Summary

1,3-Dimethoxy-2-acetoacetyl-4-hydroxynaphthalene (I) was converted to 2-methyl-3-acetyl-5-methoxy-6-acetoxy-7,8-benzochromone (III) with zinc chloride and acetic anhydride. (III) was hydrolysed to 2-methyl-3-acetyl-5-methoxy-6-hydroxy-7,8-benzochromone (IV), then methylated to 2-methyl-3-acetyl-5,6-dimethoxy-7,8-benzochromone (V). Either 1-methoxy-2-acetyl-3,4-diacetoxynaphthalene (XI) or 1,3,4-triacetoxy-2-acetylnaphthalene (XII) was converted to 2-methyl-3-acetyl-5-hydroxy-6-acetoxy-7,8-benzochromone (XIII) by heating either at 160~180° with equimolar sodium amide in toluene. Methylation of (XIII) with diazomethane in the presence of excess of methanol produced the expected methyl ether, 2-methyl-3-acetyl-5-methoxy-6-acetoxy-7,8-benzochromone (III), but methylation of (XIII) with dimethyl sulfate and potassium carbonate in acetone unexpectedly afforded 2-methyl-3-acetyl-5-acetoxy-6-methoxy-7,8-benzochromone (XIV) which is an isomer of (III).

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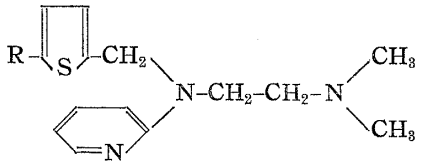
174. **Takahiro Yabuuchi**: Studies on Thiophene Derivatives. VI.*1 Syntheses of 3-Amino-1,1-di(2-thienyl)-1-alkanols and -1-alkenes.

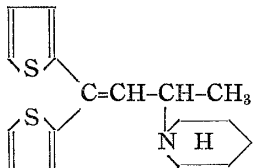
(*Chemical Research Institute, University of Kyoto**2)

Some compounds are known to become more active on nervous system and, at the same time, with less untoward side-effect, by introduction of halogen atom into the structure of the compound. For example, Chlorothen (A), in which chlorine was introduced into 5-position of thiophene ring of N,N-dimethyl-N'-(2-pyridyl)-N-(2-thenyl)ethylenediamine (Methapyrilene) (B), has more potent antihistamine effect than (B) compound without too much side-effects.

In the preceding paper,[1,2] the author reported on antitussive activity of 3-piperidino-1,1-di(2-thienyl)-1-butene (C) and its optical isomers, and it was found that this compound shows more potent antitussive action than codeine, morphine, or Methadone.



(A) R=Cl (B) R=H



(C)

Therefore, an attempt was made to synthesize 3-piperidino-1,1-di(5-chloro-2-thienyl)-1-alkenes (D), which have chlorine in 5-position of the thiophene ring in (C). Their benzene analogs were also synthesized to compare their pharmacological action with (D).

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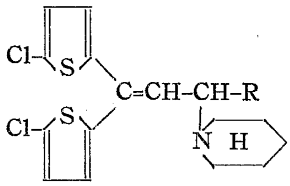
*1 This report constitutes a part of a series entitled "Studies on Thiophene Derivatives" by Ryuichi Kimura. Part V: This Bulletin, 8, 169(1960).

*2 Yoshida-konoe-cho, Sakyo-ku, Kyoto (藪内隆弘).

1) R. Kimura, T. Yabuuchi: This Bulletin, **7**, 171(1959).

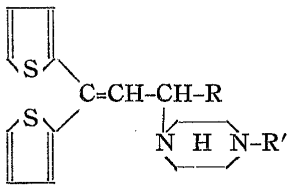
2) *Idem*: *Ibid.*, **7**, 175(1959).



(D) R=H or CH_3

It is frequently found that some derivatives of piperazine with actions on nervous system have not only more potent pharmacological action than the derivatives in which piperazine ring is replaced by alkylmonoamine or alkyldiamine in similar structure, but they also show less athwart side-effect than the latter. Especially, it is known that 1-(*p*-chlorobenzhydrol)-4-methylpiperazine, an antihistamine, also shows an antitussive action in animal test.

These interesting facts prompted the syntheses of 3-(N-alkylpiperazino)-1,1-di(2-thienyl)-1-alkenes (E), in which piperidyl group of 3-piperidino-1,1-di(2-thienyl)-1-butene is replaced with N-alkylpiperazyl group. None of (D) and (E) compounds seems to have been prepared.



