The Synthesis of 6,9-Dioxo-, 6,9- and 7,9-Dihydroxychlorpromazines, Possible Metabolites of Chlorpromazine (1)

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The syntheses of dioxogenated chlorpromazines **1**, **2**, and **3** *via* the reductive ring closure of substituted nitrodiphenyl sulfides are described.

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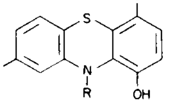
An important metabolic pathway of the major psycholeptic agent, chlorpromazine (3) in humans involves oxidation with the stepwise formation of 7-hydroxychlorpromazine (4), possibly from a non-enzymatic rearrangement of a 7,8-epoxide intermediate initially formed by microsomal oxidation of the parent drug (5), and 7,8-dihydroxychlorpromazine (6). The dihydroxylated metabolite can exist in the body *per se*, in part *O*-methylated (6) and/or further oxidized to its respective *ortho*-quinone (7), a biotransformation product which previously has been proposed as a metabolite by our group (8).

This oxidation pathway has been investigated and demonstrated *in vitro* utilizing the 7-hydroxy metabolite and enzymatic (9) or electrochemical procedures (10). Chemical and electrochemical oxidation studies of the monohydroxylated metabolite at *p*H 7 further indicated two mechanisms of formation of the *ortho*-quinone, each of which evolved from a quinoneimine intermediate (11). Interestingly, one of these processes by-passes the 7,8-dihydroxy analog as an intermediate and forms instead 6,9-dihydroxy-, **1**, and 6,9-dioxochlorpromazine, **2**, as sequential intermediates. This prompted us to report our synthesis of these two *para*-substituted compounds, which may be of interest in chemical as well as in biological studies. Furthermore, as a development from this synthesis, we wish to report the preparation of another dihydroxylated isomer, 7,9-dihydroxychlorpromazine, **3**. An analogous reaction expected to provide a 6,8-disubstituted phenothiazine gave instead the 7,9-isomer. This is also described.



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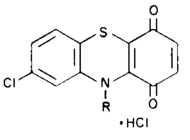

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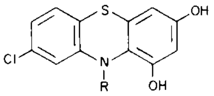
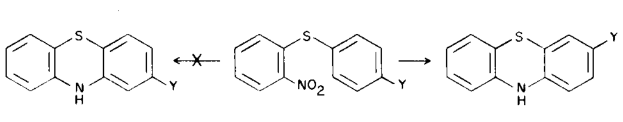


3

$R=(CH_2)_3N(CH_3)_2$

Cadogen and co-workers (12-14) found that nitrodiphenyl sulfides, such as **4**, when refluxed with triethyl phosphite in cumene, would give rise to a 3-substituted phenothiazine **5**, rather than a 2-substituted derivative **6** (Scheme I).

Scheme I

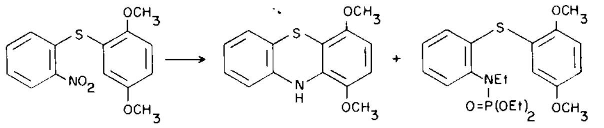


6 4 5

They found that the rearrangement was general and surmised that it proceeded through a nitrene, or nitrene precursor, as in related cyclizations occurring in decomposition reactions of azides (15,16).

As our interest was in the preparation of a 2-chloro-6,9-dioxogenated phenothiazine derivative, our synthesis was modeled according to the preparation of 1,4-dimethoxyphenothiazine **7** (12), which was obtained by the reductive ring closure of 2,5-dimethoxy-2'-nitrodiphenyl sulfide **8** (Scheme II). They also isolated diethyl *N*-ethyl-*N*-[*o*-(2,5-dimethoxyphenylthio)phenyl]phosphoramidate, **9**.

Scheme II



8 7 9

In our analogous reaction, the cyclization of 4'-chloro-2,5-dimethoxy-2'-nitrodiphenyl sulfide, **10**, provided the desired 2-chloro-6,9-dimethoxy phenothiazine, **11a**, as the major product but also small amounts of an unexpected isomer, 2-chloro-7,9-dimethoxyphenothiazine, **12a** (Scheme III).

