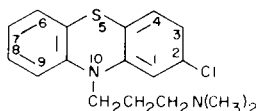


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Some Hydroxylated Derivatives of Chlorpromazine (1)

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As part of a program to determine the metabolic fate of chlorpromazine [2-chloro-10-(3-dimethylaminopropyl)phenothiazine] (I), the synthesis of several hydroxylated derivatives of I was undertaken. This paper reports the preparation and structural verification of the 1- and 6-hydroxy and the desdimethyl 3-hydroxy derivative, and summarizes unsuccessful attempts to prepare the 4-hydroxy derivative of I.



RESULTS AND DISCUSSION

Preparations of 1-, and 6-hydroxychlorpromazine (II and III) were achieved through the phenyl sulfide route to phenothiazines (3) as illustrated in Scheme 1. The route consisted of condensing the appropriate 2-bromothiophenols with the appropriate 2-chloronitrobenzenes to form 2-bromo-2'-nitrophenyl sulfide intermediates. Reduction of the nitro group to an amino, followed by intramolecular reaction of the amino group and the bromo atom afforded phenothiazines, which were subsequently alkylated to yield the desired promazine analogs. The hydroxyl groups in II and III stemmed from 2,5-dichlorophenol and 3-nitrophenol respectively, which were used as starting materials for preparation of 2-chloronitrobenzenes (IV and V) required in the phenyl sulfide syntheses. In both instances, the hydroxyl group was protected against oxidation and interference with some of the intermediate reactions by alkylation with isopropyl iodide. The isopropoxy group was retained throughout the syntheses until it was eliminated in the last step by treatment with boiling hydrochloric acid.

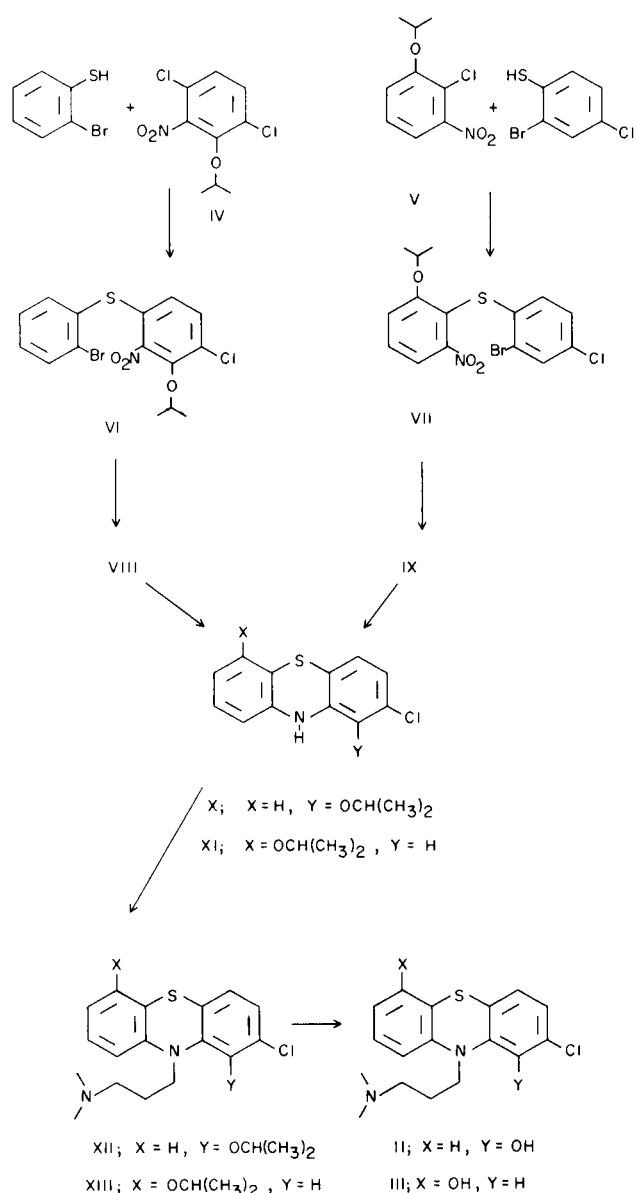
Initial attempts to react IV with 2-bromothiophenol were unsuccessful, although the method used in these attempts had been acceptable for the preparation of VII. In addition to the desired product VI, appreciable amounts of ethoxy and hydroxy analogs were formed through ether exchange with the ethanol and water. Condensation proceeded in 66% yield and produced no inseparable

by-products when carefully dried 2-propanol was used as solvent. Reduction of nitro compounds VI and VII to the corresponding amines VIII and IX was achieved with Adams' catalyst in benzene (4). The 2-bromo-2'-amino-phenylsulfides (VIII, IX) were cyclized by treatment with potassium carbonate, copper, and iodine in dimethylformamide. Finally the 3-dimethylaminopropyl side chain was introduced using sodium hydride as the basic condensing agent.

The 1-isopropoxychlorpromazine (XII) thus obtained was not isolated in pure form; nevertheless, upon cleavage with hydrochloric acid, the corresponding 1-hydroxychlorpromazine (II) was isolated in pure form. The 6-isopropoxychlorpromazine (XIII) also could not be obtained in an analytically satisfactory form. Reaction with refluxing hydrochloric acid so that only part of XIII was cleaved led to a low yield (16%) of III but ultimately gave a product of high purity containing what appeared to be a trace (< 0.5 percent) of XIII or ethanol.

