Thiophen Derivatives of Biological Interest. Part VIII. 2-Arylthiophens, 2 : 4-Diarylthiophens, and 2 : 4-Diarylselenophens.*

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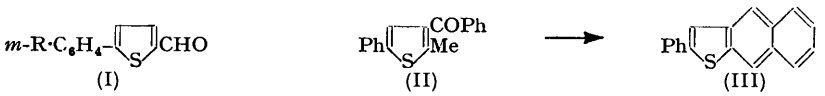
The behaviour of 2-arylthiophens, 2 : 4-diarylthiophens, and 2 : 4-diarylselenophens in formylation and Friedel–Crafts acylations, and their stability towards metal chlorides, have been investigated.

Arylthiophens offer the possibility of comparing the reactivities of thiophen and benzene nuclei in the same molecule. 2-Phenylthiophen undergoes nitration, mercuration, halogenation (Chrzaszczewska, *Roczn. Chem.*, 1925, **5**, 1, 33; Buu-Hoï and Hoán, *Rec. Trav. chim.*, 1950, **69**, 1455), and Friedel–Crafts acylation (Steinkopf and Petersdorff, *Annalen*, 1940, **543**, 119; Buu-Hoï and Hoán, *loc. cit.*) in the 5-position; 2-*p*-tolyl- and 2-*p*-chlorophenyl-thiophen behaved in the same way. It has now been found that 2-phenylthiophen with *N*-methylformanilide and phosphorus oxychloride gives 5-phenyl-2-thenaldehyde (I; R = H), which was orientated by Kishner–Wolff reduction to 2-methyl-5-phenylthiophen (Paal, *Ber.*, 1885, **18**, 367). 2-*m*-Chlorophenyl- and 2-*m*-tolyl-thiophen gave the aldehydes (I; R = Cl and Me) similarly. Acetylation of 2-*m*-chlorophenylthiophen in the presence of stannic chloride yielded 2-acetyl-5-*m*-chlorophenylthiophen, from which 2-*m*-chlorophenyl-5-ethylthiophen was obtained in the usual way.



(I) (II) (III)

2-Methyl-5-phenylthiophen resisted formylation and stannic chloride-catalysed benzoylation, but in the presence of aluminium chloride gave 3-benzoyl-2-methyl-5-phenylthiophen (II), the constitution of which followed from its conversion by an Elbs reaction into 5-phenylnaphtho(2′ : 3′-2 : 3)thiophen (III). Deactivation at the β-position by conjugation of the phenyl group was found also in other studies : 2 : 4-diphenyl- and 2 : 4-di-*p*-tolyl-thiophen with *N*-methylformanilide gave 3 : 5-diphenyl- and 3 : 5-di-*p*-tolyl-2-thenaldehyde, but 2-methyl-3 : 5-diphenyl- and -3 : 5-di-*p*-tolyl-thiophen, obtained by reduction of these aldehydes, resisted formylation and stannic chloride-catalysed acylation. It is known,

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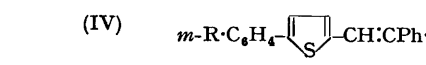
moreover, that 2 : 4 : 5-trimethylthiophen gives the aldehyde on reaction with *N*-methylformanilide (King and Nord, *J. Org. Chem.*, 1949, **14**, 638).

Several 2 : 4-diarylselenophens have been prepared. Their reactivities approximated to those of the corresponding thiophens; yields were lower in Friedel–Crafts acylation when stannic chloride was used as catalyst, but were higher with aluminium chloride. This was due to the greater stability of 2 : 4-diarylselenophens towards Lewis acids, as shown by the relative amounts of decomposition of 2 : 4-diphenylthiophen and 2 : 4-diphenylselenophen by several metal chlorides in various solvents. In the Table are listed ketones from 2 : 4-diaryl-thiophens and -selenophens, and the 2-alkyl-3 : 5-diaryl-thiophens and -selenophens derived from them by reduction.

