II, 47 g. (0.25 mole), was placed in the flask and 4 cc. of 35% methanolic benzyltrimethylammonium hydroxide (Chemlab Inc., Chicago) was added with stirring. A blue color which changed to brown was observed immediately after this addition. Recently-distilled acrylonitrile, 15 g. (0.28 mole), was added at such a rate that the temperature of the stirred reaction mixture was maintained at 38 to 40° (1.5 hr.). After the addition was completed, the mixture was stirred and warmed for an additional 2 hr., during which the temperature was maintained at 38 to 42°. The apparatus was flooded with dry nitrogen, sealed and allowed to stand at room temperature overnight. The mixture was treated with an equal volume of water, transferred to a separatory funnel, and extracted with three 100-cc. portions of ether. The extracts were combined, washed with three 150-cc. portions of water, and dried over anhydrous sodium sulfate. The ether was evaporated under reduced pressure and the residue was distilled *in vacuo* twice to yield 31.1 g. (58%)[11] of I, a pale-liquid, b.p. 112–114°/0.5 mm., n_D^{25} 1.5160.

The infrared spectrum of I (5% solution in carbon tetrachloride) showed the characteristic nitrile peak at 2250 cm.$^{-1}$ and an alkene-aromatic ring conjugation at 1580–1600 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_{18}N_2$: C, 78.50; H, 8.41; N, 13.09. Found: C, 78.61; H, 8.62; N, 13.00.

The compound was unstable when stored under ordinary conditions. A sample which had been stored in a stoppered flask exposed to diffused light for 1 week developed a strong ammoniacal odor and a dark brown color. Its infrared spectrum showed a strong conjugated carbonyl band at 1690 cm.$^{-1}$ indicating that hydrolytic changes had occurred. It was determined that the stability of the compound could be improved by storing it under dry nitrogen in a tightly-stoppered container and protecting it from light.

Hydrolysis of I. To 300 cc. of 6*M* hydrochloric acid was added 21.4 g. (0.1 mole) of the enaminonitrile (I), and the solution was warmed on the steam bath for 45 min. During this period, a white, crystalline solid which separated in the early stages of the heating process redissolved in the hot reaction mixture, and after 30 min. of heating, a white, crystalline solid separated again from the hot solution. The reaction mixture was cooled and the crystals were collected, yielding 10.9 g. (61.4%) of III, m.p. 116° after purification and drying to constant weight according to the method of Somerville and Allen.[12] The melting point was undepressed upon admixture with an authentic sample of 3-benzoylpropionic acid[12] and the infrared spectra of the two specimens (5% solution in chloroform) were identical.

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.40; H, 5.65. Found: C, 67.33; H, 5.54.

Anilide of III. The product of the hydrolysis of I was treated with freshly-distilled aniline according to the method of Klobb.[13] From this reaction, in which 6.25 g. of III and 4.0 g. of aniline were used, 2.6 g. (29.5%) of 3-benzoylpropionanilide (V) was obtained, m.p. 149–150° after recrystallization from benzene and drying to constant weight *in vacuo*.

The melting point of the anilide obtained in this case showed no depression when it was mixed with a sample of the anilide prepared from an authentic sample of 3-benzoylpropionic acid. The infrared spectra of the two specimens (5% solution in chloroform) were identical.

Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.86; H, 5.96; N, 5.53. Found: C, 75.96; H, 6.18; N, 5.75.

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(11) This yield is based upon the quantity of 2-(*N*,*N*-yellow diethylamino)-2-phenylacetonitrile employed in the cyanoethylation reaction.

(12) L. F. Somerville and C. F. H. Allen, *Org. Syntheses*, **Coll. Vol. II**, 81 (1950).

(13) T. Klobb, *Bull. soc. chim. Paris*, **19**, 391 (1898).

Pteridine Chemistry. V. The Methylation of 2-Amino-4-hydroxy-6,7-dimethylpteridine

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Although several investigators have reported on the alkylation of a number of mono- and polyhydroxypteridines[1,2] there is very little information available on the alkylation of aminohydroxypteridines. Leucopterin (2-amino-4,6,7-trihydroxypteridine) has been treated with diazomethane to give two trimethyl derivatives of unknown structure.[3] More recently we disclosed that 2-amino-4-hydroxypteridines, when treated with acrylonitrile, gave 8,9-dihydro-11H-pyrimido(2,1-b)pteridine-7-(6H),11-diones.[4] The latter reaction involved an alkylation of the 3-nitrogen of the pteridine ring and no isomeric compounds were detected.