(E) R=H or CH_3
R'=CH_3 or C_2H_5

A general synthetic route for 3-piperidino-1,1-di(5-chloro-2-thienyl)-1-alkenes (D) is shown in Chart 1.

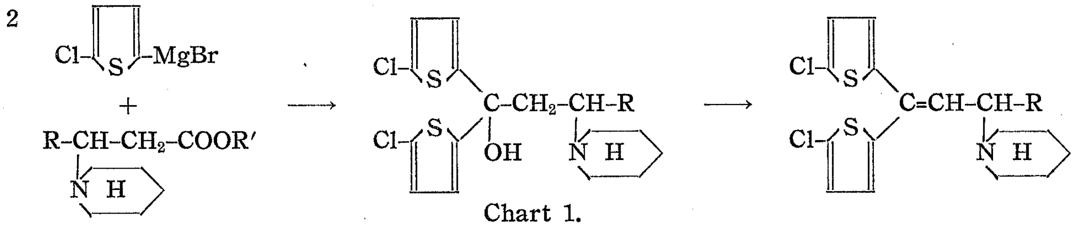


Chart 1.

3-Piperidino-1,1-di(5-chloro-2-thienyl)-1-alkanols were prepared by the condensation of 2-piperidinoalkane-1-carboxylic acid esters (see Table I) and a Grignard reagent prepared from 5-chloro-2-thienyl bromide and magnesium by the conventional method. The new compounds obtained are listed in Table II. These compounds were dehydrated by dissolving them in chloroform and introducing dry hydrogen chloride into the solutions, and various new derivatives of 3-piperidino-1,1-di(5-chloro-2-thienyl)-1-alkenes were prepared, which are shown in Table III.

Table I. 2-Aminoalkane-1-carboxylic Acid Esters
R_1-CH-CH_2-$COOR_2$
NR'R''

Compd. No.	R_1	R_1	NR'R''	Appearance	b.p. (C°/mm. Hg)
(I)	H	CH_3	-N H	Colorless oil	121～122/40
(II)	CH_3	〃	〃	〃	113～114/32
(III)	H	〃	-N H N-CH_3	〃	111～112/11
(IV)	CH_3	C_2H_5	〃	〃	110～111/5
(V)	H	CH_3	-N H N-C_2H_5	〃	126～128/12
(VI)	CH_3	C_2H_5	〃	〃	140～141/17

Table II. 3-Amino-1,1-diaryl-1-alkanols $R_1R_1>C(OH)\text{-}CH_2\text{-}CH(NR'R'')\text{-}R_2$

Compd. No.	R_1	R_2	NR′R″	m.p. (°C)	Appearance* (Crystn. Solvent)	Mol. formula	Analysis (%) C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
(VII)	Cl-C_4H_2S- (thienyl)	H	-N(piperidino) $-NC_5H_{10}$	200~201 (HBr Salt)	Prisms (EtOH + AcOEt)	$C_{16}H_{19}ONCl_2S_2\cdot HBr$	42.02	42.13	4.41	4.40	3.06	3.14
(VIII)	Cl-C_6H_4-	〃	〃	210~211 (〃)	〃	$C_{20}H_{23}ONCl_2\cdot HBr$	53.95	54.21	5.41	5.68	3.15	3.31
(IX)	Cl-C_4H_2S- (thienyl)	CH_3	〃	241~242 (HCl Salt)	〃	$C_{17}H_{21}ONCl_2S_2\cdot HCl$	49.70	49.42	5.40	5.64	3.41	3.54
(X)	Cl-C_6H_4-	〃	〃	251~252 (〃)	〃	$C_{21}H_{25}ONCl_2\cdot HCl$	60.81	60.80	6.32	6.44	3.38	3.57
(XI)	C_4H_3S- (thienyl)	H	-N(piperazine)N-CH_3	92~93 (Free base)	Needles (ligroine)	$C_{16}H_{22}ON_2S_2$	59.56	59.38	6.88	6.98	8.69	8.46
(XII)	〃	〃	-N(piperazine)N-C_2H_5	75~76 (〃)	〃	$C_{17}H_{24}ON_2S_2$	60.67	60.90	7.19	7.29	8.33	8.18
(XIII)	〃	CH_3	-N(piperazine)N-CH_3	87~88 (〃)	〃	$C_{17}H_{24}ON_2S_2$	60.67	60.71	7.19	7.30	8.33	8.24
(XIV)	C_6H_5-	H	〃	127~128 (〃)	〃	$C_{20}H_{26}ON_2$	77.38	77.33	8.44	8.63	9.03	9.15

* All are white crystals.

