

Unsaturated γ -Thiolactones

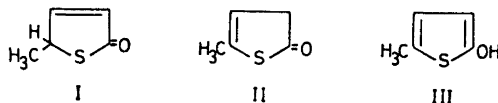
XIV.* Alkylation of the 2-Hydroxythiophene System

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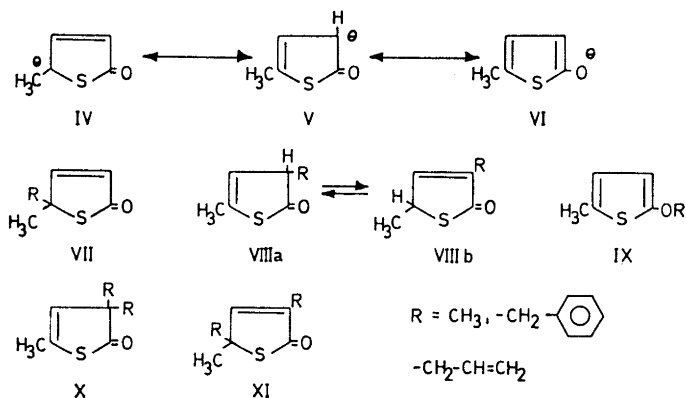
The 5-methyl-2-hydroxythiophene system has been alkylated with methyl iodide, allyl bromide, benzyl bromide, and dimethyl sulphate. The 3-position was found to be the most reactive, while *O*-alkylation was obtained only in the reaction with dimethyl sulphate.

In connection with our studies of the tautomeric hydroxythiophenes¹ it was also of interest to study some of their reactions, primarily the alkylation of the 5-methyl-2-hydroxythiophene system. For this system three tautomeric forms are possible (I - III), and the system exists in an equilibrium between the oxo-forms (I and II). These are called 5-methyl-3-thiolen-2-one and 5-methyl-4-thiolen-2-one.



A variety of methods for the alkylation of carbonyl compounds with active methylene groups has been developed. Often, however, many competing reactions take place, such as mono- and di-alkylation of carbon, *O*-alkylation, coupling reactions due to air oxidation of the salt, and Claisen condensation. By varying the choice of solvent, the reaction can be directed so that undesired side reactions are suppressed. The main purpose of this study was to obtain information on the reactivity of the anion of the 5-methyl-2-hydroxythiophene system, and thus conditions were chosen under which only alkylation took place. Since this system has a trident anion (IV - VI), three monoalkyl products are possible (VII - IX). The 3-alkyl-substituted compound (VIII) is tautomeric, with acidic properties, and it may be alkylated once again to form the dialkyl compounds X and XI.

* Part XIII, Ref. 1.



The initial alkylations of the 5-methyl-2-hydroxythiophene system were performed by a procedure analogous to that used by Löwenbein and Simonis for the alkylation of *ortho*-hydroxydiphenyl acetic acid lactone.² It proved necessary to considerably modify this procedure in order to avoid additions of Michael type. The best result was obtained when a homogeneous mixture of an excess of the alkylating reagent, ethanol-ether (1:1), and sodium was treated with 5-methyl-thiolen-2-one, and the reaction mixture refluxed for 90 min. The alkyl reagents used were methyl iodide, allyl bromide, benzyl bromide, and dimethyl sulphate and the structures of the various products were determined by NMR spectroscopy and gas chromatography in connection with mass spectroscopy. The total and relative yields are given in Table 1.

Table 1. Methylation, allylation, and benzylation of the sodium salt of the 5-methyl-2-hydroxythiophene system.

