9-Chloroanthracene-10-*d*.—To a suspension of 45 g. (0.155 mole) of 9-chloro-10-bromoanthracene in 500 ml. of anhydrous ether was added 0.153 mole (250 ml. of 0.63 *M* solution) of phenyllithium in ether. The mixture was swirled vigorously for 2 min. and intermittently for 20 min. To the resulting orange-yellow suspension was added 4 ml. (4.4 g., 0.22 mole) of deuterium oxide, and the mixture was shaken until the exothermic reaction had subsided. After a few hours, the mixture was filtered, and the solid residue was washed with ether until the washings were colorless. The ether was removed from the combined filtrates and the residue was recrystallized from cyclohexane to give, first, 2 g. of starting material, m.p. 215–216°, and second, 18 g. of the crude desired product, m.p. 98–101° (with an unmelted residue). The solid residue from the reaction mixture was extracted with boiling benzene to give another 8 g. of starting material, which made the yield of product 70%. A sample of product was recrystallized again from cyclohexane to give yellow needles, m.p. 101–102°. The infrared spectrum showed a number of differences from that of 9-chloroanthracene, including the absence of two strong bands normally present at 882 and 944 cm.$^{-1}$.

9,10′-Dichlorodianthracene-9′,10-d_2.—The photodimerization in sunlight of 9-chloranthracene-10-*d* in 68% yield was done as described before[5] for 9-chloroanthracene.

Anal. Calcd. for $C_{28}H_{16}D_2Cl_2$: D, 11.11 atom %. Found: D, 11.20 atom %.

Reaction of 9,10′-Dichlorodianthracene-9′,10-d_2 with Phenyllithium.—To a solution of 8.9 g. (0.0208 mole) of the dimer in 600 ml. of warm benzene was added 320 ml. of 0.24 *M* phenyllithium in ether. The mixture was heated under reflux (nitrogen atmosphere) for 20 hr., quenched with 150 ml. of water, and refluxed for another 30 min. The cooled reaction mixture deposited 1.7 g. of crude dianthracene-9,10′-d_2, m.p. 250–260° dec. The benzene layer was evaporated to dryness and the residue was digested with cyclohexane to leave 3.2 g. of very crude **7**, m.p. 200–280° dec., as a yellowish powder. This material was melted, recrystallized twice from cyclohexene, melted again, and recrystallized four more times from cyclohexene to give 0.116 g., m.p. 305–310°. The infrared spectrum was similar to that of undeuterated **7**, but with an extra peak at 644 cm.$^{-1}$. A 95-mg. sample of this was sublimed at 100–110° (0.6–1.0 mm.) to give a small sublimate, m.p. 290°. The temperature was raised to 240–267° (0.3 mm.), and 80 mg. of sublimate was collected in two fractions, m.p. 310–317° and 308–310°. The former was analyzed for deuterium, the latter for carbon and hydrogen.

Anal. Calcd. for $C_{34}H_{21}D$: C, 94.63; H, 5.37; D, 4.55 atom %. Found: C, 94.12; H, 5.22; D, 5.01 atom %.

In another run, using 3 g. of dimer, more care was taken to isolate dianthracene-9,10′-d_2 by successive concentration of the reaction mixture filtrate, and 0.9 g., m.p. 240–270° dec., was obtained. This was decomposed at the melting point to anthracene-9-*d*, which was recrystallized from cyclohexene to give fluorescent platelets, m.p. 212–216°. The infrared spectrum showed strong absorption at 841 and 792 cm.$^{-1}$ as reported by others.[10]

Anal. Calcd. for $C_{14}H_9D$: D, 10.0 atom %. Found: D, 9.8 atom %.

Acknowledgment.—This work was supported in part by the National Science Foundation, the Sloan Foundation, and the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is made to the two foundations and to the donors of the last-named fund.

(10) V. Gold and F. A. Long, *J. Am. Chem. Soc.*, **75**, 4543 (1953).

Ion Radicals. V. Phenothiazine, Phenothiazine 5-Oxide, and Phenothiazone-3 in Acid Solutions[1,2]

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The reactions of phenothiazine (I), phenothiazine 5-oxide (II), and phenothiazone-3 (III) in acidic solutions have been studied by ultraviolet, visible, and e.s.r. spectroscopy. Solutions of II in 96% sulfuric acid are stable; it is proposed that they contain the protonated phenazothionium ion (VI). Similarly, solutions of III in 96% sulfuric acid are stable, and it is proposed that they contain the protonated hydroxyphenazothionium ion (XIII). Solutions of I in 96% sulfuric acid contain the phenothiazine cation radical (IV) which, in time, is further oxidized to VI. It is shown that III in 59% sulfuric acid is converted to the hydroxyphenothiazine cation radical (XI). It is also shown that in aqueous sulfuric acid II is converted not only to the cation radical IV but also to XI. Mechanisms are proposed for these reactions. It is proposed that in aqueous sulfuric acid II is in equilibrium with protonated II (VII) and with the phenazothionium ion (V) arising from dehydration of VII. The cation radical IV is formed from VII by loss of the hydroxyl radical to solvent. The cation radical XI is formed in solutions of II by a sequence of reactions involving nucleophilic attack of water on V and oxidation of the hydroxylated intermediate. It is proposed that the formation of XI from solutions of III in aqueous sulfuric acid occurs by hydroxyl loss from protonated 3-hydroxyphenothiazine 5-oxide, the last being formed by the hydration of the 3-hydroxyphenazothionium ion (IX). II, IV–VI, IX, XI, and XIII are characterized by ultraviolet, visible, and, where applicable, e.s.r. spectroscopy.

The chemistry of phenothiazine (I) has enjoyed continued interest during the past 50 years, formerly because of the connection between I and numerous dyestuffs, such as Lauth's violet (3,7-diaminophenothiazine) and methylene blue, and latterly because of the pharmacological properties of substituted phenothiazines. In particular, the behavior of I toward oxidizing agents and the relationship that this behavior bears to the chemistry of phenothiazine 5-oxide (II) and phenothiazone-3 (III) have received a great deal of attention. It is now known, from the pioneering work of Michaelis,[3] that I undergoes a one-electron oxidation to form a cation radical, which was proposed to have, in sufficiently acidic solution, the structure IV.

The radical IV, prepared by the oxidation of I with bromine or lead tetracetate in acetic acid solution, was characterized spectroscopically by a series of bands between 400 and 550 mμ. Subsequently, Lewis and

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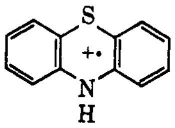
[1] Part IV: H. J. Shine, C. F. Dais, and R. J. Small, *J. Org. Chem.*, **29**, 21 (1964).

[2] (a) We thank the Directorate of Chemical Sciences, Air Force Office of Scientific Research, for the generous support of this work under Grant No. AF-AFOSR-23-63. The Beckman recording spectrophotometer used extensively in this work was purchased with funds from the Robert A. Welch Foundation. (b) Presented at the Symposium on Organic Reaction Mechanisms, Cork, Ireland, 1964.

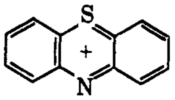
[3] L. Michaelis, S. Granick, and M. P. Schubert, *J. Am. Chem. Soc.*, **63**, 351 (1941).



IV

Bigeleisen[4] prepared the radical by photooxidation in a frozen solution and showed that it had absorption maxima in the visible region at about 520 and 500 mμ. Since that time, but only within recent years, both electron spin resonance spectroscopy and refined electrochemical techniques have been used to confirm the proposed structure, IV.

By monitoring potentiometrically the oxidative titration of I with bromine in acetic acid, Craig[5] deduced that IV underwent a second one-electron oxidation to form the phenazothionium ion, V. In the same year, the direct anodic oxidation of I in acetonitrile solution led Billon[6] to propose, also, a sequence of two one-electron oxidation steps, the second ending in protonated V. Subsequently, in a series of papers, to which we shall refer individually later, Billon has described the elegant way in which e.s.r. and absorption spectroscopy were allied in deducing the reactions taking place in the electrolysis system.