Oxidation of the 2-chlorophenothiazine to 2-chloro-3-phenothiazone (XIV), followed by reduction to 2-chloro-3-hydroxyphenothiazine (XV) proved to be a tedious step in the route (Reaction Scheme 2) employed for the synthesis of 3-hydroxydesdimethylchlorpromazine (XIX). Oxidation of 2-chlorophenothiazine with ferric chloride in dilute acetic acid (5) provided a mixture of 2-chloro-3-phenothiazone (XIV) and 2-chloro-7-phenothiazone each of which was isolated by column chromatography. Compound XIV was readily reduced to 2-chloro-3-hydroxyphenothiazine (XV) by sodium hydrosulfite. With this 3-hydroxy derivative, protection of the hydroxyl group was best achieved through the tetrahydropyranyl ether (XVI) (6). Cyanoethylation of XVI followed by reduction with lithium aluminum hydride gave the desired aminopropyl substituted compound XVIII. Treatment of XVIII with 2 N hydrochloric acid removed the dihydropyran group and yielded the 3-hydroxydesdimethylchlorpromazine.

SCHEME I. ROUTE TO 1- AND 6- HYDROXYCHLORPROMAZINE



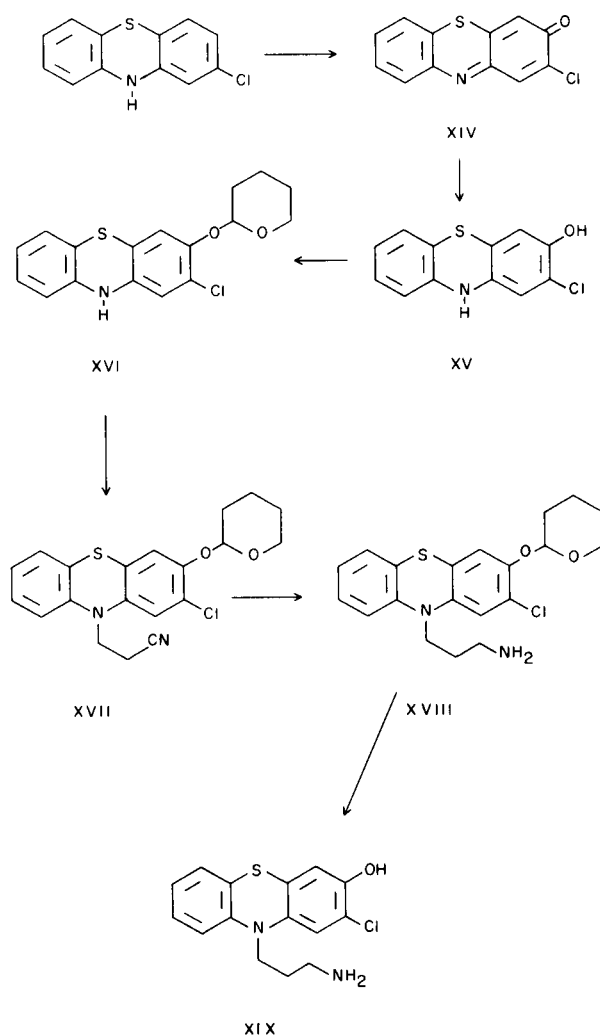
zine (XIX), which, because of its great sensitivity to light and air, could not be isolated and maintained in pure form. Even when recrystallizations were performed in a nitrogen atmosphere in the dark and with deaerated solvents, solutions were never free of color and the loss of material was very great. The best final product which could be obtained was essentially colorless but retained a trace of benzene which could not be removed *in vacuo* at room temperature.

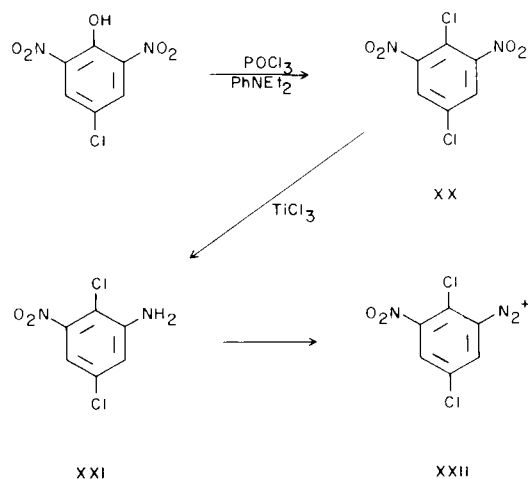
NMR data for II, III, and XIX are recorded in Table I. In all cases, the general spectral features, *i.e.*, chemical shifts, peak areas, and resonance multiplicities are in good agreement with those observed by us and others (7) for some 150 closely related compounds.

Conclusive evidence for the presence of the hydroxyl group at C-1 in II was obtained from the NMR spectrum in deuteriochloroform. An AB quartet with $J = 8.4$ cps arising from spin coupling of the protons at C-3 and C-4 was present at 6.62 and 7.04 ppm respectively. No other hydroxy isomer would have such a quartet. Absence of resonance near 1.00 ppm due to the isopropoxy methyl groups confirmed elimination of the isopropoxy group of XII.

The infrared (IR) spectrum of II showed a band at 3510 cm^{-1} , and strong absorption in the $1250\text{--}1200\text{ cm}^{-1}$ region, and confirms the presence of a phenolic hydroxyl group. General absorption in the $2600\text{--}2200\text{ cm}^{-1}$ spectral region indicated zwitterion contributions. The aromatic out-of-plane bending bands at 787 and 741 cm^{-1} were consistent with those of aromatic rings substituted at 1,2,3,4- and

REACTION SCHEME 2





1,2-positions respectively. Additional IR bands of II are reported in the experimental section.

The NMR spectrum of III in deuterated dimethylsulfoxide (DMSO- d_6) proved the presence of the hydroxyl group of III to be at C-6.

