

Investigations of Dithienylglycolic Esters

I. Preparation of Methyl Dithienylglycolates. Magnetically Nonequivalent Protons in Dithienylglycolates

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The preparations of methyl dithienylglycolates are described. Methyl 2,2'-dithienylglycolate is prepared in one step from 2-bromothiophene; the 3,3'- and 2,3'-isomers are prepared from the reaction between methyl 3-thienylglyoxalate and the Grignard reagent of the appropriate bromothiophene.

Magnetically nonequivalent thiophenic protons are observed in thienylglycolic esters of certain asymmetric alcohols.

Diarylglycolic acids and alkyl esters are important starting materials for many pharmacologically interesting compounds. Many of these acids and esters are easily available from well-known reactions. Thus diphenylglycolic acid (benzilic acid) and the methyl esters are prepared by rearrangement of benzil with potassium hydroxide in ethanol and with sodium methoxide in methanol.¹ Another general method is the reaction between a Grignard reagent and an α -ketocarboxylic acid or ester.²

The dithienylglycolic acids or esters have been described only in a few cases. Thus attempts have been made to rearrange 2,2'-thenil³ and 3,3'-thenil⁴ to 2,2'-thenilic acid and 3,3'-thenilic acid, respectively. The acids are reported to be unstable. There is also a disadvantage in using the thenils, since they are prepared in rather low yield.³⁻⁵

Ethyl 2,2'-dithienylglycolate has been prepared in 55 % yield from 2-thienylmagnesium iodide and ethyl 2-thienylglyoxalate.⁶ The glyoxalate is prepared in 50 % yield from thiophene, ethyl α -chloroglyoxalate, and aluminum chloride⁷ or in 24 % yield from 2-thienylmagnesium iodide and diethyl oxalate.⁸ Some glycolic acids bearing one 3-thienyl group and one alkyl group have been prepared from 3-thienyllithium and alkylglyoxylic acid.⁹ Thus,

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of the alkyl dithienylglycolates only ethyl 2,2'-dithienylglycolate has been reported.

In the present investigation we first checked the method of preparing ethyl 2-thienylglyoxalate by Friedel-Crafts acylation of thiophene.⁷ We were unable, however, to reproduce the reported yield of 50 % and obtained only about 20 %. Therefore we turned our attention to the reaction between 2-thienylmagnesium halide and diethyl oxalate.⁹ The reaction was run at -20° with equivalent amounts of 2-thienylmagnesium bromide and dimethyl oxalate⁸ (in order to obtain the methyl ester). The semisolid residue obtained was recrystallized from carbon tetrachloride. A white precipitate formed upon cooling. The substance was identified as methyl 2,2'-dithienylglycolate. The reaction was then repeated under various conditions. The optimum yield was obtained by adding two equivalents of 2-thienylmagnesium bromide to one equivalent of dimethyl oxalate in ether without cooling. In this way we were able to prepare methyl 2,2'-dithienylglycolate in a one step reaction in 47 % yield.

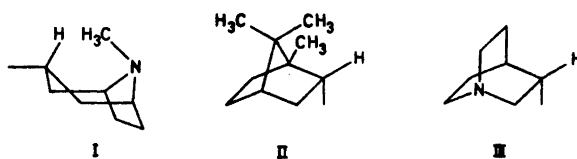
3-Thienylmagnesium bromide cannot be made directly from 3-bromothiophene and magnesium. However, by reacting 3-thienyllithium with magnesium bromide the Grignard reagent is obtained in good yield according to Gronowitz.¹⁰ Thus 3-thienylmagnesium bromide was allowed to react with dimethyl oxalate in the manner described for 2-thienylmagnesium bromide. The yield of methyl 3,3'-dithienylglycolate was poor, however. A better result was obtained when the preparation was carried out in two discrete steps. The product formed in the first step, methyl 3-thienylglyoxalate, was obtained in 53 % yield when the Grignard reagent was reacted with an excess of dimethyl oxalate at -70° . Methyl 3-thienylglyoxalate and an equivalent amount of 3-thienylmagnesium bromide gave then methyl 3,3'-dithienylglycolate in 29 % yield.

