Group II compounds have migration ratio between 0.6 and 0.7 at every pH. Most of the compounds tested belong to this group and atropine can be considered as a representative of one.

Group III contains Compounds Nos. 1, 2, 3, 5, 16, and 46, and DHNS. Their migration ratio is similar to that of group II in the region of pH 5~7, but suddenly decreases in the region of pH 7~7.5.

Group IV consists of Compounds No. 47 and 49, and papaverine.

All members of group I are trimethylammonium compounds, and have a strong C-action. No member of other groups shows C-action. This fact supports the view that existence of a cationic head would be necessary for C-action.

Compounds of group II and III, except DHNS, show A-action, but there is a wide deviation in their activity, and there is no parallelism between the activity and the migration ratio.

From this, it is supposed that the cationic property is required to some extent for A-action, but it would not be a decisive factor. Every compound of group IV, III, and II shows P-action in greater or lesser degree. No member of group IV shows A-action.

For P-action, the existence of a cationic head seems to be of little importance, and other factors such as physicochemical properties would be essential.

Among the members of group III, Nos. 1, 2, 3, 5, and 16 are characterized by the existence of a piperidino group in the molecule and by the considerable activies in both A- and P-actions. It is interesting that they show a similar migration to that of atropine at pH below 6.5 and their migration ratio lies between atropine and papaverine in the region of pH 6.5~8.5.

The author is grateful to Prof. H. Kumagai and to Prof. K. Takagi for their guidance and encouragement. He is also indebted to Miss Reiko Terada for technical assistance in the experiment.

Summary

The cationic properties of aralkylamines were compared approximately by paper electrophoresis. These compounds were broadly divisible into four groups on the basis of their mobilities. Biological characteristics of each group were discussed.

(Received November 14, 1957)

UDC 547.734.07

26. Ryuichi Kimura, Takahiro Yabuuchi, and Yasutaka Tamura : Studies on Thiophene Derivatives. I. Syntheses of 2-Amino-1,1-di(2-thienyl)alkanols.

(*Scientific Research Institute for Practical Life, University of Kyoto**)

In 1950, Adamson and Green[1,2] synthesized 3-amino-1,1-di(2′-thienyl)alkenes (A) and reported that the compounds possessed an analgesic and antispasmodic action. Moreover, Kasé[3] reporting on the result of "Coughing Dog method" said that 3-piperidino-1,1-di(2-thienyl)butene (B) had a more potent antitussive action than

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

1) D. W. Adamson : J. Chem. Soc., **1950**, 885.
2) a) D. W. Adamson, A. F. Green : Nature, **165**, 122(1950).
b) D. W. Adamson, W. H. Duffin, A. F. Green : *Ibid.*, **167**, 153(1951).
3) Y. Kasé : This Bulletin, **3**, 394(1955).

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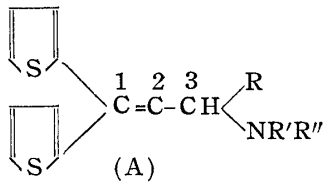
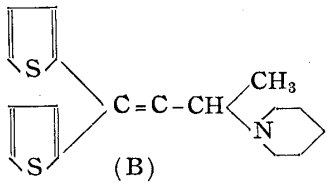
morphine or Methadon. The above interesting result promoted us to develop some clinical fields, and consequently it was found that this compound is very effective by the oral administration of 1~3 mg. for an adult..

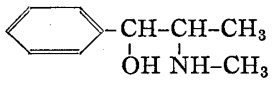


(A)

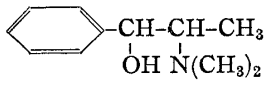


(B)

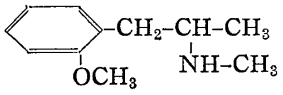
Now, if a comparison is made between the structures of (A) compounds and ephedrine group used generally as antitussives, such as ephedrine (C), methylephedrine (D), and 3-(2-methoxyphenyl)-2-methylaminopropane (E), following differences will be found in the side chain of these compounds. (1) One amino group is present in 3-position in compounds of type (A) while the same is in 2-position in ephedrines; (2) the compounds of type (A) have one double bond between 1 and 2, but ephedrines have no such double bond; (3) ephedrines have one hydroxyl group at 1-position, but the compounds of type (A) do not.



(C)



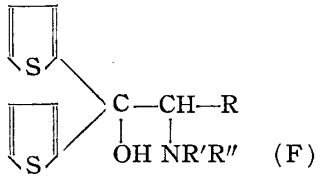
(D)



(E)

Papers on the above dithienyl derivatives possessing a side chain like that of ephedrine have not been published yet.