V

Our own interest has been in the reactions which I, II, and III undergo in acid solutions and the way in which these reactions lead to cation radicals. This interest developed from analogous work with thianthrene and its oxides.[7] Solutions of I and II in concentrated sulfuric acid were shown by Lagercrantz[8] to have e.s.r. spectra, which, although consisting of poorly resolved quartets, were interpretable in terms of coupling of the unpaired electron with the nuclei of the nitrogen and its attached hydrogen atom. Later, highly resolved e.s.r. spectra were published showing the hyperfine pattern, due to coupling with ring protons, in radicals obtained from I[9] and some of its derivatives[10,11] in sulfuric acid solutions.

The most extensive investigations of the properties of acidic solutions of I and II are to be found, however, in the work of Kehrmann. Here it was discovered[12] that, if hydrogen peroxide was added to a solution of I in sulfuric acid, in which oxidation had already ceased, further oxidation occurred to give a solution that was spectroscopically identical with one made by dissolving II in sulfuric acid. Kehrmann had earlier considered that it was *a priori* improbable that I could remain at an incomplete level of oxidation in sulfuric acid, a level which was termed semiquinoid. The instability of the semiquinoid state in sulfuric acid, which was assumed but not found in I, was found to be present in 3,7-dimethylphenothiazine, since the semiquinoid form obtained when this compound was first dissolved in sulfuric acid was rapidly converted to a higher oxidation state, one that Kehrmann termed holoquinoid. These changes were characterized by ultraviolet and visible spectroscopy. Another change that was so characterized was the behavior of II in acid solutions. It had already been noted by Barnett and Smiles[13] that a solution of II in concentrated sulfuric acid was green but became red on diluting with water. Kehrmann confirmed this change and noted that it was succeeded by yet another. He described the green solution of II as containing a diacid holoquinoid salt, and the brown-red solution, obtained by diluting with ice, as containing a monoacid holoquinoid salt. The subsequent, further change in the solution was interpreted as arising from a transformation of the last salt into the semiquinoid form. Thus, Kehrmann associated for the first time the oxidation of I with the reactions of II in acid solutions. The diacid holoquinoid salt was proposed to exist in acid solution ranging from 80% sulfuric acid to 30% oleum, and was characterized with maxima at 460 and 285 mμ. Lastly, the semiquinoid salt obtained by oxidation of I in 80–100% sulfuric acid was characterized with maxima at 513, 493, 476, 460, 438, 288, and 270 mμ. Dilution of such a solution to 10% sulfuric acid or dissolving II in 10% sulfuric acid resulted in spectral characteristics similar to the last mentioned. It is a tribute to the skill of Kehrmann's group that these absorption maxima were recorded so skillfully 50 years ago. It will be seen, though, that Kehrmann's maxima actually characterize solutions containing several components.

As for the structures of the di- and monoacid holoquinoids, these are given by Kehrmann and Sandoz,[14] along with redetermined ultraviolet and visible spectra, in which some of the earlier reported[12] maxima are no longer listed.

The oxidation of I in circumstances other than those described above can lead to high yields of III. The accepted method, using ferric chloride in aqueous solution, has been perfected by Bodea and Raileanu.[15] This method no doubt involves the oxidation of I to V followed by hydration and continued oxidation at the 3 position to give III. The reverse process is actually what concerns us here: namely, the conversion of III in acid solution to a cation radical analogous to IV. This reaction was probably achieved first by Pummerer,[16] who found that a solution of III in concentrated hydrochloric acid was initially brown but became violet on standing. The brown color was attributed to a holoquinoid salt, and the blue color to a meriquinoid salt, characterized by absorption maxima at about 450 and 550 mμ, respectively. The structures assigned by Pummerer are now recognized to be wrong. The species with the maximum at 550 mμ obtainable from III was described correctly as the semiquinone

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(4) G. N. Lewis and J. Bigeleisen, *J. Am. Chem. Soc*, **64**, 2419 (1943).

(5) J. Cymerman Craig, M. E. Tate, F. W. Donovan, and W. P. Rogers, *J. Med. Pharm. Chem.*, **2**, 669 (1960).

(6) J.-P. Billon, *Bull. soc. chim. France*, 1784 (1960).

(7) H. J. Shine and L. Piette, *J. Am. Chem. Soc.*, **84**, 4798 (1963).

(8) C. Lagercrantz, *Acta Chem. Scand.*, **15**, 1545 (1961).

(9) D. Gagnaire, H. Lemaire, A. Rassat, and P. Servoz-Gavin, *Compt. ernd.*, **255**, 1441 (1962).

(10) L. H. Piette and I. S. Forest, *Biochim. Biophys. Acta*, **57**, 419 (1962).

(11) F. W. Heineken, M. Bruin, and F. Bruin, *J. Chem. Phys.*, **37**, 1479 (1962).

(12) F. Kehrmann, J. Speitel, and E. Grandmougin, *Ber.*, **47**, 2976 (1914).

(13) E. de Barry Barnett and S. Smiles, *J. Chem. Soc.*, **95**, 1253 (1909).

(14) F. Kehrmann and M. Sandoz, *Ber.*, **50**, 1673 (1917).

(15) C. Bodea and M. Raileanu, *Acad. rep. populare Romine, Studii cercetări chim.*, **11**, 35 (1960).

(16) R. Pummerer, F. Eckert, and S. Gassner, *Ber.*, **47**, 1494 (1914).

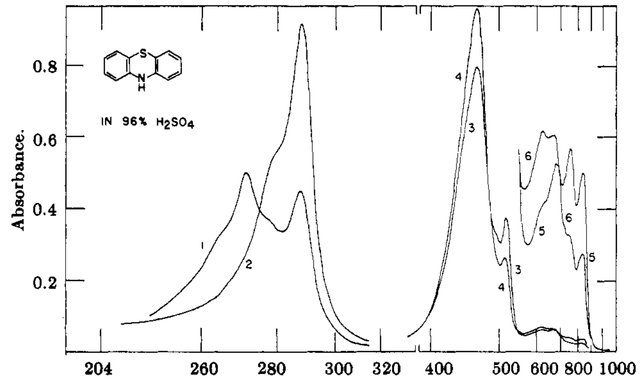


Figure 1.—Phenothiazine in 96% sulfuric acid: (1) 1 min. and (2) 8 hr. after dissolving a crystal of I in the acid already in the cuvette; (3) 22 min. and (4) 42 min. after making a 6.5 × 10^{-4} *M* solution of I; (5) 20 min. and (6) 85 min. after making a 6.5 × 10^{-5} *M* solution of I.

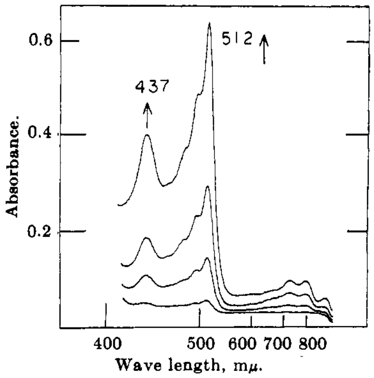


Figure 2.—The visible spectrum of a solution of phenothiazine in aqueous acetic acid after periods of 0, 5, 10, and 30 min. of irradiation with ultraviolet light.

derived from 3-hydroxyphenothiazine by Michaelis,[17] its preparation being achieved by the reduction of III in sulfuric acid with titanous sulfate. Somewhat later it was proposed[18] that III is converted to a semiquinone by heating or standing in strong acid solution.

