

JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

VOLUME 64

MARCH 6, 1942

NUMBER 3

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

α -Thienylaminoalkanes

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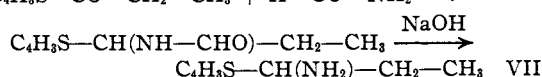
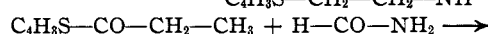
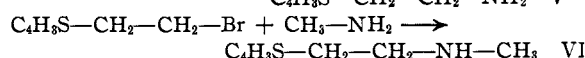
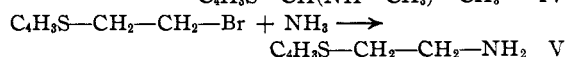
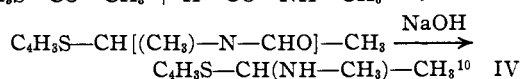
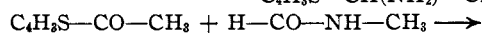
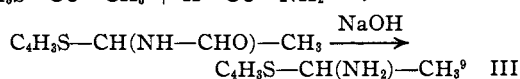
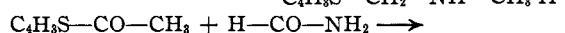
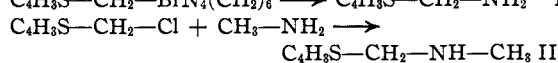
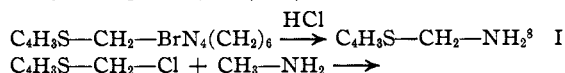
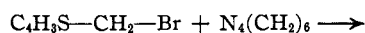
It is a matter of some interest to compare the pharmacological properties of substances which contain a phenyl radical with corresponding α -thienyl compounds.³

In this paper we have described a series of α -thienylaminoalkanes which were examined pharmacologically by L. W. Rowe in the Parke, Davis and Company laboratories. As far as ability to affect blood pressure is concerned, the behavior of a given member of the thienylaminoalkane series is remarkably similar, at least semiquantitatively, to that of the corresponding phenylaminoalkane (Table I).

Although two of our products have been reported in the chemical literature, we obtained them by different procedures. Putokhin and Egorova⁴ prepared α -thienylaminomethane but apparently did not examine it pharmacologically. The synthesis of 1-(α -thienyl)-2-aminoethane has been described by Barger and Easson⁵ and a pharmacological study was published by Tainter.⁶ It was said to be quantitatively indistinguishable from 1-phenyl-2-aminoethane from the standpoint of pressor activity.⁵ 1-(α -Phenyl- α' -thienyl)-2-aminoethane and 1-(α -*p*-anisyl- α' -thienyl)-2-

aminoethane have been shown to be pressor agents.⁷

The manner in which the α -thienylaminoalkanes were obtained is illustrated by the following formulations.



(7) Graham, *ibid.*, **13**, 305 (1940). The analogous 1-(α -phenyl- α' -furyl) and 1-(α -phenyl- α' -pyrryl) compounds also exhibited some activity. Robinson and Todd [*J. Chem. Soc.*, 1743 (1939)] prepared 2-(α' -phenyl- α -thienyl)- and 2-(α' -*p*-methoxyphenyl- α -thienyl)-ethylamine as well as a few of the corresponding furyl and pyrryl compounds.

(8) For a discussion of this reaction see Heidelberger, "An Advanced Laboratory Manual of Organic Chemistry," The Chemical Catalog Company, New York, 1923, p. 24, and Galat and Elion, *THIS JOURNAL*, **61**, 3585 (1939).

(9) Modification of Leuckart synthesis described by Ingersoll, Brown, Kim, Beauchamp and Jennings, *ibid.*, **58**, 1808 (1936).

(10) Novelli's modification of the Leuckart-Ingersoll synthesis *ibid.*, **61**, 520 (1939).

