Reaction of 2-Bromo-3,5-dimethyl-4*H*-thiopyran-4-one with Nucleophiles. 1. Sodium Hydroxide and Sodium Methoxide

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The reaction of 2-bromo-3,5-dimethyl-4*H*-thiopyran-4-one (**1**) with hydroxide ion has been investigated. Conditions have been found whereby the hydroxide could either attack at C-2, with eventual replacement of the bromine and formation of a thiopyran-1,3-dione derivative (**3**; NaOH–MeOH–Me_2SO), or at C-6, with formation of a pyran-1,3-thiodione derivative (**5**; NaOH–H_2O–Me_2SO). Spectral and chemical evidence were used to assign structures to the above compounds and to the *O*-and *S*-methyl derivatives obtained by reaction with diazomethane. Pathways for these transformations are suggested.

4*H*-Thiopyran-4-ones and their 1,1-dioxides are products of theoretical and practical synthetic interest,[2,3] especially when carrying extra functionality.[4] Our finding of a way to directly produce a bromine-substituted thiopyrone, the title compound **1**,[5] provided us with a potential access to a series of other doubly functionalized thiopyran derivatives through possible substitution of the halogen. We have, therefore, initiated a study of the reactions of **1** with various nucleophiles in order to effect such substitutions. Compound **1** possesses, however, two almost equivalent sites for nucleophilic attack, namely, positions 2 and 6. While attack at C-2 may result in substitution of the bromine, probably via addition–elimination, an attack at C-6 may lead to an exchange of the 1 heteroatom through ring-opening processes.[6] The first type of interaction has been observed with sulfide ion, which produced the thioether **2**,[5] and with several other nucleophiles, such as sodium *p*-toluenesulfinate or sodium *N,N*-diethyldithiocarbamate, which led to substitution of the bromine.[7] Other nucleophiles were, however, observed to interact with **1** in both ways.

This work is concerned mainly with the reactions of **1** with hydroxide ion, where it has been possible to selectively control the direction of attack to the 2 or 6 position. The reactions of **1** with amines, where the conditions for selectivity are still under investigation, will be reported separately.

Treatment of **1** with excess sodium hydroxide in Me_2SO–methanol yielded, after acidification, the thiopyrandione derivative **3** (Scheme I). However, a dramatic change occurred when methanol was replaced by water, the major product being the pyranthiodione derivative **5**. Both **3** and **5** are isolated as the 2-one or 2-thione derivatives, respectively, although in solution a tautomeric equilibrium with the 4-one derivatives **4** and **6** is established.

The distinction between **3** and **5** is based on the NMR chemical shifts of the *O*- and *S*-methyl derivatives **7**, **8**, and **9** (Table II) obtained by reaction with diazomethane, which gives **7** and **8** from **3**[8] but only **9** from **5**. An *S*-methyl signal appears, in fact, at higher field than that of an *O*-methyl group by over 1 ppm.

The methoxy derivative **8** could also be directly obtained from **1** by reaction with sodium methoxide in methanol, accompanied by small amounts of **3**. It was then found that under the reaction conditions of the formation of **3** from **1** that **8** is quantitatively transformed into **3**, presumably through an addition–elimination sequence, as depicted in Scheme II.

This latter reaction suggested that the formation of **3** from **1** and hydroxide ion in the presence of methanol can result from two successive substitution reactions at C-2; the first substitution is that of the bromine by a methoxide ion, generated through the equilibrium $CH_3OH + NaOH \rightleftarrows CH_3ONa + H_2O$, and the second, that of the methoxide by the hy-