In both modes of preparation, the one step and the two step, ethyl 3,3'-dithienylglycolate was formed in a side reaction. Since 3-thienyllithium was prepared from the halogen metal interconversion reaction between 3-bromothiophene and ethyllithium, lithium alcoholate may form through the cleavage of ether by the alkyl lithium reagent.¹¹ Thus the formation of the ethyl ester is probably due to the presence of ethoxide ions in the reaction mixtures.

In spite of the moderate yield the two step mode of preparation offers a convenient route to the hitherto unreported methyl 3,3'-dithienylglycolate. Moreover, this method makes it easy to prepare the third methyl dithienylglycolate, *i.e.* the one containing two different thienyl groups. Thus methyl 2,3'-dithienylglycolate was prepared in 46 % yield by adding 2-thienylmagnesium bromide to an equivalent amount of 3-thienylglyoxalate.

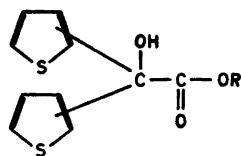
Using methyl 2,2'- and methyl 3,3'-dithienylglycolate the corresponding esters of 3-tropanol (I), borneol (II), and 3-quinuclidinol (III) were prepared through ester interchange. The 3-quinuclidinyl esters showed strong atropine like effects, peripheral as well as central nervous stimulating, when administered in small doses to dogs.¹²

When these compounds were examined with NMR (50 cps sweep width) it turned out that the aromatic ABC spin coupling pattern, typical of mono-substituted thiophenes, was doubled in the bornyl and 3-quinuclidinyl cases.



The thiophenic protons of the methyl and the 3-tropanyl esters, on the other hand, showed a normal spectrum. The doubling of the signals in cases II and III was not caused by splitting from the hydroxyl proton as was shown by deuteration of the latter. Since long range coupling with the proton at the esterified carbon atom of borneol or 3-quinuclidinol appears to be excluded (in the bornyl case this particular proton resonance had the same multiplet structure as in bornyl acetate¹³), the remaining possibility is that of magnetically nonequivalent thiophenic protons. In support of this it was found possible to account for the bands of the experimental spectra with the aid of two theoretical ABC spectra (computed with an ABC spectrum program¹⁴). The chemical shift differences thus obtained are shown in Table 1, from which the typical shift differences, 1 cps for the bornyl and 1.5–2 cps for the 3-quinuclidinyl esters, appears. Preliminary inspection of the spectra of the corresponding isobornyl esters shows the chemical shift differences to be about 0.5 and 1.5 cps for 2,2'- and 3,3'-dithienyl, respectively.

Table 1. Chemical shift differences^a in cps (0.5 M CDCl₃ at ca. 37°C) of the thiophenic protons of the bornyl (II) and 3-quinuclidinyl (III) dithienylglycolates.



2,2'-Dithienylglycolate

R	$\nu_3 - \nu_3'$	$\nu_4 - \nu_4'$	$\nu_5 - \nu_5'$
II	1.5	1.0	0.8
III	2.3	2.0	1.7

3,3'-Dithienylglycolate

R	$\nu_3 - \nu_3'$	$\nu_4 - \nu_4'$	$\nu_5 - \nu_5'$
II	1.1	0.9	0.8
III	1.8	1.4	1.4

^a The shift assignments were obtained using the following coupling constants: 2,2': $J_{34} = 3.98$ cps, $J_{35} = 1.20$ cps, $J_{45} = 5.0$ cps, 3,3': $J_{24} = 1.20$ cps, $J_{25} = 3.20$ cps, $J_{45} = 5.0$ cps.

