

## Homolytic Aromatic Substitution of Heterocyclic Compounds. Part V.<sup>1</sup> The Phenylation of Benzo[*b*]thiophen and Benzo[*b*]furan

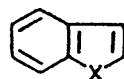
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The homolytic phenylation of benzo[*b*]thiophen and benzo[*b*]furan has been carried out with the thermal decomposition of *N*-nitrosoacetanilide as the source of phenyl radicals. The isomer ratios and the relative reactivities have been determined. Homolytic substitution in benzo[*b*]furan takes place almost exclusively in the heterocyclic ring, in contrast with benzo[*b*]thiophen, in which all the available positions show a comparable reactivity towards substitution by phenyl radicals.

The syntheses of a number of phenylbenzo[*b*]furans and phenylbenzo[*b*]thiophens are reported.

SEVERAL theoretical studies have been carried out on benzo[*b*]thiophen (I) and benzo[*b*]furan (II) and their behaviour towards attack by electrophilic and radical species may thus be predicted.<sup>2</sup> Although electrophilic substitution in these two systems<sup>3</sup> has been studied, to our knowledge there has been no systematic attempt to examine free-radical substitution. The only reported result is the phenylation of benzo[*b*]thiophen<sup>4</sup> with phenyl radicals from the thermal decomposition of *N*-nitrosoacetanilide; the reaction was, however, not thoroughly investigated, and 2-phenylbenzo[*b*]thiophen was the only product identified.

We have recently undertaken a study of the homolytic behaviour of five-membered heterocyclic compounds, and data have been reported concerning the arylation of thiophen<sup>1,5</sup> and furan.<sup>6</sup> In this paper we present the results of a similar investigation with benzo[*b*]thiophen (I) and benzo[*b*]furan (II).

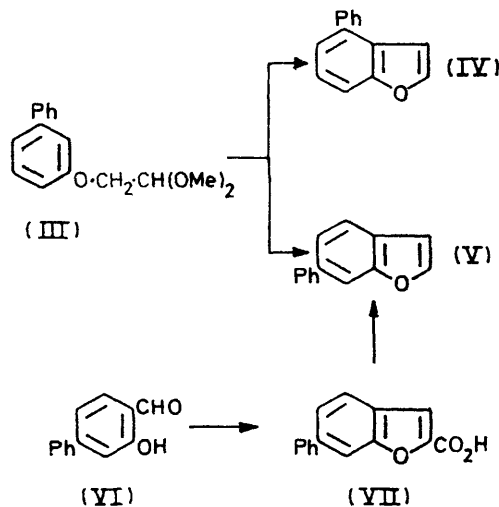


(I) X = S

(II) X = O

In order to identify the products of the phenylation of (I) and (II), the six isomeric phenylbenzo[*b*]thiophens and phenylbenzo[*b*]furans were required. The syntheses of the 4-, 5-, 6-, and 7-phenylbenzo[*b*]furans, and of 6-phenylbenzo[*b*]thiophen, not previously described, have now been carried out. 5- and 7-Phenylbenzo[*b*]furan were obtained by the cyclization of *p*- and *o*-(2,2-dimethoxyethoxy)biphenyl, respectively, with phosphorus pentoxide. Similar treatment of the *meta*-isomer (III) afforded a mixture of 4- (IV) and 6-phenyl-

benzo[*b*]furan (V), which were separated by column chromatography. The two isomers were identified by synthesizing the 6-phenylbenzo[*b*]furan (V) independently by an unambiguous route; the reaction of 2-hydroxy-4-phenylbenzaldehyde (VI) with ethyl bromomalonate afforded the acid (VII), which was readily decarboxylated to the benzofuran (V).



The cyclization of 3-(2,2-dimethoxyethylthio)iodobenzene (VIII) with phosphorus pentoxide gave a mixture of 4- (IX) and 6-iodobenzo[*b*]thiophen (X) in almost equal amounts. The mixture of the two isomers was photolysed in benzene,<sup>7</sup> and gave a mixture of 4- (XI) and 6-phenylbenzo[*b*]thiophen (XII), which were separated by column chromatography. The isomers were distinguished by comparison with an authentic sample of (XI).<sup>8</sup>

Phenyl radicals were generated *in situ* at 40° by the decomposition of *N*-nitrosoacetanilide in equimolar mixtures of benzo[*b*]thiophen and benzene, and of

<sup>1</sup> Part IV, C. M. Camaggi, R. Leardini, M. Tiecco, and A. Tundo, *J. Chem. Soc. (B)*, 1970, 1683.

