Synthesis of Possible Metabolites of Chlorpromazine. IV 7-Hydroxy-nor$_1$ - and nor$_2$ -Chlorpromazine Sulfoxide (1a,2)

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In their investigation of chlorpromazine (2) metabolism a number of authors (3-10) have encountered, in various biological media, sulfoxides of the 7-hydroxy nor$_2$ (**4**) (2) and nor$_1$ (**20**) (2) derivatives. This paper describes the synthesis of **4** (Scheme I) and provides a much improved route to **20** (Scheme III).

The synthesis of **4** was initiated with hydrogen peroxide oxidation of 7-hydroxy-nor$_2$-chlorpromazine oxalate (**2**). The resulting sulfoxide, isolated as a relatively rare hemioxalate (**3**), was subsequently converted to the hydriodide (**4**). Efforts to isolate the nor$_2$ sulfoxide as free base or as hydrochloride were in vain. Equally unproductive were attempts to reach this compound *via* a series of acylated precursors (Scheme II).

In one crystallization of **3** from hot *N,N*-dimethylformamide-xylene, thermal conversion to the formamido derivative (**5**) (Scheme I) occurred. The latter compound was identical with that obtained on oxidation of the *O,N*-diformyl derivative (**9**) (Scheme II).

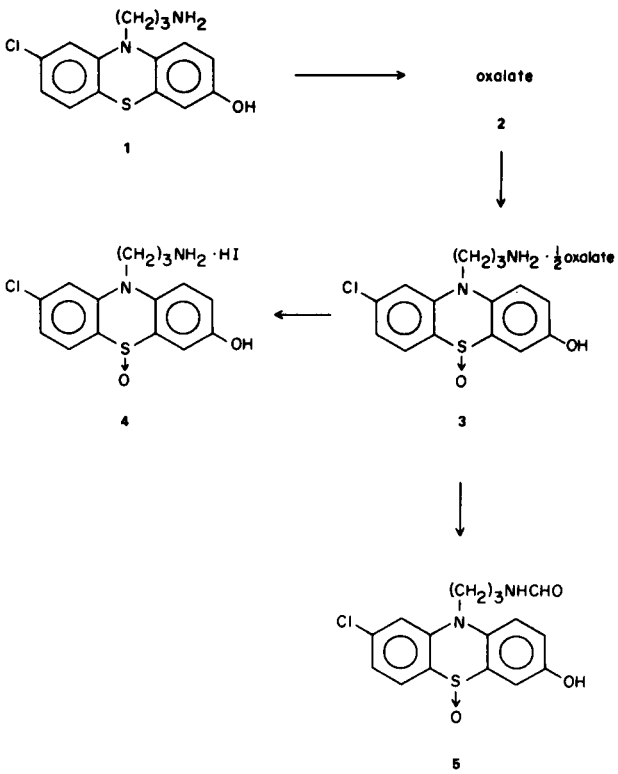
Our first synthesis of 7-hydroxy-nor$_1$-chlorpromazine sulfoxide (**20**) was described in an earlier paper (11). The need for more of this material prompted development of the simpler route outlined in Scheme III.

Infrared spectral data for the compounds of Schemes I-III and tentative structure assignments are included in Table I. As 2,7-disubstituted phenothiazines, these compounds incorporate two asymmetrically trisubstituted benzene rings each of which contains a single isolated hydrogen atom and a pair of adjacent hydrogen atoms. The presence of the isolated hydrogens is manifested by three peaks between 11.0 and 11.9 μ. One to three additional maxima between 12.0 and 12.8 μ (most frequently two peaks between 12.0 and 12.6 μ) can be attributed to the presence of the adjacent hydrogen pairs. The aromatic rings are also evidenced by a weak peak at 3.2 μ (=C-H stretch), a trio between 6.2 and 6.7 μ (C=C skeletal in-plane vibration) and a consistent quartet at 8.7-8.9, 9.0-9.2, 9.5-9.7 and 10.6-10.8 μ (in-plane C-H bending).

Although O-H stretching at about 3 μ is one of the most characteristic of the group frequencies, it is most often very weak, absent or obscured (shifted by bonding into the NH stretching regions) in the hydroxyphenothiazines.

Most of the primary and secondary amines and amides in Table I display the anticipated bands at 3 μ originating in NH stretching modes. However, the sulfoxides, **12**, **13**, **14** and **20** have the shifted NH peak at 3.1 μ suggestive of hydrogen bonding.