Protons remaining at C-7 and C-9 were each observed as one half of AB quartets due to coupling with the proton at C-8. Chemical shifts of H-7 and H-9 were 6.53 and 6.59 ppm respectively. All H-7 and H-9 resonances were further split due to spin coupling with each other. J_{78} , J_{79} , and J_{89} were measured to be 7.25, 1.4, and 7.03 cps respectively.

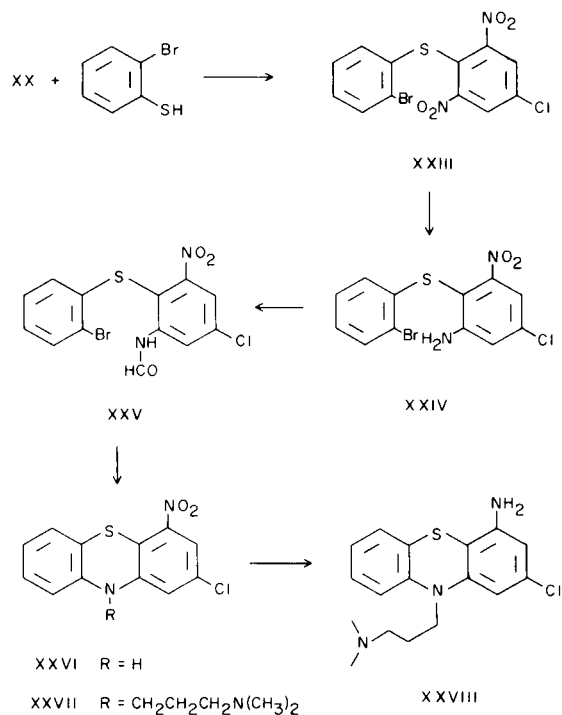
The IR spectrum of III had a strong hydroxyl absorption at 3420 cm^{-1} . A strong band at 1235 cm^{-1} confirmed the expected phenolic character of the hydroxyl group. Additional, broad absorption in the $2700\text{--}2300\text{ cm}^{-1}$ spectral region suggested significant zwitterion contribution. IR bands at 854, 807, and 773 cm^{-1} indicated isolated, two adjacent, and three adjacent aromatic ring protons thus confirming the positions of substituents on the phenothiazine nucleus. Additional IR bands for III are reported in the experimental section.

Attempts to Prepare 2-chloro-10-[3-dimethylamino-propyl]-4-hydroxyphenothiazine were not successful. The first effort was frustrated by our inability to prepare 2,5-dichloro-3-nitrophenol, which on alkaline condensation with *o*-bromothiophenol, should have provided the appropriately substituted phenyl sulfide. The latter intermediate is analogous to those employed successfully in the synthesis of 1-hydroxy and 6-hydroxychlorpromazine.

Initial efforts to prepare 1,4-dichloro-2,6-dinitrobenzene (XX) by the dinitration of *p*-dichlorobenzene (8-11) produced a mixture of isomers from which isolation of pure product proved very laborious. However, XX was readily obtained from 4-chloro-2,6-dinitrophenol by reaction with phosphorous oxychloride in diethylaniline (12), and was selectively reduced to 2,5-dichloro-3-nitroaniline

(XXI) with titanium trichloride (13). Compound XXI was converted to its diazonium salt XXII using nitrosyl sulfuric acid (14), but repeated attempts using a variety of techniques (15, 16) failed to produce the desired 2,5-dichloro-3-nitrophenol even though a successful Sandmeyer reaction was reported to have been done with XXII (13).

As an alternative, the following route was attempted:



Condensation of XX with *o*-bromothiophenol was successfully achieved and the 2-bromo-4-chloro-2,6-dinitrophenyl sulfide (XXIII) thus produced was reduced to 2-amino-2'-bromo-4-chloro-6-nitrophenyl sulfide (XXIV). Although XXIV did not undergo the Ullman condensation well, its formyl derivative (XXV) did so to produce 2-chloro-4-nitrophenothiazine (XXVI) which was alkylated (XXVII) and reduced to 4-amino-2-chloro-10-(3-dimethylamino-propyl)phenothiazine (XXVIII). All attempts to convert the diazonium salt of XXVIII to the corresponding phenolic compound were unsuccessful (15,16,17).

EXPERIMENTAL

The NMR spectra were run on a Varian Associates Model HR-60 NMR spectrometer using deuteriochloroform as the solvent unless otherwise noted. Chemical shifts are reported in parts per million (ppm) downfield from internal TMS = 0.00 ppm. The well-known sideband technique of referencing was used. The output of the audio oscillator was monitored with a Hewlett-Packard 5-decade frequency counter.

The IR spectra were obtained using a Perkin-Elmer Model 521 IR spectrometer. Liquids were run between NaCl plates and solids

TABLE I

Chemical Shift Data for Final Products (a)

Compound Proton Type	1-OH(II) (b)	6-OH(III) (c)	3-OH-desdimethyl (XIX) (c)
-CH ₂ CH ₂ CH ₂ -	1.69 (a) (e) qu, J = 6.25	1.75 (2) qu, J = ~ 6.4	1.72 (2) qu, J = ~ 6.6
-N(CH ₃) ₂	2.36 (6), s	2.09 (6), s	—
-CH ₂ CH ₂ N(CH ₃) ₂	2.71 (2) t, J = 6.5	2.28 (2) t, J = 6.6	2.62 (f) (2) t, J = 6.5
-N-CH ₂ -CH ₂ -	3.50 (2) t, J = 6.0	3.81 (2) t, J = 6.6	3.76 (2) t, J = 6.6
1	9.54 (1), s	~ 6.97, m	6.96 (h) s
3	7.04 (g) dq J = 8.4	~ 6.97, m	4.22 (j) s
4	6.62 (1) dq J = 8.4	~ 6.97, m	6.74, s
6	~ 7.15	6.3-7.2, bs	~ 7.00, m
7	~ 7.15	6.53, (k) i	~ 7.00, m
8	~ 7.15	~ 6.97, m	~ 7.00, m
9	~ 7.15	6.59, (k) i	~ 7.00, m

