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SYNTHESIS OF DITHIENO[2,3-b:3',2'-e]-8H-THIOPYRAN-8-THIONE AND DITHIENO[2,3-b:3',2'-e]-8H-THIOPYRAN-8-ONE[a]

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Abstract—This paper describes the reaction of 2,2 - di - (3 - thienyl) - 1,3 - dioxalane with butyllithium and sulphur resulting in the formation of the dithieno-dithiopyrone **3**, the dithieno - thiopyran - dioxolane **4** and the dithieno - thiopyrone **5**.

The diminished carbonyl character of the carbonyl group was studied in connection with the possibility of the dithienothiopyrone systems to form thiopyrilium structures.

Investigations for the existance of these charged structures were performed with UV and PMR spectroscopy of the thiopyrones in acidic media. By oxidation of the pyrones with hydrogen peroxide the sulphones were synthesized in which the carbonyl character was restored as was shown by the formation of the oximes. The assymetry introduced by the oximidogroup was demonstrated by the PMR spectra.

As a part of our research dealing with the synthesis of drugs with potential central activity, it was our aim to synthesize compound **2** by lithiation and sulphuration of **1**. Compound **1** was lithiated at −35° in ether, sulphur was added and the mixture allowed to warm up.

Upon acidification of the water layer during the work up procedure the colour changed from yellow through purple into orange, hydrogen sulphide was evolved and an oily layer became visible.

This oil was taken up in ether and after being dried the solvent was evaporated. The remaining red oil was chromatographed over a silica gel column with chloroform. From the first fractions red needles were obtained after slow evaporation of the eluent. The PMR spectrum of this compound showed two doublets at δ 8·26 and δ 7·48 with a coupling constant of 5·5 Hz, indicative of a 2,3 substituted thiophene. In the mass spectrum the parent peak appeared at 240.

This spectroscopic evidence, together with an elemental analysis confirms structure 3 as proposed in Scheme 1.

On further elution with chloroform a white compound was isolated with m.p. 195–198°. The IR spectrum contained an absorption at 1610 cm^{-1} and the PMR spectrum showed two doublets at δ 7·87 and δ 7·42 with a coupling constant of 5·5 Hz. The molecular weight, as determined by mass spectrometry was 224. We decided on structure **5** for this compound from which a correct elemental

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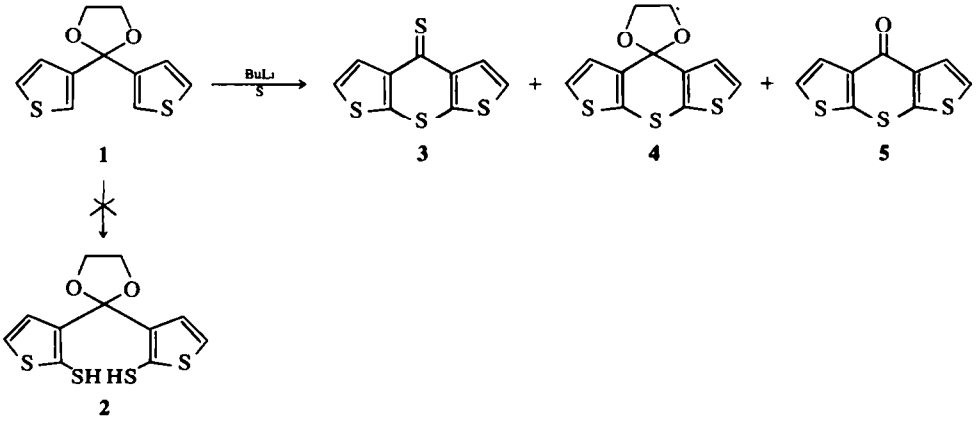


1 **3** **4** **5**

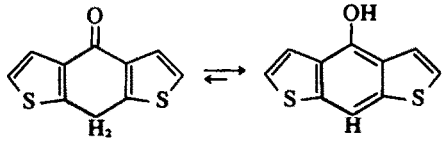
2

SCHEME 1.

analysis was obtained. From the neutral ether layer a white compound was isolated with a molecular weight of 268 and a PMR spectrum with two doublets at δ 7·17 and δ 7·28 and a singlet at δ 4·33 with an integration ratio of 2:2:4. Treatment of this compound with acidic ethanol rapidly resulted in ketone 5, as was evident from the UV and IR spectra. This result together with the spectroscopic data and an elemental analysis confirmed the proposed structure 4. As the products 3 and 5 were obtained from an alkaline aqueous solution a reaction scheme containing an acidic thiophene intermediate seems likely.

