The Synthesis of Possible Di- and Trihydroxylated Chlorpromazine Metabolites (1)

Joseph K. Suzuki (2) and Aija Zirnis

Regis Chemical Company, 8210 N. Austin Avenue, Morton Grove, Illinois 60053

and

Albert A. Manian

Psychopharmacology Research Branch, National Institute of Mental Health, Rockville, Maryland 20852

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The syntheses of di- and trihydroxychlorpromazines, I, II, III, and V, and of dioxo derivatives, IV and VI, are described.

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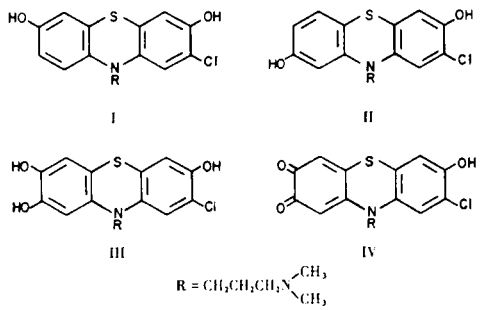
The major ring hydroxylation pathway of chlorpromazine (15) in schizophrenic humans occurs principally at the 7 position of the drug molecule; minor routes originate at the 3 and 8 positions. Further hydroxylation is indicated with the confirmed findings of 3,7- (I) and 7,8-dihydroxychlorpromazine in schizophrenic patients on chronic medication with the parent drug (3). The existence of another possible isomeric metabolite, 3,8-dihydroxychlorpromazine (II), has never been demonstrated, but this may be due in part to the unavailability of a standard for comparison in metabolic studies. Similarly, and with consideration to possible further hydroxylation of these compounds, it is conceivable that a 3,7,8-trihydroxylated biotransformation product could be formed and might be of unique pharmacological significance and activity. We wish to report our successful synthesis of I and II, and of 3,7,8-trihydroxychlorpromazine (III) and its dioxo derivative (IV).

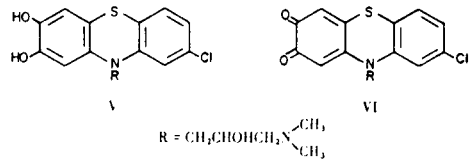


I II

III IV

R = $CH_2CH_2CH_2N(CH_3)_2$

For investigations in developing the major hydroxylation pathway of chlorpromazine we also report the preparation of two compounds which may be of relevance namely, side



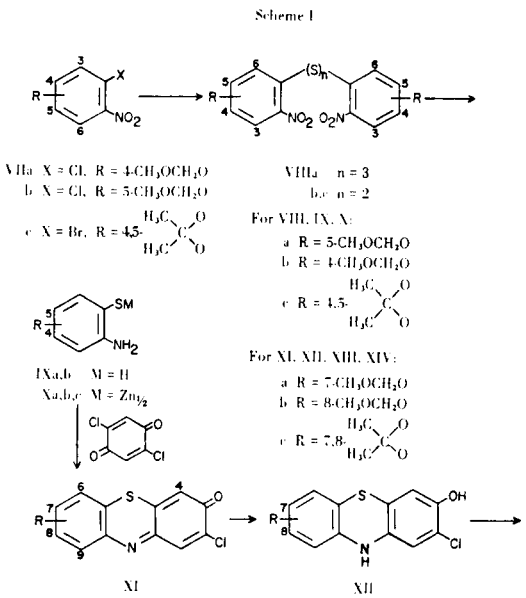
V VI

R = $CH_2CHOHCH_2N(CH_3)_2$

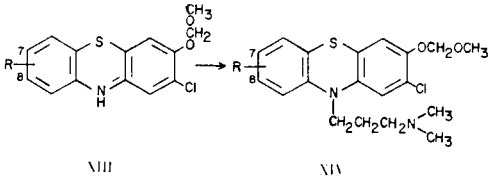
chain hydroxy analogs of 7,8-dihydroxy- and 7,8-dioxochlorpromazine (V and VI, respectively).

The synthesis of I, II, and III is founded on the reaction developed by Mine (4) and expanded upon by Nodiff and co-workers (5) as outlined in Scheme I.

Scheme I



XI XII



XIII XIV

The protective groups, methoxymethylene and dimethylmethylene, were incorporated into the starting materials, VIIa-c, without complication. These nitrohalo derivatives were treated with sodium sulfide and sulfur to give the corresponding oligosulfides. VIIIb and VIIIc were the desired disulfides, n = 2, but VIIIa analyzed as the trisulfide, n = 3. All three oligosulfides readily reduced to their aminothiophenols but the method was governed by the stability of the protective group. VIIIc, containing the dimethylmethylenedioxy moiety, could be reduced with zinc in refluxing acetic acid to Xc. Under these conditions, VIIIb, containing the methoxymethyleneoxy group, resulted in indiscernible reaction products. VIIIa and VIIIb reduced smoothly, however, with sodium dithionite at room temperature and the products were isolated as the free aminothiophenols, IXa and IXb. These compounds were not characterized but the ensuing reaction confirmed their structure.