Conjugation between benzene and thiophen nuclei is demonstrated by the bright yellow colour of α-phenyl-β-(5-*m*-tolyl-2-thienyl)- and -β-(5-*m*-chlorophenyl-2-thienyl)-acrylonitrile (IV; R = Me and Cl) (prepared from phenylacetonitrile and the appropriate arylthenaldehyde), of β-(3 : 5-diphenyl-2-thienyl)- and β-(3 : 5-di-*p*-tolyl-2-thienyl)-α-phenylacrylonitrile (V; X = S, R = H and Me) (prepared from the corresponding diarylthenaldehydes), and of chalkones obtained by condensation of the same aldehydes with ketones COArMe. The bathochromic effect on passage from the thiophen to the selenophen

(IV)  (V)

series (cf. Demerseman, Buu-Hoï, Royer, and Cheutin, *J.*, 1954, 2720) was again evident in the deep yellow-to-orange colour of α-phenyl-β-(3 : 5-diphenyl-2-selenophenyl)acrylonitrile (V; X = Se, R = H) and similar selenophen derivatives.

Experimental

5-Phenyl-2-thenaldehyde (I; R = H).—2-Phenylthiophen (16 g.), *N*-methylformanilide (19 g.), and phosphorus oxychloride (22·5 g.) were heated in toluene (100 c.c.) at 100° for 5 hr.; after decomposition with aqueous sodium acetate, and steam-distillation, the residue was taken up in benzene, dried (Na_2SO_4), and purified by vacuum-distillation. The *aldehyde* (15 g., 80%) had b. p. 200—203°/16 mm., and formed colourless needles, m. p. 92°, from ethanol (Found: C, 69·9; H, 4·4. $C_{11}H_8OS$ requires C, 70·2; H, 4·3%); its *semicarbazone* formed pale yellow needles, decomp. >215°, m. p. *ca.* 257°, from ethanol (Found: N, 17·2. $C_{12}H_{11}ON_3S$ requires

Thiophen	M. p.	Formula	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
2-Acetyl-3 : 5-di-*p*-tolyl-	150°	$C_{20}H_{18}OS$	78·3	5·9	78·4	5·8
2-Propionyl-3 : 5-di-*p*-tolyl-	116	$C_{21}H_{20}OS$	78·5	6·4	78·7	6·2
2-Methyl-3 : 5-diphenyl- *	132	$C_{17}H_{14}S$	81·5	5·7	81·6	5·6
2-Methyl-3 : 5-di-*p*-tolyl-	167	$C_{19}H_{18}S$	81·6	6·5	82·0	6·5
2-Ethyl-3 : 5-diphenyl-	144	$C_{18}H_{16}S$	81·5	5·8	81·8	6·0
3 : 5-Diphenyl-2-*n*-propyl-	115	$C_{19}H_{18}S$	82·1	6·4	82·0	6·4
2-Ethyl-3 : 5-di-*p*-tolyl-	165	$C_{20}H_{20}S$	82·0	6·6	82·1	6·8
2-*n*-Propyl-3 : 5-di-*p*-tolyl-	170	$C_{21}H_{22}S$	82·4	7·0	82·3	7·1
Selenophen						
2-*n*-Butyryl-3 : 5-diphenyl-	111	$C_{20}H_{18}OSe$	67·6	5·1	67·9	5·1
2-Acetyl-3 : 5-di-*p*-tolyl-	144	$C_{20}H_{18}OSe$	67·6	5·3	67·9	5·1
2-Propionyl-3 : 5-di-*p*-tolyl-	122	$C_{21}H_{20}OSe$	68·8	5·5	68·6	5·4
2-Acetyl-3 : 5-di-*p*-methoxyphenyl-	137	$C_{20}H_{18}O_2Se$	62·0	4·6	62·3	4·6
2-Methyl-3 : 5-diphenyl-	71	$C_{17}H_{14}Se$	68·3	4·6	68·6	4·7
2-Methyl-3 : 5-di-*p*-tolyl-	81	$C_{19}H_{18}Se$	69·8	5·5	70·1	5·5
3-Ethyl-3 : 5-diphenyl-	114	$C_{18}H_{16}Se$	69·2	5·0	69·4	5·1
2-Ethyl-3 : 5-di-*p*-tolyl-	136	$C_{20}H_{20}Se$	70·5	5·7	70·8	5·7
2-*n*-Propyl-3 : 5-di-*p*-tolyl-	143	$C_{21}H_{22}Se$	71·0	6·1	71·4	6·2