Scheme I

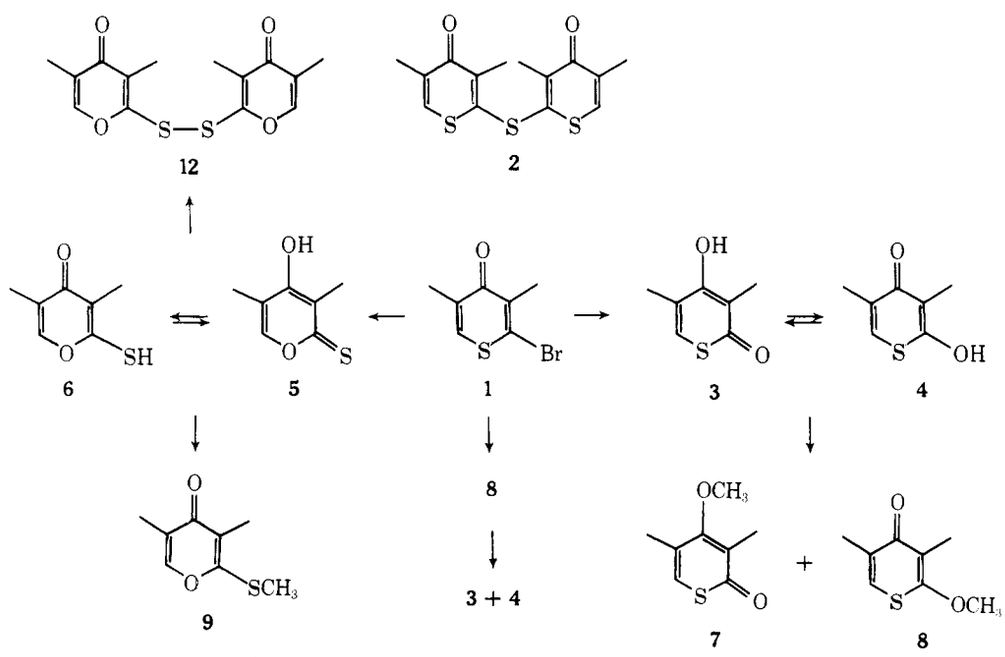

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Table I. UV Spectra of 2-Substituted 3,5-Dimethyl-4*H*-thiopyran-4-ones and Derivatives [a]

compd	registry no.	solvent	λ_{max}			
1 [b]	61170-10-3	EtOH		244 (9800)	297 (14 300) 304 (14 200)	
8	67844-81-9	isooctane	208 (13 500)	232 (7090)	289 (11 200)	
9	67844-82-0	isooctane	211 (14 300)	222 sh (8210)	275 (12 400)	
		EtOH	215 (17 000)	226 sh (11 100)	284 (13 900)	
12	67872-51-9	isooctane		223 (13 100)	257 (11 000)	
3	67844-83-1	isooctane		222 (8960) 227 (8960)		324 (1350)
		EtOH		231 (22 100) 243 sh (9700)	273 (3300) 291 (3920)	321 (4990)
5	67844-84-2	EtOH [c]	216 (10 300)	241 (15 600)	272 sh (3220)	324 (10 800)
7	67844-85-3	isooctane		224 (15 800)		332 (3080)

[a] λ is expressed in nm. Extinction coefficients are given in parentheses. [b] Reference 5. [c] Compound **5** was not soluble in isooctane.

Table II. Melting Points and NMR Chemical Shifts (δ) of 2-Substituted 3,5-Dimethyl-4*H*-thiopyran-4-ones and Derivatives

compd	mp, °C	vinyl H	OH	OCH_3 or SCH_3	3,5-dimethyl
1	91–92	7.27			2.27, 2.11
3	129–130	7.03	6.00 (brd, variable)		2.17, 2.07
5	123–126	7.55	6.16 (brd, variable)		2.18, 2.00
7	64–65	7.00		3.75	2.20, 2.10
8	80–81	7.23		3.97	2.16, 2.10
9	59–60	7.56		2.50	2.00, 1.97
12	173–174	7.57			2.13, 1.95

droxide, is as shown already in Scheme II. The hydroxide ion is thus predominantly converted first to a more nucleophilic methoxide ion which may react reversibly at C-6, but only irreversibly at C-2, to yield **8** (Scheme III).

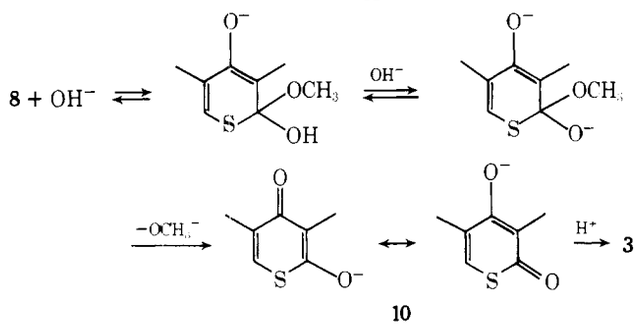
In the absence of methanol and for reasons that we cannot point out at the moment, the hydroxide ion adds preferentially at C-6, and the events leading to **5** may follow the course shown in Scheme IV. Here again two addition–elimination processes occur, the second being intramolecular. Alternatively, an elimination–addition with formation of a thioketene (**11**) may be involved at a second stage.

