

110. *Thiophen Derivatives of Potential Biological Interest. Part IV.* Tuberculostatic Thiophen Compounds.*

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Several 2-thiophenaldehyde thiosemicarbazones bearing a long-chain 5-alkyl substituent, and hydrazides and hydrazones of the thiophen series, have been prepared as potential tuberculostatic compounds.

OWING to the well-known tuberculostatic activity of analogues *in vitro*, thiophen derivatives (I—IV) were prepared in which R was a long-chain alkyl group and R'CO was nicotinoyl or isonicotinoyl. Standard methods were used.



These substances, which are lipid-soluble, are under biological investigation by Professor Welsch (Liège).

EXPERIMENTAL

Thiophen-aldehydes.—Treatment of *n*-propylthiophen (30 g.), prepared (98% yield) by Kishner-Huang-Minlon reduction of 2-propiothienone, with *N*-methylformanilide (42 g.) and phosphorus oxychloride (42 g.) yielded 5-*n*-propylthiophen-2-aldehyde (29 g.), b. p. 129°/15 mm., n_D^{25} 1.5555 [thiosemicarbazone, pale yellow needles (from ethanol), m. p. 119° (Found: C, 47.3; H, 5.5. C₉H₁₃N₃S₂ requires C, 47.6; H, 5.7%); 2:4-dinitrophenylhydrazone, prisms (from ethanol-benzene), m. p. 202° (Found: N, 16.5. C₁₄H₁₄O₄N₄S requires N, 16.8%)]. Kishner-Huang-Minlon reduction of this aldehyde (16 g.) (cf. Buu-Hoï, Hoán, and Xuong, *Rec. Trav. chim.*, 1952, 71, 285) yielded 2-methyl-5-*n*-propylthiophen (10 g.), b. p. 179°, n_D^{25} 1.5011 (cf. King and Nord, *J. Org. Chem.*, 1949, 14, 638), which with *N*-methylformanilide (12.5 g.) and phosphorus oxychloride (12.5 g.) yielded 2-methyl-5-*n*-propylthiophen-*x*-aldehyde (2 g.), b. p. 130—132°/15 mm., $n_D^{28.5}$ 1.5450 (Found: C, 64.0; H, 7.3. C₉H₁₂OS requires C, 64.3; H, 7.1%) [2:4-dinitrophenylhydrazone, prisms (from ethanol), m. p. 182° (Found: N, 16.3. C₁₅H₁₆O₄N₄S requires N, 16.1%); a semicarbazone, m. p. ca. 228° (decomp.)].

2-*n*-Undecanoylthiophen (Cagniant and Deluzarche, *Compt. rend.*, 1947, 225, 455), prepared in the usual way (cf. Buu-Hoï and Hoán, *Rec. Trav. chim.*, 1949, 68, 5) from thiophen (13.5 g.), *n*-undecanoyl chloride (32 g.), and aluminium chloride (23.5 g.) in carbon disulphide (100 c.c.), was a pale yellow oil (28 g.), b. p. 206°/15 mm., n_D^{25} 1.5139, giving a semicarbazone, needles (from methanol), m. p. 95—96° (Found: N, 13.4. C₁₆H₂₇ON₃S requires N, 13.6%). By the above reactions it gave 2-*n*-undecylthiophen (15 g. from 25 g.), b. p. 181—183°/18 mm., n_D^{25} 1.4918 (Found: C, 75.4; H, 10.8. C₁₅H₂₆S requires C, 75.6; H, 10.9%), and 5-*n*-undecylthiophen-2-aldehyde (9 g. from 14 g.), b. p. 225—226°/18 mm., n_D^{25} 1.5191 (Found: C, 72.0; H, 9.8. C₁₆H₂₆OS requires C, 72.2; H, 9.8%) [thiosemicarbazone, pale yellow needles (from ethanol), m. p. 97° (Found: C, 60.0; H, 8.5. C₁₇H₂₉N₃S₂ requires C, 60.2; H, 8.6%); 2:4-dinitrophenylhydrazone, prisms (from ethanol), m. p. 167° (Found: N, 12.3. C₂₂H₃₀O₄N₄S requires N, 12.6%)].

