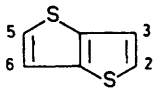
The Reactivity of Thieno[3,2-*b*]thiophen and Thieno[2,3-*b*]thiophen with Phenyl Radicals

By **P. Spagnolo, L. Testaferri,** and **M. Tiecco,*** Istituto di Chimica Organica e Industriale dell'Università, Viale Risorgimento 4, 40136 Bologna, Italy
G. Martelli, Laboratorio del C.N.R. per lo Studio di Composti del Carbonio Contenenti Eteroatomi, Ozzano Emilia, Italy

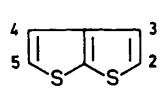
The isomeric thieno[3,2-*b*]thiophen (I) and thieno[2,3-*b*]thiophen (II) have been phenylated with phenyl radicals derived from the thermal decomposition of *N*-nitrosoacetanilide and from the reaction of aniline and pentyl nitrite. The radical substitution is favoured in the 2-position in the case of compound (I), but in structure (II) the 2- and 3-positions have comparable reactivities. The values of the relative reactivities show that for homolytic phenylation the order of decreasing reactivity is thieno[3,2-*b*]thiophen > thiophen > thieno[2,3-*b*]thiophen. The experimental results may be rationalised on the assumption that the contribution of the condensed thieno-group to the stabilisation of the intermediates is greater in (I) than in (II).

The syntheses of 2- and 3-phenylthieno[3,2-*b*]thiophens and of 2- and 3-phenylthieno[2,3-*b*]thiophens are described.

THIENO[3,2-*b*]THIOPHEN (I) and thieno[2,3-*b*]thiophen (II) have been much studied, both from the theoretical [1] and from the experimental point of view. Substitutions with electrophilic species [2] and with metallating agents [3] have been extensively investigated, but until now no attention appears to have been devoted to the homolytic substitutions of these compounds. We have recently studied the behaviour of thiophen [4] and benzo[*b*]thiophen [5] towards attack by aryl radicals, and these investigations have now been extended to include the two isomeric thienothiophens (I) and (II).



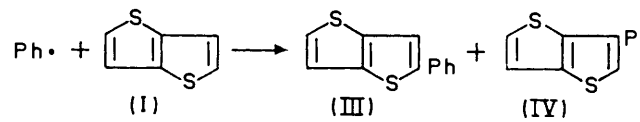
(I)



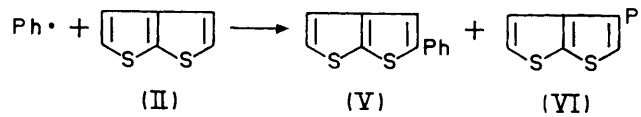
(II)

The reactivities of the various positions in the thienothiophens (I) and (II) have been calculated by Clark [1] on the basis of localisation energy values, using the semi-empirical PPP–SCF–MO method. Using a PPP–MO method, electron densities and free valence values were determined by Trinajstic and Majerski,[1] to predict the positions of electrophilic, nucleophilic, and radical attack. As far as homolytic substitutions are concerned, these investigators concluded that, as in the case of thiophen, the most reactive positions in structures (I) and (II) are those near the sulphur atom, and that the order of decreasing reactivity, as given by the site of highest reactivity in each compound, should be thiophen > thieno[3,2-*b*]thiophen > thieno[2,3-*b*]thiophen.

We generated phenyl radicals in the presence of equimolecular mixtures of either (I) and thiophen or (II) and thiophen by the reaction at 40 °C of aniline with pentyl nitrite; the mixtures were analysed directly by g.l.c., and the ratios of 2- (III) and 3-phenylthieno-[3,2-*b*]thiophen (IV) and 2- (V) and 3-phenylthieno-[2,3-*b*]thiophen (VI) produced were determined. The reactivities of compounds (I), k_{rel} [(I)/Th] and (II), k_{rel} [(II)/Th], relative to thiophen were also obtained



(I) (III) (IV)



(II) (V) (VI)

from these experiments (see Table 1). Also reported in the Table are the data obtained from experiments in which phenyl radicals were generated in an equimolecular mixture of (I) and (II); the value of k_{rel}[(I)/(II)] obtained in this way (4·38) is in good agreement with that calculated from the two previous experiments: $k_{rel}[(I)/(II)] = k_{rel}[(I)/Th]/k_{rel}[(II)/Th] = 4{\cdot}15$.

