and antimony(V) solutions, of mixed tin(II) and tin(IV) solutions, and of mixed arsenic(III) and arsenic(V) solutions, all in hydrochloric acid, have been studied. The first two systems in solution in concentrated hydrochloric acid exhibit the phenomenon of "interaction absorption."

The optical density of interaction absorption for the mixed antimony solutions is proportional to the product of the concentrations of the antimony(III) and antimony(V) implying that the absorbing species is a dimeric complex containing one Sb(III) and one Sb(V). In 3.5 *F* hydrochloric acid, there is no marked interaction absorption.

The spectroscopic results indicate that Sb(III) exists as the same ion or molecule in concentrated and 3.5 *F* hydrochloric acid but that Sb(V) undergoes hydrolysis from an ion like $SbCl_6^-$ to an ion of the type $SbCl_x(OH)_{6-x}^-$ as the hydrochloric acid concentration is decreased from *ca.* 11 *F* to 3.5 *F*.

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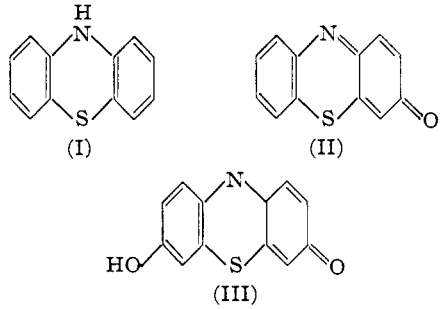
[CONTRIBUTION FROM THE WESTERN REGIONAL RESEARCH LABORATORY[1]]

Phenothiazine Derivatives: Mono-oxygenated Compounds

BY DAVID F. HOUSTON, E. B. KESTER AND FLOYD DEEDS

Phenothiazine (I) has been shown[2] to have *in vitro* tuberculostatic action which is somewhat diminished in the presence of serum. The oxidized derivatives known as phenothiazone (II) and thionol (III) also showed a moderate inhibiting effect, and it was postulated that their lesser effectiveness might be connected with their decreased solubility in lipids. Compounds having



substituents on the nitrogen were relatively ineffective, suggesting that the nitrogen should be free to take part in oxidation–reduction effects.

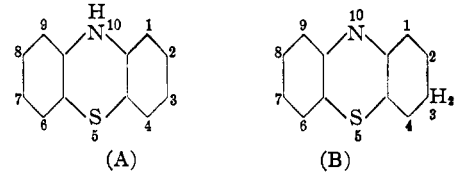
The indications are, therefore, that compounds related to phenothiazine and thionol which have unsubstituted nitrogen atoms and increased lipid solubilities might show greater tuberculostatic action. A number of compounds meeting these requirements have been synthesized, and this paper reports a series of ethers related to phenothiazone.[3]

Phenothiazone-3 was first prepared as a noncrystalline compound by Bernthsen[4] by fusion of *p*-hydroxydiphenylamine with two atoms of sulfur, recovery as 3-hydroxyphenothiazine, and oxidation with ferric chloride. Kehrmann[5] later obtained it as a crystalline product, melting at 165–166°, by ferric chloride oxidation of phenothiazine in hot aqueous alcohol. A convenient modification of this method by Pummerer and Gassner[6] gave a product melting at 162–163°. A reported improvement of this process is the subject of a recent patent.[7] The crude product is recrystallized and 45% of phenothiazone-3 melting at 163–164° is obtained. Similarly, Granick, Michaelis and Schubert[8] recrystallized the product from the reaction and found a melting point of 161°. Small-scale experiments in this Laboratory have given yields up to 62.5%, though the reaction was very susceptible to changes in process conditions.

(1) Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted. Presented at A. C. S. meeting, San Francisco, California, March 27–April 1, 1949.

(2) B. L. Friedlander, *Proc. Soc. Exptl. Biol. Med.*, **57**, 106–107 (1944).

(3) The awkwardness in naming derivatives of phenothiazine and related compounds has been pointed out by Michaelis and co-workers [THIS JOURNAL, **62**, 1802 (1940), and **63**, 351 (1941)], who also emphasized that the difficulties were greater with the quinonimine or oxidized form than with the hydroxyamine or reduced form. This trouble is largely overcome, however, by basing names of reduced-from compounds on the phenothiazine skeleton A (Ring Index No. 1860) and those of oxidized-form compounds on the theoretical 3-isophenothiazine skeleton B (Ring Index No. 1859).