(1) This paper represents part of a dissertation to be submitted to the Horace H. Rackham School of Graduate Studies by J. H. Burckhalter in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

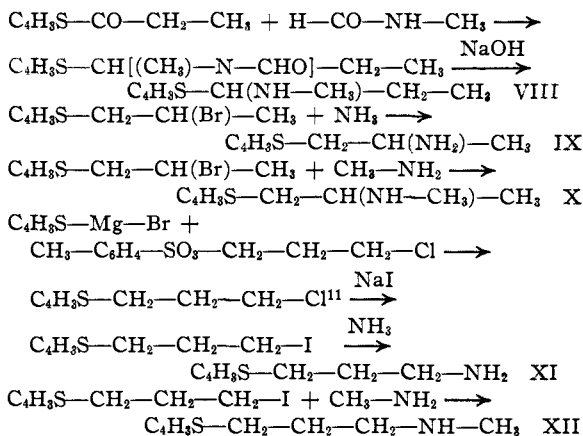
(2) Parke, Davis and Company Research Assistant.

(3) See Blicke and Zienty, *THIS JOURNAL*, **63**, 2945 (1941).

(4) Putokhin and Egorova, *J. Gen. Chem. U. S. S. R.*, **10**, 1873 (1940); *C. A.*, **35**, 4377 (1941).

(5) Barger and Easson, *J. Chem. Soc.*, 2103 (1938).

(6) Tainter, *Quart. J. Pharm. Pharmacol.*, **3**, 584 (1930).



Upon chloromethylation of thiophene, 40% of the latter was converted into α -thienylmethyl chloride and 38% into di- α -thienylmethane.

α -Thienyl bromide was obtained in 55% yield by bromination of thiophene in carbon tetrachloride solution.

1-(α -Thienyl)-2-hydroxyethane and 1-(α -thienyl)-2-hydroxypropane were prepared by interaction of α -thienylmagnesium bromide with ethylene oxide and propylene oxide, respectively. The hydroxy compounds were converted into the corresponding bromides with the aid of phosphorus tribromide.

It was hoped that 3-(α -thienyl)-propyl alcohol might be obtained from α -thienylmethylmagnesium chloride and ethylene oxide. However, after α -thienylmethyl chloride had been allowed to react with magnesium and ethylene oxide then added, only a very small quantity of a substance was obtained which might have been the desired alcohol. Evidently most of the α -thienylmethylmagnesium chloride, as fast as it was formed, reacted with α -thienylmethyl chloride since 1,2-di-(α -thienyl)-ethane was isolated in 69% yield.

Experimental

All hydrochlorides were obtained by treatment of an ether solution of the base with hydrogen chloride.

1-(α -Thienyl)-aminomethane (I).— α -Thienylcarbinol, obtained from α -thienylmagnesium iodide and formaldehyde,¹² was converted into α -thienylmethyl bromide with the aid of phosphorus tribromide.¹³ To 12.3 g. (0.07 mole) of the latter, dissolved in 40 cc. of chloroform, there was added 9.8 g. (0.07 mole) of hexamethylenetetramine; the chloroform began to reflux immediately. After the reaction had subsided, the mixture was heated on a steam-bath for one-half hour. The precipitated addition prod-

uct weighed 17 g. (72%); m. p. 160–161° (decomp.) after recrystallization from alcohol. The material was suspended in 100 cc. of absolute alcohol and treated with hydrogen chloride whereupon it dissolved and ammonium chloride soon began to precipitate. After a short time the latter was removed by filtration, the filtrate poured into a distillation flask and the solvent removed. Sodium hydroxide pellets were added to the oily residue and the latter distilled; yield 6.6 g. or 83.5% based on the addition product.

α -Thienylmethyl Chloride.—A mixture of 40 g. (0.47 mole) of thiophene and 20 cc. of concentrated hydrochloric acid was stirred vigorously, maintained at a temperature of 0–5° and treated with a rapid stream of hydrogen chloride. During the course of one hour 50 cc. of 40% formaldehyde was added. The mixture was extracted with ether, the extract washed with water and then with sodium bicarbonate solution, dried and the solvent removed. There were obtained 25 g. (40%) of α -thienylmethyl chloride which boiled at 80–81° (18 mm.)¹⁴ and 16 g. (38%) of di- α -thienylmethane the boiling point of which was 125–126° (9 mm.);¹⁵ the methane melted at 45–47° after recrystallization from alcohol.