It was of interest to determine whether the methylation of 2-amino-4-hydroxypteridines would give a single product, as occurred with acrylonitrile,[4] or several isomeric monomethyl derivatives as might be expected in this type of alkylation. 2-Amino-4-hydroxy-6,7-dimethylpteridine (I) was therefore methylated using four moles of dimethyl sulfate[5] and four moles of sodium hydroxide to give a 70% yield of a light yellow product. Chromatographic comparison with authentic compounds[6] showed that the crude product was a mixture[7] of the 1-methyl (II) and 3-methyl (III) derivatives of I, along with a very small amount of starting material. Due to the difference in the basicities of II and III (see Table I) the mixture was readily separated by crystallization from dilute acid. The yields of the products indicated that this methylation of I gave the two monomethyl derivatives in a ratio of approximately three parts of the 3-methyl derivative (III) to two parts of the 1-methyl derivative (II).

(1) H. C. S. Wood, *Chemistry and Biology of Pteridines*, Ciba Foundation Symposium, Little Brown and Co., Boston, Mass., 1954, p. 35.

(2) A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, 2066 (1956); W. Pfleiderer, *Chem. Ber.*, **90**, 2582, 2588, 2605, 2631 (1957); G. P. G. Dick, H. C. S. Wood, and W. B. Logan, *J. Chem. Soc.*, 2131 (1956).

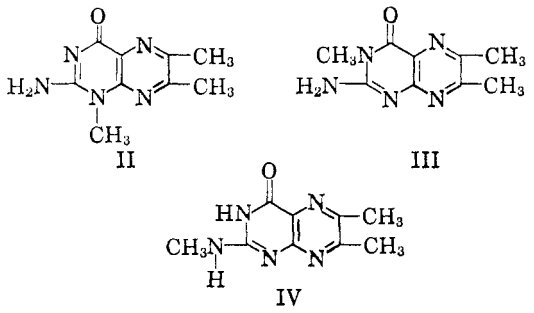
(3) H. Wieland and P. Decker, *Ann.*, **547**, 180 (1941).

(4) R. B. Angier and W. V. Curran, *J. Am. Chem. Soc.*, **81**, 5650 (1959).

(5) This large excess of dimethyl sulfate was necessary. Smaller quantities of alkylating agent always left considerable starting material in the crude product.

(6) W. V. Curran and R. B. Angier, *J. Am. Chem. Soc.*, **80**, 6095 (1958).

(7) The chromatographic examination of this mixture had to be done carefully since the 1-methyl derivative (II) was much less fluorescent than the 3-methyl derivative (III). In practice, the former compound (II) was best detected as an absorption spot using a zinc silicate plate coated with Dupont phosphor No. 609235.



II III IV

Albert *et al.*[8] have accumulated considerable data concerning the effect which substituents on the pteridine ring exert on various physical and chemical properties of the compounds. Similar data are presented here for 2-amino-4-hydroxy-6,7-dimethylpteridine (I) and its three monomethyl derivatives (II, III, IV). Table I shows the striking increase in solubility produced by substituting a methyl group for a hydrogen in the parent compound (I).[9] In addition it is interesting to note the six to seven fold difference in solubility of the isomeric 1-methyl (II) and 3-methyl (III) derivatives of I. Another difference that was observed was the increased basicity of the 1-methyl derivative (II) over the other three compounds. This was effectively confirmed, when the 1-methyl derivative (II) was found to be much more soluble than the 3-methyl derivative (III) in dilute acid despite the fact that in water alone the solubility was in the reverse order.

TABLE I

2-AMINO-6,7-DIMETHYL-4-PTERIDINONES

	pK_a Cationic	Solubility in Water At 22°	At 100°
2-Amino (I)	2.6	1 part in 280,000[a]	1 part in 9800
2-Amino-1-methyl (II)	3.2	3500[a]	440
2-Amino-3-methyl (III)	2.6	530	75
2-Methylamino (IV)	2.4	440	37

[a] Determined spectroscopically.[10]

