Thiophen Derivatives of Biological Interest. Part V. 2-Styrylthiophen, 1 : 2-Diaryl-1-2′-thienylethylenes, and Similar Compounds.*

By Ng. H. Nam, Ng. Ph. Buu-Hoï, and Ng. D. Xuong.

[Reprint Order No. 4869.]

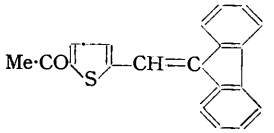
The behaviour of 2-styrylthiophen and of a series of 1 : 2-diaryl-1-2′-thienylethylenes and similar compounds towards formylation with *N*-methylformanilide, Friedel–Crafts acylations, and bromination is investigated. It is shown that, unlike their aromatic analogues, the thiophen derivatives are highly reactive. The bromo-compounds, aldehydes, ketones, thiosemicarbazones, and 4-oxo-Δ^2-thiazolin-2-ylhydrazones obtained in this study are of biological interest. The relation between the electronic structure and reactivity of several molecules in this series is discussed.

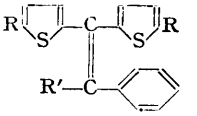
It has been demonstrated both experimentally, and by wave-mechanical calculations of π-electron densities, that in molecules such as stilbene and 1 : 1 : 2-triphenylethylene the reactivity is shifted from the benzene rings to the external double bond (cf. Buu-Hoï and Royer, *J.*, 1948, 1078; Daudel *et al.*, *Rev. Sci.*, 1946, **84**, 489; *Compt. rend.*, 1946, **223**, 947; Daudel and Pullman, *J. Phys. Radium*, 1946, **59**, 74, 105; Coulson and Daudel, *Rev. Sci.*, 1947, **85**, 29; Buu-Hoï *et al.*, *ibid.*, p. 1041). Thus, stilbene undergoes Friedel–Crafts acetylation with great difficulty (Ross, *J.*, 1945, 536), and halogenation and nitration of 1 : 1 : 2-triphenylethylene result only in the 2-bromo-, 2-chloro-, and 2-nitro-derivatives (Meisenheimer, *Annalen*, 1927, **456**, 126; Bergmann and Bondt, *Ber.*, 1931, **64**, 1455; Bergmann, Dimant, and Japhe, *J. Amer. Chem. Soc.*, 1948, **70**, 1618). It was therefore of interest to examine the reactivity of analogues of stilbene and 1 : 1 : 2-triphenylethylene in which one or more benzene nuclei would be replaced by the more reactive thiophen. A further incentive lay in the possible biological value of these thiophen compounds and their derivatives (cf. Buu-Hoï *et al.*, *Compt. rend.*, 1945, **220**, 175; Corre *et al.*, *Bull. Soc. Chim. biol.*, 1946, **28**, 716; 1948, **30**, 674; Robson, Davies, and Tebrich, *Brit. J. Pharmacol.*, 1950, **5**, 376).

The reactions studied in the present work were: phosphorus oxychloride-catalysed

* Part IV, *J.*, 1953, 547.

aldehyde syntheses by means of *N*-methylformanilide and *N*-dimethylformamide; stannic chloride-catalysed Friedel–Crafts ketone syntheses; and halogenation with free bromine. 2-Styrylthiophen was smoothly converted into 2-formyl-5-styrylthiophen under the usual conditions for the synthesis of aldehydes of alkylthiophens (cf. King and Nord, *J. Org. Chem.*, 1948, **13**, 635; Buu-Hoï, Hoán, and Lavit, *J.*, 1950, 2130); the constitution of this aldehyde was established by Kishner–Wolff reduction to the known 5-methyl-2-styrylthiophen (Buu-Hoï *et al.*, *loc. cit.*, 1950). Friedel–Crafts condensation of 2-styrylthiophen with acetyl and propionyl chloride in the presence of stannic chloride afforded excellent yields of 2-acetyl- and 2-propionyl-5-styrylthiophen, the constitution of the former ketone being similarly determined by reduction to 2-ethyl-5-styrylthiophen, which was independently prepared from 2-ethyl-5-formylthiophen and benzylmagnesium chloride, the resulting alcohol being dehydrated by formic acid. These experiments revealed the outstanding reactivity of the 5-position in the molecule of 2-styrylthiophen, as compared with stilbene which was totally inert in the same reactions. A similar reactivity was shown by 1 : 2-diphenyl-1-2′-thienylethylene, which was readily converted into the 5-acetyl-2-thienyl, 5-propionyl-2-thienyl, and 5-benzoyl-2-thienyl compounds. The constitution of the first-named ketone was determined by reduction to 1 : 2-diphenyl-1-(5-ethyl-2-thienyl)-ethylene, which was prepared separately from 2-benzoyl-5-ethylthiophen and benzylmagnesium chloride, with dehydration of the intermediate alcohol by formic acid. This behaviour was not substantially affected by the presence of halogen atoms or methyl or methoxy-groups in *para*-position on either or both of the benzene nuclei, and all these substituted ethylenes yielded ketones which, together with their derivatives, are listed in the Table. 9-2′-Thenylidenefluorene also readily underwent Friedel–Crafts acetylation, to give 9-(5-acetyl-2-thenylidene)fluorene (I); in the case of 2-phenyl-1 : 1-di-2′-thienylethylene, in whose molecule there are two thiophenic 5-positions free, a diketone (II; R = COMe, R′ = H) was obtained.

