[Contribution from the Cobb Chemical Laboratory, University of Virginia]

THE THERMAL AND PHOTOCHEMICAL AIR OXIDATION OF PHENOTHIAZINE[1]

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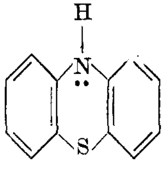
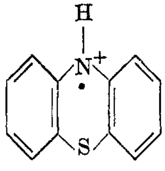
Received August 15, 1955

The sensitivity of phenothiazine to oxidation was observed in early investigations (1). While several oxidation products have been identified and others have been encountered as unstable, often highly colored substances, the course of the oxidation of phenothiazine by air alone has not been studied. In view of the current interest in phenothiazine derivatives, both as antioxidants and in medicine, we are presenting the results of experiments in which oxidation was accelerated by heating or illuminating solutions of phenothiazine in the presence of air.

Thermal oxidation. When air was passed through solutions of phenothiazine (I) in bis(2-ethylhexyl) sebacate at 200°, oxygen was absorbed, the solution turned red, and eventually a black, insoluble sludge formed. A red condensate appeared in unheated parts of the system. The reaction mixture produced brown, violet, and red bands in a chromatographic adsorption column. The red substance was apparently phenothiazone-3 (VII) for this compound was isolated from the reaction mixture.



I



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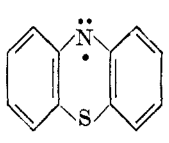

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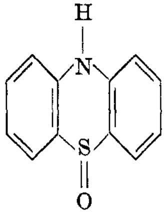

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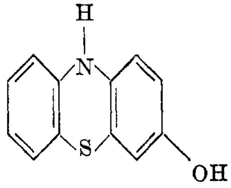

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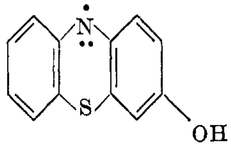

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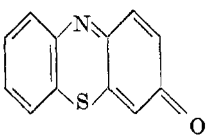
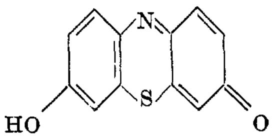


VII



VIII

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[1] From the dissertation of Gordon P. Brown, University of Virginia, 1954. This work was done under the financial sponsorship of the Materials Laboratory, Wright Air Development Center, Wright-Patterson Air Force Base, Ohio.

Although phenothiazine-5-oxide (IV), which is a colorless substance, was not isolated, 10-methylphenothiazine formed 10-methylphenothiazine-5-oxide under the same conditions and since IV was oxidized to VII, it is probable that IV was present.

Photochemical oxidation. When a 1% solution of phenothiazine in chloroform was irradiated in sunlight, a yellow-orange color was immediately observed, followed by a green color which spread downward from the surface. If, however, the solution was irradiated under a good vacuum, the yellow-orange color slowly changed to an intense blue which on contact with air, instantly became green. The green material was easily precipitated and isolated, but has not yet been identified; it is further described in the experimental section.

The manner in which the visible absorption spectrum changes with time in irradiated solutions is shown in Fig. 1. After only one minute's irradiation, well defined maxima appear at 523 and 436 mμ, with smaller peaks at 480 and 502 mμ. This spectrum is very similar to the one obtained by Michaelis, Granick, and Schubert (2) after the irradiation of I in aqueous acetic acid, producing the free radical II. The uncharged radical III, for which Lewis and Bigeleisen (2) found absorption maxima at 527 mμ and 500 mμ is probably also present in the chloroform solution.

Simultaneously with these changes, the sharp peak at 255 mμ disappeared as phenothiazine was consumed. After 15 minutes, peaks at 272, 299, and 335 mμ were observed, which correspond to the spectrum of phenothiazine-5-oxide. Finally, after three hours, the sample showed the spectrum (3) of phenothiazone-3. These two compounds, IV and VII, were isolated after the irradiation of phenothiazine in ethanol.

The violet fraction mentioned above was found here also. It seemed to be formed sooner than VII and may be the semiquinone VI, intermediate in oxidation level between the very easily oxidized 3-hydroxyphenothiazine (V) and phenothiazone-3 (VII). Hilditch and Smiles (4) have shown that IV is rearranged to V by heating with weak acids.

Thionol (VIII), obtainable by chemical oxidation (5) or by metabolism (6) of I, has not been isolated from the isoöctane-soluble fractions of our reaction mixtures.