During the determination of the pK's of these compounds using ultraviolet absorption spectroscopy[10] several observations were made concerning the possible structure of the compounds. At all pH's from 0.1N acid to pH 7 2-amino-4-hydroxy-6,7-dimethylpteridine (I) and its 3-methyl derivative (III) had essentially identical spectra whereas the spectra of the 1-methyl derivative (II) from pH 2.5 to pH 7.0 were different from the spectra of either I or III. This suggests that in its neutral and cationic forms, when it exists primarily as a pteridinone, I has its tautomeric hydrogen atom located almost entirely on the 3-nitrogen so that its chromophore is the same as the 3-methyl derivative (III). An unexpected result was obtained when the spectra were taken at higher pH's. From pH 5.0 through 0.1N sodium hydroxide the spectra of the 3-methyl derivative (III) did not change. This was expected since no tautomerism seems likely. However, although the spectra of the 1-methyl derivative (II) did not change from pH 5.0 to pH 9.2, the spectra in 0.1N sodium hydroxide did indicate that a new chromophore was being formed. This was confirmed by determining the spectra of II at various hydroxide ion concentrations from pH 9.2 to 2.0N sodium hydroxide (see Fig. 1). As the solution became more alkaline the long wave length maximum shifted from 330 mμ to 362 mμ and a new isosbestic point appeared indicating the presence of a stable, new ionic species. As further proof that no decomposition was occurring, II was dissolved in 1.0N sodium hydroxide and allowed to stand for five minutes. After adjusting to pH 9.2 the spectrum was identical with the original spectrum of II at pH 9.2. Although no proof is offered, it is suggested that the species which is present in 2.0N

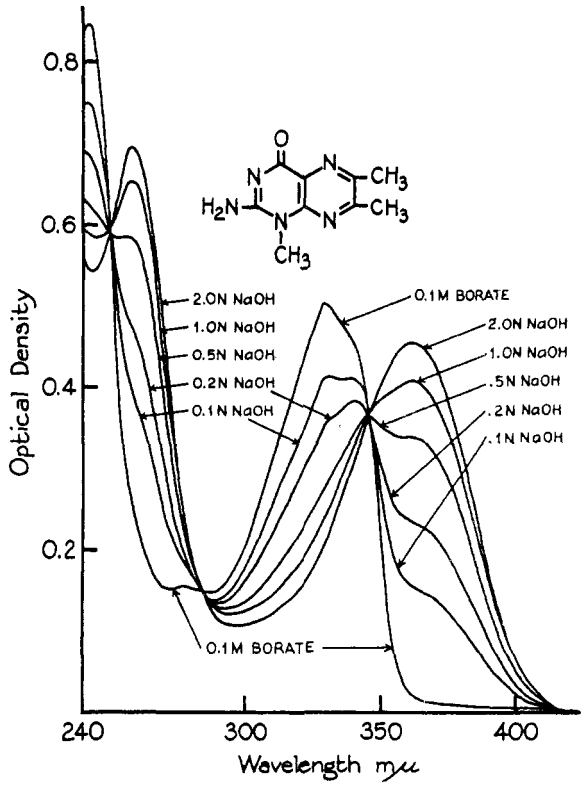


Fig. 1. Ultraviolet absorption spectra of 2-amino-1,6,7-trimethyl-4(1H)pteridinone (II) at 10 γ/ml.

(8) A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.*, 4219 (1952); A. Albert, D. J. Brown, and H. C. S. Wood, *J. Chem. Soc.*, 3832 (1954).

(9) Albert *et al.*[8] have suggested that the extremely low solubility of 2-amino-4-hydroxypteridines and other similarly substituted pteridines in water is due to strong intermolecular hydrogen bonding. The replacement of a hydrogen by a methyl group would then be expected to increase the solubilities of these compounds.

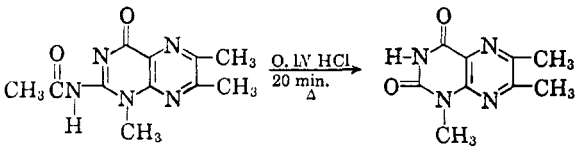
(10) G. H. Beaven, E. R. Holiday, and E. A. Johnson in *The Nucleic Acids*, Vol. I, E. Chargaff and J. N. Davidson, Academic Press, Inc., New York, N. Y., 1955, p. 496; A. Albert and J. N. Phillips, *J. Chem. Soc.*, 1294 (1956).

sodium hydroxide is the anion of the tautomeric 2-imino - 4 - hydroxy - 1,6,7 - trimethyl - 1,2 - dihydropteridine.

Further examination of the 3-methyl derivative (III) then showed that in 2.0 to 5.0*N* sodium hydroxide the solution developed a yellow color and a new maximum began to appear at about 400 mμ. However, due to the instability of the compound[4,6] under these conditions, an isosbestic point could not be determined.

