ACTA CHEMICA SCANDINAVICA 25 (1971) 3656–3662

Unsaturated γ-Thiolactones

XV.* Alkylation of the 2-Hydroxythiophene System and the 2-Hydroxyfuran System with an Ion Pair Extraction Method

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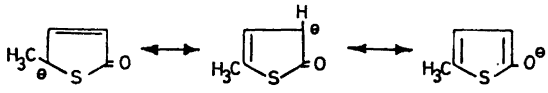
The 4- and 5-methyl-2-hydroxythiophene systems have been alkylated with methyl iodide by means of the ion pair extraction method. In both systems the 3-position was found to be the most reactive and for the 4-methyl substituted compound even a small amount of 5-methylation took place. When on the other hand dimethyl sulphate was used as alkylating reagent almost exclusive ether formation occurred. Parallel with this study the 5-methyl-2-hydroxyfuran system was methylated with the same reagents and under the same conditions. In this case the yields were much lower due to ring-opening and neither 5- nor *O*-substitution could be detected.

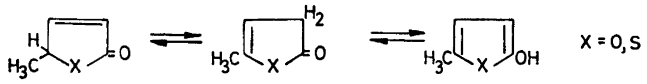
In the preceding paper the alkylation of the 5-methyl-2-hydroxythiophene system in one of the classical ways has been reported.[1] Even if this system has a trident anion (I – III), alkylation of the 5-position could only be demonstrated in one case, namely when 5-methyl-3,5-diallyl-3-thiolene-2-one was formed.



I II III

In order to obtain information about the steric effect of the substituent in the 5-position, the 4-methyl-2-hydroxythiophene system was alkylated. Parallel with this study a comparison between the 5-methyl-2-hydroxythiophene system and the corresponding furan derivatives was made. For both of the systems three tautomeric forms are possible (IV – VI), and both of the systems exist in an equilibrium between the two oxoforms (IV and V).

* Part XIV. Ref. 1.



IV V VI

The furan derivatives have long been known as β- and α-angelica lactones [2,3] while the thiophene derivatives are called 5-methyl-3-thiolen-2-one and 5-methyl-4-thiolen-2-one. It has earlier been shown that the isomerisation rate of α-angelica lactone (II) to β-angelica lactone (I) is much slower than the tautomerisation of 5-methyl-4-thiolen-2-one to 5-methyl-3-thiolen-2-one.[4] Another comparison between the two systems has been made with respect to dimerisation reactions of Michael addition type.[5] For the thiophene system the presence of the enol form has been demonstrated indirectly by treatment with acetyl chloride, whereupon acetoxythiophenes have been formed.[6,7] The angelica lactones, on the other hand, have not hitherto shown any enolic properties. For the 2-hydroxythiophene system the dissociation constants have also been determined, and it was found that they were of the same magnitude as those of the corresponding phenols.[8] However, such determinations have not been carried out on the 2-hydroxyfuran system, since ring opening is a strongly interfering reaction.

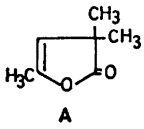
During our preliminary examinations,[1] the ion pair extraction method developed by Brändström and his collaborators was published. Using this method, a large number of anions can be extracted into a chloroform or methylene chloride phase as the counter ion in an ion pair with the tetrabutylammonium cation.[9] These authors have also shown that the ion pair extraction method can be used for weak acids, and that esters are not hydrolysed during the procedure,[10] which is an obvious advantage in work with the angelica lactones, since they easily undergo ring opening to give mainly levulinic acid esters as shown by NMR and mass spectroscopy. The water solutions of the α- and β-angelica lactones have pH values around 4.5 and 7, respectively, and in alkaline solution α-angelica lactone is hydrolysed to levulinic acid much faster than β-angelica lactone.[11]

Some ion pairs can easily be isolated as crystalline salts,[12] but this has not been possible for the 2-hydroxythiophene system nor for the 2-hydroxyfuran system, and consequently no spectroscopic data on the trident anion are available.

