3,4-Dihydro-2-isopropylidene-3-oxo-2*H*-1,4-benzothiazine (5b). To a stirred solution of **3a** (4.5 g, 0.015 mol) and 10 ml of acetone in 20 ml of methanol was added 7.5 ml of a 2.0 *N* sodium methoxide solution. The solution was stirred for 48 hr. The mixture was then diluted with 5 ml of water and subsequently filtered to obtain 2.0 g (65%) of white product: mp 217–219° (lit.[13c] mp 213–215°); NMR (DMSO-d_6) δ 7.42–6.84 (complex, 4), 2.22 (s, 3), and 2.05 (s, 3).

Registry No.—**1a,** 5325-20-2; **1b,** 37142-87-3; **1c,** 6376-75-6; **2a,** 55043-49-7; **2b,** 55043-50-0; **2c,** 55043-32-8; **3a,** 55043-33-9; **3b,** 55043-34-0; **3c,** 55043-35-1; **4a,** 55043-20-4; **4b,** 55043-21-5; **4c,** 55043-22-6; **4d,** 55043-23-7; **4e,** 55043-24-8; **4f,** 55043-25-9; **4g,** 55043-26-0; **4h,** 55043-27-1; **4i,** 55043-28-2; **4j,** 55043-29-3; **4k,** 55043-30-6; **4l,** 55043-31-7; **4m,** 55043-51-1; **5a,** 55043-52-2; **5b,** 55043-53-3; SO_2Cl_2, 7791-25-5; $P(OEt)_3$, 122-52-1; methyl iodide, 74-88-4; ethyl bromoacetate, 105-36-2; benzaldehyde, 100-52-7; *p*-methylbenzaldehyde, 104-87-0; 3,4-methylenedioxybenzaldehyde, 120-57-0; 2-thiophenecarboxaldehyde, 98-03-3; formaldehyde, 50-00-0; *p*-methoxybenzaldehyde, 123-11-5; *m*-trifluoromethylbenzaldehyde, 454-89-7; *o*-fluorobenzaldehyde, 446-52-6; *o*-nitrobenzaldehyde, 552-89-6; 9-anthracenecarboxaldehyde, 642-31-9; cinnamaldehyde, 104-55-2; acetone, 67-64-1; diethyl ketomalonate, 609-09-6.

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$$PhSCHClCONEt_2 + P(OEt)_3 \longrightarrow PhSCH(PO_3Et_2)CONEt_2 + PhSPO_3Et_2 + Et_2O_3PCH_2CONEt_2$$
i ii iii

are secondary products derived from attack of triethyl phosphite on thioether sulfur of the primary product i. Such a process would be less favored in the benzothiazinone system since there it would require opening of the ring.
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Benzopyranopyridine Derivatives. 2. Reaction of Azaxanthones with Hydroxylamine[1]

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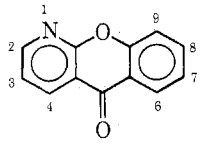
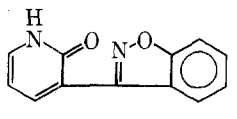
5*H*-[1]Benzopyrano[2,3-*b*]pyridin-5-one, referred to throughout this series as 1-azaxanthone (**1**), reacted in an anomalous manner with an alcoholic KOH solution of $HONH_2$·HCl to give a mixture of 3-(2-1*H*-pyridinon-3-yl)-1,2-benzisoxazole (**2**) and 3-*o*-hydroxyphenyl(2-1*H*-pyridinon-3-yl) ketoxime (**3**). The structure of **2** was established by the usual spectral analyses as well as total synthesis from 3-*o*-chlorobenzoylpyridine. It was shown that **3** is not the intermediate necessary for the formation of **2** and that **2** is formed by a direct attack of the $HONH_2$ anion on 1-azaxanthone.

5*H*-[1]Benzopyrano[2,3-*b*]pyridin-5-one, **1**, referred to throughout this series as 1-azaxanthone,[2] failed to form an oxime under the usual conditions, i.e., $HONH_2$·HCl in pyridine and EtOH. In contrast, the 2- and 4-azaxanthones were readily converted into oximes.