Anal. Calcd. for $\text{C}_9\text{H}_8\text{S}_2$: S, 35.48. Found: S, 35.16.

1-(α -Thienyl)-methylaminomethane (II).—A mixture of 6.2 g. (0.047 mole) of α -thienylmethyl chloride, 60 cc. of alcohol and 35 cc. (0.43 mole) of 40% aqueous methylamine was heated in a magnesium citrate bottle for one hour at 60°. The alcohol and excess amine were removed, the oily residue was treated with 10 cc. of 20% sodium hydroxide solution, the mixture extracted with ether and the solution dried with magnesium sulfate; yield 3.1 g. (52%).

1-(α -Thienyl)-1-aminoethane (III).—A mixture of 18.9 g. (0.15 mole) of 2-acetylthiophene¹⁶ and 27.0 g. (0.60 mole) of formamide was heated at 180–190° in an oil-bath for ten hours, treated with 80 cc. of 30% sodium hydroxide solution and heated again for ten hours at 130°. The material was extracted several times with ether and the extracts shaken with water. The ether solution was stirred and a mixture of 63 cc. of concd. hydrochloric acid and 63 cc. of water added. Unchanged ketone was recovered from the ether layer. The aqueous layer was separated and kept cold while a solution of 30 g. of sodium hydroxide in 60 cc. of water was added. The material was extracted thoroughly with ether and the ether solution dried. Upon distillation, 9.7 g. (51%) of the amine was obtained.

1-(α -Thienyl)-1-methylaminoethane (IV).—Prepared from 16.0 g. (0.127 mole) of α -acetylthiophene and 30.0 g. (0.508 mole) of methylformamide¹⁰ by the method described above; yield 7.25 g. (45%).

α -Thienyl Bromide.—A mixture of 84 g. (1 mole) of thiophene and 100 cc. of carbon tetrachloride was cooled in ice-bath, stirred, and 176 g. (1.1 moles) of bromine, dissolved in 300 cc. of carbon tetrachloride, was added during a period of four hours. The solvent was removed and the residue heated with 15 g. of powdered sodium hydroxide on a steam-bath for four hours; the mixture was stirred occasionally. The liquid was decanted from the alkali and the latter washed with carbon tetrachloride. Upon

(11) General method developed by Gilman and Beaber [THIS JOURNAL, 45, 839 (1923)] and by Rossander and Marvel [*ibid.*, 50, 1493 (1928)].

(12) Steinkopf, *Ann.*, 540, 23 (1939).

(13) Von Braun, Fussgänger and Kühn, *ibid.*, 445, 219 (1925).

(14) Biedermann [*Ber.*, 19, 639 (1886)] reported 175°.

(15) Peter, *ibid.*, 17, 1345 (1884), found 267°.

(16) "Organic Syntheses," Vol. 18, p. 1.

distillation through a column there were obtained 89.7 g. (55%) of α -thienyl bromide¹⁷ which boiled at 153–154° and 29.2 g. of α, α' -dibromothiophene; the latter boiled at 95–98° (16 mm.).¹⁸

1-(α -Thienyl)-2-hydroxyethane.— α -Thienylmagnesium bromide was prepared from 81.5 g. (0.50 mole) of α -thienyl bromide, 13.5 g. (0.55 mole) of magnesium and 300 cc. of ether. The mixture was kept cold, stirred and 44.0 g. (1 mole) of ethylene oxide was added dropwise. The ice-bath was removed, the stirring continued and 100 cc. of dry benzene added gradually in order to control the reaction. After twenty-four hours at ordinary temperature, the material was treated with a mixture of 90 cc. of concd. hydrochloric acid and an equal volume of water. The ether-benzene layer was separated, washed successively with water and sodium carbonate solution, dried and the solvents removed. The product boiled at 107–109° (14 mm.); yield 33.6 g. (53%).

The phenylurethan melted at 57–58° after recrystallization from petroleum ether (60–70°).

Anal. Calcd. for $C_{13}H_{13}O_2NS$: S, 12.96. Found: S, 13.15.