Phenothiazine as an antioxidant. Oxygen, when passed through bis(2-ethylhexyl) sebacate at 200°, was absorbed at a rapid, fairly constant rate. The introduction of 0.5–2.0% phenothiazine resulted in a short period of initial absorption, followed by a longer period of almost no absorption, after which absorption again took place rapidly. The amount of oxygen absorbed was paralleled by the change in certain properties of the solvent such as viscosity and acid content.

Two facts relevant to the present discussion were apparent from these oxidation studies. First, the amount of oxygen initially absorbed in the presence of I was roughly proportional to the amount of I present. This indicated that I, II, or III was reacting with oxygen.

The compound giving the longest period of slow oxygen absorption was

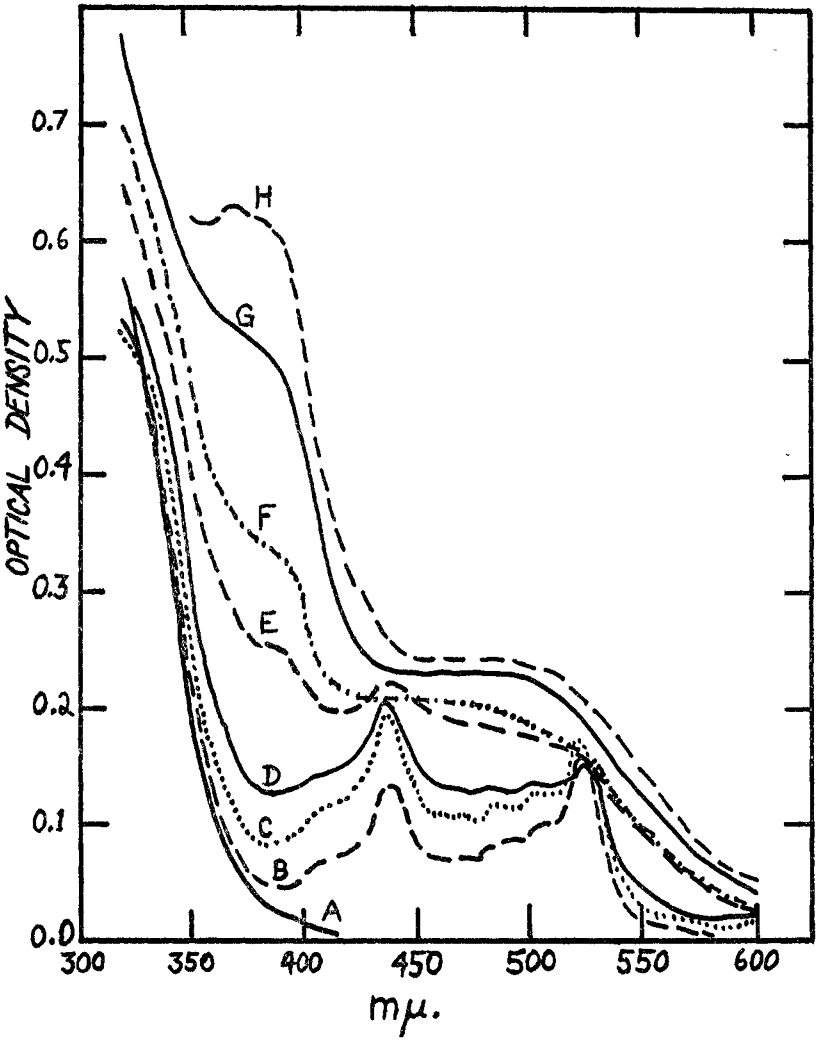

FIG. 1. CHANGE IN ABSORPTION SPECTRUM OF PHENOTHIAZINE, IRRADIATED IN CHLOROFORM, conc'n 0.0258 g./l. A, before irradiation; B, 1 min.; C, 2.5 min.; D, 10 min.; E. 30 min.; F, 60 min.; G, 120 min.; H, 210 min.

neither I nor IV, but phenothiazone-3 (VII). The exact mechanism of the antioxidant action of I cannot be given until the rate of oxidation of the solvent can be distinguished from the rate of oxidation of I. It appears possible, however, that the redox system V–VI–VII is at least partly responsible for the efficiency of phenothiazine as an antioxidant (7).