Although this has the disadvantage of naming the reduced and oxidized forms of a compound on the basis of two isomeric ring skeletons, it offers a systematic nomenclature for phenothiazine derivatives that conforms with the present usage of *Chemical Abstracts*. The disadvantage has been avoided, at least in part, in this paper by the common use of the term phenothiazine (Skeleton A) to denote the parent compound of derivatives of the reduced form, and phenothiazone-3 instead of 3-isophenothiazine-3-one (from Skeleton B) as the parent compound for derivatives of the oxidized form.

(4) A. Bernthsen, *Ann.*, **230**, 182 (1885); *Ber.*, **17**, 2860 (1884).

(5) F. Kehrmann, *Ann.*, **322**, 54 (1902).

(6) R. Pummerer and S. Gassner, *Ber.*, **46**, 2324 (1913).

(7) Nederlandische Centrale Organisatie voor Toegepast Natuurwetenschappelijk Orderzoek, Dutch Patent 59,559, June 16, 1947, *C. A.*, **41**, 5557 (1947).

(8) S. Granick, L. Michaelis and M. P. Schubert, THIS JOURNAL, **62**, 1802 (1940).

For the preparation of larger quantities, attention was turned to fusion experiments. Preliminary fusions of aniline, hydroquinone and sulfur[9] were unpromising. The preparation according to Bernthsen[4] proceeded rapidly and smoothly at 185–195° when catalyzed with iodine. Reaction was complete within a half hour, and phenothiazone-3 was consistently recovered in 41–47% yield. Recovery consisted in aeration of a suspension of the ground product in dilute aqueous alkali, and extraction of the phenothiazone-3 from the dried insoluble solids with hexane. Methods of recovery have been incompletely explored, and higher yields may be possible.

The isopropyl, octyl, dodecyl and hexadecyl ethers of 3-hydroxyphenothiazine were similarly prepared from the corresponding *p*-alkoxydiphenylamines, which were readily formed by etherification of *p*-hydroxydiphenylamine.[10] The methyl ether has previously been prepared by this fusion process by Baltzly, Harfenist and Webb[11] and by Gilman and Shirley.[12] Agreement between properties of the compounds so prepared with those of the product from methylation of 3-hydroxyphenothiazine by dimethyl sulfate[6] confirms the position of the ether group.

Sulfur fusions proceeded more smoothly with the ethers than with the free hydroxyl compound, and gave the *n*-alkoxyphenothiazines as light yellow solids in 80–84% yields. The 3-isopropoxy ether was obtained in 60% yields; more vigorous fusion conditions led to some decomposition.

The 3-alkoxyphenothiazines are insoluble in water and appreciably more soluble in organic solvents than is phenothiazone-3. They are readily susceptible to oxidation and tend to discolor when exposed to light and air. Their similarity in structure to that of phenothiazine is indicated from the similarity of the ultraviolet absorption curves.

Ultraviolet and visible absorptions of a number of compounds have been measured for control and comparison purposes. The differences between the absorption curves for phenothiazine (maxima at 254 and 318 mμ, inflection at 285), phenothiazine-5-oxide (228, 272, 302, 337 mμ) and phenothiazone-3 (236, 273, 357, 505 mμ)—all in methanol—are shown in Fig. 1. Substitution of a hydrocarbon or ether group for the hydrogen at the 3-position of phenothiazine caused only slight changes in the absorption in the range covered (maxima for 3-methylphenothiazine at 255 and 320 mμ; see also Table I). However, indications point to differences at lower wave lengths.

(9) Gesellschaft für Chemische Industry in Basel, Swiss Patent 204,521, Aug. 1, 1939.

(10) D. F. Houston, THIS JOURNAL, **71**, 395 (1949).

(11) R. Baltzly, M. Harfenist and F. Webb, *ibid.*, **68**, 2673 (1946).

(12) H. Gilman and D. Shirley, *ibid.*, **66**, 888 (1944). Professor Gilman kindly supplied samples of 3-methyl- and 3-methoxyphenothiazine.

