Factors controlling the Selectivity of *ipso*-Attack in Homolytic Aromatic Substitutions. Reactions of Alkyl Radicals with Nitrothiophen Derivatives

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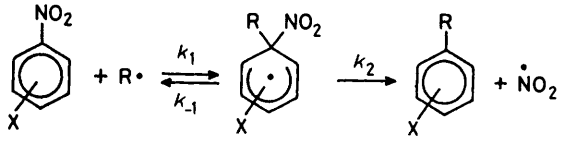
The reactions of the nearly electroneutral methyl and of the nucleophilic 1-adamantyl radical with some selected nitrothiophen derivatives have been investigated in order to elucidate the factors which control the positional selectivity of radical addition to an aromatic substrate. With 5-nitro-2-X-thiophens (II), (V), and (VI) and 3,5-dinitro-2-methoxycarbonylthiophen (III) the adamantyl radical gave exclusively the products of *ipso*-attack, whereas the methyl radical selectively added at the unsubstituted 4-position. On the other hand, with 4-nitro-2-methoxycarbonylthiophen (I) both radicals added at the 5-position and with 4,5-dinitro-2-methoxycarbonylthiophen (IV) both radicals gave the products of *ipso*-substitution by displacing the nitro-group from the 5-position. These changes in positional selectivity are explained by assuming that the nature of the transition state of the addition step changes as a function of the polar character of the radical and of the electron deficiency of the aromatic substrates.

AMONG several recently reported examples [1-3] of radical *ipso*-substitution reactions one of the most efficient and interesting processes is alkyldenitration which has been observed to occur both with heteroaromatic and homoaromatic compounds. Radical *ipso*-substitutions are



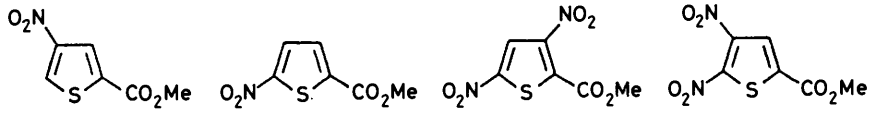
SCHEME 1

believed to occur according to the general addition–elimination mechanism for nitrobenzene derivatives shown in Scheme 1. In several cases [2,3] the addition step is reversible, but in this instance the stability of the leaving NO_2 radical greatly assists the elimination step thus leading to a practically irreversible addition.

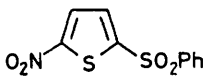
Other mechanistic aspects of radical *ipso*-substitutions, and of alkyldenitrations in particular, are not yet clear. The first and most important question to be answered concerns the factors which control competition between attack at an *ipso* or at an unsubstituted ring position of an aromatic compound. It can be suggested that both the polar character of the attacking radical and the structure of the aromatic substrate are important in determining the positional selectivity of radical addition. It has already been observed [1] that with polynitrobenzenes the nucleophilic 1-adamantyl radical (Ad·) selectively attacks *ipso*-positions bearing nitro-groups, whereas the methyl radical gives rise exclusively to products derived from addition at the unsubstituted ring positions. We have now examined the reactions of these two representative radicals with some selected nitrothiophen derivatives in the expectation that addition of Ad· at an unsubstituted position and *ipso* attack by Me· could both be observed. Compounds (I)—(VI) are suitable models in this respect and we think that the results are a contribution to the knowledge of the factors controlling the selectivity of radical addition.

RESULTS

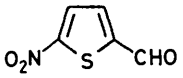
With the exception of (IV) the compounds employed in the present investigation are described in the literature; nevertheless the syntheses of compounds (I)—(IV) deserve some comment because we used procedures different from those described previously. Nitration of 2-methoxycarbonylthiophen afforded a mixture of (I) and (II) which could not be separated; small amounts of a third compound, identified as the 3-nitro-2-methoxycarbonylthiophen (VII), were also obtained. Pure (I) and (II) could be obtained easily by oxidation of the corresponding nitrothiophencarbaldehydes [4] followed by esterification with diazomethane. Compounds (III) and (IV) were instead easily separated by column chromatography of the product of the reaction of 2-methoxycarbonylthiophen with excess of