The two groups of compounds encountered here, namely, the 4-one and the 2-one or 2-thione derivatives, differ in their UV spectral properties. The difference is most easily seen (Table I) by comparing the longest wavelength absorption maxima, which for the **3, 5, 7,** and **1, 8, 9** series are above 320 nm and below 305 nm, respectively. This allowed us an assignment of structure, especially to compounds **3** and **5**, an approach that has been described and used before in related systems.[4a,8-10]

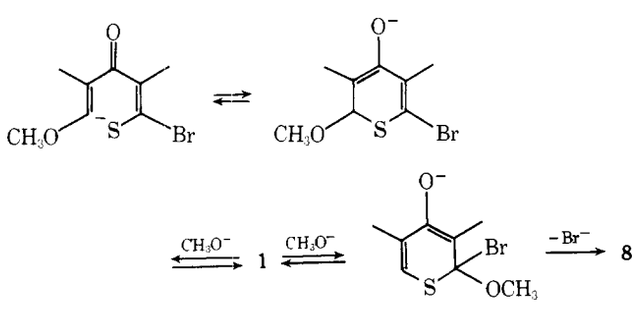
The appearance of an intermediate absorption maximum in ethanolic solutions of **3** and **5** appears to indicate the establishment of the tautomeric equilibria **3** ⇄ **4** and **5** ⇄ **6**. The latter equilibrium is also evidenced by the slow formation of disulfide **12** from solutions of **5**. The reaction presumably involves tautomerization to **6**, followed by air oxidation.

Compounds **3** and **5** differ greatly in the results of their methylation with diazomethane; **3** yields, as mentioned above, both *O*-methyl derivatives **7** and **8** while **5** yields only the *S*-methyl derivative **9**. The reaction is assumed to proceed in both cases by abstraction of a proton by the diazomethane,[11] producing **10** from **3** (or the analogous anion from **5**) and a

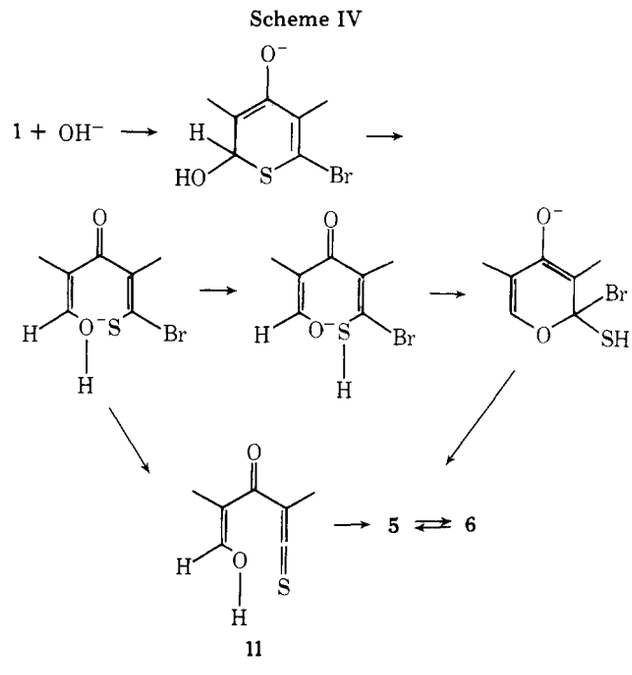
Scheme II



Scheme III



Scheme IV



Scheme V

$$^{-}CH_2—^{+}N{\equiv}N + 3 \rightarrow CH_3—^{+}N_2 + 10 \rightarrow 7 + 8$$

methyldiazonium cation (Scheme V). An S_N2 reaction of the latter with **10** at either oxygen affords the observed products. However, of the nucleophilic centers in the anion derived from **5**, the most effective is sulfur;[12] hence, attack of the methyldiazonium cation occurs at this site. Also, **9** can be inferred to be more stable than the corresponding *O*-methyl derivative, based on comparison with analogous structures.[13]

Like compound **1**, the sulfide **2** can be viewed as carrying a good leaving group in the form of a thiolate anion carried by one of the rings. Indeed, we have observed compound **2** to cleave readily with nucleophiles. These reactions, as well as other reactions of **1**, are being studied further.