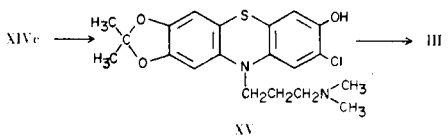
The condensation step (4,5) between the zinc salts Xa-c and 2,5-dichloro-*p*-benzoquinone proceeded as expected to the corresponding phenothiazin-3-ones, XIa-c, which are characteristically intensely dark colored compounds. Compounds IXa and IXb were converted to their zinc salts, Xa and Xb, respectively, *in situ* prior to their reaction with 2,5-dichloro-*p*-benzoquinone. An attempted condensation using the soluble sodium salt of IXb was unsuccessful and was not pursued further.

The phenothiazin-3-ones were reduced with sodium dithionite to the 3-hydroxyphenothiazine derivatives, XIIa-c. Solvent conditions were a factor in the overall rate of these reactions. The reduction of XIc in diethylene glycol required 6 hours. That of XIb was sluggish in diethylene glycol but when diluted with chloroform and water was complete within 15 minutes. The reduction of XIa in chloroform and water was complete in 30 minutes and the product was obtained analytically pure from the chloroform layer.

O-Alkylation with sodium hydride and chloromethyl methyl ether gave the fully protected derivatives XIIIa-c. *N*-Alkylation with sodium hydride and γ,*N*,*N*-dimethylaminopropyl chloride completed the formation of the chlorpromazine intermediates XIVa-c. They were isolated as the free base and/or hydrogen oxalate salt.

The cleavage of the protective groups with methanolic hydrogen chloride is exemplified in the stepwise reactions of XIVc which possesses both groups (Scheme II).

Scheme II



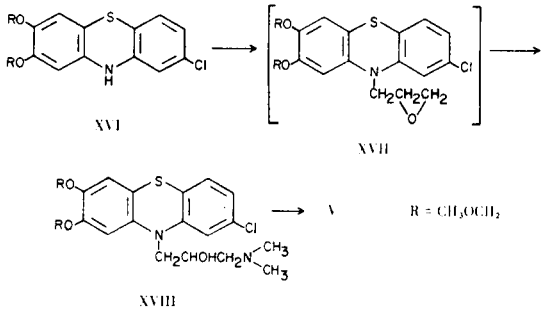
XIVc XV III

Refluxing XIVc in methanol with a moderate excess (~ 2:1) of hydrogen chloride freed the methoxymethylene group and left the more stable dimethylmethylene group intact to give XV as the hydrochloride. The latter was heated at 64°, avoiding reflux, with 10% methanolic hydrogen chloride to produce 3,7,8-trihydroxychlorpromazine, III, as the hydrochloride. When this cleavage was attempted at reflux, the product was degraded sufficiently to make isolation impossible. Compound III-hydrochloride was obtained as a glass and crystallization was not attempted.

The hydrogen oxalates of XIVa and XIVb were refluxed in methanol with a moderate excess (~ 2.5:1) of hydrogen chloride. The resulting 3,7- and 3,8-dihydroxychlorpromazines, I and II, were isolated as the free bases. The sensitivity of these compounds precluded excessive handling which tends to generate impurities which once formed were difficult to eliminate completely.

The preparation of V is an adaptation of the procedure developed for a series of 10-aminoalkanol phenothiazines by Moffett and Aspergen (8) as shown in Scheme III.

Scheme III



XVI XVII XVIII R = CH_3OCH_2

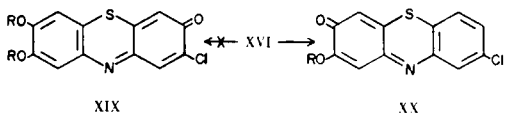
2-Chloro-7,8-dimethoxymethyleneoxyphenothiazine (XVI, 9) was converted to epoxide XVII with sodium hydride and epichlorhydrin. This intermediate was not characterized (10) and could be a mixture of XVII and the corresponding chlorohydrin as suggested by earlier work (8). Compound XVII was treated with excess dimethylamine with moderate heating to provide XVIII which after mild cleavage with methanolic hydrogen chloride yielded V-hydrochloride.

The dioxo derivatives IV and VI were prepared by oxidation of III and V, respectively, with tetrachloro-*o*-benzoquinone (11). Infrared, ultraviolet and visible spectra were compatible with the proposed structures. The structure of VI was supported by mass spectroscopy which

showed a molecular ion peak at m/e 366. Its mass spectrum was identical to that of V due to reduction prior to fragmentation. A similar phenomenon was observed in the mass spectra of 7,8-dioxo- and 7,8-dihydroxychlorpromazine (11).

In the early phase of this work an attempt was made to oxidize XVI to the phenothiazin-3-one XIX (Scheme IV) with Fremy salt (12).