1

Under forcing conditions,[3] excess KOH in EtOH, ketone-**1** reacted with $HONH_2$·HCl to give a mixture of two products, 3-(2-1*H*-pyridinon-3-yl)-1,2-benzisoxazole (**2**) and 3-*o*-hydroxyphenyl-(2-1*H*-pyridinon-3-yl) ketoxime (**3**). These compounds were separated by column chromatography on silica gel.



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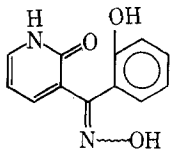
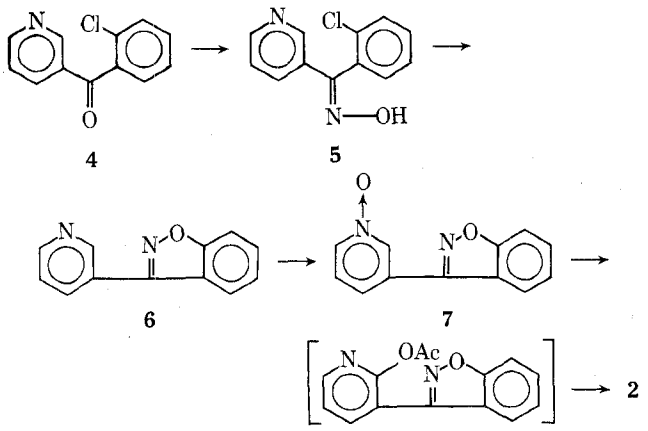


3

The benzisoxazole **2** shows a strong carbonyl frequency in the ir (6.0 μ), a C=N band at 6.2 μ, and a pair of bands at 11.1 and 11.5 μ which was subsequently found in the ir spectrum of representative 1,2-benzisoxazoles prepared in this work. The NMR spectrum of **2** showed a triplet (J = 6.7 Hz) at δ 6.40 characteristic of 3-substituted 2-pyridones.[4] Confirmation of structure **2** was established by total synthesis (Scheme I).

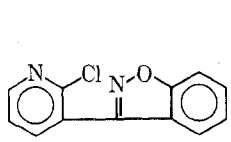
Scheme I



4 5 6 7 2

3-*o*-Chlorobenzoylpyridine (**4**) was converted into the oxime **5**. The higher melting isomer of **5**, on heating with KOH in ethylene glycol monomethyl ether by standard procedures,[5] gave the pyridylbenzisoxazole **6** in excellent yield. Rearrangement of the 1-oxide **7** with acetic anhydride and subsequent hydrolysis gave **2** identical in all respects with the original sample.

Compound **2** on reaction with phosphorus oxychloride or with phenylphosphonic dichloride was converted into the 2-chlorpyridyl analog **8**, the NMR spectrum of which did



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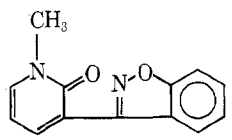
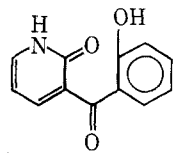


9

not show the typical pyridone resonance structure referred to above. Methylation of **2** (dimethyl sulfate in aqueous NaOH) resulted in the isolation of **9**, the NMR spectrum of which showed, in addition to the triplet at δ 6.25, a singlet at δ 3.68 (three protons), due to the *N*-methyl group. Evidence for the intact benzisoxazole ring in **8** and **9** was established by the pair of absorptions at 11.0 and 11.5 μ in the ir spectrum of both compounds.

To study the possible mechanism of this reaction 1-azaxanthone was treated with KOH in EtOH, whereby the pyridone ketone **10** was isolated as the sole product. This

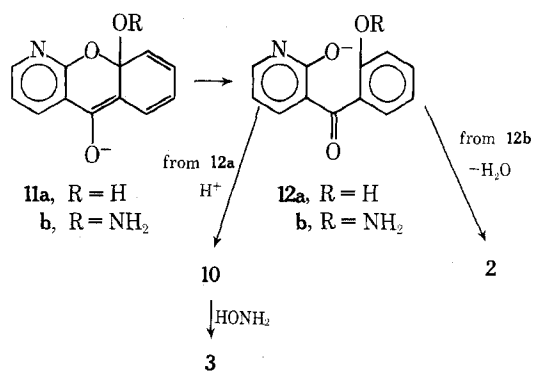


10

compound readily formed oxime **3** on reaction with $HONH_2$·HCl either in the presence of KOH in EtOH or in pyridine–EtOH. Attempts to effect closure of **3** to the benzisoxazole **2** under the original reaction conditions or under more strenuous basic conditions (KOH in ethylene glycol or fusion with KOH) were futile and compound **3** was recovered unchanged. Even under the sequential addition after 1 hr of $HONH_2$·HCl to a refluxing solution of the 1-azaxanthone in KOH and EtOH, only oxime **3** was obtained. These experiments indicate that **2** is not formed through the intermediate oxime **3.**

