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.

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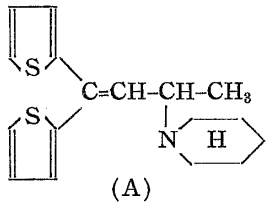
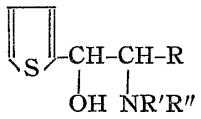
It has been reported that 3-piperidino-1,1-di(2-thienyl)-1-butene (A) has a more potent antitussive action than morphine or Methadone,[1~3] and that the action is stronger than that of benzene analogs in which thienyl group has been replaced with phenyl group.

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).

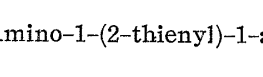
*2 Yoshida-konoe-cho, Sakyo-ku, Kyoto (藪内隆弘).

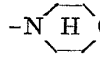
1) K. Kasé, *et al.* : This Bulletin, **3**, 394(1955).
2) R. Kimura, T. Yabuuchi : *Ibid.*, **7**, 171(1959).
3) *Idem* : *Ibid.*, **7**, 175(1959).

TABLE I. 2-Amino-1-(2-thienyl)-1-alkanones 

Compd. No.	R	NR′R″	Appearance	Free base b.p. (°C/mm. Hg)	Hydrochloride m. p. (°C)
(VII)	H	$-N(CH_3)_2$	Orange oil	150/10	
(VIII)	〃		Yellow oil	145～146/6	
(IX)	〃		Light yellow oil	161～163/6	
(X)	CH_3	$-N(CH_3)_2$	Orange oil	103～107/20	
(XI)	〃		〃	147～153/6	
(XII)	〃		Yellow oil	158～160/7	
(XIII)		$-N(CH_3)_2$	White prisms*		231
(XIV)	〃		〃 *		247
(XV)	〃		〃 *		249

* Recrystallized from $CHCl_3$–AcOEt mixture.

TABLE II. 2-Amino-1-(2-thienyl)-1-alkanols 

Compd. No.	R	NR′R″	m.p. (°C)	Crystn. solvent	Appearance*	Mol. formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
(XVI)	H		210 (dec.)	EtOH+AcOEt	needles	$C_{11}H_{17}ONS \cdot HCl$	53.31	7.32	5.65	53.47	7.53	5.61
(XVII)	〃		201 (〃)	〃	plates	$C_{10}H_{15}O_2NS \cdot HCl$	48.08	6.46	5.61	48.13	6.66	5.69
(XVIII)	CH_3		233 (〃)	〃	needles	$C_{12}H_{19}ONS \cdot HCl$	55.04	7.70	5.35	55.16	7.75	5.39
(XIX)	〃		212	〃	〃	$C_{11}H_{17}O_2NS \cdot HCl$	50.08	6.88	5.31	50.23	6.95	5.38
(XX)		$-N(CH_3)_2$	221～222	MeOH	〃	$C_{14}H_{17}ONS \cdot HCl$	59.24	6.39	4.94	59.21	6.20	4.79
(XXI)	〃		225	〃	prisms	$C_{17}H_{21}ONS \cdot HCl$	63.04	6.85	4.32	63.34	6.68	4.51
(XXII)	〃		219～220 (dec.)	$CHCl_3$+AcOEt	〃	$C_{16}H_{19}O_2NS \cdot HCl$	58.97	6.19	4.30	58.72	6.47	4.30

* All are white crystals.