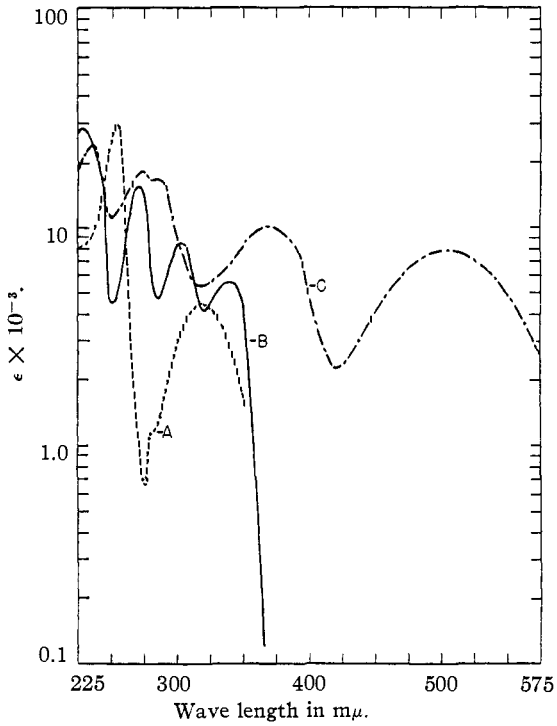


Fig. 1.—Molar extinction curves in absolute methanol (measured on solutions containing 3 to 10γ of solute per ml. of solution): (A) phenothiazine; (B) phenothiazine-5-oxide; (C) phenothiazone-3.

Phenothiazine had essentially the same maxima in isoöctane (254, 315 mμ) as in methanol. Phenothiazone-3, however, showed considerable shift with change in solvents as measured in the visible range.[13] The main absorption peak for a series of solvents was located as follows: Skellysolve B[14] (478), ether (482), benzene (490), chloroform (502), methanol (505) and water (533). The absorption of phenothiazone-3 is in agreement with the results of previous investigators.[4,8,15] The tuberculostatic properties of these compounds are the subject of other investigations, and the findings will be reported elsewhere.

Experimental[16]

A. Materials.—**Phenothiazine** was recrystallized from benzene and washed with commercial hexane before use.

***p*-Hydroxydiphenylamine,**[17] purified by distillation with superheated steam, followed by recrystallization from benzene–hexane,[10] consisted of pearly flakes melting at 69–70° in agreement with the reported[18] value of 70°.

(13) Measurements were made with a Hardy–General Electric Recording Spectrophotometer.

(14) Skellysolve B is named as part of the experimental conditions. Its use does not imply recommendation over other solvents having the same properties.

(15) (a) F. Eckert and R. Pummerer, *Z. physik. Chem.*, **87**, 612 (1914); (b) R. Pummerer, F. Eckert and S. Gassner, *Ber.*, **47**, 1498 (1914).

(16) All melting points are corrected unless otherwise indicated. Nitrogen analyses were made by the Kjeldahl procedure of White and Secor, *Ind. Eng. Chem. Anal. Ed.*, **18**, 457 (1946).

(17) Furnished by courtesy of the B. F. Goodrich Chemical Company.

(18) A. Calm, *Ber.*, **16**, 3799 (1883).

TABLE I

3-ALKOXYPHENOTHIAZINES

R in formula $C_{12}H_8NOSR$[a]	M. p., °C.	Empirical formula	Analytical data, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Absorption maxima mμ
Isopropyl	123.0–123.7	$C_{15}H_{15}NOS$	70.00	70.2	5.88	5.88	5.44	5.46	255, 320
n-Octyl	110.1–111.5	$C_{20}H_{25}NOS$	73.35	73.1	7.70	7.52	4.28	4.31	255, 320
n-Dodecyl	101–103	$C_{24}H_{33}NOS$	75.15	75.1	8.67	8.61	3.65	3.65	.....
n-Hexadecyl	101.5–103	$C_{28}H_{41}NOS$	76.48	76.4	9.40	9.30	3.19	3.21	.....

[a] The methoxy compound, $C_{13}H_{11}NOS$, has previously been reported as melting at 158–159,[12] 159,[20] 160–161[11] and 163°.[6] It shows absorption maxima at 254 and 322 mμ in methanol.

p-**Alkoxydiphenylamines** were prepared and purified by methods previously described.[10]

Phenothiazine-5-oxide (sulfoxide) was made according to Pummerer and Gassner.[6]

B. Preparation of Phenothiazone-3 by Oxidation of Phenothiazine.—The best preparation by the method of Pummerer and Gassner[6] confirmed their results; 1.0 g. of phenothiazine yielded 0.67 g. (62.5%) of coppery granular solids that melted at 160.5–162°. The filtrate was digested for one hour on the steam-bath, cooled and filtered. Rusty purple solids weighing 0.29 g. remained.

In other experiments, differing in slight details, the purplish solids formed the main precipitate in yields of 62–96%. A composite sample (2.46 g., 76% yield) was treated by extraction with and precipitation from alcohol (210 cc.) then similarly with water (3000 cc.) according to the purification scheme of Granick, Michaelis and Schubert.[3] The yield was 0.77 g. of phenothiazone-3 (25% based on phenothiazine) melting at 160–161°.

Anal. Calcd. for $C_{12}H_7ONS$: N, 6.57. Found: N, 6.52.