As reaction path we propose, therefore, a competitive direct attack of the hydroxide ion and the hydroxylamine anion on the 1-azaxanthone (Scheme II) to give a mixture

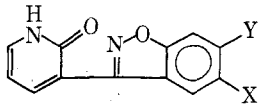
Scheme II



of intermediates of the type **11a** and **11b**, respectively, opening the oxygen bridge as in **12a** and **12b**, resulting in formation of **10**, which reacts with the excess $HONH_2$ to give **3**. The intramolecular loss of water from **12b** results in the formation of **2.**

Additional support for the proposed intermediate **11b** was obtained when the preformed anion of hydroxylamine prepared by reaction of $HONH_2$·HCl with NaH in anhydrous DMF was allowed to react with the ketone **1.** Under these conditions only the pyridone benzisoxazole **2** was ob-

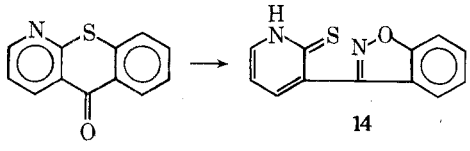
Table I
Compounds of Formula[a]



X	Y	Registry no.	Mp, °C	Yield, %	Formula[b]	Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
H	Cl	54999-81-4	238–230	65	$C_{12}H_6ClN_2O_2$	58.43	2.85	11.35	58.61	3.10	11.48
Cl	H	54999-82-5	291–292	67	$C_{12}H_7ClN_2O_2$	58.43	2.85	11.35	58.33	3.04	11.53
OCH_3	H	54999-83-6	253–255	69	$C_{13}H_{10}N_2O_3$	64.46	4.16	11.57	64.21	4.25	11.46

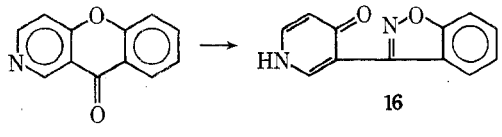
[a] From the ketones reported in ref 1, using method 1. [b] All products recrystallized from EtOH.

tained in a yield of 74%. Under similar reaction conditions 1-azathioxanthone (13) was converted into the thiopyridone benzisoxazole 14 in excellent yield. The structure 14



13 14

was assigned on the basis of spectral data and analogy with the oxygen isostere. Similarly, the benzisoxazole derived from 3-azaxanthone (15), is assigned the structure 16. The



15 16

β proton in the NMR spectrum of 16 resonates as a doublet at δ 6.38 (J = 7.2 Hz), characteristic of the structure indicated.[4]

Table I lists some substituted 2-pyridone benzisoxazoles prepared in this work.

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Unless otherwise indicated all products showed one spot on TLC [silica gel plates using $CHCl_3$ (90%)–MeOH (9%)–NH_4OH (1%) as solvent]. Ir spectra were recorded on a Perkin-Elmer Model 137 spectrometer in Nujol mulls. NMR spectra were obtained in DMSO-d_6 on a Varian A-60A spectrometer using tetramethylsilane as internal reference.

3-(2-1*H*-Pyridinon-3-yl)1,2-benzisoxazole (2) and 3-*o*-Hydroxyphenyl(2-1*H*-pyridinon-3-yl) Ketoxime (3). Method 1. In a typical experiment, a mixture of 9.9 g (0.05 mol) of 1-azaxanthone and 4.2 g (0.06 mol) of $HONH_2$·HCl was added in one portion to a solution of 38 g (0.2 mol) of KOH in 250 ml of EtOH. The mixture was heated on the steam bath for 2 hr and approximately 50% of the solvent was removed in vacuo. The residue was poured into water and the precipitated unreacted starting ketone was filtered. The filtrate was acidified with HOAc and the products were allowed to crystallize. The product was recrystallized from 600–700 ml of EtOH, yield of crude product 9.3 g, mp 220–227°.