1-(α -Thienyl)-2-bromoethane.—To a solution of 12.8 g. (0.10 mole) of the 2-hydroxyethane, which was kept cold and stirred, there was added, dropwise, 21.0 g. (0.078 mole) of phosphorus tribromide, dissolved in 10 cc. of dry benzene. The mixture was then heated for one-half hour in a boiling water-bath, cooled, stirred and treated, gradually, with 60 cc. of ice water. The benzene layer was separated, washed with water and with sodium carbonate solution, the solution dried with magnesium sulfate and the solvent removed. The bromide boiled at 98–99° (13 mm.); yield 7.1 g. (37%).

1-(α -Thienyl)-2-aminoethane (V).—A mixture of 500 cc. of alcoholic ammonia (3.9 moles) and 9.60 g. (0.05 mole) of 1-(α -thienyl)-2-bromoethane was allowed to remain at ordinary temperature for eight days. The solvent and excess ammonia were removed, the crystalline residue dissolved in water, the solution made strongly alkaline and extracted three times with 50-cc. portions of ether. The extracts were dried with magnesium sulfate; yield 3.53 g. (56%).

An amine and amine hydrochloride, identical in boiling point and melting point, respectively, with the products obtained by the process described above were obtained when α -thienylmethyl cyanide¹⁹ was reduced with sodium in boiling butyl alcohol solution.

In order to filter the hydrochloride of this amine and of amines VI, IX, X, XI and XII, a perforated platinum cone was placed in an ordinary funnel under the filter paper. When suction was applied, the salts filtered rapidly.

1-(α -Thienyl)-2-methylaminoethane (VI).—A mixture of 40 cc. of alcoholic methylamine (0.25 mole) and 9.60 g. (0.05 mole) of the bromoethane was heated in a magnesium citrate bottle at 100° for twenty-four hours and the mixture then treated as described above; yield 4.30 g. (65%).

(17) By a somewhat different procedure Krause and Renwanz [*Ber.*, **62**, 1710 (1929)] obtained the same yield.

(18) Steinkopf [*Ann.*, **430**, 98 (1923)] reported 195–206°.

(19) Blicke and Zienty, *THIS JOURNAL*, **63**, 2946 (1941).

1-(α -Thienyl)-1-aminopropane (VII).—From 56.0 g. (0.4 mole) of α -propionylthiophene²⁰ and 72 g. (1.6 mole) of formamide there was obtained, by the method described under compound III, 20.0 g. (36%) of the desired base and 24.5 g. of a substance which boiled at 174–178° (12 mm.). The latter proved to be the intermediate reaction product. $C_4H_5S-CH(NH-CHO)-CH_2CH_3$ which yielded a hydrochloride when suspended in ether and treated with hydrogen chloride; m. p. 234–235° (decomp.).²¹

Anal. Calcd. for $C_8H_{12}ONSCl$: Cl, 17.24. Found: Cl, 17.25.

Although the hydrochloride dissolves in water, the crystalline base precipitates from the solution almost immediately; the latter melts at 75–76° after recrystallization from alcohol.

Anal. Calcd. for $C_8H_{11}ONS$: S, 18.94. Found: S, 18.70.

A 16.8-g. portion of the material which boiled at 174–178° (12 mm.) was heated with 55 cc. of 30% sodium hydroxide solution on a steam-bath for three days; from the mixture there was obtained 2.8 g. of the thienylamino-propane and 10.4 g. of the unchanged intermediate product.

1-(α -Thienyl)-1-methylaminopropane (VIII).—From 22.6 g. (0.157 mole) of α -propionylthiophene and 37.0 g. (0.628 mole) of methylformamide there was obtained 6.0 g. (27%) of the pure base.

1-(α -Thienyl)-2-hydroxypropane.—Prepared in the manner described under 1-(α -thienyl)-2-hydroxyethane, 163 g. (1 mole) of α -thienyl bromide, 25 g. of magnesium, 500 cc. of ether and 116.0 g. (2 moles) of propylene oxide yielded 84.5 g. (60%) of the alcohol which boiled at 106–109° (13 mm.).

The phenylurethan melted at 62–63° after recrystallization from petroleum ether (60–70°).

