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

Antispasmodics. XII. Secondary and Tertiary Amines which Contain an ω -(2-Thienyl)-alkyl Group

By F. F. BLICKE AND FREDERICK LEONARD^{1,2}

RECEIVED JUNE 4, 1952

The preparation of 26 amines which contain an ω -(2-thienyl)-alkyl group has been described and their antispasmodic activity against intestinal strips which had been treated with acetylcholine, barium chloride and histamine has been reported.

A large number of relatively simple secondary and tertiary amines which can be represented by the general formula $R(CH_2)_xNH(alkyl)$ and $R(CH_2)_x$ - $N(alkyl)(CH_2)_xR$, in which R is phenyl or cyclohexyl, have been synthesized and some of them have been found to be active antispasmodics.⁸

In this paper a number of similar secondary and tertiary amines have been described which contain at least one ω -(2-thienyl)-alkyl group. With three exceptions (compounds 6, 25 and 26, Table I) these amines conform to the general formula C₄H₃S-(CH₂)_xNRR' in which x = 1-4 and R and R' are represented by hydrogen, alkyl, cycloalkyl, 2-thienylalkyl, phenylalkyl or cycloalkylalkyl.

thienylalkyl halide, sodium carbonate and alcohol. Since we required both the secondary and the tertiary amine, and since the two types of amines could be separated easily by distillation, this process was satisfactory for our purpose. The symmetrical secondary amines were prepared by reaction of the required halides with alcoholic ammonia.

Interaction of β -(2-thienyl)-isopropyl bromide with alcoholic ammonia yielded the expected primary and secondary amine, but a neutral, unsaturated compound was also obtained which we believe was 2-propenylthiophene⁴; the boiling point and index of refraction data corresponded

TABLE I

Amines which Contain an ω -(2-Thienyl)-alkyl Group, C4H3S–(CH2)x–NRR'

Compounds 2, 5 and 25 were recrystallized from ethanol, 21 and 24 from ether, 13 from benzene-ether, 17 from isopropyl alcohol-ether and 9 from methanol; all other compounds were recrystallized from ethanol-ether.