(I) 



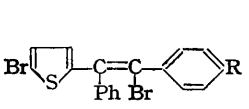
(II)

Formylation of thienyldiarylethylenes by means of *N*-methylformanilide could be effected in all instances. In the case of 2-*p*-chlorophenyl-1-phenyl-1-2′-thienylethylene, the corresponding aldehyde was obtained as a well-crystallised substance; for the other ethylenes, the aldehydes were characterised as their semicarbazones and 2 : 4-dinitrophenylhydrazones.

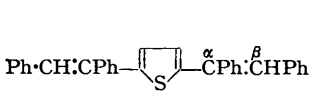
Bromination of 1 : 2-diphenyl-1-2′-thienylethylene with one or two molecules of halogen yielded a dibromo-compound which was identical with the monobromination product of 1 : 2-diphenyl-1-(5-bromo-2-thienyl)ethylene, and was therefore probably 1-bromo-2-(5-bromo-2-thienyl)-1 : 2-diphenylethylene (III; R = H); this structure is upheld by the results of bromination of a series of similar ethylenes with one thiophenic 5-position free and bearing additional halogen, methyl, or methoxy-substituents in the phenyl nuclei, all of which gave dibromo-derivatives. This behaviour confirms previous observations (Buu-Hoï and Hoán, *Rec. Trav. chim.*, 1948, **67**, 309; 1949, **68**, 441) on the bromination of diarylthienylethylenes with no thiophenic 5-positions free, which resulted in monobrominated compounds; it was therefore to be expected that 2-phenyl-1 : 1-di-2′-thienylethylene (II; R = R′ = H) would give a trisubstituted derivative with bromine, and this was in fact the case, the compound obtained being probably 2-bromo-1 : 1-di-(5-bromo-2-thienyl)-2-phenylethylene (II; R = R′ = Br). It thus appears that in the molecule of 1 : 2-diphenyl-1-2′-thienylethylene, the thiophenic 5-position is the most reactive in formylation and Friedel–Crafts acylations, and shares this property with the free position on the ethylene bond as regards bromination; this is in line with theoretical considerations, which assign high π-electron densities to the 2- and the 5-position in the thiophen nucleus.

In view of the known hepatotoxic effects of 2-arylcinchoninic acids, some similar compounds were prepared by Pfitzinger reaction on methyl ketones derived from 2-styrylthiophen

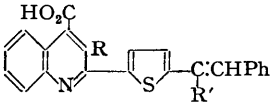
and diarylthienylethylenes, for biological testing. Whereas 5-propionyl-2-styrylthiophen readily underwent a similar reaction, 1 : 2-diphenyl-1-(5-propionyl-2-thienyl)ethylene failed to do so under the same experimental conditions; similar lack of reactivity of ketones bearing bulky substituents in the *para*-position had already been observed in the benzene series (De Clercq and Buu-Hoï, *Compt. rend.*, 1948, **227**, 1377).



(III)



(IV)



(V)

Replacement of a benzene by a thiophen nucleus in the fully conjugated polyarylethylenes is accompanied by an important bathochromic effect, shown, *e.g.*, in the yellow colour of 9-2′-thenylidenefluorene in contrast to colourless stilbene; similarly, the semicarbazones of the aldehydes and ketones described above are yellow, and the thiosemicarbazones and 4-oxo-Δ^2-thiazolin-2-ylhydrazones (cf. Buu-Hoï, Hoán, and Lavit, *J.*, 1952, 4590) are yellow to orange-yellow, in contrast to the corresponding purely aromatic compounds which are practically colourless. In this connection, it is interesting to note the orange-yellow colour of 2 : 5-di-α-stilbenylthiophen (IV), a highly conjugated compound prepared from benzylmagnesium chloride and 1-(5-benzoyl-2-thienyl)-1 : 2-diphenylethylene. A spectroscopic analysis of these observations will be published later.

In view of the pronounced tuberculostatic properties of thiosemicarbazones of 5-substituted thenaldehydes (Welsch, Buu-Hoï, Dechamps, Hoán, Le Bihan, and Binon, *Compt. rend.*, 1951, **232**, 1608), the activity against *Mycobacterium tuberculosis var. hominis* (H 37, Rv strain) *in vitro* of the thiosemicarbazones prepared has been determined. When Dubos–Davis " Tween 80 "–albumin medium was used, and the readings taken after 3 weeks at 37°, the annexed results were obtained, showing the decrease in activity corresponding to the increase in bulk of substituents.