We suggest for this intermediate the dithiol 2 which upon acidification, would expel hydrogen sulphide under formation of a sulphide bridge. In addition, the ketal function is converted into the ketone and the thioketone during the acidification procedure. The assumption of the latter step is supported by an experiment in which the ketal 4 was treated with H_2S/HCl in methanol; as shown by TLC analysis and IR spectra, a mixture of 3 and 5 was formed. The most remarkable fact of the reaction, however, is the spontaneous elimination of hydrogen sulphide to give the sulphide linkage of the thiopyrones. Likely, the stability of the formed systems lends a significant driving force to this reaction. An interesting feature of the thiopyrone 5 is found in its IR spectrum in which a carbonyl stretch vibration occurs at 1610 cm^{-1}. A similar observation was made with the thiopyrone 6[1] which showed an absorption at 1595 cm^{-1}. These rather low values are indicative of a diminished carbonyl character.[2,3] This lack of carbonyl activity was supported by the observation that oximes of the pyrones 5 and 6 could not be obtained with hydroxylamine and various bases. An explanation can be found by assuming that charged structures such as 7 and 8 contribute to the actual structure of the dithieno-thiopyrones.

As is known, the dibenzothiopyrones easily form the same kind of charged structures.[4] For their dithieno analogs an even more rapid conversion may be expected, based on the work of McDowell, who found the thiophene analogs of anthrone to possess a higher degree of enolization in comparison to their parent compounds.[5] The high tendency of the dithienothiopyrones to form a 14 Π electron aromatic structure can be shown by protonation of the thiopyrones to their thiopyrilium structures.



SCHEME 3.

The UV spectra of the thiopyrones 3, 5 and 6 were recorded in dichloromethane and in trifluoroacetic acid. As can be seen from Fig. 1(a), the protonated thiopyrones in the trifluoroacetic acid medium all show a strong resemblance in their absorption characteristics, indicating that in all cases the thiopyrilium structures determine the absorption pattern, with the mode of annelation and the substituent (SH *vs* OH) being of minor importance.[6]

The PMR spectra were recorded in deuterochloroform and in trifluoroacetic acid (Fig 2). The observed downfield shifts of the thiophene protons can be interpreted as being due to the delocalisation of the annular electrons whereby the charged thiopyrilium structures are formed.[7-9] The

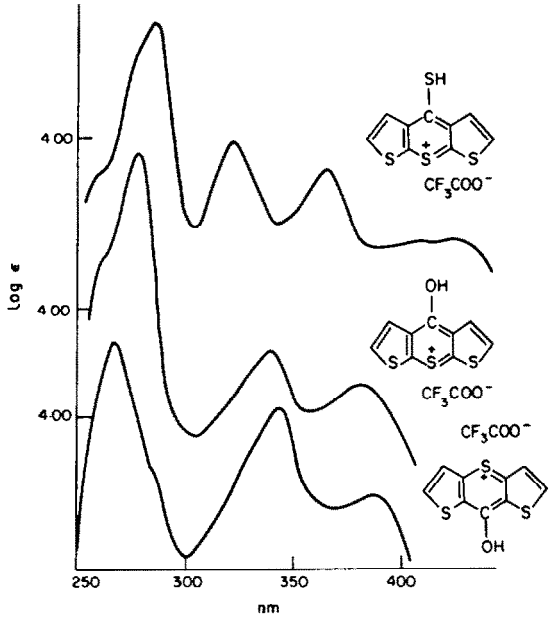
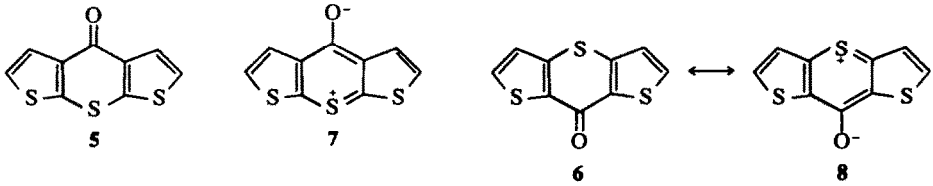


Fig 1(a).



5 7 6 8

SCHEME 2.