Nine grams of this mixture was placed on a column of silica gel (450 g) and eluted with a mixture of $CHCl_3$ (90%), MeOH (9%), and NH_4OH (1%). Fractions of 200–250 ml were collected and monitored by TLC. Similar one-spot fractions were combined. Compound 2, being less polar, was eluted first and the major portion was obtained in the first five fractions. The pure oxime 3 was collected in fractions 9–15. The combined fractions were concentrated to a residue and recrystallized from EtOH.

Compound 2 was obtained in a yield of 2.8 g (31% recovery) and 3 (2.6 g, 29% recovery).

Compound 2 had mp 230–231°. Anal. Calcd for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20. Found: C, 67.97; H, 3.89; N, 13.37.

Compound 3 had mp 257–258°. Anal. Calcd for $C_{12}H_{10}N_2O_3$: C, 62.60; H, 4.38; N, 12.17. Found: C, 62.49; H, 4.40; N, 12.42.

3-(2-1*H*-Pyridinon-3-yl)-1,2-benzisoxazole (2). NaH Method, Method 2. To a suspension of 8.5 g (0.2 mol) of 57% NaH in mineral oil in 100 ml of anhydrous DMF was added to several small portions 6.9 g (0.1 mol) of $HONH_2$·HCl and the mixture was stirred for 0.5 hr in an ice bath. A suspension of 9.9 g (0.05 mol) of 1-azaxanthone in 200 ml of DMF was added all at once and the mixture was warmed on the steam bath for 2 hr. The mixture was poured into ice water (200 ml) and extracted with $CHCl_3$. The aqueous solution was acidified with HOAc, and the product was filtered and recrystallized from EtOH, mp 230–231°. The ir was superimposable and behavior on TLC was identical with that of the sample prepared in total synthesis, yield 7.9 g (74%).

3-(2-1*H*-Thiopyridinon-3-yl)-1,2-benzisoxazole (14). Using method 2, compound 14 was obtained from 10.7 g (0.05 mol) of 1-azathiaxanthone in a yield of 8.8 g (77%), mp 235–236° (EtOH).

Anal. Calcd for $C_{12}H_8N_2OS$: C, 63.14; H, 3.53; N, 12.28. Found: C, 63.32; H, 3.59; N, 12.54.

This compound was also obtained in 53% yield using the KOH method.

3-(4-1*H*-Pyridinon-3-yl)-1,2-benzisoxazole (16) was obtained from 3-azaxanthone (15) and $HONH_2$·HCl and KOH in EtOH by method 1, mp 294–296° (EtOH). Anal. Calcd for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20. Found: C, 67.55; H, 3.88; N, 12.95.

3-*o*-Chlorobenzoylpyridine (4). Our preparation of this ketone differs from that previously reported.[6]

Step 1. A solution of 76.4 g (0.4 mol) of 2-bromochlorobenzene was converted into the Grignard reagent in Et_2O using 9.6 g (0.4 g-atom) of magnesium. 3-Pyridinealdehyde (32.1 g, 0.3 mol) was added and stirring was continued for 0.5 hr. The product was isolated in the usual manner to give 53.9 g (81%) of a white solid, mp 115–116°.

Step 2. The carbinol from step 1 was oxidized with aqueous $KMnO_4$ at 70–80° for 2 hr to give the title compound in 72% crude yield as a brown oil used directly for compound 5. The HCl salt melted at 182–185° (reported[6] mp 185–187°).

***o*-Chlorophenyl-3-pyridyl Ketoxime (5).** The crude ketone, 4 (72g), 75 g of $HONH_2$·HCl, 150 ml of pyridine, and 400 ml of EtOH was heated under reflux for 6 hr and the solvent was removed in vacuo. The residue was poured into water and allowed to crystallize. The product was filtered and recrystallized from EtOH to give 33 g of a solid, mp 204–207°.

Anal. Calcd for $C_{12}H_9ClN_2O$: C, 61.94; H, 3.90; N, 12.04. Found: C, 61.77; H, 3.93; N, 12.05.

A second crop (34 g) of oxime, mp 197–200°, was obtained by dilution with water.

3-(3-Pyridyl)-1,2-benzisoxazole (6). A mixture of 36 g of oxime 5, 390 ml of 50% aqueous KOH, and 90 ml of ethylene glycol monomethyl ether was heated under reflux with stirring for 3 hr.[5] After cooling the product was filtered and recrystallized from i-Pr_2O to give 17.2 g (84%) of 6, mp 89–90°.