Therefore, an attempt was made to synthesize 2-amino-1,1-di(2-thienyl)alkanols (F), which have both hydroxyl group at 1-position and an amino group at 2-position, in order to observe relationship between chemical structures and pharmacological activities.



(F)

The synthetic method for these compounds is as follows: First synthesis of 1-aminoalkane-1-carboxylic acid esters as starting materials is described. *dl*-Alanine ethyl ester was obtained by the esterification of *dl*-alanine (Fisher-Speier's method), and 2-aminopropionic acid esters by the amination of ethyl 2-bromopropionate, which had been obtained by the esterification of 2-bromopropionyl bromide. 2-Aminoacetic acid esters were obtained by the amination of ethyl monochloroacetate.

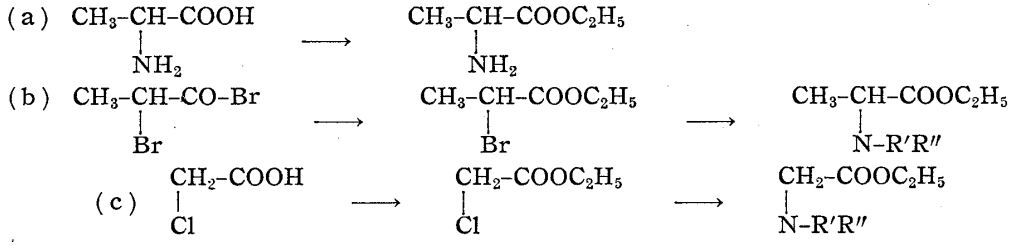


Chart 1.

1-Aminoalkane-1-carboxylic acid esters prepared in this work are listed in Table I. Next, (F) compounds were synthesized from 1-aminoalkane-1-carboxylic acid esters (see Table I) and thiophene by the lithium method.[1] Thienyllithium was prepared from thiophene and phenyllithium, which was prepared from bromobenzene and lithium, and

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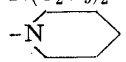
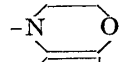
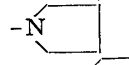
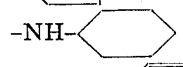
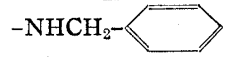
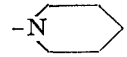
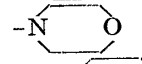
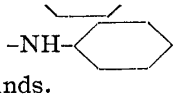
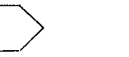
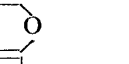
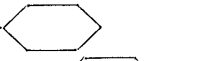
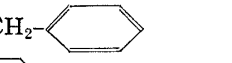
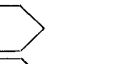
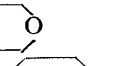
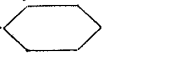
condensation of this thienyllithium with 1-aminoalkane-1-carboxylic acid esters gave (F) compounds. The new compounds obtained are listed in Table II.

Table I. Ethyl 1-Aminoalkane-1-carboxylates $R\text{-}CH(NR'R'')\text{-}COOC_2H_5$

No.	R	NR′R″	Prepar. method	b.p.(°C/mm.)	Yield (%)
1	CH_3	NH_2	a	48/11	45
2	CH_3	$N(CH_3)_2$	b	156	40
3	CH_3	$N(C_2H_5)_2$	b	200	76
4	CH_3		b	78~81.5/5	87
5	CH_3		b	91~92/4.5	84
6	CH_3		b	75~78/1	73
*7	CH_3		b	90/3	79
8	CH_3		b	109~114/1	76
9	H		c	209/273	62
10	H		c	110~120/8	25
*11	H		c	111~115/9	20

* New compounds.

Table II. 2-Amino-1,1-di(2-thienyl)alkanols, $\left(\text{thienyl}\right)_2\text{C(OH)}\text{-}\text{CH(NR'R'')}\text{-}R$

No.	R	NR′R″	Free base m.p.(°C)	Free base Yield (%)	Hydrochloride m.p.(°C)
I	CH_3	$-NH_2$	b.p. 140~141 (0.5)	13	191~191.5(decomp.)
II	CH_3	$-NHCH_3$			189(decomp.)[HI]
III	CH_3	$-N(CH_3)_2$	68~69	84	177.5~178
IV	CH_3	$-NHC_2H_5$			180~180.5
V	CH_3	$-N(C_2H_5)_2$	88~89	68	
VI	CH_3		101~102	74	181
VII	CH_3		122~123	40	
VIII	CH_3		87~88	59	
IX	CH_3		75~76	68	187.5~188(decomp.)
X	CH_3				186.5~187(decomp.)
XI	H		49.5~51.5	62	192~193(decomp.)
XII	H		84.5~85	81	149~149.5
XIII	H		70.5~71	20	128(decomp.)