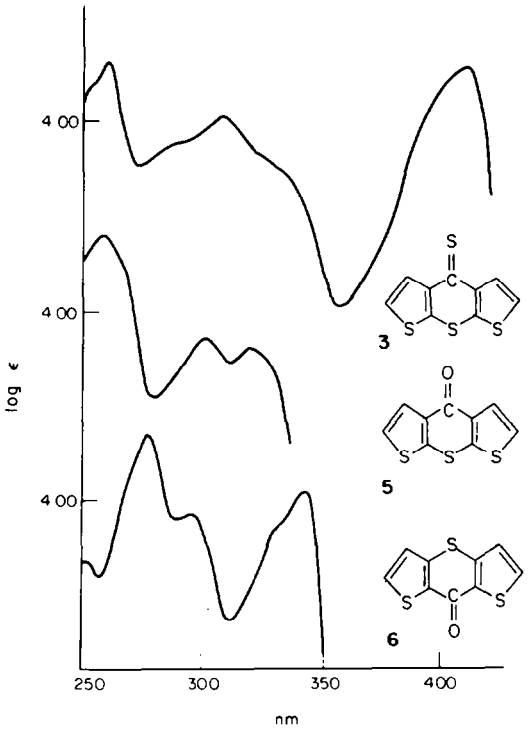


Fig 1(b).

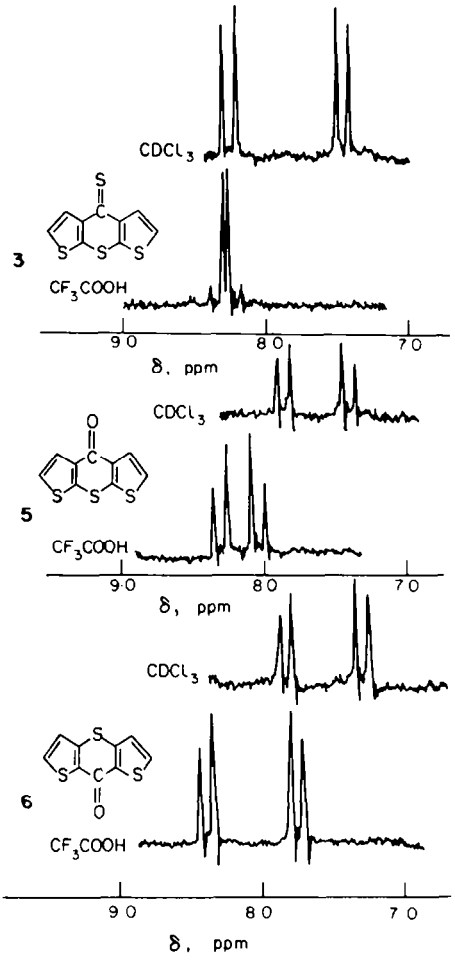
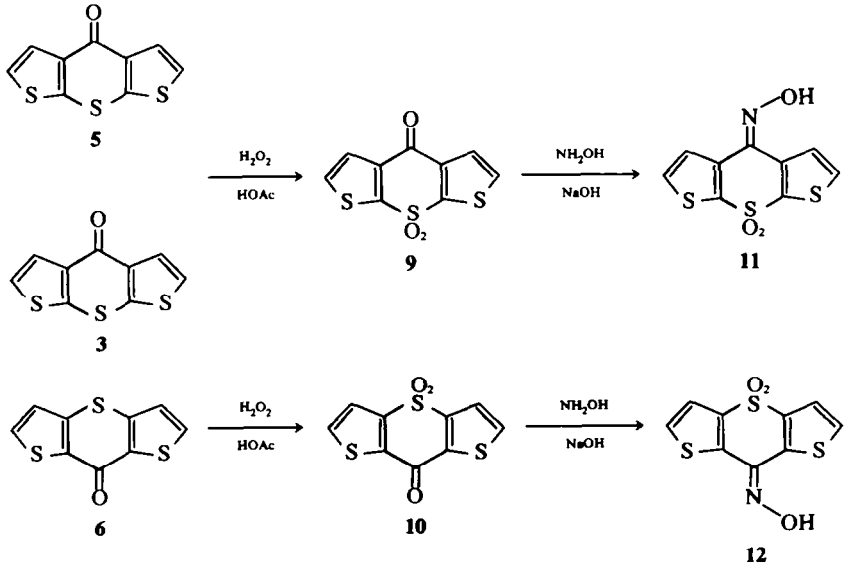


Fig 2.

thiopyrone **5** could be oxidized with hydrogen peroxide in acetic acid to the sulphone **9** in 84% yield. The same compound was also obtained by oxidation of the dithiopyrone **3**. The isomeric sulphone **10** was obtained in 75% yield by oxidation of the thiopyrone **6**. The structures of these sulphones were supported by spectroscopic evi-



SCHEME 4.

dence and correct elemental analysis. As compared to their parent thiopyrones, the sulphones **9** and **10** show a restored carbonyl character, as is evident from the carbonyl stretch vibrations in the IR spectra at 1670 and 1660 cm^{-1}, respectively and by their ability to form oximes with hydroxylamine HCl and sodium hydroxide. The PMR spectra of the oximes **11** and **12** showed an interesting aspect of assymmetry, caused by the introduction of the oximino group. The PMR spectrum of oxime **11** showed two pairs of doublets, one pair centered at δ 8·41 and δ 8·06; the other pair at δ 7·96 and δ 7·59, both with coupling constants of 5·0 Hz.

