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CYCLOADDITION REACTIONS OF 2-VINYLTHIOPHEN

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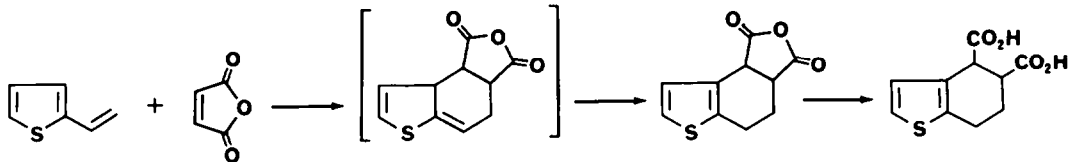
Abstract - Cycloaddition reactions between 2-vinylthiophen and the dienophiles maleic anhydride, dimethyl acetylenedicarboxylate, methyl propiolate, and methyl acrylate, are reported. Products include simple benzo[b]thiophen carboxylates (6, 13, 17) and reduced derivatives (3, 4, 18). The acetylenic dienophiles also gave a dihydrobenzthienyl-acrylate (16) or -fumarate (11), and the dithienylcyclohexene esters (7) and (14).

Cycloadditions of dienophiles to vinyl heterocycles can provide syntheses of annulated hetero-cycles with a pattern of substituents unavailable by other routes. In spite of this potential there are relatively few such cycloadditions. Monocyclic compounds which have been used are furan,[1-6] pyrroles,[4,7-10] pyridines,[11-13] and a pyrazole[14]. References to vinylthiophens are scattered;[12,15-20] these include the use of the dienophiles maleic anhydride,[15-17] alkenes,[20] benzoquinone,[17] N-phenylmaleimide,[18,20] azo compounds,[12,20] and singlet oxygen[19]. Of these only five deal with 2-vinyl thiophen itself, the most extensive recent study[19] being on the trimethyl-silyl ether of 2-acetylthiophen, using a wide variety of dienophiles. Some of the structures advanced for adducts appeared doubtful and there were no reports of the use of acetylenic dienophiles. We have now re-examined some earlier reactions, with corrected structures, and have obtained a wide range of cycloaddition products from 2-vinylthiophen and dimethyl acetylene-dicarboxylate (DMAD) and from methyl propiolate.



(1) (2) (3) (4)

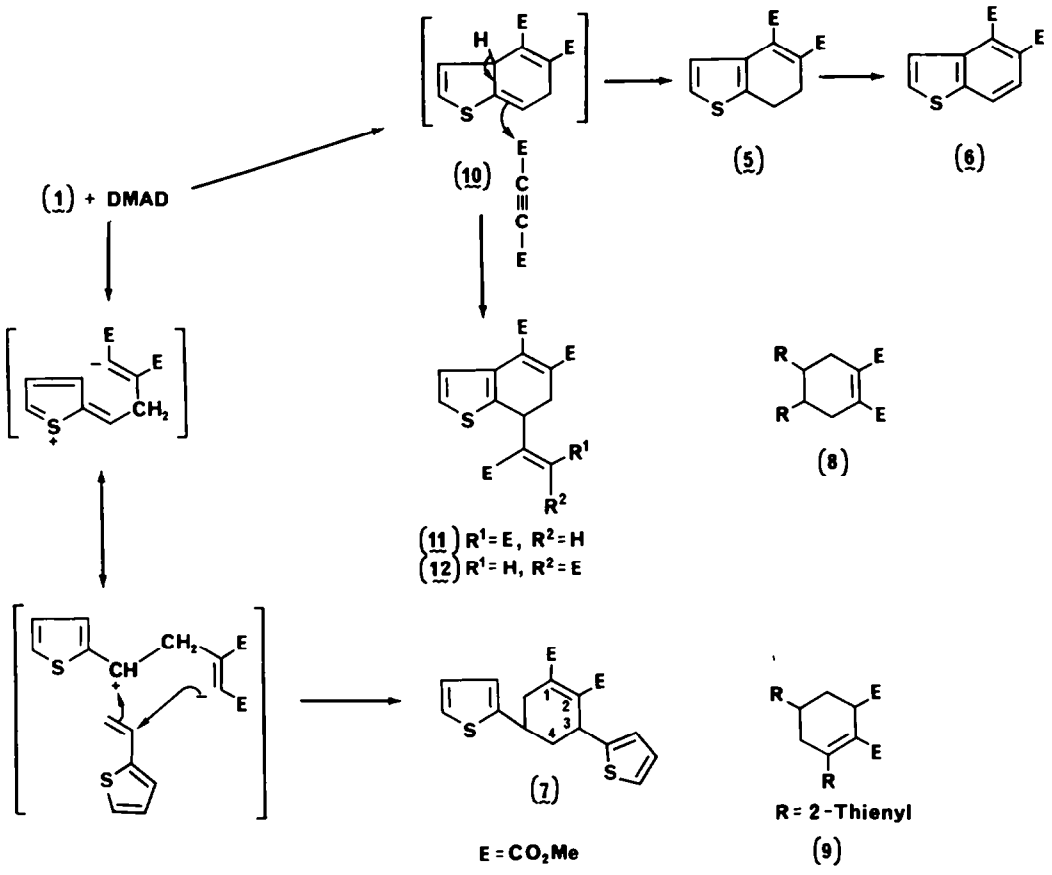
Scully and Brown reported[16] that 2-vinylthiophen (1) reacted with maleic anhydride to give an adduct which they could not purify, to which they ascribed structure (2). They converted the anhydride into a dicarboxylic acid which they further converted into benzo[b]thiophen, thus establishing that the adduct was bicyclic. Davies and Porter[17] isolated the adduct and recorded an analysis, but did not comment on the structure. We have isolated the adduct by careful chromatography on silica; two other products were also isolated.

