previously reported picrate melting at 89–90°.[2b] On treatment with thionyl chloride in chloroform IV gave the hydrochloride of 1-diethylamino-2-chloropropane, V. The free amine has been previously obtained by Kharasch and Fuchs[5] by addition of hydrogen chloride to diethylallylamine. Its picrate, which Kharasch and Fuchs compared with that from an authentic sample of 1-diethylamino-2-chloropropane, melts at 126–127°. The hydrochloride, V, which we obtained gave, on treatment with picric acid in alcohol, a crude picrate melting at 124–127°. After several crystallizations from ethanol the picrate had a constant melting point of 127°.

Basic hydrolysis of V gave a diethylaminopropanol which had the same neutral equivalent as IV but was not identical with it. Its index of refraction was higher and it gave a picrate melting at 118° whereas the picrate from IV melted at 89–90°. Its physical properties are in good agreement with those reported for 2-diethylaminopropanol-1,[6] previously prepared by the sodium and alcohol reduction of ethyl α-diethylaminopropionate, and this is the only reasonable structure which can be assigned to it. The hydrolysis of 1-diethylamino-2-chloropropane is thus accompanied by rearrangement, and the occurrence of this rearrangement constitutes evidence for II as an intermediate in the reaction.

Experimental

Preparation of 1-Diethylaminopropanol-2, IV.—Freshly distilled diethylamine (19 g., 0.26 mole) and freshly distilled propylene oxide (14.5 g., 0.25 mole) were sealed in a Carius tube and heated for thirty hours at 210°. On distillation 28.5 g. of material boiling at 49–51° at 15 mm. was obtained. Redistillation at atmospheric pressure gave 23.5 g. (72% of the theoretical) of the amino alcohol boiling at 155–157°. Another distillation gave a product boiling at 156–157°; $n^{25}D$ 1.4244; neutral equivalent: calcd. for $C_7H_{17}ON$ 131, found 133. The amino alcohol gave the known picrate melting at 89–90°.[2b]

Preparation of 1-Diethylamino-2-chloropropane Hydrochloride, V.—Thionyl chloride (14.3 g., 0.12 mole) in 50 cc. of chloroform was added dropwise to 1-diethylaminopropanol-2 (13.1 g., 0.10 mole). The reaction mixture was cooled in an ice-bath during the addition. The mixture was then refluxed for two hours. The solvent was removed *in vacuo* and the crude product was crystallized twice from acetone. The yield was 10.3 g. (55%) of a white, hygroscopic, crystalline solid.

Anal. Calcd. for $C_7H_{17}NCl_2$: ionic chloride 19.0. Found: Cl^-, 18.7.

On treatment with picric acid in ethanol the amine hydrochloride gave a crude picrate melting at 124–127°. After several crystallizations from etlianol the picrate had a constant melting point of 127°.

Hydrolysis of 1-Diethylamino-2-chloropropane Hydrochloride.—1-Diethylamino-2-chloropropane hydrochloride (5 g., 0.027 mole) was treated with sodium hydroxide (4 g., 0.10 mole) in 75 cc. of water and 75 cc. of acetone. The mixture was left standing for forty hours and then extracted continuously with ether for twenty hours. The ether extract consisted of two phases. Concentrated hydrochloric acid (3 cc., 0.036 mole) was added and the solution was taken to dryness. A sirup was obtained and all attempts to obtain the crystalline hydrochloride failed. An aqueous solution of the sirup was made strongly alkaline and extracted with benzene. The benzene extract was dried and distilled, giving 2 g. (56.8%) of 2-diethylaminopropanol-1; b. p. 66° at 25 mm.; $n^{25}D$ 1.4290; neutral equivalent, calcd. for $C_7H_{17}ON$ 131, found 134. The product gives a deep yellow picrate which melts at 118° and shows a depression to 85° on mix melting with picric acid (m. p. pure, 121.8°).

Anal. Calcd. for $C_{13}H_{20}N_4O_8$: C, 43.33; H, 5.60. Found: C, 43.22; H, 5.56.

Summary

1-Diethylamino-2-chloropropane gives on hydrolysis the rearranged product 2-diethylaminopropanol-1. This constitutes evidence for the occurrence of N,N-diethyl-α-methylethylenimmonium chloride as an intermediate in the reaction.

NORTH ADAMS, MASS. RECEIVED DECEMBER 6, 1946

(5) Kharasch and Fuchs, *J. Org. Chem.*, **10**, 159 (1945).

