General Procedure for the Preparation of 3-(1-Methyl-2-pyridylimino)-3H-[1,2,4]thiadiazolo[4,3-*a*]pyridinium Iodides.—A 1:1 mixture of the above bases and CH_3I was refluxed in chloroform. The salt crystallized from the hot reaction mixture and, on recrystallization from ethanol, gave the products described in Table III.

Bromination of 3-(2-Pyridylimino)-3H-[1,2,4]thiadiazolo-[4,3-*a*]pyridines.—The fused-ring system (0.02 mol) in glacial acetic acid (200 ml) was stirred at room temperature while a solution of Br_2 (0.02 mol) in glacial acetic acid (10 ml) was added slowly. An immediate reaction occurred and the reaction mixture was heated at 100° for 1 hr during which time it became a bright yellow color. The reaction mixture was poured over ice and the precipitate recrystallized from acetone.

Registry No.—1, 24097-57-2; 2, 24097-94-7; 3, 24097-95-8; 4, 24097-96-9; 4 (perchlorate), 24097-74-3; 5, 24162-35-4; 6, 24097-97-0; 7, 24097-98-1; 8, 24097-99-2; 9, 24162-36-5; 10, 24097-58-3; 11, 24097-59-4; 12, 24097-60-7.

Thiapyrone Chemistry. III.[1] The Reaction of 2,6-Dimethylthio-3,5-diphenylthiapyrone with Hydroxide Ion

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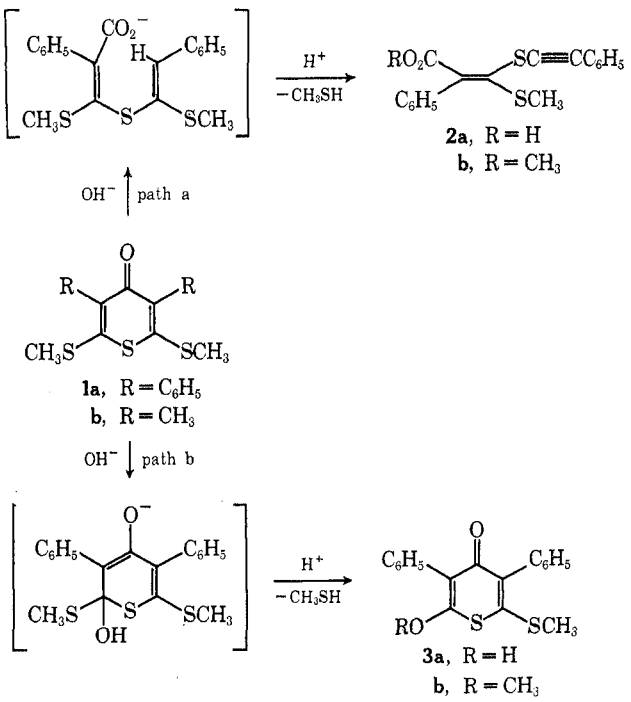
The reaction of 2,6-dimethylthio-3,5-diphenylthiapyrone (**1a**) with hydroxide ion has been reinvestigated. The major product of the reaction is shown to be the hydroxythiapyrone **3a**, which on treatment with diazomethane gives the isomeric enol ethers **3b** and **4b**. Spectral and chemical evidence used to support these conclusions are discussed.

In the course of our studies on the chemistry of thiapyrones, we have had occasion to reinvestigate the reaction of 2,6-dimethylthio-3,5-diphenylthiapyrone (**1a**) with hydroxide ion. Schönberg and Asker[2] described this reaction as leading to the complex thio ether **2a** *via* ring cleavage followed by the acid-catalyzed elimination of methanethiol. This sequence is indicated in path a. However, the only evidence offered in support of the assigned structure was an elemental analysis and demonstration of the acidic character of the product by its solubility properties and its reaction with diazomethane to form the "ester" **2b**.