It appears that the chemical shift difference in the present cases is structure dependent and more sensitive to a change of the R group than to changing 2-thienyl for 3-thienyl. The data so far obtained do not answer the question whether in addition the esterified carbon atom of the alcohol has to be asymmetric, as it is in the 3-quinuclidinyl, bornyl, and isobornyl cases.

Vlies¹⁵ states in his study of magnetically nonequivalent methyl protons of isopropyl esters of various glycolic acids that the ester must possess an asymmetric center, which in addition should be bonded to a phenyl nucleus for doubling of the methyl doublet to occur. Thus Vlies reports this doubling to be (in CCl₄ at 37°C) 10.5 cps in isopropyl mandelate and 4.5 cps in isopropyl phenylcyclohexylglycolate, whereas no doubling could be observed in isopropyl benzilate or isopropyl dicyclohexylglycolate, for example. To the extent that the presence of an asymmetric carbon is necessary for the occurrence of magnetically nonequivalent protons "at the other end" of the glycolic link, our results show that if these protons are thiophenic (conceivably aromatic in general) a phenyl group is no longer required at the asymmetric center.

If the small differences between the figures given in Table 1 are considered significant, it appears that the magnetic nonequivalence is seen to increase (for 2,2'-dithienyl cases) for the positions in the order $5 < 4 < 3$. It is noteworthy that this is also the order of decreasing distance through space between the protons concerned and the asymmetric carbon in 3-quinuclidinyl 2,2'-dithienylglycolate according to the X-ray crystallographic investigation of this compound by Meyerhöffer¹⁶ (Part II of this series). Work is in progress to study further the problems concerning magnetic nonequivalence in glycolic esters of the type described.

EXPERIMENTAL

NMR spectra were obtained with a Varian A 60A Analytical NMR Spectrometer at ambient temperature using deuteriochloroform as solvent and with tetramethylsilane as internal standard. Infrared spectra were recorded with a Perkin Elmer Model 225 Grating Infrared Spectrometer. Mass spectra were obtained with the LKB model 9000 gas-chromatograph-mass spectrometer operating at 70 eV (SE 30, 3 m × 2.5 mm; 220°C). The elemental analyses were carried out at the Department of Analytical Chemistry, University of Lund. All melting points and boiling points are uncorrected.

Preparation of methyl dithienylglycolates. In all experiments sodium dried ether was used. Ethyllithium was prepared from ethyl bromide and lithium in ether at -20°C, 3-bromothiophene was prepared according to Gronowitz.¹⁷

Methyl 2,2'-dithienyl glycolate. 2-Thienylmagnesium bromide was made in the usual way from 2.7 g (0.11 g-atoms) of magnesium and 16.3 g (0.1 mole) of 2-bromothiophene in 100 ml of ether. The Grignard solution was then added dropwise to a stirred solution of 5.9 g (0.05 moles) of dimethyl oxalate in 150 ml of ether. After the addition the reaction mixture was refluxed for 30 min. After cooling 150 ml of dilute sulfuric acid was slowly added. The ether layer was separated, washed with dilute sodium bicarbonate and water, and dried over anhydrous sodium sulfate. After filtration and evaporation of the solvent the solid residue was dissolved in a small amount of warm carbon tetrachloride. This solution was cooled to 0° whereupon crystals precipitated. These were collected and dried. The substance was identified as methyl 2,2'-dithienylglycolate, m.p. 94–95° (5.9 g; 47%). (Found: C 51.9; H 3.93; S 25.1. Calc. for C₁₁H₁₀O₃S₂: C 51.9; H 3.96; S 25.2).

The IR spectrum (CCl₄) showed absorption for hydroxyl at 3580 cm⁻¹ (w) and 3500 cm⁻¹ (m) and for carbonyl at 1735 cm⁻¹. The NMR shifts are given in Table 2. Integrated areas were in the ratio 6:1:3.