Table III. 3-Amino-1,1-diaryl-1-alkenes $R_1R_1>C{=}CH\text{-}CH(NR'R'')\text{-}R_2$

Compd. No.	R_1	R_2	NR′R″	m.p. (°C) (HCl Salt)	Appearance*	Mol. formula	Analysis (%) C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
(XV)	Cl-C_4H_2S- (thienyl)	H	-N(piperidino) $-NC_5H_{10}$	192~193	Prisms	$C_{16}H_{17}NS_2Cl_2\cdot HCl$	48.68	48.51	4.59	4.47	3.55	3.48
(XVI)	Cl-C_6H_4-	〃	〃	191~192	〃	$C_{20}H_{21}NCl_2\cdot HCl$	62.76	63.04	5.79	5.98	3.66	3.92
(XVII)	Cl-C_4H_2S- (thienyl)	CH_3	〃	195~196	Needles	$C_{17}H_{19}NS_2Cl_2\cdot HCl$	49.94	49.71	4.93	5.18	3.43	3.71
(XVIII)	Cl-C_6H_4-	〃	〃	249~250	〃	$C_{21}H_{23}NCl_2\cdot HCl$	63.58	63.38	6.10	6.08	3.53	3.77
(XIX)	C_4H_3S- (thienyl)	H	-N(piperazine)N-CH_3	196~197	Prisms	$C_{16}H_{20}N_2S_2\cdot H_2O\cdot 2HCl$	48.60	48.31	6.12	6.41	7.08	6.78
(XX)	〃	〃	-N(piperazine)N-C_2H_5	208~209	〃	$C_{17}H_{22}N_2S_2\cdot H_2O\cdot 2HCl$	49.87	50.14	6.40	6.20	6.84	6.91
(XXI)	〃	CH_3	-N(piperazine)N-CH_3	185~186	Needles	$C_{17}H_{22}N_2S_2\cdot H_2O\cdot 2HCl$	49.87	49.71	6.40	6.55	6.84	7.00
(XXII)	C_6H_5-	H	〃	226~227	Prisms	$C_{20}H_{24}N_2\cdot H_2O\cdot 2HCl$	62.66	62.39	7.36	7.56	7.31	7.49

* Crystallized from $CHCl_3$–AcOEt mixture. All are white crystals.

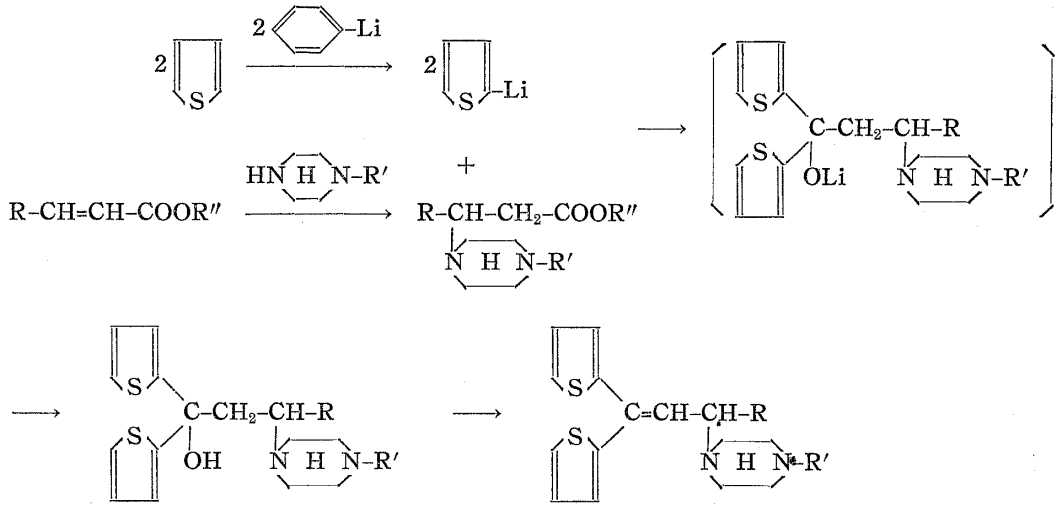


Chart 2.

