

*Thiophen Derivatives of Biological Interest. Part X.**
5-Substituted 2-Thenaldehydes and Derivatives.

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A number of new 2-thenaldehydes bearing alkyl, arylalkyl, and *cyclohexylalkyl* substituents at position 5 have been synthesised, and their thiosemicarbazones and 4-oxo- Δ^2 -thiazolin-2-ylhydrazones prepared for testing for tuberculostatic and tumour-growth inhibiting activity.

THIOSEMICARBAZONES of many 5-substituted 2-thenaldehydes display high tuberculostatic activity *in vitro* (Welsch, Buu-Hoï, Dechamps, Hoán, Le Bihan, and Binon, *Compt. rend.*, 1951, **232**, 1608). This activity decreases with the length of the chain in position 5, e.g., against *Mycobacterium tuberculosis, var. hominis* (strain H37 Rv), as 5-*n*-propyl-2-thenaldehyde thiosemicarbazone (Buu-Hoï, Xuong, Royer, and Lavit, *J.*, 1953, 547) is active at the concentration 1 : 10⁶—10⁷, and the undecyl, dodecyl, and tetradecyl analogues at 1 : 10⁴; also 5-*n*-tetradecyl-2-thenaldehyde thiosemicarbazone shows a slight inhibitory activity towards the growth of grafted sarcoma 180 in mice at a daily dose of 200 mg./kg. (personal communication from Dr. Chester Stock, Sloan-Kettering Institute, New York). A number of new 5-substituted 2-thenaldehydes, their thiosemicarbazones (I), and their 4-oxo- Δ^2 -thiazolin-2-ylhydrazones (II) have now been prepared for further biological experiments. The substituents at position 5 include straight and branched alkyl, arylalkyl, and *cyclohexylalkyl* groups. The aldehydes were synthesised by the

* Part IX, Sy, Buu-Hoï, and Xuong, *J.*, 1955, 21.

N-methylformanilide reaction (King and Nord, *J. Org. Chem.*, 1948, **13**, 635; Buu-Hoï *et al.*, *J.*, 1952, 4590; 1953, 547) on the appropriate 5-substituted thiophens, prepared by reduction of 2-acylthiophens. Condensation of the new thienaldehydes with isonicotinoylhydrazine gave the hydrazones, listed on p. 1583. The 4-oxo- Δ^2 -thiazolin-2-ylhydrazones



of the aldehydes described were prepared from the corresponding thiosemicarbazones and chloroacetic acid (Chabrier *et al.*, *Bull. Soc. chim. France*, 1947, **14**, 797; 1950, **17**, 48; Buu-Hoï *et al.*, *loc. cit.*).

EXPERIMENTAL

Friedel-Crafts Acylations of Thiophen.—The reactions between thiophen and acid chlorides were catalysed with stannic chloride in carbon disulphide solution, in the usual way (cf. Sy, Buu-Hoï, and Xuong, *J.*, 1954, 1975); some of the ketones thus prepared were insufficiently characterised or were unknown, *viz.*: 2-Hexanoylthiophen, b. p. 159°/13 mm., n_D^{24} 1.5285 (Schleicher, *Ber.*, 1886, **19**, 660, gave b. p. 304°/760 mm.) [*semicarbazone*, needles, m. p. 117°, from ethanol (Found: N, 16.3. $C_{12}H_{19}ON_3S$ requires N, 16.6%)]. 2-*n*-Decanoylthiophen, b. p. 205°/22 mm., n_D^{27} 1.5170 (cf. Cagniant and Deluzarche, *Compt. rend.*, 1947, **225**, 455) [*semicarbazone*, m. p. 114° (Hartough and Kosak, *J. Amer. Chem. Soc.*, 1947, **69**, 3098, gave m. p. 110—110.5°)]. 2-Hexahydrobenzoylthiophen, b. p. 162°/13 mm., prisms, m. p. 44°, from ligroin (Found: C, 68.0; H, 7.4. $C_{11}H_{14}OS$ requires C, 68.0; H, 7.2%) [*semicarbazone*, prisms, m. p. 152°, from ethanol (Found: N, 16.9. $C_{12}H_{17}ON_3S$ requires N, 16.7%)]. 2- β -cycloHexylpropionylthiophen, b. p. 188°/13 mm., n_D^{18} 1.5542 (Found: C, 70.0; H, 8.3. $C_{13}H_{18}OS$ requires C, 70.3; H, 8.1%). 2-4'-cycloHexylhexanoylthiophen, b. p. 217°/14 mm., n_D^{24} 1.5428 (Found: C, 72.4; H, 9.2. $C_{16}H_{24}OS$ requires C, 72.7; H, 9.1%) [*semicarbazone*, prisms, m. p. 149°, from methanol (Found: N, 13.2. $C_{17}H_{27}ON_3S$ requires N, 13.1%)]. 2- ω -cycloPentyltridecanoylthiophen, b. p. 260—263°/13 mm., n_D^{25} 1.5205 (Found: C, 75.6; H, 10.3. $C_{22}H_{36}OS$ requires C, 75.9; H, 10.3%).