The adduct melted over a range, close to that reported by Davies and Porter[17], but appeared pure from its ^{1}H n.m.r. spectrum. The most immediately relevant observation was the presence of a singlet (2H) at δ7.0 due to two coincidental thiophen protons, with no other signals below δ5.0, which excludes structure (2). Two multiplets (each 1H) at δ4.2 and δ3.65 were seen to be doublets

of triplets, the signal at lower field, H^A, having J 8 and 1Hz, and that at higher field, H^B, J 8 and 5Hz. These data accord well with the structure of an isomer (3) of compound (2) in which the thiophen ring has re-aromatized, and the major coupling constant of 8Hz between H^A and H^B is in good agreement with that expected for a cis(e,a) arrangement of the anhydride derived hydrogen atoms. The remaining signals, a distorted triplet at δ2.6-2.9 (H7a and H7b), and a multiplet (2H) δ1.8-2.6 agree equally well with the structure proposed. The second product isolated was a dicarboxylic acid, with a melting point very close to that recorded by Scully and Brown[16] for their compound produced by hydrolysis of the anhydride. The removal of the constraint on the carbonyl group (now no longer held in the anhydride ring), allowed a greater deshielding of H3, and the thiophen protons were clearly seen as a pair of doublets at δ7.0 and 7.25. The alicyclic protons were less resolved but H4 was again visible as a deformed doublet (J 6Hz) at δ4.15 and there seems no doubt that the acid has structure (4), probably still with a cis arrangement of carboxyl groups. The third compound, isolated only in small amounts was a mono ethyl ester of the dicarboxylic acid (4), probably formed on chromatography using chloroform as eluant.

