UDC 615.782-012

171. Norio Sugimoto, Kentaro Okumura, Noboru Shigematsu, and Goro Hayashi: Studies on the Synthetic Analgesics. XVII. Syntheses of 2-(N-*tert*-Aminoalkylacylamino)thiophene.

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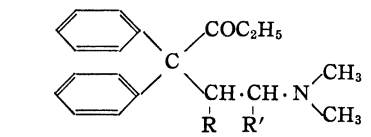
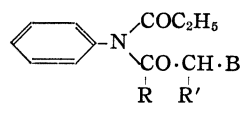
Recently, Wright and co-workers[1] reported a new series of potent analgesics of novel chemical structure, N-*tert*-aminoalkylpropionanilide (A). The compounds in this series are considered as analogs of methadone or isomethadone, in which the quaternary carbon atom and one of the phenyl groups have been replaced by a nitrogen atom. On the other hand, it is well known that the series of 2,2′-(3-*tert*-amino-1-propenylidene)dithiophene (B)[2] have the same order of analgesic activities as that of morphine and hence the thienyl group is presumably a pharmacological isoster of the phenyl group in the field of analgesics.[3] These two facts prompted us to undertake the synthesis of a series of 2-(N-*tert*-aminoalkylacylamino)thiophene (C), which may be considered as thiophene-analogs of the anilides (A), for analgesic testing.

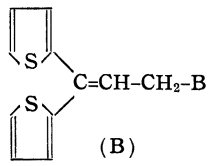


R : H R′ : CH_3 ···methadone
R : CH_3 R′ : H·····isomethadone



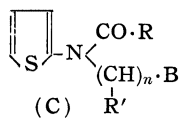
(A)

R, R′ : H, CH_3
B : *tert*-amine



(B)

B : *tert*-amine



(C)

R : CH_3, C_2H_5, OC_2H_5 n : 2～3
R′ : H, CH_3
B : *tert*-amine

Chart 1.

The synthesis of the compounds was accomplished according to the route shown in Chart 2. The compounds prepared are listed in Tables I, II, and III. Reduction of 2-nitrothiophene with stannous chloride according to the direction of Steinkopf[4] afforded 2-aminothiophene hydrochloride as a double salt of stannic chloride. The salt was directly treated with acetic anhydride, propionic anhydride and ethyl chloroformate in the presence of alkali to yield acetyl, propionyl and ethoxycarbonyl amides respectively. The amides were converted to the sodium or potassium salts with sodium hydride or potassium metal, and the salts were condensed with the *tert*-aminoalkyl halides to give the desired 2-(N-*tert*-aminoalkylacylamino)thiophene (C).

The hydrochlorides of these compounds were submitted to the analgesic test. They were tested according to the mouse hot plate method modified by Woolfe, Mac Donald

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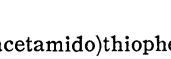
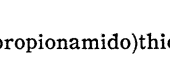
1) W.B. Wright, H.J. Brabander, R.A. Hardy: J. Am. Chem. Soc., **81**, 1518 (1959); J. Org. Chem., **26**, 476 (1961); *Ibid.*, **26**, 485 (1961).
2) V.B. Schatz.: Medecinal Chemistry p. 72 (1960) published by Interscience Publishers Inc., New York.
3) D.W. Adamson, A.F. Green: Nature, **1950**, 122.
4) W. Steinkopf: Ann., **403**, 17 (1914).

TABLE I. 2-(N-*tert*-Aminoalkylacetamido)thiophene 

No.	R	b.p. °C/mm.Hg	Yield(%)	Deriv.	m.p. °C	Recryst. solvent	Formula	Analysis % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Analgesic activity* and toxicity* LD_{50} mg./kg.	ED_{50} mg./kg.
1	$-CH_2CH_2\cdot N$ 	138~140/0.04	50.4	Picrate	134~135	EtOH	$C_{19}H_{17}O_8N_5S$	48.00	3.60	14.73	47.72	3.97	14.55	>150.0	none
2	$-CH_2CH(CH_3)\cdot N(CH_3)_2$	103~106/0.08	25.1	〃	113~114	〃	$C_{17}H_{21}O_8N_5S$	44.84	4.65	15.38	45.04	4.78	15.52	>150.0	>150.0
3	$-CH_2CH(CH_3)\cdot N(CH_3)CH_2Ph$	150~156/0.04	52.4	Oxalate	150~152	iso-PrOH	$C_{19}H_{24}O_5N_2S$	58.15	6.17	7.14	57.97	6.03	6.94	>150.0	none
4	$-CH_2CH(CH_3)\cdot N(CH_3)CH_2CH_2Ph$	165~170/0.04	63.8	〃	110~111	〃	$C_{20}H_{26}O_5N_2S$	59.10	6.45	6.89	58.79	6.35	6.75	>150.0	>100.0

