Summary

Twenty new derivatives of nitrogen mustard, including six N-oxides, were prepared and tested for their *in vivo* and *in vitro* antitumor activity against the Yoshida sarcoma.

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19. Ryuichi Kimura, Takahiro Yabuuchi, and Yasutaka Tamura: Studies on Thiophene Derivatives. IV.[1] Syntheses of 2-Aminoethyl 3,3-Diaryl-3-hydroxypropanoates and 3,3-Diaryl-2-propenoates.

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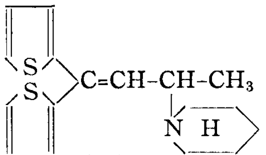
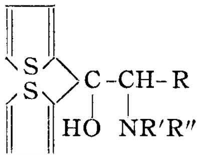
It is known that some thiophene derivatives have an interesting pharmacological action. For example, 3-piperidino-1,1-di(2-thienyl)-1-butene (A) has a more potent antitussive action than morphine or Methadone.

In previous papers[1,2] of this series, it has been shown that the antitussive effect of the dextro form obtained by optical resolution of (A) compound was twice as strong as the racemic form and also several times stronger than codeine in clinical application.

In a later work,[3] many derivatives of 2-amino-1,1-(2-thienyl)alkanol (B) having structures similar to both ephedrine and (A) compound were synthesized in order to obtain new active antitussive agents in this field.


(A)


(B)

As the inhibitor of parasympathetic system generally relieves convulsion of the bronchus, some of them exert an antitussive action. For example, 2′-diethylaminoethyl 1-phenylcyclopentane-1-carboxylate (C) and 2-aminoalkyl 3,3-diphenyl 2-propenoic acids (D) have antitussive effect. Therefore, it seemed of interest to synthesize some derivatives of 2-aminoethyl 3,3-diaryl-2-propenoates (F), in which R_1 represents thienyl group, R_2 the thienyl group or phenyl group, and NR′R″ the aliphatic amine or cycloamine. None of these compounds seem to have been prepared.

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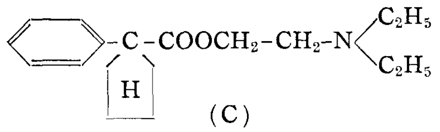
* Yoshida-Konoe-cho, Sakyo-ku, Kyoto (木村隆一, 藪内隆弘, 田村泰隆).

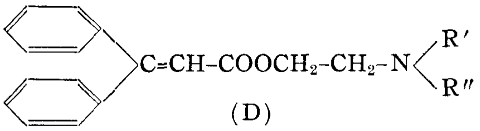
[1] Part III: This Bulletin, **7**, 175(1959).

[2] R. Kimura, T. Yabuuchi: *Ibid.*, **7**, 171(1959).

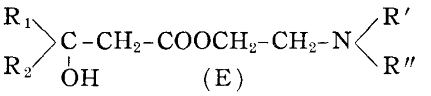
[3] *Idem.*: *Ibid.*, **6**, 159(1958).



(C)

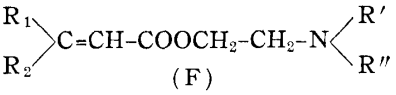


(D)



$$\begin{matrix}R_1\\R_2\end{matrix}>\underset{OH}{C}-CH_2-COOCH_2-CH_2-N<\begin{matrix}R'\\R''\end{matrix}$$

(E)



$$\begin{matrix}R_1\\R_2\end{matrix}>C=CH-COOCH_2-CH_2-N<\begin{matrix}R'\\R''\end{matrix}$$

(F)

A general synthetic route for these compounds is shown in Chart 1.