			Base		Hydrohalide						
		_		B.p.,		M.p.,		Nitrogen, %		Halogen, %	
		R	R'	°C.	Mm.	°C.	Formula	Calcd.	Found	Caled.	Found
1	C4H3SCH2	H	C8H17	150 - 155	5	188-190	$C_{13}H_{24}SNC1$	5.35	5.32	13.54	13.57
2	C4H3SCH2	н	C4H3SCH2	183 - 188	17	247	$C_{10}H_{12}S_2NC1$	5.70	5.68	14.42	14.37
3	$C_4H_3S(CH_2)_2$	н	C_2H_5	103 - 105	22	167 - 168	C8H14SNC1	7.31	7.40	18.50	18.31
4	$C_{4}H_{3}S(CH_{2})_{2}$	н	C4H9	129 - 132	18	260 - 261	C10H18SNC1	6.37	6.66	16.13	16.43
5	$C_4H_3S(CH_2)_2$	н	$C_6H_{11}^a$	139 - 142	5	233 - 234	C ₁₂ H ₂₀ SNCI	5.70	5.75	14.42	14.36
6	C4H3SC(CH3)2b	H	$C_4H_3SC(CH_3)_2$	171 - 174	5	162 - 167	$C_{14}H_{20}S_2NC1$	4.64	4.66	11.74	11.68
7	$C_4H_3S(CH_2)_8$	н	CH3	86-89	3	129-130	C ₈ H ₁₄ SNC1	7.31	7.24	18.50	18.30
8	C4H2S(CH2)3	н	C_2H_5	97-98	5	138-139	C ₉ H ₁₆ SNCI	6.81	6.75	17.23	17.15
9	C ₄ H ₃ S(CH ₂) ₂	н	CH2CH2NH2	143 - 145	6	241-242°	$C_9H_{18}SN_2Cl_2$	10.90	10.78	27.57	27.40
10	$C_4H_3S(CN_2)_3$	н	C4H9	109-113	2	225 - 227	$C_{11}H_{20}SNC1$	5.99	6.00	15.16	15.06
11	$C_4H_3S(CH_2)_3$	н	$C_{6}H_{13}$	142 - 144	3	248 - 250	$C_{18}H_{24}SNC1$	5.35	5.34	13.54	13.46
12	$C_4H_3S(CH_2)_4$	н	$C_{3}H_{7}^{d}$	123 - 126	8	126 - 127	$C_{11}H_{20}SNC1$	6.02	5.95	15.23	15.14
13	C4H3SCH2	C4H3SCH2	C8H17	214 - 218	7	84-86	C18H28S2NC1	3.91	3.84	9.90	9.90
14	C ₄ H ₃ SCH ₂	$C_4H_3S(CH_2)_2$	CH3	185 - 189	16	142 - 143	$C_{12}H_{16}S_2NC1$	5.12	5.05	12.94	12.79
15	$C_4H_3S(CH_2)_2$	$C_4H_3S(CH_2)_2$	CH₃	194 - 196	15	128-130	C13H18S2NC1	4.87	4.70	12.31	12.22
						103-106	C14H20S2NBr	4.04	4.04	23.07	23.01*
16	$C_4H_3S(CH_2)_2$	$C_4H_3S(CH_2)_2$	C ₂ H ₅	181 - 183	7	119 - 120	$C_{14}H_{20}S_2NCl$	4.64	4.51	11.74	11.66
17	$C_4H_3S(CH_2)_2$	$C_4H_3S(CH_2)_2$	C4H3	196 - 198	8	126 - 128	$C_{16}H_{24}S_2NC1$	4.25	4.26	10.74	10.46
18	$C_4H_3S(CH_2)_2$	$C_{6}H_{11}(CH_{2})_{2}$	C ₂ H ₅	171 - 172	6	133-134	C ₁₆ H ₂₈ SNC1	4.64	4.68	11.74	11.64
19	$C_4H_3S(CH_2)_2$	$C_6H_5(CH_2)_2$	C6H11	232 - 234	8	119 - 121	C20H28SNC1	4.00	4.00	10.13	10.15
20	$C_4H_3S(CH_2)_2$	$C_4H_3S(CH_2)_4$	C3H7d	198 - 202	4	97-98	$C_{17}H_{26}S_2NC1$	3.61	3.60	20.57	20.63
21	C4H3S(CH2)3	$C_6H_5(CH_2)_2$	$C_{2}H_{5}$	187 - 188	6	118-120	C17H24SNBr	3.95	3.88	22.55	22.30
22	C ₄ H ₃ S(CH ₂) ₃	$C_4H_3S(CH_2)_3$	CH3	185 - 186	3	108-110	$C_{15}H_{22}S_2NBr$	3,89	3.96	22.18	22.16
						111113	C16H24S2NBr	3.71	3.92	21.35	22.03°
23	$C_4H_3S(CH_2)_3$	$C_4H_2S(CH_2)_3$	C ₂ H ₅	204 - 206	6	90 - 92	C16H24S2NBr	3.71	3.77	21.35	21.24
24	C ₄ H ₃ S(CH ₂) ₃	C4H3S(CH2)3	C ₄ H ₂	197 - 200	2	64 - 65	C18H28S2NBr	3.56	3.56	19.86	19,73
25	C4H3SCH2	-CH2CH2OCH	I2CH2-	140-143	20	220-221	C ₉ H ₁₄ OSNC1	6.38	6,34	16.14	16.02
26	C ₄ H ₃ S(CH ₂) ₃	-CH2CH2CH2	CH2CH2-	135-138	7	189-190	$C_{12}H_{20}SNC1$	5.69	5.64	14.39	14.38
	^a Cycloheyyl	b B-(2-Thiens	v1)-isonronv1	The struct	ural fo	rmula for t	his amine does	not confe	to the	a mamaral	formula

^a Cyclohexyl. ^b β -(2-Thienyl)-isopropyl. The structural formula for this amine does not conform to the general formula in the heading. ^c Dihydrochloride. ^d Isopropyl. ^e Methobromide.

A mixture of alkyl-(2-thienyl)-alkyl- and alkyldi-(2-thienyl)-alkylamines was obtained by heating one molecular equivalent of the required alkylamine with two molecular equivalents of the

(1) This paper represents part of a dissertation submitted by Frederick Leonard in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan, 1946.