(a) All chemical shifts are reported in ppm downfield from internal TMS. All coupling constants are reported in cycles per second. (b) Solvent was deuteriochloroform. (c) Solvent was DMSO-d₆. (d) In all cases, this resonance was observed as a broadened quintet due to unequal coupling with adjacent methylene groups. The observed coupling was about the average of the individual couplings under the experimental conditions. (e) Numbers in parenthesis are relative areas. (f) -CH₂NH₂. (g) Integrated with 6, 7, 8, 9 H's. (h) Integrated with 4, 6, 8, 9 H's. (j) -OH and -NH₂ protons. Corrected for solvent water. (k) J₇₈ = 7.25; J₇₉ = 1.4; J₈₉ = 7.03; qu = quintet; s = singlet; t = triplet; b = broad; dq = 1/2 AB quartet; m = multiplet; i = four lines of an ABX spectrum.

were run as potassium bromide discs.

3,6-Dichloro-2-nitrophenol.

This compound was prepared by a modification of the procedure of Hodgson and Kershaw (18) which was unworkable as described. One mole of 2,5-dichlorophenol (163 g.) was added to a mixture of 250 g. of 30% oleum and 200 g. of 96% sulfuric acid at 0°, and the mixture then heated to 80-90° for 30 minutes. After cooling to 0°, this slurry was diluted with 200 ml. of sulfuric acid, then treated during 30 minutes with good agitation with a mixture of 70 g. of 90% nitric acid and 106 ml. of 20% oleum. The mixture was held at 0° for an additional 30 minutes then allowed to warm to room temperature and stirred for 17 hours. Finally the mixture was heated to 60° during 2 hours and held at that temperature for 3 hours to complete the nitration. After cooling,

200 ml. of water was added and the product was steam distilled at 150°. A lower temperature for steam distillation was ineffective in hydrolyzing the sulfonic acid. The product was isolated by ether extraction of the steam distillate, evaporated of the ether, and crystallization of the product from petroleum ether (b.p. 60-110°); yield 107 g. (51%), m.p. 70-72° (lit. 70°) (18).

Chloroisopropoxynitrobenzenes (IV and V).

Compounds IV and V were prepared by refluxing 3,6-dichloro-2-nitrophenol and 2-chloro-3-nitrophenol (the latter prepared by the procedure of van Erp (19)) respectively for 2.5 days in dry acetone (1 liter per mole of phenol) containing 20% excess each of isopropyl iodide and potassium carbonate. The cooled acetone solutions were filtered, solvent and excess isopropyl iodide evaporated and the residues dissolved in benzene. The benzene solutions

were extracted with water, dried and distilled.

Compound IV: 92% yield; boiling range 84-88.5°/0.18-0.28 mm.

Anal. Calcd. for C₉H₉Cl₂NO₃: C, 43.2; H, 3.6; N, 5.6. Found: C, 43.5; H, 3.6; N, 5.4.

IR and NMR data were in agreement with the structure of IV. The NO₂ bands were observed in the former at 1548 and 1374 cm⁻¹.

Compound V: 91% yield; boiling range 79-81°/0.05 mm. The NMR spectrum of V showed all the expected resonances. The IR spectrum was similar to that of the starting phenol except for loss of absorption associate with the phenolic hydroxyl group and appearance of new bands corresponding to formation of the ether linkage.

2'-Bromo-4-chloro-3-isopropoxy-2-nitrophenyl Sulfide (VI).

To a warm solution of 3.68 g. (0.16 g.-atom) of sodium in 130 ml. of dry isopropyl alcohol, 30.24 g. (0.16 mole) of 2-bromothiophenol was added dropwise, followed, after a few minutes, by a solution of 40.0 g. (0.16 mole) of IV in 80 ml. of isopropyl alcohol added all at once. This mixture was refluxed with stirring for 44 hours then cooled, diluted with sufficient benzene to keep the organic material in solution, and filtered to remove sodium chloride. The solvent was evaporated and the residue dissolved in 450 ml. of benzene. The benzene solution was washed with 90 ml. of water then with 500 ml. of 10% aqueous sodium hydroxide in three portions, and finally with water. The benzene solution was dried, the solvent evaporated, and the residue crystallized from isopropyl alcohol to give 36.0 g. of VI m.p. 86-86.5°, yield, 66%

Anal. Calcd. for C₁₅H₁₃BrClNO₃S: C, 44.7; H, 3.25; N, 3.5. Found: C, 45.1; H, 3.1; N, 3.3.

NMR and IR data were in agreement with the structure of VI. The -NO₂ bands appeared in the IR spectrum at 1544 and 1476 cm⁻¹.

2-Bromo-4-chloro-2'-isopropoxy-6'-nitrophenyl Sulfide (VII) (20).

To a solution of sodium ethoxide (4.6 g., (0.2 g.-atom) of sodium dissolved in 160 ml. of ethanol) was added first 44.8 g. (0.2 mole) of 2-bromo-4-chlorothiophenol (21) then, after about 30 minutes, 43.2 g. of V in 280 ml. of ethanol. The mixture was heated at reflux for 25 hours, filtered to remove sodium chloride, cooled, and the solvent evaporated. The residue was dissolved in ether, extracted twice with 10% aqueous sodium hydroxide to remove any unreacted thiol, washed with water until free of alkali and the ether then evaporated. Recrystallization of the residue from ethanol provided 44.5 g. (51%) of bright yellow crystalline solid (VII) m.p. 81-82°.