All compounds were purified by distillation in a high vacuum and recrystallised from ethanol as colourless prisms. The halochromy in sulphuric acid was yellow (thiophen ketones and 2-alkyl-3 : 5-diarylthiophens), orange-yellow (selenophen ketones) and orange (5-alkyl-2 : 4-diarylselenophens). Yields in Friedel–Crafts acylations of 2 : 4-diarylselenophens (72—82%) were slightly higher with aluminium chloride than by the stannic chloride method (65—79%).

* This compound could not be formylated or acylated in the presence of stannic chloride; its selenophen analogue showed the same inertia.

N, 17·1%), its *thiosemicarbazone*, yellow prisms, decomp. >190°, m. p. *ca.* 209°, from ethanol (Found : C, 54·9; H, 4·2. $C_{12}H_{11}N_3S_2$ requires C, 55·2; H, 4·2%), and its 2 : 4-*dinitrophenylhydrazone* crimson needles, m. p. 288°, from acetic acid (Found : N, 15·0. $C_{17}H_{12}O_4N_4S$ requires N, 15·2%).

2-*Methyl*-5-*phenylthiophen*.—The foregoing aldehyde (6 g.) was heated with 85% hydrazine hydrate (2·4 g.) in diethylene glycol (20 c.c.) for a few minutes at 100°; after cooling, potassium hydroxide (2·7 g.) was added, and the mixture heated with removal of water up to 190—200°, then refluxed for 2 hr. Dilute hydrochloric acid was added after cooling, and the product taken up in benzene and vacuum-distilled. It crystallised as colourless needles (4·8 g.), m. p. 51°, from ethanol; Paal (*loc. cit.*) gave m. p. 49—51°.

3-*Benzoyl*-2-*methyl*-5-*phenylthiophen* (II).—To an ice-cooled solution of 2-methyl-5-phenylthiophen (8·7 g.) and benzoyl chloride (7·7 g.) in carbon disulphide, aluminium chloride (7·4 g.) was added portionwise with stirring; the mixture was kept at room temperature for 1½ hr., then decomposed with dilute hydrochloric acid, the organic layer washed with aqueous sodium hydroxide and dried (Na_2SO_4), the solvent removed, and the residue fractionated in a vacuum. The *ketone* formed colourless leaflets (9·5 g.), m. p. 129°, from ethanol (Found : C, 77·3; H, 5·1. $C_{18}H_{14}OS$ requires C, 77·6; H, 5·0%). No ketone was obtained by the stannic chloride procedure, whereas 2-benzoyl-5-phenylthiophen (3 g.), m. p. 131°, from ethanol, was readily prepared from 2-phenylthiophen (4 g.), benzoyl chloride (4 g.), and stannic chloride (7·2 g.) in carbon disulphide.

5-*Phenylnaphtho*(2′ : 3′-2 : 3)*thiophen* (III).—3-Benzoyl-2-methyl-5-phenylthiophen (8 g.) was gently refluxed for 3 hr., and the *product* was vacuum-distilled and recrystallised from benzene; it formed colourless, sublimable leaflets (3 g.), m. p. 297° (Found : C, 82·8; H, 4·6. $C_{18}H_{12}S$ requires C, 83·0; H, 4·6%).

2-m-*Chlorophenylthiophen*.—This was prepared by the Gomberg–Bachmann method (*J. Amer. Chem. Soc.*, 1924, **46**, 2339) : 5N-sodium hydroxide (232 c.c.) was added dropwise to a well-stirred mixture of thiophen (250 c.c.) and a diazonium solution from *m*-chloroaniline (127·5 g. in 80 c.c. of water), hydrochloric acid (200 c.c.), and sodium nitrite (72 g. in 140 c.c. of water); the product (13 g.), purified by steam-distillation and vacuum-fractionation, formed colourless leaflets, m. p. 30°, b. p. 154—156°/15 mm., from ethanol (Found : C, 61·5; H, 3·8. $C_{10}H_7SCl$ requires C, 61·7; H, 3·6%).