(I) (II) (III) (IV)

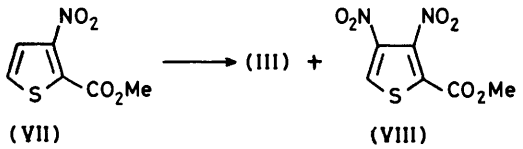


(V)



(VI)

nitric acid. Their identities were confirmed by the results of nitration of the three isomeric nitromethoxycarbonylthiophens (Scheme 2). 3-Nitro-2-methoxycarbonylthiophen (VII) afforded (III) and small amounts of 3,4-dinitro-



SCHEME 2

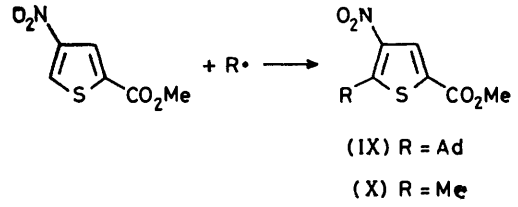
2-methoxycarbonylthiophen (VIII); 4-nitro-2-methoxycarbonylthiophen (I) gave 4,5-dinitro-2-methoxycarbonylthiophen (IV) and traces of (VIII). Finally the nitration of 5-nitro-2-methoxycarbonylthiophen (II) afforded the 3,5-dinitro-derivative (III) as the sole reaction product.

1-Adamantyl, methyl, and cyclohexyl radicals were produced by the silver-catalysed oxidative decarboxylation of the corresponding carboxylic acids [5] and the reactions with compounds (I)—(VI) were carried out in acetonitrile–water solution. Reaction yields were generally lower than those observed previously,[1] but this is due to the fact that both the substrates and the products were sensitive to the reaction conditions and were partially consumed to give unidentified products.

The reactions of 4-nitro-2-methoxycarbonylthiophen (I) with Ad• and Me• radicals afforded 4-nitro-5-(1-adamantyl)-2-methoxycarbonylthiophen (IX) and 4-nitro-5-methyl-2-methoxycarbonylthiophen (X) in 47 and 50% yield, respectively (Scheme 3).

From this latter reaction a further interesting compound was also obtained in low yield (8%); this was identified as the 5-(1-adamantyl)-5-methoxycarbonylthiophen-2(5*H*)-one (XIII). Similarly, 5-nitro-2-phenylsulphonylthiophen (V) reacted with methyl radical to give 4-methyl-5-nitro-2-phenylsulphonylthiophen (XIV) (32%), and with adamantyl radical to give 5-(1-adamantyl)-2-phenylsulphonylthiophen (XV) (43%). Cyclohexyl radical also reacted with (V) to give the *ipso*-substitution product, 5-cyclohexyl-2-phenylsulphonylthiophen (XVI) (38%). Finally, from the reaction of 5-nitrothiophen-2-carbaldehyde (VI) with Ad• the only observed product was the 5-(1-adamantyl)-thiophen-2-carbaldehyde (XVII) (46%).