Anal. Calcd. for C₁₅H₁₃BrClNO₃S: C, 44.7; H, 3.25; N, 3.5. Found: C, 44.7; H, 3.4; N, 3.1.

The NMR spectrum confirmed the presence of six aromatic protons. The IR spectrum showed -NO₂ bands at 1535 and 1456 cm⁻¹. Other NMR and IR data further confirmed the structure of VII.

Aminobromochloroisopropoxyphenyl Sulfides (VIII and IX).

Ten to 15 g. portions of VI and VII were reduced by shaking at room temperature in benzene (100-200 ml.) under 50 psig of hydrogen for 24 hours with 2 g. of pre-reduced Adams catalyst (4); the benzene solutions were filtered and the solvent evaporated. The residues were taken up in petroleum ether (VIII) or ether (IX) and the products precipitated as their salts by addition of dry hydrogen chloride at ice-bath temperature.

Compound VIII: 80% yield of free base was isolated; m.p. 91-93° (from isopropyl alcohol).

Anal. Calcd. for C₁₅H₁₅BrClNOS: C, 48.5; H, 4.0; N, 3.8. Found: C, 48.3; H, 3.8; N, 3.7.

The NMR spectrum showed a two proton, concentration dependent resonance, from the NH₂ group, at 4.51 ppm. The IR spectrum showed NH₂ bands at 3455, 3355, and 1597 cm⁻¹. Other NMR and IR spectral data were in agreement with the structure of VIII.

Compound IX: The hydrochloride was recrystallized from ethanol, m.p. 199-202° dec. The free base, extracted with ether from aqueous bicarbonate was an oil which was used without further purification.

Anal. Calcd. for C₁₅H₁₅BrClNOS: C, 48.5; H, 4.0; N, 3.8. Found: C, 48.7; H, 3.9; N, 3.3.

The NMR spectrum showed a singlet (4.38 ppm) from the -NH₂ protons. The IR spectrum showed -NH₂ bands at 3484 and 3282 cm⁻¹. Other NMR and IR data further confirmed the structure of IX.

2-Chloroisopropoxyphenothiazines (X and XI).

Cyclization of VIII and IX was achieved by refluxing each with 1.2 mole of potassium carbonate, 0.5 gram atom of copper powder and a small crystal of iodine in 2.5 l/mole of dimethylformamide under a stream of nitrogen for 2 days. The solutions were filtered, diluted with water and extracted with benzene. The benzene solutions were washed with water, dried, and evaporated. The residues were dissolved in petroleum ether (X) or ether (XI) and treated with hydrogen chloride to precipitate uncyclized amine.

Compound X: 75% yield, m.p. 109-111° (from ethanol).

Anal. Calcd. for C₁₅H₁₄ClNOS: C, 61.8; H, 4.8; N, 4.8. Found: C, 62.0; H, 4.6; N, 5.6.

The NMR spectrum exhibited the >NH resonance at about 6.45 ppm. The IR spectrum showed an absorption at 3355 cm⁻¹ due to the >NH group. Other spectral data confirmed the structure of X.

Compound XI: The dark viscous oil recovered by evaporation of the ether could not be induced to crystallize and was used for preparation of XIII without further purification. Its NMR spectrum in DMSO-d₆ showed a one proton singlet due to the >NH proton at 6.00 ppm. The IR spectrum showed the >NH band at 3380 cm⁻¹. Other NMR and IR data confirmed the structure of XI.

2-Chloro-10-(3-dimethylaminopropyl)isopropoxyphenothiazines (XII and XIII).

Compounds X and XI were each alkylated by refluxing in dry xylene first for 30-60 minutes with about fourfold excess of sodium hydride (mineral oil dispersion) then for 4 hours after adding a 20% excess of 3-dimethylaminopropyl chloride (as a xylene solution). The solutions were cooled, treated with water, and after drying and solvent evaporation, produced dark oily residues which could not be crystallized.

Compound XII: Attempts to prepare the hydrochloride in pure form were unsuccessful. IR and NMR spectra of the free base indicated reasonable purity and were in good agreement with the assigned structure.

Compound XIII: Attempts to prepare pure the hydrochloride of this compound were also unsuccessful. Its approximate m.p. is 114-116° (ethanol-ether). The NMR spectrum of XIII in methanol-d₄ exhibited a multiplet at 1.78 ppm, the -CH₂-CH₂-CH₂-proton, a singlet at 2.08 ppm, the -CH₂-N(CH₃)₂ proton, a multiplet at 2.36, the -CH₂-CH₂N(CH₃)₂ protons, and a two proton triplet (J = 6.2 cps) at 3.60 ppm, the >N-CH₂-CH₂-CH₂N(CH₃)₂ protons. No N-H absorption was observed in the IR spectrum. However, bands not present in the spectrum of XI at 2960-2750 cm⁻¹ from the aliphatic side chain were present. Other spectral data further confirmed the assigned structure.

2-Chloro-10-(3-dimethylaminopropyl)-1-hydroxyphenothiazine (II).

Cleavage of the ether XII was achieved by boiling a 4.1 g. portion in 45 ml. of concentrated hydrochloric acid for 30 minutes, diluting with water and neutralizing with sodium bicarbonate to give a final volume of about 600 ml. which was extracted with ether. The ether solution was dried and evaporated and the residue crystallized from ethanol to give 1.0 g. of II, m.p. 170-173° (darkens). Recrystallization from ethanol (Norite) raised the m.p. to 176-177°. Residues from the solvent appeared to contain both XII and X.