Apparently, the formation of the oxime has resulted in four nonequivalent protons. We assume that the absorptions at low field are caused by the α- and β-protons closest to the N-hydroxyl-group.[10,11]. The fact that in this case both α and β protons are affected, is in contrast with the oximes of cyclopentadithiophenone in which only the α-protons absorb at different field.[12] This may be caused by the different geometries of the molecules.

The dithienothiopyrone oximes are probably bent about an axis through the S atom of the sulphone and the C atom of the oxime.

In this way the OH group of the oxime can exert its influence via the thiophene ring to both α and β protons of the "syn" thiophene ring.

EXPERIMENTAL

The PMR spectra were obtained using a Varian A-60 spectrometer (TMS as internal standard). IR spectra were measured with a Beckmann IR-33 spectrophotometer. UV spectra were determined in 96% EtOH (unless otherwise stated) using a Zeiss PMQ II spectrophotometer. Melting points are uncorrected. Microanalyses were performed by the Analytical Department of the Organic Laboratory (Mr.'s H. Draayer, J. Ebels, W. M. Hazenberg and J. E. Vos).

Dithieno [2,3 - b:3',2' - e] - 8H - *thiopyran* - 8 - *spiro* - 2' - 1,3' - *dioxolane* (**4**), *dithieno* [2,3 - *b*:3',2' - e] - 8H-*thiopyran* - 8 - *thione* (**3**), *dithieno* [2,3 - b:3',2' - e] - 8H-*thiopyran* - 8 - *one* (**5**). To a soln of 2,2 - di(3 - thienyl) - 1,3 - dioxolane (3·0 g, 12·6 mmole) in 180 ml abs ether was added at −35°, 17 ml of 1·6 N (25 mmoles) n-butyllithium in ether. After stirring for 20 min at −25° the soln became turbid and 0·8 g (26 mmoles) of sulphur was added in one portion, after 5 min the clear soln became yellow. The mixture was warmed over 30 min to 10°C and then poured into 100 ml water. The light purple ethereal layer was washed with 50 ml 2 N NaOH and dried ($MgSO_4$). The water layer together with the basic layer were acidified with 2 N H_2SO_4, during this acidification the colour turned through purple into orange and H_2S was evolved. The soln was extracted with chloroform and the chloroform was washed with water and was dried ($MgSO_4$). The solvent was evaporated and the red oil chromatographed over a silica gel column with chloroform (R_f 0·72 in $CHCl_3$). The first orange-red fractions were collected and the solvent evaporated to give 1·0 g of a red compound which was crystallized from chloroform to give an analytical sample of **3**. (Found C, 45·1; H, 1·7; S, 53·2. Calc. for $C_9H_4S_4$ (240·39): C, 44·96; H, 1·68; S, 53·36%); PMR ($CDCl_3$) δ 8·26 (d, 2H, J = 5·5 Hz): δ7·48 (d, 2H, J = 5·5 Hz). UV (CH_2Cl_2): sh 253 (log ϵ 4·18): λ_{max} 259 (4·24) sh 285 (3·95) 3·10 (4·03) sh 344 (3·75) 412 (4·24) 310 (4·03) sh 344 (3·75) 412 (4·24). The following fractions (R_f 0·29) were collected and the solvent evaporated leaving 0·3 g of a yellow compound 192–194°. After recrystallisation from chloroform light yellow platelets were obtained with m.p. 197–198°. (Found: C, 47·9; H, 1·9; S, 43·0. Calc. for $C_9H_4OS_3$ (224·32): C, 48·20; H, 1·82; S, 42·88%); PMR ($CDCl_3$): δ 7·87 (d, 2H, J = 5·5 Hz): δ 7·42 (d, 2H, J = 5·5 Hz). UV (CH_2Cl_2): λ_{max} 260 nm (log ϵ 4·34): 303 (3·90): 322 (3·85).

The neutral ether layer was evaporated to give 0·3 g of a reddish oil from which by treatment with $CHCl_3$ some crystals were obtained. After recrystallization from EtOH 0·2 g (6%) of grey-white crystals of **4** were isolated, m.p. 150–151. (Found: C, 49·0; H, 3·2; S, 35·9. Calc. for $C_{11}H_8O_2S_3$ (268·37): C, 49·24; H, 3·03; S, 35·84%); PMR ($CDCl_3$): δ 7·28 (d, 2H, J = 6·0 Hz): δ 7·17 (d, 2H, J = 5·0 Hz) δ 4·33 (s, 4H); UV (CH_2Cl_2): λ_{max} 290 (log ϵ 2·08).