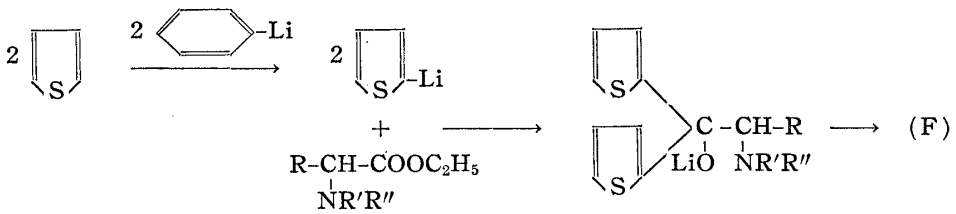


Chart 2.

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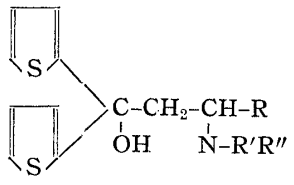
Furthermore 3-amino-1,1-di(2′-thienyl)alkan-1-ols (G) previouly reported by Adamson[1] was readily converted into (A) compound by dehydration with hydrogen chloride, but (F) compounds could not form alkenes by the same procedure as above.



(G)

The authors express their gratitude to Prof. Dr. Saikachi, Pharmaceutical Institute, University of Kyushu, for guidance and encouragement throughout this work. The authors' thanks are also due to the members of the Analysis Room of the Pharmaceutical Institute, University of Kyoto, for the microanalysis.

Experimental

Preparation of 1-Aminoalkane-1-carboxylic Acid Esters—To 1 mole of ethyl 2-bromopropionate[4] or ethyl monochloroacetate,[5] 2 moles of the amines was added in a desired quantity of benzene and in general the mixtures were heated on a boiling water bath for 2 hrs., except dimethylamine or diethylamine (at 100° in a sealed tube). After cooling, the separated crystals were removed by filtration. The pure esters obtained by distillation of the filtrate are listed in Table I. Alanine ethyl ester[6] was prepared from a mixture of 10 g. of *dl*-alanine and 30 cc. of dehyd. EtOH in presence of dry HCl.

2-Amino-1,1-di(2-thienyl)propanol (I)—A three-necked flask was equipped with a stirrer, a reflux condenser carrying a nitrogen inlet, a thermometer, and a dropping funnel. The apparatus was swept with dry O_2-free N_2, and 300 cc. of dehyd. ether was placed. While the flow of N_2 continued, 8.5 g. (1.2 atoms) of Li metal was cut into small pieces and added into the flask. The stirrer was started, a solution of 9.4 g. (0.6 mole) of bromobenzene in 100 cc. of dehyd. ether was added to the ether solution at such a rate as to maintain a constant reflux. After addition of bromobenzene reflux was continued for additional 2 hrs., the flask was chilled in an ice bath, and a slow stream of N_2 was led into the apparatus. Fifty grams (0.6 mole) of thiophene in equal amount of ether was added to the flask, the mixture was refluxed for 2 hrs., chilled to −20° in a dry-ice bath, and then 23.4 g. (0.2 mole) of *dl*-alanine ethyl ester in equal amount of ether was gradually added to the mixture, stirring was continued for additional 2 hrs. at room temperature, and the reaction mixture was allowed to stand over night. After pouring the reaction mixture into ice water, the ethereal layer was separated and the aqueous layer was extracted with ether. The combined extracts were dried over anhyd. Na_2SO_4 and removal of the solvent gave a dark brown material. Distillation of the crude product so obtained gave colorless oil, b.$p_{0.5}$ 140～141°. Yield, 6.2 g. To the solution of basic oil in $CHCl_3$, dry HCl gas was introduced under cooling until it became neutral and then the solvent was evaporated to dryness under diminished pressure. The residue was recrystallized from MeOH to obtain colorless prisms, m.p. 191～191.5°(decomp.). *Anal.* Calcd. for $C_{11}H_{14}ONClS_2$: C, 47.88; H, 5.11; N, 5.08. Found: C, 48.26; H, 5.25; N, 4.99.