Anal. Calcd. for $C_{17}H_{19}ClN_2OS$: C, 61.0; H, 5.7; N, 8.4. Found: C, 61.1; H, 5.7; N, 8.4.

Structure confirmation of II is discussed in the text. Additional IR bands (in cm^{-1}) not reported in the text were 3075, and 3030, aromatic CH "stretch"; 3000-2700, alkyl CH "stretch"; 1450-1400, 1352 and 1322 alkyl CH "bend"; 1590, 1554, 1480, and 1460, aromatic -C=C- "stretch"; 1032 phenyl-S- "stretch".

2-Chloro-10-(3-dimethylaminopropyl)-6-hydroxyphenothiazine (III).

Twenty-nine grams of XIII was heated to boiling during 10 minutes in 400 ml. of concentrated hydrochloric acid and refluxed for 40 minutes. The mixture was then diluted with water and extracted with benzene to remove neutral materials. The aqueous layer including a dense oily layer of amine salt was neutralized with sodium carbonate and extracted with benzene. The residue resulting from evaporation of the benzene was dissolved in isopropyl alcohol and crystallization induced by addition of ether. The 10.4 g. sample of crude III obtained in this way was recrystallized to constant melting point, 172-173° from ethanol to give 4.1 g. (16%) of purified III.

Anal. Calcd. for $C_{17}H_{19}ClN_2OS$: C, 60.9; H, 5.7; N, 8.4. Found: C, 60.9; H, 5.8; N, 8.5.

NMR and IR spectroscopic data used to confirm the structure of III are reported in the text. Additional IR bands not reported in the text are (in cm^{-1}): 3060-3000, aromatic CH "stretch"; 3000-2700 aliphatic CH "stretch"; 1460-1430 and 1402, aliphatic CH "bend"; 1578, 1555, 1470-1460, aromatic -C=C- "stretch".

2-Chloro-3-phenothiazine (XIV).

To a stirred solution of 75 g. of ferric chloride hexahydrate in 9 l. of water and 1 l. acetic acid at 95°, 14.8 g. of 2-chlorophenothiazine was added, and heating was continued for 15 minutes. On cooling and filtration, 13.9 g. of red-brown solid was recovered. A 5 g. portion of this material was chromatographed on a silica gel column using chloroform as eluent to separate first, 1.3 g. of unoxidized 2-chlorophenothiazine and then, as an intensely colored purple band on the column which produced a deep red eluate, 2.9 g. of mixed 2-chloro-3- and 7-phenothiazines. These isomers were separated on a column of silica gel which had first been wet with water then air dried at room temperature. A 396 mg. sample of the mixture applied to such a column in methylene chloride solution and eluted with the same solvent gave two red bands the first of which yielded, on evaporation of the solvent, 103 mg. of XIV a red-brown powder, recrystallized from cyclohexane to m.p. 232-234°. The second band provided 179 mg. of 2-chloro-7-phenothiazine, a red-brown powder recrystallized from aqueous acetic acid to m.p. 212-213°. Compound XIV alone can be prepared with much greater convenience by the condensation of the zinc salt of 2-aminothiophenol with 2,5 dichlorobenzoquinone (22).

Anal. Calcd. for $C_{12}H_6ClNOS$: C, 58.1; H, 2.4; N, 5.7. Found: C, 58.1; H, 2.8; N, 5.7.

The NMR spectrum showed a one proton singlet at 6.86 ppm,

H-1 and a one proton singlet at 7.88 ppm, H-4. The IR spectrum showed a band at 1625 cm^{-1} from the C=O group. Other NMR and IR data further confirmed the structure of XIV.

2-Chloro-3-hydroxyphenothiazine (XV).

A solution of 5 g. of XIV in 600 ml. of methylene chloride was shaken with excess saturated aqueous sodium hydrosulfite solution until the red color disappeared. The methylene chloride solution was separated, dried over magnesium sulfate and the solvent evaporated. The residue was recrystallized from benzene to give 3.5 g. of glistening silvery platelets which darken at 190°, melt at 197-198° (dec.) and slowly turn red on exposure to air at room temperature.

Anal. Calcd. for $C_{12}H_8ClNOS$: C, 57.7; H, 3.2; N, 5.6. Found: C, 57.9; H, 3.1; N, 5.6.

The corresponding reduction of 2-chloro-7-phenothiazine, requiring larger volumes of methylene chloride due to limited solubility, provided from 98 mg. of the phenothiazine, 45 mg. of 2-chloro-7-hydroxyphenothiazine, recrystallized from benzene-cyclohexane as a white solid which turns purple very rapidly.

The NMR spectrum of a red solution of XV in methanol- d_4 exhibited three major broadened resonances. The ESR spectrum of a colored carbon disulfide solution clearly indicated the presence of free radicals. Stabilization with sodium hydrosulfite eliminated the color and the radicals. Sodium hydrosulfite stabilization of the original methanol- d_4 solution also eliminated the color and a well resolved NMR spectrum was obtained. The latter showed singlets at 6.54 ppm, H-4; and 6.66, H-1. The -NH and -OH protons were concentration dependent and were coincident with the water and methanol -OH at about 4.7 ppm. The IR spectrum showed phenolic -OH bands at 3508 and 1188 cm^{-1} . Other NMR and IR data confirmed the structure of XV.

2-(2-Chloro-3-phenothiazinoyl)tetrahydropyran (XVI).