(2) Frederick Stearns and Company Fellow.

(3) Profenil (Sestron) is ethyldi- $(\gamma$ -phenylpropyl)-amine hydrochloride. Methyldi- $(\beta$ -cyclohexylethyl)-amine hydrochloride was formerly marketed under the name Cyverine. very closely to those reported for propenylbenzene⁵ and were different from those published for 2-allyl-thiophene.⁶

(4) G. Errera (Gazz. chim. ital., 14, 506 (1884)) and M. P. Genvresse (Bull. soc. chim., [3] 9, 220 (1893)) found that β -phenylisopropyl chloride is converted into propenylbenzene by alcoholic potassium hydroxide, and also by the action of heat (G. Errera, Gazz. chim. ital., 16, 318 (1886)).

(5) A. Klages, Ber., 36, 2574 (1903).

(6) E. Grischkewitsch-Trochimowski, J. Russ. Phys. Chem. Soc., 43, 201 (1911); Chem. Zentr., 82, I, 1851 (1911).

The antispasmodic activity of the amines, which was determined under the supervision of Dr. A. M. Lands in the Frederick Stearns and Company Laboratories, is reported in Table II.

TABLE II ANTISPASMODIC ACTIVITY^a

Com- pound	Acetylcholine	Barium chloride	Hist- amine
1	100-200	100-200	400-800
2	5 0	50	50
3	N.E. ^b	N.E.	N.E.
4	200	100 - 200	100
5	50-100	N.E.	50 - 100
6	100	100	100
7	N.E.	N.E.	N.E.
8	N.E.	N.E.	N.E.
9	50	50	50-100
10	50-100	N.E.	50-100
11	100 - 200	100	200
12	N.E.	N.E.	N.E.
13	N.E.	N.E.	N.E.
14	50-100	50	100
15	50-100	50-100	200
15^{c}	N.E.	N.E.	100
16	100-200	50 - 100	100-200
17	100	50	100-200
18	1000-2000	200-400	400
19	100	50	100
20	400-800	100 - 200	400
21	200	200	200
22	200-400	100 - 200	400
22^{c}	2 00	100	200 - 400
23	800	200 - 400	400
24	200	100-200	200 - 400
25	N.E.	N.E.	N.E.
26	200	50	100
Methyld	li-(β-cyclohexyl-		
ethyl)	-amine hydrochlorid	e 400	

Papaverine

^a Isolated segments of rabbit ileum were used to determine the spasmolytic activity against acetylcholine- and barium chloride-induced contractures, while guinea pig ileum was employed to determine the effect against histamineinduced contractures. Spasmolytic potency is reported in terms of maximum effective dilution. Each dilution value in the table is to be *multiplied by 1000.* ^b No effect with a dilution of 1-50,000. • Methobromide.

200

Experimental Part

(2-Thienyl)-alkyl Halides.-(2-Thienyl)-methyl,⁷ B-(2thienyl)-ethyl⁷ and γ -(2-thienyl)-propyl chloride,⁸ as well as β -(2-thienyl)-isopropyl bromide,⁸ have already been described.

In order to obtain δ -(2-thienyl)-butyl chloride, a solution of β -(2-thienyl)-ethylmagnesium chloride, prepared from 80.7 g. of β -(2-thienyl)-ethyl chloride, 14.0 g. of magnesium and 360 cc. of ether, was stirred and 235 g. of β -chloroethyl p-toluenesulfonate, β dissolved in 235 cc. of ether, was added, dropwise, during a 2-hour period. After the mixture had

- (7) F. F. Blicke and F. Leonard, THIS JOURNAL, 68, 1934 (1946).
- (8) F. F. Blicke and J. H. Burckhalter, ibid., 64, 477 (1942).
- (9) G. R. Clemo and C. R. Tenniswood, J. Chem. Soc., 2549 (1931).

been stirred and refluxed for 17 hours, 96 cc. of concd. hydrochloric acid, diluted with 330 cc. of water, was added, followed by enough water to dissolve the precipitate. The organic layer and the ether extract of the aqueous layer were combined, washed with dilute sodium carbonate solution, then with water, and dried over potassium carbonate. Upon fractionation, 28.6 g. of the chloride was obtained; b.p. 117-118° (14 mm.).