<sup>2</sup> R. Zahradnik, C. Parkányi, V. Horak, and J. Koutecky, *Coll. Czech. Chem. Comm.*, 1963, **28**, 776; F. Momicchioli and A. Rastelli, *J. Mol. Spectroscopy*, 1967, **22**, 310; C. Aussems, S. Jaspers, G. Leroy, and F. Van Remoortere, *Bull. Soc. chim. belges*, 1969, **78**, 479; R. Zahradnik, *Adv. Heterocyclic Chem.*, 1965, **5**, 1.

<sup>3</sup> B. Iddon and R. M. Scowston, *Adv. Heterocyclic Chem.*, 1970, **11**, 177; R. C. Elderfield and V. B. Meyer, in 'Heterocyclic Compounds,' ed. R. C. Elderfield, vol. 2, Wiley, London, 1951, p. 1; N. P. Buu-Hoi, N. D. Xuong, and N. V. Bac, *J. Chem. Soc.*, 1964, 173.

<sup>4</sup> R. Gaertner, *J. Amer. Chem. Soc.*, 1952, **74**, 4950.

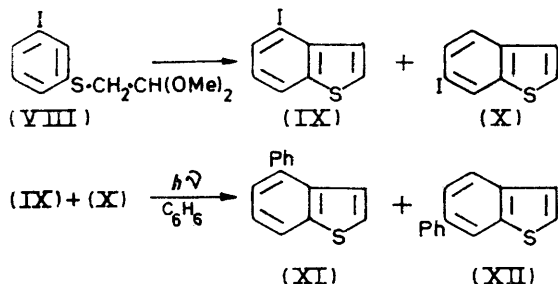
<sup>5</sup> C. M. Camaggi, R. Leardini, M. Tiecco, and A. Tundo, *J. Chem. Soc. (B)*, 1969, 1251.

<sup>6</sup> L. Benati, N. La Barba, M. Tiecco, and A. Tundo, *J. Chem. Soc. (B)*, 1969, 1253.

<sup>7</sup> G. Martelli, P. Spagnolo, and M. Tiecco, *J. Chem. Soc. (B)*, 1970, 1413.

<sup>8</sup> M. C. Kloetzel, J. E. Little, and D. M. Frisch, *J. Org. Chem.*, 1953, **18**, 1511.

benzo[*b*]furan and benzene. The mixtures were analysed by g.l.c. and the isomer ratios and the reactivity



of benzo[*b*]thiophen  $K_{bt/b}$  and benzo[*b*]furan  $K_{bf/b}$  relative to benzene were thus determined (see Table 1).

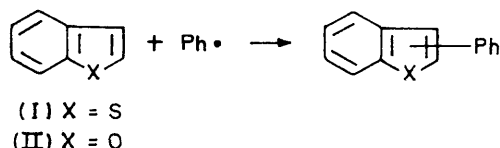


TABLE 1

Isomer ratios, partial rate factors ( $k$ ), and relative reactivities for the phenylation of benzo[*b*]thiophen ( $K_{bt/b}$ ) and of benzo[*b*]furan ( $K_{bf/b}$ )

Substrate	Position of substitution	Isomer ratios (%)	$k$	$K_{bt/b}$ or $K_{bf/b}$
(I)	2	20.6	9.0	7.3
	3	21.1	9.25	
	4	28.1	12.3	
	5 and/or 6	11.8	5.2	
	7	18.4	8.1	
(II)	2	75.9	37.8	8.3
	3*			
	4	17.5	8.7	
	5*			
	6*			
	7	6.6	3.3	

\* Traces of the product were detected by g.l.c.