EXPERIMENTAL

Thermal oxidation. To 100 ml. of bis(2-ethylhexyl) sebacate was added 5.0 g. of phenothiazine. The solution was placed in a Pyrex cell fitted with a reflux condenser and an air inlet tube extending nearly to the bottom of the cell. After one hour of preliminary heating at 200° in an aluminum-block thermostat, the air flow was started at a rate of 5 liters per hour and was maintained for 12 hours. The oxidized sample was filtered and the filtrate was taken up in isoöctane and refiltered. After distilling off the isoöctane, the oil was continuously extracted with water for 12 days. The red aqueous extract was extracted with ether and the ether solution was dried over sodium carbonate. The 35 mg. of red-brown material remaining after removal of the ether was dissolved in benzene-petroleum ether (1:1) and chromatographed. The red band was eluted from the alumina with ethanol. Upon adding a little water and cooling, 15 mg. of phenothiazone-3 was obtained; m.p. 160–161°, corr., alone and in mixture with authentic VII. The x-ray diffraction pattern indicated that the material consisted chiefly of VII, as did the ultraviolet absorption spectrum.

The same procedure and evidence of structure were used in the oxidation of phenothiazine-5-oxide (IV) to VII; m.p. of product, 157.5–158°, corr. Mixture m.p. 158.5–159°.

The isoöctane-insoluble fraction of the reaction mixture was a high-melting, apparently polymeric, sulfur-containing substance.

After the oxidation, by the same procedure, of 10-methylphenothiazine, enough water was added to the isoöctane solution to cover the bottom of the flask. Over a 3–4 day period white needles crystallized at the interface, m.p. 174.5–175.7°; after crystallizing from ethanol, 179–179.3°, corr. The m.p. of a sample of 10-methylphenothiazine-5-oxide was 190.5–191.5° corr. The oxidation product was therefore mixed with a trace of the known sample; the m.p. rose to 191.5–192.5°, corr., showing it to be an isomorph of 10-methylphenothiazine-5-oxide.

Anal. Calc'd for $C_{13}H_{11}NSO$: C, 68.09; H, 4.84.
Found: C, 68.02; H, 5.01.

Photochemical studies. Commercial phenothiazine was recrystallized from an acetone-isoöctane mixture and was vacuum-sublimed twice; m.p. 185–185.5°, corr. The spectra shown in Fig. 1 were obtained by illuminating solutions of phenothiazine in chloroform (0.0258 g./l.) in 25-ml. Pyrex flasks, maintained at 20°, and 30 cm. from a General Electric sunlamp. The undiluted samples were placed in the spectrophotometer.

Samples, containing about 0.005 g./l. of phenothiazine did not give a green color while illuminated. However, the green did appear if, after one minute's illumination, the solution was allowed to stand in the dark for 4 hours.

Samples containing 10 g./l. of phenothiazine in chloroform yielded a green precipitate which melted with decomposition at about 250° after two vacuum sublimations; this solid was slightly soluble in chloroform, ethanol, and acetone.

Irradiation of solutions of phenothiazine in carbon tetrachloride caused the separation of a very dark green precipitate. An alcohol solution of this material was intense green at first, changing to blue and finally to red. The green crystals obtained from the red solution became lighter with successive crystallizations until a very pale green material, m.p. 166–167°, was obtained, which was not identified.

Irradiation of 2 gm. of phenothiazine in 200 ml. of 95% ethanol for 23 hours in a stream of air gave a red solution from which was recovered by recrystallization 0.3 g. of white needles, m.p. 255°, dec.; mixture m.p. with phenothiazine-5-oxide (IV) 252.5° dec.

Irradiation of 50 gm. of phenothiazine in 5 liters of 95% ethanol in a stream of air for 48 hours gave a red-brown residue after distilling off the ethanol. This material was adsorbed on alumina from a 1:1 petroleum ether-benzene solution. When the column was developed with this solvent and with pure benzene, a gold band appeared at the top, then a narrow purple band, and below this, a dark red band, contaminated with purple at its upper surface. Elution of the red band and recrystallization gave 25 mg. of phenothiazone-3, m.p. 159–159.5°, corr. Ultraviolet spectra and x-ray diffraction patterns confirmed the identity of the product.

Acknowledgement. We are indebted to Dr. Kenneth R. Lawless for the x-ray diffraction patterns.

SUMMARY

The oxidation of phenothiazine by air at 200°, in a diester solvent, yields phenothiazone-3 and intermediate oxidation products. Phenothiazine-5-oxide and phenothiazone-3 were isolated from alcoholic solutions of phenothiazine irradiated at room temperature, and the spectra of certain free radicals were observed in chloroform solution.

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