Scheme IV



XIX XX

R = CH_3OCH_2

Oxidation, however, took place in the blocked 7-position to give XX. Similar oxidative cleavages of isopropoxy- (5) and methoxyphenothiazines (13) using ferric chloride have been observed. These examples suggest the potential usefulness of this reaction in the structure proof of polyalkoxy heterocyclic compounds as well as a route for the selective derivatization of alkoxy substituents.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover melting point apparatus in open capillaries and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Infracord Model 137. Ultraviolet and visible spectra were recorded on a Perkin-Elmer spectrophotomer Model 202. Electron-impact mass spectra were obtained on a Hitachi RMU-6D mass spectrometer. Chemical ionization mass spectra were obtained in a Finnegan 1015 mass spectrometer. Analyses were performed by Micro-Tech Laboratories, Skokie, Illinois.

2-Chloro-4-methoxymethyleneoxynitrobenzene (VIIa).

A mixture of 43.7 g. (0.25 mole) of 3-chloro-4-nitrophenol (7), 645 ml. of anhydrous dimethylformamide, and 13.2 g. (0.275 mole) of 50% sodium hydride was stirred under nitrogen for 45 minutes and then chilled in an ice bath as 23.2 g. (0.28 mole) of chloromethyl methyl ether in 80 ml. of dimethylformamide was added in 20 minutes. After another 6 g. of chloromethyl methyl ether was added, the reaction mixture was stirred for 15 minutes and poured into 2 l. of water. The product was extracted with benzene and the latter washed with water, dried and stripped to a red oil weighing 50 g. (92%). A 2 g. portion was passed through a 50 g. silica gel/benzene column. The homogeneous fractions were stripped to a pale yellow oil which was distilled at 124°/0.4 mm.

Anal. Calcd. for $C_8H_8ClNO_4$: C, 44.15; H, 3.70; N, 6.43. Found: C, 44.10; H, 3.64; N, 6.37.

2-Chloro-5-methoxymethyleneoxynitrobenzene (VIIb).

In the above manner 20.3 g. (0.12 mole) of 3-nitro-4-chlorophenol (14) was converted to 27.7 g. (>100%) of crude VIIb as a red oil. Crystallization from benzene-hexane gave an analytical sample, m.p. 28-30°.

Anal. Calcd. for $C_8H_8ClNO_4$: C, 44.15; H, 3.70; N, 6.43. Found: C, 44.13; H, 3.62; N, 6.43.

Bis(2-nitro-5-methoxymethyleneoxyphenyl) Trisulfide (VIIIa).

A mixture of 7.06 g. (0.22 mole) of sulfur, 52.8 g. (0.22 mole) of sodium sulfide nonahydrate and 250 ml. of diethylene glycol was stirred for one hour. The resulting cloudy solution was added to a solution of 48 g. (0.22 mole) of 2-chloro-4-methoxymethyleneoxynitrobenzene (VIIa) in 100 ml. of diethylene glycol in 20 minutes to give a black reaction mixture which was stirred overnight. The latter was poured into 4 l. of water and treated with 12 ml. of glacial acetic acid, discharging the dark color. Sodium chloride was added and the mixture extracted with benzene and the benzene extract washed with water, dried and stripped to a yellow residue weighing 41.2 g. (81%), m.p. 130-134.5°. A small sample was extracted with benzene at room temperature, filtered and concentrated at room temperature to give a yellow solid, m.p. 147-148°, which analyzed for the trisulfide.

Anal. Calcd. for $C_{16}H_{16}N_2O_8S_3$: C, 41.73; H, 3.50; N, 6.08. Found: C, 42.03; H, 3.49; N, 6.15.

Bis(2-nitro-4-methoxymethyleneoxyphenyl) Disulfide (VIIIb).

In the above manner 27.7 g. (0.13 mole) of 2-chloro-5-methoxymethyleneoxynitrobenzene (VIIb) was converted to 27.7 g. (98%) of VIIIb as a red-orange oil. For analysis, a sample was purified *via* a silica gel/benzene column and crystallization from benzene-hexane, m.p. 87-89°.

Anal. Calcd. for $C_{16}H_{16}N_2O_8S_2$: C, 44.85; H, 3.76; N, 6.54. Found: C, 44.82; H, 3.73; N, 6.63.

Bis(4,5-dimethylmethylenedioxy-2-nitrophenyl) Disulfide (VIIIc).

In the above manner 46 g. (0.17 mole) of 2-bromo-4,5-dimethylmethylenedioxynitrobenzene (VIIc, 6) was converted to 23.9 g. (62%) of VIIIc, m.p. 241-243.5° dec. An analytical sample was obtained by crystallizing from benzene, m.p. 248-248.5° dec.

Anal. Calcd. for $C_{18}H_{16}N_2O_8S_2$: C, 47.78; H, 3.56; N, 6.19. Found: C, 48.49; H, 3.62; N, 6.33.

2-Amino-5-methoxymethyleneoxythiophenol (IXa).