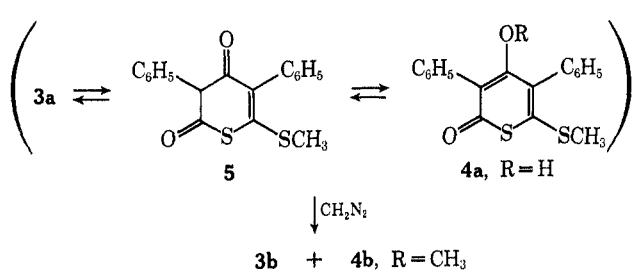


Our investigation of this reaction has revealed that the product is not **2a** but rather is the thiapyrone derivative **3a**, existing in solution in equilibrium with its tautomeric forms **4a** and **5**. When treated with diazomethane, this mixture produces the isomeric enol ethers **3b** and **4b**. The structural assignments of these products based on chemical and spectroscopic data are the subject of this report.

Results and Discussion

2-Methylthio-3,5-diphenyl-6-hydroxy-4-thiapyrone (**3a**) is produced in 38% yield by treatment of **1a** with alcoholic potassium hydroxide by the procedure described by Schönberg.[2] Path b, involving a Michael addition of hydroxide ion to **1a** followed by acidification and consequent elimination of methanethiol, suggests a possible route for its formation. This yellow crystalline material has the same melting point and other properties previously attributed to the incorrectly assigned structure **2a**.[2]

A key to the characterization of the acidic thiapyrone **3a** was its reaction with diazomethane. Since it seemed likely that **3a** should also exist as **4a**,[3] both tautomeric forms of the parent thia-2,4-pyrone **5**, methylation of



the tautomeric mixture was expected to produce the isomeric enol ethers **3b** and **4b**.[4] Careful chromatographic separation of the total reaction mixture afforded

(1) Paper II of this series: H. J. Teague and W. P. Tucker, *J. Org. Chem.*, **32**, 3144 (1967).

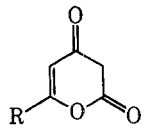
(2) A. Schönberg and W. Asker, *J. Chem. Soc.*, 604 (1946).

(3) The yellow hydrolysis product probably exists mainly as tautomer **4a** in both the solid state and in solution. Its visible absorption maximum (370 mμ) closely resembles that (380 mμ) of the α-thiapyrone ether **4b** (Table I).

(4) D. Herbert, W. B. Mors, O. R. Gottlieb, and C. Djerassi, *J. Amer. Chem. Soc.*, **81**, 2427 (1959).

these isomers, one (**3b**) as white crystals, mp 156–158°, in 19% yield, and the other (**4b**) as a bright yellow solid, mp 151–153°, in 75% yield. This second product is the only one obtained when the work-up procedure described by Schönberg is employed, and is the product to which he assigned structure **2b**.[2]

Our assignment of structures to the products is based largely on a study of the ultraviolet–visible absorption spectra of these and similar compounds and on their nuclear magnetic resonance spectra. Djerassi and coworkers[4] have demonstrated that electronic absorption spectra can be used in distinguishing between the enol ethers produced by methylation of 2,4-pyrones **6** showing that the isomer with the longer wavelength absorption maximum represents the 2-pyrone derivative, **7b**.[5] Table I gives the ultraviolet–visible maxima of



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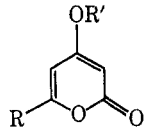
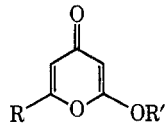