5-m-*Chlorophenyl*-2-*thenaldehyde* (I; R = Cl).—Prepared in 70% yield from the foregoing compound (5 g.), *N*-methylformanilide (5·3 g.), and phosphorus oxychloride (6 g.) in toluene, this *aldehyde* formed colourless needles, m. p. 91°, b. p. 215—218°/14 mm., from ethanol (Found : C, 59·6; H, 3·1. $C_{11}H_7OSCl$ requires C, 59·3; H, 3·1%) and gave a thiosemicarbazone, yellowish needles, m. p. 186°, from ethanol and 2 : 4-*dinitrophenylhydrazone*, dark red needles, m. p. 276°, from acetic acid (Found : N, 13·6. $C_{17}H_{11}O_4N_4SCl$ requires N, 13·9%).

β-(5-m-*Chlorophenyl*-2-*thienyl*)-α-*phenylacrylonitrile* (IV; R = Cl).—To a warm ethanol solution of equimolecular amounts of the foregoing aldehyde and phenylacetonitrile, a few drops of concentrated aqueous sodium hydroxide were added; the precipitated *nitrile* crystallised as yellow needles, m. p. 161°, from ethanol (Found : C, 70·8; H, 3·9. $C_{19}H_{12}NSCl$ requires C, 70·9; H, 3·7%).

5-m-*Chlorophenyl*-2-*methylthiophen*.—Obtained in 81% yield from the foregoing aldehyde (2·2 g.), hydrazine hydrate (1 g.), and potassium hydroxide (1 g.) in diethylene glycol, this *compound* had b. p. 170—174°/14 mm., n_D^{24} 1·6465 (Found : C, 63·3; H, 4·0. $C_{11}H_9SCl$ requires C, 63·3; H, 4·3%).

2-*Acetyl*-5-m-*chlorophenylthiophen*.—To an ice-cooled solution of 2-*m*-chlorophenylthiophen (4·5 g.) and acetyl chloride (2 g.) in carbon disulphide, stannic chloride (7 g.) was added portionwise; the mixture was kept at room temperature for 12 hr., then decomposed with dilute hydrochloric acid, the organic layer was washed with water and dried (Na_2SO_4), the solvent removed, and the residue vacuum-distilled. The *ketone* (4·3 g.), b. p. 217—220°/13 mm., formed colourless leaflets, m. p. 99°, from ethanol (Found : C, 60·6; H, 3·6. $C_{12}H_9OSCl$ requires C, 60·8; H, 3·8%) and a 2 : 4-*dinitrophenylhydrazone*, dark red prisms, m. p. 228°, from acetic acid (Found : N, 13·0. $C_{18}H_{13}O_4N_4SCl$ requires N, 13·4%), and thiosemicarbazone, almost colourless needles, m. p. 190°, from ethanol. The *chalkone* obtained from this ketone and 5-*m*-chlorophenyl-2-thenaldehyde formed golden-yellow prisms, m. p. 213°, from ethanol (Found : C, 62·1; H, 3·2. $C_{23}H_{14}OS_2Cl_2$ requires C, 62·5; H, 3·1%).

The following were also prepared :

2-m-*Chlorophenyl*-5-*ethylthiophen* (77% yield), b. p. 178°/14 mm., n_D^{21} 1·6261 (Found : C, 64·5; H, 5·1. $C_{12}H_{11}SCl$ requires C, 64·7; H, 4·9.

2-m-*Tolylthiophen* [poor yield (6 g.) in the diazo-reaction of *m*-toluidine (107 g.) and thiophen (168 g.)], b. p. 143—145°/12 mm., n_D^{20} 1·6249 (Found: C, 75·5; H, 5·9. $C_{11}H_{10}S$ requires C, 75·8; H, 5·7%).