2-Monomethylamino-1,1-di(2-thienyl)propanol (II)—To 2-amino-1,1-di(2-thienyl)propanol was added equal moles of CH_3I in acetone and the mixture was heated at 100° for 15 hrs. in a sealed tube. After cooling, 5 volumes of ether was added, the crystals that separated were collected by suction, and recrystallization of the crude crystals from AcOEt gave the hydriodide as colorless microprisms, m.p. 189°(decomp.). *Anal.* Calcd. for $C_{12}H_{16}ONIS_2$: C, 37.78; H, 4.23; N, 3.68. Found: C, 37.91; H, 4.34; N, 3.51.

2-Dimethylamino-1,1-di(2-thienyl)propanol (III)—This compound was prepared from 4.3 g. (0.6 atom) of Li, 47 g. (0.3 mole) of bromobenzene, 25 g. (0.3 mole) of thiophene, and 17.3 g. (0.1 mole) of ethyl 2-dimethylaminopropionate in the same manner as for (I). The residue obtained by evaporation of the solvent was washed well with MeOH and recrystallized from $CHCl_3$ to colorless scales, m.p. 68～69°. Yield, 22.4 g. Hydrochloride of the base was obtained likewise and recrystallized from $CHCl_3$ to colorless needles, m.p. 177.5～178°. *Anal.* Calcd. for $C_{13}H_{18}ONClS_2$: C, 51.36; H, 5.97; N, 4.61. Found: C, 51.39; H, 5.97; N, 5.01.

2-Monoethylamino-1,1-di(2-thienyl)propanol (IV)—To 2-amino-1,1-di(2-thienyl)propanol an equal mole of EtI in acetone was added and the mixture was heated at 100° for 8 hrs. in a sealed tube. After cool, the mixture was poured into ice water, acidified with HCl, and insoluble matter inthe

4) M. Wernig: Ann. Chem. Liebigs, **280**, 250(1894).
5) M. Conarad: *Ibid.*, **188**, 218(1877).
6) C. Harries, M. Neiss: *Ibid.*, **327**, 381(1903).

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aqueous phase was removed by shaking with ether. The aqueous layer was made alkaline with NH_4OH under cooling and extracted with ether. The ethereal extract was dried over anhyd. Na_2SO_4 and ether was completely evaporated. Its hydrochloride was prepared by the method described for (I) and recrystallized from a mixture of AcOEt and MeOH to colorless needles, m.p. 180~180.5°. *Anal.* Calcd. for $C_{13}H_{18}ONClS_2$: C, 51.36; H, 5.97; N, 4.61. Found: C, 50.08; H, 5.52; N, 4.84.

2-Diethylamino-1,1-di(2-thienyl)propanol (V)—This compound was prepared from 4.3 g. of Li, 47 g. of bromobenzene, 25 g. of thiophene, and 15.9 g. of ethyl 2-diethylaminopropionate in the same way as for (I). The residue obtained by evaporation of the ether was washed with MeOH and recrystallized from MeOH to colorless prisms, m.p. 88~89°. Yield, 20 g. *Anal.* Calcd. for $C_{15}H_{21}ONS_2$: C, 60.94; H, 7.16; N, 4.74. Found: C, 61.05; H, 7.37; N, 4.44.

2-Piperidino-1,1-di(2-thienyl)propanol (VI)—This compound was prepared from 18.5 g. of ethyl 2-piperidinopropionate in the same manner as for (I). The residue obtained by evaporation of the ether was washed with MeOH and recrystallized from $CHCl_3$ to colorless prisms, m.p. 101~102°. Yield, 22.7 g. Hydrochloride: Colorless prisms (from $CHCl_3$), m.p. 181°. *Anal.* Calcd. for $C_{16}H_{22}ONClS_2$: C, 55.86; H, 6.43; N, 4.08. Found: C, 55.68; H, 6.62; N, 3.94.

2-Morpholino-1,1-di(2-thienyl)propanol (VII)—This compound was prepared from 18.7 g. of ethyl 2-morpholinopropionate in the same manner as for (I). The residue obtained by evaporation of ether was washed with MeOH and recrystallized from $CHCl_3$ to colorless prisms, m.p. 122~123°. Yield, 12.3 g. *Anal.* Calcd. for $C_{15}H_{19}O_2NS_2$: C, 58.20; H, 6.19; N, 4.21. Found: C, 57.88; H, 6.36; N, 4.30.