Reaction between 2-vinylthiophen (2) and dimethyl acetylene dicarboxylate (DMAD) required a longer time than that with maleic anhydride. The crude product contained much polymer but four products were isolated by chromatography in low yield, and are described in the order of elution. The first compound was a solid, of formula $C_{12}H_{10}O_4S$, with a strong carbonyl absorption in the infrared, and a simple ^1H n.m.r. spectrum. Two methyl singlets at δ3.85 and 3.9 indicated the presence of two methyl esters and the only other signals (4H) were in the region δ7.4-8.0. Two coincidental signals at δ7.4 were assigned to H2 and H3 (thiophen protons) and a very distorted pair of doublets at δ7.7 and 7.85 (J 8Hz) to H6 and H7 in the benzothiophen diester (6). This product is formed by dehydrogenation of the 'normal' cycloaddition product (5) which was not itself isolated. The second material eluted from the column, was purified further by p.l.c. and h.p.l.c., and shown to have the formula $C_{18}H_{18}O_4S_2$. The ^1H n.m.r. spectrum showed the presence of only two ester groups, signals due to six aromatic protons δ6.55-7.2, and a total of six protons absorbing in the region δ1.15-3.5, presumed to be in an alicyclic ring. Assembling these units on the most reasonable mechanistic grounds, the preferred structure would be a di-(2-thienyl)-cyclohexene-dicarboxylate (7). The chemical shifts of the alicyclic protons show two of them at δ1.0-1.15 to be remote from deshielding groups (H4,4'). The remaining four protons are all to some extent deshielded, the furthest downfield being H3, but none are alkene protons. The only alternative structures considered were (8) and (9). The former was excluded because of the absence of 'shielded' protons, and the latter because of the similarity of the ester groups both in infrared absorption maxima and in chemical shift of the methyl signals. A mechanism for formation of this product is given in Scheme 1. This type of product is unique in reported cycloaddition of simple vinylheterocycles.

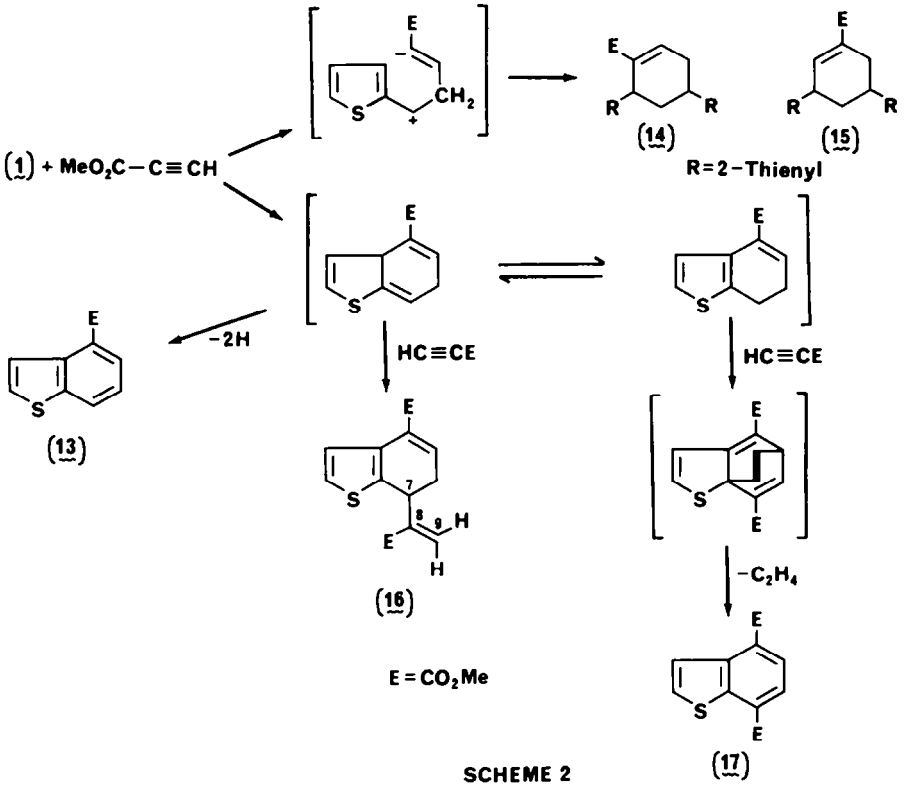
The third product was a crystalline solid. Analysis showed a molecular formula of $C_{18}H_{18}O_8S$, and there were four methyl ester groups in similar environments. The presence of an AB system in the ^1H n.m.r. spectrum (J 6Hz) at δ7.45 and 7.55 is characteristic of an annulated thiophen, and a sharp singlet at δ7.75 was assigned to the proton on a fumarate residue (maleate δ5.5). The only other signals were an ABM system; H^A centred at δ2.8 as a double doublet (J 18 and 6Hz), H^B at δ3.4 as a double doublet (J 18 and 9Hz), and H^M at δ4.5 (J 9 and 6Hz). All these data are satisfied by the structure (11), and the product could be formed by an ene reaction on the intermediate (10) formed by the $\pi_4 + \pi_2$ cycloaddition. A similar product was reported by Davidson and Elix from the reaction between 2-vinyl-furan and DMAD[5]. The fourth component was not obtained analytically pure, but the n.m.r. spectrum shows quite clearly that it is the (Z)-isomer (12) of compound (11). The most significant differences from the spectrum of the (E) isomer are in the position of the isolated alkene signal (at δ5.55 (maleate) instead of δ7.75), and in a simplification of the alicyclic portion of the spectrum because of the near coincidence of the signals for H6 and H6'.