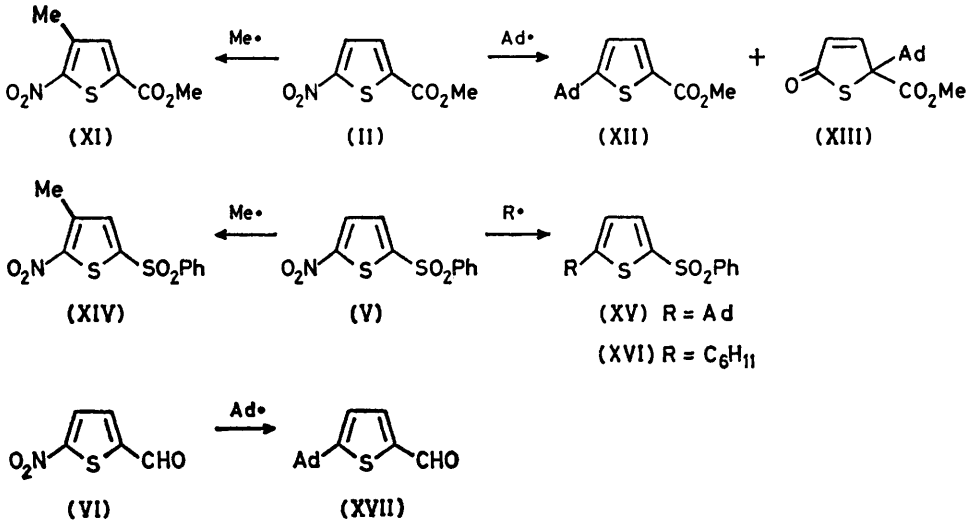
The different behaviour of Me• and Ad• was also observed in the case of the 3,5-dinitro-2-methoxycarbonylthiophen (III) (Scheme 5). Methyl radical added to the unsubstituted position to give 4-methyl-3,5-dinitro-2-methoxycarbonylthiophen (XVIII) (35%), whereas the bridgehead



SCHEME 3

alkyl radical effected the displacement of the nitro-group from the 5-position to afford 5-(1-adamantyl)-3-nitro-2-methoxycarbonylthiophen (XIX) (45%).

Finally, both radicals reacted with the 4,5-dinitro-2-methoxycarbonylthiophen (IV) to give the products of



SCHEME 4

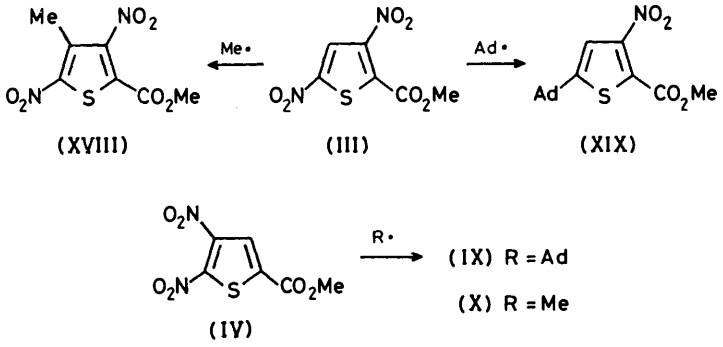
Different behaviour was shown by the 2,5-disubstituted thiophen derivatives (Scheme 4). Methyl radical reacted with 5-nitro-2-methoxycarbonylthiophen (II) to give the product of substitution at the 4-position, 4-methyl-5-nitro-2-methoxycarbonylthiophen (XI) (35%), whereas Ad• effected the displacement of the nitro-group giving the 5-(1-adamantyl)-2-methoxycarbonylthiophen (XII) (55%). alkyldenitration (IX) (55%) and (X) (35%), identical to the compounds obtained from the reaction of (I) with adamantyl and methyl radical, respectively.

Structural assignment of the products was carried out by n.m.r. spectroscopy. In the case of the adamantane derivatives (IX) and (XIX) assignment was facilitated by the appearance of the absorptions of the hydrogens of the bridgehead alkyl group. It has already been observed [1] in several cases that the β, γ, and δ protons generally give rise

to distinct absorptions; however, if a group is present in the position *ortho* to adamantyl, the β-hydrogen atoms are deshielded and the adamantyl group gives rise to two broad singlets, of relative intensity 6 : 9 due to the δ and to the β + γ protons, respectively.