Thiosemicarbazone of	Active concn.
2-Formyl-5-styrylthiophen	$1 : 10^5$
2-Acetyl-5-styrylthiophen	$1 : 10^5$
2-*p*-Chlorostyryl-5-formylthiophen	$1 : 10^5$
1-(5-Formyl-2-thienyl)-1 : 2-diphenylethylene	$1 : 10^4$
2-*p*-Chlorophenyl-1-(5-formyl-2-thienyl)-1-phenylethylene	$1 : 10^4$
1(5-Acetyl-2-thienyl)-1 : 2-diphenylethylene	$1 : 10^3$
1-(5-Acetyl-2-thienyl)-2-phenyl-1-*p*-tolylethylene	$1 : 10^3$
1-(5-Acetyl-2-thienyl)-2-*p*-chlorophenyl-1-phenylethylene	$1 : 10^3$

Experimental

2-Formyl-5-styrylthiophen.—To a solution of 2-styrylthiophen (9·3 g.) and dimethylformamide (4·4 g.) in *o*-dichlorobenzene (15 c.c.), phosphorus oxychloride (9·2 g.) was added, and the mixture cautiously warmed on the water-bath until an exothermic reaction set up; when this had subsided, the mixture was heated for a further hour, then treated with saturated aqueous sodium acetate, and the solvent removed in steam. The residue was taken up in benzene, dried (Na_2SO_4), and purified by vacuum-distillation to yield *2-formyl-5-styrylthiophen* (9·7 g., 90%), b. p. 208—210°/1 mm., which crystallised as shiny, pale yellow needles, m. p. 84°, from methanol (Found: C, 73·6; H, 4·7. $C_{13}H_{10}OS$ requires C, 72·9; H, 4·7%). The corresponding *semicarbazone* crystallised as pale yellow leaflets, m. p. 269—271° (decomp.), from ethanol–benzene (Found: N, 15·3. $C_{14}H_{13}ON_3S$ requires N, 15·5%); the *thiosemicarbazone* formed shiny yellow needles, m. p. 186—187°, from ethanol (Found: N, 14·4. $C_{14}H_{13}N_3S_2$ requires N, 14·6%); the *4-oxo-Δ^2-thiazolin-2-ylhydrazone*, prepared by heating a solution of the thiosemicarbazone (1·2 g.), chloroacetic acid (1·6 g.), and sodium acetate (1·4 g.) in ethanol for 1 hr., crystallised as greenish-yellow prisms, m. p. 296—298° (decomp.), from acetic acid (Found: N, 12·7. $C_{16}H_{13}ON_3S_2$ requires N, 12·8%).

2-Methyl-5-styrylthiophen.—A mixture of the foregoing aldehyde (8·5 g.), 85% hydrazine hydrate (12 g.), and diethylene glycol (60 c.c.) was heated at 100° for 5 min.; after addition of potassium hydroxide (12 g.), the mixture was heated with removal of water up to 190—200° and refluxed for 3 hr. Dilute hydrochloric acid was added after cooling, and the product taken

up in benzene and purified by vacuum-distillation; 2-methyl-5-styrylthiophen (6·8 g., 85% yield) had b. p. 155—157°/0·8 mm., and crystallised from ethanol as colourless leaflets, m. p. 85° (cf. Buu-Hoï, Hoán, and Lavit, *loc. cit.*, 1950).

2-*Acetyl*-5-*styrylthiophen*.—To an ice-cooled solution of acetyl chloride (7·5 g.) and 2-styrylthiophen (14·9 g.) in dry benzene (150 c.c.), stannic chloride (25 g.) was added during 15 min. with stirring; the dark red mixture was kept at room temperature for 1½ hr. and decomposed with dilute hydrochloric acid. The product gave on vacuum-fractionation a *ketone* (12·8 g., 70%), b. p. 238—240°/13 mm., crystallising as shiny, pale yellow needles, m. p. 134°, from methanol (Found: C, 73·5; H, 5·4. $C_{14}H_{12}OS$ requires C, 73·7; H, 5·3%). The *semicarbazone* formed yellow needles, m. p. 228° (decomp.), from methanol (Found: N, 14·7. $C_{15}H_{15}ON_3S$ requires N, 14·7%); the 2 : 4-*dinitrophenylhydrazone* formed red needles, m. p. 242° (decomp.), from benzene (Found: N, 13·6. $C_{20}H_{16}O_4N_4S$ requires N, 13·7%).

2-*Ethyl*-5-*styrylthiophen*.—Wolff–Kishner–Huang-Minlon reduction of 5-acetyl-2-styrylthiophen gave a product which formed a pale yellow oil, b. p. 154—156°/0·6 mm., solidifying to a crystalline mass, m. p. 30° (87% yield); the same *product* was obtained by the reaction of benzylmagnesium chloride with 5-ethyl-2-thenaldehyde in the usual way (Found: C, 78·3; H, 6·5. $C_{14}H_{14}S$ requires C, 78·5; H, 6·5%).

2-*Propionyl*-5-*styrylthiophen*.—Obtained in 70% yield from 2-styrylthiophen (14·9 g.), propionyl chloride (8·9 g.), and stannic chloride (25 g.) in benzene (150 c.c.), this *ketone* had b. p. 253—254°/13 mm., and formed pale yellow needles, m. p. 108°, from methanol (Found: C, 74·2; H, 6·0. $C_{15}H_{14}OS$ requires C, 74·4; H, 5·8%); the *semicarbazone* formed yellow needles, m. p. 216—217° (decomp.) (Found: N, 13·9. $C_{16}H_{17}ON_3S$ requires N, 14·0%). 2-*Benzoyl*-5-*styrylthiophen*, similarly prepared in 55% yield from benzoyl chloride, had b. p. 238—239°/0·5 mm., and formed greenish-yellow leaflets, m. p. 116° (Found: C, 78·0; H, 5·1. $C_{19}H_{14}OS$ requires C, 78·6; H, 4·8%).