During the determination of the structure of the pyrimido(2,1-b)pteridines produced from acrylonitrile and 2-amino-4-hydroxypteridines[4] the acetyl derivatives of II and III were prepared. Attempts to recrystallize the acetyl derivative of II from water resulted in decomposition of the compound. This led to a study of the stability of the acetyl derivatives of 2-amino-4-hydroxy-6,7-dimethylpteridine (I) and its three monomethyl derivatives (II, III, and IV).

When 2-acetamido-1,6,7-trimethyl-4(1H)pteridinone (V) was dissolved in 0.1*N* hydrochloric acid and heated twenty minutes on a steam bath it was completely hydrolyzed to give, as the sole product, 1,6,7-trimethyl-2,4-(1H,3H)pteridinedione (VI), isolated and identified by comparison with an authentic sample.[6] On the other hand, the parent compound, 2-amino-1,6,7-trimethyl-4(1H)pteridinone (II) was completely stable under similar conditions, *e.g.*, when II was heated on the steam bath in either 0.1*N* or 1.0*N* hydrochloric acid for one hour only starting material was present as shown by paper chromatography. Obviously, then, the acid hydrolysis of V to VI did not involve the formation of the 2-amino derivative, II, as an intermediate but rather proceeded by direct cleavage of the bond between the exocyclic nitrogen and the ring carbon.



V VI

In comparison with these results, when 2-acetamido-3,6,7-trimethyl-4(3H)pteridinone[4] (VII) was heated on the steam bath for twenty minutes in 0.1*N* hydrochloric acid, chromatographic examination of the solution showed the presence of approximately equal amounts of 3,6,7-trimethyl-2,4-(1H,3H)pteridinedione (VIII)[6] and 2-amino-3,6,7-trimethyl-4(3H)pteridinone (III).

In this case there was some of the normal type of hydrolysis of the 2-acetamido derivative (VII) to give the 2-amino derivative (III). However, there was again considerable direct cleavage at the exocyclic nitrogen-ring carbon bond since III was completely stable under these conditions. Finally, although 2-acetamido-4-hydroxy-6,7-dimethylpteridine and 2-(*N*-methylacetamido)-4-hydroxy-6,7-dimethylpteridine under the conditions described above gave primarily the parent 2-amino compounds, I and IV, there were small amounts of 2,4-dihydroxy-6,7-dimethylpteridine produced in each case whereas I and IV themselves were entirely stable. Thus each of these acetyl derivatives undergoes acid catalyzed cleavage of the exocyclic nitrogen-ring carbon bond more readily than its parent 2-amino derivative although the relative rates of the two reactions vary depending upon the substituents on the pyrimidine ring.[11]

EXPERIMENTAL[12]

Methylation of 2-amino-4-hydroxy-6,7-dimethylpteridine (I). Compound I (3.8 g., 0.02 mole) was mixed with 50 ml. of water and stirred vigorously. Dimethyl sulfate (8.0 ml., 86.0 mmoles) was added in eight portions over a period of 1.75 hr. while simultaneously adding, dropwise, 80 ml. of 1*N* sodium hydroxide.[5] The mixture was stirred for an additional hour. At the end of the stirring a precipitate was present and the *p*H was 6.8–7.0.[13] The reaction mixture was heated to affect solution and 1.2 ml. of concd. hydrochloric acid was added to give *p*H 2. The hot solution was treated with Norit, filtered, and the filtrate stored in the cold overnight. The resulting crystalline product was collected and dried; yield 0.90 g. (Fraction A). Paper chromatography showed this crop to be mainly the 3-methyl isomer (III) with a small amount of starting material.[14]

The filtrate to Fraction A was brought to *p*H 5.5–6.0 with solid sodium acetate and cooled; yield 1.75 g. (Fraction B). Fraction B was a mixture of II and III with a small amount of starting material. This product was dissolved in 25 ml. of boiling water containing 0.60 ml. of concd. hydrochloric acid, treated with Norit, and filtered. After the filtrate had been cooled for several days the crystals were collected; yield 0.65 g. (Fraction C). This fraction also contained all three compounds. The filtrate was heated to 80° and brought to *p*H 5.5–6.0 with solid sodium acetate and cooled; yield 0.65 g. (Fraction D). This was primarily the 1-methyl derivative (II).