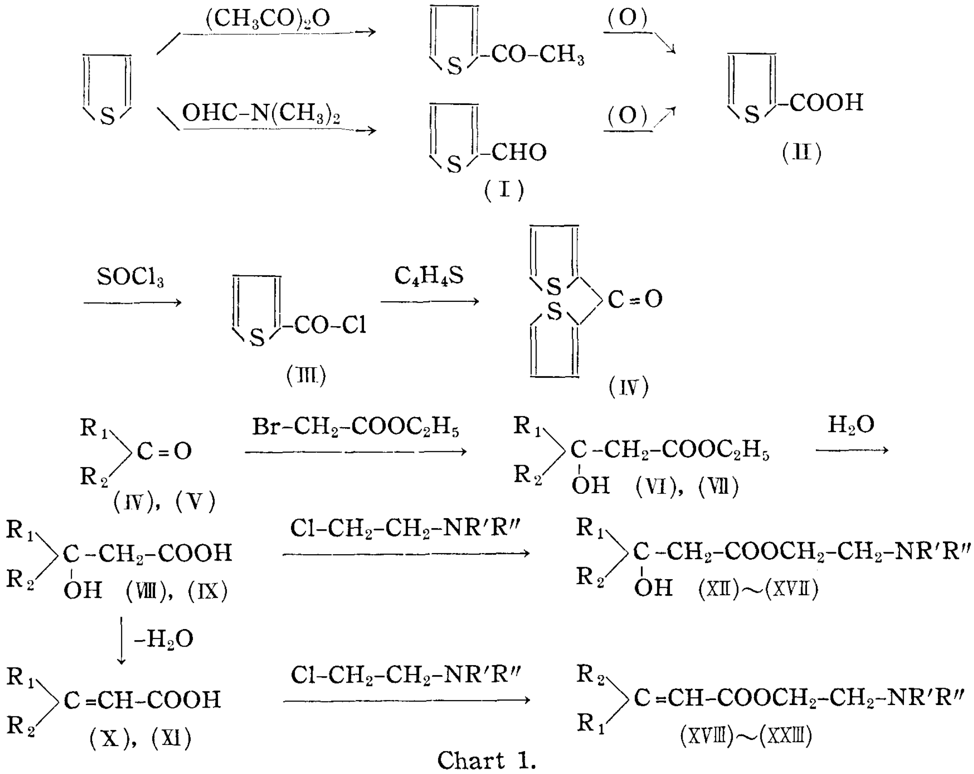


Chart 1.

Di(2-thienyl) ketone (IV)[4] and phenyl 2-thienyl ketone (V)[5] as starting materials were synthesized by the Friedel-Crafts condensation of thiophene with 2-thenoyl chloride (III) and benzoyl chloride, respectively. The condensation was more successfully carried out in the presence of anhydrous stannic chloride than anhydrous aluminum chloride as a condensation agent. 2-Thiophenecarboxylic acid (II) has generally been synthesized by oxidation of 2-acetylthiophene,[6] but it was confirmed that air oxidation process for 2-thiophenecarboxaldehyde in alkaline solution (medium) gave the corresponding carboxylic acid in the presence of silver oxide-copper oxide catalyst, in a good yield. Direct preparation of 2-thiophenecarboxaldehyde (I) from thiophene with dimethylformamide[7] was effected easily.

Furthermore, ethyl 3,3-di(2-thienyl)-3-hydroxypropanoate (VI) and ethyl 3-phenyl-3-hydroxypropanoate (VII) were synthesized by the Reformatsky reaction of ethyl 2-bromoethanoate with di(2-thienyl) ketone and phenyl 2-thienyl ketone, respectively. The reaction was carried out in the presence of zinc powder, with a small amount of copper powder and iodine, in a mixture of dehyd. benzene and toluene.

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[4] F. F. Blicke, F. E. Anderson : J. Am. Chem. Soc., **74**, 1733(1952).

[5] Org. Syntheses, Coll. Vol. II, 247.

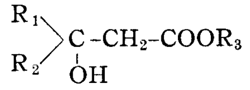
[6] H. D. Hartough, L. G. Conley : J. Am. Chem. Soc., **69**, 3096(1947), *et seq.*

[7] E. Campaigne, *et al.* : *Ibid.*, **75**, 989(1953).

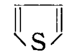
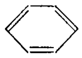
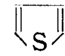
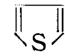
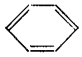
It was found that purification of zinc powder[8] with conc. sulfuric acid containing a few drops of nitric acid resulted in excellent results, otherwise in very poor yield. The esters thus obtained were hydrolyzed with 25% potassium hydroxide in methanol to the corresponding acids. Dehydration of 3,3-diphenyl-3-hydroxypropanoic acid was usually carried out by heating with formic acid,[9] while dehydration of both 3,3-di(2-thienyl)-3-hydroxypropanoic acid (VIII) and 3-phenyl-3-(2-thienyl)-3-hydroxypropanoic acid (IX) did not succeed in isolation of individuals from each reaction mixture due to resinous matter. It was found, however, that 3,3-di(2-thienyl)-2-propenoic acid (X) and 3-phenyl-3-(2-thienyl)-2-propenoic acid (XI) are obtained in a good yield by bubbling dry hydrogen chloride into cold chloroform suspension. These new compounds (VI to XI) are shown in Table I.

The compounds (VIII) to (VI) were esterified with 2-aminoethyl chloride in dry isopropanol, resulting in the corresponding new aminoesters as shown in Tables II and III.