Anal. Calcd. for $C_{14}H_{16}O_2NS$: S, 12.27. Found: S, 12.55.

1-(α -Thienyl)-2-bromopropane.—Prepared in the manner described under the 2-bromoethane, 21 g. (34%) of the bromide was obtained from 42.6 g. (0.30 mole) of the alcohol, 29.7 g. (0.11 mole) of phosphorus tribromide and 45 cc. of chloroform; b. p. 98–99° (11 mm.).

1-(α -Thienyl)-2-aminopropane (IX).—A mixture of 500 cc. of alcoholic ammonia (3.9 moles) and 14.7 g. (0.071 mole) of 1-(α -thienyl)-2-bromopropane was treated in the manner described under compound V; yield 5.25 g. (53%).

1-(α -Thienyl)-2-methylaminopropane (X).—Prepared in the same manner as compound VI, there was obtained 4.2 g. (41%) of the amine from 13.5 g. (0.066 mole) of 1-(α -thienyl)-2-bromopropane and 53 cc. of alcoholic methylamine (0.330 mole).

1-(α -Thienyl)-3-aminopropane (XI).— α -Thienylmagnesium bromide was prepared from 57.0 g. (0.35 mole)

(20) Isolated in 79% yield when prepared according to the directions given in "Organic Syntheses" (Vol. 18, p. 1) for α -acetylthiophene.

(21) In addition, a small amount of oil was obtained which soon crystallized and melted at 173–175°, which is the melting point of the hydrochloride of the thienylaminopropane. The formation of the latter was due to a cleavage of the material by cold hydrogen chloride.

TABLE I
 1-(α -THIENYL)-AMINOALKANE BASES AND HYDROCHLORIDES

1-(α -Thienyl)-	B. p. base,		M. p., °C. ^a	Hydrochloride		Pressor activity:		
	°C.	Mm.		Formula	% Chlorine Calcd. Found	I ^b	II ^c	
1 Aminomethane	73-75	11 ^d	193-194	C ₅ H ₅ NSCl	23.69	23.54	0	0 ^e
2 Methylaminomethane	75-80	14	189-190	C ₆ H ₁₀ NSCl	21.66	21.66	0	
3 1-Aminoethane	83-84	16	140-142	C ₆ H ₁₀ NSCl	21.66	21.51	0	0 ^e
4 1-Methylaminoethane	75-76	10	133-134	C ₇ H ₁₂ NSCl	19.95	20.04	0	
5 2-Aminoethane	88-90	13 ^f	200-202 ^f	C ₆ H ₁₀ NSCl	21.66	21.71	++	++ ^{g,o}
6 2-Methylaminoethane	90-91	13	154-155	C ₇ H ₁₂ NSCl	19.95	19.94	++	++ ^e
7 1-Aminopropane	89-91	13	173-175	C ₇ H ₁₂ NSCl	19.95	20.09	0	0 ^e
8 1-Methylaminopropane	90-92	12	121-122	C ₈ H ₁₄ NSCl	18.50	18.68	0	
9 2-Aminopropane	94-96	15	139-141	C ₇ H ₁₂ NSCl	19.95	20.19	++	++ ^{g,h}
10 2-Methylaminopropane	85-88	14	133-135	C ₈ H ₁₄ NSCl	18.50	18.56	++	
11 3-Aminopropane	110-112	19	194-195	C ₇ H ₁₂ NSCl	19.95	19.99	+	+ ^{e,o}
12 3-Methylaminopropane	112-114	19	127-128	C ₈ H ₁₄ NSCl	18.50	18.50	+	