(6) V. Braun, Leistner and Münch, *Ber.*, **59**, 1954 (1926); V. Braun, Joster and Wagner, *ibid.*, **61**, 1426 (1928); Grignard, Dupont and Locquin, "Traite de Chimie Organique," Vol. 12, p. 478.

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

Thionol and its Semiquinone Radical

BY S. GRANICK AND L. MICHAELIS

In previous papers from this Laboratory the formation of semiquinone radicals by partial reduction of thiazine dyestuffs has been studied for many representatives of dyes of this class (and also of the class of oxazines and that of selenazines).[1] The various types of representatives may be characterized as follows: they may have no "auxochromic" group at all (phenthiazine itself, unsubstituted); or they may have one auxochromic group, either an amino group[2] (3-aminothiazine), or a hydroxyl group (3-hydroxthiazine); or they may have two auxochromic groups, either two amino groups (3,9-diaminothiazine or thionine, and also methylene blue), or one amino and one hydroxyl group (thionolin) or two hydroxyl groups (3,9-dihydroxythiazine or thionol). Representatives of all these groups were investigated except for the last mentioned one, thionol, which could not be obtained in a sufficiently pure condition. For theoretical reasons to be discussed later, it seemed desirable to fill in this gap.

(1) (a) L. Michaelis and M. P. Schubert, THIS JOURNAL, **62**, 204 (1940); (b) S. Granick, L. Michaelis and M. P. Schubert, *ibid.*, **62**, 1802 (1940); (c) L. Michaelis, S. Granick and M. P. Schubert, *ibid.*, **63**, 351 (1941); (d) L. Michaelis and S. Granick, *ibid.*, **65**, 1636 (1941); (e) *ibid.*, **64**, 1861 (1942).

(2) As in previous papers, the nomenclature refers to the corresponding leuco dye, instead of the dye itself, for the sake of simplicity.

Thionol was first prepared by Bernthsen,[2a] however the purity of the preparation obtained with his method in this Laboratory was not satisfactory. De Eds and Eddy[3] also prepared this dye but the product obtained was amorphous and did not have the purity necessary for the present task. A pure crystalline product was obtained as follows: Thiodiphenylamine (practical, Eastman Kodak Co.) is recrystallized from hot acetone. According to Bernthsen 22 g. is refluxed at 160–170° for thirty hours with a mixture of 440 g. of concentrated sulfuric acid plus 88 cc. of water. The solution is poured into 700 cc. of water and the resulting precipitate filtered and washed with water. The precipitate is then extracted once with 7 g. of sodium carbonate in 1 liter of boiling water, and again with 6 g. of sodium carbonate in 1 liter of boiling water, filtering rapidly each time. The further purification of the crude material is achieved by utilizing the advantageous properties of the lithium salt of the dye. To the deep purple hot filtrate is added 25 g. of lithium chloride. On cooling, long purple needles of the lithium salt crystallize out together with an amorphous brownish impurity. After the crystals have settled, most of the mother liquor is sucked off and discarded, the remainder centrifuged. The amorphous material forms a top layer. It is sucked off. The crystalline material is at the bottom. The yield of the crude lithium salt is 2.01 g. It is converted into the lithium-free dye by recrystallizing from boiling glacial acetic acid. Yield was 1.1 g. of thionol, in long reddish-yellow needles. *Anal.* for $C_{12}H_7O_2NS$: Calcd.: N, 6.12; S, 13.9. Found: N, 6.02; S, 13.7. The molar extinction coefficient in 0.01 *N* sodium hydroxide, in a highly diluted solution, at its maximum absorption at 590 mμ is 63,000 (Fig. 1). (For the cation of thionine the location of the peak of absorption (at 597 mμ) and E_{mol} for extremely diluted aqueous solution are very similar to those of the anion of thionol.) The pure lithium salt forms long purple rods, without water of crystallization. It is very sparingly soluble. The crystals, under a polarizer, are dichroitic bluish-black and purple-red. *Anal.* Calcd. for $C_{12}H_6O_2NSLi$: N, 5.95. Found: N, 6.03. The sodium salt is highly soluble. It forms crystalline rods of brownish-red color, dichroitic pale red and dark red. It is also water-free. *Anal.* Calcd. for $C_{12}H_6O_2NSNa$: N, 5.57. Found: N, 5.58. The difference of the crystalline lithium and sodium salts, especially with respect to color in the solid state, is striking, although in the dissolved state they are indistinguishable. The absorption spectrum of the free radical is shown in Fig. 2. The mode of its preparation is described in the legend to this figure.

