[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

SOME DERIVATIVES OF 10-ALKYLPHENOTHIAZINES

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It has been reported (1) that sodamide in liquid ammonia is a useful condensing agent for the preparation of 10-ethyl- and 10-benzyl-phenothiazine from phenothiazine and the appropriate organic halide. The preparation of 10-ethylphenothiazine by this method has now been improved and made especially applicable to large runs. This sodamide-condensation type of reaction also has been applied to the preparations of 10-(*n*-propyl)-, 10-isopropyl- and 10-(*p*-methoxybenzyl)-phenothiazine.

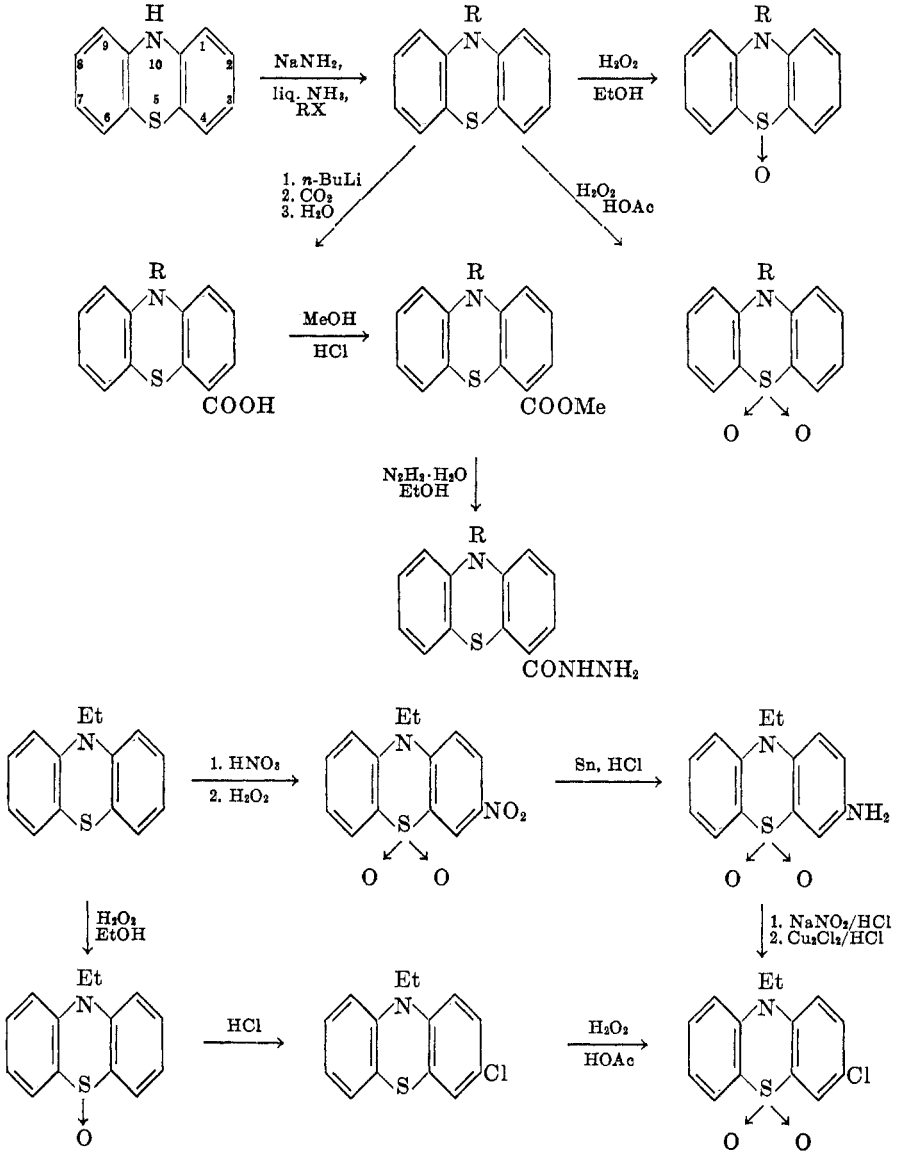
The oxidation of 10-ethylphenothiazine by potassium permanganate in boiling water to give the sulfoxide has been reported (2). It has been found that 10-ethylphenothiazine-5-oxide can be obtained in good yield by the treatment of 10-ethylphenothiazine with 30% hydrogen peroxide in an ethanolic medium. By the use of this oxidation procedure, several new N-substituted phenothiazine sulfoxides have been prepared. A number of phenothiazine derivatives were found to be readily oxidized to the corresponding sulfones by 30% hydrogen peroxide with acetic acid as the solvent.