A mixture of 4.6 g. of XV and 40 ml. of dihydropyran was treated with two drops of hydrochloric acid, stirred overnight, refluxed for 1 hour, diluted with ether and shaken with three 50 ml. portions of 2 N sodium hydroxide. The ether solution was dried over magnesium sulfate, and the solvent evaporated. The dark oily residue was dissolved in hot ethanol and on chilling, 2.5 g. of reddish crystalline product was obtained. Successive crystallizations from ethanol gave a slightly pink product which appeared to soften at 144°, and melted at 193-194° (dec.). Its behavior on heating suggests the possibility that thermal decomposition may occur at 144° and the final melting point may be that of XV.

Anal. Calcd. for $C_{17}H_{16}ClNO_2S$: C, 61.1; H, 4.8; N, 4.2. Found: C, 61.5; N, 4.7; N, 5.0.

The NMR spectrum in DMSO- d_6 showed a one proton concentration dependent singlet at 8.50 ppm due to the N-H proton, a one proton multiplet at 5.41 ppm; the 2' proton; a two proton multiplet at 3.60 ppm; the 6' protons and a six proton complex multiplet near 1.75 ppm; the 3', 4', and 5' protons. The IR spectrum showed an NH band at 3350 cm^{-1} . Other NMR and IR data further confirmed the structure of XVI.

2-[2-Chloro-10-(2-cyanoethyl)phenothiazinoyl]tetrahydropyran (XVII).

A slurry of 0.5 g. of XVI in 10 ml. of acrylonitrile (hydroquinone inhibited) was treated at ice bath temperature with one drop of 40% benzyl trimethylammonium methoxide in methanol. The solid appeared to dissolve, then, after a few minutes, a voluminous precipitate formed. An additional 5 ml. of acrylonitrile was added to facilitate agitation and the mixture was stirred over-

night at room temperature. Excess acrylonitrile was removed by evaporation, and the residue dissolved in benzene-ethyl acetate (2:1). Approximately 0.1 g. of insoluble yellow material was removed from the solution by filtration, the solvents were evaporated, and the residue recrystallized from the minimum amount of boiling ethyl acetate. The product slowly crystallized on refrigeration to give 0.35 g. of pink solid and a small additional quantity on evaporation of part of the solvent. Repeated recrystallization from ethyl acetate produced XVII as an almost white material which decomposed at 143-144°.

Anal. Calcd. for $C_{20}H_{19}ClN_2O_2S$: C, 62.0; H, 4.9; N, 7.2. Found: C, 61.9; H, 4.9; N, 8.0.

The NMR spectrum of XVII in DMSO- d_6 confirmed retention of the tetrahydropyranyl group, and also showed a two proton triplet ($J = 6.4$ cps) at 2.89 ppm due to the $-CH_2C\equiv N$ protons. The IR spectrum was generally very similar to XVI and showed a $-C\equiv N$ bond at 2252 cm^{-1} . Other NMR and IR data further confirmed the structure of XVII.

2-[10-(3-Aminopropyl)-2-chloro-3-phenothiazinoxy] tetrahydropyran (XVIII).

A warm solution of 8.0 g. of XVII in 180 ml. of benzene was added during 1.5 hours to 2.6 g. of lithium aluminum hydride slurried in 150 ml. of ether. The stirred mixture was then refluxed for 3 hours, cooled, treated first with a little ethanol then with water to decompose the excess lithium aluminum hydride, then filtered. The aqueous layer was separated, washed with a little benzene and the combined organic extracts dried over magnesium sulfate. Evaporation of the solvent left 6.8 g. of a tan oil which was recrystallized from methanol to give, in three crops which did not vary in melting point appreciably, 6.8 g. of crystalline product. An additional crystallization from methanol gave white crystalline XVIII, m.p. 70-72°.

The sensitivity of this material to oxidation presumably accounts for the relatively poor analytical values.

Anal. Calcd. for $C_{20}H_{23}ClN_2O_2S$: C, 61.4; H, 5.9; N, 7.2. Found: C, 60.0; H, 6.0; N, 7.9.

The NMR spectrum of XVIII in DMSO- d_6 exhibited a broad concentration dependent singlet at 2.36 ppm due to the $-NH_2$ protons. No resonance at 2.89 ppm was observed. The $-C\equiv N$ absorption observed in the IR spectrum of XVII was absent and $-NH_2$ bands were observed at 3630 and 3400 cm^{-1} for a dilute carbon tetrachloride solution.

10-(3-Aminopropyl)-2-chloro-3-hydroxyphenothiazine (XIX).

Agitation of an 8 g. sample of XVIII with 200 ml. of 2 *N* hydrochloric acid under nitrogen in subdued light for about 2 hours produced a blue tarry material. This semisolid was recrystallized repeatedly from benzene and from ethanol in the dark under nitrogen, the solvents having been boiled and cooled under nitrogen prior to use to minimize their oxygen content. Despite these precautions, a little color remained in even the most highly purified sample. Only 130 mg. of XIX, m.p. (in vacuo) 171-173° (dec.), were isolated.

Anal. Calcd. for $C_{15}H_{15}ClN_2OS$: C, 58.7; H, 4.9; N, 9.1. Found: C, 59.4; H, 5.1; N, 8.7.

The NMR spectrum indicated the presence of about 2.5 wt. % of benzene which could not be removed by prolonged exposure *in vacuo* at room temperature. Correction of the analytical values for the benzene content of the sample give C, 59.4; H, 5.0; N, 8.9, in close agreement with the determined values.

1,4-Dichloro-2,6-nitrobenzene (XX).