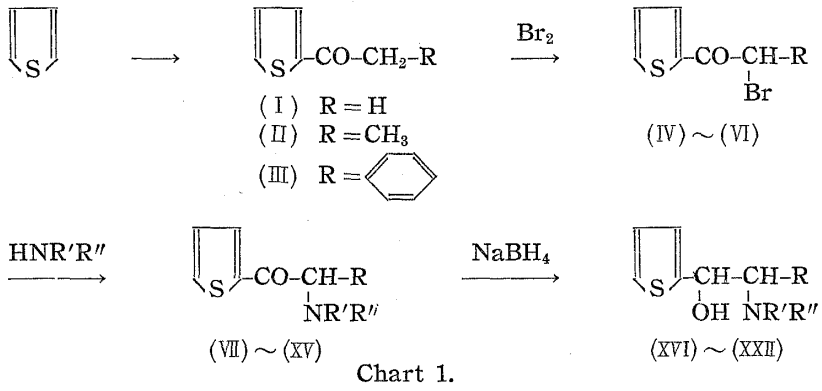
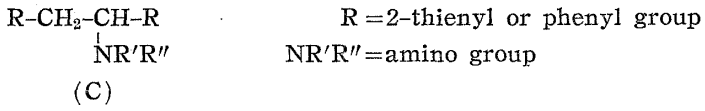


Chart 1.

were then brominated with bromine under cooling to 2-bromo-1-(2-thienyl)-1-alkanones and the bromine in these compounds was replaced by various amines, resulting in the formation of 2-amino-1-(2-thienyl)-1-alkanones shown in Table I. The amino ketones obtained were reduced with sodium borohydride to the corresponding 2-amino-1-(2-thienyl)-1-alkanols (B) shown in Table II.

It is known that some compounds in which hydroxyl group has been reduced exert more potent antitussive or analgesic action than the corresponding hydroxyl derivatives, as seen in β-(*o*-methoxyphenyl)isopropylamine or 2-dimethylamino-1,2-diphenylethane, etc. Therefore, attempt was made to synthesize aminodiarylalkanes, shown by the general formula (C), in order to observe the relationship between chemical structure and pharmacological activity. None of the (B) and (C) compounds seems to have been prepared.



(C)

The synthetic method for (C) compound is shown in Chart 2.

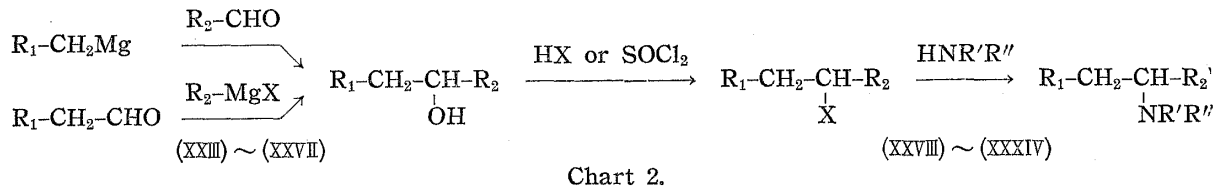


Chart 2.

Either arylalkyl- or aryl-magnesium halide was condensed with one of thienoaldehyde, phenoaldehyde, or β-phenylpropionaldehyde to diarylalkanols listed in Table III. The hydroxyl group in the compounds obtained was replaced by various amines after halogenation with hydrogen chloride, hydrogen bromide, or thienyl chloride. The resulting aminodiarylalkanes are listed in Table IV.

Experimental

Syntheses of 2-Amino-1-(2-thienyl)-1-alkanones (VII～XV)—To a dehyd. Et_2O solution of either 1-(2-thienyl)-1-ethanone*3 (I), 1-(2-thienyl)-1-propanone*4 (II), or 1-(2-thienyl)-2-phenyl-1-ethanone*5 (III), molar equivalent of Br_2 was added dropwise with stirring under cooling, stirring was continued for additional 1 hr., and the solvent was evaporated to dryness under a diminished pressure. A dehyd.

*3 This was prepared from thiophene and Ac_2O (catalyst, H_3PO_4); b.p_4 77°.

*4 This was prepared from the Friedel-Crafts reaction of thiophene and propionyl chloride (catalyst, $SnCl_4$); b.p. 223～225°.

*5 This was prepared from thiophene and phenylacetyl chloride (catalyst, $SnCl_4$), b.p_{12} 196～198; m.p. 49～50°.