The melting point, 284.5–286°, of 10-benzylphenothiazine-5-dioxide prepared by hydrogen peroxide oxidation of 10-benzyl-phenothiazine in acetic acid does not agree with that, 211–212°, reported (3). This compound was therefore prepared using the reported reagents and as nearly as possible the same conditions; the product showed the higher melting point and a mixture with the dioxide from hydrogen peroxide oxidation melted without depression. A small amount of 10-benzylphenothiazine-5-oxide also was oxidized to the sulfone (mixture melting point). Infrared absorption measurements of the samples prepared by peroxide oxidation in acetic acid indicated the presence of the sulfone group in the molecule.

4-Carbomethoxy-10-ethylphenothiazine was prepared in good yield by the saturation of a methanolic solution of 10-ethylphenothiazine-4-carboxylic acid with hydrogen chloride followed by a one-hour reflux period. The hydrazide was readily prepared from this ester by treatment with hydrazine hydrate in an ethanolic medium. The sulfoxide and sulfone derivatives were prepared of both the ester and the hydrazide.

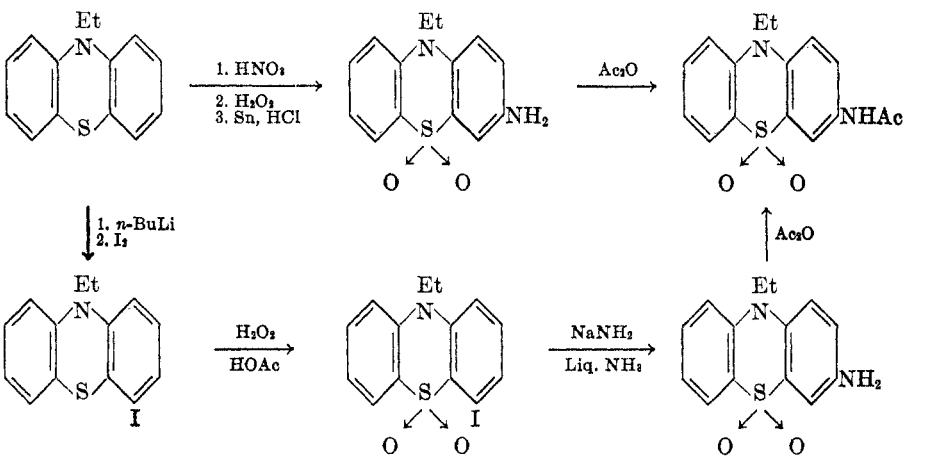
10-Ethylphenothiazine-5-oxide when treated with hydrochloric acid yielded a monochloro-10-ethylphenothiazine. A similar reaction has been reported for the 10-methyl analog (4). The position of the chlorine atom was established by the following sequence of reactions. The chloro-10-ethylphenothiazine was oxidized by the usual procedure to the corresponding sulfone. 3-Nitro-10-ethylphenothiazine-5-oxide was prepared (5) and oxidized to the sulfone; reduction of this sulfone derivative with tin and hydrochloric acid gave the 3-amino-10-ethylphenothiazine-5-dioxide. A Sandmeyer reaction with this compound gave

3-chloro-10-ethylphenothiazine-5-dioxide; a mixture melting point determination with the -5-dioxide of the above monochloro-10-ethylphenothiazine showed no depression. Additional evidence was furnished by infrared absorption measurements which indicated 1,2,4-substitution in the molecule.



4-Iodo-10-ethylphenothiazine was prepared by the metalation of 10-ethylphenothiazine using *n*-butyllithium and subsequent treatment with iodine. The compound was oxidized to the -5-dioxide and the 4-iodo-10-ethylphenothiazine-5-dioxide was subsequently reacted with sodamide in liquid ammonia

to give an amino-10-ethylphenothiazine-5-dioxide. Rearrangement reactions of *ortho*-halogenoaryl ethers and sulfides have been reported (6, 7). The reaction has been extended to include *ortho*-halogenoaryl sulfones (7c). Recent evidence indicates that some rearrangement occurs with aryl halides in general (7d). That rearrangement had occurred in this case was shown by acetylating both this amino derivative and the above-described 3-amino-10-ethylphenothiazine-5-dioxide; a mixture melting point of the two derivatives was not depressed. The acetamido derivative was prepared since the free amine, in the presence of air, slowly darkens on standing.



EXPERIMENTAL[1]

10-Ethylphenothiazine. The following procedure offers some refinements in the described method (1) and is the result of a rather thorough study of the effects of variations in the conditions and the amounts of reactants. To a previously calibrated 5-liter, three-necked flask was added 4,360 ml. of anhydrous liquid ammonia. The flask was fitted with a Trubore stirrer and a Dewar-type condenser; in the condenser a Dry Ice-acetone mixture was maintained throughout the reaction. The lower half of the flask was immersed in a mineral oil bath cooled with Dry Ice; this oil bath also contained an electric heater to aid later in the removal of the liquid ammonia. The upper portion of the flask was covered with several layers of cotton towels to give some insulation.