Anal. Caled. for C₈H₁₁SC1: Cl, 20.30. Found: Cl, 19.96.

Amines (Table I).—Compounds 1, 3, 4, 5, 7, 8, 10, 11, 12, 13, 15, 16, 17, 22, 23 and 24 were prepared from alkylamine, R'NH₂, and the required (2-thienyl)-alkyl chloride. Compound 9 was obtained from ethylenediamine, 14 from methylpound 9 was obtained from entrytenediatinic, 14 from accent β -(2-thienyl)-ethylamine,⁸ 18 from 3 and β -cyclohexylethyl bromide, 19 from 5 and β -phenylethyl bromide, 20 from 12, and 2, 25 and 26 from the required halide and ammonia, morpholine or piperidine.

Typical procedures are described below. Hexyl- and Octylamine.—These amines were obtained in about 53% yield when 0.5 mole of the required bromide was dissolved in 800 cc. of absolute methanol, the solution saturated with ammonia, and then allowed to remain at room temperature for 8 days.

Butyl- β -(2-thienyl)-ethyl- (4) and Butyldi- β -(2-thienyl)-ethylamine (17).—A mixture of 7.3 g. (0.1 mole) of butyl-amine, 29.3 g. (0.2 mole) of β -(2-thienyl)-ethyl chloride, 21.2 g. (0.2 mole) of anhydrous sodium carbonate and 30 cc. of absolute alcohol was heated in a citrate bottle on a steambath for 40 hours. Water was added to dissolve the pre-cipitate, and the oily layer was separated. The aqueous layer was made strongly alkaline, and then extracted with ether. The combined organic layers were washed with water, and then treated with 40 cc. of 10% hydrochloric acid. The aqueous layer was extracted with ether, and then wade strongly alkaline. The precipitated, oilly amines were extracted with ether, and the extracts dried with anhydrous potassium carbonate. Upon fractionation there were obtained 5.0 g. of butyl- β -(2-thienyl)-ethylamine, b.p. 129–132° (18 mm.), and 11.5 g. of butyldi- β -(2-thienyl)-ethylamine, b.p. 196–198° (8 mm.).

Di- β -(2-thienyl)-isopropylamine (6).—A mixture of 36.4 (0.178 mole) of β -(2-thienyl)-isopropyl bromide, 14 cc. of alcoholic ammonia which contained 1.66 g. of ammonia and 18.8 g. (0.178 mole) of anhydrous sodium carbonate was heated on a steam-bath for 40 hours, and then treated was neated on a steam-bath for 40 hours, and then treated as described above. From the acid-soluble portion, 4.9 g, of the secondary amine and a very small amount of the pri-mary amine were obtained. Fractionation of the acid-insoluble material yielded 7.4 g, of a product, presumably 2-propenylthiophene, which decolorized bromine and po-tassium permanganate instantly; b.p. $175-177^{\circ}$, n^{20} p $1.5547.^{10}$

N-(γ -2-Thienylpropyl)-piperidine (26) and N-(2-Thienyl-methyl)-morpholine (25).—Piperidine (8.5 g., 0.1 mole), 16.1 g. (0.1 mole) of γ -(2-thienyl)-propyl chloride, 10.6 g. (0.1 mole) of anhydrous sodium carbonate and 20 cc. of absolute ethanol were heated for 24 hours on a steam-bath; yield 15 g. (72%).

The morpholine compound was obtained in 68% yield by the same general procedure except that benzene was used as a solvent, and the mixture was heated for 6 hours.

The amine hydrochlorides were prepared by addition of 5% more than the calculated amount of normal alcoholic hydrogen chloride to the amine (0.03 mole) dissolved in 30 cc. of anhydrous ether. The mixture was placed in a refrigerator whereupon the salt precipitated. In those instances in which the salt did not precipitate, the solvents were removed, and the oily residue was covered with ether and placed in a refrigerator.

ANN ARBOR, MICHIGAN

(10) The constants for propenylbenzene are b.p. $176-177^{\circ}$, $n^{20}D$ 1.54925; for 2-allylthiophene, b.p. 158-159°, n20 D 1.5281.6