Experiments were also carried out in which (I) and (II) competed for the phenyl radicals; the experimental

Thiophen<sup>4,5</sup> and furan<sup>6</sup> behave differently in their reactions with phenyl radicals. With thiophen, substitution takes place at the 2-position (93%) and at the 3-position (7%), whereas furan is only arylated in the 2-position; the reactivities of the two compounds relative to benzene are 2.6 and 11.5, respectively. Fusion with a benzene ring decreases this difference between the relative reactivities; the values are 7.3 and 8.3 for benzo[*b*]thiophen and benzo[*b*]furan, respectively. The orientations are considerably different in the two cases. In benzo[*b*]furan, the attack by the phenyl radical is mainly limited to the 2-position, which has almost the same relative reactivity (37.8) as the 2-position of furan<sup>6</sup> (34.5).† No substitution occurs in the 3-position, as is observed with furan. In the case of benzo[*b*]thiophen, the two aromatic fused rings show a comparable reactivity and, in contrast to thiophen, the 2- and 3-positions have almost the same reactivity. Both in (I) and (II) the most reactive position of the benzene ring is the 4-position, followed by the 7-position; substitution at the 5- and 6-positions occurs to a much lesser extent in benzo[*b*]thiophen, and is negligible in benzo[*b*]furan.

From a qualitative point of view the results obtained with (I) and (II) are consistent with the known substitution patterns and reactivities of the thiophen and furan rings relative to benzene. Theoretical treatments<sup>2</sup> of the benzo[*b*]thiophen and benzo[*b*]furan predict that the two molecules should show a very similar behaviour towards substitution by free radicals; in both cases the expected reactivity order is 2 > 3 ~ 4 > 7 > 6 > 5. Although the qualitative trend is roughly as predicted, the experimental results do not confirm these predictions with any precision, particularly with reference to the reactivity of the 3-position of benzo[*b*]furan.

## EXPERIMENTAL

2- and 3-Phenylbenzo[*b*]furan,<sup>9</sup> and 2-,<sup>10</sup> 3-,<sup>11</sup> 4-,<sup>8</sup> and 5-phenylbenzo[*b*]thiophen,<sup>12</sup> were prepared as described in

TABLE 2

Isomer ratios and relative reactivities for the phenylation of benzo[*b*]thiophen (I) and benzo[*b*]furan (II)

Competitive experiment	Isomer ratios (%)						$K_{bt/b}$ or $K_{bf/b}$	Column *
	2-	3-	4-	5-	6-	7-		
Benzothiophen-benzene	20.55	21.15	28.15		11.75	18.40	7.3	B, C
	20.63	21.09	27.97		11.88	18.43	7.3	
	Benzofuran-benzene	75.31	Trace	17.59	Trace	Trace	7.08	8.3
76.63		Trace	17.33	Trace	Trace	6.03	8.15	A
75.71		Trace	17.67	Trace	Trace	6.61	8.45	A
Benzothiophen-benzofuran			Not determined				1.23	B
			Not determined				1.23	B
			Not determined				1.32	B

\* A, 5% Free fatty acid phase (FFAP) on Aeropak 30, 80-100 mesh (3 m). B, 5% Free fatty acid phase (FFAP) on Aeropak 30, 80-100 mesh (1.5 m). C, 5% Diethylene glycol succinate (LAC 728) on Aeropak 30, 80-100 mesh (2 m).

(average) value (see Table 2) of  $K_{bt/bt} = 1.26$  is in good agreement with the calculated value ( $K_{bt/b}/K_{bf/b} = 1.14$ ).

† This value was obtained from the expression:

$$k_2 = K \cdot \frac{(\% \text{ 2-isomer})}{100} \cdot \frac{1}{2} = 11.5 \times 1 \times 3 = 34.5$$

the literature. Light petroleum refers to that fraction with b.p. 40-60°.

<sup>9</sup> W. Davies and S. Middleton, *J. Chem. Soc.*, 1958, 822.

<sup>10</sup> J. E. Banfield, W. Davies, N. W. Gamble, and S. Middleton, *J. Chem. Soc.*, 1956, 4791.

<sup>11</sup> S. Middleton, *Austral. J. Chem.*, 1959, 12, 218.

<sup>12</sup> L. J. Pandya, D. S. Rao, and B. D. Tilak, *J. Sci. Ind. Res., India*, 1959, 18B, 516 (*Chem. Abs.*, 1960, 54, 17,391d).