Sodium (78 g., 3.39 g.-atom; ¼ to ⅜ inch cubical pieces) was added to the rapidly stirred liquid ammonia over a 20-minute period. After the first few pieces of sodium had been added, 1 g. of ferric nitrate catalyst was added. One hour after all of the sodium had been added, during which time the color of the solution changed from blue to gray, 600 g. (3.0 moles) of phenothiazine[2] was added over a 20-minute period. The solution now became orange in color. One hour after the addition of the phenothiazine had been completed, 491 g. (4.5 moles) of ethyl bromide was added dropwise over a 1-hour period. During this time an orange precipitate appeared, later becoming cream-colored as the ammonia was allowed to evaporate. Immediately after all of the ethyl bromide had been added, the flask was opened to the atmosphere and the heater in the oil-bath was turned on to evaporate the ammonia. The removal of the liquid ammonia in this manner required 8–10 hours.

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[1] All melting points are uncorrected.

[2] Eastman Kodak Co. Practical, m.p. 184–185° (this m.p. has varied with different lots), sifted to 16 mesh or smaller particles.

The residual solid was then extracted with one 1-liter portion and two 500-ml. portions of refluxing, thiophene-free benzene. The combined extracts were cooled and the orange to red solution was chromatographed on an 80 × 330 mm. column of alumina[3] which had been previously wet with benzene. The column was eluted with additional benzene until no 10-ethylphenothiazine remained on the column; this required about 2 liters of benzene. The eluate was a golden yellow color. Removal of the benzene left 678 g. (99%) of white solid melting at 103–104.5°.

10-(n-Propyl)phenothiazine. Phenothiazine (19.9 g., 0.10 mole) was added, with stirring, to 0.11 mole of sodamide (8) (prepared from 2.6 g. of sodium in liquid ammonia) in 500 ml. of liquid ammonia. The resulting mixture was stirred for 2 hours and subsequently 18.45 g. (0.15 mole) of *n*-propyl bromide was added in small portions over a period of 20 minutes. The stirring was continued for an additional 2 hours. The ammonia was then allowed to evaporate. The yellow-brown residue was extracted with 150 ml. of hot benzene. The cooled benzene extract was chromatographed on a 38 × 180 mm. column of alumina[4] using benzene as the eluting agent. From the eluates, 22.7 g. (94%) of a yellow oil was obtained. Upon cooling this oil solidified, m.p. 48–50°. Recrystallization from ethanol gave 20.0 g. (83%) of crystals melting at 49–50°. 10-(*n*-Propyl)phenothiazine has been prepared from 10-allylphenothiazine (9) and from 10-(β-bromopropyl) phenothiazine (9); the reported m.p. is 49.5–50°.

10-Isopropylphenothiazine. Sodamide (prepared from 2.6 g. of sodium and 500 ml. of liquid ammonia), phenothiazine (19.9 g., 0.10 mole), and isopropyl bromide (18.45 g., 0.15 mole) were reacted according to the above procedure. Following chromatographic separation as above, there was obtained 18.3 g. (76%) of crystals, m.p. 58–60°. A small amount of unreacted phenothiazine (mixture melting point) also was recovered from the eluate. The 10-isopropylphenothiazine was recrystallized from ethanol to give 16.2 g. (67%) of crystals melting at 59–60°.

Anal. Calc'd for $C_{15}H_{15}NS$: S, 13.28. Found: S, 13.43, 13.51.

An infrared spectrum[5] of this compound indicated the presence of a tertiary nitrogen atom in the molecule.

10-(p-Methoxybenzyl)phenothiazine. Sodamide (0.055 mole, prepared from 1.3 g. of sodium in 250 ml. of liquid ammonia), phenothiazine (10.0 g., 0.05 mole), and *p*-methoxybenzyl chloride (11.75 g., 0.075 mole) were reacted by a procedure similar to that described for the preparation of 10-*n*-propylphenothiazine. Subsequent to chromatographic purification there was obtained a quantitative yield of an oil which solidified, m.p. 100–102°. Recrystallization from ethanol gave 14.5 g. (91%) of 10-(*p*-methoxybenzyl)phenothiazine melting at 101.5–103°.

Anal. Calc'd for $C_{20}H_{17}NOS$: S, 10.04. Found: S, 10.01, 10.08.

A tertiary nitrogen atom was indicated by the infrared spectrum of the compound.