3-*Methyl*-2-(5-*styryl*-2-*thienyl*)*cinchoninic Acid* (V; R = Me, R′ = H).—A mixture of 2-propionyl-5-styrylthiophen (2·5 g.), isatin (1·8 g.), and potassium hydroxide (2·3 g.) in ethanol (30 c.c.) was refluxed for 24 hr.; water was added, and the aqueous solution extracted with ether and acidified with acetic acid. The *acid* (2·5 g.) crystallised as yellow prisms, m. p. 268° (decomp.), from ethanol (Found: C, 74·2; H, 4·4. $C_{23}H_{17}O_2NS$ requires C, 74·4; H, 4·6%).

9-2′-*Thenylidenefluorene*.—Sodium (10·1 g.) was treated with absolute ethanol (500 c.c.), and to this solution fluorene (37·5 g.) was added, and the mixture heated on the water-bath until the hydrocarbon had completely dissolved; 2-thenaldehyde (22·4 g.) was then added dropwise with stirring, and the mixture kept for 1 hr. at 75—80°, and overnight at room temperature. The residue from distillation of the ethanol was treated with dilute sulphuric acid, and the product taken up in benzene and purified by vacuum-distillation. 9-2′-*Thenylidenefluorene*, obtained in 63% yield, formed from ethanol greenish-yellow needles, m. p. 72°, and gave a blood-red colour in sulphuric acid (Found: C, 83·1; H, 4·6. $C_{18}H_{12}S$ requires C, 82·9; H, 4·6%).

9-(5-*Acetyl*-2-*thenylidene*)*fluorene* (III).—To a cooled solution of 9-2′-thenylidenefluorene (13 g.) and acetyl chloride (4·7 g.) in benzene (200 c.c.), stannic chloride (15·6 g.) was added portionwise with stirring, and the mixture kept for 75 min. at room temperature. After the usual treatment, the ketone obtained in 82% yield formed orange-yellow needles, m. p. 116°, from ethanol (Found: C, 79·6; H, 4·6. $C_{20}H_{14}OS$ requires C, 79·5; H, 4·6%). The *oxime* formed yellow prisms, m. p. 166°, from ethanol (Found: N, 4·4. $C_{20}H_{15}ONS$ requires N, 4·4%); the *semicarbazone* formed yellow prisms, m. p. 257° (decomp.), from ethanol–benzene (Found: N, 11·6. $C_{21}H_{17}ON_3S$ requires N, 11·7%); the 2 : 4-*dinitrophenylhydrazone* formed crimson needles, m. p. 278° (decomp.), from nitrobenzene (Found: N, 11·6. $C_{26}H_{18}O_4N_4S$ requires N, 11·6%). An attempt to perform a Pfitzinger reaction with isatin and this ketone failed on account of resinification.

1-(5-*Bromo*-2-*thienyl*)-1 : 2-*diphenylethylene*.—To an ethereal solution of benzylmagnesium chloride (from 4·8 g. of magnesium and 25·3 g. of benzyl chloride) a solution of 2-benzoyl-5-bromothiophen (26·7 g.) (cf. Buu-Hoï, Hoán, and Xueng, *Rec. Trav. chim.*, 1950, **69**, 1083) in ether (250 c.c.) was added portionwise, and the mixture refluxed on the water-bath for 15 min. The crude alcohol obtained on decomposition with dilute sulphuric acid was heated for 5 min. with 99% formic acid (60 g.), the mixture poured into water, and the *ethylene* formed taken up in benzene and vacuum-distilled. It formed a thick, pale yellow oil (29·5 g. 86%), b. p. 192—194°/0·5 mm., n_D^{25} 1·6887, giving an orange colour in sulphuric acid (Found: C, 63·0; H, 3·9. $C_{18}H_{13}SBr$ requires C, 63·3; H, 3·8%).

1-*Bromo*-2-(5-*bromo*-2-*thienyl*)-1 : 2-*diphenylethylene* (III; R = H).—(*a*) To an ice-cooled solution of the foregoing ethylene (3·4 g.) in acetic acid (20 c.c.), bromine (1·6 g. in 20 c.c. of

acetic acid) was added portionwise with stirring, and the mixture kept for ½ hr. at room temperature; the precipitate obtained was collected, washed with water, and crystallised as colourless needles (3 g.), m. p. 127°, from acetic acid (Found: C, 51·6; H, 2·8; Br, 37·9. $C_{18}H_{12}SBr_2$ requires C, 51·4; H, 2·9; Br, 38·1%).

(*b*) A solution of 1 : 2-diphenyl-1-2′-thienylethylene (2·6 g.) in cold acetic acid (20 c.c.) was treated in the same way with bromine (2·9 g. in 20 c.c. of acetic acid); the product obtained was identical with the above.