In addition, we isolated a phosphoramidate which, lacking nmr analysis, is assumed to have the *para*-di-

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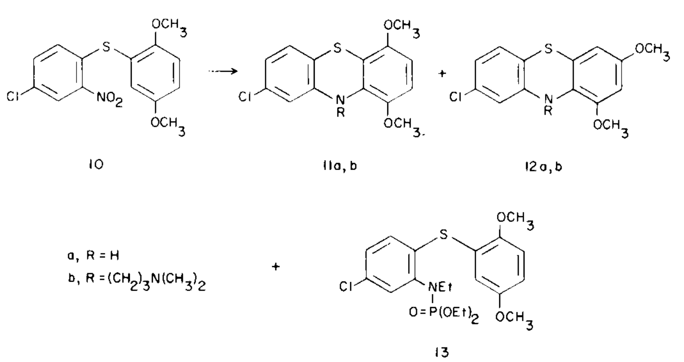
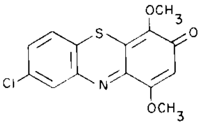
Scheme III

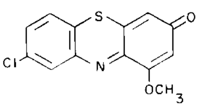


methoxy structure, **13**. Nmr analysis (Table I) of pure **11a** displayed a complex pattern at δ 6.3-6.8 (methanol-d_4) containing a quartet having *ortho*-coupling, $J_{7,8}$ = 10 Hz (for **7**, $J_{2,3}$ = 3.8 Hz) (12). Due to difficult separation problems, we obtained an nmr spectrum of **12a** superimposed on the spectrum of **11a**, from a mixture of **12a** and **11a** in approximately a 1:1 ratio. A quartet was distinguishable, showing that **12a** had *meta*-coupling, $J_{6,8}$ = 3 Hz. Corresponding samples of **11b** and **12b** had similar coupling constants. In thin layer chromatography, **11a** and **12a** could be separated in SB/CD chamber (17) and their spots as developed with iodine had distinct color differences.

Furthermore, Fremy's salt oxidations (18,19) of **11a** and **12a** provided the required quinoneimines, **14** and **15**, respectively, which gave satisfactory elemental analyses.



14



15

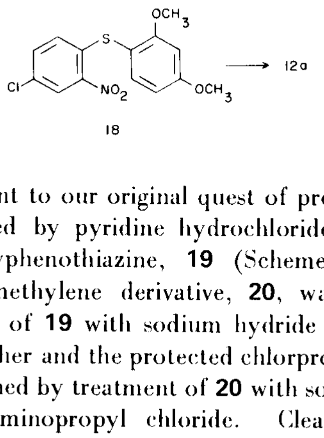
Oxidation of chlorophenothiazines generally occur in the ring which does not have the chloro substituent and are accommodated by concomitant dealkylation when the 7-position is blocked by an alkoxyl group (19-21). The quinoneimines possessed the characteristic dark red color and showed strong absorption in the carbonyl region of their infrared spectra as well as the absence of the strong N-H band present in phenothiazine spectra.

An attempt was made to prepare the 2-chloro-6,8-dimethoxy isomer, **16**, from 4′-chloro-3, 5-dimethoxy-2′-nitrodiphenyl sulfide, **17** (Scheme IV). The anticipated rearrangement did not take place and **12a** was obtained as the sole phenothiazine derivative as confirmed by Fremy's salt oxidation to **14**. It may be that this is due to the strong *ortho-para* directive effects of the two methoxyl groups (15) on the available 2- and 5- positions.

Scheme IV

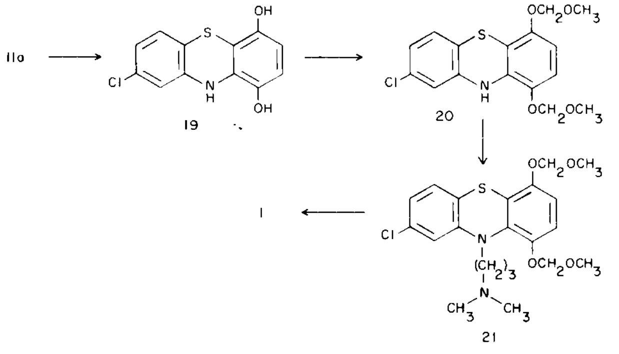
In addition, the ring closure of 4′-chloro-2,4-dimethoxy-2′-nitrodiphenyl sulfide, **18**, yielded **12a** as the major product and **11a** as a minor product. (Scheme V). Obtaining **11a** from **18** and **12a** from **10** is not readily explainable, although it is interesting to note that methoxyl shifts have been observed in this type of ring closure (12,22).