A similar experiment in which *N*-nitrosoacetanilide was employed as the source of phenyl radicals afforded almost identical results.

The data in the Table show that thieno[3,2-*b*]thiophen and thieno[2,3-*b*]thiophen behave differently in their reaction with phenyl radicals. In the case of (I), radical attack is favoured in the 2-position, while in (II) the reactivities of the 2- and 3-positions are very similar; the change in orientation is similar to that encountered in passing from thiophen [4] to benzo[*b*]thiophen.[5] This difference may be explained by assuming that in substitution by phenyl radicals at the 2-position of thieno-[3,2-*b*]thiophen, the σ-complex (VII) is stabilised by the delocalisation of the odd electron over the whole molecule, while in the corresponding σ-complex (VIII), formed by attack of the phenyl radical at the 2-position of the thieno[2,3-*b*]thiophen, the condensed thieno-group is

[1] D. T. Clark, *Tetrahedron*, 1968, **24**, 2567; N. Trinajstic and Majerski, *Z. Naturforsch.*, 1967, 1475; N. Trinajstic and A. Hinchliffe, *Croat. Chemica Acta*, 1967, **39**, 119; M. J. S. Dewar and N. Trinajstic, *J. Amer. Chem. Soc.*, 1970, **92**, 1453; R. A. W. Johnstone and S. D. Ward, *Tetrahedron*, 1969, **25**, 5485.

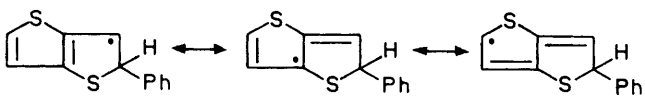
[2] F. Challenger, *Sci. Progr.*, 1953, **41**, 593; A. Bugge, *Acta Chem. Scand.*, 1969, **23**, 2704.

[3] A. Bugge, *Acta Chem. Scand.*, 1968, **22**, 63.

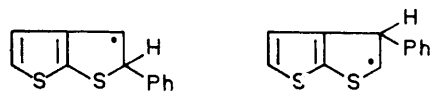
[4] C. M. Camaggi, R. Leardini, M. Tiecco, and A. Tundo, *J. Chem. Soc.* (*B*), 1969, 1251; 1970, 1682.

[5] G. Martelli, P. Spagnolo, M. Tiecco, and A. Tundo, in the press.

scarcely involved. This assumption accounts for the preferred 2-substitution in thieno[3,2-*b*]thiophen, and at the same time accounts for the orientation found in (II), since, if the condensed thieno-group does not



(VII)



(VIII) (IX)

appreciably contribute to the delocalisation of the odd electron, the σ-complex (VIII) would be expected to have a stability very similar to that of the intermediate (IX), formed by radical attack at the 3-position.

These results support the foregoing explanation of the different orientation observed in the homolytic substitution of (I) and (II).

As far as the relative reactivities are concerned, the theoretically predicted sequence thiophen > (I) > (II) is not found: thieno[3,2-*b*]thiophen (I) is considerably more reactive than thiophen, k_{rel}[(I)/Th] = 2·97. The experimental order of decreasing reactivity is (I) > thiophen > (II).