1-p-*Chlorophenyl*-2-*phenyl*-1-2′-*thienylethylene*.—Prepared in 75% yield from benzylmagnesium chloride (from 17·7 g. of benzyl chloride and 3·4 g. of magnesium in 100 c.c. of ether) and 2-*p*-chlorobenzoylthiophen (15·6 g.; cf. Buu-Hoï, Hoán, and Xuong, *loc. cit.*), the *ethylene* formed colourless prisms, m. p. 78°, b. p. 243—244°/12 mm., from methanol (Found: C, 72·8; H, 4·4; Cl, 11·9. $C_{18}H_{13}SCl$ requires C, 72·8; H, 4·4; Cl, 12·0%). 1-*Bromo*-2-(5-*bromo*-2-*thienyl*)-2-p-*chorophenyl*-1-*phenylethylene*, obtained from the foregoing ethylene with bromine, formed colourless prisms, m. p. 124°, from acetic acid (Found: C, 47·7; H, 2·5. $C_{18}H_{11}SBr_2Cl$ requires C, 47·5; H, 2·4%).

1-p-*Bromophenyl*-2-*phenyl*-1-2′-*thienylethylene*.—Prepared in 86% yield from 2-*p*-bromobenzoylthiophen (26·7 g.; cf. Buu-Hoï, Hoán, and Xuong, *loc. cit.*) and benzylmagnesium chloride (from 25·3 g. of benzyl chloride and 4·8 g. of magnesium), this *compound* formed colourless prisms, m. p. 108°, from methanol; it gave a dark orange colour in sulphuric acid (Found: C, 63·2; H, 3·9; Br, 23·3. $C_{18}H_{13}SBr$ requires C, 63·3; H, 3·8; Br, 23·5%). 2-*Bromo*-1-p-*bromophenyl*-1-(5-*bromo*-2-*thienyl*)-2-*phenylethylene* formed colourless prisms, m. p. 149°, from acetic acid (Found: C, 43·0; H, 2·1; Br, 47·8. $C_{18}H_{11}SBr_3$ requires C, 43·3; H, 2·2; Br, 48·1%).

2-p-*Chlorophenyl*-1-*phenyl*-1-2′-*thienylethylene*.—Prepared in 89% yield from 2-benzoylthiophen (62 g.) and *p*-chlorobenzylmagnesium chloride (from 12·7 g. of magnesium and 85·5 g. of *p*-chlorobenzyl chloride in 400 c.c. of ether), this *product* formed colourless prisms, m. p. 64°, b. p. 237—238°/12 mm., from methanol; it gave an orange colour with sulphuric acid (Found: C, 72·8; H, 4·5; Cl, 11·9%). 2-*Bromo*-1-(5-*bromo*-2-*thienyl*)-2-p-*chlorophenyl*-1-*phenylethylene* (III; R = Cl) formed colourless needles, m. p. 148° (Found: C, 47·5; H, 2·5%).

2-p-*Toluoylthiophen*.—To an ice-cooled solution of thiophen (25·2 g.) and *p*-toluoyl chloride (38·6 g.) in benzene (200 c.c.), stannic chloride (78 g.) was added during 45 min. with stirring; the mixture was kept for 2 hr. at room temperature, and worked up in the usual way, the *ketone* (45 g., 89%), b. p. 196—197°/14 mm., crystallising as colourless needles, m. p. 72°, from methanol (Found: C, 71·3; H, 5·0. $C_{12}H_{10}OS$ requires C, 71·3; H, 5·0%).

2-*Phenyl*-1-2′-*thienyl*-1-p-*tolylethylene*.—Prepared in 88% yield from 2-*p*-toluoylthiophen (20·1 g.) and benzylmagnesium chloride (from 4·8 g. of magnesium and 25·3 g. of benzoyl chloride in 150 c.c. of ether) this *stilbene* derivative formed colourless leaflets, m. p. 61°, b. p. 206—207°/0·6 mm., from methanol (Found: C, 82·5; H, 5·8. $C_{19}H_{16}S$ requires C, 82·6; H, 5·8%). 1-*Bromo*-2-(5-*bromo*-2-*thienyl*)-1-*phenyl*-2-*p*-*tolylethylene* formed colourless needles, m. p. 134°, from acetic acid (Found: C, 52·5; H, 3·2; Br, 36·7. $C_{19}H_{14}SBr_2$ requires C, 52·5; H, 3·2; Br, 36·9%).

1-*Bromo*-2-(5-*bromo*-2-*thienyl*)-2-p-*methoxyphenyl*-1-*phenylethylene*, prepared from 1-*p*-methoxyphenyl-2-phenyl-1-2′-thienylethylene (Buu-Hoï, Hoán, and Xuong, *loc. cit.*) with bromine, formed colourless needles, m. p. 120°, from acetic acid (Found: C, 50·8; H, 3·2; Br, 35·4. $C_{19}H_{14}OSBr_2$ requires C, 50·7; H, 3·1; Br, 35·5%).