3-Bromo-10-ethylphenothiazine. 3-Acetoxymercuri-10-ethylphenothiazine (10) (4.5 g., 0.0094 mole) was suspended in an excess of 10% potassium bromide solution. This light gray mixture was allowed to stand on a steam-bath for 6 hours with occasional stirring. The filtered solid was suspended in 25 ml. of a *molar* solution of potassium bromide and 50 ml. of carbon tetrachloride was added. Subsequently, 17.0 g. of bromine was added slowly. After 1 hour, the deep red carbon tetrachloride layer was separated, washed with 10% sodium sulfite and filtered; the filtrate was washed with water and dried over sodium sulfate. The solution was filtered and allowed to evaporate to dryness. A small amount of dark green crystals was isolated, melting from 115–119°, with preliminary softening at 110°. Recrystallization from petroleum ether (b.p. 60–70°) raised the m.p. to 121–122°. A mixture melting point determination with an authentic sample of 3-bromo-10-ethylphenothiazine[6] (m.p. 121.5–123°) showed no depression.

[3] Chicago Apparatus Co., Activated Alumina, 80–200 mesh.

[4] Alcoa Activated Alumina, Grade: F-20.

[5] The authors are grateful to Dr. V. A. Fassel and Messrs. M. Margoshes and R. M. Hedges for the infrared analyses.

[6] This sample was prepared by Mr. John Eisch, unpublished studies, by the action of

3-Chloro-10-ethylphenothiazine. 10-Ethylphenothiazine-5-oxide (48.6 g., 0.20 mole) was treated with 100 ml. of 6 *N* hydrochloric acid; a similar procedure has been described (4) for the preparation of chloro-10-methylphenothiazine. A tarry solution resulted and was refluxed and stirred for 1 hour. The dark brown mixture was extracted portionwise with 500 ml. of ether. A purple liquid with some insoluble white material remained. The combined ether extracts were washed twice with 20% sodium hydroxide and were dried over sodium sulfate. Evaporation of the solvent gave 35.5 g. (67.9%) of light brown crystals, m.p. 104–109°. Two recrystallizations from methanol yielded 27.0 g. (51.5%) of light green needles melting at 111–113°.

Anal. Calc'd for $C_{14}H_{12}ClNS$: S, 12.25; Cl, 13.54.
Found: S, 12.38, 12.60; Cl, 13.32, 13.21.

Infrared absorption measurements confirmed the absence of the sulfoxide grouping and indicated 1,2,4-substitution.

4-Iodo-10-ethylphenothiazine. 4-Lithio-10-ethylphenothiazine was prepared according to the previously published procedure (11) using 31.7 g. (0.13 mole) of 10-ethylphenothiazine-5-oxide and a total of 0.39 mole of *n*-butyllithium at 0°. To the metalation mixture was added 19.0 g. (0.075 mole) of iodine. The mixture was refluxed for 2 hours and then poured into a large volume of distilled water. Following the removal by filtration of a small amount of insoluble material, the layers were separated and the ethereal layer washed with two 100-ml. portions of 10% sodium bisulfite. The ethereal layer was light orange in color. The ether was distilled off leaving a yellow solid which melted from 109–114°. Recrystallization, first from petroleum ether (b.p. 60–70°) and then from ethanol, yielded 10.7 g. (23.4%) of a yellow powder melting at 118–119°. A qualitative test for iodine was positive.

Anal. Calc'd for $C_{14}H_{12}INS$: S, 9.06. Found: S, 9.38, 9.21.

Infrared absorption measurements showed the absence of the sulfoxide group and indicated 1,2,3-substitution.

4-Carbomethoxy-10-ethylphenothiazine and 10-ethylphenothiazine-4-carboxylic acid hydrazide. 10-Ethylphenothiazine-4-carboxylic acid was prepared by reacting 10-ethylphenothiazine-5-oxide with *n*-butyllithium followed by carbonation (11). A solution of 5.42 g. (0.02 mole) of this acid in 120 ml. of hot absolute methanol was saturated with anhydrous hydrogen chloride and then refluxed for 1 hour. The resulting solution was cooled and then poured into 250 ml. of water. A yellow oil soon separated and solidified on standing overnight. Filtration gave 5.57 g. (98%) of product, m.p. 110.5–112°. Recrystallization from the minimum amount of absolute methanol raised the m.p. to 111.5–113°. 4-Carbomethoxy-10-ethylphenothiazine (m.p. 111–112°) has been prepared in 57% yield by treatment of the acid with diazomethane (10). A mixture melting point of the two samples was not depressed.

Treatment of the above ester with hydrazine hydrate in ethanol gave an 86% yield of 10-ethylphenothiazine-4-carboxylic acid hydrazide, m.p. 155.5–157°.

Anal. Calc'd for $C_{15}H_{15}N_3OS$: S, 11.24. Found: S, 11.36, 11.48.