Reduction of 2-Acylthiophens.—This was performed by Huang-Minlon's method in diethylene glycol; yields were excellent (80—98%), except with the long-chain ketones.

Formylation of 5-Substituted Thiophens.—This was effected equally well with *N*-methylformanilide or dimethylformamide, provided that with the latter agent the heating was prolonged (10—12 hr.).

Products.—See Tables.

2-Alkyl-, 2-arylalkyl-, and 2-cycloalkyl-thiophens.

Substituent *	B. p./mm.	n_D (temp.)	Formula	Found (%)		Reqd. (%)	
				C	H	C	H
<i>n</i> -Butyl- ^a	182°	1.5070 (24)	$C_8H_{12}S$	—	—	—	—
<i>iso</i> Pentyl- ^b	196—198	1.5040 (24)	$C_9H_{14}S$	—	—	—	—
<i>n</i> -Pentyl	204	1.5055 (20)	$C_9H_{14}S$	70.0	9.2	70.1	9.1
<i>n</i> -Hexyl- ^c	114/14	1.5026 (24)	$C_{10}H_{16}S$	—	—	—	—
<i>n</i> -Heptyl	127/18	1.4998 (24)	$C_{11}H_{18}S$	72.3	9.9	72.5	9.9
<i>n</i> -Octyl- ^d	139/15	1.4970 (23)	$C_{12}H_{20}S$	73.5	10.1	73.5	10.2
<i>n</i> -Decyl	170/16	1.4932 (27)	$C_{14}H_{24}S$	74.8	10.8	75.0	10.7
4'- <i>tert</i> -Butylbenzyl	177/14	1.5635 (26)	$C_{15}H_{18}S$	78.2	7.8	78.3	7.8
<i>cyclo</i> Hexylmethyl	129/18	1.5350 (24)	$C_{11}H_{16}S$	73.5	8.8	73.3	8.9
3'- <i>cyclo</i> Hexyl- <i>n</i> -propyl	157/13	1.5272 (21)	$C_{13}H_{20}S$	75.1	9.8	75.0	9.6
4'- <i>cyclo</i> Hexyl- <i>n</i> -hexyl	185—187/15	1.5220 (21)	$C_{16}H_{26}S$	76.8	10.6	76.8	10.4
ω - <i>cyclo</i> Pentyl- <i>n</i> -tridecyl	242—248/20	1.5045 (24)	$C_{22}H_{38}S$	78.8	11.5	79.0	11.4
2- <i>n</i> -Hexyl-5-methyl	116/14	1.5010 (24)	$C_{11}H_{16}S$	72.3	9.9	72.5	9.9
2- <i>n</i> -Heptyl-5-methyl	129/15	1.4982 (24)	$C_{12}H_{20}S$	73.5	10.5	73.5	10.2
2- <i>cyclo</i> Hexylmethyl-5-methyl	141/22	1.5330 (20)	$C_{12}H_{18}S$	74.0	9.3	74.2	9.3
β -Phenethyl- ^e	152/15	1.5854 (24)	$C_{12}H_{12}S$	—	—	—	—

* At position 2 unless otherwise stated.

^a Meyer and Kreis (*Ber.*, 1884, **17**, 1559) gave b. p. 181—182°. ^b Steinkopf and Schubart (*Annalen*, 1920, **424**, 1) gave b. p. 74—75°/11 mm. ^c Campaigne and Diedrich (*J. Amer. Chem. Soc.*, 1948, **70**, 391) gave b. p. 79—82°/1 mm., n_D^{20} 1.4970. ^d von Schweinitz (*Ber.*, 1886, **19**, 644) gave b. p. 257—259°, and Campaigne and Diedrich (*loc. cit.*) gave b. p. 106—108°/1 mm., n_D^{20} 1.4824. ^e Buu-Hoï, Hoán, and Jacquignon (*J.*, 1951, 1381) gave b. p. 159—160°/13 mm.; this substance is a liquid, and the m. p. cited was a clerical error.

5-Substituted 2-thenaldehydes.