2-p-*Chlorophenyl*-1-2′-*thienyl*-1-p-*tolylethylene*, prepared in 86% yield from 2-*p*-toluoylthiophen (18·2 g.) and *p*-chlorobenzylmagnesium chloride (from 3·6 g. of magnesium and 24·5 g. of *p*-chlorobenzyl chloride in 200 c.c. of ether), formed colourless needles, m. p. 76°, b. p. 212—213°/0·5 mm., from methanol and gave an orange-red colour with sulphuric acid (Found: C, 73·5; H, 4·7; Cl, 11·4. $C_{19}H_{15}SCl$ requires C, 73·4; H, 4·8; Cl, 11·4%). 1-*Bromo*-2-(5-*bromo*-2-*thienyl*)-1-p-*chlorophenyl*-2-p-*tolylethylene* formed colourless needles, m. p. 161°, from acetic acid (Found: C, 48·7; H, 2·9. $C_{19}H_{13}SBr_2Cl$ requires C, 48·7; H, 2·8%).

2-p-*Chlorophenyl*-1-p-*methoxyphenyl*-1-2′-*thienylethylene*, prepared in 94% yield from 2-*p*-anisoylthiophen (32·7 g.) and *p*-chlorobenzylmagnesium chloride (from 38·7 g. of *p*-chlorobenzyl chloride and 5·8 g. of magnesium), formed silky colourless needles, m. p. 112°, b. p. 230—231°/0·6 mm., from methanol (Found: C, 69·9; H, 4·6; Cl, 10·7. $C_{49}H_{15}OSCl$ requires C, 69·8; H, 4·6; Cl, 10·9%). 1-*Bromo*-2-(5-*bromo*-2-*thienyl*)-1-p-*chlorophenyl*-2-p-*methoxyphenylethylene* formed colourless prisms, m. p. 150°, from acetic acid (Found: C, 47·2; H, 2·8. $C_{19}H_{13}OSBr_2Cl$ requires C, 47·0; H, 2·7%).

2-*Bromo*-1 : 1-*di*-(5-*bromo*-2-*thienyl*)*ethylene* (II; R = R′ = Br), obtained from 2-phenyl-1 : 1-di-2′-thienylethylene (Buu-Hoï and Hoán, *loc. cit.*) and 3 mol. of bromine in acetic acid,

Ketones[a] *and aldehydes*[b] *derived from* 1 : 2-*diaryl*-1-2′-*thienylethylenes.*