10-Ethylphenothiazine-5-oxide (2). Hydrogen peroxide (50 ml. of 30%) was added to a hot solution of 36.3 g. (0.16 mole) of 10-ethylphenothiazine in 1,200 ml. of ethanol. The mixture was refluxed for 5 hours[7] and was then allowed to stand overnight before removal of 800 ml. of solvent by distillation with the aid of a water-pump. The residual solution was poured into 2 liters of cold water, then placed in the refrigerator and allowed to crystallize. The white crystals which formed were filtered and dried to yield 31.9 g. (82%) of 10-ethylphenothiazine-5-oxide, m.p. 162–164°. An addition 2.5 g. (6%) of white crystals, m.p. 162–164°, was obtained from the filtrate after further cooling. The total yield of pure product was 34.4 g. (88%). With larger runs, yields of 90–97% were obtained by this procedure.

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hydrobromic acid on 10-ethylphenothiazine-5-oxide. The position of the bromine atom was established by the preparation of the Grignard reagent and subsequent carbonation to yield the known 10-ethylphenothiazine-3-carboxylic acid (ref. 10).

[7] If too large an excess of hydrogen peroxide is used or if refluxing is continued to a longer period, some of the sulfone is formed.

TABLE I

SOME N-SUBSTITUTED PHENOTHIAZINE-5-OXIDES

COMPOUND OXIDIZED	M.P. OF OXIDE, °C.	PHENOTHIAZINE DERIVATIVES, moles	30% H_2O_2 ml.	SOLVENT (EtOH), ml.	REFLUX TIME, hrs.	YIELD,[a] %	SULFUR ANALYSES	
							Calc'd	Found
10-Benzylphenothiazine	226.5–228	0.01	10	100	1	82	10.50	10.63, 10.64
10-(*p*-Methoxybenzyl)-phenothiazine	202.5–204	.01	10	100	1	89	9.56	9.63, 9.70
3-Chloro-10-ethylphenothiazine	112–114[b]	.038	15	200	5	56.8	11.51	11.72, 11.67
10-Ethylphenothiazine-4-carboxylic acid	226 (dec.)	.0365	15	300	5	86	11.10[c]	11.02, 11.00
4-Carbomethoxy-10-ethylphenothiazine	168–169	.0175	20	100	5	83	10.52	10.68, 10.75

[a] Ethanol was the recrystallization solvent for all of these sulfoxides except the 4-carbomethoxy-10-ethylphenothiazine-5-oxide, which was recrystallized from methanol. [b] A mixture melting point with the starting 3-chloro-10-ethylphenothiazine was depressed. Also infrared absorption measurements indicated the presence of the sulfoxide grouping. [c] Calc'd for $C_{15}H_{13}NO_3S$: Neut. equiv., 288.3. Found: Neut. equiv., 283.6, 286.0.

Some additional N-substituted phenothiazine-5-oxides prepared essentially in accordance with this procedure are listed in Table I.

10-(n-Propyl)phenothiazine-5-oxide. To a hot solution of 2.41 g. (0.01 mole) of 10-(*n*-propyl)phenothiazine in 100 ml. of ethanol was added 10 ml. of 30% hydrogen peroxide. The mixture was refluxed for 10 hours and subsequently was concentrated by distilling off 60 ml. of the solvent. The residual liquid was poured into 100 ml. of cold water, thus precipitating 2.4 g. (93%) of white crystals, melting over the range 128–137°. Recrystallization from dilute ethanol gave 2.1 g. (82%) of crystals, melting over the range 131–138°. The crude material was dissolved in 75 ml. of benzene and the solution was chromatographed on a 19 × 160 mm. column of alumina.[8] The column was eluted with benzene and finally with ethanol. From the eluates was obtained 1.65 g. (64%) of 10-(*n*-propyl)phenothiazine-5-oxide, m.p. 138–140°.

Anal. Calc'd for $C_{15}H_{15}NOS$: S, 12.43. Found: S, 12.52, 12.54.

Repetition of the procedure with only 5 hours of refluxing gave a 92% yield of crude material and a 68% yield of product, m.p. 137.5–139.5°, after chromatographic purification.

10-Ethylphenothiazine-4-carboxylic acid hydrazide-5-oxide. Absolute ethanol (10 ml.) and 10 g. of hydrazine hydrate (99%) were heated to reflux. Then 5 g., (0.0164 mole) of 4-carbomethoxy-10-ethylphenothiazine-5-oxide (Table I) was added in small portions to the solution. Each addition was made only after the preceding amount had dissolved. The very light green solution was then refluxed for 2 hours. The solution was allowed to cool; crystals weighing 4.0 g. (80%) and melting at 214–217° were formed. After one recrystallization from methanol the white crystals melted sharply at 217–217.5°.

Anal. Calc'd for $C_{16}H_{15}NO_3S$: S, 10.52. Found: S, 10.43, 10.31.

Infrared absorption measurements gave bands indicating the presence of the imino, sulfoxide, and carbonyl groupings in the molecule.