SCHEME I



The region 7.5-8.5 μ contains four to seven bands of varying intensity. Absorption in the low wavelength half of this range can be assigned to C-N stretch while the peaks in the other half are indicative of C-O stretch.

The S=O stretching bands at 9.8-10.4 μ are at the high wavelength extreme for sulfoxide absorption.

TABLE I

Infrared Spectral Data (μ) (a)

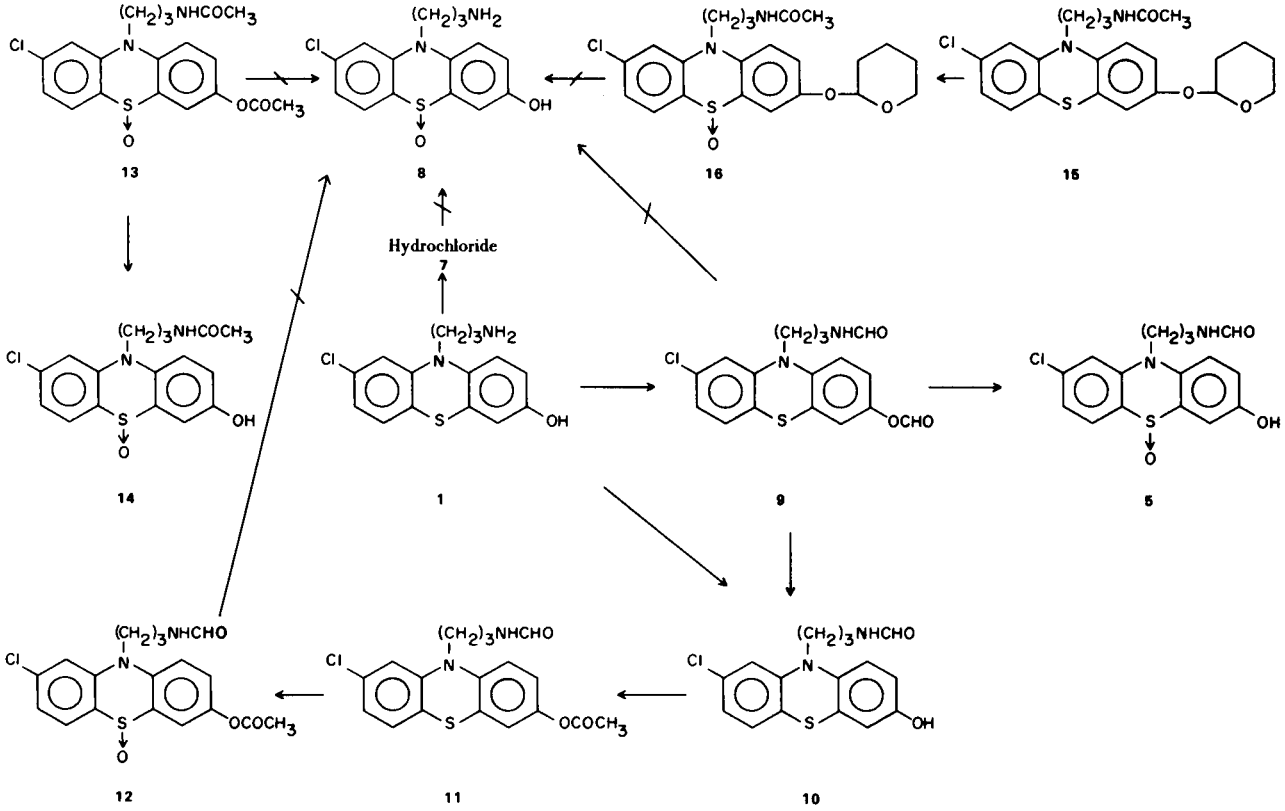
No.	Amine and Amide N-H (b)	Aromatic =C-H (b)	Amide C=O (b)	Aromatic C=C (b)	Sulfoxide S=O (b)	Aromatic I.P. Def. (a) C-H
1	(a)			6.3 (s), 6.4 (s), 6.7 (m)		8.9 (m), 9.1 (m), 9.5 (m), 10.6 (m)
2	(f)	3.2 (w)		6.2 (m), 6.4 (m), 6.7 (m)		8.9 (w), 9.2 (w), 9.6 (w), 10.8 (w)
3	(f)	3.2 (w)		6.3 (s), 6.5 (s), 6.7 (w)	10.4 (s) (h)	8.7 (w), 9.0 (w), 9.7 (w), 10.7 (m)
4	(f)			6.3 (s), 6.5 (s), 6.7 (s)	10.2 (m)	8.7 (w), 9.0 (w), 9.6 (w), 10.7 (m)
5	3.0 (w)	3.2 (w)	6.0 (s)	6.3 (m), 6.5 (m), 6.7 (w)	10.2 (s)	8.7 (w), 9.0 (m), 9.6 (m), 10.6 (w)
7	(f)			6.3 (m), 6.5 (m), 6.7 (s)		8.9 (m), 9.1 (m), 9.6 (m), 10.8 (m)