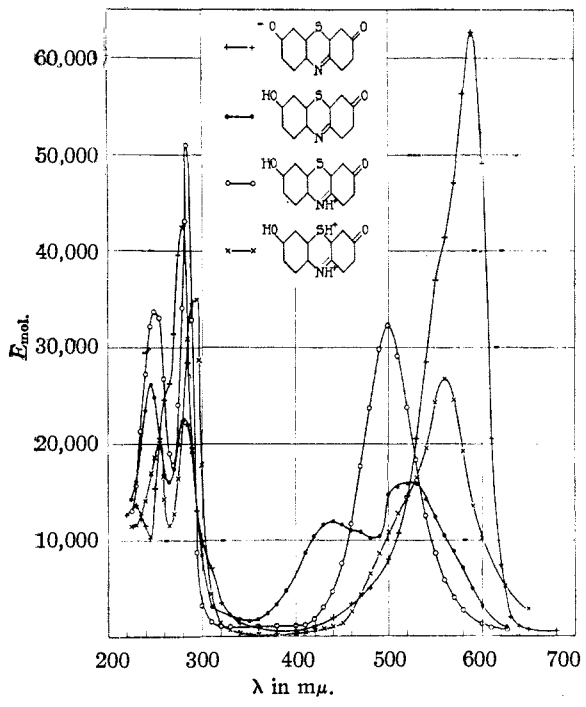


Fig. 1.—Molar extinction coefficient of thionol: +—+, from measurement in a 5×10^{-6} *M* concentration in 0.01 *N* sodium hydroxide; ●—●, from measurement in 3×10^{-5} *M* concentration in a 40% alcohol solution, 0.04 *N* with respect to hydrochloric acid; O—O, from measurement in 5×10^{-6} *M* concentration in 8 *N* sulfuric acid; x—x, from measurement in 5×10^{-6} *M* concentration in 20 *N* sulfuric acid.

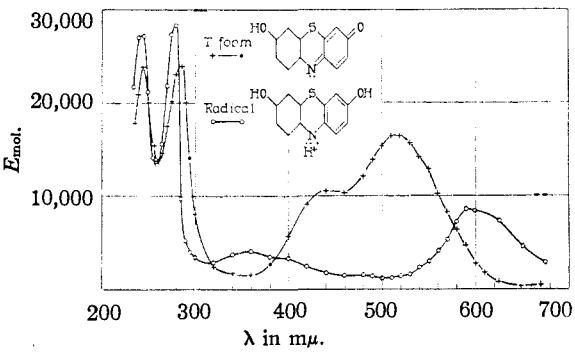


Fig. 2.—O—O, molar extinction coefficient of the semiquinone radical of thionol, prepared as follows: Solution A, 10 cc. of a 2.35×10^{-4} molar solution of lithium thionol + 40 cc. of 95% ethanol + 35 cc. water is titrated with titanium trichloride precisely to complete reduction. The titanium trichloride solution used is prepared from 0.5 cc. of the commercial 15% solution + 5 cc. of 2.4 *N* hydrochloric acid. Solution B, 10 cc. of 2.35×10^{-4} molar solution of lithium-thionol + 5 cc. of 2 *N* hydrochloric acid. Solutions A and B are mixed and diluted with water to a volume of 10 cc. giving a clear blue solution. It is assumed, as an approximation permissible for this purpose, that in such an acid solution no appreciable amount of the dye and the leucodye exists in equilibrium with the free radical. Furthermore, advantage is taken of the fact that in such an acid solution no autoxidation on exposure to the air takes place. The readings are taken against a blank of a solution of titanium trichloride of the same composition but without dye. +—+, molar extinction of the dye (in its quinonoid, or T-, form) in the same acid solvent as the other curve.

Potentiometric titration was carried out with the method in use for many years in this Laboratory, recently summarized.[4] The details are given in Table I. In all experiments except the last, the potentials at three bright platinum electrodes were established rapidly and agreed between 20 and 80% of the titration within 0.1 to 0.2 millivolt; in the last experiment within 2 mv. For the acid solution the solvent contained 20% alcohol because of the sparing solubility of the dye. Therefore the significance of the "*p*H"

(2a) A. Bernthsen, *Ann.*, **230**, 100 (1885).

(3) F. De Eds and C. W. Eddy, THIS JOURNAL, **60**, 1448 (1938).

(4) L. Michaelis, in "Physical Methods of Organic Chemistry," edited by A. Weissberger, Vol. II, 1051 (1946).