^a Hydrochlorides 1, 2 and 7 were recrystallized from a mixture of alcohol and acetone; 3, 4, 11 and 12 from acetone; 5, 6 and 10 were dissolved in alcohol and precipitated with ether; 8 and 9 from a mixture of acetone and ether. ^b Activity of thienyl amine. ^c Activity of corresponding phenyl amine. ^d Putokhin and Egorova [*J. Gen. Chem. U. S. S. R.*, **10**, 1873 (1940); *C. A.*, **35**, 4377 (1941)] found 77° (16 mm.) and 88° (26 mm.). ^e Barger and Dale, *J. Physiol.*, **41**, 29 (1910). ^f Barger and Easson [*J. Chem. Soc.*, 2103 (1938)] reported the boiling point to be 200-201° (750 mm.) and the melting point 200-202°. ^g Hartung and Munch, *THIS JOURNAL*, **53**, 1875 (1931). ^h Alles, *J. Pharm. Exp. Therap.*, **47**, 339 (1933); Alles and Feigen, *ibid.*, **72**, 267 (1941). ⁱ 0 = inactive or slightly active; + = moderately active, ++ = good activity.

of α -bromothiophene, 8.5 g. of magnesium and 200 cc. of ether in a liter, three-necked flask. The solution was stirred and 173.0 g. (0.70 mole) of γ -chloropropyl *p*-toluenesulfonate¹¹ added at such a rate that the mixture boiled gently. A solid began to separate as soon as the ester was added. After about one-half of the ester had been added, external heat was applied and the material was heated and stirred for five hours; 60 cc. of hydrochloric acid, diluted with 200 cc. of water, was added to the cold, stirred mixture, followed by enough water to dissolve all of the precipitated solid. The ether layer was separated, shaken with sodium bicarbonate solution, dried over calcium chloride, the solvent removed and the 3-(α -thienyl)-propyl chloride distilled; yield 34 g. (61%); b. p. 84-86° (4 mm.).

In order to obtain 3-(α -thienyl)-propyl iodide, 32 g. of sodium iodide, dissolved in 90 cc. of acetone, and 16 g. (0.10 mole) of the propyl chloride were heated for six hours on a steam-bath; 5.69 g. (calcd. 5.86 g.) of precipitated sodium chloride was removed by filtration and the acetone removed from the filtrate. The residue, which consisted of the oily propyl iodide and the excess sodium iodide, was mixed with 1000 cc. of alcoholic ammonia (7.8 moles) and after eight days treated in the manner described under compound V. The yield of amine was 7.4 g. (53%).

1-(α -Thienyl)-3-methylaminopropane (XII).—This compound was obtained when the mixture of 3-(α -thienyl)-propyl iodide and excess sodium iodide, described under compound XI, was heated with 78 cc. of alcoholic methylamine (0.50 mole) for twenty-four hours at 100°. There was obtained 9.9 g. (64%) of amine.

Attempt to Prepare 3-(α -Thienyl)-propyl Alcohol from α -Thienylmethylmagnesium Chloride and Ethylene Oxide; Formation of 1,2-Di-(α -thienyl)-ethane.—To 30 g. (1.23 moles) of magnesium and 300 cc. of ether, which was

stirred, there was added 54.6 g. (0.41 mole) of α -thienylmethyl chloride during the course of two hours.²² A heavy, white precipitate formed and the mixture refluxed spontaneously; no external heat was applied. After the chloride had been added, the mixture was allowed to remain for two hours at ordinary temperature. It was then stirred and 36 g. of ethylene oxide added. There was no apparent reaction. After the mixture had been stirred for four hours, it was allowed to remain at ordinary temperature for twelve hours; 214 cc. of concentrated hydrochloric acid, diluted with 100 cc. of water, was added, the ether layer separated, shaken with water and then with sodium bicarbonate solution, dried and the solvent removed. There was obtained 8.1 g. of product which boiled at 100-112° (18 mm.); because of the low yield, this material, which might be desired propyl alcohol, was not investigated further. A second fraction boiled at 152-156° (20 mm.) and weighed 27.4 g. (69%); this product melted at 64-65° after recrystallization from methyl alcohol and proved to be the dithienylethane.

Anal. Calcd. for C₁₀H₁₀S₂: S, 33.00. Found: S, 32.50.

Summary

The preparation of twelve α -thienylaminoalkanes has been described.

From comparisons, in those instances in which pharmacological data are available, it has been found that the thienyl amines behave entirely similarly to analogous amines of the benzene series as far as pressor activity is concerned.

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(22) When the chloro compound and magnesium were used in equimolecular amounts the ethane was obtained in 40% yield.