9	3.0 (m)	3.2 (w)	6.1 (s)	6.3 (w), 6.5 (m), 6.7 (m)		8.8 (w), 9.1 (s), 9.6 (w), 10.8 (w)
10	3.0 (w)		6.1 (s)	6.3 (w), 6.4 (m), 6.7 (m)		8.9 (w), 9.1 (w), 9.5 (w), 10.8 (w)
11	3.0 (m)	3.2 (w)	6.1 (s)	6.3 (w), 6.5 (s), 6.7 (w)		8.9 (m), 9.1 (w), 9.5 (w), 10.6 (m)
12	3.1 (m)	3.2 (w)	6.0 (s), 6.1 (s) (c)	6.3 (m), 6.5 (w), 6.7 (w)	9.9 (s)	8.9 (w), 9.1 (w), 9.6 (m), 10.7 (m)
13	3.1 (m)	3.2 (w)	6.0 (s), 6.1 (s) (c)	6.2 (s), 6.4 (s), 6.7 (m)	9.8 (s)	8.8 (w), 9.0 (m), 9.5 (s), 10.7 (m)
14	3.1 (w)	3.2 (w)	6.1 (s)	6.3 (s), 6.5 (s), 6.7 (s)	10.1 (s)	8.9 (w), 9.1 (w), 9.6 (m), 10.6 (m)
15	3.0 (m)		6.1 (s)	6.4 (m), 6.5 (m), 6.7 (m)		8.9 (w), 9.0 (m), 9.6 (m), 10.7 (w)
16	3.0 (m)		6.0 (s)	6.4 (m), 6.5 (m), 6.7 (m)	10.0 (s)	9.0 (b-s), 9.6 (s), 10.7 (w)
17	3.0 (w)			6.2 (m), 6.4 (m), 6.7 (m)		8.9 (m), 9.1 (m), 9.7 (s), 10.7 (m)
18 (1)		3.2 (w)	6.0 (s)	6.2 (m), 6.3 (m), 6.7 (s)		8.9 (m), 9.0 (m), 9.7 (m), 10.8 (m)
19			5.9 (s)	6.2 (m), 6.4 (m), 6.7 (m)	10.2 (b-m) (i)	8.9 (m), 9.1 (w), 9.5 (s), 10.7 (m)
20	3.1 (m)	3.2 (w)		6.3 (s), 6.5 (m), 6.7 (s)	9.9 (s)	8.9 (w), 9.1 (m), 9.6 (m), 10.8 (w)

