. Found: C, 63.78; H, 6.26; N, 7.83; S, 9.07. NMR ($CDCl_3$) δ: 1.23 (3H, t, Me), 1.63 (6H, broad s, piperidino), 3.53 (4H, broad s, piperidino), 4.22 (2H, q, CH_2), 5.57 (1H, broad s, OH), 6.85 (1H, s, CH), 7.15—7.77 (5H, m, Ph). IR ν_{max}^{KBr} cm^{-1}: 3400, 1670.

α-Hydroxy-β-(4-phenyl-2-piperidinothiazol-5-yl)acrylic Acid (**8**)——A suspension of 358 mg of **7** in 50 ml of 10% hydrochloric acid solution was refluxed for 20 min. The mixture became a solution and was allowed to stand overnight. The precipitated product was collected by filtration. Drying over P_2O_5 gave 240 mg (65%) of **8**, mp 215—217°. *Anal.* Calcd. for $C_{17}H_{18}N_2O_3S \cdot HCl$: C, 55.68; H, 5.22; N, 7.64; S, 8.74. Found: C, 55.68; H, 5.27; N, 7.70; S, 8.81. NMR (d_6-DMSO) δ: 1.78 (6H, broad s, piperidino), 3.78 (4H, broad s, piperidino), 6.53 (1H, s, CH), 7.53 (5H, s, Ph). IR ν_{max}^{KBr} cm^{-1}: 1700.

4-Phenyl-2-piperidinothiazol-5-ylacetic Acid Hydrochloride (**3a**)——Keto acid (**8**, 370 mg) was dissolved in 5.0 ml of 5% sodium hydroxide solution. To this, 1.0 ml of 30% H_2O_2 solution was added and the mixture was stirred for 30 min at room temperature. The mixture was acidified with 10% hydrochloric acid and the precipitate was collected by filtration (45 mg of **3a**, 13%). The IR spectrum of this product was identical to that of the authentic sample, **3a**, which was prepared by method a in Chart 1.

***S*-β-*p*-Chlorophenyl-β-ethoxycarbonylmethyloxyethenyl 4-Morpholinethiocarbonate** (**9**)——To a cooled (−70°) solution of 7.0 g of **5b′** in 40 ml of THF was added 20 ml of 15% *n*-BuLi hexane solution dropwise. The yellow mixture was stirred for 20 min at −70°. Then a solution 4.3 g of ethyl bromoacetate in 6.0 ml of THF was added dropwise. The cooling bath was removed and the mixture was stirred for 1 hr at room temperature. To the reddish mixture, 5% hydrochloric acid solution and excess ether were added. The etherial solution was separated, washed with saturated sodium bicarbonate solution, separated and dried over sodium sulfate. Concentration of the solvent followed by recrystallization from ethanol gave 5.6 g (68%) of **9**, mp 104—105°. *Anal.* Calcd. for $C_{17}H_{18}ClNO_5S$: C, 53.19; H, 4.73; N, 3.65; S, 8.35. Found: C, 53.46; H, 4.89; N, 3.75; S, 8.55. NMR ($CDCl_3$) δ: 1.27 (3H, t, Me), 3.43 (2H, s, CH_2), 3.70 (8H, broad s, morpholino), 4.22 (2H, q, CH_2), 6.50 (1H, s, CH), 7.27 (4H, s, Ar).

Ethyl 2-Morpholino-4-(2-thienyl)thiazol-5-ylacetate (**21**)——Ester **4l** was synthesized from β-2-thienylcarbonylpropionic acid[16] by the same procedure as for **4d** and used without further purification. A mixture

---

[16] L.F. Fieser and R.G. Kennelly, *J. Am. Chem. Soc.*, **57**, 1611 (1935).

of 2.90 g of **41** and 1.61 g of morpholinothiourea[17] in 20 ml of ethanol was refluxed for 3 hr. The mixture was filtrated and the filtrate was concentrated *in vacuo*. The residual oil was separated by column chromatography on silica gel with chloroform as an eluant. Recrystallization from ethanol gave 1.80 g (54% from **41**) of **21**, mp 58—59°. NMR ($CDCl_3$) δ: 1.23 (3H, t, Me), 3.25—3.90 (8H, m, morpholino), 3.82 (2H, s, CH_2), 4.15 (2H, q, CH_2), 6.88—7.33 (3H, m, thienyl).

2-Morpholino-4-(2-thienyl)thiazol-5-ylacetic Acid (31)——A suspension of 700 mg of **21** in 10% sodium hydroxide solution was refluxed until it became clear. Then the solution was cooled to room temperature and neutralized with 5% hydrochloric acid solution. The mixture was extracted with chloroform, dried and concentrated. Recrystallization from petroleum ether afforded 420 mg (65%) of **31**, dec. 110—111°.

Ethyl 4-*p*-Chlorophenyl-2-morpholinothiazol-5-ylacetate (2g)——A mixture of 3.9 g of morpholinothiourea and 6.1 g of **4g** in 40 ml of ethanol was refluxed for 3 hr, then allowed to stand overnight. Next, the mixture was concentrated and excess saturated sodium bicarbonate solution was added. The organic layer was separated, dried and concentrated *in vacuo*. Recrystallization from ethanol gave 5.7 g (82% to **4g**) of **2g**, mp 113—114°. NMR ($CDCl_3$) δ: 1.43 (3H, t, Me), 3.32—3.93 (8H, m, morpholino), 3.72 (2H, s, CH_2), 4.22 (2H, q, CH_2), 7.13—7.63 (4H, m, Ar).

4-*p*-Chlorophenyl-2-morpholinothiazol-5-ylacetic Acid Hydrochloride (3g)——Hydrolysis of **2g** was carried out as for **3d**. The acid **3g** was obtained in 80% yield, dec 212—214°. NMR (d_6-DMSO) δ: 3.47—3.87 (8H, m, morpholino), 3.72 (2H, s, CH_2), 7.47 (4H, s, Ar).

Acids **3h**—**k** were synthesized by the same procedure and the results are summarized in Tables II and III.

Acknowledgement The authors are grateful to the members of the analytical and physical chemistry sections of this laboratory for elemental analyses and spectral measurements. We also express our appreciation to Dr. K. Hirose and his colleagues for the pharmacological assays.

---

[17] H. Hartmann and I. Reuther, *J. Prakt. Chem.*, **315**, 144 (1973).