Ethylene derivative	M. p.	Formula	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
1-(5-Acetyl-2-thienyl)-1 : 2-diphenyl	112°	$C_{20}H_{16}OS$	78·9	5·4	78·9	5·3
oxime	201	$C_{20}H_{17}ONS$	N, 4·3		N, 4·4	
semicarbazone	200 *	$C_{21}H_{19}ON_3S$	N, 11·4		N, 11·6	
thiosemicarbazone	196	$C_{21}H_{19}N_3S_2$	66·7	4·9	66·8	5·0
2 : 4-dinitrophenylhydrazone	229	$C_{26}H_{20}O_4N_4S$	N, 11·4		N, 11·6	
1-(5-Propionyl-2-thienyl)-1 : 2-diphenyl	78	$C_{21}H_{18}OS$	79·4	5·7	79·2	5·7
oxime	174	$C_{21}H_{19}ONS$	N, 4·0		N, 4·2	
semicarbazone	170 *	$C_{22}H_{21}ON_3S$	N, 11·1		N, 11·2	
1-(5-Benzoyl-2-thienyl)-1 : 2-diphenyl	123	$C_{25}H_{18}OS$	81·9	4·9	82·0	4·9
oxime	182	$C_{25}H_{19}ONS$	N, 3·5		N, 3·7	
1-(5-Acetyl-2-thienyl)-1-*p*-chlorophenyl-2-phenyl	120	$C_{20}H_{15}OSCl$	71·0	4·5	70·9	4·4
oxime	221	$C_{20}H_{16}ONSCl$	N, 3·9		N, 4·0	
semicarbazone	211 *	$C_{21}H_{18}ON_3SCl$	N, 10·5		N, 10·5	
2 : 4-dinitrophenylhydrazone	269 *	$C_{26}H_{19}O_4N_4SCl$	N, 10·5		N,10·8	
1-(5-Acetyl-2-thienyl)-2-phenyl-1-*p*-tolyl	122	$C_{21}H_{18}OS$	79·2	5·8	79·2	5·7
oxime	193	$C_{21}H_{19}ONS$	N, 4·1		N, 4·2	
semicarbazone	238 *	$C_{22}H_{21}ON_3S$	N, 11·1		N, 11·2	
thiosemicarbazone	226 *	$C_{22}H_{21}N_3S_2$	67·5	5·3	67·5	5·4
1-(5-Acetyl-2-thienyl)-1-*p*-methoxyphenyl-2-phenyl	103	$C_{21}H_{18}O_2S$	75·4	5·4	75·4	5·4
oxime	182	$C_{21}H_{19}O_2NS$	N, 4·0		N, 4·0	
semicarbazone	228 *	$C_{22}H_{21}O_2N_3S$	N, 10·7		N, 10·7	
2 : 4-dinitrophenylhydrazone	252	$C_{27}H_{22}O_5N_4S$	N, 10·7		N, 10·9	
1-(5-Acetyl-2-thienyl)-2-*p*-chlorophenyl-1-phenyl	105	$C_{20}H_{15}OSCl$	71·1	4·5	70·9	4·4
oxime	199	$C_{20}H_{16}ONSCl$	N, 3·9		N, 4·0	
semicarbazone	214	$C_{21}H_{18}ON_3SCl$	N, 10·5		N, 10·6	
thiosemicarbazone	196 *	$C_{21}H_{18}N_3S_2Cl$	61·0	4·3	61·2	4·4
2-*p*-Chlorophenyl-1-phenyl-1-(5-propionyl-2-thienyl)	92	$C_{21}H_{17}OSCl$	71·4	4·7	71·5	4·8
oxime	147	$C_{21}H_{18}ONSCl$	N, 3·6		N, 3·8	
semicarbazone	187 *	$C_{22}H_{20}ON_3SCl$	N, 10·0		N, 10·2	
1-(5-Acetyl-2-thienyl)-2-*p*-chlorophenyl-1-*p*-tolyl-	124	$C_{21}H_{17}OSCl$	71·4	4·9	71·5	4·8
oxime	187	$C_{21}H_{18}ONSCl$	N, 3·7		N, 3·8	
semicarbazone	244 *	$C_{22}H_{20}ON_3SCl$	N, 10·1		N, 10·2	
2 : 4-dinitrophenylhydrazone	262	$C_{27}H_{21}O_4N_4SCl$	N, 10·5		N, 10·5	
1-(5-Acetyl-2-thienyl)-2-*p*-chlorophenyl-1-*p*-methoxyphenyl-	100	$C_{21}H_{17}O_2SCl$	68·3	4·6	68·4	4·6
oxime	184	$C_{21}H_{18}O_2NSCl$	N, 3·6		N, 3·6	
semicarbazone	224 *	$C_{22}H_{20}O_2N_3SCl$	N, 9·8		N, 9·9	
2 : 4-dinitrophenylhydrazone	253 *	$C_{27}H_{21}O_5N_4SCl$	N, 10·1		N, 10·2	
1 : 1-Di-(5-acetyl-2-thienyl)-2-phenyl[c]	169	$C_{26}H_{16}O_2S_2$	68·3	4·6	68·2	4·5
disemicarbazone	>310	$C_{22}H_{22}O_2N_6S_2$	N, 17·8		N, 18·0	
2-*p*-Chlorophenyl-1-(5-formyl-2-thienyl)-1-phenyl-	114	$C_{19}H_{13}OSCl$	70·1	4·3	70·3	4·0
oxime	164	$C_{19}H_{14}ONSCl$	N, 4·0		N, 4·1	
semicarbazone	240—242	$C_{20}H_{16}ON_3SCl$	N, 10·9		N, 11·1	
thiosemicarbazone	212 *	$C_{20}H_{16}N_3S_2Cl$	60·2	3·9	60·4	4·0
4-oxo-Δ^3-thiazolin-2-ylhydrazone	272—274	$C_{22}H_{16}ON_3S_2Cl$	N, 9·4		N, 9·6	
2 : 4-dinitrophenylhydrazone	266 *	$C_{25}H_{17}O_4N_4SCl$	N, 10·8		N, 11·1	
1-(5-Formyl-2-thienyl)-1 : 2-diphenylethylene	B. p. 209—210°/0·7 mm.	—	—		—	
semicarbazone	220—221 *	$C_{20}H_{17}ON_3S$	N, 11·9		N, 12·1	
2 : 4-dinitrophenylhydrazone	232 *	$C_{25}H_{18}O_4N_4S$	N, 11·7		N, 11·9	
2-*p*-Chlorophenyl-1-(5-formyl-2-thienyl)-1-*p*-methoxyphenyl-	B. p. 258—260°/0·6 mm.	—	—		—	
semicarbazone	199—200	$C_{21}H_{18}O_2N_3SCl$	N, 10·0		N, 10·2	

[a] The ketones, prepared as for 9-(2-thenylidene)fluorene, were recrystallised from methanol and were pale yellow; the corresponding oximes, semicarbazones, and thiosemicarbazones, recrystallised from ethanol, were yellow or orange-yellow, and the 2 : 4-dinitrophenylhydrazones (toluene) were red. [b] The pale yellow aldehydes were prepared from the appropriate ethylene, phosphorus oxychloride, and *N*-methylformanilide or dimethylformamide, as for formylation of 2-styrylthiophen; the oximes and 4-oxo-Δ^2-thiazolin-2-ylhydrazones were yellow, the semicarbazones and thiosemicarbazones orange-yellow, and the 2 : 4-dinitrophenylhydrazones red. Recrystallisation from ethanol (oximes, semicarbazones, thiosemicarbazones) or acetic acid or toluene (4-oxo-Δ^2-thiazolin-2-ylhydrazones and 2 : 4-dinitrophenylhydrazones). [c] This ketone (b. p. 259—261°/0·3 mm.) was orange-yellow, its semicarbazone yellow. * With decomp.

formed colourless prisms, m. p. 74° (Found : C, 37·9; H, 1·9; Br, 47·0. $C_{16}H_9S_2Br_3$ requires C, 38·0; H, 1·8; Br, 47·5%).