Methyl 3-thienylglyoxalate. 3-Thienyllithium was prepared from 27.7 g (0.17 moles) of 3-bromothiophene in 75 ml of ether and 0.15 moles of ethyllithium in 230 ml of ether at -70° according to Gronowitz¹⁸ and was subsequently added (at -70°) under nitrogen to a well-stirred solution of magnesium bromide in ether-benzene. The latter was prepared by carefully adding 41.4 g ethylene bromide in a mixture of 100 ml of ether and 10 ml of benzene to 8.2 g of magnesium in 50 ml of ether. A clear solution of 3-thienylmagnesium bromide was formed,¹⁰ which after 30 min was cooled to -70° . It was added dropwise (under nitrogen) to a solution of 41.3 g (0.35 moles) of dimethyl oxalate in 400 ml of ether cooled to -70° . After stirring for an additional hour the cooling-bath was removed. When the temperature reached 0° , 250 ml of dilute sulfuric acid was added. The ether layer was separated, washed with dilute sodium bicarbonate and water, and dried over anhydrous sodium sulfate. After filtration and evaporation of the solvent the residue was distilled through a short column. 13.6 g (53 %) of methyl 3-thienylglyoxalate was collected at $88-94^{\circ}/0.1$ mm. On standing the substance solidified. For analytical purpose a small amount was recrystallized from petroleum ether, m.p. $38-39^{\circ}$. (Found: C 49.2; H 3.33; S 18.6. Calc. for $C_7H_6O_3S$: C 49.4; H 3.55; S 18.8).

The IR spectrum showed absorption for carbonyl at 1735 cm^{-1} and for carbonyl (ketone) at 1685 cm^{-1} . The NMR spectrum showed a singlet at 4.02 ppm and three quartets at 7.42 ppm, 7.77 ppm, and 8.67 ppm. These were assigned as the CH_3 protons, the thiophene protons in the 5-position, those in the 4-position, and those in the 2-position, respectively ($J_{24}=1.2$ cps, $J_{25}=2.8$ cps, $J_{45}=5.0$ cps). The integrated areas were in the ratios 3:1:1:1.

Methyl 3,3'-dithienylglycolate. A solution of 3-thienyllithium in ether was prepared in the usual way from 17.9 g (0.11 moles) of 3-bromothiophene in 50 ml of ether and 0.1 mole of ethyllithium in 150 ml of ether at -70°C . Magnesium bromide was prepared as above from 5.8 g (0.24 g-atoms) of magnesium in 50 ml of ether and 30.0 g (0.16 moles) of ethylene bromide in 75 ml of ether and 10 ml of benzene. From these two solutions 3-thienylmagnesium bromide was prepared as previously described. The clear solution of the Grignard reagent was cooled to 0°C and added dropwise to a stirred solution of 18.1 g (0.106 moles) of methyl 3-thienylglyoxalate in 300 ml of ether cooled to 0°C . After stirring for an additional hour, 250 ml of dilute sulfuric acid was slowly added. The ether layer was separated, washed with dilute sodium bicarbonate solution and water, and dried over anhydrous sodium sulfate. After filtration and evaporation of the solvent 22.4 g substance remained, which upon cooling became semisolid.

Recrystallization from a small amount of carbon tetrachloride gave 7.4 g (29 %) of methyl 3,3'-dithienylglycolate, m.p. $78-79^{\circ}\text{C}$. (Found: C 51.7; H 4.28; S 25.3. Calc. for $C_{11}H_{10}O_3S_2$: C 51.9; H 3.96; S 25.2).

The IR spectrum showed absorption for hydroxyl at 3590 cm^{-1} (w) and 3520 cm^{-1} (m), for carbonyl at 1735 cm^{-1} . The NMR shifts are given in Table 2. The integrated areas were in the ratio 6:1:3.