The products (III)—(VI), obtained from the phenylation of the thienolthiophens (I) and (II), were identified by comparison (i.r., u.v., and g.l.c.) with authentic samples; for this purpose they were separated from product mixtures by a combination of column chromatography and preparative g.l.c. The 2-phenyl derivatives of (I) and (II) were synthesised in two ways. The first method was the homolytic substitution in benzene of the radicals 2-thieno[3,2-*b*]thienyl and 2-thieno[2,3-*b*]-thienyl, produced by photolysis of the corresponding

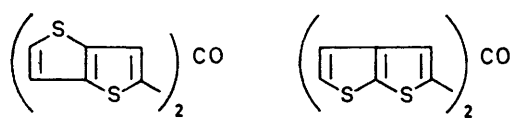
TABLE 1

Isomer distributions and relative reactivities for the phenylation of thieno[3,2-*b*]thiophen (I) and thieno-[2,3-*b*]thiophen (II)

	Isomer distributions (%)						Relative rates		
	Thiophen		(I)		(II)				
Substrates	2-	3-	2-	3-	2-	3-	k_{rel} [(I)/Th]	k_{rel} [(II)/Th]	k_{rel} [(I)/(II)]
(I), Thiophen	91·4	8·6	88·7	11·3			2·97		
(II), Thiophen	90·5	9·5			40·5	59·5		0·71	
(I), (II)			89·2	10·8	44·5	55·5			4·38
(I), (II) *			87·2	12·8	43	57			4·32

* With *N*-nitrosoacetanilide as the source of phenyl radicals.

This assumption finds considerable support in some recently obtained spectroscopic results. In the course of an e.s.r. investigation, the radical anions derived from the reduction of the condensed thiophens (I) and (II) were studied.[6] Attempts to produce the radical anion of thieno[2,3-*b*]thiophen failed but the reduction of thieno[3,2-*b*]thiophen was possible under particular experimental conditions. The difference in stability between the two radical anions is the result of a greater conjugation between the two rings in structure (I) than in (II). The results of the reduction of the ketones (X) and

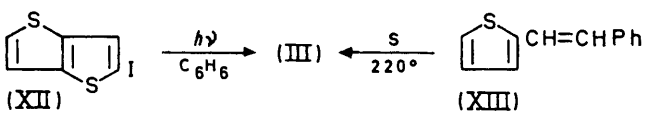


(X) (XI)

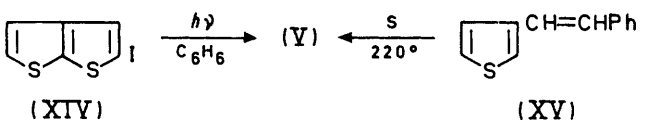
(XI) are even more revealing.[7] The e.s.r. spectrum of the ketyl corresponding to (X) is analysable in terms of three coupling constants (4·47, 2·34, and 0·6 G), attributed to the 3-, 5-, and 6-positions, respectively; in the ketyl corresponding to (XI) the coupling constants of the 4- and 5-positions were very small (0·1 and 0·5 G) and the odd electron was almost exclusively delocalised in the 3-position, which had a coupling constant of 5·1 G.

[6] L. Lunazzi, G. Martelli, G. Placucci, and M. Tiecco, *J. Chem. Soc.* (*B*), 1971, 1820.

iodo-derivatives (XII) and (XIV), under conditions similar to those used in the photolysis of the iodothiophens.[8] The 2-phenylthienothiophens (III) and (V) were also obtained from the cyclisation, with sulphur at 220°, of the easily available 2- (XIII) and 3-styrylthiophen (XV), respectively.



(XII) (III) (XIII)



(XIV) (V) (XV)

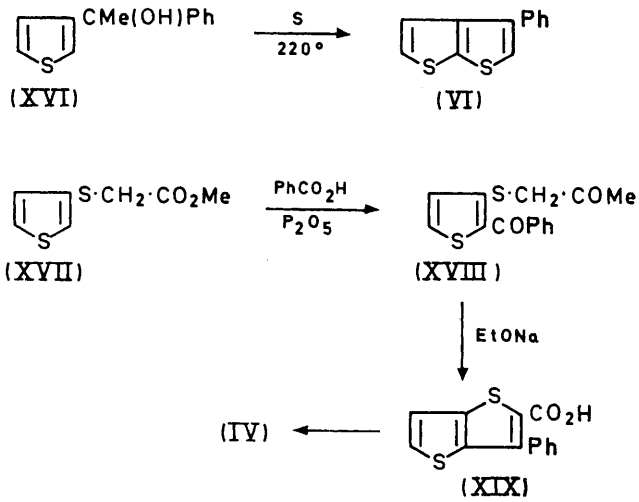
This cyclisation was also employed to synthesise 3-phenylthieno[2,3-*b*]thiophen (VI) from 1-phenyl-1-(3-thienyl)ethanol (XVI), which, under the reaction conditions, was probably first dehydrated to the ethylene and then cyclised.