TABLE I (Continued)

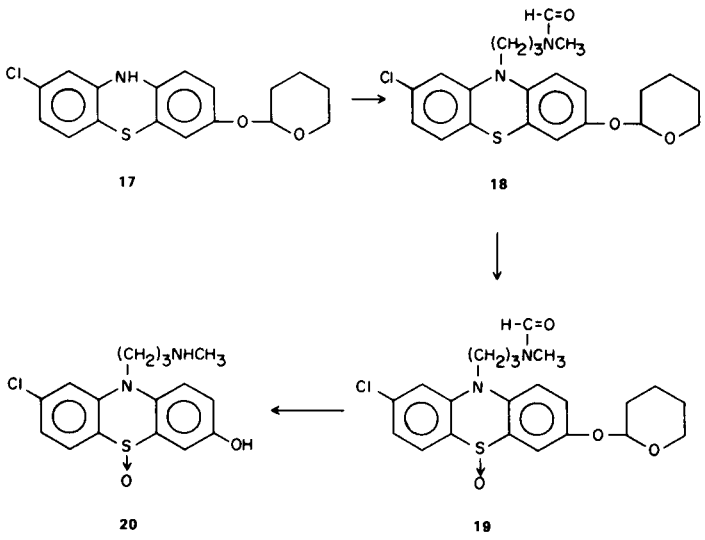
No.	Aromatic C-H O.O.P. Def. (a)		Miscellaneous
	Isolated H	2 Adjacent H	
1	11.4 (m), 11.6 (m), 11.8 (s)	12.3 (s), 12.5 (s), 12.8 (m)	3.9 (b-w) (e)
2	11.1 (s), 11.6 (w), 11.8 (w)	12.0 (w), 12.5 (s)	2.8 (w-sharp) (g)
3	11.2 (m), 11.6 (w), 11.8 (w)	12.2 (w), 12.6 (m)	
4	11.1 (s), 11.8 (m)	12.3 (m), 12.5 (m)	
5	11.1 (m), 11.5 (w), 11.9 (w)	12.0 (w), 12.6 (m)	
7	11.1 (s), 11.6 (m), 11.8 (m)	12.3 (s), 12.5 (m), 12.6 (m)	3.0 (w) (OH)
9	11.2 (m), 11.5 (w), 11.8 (s)	12.1 (w), 12.4 (s), 12.6 (m)	5.8 (s) (j)
10	11.1 (m), 11.5 (w), 11.8 (m)	12.4 (b-s)	
11	11.2 (m), 11.4 (w), 11.8 (m)	12.3 (m), 12.6 (s)	5.7 (s) (j)
12	11.1 (w), 11.5 (w), 11.8 (m)	12.2 (w), 12.4 (m), 12.6 (w)	5.7 (s) (j)
13	11.0 (m), 11.4 (m), 11.8 (s)	12.4 (w), 12.5 (s), 12.9 (w)	5.7 (s) (j)
14	11.1 (m), 11.5 (m)	12.0 (m), 12.4 (s)	
15	11.1 (m), 11.4 (w), 11.7 (m)	12.2 (s), 12.4 (s)	10.4 (s) (k)
16	11.0 (m), 11.3 (w), 11.8 (m)	12.2 (m), 12.4 (m), 12.9 (m)	10.4 (m) (k)
17	11.2 (w), 11.5 (m), 11.8 (m)	12.1 (w), 12.5 (m)	10.4 (s) (k)
18 (l)	11.2 (w), 11.5 (m), 11.7 (w)	12.2 (m), 12.4 (m)	10.4 (s) (k)
19	11.1(w), 11.3 (m), 11.6 (w), 11.9 (w)	12.1 (w), 12.4 (m), 12.6 (m)	10.2 (b-m) (i,k)
20	11.1 (m), 11.7 (b-s)	12.4 (m), 12.5 (m)	4.0 (b-w) (e)

(a) w = weak, m = medium, s = strong, b = broad, I.P. Def. = in-plane deformation, O.O.P. Def. = out-of-plane deformation. (b) Stretching vibration. (c) The reason for this apparent band split is not clear. (d) This spectrum contains a weak doublet at 2.9 and 3.0 μ attributable to the symmetric and assymetric stretching vibrations of a primary amine. (e) The location, shape and intensity of this band are suggestive of a zwitterionic structure involving the amino and phenol groups. (f) The primary amine salts, **2**, **3**, **4** and **7** all exhibit three weak peaks between 3.6 and 4 μ and a broad slightly stronger peak near 5 μ. This pattern, most obvious in the hydrochloride (**7**), is unique for the primary amine ion, NH_3^+. [W. E. Thompson, R. J. Warren, I. B. Eisdorfer and J. E. Zarembo, *J. Pharm. Sci.*, 54, 1819 (1965)]. (g) Unassociated OH stretch. (h) The few other peaks between 8.2 and 10.5 μ are all quite weak. (i) This broad (4 μ wide) band is probably an overlap of the S=O (sulfoxide) and C-O (tetrahydropyranyloxy) stretching bands. (j) Ester C=O stretching vibration. (k) Ether C-O stretch arising from the tetrahydropyranyloxy group. (l) Film (crude).

SCHEME II



SCHEME III



EXPERIMENTAL

Melting points were determined in sealed, evacuated capillary tubes in an electrically heated Thiele-Dennis apparatus and are uncorrected. All reactions were mechanically or magnetically stirred under dry nitrogen and in the absence of strong, direct light. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. and Microanalysis, Inc., Wilmington, Delaware. Infrared spectra were taken as Nujol mulls on a Perkin-Elmer Model 137B Infracord Spectrophotometer. Organic solutions were dried with anhydrous magnesium sulfate and decolorized with Darco G-60. Concentration and complete solvent removal were always carried out under reduced pressure.

