ACTA CHEMICA SCANDINAVICA 22 (1968) 2445–2452

Nitration of 4,5-Dihydro-5-methyl-6H-cyclopenta[b]thiophene-6-one and Nitration and Acetylation of α-Methyl-β-(3-thienyl)propanoic Acid. A Reinvestigation

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Contrary to the results obtained by others, the nitration of 4,5-dihydro-5-methyl-6H-cyclopenta[b]thiophene-6-one is shown to give two isomers, making this reaction analogous to the nitration of 2-acetylthiophene. The nitration and acetylation of α-methyl-β-(3-thienyl)propanoic acid is in the same way shown to be analogous to the nitration and acetylation of 3-methylthiophene, giving in each case the 2-substituted derivative as the major product.

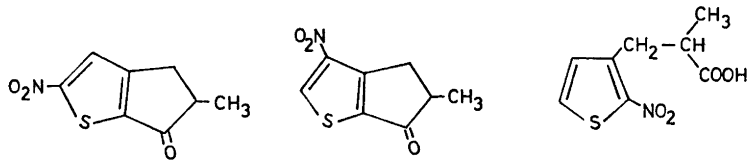
An interesting *ortho*-effect was observed in the mass spectrum of 4,5-dihydro-5-methyl-6H-cyclopenta[b]thiophene-6-one, and is compared with a similar effect in *o*-nitrotoluene. Even in the case of the other pair of isomers large differences in the mass spectra were noticed.

During work on the chemistry of cyclopenta-thiophenes now in progress in this laboratory, our attention was called to a publication by Sam and Thompson.[1] These authors report the nitration of 4,5-dihydro-5-methyl-6H-cyclopenta[b]thiophene-6-one and the nitration and acetylation of α-methyl-β-(3-thienyl)propanoic acid. As their results to some extent seem to be at variance with the normal substitution pattern in thiophene derivatives, and as they give no structural proofs of the reaction products, we thought it worthwhile to reinvestigate their work.

The synthesis of 4,5-dihydro-5-methyl-6H-cyclopenta[b]thiophene-6-one was accomplished in one step from thiophene and methacrylic acid in polyphosphoric acid according to Meth-Cohn and Gronowitz.[2] α-Methyl-β-(3-thienyl)propanoic acid[3] was prepared from 3-bromomethylthiophene and diethyl methylmalonate by the usual malonic ester synthesis, followed by hydrolysis and decarboxylation.

Sam and Thompson carried out the nitration of 4,5-dihydro-5-methyl-6H-cyclopenta[b]thiophene-6-one in acetic anhydride with a mixture of fuming nitric acid and acetic anhydride. They prepared this nitration mixture at −6°C, and considered it to be an acetyl nitrate solution in acetic anhydride.

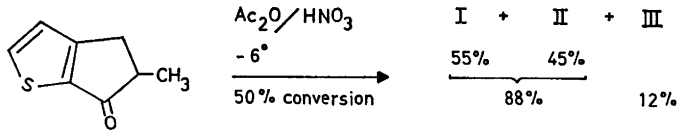
According to Bordwell and Garbisch,[4] however, it is not likely that acetyl nitrate is formed at temperatures below 10°C. In any event Sam and Thompson obtained nitrated products. With a reaction temperature between −6°C and −15°C they claim the formation of a single product (m.p. 98—100°C) to which they assigned structure I. Apparently they failed to detect any of the isomeric compound II. At temperatures between 0°C and 10°C Sam and Thompson obtained a ring-opened nitrated product III (m.p. 135—136°C) together with



I II III

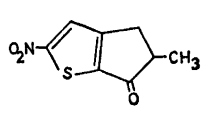
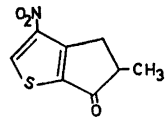
I. The position occupied by the nitro group in I and III was not proved, but deduced by analogy with Rinkes' nitration of 2-acetylthiophene [5] (in which about equal amounts of 4-nitro- and 5-nitro-2-acetylthiophene were obtained). Neither are these results analogous with Tirouflet's nitration of acetylthiophene,[6] which gave 52 % of 4-nitro-2-acetylthiophene.

