

## Preparation of Some Thiophene-, Selenophene- and Furanthiols. Ionisation Potentials in Tautomer Analysis

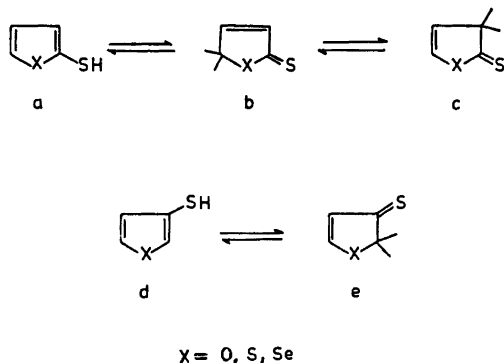
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5-Methyl-2-mercapto and 2,5-dimethyl-3-mercapto derivatives of furan, thiophene and selenophene have been prepared by treatment of the corresponding aryllithiums with sulfur. Upon alkylation by an ion pair extraction method, only the *S*-alkylated compounds were obtained. The potentially tautomeric thiol systems exist mainly in the thiol form in liquid solution and gas phase, as found by IR and NMR spectroscopy and by a study of ionization potentials.

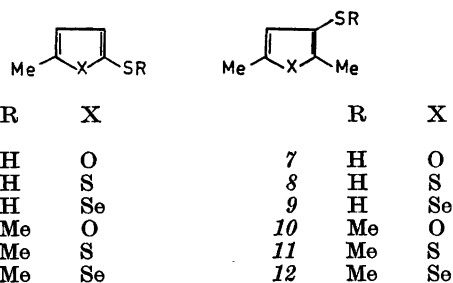
Analysis of some tautomeric 2- and 3-hydroxythiophenes, -selenophenes, and -furans by ionisation potential measurements in the gas phase in the mass spectrometer have shown that the 2-isomers are largely present in the lactone forms, whereas the 3-isomers are present in both the ketone and hydroxy forms.<sup>1,2</sup>

We report herein comparative studies of tautomeric thiol analogues (Scheme 1) in the mass spectrometer as well as studies of tautomeric equilibria in liquid state and in solutions.



Scheme 1.

The thiol compounds studied are the 5-methyl-2-mercapto and 2,5-dimethyl-3-mercapto derivatives of furan, thiophene and selenophene. As unsubstituted 3-hydroxythiophene decomposes the methyl substituents were introduced in order to obtain stable compounds.<sup>3,4</sup> Thiophenethiols can be prepared in various ways,<sup>5–12</sup> but the method used in this work is treatment of an aryllithium with sulfur followed by hydrolysis. The aryllithium was obtained by direct metalation in the 2-series,



Scheme 2.

and by halogen-metal exchange in the 3-series. The halogen-metal exchange was performed at  $-70^{\circ}\text{C}$  in the furan and thiophene case, and at  $-110^{\circ}\text{C}$  in the selenophene case to avoid ring-opening.<sup>13</sup> Three of the six resulting thiol systems were not previously known (*cf.* Experimental part). Upon alkylation of these potentially tautomeric systems by an ion pair extraction method, only *S*-alkylated products were obtained with either dimethyl sulfate or methyl iodide as the alkylating agents.

Table 1.  $^1\text{H}$  NMR parameters for 5-methyl-2-mercapto and 2,5-dimethyl-3-mercapto derivatives of furan, thiophene and selenophene at 60 MHz.

	$\delta$ -Values					$J$ -Values								
	2CH <sub>3</sub>	5CH <sub>3</sub>	SH	3H	4H	3,4	3,SH	4,SH	2CH <sub>3</sub> ,SH	5CH <sub>3</sub> ,SH	4,5CH <sub>3</sub>	3,5CH <sub>3</sub>	2CH <sub>3</sub> ,5CH <sub>3</sub>	
1	<sup>a</sup> —	2.23	3.40	6.31	5.88	3.0	1.9	—	0.5 <sup>c</sup>	1.0 <sup>c</sup>	1.0	0.4 <sup>c</sup>	—	
2	<sup>a</sup> —	2.37	3.40	6.81	6.50	3.4	1.6	—	—	1.1	1.1	0.4	—	
3	<sup>a</sup> —	2.46	3.63	6.96	6.63	3.6	1.4	—	—	1.1	1.2	—	—	
7	<sup>b</sup> 2.20	2.14	2.49	—	5.74	—	—	—	1.2	—	0.9	—	0.5	
8	<sup>b</sup> 2.28	2.28	2.83	—	6.37	—	—	0.4	0.8	—	1.0	—	—	
9	<sup>b</sup> 2.37	2.36	2.88	—	6.53	—	—	0.4	0.8	—	1.1	—	0.7	

<sup>a</sup> Deuteriochloroform solution. <sup>b</sup> Carbon disulfide solution. <sup>c</sup> Obtained by decoupling experiments at 100 MHz.