SCHEME 1

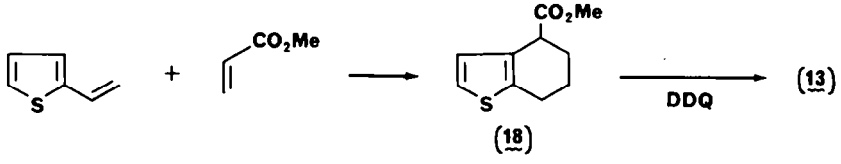
The reaction between methyl propiolate and vinylthiophen (1) was conducted at 100 °C under pressure, and was also accompanied by polymer formation. Four products were isolated and characterised spectroscopically, all being obtained analytically pure. In order of elution, the first compound was a methyl benzo[b]thiophencarboxylate. In the n.m.r. spectrum all signals except the methyl ester singlet at δ3.85 were in the aromatic region. In the region δ7.0-7.6 were a doublet (J 6Hz) assigned to H2, and a doublet of doublets (J 7 and 8Hz) assigned to H6. The second thiophen signal was at δ8.3 and the deshielding presents a clear indication that the methoxycarbonyl substituent is at C4. The other two signals were two overlapping doublets of doublets (J 8 or 7 and 1Hz) which must be H5 and H7, thus establishing the compound as methyl benzo[b]thiophen-4-carboxylate (13). Cycloaddition of methyl propiolate thus appears regio-specific in the sense expected from a simple HMO calculation. The second compound eluted was further purified by HPLC; analysis and mass spectrum showed it to have the molecular formula $C_{16}H_{16}O_2S_2$. Inspection of the ^1H n.m.r. spectrum showed a close similarity with that of compound (7) but with only one ester signal, and a multiplet (7H) in the aromatic region, which includes H2, β to the ester. The signals were more difficult to assign than those of compound (7) but the general shifts leave us with no doubt that structure (14) is correct. Our spectral data do not entirely exclude the isomeric structure (15), but our suggested stepwise mechanism would lead to the placing of the ester group as shown in structure (14). The third compound eluted, also purified by HPLC, had a molecular formula $C_{14}H_{14}O_4S$ and two virtually identical ester groups. The n.m.r. spectrum showed a pattern of ester and alkene protons almost identical with that of methyl methacrylate, with an additional triplet (or double doublet) at δ6.7 (J 5Hz) which was assigned to a proton β to an ester. The compound was clearly analogous to that obtained from DMAD - compound (11) - and is assigned structure (16), the position of the ester on the six membered ring being assigned on the basis of the mechanism of formation, and of the observed coupling of H5. The

fourth component was difficult to separate, but proved most interesting. With a molecular formula of $C_{12}H_{10}O_4S$ and two almost identical ester groups, it must be a benzothiophendicarboxylate, and the symmetry of the spectrum leads to its formulation as the 4,7-dicarboxylate (17). A similar product has been reported as arising from N-substituted 2-vinylpyrroles[7], and can be derived by addition of a second molecule of methyl propiolate to the expected adduct followed by retro Diels-Alder elimination of ethylene. All these reactions are summarized in Scheme 2.