We have repeated Sam and Thompson's experiment under their conditions. Our results are expressed in the following scheme:

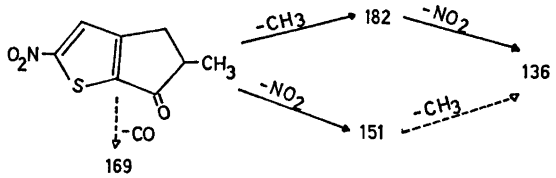


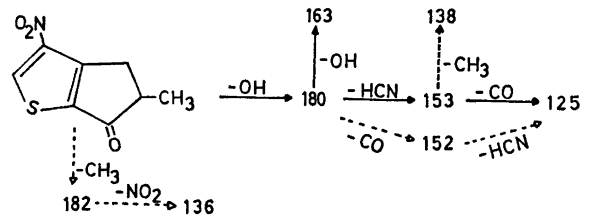
The products were identified by NMR, elementary analyses and mass spectra. I and II were separated by fractional crystallization from ethanol/water. The least soluble isomer (m.p. 99—101°C) gave an NMR spectrum ($CDCl_3$) with an 1 H singlet at $\tau=2.05$ ppm and the other (m.p. 94—96°C) possessed an 1 H singlet at $\tau=1.16$ ppm. The NMR spectrum ($CDCl_3$) of the starting material shows thiophenic absorptions at $\tau=2.21$ ppm and $\tau=2.97$ ppm due to the 2- and 3-hydrogens, respectively.[2] Since it is known that a nitro group shifts an *ortho* hydrogen approximately 1 ppm to lower field in mononitrated thiophenes,[7] it is evident that the compound melting at 99—101°C is the 2-nitro isomer (I) and that the compound melting at 94—96°C is the 3-nitro isomer (II). The acid (m.p. 133—135°C) gave an NMR spectrum with a typical 4,5-coupling constant of 5.4 c/s characteristic of 2,3-disubstituted thiophenes,[8] which confirms the structure III. The structure assignments made by Sam and Thompson regarding I and III are thus substantiated. We have also carried out the nitration with the same nitrating mixture prepared at 20°C. According to the literature [4] this should then contain appreciable amounts of acetyl nitrate. Within experimental error, however, the same isomer distribution was obtained.

Table 1. Dominant fragments in the mass spectrum of 4,5-dihydro-5-methyl-2-nitro (and -3-nitro) -6H-cyclopenta[b]thiophene-6-one. Relative intensity taken as ion current for each fragment in percent of total ion current from $m/e = 25$ and above.

Mass (m/e)	Probable origin	Relative intensity 	
197	Parent ion	16.96	11.85 (base peak)
182	$197^+ - CH_3$	17.83 (base peak)	2.53
180	$197^+ - OH$	0.16	3.16
169	$197^+ - CO$	1.72	0.21
163	$180^+ - OH$	0.09	1.01
153	$180^+ - HCN$	0.15	2.44
152	$180^+ - CO$	0.55	1.19
151	$197^+ - NO_2$	1.93	0.51
138	$153^+ - CH_3$	0.26	2.07
136	$182^+ - NO_2$	2.79	0.80
125	$153^+ - CO$ / $152^+ - HCN$	0.18	5.91

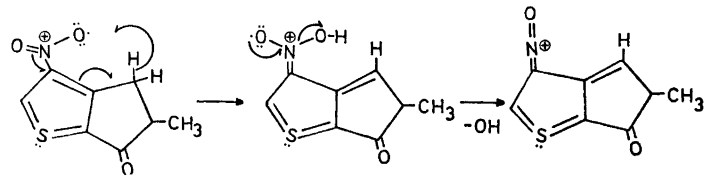
An interesting difference in the fragmentation pattern during electron impact in the mass spectrometer was observed between the two nitrated cyclopenta[b]thiophenes. Table 1 records the relative intensities of dominant fragments in percentage of total ion current for the two isomers. These data may be visualized in the following manner:





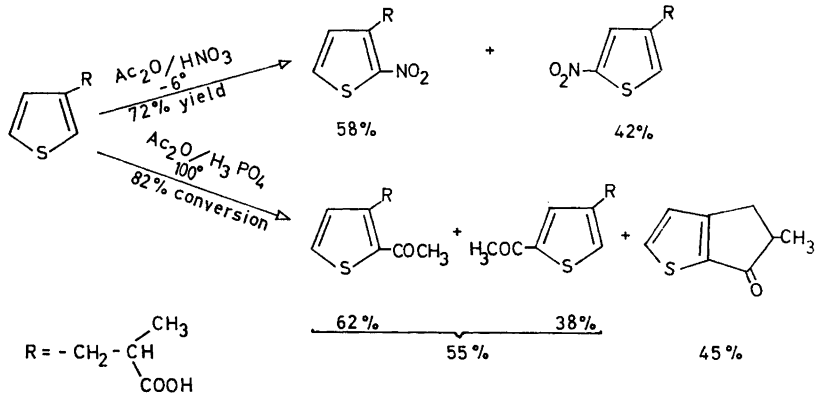
Solid arrows indicate processes whose occurrence is supported by metastable peaks. The fragmentation of the 3-nitro derivative outlined above is quite similar to the fragmentation pattern of *o*-nitrotoluene.[9] The primary fragmentation of *o*-nitrotoluene is the loss of OH from the molecular ion followed