2-β-*Naphthoylthiophen*.—Prepared in 75% yield from β-naphthoyl chloride (38·1 g.), thiophen (20·2 g.) and stannic chloride (62·8 g.) in benzene (300 c.c.) in the usual way, except that the mixture was kept for 4 hr. at room temperature, the *ketone* crystallised as colourless leaflets, m. p. 89°, from methanol (Found : C, 75·6; H, 4·0. $C_{15}H_{10}OS$ requires C, 75·6; H, 4·2%).

1-β-*Naphthyl-2-phenyl-1-2′-thienylethylene*, prepared from the foregoing ketone (23·8 g.) and benzylmagnesium chloride (from 25·3 g. of benzyl chloride and 4·8 g. of magnesium in 150 c.c. of ether), formed colourless needles, m. p. 95° (Found : C, 84·4; H, 5·0. $C_{22}H_{16}S$ requires C, 84·6; H, 5·1%).

9-(5-*Acetyl-2-thenylidene*)*fluorene*.—To an ice-cooled solution of 9-2′-thenylidenefluorene (13 g.) and acetyl chloride (4·7 g.) in benzene (200 c.c.), stannic chloride (15·6 g.) was added portionwise with stirring; the mixture was kept for 75 min. at room temperature, and worked up in the usual way, to yield 82% of a *ketone*, b. p. 270—272°/0·6 mm., forming orange-yellow needles, m. p. 115°, from ethanol (Found : C, 79·6; H, 4·6. $C_{20}H_{14}OS$ requires C, 79·5; H, 4·6%). The *oxime* crystallised as yellow prisms, m. p. 165°, from ethanol (Found : N, 4·4. $C_{20}H_{15}ONS$ requires N, 4·4%); the *semicarbazone* formed yellow needles, m. p. 257° (decomp.), from ethanol–benzene (Found : N, 11·5. $C_{21}H_{17}ON_3S$ requires N, 11·7%).

1-(5-*Ethyl-2-thienyl*-1 : 2-*diphenylethylene*.—(a) *By reduction of* 1-(5-*acetyl-2-thienyl*)-1 : 2-*diphenylethylene*. This ketone (9·1 g.), on reduction in the usual way with 85% hydrazine hydrate (15 g.) and potassium hydroxide (15 g.) in diethylene glycol (80 c.c.), gave the *stilbene* derivative as a pale yellow oil (8 g.), b. p. 187—188°/0·5 mm., n_D^{26} 1·6667 (Found : C, 82·6; H, 6·1. $C_{20}H_{18}S$ requires C, 82·7; H, 6·2%). (b) *By Grignard synthesis*. The same product was obtained in 75% yield from benzylmagnesium chloride (25·3 g. of benzyl chloride and 4·8 g. of magnesium in 200 c.c. of ether) and 2-benzoyl-5-ethylthiophen.

2 : 5-*Di-α-stilbenylthiophen* (IV).—To a cooled Grignard reagent made from benzyl chloride (7·6 g.) and magnesium (1·45 g.) in ether (100 c.c.), a solution of 1-(5-benzoyl-2-thienyl)-1 : 2-diphenylethylene (11 g.) in dry benzene (100 c.c.) was added portionwise, and the mixture refluxed for 15 min. on the water-bath. After decomposition with dilute sulphuric acid, the alcohol obtained was dehydrated with 98% formic acid (20 g.), and the product vacuum-fractionated. The *ethylene* (71%), b. p. 290—292°/0·8 mm., forming orange-yellow needles, m. p. 142°, from acetic acid (Found : C, 86·8; H, 5·3. $C_{32}H_{24}S$ requires C, 87·3; H, 5·4%). This compound was highly sensitive to oxygen and light and gave a deep violet colour in sulphuric acid.

2-(5-α-*Stilbenyl-2-thienyl*)*cinchoninic Acid* (V; R = H, R′ = Ph).—A mixture of 1-(5-acetyl-2-thienyl)-1 : 2-diphenylethylene (3 g.), isatin (1·8 g.), and potassium hydroxide (2·2 g.) in ethanol (15 c.c.) was refluxed for 24 hr.; the precipitate obtained on dilution with water, ether-extraction, and acidification with acetic acid formed yellow prisms, m. p. 225—226° (decomp.), from ethanol (Found : C, 77·3; H, 4·6. $C_{28}H_{19}O_2NS$ requires C, 77·6; H, 4·4%). 1 : 2-Diphenyl-1-(5-propionyl-2-thienyl)ethylene, treated in the same way with isatin, was recovered unchanged even after 48 hours' heating.

Various.—Other *compounds* prepared are listed in the Table.

Thanks are offered to Prof. M. Welsch, Bacteriological Institute, University of Liége, for having tested the compounds for tuberculostatic activity. Results of biological tests for œstrogenic and progesterone-like activity will be reported elsewhere.

THE RADIUM INSTITUTE, UNIVERSITY OF PARIS. [*Received, December 7th*, 1953.]