Even if the ion pair extraction method is used for the alkylation of the angelica lactones, the ring opening reaction dominates. The best results were obtained when the reaction temperature was maintained at 30° for 10 min. The total and relative yields of the various products on alkylation with methyl iodide and dimethyl sulphate are given in Table 1. As shown in the table the isomer distribution is rather different for the two reagents. Dimethyl sulphate gives only 3-methyl-β-angelica lactone, while 5-methyl-2-methoxyfuran could not be detected, although dimethyl sulphate, in contrast to methyl iodide, is known to give mainly *O*-alkylations in many cases.[9,13,14] It is pertinent to note that the two 2-hydroxythiophene systems described below give *O*-alkylation even with methyl iodide as the alkyl reagent, which shows that the ion pair extraction method itself is no hindrance to *O*-alkylation. When the

Table 1. Alkylation of α-angelica lactone with methyl iodide and dimethyl sulphate.

Alkyl reagent	Yield %	Products and relative yields		
		A	B	C
CH_3I	26	46	30	24
$(CH_3O)_2SO_2$	7	–	–	100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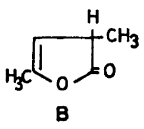
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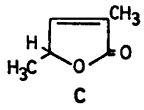
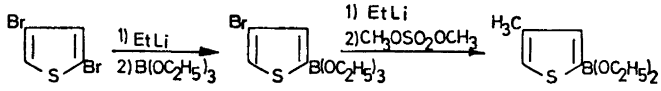
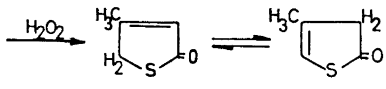

C

5-methyl-2-hydroxythiophene system was alkylated in the classical way by treating the sodium salt with dimethyl sulphate in a homogeneous solution, *O*-alkylation was the dominant reaction.[1]

4-Methyl-3-thiolen-2-one has previously been prepared by metalation of 3-methylthiophene followed by treatment with butyl borate and oxidation of the resulting boronic acid. NMR spectral analysis gave a product consisting of 16 % 2,3-isomer and 84 % 3,5-isomer.[6] In order to obtain an isomer-free product a new method was developed starting with 2,4-dibromothiophene. All the reaction steps in the scheme were carried out in the same flask without


VII VIII IX


X XI

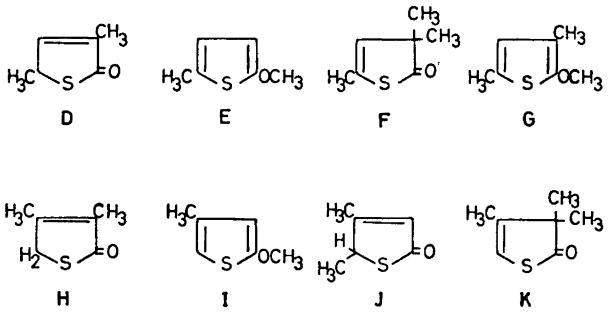
isolation of the intermediate products. Only the conjugated form, 4-methyl-3-thiolen-2-one, could be detected.

At this point it should be pointed out that while metalation of 3-methylthiophene takes place in both the 2- and the 5-positions, halogen-metal exchange followed by hydrolysis of 2,5-dibromo-3-methyl-thiophene gives isomer free 2-bromo-3-methylthiophene, shown by gas chromatography analysis. This gives another route for preparing the 4-methyl-2-boronic acid. 2,5-Dibromo-3-methylthiophene is treated by one equivalent butyllithium followed by triethylborate and another equivalent butyllithium followed by hydrolysis.

The total and relative yields of the products obtained when the 4-methyl- and 5-methyl-thiolene systems were alkylated with methyl iodide and dimethyl sulphate by the ion pair extraction method are given in Table 2. The structures

Table 2. Alkylation of 4-methyl- and 5-methyl-2-hydroxythiophene with methyl iodide and dimethyl sulphate.