by loss of either CO and/or HCN. Analogous to the mechanism given for loss of OH from the *o*-nitrotoluene ion, the following mechanism is proposed:



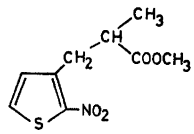
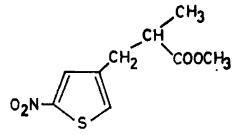
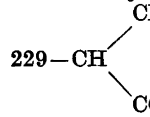
This behaviour then represents a confirmation of the structure assignments since only the 3-nitro compound should give such an *ortho*-effect.

The most surprising part of Sam and Thompson's work is their conclusions from nitration and acetylation of α-methyl-β-(3-thienyl)propanoic acid. They claim that this exclusively gives 5-substitution. Giving no structural proofs, they base their reasoning on an analogy with the nitration [10] and the acetylation [11] of 3-methylthiophene. As has been known for a rather long time, electrophilic substitution in 3-methylthiophene always gives the 2-isomer as the major product, and that is also the case in the work to which Sam and Thompson make references. Our repetition of these experiments gave quite different results, which are shown in the scheme:



The structure determinations of the isomers are based on their NMR spectra. In the case of nitration, two solids were isolated, one of which was identical with the previously mentioned α-methyl-β-(2-nitro-3-thienyl)-propanoic acid (III). The other had the same melting point as the one considered by Sam and Thompson to be α-methyl-β-(5-nitro-3-thienyl)propanoic acid. Its NMR spectrum showed, however, that this was a 50:50 mixture of the 2-nitro and the 5-nitro isomer, the latter having a characteristic 2,4-coupling constants of 1.5 c/s. The 2-acetyl derivative showed a 4,5-coupling constant of 5.0 c/s and finally the 5-acetyl compound had a coupling constant of 1.2 c/s, which is due to a 2,4-coupling. Our results are thus closely analogous to Rinkes' [10] nitration and Kosak's [11] acetylation of 3-methylthiophene. It should also be mentioned that Meth-Cohn and Gronowitz [2] obtained mostly 2-

Table 2. Dominant fragments in the mass spectrum of methyl α-methyl-β-(2-nitro (and 5-nitro) -3-thienyl)propanoate. Relative intensity defined as in Table 1.

Mass (*m/e*)	Probable origin	Relative intensity 	
229	Parent ion	0.12	4.06
212	229−OH	0.12	0.81
198	229−OCH_3	1.94	0.86
183	229−NO_2	7.16 (base peak)	0.32
170	229−$COOCH_3$	1.76	5.52
169	229−$HCOOCH_3$	0.55	7.66
152	183−OCH_3	3.46	0.17
142	229− 	2.55	14.65 (base peak)
97		2.00	1.60
96		1.34	4.96

acetylated product when they reacted acetic acid with β-(3-thienyl)propanoic acid in PPA. The neutral product formed in our acetylation reaction was shown (NMR, IR) to be identical with an authentic sample of 4,5-dihydro-5-methyl-6H-cyclopenta[b]thiophene-6-one.

As a further structural proof the mass spectra of the nitrated and acetylated isomers were recorded. All of the acids were first converted to methyl esters

Table 3. Dominant fragments in the mass spectrum of methyl-α-methyl-β-(2-acetyl (and 5-acetyl) -3-thienyl)propanoate. Relative intensity defined as in Table 1.