DISCUSSION

In reactions with polynitrobenzenes it was observed that adamantyl radicals add to the *ipso*-positions while methyl radicals add to the unsubstituted positions.[1]

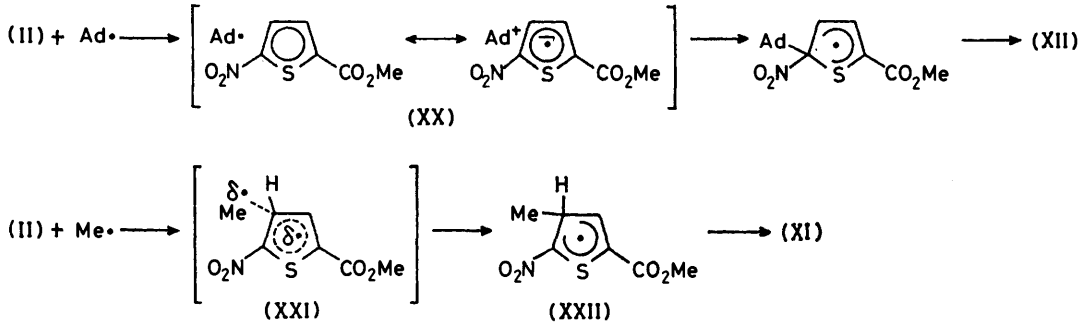


SCHEME 5

From our results we now have a more complete picture of the consequences of the interaction of a radical with an aromatic compound. Important examples are presented in which all the various possibilities are observed depending on the nature of the radical and the substrate. Thus, for 4-nitro-2-methoxycarbonylthiophen (I) both Me• and Ad• add to the unsubstituted 5-position and for 4,5-dinitro-2-methoxycarbonylthiophen (IV) both radicals add to the *ipso* 5-position; on the other hand, for compounds (II), (III), and (V), Ad• effects *ipso*-substitution of the nitro-group in the 5-position and Me• adds to the unsubstituted 4-position.

We suggest that these results can be explained by assuming that polar effects intervene and stabilize the transition state of the addition step with the strongly nucleophilic adamantyl radical, whereas they are negligible with the scarcely nucleophilic methyl radical. When dealing with nucleophilic radicals and strongly electron-deficient substrates the transition state leading to the σ-complex intermediates is similar to a charge transfer complex [6] with a considerable contribution from the polar forms (XX) (Scheme 6); in this case the major factor which controls the positional selectivity is the local charge density at the ring positions which suffer attack. This explains the preference for the 5-position bearing a nitro-group in compounds (II)—(VI). In the case of compound (I) also the 5-position is very likely the most positive centre of the molecule and it is therefore the preferred site of attack by the nucleophilic adamantyl radical.

This description of the transition state cannot be applied to the case of the reactions of the methyl radical. With this species the transition state of the addition step (XXI) is close to the σ-complex intermediate (XXII); it follows that the positional selectivity is governed by the stability of the σ-complex and addition will therefore occur at the ring positions from which the most stable

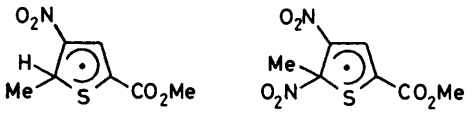


SCHEME 6

intermediates can be formed. Thus, the reaction with (I) will proceed through (XXIII) so that the unpaired electron can be delocalized by the two conjugated substituents. Similarly Me• will preferentially attack the unsubstituted 4-position of compounds (II)—(IV); it is well known that the nitro-group is very efficient in delocalizing an odd electron and exhibits strong *ortho*-directing properties.[7,8] This argument suggests that selective *ipso*-attack by methyl radicals (and by neutral radicals in general) will occur only in those particular cases in which addition at the *ipso*-carbon atom affords the most stable σ-complex. Indeed the reaction with 4,5-dinitro-2-methoxycarbonylthiophen (IV) does give

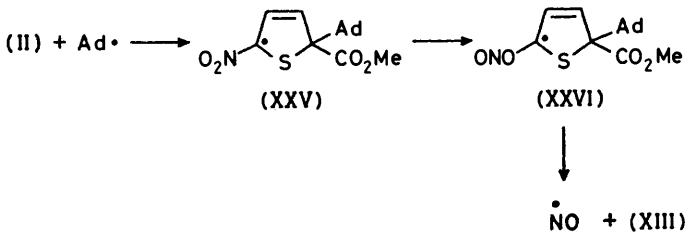
the methyldenitration product (X); the intermediate (XXIV) is the most stable radical which can be formed from (IV).

