Thiophen Derivatives of Biological Interest. Part IX. Odour and Chemical Structure in the Thiophen Series.*

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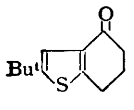
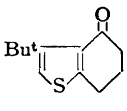
The relation between odour and chemical constitution in thiophen compounds has been investigated. 2- and 3-*tert.*-Butyl-4 : 5 : 6 : 7-tetrahydro-4-oxothionaphthen were synthesised from 2- and 3-*tert.*-butylthiophen by the succinic anhydride method; their vapours have an odour reminiscent of 7-*tert.*-butyl-1-tetralone; 5-*iso*propyl-2-thenaldehyde, 2-2′-thienylideneheptanal, and a series of esters of 2-thenoic acid have odours similar to those of the benzene isologues. Other reactions of 3-*tert.*-butylthiophen and 2 : 5-di-*tert.*-butylthiophen were investigated.

7-*tert.*-BUTYL-1-TETRALONE has an odour reminiscent of smouldering sandalwood (Buu-Hoï and Cagniant, *Compt. rend.*, 1942, **214**, 115; Cagniant and Buu-Hoï, *Bull. Soc. chim.*, 1942, **9**, 111, 841). It was of interest to examine the odour of its isologues. 2-*tert.*-Butyl-4 : 5 : 6 : 7-tetrahydro-4-oxothionaphthen (I), prepared from 2-*tert.*-butylthiophen by the succinic anhydride method (cf. Buu-Hoï, Hoán, and Khôi, *J. Org. Chem.*, 1950, **15**, 957), did in fact, in the vapour state, have the characteristic burning-sandalwood smell. The 3-*tert.*-butyl isomer, prepared from 3-*tert.*-butylthiophen, had a less marked and less pleasant odour. A chemical difference was that the former readily underwent a Pfitzinger reaction with isatin to give 5′-*tert.*-butyl-3 : 4-dihydrothiopheno(3′ : 2′-1 : 2)acridine-5-carboxylic acid (III), whereas the latter gave a negligible yield, probably on account of steric hindrance by the *tert.*-butyl group.



(I)



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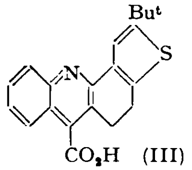

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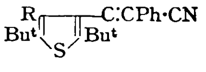

(IV)

The successful synthesis of the thionaphthen (II) showed that succinoylation of 3-*tert.*-butylthiophen, which yielded only one reaction product, occurred at position 5, in contrast with the acylation of 3-methylthiophen which takes place mostly at position 2 (Hartough and Kosak, *J. Amer. Chem. Soc.*, 1947, **69**, 3093), a discrepancy probably due to the steric effect of the *tert.*-butyl radical. Formylation of 3-*tert.*-butylthiophen readily gave a single aldehyde, which was therefore taken to be 4-*tert.*-butyl-2-thenaldehyde; likewise, acetylation gave a single ketone, considered on the same grounds to be 2-acetyl-4-*tert.*-butylthiophen. This ketone underwent a Pfitzinger reaction with isatin to give 2-(4-*tert.*-butyl-2-thienyl)cinchoninic acid, and oxidation with sodium hypobromite to give 4-*tert.*-butyl-2-thenoic acid.

Formylation of 2 : 5-di-*tert.*-butylthiophen gave a good yield of 2 : 5-di-*tert.*-butyl-3-thenaldehyde; condensation with benzyl cyanide gave the acrylonitrile (IV; R = H). 2 : 5-Di-*tert.*-butyl-3-methylthiophen, prepared from the aldehyde by Wolff–Kishner reduction, also gave the aldehyde, and thence the acrylonitrile (IV; R = Me) and 2 : 5-di-*tert.*-butyl-3 : 4-dimethylthiophen. 3-Acetyl-2 : 5-di-*tert.*-butylthiophen, unlike the aldehydes, gave no ketonic derivatives or cinchoninic acid, nor could it be oxidised by sodium hypobromite.

5-*iso*Propyl-2-thenaldehyde was prepared; its odour was like that of *p*-*iso*propylbenzaldehyde. Both 2-2′-thienylideneheptanol, prepared by condensing 2-thenaldehyde with heptanal, and α-*n*-pentylcinnamaldehyde (Rutowski and Korolew, *J. prakt. Chem.*,

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1928, **119**, 273) had a jasmin-like scent; similarly, a series of esters prepared from 2-thenoic acid had odours resembling those of their benzene isologues.