Experimental Section

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. NMR spectra (Table II) were recorded in $CDCl_3$ on a Varian T-60 spectrometer with Me_4Si as an internal standard. All signals appeared as singlets or broadened singlets. Mass spectra were obtained on a MAT 731 spectrometer. Ultraviolet spectra (Table I) were recorded on a Cary 118 spectrophotometer. Infrared spectra were determined in 5–10% chloroform solutions on a Perkin-Elmer 457A grating spectrometer. Elemental analyses were performed by Mr. Raoul Heller of The Weizmann Institute of Science, Microanalytical Laboratory. TLC was done on Merck Kieselgel 60-F254 precoated aluminum plates. The adsorbent for column chromatography was Merck Kieselgel 60, 70–230 mesh.

4-Hydroxy-3,5-dimethyl-2*H*-thiopyran-2-one (3). The bromide **1** (499 mg, 2.28 mmol) was added to a mixture of sodium hydroxide (325 mg, 8.12 mmol) in 9 mL of dry Me_2SO and 5 mL of methanol. No effort was made to dry the methanol. After heating with stirring at 100 °C for 19 h, the brown mixture was cooled, diluted with water to 100 mL, and extracted with ethyl ether (3 × 15 mL). Evaporation of the water-washed and dried (Na_2SO_4) extract yielded only a trace of **1**. The basic, aqueous phase was acidified with 1 mL of 12 M hydrochloric acid and extracted with ethyl ether (4 × 20 mL). The combined extracts were washed with water (1 × 10 mL) and dried (Na_2SO_4). Removal of the solvent at reduced pressure yielded 307 mg of a brown solid which on TLC displayed only one spot beyond the origin. Chromatography on 15 g of silica gel with ethyl ether as the eluant afforded 268 mg (75%) of an off-white solid, mp 128–130 °C. An analytical sample was obtained by sublimation at 1 torr at a bath temperature of 120 °C: mass spectrum, *m/e* 156 (M^+); IR 3580 (OH), 3330 (OH), 1611 (C=O), 1580 (C=C), 1532, 1200, 1032 cm^{-1}. Anal. Calcd for $C_7H_8O_2S$: C, 53.83; H, 5.16. Found: C, 54.14; H, 5.28.

4-Hydroxy-3,5-dimethyl-2*H*-pyran-2-thione (5) and Bis[3,5-dimethyl-4*H*-pyran-4-one] 2-Disulfide (12). A solution of **1** (549 mg, 2.52 mmol) in 10 mL of Me_2SO was added to 15.5 mL of water containing NaOH[14] (218 mg, 5.45 mmol), and the resulting mixture was heated with stirring at 102 °C for 18 h. The yellow solution was then worked up as in the preparation of **3**. No more than a trace of unreacted **1** was recovered. Acidification of the basic aqueous fraction produced an intense yellow color. Evaporation of the ether extracts in vacuo afforded 277 mg of a deep yellow oil that solidified on standing. TLC showed the presence of one major component. Several recrystallizations from an ethyl acetate–hexane mixture gave a few milligrams of a yellow solid, mp 123–126 °C, shown by TLC to be slightly contaminated by **12**: mass spectrum, *m/e* 156 (M^+); IR 3350 (OH), 2580 (SH, weak), 1642 (C=O), 1605, 1080 (COC) cm^{-1}. Anal. Calcd for $C_7H_8O_2S$: C, 53.83; H, 5.16. Found: C, 53.31; H, 5.52.

On standing, the filtrates from recrystallization of **5** deposited a white solid (**12**) that was recrystallized from the same solvent mixture: mp 173–174 °C; mass spectrum, *m/e* 310 (M^+); IR 1640 (C=O), 1611 (C=C) cm^{-1}. Anal. Calcd for $C_{14}H_{14}O_4S_2$: C, 54.18; H, 4.55. Found: C, 53.66; H, 4.53.