3-Phenylthieno[3,2-*b*]thiophen (IV) was synthesised

[7] G. F. Pedulli and M. Tiecco, unpublished results.

[8] L. Benati and M. Tiecco, *Boll. sci. Fac. Chim. ind. Bologna*, 1966, **24**, 255; G. Martelli, P. Spagnolo, and M. Tiecco, *J. Chem. Soc.* (*B*), 1968, 901.

in a similar manner to the thieno[3,2-*b*]thiophen itself. Methyl (3-thienylthio)acetate (XVII) was benzoylated with benzoic acid and phosphorus(v) oxide; the resulting



methyl (2-benzoyl-3-thienylthio)acetate (XVIII) was not isolated, but directly subjected to a Dieckman condensation to afford 3-phenylthieno[3,2-*b*]thiophen-2-carboxylic acid (XIX), which was then decarboxylated.

EXPERIMENTAL

Thieno[3,2-*b*]thiophen [9] and thieno[2,3-*b*]thiophen [10] were prepared as described in the literature.

2-*Phenylthieno*[3,2-b]*thiophen* (III).—(*a*) A solution of 2-iodothieno[3,2-*b*]thiophen [11] (XII) (0·4 g) in benzene (100 ml) was irradiated with a high-pressure mercury lamp [8] for 3 h. The reaction was monitored by u.v. spectroscopy. Iodine was removed by washing with sodium thiosulphate solution and the benzene was removed by distillation. The residue was chromatographed through a silica gel column with light petroleum (b.p. 40—60°) as eluant to afford 2-*phenylthieno*[3,2-b]*thiophen* (III) (0·2 g), m.p. 164—166° (Found: C, 66·9; H, 3·75; S, 29·55. $C_{12}H_8S_2$ requires C, 66·65; H, 3·7; S, 29·65%).

(*b*) A mixture of benzyl chloride (18·7 g) and triethyl phosphite (25 ml) was boiled under reflux for 7 h and then distilled to afford diethyl benzylphosphonate (30 g), an oil, b.p. 157—158° at 15 mmHg. To a solution of this compound (30 g) and thiophen-2-carbaldehyde (13 g) in dimethoxyethane (100 ml), sodium hydride (2·4 g) was added in small portions. The resulting mixture was boiled under reflux for 1 h, poured into water, and extracted with ether. The organic layer was washed with water and evaporated. The residue was chromatographed through a silica gel column with light petroleum (b.p. 40—60°) as eluant to afford 2-styrylthiophen (XIII) (18 g), m.p. 108—110° (lit.,[12] 111°) (Found: C, 77·4; H, 5·35; S, 17·05. Calc. for $C_{12}H_{10}S$: C, 77·4; H, 5·4; S, 17·2%). A mixture of the olefin (XIII) (10 g) and sulphur (3 g) was kept at 220° on an oil-bath for 3 h, and then chromatographed through silica gel with light petroleum (b.p. 40—60°) as eluant to afford 2-phenylthieno[3,2-*b*]thiophen (III) (1·6 g), m.p. 164—166° (from ethanol), identical with that obtained in (*a*).

2-*Phenylthieno*[2,3-b]*thiophen* (V).—(*a*) A solution of 2-iodothieno[2,3-*b*]thiophen [13] (XIV) (0·6 g) in benzene (100 ml), treated as described before, gave 2-*phenylthieno*[2,3-b]*thiophen* (V) (0·2 g), m.p. 165—166° (Found: C, 66·6; H, 3·75; S, 29·65. $C_{12}H_8S_2$ requires C, 66·65; H, 3·7; S, 29·65%).