Anal. Calcd for $C_{12}H_8N_2O$: C, 73.46; H, 4.11; N, 14.28. Found: C, 73.10; H, 4.25; N, 14.17.

3-(3-Pyridyl 1-oxide)-1,2-benzisoxazole (7). To a solution of 17.0 g (0.087 mol) of 6 in 60 ml of acetic acid was added dropwise 30 ml of 30% H_2O_2 and the mixture was heated for 20 hr at 60°. The mixture was poured into ice water and the precipitated product was recrystallized from benzene–hexane, yield 11.6 g (63%), mp 149–151°.

Anal. Calcd for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20. Found: C, 67.61; H, 3.86; N, 13.21.

Rearrangement of 7 to 2. The 1-oxide 7 (4.2 g, 0.02 mol) was added portionwise to 25 ml of Ac_2O and the mixture was heated under reflux for 3 hr. At the end of 2.5 hr an aliquot was removed, poured into water, made alkaline ($NaHCO_3$), and extracted with $CHCl_3$. The $CHCl_3$ was removed and the residue was examined in the ir, showing carbonyl bands at 5.75 and 6.0 μ. Heating of the main batch was discontinued after 3 hr and the excess Ac_2O was removed in vacuo. To the residue 25 ml of concentrated HCl was added and the mixture was allowed to reflux overnight. A white precipitate formed on pouring the mixture into ice water, which was filtered and recrystallized from EtOH, yield 3.3 g (78%), mp 228–230°. An additional crystallization from EtOH brought the melting point to 230–231°. This product was identical (TLC, mixture melting point, ir, NMR) with the material previously isolated.

3-(2-Chloro-3-pyridyl)-1,2-benzisoxazole (8). A mixture of 8.4 g (0.043 mol) of 2 and 12 g of phenylphosphoric dichloride was heated at 180° for 2.5 hr, poured into water, and warmed on the steam bath to dissolve the tar-like material. After cooling, the solution was basified (NH_4OH) and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with water and concentrated to a residue which was recrystallized from hexane, yield 6 g (66%), mp 92–93°.

Anal. Calcd for $C_{12}H_7ClN_2O$: C, 62.48; H, 3.06; N, 12.15. Found: C, 62.60; H, 3.14; N, 12.31.

This same product was obtained in comparable yield from 2 by refluxing with a large excess of phosphorus oxychloride for 3 hr.

3-(1-Methyl-2-1*H*-pyridinon-3-yl)-1,2-benzisoxazole (9). To a solution of 2.5 g of 2 dissolved in 200 ml of 2 N NaOH was added 5 ml of dimethyl sulfate and the mixture was stirred for 3 hr at room temperature. A heavy white precipitate formed which was filtered and recrystallized from EtOAc–hexane to give 2.0 g of product, mp 146–147°.

Anal. Calcd for $C_{13}H_{10}N_2O_2$: C, 69.01; H, 4.46; N, 12.38. Found: C, 69.22; H, 4.37; N, 12.52.

3-(*o*-Hydroxybenzoyl)-2-pyridone (10). 1-Azaxanthone (19.7,

0.1 mol), 50 g of KOH, and 300 ml of EtOH was heated under reflux for 2 hr and poured into water. The clear solution was acidified (HOAc), cooled, and filtered, and the precipitate was washed with water and recrystallized from EtOH, mp 236–238°, yield 16.3 g (76%).

Anal. Calcd for $C_{12}H_9NO_3$: C, 66.97; H, 4.22; N, 6.51. Found:, 67.27; H, 4.26; N, 6.72.

3-*o*-Hydroxyphenyl(2-1*H*-pyridinon-3-yl) Ketoxime (3). A solution of 21.5 g (0.1 mol) of ketone **10**, 10.4 g (0.15 mol) of $HONH_2$·HCl, and 36 g of KOH in 200 ml of EtOH was refluxed for 2 hr, poured into 250 ml of H_2O, and acidified (HOAc). The precipitated product was recrystallized from EtOH, mp 257–258°.

This same product was obtained from **10** (0.1 mol) by refluxing with 0.15 mol of $HONH_2$·HCl in 200 ml of pyridine and 100 ml of EtOH.