There is thus an analogy between the benzene and thiophen derivatives in respect of odour; but no attempt was made in the present work at a precise assessment on a physiological basis.

EXPERIMENTAL

*β-(5-*tert.*-Butyl-2-thenoyl)propionic Acid.*—To an ice-cooled, stirred solution of 2-*tert.*-butylthiophen (22 g.) and succinic anhydride (20 g.) in nitrobenzene (120 c.c.), finely powdered aluminium chloride (50 g.) was added portionwise. The mixture was kept for 16 hr. at room temperature, then decomposed with ice, and the nitrobenzene steam-distilled. The *keto-acid* was taken up in aqueous sodium carbonate and recrystallised from benzene, giving colourless prisms (31 g.), m. p. 114° (Found: C, 59·7; H, 6·8. $C_{12}H_{16}O_3S$ requires C, 60·0; H, 6·7%).

*γ-(5-*tert.*-Butyl-2-thienyl)butyric Acid.*—The foregoing acid (28 g.) was heated with 85% hydrazine hydrate (30 g.) and potassium hydroxide (25 g.) in diethylene glycol (100 c.c.) to 190—200° with removal of water, and the mixture then refluxed for 2 hr., diluted with water, and acidified with dilute hydrochloric acid. The reduction *product*, taken up in benzene, was purified by vacuum-distillation, and formed colourless leaflets (20 g.), m. p. 47°, b. p. 214°/24 mm., from ligroin (Found: C, 63·5; H, 8·2. $C_{12}H_{18}O_2S$ requires C, 63·7; H, 8·0%).

*2-*tert.*-Butyl-4 : 5 : 6 : 7-tetrahydro-4-oxothionaphthen* (I).—The butyric acid (10 g.) was converted into the acid chloride by thionyl chloride (20 g.) and a few drops of pyridine, treated in cold carbon disulphide (50 c.c.) with stannic chloride (25 g., dissolved in 20 c.c. of carbon disulphide), refluxed for 2 hr., and worked up in the usual way. The *ketone* (4 g.) formed a pale yellow oil, b. p. 170—171°/13 mm., n_D^{25} 1·5699 (Found: C, 68·9; H, 7·8. $C_{12}H_{16}OS$ requires C, 69·2; H, 7·7%). The *semicarbazone* formed needles, m. p. 249°, from ethanol (Found: N, 15·6. $C_{13}H_{19}ON_3S$ requires N, 15·8%).

*5′-*tert.*-Butyl-3 : 4-dihydrothiopheno(3′ : 2′-1 : 2)acridine-5-carboxylic Acid* (III).—A solution of the foregoing ketone (2·1 g.), isatin (1·5 g.), and potassium hydroxide (1·7 g.) in ethanol (15 c.c.) was gently refluxed for 12 hr. After dilution with water and ether-extraction of neutral impurities, acidification with acetic acid gave a precipitate (2 g.) which crystallised as pale yellow prisms, m. p. 231°, from ethanol (Found: C, 71·0; H, 5·6. $C_{20}H_{19}O_2NS$ requires C, 71·2; H, 5·6%).

*4-*tert.*-Butyl-2-thenaldehyde.*—A mixture of 3-*tert.*-butylthiophen (17·5 g.), *N*-methylformanilide (22·5 g.), and phosphorus oxychloride (24 g.) was refluxed for 2 hr., then poured into aqueous sodium acetate, and the mixture was steam-distilled. The *aldehyde* was taken up in ether, washed with dilute hydrochloric acid, then with water, dried (Na_2SO_4), and purified by distillation, to form a pale yellow oil (18 g.), b. p. 249—250°, n_D^{22} 1·5320 (Found: C, 64·2; H, 7·2. $C_9H_{12}OS$ requires C, 64·3; H, 7·1%). It gave a *semicarbazone*, leaflets, m. p. 221°, from ethanol (Found: N, 18·4. $C_{10}H_{15}ON_3S$ requires N, 18·7%), *thiosemicarbazone*, colourless prisms, m. p. 186°, from ethanol (Found: C, 49·5; H, 6·2. $C_{10}H_{15}N_3S_2$ requires C, 49·8; H, 6·2%), *4-oxo-Δ^2-thiazolin-2-ylhydrazone*, colourless prisms, m. p. 315°, from ethanol (Found: C, 51·0; H, 5·2. $C_{12}H_{15}ON_3S_2$ requires C, 51·2; H, 5·3%), *2 : 4-dinitrophenylhydrazone*, red needles, m. p. 221°, from acetic acid (Found: N, 16·2. $C_{15}H_{16}O_4N_4S$ requires N, 16·1%), and *oxime*, colourless needles, m. p. 79°, from methanol (Found: C, 58·8; H, 7·4. $C_9H_{13}ONS$ requires C, 59·0; H, 7·1%).