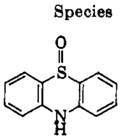
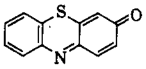
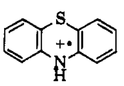
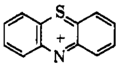
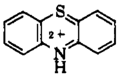
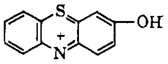
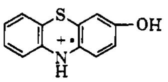
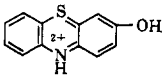
We wish to report on our work with I-III in acid solutions, from which we believe that, with the combination of absorption and e.s.r. spectroscopy, all of the transformations observed by the earlier workers can be better defined.

Results. Absorption Spectra

We shall record below and in the accompanying figures the ultraviolet, visible, and near-infrared spectra of solutions of I-III. The spectra of these compounds in some solvents change with time, but in others they remain stable. We shall be concerned particularly with a number of absorption peaks and bands which are common to solutions of all three compounds, but whose presence or absence depend upon the acidity and age of the solutions. We shall use these spectra in conjunction with the e.s.r. spectra which follow to deduce the nature of the species which are present in these solutions and to put forward an explanation of how they are formed. It will be convenient to assign to the spectra, as we come to them, those species which we believe were present in solution. In order to assist in correlating the assignments, however, they are listed, now, in Table I. We shall say now, also, that the assignments for the cation radical IV were made principally from the absorption and e.s.r. spectra of solutions of I, the assignments for V and VI from solutions of II, and for IX, XI, and XIII from solutions of III. Further, we shall present our data for the compounds I and III first and then show how the data are used for deducing what species are present in solutions of II.

Table I

Major Absorption Maxima

	Species	Maxima, mμ				
II		225	270	302	336	
III^a		237	270-287		369	500
IV		271	437	515		
V		281	420^b	437^c		
VI		287	455			
IX		287	444			
XI		276	554			
XIII		296	502			

^{a} III is listed here for comparison with assigned peaks. We do not believe that III itself was detected in the spectra of acid solutions of II or III. The peaks listed here are for III in 95% ethanol. The values of $10^4\epsilon$ at the listed wave lengths were 3.9 (237 mμ), 2.8 (270-287 mμ, broad flat band), 1.7 (369 mμ), and 1.3 (500 mμ). ^{b} In formic acid. ^{c} Approximate value, in aqueous sulfuric acid.

I in Sulfuric Acid.—I dissolved rapidly in 96% sulfuric acid. The solution was initially golden in color but became green on standing. The absorption spectra associated with this change are summarized in Figure 1. Maxima at 271, 515, 760, and 825 mμ disappeared with time and were replaced by others at 287, 455, 625, and 675 mμ. The changes in the spectra went through isosbestic points, the most clearly defined being at 274 mμ. The golden-colored solution of I also had an e.s.r. spectrum (this is dealt with later) whose intensity diminished as the color of the solution changed. We assign the absorption peaks 271, 515, 760, and 825 mμ to the cation radical IV. The changes in spectra are attributed to the oxidation of IV with the formation of the dication VI.

I in Acetic Acid. Irradiation with Ultraviolet Light.—A dilute solution of I in aqueous acetic acid was colorless. Irradiation with ultraviolet light caused the solution to become colored, the depth of the color increasing with the time of irradiation. The visible

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(17) S. Granick, L. Michaelis, and M. P. Schubert, *J. Am. Chem. Soc.*, **62**, 1802 (1940).

(18) H. B. Collier, D. E. Allen, and W. E. Swales, *Can. J. Res.*, **D21**, 151 (1943).

spectrum of the colored solution is recorded in Figure 2. The four curves represent scans taken at increasing time intervals. The character of the spectrum did not change; only its intensity increased. In particular, the relative intensities of the two prominent peaks at 437 and 512 mμ did not change. The solution also showed an e.s.r. spectrum whose intensity increased with the time of irradiation. The spectrum in Figure 2 is assigned to the cation radical IV.

We will note here that the 437-mμ peak of Figure 2 was not observable in the spectra of solutions of I in 96% sulfuric acid (Figure 1) because of the large overshadowing absorption at 455 mμ, due to VI.

The peaks assigned to the cation radical IV are summarized then as 271, 437, 515, 760, and 825 mμ. Small wave-length differences for the sulfuric and acetic acid solutions due, possibly, to the influence of solvent or instrument error are disregarded.

III in Sulfuric Acid.—Solutions of III in 96% sulfuric acid were stable for months. The ultraviolet and visible spectra are given in Figure 3. We assign these spectra, with major peaks at 296 and 502 mμ, to the hydroxy dication XIII. The solutions did not give an e.s.r. signal.

Solutions of III in aqueous sulfuric acid were not stable. The ultraviolet spectra were not only initially unlike those of the 96% sulfuric acid solution, but they also changed with time. The behavior of III in 59% sulfuric acid is shown in Figure 4. The initial peaks at 288 and 244 mμ decreased slowly with time to give place to new peaks at 276 and 554 mμ. Accompanying this change was the appearance of a well-defined e.s.r. spectrum which we shall deal with further on. We assign the peaks at 288 and 444 mμ to the hydroxy cation IX, and those at 276 and 554 mμ to the hydroxy cation radical XI.

II in Solvents Other than Strong Acids.—The ultraviolet absorption maxima of solutions of II in several solvents are listed in Table II. The spectrum of the ethanol solution is given in Figure 5. The data for the 15 and 28% sulfuric acid solutions listed in Table II are for solutions in which the changes which we shall discuss below had not yet become pronounced. The purpose of giving the collected data in Table II is to establish the peaks characteristic of II in solution and to show that they are present in newly made solutions of II in 15 and 28% sulfuric acid. We assign to II, therefore, peaks in the regions of 225, 270, 302, and 336 mμ.

TABLE II

ULTRAVIOLET DATA FOR SOLUTIONS OF II

Solvent	λ ($10^{-3}\epsilon$)	λ ($10^{-3}\epsilon$)	λ ($10^{-3}\epsilon$)	λ
H_2O	...	305	270	226
AcOH	340 (6.5)	304 (10.2)	270 (19.7)	...
EtOH	337 (6.0)	303 (8.7)	270 (16.2)	229[a]
$CHCl_3$	335 (5.0)	300 (7.0)	272 (14.0)	...
Benzene	340 (4.5)	300 (6.5)	...	...
CCl_4	340[b] (4.7)	310 (7.5)	275 (11.5)	230
Cyclohexane	340[c] (3.0)	305[c] (5.3)	273 (9.5)	...
15% H_2SO_4	336	302	...	225
28% H_2SO_4	339	305	...	225

[a] $10^{-3}\epsilon$ 33.0. [b] There was a second maximum at 353 mμ (ϵ 4.5×10^3). [c] Broad band.

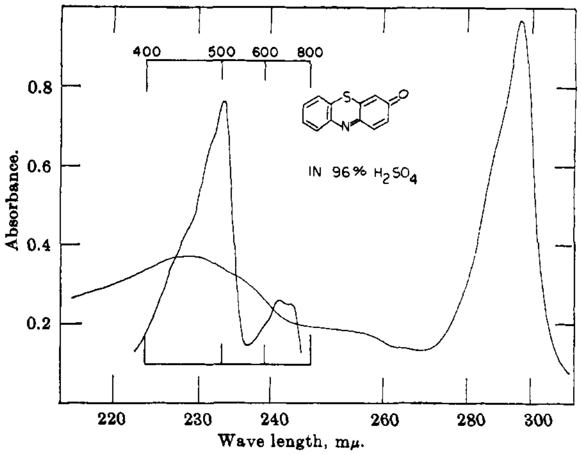

Figure 3.—Phenothiazone-3 in 96% sulfuric acid: ultraviolet spectrum of a 1.6×10^{-5} *M* solution; visible spectrum of a 4.7×10^{-5} *M* solution.