SCHEME 2

Our final experiments were with methyl acrylate as dienophile. Under the same drastic conditions (100 °C, sealed tube, CH_2Cl_2 solvent, 72h) only one product was obtained, in 7% yield. By increasing the reaction temperature to 160 °C the yield of ester (18) could be increased to 28%. Analysis showed it to have the formula $C_{10}H_{12}O_2S$, and the presence of one methyl singlet indicated a mono-ester. The characteristic AB system of a 2,3-disubstituted thiophen at δ6.8 and 6.95 indicated a slight deshielding of H3. The rest of the ^1H n.m.r. spectrum, a series of multiplets at δ2.0-2.5 (4H), at δ2.8-3.2 (2H) and near δ3.8 suggest that the ester group is adjacent to the thiophen ring, and calculations show that the most likely mode of cycloaddition, as with the methyl propiolate would place the ester group at position 4. Thus the cycloaddition product is methyl 4,5,6,7-tetrahydrobenzo[b]thiophen-4-carboxylate (18), and dehydrogenation gave ester (13).



In summary, we have shown that 2-vinylthiophen reacts with a number of simple dienophiles to give a variety of products. Of these the 2:1 adducts (7) and (14) have not been previously observed for vinyl heterocycles, and the adduct (16) is of a type only previously reported with vinylpyrroles.

EXPERIMENTAL

M.p.s. were determined on a Kofler heated stage and are uncorrected. Column chromatography was performed on Merck silica gel or alumina. P.l.c. was on plates (20 x 20 or 40 x 20 cm) of Merck silica gel $60PF_{254}$. HPLC was performed on a Waters instrument, using a semipreparative silica carbowax column eluting with a 1:4 mixture of ethyl acetate and hexane. N.m.r. spectra were recorded for $CDCl_3$ solutions unless otherwise stated.

1-(2-Thienyl)ethanol and 2-Vinylthiophen. -

(a) The thienyl ethanol was prepared in 90% yield by reduction of 2-acetyl thiophen with sodium borohydride in methanol, b.p. 100 °C/1.5 mm Hg (lit.[21] b.p. 90-92°/6 mm Hg).

(b) The thienyl ethanol was dehydrated by distillation (50 mm Hg) through an activated alumina column kept at 250°. The yield was 80%, b.p. 65-67 °C/50 mm Hg (lit.[21] b.p. 50.5-51 °C/28 mm Hg).

Reaction between 2-Vinylthiophen and Maleic Anhydride. - A mixture of vinylthiophen (0.77 g.), maleic anhydride (0.69 g.) and dry benzene (3 ml), was boiled under reflux (6 h.) and then left overnight (10 h.) Polymeric material was filtered off and washed with benzene, and the combined benzene solutions evaporated to give an oil (1.46 g.), which was separated by chromatography on a silica column (eluant $CHCl_3$). The first fraction from the column was the anhydride (3) m.p. 150-160 °C (0.14 g., 10%) (lit.[17] m.p. 164-166 °C) ν_{max} (CCl_4)1870, 1800, 710 cm^{-1}. δ1.8-2.6 (2H, m), 2.6-2.9 (2H, m), 3.5 (1H, dt, J5 and 8Hz, H5), 4.2 (1H, dt, J8 and 1Hz, H4), 7.0 (2H, s). The second fraction (0.4 g., 32%) was the 4,5,6,7-tetrahydrobenzo[b]thiophen-4,5-dicarboxylic acid, m.p. 183-185 °C (lit.[17] m.p. 180-185 °C). ν_{max}^{KBr} 1690 cm^{-1} δ(d_6-DMSO + d_6-acetone) 2.1-3.1 (5H, m), 4.15 (1H, d, J 6 Hz, H4), 7.0 (1H, d, J 6Hz, H2), 7.25 (1H, d, J 6Hz, H3). The third fraction was a colourless oil, b.p. 250°/0.5 mm Hg, identified tentatively as a monoethyl ester of tetrahydrobenzthiophen-4,5-dicarboxylic acid (0.04 g., 2%) ν_{max} 1750, 1710 cm^{-1}. δ1.05-1.4 (t, 3, $CH_2\underset{\sim}{CH_3}$), 2.2-2.55 (2H, m), 2.55-3.0 (3H, m), 3.8-4.3 (3H, m, $\underset{\sim}{CH_2}CH_3$ + H4) 7.0 (1h, d, J 5Hz, H2), 7.15 (1H, d, J 5Hz, H3), 8.8 (1H, brs, exch. D_2O, CO_2H).