C. Phenothiazone-3 by Sulfur Fusion of *p*-Hydroxydiphenylamine.—Fusion was essentially according to Bernthsen[4] except that iodine was added as catalyst. A mixture of 3.7 g. (0.02 mole) of *p*-hydroxydiphenylamine and 1.4 g. (0.044 g. atom) of sulfur was ground in a mortar and placed in a 50-cc. distilling flask carrying a bubbler tube on the side-arm. Then 0.04 g. of iodine was added, and the flask was stoppered and placed in a metal-bath preheated to 180°. Bath temperature was held at 185–195° during the fifteen to twenty minutes that gas evolution continued, and for an added ten minutes. The reaction mixture was poured into a porcelain dish and allowed to cool. It crystallized in a cake of dark greenish-brown solid which melted at 170–175° (rapid heating in capillary tube, uncorrected). DeEds and Thomas[19] reported a melting point of 172–174° for 3-hydroxyphenothiazine.

The fusion product was ground with 200 cc. of 0.5% potassium hydroxide per gram, aerated for thirty to forty-five minutes, filtered and washed with cold water. The dried solids were extracted with commercial hexane until the extracts were no longer orange. Evaporation of the solvent left a rust-red crystalline residue of phenothiazone-3. Further purification was achieved by crystallization from aqueous alcohol or—for small amounts—from water. The product melted at 161°, and was identical with the phenothiazone from the oxidation reaction. Yields varied from 40–45%.

Anal. Calcd. for $C_{12}H_7ONS$: N, 6.57. Found: N, 6.53.

Use of this recovery process has shown that the reaction is relatively insensitive to a small excess of either reactant.

Phenothiazone-3 can be separated from congeners by adsorption from hexane or benzene solutions on alumina, followed by elution with benzene containing 20% of chloroform. The phenothiazone-3 is collected in the eluate and recrystallized by concentration of the solution. It may be sublimed slowly at boiling xylene temperatures in the vacuum of a mechanical pump.

D. 3-Isopropoxyphenothiazine.—A ground mixture of 4.55 g. (0.02 mole) of *p*-isopropoxydiphenylamine[10] and 1.30 g. (0.041 g. atom) of sulfur was fused with 0.1 g. iodine at 160–170° as for phenothiazone-3. After forty-five minutes the odor of the evolving gases changed from that of hydrogen sulfide to one suggesting organic sulfides, and heating was stopped. The cooled reaction mass was an olive-brown resin which partially crystallized on mechanical working. Extraction of the solids with hexane until extracts were nearly colorless (eleven hours) left 10.5% of insoluble residue. From the solution was obtained 58.5% of clusters of yellow crystals. Evaporation left 26% of reddish oil. The crystals were purified by solution in hot benzene (5 cc./g.), addition of hexane (200 cc./g.) and cooling to 0°. The faintly tan crystalline powder melted at 123.0–123.7°. On exposure to the atmosphere it gradually becomes discolored. Vacuum sublimation at 110° first removes the colored portion. The 3-isopropoxyphenothiazine sublimes very slowly under these conditions.

Aeration for thirty minutes of a suspension of 0.5 g. of the ether in 100 cc. of 0.5% potassium hydroxide, and extraction of the dried insoluble solids with hexane, yielded 0.39 g. composed of phenothiazone-3 and the original ester.

E. 3-*n*-Alkoxyphenothiazines.—These were also prepared by iodine-catalyzed fusion of the appropriate amine with two atom-equivalents of sulfur. At temperatures of 160–170° gas evolution ended in fifty to sixty minutes. No sulfide odors developed. Extraction with and crystallization from hexane gave 80–84% of nearly white powders, and left residues of yellow oil. Melting points and analytical data are collected in Table I.

Acknowledgment.—The authors are indebted to Dr. E. J. Eastmond, Mrs. Bernice Williams and Mr. G. F. Bailey for the measurement of spectral absorptions, to Mr. L. M. White and Miss Geraldine Secor for microchemical analyses, and to Dr. F. T. Jones for microscopical examinations of numerous products.

Summary

Phenothiazone-3 has been prepared by the oxidation of phenothiazine with ferric chloride and by the iodine-catalyzed condensation of *p*-hydroxydiphenylamine with sulfur. Similar condensations of *p*-alkoxydiphenylamines and sulfur have given the isopropyl and the normal octyl, dodecyl and hexadecyl ethers of 3-hydroxyphenothiazine.

ALBANY, CALIFORNIA RECEIVED APRIL 11, 1949

(19) F. DeEds and J. O. Thomas, *J. Parasitol.*, **28**, 363 (1942).

(20) F. Kehrmann, and L. Diserens, *Ber.*, **48**, 327, footnote 4 (1915).