5-m-*Tolyl*-2-*thenaldehyde* (I; R = Me) [4·5 g. from 2-*m*-tolylthiophen (5 g.), *N*-methylformanilide (5·7 g.), and phosphorus oxychloride (6·5 g.)], colourless prisms, m. p. 48°, b. p. 196—198°/12 mm., from ethanol (Found: C, 71·4; H, 5·0. $C_{12}H_{10}OS$ requires C, 71·3; H, 5·0%); *thiosemicarbazone*, yellowish prisms, m. p. 190—191°, from ethanol (Found: C, 56·4; H, 4·8. $C_{13}H_{13}N_3S_2$ requires C, 56·7; H, 4·7%).

α-*Phenyl*-β-(5-m-*tolyl*-2-*thienyl*)*acrylonitrile* (IV; R = Me), yellow prisms, m. p. 139°, from ethanol (Found: C, 79·5; H, 5·3. $C_{20}H_{15}NS$ requires C, 79·7; H, 5·0%).

2-*Methyl*-5-m-*tolylthiophen*, b. p. 153°/13 mm., n_D^{22} 1·6240 (Found: C, 76·3; H, 6·3. $C_{12}H_{12}S$ requires C, 76·5; H, 6·4%).

2 : 4-Diphenyl-5-thenaldehyde [from 2 : 4-diphenylthiophen (23·5 g.), *N*-methylformanilide (19 g.; or dimethylformamide), and phosphorus oxychloride (22·5 g.) in hot dry toluene (100 c.c.) (5 hr.)]; 2 : 4-*dinitrophenylhydrazone*, crimson needles, m. p. 269°, from acetic acid (Found: N, 12·5. $C_{23}H_{16}O_4N_4S$ requires N, 12·6%); 4-*oxo*-Δ^2-*thiazolin*-2-*ylhydrazone*, yellow needles, m. p. 272°, from acetic acid (Found: N, 11·3. $C_{20}H_{15}ON_3S_2$ requires N, 11·1%).

β-(2 : 4-*Diphenyl*-5-*thienyl*)-α-*phenylacrylonitrile*, lemon-yellow needles, m. p. 178°, from ethanol (Found: C, 82·3; H, 4·5. $C_{25}H_{17}NS$ requires C, 82·6; H, 4·7%).

3 : 5-*Di*-p-*tolyl*-2-*thenaldehyde* [from 2 : 4-di-*p*-tolylthiophen (5 g.), *N*-methylformanilide (4 g.), and phosphorus oxychloride (4·6 g.) in toluene (30 c.c.); 82% yield], yellowish leaflets, m. p. 165°, from ethanol (Found: C, 78·3; H, 5·7. $C_{19}H_{16}OS$ requires C, 78·1; H, 5·5%); *semicarbazone*, yellow prisms (from ethanol), decomp. >242° (Found: N, 11·7. $C_{20}H_{19}ON_3S$ requires N, 12·0%); thiosemicarbazone, yellow prisms, decomp. >196°; the acrylonitrile with phenylacetonitrile formed yellow needles from ethanol.

2-Formyl-3 : 5-diphenylselenophen [83·5% yield from 2 : 4-diphenylselenophen (28 g.), *N*-methylformanilide (19 g.), and phosphorus oxychloride (22·5 g.) in toluene (100 c.c.)]; 4-*oxo*-Δ^2-*thiazolin*-2-*ylhydrazone*, yellow needles, m. p. 275°, from acetic acid (Found: N, 9·6. $C_{20}H_{15}ON_3SSe$ requires N, 9·9%); β-(3 : 5-*diphenyl*-2-*selenophenyl*)-α-*phenylacrylonitrile*, deep yellow prisms, m. p. 171°, from ethanol (Found: C, 71·0; H, 4·4. $C_{25}H_{17}NSe$ requires C, 71·2; H, 4·1%).