*o*-(2,2-Dimethoxyethoxy)biphenyl.—A solution of *o*-hydroxybiphenyl<sup>13</sup> (11 g) and 2-bromacetaldehyde dimethyl acetal (14 g) in sodium ethoxide [from sodium (1.5 g) in ethanol (200 ml)] was boiled under reflux for 17 h. The solvent was evaporated and the residue poured into water (200 ml) and extracted with ether. The extract was washed with 5% sodium hydroxide and evaporated, and the residue was distilled to give *o*-(2,2-dimethoxyethoxy)biphenyl (5.6 g), an oil, b.p. 168—170° at 2 mmHg (Found: C, 74.2; H, 6.95. C<sub>16</sub>H<sub>18</sub>O<sub>3</sub> requires C, 74.4; H, 7.0%).

*m*-(2,2-Dimethoxyethoxy)biphenyl (III).—*m*-Hydroxybiphenyl<sup>14</sup> (3 g), treated as described for the *o*-isomer, afforded a crude product (3.2 g), which was purified by distillation to give *m*-(2,2-dimethoxyethoxy)biphenyl, b.p. 149—151° at 1 mmHg (Found: C, 74.0; H, 7.1%).

*p*-(2,2-Dimethoxyethoxy)biphenyl.—*p*-Hydroxybiphenyl<sup>15</sup> (11 g), treated as described for the *o*-isomer, afforded a product which was purified by chromatography [silica gel; light petroleum-ether (9:1)] to give *p*-(2,2-dimethoxyethoxy)biphenyl (2 g), m.p. 54—56° (Found: C, 74.7; H, 7.0%).

*o*-(2,2-Diethoxyethylthio)biphenyl.—*o*-Mercaptobiphenyl<sup>16</sup> (12 g) and 2-bromacetaldehyde diethyl acetal (15 g) were treated as before to give crude *o*-(2,2-diethoxyethylthio)biphenyl (9 g), purified by distillation, b.p. 188—190° at 3 mmHg (Found: C, 71.0; H, 7.25; S, 10.3. C<sub>18</sub>H<sub>22</sub>O<sub>2</sub>S requires C, 71.5; H, 7.31; S, 10.5%).

*m*-(2,2-Dimethoxyethylthio)iodobenzene.—*m*-Iodobenzene-thiol<sup>17</sup> (21 g) was treated with 2-bromacetaldehyde dimethyl acetal (21 g) to give a crude product (14.4 g), b.p. 162—172° at 14 mmHg, which was purified by chromatography [silica gel; light petroleum-ether (9:1)]. The first 500 ml of solution contained small quantities of unidentified material; the following 200 ml contained *m*-(2,2-dimethoxyethylthio)iodobenzene (10.5 g), b.p. 168—170° at 14 mmHg (Found: C, 36.95; H, 4.0; I, 39.05; S, 9.8. C<sub>10</sub>H<sub>13</sub>IO<sub>2</sub>S requires C, 37.05; H, 4.05; I, 39.15; S, 9.9%).

2-Hydroxy-4-phenylbenzaldehyde (VI).—A solution of 3-hydroxy-4-methylbiphenyl<sup>18</sup> (6 g) in acetic anhydride (40 ml) was boiled under reflux for 12 h. The solution was stirred with an excess of 20% sodium hydroxide and then extracted with ether; the solvent was evaporated off to leave 3-acetoxy-4-methylbiphenyl (5 g), m.p. 46—48° (from light petroleum) (Found: C, 79.65; H, 6.2. C<sub>15</sub>H<sub>14</sub>O<sub>2</sub> requires C, 79.6; H, 6.25%). To a stirred solution of this compound in acetic anhydride-acetic acid (140 ml; 1:1 v/v) at 5°, chromium trioxide (12.5 g) was added in small portions. The resulting mixture was stirred overnight, then poured into water, and extracted with ether. The organic solution was washed with 10% sodium hydroxide, dried, and evaporated; the residue was boiled under reflux with conc. sulphuric acid and ethanol and then purified by chromatography [silica gel; light petroleum-ether (85:15)] to give 2-hydroxy-4-phenylbenzaldehyde (VI) (0.7 g), m.p. 82—83° (from light petroleum) (Found: C, 78.85; H, 4.95. C<sub>13</sub>H<sub>10</sub>O<sub>2</sub> requires C, 78.8; H, 5.1%).