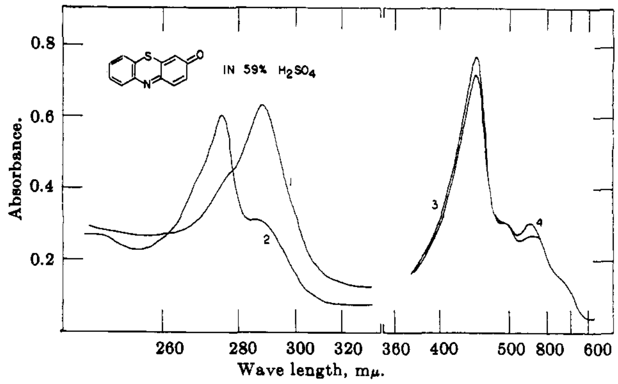

Figure 4.—Phenothiazone-3 in 59% sulfuric acid: ultraviolet spectra of a 1.4×10^{-5} *M* solution after (1) 10 min. and (2) 6 days; visible spectra of a 4.6×10^{-5} *M* solution after (3) 10 min. and (4) 16 hr.

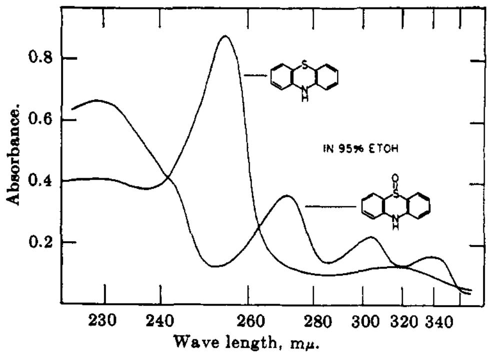

Figure 5.—The ultraviolet spectra of 1.6×10^{-5} *M* phenothiazine and 2×10^{-5} *M* phenothiazine 5-oxide in 95% ethanol.

II in Sulfuric Acid.—The spectra of solutions of II in aqueous sulfuric acid changed with time. The spectrum in 96% sulfuric acid did not. The changes in the spectra of the aqueous acid solutions are complicated because their nature depends on the acidity of the solution. We record in the accompanying figures the ultraviolet and visible spectra of II in 15, 28, 59, and 96% sulfuric acid. The data for 15% sulfuric acid (Figures 6 and 7) are given in detail so as to establish the way in which the changes were followed. The changes that occurred in 28 and 59% sulfuric acid are summarized only by the initial and final scans made.

Figure 6 shows that the initial spectrum with maxima at 225, 302, and 336 mμ gave way to one with maxima

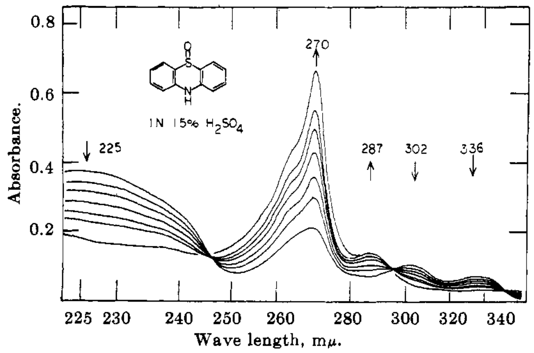

Figure 6.—Changes in the ultraviolet spectrum of phenothiazine 5-oxide, $7.6 \times 10^{-6}\ M$, in 15% sulfuric acid, with time. Scans were made at 6, 36, 96, 136, 186, and 240 min. and 14.5 hr. after making the solution.

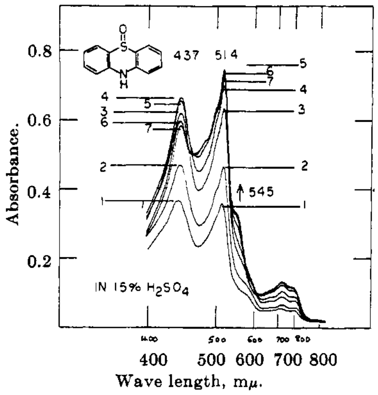

Figure 7.—Changes in the visible spectrum of phenothiazine 5-oxide, $5.1 \times 10^{-5}\ M$, in 15% sulfuric acid, with time. Scans were made in the order shown at 1, 2, 5, 9, 22, and 46 hr. and 3 days after making the solution.

at 270 and 287 mμ. The small band at 287 mμ also disappeared eventually, but this is not shown in Figure 6. From the data in Table II we are able to assign the disappearing maxima at 225, 302, and 306 mμ to II itself. Table II shows that a fourth band at 270 mμ characterizes II. This band is seen in Figure 6, but its disappearance is recognizable only in the change with time in the shape of the new peak that grew in the same region. Our assignments to Figure 6, therefore, are the disappearance of II (maxima at 225, 270, 302, and 306 mμ) and the appearance of IV (maximum at 270 mμ). The band at 287 mμ which is seen to have grown in Figure 6 is assigned to the hydroxy cation IX; the reason for this assignment is given below.

The changes with time in the visible spectrum of a 15% sulfuric acid solution are also given in detail so as to establish the pattern and to help in justifying our assignments. Figure 7 shows the growth which occurred in the peaks of IV at 437 and 514 mμ. The relative intensities are not suitable to IV, however, since the 437-mμ peak is too intense, but, after a while, absorption at 437 mμ decreased although that at 514 mμ remained unchanged. While absorption at 437 mμ reached a maximum intensity and then declined, a new absorption developed as a shoulder at 545 mμ. Our conclusion is as follows. The growth at 514 mμ was due to the formation of the cation radical, IV. The growth at 437 mμ was due both to IV and another species, which we assign as the hydroxy cation, IX. The subsequent fall at 437 mμ and the rise at 545 mμ were due to the disappearance of IX by its conversion to the hydroxy cation radical XI. Table I and Figure 4 show that this cation radical has a peak in the ultraviolet (at 276 mμ). This peak cannot be seen in the spectrum of the 15% sulfuric acid solution (Figure 6) because of the overshadowing absorption due to IV.

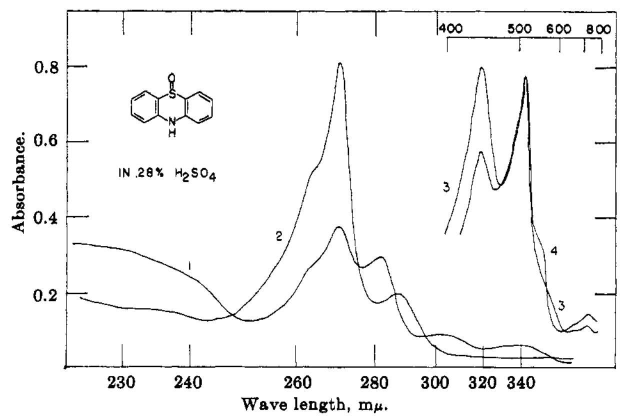

Figure 8.—Phenothiazine 5-oxide in 28% sulfuric acid: ultraviolet spectra of a $7.6 \times 10^{-6}\ M$ solution after (1) 6 min. and (2) 186 min.; visible spectra of a $5.1 \times 10^{-5}\ M$ solution after (3) 1.5 hr. and (4) 22.5 hr.

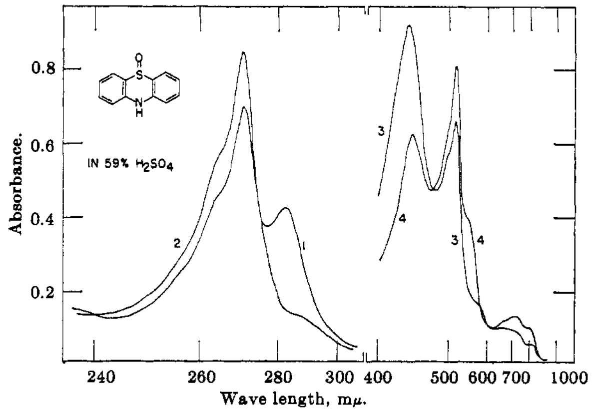

Figure 9.—Phenothiazine 5-oxide in 59% sulfuric acid: ultraviolet spectra of a $7.6 \times 10^{-6}\ M$ solution after (1) 6 min. and (2) 12 hr.; visible spectra of a $5.1 \times 10^{-5}\ M$ solution after (3) 7 min. and (4) 24 hr.