Fraction C was dissolved in a hot solution of 22 ml. of water and 0.17 ml. of concd. hydrochloric acid and cooled overnight; yield 0.20 g. (Fraction E). The filtrate was brought to *p*H 4.5–5.0 with sodium acetate to give 0.37 g. of material (Fraction F).

(11) After this work was completed it was found that D. M. Brown, A. Todd, and S. Varadarajan, *J. Chem. Soc.*, 2384 (1956) had observed a similar reaction when they found that 4-acetamido-2-hydroxypyrimidine heated two hours at 100° in 85% acetic acid gave a 50:50 mixture of 2,4-dihydroxypyrimidine and 2-hydroxy-4-aminopyrimidine.

(12) The melting points have been corrected for the exposed stem of the thermometer.

(13) In one experiment the product was collected at this point; yield 2.9 g. (70%). Chromatographic examination of this product showed it to be a mixture[7] of the 1-methyl (II) and 3-methyl (III) derivatives of I with a trace of I also present. Many other sets of conditions were examined but none gave more satisfactory results than those described.

(14) The paper chromatography for all of the fractions mentioned was carried out in 0.5% Na_2CO_3, and in isopropyl alcohol—1*N* NH_4OH(7–3), by spotting solutions of 20 mg./ml. of material[7] on Whatman No. 1 filter paper and using the descending technique. The first solvent system separated the 1-methyl isomer (II) from the starting material and the 3-methyl derivative (III), while the second system separated starting material from the two methylated derivatives.

Fractions A and E were combined and recrystallized from 50 ml. of hot water, using Norit, to yield 0.90 g. (22%) of 2-amino-3,6,7-trimethyl-4(3H)pteridinone (III) which contained only a trace of the starting material. Fractions D and F were combined and recrystallized from 350 ml. of boiling water to give 0.65 g. (16%) of 2-amino-1,6,7-trimethyl-4(1H)pteridinone (II) containing only traces of I and III. The identities of these recrystallized products were corroborated by ultraviolet and infrared comparisons with authentic samples[6] of II and III.

The infrared spectra of these two products are distinctively different in the C=O and C=N regions. The 3-methyl derivative (III) has bands at 5.78, 6.07, and 6.43 μ while the 1-methyl derivative (II) has bands at 5.92 (shoulder), 6.0, 6.18, 6.25 (shoulder), and 6.51 μ.

2-Acetamido-1,6,7-trimethyl-4-(1H)pteridinone (V). 2-Amino-1,6,7 trimethyl-4-(1H)pteridinone (1.0 g., 4.9 mmoles) and 20 ml. of acetic anhydride were mixed and heated to reflux for 4 hr. The solution was then cooled well and the crystalline product was collected; yield 0.4 g. The filtrate was evaporated to dryness. The residue was slurried with ether and the solid product was collected; yield 0.5 g. (combined yield 75%).

The two products were combined and recrystallized from 7 ml. of ethanol; yield 0.45 g. (37%); m.p. 171–172°. R_f 0.90 (0.5% sodium carbonate); R_f 0.79 (3% ammonium chloride). Ultraviolet absorption spectra in 0.1*N* sodium hydroxide 262 mμ (ϵ 15,100), 338 mμ (ϵ 12,700); methanol λ_{max} 230 mμ (ϵ 15,800), 278 mμ (ϵ 20,800), 325 mμ (ϵ 13,300).

Anal. Calcd. for $C_{11}H_{13}N_5O_2$ (247): C, 53.4; H, 5.3; N, 28.3. Found: C, 53.3; H, 5.3; N, 28.3.

Acid hydrolysis of 2-acetamido-1,6,7-trimethyl-4-(1H)pteridinone (V). 2-Acetamido-1,6,7-trimethyl-4-(1H)-pteridinone (100 mg., 0.4 mmole) was dissolved in 100 ml. of 0.1*N* hydrochloric acid and heated on the steam bath for 20 min. This was cooled overnight and the crystalline product was collected; yield 30 mg. (36%). Infrared absorption spectra and chromatography showed this to be 1,6,7-trimethyl-2,4-(1H,3H)pteridinedione.[6]

Anal. Calcd. for $C_9H_{10}N_4O_2$ (206): C, 52.4; H, 4.9; N, 27.2. Found: C, 52.3; H, 5.1; N, 26.9.

Chromatographic and spectroscopic examination of the filtrate indicated that no other product was present.