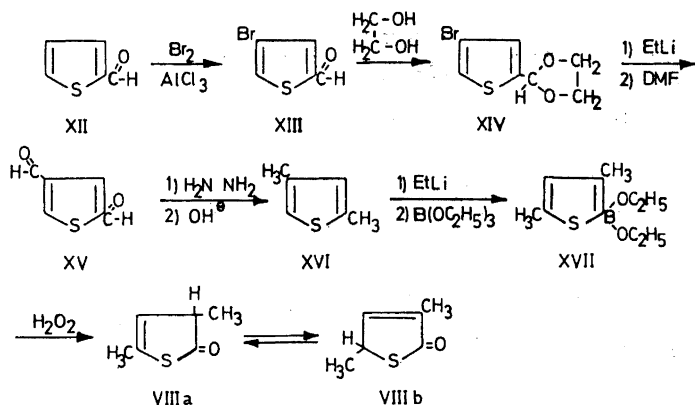
Alkyl reagent	Yield %	VIII	X	XI	IX
Methyl iodide	18 ^a	83	17	—	—
Allyl bromide	33 ^a	69	26	5	—
Benzyl bromide	28 ^a	89	11	—	—
Dimethyl sulphate	77 ^a	36	—	—	64
Dimethyl sulphate	79 ^b	47	—	—	53

^a In ether-ethanol (1:1).

^b In water.

An authentic sample of the tautomeric monomethylated product was prepared according to the route, shown below.

2,4-Diformylthiophene (XV) was prepared according to Gol'dfarb *et al.*⁷ in the following way. 2-Thiophenealdehyde (XII) was brominated with bromine and AlCl_3 without solvent giving 4-bromo-2-thiophenealdehyde (XIII). After protection of the aldehyde function with ethyleneglycol and halogen-metal



exchange followed by formylation with dimethylformamide and hydrolyses, XV was obtained. After Wolff-Kishner reduction.⁸ of the two aldehyde groups in one step 2,4-dimethylthiophene (XVI) was formed. This is the most convenient way for preparation of pure 2,4-dimethylthiophene. The 3,5-dimethyl-thiolen-2-one was prepared according to Ref. 11 from XVI, and only the α,β -unsaturated form was observed.

Even if the introduction of the first alkyl group should make the compound less acidic,³ a considerable amount of the dialkylated product, X, is formed. One of the reasons for this is that the dialkyl product may be more stable to ring-opening reactions than the monoalkylated product. In Table 1 it is shown that by using dimethylsulphate as alkyl reagent the yields become larger and the *O*-alkylation becomes more important than the *C*-alkylation.^{9,10}

Alkylation of the 5-position was not observed except for one case, namely when small amounts of 5-methyl-3,5-diallyl-3-thiolen-2-one were obtained (*cf.* Table 1). These results are rather surprising, since Michael additions gave both 3- and 5-coupled products in these systems.⁴ The most important reason for this difference in reactivity is probably the reversibility of the Michael reaction, with the consequence that product formation is thermodynamically controlled, whereas the alkylation is a kinetically controlled reaction. The greater reactivity of the 3-position is in accord with dissociation constant measurements, which demonstrated that the 3-position is most acidic.⁵

EXPERIMENTAL

Alkylation of 5-methyl-thiolen-2-one with methyl iodide in ethanol-ether (Procedure A). 23 g (0.16 mol) of methyl iodide, 45 ml of dry ether and 50 ml of absolute ethanol were heated with 0.9 g (0.04 mol) of sodium under nitrogen. When the solution was homogeneous, 4.5 g (0.04 mol) of 5-methyl-thiolen-2-one solved in 5 ml of dry ether was added and the mixture was refluxed for 90 min at 42°. The reaction mixture was carefully poured into 2 N hydrochloric acid covered with cooled ether. The phases were separated and the water phase extracted with ether. The combined ether phases were washed with water to neutral reaction, dried over magnesium sulphate and distilled, giving 0.93 g (18 %) of alkyl product, b.p. 80–95°/10 mmHg, $n_D^{25} = 1.5170$. The composition of the product as determined by gas chromatography is given in Table 1. The retention

time for 3,5-dimethyl-3-thiolene-2-one was identical with that of an authentic sample described below.