Finally, the formation of the thiolactone (XIII) from the reaction of Ad· with the 5-nitro-2-methoxycarbonylthiophen (II) deserves some comment. This clearly indicates that addition can also occur at the 2-position to give the *ipso*-intermediate (XXV) (Scheme 7); in this



(XXIII) (XXIV)

case, however, the elimination step is not so easy as in the other examples in which one of the *ipso*-substituents is a nitro-group. Both the Ad and CO_2Me groups form strong bonds with the *ipso*-carbon atom so that neither can be easily eliminated and the intermediate (XXV) is forced to decay through other processes different from reversibility or *ipso*-substitution. Quite similar situations have been encountered in the case of the 2,5-disubstituted furan derivatives.[9] On the basis of



SCHEME 7

evidence obtained from the furan series we tentatively suggest that the thiolactone (XIII) is formed from (XXV) through the rearrangement of the nitro group to a nitrite (XXVI) which then fragments losing the NO radical.

EXPERIMENTAL

Product characterization was accomplished by n.m.r. (JEOL C60HL; $CDCl_3$ solutions) and mass spectrometry (Varian MAT 311A at 70 eV using an all-glass inlet system). M.p.s are uncorrected.

Materials.—5-Nitro-2-phenylsulphonylthiophen [10] (V) and 4-nitro- and 5-nitrothiophen-2-carbaldehyde [5] were prepared as described in the literature.

3-Nitro- (VII), *4-nitro-* (I), *and 5-nitro-2-methoxycarbonylthiophen* (II). To a stirred mixture of nitric acid (*d* 1.51; 4.6 ml) and acetic anhydride (14 ml) at −10 °C, 2-methoxycarbonylthiophen (3 g) was added dropwise. The mixture was stirred at −10 °C for 0.5 h, poured into ice, and extracted with ether. The organic layer was washed with water, sodium carbonate solution, and water and dried (Na_2SO_4). The solvent was removed and the residue chromatographed on silica gel using light petroleum (b.p. 40—60°)–diethyl ether (8 : 2) as eluant. Fractions were collected which contained a mixture (3 g) of 4-nitro- and 5-nitro-2-methoxycarbonylthiophen in 3 : 2 ratio (by n.m.r.); attempts to separate the two isomers by further column chromatography, under several different conditions, were unsuccessful. Later fractions contained a third compound (0.25 g), identified as *3-nitro-2-methoxycarbonylthiophen* (VII), m.p. 50—51°, δ 7.4 (1 H, d), 7.3 (1 H, d, *J* 5.5 Hz), and 3.85 (3 H, s) (Found: C, 38.9; H, 2.7; N, 7.55. $C_6H_5NO_4S$ requires C, 38.5; H, 2.7; N, 7.5%).

4-Nitro-2-methoxycarbonylthiophen (I). To a solution of 4-nitrothiophen-2-carbaldehyde [5] (1.1 g) in pyridine (60 ml) a solution of tetrabutylammonium permanganate (1.3 g) in pyridine was added dropwise and the resulting mixture was poured into diluted HCl containing sodium hydrogensulphite. Extraction with ether followed by washing with water, drying, and evaporation afforded a solid residue which was directly treated with an excess of diazomethane. Evaporation of the solvent left the desired product (I) (1 g), m.p. 98—100° (lit.,[11] 100—101°), δ 8.4 (1 H, d), 8.1 (1 H, d, *J* 1.5 Hz), and 3.95 (3 H, s).

5-Nitro-2-methoxycarbonylthiophen (II). Following the procedure described above for the 4-isomer, this compound was obtained in 85% yield starting from 5-nitrothiophen-2-carbaldehyde [5] (VI). Compound (II) had m.p. 78—79° (lit.,[12] 76°), δ 7.8 (1 H, d), 7.6 (1 H, d, *J* 4.5 Hz), and 3.95 (3 H, s).