10-(3-Aminopropyl)-2-chloro-7-hydroxyphenothiazine Oxalate (**2**).

A solution of 0.54 g. (0.006 mole) of oxalic acid in 10 ml. of ethanol and 80 ml. of ether was added, dropwise, at room temperature, to a solution of 1.9 g. (0.006 mole) of **1** (11) in 50 ml. of ethanol. After 2 hours at room temperature the solid was filtered and extracted with boiling ethyl acetate (removal of starting material) leaving 2.0 g. (84%) of **2**, m.p. 218-220°. Crystallization from ethanol provided an analytical sample, m.p. 220-221° dec.

Anal. Calcd. for $C_{17}H_{17}ClN_2O_5S$: C, 51.39; H, 4.28; N, 7.05. Found: C, 51.54; H, 4.32; N, 7.02.

From the mother liquor there separated a small second crop of crystals which was dimorphic with the first. The second crop had an identical melting point (no mixture m.p. depression), the same empirical formula (C, H, N analyses) and a different infrared spectrum. On oxidation, both crops gave the same sulfoxide (**3**).

10-(3-Aminopropyl)-2-chloro-7-hydroxyphenothiazine Sulfoxide Hemi-oxalate (**3**).

A solution of 2.7 g. (0.026 mole) of 30% hydrogen peroxide was added to a suspension of 3.5 g. (0.0088 mole) of **2** in 125 ml. of ethanol and the mixture was heated to reflux. After about 0.5 hour the mixture cleared and in another 0.5 hour a white solid began to separate. After a total of 2 hours under reflux the mixture was cooled and filtered to give 3.2 g. (99%) of **3**, m.p. 225-228°. This material was used without further purification. Crystallization from water afforded an analytical sample, m.p. 235-236° dec.

Anal. Calcd. for $C_{16}H_{16}ClN_2O_4S$: C, 52.24; H, 4.35; N, 7.61. Found: C, 51.94; H, 4.32; N, 7.45.

Attempted crystallization of **3** from hot DMF-xylene gave 52% of the desired compound (**3**) and 43% of a white solid, m.p. 204-206°, (acetonitrile) whose infrared and elemental analyses indicated that it was 2-chloro-10-(3-formamidopropyl)-7-hydroxyphenothiazine 5-oxide (**5**).

Anal. Calcd. for $C_{16}H_{15}ClN_2O_3S$: C, 54.77; H, 4.28; N, 7.98. Found: C, 54.55; H, 4.20; N, 8.01.

The infrared spectrum of **5** [peaks at 3.0 μ (-NH-), 6.0 μ (>C=O) and 10.3 μ (>S → O)] was identical with that of the material obtained on oxidation of **9** (30% hydrogen peroxide-acetic acid, 75-80°, 5 hours).

10-(3-Aminopropyl)-2-chloro-7-hydroxyphenothiazine Sulfoxide Hydriodide (**4**).

The oxalate (**3**) (1 g., 0.0026 mole) was dissolved in 400 ml. of hot water and the cooled solution was extracted with benzene (discarded) and basified (*p*H 9-10) with 10% potassium carbonate. The solution was taken to dryness and the yellow, solid residue was extracted with hot methanol. The extract was treated with neutral alumina and concentrated to 20 ml. The hot concentrate was treated, dropwise, with freshly distilled concentrated hydriodic acid (47%) until the solution became pale yellow or colorless. The solution was heated under reflux for an additional 0.5 hour, cooled and poured into ether. The resulting yellow-white solid was dried and extracted repeatedly with acetonitrile (discarded) to remove inorganic material. The insoluble residue was then crystallized several times from ethanol-cyclohexane to provide 0.51 g. (43%) of **4** as off-white solid, m.p. 254-255°.

Anal. Calcd. for $C_{15}H_{16}ClIN_2O_2S$: C, 39.95; H, 3.55; N, 6.21. Found: C, 40.06; H, 3.76; N, 6.34.

2-Chloro-10-(3-formamidopropyl)-7-formoxyphenothiazine (**9**).