Figures 6 and 7 are summarized, then, as showing the disappearance of II (225, 270, 302, and 336 mμ), the formation of IV (270, 437, and 514 mμ), the formation of IX (287 and 437 mμ), and the conversion of IX to XI (276 and 545 mμ).

Figures 8 and 9 show the trend in the initial state of II in sulfuric acid as the acidity was increased. A new peak was seen at 281 mμ. In Figure 8 this peak accompanies those of II. The 225-, 281-, 305-, and 339-mμ maxima disappeared with time. The peaks due to II were not at all pronounced in the initial spectrum of the 59% sulfuric acid solution, but the peak at 281 mμ was present (Figure 9) and it disappeared with time. The peak at 281 mμ is assigned to the cation V. Figure 8 also shows the growth at 287 mμ which we have attributed to the formation of IX. The visible-region portion of Figure 8, recorded over a later period of time, is interpreted as showing not only the presence of IV in solution but also the presence of IX and its transformation to XI. These transformations are also seen in Figure 9. The changes in the region near 440 mμ are complicated. Not only do IV and IX have

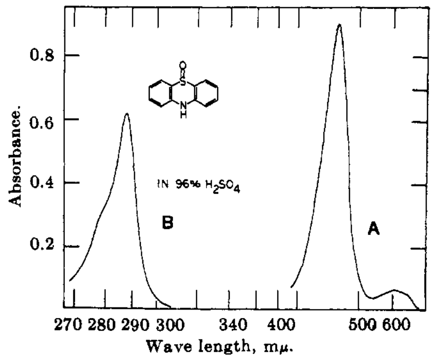

Figure 10.—Spectra of phenothiazine 5-oxide in 96% sulfuric acid: ultraviolet (B), 7.6×10^{-6} M; visible (A), 5.3×10^{-5} M.

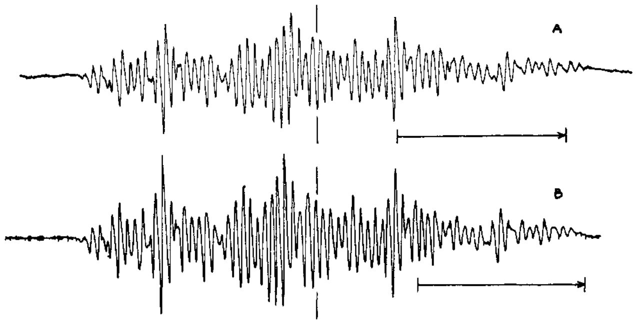

Figure 11.—E.s.r. spectra of (A) a solution of phenothiazine in 59% sulfuric acid, 26 hr. old; (B) phenothiazine 5-oxide in 59% sulfuric acid, 2 hr. old. For scale marks see Experimental.

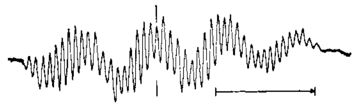

Figure 12.—The e.s.r. spectrum of phenothiazone-3 in 59% sulfuric acid. The solution was 2 hr. old. For scale marks see Experimental.

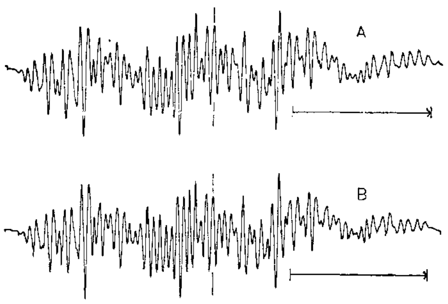

Figure 13.—The e.s.r. spectra of (A) a 3-day-old, 2×10^{-3} M solution of phenothiazine 5-oxide in 59% sulfuric acid and (B) a solution made from mixing equal volumes of 11-hr.-old solutions of 2×10^{-3} M phenothiazine and 1×10^{-3} M phenothiazone-3 in 59% sulfuric acid. For scale marks see Experimental.

maxima in this region, but we conclude from the work with formic acid (below) that V has a peak in this region, too.

Figure 10 shows the spectra of II in 96% sulfuric acid. The solutions were quite stable. The peaks at 287 and 455 mμ are assigned to the dication VI.

II in Formic Acid.—We were able to follow the rapid disappearance of II in 97% formic acid. The initial spectrum with bands at 270 and 306 mμ gave place rapidly to one with a peak at 281 mμ. This in turn was replaced in time with a peak again at 270 mμ. Our assignments here are the rapid transformation of II (270 and 306 mμ) to the cation V (281 mμ) and the slower conversion of the cation V to the cation radical IV (270 mμ).

II in Trifluoroacetic Acid.—II dissolved rapidly in trifluoroacetic acid and the solution became colored immediately. A strong peak at 281 mμ gave place in time to one at 270 mμ. The assignments are like those above.

II in Phosphoric Acid.—A solution of II in 85% phosphoric acid behaved very much like one of II in 59% sulfuric acid. A peak at 283 mμ gave place with time to one at 271 mμ. At the same time the e.s.r. spectrum of the solution grew in intensity.

Irradiation of II in Sulfuric Acid.—Although the absorption spectrum of solutions of II in 96% sulfuric acid did not change with time, a change could be caused by irradiation with ultraviolet light. The change was not noticed in light intensities as low as those used in the recording spectrophotometers, but occurred if a more intense beam was shone on solutions in the spectrophotometer cuvettes. The 287- and 455-mμ peaks decreased while shoulders developed at 271 and 515 mμ. If an irradiated solution was allowed to stand away from the ultraviolet lamp, the change was reversed, the spectra returning in time to what they were initially.

Results. E.s.r. Spectra

The e.s.r. spectrum (A) of I in 59% sulfuric acid is given in Figure 11. The e.s.r. spectrum (B) of a 2-hr.-old solution of II in 59% sulfuric acid is also given. As far as we can tell, the spectra have identical characteristics. The fall in intensity and resolution in going from lower to higher field, characteristic of phenothiazines in concentrated sulfuric acid,[11,19] is seen, but is not so pronounced in the more aqueous acid.

An e.s.r. signal could not be detected from a solution of III in 96% sulfuric acid. On the other hand, a signal was obtained from a solution of III in 59% sulfuric acid, and the signal intensity grew with time. The e.s.r. spectrum is given in Figure 12. In Figure 13 are given (A) the e.s.r. spectrum of a 3-day-old solution of II in 59% sulfuric acid and (B) the spectrum of a mixture of 11-hr.-old solutions of I and III in the same solvent.

Whether or not an e.s.r. spectrum with good resolution was obtained by dissolving II in 96% sulfuric acid depended on the sample of acid. One lot of acid gave solutions for which high instrument signal levels were needed to detect the presence of a radical, and the e.s.r. spectrum recorded consisted of four broad bands. A solution such as this showed electronic absorption spectra only as recorded in Figure 10. Irradiation of such a solution with ultraviolet light caused an increase in radical concentration and enabled a much easier detection of an e.s.r. signal; the e.s.r. spectrum was identical with one from I in 96% sulfuric acid. Where II in another lot of 96% sulfuric acid gave an easily detectable e.s.r. signal without irradiation, the

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(19) J.-P. Billon, G. Cauquis, and J. Combrisson, *J. chim. phys.*, **61**, 374 (1964).

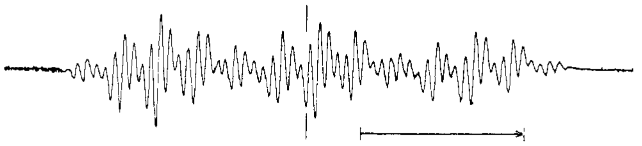


Figure 14.—The e.s.r. spectrum of a solution of phenothiazine in 95% ethanol after irradiation with ultraviolet light. For scale marks see Experimental.

e.s.r. spectrum was again like that of I in 96% sulfuric acid. Irradiation in this case caused an increase in the intensity of the e.s.r. signal. Quantitative measurements of radical concentrations were not made. The variation noted in going from one lot of 96% sulfuric acid to another has been followed carefully in work with thianthrene monoxide, and will be discussed in a future communication.