To a stirred suspension of 38 g. (0.088 mole) of bis(2-nitro-5-methoxymethyleneoxyphenyl) trisulfide (VIIIa) in 1 l. of ethanol was added a solution of 120 g. (3 moles) of sodium hydroxide in 480 ml. of water followed by a slurry of 306 g. (1.76 moles) of sodium dithionite in 600 ml. of water. Stirring for 2.5 hours gave a creamy suspension which was added to 2.5 l. of water. The basic mixture was extracted with benzene and adjusted to neutral *p*H with 125 ml. of glacial acetic acid to extract the product with benzene, adding acetic acid and sodium chloride as needed. The benzene extract was washed with water, dried and stripped to a yellow oil which weighed 22.3 g. (68%) and which was used as such.

2-Amino-4-methoxymethyleneoxythiophenol (IXb).

A mixture of 27.7 g. (0.064 mole) bis(2-nitro-4-methoxymethyleneoxyphenyl) disulfide (VIIIb) in 1 l. of ethanol and 420 ml. of 20% aqueous sodium hydroxide was stirred as a slurry of 222 g. (1.28 moles) of sodium dithionite in 400 ml. of water and 420 ml. of 20% sodium hydroxide was added. After one hour, the resulting creamy suspension was diluted with 2.5 l. of water, extracted with benzene and neutralized with 200 ml. of glacial acetic acid. The product was extracted with benzene, adding sodium chloride and acetic acid as necessary. The benzene extract was washed with water, dried and stripped to a yellow oil weighing 16 g. (69%).

2-Amino-4,5-dimethylmethylenedioxybenzenethiol Zinc Salt (Xc).

To a suspension of 23.8 g. (0.053 mole) bis(4,5-dimethylmethylenedioxy-2-nitrophenyl) disulfide (VIIIc) in 1.8 l. of glacial

acetic acid was added 106 g. (1.63 moles) of zinc dust at reflux. Refluxing was continued for 45 minutes, the hot mixture filtered and the insoluble mixture washed with hot acetic acid and water. The filtrate was diluted with 8 l. of water and the resulting precipitate filtered and washed with water. The product was dried to weigh 17.3 g. (83%) and used without further purification.

2-Chloro-7-methoxymethyleneoxyphenothiazin-3-one (XIa).

To a solution of 22 g. (0.12 mole) of 2-amino-5-methoxymethyleneoxythiophenol (IXa) in 400 ml. of ethanol was added a solution of 5.2 g. (0.13 mole) of sodium hydroxide in 8 ml. of water under nitrogen. To the resulting solution was added a cloudy solution of 9.5 g. (0.07 mole) of zinc chloride in 240 ml. of ethanol in 25 minutes to give a creamy suspension. To the latter was added a slurry of 23 g. (0.13 mole) of 2,5-dichloro-*p*-benzoquinone in 200 ml. of ethanol. Dilution with 150 ml. of ethanol and stirring for 3 hours gave a red suspension which was filtered to give 36.2 g. (98%) of crude product. An analytical sample was obtained from chloroform, m.p. 180-181° dec.

Anal. Calcd. for $C_{14}H_{10}ClNO_3S$: C, 54.63; H, 3.28; N, 4.55. Found: C, 54.41; H, 3.30; N, 4.57.

2-Chloro-8-methoxymethyleneoxyphenothiazin-3-one (XIb).

In the above manner 16 g. (0.086 mole) of 2-amino-4-methoxymethyleneoxythiophenol (IXb) was converted to 17 g. (64%) of XIb. Crystallization from ethanol gave an analytical sample as purple crystals, m.p. 175° dec.

Anal. Calcd. for $C_{14}H_{10}ClNO_3S$: C, 54.63; H, 3.28; N, 4.55. Found: C, 54.82; H, 3.38; N, 4.62.

2-Chloro-7,8-dimethylmethylenedioxyphenothiazin-3-one (XIc).

A suspension of 17.3 g. (0.044 mole) of 2-amino-4,5-dimethylmethylenedioxybenzenethiol zinc salt (Xc) in 860 ml. of ethanol was stirred with 15.7 g. (0.088 mole) of 2,5-dichloro-*p*-benzoquinone for 1.5 hours. The dark solid was collected, washed with ethanol and dried to yield 18.2 g. (65%) of crude product which was used as such. An analytical sample crystallized from chloroform, m.p. $>280°$.

Anal. Calcd. for $C_{15}H_{10}ClNO_3S$: C, 56.34; H, 3.15; N, 4.38. Found: C, 56.24; H, 3.21; N, 4.31.

2-Chloro-3-hydroxy-7-methoxymethyleneoxyphenothiazine (XIIa).

A mixture of 33 g. (0.11 mole) of 2-chloro-7-methoxymethyleneoxyphenothiazin-3-one (XIa), 3 l. of chloroform, 57 g. (0.33 mole) of sodium dithionite and 500 ml. of water was stirred for about 30 minutes when the original dark red color had dissipated. The chloroform layer was separated, dried and concentrated to about 500 ml. The resulting mush was filtered and the solid collected and washed with chloroform. After drying the analytically pure product weighed 20.3 g. (60%), m.p. 145-145.5° dec.

Anal. Calcd. for $C_{14}H_{12}ClNO_3S$: C, 54.28; H, 3.91; N, 4.52. Found: C, 54.38; H, 3.95; N, 4.58.