Reaction between 2-Vinylthiophen (1) and DMAD. - A solution of vinylthiophen (1) (1.5 g.) and DMAD (1.905 g.) in anhydrous benzene (15 ml) was boiled and stirred under reflux (8 h.) then left at room temperature (10 h.). Evaporation gave 2.5 g. of crude product, which was purified on a silica column, eluting first with dichloromethane/cyclohexane (1:1), and then with increasing proportions of dichloromethane. The first fraction was a mixture of starting materials (~ 0.2 g.). The second fraction (0.14 g.) was further purified by p.l.c. (ethyl acetate/toluene 1:9), to give dimethyl benzo[b]thiophen-4,5-dicarboxylate, (6), m.p. 64-66 °C (from cyclohexane)(5% yield). (Found: C, 57.5; H, 3.8. $C_{12}H_{10}O_4S$ requires C, 57.6; H, 4.0%). ν_{max} (CCl_4) 1740 cm^{-1}. δ(CCl_4) 3.85 (3H, s), 3.9 (3H, s), 7.4 (2H, s), 7.7 (1H, d, J 8Hz) 7.9 (1H, d, J 8Hz). The third fraction eluted was further purified by p.l.c. (eluent ethyl acetate/cyclohexane, 1:9), and then HPLC to give dimethyl-3,5-di(2-thienyl)cyclohex-1-en-1,2-dicarboxylate (7), (4% yield). (Found: C, 60.05; H, 4.75. $C_{18}H_{18}O_4S_2$ requires C, 59.65; H, 4.95%). ν_{max} (CCl_4) 1740 cm^{-1}. δ1.15-1.5 (2H, m), 2.55-3.05 (2H, m), 3.05-3.50 (2H, m), 3.70 (3H, s), 3.80 (3H, s) 6.55-7.2 (6H, m). The fourth fraction eluted (0.08 g. 15%) was crystallized from cyclohexane, giving tetramethyl (E)-7-(2-butendionato)-6,7-dihydrobenzo[b]thiophen-4,5-dicarboxylate (11), m.p. 115-116 °C. (Found: C, 54.85; H, 4.65. $C_{18}H_{18}O_8S$ requires C, 54.8; H, 4.55%). ν_{max} (CCl_4) 1740, 1200 cm^{-1} δ2.8 (1H, dd, J18 and 6Hz, H6), 3.4 (1H, dd, J18 and 9Hz, H6'), 3.65 (6H, s, 2 x CO_2CH_3), 3.85, (3H, s, CO_2CH_3), 3.95 (3H, s, CO_2CH_3), 4.5 (dd, J9 and 6Hz, H7), 7.45 (1H, d, J 6Hz, H2), 7.55 (1H, d, J 6Hz, H3), 7.75 (1H, s, $\underset{\sim}{CH}(CO_2Me)=C(CO_2Me)$). The fifth fraction was further purified by p.l.c. (CCl_4/ethyl acetate, 9:1) and gave the (Z) isomer of compound (11), diester (12) (2%). δ2.8-3.1 (2H, m), 3.55 (3H, s), 3.65 (3H, s), 3.7 (3H, s), 3.8 (3H, s), 3.9-4.25 (1H, m, H7), 5.5 (1H, d, J 0.5Hz, H9), 6.85 (1H, d, J 5Hz, H2), 7.15 (1H, d, J 5Hz, H3).