A solution of I in aqueous acetic acid which had been irradiated with ultraviolet light had an e.s.r. spectrum similar to A in Figure 11. In contrast the irradiation of I in 95% ethanol led to the e.s.r. spectrum shown in Figure 14.

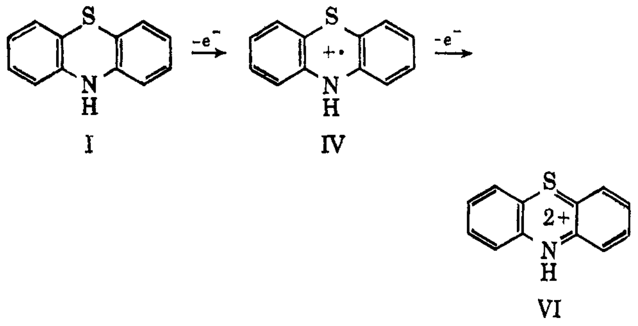
Results. Products

From the analogous work on thianthrene and thianthrene 5-oxide,[7] it was anticipated that the products recoverable from solutions of I and II would be I, II, and III. Our attempts to isolate products quantitatively in the present case were quite unsuccessful. These attempts suffered from inherent difficulty in that the cations and cation radicals of the phenothiazine series are not readily hydrolyzed in dilute acidic solutions. Extraction with cyclohexane and benzene of the aqueous solutions obtained by pouring 10^{-2} M solutions of I or II in 96% sulfuric acid onto ice enabled the recovery of some I and some III. Product balance was never achieved. Analysis of the organic extracts by ultraviolet spectroscopy was carried out. The results, however, were not reproducible. Therefore, it is not possible to present here the kind of product balance that was achieved in the thianthrene system.

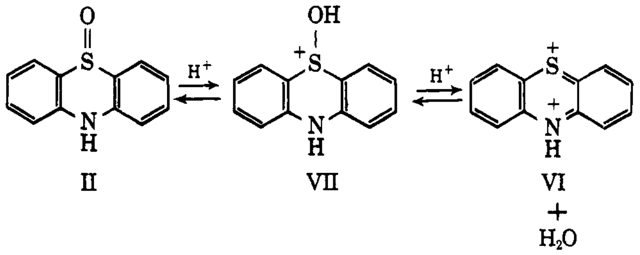
Discussion. Optical Spectra

I and II in 96% Sulfuric Acid.—There seems to be little doubt that Figure 1 shows that the cation radical IV was formed in 96% sulfuric acid and underwent further oxidation. The assignment of peaks for IV in 96% sulfuric acid and in aqueous acetic acid (Figure 2) agrees with the data obtained by Billon[20,21] from anodic oxidation of I in acetonitrile. Billon also reported the second oxidation stage, V, and characterized it with absorption maxima at 281 and 419 $m\mu$. Our results from experiments with II lead to a similar assignment. The final absorption maxima of solutions of I in 96% sulfuric acid as well as those of II in 96% sulfuric acid (287 and 455 $m\mu$) do not differ largely from the aforementioned, but we feel that the difference is significant enough to propose that the maxima at 287 and 455 $m\mu$ characterize not V but its conjugate acid, VI.

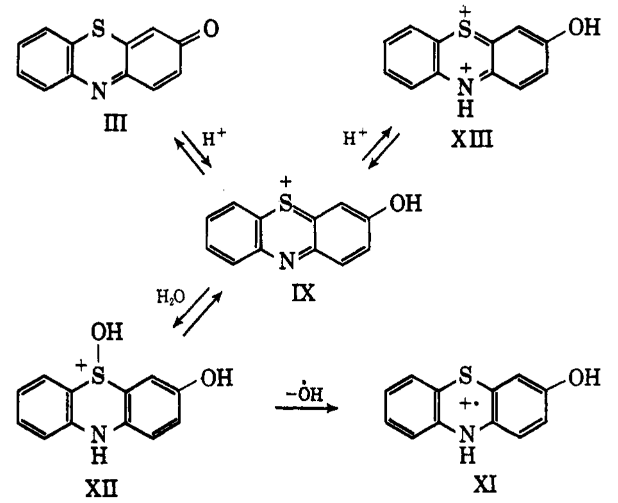
The transformations of I are formulated as follows.



The conversion of II to VI in 96% sulfuric acid is formulated as the carrying of the following equilibria virtually completely to the right.



III in Sulfuric Acid.—The fate of III in sulfuric acid depends on the strength of the acid. We propose that in 96% sulfuric acid (Figure 3) III exists as the dication XIII, but in aqueous acid, for example 59%, the monocation is initially predominant and is the origin of the transformation we have observed (Figure 4). The system is formulated below. We represent, here,



the formation of the cation radical XI from the cation IX as occurring by the homolysis of the intermediate, XII. We are not certain that XII is an intermediate or that, if it is, homolysis is the reaction which converts it to XI. Earlier work[22] and work in progress on the effect of the concentration of thianthrene 5-oxide on its conversion to the thianthrene cation radical in sulfuric acid indicate that the homolysis of a protonated sulfoxide is reasonable. We shall propose further on that this is the reaction that carries II to IV, and we shall also propose that the hydroxyl radical is donated to the solvent and stored as an oxidizing agent.[23] Our formulation of the path from

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(20) J.-P. Billon, *Bull. soc. chim. France*, 1923 (1961).

(21) J.-P. Billon, *Ann. chim.* (Paris), **7**, 183 (1962).

(22) H. J. Shine and T. A. Robinson, *J. Org. Chem.*, **28**, 2828 (1963).

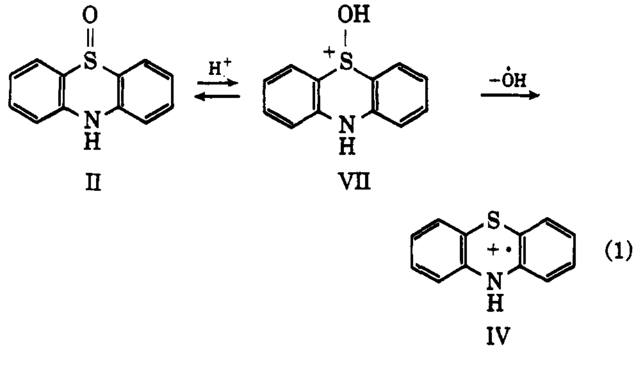
(23) A referee has suggested that the homolysis may be of the sulfate ester.

$$>\overset{+}{S}—OSO_3H \longrightarrow >S^{+\cdot} + \cdot OSO_3H \longrightarrow H_2S_2O_8$$

III to XI is made in part on the basis of our results with III and in part on the basis of our work with the thianthrene oxides.[7,22]

We have seen now that a solution of III in 96% sulfuric acid (Figure 3) is quite different from both a solution of II (Figure 10) and a solution finally achieved from I (Figure 1) in 96% sulfuric acid. It is apparent, therefore, that, although III is prepared by oxidizing I[15] and although solutions of II in 96% sulfuric acid give some III when they are poured onto ice, very little, if any, of III can be present in solutions of I or II in 96% sulfuric acid. When III is formed by pouring a solution of II in 96% sulfuric acid onto ice it must arise from reactions of II in aqueous sulfuric acid. These are, indeed, the very same reactions which we have been following with II and to which we shall now turn.