3,5-Dimethyl-3-thiolene-2-one. 345 ml of 0.6 N butyllithium was added dropwise to 21.1 g (0.19 mol) of 2,4-dimethylthiophene (see below) in 200 ml of dry ether under nitrogen at room temperature, at such a rate that gentle reflux was maintained. The resulting thienyllithium compound was refluxed for a further half an hour, then cooled to -70° , and treated with 30.3 g (0.21 mol) of triethylborate in 200 ml of dry ether. After stirring at -70° for 4 h, the reaction mixture was allowed to warm to room temperature and then treated with 38 ml of 30 % hydrogen peroxide solution. After complete addition the mixture was refluxed for 1 h with vigorous stirring. The reaction mixture was cooled, the layers separated and the aqueous phase extracted with ether. The combined ethereal phases were washed with cold water until the separating water did not oxidize ferrous ammonium sulphate, dried over magnesium sulphate and distilled. 12.9 g (53 %) of 3,5-dimethyl-3-thiolene-2-one, b.p. $86-87^\circ/9$ mmHg, $n_D^{22}=1.5210$, was obtained. NMR data (CDCl_3): $\tau_{5-\text{CH}_3}=8.43$, $\tau_{3-\text{CH}_3}=8.17$, $\tau_{\text{H}_1}=2.73$, $\tau_{\text{H}_2}=5.59$, $J_{45}=3.0$ c/s, $J_{4-3\text{CH}_3}=1.4$ Hz, $J_{5-5\text{CH}_3}=7.2$ Hz and $J_{5-3\text{CH}_3}=2.0$ Hz. (Found: C 56.14; H 6.01; S 25.65. Calc. for $\text{C}_8\text{H}_{10}\text{OS}$: C 56.22; H 6.29; S 25.01.)

2,4-Dimethylthiophene was prepared by Wolff-Kishner reduction according to Ref. 6 from 47.9 g (0.34 mol) of 2,4-diformylthiophene,⁷ 137 ml of hydrazin hydrate (85 %) and 140 g of potassium hydroxide. Distillation gave 21 g (56 %) of 2,4-dimethylthiophene, b.p. $143-144^\circ$, $n_D^{20}=1.5117$ (lit. values⁸ b.p. $137-138$, $n_D^{20}=1.5130$). NMR spectrum (CDCl_3): $\tau_{2-\text{CH}_3}=7.60$, $\tau_{4-\text{CH}_3}=7.83$, $\tau_{\text{H}_1}=3.46$, $\tau_{\text{H}_2}=3.40$, $J_{34}=1.2$ Hz, $J_{3-3\text{CH}_3}=1.1$ Hz.

Alkylation of 5-methyl-thiolene-2-one with allyl bromide in ethanol-ether. 4.5 g (0.04 mol) of 5-methyl-thiolene-2-one was alkylated with 20 g (0.16 mol) of allyl bromide as described in procedure A, giving 2.2 g (33 %) of alkyl product, b.p. $120-125^\circ/12$ mmHg. The composition of the product as determined by gas chromatography is given in Table 1. The components were isolated by preparative gas chromatography and analyzed.

5-Methyl-3-allyl-3-thiolene-2-one, $n_D^{21}=1.5350$. Carbonyl frequency in IR (film): 1680 cm^{-1} . NMR data (CDCl_3): $\tau_{\text{H}_1}=2.90$, $\tau_{\text{H}_2}=5.62$, $\tau_{5-\text{CH}_3}=8.48$, $\tau_{3-\text{CH}}=7.01$, $J_{45}=3.04$ Hz, $J_{4-3\text{CH}}=1.4$ Hz, $J_{5-5\text{CH}_3}=7.2$ Hz, $J_{5-3\text{CH}}=1.8$ c/s. (Found: C 63.0; H 6.50; S 19.4. Calc. for $\text{C}_8\text{H}_{10}\text{OS}$ (154.2): C 62.30; H 6.54; S 20.79.)

5-Methyl-3,3-diallyl-4-thiolene-2-one, $n_D^{21}=1.5168$. Carbonyl frequency in IR (film): 1715 cm^{-1} . NMR data (CDCl_3): $\tau_{\text{H}_1}=4.59$, $\tau_{5-\text{CH}_3}=7.88$, $\tau_{3-\text{CH}}=7.63$, $J_{4-5\text{CH}_3}=1.6$ c/s. (Found: C 67.3; H 7.28; S 15.8. Calc. for $\text{C}_{11}\text{H}_{14}\text{OS}$ (194.2): C 68.01; H 7.26; S 16.50.)