*4-*tert.*-Butyl-2-methylthiophen.*—Obtained by reduction of the foregoing aldehyde (8·5 g.) by means of hydrazine hydrate (14 g.) and potassium hydroxide (14 g.) in diethylene glycol (60 c.c.), this *compound* formed a pale yellow oil (7 g.), b. p. 195°, n_D^{24} 1·5025 (Found: C, 70·0; H, 9·2. $C_9H_{14}S$ reuires C, 70·1; H, 9·1%).

*2-Acetyl-4-*tert.*-butylthiophen.*—To an ice-cooled solution of 3-*tert.*-butylthiophen (14 g.) and acetyl chloride (8 g.) in carbon disulphide (200 c.c.), stannic chloride (30 g.) was added portionwise. The mixture was kept at room temperature for 1 hr., poured on ice, then worked up in the usual way. The *ketone* (15 g.) was a pale yellow oil, b. p. 259°, n_D^{23} 1·5322 (Found C, 65·8; H, 7·7. $C_{10}H_{14}OS$ requires C, 65·9; H, 7·7%). It gave a *2 : 4-dinitrophenylhydrazone*, red needles, m. p. 226°, from acetic acid (Found: N, 15·8. $C_{16}H_{18}O_4N_4S$ requires N, 15·5%), *oxime*, colourless needles, m. p. 113°, from ethanol (Found: C, 60·6; H, 7·5. $C_{10}H_{15}ONS$ requires C, 60·9; H, 7·6%), semicarbazone, m. p. 249°, thiosemicarbazone, m. p. 192°, and 4-oxo-Δ^2-thiazolin-2-ylhydrazone, m. p. 305°. *2-(4-*tert.*-Butyl-2-thienyl)cinchoninic acid*, prepared in 90% yield by means of isatin, formed pale yellow prisms, m. p. 172°, from ethanol (Found: C, 69·1; H, 5·3. $C_{18}H_{17}O_2NS$ requires C, 69·5; H, 5·5%).

4-tert.-*Butyl-2-thenoic Acid.*—2-Acetyl-4-*tert.*-butylthiophen (19 g.) was oxidised with aqueous sodium hypobromite (from 16 g. of sodium hydroxide and 8·2 c.c. of bromine); the *acid* obtained (60% yield) formed prisms, m. p. 77°, from water (Found: C, 58·5; H, 6·6. $C_9H_{12}O_2S$ requires C, 58·7; H, 6·5%).

β-(4-tert.-*Butyl-2-thenoyl)propionic Acid.*—Prepared from 3-*tert.*-butylthiophen as for the 2-isomer and in similar yield, this *acid* formed colourless prisms, m. p. 119°, from benzene (Found: C, 59·7; H, 6·5%). γ-(3-tert.-*Butyl-5-thienyl)butyric acid* formed a pale yellow, viscous oil, b. p. 200—201°/13 mm. (Found: C, 63·5; H, 8·3%).

3-tert.-*Butyl*-4 : 5 : 6 : 7-*tetrahydro-4-oxothiophen.*—This *ketone* formed a pale yellow oil, b. p. 179°/13 mm., $n_{\rm D}^{25}$ 1·5669, whose vapours had a less pleasant odour than the isomeric ketone (Found: C, 69·0; H, 8·0%); it gave no cinchoninic acid with isatin. The *semicarbazone* formed needles, m. p. 238° (Found: C, 58·6; H, 7·3%).

2 : 5-*Di*-tert.-*butyl-3-thenaldehyde.*—A mixture of 2 : 5-di-*tert.*-butylthiophen (25 g.), phosphorus oxychloride (25 g.), and *N*-methylformanilide (24 g.) was heated for 3 hr. on the water-bath and worked up in the usual way; the *aldehyde* formed a pale yellow oil, b. p. 137°/13 mm., $n_{\rm D}^{21}$ 1·5147 (Found: C, 69·5; H, 9·0. $C_{13}H_{20}OS$ requires C, 69·6; H, 8·9%), and gave a *semicarbazone*, prisms, m. p. 231° (Found: N, 14·6. $C_{14}H_{23}ON_3S$ requires N, 14·9%), *oxime*, prisms, m. p. 106°, from ethanol (Found: C, 65·0; H, 9·0. $C_{13}H_{21}ONS$ requires C, 65·3; H, 8·8%), and 2 : 4-*dinitrophenylhydrazone*, red needles, m. p. 219°, from acetic acid (Found: N, 14·2. $C_{19}H_{24}O_4N_4S$ requires N, 13·9%).