(*b*) A mixture of diethyl benzylphosphonate (12 g), thiophen-3-carbaldehyde (7 g), sodium hydride (2 g), and dimethoxyethane (40 ml) was treated as described in (*b*) before. Column chromatography afforded 3-*styrylthiophen* (XV) (4 g), m.p. 120—122° (from ethanol) (Found: C, 77·6; H, 5·55; S, 17·15. $C_{12}H_{10}S$ requires C, 77·4; H, 5·4; S, 17·2%). A mixture of the olefin (XV) (3·5 g) and sulphur (1·2 g) kept on an oil-bath for 3 h at 220° gave 2-phenylthieno[2,3-*b*]thiophen (V) (0·2 g), m.p. 166—167°, identical with that obtained in (*a*).

3-*Phenylthieno*[2,3-b]*thiophen* (VI).—To a solution of n-butyllithium [from lithium (1 g)], cooled at −70°, 3-bromothiophen (10 g) was added dropwise; after 20 min, a solution of acetophenone (7·3 ml) in ether (30 ml) was added and the mixture was stirred at −70° for 2 h. The coolant was removed and the mixture was left to reach room temperature; it was then poured into water. The organic layer was separated, washed, dried, and evaporated; the residue was crystallised from light petroleum (b.p. 100—120°) to afford 1-*phenyl*-1-(3-*thienyl*)*ethanol* (XVI) (8·5 g), m.p. 75—77° (Found: C, 70·65; H, 6·0; S, 15·75. $C_{12}H_{12}OS$ requires C, 70·55; H, 5·9; S, 15·7%). This compound (3 g) was mixed with sulphur (0·9 g) and then heated on an oil-bath, the temperature of which was gradually raised to 220°. The mixture was kept at this temperature for 2 h, cooled, and then chromatographed through a silica gel column. Elution with light petroleum (b.p. 40—60°) afforded 3-*phenylthieno*[2,3-b]*thiophen* (VI) (0·5 g), m.p. 55—56° (Found: C, 66·55; H, 3·7; S, 29·65. $C_{12}H_8S_2$ requires C, 66·65; H, 3·7; S, 29·65%).

3-*Phenylthieno*[3,2-b]*thiophen* (IV).—A mixture of methyl (3-thienylthio)acetate [3] (XVII) (12 g), benzoic acid (8 g) phosphorus pentoxide (9 g), and benzene (90 ml) was boiled under reflux for 6 h and then washed several times with aqueous saturated sodium hydrogen carbonate solution. The solvent was removed by evaporation and the residue chromatographed through a silica gel column with cyclohexane–ethyl acetate (85 : 15 v/v) as eluant. The first 400 ml of eluate contained small amounts of unidentified products and was discarded; the following 200 ml contained impure methyl (2-benzoyl-3-thienylthio)acetate (m.p. 105—130°), which without further purification was dissolved in ethanolic sodium ethoxide (80 ml) [from sodium (1·8 g)] and boiled under reflux for 2 h. The mixture was poured into water, acidified with hydrochloric acid, and extracted with ether. The solution was dried and evaporated. Crystallisation of the residue from nitromethane afforded 3-*phenylthieno*[3,2-b]*thiophen*-2-*carboxylic acid* (XIX) (1·8

[9] Ya. L. Goldfarb, V. P. Litvinov, and S. A. Ozolin, *Izvest. Akad. Nauk S.S.S.R., Otdel. khim. Nauk*, 1965, 510 (*Chem. Abs.*, 1965, **63**, 592f).

[10] S. Gronowitz and B. Persson, *Acta Chem. Scand.*, 1967, **21**, 812.

[11] F. Challenger and R. Emmot, *J. Inst. Petroleum*, 1951, **37**, 396.

[12] Ng. Ph. Buu-Hoï, Ng. Hoán, and D. Larit, *J. Chem. Soc.*, 1950, 2130.