Substrate	Reagent	Yield %	Products and relative yields			
			D	E	F	G
5-Methyl-thiolen-2-one	CH_3I	53 %	86	12	2	–
»	$(CH_3O)_2SO_2$	89 %	4	90	2	4
			H	I	J	K
4-Methyl-thiolen-2-one	CH_3I	49 %	84	9	3	4

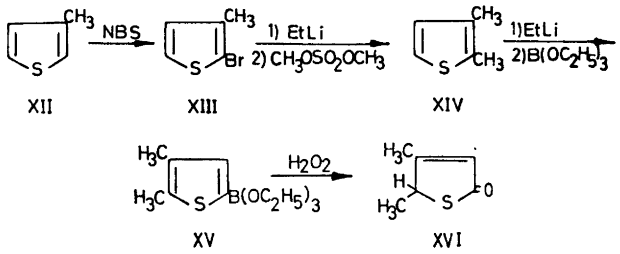


of the various products were determined by NMR spectroscopy and by gas chromatography in connection with mass spectroscopy.

A comparison of Tables 1 and 2 shows that the furan system gives both α- and β-unsaturated forms of the 3-alkyl product, while the thiophene system gives only the conjugated form. This is probably a reflection of the fact that the thiophene system rearranges much faster than the furan system.[4] The different behaviour towards *O*-alkylation has already been pointed out, and is stressed once again. When treated with dimethyl sulphate the 5-methyl-2-hydroxythiophene system gives mainly the *O*-alkylated product.

A comparison of the results in Table 2 shows that alkylation of the 4-methyl- and 5-methyl-thiolen-2-ones occurs mainly in the 3-position. Alkylation of the 5-position only takes place in the 4-methyl substituted compound, but not in the 5-methyl substituted isomer. Even if the amount of 5-alkylated product is rather small it may be formed due to less steric hindrance.

As the unconjugated form of the 3-methylated 4-methylthiolene-2-one would be expected to have an NMR spectrum similar to that of the 5-methylated product, an authentic sample of 4,5-dimethyl-3-thiolen-2-one (XVI) was prepared and the above interpretation was shown to be correct. The following route was used for its synthesis.



3-Methylthiophene was brominated with *N*-bromosuccinimide, and the so obtained 2-bromo-3-methylthiophene was after halogen-metal exchange treated with dimethyl sulphate.[19] After metallation the 3,4-dimethylthiophene was reacted with triethyl borate. The thienylboronic ester was, without isolation, oxidized with hydrogen peroxide to the 4,5-dimethyl-3-thiolen-2-one.

EXPERIMENTAL

Alkylation of α-angelica lactone with methyl iodide. A freshly prepared solution of 50 ml of water, 17.0 g (0.05 mol) of tetrabutylammonium hydrogen sulphate and 4.0 g (0.10 mol) of sodium hydroxide was added dropwise to 4.3 g (0.044 mol) of α-angelica lactone and 14.2 g (0.10 mol) of methyl iodide, dissolved in 50 ml of chloroform. During the addition, which took 10 min, the temperature was maintained at 30°. When the addition was complete, the phases were separated and the water phase was extracted with chloroform. The combined chloroform phases were evaporated, and when the residue was treated with ether the tetrabutylammonium iodide precipitated. The solid was filtered off and washed with ether, whereupon the filtrate was washed with water, dried over magnesium sulphate and evaporated. The residue was distilled from a Claisen-flask and during the distillation the receiver was cooled. The fraction boiling at 20 – 100°/8 mmHg was collected and analyzed by gas chromatography and NMR spectroscopy. The total and relative yields are given in Table 1. After separation by preparative gas chromatography it was found that one of the components had a carbonyl stretching band at 1790 cm^{-1} and the mass number 112 *m/e*, in accordance with 3-methyl-α-angelica lactone. The retention time and spectroscopic data for the other component were identical with those of an authentic sample of 3,3-dimethyl-α-angelica lactone, described below.