7a, R′ = H
b, R′ = CH_3



8a, R′ = H
b, R′ = CH_3

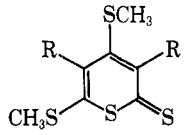
TABLE I

SPECTRAL PROPERTIES OF PYRONES AND THIAPYRONES

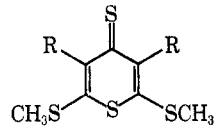
Compound	Uv–visible,[a,b] λ_{max}, mμ (log ε)	Pmr, δ[c] 2(6)-CH_3	Pmr, δ[c] 4-CH_3
1a	280 (4.23)	2.40	
1b	285 (3.69)	(2.46, 2.22)[d]	
3a	370 (3.87)	2.41	
3b	275 (4.07)	2.40 (3.82)	
4b	380 (3.96)	2.44	3.00
7b, R = CH_3	280 (3.80)[e]		
7b, R = C_6H_5	314 (4.13)[e]		
8b, R = CH_3	240 (4.13)[e]		
8b, R = C_6H_5	276 (4.29)[e]		
9a	498 (3.57)	(2.33, 2.52, 2.59, 2.72)[d]	
9b	500 (4.61)[f]	2.49	1.51
10a	405 (4.19)	(2.54, 2.62)[d]	
10b	408 (4.33)[f]	2.47	
11	480	2.52	2.98

[a] Ethanol solutions. [b] Longest wavelength absorption maxima. [c] Deuteriochloroform solvent with internal tetramethylsilane. [d] Rigorous assignment of these signals was not made. [e] These are only several of the examples given in ref 4. [f] Reference 7.

longest wavelength for a number of structurally similar pyrones and thiapyrones. Compounds **3b** and **4b**, as well as the previously reported thiothiapyrones **9b** and **10b**,[6] show the same correlation of structure with visible



9a, R = CH_3
b, R = C_6H_5



10a, R = CH_3
b, R = C_6H_5

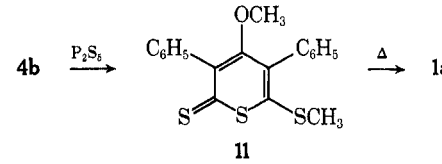
absorption as those studied by Djerassi.[4,7] Based on these data, the isomer with the longer wavelength absorption maximum is assigned structure **4b**. The similarity of the ultraviolet spectra of thiapyrones **1a** (λ_{max} 280 mμ), **1b** (λ_{max} 285 mμ), and **3b** (λ_{max} 275 mμ) reflects their structural resemblance.

It is interesting to note that the position of the absorption band of longest wavelength of the thiapyrones in Table I is not appreciably altered by substitution of methyl for phenyl in the 3 and 5 positions. (Compare for example, **1a** and **1b**, **9a** and **9b**, and **10a** and **10b**.) An examination of models indicates that the phenyl substituents cannot gain coplanarity with the heterocyclic ring and indeed must remain nearly perpendicular to it. Consequently, conjugation is minimized and its effect on the absorption spectra is very small.

The assignments of structures **3b** and **4b** are supported by the nmr data given in Table I. The presence of phenyl substituents in the 3 and 5 positions of the thiapyrones causes a marked difference in the chemical shifts of the protons of the adjacent S–CH_3 or O–CH_3 groups. The nmr spectra of a number of thiapyrones showed that the S–CH_3 group in the 2 position absorbs at *ca.* 2.4–2.5 ppm. However, when the S–CH_3 group is located in the 4 position and is flanked by phenyl substituents (as in **9b**) the methyl signal is shifted upfield by almost 1 ppm. A study of models shows that such an effect is to be expected in these compounds. Substituents in the 4 position are forced to remain above the plane of the phenyl rings where they are shielded because of the ring current effect.[8] In isomers **9a** and **10a**, which contain no phenyl substituents, little difference in the chemical shifts of the various methyl groups was observed.

The enol ethers produced by methylation of **3a** also exhibited a sharp difference in the chemical shifts of the O–CH_3 groups. In both isomers the absorption of O–CH_3 is lower than the corresponding S–CH_3 groups; however, in **4b**, the O–CH_3 group is shielded nearly 0.8 ppm more than that in **3b**. That this difference in O–CH_3 absorption is due to the ring currents of the phenyl substituents is borne out by an examination of models. The O–CH_3 group in the 4 position is shielded by the phenyl substituents to a greater degree than that in the 2 position. Thus, the nmr data support the assignments for **3b** and **4b** made on the basis of the ultraviolet–visible absorption data.