2-Acetamido-4-hydroxy-6,7-dimethylpteridine. 2-Amino-4-hydroxy-6,7-dimethylpteridine (1.0 g., 5.2 mmoles) and 40 ml. of acetic anhydride were mixed and heated to reflux for 4.5 hr. After cooling for several hours the crystalline product was collected and washed with ether; yield 0.9 g. (75%).

A portion (0.5 g.) of this material was recrystallized once from 10 ml. of water and a second time from 15 ml. of water; yield 0.4 g.; light yellow needle-like crystals; m.p., placed in a bath at 250° it melts and resolidifies and melts at 298–299° dec. R_f 0.71 (0.5% sodium carbonate), R_f 0.62 (3% ammonium chloride). Ultraviolet absorption spectra in 0.1*N* sodium hydroxide, λ_{max} 252 mμ (ϵ 29,400), 342 mμ (ϵ 9700); 0.1*N* HCl, λ_{max} 280 mμ (ϵ 17,000), 331 mμ (ϵ 10,700).

Anal. Calcd. for $C_{10}H_{11}N_5O_2.6H_2O$: C, 35.2; H, 6.8; N, 20.5; H_2O, 31.7. Found: C, 35.3; H, 7.1; N, 20.6; H_2O (Karl Fischer) 35.2.

2-(N-Methylacetamido)-4-hydroxy-6,7-dimethylpteridine. 2-Methylamino-4-hydroxy-6,7-dimethylpteridine (0.65 g., 3.2 mmoles) and 15 ml. of acetic anhydride were mixed and heated to reflux for 3 hr. The solution was filtered to remove a trace of insoluble material and cooled overnight; yield of crystalline product 0.49 g. This was recrystallized from 20 ml. of ethanol; yield 0.28 g. (36%); m.p. 222–225°; R_f 0.88 (0.5% sodium carbonate), 0.74 (3% ammonium chloride); ultraviolet absorption spectra in 0.1*N* hydrochloric acid, λ_{max} 280 m, (ϵ 12,100), 327 mμ (ϵ 8000); methanol, λ_{max} 279 mμ (ϵ 11,600), 330 mμ (ϵ 7900); 0.1*M* sodium tetraborate, 248 mμ (ϵ 21,800), 333 mμ (ϵ 8000).

Anal. Calcd. for $C_{11}H_{13}N_5O_2$ (247): C, 53.4; H, 5.3; N, 28.3. Found: C, 53.5; H, 5.4; N, 28.4.

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Reductive Halogenation of Thiaxanthene 5-Oxide

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During an investigation of the orientation of monosubstituents in the 10-thiaxanthenone[1] nucleus, we had occasion to allow aqueous hydrobromic acid to react with thiaxanthene-5-oxide (I) in an attempt to halogenate reductively thiaxanthene-5-oxide. It was found that treatment of I with a 33% solution of hydrobromic acid gave a 26% yield of 10-thiaxanthenone (V) and a 29% yield of thiaxanthene (II).

Hilditch and Smiles[2] originally studied the intramolecular acid-induced rearrangements of thiaxanthene-5-oxide and 10-thiaxanthenol compounds. These workers found, for example, that the reaction of alcoholic hydrogen chloride on thiaxanthene-5-oxide afforded a colored thiaxanthylium salt which slowly changed to a colorless 10-chlorothiaxanthene. By treating thiaxanthene-5-oxide with hydrobromic acid, we isolated almost equimolar quantities of II and V.

A possible mechanistic interpretation of the reaction of hydrobromic acid on thiaxanthene-5-oxide is presented below.

Initial protonation of the sulfoxide grouping in I with subsequent reduction would form II and one molar equivalent of bromine (or hypobromous acid). The reductive halogenation of other systems in which the sulfoxide grouping is reduced to a sulfide have been reported.[3–5] An electrophilic attack by bromine on II would then yield the unstable 10-bromothiaxanthene (III) which could readily hydrolyze under the conditions of the experiment giving 10-thiaxanthenol (IV). Disproportionation of IV would afford the observed products,

(1) The numbering and nomenclature is that recommended by *Chemical Abstracts*.

(2) T. P. Hilditch and S. Smiles, *J. Chem. Soc.*, **99**, 145 (1911).

(3) H. J. Page and S. Smiles, *J. Chem. Soc.*, **97**, 1112 (1910).

(4) H. Gilman and J. Eisch, *J. Am. Chem. Soc.*, **77**, 3862 (1955).

(5) H. Gilman and D. R. Swayampati, *J. Am. Chem. Soc.*, **77**, 5944 (1955).