4-Methoxy-3,5-dimethyl-2*H*-thiopyran-2-one (7) and 2-Methoxy-3,5-dimethyl-4*H*-thiopyran-4-one (8). To a stirred solution of **3** (238 mg, 1.53 mmol) in 15 mL of ether was added in small portions a large excess of ethereal diazomethane. After 2 h the solvent was evaporated, giving an oil that solidified on standing. The NMR spectrum of this mixture showed two methoxyl peaks at δ 3.72 and 3.93 in a 1:2 ratio. Chromatography of the mixture on 20 g of adsorbent with the eluant 4:1 ether–hexane yielded in fractions 7–9 75 mg of the white solid **7**, mp 63–64 °C. Sublimation at reduced pressure gave an analytical sample: mass spectrum, *m/e* 170 (M^+); IR 1614 (C=O), 1585 (C=C), 1155 cm^{-1}. Anal. Calcd for $C_8H_{10}O_2S$: C, 56.45; H, 5.92. Found: C, 56.80; H, 6.10.

Fractions 17–23 furnished 151 mg of the white solid **8**, mp 79–80 °C, purified in part by sublimation at reduced pressure: mass spectrum, *m/e* 170 (M^+); IR 1593 (C=O), 1548 (C=C), 1230 (C–O), 1160 cm^{-1}. Anal. Calcd for $C_8H_{10}O_2S$: C, 56.45; H, 5.92. Found: C, 56.26; H, 5.91.

2-Methylthio-3,5-dimethyl-4*H*-pyran-4-one (9). To a stirred ether solution of 300 mg of the product mixture from the reaction of **1** with hydroxide ion in aqueous Me_2SO, containing mainly **5**, was added in small portions an excess of ethereal diazomethane. TLC showed that all of **5** had reacted. Chromatography of 281 mg on 30 g of silica gel, on elution with 2:1 ether–hexane, gave 186 mg of white solid **9** that was recrystallized from hexane: mass spectrum, *m/e* 170 (M^+); IR 1648 (C=O), 1605 (C=C), 1260 (C–S), 1178 cm^{-1}. Anal. Calcd for $C_8H_{10}O_2S$: C, 56.45; H, 5.92. Found: C, 56.45; H, 6.14. Another 75 mg was distributed in five other small fractions, of which only **12** was identified.

Reaction of 1 with Sodium Methoxide in Methanol. Formation of 8 and 3. To a solution of sodium methoxide in 10 mL of methanol (prepared by dissolving 143 mg (6.22 mmol) of sodium in methanol) was added **1** (340 mg, 1.55 mmol). After heating at reflux for 18 h, the mixture was cooled, concentrated at reduced pressure, diluted with water, and extracted with methylene chloride (4 × 10 mL). The combined extracts were washed with water and dried (Na_2SO_4). Evaporation of the solvent in vacuo gave 132 mg (52%) of **8**, identified by its NMR spectrum. The basic, aqueous phase was acidified with 1 mL of 12 M hydrochloric acid and extracted with methylene chloride (4 × 10 mL). Workup of the extracts as above gave 85 mg of a yellow oil that became solid. Recrystallization from benzene yielded a white solid, mp 126–129 °C, whose NMR spectrum was that of **3**. When the methanol was dried over and distilled from magnesium methoxide, **8** was obtained in 57% yield and the formation of **3** was suppressed. However, acidification of the basic solution yielded lesser amounts of a yellow oil that gave several spots on TLC and whose NMR spectrum may indicate addition products to **1**. These materials were not examined further.

Reaction of 8 with Potassium Hydroxide in Methanol–Me_2SO. A solution of **8** (98 mg, 0.58 mmol) and potassium hydroxide (106 mg, 1.89 mmol) in 5 mL of dried Me_2SO and 5 mL of untreated methanol was heated at 110 °C for 19 h. After cooling, the yellow solution was poured into 100 mL of water and worked up as described for the conversion of **1** to **3**. Evaporation of the extracting solvent gave 81 mg (90%) of a yellow-white solid, mp 127–129 °C, whose IR spectrum was identical with that of **3**.

Registry No.—Diazomethane, 334-88-3; sodium methoxide, 124-41-4; sodium hydroxide, 1310-73-2.

References and Notes

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(7) Unpublished observations in this laboratory.
(8) For a reaction of diazomethane with the structurally related 3,5-dimethyl-4-hydroxy-2*H*-pyran-2-one, yielding a mixture of 3,5-dimethyl-2-methoxy-4*H*-pyran-4-one and 3,5-dimethyl-4-methoxy-2*H*-pyran-2-one, see E. Niccoli, U. Vaglini, and G. Ceccarelli, *Ann. Chim.*, **58**, 664 (1968).
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