Synthetic method for 3-(N-alkylpiperazino)-1,1-di(2-thienyl)-1-alkenes (E) is shown in Chart 2.

3-(N-Alkylpiperazino)-1,1-di(2-thienyl)-1-alkanols were prepared from 2-(N-alkylpiperazino)alkane-1-carboxylic acid esters (see Table I) and thiophene by the lithium method. 2-Thienyllithium was prepared from thiophene and phenyllithium, obtained from bromobenzene and lithium, and condensation of 2-thienyllithium with 2-(N-alkylpiperazino)-alkane-1-carboxylic acid esters gave 3-(N-alkylpiperazino)-1,1-di(2-thienyl)-1-alkanols. Benzene analogs of these compounds were also prepared by condensation of phenylmagnesium bromide and 2-(N-alkylpiperazino)alkane-1-carboxylic acid ester. The above new compounds are listed in Table II. These carbinols were dehydrated by bubbling dry hydrogen chloride into their cold chloroform solution. The new compounds obtained are shown in Table III.

Experimental

Syntheses of 2-Aminoalkane-1-carboxylic Acid Esters (I~VI)—Molar equivalent of either methyl crotonate, ethyl crotonate, or methyl acrylate was mixed with one of piperidine, N-methylpiperazine, or N-ethylpiperazine, the mixture was refluxed in an oil bath for 5 hr., and the pure esters were obtained by fractional distillation of the reaction products, as listed in Table I.

3-Piperidino-1,1-di(5-chloro-2-thienyl)-1-propanol (VII)—To an Et_2O solution of the Grignard reagent, prepared from 29.6 g. (0.15 mole) of 5-chloro-2-bromothiophene and 3.6 g. (0.15 atom) of Mg in 30 cc. of dehyd. Et_2O, 8.6 g. (0.05 mole) of methyl β-piperidinopropionate in 10 cc. of dehyd. Et_2O was dropped in gradually with stirring at 0°, the mixture was boiled under reflux for 5 hr., and kept overnight at room temperature. After cool, 25 g. of crushed ice was added, followed by 25 cc. of 25% NH_4Cl solution, and AcOH was added dropwise with stirring until the solution became acid to litmus. A precipitate collected by suction was washed with Et_2O and recrystallized from a mixture of EtOH and AcOEt to white prisms, m.p. 200~201° (hydrobromide). Yield, 4 g.

3-Piperidino-1,1-di(*p*-chlorophenyl)-1-propanol (VIII) was prepared by the method described for (VII) (see Table II).

3-Piperidino-1,1-di(5-chloro-2-thienyl)-1-butanol (IX)—A solution of 9.3 g. (0.05 mole) of methyl β-piperidinobutyrate in 10 cc. of dehyd. Et_2O was added dropwise into Et_2O solution of the Grignard reagent, prepared from 29.6 g. (0.15 mole) of 5-chloro-2-bromothiophene and 3.6 g. (0.15 mole) of Mg in 70 cc. of dehyd. Et_2O, stirred and cooled in an ice bath at 0°. The reaction mixture was boiled under reflux for 2 hr., kept overnight at room temperature, and 50 cc. of 25% NH_4Cl solution was added gradually with stirring under cooling. After pouring the whole mixture into ice water, the Et_2O layer was separated and the aqueous layer was extracted with Et_2O. Crushed ice was added to the combined extract, which was acidified with 10% HCl and insoluble matter in the aqueous phase was removed by Et_2O, The aqueous layer was made alkaline with NH_4OH under cooling and extracted with Et_2O. The Et_2O extract was dried over anhyd. Na_2SO_4 and evaporated. To the

residue dissolved in $CHCl_3$, 25% EtOH-HCl was added under cooling until the solution became neutral and the solvent was evaporated to dryness under a diminished pressure. The residue was recrystallized from a mixture of EtOH and AcOEt to white prisms, m.p. 241~242° (hydrochloride). Yield, 7 g.

3-Piperidino-1,1-di(*p*-chlorophenyl)-1-butanol (X) was prepared in the same manner as for (IX) (see Table II).