2-(1-Pyrrolidyl)-1,1-di(2-thienyl)propanol (VIII)—This compound was prepared from 17.1 g. of ethyl 2-(1-pyrrolidyl)propionate in the same way as for (I). The residue obtained by evaporation of ether was washed with MeOH and recrystallized from AcOEt to colorless prisms, m.p. 87~88°. Yield, 17.3 g. *Anal.* Calcd. for $C_{15}H_{19}ONS_2$: C, 61.38; H, 6.53; N, 4.78. Found: C, 61.64; H, 6.28; N, 4.81.

2-Cyclohexylamino-1,1-di(2-thienyl)propanol (IX)—This compound was prepared by condensation of 4.3 g. of Li, 47 g. of bromobenzene, 25 g. of thiophene, and 19.9 g. of ethyl 2-cyclohexylaminopropionate following the same procedure as described for (I). The residue obtained by evaporation of the solvent was washed with MeOH and recrystallized from $CHCl_3$ to colorless prisms, m.p. 75~76°. Yield, 21.8 g. Hydrochloride: Colorless prisms (from MeOH), m.p. 187.5~188°(decomp.). *Anal.* Calcd. for $C_{17}H_{24}ONClS_2$: C, 57.02; H, 6.76; N, 3.92. Found: C, 57.20; H, 6.89; N, 3.61.

2-Benzylamino-1,1-di(2-thienyl)propanol (X)—This compound was prepared from 20.7 g. of ethyl 2-benzylaminopropionate in the same manner as the procedure for (I). After removal of the solvent the oily matter obtained was dissolved in $CHCl_3$ treated with dry HCl under cooling, and then crystalline mass separated. This was collected by suction, washed with $CHCl_3$, and recrystallized from MeOH to colorless prisms, m.p. 186.5~187°(decomp.). *Anal.* Calcd. for $C_{18}H_{20}ONClS_2$: C, 59.06; H, 5.51; N, 3.83. Found: C, 59.16; H, 5.72; N, 3.54.

2-Piperidino-1,1-di(2-thienyl)ethanol (XI)—This compound was prepared from 17.1 g. of ethyl 2-piperidinoacetate in the same manner as for (I). The residue obtained by evaporation of the solvent was washed with MeOH and recrystallized from MeOH to colorless needles, m.p. 49.5~51.5°. Yield, 18.2 g. Hydrochloride: Colorless needles (from MeOH), m.p. 192~193°(decomp.). *Anal.* Calcd. for $C_{15}H_{20}ONClS_2$: C, 54.59; H, 6.10; N, 4.25. Found: C, 54.49; H, 5.97; N, 3.99.

2-Morpholino-1,1-di(2-thienyl)ethanol (XII)—This compound was prepared from 17.4 g. of ethyl 2-morpholinoacetate in the similar manner as for (I). The residue obtained by evaporation of the ethereal solution was recrystallized from MeOH to colorless microprisms, m.p. 84.5~85°. Yield, 24.0 g. Hydrochloride: Colorless microprisms (from MeOH-AcOEt), m.p. 149~149.5°. *Anal.* Calcd. for $C_{14}H_{18}ONClS_2$: C, 50.65; H, 5.47; N, 4.22. Found: C, 50.95; H, 5.30; N, 3.99.

2-Cyclohexylamino-1,1-di(2-thienyl)ethanol (XIII)—This compound was prepared from 18.4 g. of ethyl 2-cyclohexylaminoacetate following the same procedure as mentioned for (I). The residue obtained by evaporation of the ethereal solution was recrystallized from MeOH to colorless needles, m.p. 70.5~71°. Yield, 6.2 g. Hydrochloride: Colorless needles (from MeOH), m.p. 128°(decomp.). *Anal.* Calcd. for $C_{16}H_{21}ONClS_2$: C, 55.54; H, 6.70; N, 4.05. Found: C, 55.62; H, 6.49; N, 3.78.

Summary

It was found that 3-piperidino-1,1-di(2-thienyl)butene prepared by Adamson possessed an antitussive action. The compound has one amino group at the 3-position, and one double bond between 1 and 2. However, ephedrine used as an antitussive for a long time has one amino group at 2-position and a hydroxyl group at 1-position.

Therefore, 2-amino-1,1-di(2-thienyl)propanols and 2-amino-1,1-di(2-thienyl)-ethanols which have one amino group at 2-position and hydroxyl group at 1-position were synthesized, in order to investigate the structure-activity relationship of the antitussive. The compounds were synthesized by the condensation of 1-aminoalkane-1-carboxylic acid esters and thiophene(the lithium method).

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