2-Chloro-3-hydroxy-8-methoxymethyleneoxyphenothiazine (XIIb).

A mixture of 17 g. (0.055 mole) of 2-chloro-8-methoxymethyleneoxyphenothiazin-3-one (XIb), 250 ml. of diethylene glycol and 60 g. (0.34 mole) of sodium dithionite was stirred for 2 hours and another 30 g. portion of sodium dithionite added. After 4 hours, the dark reaction mixture was diluted with 50 ml. of water and 50 ml. of chloroform. After 15 minutes, the dark color was replaced by a creamy suspension which was added to 1 l. of water, filtered, washed with water and dried to yield 8.82 g. (51%) of product, m.p. 148-151°. Pink crystals were obtained from hexane-benzene, m.p. 149-149.5° dec., for analysis.

Anal. Calcd. for $C_{14}H_{12}ClNO_3S$: C, 54.28; H, 3.91; N, 4.52. Found: C, 54.51; H, 3.82; N, 4.55.

2-Chloro-7,8-dimethylmethylenedioxy-3-hydroxyphenothiazine (XIIc).

A mixture of 18 g. (0.056 mole) of 2-chloro-7,8-dimethylmethylenedioxyphenothiazin-3-one (XIc), 270 ml. of diethylene glycol, and 60 g. (0.34 mole) of sodium dithionite was stirred for 6 hours and then added to 1.2 l. of water containing sodium dithionite. The resulting precipitate was collected, washed with water, and extracted with chloroform. The extract was dried and evaporated to give 10.4 g. (58%) of XIIc. An analytical sample was crystallized from benzene-hexane, m.p. 191-192°.

Anal. Calcd. for $C_{15}H_{12}ClNO_3S$: C, 55.98; H, 3.76; N, 4.35. Found: C, 56.04; H, 3.78; N, 4.33.

2-Chloro-3,7-dimethoxymethyleneoxyphenothiazine (XIIIa).

A mixture of 20.2 g. (0.065 mole) of 2-chloro-3-hydroxy-7-methoxymethyleneoxyphenothiazine (XIIa), 200 ml. of anhydrous dimethylformamide and 3.46 g. (0.072 mole) of 50% sodium hydride was stirred under nitrogen for 3.5 hours and then chilled in an ice bath as a solution of 6.22 g. (0.075 mole) of chloromethyl methyl ether in 25 ml. of dimethylformamide was added in 40 minutes. Another 0.5 ml. of chloromethyl methyl ether was added to the mixture which was stirred at room temperature for 0.5 hours before pouring into 2 l. of water. The resulting mixture was extracted with benzene with the aid of sodium chloride and the benzene extract washed with water, dried and stripped to a dark oil weighing 25.7 g. This was extracted several times with hot hexane to give 8.8 g. (38%) of product, m.p. 85-86°. Further extraction gave a second crop weighing 6.5 g. (28%), m.p. 80-84°. An analytical sample from hexane melted at 85-86°.

Anal. Calcd. for $C_{16}H_{16}ClNO_4S$: C, 54.31; H, 4.56; N, 3.96. Found: C, 54.19; H, 4.38; N, 4.00.

2-Chloro-3,8-dimethoxymethyleneoxyphenothiazine (XIIIb).

In the above manner 8.62 g. (0.028 mole) of 2-chloro-3-hydroxy-8-methoxymethyleneoxyphenothiazine (XIIb) was converted to 9.52 g. (96%) of XIIIb which was an oil. For analysis, an aliquot was purified on a silica gel/benzene column. Homogeneous fractions were stripped to an oil which was redissolved in ether, filtered, evaporated and dried *in vacuo* at 100°.

Anal. Calcd. for $C_{16}H_{16}ClNO_4S$: C, 54.31; H, 4.56; N, 3.96. Found: C, 54.02; H, 4.62; N, 4.05.

2-Chloro-7,8-dimethylmethylenedioxy-3-methoxymethyleneoxyphenothiazine (XIIIc).

In the above manner 10 g. (0.031 mole) of 2-chloro-7,8-dimethylmethylenedioxy-3-hydroxyphenothiazine (XIIc) was converted to 7.7 g. (70%) of XIIIc, m.p. 164-166° dec. An analytical sample crystallized from benzene, m.p. 167-169° dec.

Anal. Calcd. for $C_{17}H_{16}ClNO_4S$: C, 55.81; H, 4.41; N, 3.83. Found: C, 55.80; H, 4.36; N, 3.83.

3,7-Dimethoxymethyleneoxychlorpromazine Hydrogen Oxalate ($XIVa \cdot C_2H_2O_4$).