3,5-Dinitro- (III) *and 4,5-dinitro-2-methoxycarbonylthiophen* (IV). To a stirred mixture of concentrated H_2SO_4 (40 ml) and HNO_3 (*d* 1.51; 40 ml), cooled in ice, 2-methoxycarbonylthiophen (3.7 g) was added dropwise. The mixture was stirred for 30 min, poured into ice, and extracted with chloroform. After the usual work-up the residue was chromatographed on silica gel using light petroleum–ether (1 : 1) as eluant. Fractions were collected which contained pure *3,5-dinitro-2-methoxycarbonylthiophen* (III) (2.7 g), oil (lit.,[13] b.p. 61—62°), δ 8.1 (1 H, s) and 3.95 (3 H, s). After some fractions containing a mixture of (III) and (IV), pure *4,5-dinitro-2-methoxycarbonylthiophen* (IV) (1 g) was collected, m.p. 57—58°, δ 7.8 (1 H, s) and 3.95 (3 H, s) (Found: C, 31.2; H, 1.6; N, 12.3. $C_6H_4N_2O_6S$ requires C, 31.0; H, 1.7; N, 12.1%).

Nitration of 3-nitro-2-methoxycarbonylthiophen (VII). The reaction was carried out with H_2SO_4 and HNO_3 as described above, using (VII) (0.1 g). Column chromatography afforded (III) (56%) and *3,4-dinitro-2-methoxycarbonylthiophen* (VIII) (14%), m.p. 86—88°, δ 8.4 (1 H, s) and 3.9 (3 H, s) (Found: C, 31.4; H, 1.8; N, 12.0%).

Nitration of 4-nitro-2-methoxycarbonylthiophen (I). Under the same conditions (I) afforded a mixture of (IV) (50%) and (VIII) (15%) which was separated by column chromatography.

Nitration of 5-nitro-2-methoxycarbonylthiophen (II). The reaction was effected under the same experimental conditions using (II) (0.2 g). The only product isolated was (III), identical with the product obtained from the nitration of (VII) and of 2-methoxycarbonylthiophen.

Reactions of Compounds (I)—(VI) *with Alkyl Radicals.*—All the reactions were carried out by the following general procedure. To a stirred solution of the nitro-compound (3 mmol), the acid (adamantane-1-carboxylic, acetic, or cyclohexanecarboxylic) (15 mmol) and $AgNO_3$ (0.3 mmol) in 4 : 1 v/v acetonitrile–water (50 ml), a saturated solution of $(NH_4)_2S_2O_8$ (20 mmol) in water was added dropwise, under reflux, over *ca.* 20 min. Stirring and heating were continued for 30 min and the cooled solution was then poured onto ice and NH_3; the mixture was extracted with chloroform and the organic layer was washed with 5% NaOH and with water. The solution was dried and the