The  $^1\text{H}$  NMR data of the thiols and their sulfide analogues are given in Tables 1 and 2, respectively. It can be seen that the chemical shifts as well as the coupling constants increase in the series furan < thiophene < selenophene. The only exceptions are the thiol *ortho* couplings in the two furan thiol systems,  $J_{3\text{S,H}}$  and  $J_{2\text{CH}_3,\text{SH}}$ , which are larger than those of the thiophene and selenophene derivatives.

The  $^1\text{H}$  NMR spectra of the potentially tautomeric thiols showed only the presence of the thiol tautomer. The same conclusion was reached from the IR spectra, which had absorptions in the region 2525–2545  $\text{cm}^{-1}$  characteristic for the thiol form. The spectral data support earlier conclusions reached from dipole moment measurements that the thiol form of the five-membered heterocyclic thiols predominates to more than 95%.<sup>14,15</sup> In potentially tautomeric hydroxy derivatives of five-membered heterocyclic compounds, how-

ever, the relative concentration of the hydroxy form may be small, and in some cases the hydroxy form is not seen by the usual spectroscopic techniques.<sup>3–5,16</sup> These findings agree with the general observation that in thione-enethiol tautomeric equilibria, a higher percentage of the enethiol tautomer will be present than of the enol in an analogous keto-enol system.<sup>17</sup> Furthermore, the physical data for the monothiated carboxylic acids favour the thiolcarboxylic acid rather than the thionocarboxylic acid structure.<sup>18</sup> As expected from the above results the thiol form of the heterocyclic thiols was found to predominate in the gas phase in the mass spectrometer by measurements of ionisation potentials (IP). From Table 3 it is seen that in both the 2- and 3-series the methylthio derivatives of furan and thiophene (4 and 5) and (10 and 11), respectively, have closely similar IP values whereas the values for the corresponding selenophenes

Table 2.  $^1\text{H}$  NMR parameters for 5-methyl-2-methylmercapto and 2,5-dimethyl-3-methylmercapto derivatives of furan, thiophene and selenophene at 60 MHz in deuteriochloroform solution.

	$\delta$ -Values					$J$ -Values				
	2CH <sub>3</sub>	5CH <sub>3</sub>	SCH <sub>3</sub>	3H	4H	3,4	4,5CH <sub>3</sub>	3,5CH <sub>3</sub>	4,2CH <sub>3</sub>	2CH <sub>3</sub> ,5CH <sub>3</sub>
4	—	2.25	2.32	6.28	5.90	3.0	1.0	0.4	—	—
5	—	2.37	2.35	6.81	6.50	3.4	1.1	0.4	—	—
6	—	2.46	2.40	6.93	6.65	3.6	1.2	—	—	—
10	2.26	2.20	2.21	—	6.24	—	0.8	—	0.4	0.6
11	2.36	2.35	2.28	—	6.58	—	1.0	—	—	0.5
12	2.48	2.44	2.29	—	6.79	—	1.2	—	—	—

**Table 3.** Ionisation potentials of 2-methyl-2-thiol, 2,5-dimethyl-3-thiol and the corresponding methylthio derivatives of furan, thiophene and selenophene.

Compound	IP $\pm$ 0.05 eV
1	8.45
2	8.48
3	8.17
4	8.15
5	8.13
6	7.84
7	8.23
8	8.22
9	7.90
10	7.91
11	7.96
12	7.73

(6 and 12) are 0.2–0.3 eV lower. These findings are in accordance with previous results obtained for the parent heterocycles and 3-methoxy derivatives.<sup>3,7</sup> The IP values for the thiols vary in the same manner as the IP values for the respective methylthio analogues and are *ca.* 0.3 eV higher. This difference is similar to that between thiophenol (8.93 eV) and thioanisol (8.60 eV), and between pyridine-3-thiol and 3-methylthio pyridine.<sup>20</sup> The IP values for the thione tautomers in the 2-series (*b* and *c*) and in the 3-series (*e*), or of model compounds thereof, are expected to vary significantly with the nature of the heteroatom.<sup>1,2</sup> Unfortunately, suitable compounds were not available for study, but the available data show that the thiol tautomers *a* and *d* are the predominant species in the gas phase. Their hydroxy analogues, however, are mainly present as lactones or ketones.<sup>1,2</sup> The difference in tautomeric preferences is another reflection of the relative tendencies of oxygen and sulfur for double bond formation.<sup>18</sup>