5-Substituent	B. p./mm.	n (temp.)	Formula	Found (%)		Reqd. (%)	
				C	H	C	H
<i>n</i> -Butyl-	145°/18	1.5517 (26)	C ₉ H ₁₂ OS	64.1	7.3	64.3	7.1
<i>iso</i> Pentyl-	152—154/18	1.5460 (25)	C ₁₀ H ₁₄ OS	65.8	7.6	65.9	7.7
<i>n</i> -Pentyl-	150/14	1.5480 (19)	C ₁₀ H ₁₄ OS	65.8	7.9	65.9	7.7
<i>n</i> -Hexyl-	160/13	1.5415 (23)	C ₁₁ H ₁₆ OS	67.1	8.1	67.3	8.2
<i>n</i> -Heptyl-	173/13	1.5338 (26)	C ₁₂ H ₁₈ OS	68.5	8.5	68.6	8.6
<i>n</i> -Octyl-	190/14	1.5310 (25)	C ₁₃ H ₂₀ OS	69.3	9.1	69.6	8.9
<i>n</i> -Decyl-	210—212/14	1.5250 (24)	C ₁₃ H ₂₄ OS	71.3	9.6	71.4	9.5
Phenethyl-	208/14	1.6165 (24)	C ₁₃ H ₁₂ OS	72.2	5.5	72.2	5.6
4'- <i>tert.</i> -Butylbenzyl-	218—220/13	1.5910 (24)	C ₁₆ H ₁₈ OS	74.3	6.9	74.4	7.9
<i>cyclo</i> Hexylmethyl-	180/13	1.5708 (23)	C ₁₅ H ₁₆ OS	69.0	7.9	69.2	7.7
3'- <i>cyclo</i> Hexyl- <i>n</i> -propyl-	215/18	1.5550 (24)	C ₁₄ H ₂₀ OS	71.2	8.8	71.2	8.5
4'- <i>cyclo</i> Hexyl- <i>n</i> -hexyl-	236/17	1.5470 (23)	C ₁₇ H ₂₆ OS	73.3	9.3	73.4	9.4
ω - <i>cyclo</i> Pentyl- <i>n</i> -tridecyl- ^a	270—275/15	1.5219 (22)	C ₂₃ H ₃₈ OS	76.0	10.3	76.2	10.5

^a The 2:4-dinitrophenylhydrazone formed red needles, m. p. 155°, from acetic acid (Found: N, 10.6. C₂₉H₄₂O₄N₄S requires N, 10.3%); the *p*-chlorobenzoylhydrazone, prisms, m. p. 126°, from ethanol (Found: C, 69.6; H, 8.5. C₃₀H₄₃ON₂SCI requires C, 69.9; H, 8.3%); the *salicyloylhydrazone*, prisms, m. p. 151°, from ethanol (Found: N, 5.7. C₃₀H₄₃O₂N₂S requires N, 5.6%); and the 5-*chloro*-*salicyloylhydrazone*, prisms, m. p. 170°, from ethanol (Found: C, 67.5; H, 8.3. C₃₀H₄₃O₂N₂SCI requires C, 67.8; H, 8.1%).

5-Substituted 2-thenaldehyde thiosemicarbazones.^a

Substituent	M. p.	Formula	Found (%)		Reqd. (%)	
			C	H	C	H
<i>n</i> -Butyl-	105°	C ₁₀ H ₁₅ N ₃ S ₂	56.2	6.5	56.0	6.2
<i>iso</i> Amyl-	121	C ₁₁ H ₁₇ N ₃ S ₂	51.5	6.9	51.8	6.7
<i>n</i> -Amyl-	106	C ₁₁ H ₁₇ N ₃ S ₂	51.8	6.9	51.8	6.7
<i>n</i> -Hexyl-	99	C ₁₂ H ₁₉ N ₃ S ₂	53.2	7.0	53.5	7.1
<i>n</i> -Heptyl-	102	C ₁₃ H ₂₁ N ₃ S ₂	55.0	7.7	55.1	7.4
<i>n</i> -Octyl-	94	C ₁₄ H ₂₃ N ₃ S ₂	56.8	7.7	56.6	7.7
<i>n</i> -Decyl-	92	C ₁₆ H ₂₇ N ₃ S ₂	59.3	8.5	59.1	8.3
Phenethyl-	141	C ₁₄ H ₁₅ N ₃ S ₂	58.0	5.4	58.1	5.2
4'- <i>tert.</i> -Butylbenzyl-	170 (dec.)	C ₁₇ H ₂₁ N ₃ S ₂	61.3	6.5	61.6	6.3
<i>cyclo</i> Hexylmethyl-	147	C ₁₃ H ₁₉ N ₃ S ₂	55.4	6.8	55.5	6.8
3'- <i>cyclo</i> Hexylpropyl-	150	C ₁₅ H ₂₃ N ₃ S ₂	58.5	7.2	58.2	7.4
4'- <i>cyclo</i> Hexyl- <i>n</i> -hexyl-	91	C ₁₈ H ₂₉ N ₃ S ₂	61.6	8.6	61.5	8.3
ω - <i>cyclo</i> Pentyl- <i>n</i> -tridecyl-	82	C ₂₄ H ₄₁ N ₃ S ₂	66.5	9.7	66.2	9.4