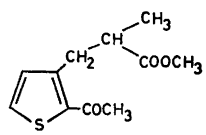
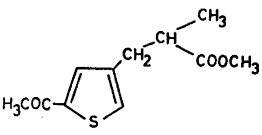
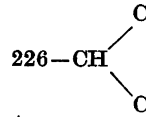
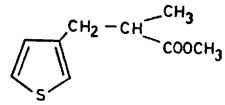
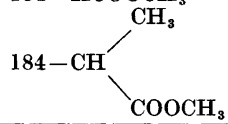
Mass (*m/e*)	Probable origin	Relative intensity 	
226	Parent ion	1.76	7.24
211	226−CH_3	0.04	4.62
167	226−$COOCH_3$	3.88	6.64
166	226−$HCOOCH_3$	7.93	2.92
153		5.40	0.66
151		13.84 (base peak)	1.65
139	226− 	4.56	18.50 (base peak)
43	$^+O{\equiv}C-CH_3$	11.14	15.28

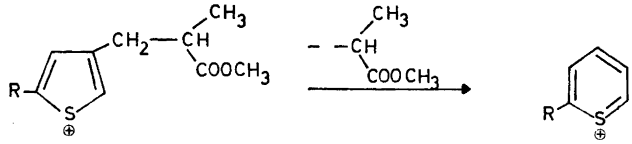
Table 4. Dominant fragments in the mass spectrum of methyl-α-methyl-β-(3-thienyl) propanoate. Relative intensity defined as in Table 1.

Mass (m/e)	Probable origin	Relative intensity 
184	Parent ion	8.41
153	$184-OCH_3$	1.42
125	$184-COOCH_3$	12.46
124	$184-HCOOCH_3$	5.78
97		35.46 (base peak)

by the action of methanol and dry hydrogen chloride and then injected into the gas chromatographic part of the mass spectrometer. As can be seen from the partial spectra (Tables 2 and 3), the isomers exhibit quite large differences in fragmentation pattern. The mass spectrum of the methyl ester of the starting material is recorded in Table 4.

From these results it is quite obvious that the 5-substituted isomers have a fragmentation pattern similar to that of the starting material. By analogy with the mass spectrum [12] of 3-methylthiophene it is proposed that the main fragmentation involves a rearrangement to the corresponding thiopyrylium ion. The compounds substituted in the 2-position behave differently upon electron impact. Regarding the 2-nitro isomer (Table 2, left column), primary loss of OH from the molecular ion (which may be expected by analogy with *o*-nitrotoluene as mentioned above) occurs to a negligible extent. The base peak at $m/e=183$ can be explained by a loss of NO_2 from the molecular ion. It is interesting to note that even the acid (III, M=215) has a base peak ($m/e=169$) corresponding to the loss of NO_2 from the molecular ion.

As for the 2-acetyl compound (Table 3, left column) the base peak at $m/e=151$ may be explained by a fragmentation involving loss of $COCH_3$ and CH_3OH from the molecular ion. Even in the case of the ethyl ester, the base peak occurred at $m/e=151$.



R = H	m/e = 184	m/e = 97 (base peak)
R = NO_2	m/e = 229	m/e = 142 (-"-)
R = $COCH_3$	m/e = 226	m/e = 139 (-"-)

More material is needed before the fragmentation pattern of these compounds can be outlined, and we are therefore pursuing our investigations of these problems.

EXPERIMENTAL

4,5-Dihydro-5-methyl-6H-cyclopenta[b]thiophene-6-one.[2] NMR ($CDCl_3$): $\tau_{2H}=2.21$ ppm (d), $\tau_{3H}=2.97$ ppm (d), $\tau_{CH_3CH}=6.4-7.6$ ppm (m), $\tau_{CH_3}=8.65$ ppm (d); $J_{2H-3H}=5.0$ c/s, $J_{CH_3-CH}=7.5$ c/s. IR (CCl_4): ν, cm^{-1}, in order of decreasing absorbance: 1710 (carbonyl), 1430, 1265, 1445, 925, 720, 1305, 1375, 1190, 1085.

Nitration of 4,5-dihydro-5-methyl-6H-cyclopenta[b]thiophene-6-one. To 5.0 g (0.033 mole) of 4,5-dihydro-5-methyl-6H-cyclopenta[b]thiophene-6-one in 18.5 ml of acetic anhydride a solution of 10 g of fuming nitric acid (*d* 1.50) and 12.5 ml of acetic anhydride (prepared by addition of the nitric acid to the anhydride at −6°C) was added dropwise with stirring at −6°C. After the addition was completed, the reaction mixture was stirred for 30 min at −6°C and then poured, with stirring, into 100 ml of cold water. The resulting oil was taken up in ether, the ether extract washed with 10 % sodium bicarbonate solution and water. After drying ($MgSO_4$), the ether phase was evaporated *in vacuo*, giving 5.4 g of a semicrystalline solid. The NMR spectrum of this crude product showed it to be a mixture of starting material (2.5 g, 50 %) and two mononitro derivatives (2.9 g, 44 %) in relative proportion 45:55. Fractional crystallization from ethanol/water gave two faint yellow solids. The least soluble isomer had m.p. 99−101°C and respresented the major portion. This isomer was identified as *4,5-dihydro-5-methyl-2-nitro-6H-cyclopenta[b]thiophene-6-one.* NMR ($CDCl_3$): $\tau_{3H}=2.05$ ppm (s), $\tau_{CH_3CH}=6.3-7.5$ ppm (m), $\tau_{CH_3}=8.60$ ppm (d); $J_{CH_3-CH}=7.0$ c/s. IR (CCl_4): ν, cm^{-1}, in order of decreasing absorbance: 1725 (carbonyl), 1345, 1525, 1240, 1410, 1070, 1540, 1445, 1280, 1305. (Found: C 49.03; H 3.59; N 7.20; S 16.04; Mol.wt. 197 (mass spectrum, see Table 1). Calc. for $C_8H_7NO_3S$ (197.2): C 48.72; H 3.58; N 7.10; S 16.26).