A mixture of 20.4 ml. of acetic anhydride and 8.5 ml. of 98% formic acid was heated at 50-60° for 2 hours. To 15 ml. of this solution was added, at room temperature, 1.75 g. (0.0056 mole) of **1** (11). The mixture was kept at room temperature for 1 hour, poured into 150 ml. of ice water, adjusted to *p*H 8 with 20% sodium hydroxide solution and extracted with ethyl acetate. The extract was washed with water, dried and concentrated. The residue was dissolved in ether-methanol and diluted with petroleum ether to give 1 g. of **9**, m.p. 113-115°. This material was used without further purification. An analytical sample was obtained from hot ligroin (b.p. 60-90°)-ethanol as white needles, m.p. 124.5-126°.

Anal. Calcd. for $C_{17}H_{15}ClN_2O_3S$: C, 56.30; H, 4.16; N, 7.72. Found: C, 56.65; H, 4.16; N, 7.96.

2-Chloro-10-(3-formamidopropyl)-7-hydroxyphenothiazine (**10**).

A mixture of 90 mg. of **9**, 15 ml. of ethanol and 16 mg. of potassium hydroxide (85% assay) was heated under reflux for 1 hour, poured into 10 ml. of ice-water and neutralized with 10% hydrochloric acid. The resulting off-white solid was washed with water, dried and crystallized from petroleum ether-ethanol to give a small quantity of white cyrstals, m.p. 163-164.5°. This material was identified as the *N*-monoformyl derivative (**10**), by infrared analysis (disappearance of ester carbonyl peak at 5.8 μ, retention of amide carbonyl peak at 6.1 μ).

The same compound (**10**) was obtained by heating **1** with 97% formic acid, containing a catalytic quantity of pyridine, for 20 hours at 100°.

7-Acetoxy-2-chloro-10-(3-formamidopropyl)phenothiazine (**11**).

The *N*-monoformyl derivative (**10**) (0.5 g., 0.0015 mole) was dissolved in 5 ml. of 5% sodium hydroxide solution. Within minutes off-white crystals of the corresponding sodium phenoxide separated. This material was washed with ether, dissolved in 50 ml. of cool water and treated with 0.16 g. (0.0015 mole) of acetic anhydride. The resulting pale pink solid was crystallized from ligroin (b.p. 60-90°)-ethanol to give 0.3 g. (53%) of **11** as white needles, m.p. 157-159.5°. Additional crystallization from the same solvent mixture provided the analytical sample, m.p. 159-160°.

Anal. Calcd. for $C_{18}H_{17}ClN_2O_3S$: C, 57.36; H, 4.54; N, 7.43. Found: C, 57.34; H, 4.43; N, 7.24.

The mixture melting point of **11** and 10-(3-acetamidopropyl)-7-acetoxy-2-chlorophenothiazine (11) (m.p. 165.5-166.5°) was 130-133°.

7-Acetoxy-2-chloro-10-(3-formamidopropyl)phenothiazine 5-Oxide (**12**).

A mixture of 0.9 g. (0.0024 mole) of **11**, 30 ml. of acetic acid and 0.28 g. (0.0024 mole) of 30% hydrogen peroxide was heated at 70-80° for 5 hours and evaporated to dryness. Trituration of the resulting dark red oil with acetone afforded 0.65 g. (69%) of **12** as white solid, m.p. 217-220°. Crystallization (benzene-ethanol)

provided an analytical sample as fine white needles, m.p. 223-224°.

Anal. Calcd. for $C_{18}H_{17}ClN_2O_4S$: C, 55.03; H, 4.36; N, 7.13. Found: C, 55.28; H, 4.35; N, 7.52.

10-(3-Acetamidopropyl)-2-chloro-7-hydroxyphenothiazine 5-Oxide (**14**).

A mixture of 0.8 g. (0.002 mole) of **13** (11), 20 ml. of ethanol and 10 ml. (0.002 mole) of 0.2 *N* ethanolic sodium hydroxide was heated under reflux for 0.5 hour, poured into 300 ml. of water, and acidified with 10% hydrochloric acid. The resulting white solid was washed with water and dried to give 0.65 g. (89%) of **14**, m.p. 240-244°. Crystallization from aqueous ethanol provided an analytical sample as white needles, m.p. 244-245.5°.

Anal. Calcd. for $C_{17}H_{17}ClN_2O_3S$: C, 55.96; H, 4.68; N, 7.67. Found: C, 55.88; H, 4.64; N, 7.81.

A small quantity of **14** was obtained previously (11) as a by-product in the oxidation of 10-(3-acetamidopropyl)-7-acetoxy-2-chlorophenothiazine (11) to its sulfoxide (**13**).