1-*Phenyl*-2-(2 : 5-*di*-tert.-*butyl-3-thienyl)acrylonitrile* (IV; R = H).—This *compound* crystallised as pale yellow needles, m. p. 136°, from ethanol, giving a deep orange solution with sulphuric acid (Found: C, 78·2; H, 7·6. $C_{21}H_{25}NS$ requires C, 78·0; H, 7·7%).

2 : 5-*Di*-tert.-*butyl-3-methylthiophen.*—Prepared from 2 : 5-di-*tert.*-butyl-3-thenaldehyde (10 g.), hydrazine hydrate (15 g.), and potassium hydroxide (15 g.) in diethylene glycol (50 c.c.), this *compound* formed a pale yellow oil (8 g.), b. p. 119°/13 mm., $n_{\rm D}^{23}$ 1·4952 (Found: C, 74·2; H, 10·5. $C_{13}H_{22}S$ requires C, 74·3; H, 10·5%).

2 : 5-*Di*-tert.-*butyl-4-methyl-3-thenaldehyde.*—Prepared from the foregoing compound (8 g.), phosphorus oxychloride (8 g.), and *N*-methylformanilide (7 g.), the *aldehyde* (7 g.) was a pale yellow, viscous oil, b. p. 155°/13 mm., $n_{\rm D}^{21}$ 1·5091 (Found: C, 70·4; H, 9·5. $C_{14}H_{22}OS$ requires C, 70·6; H, 9·2%); it gave a *semicarbazone*, needles, m. p. 225°, from ethanol (Found: N, 13·9. $C_{15}H_{25}ON_3S$ requires N, 14·2%), *oxime*, prisms, m. p. 95°, from ethanol (Found: C, 66·3; H, 9·3. $C_{14}H_{23}ONS$ requires C, 66·4; H, 9·1%), and orange-red 2 : 4-dinitrophenylhydrazone, m. p. 221°.

2-(2 : 5-*Di*-tert.-*butyl-4-methyl-3-thienyl)-1-phenylacrylonitrile* (IV; R = Me).—This *compound* crystallised as yellow needles, m. p. 144° from ethanol, giving an orange-red solution with sulphuric acid (Found: C, 78·0; H, 8·3. $C_{22}H_{27}NS$ requires C, 78·3; H, 8·0%).

2 : 5-*Di*-tert.-*butyl*-3 : 4-*dimethylthiophen.*—Obtained in only 60% yield, this *compound* was a pale yellow oil, b. p. 139°/13 mm., $n_{\rm D}^{19}$ 1·4832 (Found: C, 74·9; H, 10·9. $C_{14}H_{24}S$ requires C, 75·0; H, 10·7%).

5-iso*Propyl-2-thenaldehyde.*—Prepared in the usual way from 2-*iso*propylthiophen (Schleicher, *Ber.*, 1886, **19**, 672) (b. p. 154°, $n_{\rm D}^{20}$ 1·5630), the *aldehyde* (78% yield) was a pale yellow oil, b. p. 239°, $n_{\rm D}^{19}$ 1·5604, with a strong cumin odour resembling that of *p*-*iso*propylbenzaldehyde (Found: C, 62·3; H, 6·5. $C_8H_{10}OS$ requires C, 62·3; H, 6·5%). The *semicarbazone* formed needles, m. p. 219°, from ethanol (Found: C, 51·0; H, 6·3. $C_9H_{13}ON_3S$ requires C, 51·2; H, 6·2%), the *thiosemicarbazone* yellowish prisms, m. p. 203°, from ethanol (Found: C, 47·3; H, 5·5. $C_9H_{13}N_3S_2$ requires C, 47·6; H, 5·7%); and the 4-*oxo*-Δ^2-*thiazolin-2-ylhydrazone* colourless needles, m. p. 257° (decomp.) (Found: C, 49·1; H, 5·0. $C_{11}H_{13}ON_3S_2$ requires C, 49·4; H, 4·9%). 1-*Phenyl*-2-(5-iso*propyl-2-thienyl)acrylonitrile*, obtained by use of benzyl cyanide, formed yellowish needles, m. p. 72°, from ethanol, giving an orange colour with sulphuric acid (Found: C, 75·8; H, 6·2. $C_{16}H_{15}NS$ requires C, 75·9; H, 5·9%).