10-Benzylphenothiazine-5-dioxide. (*a*) Hydrogen peroxide (3 ml. of 30%) was added to a warm solution of 1.91 g. (0.0066 mole) of 10-benzylphenothiazine (1) in 25 ml. of glacial acetic acid and the resulting solution was refluxed for 30 minutes. The color of the solution changed from light green to red and then to orange. On cooling, 1.96 g. (92%) of orange

[8] Fisher Scientific Co., A-541/2, 80–200 mesh.

crystals, m.p. 280–282°, separated. The product was recrystallized from approximately 150 ml. of dioxane to give 1.45 g. (68%) of fine white needles melting at 284.5–286°.

Anal. Calc'd for $C_{19}H_{15}NO_2S$: S, 9.97. Found: S, 9.99, 10.07.

The above procedure was employed for the preparation of 10-*n*-propylphenothiazine-5-dioxide and 10-isopropylphenothiazine-5-dioxide, the only major modification being that considerable acetic acid was distilled off before the products crystallized. The results of these two preparations are given in Table II.

(*b*) *Oxidation with potassium permanganate.* 10-Benzylphenothiazine-5-dioxide has been reported (3) to melt at 211–212°. In view of the disagreement concerning the m.p. of this compound, oxidation was carried out with the reported reagents; however, the conditions may not have been duplicated as adequate information was not available.

Potassium permanganage (40 ml. of a 3% solution) was added to 1.45 g. (0.005 mole) of 10-benzylphenothiazine (1) dissolved in a refluxing solution of 10 ml. of acetone and 5 ml. of acetic acid. The mixture was refluxed for 1.5 hours with additions, from time to time, of small amounts of powdered potassium permanganate. The hot mixture was filtered and the residue was extracted with hot acetone and then with hot dioxane. The extracts were concentrated and cooled; 0.6 g. (37%) of material, melting over the range 227–264°, crystallized from the acetone extract and 0.46 g. (29%) of crystals, melting over the range 268–277°, was obtained from the dioxane extract. Recrystallization of the latter product from dioxane and then acetone gave a small amount of product, m.p. 284–286°. A mixture melting point with the 10-benzylphenothiazine-5-dioxide obtained by hydrogen peroxide oxidation of 10-benzylphenothiazine was not depressed. Also mixture melting point determinations of these samples with material obtained by oxidation of 10-benzylphenothiazine-5-oxide with hydrogen peroxide in acetic acid showed no depression. Infrared analyses of the samples indicated the presence of the sulfone grouping.

10-Ethylphenothiazine-4-carboxylic acid-5-dioxide. 10-Ethylphenothiazine-4-carboxylic acid (10 g., 0.0366 mole) was dissolved in 250 ml. of glacial acetic acid. To the solution was added 15 ml. of 30% hydrogen peroxide; the reaction mixture was then warmed to 80° and there was maintained, with stirring, for 2 hours. The solution became amber-colored and a pinkish precipitate appeared but soon dissolved. Then an additional 12 ml. of 30% hydrogen peroxide was added and the solution was allowed to stand for 6 hours. A white solid formed which after filtration and drying weighed 10.3 g. (92%) and melted at 227–228°. A mixture melting point with 10-ethylphenothiazine-4-carboxylic acid-5-oxide melted at 212°, with decomposition. One recrystallization from glacial acetic acid gave 9.6 g. (85.6%) of a white powder, m.p. 228–229°.

Anal. Calc'd for $C_{15}H_{13}NO_4S$: S, 10.52; Neut. equiv., 304.4.
Found: S, 10.36, 10.52; Neut. equiv., 307.4, 306.2.

3-Chloro-10-ethylphenothiazine-5-dioxide and 4-iodo-10-ethylphenothiazine-5-dioxide were prepared from the corresponding sulfides by the above procedure. The results of these two preparations are given in Table III.

10-Ethylphenothiazine-4-carboxylic acid-5-dioxide was also prepared by the oxidation of the corresponding monoxide with hydrogen peroxide in acetic acid to give a product melting at 228° and by the treatment (12) of 10-ethylphenothiazine-5-dioxide with *n*-butyllithium in the presence of *n*-butylmagnesium bromide, followed by carbonation to give a solid melting at 227–228°. Mixture melting point determinations of these two samples with the sample obtained by oxidation of 10-ethylphenothiazine-4-carboxylic acid showed no depression. Infrared absorption measurements of these samples indicated the sulfone group to be present in the molecule.