6-Phenylbenzo[b]furan (V).—A solution of the aldehyde (VI) (0.5 g) and ethyl bromomalonate (1.25 g) in ethyl methyl ketone (10 ml) was boiled under reflux for 12 h with anhydrous potassium carbonate (1 g).<sup>19</sup> The solvent was

evaporated, the residue was poured into dil. sulphuric acid, and the mixture was extracted with ether. The extract was evaporated and the resulting oil was boiled under reflux for 1 h with ethanolic sodium hydroxide (2 ml; 10%). The ethanol was removed by evaporation and the residue was treated with dil. hydrochloric acid; the organic product was extracted with ether and the extract was dried and evaporated to leave 6-phenylbenzo[b]furan-6-carboxylic acid (VII) (0.5 g), m.p. 260—262° (from nitromethane) (Found: C, 75.5; H, 4.2. C<sub>15</sub>H<sub>10</sub>O<sub>3</sub> requires C, 75.6; H, 4.25%). A solution of this acid in quinoline (5 ml) was heated under reflux for 1 h with copper-bronze. The cooled solution was poured into an excess of dil. hydrochloric acid, and the mixture was extracted with ether. The organic layer was washed with dil. hydrochloric acid and water, dried, and evaporated. The residue was distilled to afford 6-phenylbenzo[b]furan (V) (0.2 g), b.p. 98—100° at 0.3 mmHg (Found: C, 86.45; H, 5.15. C<sub>14</sub>H<sub>10</sub>O requires C, 86.55; H, 5.2%).

4- (IV) and 6-Phenylbenzo[b]furan (V).—A mixture of *m*-(2,2-dimethoxyethoxy)biphenyl (3 g), phosphorus pentoxide (26 g), phosphoric acid (16 ml; 85%), and chlorobenzene was stirred at 150° for 5 h, and then poured into water.<sup>12</sup> The mixture was extracted with ether and the extract was washed with water, dried, and evaporated. The residue (1 g) was shown by g.l.c. to be a 2:3 mixture of (IV) and (V), and was chromatographed (silica gel; pentane). The first 100 ml of eluate contained no product; the following 100 ml contained 4-phenylbenzo[b]furan (IV), b.p. 130—132° at 1 mmHg (Found: C, 86.5; H, 5.2%). The next 100 ml of eluate contained a mixture of (IV) and (V), and this was followed by 100 ml containing 6-phenylbenzo[b]furan (V), identical (g.l.c., i.r., and u.v.) with that obtained independently as described before.

5-Phenylbenzo[b]furan.—The cyclisation of the *o*-(2,2-dimethoxyethoxy)biphenyl (2 g) with polyphosphoric acid was carried out as before and afforded a crude product. Column chromatography (silica gel; light petroleum) gave 5-phenylbenzo[b]furan (0.5 g), m.p. 64—66° (Found: C, 85.95; H, 5.15%).

7-Phenylbenzo[b]furan.—The reaction of *o*-(2,2-dimethoxyethoxy)biphenyl (3.5 g) with polyphosphoric acid afforded an oil which was filtered through a silica gel column with light petroleum as eluant to give 7-phenylbenzo[b]furan (1.2 g), b.p. 120° at 0.5 mmHg (Found: C, 86.35; H, 5.2%).

4- (XI) and 6-Phenylbenzo[b]thiophen (XII).—The crude product obtained from the cyclisation of the *m*-(2,2-dimethoxyethylthio)iodobenzene (4 g) with polyphosphoric acid was purified by chromatography on silica gel with light petroleum as eluant. The oil obtained was distilled *in vacuo* to afford a mixture (1.85 g) of 4- (IX) and 6-iodoiodobenzothiothiophen (X) in almost equal amounts (by g.l.c.) (Found: C, 37.05; H, 1.9; I, 48.65; S, 12.3. Calc. for C<sub>8</sub>H<sub>5</sub>IS: C, 36.95; H, 1.95; I, 48.8; S, 12.35%). A solution of the mixture (1.5 g) in benzene (200 ml) was irradiated with u.v. light<sup>7</sup> for 15 h. The iodine produced was removed by treating the mixture with charcoal and, after filtration, the solvent was removed by distillation. The residue was chromatographed (silica gel; light petroleum). The first 300 ml contained no product; the following 200

<sup>13</sup> O. Hönigschmid, *Monatsh.*, 1901, **22**, 568.