Table III. Diarylalkanols R_1-CH(OH)-R_2

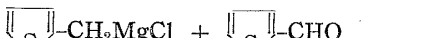
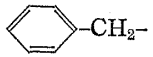
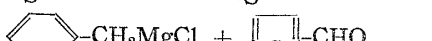
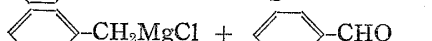
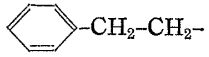
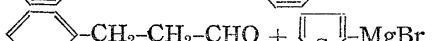
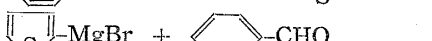
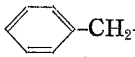
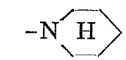
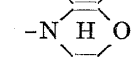
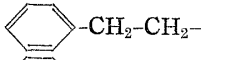
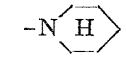
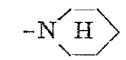
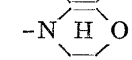
Compd. No.	R_1	R_2	Prep. method	Appearance	b.p. (°C/mm. Hg)	m.p. (°C)
(XXIII)				Viscous oil	128~130/8	
(XXIV)				White prisms	190~193/30	52.5~53
(XXV)	〃			〃	177/15	65~66
(XXVI)				Viscous oil	115~116/11	
(XXVII)				White prisms		57~58

Table IV. Aminodiarylalkanes R_1-CH($NR'R''$)-R_2 ·HX

Compd. No.	R_1	R_2	$NR'R''$	HX	m.p. (°C)	Crystn. Solvent	Appearance	Mol. formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
(XXVIII)				picrate	178	EtOH	Yellow prisms	$C_{23}H_{24}O_7N_4S$	55.18	4.83	11.19	55.46	5.095	11.30
(XXIX)	〃	〃		HCl	203	EtOH+ AcOEt	White prisms	$C_{16}H_{20}ONClS$	62.01	6.51	4.52	61.79	6.69	4.33
(XXX)	〃		〃	〃	219	EtOH	〃	$C_{18}H_{22}ONCl$	71.15	7.30	4.61	70.95	7.24	4.47
(XXXI)				picrate	146~147	〃	Yellow prisms	$C_{24}H_{26}O_7N_4S$	56.02	5.09	10.88	55.76	5.23	11.13
(XXXII)		〃	$-N(CH_3)_2$	〃	172	〃	Yellow plates	$C_{19}H_{18}O_7N_4S$	51.12	4.06	12.55	51.19	4.21	12.71
(XXXIII)	〃	〃		〃	186	〃	Yellow prisms	$C_{22}H_{22}O_7N_4S$	54.31	4.56	11.51	54.47	4.72	11.66
(XXXIV)	〃	〃		〃	199	〃	Yellow needles	$C_{21}H_{20}O_8N_4S$	51.63	4.13	11.47	51.89	4.19	11.40

benzene solution of the residue so obtained (IV～VI) and 2 moles of the amine were heated on a steam bath for 8 hr., except for dimethylamine (at 100° in a sealed tube). After cool, the separated crystals were removed by filtration and pure amino ketones (VII～XII) were obtained by distillation of the filtrate. 2-Amino-1-(2-thienyl)-2-phenyl-1-ethanones (XIII～XV) were obtained as the hydrochloride by neutralization with 20% HCl-EtOH solution (see Table I).

Syntheses of 2-Amino-1-(2-thienyl)-1-alkanols (XVI～XXII)—A dehyd. EtOH solution of 2/3 mole of $NaBH_4$ was added to dehyd. EtOH solution of 2-amino-1-(2-thienyl)-1-alkanones (VII～XV) and the mixture was allowed to stand for over 1 hr. The residue obtained by removal of EtOH was made alkaline with 20% NaOH solution, extracted with Et_2O, and the Et_2O extract was dried over anhyd. Na_2SO_4. The residue obtained by evaporation of the solvent was neutralized with 20% HCl-EtOH, the solvent was removed under a diminished pressure, and the crude material was recrystallized from a suitable solvent (see Table II). The yield of pure products was usually 45～75%.