Syntheses of 3-(N-Alkylpiperazino)-1,1-di(2-thienyl)-1-alkanols (XI~XIII)—Preparation of 3-(N-methylpiperazino)-1,1-di(2-thienyl)-1-propanol (XI): A flask equipped with a stirrer, a reflux condenser carrying a nitrogen inlet, a thermometer, and a dropping funnel was swept with dry O_2-free N_2, and 100 cc. of dehyd. Et_2O was placed in the flask. While the flow of N_2 continued, 2.1 g. (0.3 atom) of Li metal cut into small pieces was added into the flask. The stirrer was started and a solution of 23.5 g. (0.15 mole) of bromobenzene in 30 cc. of dehyd. Et_2O was added to the Et_2O solution at such a rate as to maintain a constant reflux. After addition of bromobenzene, refluxing was continued for additional 2 hr., the flask was chilled in an ice bath, and a slow stream of N_2 was led into the flask. Dehyd. Et_2O solution of 12.5 g. (0.15 mole) of thiophene was added to the flask, the mixture was refluxed for 2 hr., chilled to −20° in a dry-ice bath, and then 9.3 g. (0.05 mole) of methyl β-(N-methylpiperazino)propionate in 10 cc. of dehyd. Et_2O was gradually added to the mixture. Stirring was continued for additional 2 hr. at room temperature and the reaction mixture was allowed to stand overnight. After pouring the reaction mixture into ice water, the Et_2O layer was separated and the aqueous layer was extracted with Et_2O. The combined extract was dried over anhyd. Na_2SO_4 and removal of the solvent gave a dark brown material. Recrystallization of the crude product so obtained from ligroine gave white needles, m.p. 92~93°. Yield, 9.5 g.

3-(N-Ethylpiperazino)-1,1-di(2-thienyl)-1-propanol (XII) and 3-(N-methylpiperazino)-1,1-di(2-thienyl)-1-butanol (XIII) were prepared in the same way as for (XI) (see Table II).

3-(N-Methylpiperazino)-1,1-diphenyl-1-propanol (XIV)—A solution of 9.3 g. (0.05 mole) of methyl β-(N-methylpiperazino)propionate dissolved in equal quantity of dehyd. Et_2O was added gradually to Et_2O solution of the Grignard reagent, prepared from 20 g. of bromobenzene and 3.3 g. of Mg, and stirred and cooled in a bath at 0°. After stirring in the cold for 1 hr., the mixture was heated under reflux for 2 hr. and then kept overnight at room temperature. The mixture was poured with stirring into 30 g. of crushed ice and 30 cc. of 25% NH_4Cl solution, the Et_2O layer was separated, and the aqueous layer was extracted with Et_2O. The combined extract was dried over anhyd. Na_2SO_4 and removal of the solvent gave a dark material. Recrystallization of the crude product from ligroine gave white needles, m.p. 127~128°. Yield, 10.2 g.

3-Piperidino-1,1-di(5-chloro-2-thienyl)-1-propene (XV)—The Grignard reagent prepared from 29.6 g. of 2-chloro-5-bromothiophene and 3.3 g. of Mg was condensed with 8.6 g. (0.05 mole) of methyl β-piperidinopropionate, and the decomposition of the complex with NH_4Cl solution gave the crude 3-piperidino-1,1-di(5-chloro-2-thienyl)-1-propanol.

After pouring the reaction mixture into ice water, Et_2O layer was separated and the aqueous layer was extracted with Et_2O. The combined extract was acidified with HCl under cooling and insoluble mater in the aqueous phase was removed by shaking with Et_2O. The aqueous layer was made alkaline with NH_4OH with cooling and extracted with Et_2O. The Et_2O extract was dried over anhyd. Na_2SO_4 and Et_2O was completely evaporated. Dry HCl gas was introduced and saturated into the solution of the residue dissolved in $CHCl_3$ (50 cc.), and the solvent was evaporated to dryness under a diminished pressure. The residue was recrystallized from a mixture of $CHCl_3$ and AcOEt to white prisms, m.p. 192~193°. Yield, 4.3 g.

3-Piperidino-1,1-di(*p*-chlorophenyl)-1-propene (XVI) was prepared in a similar manner as for (XV) (see Table III).

3-Piperidino-1,1-di(5-chloro-2-thienyl)-1-butene (XVII)—To a mixture of 4.7 g. (0.01 mole) of 3-piperidino-1,1-di(5-chloro-2-thienyl)-1-butanol hydrobromide and 20 cc. of $CHCl_3$, 15 cc. of 10% NH_4OH was added with shaking, the $CHCl_3$ layer was separated, and the aqueous layer was extracted with $CHCl_3$. The combined extract was dried over anhyd. Na_2SO_4 and dry HCl gas was saturated under cooling. The residue obtained by evaporation of the solvent under a diminished pressure was recrystallized from a mixture of $CHCl_3$ and AcOEt to white needles, m.p. 195~196°. Yield, 2.8 g.