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2-Dodecanoylthiophen (35 g.; cf. Ralston and Christensen, *Ind. Eng. Chem.*, 1937, **29**, 194), b. p. 212—215°/15 mm., n_D^{25} 1.5060, was similarly prepared and yielded 2-n-dodecylthiophen (18 g. from 35 g.), b. p. 184—188°/18 mm., n_D^{25} 1.4783 (Found: C, 76.0; H, 11.3. $C_{18}H_{28}S$ requires C, 76.2; H, 11.1%), and 5-n-dodecylthiophen-2-aldehyde (6 g. from 15 g.), b. p. 224—228°/15 mm., pale yellow leaflets (from methanol), m. p. 34° (Found: C, 72.7; H, 10.3. $C_{17}H_{28}OS$ requires C, 72.9; H, 10.0%) [thiosemicarbazone, pale yellow needles (from ethanol), m. p. 95° (Found: C, 60.9; H, 9.0. $C_{18}H_{31}N_3S_2$ requires C, 61.2; H, 8.8%); 2:4-dinitrophenylhydrazones, prisms (from ethanol), m. p. 162° (Found: N, 11.9. $C_{23}H_{32}O_4N_4S$ requires N, 12.2%)].

Similarly were obtained 2-tetradecanoylthiophen (cf. Ralston and Christensen, *loc. cit.*), leaflets (from light petroleum), m. p. 36° [semicarbazone, needles (from ethanol), m. p. 108° (Found: N, 11.7. $C_{19}H_{33}ON_3S$ requires N, 12.0%)], 2-n-tetradecylthiophen (7 g. from 12 g.), b. p. 212—214°/15 mm., n_D^{25} 1.4845 (Found: C, 76.9; H, 11.3. $C_{18}H_{32}S$ requires C, 77.1; H, 11.4%), and 5-n-tetradecylthiophen-2-aldehyde (5.5 g. from 7 g.), b. p. 250—252°/20 mm., leaflets (from ethanol), m. p. 43° (Found: C, 73.7; H, 10.4. $C_{19}H_{32}OS$ requires C, 74.0; H, 10.4%) [thiosemicarbazone, needles (from ethanol), m. p. 97° (Found: C, 62.7; H, 9.2. $C_{20}H_{35}N_3S_2$ requires C, 63.0; H, 9.2%); 2:4-dinitrophenylhydrazones, prisms (from ethanol), m. p. 158° (Found: N, 11.2. $C_{25}H_{36}O_4N_4S$ requires N, 11.5%)].

4-Keto-2-thiazolylhydrazones of 5-Alkylthiophen-2-aldehydes.—These were prepared by refluxing for 3 hours 1 mol. each of the thiosemicarbazones and chloroacetic acid in ethanol; the precipitates obtained on cooling were recrystallised from acetic acid or ethanol, yielding the hydrazones (IV) in which R was n-propyl, prisms, m. p. 221° (decomp.) (Found: C, 49.3; H, 4.6. $C_{11}H_{13}ON_3S_2$ requires C, 49.4; H, 4.9%), n-undecyl, pale yellow needles, m. p. 163° (Found: C, 60.0; H, 7.8. $C_{19}H_{29}ON_3S_2$ requires C, 60.2; H, 7.7%), n-dodecyl, almost colourless needles, m. p. 155° (Found: C, 61.0; H, 7.8. $C_{20}H_{31}ON_3S_2$ requires C, 61.1; H, 7.9%), and n-tetradecyl, m. p. 154° (Found: C, 62.6; H, 8.1. $C_{22}H_{35}ON_3S_2$ requires C, 62.7; H, 8.3%).

Hydrazides.—2-Thenoylhydrazine, m. p. 137°, was prepared according to Curtius and Thyssen (*J. pr. Chem.*, 1903, **65**, 7). 5-Chloro-2-thenoylhydrazine (38 g.) was obtained by refluxing ethyl 5-chloro-2-thenoate (40 g.) and 85% hydrazine hydrate (15 g.) in methanol