^a Recrystallised from ethanol.

5-Substituted 2-thenaldehyde derivatives.

Substituent	M. p.	Formula	4-Oxo- Δ^2 -thiazolin-2-ylhydrazones. ^a				<i>iso</i> Nicotinoylhydrazones ^b					
			Found (%)		Reqd. (%)		M. p.	Formula	Found (%)		Reqd. (%)	
			C	H	C	H			N	N	N	N
<i>n</i> -Butyl-	195° (dec.)	C ₁₂ H ₁₅ ON ₃ S ₂	51.0	5.2	51.2	5.3	148°	C ₁₅ H ₁₇ ON ₃ S	14.5	14.6	14.5	14.6
<i>iso</i> Pentyl-	198	C ₁₃ H ₁₇ ON ₃ S ₂	52.6	6.0	52.9	5.8	162	C ₁₆ H ₁₉ ON ₃ S	14.0	14.0	14.0	14.0
<i>n</i> -Pentyl-	194	C ₁₃ H ₁₇ ON ₃ S ₂	52.6	5.8	52.9	5.8	130	C ₁₆ H ₁₉ ON ₃ S	14.2	14.0	14.2	14.0
<i>n</i> -Hexyl-	178	C ₁₄ H ₁₉ ON ₃ S ₂	54.3	6.1	54.4	6.2	121	C ₁₇ H ₂₁ ON ₃ S	13.0	13.3	13.0	13.3
<i>n</i> -Heptyl-	180	C ₁₅ H ₂₁ ON ₃ S ₂	55.9	6.5	55.7	6.5	122	C ₁₈ H ₂₃ ON ₃ S	12.6	12.8	12.6	12.8
<i>n</i> -Octyl-	168	C ₁₆ H ₂₃ ON ₃ S ₂	56.8	7.0	57.0	6.8	122	C ₁₉ H ₂₅ ON ₃ S	12.1	12.2	12.1	12.2
<i>n</i> -Decyl-	157	C ₁₈ H ₂₇ ON ₃ S ₂	59.1	7.3	59.2	7.4	124	C ₂₁ H ₂₉ ON ₃ S	11.1	11.3	11.1	11.3
Phenethyl-	217	C ₁₆ H ₁₅ ON ₃ S ₂	58.1	4.9	58.4	4.6	180	C ₁₉ H ₁₇ ON ₃ S	12.2	12.5	12.2	12.5
4'- <i>tert.</i> -Butylbenzyl- (dec.)	238	C ₁₉ H ₂₁ ON ₃ S ₂	61.3	5.8	61.5	5.7	183	C ₂₂ H ₂₅ ON ₃ S	11.0	11.1	11.0	11.1
<i>cyclo</i> Hexylmethyl- (dec.)	240	C ₁₅ H ₁₉ ON ₃ S ₂	56.3	5.8	56.1	5.9	187	C ₁₈ H ₂₁ ON ₃ S	12.6	12.8	12.6	12.8
3'- <i>cyclo</i> Hexylpropyl- (dec.)	218	C ₁₇ H ₂₃ ON ₃ S ₂	58.6	6.9	58.5	6.6	144	C ₂₀ H ₂₅ ON ₃ S	12.0	11.8	12.0	11.8
4'- <i>cyclo</i> Hexyl- <i>n</i> -hexyl- ω - <i>cyclo</i> Pentyl- <i>n</i> -tri- decyl-	170	C ₂₀ H ₂₉ ON ₃ S ₂	61.1	7.6	61.4	7.4	116	C ₂₉ H ₄₃ ON ₃ S	9.0	8.7	9.0	8.7
	152	C ₂₆ H ₄₁ ON ₃ S ₂	66.0	8.4	65.7	8.6						

^a Recrystallised from ethanol or acetic acid.

^b Recrystallised from ethanol.