solvent evaporated. The residue was chromatographed through a silica gel column using light petroleum–diethyl ether (7 : 3) as eluant. The separation of the products was monitored by t.l.c. Yields are reported in the Results section: *4-nitro-5-(1-adamantyl)-2-methoxycarbonylthiophen* (IX), obtained from the reaction of 1-adamantyl radicals with (I) and with (IV), m.p. 101—103°, δ 8.0 (1 H, s), 3.9 (3 H, s), 2.2br (9 H, s, β- and γ-H), and 1.8br (6 H, s, δ-H) (Found: C, 60.0; H, 5.85; N, 4.3. $C_{16}H_{19}NO_4S$ requires C, 59.8; H, 6.0; N, 4.4%); *4-nitro-5-methyl-2-methoxycarbonylthiophen* (X), obtained from the reaction of methyl radicals with (I) and with (IV), m.p. 75—76°, δ 8.1 (1 H, s), 3.9 (3 H, s), and 2.8 (3 H, s) (Found: C, 41.5; H, 3.5; N, 6.5. $C_7H_7NO_4S$ requires C, 41.8; H, 3.5; N, 6.7%); *5-nitro-4-methyl-2-methoxycarbonylthiophen* (XI), m.p. 89—90°, δ 7.45 (1 H, s), 3.9 (3 H, s), and 2.6 (3 H, s) (Found: C, 41.2; H, 3.7; N, 6.6%); *5-(1-adamantyl)-2-methoxycarbonylthiophen* (XII), m.p. 112—113°, δ 7.5 (1 H, d), 6.75 (1 H, d, *J* 4 Hz), 3.85 (3 H, s), 2.1br (3 H, s, γ-H), 1.95br (6 H, s, β-H), and 1.7br (6 H, s, δ-H) (Found: C, 69.8; H, 7.2. $C_{16}H_{20}O_2S$ requires C, 69.5; H, 7.3%); *5-(1-adamantyl)-5-methoxycarbonylthiophen-2(5H)-one* (XIII), m.p. 96—98°, δ 7.45 (1 H, d), 6.05 (1 H, d, *J* 6 Hz), 3.7 (3 H, s), 2.1—1.9 (9 H, m), and 1.75 (6 H, s), $\nu_{max.}$ 1 630 cm^{-1} (α,β-unsaturated thiolactone),[14] *m/e* 292 (1.7%, *M*), 233 (12, *M* − CO_2Me), 232 (3), 205 (7), 136 (78), 135 (100), 107 (72), 93 (72), 79 (72), and 67 (67); *4-methyl-5-nitro-2-phenylsulphonylthiophen* (XIV), m.p. 103—105°, δ 8.1—7.9 (2 H, m), 7.7—7.5 (3 H, m), 7.4 (1 H, s), and 2.6 (3 H, s), *m/e* 283 (30%, *M*), 269 (5), 266 (4), 125 (100), 97 (21), and 77 (68); *5-(1-adamantyl)-2-phenylsulphonylthiophen* (XV), m.p. 157—159°, δ 8.0—7.8 (2 H, m), 7.6—7.35 (4 H, m), 6.75 (1 H, d, *J* 4.5 Hz), 1.9br (9 H, s), and 1.7br (6 H, s), *m/e* 358 (100%, *M*), 315 (3, *M* − C_3H_7), 301 (22, *M* − C_4H_9), 160 (35), 135 (6.5), 94 (14), 93 (8.5), 79 (13), and 67 (7.5); *5-cyclohexyl-2-phenylsulphonylthiophen* (XVI), m.p. 100—101°, δ 8.05—7.85 (2 H, m), 7.6—7.4 (4 H, m)), 6.75 (1 H, d, *J* 4.5 Hz), and 1.5—1.0 (11 H, m), *m/e* 306 (100%, *M*), 263 (27), 250 (14), 237 (3), 225 (3), 165 (42), 125 (44), 97 (36), and 82 (9); *5-(1-adamantyl)thiophen-2-carbaldehyde* (XVII), m.p. 131—133°, δ 9.6 (1 H, s), 7.5 (1 H, d) 6.85 (1 H, d, *J* 4.5 Hz), 2.05br (3 H, s, γ-H), 1.95br (6 H, s, β-H), and 1.75br (6 H, s, δ-H) (Found: C, 73.2; H, 7.5. $C_{15}H_{18}OS$ requires: C, 73.1; H, 7.4%); *4-methyl-3,5-dinitro-2-methoxycarbonylthiophen* (XVIII), m.p. 63—64°, δ 3.9 (3 H, s) and 2.55 (3 H, s) (Found: C, 34.3; H, 2.5; N, 11.2. $C_7H_6N_2O_6S$ requires: C, 34.1; H, 2.5; N, 11.4%); *5-(1-adamantyl)-3-nitro-2-methoxycarbonylthiophen* (XIX), m.p. 131—132°, δ 7.1 (1 H, s), 3.9 (3 H, s), 2.1br (3 H, s, γ-H), 2.0br (6 H, s, β-H), and 1.8br (6 H, s, δ-H) (Found: C, 59.5; H, 6.2; N, 4.6%).

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