2-2′-*Thienylideneheptanal.*—To a solution of 2-thenaldehyde (11·2 g.) and heptanal (11·4 g.) in ethanol (100 c.c.) and water (500 c.c.), 10% aqueous sodium hydroxide (25 c.c.) was added, and the mixture was kept at room temperature for 2 days, with frequent shaking. After acidification with acetic acid, the *product* was taken up in ether and vacuum-fractionated, giving a colourless oil (15 g.), b. p. 192—194°/35 mm., $n_{\rm D}^{25}$ 1·5686 (Found: C, 69·0; H, 7·8. $C_{12}H_{16}OS$ requires C, 69·2; H, 7·7%). The *semicarbazone* formed colourless prisms, m. p. 132—133°, from ethanol (Found: C, 58·6; H, 7·4. $C_{13}H_{19}ON_3S$ requires C, 58·9; H, 7·2%).

Esters of 2-Thenoic and 5-tert.-*Butyl-2-thenoic Acid.*—These *esters* were prepared by the reaction of 2-thenoyl chloride or 5-*tert.*-butyl-2-thenoyl chloride on the appropriate alcohol in ether or benzene; they are listed in the Table.

Alkyl	B. p./mm.	n_D (temp.)	Formula	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
		Esters of 2-thenoic acid.					
Pr^n	124—125°/24	1·5137 (28°)	$C_8H_{10}O_2S$	56·3	6·1	56·5	5·9
Pr^i	110°/22	1·5128 (26)	$C_8H_{10}O_2S$	56·2	6·0	56·5	5·9
Bu^n	137—138°/24	1·5112 (27)	$C_9H_{12}O_2S$	58·8	6·6	58·7	6·5
Bu^t	129°/22	1·5088 (27)	$C_9H_{12}O_2S$	58·4	6·7	58·7	6·5
n-Pentyl	152—153°/27	1·5079 (27)	$C_{10}H_{14}O_2S$	60·5	7·3	60·6	7·1
*iso*Pentyl	142—143°/22	1·5049 (28)	$C_{10}H_{14}O_2S$	60·8	7·0	60·6	7·1
n-Decyl	207—208°/20	1·4943 (26)	$C_{15}H_{24}O_2S$	67·0	8·8	67·2	9·0
Tetrahydrogeranyl	198°/22	1·4986 (27)	$C_{15}H_{24}O_2S$	67·3	9·2	67·2	9·0
n-Dodecyl	224—225°/20	1·4901 (28)	$C_{17}H_{28}O_2S$	68·6	9·4	68·9	9·5
n-Tetradecyl	245—246°/20	1·4891 (27)	$C_{19}H_{32}O_2S$	70·3	10·2	70·4	9·9
n-Hexadecyl	266—268°/22	1·4882 (26)	$C_{21}H_{36}O_2S$	71·3	10·2	71·6	10·2
Citronellyl	198—199°/20	1·4981 (26)	$C_{15}H_{22}O_2S$	67·5	8·5	67·7	8·3
Benzyl	195—196°/24	1·5786 (25)	$C_{12}H_{10}O_2S$	66·0	4·7	66·1	4·6
2-Phenylethyl	199—201°/18	1·5731 (26)	$C_{13}H_{12}O_2S$	67·0	5·5	67·2	5·2
3-Phenylpropyl	222°/24	1·5649 (26)	$C_{14}H_{14}O_2S$	68·2	5·8	68·3	5·7
		Esters of 5-tert.*-butyl-2-thenoic acid.*					
Et	150—151°/20	1·5138 (26)	$C_{11}H_{16}O_2S$	62·0	7·3	62·3	7·5
*iso*Pentyl	174—175°/20	1·5025 (25)	$C_{14}H_{22}O_2S$	66·0	8·8	66·1	8·7
Benzyl	226—227°/29	1·5608 (27)	$C_{16}H_{18}O_2S$	70·3	6·6	70·1	6·6
2-Phenylethyl	238—239°/31	1·5493 (27)	$C_{17}H_{20}O_2S$	70·5	7·2	70·8	6·9

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