## EXPERIMENTAL

**General.** <sup>1</sup>H 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 gas chromatograph used was a Perkin-Elmer 900 analytical instrument. Mass spectra were obtained with an LKB 9000 mass spectrometer. The ionisation efficiency curves were recorded with an

AEI MS-902 mass spectrometer and the IPs obtained by the semilog-plot method as previously described,<sup>28</sup> with xenon as the reference gas. The reservoir and the connecting tubes were kept at 130 °C and the ion source at 230 °C. The IPs are the average of three determinations, the deviation being 0.05 eV. Elemental analyses were carried out at the Analytical Department at the Chemical Center, Lund, and by Dornis und Kolbe, Mikro-analytisches Laboratorium, Mülheim/Ruhr.

**5-Methyl-2-mercaptofuran, 1** (Procedure A). To a solution of 24.6 g (0.300 mol) of 2-methylfuran (Aldrich) in 250 ml of dry diethyl ether, 235 ml of 1.40 N butyllithium in hexane was added at such a rate that the reaction mixture was gently refluxing. When the addition was complete, the reaction mixture was refluxed for another 2.5 h, whereupon it was cooled to –70 °C and 9.6 g (0.30 mol) of sulfur was added in one portion. The reaction mixture was stirred for half an hour at –70 °C and then slowly warmed to –30 °C, whereupon it was hydrolyzed with 750 ml of water and ice. The phases were separated and the water phase was extracted twice with ether. The combined water phases were covered with ice and ether and acidified with one equivalent of cold 2 N hydrochloric acid. The ether phase was separated and the water phase extracted twice with ether. The combined ether phases were washed with water until neutral reaction and dried over magnesium sulfate. VPC analysis of the ether solution showed only one component. Upon distillation under nitrogen, 13.7 g (40 %) of 5-methyl-2-mercaptofuran was obtained, b.p. 43–44 °C/1.6 kPa,  $n_D^{20} = 1.5165$ , IR (film), SH = 2525 cm<sup>-1</sup>, for NMR data see Table 1. Anal. C<sub>5</sub>H<sub>6</sub>OS: C, H, M. Wt. 114.

**5-Methyl-2-mercapto thiophene, 2**, was prepared according to procedure A from 18.5 g (0.190 mol) of 2-methylthiophene, 135 ml of 1.40 N butyllithium and 6.1 g (0.190 mol) of sulfur, yielding 11.9 g (48 %) of the product, b.p. 72–73 °C/1.7 kPa,  $n_D^{20} = 1.5850$  (lit.<sup>5</sup> 64 °C/1.3 kPa,  $n_D^{20} = 1.5904$ ) IR (film): SH = 2525 cm<sup>-1</sup>, for NMR data see Table 1.

**5-Methyl-2-mercapto selenophene, 3**, was prepared according to procedure A from 11.8 g (0.040 mol) of 2-methylselenophene,<sup>21</sup> 65 ml of 1.40 N butyllithium and 2.9 g (0.090 mol) of sulfur, yielding 5.6 g (35 %) of the product, b.p. 93–94 °C/1.6 kPa,  $n_D^{20} = 1.6320$ . IR (film): SH = 2525 cm<sup>-1</sup>. For NMR data see Table 1. Anal. C<sub>5</sub>H<sub>6</sub>SSe: C, H, S, M.Wt. 178 (<sup>78</sup>Se).

**2,5-Dimethyl-3-mercaptofuran, 7**, (Procedure B). To a solution of 11.1 g (0.068 mol) of 2,5-dimethyl-3-iodofuran<sup>23</sup> in 75 ml of dry diethyl ether at –70 °C, 55 ml of 1.37 N butyllithium in hexane was added dropwise with stirring under nitrogen. 15 min after the addition was complete, 2.4 g (0.075 mol) of sulfur was added in one portion. The stirring was

continued at  $-70^{\circ}\text{C}$  for another 90 min, whereupon the temperature was raised to  $-15^{\circ}\text{C}$ , and the reaction mixture poured into 200 ml of cold water. The phases were separated and the ether phase extracted with small portions of cold 10% potassium hydroxide solution. The combined aqueous phases were acidified with cold dilute hydrochloric acid and immediately extracted with ether. The combined ether phases were washed with cold water and dried over magnesium sulfate. Distillation under nitrogen gave 4.5 g (78%) of the product, b.p.  $54-56^{\circ}\text{C}/1.6\text{ kPa}$ ,  $n_{\text{D}}^{20} = 1.5084$ . For NMR data see Table 1.