TABLE I

POTENTIOMETRIC OXIDATIVE AND REDUCTIVE TITRATIONS OF DIHYDROXYTHIAZINE AT 30°

Molar concn. of dye × 10^4	Buffer medium, 50 cc.	pH	Method of titration	E_m, mean normal potential (against the normal H_2-electrode) in volts	E_i, index potential. Potential diff. of 50, and of 25 (or 75%) of oxidation in millivolts	k, semi-quinone formation constant[a]	$(s/a)_{max}$ maximum ratio of semi-quinone to total dye[a]
2.4	0.0986 N NaOH	12.67	Reduction with $Na_2S_2O_4$	−0.2992	13.8; 14.0		
2.7	M/15 alkaline phosphate buffer	11.09	Reduction with $Na_2S_2O_4$	− .2512	13.9; 14.1		
2.4	Dimethylglycine buffer,[b] μ = 0.1	10.03	Reduction with $Na_2S_2O_4$	− .2075	13.5; 13.8		
2.4	Dimethylglycine buffer,[b] μ = 0.1	9.42	Reduced with H_2, Pd and titrated with $K_3Fe(CN)_6$	− .1700	14.4; 14.6		
2.5	Dimethylglycine buffer,[b] μ = 0.1	9.02	Reduced with $Na_2S_2O_4$	− .1395	13.8; 14.0		
2.7	Veronal buffer, μ = 0.1	7.99	Reduced with $Na_2S_2O_4$	− .0537	13.6; 13.9		
1.0	10 cc. 95% ethanol + 40 cc. of $\frac{M}{15}$ phosphate buffer	6.52	Reduced with H_2Pd and titrated with $K_3Fe(CN)_6$	+ .0825	16.2; 15.8		
0.70	10 cc. of 95% ethanol + 40 cc. acetate buffer, μ = 0.1	4.82	Reduced with H_2Pd and titrated with $K_3Fe(CN)_6$	+ .2085	15.7; 15.4	0.02	0.06
1.0	10 cc. 95% ethanol + 40 cc. glycine buffer, μ = 0.1	2.28	Reduced with $TiCl_3$	+ .3613	18.6; 19.0	.326	.19
0.7	10 cc. 95% ethanol + 40 cc. citrate buffer, μ = 1.0	2.01	Reduced with $TiCl_3$	+ .3768	20.8; 21.1	1.0	.33
.4	10 cc. 95% ethanol + 40 cc. glycine buffer, μ = 0.1	1.46	Reduced with $TiCl_3$	+ .405	32.0; 32.0	6.5	.56

[a] Calculated from the mean value of E_i according to the equations $k = [10^{E_i/60} - 3 \times 10^{-E_i/60}]^2$ and $(s/a)_{max} = \sqrt{k}/(2 + \sqrt{k})$. [b] L. Michaelis and M. P. Schubert, *J. Biol. Chem.*, 115, 221 (1936).

scale in solutions with and without alcohol is not quite the same. Since, however, all those experiments in which a measurable amount of semiquinone was formed (between pH 6 and 1.5) were carried out in the 20% alcohol solution, they are comparable with each other and the plotting of the three normal potentials in Fig. 1 within this pH range is justifiable.

The acidic ionization constants of the dye in all its three levels of oxidation can be recognized from the change of the slopes of the potential curves, the change being either from 0.06 to 0.03 v. per pH unit, or from 0.03 to 0 (Fig. 3).

It is obvious that the separation of the two steps of oxidation becomes the more distinct the more acid the solution. This is the same as, *e. g.*, for thionine, but there is a large quantitative difference which requires comment. The degree to which decreasing pH influences the separation of the two steps in the various dyestuffs may be expressed in terms of that pH at which the three normal potential curves intersect, *i. e.*, where the normal potential of the first step of oxidation, E_1, equals that of the second step, E_2, and also the over-all normal potential of the bivalent system, E_m. In comparing various thiazine dyestuffs in this respect, utilizing the data of previous papers[1-b,d,e] the result is shown in Table II.

TABLE II

	Dyestuff, named in the form of the leuco dye	Alternate name	pH at the point of intersection of the three normal potentials
1	3,9-Dihydroxythiazine	Thionol	+2.0
2	3-Hydroxythiazine		+1.8
3	3-Amino-9-hydroxythiazine	Thionoline	−1 approx.[a]
4	3-Aminothiazine		−1.5
5	3,9-Diaminothiazine	Thionine	−4.2
6	3,9-Di-(dimethylamino)-thiazine	Methylene blue	−5

[a] Estimated by comparing the data of (1b) and (1e).