3,3-Dimethyl-α-angelica lactone was prepared from 4.0 g (0.028 mol) of 2,2-dimethyllevulinic acid,[15] which was placed in a distillation flask and slowly heated. First water was distilled off, followed by the product at 167°. The distillate was taken up in ether, dried over magnesium sulphate and redistilled, yielding 2.9 g (83 %) of lactone, b.p. 167 – 168°, $n_D^{20} = 1.4140$. Carbonyl frequency in IR (film): 1802 cm^{-1}. NMR spectrum ($DCCl_3$): $\tau_{3-(CH_3)_2} = 8.71$, $\tau_{5-CH_3} = 8.00$, $\tau_{H_4} = 4.80$, $J_{H-5CH_3} = 1.5$ Hz. (Found: C 66.5; H 8.0; O 25.5; M.w. 126. Calc. for $C_7H_{10}O_2$: C 66.65; H 7.99; O 25.36; Mv 126.15.)

Alkylation of α-angelica lactone with dimethyl sulphate. 4.3 g (0.044 mol) of α-angelica lactone was alkylated with 9.47 ml (0.10 mol) of dimethyl sulphate according to procedure B, giving a 7 % yield of 3-methyl-β-angelica lactone. The product was isolated by preparative gas chromatography and analyzed. NMR data ($DCCl_3$): $\tau_{3-CH_3} = 8.58$, $\tau_{4-CH_3} = 8.09$, $\tau_{H_5} = 4.98$, $\tau_{H_4} = 2.82$, $J_{45} = 1.6$ Hz, $J_{3-4CH_3} = 1.7$ Hz, $J_{5-5CH_3} = 6.8$ Hz and $J_{3-5CH_3} = 1.8$ Hz. (Found: M.w. 112. Calc. for $C_6H_8O_2$: M.w. 112.12).

4-Methyl-3-thiolen-2-one. 200 ml of ethereal 1.0 N ethyllithium was added under nitrogen at −70° in a slow stream to 48.4 g (0.20 mol) of 2,4-dibromothiophene [16] in 100 ml of dry ether. After stirring for 30 min, 50.7 g (0.22 mol) of butylborate in 150 ml of dry ether was added dropwise. The reaction mixture was then stirred for 3 h, whereupon 230 ml of 1.0 N ethyllithium was added dropwise. The stirring was continued at −70° for 30 min and 35.4 g (0.28 mol) dimethyl sulphate in 100 ml of dry ether was added, and the reaction mixture was left at −70° for 90 min and then allowed to warm slowly to

0°. It was then treated with 200 ml of 2 N hydrochloric acid. The aqueous phase was extracted twice with ether, the combined ethereal phases extracted with cold 2 N sodium hydroxide solution and the alkaline solution acidified with cold hydrochloric acid. The precipitated oily boronic acid was immediately taken up in ether.

96 ml of 10 % hydrogen peroxide solution was added dropwise with stirring under nitrogen to the ethereal boronic acid. When the addition was complete, the reaction mixture was refluxed for 1 h with rather vigorous stirring. After separating the phases, the water phase was extracted with ether and the combined ethereal phases were washed with water four or five times until the washings did not oxidize ferrous ammonium sulphate. The ethereal phase was dried over magnesium sulphate, evaporated and distilled giving 8.4 g of a product, b.p. 85 – 90°/3 mmHg, consisting of 75 % 4-methyl-3-thiolen-2-one, 12 % 4-bromo-3-thiolen-2-one,[6] 6 % 3-thiolen-2-one [17] and 7 % of undefined products. The proportions of the components were determined by gas chromatography using an OV 17 (3 %) column at 110°.