*2,5-Dimethyl-3-mercaptothiophene, 8*, was prepared according to procedure B from 17.0 g (0.071 mol) of 2,5-dimethyl-3-iodothiophene,<sup>24</sup> 55 ml of 1.34 N butyllithium and 2.4 g (0.075 mol) of sulfur, yielding 7.6 g (74%) of the product, b.p.  $80-82^{\circ}\text{C}/1.36\text{ kPa}$ ,  $n_{\text{D}}^{20} = 1.5776$  (lit.<sup>25</sup> b.p.  $95-96^{\circ}\text{C}/2.6\text{ kPa}$ ,  $n_{\text{D}}^{27} = 1.566$ ). For NMR data see Table 1.

*2,5-Dimethyl-3-mercaptoselenophene, 9*, was prepared according to procedure B from 20.0 g (0.700 mol) of 2,5-dimethyl-3-iodoselenophene,<sup>26</sup> 55 ml of 1.34 N butyllithium and 2.4 g (0.075 mol) of sulfur at  $-110^{\circ}\text{C}$ , yielding 4.0 g (30%) of the product, b.p.  $94-97^{\circ}\text{C}/1.3\text{ kPa}$ ,  $n_{\text{D}}^{20} = 1.6122$ . For NMR data see Table 1. Anal.  $\text{C}_8\text{H}_{10}\text{SSe}$ : C, H, Se. M.Wt. 192 (<sup>80</sup>Se).

*Alkylation of the 5-methyl-2-mercaptofuran system with methyl iodide* (Procedure C). A freshly prepared solution of 13.5 g (0.04 mol) of tetrabutylammonium hydrogen sulfate and 3.20 g (0.08 mol) of sodium hydroxide in 40 ml of water was added dropwise and with stirring to 4.55 (0.04 mol) of 5-methyl-2-mercaptofuran and 11.40 g (0.08 mol) of methyl iodide in 40 ml of chloroform at  $30^{\circ}\text{C}$ . The reaction mixture was stirred vigorously for another 10 min, whereupon the phases were separated and the water phase extracted with chloroform. When the combined organic phases were concentrated and the residue treated with diethyl ether, tetrabutylammonium iodide precipitated. After filtration, the filtrate was washed with water and dried over magnesium sulfate. Distillation under nitrogen gave 3.5 g (68%) of 5-methyl-2-methylthiofuran, 4, b.p.  $56-57^{\circ}\text{C}/1.6\text{ kPa}$ ,  $n_{\text{D}}^{20} = 1.5190$ . For NMR data see Table 2. Anal.  $\text{C}_6\text{H}_8\text{OS}$ : C, H. M.Wt 128.

*Alkylation of the 5-methyl-2-mercapto thiophene system with methyl iodide* was carried out according to procedure C, using 3.25 g (0.025 mol) of 5-methyl-2-thiophenethiol, 7.1 g (0.050 mol) of methyl iodide, 8.5 g (0.025 mol) of tetrabutylammonium hydrogen sulfate and 2.0 g (0.05 mol) of sodium hydroxide, to yield 2.6 g (72%) of 5-methyl-2-methyl-thiophene 5, b.p.  $83-84^{\circ}\text{C}/1.6\text{ kPa}$ ,  $n_{\text{D}}^{20} = 1.5785$  (lit.<sup>27</sup> b.p.  $76-77^{\circ}\text{C}/1.3\text{ kPa}$ ,  $n_{\text{D}}^{20} = 1.5785$ ). For NMR data see Table 2.