4-Azaxanthone 5-Oxime. One gram of 4-azaxanthone, 0.5 g of $HONH_2$·HCl, 20 ml of pyridine, and 40 ml of EtOH were refluxed on the steam bath for 6 hr. The excess solvents were removed in vacuo and ice water was added. The product was filtered, washed with H_2O, and recrystallized from dilute EtOH, yield 0.8 g, mp 152–154°.

Anal. Calcd for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20. Found: C, 68.30; H, 3.78; N, 13.47.

2-Azaxanthone 5-Oxime. This compound was prepared by same method as above, yield 0.6 g, mp 259–260°.

Anal. Calcd for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20. Found: 67.88; H, 3.66; N, 13.21.

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Registry No.—**1**, 6537-46-8; **2**, 54999-68-7; **3**, 54999-69-8; **4**, 42374-49-2; **5**, 54999-70-1; **6**, 54999-71-2; **7**, 54999-72-3; **8**, 54999-73-4; **9**, 54999-74-5; **10**, 54999-75-6; **13**, 5698-68-0; **14**, 54999-76-7; **15**, 54629-30-0; **16**, 54999-77-8; 2-bromochlorobenzene, 694-80-4; 3-pyridinealdehyde, 500-22-1; α-(3-pyridyl)-2-chlorobenzyl alcohol, 54999-78-9; 4-azaxanthone 5-oxime, 54999-79-0; 4-azaxanthone, 54629-31-1; 2-azaxanthone 5-oxime, 54999-80-3; 2-azaxanthone, 54629-29-7.

References and Notes

(1) For part 1 in this series see F. J. Villani et al., *J. Med. Chem.*, **18**, 1 (1975).
(2) For convenience and consistent with the numbering system adopted in this and related series of compounds (see ref 1 and references cited therein), we prefer to use the numbering system shown in **1**.
(3) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds", 4th ed, Wiley, New York, N.Y., 1956, p 255.
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The Behavior of Thioxanthenol Sulfoxides and Related Compounds in 96% Sulfuric Acid[1]

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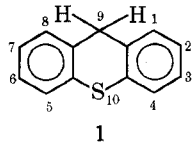
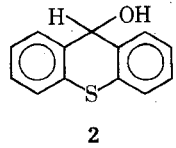
Thioxanthen-9-ol 10-oxides react with 96% sulfuric acid to produce, after quenching, thioxanthone (85%) as the major product. The mechanism, studied by NMR, absorption, and fluorescence spectroscopy, involves the loss of H_3O^+ from sulfinyl-O-protonated thioxanthen-9-ol 10-oxide. Minor components arise via a hydride transfer from starting material to O-protonated thioxanthone. Based upon isotope exchange studies, a thiaanthracene analog of thioxanthenol sulfoxide is considered an unlikely intermediate in this dehydration.

The course of the reaction of derivatives of thioxanthene (**1**) with acids depends upon the nature of both the derivative and the acid. For example, **1** and its 9-alkyl and 9,9-dialkyl derivatives react with "magic acid" to produce the corresponding S-protonated thioxanthene derivatives (and *not* thiaanthracenes).[2] Sulfuric acid converts 9,9-dialkylthioxanthenes into the corresponding radical cations.[3] On the other hand, **1**, thioxanthenol (**2**), and thioxanthene sulfoxide (**3**) react with concentrated sulfuric acid to produce the thioxanthylium cation (**4**).[4] In contradistinction, trifluoroacetic acid converts **2**, but not **3**, into **4**.[5]

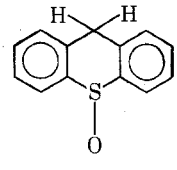
As part of our continuing study of the chemistry of the thioxanthene ring system and of the reactions of organosulfur compounds in acidic media,[6] we now present an account of the behavior of the isomeric thioxanthenol sulfoxides (**5**)[7] and related compounds in concentrated (96%) sulfuric acid.[8]



1



2



3

Results

cis- or *trans*-thioxanthenol sulfoxide (**5**) reacts with concentrated sulfuric acid (or its deuterated analog) to produce, after 1 hr, a solution whose NMR spectrum is similar to, but not identical with, that of thioxanthone (**6**) in the same medium.[9] A salient difference is the presence, in solutions of **5**, of a highly structured group of absorptions in the aryl region and a sharp singlet at δ 9.98. Both of these features are characteristic of solutions of the thioxanthylium