A mixture of 8.8 g. (0.025 mole) of 2-chloro-3,7-dimethoxymethyleneoxyphenothiazine (XIIIa), 225 ml. of anhydrous dimethylformamide, and 1.41 g. (0.029 mole) of 50% sodium hydride was stirred under nitrogen for 2 hours. A second portion of 1.41 g. of 50% sodium hydride was added and followed with 4.45 g. (0.027 mole) of dimethylaminopropyl chloride hydrochloride. The resulting mixture was heated in an oil bath maintained at 80° for 2 hours and added to 2 l. of water. A dark gummy precipitate

was obtained, collected by filtration and taken up in benzene. The benzene solution was washed with water giving a thick emulsion which separated very slowly. The benzene layer was dried and stripped to a dark oil weighing 10.5 g. A portion weighing 6.2 g. (0.014 mole) was taken up in 150 ml. of ether, filtered and added dropwise to a solution of 1.27 g. (0.014 mole) of oxalic acid in 40 ml. of ether to obtain a gummy precipitate and a suspended solid. The latter was collected and washed with ether to give 5.29 g. (40%) of product, m.p. 145-146.5°.

The gummier material was washed with ether and crystallized from ethanol to give 0.52 g. (4%) of product, m.p. 144.5-146°. Concentrating the mother liquor gave another 0.54 g. (4%), m.p. 148-148.5°.

Anal. Calcd. for $C_{21}H_{26}ClN_2O_4S \cdot C_2H_2O_4$: C, 52.32. H, 5.34; N, 5.31. Found: C, 52.32; H, 5.51; N, 5.18.

3,8-Dimethoxymethyleneoxychlorpromazine (XIVb) and its Hydrogen Oxalate Salt (XIVb·$C_2H_2O_4$).

In the above manner 9.0 g. (0.025 mole) of 2-chloro-3,8-dimethoxymethyleneoxyphenothiazine (XIIIb) was converted to crude XIVb which was purified on a 360 g. silica gel/benzene column. Elution with benzene and benzene-ethyl acetate mixtures removed fast-moving impurities. Elution with ethyl acetate-methanol mixtures (9:1, 4:1, 3:2) gave product fractions which were stripped to 9.7 g. of brown oil. Further purification through an alumina/benzene column, eluting with benzene and then a benzene-ethyl acetate mixture (9:1 and 4:1) gave 7.02 g. (63%) of product as the free base.

Anal. Calcd. for $C_{21}H_{26}ClN_2O_4S$: C, 57.59; H, 5.98; N, 6.40. Found: C, 57.41, 57.43; H, 6.22, 6.21; N, 6.20, 6.36.

The hydrogen oxalate (XIVb·$C_2H_2O_4$) was formed by adding 2.58 g. (0.0059 mole) of XIVb in 100 ml. of ether to a stirred solution of 0.60 g. (0.00062 mole) of oxalic acid in 15 ml. of ether. The resulting precipitate was collected and washed with ether to weigh 2.43 g., m.p. 112-119°.

Anal. Calcd. for $C_{21}H_{26}ClN_2O_4S \cdot C_2H_2O_4 \cdot \frac{1}{2}H_2O$: C, 51.44; H, 5.44; N, 5.22. Found: C, 51.66; H, 5.44; N, 5.26.

2-Chloro-7,8-dimethylmethylenedioxy-3-methoxymethyleneoxychlorpromazine (XIVc).

In a manner similar to the above, 7.5 g. (0.020 mole) of 2-chloro-7,8-dimethylmethylenedioxy-3-methoxymethyleneoxyphenothiazine (XIIIc) gave 6.79 g. (73%) of XIVc as the free base. For analysis, a small sample was washed with 5% sodium hydroxide solution and with water, dried and stripped to a light brown oil. The oil was extracted with hexane and the extract evaporated to an oil which was dried *in vacuo* at 78°.

Anal. Calcd. for $C_{23}H_{27}ClN_2O_4S$: C, 58.59; H, 6.04; N, 6.21. Found: C, 58.46; H, 6.19; N, 5.94.

3,7-Dihydroxychlorpromazine (I).

To a refluxing solution of 0.476 g. (0.00090 mole) of 3,7-dimethoxymethyleneoxychlorpromazine hydrogen oxalate (XIVa·$C_2H_2O_4$) in 25 m. of methanol was added 1.1 ml. of 9% methanolic hydrogen chloride under nitrogen. After refluxing for 1.75 hours, the reaction mixture was stripped at room temperature to a blue film which in turn was stripped twice with methanol and dried *in vacuo* with sodium hydroxide. The resulting hard glassy residue was taken up in 25 ml. of water, extracted with ether, diluted with 25 ml. of water and treated with 3 ml. of 1*N* ammonium hydroxide to obtain a light blue green precipitate. The latter was collected, washed with water and dried *in vacuo* at room temperature. It was then extracted with 200 ml. of ether, filtered and concentrated to about 25 ml. to obtain the product which was collected, washed with ether and dried *in vacuo* at 78° to weigh 0.109 g. (35%), m.p. 144-148° dec. The mother liquor on further concentration yielded a second crop weighing 0.04 g. (13%), m.p. 142-146° dec.; uv λ max (ethanol): mμ (ε max): 216 (22,100), 251 (26,400), 311 (5,080).