Reaction between 2-Vinylthiophen (1) and Methyl Propiolate. - A solution of vinylthiophen (1) (1 g.) and methyl propiolate (0.98 g.) in dichloromethane (10 ml) was heated in a sealed tube at 100° (5 atmos. pressure) (60 h.). Evaporation gave a crude product (1.76 g.) separated on a silica column, eluent hexane with increasing proportions of chloroform. First fraction eluted was methyl benzo[b]thiophen-4-carboxylate (13) (0.04 g., 3%). (Found: C, 62.9; H, 4.0. $C_{10}H_8O_2$

requires C, 62.45; H, 4.2%) m/z 194 (M^+) ν_{max} (CCl_4) 1740 cm^{-1} δ(CCl_4) 3.85 (3H, s), 7.4 (1H, dd, J7 and 8Hz, H6), 7.45 (1H, d, J 6Hz, H2), 7.9 (1H, br d, J 7Hz, H5 or H7), 8.0 (1H, br d, J 7Hz, H7 or H5), 8.2 (1H, d, J 6Hz, H3). The second fraction eluted was further purified by p.l.c. (cyclohexane) and HPLC to give methyl 4,6-di(2-thienyl)cyclohex-1-en-1-carboxylate (14) (1.5%). (Found: C, 63.3; H, 5.1. $C_{16}H_{16}O_2S_2$ requires C, 63.15; H, 5.25%). m/z 306 (1.9%) 305 (2.6%) 304 (10%), 192 (100%) 161 (88%). δ1.2-1.4 (2H, dd, J 7 and 1Hz, H4, 4'), 2.4-3.0 (4H, m), 3.7 (3H, s), 6.6-7.4 (7H, m). The third fraction, further purified by p.l.c. (cyclohexane/ether; 7:3), and HPLC gave dimethyl 7-(2-propenoato)-6,7-dihydrobenzo[b]thiophen-4--carboxylate (16) (15%). (Found: C, 59.9; H, 4.85. $C_{14}H_{14}O_4S$ requires C, 60.45; H, 5.05%). ν_{max} (CCl_4) 1730, 1280 cm^{-1}. δ2.5-2.8 (2H, m), 3.7 (6H, s), 4.15 (1H, t, J 7Hz, H7), 5.2 (1H, br s, H9), 6.1 (1H, s, H9'), 6.7 (1H, t, J 5Hz, H5), 6.9 (1H, d, J 6Hz), 7.45 (1H, d, J 6Hz; H3). The last fraction eluted, further purified by HPLC, gave dimethyl benzo[b]thiophen-4,7-dicarboxylate (17) m.p. 128-130 °C m/z 250.0299 ($C_{12}H_{10}O_4S$, requires 250.0299; M^+, 100%), 191.0165 ($M-CO_2CH_3$, 13%). δ4.0 (3H, s), 4.05 (3H, s), 7.55 (1H, d, J 6Hz, H2), 7.9 (2H, s, H5 and H6), 8.1 (1H, d, J 6Hz, H3). Our thanks are due to the PCMU for an exact mass determination.

Reaction between 2-Vinylthiophen (1) and Methyl Acrylate. - A solution of vinylthiophen (1) (0.94 g.) and methyl acrylate (0.74 g.) in dichloromethane (10 ml) was heated in a sealed tube at 100 °C (5 atmospheres, 72 h.). Evaporation gave crude product, purified by p.l.c. (chloroform eluent). The only product isolated was again subjected to p.l.c. (CCl_4/CH_2Cl_2, 1:9) and gave, in 7% yield, methyl 5,6,7,8-tetrahydrobenzo[b]thiophen-4-carboxylate (18). (Found: C, 61.75; H, 6.45. $C_{10}H_{12}O_2S$ requires C, 61.2; H, 6.1%). ν_{max} (CCl_4) 1750 cm^{-1}. δ2.1-2.7 (4H, m), 2.7-3.0 (2H, m), 3.4-3.6 (1H, m), 3.65 (3H, s), 6.8 (1H, d, J 5Hz, H2), 6.95 (1H, d, J 5Hz, H3). By raising the reaction temperature to 160 °C the yield of ester (18) could be raised to 28%.

Dehydrogenation of Ester (18). - A solution of the ester (18) (0.41 g.) and DDQ (0.098 g.) in anhydrous benzene (10 ml) was boiled under reflux (4.5 h.). The mixture was filtered, and the filtrate evaporated. Purification by p.l.c. (eluent hexane/methanol, 9:1) gave ester (13) (0.11 g., 28%), identical with specimens prepared by addition of methyl propiolate to 2-vinylthiophen.

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