5-Methyl-3,5-diallyl-3-thiolene-2-one. Carbonyl frequency in IR (film): 1685 cm^{-1} . M. wt. 194.

Benylation of 5-methyl-thiolene-2-one in ethanol-ether. 4.5 g (0.04 mol) of 5-methyl-thiolene-2-one was alkylated with 28 g (0.16 mol) of benzylbromide according to procedure A, giving 2.3 g of product (28 %). The composition of the product as determined by gas chromatography is given in Table 1. The components were isolated by preparative gas chromatography and analyzed.

5-Methyl-3-benzyl-thiolene-2-one, b.p. $187-190^\circ/8$ mmHg, $n_D^{21}=1.5872$. Carbonyl frequency in IR (film): 1678 cm^{-1} . NMR data (CDCl_3): $\tau_{\text{H}_1}=3.23$, $\tau_{\text{H}_2}=5.82$, $\tau_{5-\text{CH}_3}=8.58$, $\tau_{3-\text{CH}_2}=6.41$, $J_{45}=2.8$ Hz, $J_{4-3\text{CH}_2}=1.6$ Hz, $J_{5-5\text{CH}_3}=7.1$ Hz, $J_{5-3\text{CH}_2}=1.8$ Hz. (Found: C 70.4; H 5.88; S 14.03. Calc. for $\text{C}_{12}\text{H}_{12}\text{OS}$ (204.3): C 70.55; H 5.92; S 15.70.)

5-Methyl-3,3-dibenzyl-4-thiolene-2-one, b.p. $232-238^\circ/8$ mmHg, recrystallized from ethanol, m.p. $135.5-136^\circ$. Carbonyl frequency in IR (KBr): 1700 cm^{-1} . NMR data (CDCl_3): $\tau_{\text{H}_1}=4.56$, $\tau_{5-\text{CH}_3}=8.18$, $\tau_{3-\text{CH}_2}=6.86$ and 7.18 , $J_{4-5\text{CH}_3}=1.6$ c/s. (Found: C 77.4; H 6.16; S 10.9. Calc. for $\text{C}_{19}\text{H}_{18}\text{OS}$ (294.4): C 77.5; H 6.12; S 10.9.)

Alkylation of 5-methyl-thiolene-2-one with dimethyl sulphate in ethanol-ether. 4.5 g (0.04 mol) of 5-methyl-thiolene-2-one in 5 ml of dry ether was treated with 20.4 g (0.16 mol) of dimethyl sulphate according to procedure A, giving 3.9 g (77 %) of product. The composition of the product as determined by gas chromatography is given in Table 1. The retention times, IR and NMR spectra of the components were identical with those of authentic samples of 5-methyl-2-methoxythiophene¹² and 3,5-dimethyl-thiolene-2-one (see above).

Alkylation of 5-methyl-thiolene-2-one with dimethyl sulphate in sodium hydroxide solution. 4.5 g (0.04 mol) of 5-methyl-thiolene-2-one was dropped into a solution of 40 ml of water, 1.7 g (0.04 mol) of sodium pellets and 20.4 g (0.16 mol) of dimethyl sulphate under a nitrogen atmosphere. The reaction mixture was refluxed for 90 min and poured

into cold 2 N hydrochloric acid covered with ether. The water phase was extracted with ether, and the combined ether phases were washed with water until neutral, dried on magnesium sulphate and distilled. The yield was 4.0 g (79 %), containing 5-methyl-2-methoxythiophene and 3,5-dimethyl-3-thiolene-2-one in the proportions given in Table 1.

The NMR spectra were obtained with a Varian A-60 high resolution spectrometer. The IR spectra were recorded on a Perkin-Elmer Model 257 instrument. The mass spectra were recorded on an LKB A 9000 mass spectrometer and the ion-source voltage was 70 eV. The gas chromatographs used were a Perkin-Elmer 900 analytical instrument and a Perkin-Elmer F 21 preparative instrument. The elementary analyses were carried out at the Analytical Department at the Chemical Center and at Ilse Beetz, Mikro-analytisches Laboratorium, Kronach.

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