10-(3-Acetamidopropyl)-2-chloro-7-(perhydro-2-pyranyloxy)phenothiazine 5-Oxide (**16**).

A mixture of 5 g. (0.0115 mole) of **15** (11), 70 ml. of 95% ethanol and 1.9 g. (0.017 mole) of 30% hydrogen peroxide was heated under reflux for 7 hours and allowed to stand at room temperature overnight. Removal of the solvent, trituration of the residual deep red oil with ether-chloroform (1:1) and washing the resulting solid with acetone gave 3.5 g. (67%) of **16** as pale pink solid, m.p. 136-138.5°. This was used without further purification. Crystallization from acetone-ethanol provided an analytical sample as white solid, m.p. 149-151°.

Anal. Calcd. for $C_{22}H_{25}ClN_2O_4S$: N, 6.24. Found: N, 6.54.

2-Chloro-10-[3-(*N*-methylformamido)propyl]-7-(perhydro-2-pyranyloxy)phenothiazine (**18**).

To a suspension of 2.65 g. (0.055 mole) of a 50% dispersion of sodium hydride (mineral oil) in 25 ml. of dimethyl sulfoxide was added a solution of 15 g. (0.045 mole) of 2-chloro-7-tetrahydropyranyloxyphenothiazine (**17**) (11) in 100 ml. of dimethyl sulfoxide. After 2 hours at room temperature, the mixture was treated with a solution of 9.2 g. (0.070 mole) of *N*-(3-chloropropyl)-*N*-methylformamide (11) in 25 ml. of dimethyl sulfoxide. The mixture was maintained at 125° for 5 hours, allowed to stand at room temperature overnight and poured into a solution of 20 g. of ammonium chloride in 2 l. of water. The resulting oil was extracted with ether (3 x 200 ml.) and the extract was dried and decolorized. Removal of the solvent left 17 g. of **18** as a pale brown oil which was used without further purification.

2-Chloro-10-[3-(*N*-methylformamido)propyl]-7-(perhydro-2-pyranyloxy)phenothiazine 5-Oxide (**19**).

To a solution of 20 g. (0.046 mole) of **18** in 200 ml. of pyridine was added, during 3 hours, 23 g. (0.23 mole) of chromic anhydride (12). After 70 hours at room temperature the mixture was poured into 2 l. of water and extracted with ethyl acetate. The extract was dried and concentrated to give a red oil. Stirring the oil with ether provided 15.5 g. (75%) of **19** as a pink solid, m.p. 122-126°. Crystallization from ethyl acetate-ether gave the analytical sample as off-white crystals, m.p. 136-138°.

Anal. Calcd. for $C_{22}H_{25}ClN_2O_4S$: C, 58.85; H, 5.61; N, 6.24. Found: C, 58.82; H, 5.54; N, 6.25.

2-Chloro-7-hydroxy-10-(3-methylaminopropyl)phenothiazine 5-Oxide (**20**).

A mixture of 11.5 g. (0.026 mole) of **19**, 360 ml. of ethanol and 60 ml. of 10% sodium hydroxide was heated under reflux for 4 hours. Half of the solvent was removed and the residue was poured into 800 ml. of water. The resulting off-white precipitate was redissolved by addition of concentrated hydrochloric acid to *p*H 2. The almost clear solution was extracted with ether (discarded), adjusted to *p*H 8 with solid potassium carbonate and evaporated to dryness. The residue was extracted with 500 ml. of chloroform. The solvent was removed and the residue was stirred overnight with 200 ml. of ether. Filtration provided 7 g. (80%) of **20**, m.p. 180-183°. Crystallization from ethanol-ether raised the melting point to 191-192°. The infrared spectrum of this material was identical with that of the solid described earlier (11).

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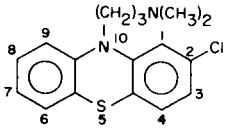
(1a) This investigation was supported by the Psychopharmacology Research Branch, National Institute of Mental Health, Contract SA-43-pH-3758; (b) Pharmacology Section, Psychopharmacology Research Branch, National Institute of Mental Health, Chevy Chase, Maryland 20015.

(2) Chlorpromazine is the generic name for 2-chloro-10-(3-dimethylaminopropyl)phenothiazine.



Nor_1- and nor_2-chlorpromazine are derivatives of chlorpromazine in which the 10-side chain has lost, respectively, one or both methyl groups.

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