To explain this order of sequence, the following argument will be helpful. It has been pointed out previously that the attachment of a proton to the bridge-N brings about a special type of resonance which is essential for the stability of the free radical. If there is no amino group in the molecule (no. 1 and no. 2 of Table II) and therefore no competition for the bridge-N to capture a proton, a lesser acidity is sufficient to attach the proton at the bridge-N and thus to stabilize the radical, than when there is an amino group present (no. 3 and no. 4), and the acidity requisite for stabilization of the radical is still greater if there are two amino groups (no. 5 and no. 6) to compete with.

As regards the type of absorption spectrum exhibited by the free radicals, the results obtained previously[1c] supplemented by the present paper, permit the following generalizations. The radicals of thiazine compounds containing either no auxochromic group, or, if containing such, having

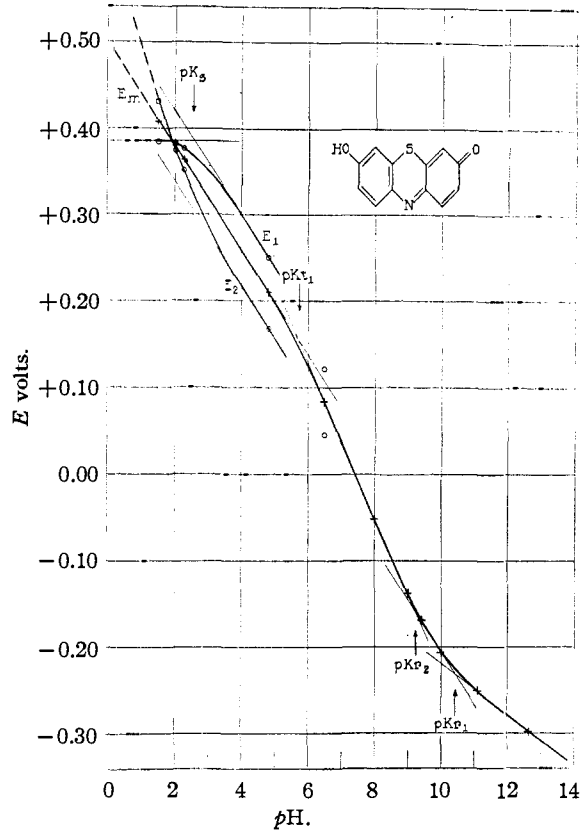
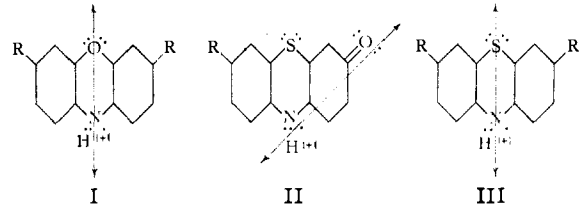


Fig. 3.—Normal potential of thionol plotted against pH: E_1, normal potential of the lower step of oxidation, leuco-dye ⇄ semiquinone; E_2, normal potential of the higher step of oxidation, semiquinone ⇄ (quinonoid) dye; $E_m = {}^1/_2(E_1 + E_2)$, or normal potential of the bivalent oxidation leuco dye ⇄ dye; pKr_1, pKr_2, acidic ionization exponents of the leuco dye; pK_s, acidic ionization exponent of the semiquinone; pK_t, acidic ionization exponent of the (quinonoid) dye.

only nitrogenous groups, have one common type of spectrum: a complicated series of bands lying between 4,200 and 5,300 Å. On the other hand, all radicals derived from thiazine containing at least one oxygen atom have all one single, rather sharp band somewhere between 5,500 and 5,900 Å. The same rule holds for selenazines. On the other hand, all radicals derived from oxazine compounds have always only one single rather sharp absorption band lying somewhere between 5,400 and 5,700 Å. It seems that the participation of an oxygen atom in the oscillator responsible for the absorption brings about the one-band type of the spectrum (I and II), whereas the participation of a sulfur (or selenium) atom brings about the other, complicated type of spectrum. Furthermore, the one end of the oscillator is always the bridge nitrogen (with its attached proton), whereas the other end is always an oxygen atom if there is one, thus establishing an oscillator either as in I, or in II, and only if there is no oxygen atom (as in III) will the sulfur (or selenium) atom be used to form the other end of the oscillator, and in this case always the complicated poly-band spectrum is produced.



Summary

The normal oxidation–reduction potentials of thionol have been measured, especially with respect to the semiquinone formed as an intermediate step of reduction. A comparison of the data obtained with those of previous papers is used to explain why some thiazine dyes show a distinct separation of the two steps of oxidation only in strongly acid solutions, others already in weakly acid solutions. Some comments about the absorption spectra of the semiquinone radicals are added.

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