Anal. Calcd. for $C_{17}H_{19}ClN_2O_2S$: C, 58.19; H, 5.46; N, 7.98. Found: C, 58.09, 58.05; H, 5.46, 5.47; N, 7.93, 7.83.

3,8-Dihydroxychlorpromazine (II).

In the above manner 1.01 g. (0.0019 mole) of 3,8-dimethoxymethyleneoxychlorpromazine hydrogen oxalate (XIVb·$C_2H_2O_4$) was converted to II. After evaporation of the ether extract, the light green residue was stirred with 7.5 ml. of acetone to an off-white solid which was dried *in vacuo* at 78° overnight. The resulting light grey product weighed 0.409 g. (61%), m.p. 191-192° dec.; uv λ max (ethanol): mμ (ε max): 244 (21,700), 309 (5,730).

Anal. Calcd. for $C_{17}H_{19}ClN_2O_2S$: C, 58.19; H, 5.46; N, 7.98. Found: C, 58.23; H, 5.49; N, 7.77.

2-Chloro-7,8-dimethylmethylenedioxy-3-hydroxychlorpromazine Hydrochloride 1½ Hydrate (XV·HCl·$1\frac{1}{2}H_2O$).

A solution of 5.11 g. (0.0113 mole) of 2-chloro-7,8-dimethylmethylenedioxy-3-methoxymethyleneoxychlorpromazine (XIVc) was refluxed under nitrogen and 10 ml. of 10% methanolic hydrogen chloride was added. Within five minutes the resulting green solution was stripped at mild temperatures to a green gel which was dried *in vacuo* to a light blue-green glass weighing 5.84 g. (theory: 5.3 g.) which was useable as such. An analytical sample crystallized from water (Norite and sulfur dioxide) as a pale yellow solid, m.p. 154-156° dec.

Anal. Calcd. for $C_{20}H_{23}ClN_2O_3S \cdot HCl \cdot 1\frac{1}{2}H_2O$: C, 51.06; H, 5.79; N, 5.96. Found: C, 51.13; H, 5.50; N, 6.03.

3,7,8-Trihydroxychlorpromazine Hydrochloride (III·HCl).

A solution of 2.54 g. (0.0054 mole) of 2-chloro-7,8-(dimethylmethylenedioxy)-3-hydroxychlorpromazine hydrochloride 1½ hydrate (XV) in 125 ml. of 10% methanolic hydrogen chloride was stirred and heated under nitrogen in an oil bath maintained at 64° for 5 hours. It was then stripped to a heavy green oil which on drying *in vacuo* at room temperature converted to a glass. Trituration with ether and drying at 100° overnight gave 1.92 g. of product (88%) as a purple glass, m.p. 130-135° dec.; uv λ max (ethanol): mμ (ε max): 219 (14,500), 241 (23,200), 320 (9,500).

Anal. Calcd. for $C_{17}H_{19}ClN_2O_3S \cdot HCl$: C, 50.62; H, 5.00; N, 6.95. Found: C, 50.34; H, 4.90; N, 6.79.

2-Chloro-7,8-dimethoxymethyleneoxy-10-(2,3-epoxypropyl)phenothiazine (XVII).

A mixture of 10 g. (0.0283 mole) of 2-chloro-7,8-dimethoxymethyleneoxyphenothiazine (XVI, 9), 200 ml. of anhydrous dimethylformamide, and 1.5 g. (0.031 mole) of 50% sodium hydride was stirred at room temperature under nitrogen for 4 hours. It was then added to a stirred solution of 13.1 g. (0.141 mole) of epichlorhydrin in 200 ml. of anhydrous dimethylformamide at 5-8° in 45 minutes and the resulting mixture stirred at room temperature overnight and poured into 2 l. of water. The crude product was extracted with ether and the latter washed with water, dried and stripped to a heterogeneous oil which was washed with hexane. The oil was then applied to a 300 g. silica gel/chloroform column. Elution with chloroform gave product fractions which were evaporated to 8.94 g. (77%) red, oily product which was used as such.

2-Chloro-7,8-dimethoxymethyleneoxy-10-(3-dimethylamino-2-hydroxypropyl)phenothiazine (XVIII).

A mixture of 8.94 g. (0.022 mole) of 2-chloro-7,8-dimethoxymethyleneoxy-10-(2,3-epoxypropyl)phenothiazine (XVII), 90 ml. of benzene, and 3 g. (0.066 mole) of dimethylamine was shaken in a Parr apparatus at heat lamp temperatures for 30 hours and then stripped to a red, viscous oil. This was passed through a 300 g. silica gel/methanol column. Major fractions containing the bulk of the product and a fast moving impurity were stripped to a dark oil (A) weighing 6.75 g. Later fractions were stripped to a heterogeneous mixture (B). Oil (A) was passed through a 240 g. alumina (+6% water, neutral, Brockman)/benzene column. Elution with benzene was followed by benzene-ethyl acetate mixtures (4:1; 3:2; 2:3; 1:4) to obtain clean product fractions which were combined and stripped to a tan oil. The latter was alternately taken up in benzene, methanol, and benzene, filtering and evaporating to obtain 5.29 g. (53%) of product (XVIII) as an olive oil.