2-*Formyl*-3 : 5-*di*-p-*tolylselenophen* [4·5 g. from 2 : 4-di-*p*-tolylselenophen (5 g.)], yellowish prisms, m. p. 121° (from methanol), giving a brown-red colour in sulphuric acid (Found: C, 67·2; H, 4·7. $C_{19}H_{16}OSe$ requires C, 67·0; H, 4·9%); *semicarbazone*, yellow prisms (from ethanol), decomp. >230°, m. p. 249° (Found: N, 10·3. $C_{20}H_{19}ON_3Se$ requires N, 10·6%); *thiosemicarbazone*, yellow prisms, m. p. 192°, from ethanol (Found: N, 10·5. $C_{20}H_{19}N_3SSe$ requires N, 10·2%); 2 : 4-dinitrophenylhydrazone, crimson needles, m. p. 288°, from acetic acid; deep yellow condensation product with phenylacetonitrile.

2-*Formyl*-3 : 5-*di*-p-*methoxyphenylselenophen* [4·5 g. from 2 : 4-di-*p*-methoxyphenylselenophen (6 g.)], pale yellow needles, m. p. 131°, from ethanol, giving dark red halochromy in sulphuric acid (Found: C, 61·3; H, 4·4. $C_{19}H_{16}O_3Se$ requires C, 61·4; H, 4·3%); *thiosemicarbazone*, orange-yellow prisms (from ethanol), decomp. >210°, m. p. 244° (Found: N, 9·4. $C_{20}H_{19}O_3N_3SSe$ requires N, 9·5%); 4-*oxo*-Δ^2-*thiazolin*-2-*ylhydrazone*, yellow needles (from acetic acid), m. p. 266° (Found: N, 8·4. $C_{22}H_{19}O_3N_3SSe$ requires N, 8·6%); 2 : 4-dinitrophenylhydrazone, red needles, m. p. 231°, from acetic acid; orange-yellow condensation product with phenylacetonitrile.

2-β-(3 : 5-*Diphenyl*-2-*thienyl*)*acryloyl*-3 : 5-*diphenylthiophen*.—A solution in warm ethanol of equimolecular amounts of 3 : 5-diphenyl-2-thenaldehyde and 2-acetyl-3 : 5-diphenylthiophen was shaken with a few drops of a 20% aqueous sodium hydroxide; the precipitated *ketone* crystallised as yellow needles, m. p. 182°, from ethanol (Found: C, 80·0; H, 4·7. $C_{35}H_{24}OS_2$ requires C, 80·1; H, 4·5%).

2 : 4-*Di*-(p-*hydroxyphenyl*)*selenophen*.—2 : 4-Di-*p*-methoxyphenylselenophen (3 g.) and redistilled pyridine hydrochloride (10 g.) were refluxed for 20 min.; the precipitate obtained on addition of water (2 g.) was purified by dissolution in aqueous sodium hydroxide and reprecipitation with hydrochloric acid. Repeated crystallisation from acetic acid gave the *product* as colourless prisms, m. p. 218° (Found: C, 60·5; H, 3·6. $C_{16}H_{12}O_2Se$ requires C, 60·9; H, 3·8%).

Stability of 2 : 4-*Diarylthiophens and* 2 : 4-*Diarylselenophens towards Metal Chlorides*.—2 : 4-Diphenyl-thiophen and -selenophen (0·01 mol.) were severally kept for 45 min. in contact with aluminium or stannic chloride (0·012 mol.) in dry carbon disulphide or benzene (50 c.c.). After treatment with ice and hydrochloric acid, the organic layer was washed with water and dried

(Na_2SO_4), and the unchanged substance isolated by distillation in a high vacuum. 2 : 4-Diphenylthiophen is scarcely affected by stannic chloride up to 25° but undergoes extensive decomposition by aluminium chloride even at room temperature; 2 : 4-diphenylselenophen is stable towards aluminium chloride up to 25° but decomposes almost completely above 40°. 2 : 4-Diphenyl-thiophen and -selenophen formed dark brown complexes with aluminium chloride; the complex with stannic chloride was brown-yellow with the thiophen, and red with the selenophen. 2 : 4-Diphenyl-thiophen and -selenophen are stable towards fused zinc chloride (in chloroform) and ferric chloride (in light petroleum) up to 60°.

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