In an effort to distinguish chemically between **3b** and **4b**, **4b** was allowed to react with phosphorus pentasulfide in refluxing dioxane to produce the thiothiapyrone **11**. Heating **11** to the melting point (150°) resulted in



11

rearrangement to compound **1a**, the thiapyrone which was originally treated with hydroxide ion. Similar thion–thiol rearrangements have been previously studied.[7] This sequence of reactions confirms the structural assignments of the enol ethers. It seems unlikely that isomer **3b** could provide such a result since extensive rearrangement of atoms would be required.

(5) Infrared spectra can also be used to distinguish between these derivatives (ref 4) but are not sufficiently different for the thiapyrones to be useful in the present investigation.

(6) H. J. Teague and W. P. Tucker, *J. Org. Chem.*, **32**, 3140 (1967).

(7) Other examples illustrating this correlation and a theoretical discussion of it are found in a review by R. Mayer, W. Broy, and R. Zahradnik, *Advan. Heterocycl. Chem.* **8**, 247 (1967).

(8) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y. 1959, Chapter 7.

Experimental Section[9]

2,6-Dimethylthio-3,5-diphenyl-4-thiapyrone (1a).—The preparation of this compound is described in ref 6.

2,6-Dimethylthio-3,5-dimethyl-4-thiapyrone (1b).—This compound was prepared in 67% yield by the method of Apitzsch,[10] mp 122–123° (lit.[10] 123°).

2-Methylthio-3,5-diphenyl-6-hydroxy-4-thiapyrone (3a).—As described by Schönberg,[2] a solution containing 2.0 g of 1a and 3.0 g of potassium hydroxide in 60 ml of ethanol was refluxed for 1 hr. The solution was acidified with dilute hydrochloric acid and allowed to stand for 1 day. The product which precipitated was collected and dried. Recrystallization from benzene afforded 0.35 g (38.5%) of 3a as pale yellow crystals, mp 198–200° (lit.[2] 200°).

Anal. Calcd for $C_{18}H_{14}O_2S_2$: C, 66.23; H, 4.32; S, 19.65. Found: C, 66.44; H, 4.32; S, 19.40.

Methylation of 3a.—Compound 3a (115.0 mg, 0.353 mmol) was added to a cold solution of diazomethane in ether and the solution maintained at 0° for 24 hr. Slow evolution of nitrogen was noted during this time. Removal of the solvent left a bright yellow residue. This residue contained two compounds and was separated by preparative thin layer chromatography (ptlc) (silica gel H with chloroform as developer). The faster moving band was yellow and yielded 90.2 mg (75%) of 2-methylthio-3,5-diphenyl-4-methoxy-2-thiapyrone (4b); recrystallization from heptane gave bright yellow crystals, mp 151–153° (lit.[2] 153°).

Anal. Calcd for $C_{19}H_{16}O_2S_2$: C, 67.01; H, 4.72; nuclidic mass, 340.0591. Found: C, 66.95; H, 4.61; nuclidic mass, 340.0597.

A second homogenous fraction, colorless, was removed from the silica gel and yielded 22.2 mg (18.5%) of 2-methylthio-3,5-diphenyl-6-methoxy-4-thiapyrone (3b); recrystallization from acetonitrile gave white needles, mp 156–158°.

Anal. Calcd for $C_{19}H_{16}O_2S_2$: C, 67.01; H, 4.72; nuclidic mass, 340.0591. Found: C, 66.86; H, 4.90; nuclidic mass, 340.0597.

2,6-Dimethylthio-3,5-dimethyl-4-thiothiapyrone (10a).—This compound was prepared from 1b by the general procedure previously reported.[6] It was obtained in nearly quantitative yield; recrystallization from acetonitrile yielded bright red needles, mp 176–178°.

Anal. Calcd for $C_9H_{12}S_4$: C, 43.51; H, 4.87. Found: C, 43.25; H, 4.81.