TABLE II. 2-(N-*tert*-Aminoalkylpropionamido)thiophene 

No.	R	b.p. °C/mm.Hg	Yield(%)	Deriv.	m.p. °C	Recryst. solvent	Formula	Analysis % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Analgesic activity* and toxicity* LD_{50} mg./kg.	ED_{50} mg./kg.
5	$-CH_2CH_2\cdot N$ 	127~130/0.09	45.5	Oxalate	185~188	EtOH	$C_{16}H_{24}O_5N_2S$	53.92	6.79	7.86	54.20	6.59	7.82	>150.0	150.0
6	$-CH_2CH(CH_3)\cdot N(CH_3)_2$	94~97/0.08	48.1	Picrate	118~119	〃	$C_{17}H_{21}O_8N_5S$	44.84	4.65	15.38	45.23	4.43	15.10	>150.0	150.0
7	$-CH_2CH(CH_3)\cdot N$ 	142~145/0.5	66.6	Oxalate	163~164	〃	$C_{17}H_{26}O_5N_2S$	55.12	7.08	7.56	55.02	6.66	7.70	399.0	32.0
8	$-CH_2CH(CH_3)\cdot N(CH_3)_2$	110~112/0.09	45.2	Picrate	134~136	〃	$C_{18}H_{23}O_8N_5S$	46.05	4.94	14.92	46.29	4.87	15.04	508.0	46.5
9	$-CH_2CH(CH_3)\cdot N(C_2H_5)_2$	122~125/0.2	85.7	Base			$C_{14}H_{24}ON_2S$	62.66	9.02	10.44	62.23	8.67	10.39	>150.0	none
10	$-CH_2CH(CH_3)\cdot N(CH_3)CH_2Ph$	158~165/0.07	80.3	Oxalate	139~141	iso-PrOH	$C_{20}H_{26}O_5N_2S$	59.10	6.45	6.89	59.52	6.05	6.81	511.5	29.9
11	$-CH_2CH(CH_3)\cdot N(CH_3)CH_2CH_2Ph$	162~167/0.05	85.7	〃	116~122	〃	$C_{21}H_{28}O_5N_2S$	59.99	6.71	6.66	59.80	6.67	6.59	265.0	7.1

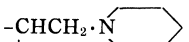
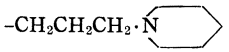
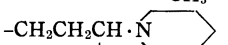
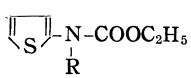
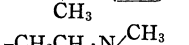
No.	R	b.p. °C/mm.Hg	Yield(%)	Deriv.	m.p. °C	Recryst. solvent	Formula	Analysis % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Analgesic activity* and toxicity* LD_{50} mg./kg.	ED_{50} mg./kg.
12	$-CHCH_2\cdot N$ (CH$_3$) 	148~150/0.5	62.2	〃	169~170	EtOH	$C_{17}H_{26}O_5N_2S$	55.12	7.08	7.56	55.18	6.52	7.75	408.0	17.4
13	$-CHCH_2\cdot N(CH_3)_2$ (CH$_3$)	100~105/0.07	88.3	Picrate	131~134	〃	$C_{18}H_{23}O_8N_5S$	46.05	4.94	14.92	46.34	4.50	14.95	468.6	45.2
14	$-CHCH_2\cdot N(CH_3)CH_2Ph$ (CH$_3$)	175~180/0.07	88.2	Oxalate	137~138	〃	$C_{20}H_{26}O_5N_2S$	59.10	6.45	6.89	59.00	6.05	7.17	300.0	35.4
15	$-CHCH_2\cdot N(CH_3)CH_2CH_2Ph$ (CH$_3$)	165~169/0.06	90.6	〃	112~115	iso-PrOH	$C_{21}H_{28}O_5N_2S$	59.99	6.71	6.66	60.25	6.32	6.55	139.0	9.7
16	$-CH_2CH_2CH_2\cdot N$ 	154~157/0.4	90.7	〃	161~165	EtOH	$C_{17}H_{26}O_5N_2S$	55.12	7.08	7.56	55.44	6.97	7.74	>150.0	none
17	$-CH_2CH_2CH_2\cdot N(CH_3)_2$	120~123/0.09	88.3	〃	143~146	〃	$C_{14}H_{22}O_5N_2S$	50.90	6.71	8.48	50.77	6.74	8.57	>150.0	〃
18	$-CH_2CH_2CH\cdot N$ (CH$_3$) 	158~162/0.1	73.2	〃	184~185	〃	$C_{18}H_{28}O_5N_2S$	56.24	7.34	7.29	56.62	7.25	7.44	120.0	〃
19	$-CH_2CH_2CH\cdot N(CH_3)_2$ (CH$_3$)	125~128/0.4	81.6	Picrate	142~143	〃	$C_{19}H_{25}O_8N_5S$			14.86			14.93	>150.0	〃
20	$-CH_2CH_2CH\cdot N(CH_3)CH_2Ph$ (CH$_3$)	175~178/0.09	50.0	Oxalate	126~128	iso-PrOH	$C_{21}H_{28}O_5N_2S$	59.99	6.71	6.66	59.84	6.48	6.58	>150.0	〃
21	$-CH_2CH_2CH\cdot N(CH_3)CH_2CH_2Ph$ (CH$_3$)	183~186/0.07	70.0	〃	128~130	EtOH	$C_{22}H_{30}O_5N_2S$	60.81	6.96	6.45	60.75	6.84	6.53	>675.0	57.7