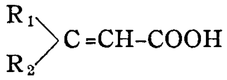
Table I. 3,3-Diarylpropanoic Acid and its Ethyl Esters



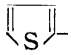
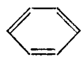
$$\begin{matrix}R_1\\R_2\end{matrix}\!\!>\underset{\displaystyle OH}{C}-CH_2-COOR_3$$

Compd. No.	R_1	R_2	R_3	m.p. (°C)	Yield* (%)	Crystn. Solvent	Appearance
(VI)			C_2H_5	49~50	63.8	EtOH	Colorless prisms
(VII)			C_2H_5	62~63	67.9	70% EtOH	Colorless needles
(VIII)			H	153.5	81.1	EtOH-benzene (1:4) mixt.	Colorless prisms
(IX)			H	171	87.9	〃	〃

* Calcd. on the basis of diaryl ketone or ethyl 3,3-diaryl-3-hydroxypropanoate



$$\begin{matrix}R_1\\R_2\end{matrix}\!\!>C=CH-COOH$$

Compd. No.	R_1	R_2	m.p. (°C)	Yield* (%)	Crystn. Solvent	Appearance
(X)			139.5 (d.)	87.3	Benzene-ligroine (3:1)	Colorless prisms
(XI)			147.5~148	91.4	〃	〃

* Calcd. on the basis of 3,3-diaryl-3-hydroxypropanoic acid

Experimental

2-Thiophenecarboxylic Acid (II)—A mixture of 10 g. of Ag_2O-CuO catalyst,[10] 10 g. of NaOH, and 250 cc. of water was placed in a 500-cc. three-necked flask equipped with a stirrer, a dropping funnel, and a thermometer. Stirring was started and 25.5 g. (0.25 mole) of 2-thiophenecarboxaldehyde was added to the mixture at 40° during 30 min., and stirring was continued for additional 5 hr. The reaction mixture was filtered and acidification of the filtrate with conc. HCl gave a precipitate, which was collected by suction. This mother liquor was extracted with ether and more 2-thiophenecarboxylic acid was obtained. The combined crude crystals were recrystallized from hot water to colorless prisms, m.p. 128~129°. Yield, 20 g.

Ethyl 3,3-Di(2-thienyl)-3-hydroxypropanoate (VI)—In a clean, dry three-necked flask of 500-cc. capacity, fitted with a mechanical stirrer, a 250-cc. dropping funnel, and a reflux condenser, the top of which was protected by a $CaCl_2$-tube, 16 g. of activated Zn dust, 1.5 g. of Cu dust, and few small crystals of iodine were placed. A solution of 38.4 g. (0.2 mole) of di(2-thienyl) ketone and 38 g. of ethyl 2-bromoethanoate[11] in 100 cc. of dehyd. benzene and 80 cc. of dehyd. toluene was placed in

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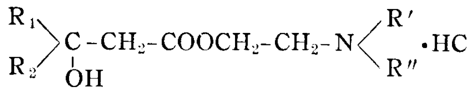
[8] L. F. Fieser, W. S. Johnson: J. Am. Chem. Soc., **62**, 575(1940).
[9] H. Ruppe: Ann., **395**, 136(1913).
[10] H. Narazaki, N. Ito: Tokyo Kôgyô Shikensho Hôkoku, **46**, 13(1951).
[11] Org. Syntheses, **23**, 37.

Table II. 2-Aminoethyl 3,3-Diaryl-3-hydroxypropanoates



$\begin{matrix}R_1\\R_2\end{matrix}\!>\underset{\mathrm{OH}}{\mathrm{C}}\text{-CH}_2\text{-COOCH}_2\text{-CH}_2\text{-N}\!<\!\begin{matrix}R'\\R''\end{matrix}\cdot\mathrm{HCl}$