3-Piperidino-1,1-di(*p*-chlorophenyl)-1-butene (XVIII) was prepared in the same manner as for (XVII) (see Table III).

Syntheses of 3-(N-Alkylpiperazino)-1,1-diaryl-1-alkenes (XIX~XXII)—Preparation of 3-(N-methylpiperazino)-1,1-di(2-thienyl)-1-butene (XXI): Dry HCl gas was introduced and saturated into a cooled solution of 6.7 g. (0.02 mole) of 3-(N-methylpiperazino)-1,1-di(2-thienyl)-1-butanol in 50 cc. of $CHCl_3$ and the solvent was evaporated under a reduced pressure. The residue obtained was recrystallized from a mixture of $CHCl_3$ and AcOEt to white needles, m.p. 185~186°. Yield, 5.4 g.

3-(N-Methylpiperazino)-1,1-di(2-thienyl)-1-propene (XIX), 3-(N-ethylpiperazino)-1,1-di(2-thienyl)-1-propene (XX), and 3-(N-methylpiperazino)-1,1-diphenyl-1-propene (XXII) were prepared in the same way as for (XXI).

The author is deeply grateful to Prof. Dr. T. Takahashi, Pharmaceutical Institute, University of Kyoto, for his kind encouragement and especially to Prof. Dr. H. Saikachi, Pharmaceutical Institute, University of Kyushu, for his helpful guidance and advice througout this work. The author is indebted to the Analysis Center of the University of Kyoto for microanalysis.

Summary

In the hope of finding more active antitussives that exhibit less side-effects than 3-piperidino-1,1-di(2-thienyl)-1-butene, which also possesses potent antitussive effect, 3-amino-1,1-di(5-chloro-2-thienyl)-1-alkanols and -1-alkenes, and 3-(N-alkylpiperazino)-1,1-di(2-thienyl)-1-alkanols and -1-alkenes were synthesized. Carbinols were prepared by the condensation of 5-chloro-2-thienylmagnesium bromide and 2-piperidinoalkane-1-carboxylic acid ester, or of 2-thienyllithium and 2-(N-alkylpiperazino)alkene-1-carboxylic acid ester, and the products were dehydrated with hydrogen chloride to alkenes.

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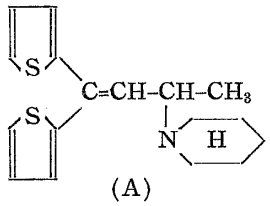
175. **Takahiro Yabuuchi**: Studies on Thiophene Derivatives. VII.*1 Syntheses of 2-Amino-1-(2-thienyl)-1-alkanols and Aminodiarylalkanes.

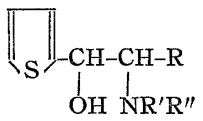
(*Chemical Research Institute, University of Kyoto**2)

It has been reported that 3-piperidino-1,1-di(2-thienyl)-1-butene (A) has a more potent antitussive action than morphine or Methadone,[1~3] and that the action is stronger than that of benzene analogs in which thienyl group has been replaced with phenyl group.

This interesting result prompted the synthesis of thiophene derivatives having a structure similar to ephedrine which is commonly used as an antitussive, in order to compare them in the pharmacological field, and consequently an attempt was made to synthesize 2-amino-1-(2-thienyl)-1-alkanols (B : R=H, CH_3 or phenyl). The synthetic method for these compounds is shown in Chart 1.



(A)



(B)

Thienyl alkyl ketones were prepared from thiophene and acetic anhydride, propionyl chloride, or phenylacetyl chloride by the Friedel-Crafts reaction. These three compounds

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*1 This constitutes a part of a series entitled "Studies on Thiophene Derivatives" by Ryuichi Kimura. Part VI : This Bulletin, 8, 1041(1960).

*2 Yoshida-konoe-cho, Sakyo-ku, Kyoto (藪内隆弘).

1) K. Kasé, *et al.* : This Bulletin, **3**, 394(1955).
2) R. Kimura, T. Yabuuchi : *Ibid.*, **7**, 171(1959).
3) *Idem* : *Ibid.*, **7**, 175(1959).