*Alkylation of the 5-methyl-2-mercaptoselenophene system with methyl iodide* was carried out according to procedure C, from 2.00 g (0.01

mol) of 5-methyl-2-mercaptoselenophene, 3.25 g (0.022 mol) of methyl iodide, 3.82 g (0.01 mol) of tetrabutylammonium hydrogen sulfate and 0.90 g (0.023 mol) of sodium hydroxide, yielding 1.3 g (60%) of 5-methyl-2-methylthio-selenophene, 6, b.p.  $100-102^{\circ}\text{C}/1.6\text{ kPa}$ ,  $n_{\text{D}}^{20} = 1.6140$ . For NMR data see Table 2. Anal.  $\text{C}_8\text{H}_8\text{SSe}$ : C, H, S. M.Wt 192 (<sup>80</sup>Se).

*Alkylation of the 2,5-dimethyl-3-mercaptofuran system with methyl iodide* was carried out according to procedure C, using 1.3 g (0.010 mol) of 2,5-dimethyl-3-mercaptofuran, 3.3 g (0.023 mol) of methyl iodide, 4.0 g (0.012 mol) of tetrabutylammonium hydrogen sulfate and 0.9 g (0.023 mol) of sodium hydroxide, to yield 0.9 g (63%) of 2,5-dimethyl-3-methylthiofuran, 10, b.p.  $62-64^{\circ}\text{C}/1.3\text{ kPa}$ ,  $n_{\text{D}}^{20} = 1.5057$ . For NMR data see Table 2. Anal.  $\text{C}_7\text{H}_{10}\text{OS}$ : C, H, S. M.Wt 142.

*Alkylation of the 2,5-dimethyl-3-mercaptofuran system with dimethyl sulfate* was carried out according to procedure C with a small modification in the work-up, using 1.3 g (0.010 mol) of 2,5-dimethyl-3-mercaptofuran, 3.1 g (2.3 ml, 0.025 mol) of dimethyl sulfate, 4.0 g (0.012 mol) of tetrabutylammonium hydrogen sulfate and 0.9 g (0.023 mol) of sodium hydroxide. Upon treatment with diethyl ether the ammonium salt forms an oily slurry, which was separated and the ether phase was worked up as described for procedure C, yielding 1.2 g (85%) of 2,5-dimethyl-3-methylthiofuran, 10, b.p.  $60-63^{\circ}\text{C}/1.5\text{ kPa}$ , identical with the compound described above.

*Alkylation of the 2,5-dimethyl-3-mercaptothiophene system with methyl iodide* was carried out according to procedure C, from 1.4 g (0.0097 mol) of 2,5-dimethyl-3-mercaptothiophene, 3.3 g (0.023 mol) of methyl iodide, 4.0 g (0.012 mol) of tetrabutylammonium hydrogen sulfate and 0.9 g (0.023 mol) of sodium hydroxide, yielding 0.7 g (45%) of 2,5-dimethyl-3-methylthiothiophene, 11, b.p.  $100-101^{\circ}\text{C}/1.7\text{ kPa}$ ,  $n_{\text{D}}^{23} = 1.1507$ . For NMR data see Table 2. Anal.  $\text{C}_7\text{H}_{10}\text{S}_2$ : C, H, S. M.Wt 158.

*Alkylation of the 2,5-dimethyl-3-mercaptoselenophene system with methyl iodide* was carried out according to procedure C, using 1.0 g (0.010 mol) of 2,5-dimethyl-3-mercaptoselenophene, 3.3 g (0.023 mol) of methyl iodide, 4.0 g (0.012 mol) of tetrabutylammonium hydrogen sulfate and 0.9 g (0.023 mol) of sodium hydroxide, to yield 1.1 g (55%) of 2,5-dimethyl-3-methylthioselenophene, 11, b.p.  $104-106^{\circ}\text{C}/1.3\text{ kPa}$ ,  $n_{\text{D}}^{20} = 1.6005$ . For NMR data see Table 2. Anal.  $\text{C}_7\text{H}_{10}\text{SSe}$ : C, H, Se. M.Wt 206 (<sup>80</sup>Se).

*Alkylation of the 2,5-dimethyl-3-mercaptoselenophene system with dimethyl sulfate* was carried out according to the modified procedure C described above for the furan system, using 1.2 g (0.0063 mol) of 2,5-dimethyl-3-mercaptoselenophene, 2.0 g (1.5 ml, 0.016 mol) of dimethyl sulfate, 2.5 g (0.0074 mol) of tetrabutylammonium hydrogen sulfate and 0.6 g (0.015 mol) of sodium hydroxide, to yield

0.7 g (54 %) of 2,5-dimethyl-3-methylthio-selenophene, 12, b.p. 104–106 °C/1.3 kPA, identical with the compound described above.

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