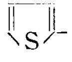
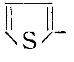
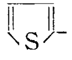
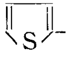
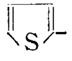
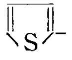
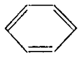
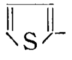
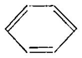
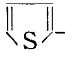
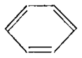
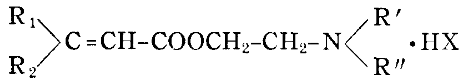
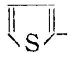
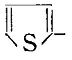
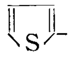
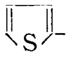
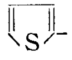
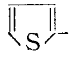
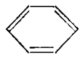
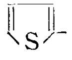
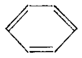
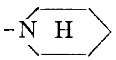
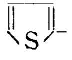
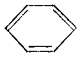
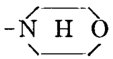
Compd. No.	R_1	R_2	NR'R''	m.p. (°C)	Crystn. Solvent	Appearance	Formula	Analysis (%)					
								C		H		N	
								Calcd.	Found	Calcd.	Found	Calcd.	Found
(XII)			$-N(C_2H_5)_2$	147~147.5	iso-PrOH	Colorless prisms	$C_{17}H_{24}O_3NClS_2$	52.34	52.37	6.207	6.332	3.594	3.323
(XIII)				166~167(d.)	MeOH-AcOEt	〃	$C_{18}H_{24}O_3NClS_2$	53.78	54.03	6.018	6.108	3.484	3.545
(XIV)			$-N(CH_3)_2$	128~129	$CHCl_3$ + benzene mixt.	Colorless needles	$C_{17}H_{22}O_3NClS$	57.35	57.20	6.233	6.353	3.938	3.666
(XV)			$-N(C_2H_5)_2$	122	〃	〃	$C_{19}H_{26}O_3NClS$	59.41	59.55	6.828	6.842	3.651	3.820
(XVI)				148~149	〃	Colorless prisms	$C_{20}H_{26}O_3NClS$	60.65	60.47	6.621	6.805	3.540	3.481
(XVII)				151.5(d.)	$CHCl_3$	Colorless needles	$C_{19}H_{24}O_4NClS$	57.33	57.09	6.082	6.224	3.522	3.381

Table III. 2-Aminoethyl 3,3-Diaryl-2-propenoates



$\begin{matrix}R_1\\R_2\end{matrix}\!>\mathrm{C{=}CH\text{-}COOCH_2\text{-}CH_2\text{-}N}\!<\!\begin{matrix}R'\\R''\end{matrix}\cdot\mathrm{HX}$

Compd. No.	R_1	R_2	NR'R''	HX	m.p. (°C)	Crystn. Solvent	Appearance	Formula	Analysis (%)					
									C		H		N	
									Calcd.	Found	Calcd.	Found	Calcd.	Found
(XVIII)			$-N(CH_3)_2$	picrate	166~167	MeOH	Yellow prisms	$C_{21}H_{20}O_9N_4S_2$	47.01	47.18	3.757	3.996	10.44	10.47
(XIX)			$-N(C_2H_5)_2$	〃	109.5~110.5	〃	〃	$C_{23}H_{24}O_9N_4S_2$	48.93	48.69	4.285	4.398	9.924	9.818
(XX)			$-N(CH_3)_2$	HCl	179~179.5	$CHCl_3$ + AcOEt mixt.	Colorless prisms	$C_{17}H_{20}O_2NClS$	60.41	60.54	5.969	6.050	4.148	4.034
(XXI)			$-N(C_2H_5)_2$	picrate	118~119	MeOH	Yellow prisms	$C_{25}H_{26}O_9N_4S$	53.76	53.88	4.692	4.951	10.030	9.882
(XXII)				HCl	160~161	$CHCl_3$ + AcOEt mixt.	Colorless prisms	$C_{20}H_{24}O_2NClS$	63.54	63.64	6.404	6.473	3.709	3.956
(XXIII)				〃	172	$CHCl_3$ + ligroine mixt.	〃	$C_{19}H_{22}O_3NClS$	60.02	60.32	5.839	6.130	3.689	3.869

the dropping funnel. About 20 cc. of this solution was added to the flask and warmed until the reaction started. The mixture was then stirred and the rest of the solution was introduced at such a rate that a gentle refluxing occurs, during about 1 hr. The flask was then cooled in an ice-bath and the content was poured into 300 cc. of ice-cold 10% H_2SO_4 with vigorous stirring. The acid layer was drawn off and the benzene solution was extracted with two 50-cc. portions of ice-cold 5% H_2SO_4. The benzene solution was washed consecutively with 25 cc. of cold 10% $NaHCO_3$ solution, 25 cc. of cold 5% H_2SO_4, and two 25-cc. portions of water. The combined acid extract was washed with two 50-cc. portions of benzene and the combined benzene solution was dried over anhyd. Na_2SO_4. After filtration, the solvent was removed by distillation under a diminished pressure on a water-bath. The residue was recrystallized from EtOH to colorless prisms, m.p. 49$\sim$50°. Yield, 36 g. *Anal.* Calcd. for $C_{13}H_{14}O_3S_2$: C, 55.27; H, 4.999. Found : C, 55.44; H, 5.289.