Dithieno [2,3 - b: 3', 2' - e] - 8H - *thiopyron* - 8 - *one* 4,4 *dioxide* (**9**). To a soln of **3** (0·3 g; 1·25 mmoles) in 35 ml AcOH 30% H_2O_2 (2·5 ml) was added. The mixture was refluxed until the red colour disappeared and turned through green into yellow. The soln was poured into water and extracted twice with chloroform. The chloroform was washed with $NaHCO_3$ until neutral and was dried ($MgSO_4$). Evaporation of the solvent yielded 0·26 g (81%) of light yellow crystals, m.p. 221–222.° (Found C, 41·9; H, 1·6; S, 37·2. Calc. for $C_9H_4O_3S_3$ (256·32): C, 42·17; H, 1·57; S, 37·53%); PMR (CD_3COCD_3): δ 7·86 (d, 2H, J = 5·1 Hz): δ 7·42 (d, 2H, J = 5·1 Hz).

Dithieno [3,2 - b: 2',3' - e] - 8H - *thiopyran* - 8 - *one* 4,4 - *dioxide* (**10**). A soln of **6** (1·0 g; 4·5 mmole) in 50 ml AcOH was heated at 100° and 30% H_2O_2 (2 ml) was added. The soln was refluxed for 1 hr, cooled, poured into 100 ml water, and extracted twice with chloroform. The chloroform was washed with water and dried ($MgSO_4$). Evaporation of the solvent yielded 0·9 g (76%) of a light-yellow solid which was recrystallized from EtOH. (Found: C, 41·9; H, 1·7; S, 37·1. Calc. for $C_9H_4O_3S_3$ (256·32): C, 42·17; H, 1·57; S, 37·53%); PMR (CD_3COCD_3): δ 8·33 (d, 2H, J = 5·1 Hz): δ 7·76 (d, 2H, J = 5·1 Hz).

Dithieno [2,3 - b: 3',2' - e] - 8H - *thiopyron* - 8 - *one* 4,4 *dioxide oxime* (**11**). To a soln of **9** (100 mg; 4 mmoles) in 20 ml EtOH and 4 ml water hydroxylamine hydrochloride (100 mg) was added. To the stirred mixture powdered NaOH (100 mg) was added. The soln was refluxed for 30 min and then poured into a mixture of 2 N HCl and ice. The water layer was extracted with chloroform and the chloroform dried ($MgSO_4$) and evaporated. The oil obtained was chromatographed over Al_2O_3 (neutral) with chloroform giving 30% of a light brown solid; PMR (CD_3COCD_3): δ 7·59 (d, 1H, J = 5·1 Hz); δ 7·96 (s, 1H, J = 5·1 Hz) δ 8·06 (d, 1H, J = 5·1 Hz); δ 8·41 (d, 1H, J = 5·1 Hz) δ 12·2 (s, 1H): *m/e* M^+ 271. UV: λ_{max} 274 nm (log ϵ 4·05) sh 300 (3·95).

Dithieno [3,2 - b: 2',3' - e] - 8H - *thiopyron* - 8 - *one* 4,4-*dioxide oxime* (**12**). To a soln of **10** (200 mg; 8 mmol) in 35 ml EtOH and 4 ml water hydroxylamine hydrochloride (160 mg) was added. To the mixture powdered NaOH (200 mg) was added portionwise. The soln turned green on addition of each portion but became suddenly dark

brown. The mixture was then refluxed for 1 hr, then cooled and poured into 2 N HCl. After standing overnight the light brown needles were collected. After chromatography over a neutral Al_2O_3 column with $CHCl_3$–MeOH (4:1) the oxime was recrystallised from EtOH–water to give 120 mg (54%) of white needles, m.p. 237–239°. (Found: C, 39·7; H, 2·0; N, 5·1; S, 35·0. Calc. for $C_9H_5NO_3S_3$ (271·34): C, 39·84; H, 1·81; N, 5·16; S, 35·45%); PMR (CD_3COCD_3): δ 7·55 (d, 1H, J = 5·2 Hz); δ 7·68 (d, 1H, J = 5·2 Hz); δ 7·75 (d, 1H, J = 5·2 Hz); δ 8·04 (d, 1H, J = 5·2 Hz); δ 12·7 (s, 1H). UV: λ_{max} 271 nm (log ϵ 4·17) 3·12 (3·98).

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