2,4-Dimethylthio-3,5-dimethyl-6-thiothiapyrone (9a).—The preparation of this compound also followed the general procedure reported earlier.[6] In contrast to the thiapyrone derivatives with phenyl groups in the 3 and 5 positions, 9a and 10a possessed nearly identical R_f values in several solvent systems (chloroform, chloroform–hexane, benzene) making purification by ptlc more difficult. Purification was accomplished using silica gel H with ethyl acetate as developer. The 2-thiapyrone isomer (9a) moved slightly ahead of the 4 isomer (10a) and could be isolated in pure form by removing the top portion of the band (that portion which was homogenous in 9a). Recrystallization from hexane yielded a red solid, mp 88–90°.

Anal. Calcd for $C_9H_{12}S_4$: C, 43.51; H, 4.87. Found: C, 43.40; H, 4.90.

2-Methylthio-4-methoxy-3,5-diphenyl-6-thiothiapyrone (11).—A solution of 100 mg of 4b and 90 mg of phosphorus pentasulfide in 30 ml of *p*-dioxane was gently refluxed. The progress of the reaction was followed by tlc (silica gel H–chloroform) and the reaction was continued until all starting material disappeared or until more than one product appeared. The solvent was removed *in vacuo* and the reaction mixture leached with chloroform. This solution was concentrated and the products were separated by ptlc (aluminum oxide G–ethyl acetate) yielding approximately 60 mg (57%) of 11. Recrystallization from methylene chloride–hexane gave red crystals, mp 150–152°.

Anal. Calcd for $C_{19}H_{16}OS_3$: C, 64.00; H, 4.50; S, 27.00; nuclidic mass, 356.0363. Found: C, 63.89; H, 4.39; S, 26.90; nuclidic mass, 356.0352.

Thermal Rearrangement of 11.—Under nitrogen, 50 mg of 11 was heated at 150° for 30 min; some decomposition was evidenced by a foul odor and by evolution of a colored gas. After this time analysis by tlc (silica gel H–chloroform) indicated that nearly all the red starting material had disappeared. The majority of the residue was an almost colorless material; small amounts of other compounds also appeared. The major component (80%) was isolated by ptlc (silica gel H–chloroform). Recrystallization from ethyl acetate yielded light yellow crystals, mp 163–165°, which proved to be 1a. The identity of this product and 1a was confirmed by tlc (many different solvents systems) and mixture melting point, 163–165°, and verified by identical ir spectra.

Registry No.—1a, 24097-29-8; 1b, 24215-64-3; 3a, 24097-30-1; 3b, 24097-31-2; 4b, 24097-32-3; 7b (R = CH_3), 672-89-9; 7b (R = C_6H_5, 4225-45-0; 8b, (R = CH_3), 4225-42-7; 8b, (R = C_6H_5), 4225-43-8; 9a, 24097-37-8; 9b, 24162-38-7; 10a, 24162-39-8; 10b, 14172-81-7; 11, 24097-39-0; hydroxide ion, 14280-30-9.

Acknowledgment.—We wish to thank the National Science Foundation for a research grant (GP-7460) partially supporting these studies. We also thank Dr. David Rosenthal of the Research Triangle Center for Mass Spectrometry for the mass spectral analyses.

(9) Melting points were taken on a Thomas–Hoover melting point apparatus and are uncorrected. Ultraviolet and visible spectra were measured in ethanol on a Beckman Model DK-2 spectrophotometer. The nmr spectra were determined in deuteriochloroform on a Varian HA-100 spectrometer and are reported in parts per million downfield from tetramethylsilane internal standard. Pertinent spectral data are included in Table I. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. High resolution mass spectral analyses were obtained on an Associated Electrical Industries MS-902 instrument. The absorbants used in thin layer chromatography separations were products of E. Merck (West Germany).

(10) H. Apitzsch, *Chem. Ber.*, **38**, 2888 (1905).