The other isomer had m.p. 94−96°C and was identified as *4,5-dihydro-5-methyl-3-nitro-6H-cyclopenta[b]thiophene-6-one.* NMR ($CDCl_3$): $\tau_{2H}=1.16$ ppm (s), $\tau_{CH_3CH}=6.0-7.3$ ppm (m), $\tau_{CH_3}=8.58$ ppm (d); $J_{CH_3-CH}=7.0$ c/s. IR (CCl_4): ν, cm^{-1}, in order of decreasing absorbance: 1725 (carbonyl), 1555, 1355, 1520, 1255, 1440, 930, 850, 890, 3110. (Found: C 49.07; H 3.57; N 7.19; S 16.31; Mol.wt. 197 (mass spectrum, see Table 1). Calc. for $C_8H_7NO_3S$ (197.2): C 48.72; H 3.58; N 7.10; S 16.26).

The sodium bicarbonate wash solution obtained above was acidified with 5 N hydrochloric acid to give an oil which was extracted with ether. Drying ($MgSO_4$) and evaporation of the ether yielded 0.43 g (6 %) of a product, which after crystallization from acetone/water melted at 133−135°C. This compound was *α-methyl-β-(2-nitro-3-thienyl)propanoic acid.* NMR ($(CD_3)_2CO$): $\tau_{COOH}=-0.10$ ppm (s), $\tau_{5H}=2.21$ ppm (d), $\tau_{4H}=2.86$ ppm (d), $\tau_{CH_3CH}=6.2-7.5$ ppm (m), $\tau_{CH_3}=8.78$ ppm (d); $J_{4H-5H}=5.4$ c/s, $J_{CH_3-CH}=6.5$ c/s. IR (CCl_4): ν, cm^{-1}, in order of decreasing absorbance: 1340, 1714 (CO), 1509, 1400, 1550. (Found: C 44.42; H 4.02; N 6.86; S 14.70; Mol.wt. 215 (mass spectrum). Calc. for $C_8H_9NO_4S$ (215.2): C 44.64; H 4.22; N 6.51; S 14.90).

Nitration of α-methyl-β-(3-thienyl)propanoic acid. The procedure employed was that of Sam and Thompson. A solution of 5.0 g (0.029 mole) of α-methyl-β-(3-thienyl)propanoic acid [3] in 10 g of acetic anhydride was added dropwise with stirring at −6°C to a mixture of 5 g of nitric acid (*d* 1.5) and 8 g of acetic anhydride (prepared as above at −6°C). After an additional 30 min of stirring at −6°C, the resulting solution was poured into ice water. The oil that separated was taken up in ether and the water phase was extracted thoroughly with ether. The combined ether phases were dried ($MgSO_4$) and the ether evaporated *in vacuo* to give 4.5 (72 %) of product. The NMR spectrum of this crude material revealed the existence of two mononitro derivatives: *α-methyl-β-(2-nitro-3-thienyl)propanoic acid* (2.6 g, 58 %), *α-methyl-β-(5-nitro-3-thienyl)propanoic acid* (1.9 g, 42 %). Crystallization from acetone/water gave two sharply melting solids. One of them, with m.p. 133−135°C, was identical with α-methyl-β-(2-nitro-3-thienyl)propanoic acid (prepared above). The other solid had m.p. 94−96°C. NMR showed that it was a 50:50 mixture of the 2-nitro and the 5-nitro compound. In spite of several attempts to separate this mixture into its components by fractional crystallization from various solvents, it remained unseparated. NMR ($(CD_3)_2CO$): Peaks belonging to the 5-nitro isomer only:

$\tau_{COOH} = -0.10$ ppm (s), $\tau_{2H} = 2.05$ ppm (d), $\tau_{4H} = 2.37$ ppm (broad singlet), $\tau_{CH_3CH} = 6.2-7.5$ ppm (m), $\tau_{CH_3} = 8.82$ ppm (d); $J_{2H-4H} = 1.5$ c/s, $J_{CH_3-CH} = 6.5$ c/s. Absorptions due to the 2-nitro isomer were identical with those given above. IR (CCl_4): ν, cm^{-1}, in order of decreasing absorbance: 1340, 1715, 1510, 1420, 2980, 1400, 2940, 1550. (Found: C 44.24; H 4.09; N 6.13; S 14.59. Calc. for $C_8H_9NO_4S$ (215.2): C 44.64; H 4.22; N 6.51; S 14.90). For the mass spectrum of the methyl esters, see Table 2.

Acetylation of α-methyl-β-(3-thienyl)propanoic acid. Following the procedure of Sam and Thompson 5.0 g (0.029 mole) of α-methyl-β-(3-thienyl)propanoic acid [3] and 3.0 g (0.029 mole) of acetic anhydride was mixed and heated to 60°C with stirring. Then 0.3 ml of 85 % orthophosphoric acid was added and the mixture heated to 100°C for 2 h. After cooling to 50°C, water was added and stirring continued for a further 30 min. Then the oily layer was taken up in ether and the ether extracted several times with 10 % sodium bicarbonate solution. The combined extracts were acidified with 10 % hydrochloric acid. This gave 3.5 g of acidic material. From the ether extract was isolated 1.5 g (35 %) neutral product, which was proved (IR, NMR) to be the cyclised acid, *4,5-dihydro-5-methyl-6H-cyclopenta[b]thiophene-6-one*. NMR analyses of the crude acidic product showed that it consisted of 0.9 g (25 %) of starting material and 2.6 g (75 %) of a mixture of monoacetylated products in relative proportion (38:62) with the 2-acetyl derivative dominating. This gives 42 % yield of acetylation and 18 % recovery of starting material. NMR ($CDCl_3$): *α-methyl-β-(2-acetyl-3-thienyl)propanoic acid:* $\tau_{5H} = 2.66$ ppm (d), $\tau_{4H} = 3.08$ ppm (d), $\tau_{CH_3CH} = 6.3-7.5$ ppm (m), $\tau_{COCH_3} = 7.45$ ppm (s), $\tau_{CH_3} = 8.75$ ppm (d); $J_{4H-5H} = 5.0$ c/s, $J_{CH_3-CH} = 7.5$ c/s. *α-Methyl-β-(5-acetyl-3-thienyl)propanoic acid:* $\tau_{4H} = 2.53$ ppm (d), $\tau_{2H} = 2.77$ ppm (d), $\tau_{CH_3-CH} = 6.3-7.5$ ppm (m), $\tau_{COCH_3} = 7.45$ ppm (s), $\tau_{CH_3} = 8.77$ ppm (d); $J_{2H-4H} = 1.2$ c/s, $J_{CH_3-CH} = 7.0$ c/s. For the mass spectrum of the methyl esters, see Table 3.

The melting points are uncorrected. The IR spectra were recorded on a Perkin Elmer grating infrared spectrophotometer type 257, the NMR spectra on a Varian A 60 (with TMS as an internal standard). The elementary analyses were carried out by Ilse Beetz, Mikroanalytisches Laboratorium, Kronach. The mass spectra were obtained with an LKB 9000 with an ionization energy of 70 eV. In the case of the nitrated cyclopentathiophenes (I and II) a direct inlet system was used. In the other cases the isomers were first separated by VPC on a 3 m SE 30 (1 %) column before injection into the ion source. The column temperature was 165°C for the nitro derivatives and 140°C for the other esters. In each case the 2-isomer had shorter retention time than the corresponding 5-isomer.

Acknowledgement. The author is indebted to Professor Salo Gronowitz for suggesting the topic, for valuable discussions and for all the facilities placed at the author's disposal. The mass spectra were recorded by Mrs. Gun-Britt Lindahl and the NMR spectra by Mr. Jan Glans. This work has been supported by a grant (rekrutteringsstipendium) from *Norwegian Research Council for Science and Humanities*, which is gratefully acknowledged. Financial support from the *Faculty of Science of the University of Lund* is also acknowledged.

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Received March 25, 1968.