II in Acids and Other Solvents.—The ultraviolet spectra of solutions of II in the solvents listed in Table I, with the exception of aqueous sulfuric acid, did not change on standing. Changes in these solutions will occur if they are placed in sunlight, but the lack of change to which we refer is in contrast to the behavior in the more acidic solutions. It can be seen that the character of the ultraviolet spectrum of a stable solution of II does not depend much on the solvents used. Solutions of II in 15 and 28% sulfuric acid showed these ultraviolet characteristics during the early part of their life, as shown in Figures 6 and 8. The 270- and 306-mμ peaks were also seen briefly in the spectrum of the formic acid solution. These data indicate that the four peaks recorded in Table I and which disappear from the spectra of the acid solutions are due to the oxide II. Thus, in Figure 6 we are witnessing the disappearance of II and the appearance of the ion radical IV. We propose that IV arises from the loss of hydroxyl from the protonated oxide VII, as shown in eq. 1.

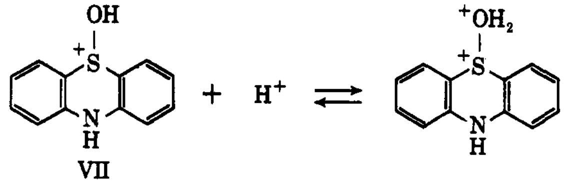


II VII IV (1)

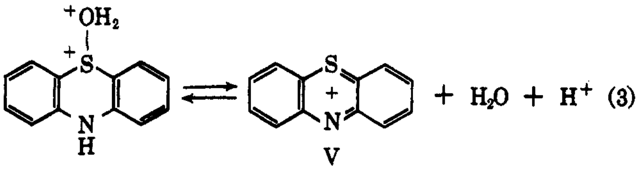
If the disappearing peaks in Figure 6 are those of II, as we propose, we must conclude that VII either absorbs in the same regions as II or that the concentration of VII is too low for the VII to be seen.

When II was dissolved in the acids stronger than 15% sulfuric acid (except 96% sulfuric acid) a new peak was seen which we assigned to the cation V. We propose that V is formed in these solutions by the protonation and dehydration of VII (eq. 2 and 3).

In these solutions, therefore, VII can go either to IV by hydroxyl loss or to V by dehydration. That these reactions can occur both in strong acids such as aqueous sulfuric and weak acids such as formic and phosphoric is relatable to the H_0 and J_0 values of the acids.



VII (2)



V (3)

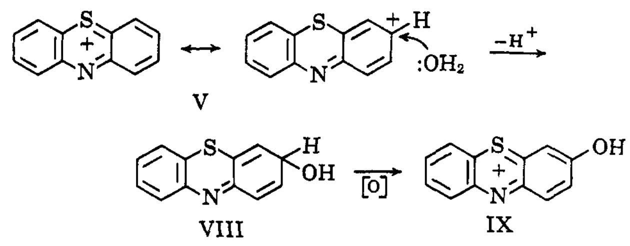
We relate, qualitatively, the ability of an acid to cause reactions 2 and 3 to J_0 values for the want of a more applicable term, recognizing that J_0 applies to carbinols and that, furthermore, the carbinols are not charged. In 15% sulfuric acid protonation can occur but not dehydration; the H_0 and J_0 values are -0.66 and -1.32.[24] In 28% sulfuric acid the corresponding values are about -1.7 and -3.2, while in 59% sulfuric acid they are about -4.4 and -8.9. In line with this, partial dehydration to V is seen in Figure 8 and predominant dehydration in Figure 9. The H_0 and J_0 values of 97% formic acid are about -1.3 and -6.2,[25] so that one can understand that the changes we were following in the ultraviolet and visible spectra of the formic acid solutions were the fast dehydration of VII to equilibrium with V (reactions 2 and 3) and the slower radical formation (1).

The H_0 values for 85% phosphoric[26] and anhydrous trifluoroacetic acid[27] are -3.8 (approximately) and -3.0, respectively. The J_0 values do not appear to be available. Our interpretation of the behavior of II in these acids is the rapid equilibration of V and VII, the VII concentration being too low for appearance in the ultraviolet, followed by the slow conversion of VII to IV.

As for the 96% sulfuric acid, with H_0 and J_0 values of -10.0 and -18, it is not unreasonable to propose the dehydration of VII and the maintaining of V as its conjugate acid, VI.

It remains now to correlate with the behavior of II those features of solutions of III which we also find in solutions of II. We have proposed that some of the spectral changes recorded in Figure 6–9 involve the hydroxy cation IX and the hydroxy cation radical XI. Our view is that IX is formed in aqueous acid solutions of II by the steps set out below.

$$H^+ + \text{II} \rightleftharpoons \text{VII} \overset{H^+}{\rightleftharpoons} \text{V} + H_2O + H^+$$



V VIII IX

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[24] M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957); M. J. Jorgenson and D. R. Hartter, *J. Am. Chem. Soc.*, **85**, 882 (1963).

[25] R. Stewart and T. Mathews, *Can. J. Chem.*, **38**, 602 (1960).

[26] E. Heilbronner and S. Weber, *Helv. Chim. Acta*, **32**, 1513 (1949).

[27] H. H. Hyman and R. A. Garber, *J. Am. Chem. Soc.*, **81**, 1847 (1959).

The nucleophilic reaction of water with V is analogous to the proposal that has been made for reductive chlorination of oxides of phenothiazine and thianthrene.[28] The last step, the conversion of VIII to IX, is an oxidation. Whether this occurs directly on VIII, or whether VIII tautomerizes to 3-hydroxyphenothiazine (X) first, cannot be said. In either case, the oxidant is available from the sequence of reactions proposed earlier (eq. 1) in which a hydroxyl group is lost and stored either as a peroxysulfuric acid or hydrogen peroxide. Oxidations which occur in solutions of II cannot be of the kind that give rise to sulfur dioxide, because this compound is not detected. This is also true in the analogous reactions of thianthrene 5-oxide.[7] The transformation of IX to the cation radical XI is formulated in the discussion of the fate of III in sulfuric acid.

It will be noted that our proposals for the reactions of II in acid solution are similar in kind, but not in detail, to those made by Kehrmann.[12] Kehrmann's mono- and diacid holoquinoid salts are our V and VI, and his semiquinoid salt is, of course, the ion radical IV. Kehrmann's assignments, made without the use of instruments available to modern workers, are to be admired.

It was suggested recently[29] that the ultraviolet spectrum of solutions of phenothiazine derivatives in 50% sulfuric acid, together with paper chromatography, will provide a technique for the estimation and identification of the derivatives in clinical chemistry. It was noted also[29] that fluopromazine and its oxide had the same ultraviolet spectrum but different visible spectra in this solvent. The last observation can be understood on the basis of our present work. If the fluopromazine cation radical and thionium ion have somewhat similar ultraviolet spectra but different visible spectra, it may have been that both species were present and were observed in the sulfoxide solution. It appears to us, in view of the changes in, and interrelationships of, the spectra of I, II, and III in sulfuric acid solutions, that the quantitative estimation of phenothiazine derivatives in 50% sulfuric acid may be unachievable.

Irradiation of I and II in Acid Solutions.—The formation of IV by the ultraviolet irradiation of I in solution was proposed some years ago.[4] The spectra in Figure 2 were recorded after periods of irradiating a solution in aqueous acetic acid. The uniformity in the spectra obtained after increasing periods of irradiation and the e.s.r. spectrum indicated that photooxidation to IV without further reactions was occurring.

We have found that acidic solutions of II will also give IV if irradiated. Solutions of II in 96% sulfuric acid do not show a high radical concentration. The concentration can be increased by irradiation with an ultraviolet lamp and the formation of IV can be detected in the ultraviolet and visible regions, and by e.s.r. spectroscopy. The development of IV by irradiation is accompanied by a decrease in the concentration of VI. The reaction occurring we believe is as in eq. 1 but is now photoinduced. IV will slowly revert to VI if irradiation is stopped, and this is due to oxidation of IV, just as is seen in Figure 1.