<sup>14</sup> P. Jacobson and A. Loeb, *Ber.*, 1903, **36**, 4082.

<sup>15</sup> H. Hübner, *Annalen*, 1881, **209**, 348.

<sup>16</sup> E. Campaigne and S. W. Osborn, *J. Org. Chem.*, 1957, **22**, 561.

<sup>17</sup> G. Schwarzenbach and H. Egli, *Helv. Chim. Acta*, 1934, **17**, 1176.

<sup>18</sup> F. Wessely, L. Holzer, and H. Vilček, *Monatsh.*, 1952, **83**, 1253.

<sup>19</sup> R. Andrisano and F. Duro, *Gazzetta*, 1955, **85**, 381.

ml of eluate contained 4-phenylbenzo[*b*]thiophen (XI) (0.2 g), m.p. 42–44° (lit.,<sup>11</sup> 46–47°), identical (m.p., mixed m.p., i.r., and u.v.) with an authentic sample.<sup>11</sup> Further elution (300 ml) gave 6-phenylbenzo[*b*]thiophen (XII) (0.33 g) contaminated with the 4-isomer. This fraction was purified by chromatography on silica gel to give 6-phenylbenzo[*b*]thiophen (XII) (0.25 g), m.p. 43–45° (from light petroleum) (Found: C, 79.9; H, 4.75; S, 15.15. C<sub>14</sub>H<sub>10</sub>S requires C, 79.95; H, 4.8; S, 15.25%).

*7-Phenylbenzo[*b*]thiophen.*—*o*-(2,2-Diethoxyethylthio)biphenyl (2.5 g), phosphorus pentoxide (26 g), phosphoric acid (16 ml; 85%), and chlorobenzene (16 ml) were kept at 160° for 5 h. After the usual work-up, the residue was chromatographed (alumina; light petroleum) to give 7-phenylbenzo[*b*]thiophen (1 g), m.p. 37–38° (lit.,<sup>20</sup> 37.5–38.5°) (Found: C, 79.95; H, 4.8; S, 15.5. Calc. for C<sub>14</sub>H<sub>10</sub>S: C, 79.95; H, 4.8; S, 15.25%).

*Phenylation of Benzo[*b*]thiophen and Benzo[*b*]furan.*—*N*-Nitrosoacetanilide (0.16 g) decomposed at 40 °C over 50 h in equimolar mixtures of (i) benzo[*b*]thiophen (25 mol. equiv.) and benzene (25 mol. equiv.), (ii) benzo[*b*]furan and benzene,

<sup>20</sup> D. W. H. MacDowell and T. D. Greenwood, *J. Heterocyclic Chem.*, 1965, **2**, 44.

and (iii) benzo[*b*]thiophen and benzo[*b*]furan. The mixtures were analysed by g.l.c., with a Varian Aerograph 1520 instrument equipped with flame ionization detector; a calibration for area response differences between biphenyl, phenylbenzo[*b*]thiophens, and phenylbenzo[*b*]furans was effected for each reaction with an internal standard. The columns used are indicated in Table 2. From the relative amounts of biphenyl and phenylbenzo[*b*]thiophens or phenylbenzo[*b*]furan thus determined were calculated<sup>21</sup> the isomer ratios, the relative reactivities, and the partial rate factors (see Table 2). Two or three independent experiments were carried out in each case, and the average values are reported in Table 1.

The components of the mixtures (i) and (ii) were separated by preparative g.l.c., and their i.r. spectra were compared with those of the authentic phenylbenzo[*b*]thiophens and phenylbenzo[*b*]furans.

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

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<sup>21</sup> G. H. Williams, 'Homolytic Aromatic Substitution,' Pergamon, Oxford, 1960.