The crude product described above was chromatographed on silica gel column using toluene as eluent. The separation was followed by gas chromatography. Pure 4-methyl-3-thiolene-2-one, b.p. 69 – 70°/0.9 mmHg, $n_D^{20} = 1.5555$ was obtained. NMR spectrum ($DCCl_3$): $\tau_{H-CH_3} = 7.78$, $\tau_{5-CH_2} = 5.98$, $\tau_{H_3} = 3.95$, $J_{3-5CH_2} = 1.5$ Hz, $J_{3-4CH_3} = 1.5$ Hz, $J_{5CH_3-4CH_3} = 0.75$ Hz. (Found: C 52.4; H 5.39; S 28.2; M.w. 114. Calc. for C_5H_6OS: C 52.60; H 5.30; S 28.07; M.w. 114.17.)

Alkylation of 5-methyl-thiolene-2-one with methyl iodide. A freshly prepared solution, 17.0 g (0.05 mol) of tetrabutylammonium hydrogen sulphate and 4.0 g (0.10 mol) of sodium hydroxide in 50 ml of water, was added dropwise to 5.7 g (0.05 mol) of 5-methyl-thiolen-2-one [7] and 14.2 g (0.10 mol) of methyl iodide, dissolved in 50 ml of chloroform. When the addition was complete 50 ml of 2 N hydrochloric acid was added. The phases were separated and the water phase was extracted twice with chloroform. The combined chloroform phases were evaporated, and when the residue was treated with ether the tetrabutylammonium iodide precipitated. The solid was filtered off and washed with ether, whereupon the filtrate was washed with water, dried over magnesium sulphate and evaporated. The residue was distilled and the fraction boiling at 82 – 97°/11 mmHg was collected and analyzed by gas chromatography and NMR spectroscopy. The total and relative yields are given in Table 2. After separation by preparative gas chromatography it was found that retention times and spectroscopic data were identical with those of autentic samples of 3,5-dimethyl-3-thiolen-2-one [1] and 5-methyl-2-methoxythiophene.[18]

Alkylation of 5-methyl-3-thiolene-2-one with dimethyl sulphate was carried out as above from 4.0 g (0.035 mol) 5-methyl-thiolen-2-one,[7] 8.8 g (0.07 mol) of dimethyl sulphate, 35 ml of chloroform, 11.9 g of tetrabutylammonium hydrogensulphate, 2.8 g of sodium hydroxide and 35 ml of water. Upon distillation the fraction boiling at 48 – 70°/8 mmHg was collected and analyzed by gas chromatography and NMR spectroscopy. The total and relative yields are given in Table 2.

Alkylation of 4-methyl-3-thiolen-2-one was carried out as above from 4.56 g (0.04 mol) of 4-methyl-3-thiolen-2-one, 11.4 g (0.08 mol) of methyl iodide, 40 ml of chloroform, 13.6 g (0.04 mol) of tetrabutylammonium hydrogensulphate, 3.2 g (0.08 mol) of sodium hydroxide and 40 ml of water. Upon distillation the fraction boiling at 74 – 78°/0.9 mmHg was collected and analyzed by gas chromatography and NMR spectroscopy. The total and relative yields are given in Table 2.

4,5-Dimethyl-3-thiolen-2-one was prepared in a manner analogous to that described for 5-methyl-β,γ-butenolide,[4] from 44.8 g (0.040 mol) of 2,3-dimethyl-thiophene,[19] 475 ml of 1.02 N ethyllithium, 64.2 g (0.48 mol) of triethyl borate, and 80 ml of 30 % hydrogen peroxide. Distillation gave 33.0 g (65 %) b.p. 68 – 69°/0.9 mmHg, $n_D^{20} = 1.5375$. NMR spectrum ($CDCl_3$): $\tau_{5-CH_3} = 8.42$, $\tau_{4-CH_3} = 7.86$, $\tau_{H_3} = 4.05$, $\tau_{H_5} = 5.68$, $J_{5-5CH_3} = 7.3$ Hz, $J_{5-4CH_3} = 0.7$ Hz, $J_{3-4CH_3} = 1.4$ Hz. (Found: C 55.6; H 6.26; S 24.9; M.w. 128. Calc. for C_6H_8OS: C 56.22; H 6.29; S 25.01; M.w. 128.19.)