4-Carbomethoxy-10-ethylphenothiazine-5-dioxide and 10-ethylphenothiazine-4-carboxylic acid hydrazide-5-dioxide. 10-Ethylphenothiazine-4-carboxylic acid-5-dioxide (6.1 g., 0.020 mole) was dissolved in 200 ml. of hot absolute methanol. The solution was saturated with anhydrous hydrogen chloride and then refluxed for 2 hours. The light yellow solution was allowed to cool and was poured into 250 ml. of distilled water. A white oil separated which solidified on standing in the refrigerator. The white powder was filtered and dried to give

TABLE II

SOME N-SUBSTITUTED PHENOTHIAZINE-5-DIOXIDES

COMPOUND OXIDIZED	M.P. OF DIOXIDE, °C.	PHENOTHIAZINE DERIVATIVE, moles	30% H_2O_2, ml.	SOLVENT (HOAc), ml.	TEMP. AND TIME OF HEATING	YIELD,[a] %	SULFUR ANALYSES	
							Calc'd	Found
10-*n*-Propylphenothiazine	193–195	0.0066	3	25	Reflux, 30 min.	78	11.73	11.79, 11.90
10-Isopropylphenothiazine	174–176	.0066	3	30	Reflux, 30 min.	36	11.73	11.73, 11.82
3-Chloro-10-ethylphenothiazine	154–156	.038	15	300	80° 2 hrs.	54.9	10.88	10.95, 10.73
4-Iodo-10-ethylphenothiazine	194–195	.0282	20	80	80° 3 hrs.	57.8	[b]	

[a] Absolute ethanol was the recrystallization solvent for all of these sulfones except the 10-isopropylphenothiazine-5-dioxide, which was recrystallized from dilute ethanol. The 4-iodo-10-ethylphenothiazine-5-dioxide required two recrystallizations.

[b] *Anal.* Calc'd for $C_{14}H_{12}IN_2OS$: C, 43.62; H, 3.16; N, 3.63.
Found: C, 43.81, 43.66; H, 3.11, 3.09; N, 3.65, 3.59.

6.1 g. (96%) of 4-carbomethoxy-10-ethylphenothiazine-5-dioxide melting at 135–138°. Two recrystallizations from ethanol raised the m.p. to 140–141°.

Anal. Calc'd for $C_{16}H_{15}NO_4S$: S, 10.08. Found: S, 10.38, 10.30.

Treatment of the above ester with hydrazine hydrate in ethanol gave a 69% yield of 10-ethylphenothiazine-4-carboxylic acid hydrazide-5-dioxide, m.p. 225–226°.

Anal. Calc'd for $C_{15}H_{15}N_3O_3S$: S, 10.08. Found: 10.28, 10.38.

Infrared measurements indicated the presence of the imino, sulfone, and carbonyl groups in the molecule.

3-Nitro-10-ethylphenothiazine-5-dioxide. In 600 ml. of glacial acetic acid was dissolved 20.0 g. (0.069 mole) of 3-nitro-10-ethylphenothiazine-5-oxide and the yellow-colored solution was heated to 80°. Hydrogen peroxide (32 ml. of 30%) was added over a period of 10 minutes and the solution was then kept at 80° for 3 hours. A slight cloudiness had developed after 2 hours and a precipitate had formed at the end of the 3-hour period. An additional 6 ml. of 30% hydrogen peroxide was added and the solution was allowed to stand overnight at room temperature. Filtration gave 19.4 g. (91.8%) of a light yellow powder melting at 243–246°. One recrystallization from ethanol yielded 18.1 g. (85.7%) of solid melting at 245–246.5°.

Anal. Calc'd for $C_{14}H_{12}N_2O_4S$: S, 10.55. Found: S, 10.75, 10.83.

An infrared analysis of this compound indicated the presence of the sulfone group and of 1,2,4-substitution.

3-Amino-10-ethylphenothiazine-5-dioxide. 3-Nitro-10-ethylphenothiazine-5-dioxide (20 g., 0.066 mole) was added to 300 ml. of ethanol forming a slurry; 10.0 g. of tin then was added. The mixture was warmed slightly, with stirring, and 100 ml. of conc'd hydrochloric acid was added slowly over a period of 1 hour. After refluxing for 2 hours, the transparent, greenish solution was filtered free from unreacted tin. On cooling, a white solid formed; filtration and drying gave 17.0 g. of the amine hydrochloride melting at 188–192°, with decomposition. This salt was suspended in 300 ml. of distilled water; the mixture was warmed and made basic with ammonium hydroxide. Filtration of the resulting mixture gave 13.0 g. (71.0%) of a light brown solid melting at 184–185.5°. One recrystallization from ethanol raised the melting point to 186–187°. The light brown crystals darkened in color on prolonged exposure to air.

Anal.[9] Calc'd for $C_{14}H_{15}ClN_2O_2S$: C, 54.00; H, 4.84; N, 9.02.
Found: C, 54.75, 54.78; H, 4.55, 4.47; N, 9.27, 9.15.