[13] F. Challenger, P. H. Chapham, and R. Emmot, *J. Inst. Petroleum*, 1948, **34**, 922.

g), m.p. 230—231° (Found: C, 58·35; H, 3·15; S, 25·55. $C_{13}H_8O_2S_2$ requires C, 58·25; H, 3·2; S, 25·7%). A solution of the acid (1·1 g) in quinoline (15 ml) was kept at 220° for 3 h in the presence of copper bronze (1 g). The cooled solution was poured into an excess of dilute hydrochloric acid and ether was added; the organic layer was separated, washed with dilute hydrochloric acid, water, 10% sodium hydrogen carbonate solution, and water. The solution was dried and evaporated to leave a residue which was purified by chromatography on a silica gel column. Elution with light petroleum (b.p. 40—60°) afforded 3-*phenylthieno*-[3,2-b]*thiophen* (IV) (0·7 g), m.p. 62—63° (Found: C, 66·55; H, 3·65; S, 29·75. $C_{12}H_7S_2$ requires C, 66·65; H, 3·7; S, 29·65%).

Phenylation of Thieno[3,2-b]*thiophen and Thieno*[2,3-b]-*thiophen.*—Aniline (1 mol. equiv., 0·12 ml) and pentyl nitrite (0·25 ml) were added to mixtures (25 mol. equiv. of each component) of (*a*) thiophen and thieno[3,2-*b*]thiophen, (*b*) thiophen and thieno[2,3-*b*]thiophen, and (*c*) thieno[3,2-*b*]-thiophen and thieno[2,3-*b*]thiophen. The mixtures, in sealed ampoules, were kept at 40° on an oil-bath for 40 h, and then analysed directly by g.l.c. Three independent experiments were carried out in each case; and the isomer ratios and the relative reactivities thus determined are reported in Table 2 (*cf.* the averaged values in Table 1). The phenylthienothiophens (III)—(VI) were identified by comparison of their retention times with those of authentic compounds; from experiments carried out on a preparative scale, the single isomers were also isolated by a combination of column chromatography and preparative g.l.c., and their i.r. spectra were compared with those of the independently prepared phenylthienothiophens. The g.l.c. analyses were carried out with a Varian Aerograph 1520 instrument equipped with flame-ionisation detector; calibration for area response differences between phenylthiophens and phenylthienothiophens was effected for every reaction with an internal standard. The column used was 5% FFAP (free fatty acid phase) (3 m) on Aeropak 30 (80—100 mesh).

TABLE 2

Isomer distributions and relative reactivities for the phenylation of thieno[3,2-*b*]thiophen (I) and thieno-[2,3-*b*]thiophen (II)

	Isomer distributions (%)						Relative rates		
	Thiophen		(I)		(II)				
Substrates	2-	3-	2-	3-	2-	3-	k_{rel} [(I)/Th]	k_{rel} [(II)/Th]	k_{rel} [(I)/(II)]
(I), Thiophen	91·3	8·7	89	11			3·0		
	91·2	8·8	88	12			3·0		
	91·7	8·3	89	11			2·92		
(II), Thiophen	90·3	9·7			39·8	60·2		0·69	
	90·3	9·7			39·1	60·9		0·67	
	90·8	9·2			42·6	57·4		0·76	
(I), (II)			87·9	12·1	45·8	54·2			4·43
			89·6	10·4	44	56			4·5
			90	10	43·7	56·3			4·21
(I), (II) [a]	*b*		87·8	12·2	41·6	58·4			4·3
	c		86·1	13·9	42·8	57·2			4·35
	d		87·2	12·8	44·6	55·4			4·3

[a] With *N*-nitrosoacetanilide as the source of phenyl radicals. [b] Molar ratio thienothiophens : *N*-nitrosoacetanilide = 20 : 1. Molar ratio = 40 : 1. [d] Molar ratio 80 : 1.

We thank Dr. D. I. Davies, King's College, London, for discussions.

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