Table III. Ethyl N-*tert*-Aminoalkyl-2-thiophenecarbamate 

No.	R	b.p. °C/mm.Hg	Yield(%)	Deriv.	m.p. °C	Recryst. solvent	Formula	Analysis % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Analgesic activity* and toxicity* LD_{50} mg./kg.	ED_{50} mg./kg.
22	$-CH_2CH\cdot N$ (CH$_3$) 	140~145/0.5	49.4	Oxalate	150~153	EtOH	$C_{17}H_{26}O_6N_2S$	52.84	6.78	7.25	52.84	7.01	6.95	>150.0	>100.0
23	$-CH_2CH\cdot N(CH_3)_2$ (CH$_3$)	115~117/0.08	53.4	〃	165~166	〃	$C_{14}H_{22}O_6N_2S$	48.55	6.40	8.09	49.01	6.45	7.79	>150.0	none
24	$-CH_2CH\cdot N(CH_3)CH_2CH_2Ph$ (CH$_3$)	165~170/0.07	41.6	〃	124~126	〃	$C_{20}H_{26}O_6N_2S$	56.86	6.20	6.63	56.64	6.12	6.18	>150.0	>100.0
25	Morphine hydrochloride													450.0	6.8

* subcutaneous administration

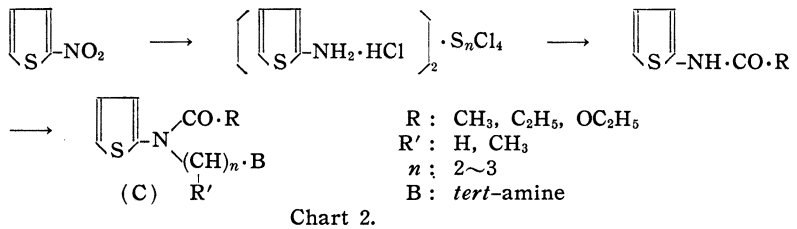


Chart 2.

and Eddy[5] and the results obtained are shown in Tables I, II and III. Among these compounds of this series, No. 11 was observed to have the activity approximately equal to that of morphine and No. 12 showed the activity between those of meperidine and codeine. The propionyl group attached to amine was apparently the most important for the activity because several propionamides (Table II) had the analgesic activity while all acetyl (Table I) and ethoxycarbonyl (Table III) amides were devoid of the activity. Variation in the alkylene chain between the two nitrogen atoms affected markedly the analgesic activity. The ethylene group was found to be the most effective for the activity while the propylene group caused to reduce the activity. This structure-activity relationship in this series of compounds was similar to those in the series of methadones and N-*tret*-aminoalkylpropionanilide (A).

Experimental

2-(N-*tert*-Aminoalkylacetamido)thiophene——The K salts of 2-acetamidothiophenes were prepared by heating with K metal (0.78 g.; 0.02 mole) and 2-acetamidothiophenes (2.28 g.; 0.02 mole) in 28 cc. of anhyd. xylene at 120~130° for 2 hr. with stirring.

To this salts solution was added dropwise with stirring at 120° a solution of *tert*-aminoalkyl chlorides (0.026 mole) in 14 cc. of anhyd. xylene and the mixture was kept at 120~130° for 2 hr.

After cooling, the reaction mixture was filtered and the inorganic salt washed with xylene. The combined solution was extracted with 5% HCl. The extract was made alkaline with K_2CO_3, and the oil separated was extracted with Et_2O. After evaporation of the dried Et_2O solution, the remaindal syrup was purified by vacuum distillation.

2-(N-*tert*-Aminoalkylpropionamido)thiophene——To a hot solution of 2-propionamidothiophene (3.1 g.; 0.02 mole) in 35 cc. of xylene was added NaH (0.53 g,; 0.022 mole), and the mixture was heated at 110~120° for about 2 hr. with stirring, when the white crystals of the Na salts of 2-propionamidothiophene were completely separated. To the Na salt suspension was added a solution of *tert*-aminoalkyl chloride (0.026 mole) in 15 cc. of xylene and the reaction mixture was heated at 120~130° for 3 hr. with stirring. Then the mixture was worked up as described above to give the oily crude amide which was purified by vacuum distillation.

Ethyl N-*tert*-Aminoalkyl-2-thiophenecarbamate—— To a solution of ethyl 2-thiophenecarbamate (3.42 g.; 0.02 mole) in 25 cc. of anhyd. toluene was added NaH (0.53 g.; 0.022 mole) with stirring, and then was refluxed for 1.5 hr. when the crystalline Na salt was completely separated. To the Na salt suspension was added a solution of *tert*-aminoalkyl chloride (0.026 mole) in 35 cc. of xylene and the heating of this mixture was continued for 2 hr. For the purification of the crude materials also was used vacuum distillation in this case.

Summary

Acyl-derivatives of thienylaminoethyl (or propyl) amines have been synthesized. Some of the compounds tested for analgesic activity showed the almost equal as morphine.

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5) N. B. Eddy, D. Leinbach : J. Pharmacol. Expl. Therap., **107**, 385 (1953).