R	M. p.	Found, %		Formula	Required, %	
		C	H		C	H
5-R-Thiophen-2-aldehyde N'-nicotinoylhydrazones (III). ^a						
Pr	138°	61.2	5.6	$C_{14}H_{15}ON_3S$	61.5	5.5
$C_{11}H_{23}$	118	68.5	8.2	$C_{22}H_{31}ON_3S$	68.6	8.1
$C_{12}H_{25}$	126	69.1	8.3	$C_{23}H_{33}ON_3S$	69.2	8.3
$C_{14}H_{29}$	129	70.0	8.8	$C_{25}H_{37}ON_3S$	70.3	8.7
5-R-Thiophene-2-aldehyde N'-isonicotinoylhydrazones (III). ^a						
Pr	192	61.4	5.5	$C_{14}H_{15}ON_3S$	61.5	5.5
$C_{11}H_{23}$	128	68.6	8.4	$C_{22}H_{31}ON_3S$	68.6	8.1
$C_{12}H_{25}$	119	69.0	8.4	$C_{23}H_{33}ON_3S$	69.2	8.3
$C_{14}H_{29}$	121	70.1	9.0	$C_{25}H_{37}ON_3S$	70.3	8.7
Thiophen-2-aldehyde N'-5-R-thenoylhydrazones (IV). ^a						
Pr	173	56.0	5.2	$C_{13}H_{14}ON_2S_2$	56.1	5.0
$C_{11}H_{23}$	105	64.3	7.8	$C_{21}H_{30}ON_2S_2$	64.6	7.7
$C_{12}H_{25}$	102	65.2	7.8	$C_{22}H_{32}ON_2S_2$	65.3	7.9
$C_{14}H_{29}$	106	66.4	8.5	$C_{24}H_{36}ON_2S_2$	66.7	8.3
Various N'-2-thenoylhydrazones (IV; R = H). ^b						
Parent X·CHO						
9-Ethylcarbazole-3-aldehyde ...	227°	69.4	4.8	$C_{20}H_{17}ON_3S$	69.2	4.9
Pyrene-3-aldehyde °	270	74.3	4.1	$C_{22}H_{14}ON_2S$	74.6	4.0
p-HO·C ₆ H ₄ ·CHO	> 262 ^f	58.2	4.0	$C_{12}H_{10}O_2N_2S$	58.5	4.1
4 : 3 : 5 : 1-HO·C ₆ H ₃ ·Br ₂ ·CHO ...	> 264 ^f	35.5	2.3	$C_{12}H_8O_2N_2SBr_2$	35.6	2.0
4 : 3 : 5 : 1-HO·C ₆ H ₃ ·I ₂ ·CHO	> 237 ^f	28.6	2.0	$C_{12}H_8O_2N_2SI_2$	28.9	1.6
p-NMe ₂ ·C ₆ H ₄ ·CHO	203	61.6	5.5	$C_{14}H_{15}ON_3S$	61.5	5.5
o-C ₆ H ₄ Cl·CHO	186	54.2	3.6	$C_{12}H_9ON_2S$	54.4	3.4
p-MeO·C ₆ H ₄ ·CHO	185	60.0	4.8	$C_{13}H_{12}O_2N_2S$	60.0	4.6
3 : 4 : 1-(MeO) ₂ C ₆ H ₃ ·CHO	171	57.6	4.9	$C_{14}H_{14}ON_3S$	57.9	4.8
3 : 4 : 1-C ₆ H ₃ Cl ₂ ·CHO	219	48.0	2.9	$C_{12}H_8ON_2S$	48.2	2.7
Ph·CHO ^d	189	54.1	3.5	$C_{12}H_9ON_2S$	54.4	3.4
Ph·CHO ^e	201	46.3	3.2	$C_{12}H_9ON_2SBr$	46.6	2.9
3 : 4 : 1-CH ₂ O ₂ ·C ₆ H ₃ ·CHO	199	56.8	3.5	$C_{13}H_{10}O_2N_2S$	56.9	3.6
X·CH = 5-Acenaphthylidene °	240	70.5	4.6	$C_{18}H_{14}ON_2S$	70.6	4.6

^a Yellow needles. ^b Colourless unless otherwise stated. ^c Yellow prisms, sparingly sol. in EtOH.
^d 5-Cl in the thenoyl nucleus. ^e 5-Br in the thenoyl nucleus. ^f Decomp.

(30 c.c.) for 12 hours, and crystallised from methanol as leaflets, m. p. 151°, decomp. >146° (Found: N, 15.6. $C_5H_8ON_2SCl$ requires N, 15.9%); *ethyl 5-chloro-2-thenoate*, prepared by treating 5-chloro-2-thenoyl chloride with ethanol, had b. p. 234—236° and an aromatic odour (Found: C, 44.0; H, 3.7. $C_7H_7O_2SCl$ requires C, 44.1; H, 3.7%).

5-Bromo-2-thenoylhydrazine, leaflets (from methanol), m. p. 144° (decomp. from 132°) (Found: N, 12.5. $C_5H_8ON_2SBr$ requires N, 12.7%), and ethyl 5-bromo-2-thenoate, b. p. 134—136°/30 mm., were similarly prepared.

Hydrazones.—One mol. each of the hydrazide and aldehyde in ethanol were refluxed for 10 minutes. The precipitates obtained on cooling were recrystallised from ethanol. The *products* are tabulated.

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