The heterogeneous mixture (B) and other impure fractions were combined and purified through a 50 g. alumina (+6% water, neutral, Brockman)/benzene column eluting with benzene and benzene-ethyl acetate mixtures to give 0.74 g. (7.4%) of product.

A hydrogen oxalate (XVIII·$C_2H_2O_4$) was prepared in ether for analysis.

Anal. Calcd. for $C_{21}H_{27}ClN_2O_5S \cdot C_2H_2O_4$: C, 50.68; H, 5.36; N, 5.14. Found: C, 50.76; H, 5.27; N, 5.75.

2-Chloro-7,8-dihydroxy-10-(3-dimethylamino-2-hydroxypropyl)-phenothiazine Hydrochloride (V·HCl).

To a refluxing solution of 0.225 g. (0.000494 mole) of 2-chloro-7,8-dimethoxymethyleneoxy-10-(3-dimethylamino-2-hydroxypropyl)phenothiazine (XVIII) in 25 ml. of methanol was added 0.5 ml. of methanolic hydrogen chloride. Refluxing under nitrogen was continued for 30 minutes. Stripping gave a light blue oil which was taken up in 1-butanol, concentrated and chilled overnight. A light purple solid was obtained and washed with 1-butanol and ether. Drying at 100° *in vacuo* provided 0.122 g. (61%) of product, m.p. 93-105°; uv λ max (ethanol): mμ (ε max): 216 (20,200), 237 (26,000), 280 (18,300), 316 (6,060).

Anal. Calcd. for $C_{17}H_{19}ClN_2O_3S \cdot HCl$; C, 50.62; H, 5.00; N, 6.95. Found: C, 50.44; H, 5.17; N, 6.69.

2-Chloro-7,8-dioxo-3-hydroxychlorpromazine Hydrochloride (IV·HCl).

A solution of 0.05 g. (0.000124 mole) of 3,7,8-trihydroxychlorpromazine hydrochloride (III·HCl) in 2 ml. of methanol was treated with a solution of 0.03 g. (0.000124 mole) of tetrachloro-*o*-benzoquinone in 1 ml. of methanol. The resulting thick suspension was diluted with a few ml. of methanol, stirred manually and centrifuged. The supernate was removed, the solid washed with methanol and with ether and dried at 100° for 4 hours to obtain 0.024 g. of product (48%), m.p. 200° dec.; ir (potassium bromide): c=o, broad band at 6.0-6.3μ; uv-visible λ max (ethanol): mμ (ε max): 220 (7,700), 265 (24,600), 542 (9,600).

Anal. Calcd. for $C_{17}H_{17}ClN_2O_3S \cdot HCl$: C, 50.88; H, 4.52; N, 6.98. Found: C, 50.75; H, 4.65; N, 6.68.

2-Chloro-7,8-dioxo-10-(3-dimethylamino-2-hydroxypropyl)phenothiazine Hydrochloride Hemihydrate (VI·HCl·½H_2O).

To a solution of 0.495 g. (0.00123 mole) of 2-chloro-7,8-dihydroxy-10-(3-dimethylamino-2-hydroxypropyl)phenothiazine hydrochloride (V·HCl) in 10 ml. of methanol was added a solution of 0.30 g. (0.00123 mole) of tetrachloro-*o*-benzoquinone in 2 ml. of methanol. After diluting with 3 ml. of methanol, the mixture was stirred for one hour and then filtered. The product was washed with methanol and with ether and dried *in vacuo* at 100° to weigh 0.361 g. (70%), m.p. 218° dec.; ir (potassium bromide): c=o, broad band at 6.0-6.3 μ; uv-visible λ max (ethanol): mμ (ε max): 228 (23,700), 260 (47,500), 500 (16,000).

Anal. Calcd. for $C_{17}H_{17}ClN_2O_3S \cdot HCl \cdot \frac{1}{2}H_2O$: C, 49.76; H, 4.66; N, 6.83. Found: C, 49.24; H, 4.33; N, 6.78.

2-Chloro-8-methoxymethyleneoxyphenothiazin-7-one (XX).

To a solution of 0.83 g. (0.003 mole) of freshly prepared Fremy salt in 65 ml. of water and 13 ml. of 1/6*M* dipotassium hydrogen phosphate was added a solution of 0.5 g. (0.0014 mole) of 2-chloro-7,8-dimethoxymethyleneoxyphenothiazine (XVI, 9) in 20 ml. of diethylene glycol. After 4.5 hours the precipitate was collected, washed with water and dried *in vacuo* to weigh 0.22 g. (51%), m.p. 182° dec. Crystallization from chloroform provided an analytical sample as a bright red solid, m.p. 189-190° dec.; ir (potassium bromide): c=o, group of bands at 6.0-6.2 μ.

Anal. Calcd. for $C_{14}H_{10}ClNO_3S \cdot \frac{1}{2}H_2O$: C, 53.08; H, 3.50; N, 4.42. Found: C, 53.00; H, 3.18; N, 4.47.

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