Ethyl 3-Phenyl-3-(2-thienyl)-3-hydroxypropanoate (VII)—This was prepared by the Reformatsky reaction of 37.6 g. (0.2 mole) of phenyl 2-thienyl ketone in the same manner as for ethyl 3,3-di(2-thienyl)-3-hydroxypropanoate. Recrystallization of crude crystals from 70% EtOH gave colorless needles, m.p. 62$\sim$63°. Yield, 37.5 g. *Anal.* Calcd. for $C_{15}H_{16}O_3S_2$: C, 65.17; H, 5.838. Found : C, 64.98; H, 5.913.

3,3-Di(2-thienyl)-3-hydroxypropanoic Acid (VIII)—A mixture of 28.2 g. (0.1 mole) of ethyl 3,3-di-(2-thienyl)-3-hydroxypropanoate and 25% KOH-MeOH solution was heated on a boiling water bath for 12 hr., 100 cc. of water was added to the residue obtained by removal of the solvent, and insoluble matter was removed by filtration. The filtrate was neutralized with 10% HCl under attentive cooling and the resulting crystals were collected by suction were recrystallized from benzene-EtOH to colorless prisms, m.p. 153.5°. Yield, 20.6 g. *Anal.* Calcd. for $C_{11}H_{10}O_3S_2$: C, 51.93; H, 3.965. Found: C, 52.09; H, 4.097.

3-Phenyl-3-(2-thienyl)-3-hydroxypropanoic Acid (IX)—This was prepared from 27.6 g. (0.1 mole) of ethyl 3-phenyl-3-(2-thienyl)-3-hydroxypropanoate by the same procedure as for 3,3-di(2-thienyl)-3-hydroxypropanoate. Recrystallization from a mixture of EtOH and benzene gave colorless prisms, m.p. 171° (decomp.). Yield, 21.8 g. *Anal.* Calcd. for $C_{13}H_{12}O_3S$: C, 62.84; H, 4.874. Found : C, 62.61; H, 4.860.

3,3-Di(2-thienyl)-2-propenoic Acid (X)—To a mixture of 12.7 g. (0.05 mole) of 3,3-di(2-thienyl)-3-hydroxypropanoic acid and 100 cc. of $CHCl_3$, dry HCl gas was introduced under cooling for 20 min. and the solvent was evaporated to dryness under a diminished pressure. The residue was recrystallized from a mixture of benzene-ligroine to colorless prisms, m.p. 139.5°(decomp.). Yield, 10.3 g. *Anal.* Calcd. for $C_{11}H_8O_2S_2$: C, 55.89; H, 3.411. Found : C, 55.83; H, 3.621.

3-Phenyl-3-(2-thienyl)-2-propenoic Acid (XI)—This was prepared from 12.4 g. (0.05 mole) of 3-phenyl-3-(2-thienyl)-3-hydroxypropanoic acid, following the same procedure as described for 3,3-di(2-thienyl)-3-hydroxypropanoic acid. Recrystallization from a mixture of benzene and ligroine gave colorless prisms, m.p. 147.5$\sim$148°. Yield, 10.1 g. *Anal.* Calcd. for $C_{13}H_{10}O_2S$: C, 67.78; H, 4.379. Found : C, 68.05; H, 4.561.

Syntheses of the Aminoethyl Esters (XII$\sim$XXIII)—Molar equivalents (0.03$\sim$0.05 mole) of 3,3-diaryl-3-hydroxypropanoic acids (VIII, IX) or 3,3-diaryl-2-propenoic acids (X, XI) and the basic chloride (2-dimethylamino-1-chloroethane,[12] 2-diethylamino-1-chloroethane,[12] 2-piperidino-1-chloroethane,[13] and 2-morpholino-1-chloroethane[14]) were dissolved in about 50 cc. of isopropanol, which had been dried over CaO, and refluxed on a water bath for 12 hr. The solvent was removed under a reduced pressure, the residue was washed with dehyd. ether, and the crude material was recrystallized from suitable solvent (see Tables II and III). The yield of recrystallized products was usually 50$\sim$65%.

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Summary

As some thiophene derivatives have interesting pharmacological action, 2-aminoethyl 3,3-diaryl-3-hydroxypropanoates and 2-aminoethyl 3,3-diaryl-2-propenoates having thiophene ring were synthesized. Esterification of 3,3-diaryl-3-hydroxypropanoic acids, prepared by the Reformatsky reaction of diaryl ketones, and 3,3-diaryl-2-propenoic acid prepared by dehydration of these hydroxypropanoic acid gave aminoethyl esters of the corresponding acids.

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[13] F. F. Blick, E. Maxwell : J. Am. Chem. Soc., **64**, 429(1942).
[14] J. P. Mason, H. W. Block : *Ibid.*, **62**, 1445(1940).