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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, CH₃ or phenyl). The synthetic method for these compounds is shown in Chart 1.

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) K. Kasé, *et al.* : This Bulletin, 3, 394(1955).

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

TABLE I. 2-Amino-1-(2-thienyl)-1-alkanones $\text{S} \begin{array}{c} \diagup \\ \diagdown \end{array} \text{CO-CH-R}$

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)	"	-N $\begin{array}{c} \diagup \\ \diagdown \end{array}$ H	Yellow oil	145~146/6	
(IX)	"	-N $\begin{array}{c} \diagup \\ \diagdown \end{array}$ H O	Light yellow oil	161~163/6	
(X)	CH ₃	-N(CH ₃) ₂	Orange oil	103~107/20	
(XI)	"	-N $\begin{array}{c} \diagup \\ \diagdown \end{array}$ H	"	147~153/6	
(XII)	"	-N $\begin{array}{c} \diagup \\ \diagdown \end{array}$ H O	Yellow oil	158~160/7	
(XIII)		-N(CH ₃) ₂	White prisms*		231
(XIV)	"	-N $\begin{array}{c} \diagup \\ \diagdown \end{array}$ H	"	"	247
(XV)	"	-N $\begin{array}{c} \diagup \\ \diagdown \end{array}$ H O	"	"	249

* Recrystallized from CHCl₃-AcOEt mixture.TABLE II. 2-Amino-1-(2-thienyl)-1-alkanols $\text{S} \begin{array}{c} \diagup \\ \diagdown \end{array} \text{CH-CH-R} \cdot \text{HCl}$
OH NR'R''

Compd. No.	R	NR'R''	m.p. (°C)	Crystn. solvent	Appearance*	Mol. formula	Analysis (%)					
							Calcd.			Found		
(XVI)	H	-N $\begin{array}{c} \diagup \\ \diagdown \end{array}$ H	210 (dec.)	EtOH + AcOEt	needles	C ₁₁ H ₁₇ ONS·HCl	C	H	N	C	H	N
(XVII)	"	-N $\begin{array}{c} \diagup \\ \diagdown \end{array}$ H O	201 (")	"	plates	C ₁₀ H ₁₅ O ₂ NS·HCl	53.31	7.32	5.65	53.47	7.53	5.61
(XVIII)	CH ₃	-N $\begin{array}{c} \diagup \\ \diagdown \end{array}$ H	233 (")	"	needles	C ₁₂ H ₁₉ ONS·HCl	48.08	6.46	5.61	48.13	6.66	5.69
(XIX)	"	-N $\begin{array}{c} \diagup \\ \diagdown \end{array}$ H O	212	"	"	C ₁₁ H ₁₇ O ₂ NS·HCl	55.04	7.70	5.35	55.16	7.75	5.39
(XX)		-N(CH ₃) ₂	221~222	MeOH	"	C ₁₄ H ₁₇ ONS·HCl	50.08	6.88	5.31	50.23	6.95	5.38
(XXI)	"	-N $\begin{array}{c} \diagup \\ \diagdown \end{array}$ H	225	"	prisms	C ₁₇ H ₂₁ ONS·HCl	59.24	6.39	4.94	59.21	6.20	4.79
(XXII)	"	-N $\begin{array}{c} \diagup \\ \diagdown \end{array}$ H O	219~220 (dec.)	CHCl ₃ + AcOEt	"	C ₁₆ H ₁₉ O ₂ NS·HCl	63.04	6.85	4.32	63.34	6.68	4.51
							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.

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. Et₂O 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 Br₂ 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 Ac₂O (catalyst, H₃PO₄); b.p.₄ 77°.

*⁴ This was prepared from the Friedel-Crafts reaction of thiophene and propionyl chloride (catalyst, SnCl₄); b.p. 223~225°.

*⁵ This was prepared from thiophene and phenylacetyl chloride (catalyst, SnCl₄), b.p.₁₂ 196~198; m.p. 49~50°.

TABLE III. Diarylalkanols R_1-CH-R_2
OH

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 $R_1-CH-R_2 \cdot HX$
NR'R''

Compd. No.	R_1	R_2	NR'R''	HX	m.p. (°C)	Crystn. Solvent	Appearance	Mol. formula	Analysis (%)					
									Calcd.			Found		
									C	H	N	C	H	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	"	$C_{19}H_{22}ONCl$	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)		"		"	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 NaBH₄ 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 Et₂O, and the Et₂O extract was dried over anhyd. Na₂SO₄. 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-thienyl chloride⁴⁾ and 2.5 g. of Mg in a usual manner, dehyd. Et₂O solution of 11.2 g. (0.1 mole) of 2-thiophenecarboxaldehyde⁵⁾ was added gradually with stirring at 0° and the reaction mixture was allowed to stand overnight. To the reaction flask, 50 cc. of 25% NH₄Cl solution was added with stirring under cooling, the Et₂O layer was separated, the aqueous layer was extracted with Et₂O, and the combined extract was dried over anhyd. Na₂SO₄. Distillation of the crude product obtained by removal of the solvent gave viscous oil, b.p. 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. CaCl₂, 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 SOCl₂ 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%.

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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 halogenation of diarylalkanols followed by amination.

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