Methyl 2,3'-dithienylglycolate. 2-Thienylmagnesium bromide was prepared in the usual way from 0.6 g (0.025 g-atoms) of magnesium and 2.9 g (0.018 moles) of 2-bromothiophene in 25 ml of ether. The Grignard solution was transferred to a dropping funnel and slowly added to a solution of 3.0 g (0.018 moles) of methyl 3-thienylglyoxalate in 50 ml of ether. The reaction mixture was then refluxed for 1 h followed by hydrolysis with dilute sulfuric acid. The reaction mixture was then worked up in the usual way. The residue was treated with charcoal in boiling acetone and recrystallized from carbon tetrachloride; 2.1 g (46 %) of methyl 2,3'-dithienylglycolate was obtained, m.p. $92-94^{\circ}\text{C}$. (Found: C 51.5; H 4.05; S 25.2. Calc. for $C_{11}H_{10}O_3S_2$: C 51.9; H 3.96; S 25.2).

The IR spectrum showed absorption for hydroxyl at 3590 cm^{-1} (w) and at 3510 cm^{-1} , for carbonyl at 1735 cm^{-1} . The NMR spectrum showed signals at 3.92 ppm, 4.50 ppm, and a complex spectrum between 6.97 and 7.53 ppm. These were assigned to the CH_3 protons, OH, and the thiophene ring protons, respectively. The integrated areas were in the ratio 3:1:6.

Ester interchange of methyl dithienylglycolates. The 3-tropanyl, bornyl, and 3-quinuclidinyl dithienylglycolates were prepared from methyl 2,2'-dithienyl-, or methyl 3,3'-dithienylglycolate and the appropriate alcohols in the presence of sodium hydride.¹⁹ Approximately equimolar amounts of the methyl ester, the alcohol and sodium hydride were used in the concentration range of 2–60 mM. The solvent was heptane except in the preparation of bornyl 3,3'-dithienylglycolate where petroleum ether was used. The

reactions were carried out at reflux temperature. Yields ranged from 25 % to 50 %. The product obtained was uniform in each one of the preparations as evidenced by GLC. Melting points: 2,2'-dithienyl derivatives: 255–260° (decomp.) (I); 80–82° (II); 154–155° (III). 3,3'-dithienyl derivatives: 221–223° (I); 55–56° (II); 138–139° (III). Mass spectral analyses gave the following values (*m/e*, % of base peak) for the M⁺ ions of the compounds. 2,2'-dithienyl derivatives: 363, 6.5 % (I); 376, 1.6 % (II); 349, 2.1 % (III). 3,3'-dithienyl derivatives: 363, 6.7 % (I); 376, 1 % (II); 349, 5.7 % (III). The NMR shifts of proton resonances are given in Table 2.

Table 2. Chemical shifts ^a (ppm downfield from TMS) in CDCl₃ of proton resonances of dithienylglycolic esters.

2,2'-Dithienylglycolate						
R	H ₃	H ₄	H ₅	OH	OCH	Residue of R
CH ₃	7.28	7.06	7.38	4.8	3.90	—
I	7.22	7.03	7.36	5.6	5.1	3.2–1.2 (13 H)
II	7.09	6.86	7.18	4.7	4.9	2.6–0.8 (16 H)
	7.12	6.88	7.19			
III	7.11	6.91	7.21	6.4	4.9	3.3–1.1 (11 H)
	7.15	6.94	7.24			
3,3'-Dithienylglycolate						
R	H ₂	H ₄	H ₅	OH	OCH	Residue of R
CH ₃	7.41	7.21	7.36	4.4	3.87	—
I	7.40	7.24	7.40	4.8	5.1	3.1–1.1 (13 H)
II	7.32	7.13	7.27	4.3	5.0	2.7–0.6 (16 H)
	7.34	7.14	7.29			
III	7.28	7.09	7.23	5.4	4.9	3.3–1.0 (11 H)
	7.31	7.11	7.25			

^a The coupling constants used for the assignments of the shifts of the thiophenic protons are those given in Table 1.

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