2-Bromo-3-methylthiophene. 285 ml of 0.6 N butyllithium was dropped under nitrogen into a solution of 43.1 g (0.17 mol) of 2,5-dibromo-3-methylthiophene [20] in 100 ml of dry ether at −70°. After complete addition, stirring was continued for 20 min. The reaction mixture was then allowed to warm to room temperature and hydrolysed with 100 ml of cold 2 N hydrochloric acid. The phases were separated and the water phase extracted with ether. The combined ethereal phases were washed with water and dried over magnesium sulphate. Distillation gave 23.6 g (80 %) of an isomer-free product, b.p.

55 – 56°/9 mmHg, $n_D^{24} = 1.5700$. Gas chromatography analysis on both an OV 17 and an NPGS column showed only one peak and the spectroscopic data were identical with those of an authentic sample.[19]

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 quantitative analyses were corrected for the differences of the sensitivity of the detector for the different compounds. The elemental analyses were carried out at the Analytical Department at the Chemical Center, Lund and at Ilse Beetz Mikroanalytisches Laboratorium, Kronach.

Acknowledgements. We wish to express our thanks to Professor Salo Gronowitz for his interest in this work and for all facilities placed at our disposal.

Grants from the *Swedish Natural Science Research Council* to A.-B. H. and from the *Faculty of Science of the University of Lund* to B. C. are gratefully acknowledged.

REFERENCES

1. Cederlund, B. and Hörnfeldt, A.-B. *Acta Chem. Scand.* **25** (1971) 3324.
2. Wolff, L. *Ann.* **229** (1885) 249.
3. Thiele, I., Tischbein, R. and Lossow, E. *Ann.* **319** (1920) 180.
4. Hörnfeldt, A.-B. *Arkiv Kemi* **29** (1968) 229.
5. Hörnfeldt, A.-B. *Arkiv Kemi* **28** (1968) 363.
6. Hörnfeldt, A.-B. *Arkiv Kemi* **21** (1963) 239.
7. Hörnfeldt, A.-B. *Arkiv Kemi* **22** (1964) 211.
8. Hörnfeldt, A.-B. *Arkiv Kemi* **29** (1968) 247.
9. Brändström, A. and Junggren, U. *Acta Chem. Scand.* **23** (1969) 2203.
10. Brändström, A. and Junggren, U. *Acta Chem. Scand.* **23** (1969) 2204.
11. Kuehl, Jr., F. A., Linstead, R. P. and Orkin, B. A. *J. Chem. Soc.* **1950** 2213.
12. Brändström, A. and Junggren, U. *Acta Chem. Scand.* **23** (1969) 2536.
13. Briegen, G. and Pelletier, W. M. *Tetrahedron Letters* **1965** 3555.
14. Brändström, A. *Arkiv Kemi* **6** (1953) 155.
15. Caralito, C. J. and Haskell, T. H. *J. Am. Chem. Soc.* **67** (1945) 1991.
16. Lawesson, S. O. *Arkiv Kemi* **11** (1957) 317.
17. Gronowitz, S. and Hoffman, R. A. *Arkiv Kemi* **15** (1960) 499.
18. Sicé, J. *J. Am. Chem. Soc.* **75** (1953) 3697.
19. Wiersema, A. and Gronowitz, S. *Acta Chem. Scand.* **24** (1970) 2593.
20. Steinkopf, W. and Jacob, H. *Ann.* **515** (1935) 293.

Received March 24, 1971.