One gram (0.0036 mole) of the above amine was suspended in 20 ml. of benzene. To the mixture was added 1.0 g. (0.019 mole) of acetic anhydride. The mixture was refluxed for 2 hours; the solution remained cloudy throughout the reflux period. On cooling, a light brown solid separated and was filtered off to give 0.9 g. (78%) of a 3-acetamido-10-ethylphenothiazine-5-dioxide melting at 213–214.5°. One recrystallization from ethanol yielded 0.8 g. (69.4%) of white crystals melting at 214.5–215.5°.

Anal. Calc'd for $C_{16}H_{17}N_2O_3S$: C, 60.70; H, 5.06; N, 8.87.
Found: C, 60.60, 60.66; H, 5.10, 5.16; N, 8.91, 8.98.

3-Amino-10-ethylphenothiazine-5-dioxide (5 g., 0.0183 mole) was placed in 75 ml. of benzene. To the mixture was added 2.1 g. (0.0183 mole) of chloroacetyl chloride. The dark brown solution was refluxed for 2 hours, then filtered free from a small amount of insoluble material and the filtrate was allowed to cool overnight. A light brown solid, m.p. 183–186° (3 g., 46.8%), was isolated. One recrystallization from absolute ethanol gave 1.5 g. (23.4%) of white needles melting at 184.5–186°.

Anal. Calc'd for $C_{16}H_{15}ClN_2O_3S$: S, 9.05. Found: S, 9.23, 9.33.

3-Chloro-10-ethylphenothiazine-5-dioxide from 3-amino-10-ethylphenothiazine-5-dioxide. 3-Amino-10-ethylphenothiazine-5-dioxide (5 g., 0.0182 mole) was added slowly to 30 ml. of a 2:1 mixture of hydrochloric acid and water. The brown solution was cooled to 0° and a solution of 5 g. of sodium nitrite in 25 ml. of water was added slowly, with stirring, until a positive starch-iodide test for nitrous acid was obtained. This mixture was then added cautiously to a freshly prepared cuprous chloride solution previously cooled to −10° (13). The reddish-brown solution was vigorously shaken and warmed on a steam-bath for 15 minutes. After cooling, the solution was neutralized with sodium carbonate and extracted with three 100-ml. portions of ether. The ethereal layer was washed with sodium hydroxide and dried over sodium sulfate. Removal of the solvent gave a few greenish-brown crystals which melted at 150–154°. A mixture melting point with 3-chloro-10-ethylphenothiazine-5-dioxide (see Table II) was not depressed.

Reaction of 4-iodo-10-ethylphenothiazine-5-dioxide with sodamide in liquid ammonia. 4-Iodo-10-ethylphenothiazine-5-dioxide (8 g., 0.0268 mole) was added slowly, with stirring, to a suspension of 0.10 mole of sodamide (prepared from 2.3 g. of sodium) in 150 ml. of liquid ammonia. The solution became orange-red in color. After stirring for 3 hours, the liquid ammonia was allowed to evaporate; the residual dark brown material was extracted with five 100-ml. portions of hot benzene. The remaining dark solid was insoluble in the common organic solvents. The benzene solution was a dark orange color; this solution was filtered free of some insoluble matter. Treatment of the benzene filtrate with anhydrous hydrogen chloride created a very slight turbidity; however, attempts to induce crystallization were unsuccessful. Evaporation of the solvent gave a small amount of light orange material. This solid slowly darkened on exposure to air; the substance was dissolved in 50 ml. of benzene and 5 ml. of acetic anhydride was added. After refluxing for 1 hour, the solution was allowed to cool. A gray powder weighing 1.2 g. (19%) and melting at 211–213.5° was isolated. A mixture melting point with 3-acetamido-10-ethylphenothiazine-5-dioxide prepared from the corresponding 3-nitro derivative (see above) was not depressed.

SUMMARY

An improved procedure for the preparation of 10-ethylphenothiazine is given; the preparation of 10-(*n*-propyl)-, 10-isopropyl-, and 10-(*p*-methoxybenzyl)-phenothiazine is described.

An improved procedure for the preparation of 10-ethylphenothiazine-5-oxide

[9] The salt was analyzed rather than the free amine since the latter in the presence of air slowly turns brown.

is presented. Oxidation procedures are described for the preparation of a number of new phenothiazine-5-oxides and -5-dioxides.

The melting point of 10-benzylphenothiazine-5-dioxide has been found to be 284.5–286° rather than the reported 211–212°.

4-Carbomethoxy-10-ethylphenothiazine and 10-ethylphenothiazine-4-carboxylic acid hydrazide as well as their sulfoxide and sulfone derivatives have been prepared.

The treatment of 10-ethylphenothiazine-5-oxide with hydrochloric acid gives a monochloro-10-ethylphenothiazine. The chlorine atom has been established to be in the 3-position.

4-Iodo-10-ethylphenothiazine-5-dioxide on reaction with sodamide in liquid ammonia has been shown to undergo rearrangement to give 3-amino-10-ethylphenothiazine-5-dioxide.

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