Syntheses of Diarylalkanols (XXIII～XXVII)—Preparation of 1,2-di(2-thienyl)-1-ethanol (XXIII): To the Grignard reagent, prepared from 17 g. of 2-thenyl chloride[4] and 2.5 g. of Mg in a usual manner, dehyd. Et_2O solution of 11.2 g. (0.1 mole) of 2-thiophenecarboxaldehyde[5] was added gradually with stirring at 0° and the reaction mixture was allowed to stand overnight. To the reaction flask, 50 cc. of 25% NH_4Cl solution was added with stirring under cooling, the Et_2O layer was separated, the aqueous layer was extracted with Et_2O, and the combined extract was dried over anhyd. Na_2SO_4. Distillation of the crude product obtained by removal of the solvent gave viscous oil, b.p_8 128～130°. Yield, 10.9 g.

2-Phenyl-1-(2-thienyl)-1-ethanol (XXIV), 1,2-diphenyl-1-ethanol (XXV), 3-phenyl-1-(2-thienyl)-1-propanol (XXVI), and phenyl-(2-thienyl)methanol (XXVII) were prepared by the same method as for (XXIII) (see Table III). The yield of each product was usually 50～70%.

Syntheses of Aminodiarylalkanes (XXVIII～XXXIV)—Preparation of 2-morpholino-2-(2-thienyl)-1-phenylethane (XXIX): Dry HCl gas was saturated in a mixture of 9.9 g. (0.05 mole) of 2-phenyl-1-(2-thienyl)-1-ethanol, 3 g. of anhyd. $CaCl_2$, and 30 cc. of petr. ether under cooling. After filtration, the solvent was removed by distillation under a diminished pressure. To the residue was added 8.7 g. of morpholine dissolved in 20 cc. of dehyd. benzene and the mixture was heated on a steam bath for 10 hr. After cool, the separated crystals were removed by filtration. The residue obtained by evaporation of the filtrate was neutralized with 20% EtOH-HCl and the solvent was evaporated to dryness under a diminished pressure. Recrystallization of the crude material from a mixture of EtOH and AcOEt gave white prisms, m.p. 203°. Yield, 4.9 g.

2-Piperidino-2-(2-thienyl)-1-phenylethane (XXVIII) and 2-morpholino-1,2-diphenylethane (XXX) were prepared from 1,2-diaryl-1-ethanol in the same manner as for (XXIX). 3-Piperidino-3-(2-thienyl)-1-phenylpropane (XXXI) was prepared by chlorination with $SOCl_2$ and dimethyl(2-thienyl)phenylmethane (XXXII), piperidino(2-thienyl)phenylmethane (XXXIII), and morpholino(2-thienyl)phenylmethane (XXXIV) were prepared by bromination with dry HBr, followed by amination (see Table IV). The yield of the pure product was usually 30～60%.

The author is deeply grateful to Prof. Dr. T. Takahashi, Faculty of Pharmacy, Kyoto University for his kind encouragement and especially to Prof. Dr. H. Saikachi, Pharmaceutical Institute, University of Kyushu, for his helpful guidance and advice throughout this work. The author wishes to thank Mr. Yasutaka Tamura for his technical assistance in these experiments and to the Analysis Center of the Kyoto University for microanalyses.

Summary

It has been found that 3-piperidino-1,1-di(2-thienyl)-1-butene exhibits a potent antitussive effect. It seemed interesting to investigate pharmacological action of 2-amino-1-(2-thienyl)-1-alkanols, in which phenyl group in ephedrine, long used as an antitussive, is substituted with thienyl group. The compounds were prepared by reduction of 2-amino-1-(2-thienyl)-1-alkanones obtained by amination of 2-bromo-1-(2-thienyl)-1-alkanones. Aminodiarylalkanes were also synthesized in the hope of finding a more potent antitussive. These compounds were synthesized by halogention of diarylalkanols followed by amination.

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4) F. F. Blick, T. H. Burckhalter: J. Am. Chem. Soc., **64**, 478(1942).
5) E. Campaigne, *et al.*: *Ibid.*, **75**, 989(1953).