Following the method of Barrows, *et al.*, (12) 50 ml. of diethylaniline were added to a stirred solution of 21.9 g. of 4-chloro-2,6-

dinitrophenol in 100 ml. of phosphorus oxychloride. The temperature rose to about 50° and the reaction mixture was then heated at 80° for 1 hour, cooled, and poured slowly on ice. Completion of hydrolysis at ice temperature required a considerable period of agitation in ice water. The resulting slurry was then filtered and the residue slurried repeatedly with concentrated aqueous sodium carbonate until the filtrate was colorless. The filtrate was washed with water and dried to give 21.3 g. of crude XX, m.p. 102-103°. Recrystallization from ethanol provided 15.7 g. of tan needles, m.p. 105-107°.

Anal. Calcd. for $C_6H_2Cl_2N_2O_4$: C, 30.4; H, 0.85; N, 11.8. Found: C, 30.4; H, 0.8; N, 11.5.

2'-Bromo-4-chloro-2,6-dinitrophenyl Sulfide (XXIII).

A solution of 2.3 g. (0.1 g.-atom) of sodium in 80 ml. of ethanol was first treated dropwise with 18.9 g. (0.1 mole) of 9-bromothiophenol then brought to reflux and a hot solution of 23.7 g. (0.1 mole) of XX in 200 ml. of ethanol added all at once. After 20 minutes at reflux during which the color changed from orange to yellow green, and finally to yellow, the mixture was cooled and filtered. The solid was dissolved in benzene, extracted twice with 5% sodium hydroxide and twice with water, dried on magnesium sulfate and the benzene evaporated. The residue was recrystallized from ethanol to give 27 g. of bright yellow crystals, m.p. 148-149°. If the reaction was conducted for longer periods of time, the yield was markedly decreased through the formation of unidentified by-products.

In addition to a complex multiplet, a two proton singlet at 7.91 ppm was observed for H-3 and H-5. The IR spectrum showed $-NO_2$ bands at 1560 and 1343 cm^{-1} , and confirmed the aromatic ring's substitution.

2-Amino-2'-bromo-4-chloro-6-nitrophenyl Sulfide (XXIV).

A solution of 71.8 g. (0.18 mole) of XXIII in 2600 ml. of ethanol at 70-75° was treated during 1 hour with 940 g. of 20% titanium trichloride solution added below the surface, while carbon dioxide was continually bubbled through the reaction. Heating and passage of carbon dioxide through the solution were continued for two additional hours and the mixture then cooled and filtered to give 35.3 g. of yellow crystalline solid. The filtrate was diluted to 14 l. and the resulting solid obtained on filtration weighed 29.2 g. A little titania was present in the product which was purified by chromatography on activated alumina. From 40 g. of crude reaction product, 36 g. was eluted with chloroform, m.p. 157-159°. Recrystallization from ethanol did not improve the melting point but recrystallization from ethanol alone (omitting chromatography) gave a lower melting product.

The NMR spectrum showed a two proton concentration dependent, $-NH_2$ resonance at 4.55 ppm in addition to the aromatic resonances. The IR spectrum exhibited strong NH_2 bands at 3455 , 3350 , and 1602 cm^{-1} , $-NO_2$ bands at 1532 and 1368 cm^{-1} , and confirmed the aromatic rings' substitution.

2'-Bromo-4-chloro-2-formamid-o-6-nitrophenyl Sulfide (XXV).

Thirty-six grams of XXIV were refluxed for 10 hours in 350 ml. of formic acid. The reaction mixture was cooled and filtered to provide a solid product m.p. 218-223°, the melting point of which was only slightly elevated 219-223° on recrystallization from large volumes of ethanol. Only 7 g. of product crystallized from about 3 l. of ethanol, the low yield probably occasioned by the high solvent dilution.

2-Chloro-4-nitrophenothiazine (XXVI).

A mixture of 3.9 g. (0.01 mole) of XXV, 2.1 g. of potassium carbonate, 0.2 g. of copper powder, and a very small crystal of

iodine in 100 ml. of dimethylformamide was refluxed under nitrogen for 5.5 hours, cooled and filtered. The purple filtrate was diluted to one liter with water to precipitate a purple solid which was recrystallized from benzene to give 1.8 g. of XXVI.

The NMR spectrum showed a one proton, concentration dependent singlet due to the NH proton and a one proton doublet ($J = 2.0$ cps) at 7.74 ppm due to H-5. The IR spectrum showed an NH band at 3360 cm^{-1} and -NO_2 bands at 1498 and 1314 cm^{-1} . The remainder of the IR spectrum confirmed the aromatic rings' substitution.

2-Chloro-10-(3-dimethylaminopropyl)-4-nitrophenothiazine (XXVII).

A solution of 2.79 g. (0.01 mole) of XXVI in 100 ml. of xylene was treated with 0.5 g. of 54% suspension of sodium hydride in mineral oil, and the mixture refluxed 15 minutes. Five g. of a 50% solution of 3-dimethylaminopropylchloride in xylene was then added, and refluxing continued for 4.5 hours. The reaction mixture was then cooled, washed with water and then extracted with aqueous hydrochloric acid. The aqueous phase and the darker oily phase which separated from the xylene were collected, the acid extraction repeated, and the combined aqueous and oily phases made alkaline (sodium carbonate). The alkaline mixture was extracted with xylene, dried (magnesium sulfate), and the solvent evaporated to leave a dark oil (1.5 g.) which could not be crystallized and was used without further purification for reduction to XXVIII.

4-Amino-2-Chloro-10-(3-dimethylaminopropyl)phenothiazine (XXVIII).

Reduction of XXVII was effected by shaking 6.5 g. of the oily nitro compound in 200 ml. of benzene with 0.9 g. of Adams' catalyst for 20 hours at room temperature under 40 psig hydrogen. The catalyst was removed by filtration and the solvent evaporated to leave 5.9 g. of oily residue which could not be crystallized.

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