Discussion. E.s.r. Spectra

The e.s.r. spectrum of IV has been discussed most recently by Odiot and Tonnard.[30] The spectrum (A) given in Figure 11 is very similar to those reported for IV by others. We found that the more aqueous the acid the better was the resolution of the e.s.r. spectrum in the higher field region. This may have been due to the removal of anisotropy effects as the viscosity of the solution was lowered. The spectrum of the corresponding anion radical has been reported,[31] and the asymmetry of the spectrum, like that of IV, has been commented on.

The e.s.r. spectrum of XI, seen in Figure 12, appears to be identical with that recently obtained by Billon[19] by the cathodic reduction of III in acidic acetonitrile. Billon[21] observed changes in color and optical spectra of solutions of III in aqueous acid but was unable to detect a radical. The e.s.r. spectrum in Figure 12, obtained from III in 59% sulfuric acid, is a quartet, arising from approximately equal coupling with the nitrogen and hydrogen of the -NH group and further splittings by the ring protons. We are not sure that coupling with the hydroxyl proton occurs, as proposed by the French group,[19,30] since our spectrum is very similar to that of the 3-methoxyphenothiazine cation radical.[32]

The spectrum (B, Figure 11) obtained from a 2-hr.-old solution of II in 59% sulfuric acid is, as far as we can tell, identical with that of I in 59% sulfuric acid. From our foregoing discussion and optical spectra we would have expected that the e.s.r. spectrum of the solution of II would show the presence of some XI. This is indeed the case in aged solutions of II as shown in Figure 13. In the spectrum of the mixture of I and III distortion of the spectrum of IV is caused by overlap with that of XI. Although the solution in which the overlapping of spectra is seen was initially 1×10^{-3} M in I and 0.5×10^{-3} M in III, we do not know what the concentrations of the derived radicals IV and XI were. The similarity between the spectrum of this solution and that of the aged 2×10^{-3} M II is striking.

Thus, on all counts, from ultraviolet, visible, and e.s.r. spectroscopy the formation of the radical XI as part of the system of II in acids is demonstrable.

The irradiation of solutions of I in aqueous acetic acid led to IV; the e.s.r. spectrum, like the visible spectrum, was that of IV. On the other hand, irradiation in ethanol gave a radical whose e.s.r. spectrum (Figure 14) appears to be a major triplet split into two sets of overlapping quintets. This spectrum may be that of the free radical XIV. If this is so, XIV must be a strong enough base to be protonated in aqueous acetic acid. The photooxidation of I in these solvents requires

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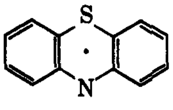
[28] Part VII: H. J. Shine and C. F. Dais, *J. Org. Chem.*, **30**, 2145 (1965).

[29] H. V. Street, *Chem. Ind.* (London), 1501 (1962).

[30] S. Odiot and F. Tonnard, *J. chim. phys.*, **61**, 382 (1964).

[31] M. Bruin, F. Bruin, and F. W. Heineken, *J. Org. Chem.*, **29**, 507 (1964). The hyperfine splitting[1] for the thianthrene cation radical is quoted in this paper as 1.62 instead of 1.32 gauss.

[32] L. H. Piette, G. Bulow, and I. S. Forrest, International Conference on Metabolism Excretion and Action Mechanism of Psychoactive Drugs Derived from Phenothiazine or Structurally Related Compounds, Paris, Sept. 1962. We are indebted to Dr. Piette for copies of his spectra and manuscript.



XIV

the removal of a hydrogen atom, but we have not investigated this facet of the reaction. The formation of the hexamethylbenzene cation radical by the photolysis of a solution of hexamethylbenzene in sulfuric acid has been reported.[33] The photoxidation of I in aqueous acetic acid occurs very readily, even in indirect sunlight.

Piette and Forrest have reported[10] that the ultraviolet irradiation of phenothiazine derivatives in aqueous solution gave different colors and e.s.r. spectra from the chemical, enzymatic, and anodic oxidation of the same derivatives. The e.s.r. spectra from photooxidation were not given.[34]

Experimental

Materials.—Phenothiazine, practical grade, Distillation Products Industries, was recrystallized from butanol and had m.p. 182–184°. Phenothiazine 5-oxide, practical grade, Matheson Coleman and Bell, was recrystallized from 95% ethanol and had m.p. 251–253°. Phenothiazone-3 was prepared by the method of Bodea and Raileanu,[15] with some modification. The product first deposited from solution had m.p. 161–163°, but was found by thin layer chromatography to contain more than one component, and left a residue on ignition. The product, therefore, was sublimed under vacuum with heating from boiling xylene. Fine, dark red needles were obtained, m.p. 162–163°, lit.[15] m.p. 161–162°. Sulfuric acid was Baker's analyzed reagent grade, 95.9%. Trifluoroacetic acid was from Matheson Coleman and Bell. A solution of thianthrene in the acid did not become colored on standing,[7] and the acid was, therefore, considered acceptable for use without purification. Formic acid was Baker and Adamson's C.P. grade; titration showed it to be 96.5%. Phosphoric acid (85%) was from Baker and Adamson.

Absorption Spectra.—Changes in the absorption spectra that occurred with time were recorded for the most part with a Beckman Model DK-2 spectrophotometer. This instrument permitted the repeated recording of scans on the same chart. In some of the work with trifluoroacetic and formic acids, where more rapid scanning was required, a Cary Model 14 spectrophotometer was used. In this case spectra were recorded on a moving strip chart and are, therefore, not presented as figures. Acidic solutions in which spectral changes were recorded were made as follows. A stock solution of the substrate in a volatile solvent was made. An appropriate aliquot was evaporated to dryness at reduced pressure in a volumetric flask, to which the required acid was then added. Stock solutions of phenothiazine 5-oxide were in ethanol and were kept in the dark. Stock solutions of phenothiazine and phenothiazone were in ethanol, benzene, or cyclohexane. The solutions were made immediately before use. Where there was a delay before use the solutions were kept in the dark.

The ultraviolet data in Table I were obtained with the Cary instrument. This instrument was also used in attempts to determine by ultraviolet spectroscopy the yields of products obtained by pouring acid solutions onto ice.

Products.—Attempts were made to isolate products from solutions of I or II in 96% sulfuric acid by pouring them onto ice. The use of concentrated solutions, such as 10^{-1} *M*, gave very deeply colored solutions after pouring onto ice, from which very little solid matter precipitated. Extraction of these solutions with cyclohexane enabled the recovery of phenothiazine, as demonstrated by the ultraviolet spectrum and melting point of the recovered solid. Subsequent extraction with benzene gave red solutions from which some phenothiazone was recovered by chromatography. However, product balance was never achieved. It was not possible, for example, to find phenothiazine 5-oxide in the extracts from the aqueous acid.

It was found that known mixtures of phenothiazine and phenothiazone in cyclohexane and benzene could be quantitatively analyzed by ultraviolet and visible spectroscopy. Therefore, attempts were made to analyze for reaction products by pouring 10^{-2} *M* solutions of I or II onto ice and extracting first with several portions of cyclohexane and next with several portions of benzene. Spectroscopic analysis of the two solutions was carried out, but in 15 separate experiments product balance and reproducibility were poor. It was found that the incorporation of ferrous sulfate in the ice slurry uniformly, but not reproducibly, increased the amount of recovered phenothiazine. This technique has been used very successfully in work with thianthrene 5-oxide and will be reported in a future communication.

E.s.r. Spectra.—The equipment and calibration methods have been described earlier.[1] The scale mark on the figures is 10 gauss and shows increasing field. The vertical line indicates the center of a potassium nitrosodisulfonate spectrum. The spectrum of a solution of phenothiazine in 59% sulfuric acid was not changed after bubbling nitrogen through the solution for 5 min. while the cell remained in the instrument.

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(33) R. Hulme and M. C. R. Symons, *Proc. Chem. Soc.*, 241 (1963).

(34) Dr. Piette has informed us, further, that the irradiation of phenothiazine in ethanol has been investigated in this laboratory.