Scheme V



Pursuant to our original quest of preparing **1**, **11a** was dealkylated by pyridine hydrochloride to 2-chloro-6,9-dihydroxyphenothiazine, **19** (Scheme VI). The dimethoxymethylene derivative, **20**, was obtained upon treatment of **19** with sodium hydride and chloromethyl methyl ether and the protected chlorpromazine derivative **21**, obtained by treatment of **20** with sodium hydride and dimethylaminopropyl chloride. Cleavage of the acid labile protective groups was effected with methanolic hydrogen chloride and the product **1**, was isolated as the free base qupon treatment with ammonia.

Scheme VI

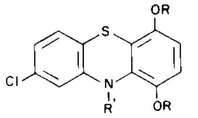


By a similar synthetic route, 7,9-dihydroxychlorpromazine, **3**, was obtained starting from **12a**. The 6,9-dioxochlorpromazine, **2**, was obtained by reaction of **1** with *p*-chloranil. This is analogous to the oxidation of 7,8-dihydroxychlorpromazine, which on treatment with *o*-chloranil give 7,8-dioxochlorpromazine.

Nmr data are presented in Table I and assignments are based on observed coupling constants and substituent factors (8,12,24-26). The influence of the quinonoid system in **2** is particularly interesting not only in the

Table I

NMr Data for Phenothiazine Derivatives (a)

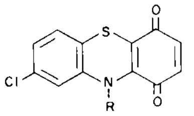


1, 11a, 11b

1, $R=H, R'=(CH_2)_3N(CH_3)_2$

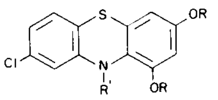
11a, $R=CH_3, R'=H$

11b, $R=CH_3, R'=(CH_2)_3N(CH_3)_2$



2

2, $R=(CH_2)_3N(CH_3)_2 \cdot HCl$



3, 12a, 12b

3, $R=H, R'=(CH_2)_3N(CH_3)_2$

12a, $R=CH_3, R'=H$

12b, $R=CH_3$,
$R'=(CH_2)_3N(CH_3)_2 \cdot HCl$

Compound Proton Type	**1** (b)	**11a** (c)	**11b** (c)	**2** (b,e)	**3** (b)	**12a** (c,f)	**12b** (c,g)
H_1	7.01 (d) $J_{1'3} = 2.5$	6.64- -6.79 (m)	6.88- -7.05 (m)	7.24 (s)	7.02 (d) $J_{1'3} = 2.5$	6.44- -6.80 (m)	7.05 (d) $J_{1'3} = 3$
H_3	6.92 (dd) $J_{1'3} = 2.5$, $J_{3'4} = 8$	"	"	7.12 (s)	6.89 (dd) $J_{1'3} = 2.5$, $J_{3'4} = 10$	"	6.91 (dd) $J_{1'3} = 3$, $J_{3'4} = 8$
H_4	7.08 (d) $J_{3'4} = 8$	"	"	"	7.07 (d) $J_{3'4} = 10$	"	7.25 (d) $J_{3'4} = 8$
H_6					6.22 (d) $J_{6'8} = 3$	6.32 (d) $J_{6'8} = 3$	6.46 (d) $J_{6'8} = 3$
H_7	6.52 (d) $J_{7'8} = 10$	6.59 (d) $J_{7'8} = 10$	6.76 (d) $J_{7'8} = 10$	6.79 (s)			
H_8	6.40 (d) $J_{7'8} = 10$	6.35 (d) $J_{7'8} = 10$	6.65 (d) $J_{7'8} = 10$	"	6.04 (d) $J_{6'8} = 3$	6.10 (d) $J_{6'8} = 3$	6.39 (d) $J_{6'8} = 3$
C_6-OCH_3		3.78 (s)	3.79 (s)				
C_7-OCH_3						3.84 (s)	3.84 (s)
C_9-OCH_3		3.72 (s)	"			3.69 (s)	3.72 (s)

(a) Chemical shifts in δ, coupling constants in Hz. (b) In deuterodimethyl sulfoxide. (c) In deuteromethanol. (d) doublet. (dd) doublet of doublets. (e) With 15-20% of **1**. (f) With **11a** in approximately a 1:1 ratio. (g) With **11b** in a 1:2 ratio. (m) Multiplet. (s) Singlet.

markedly downfield shift of aromatic protons but also in the simplified absorption pattern. The lowest field signal, δ 7.24, appears as a singlet and has been assigned to H_1 which would be most affected by a substantial partial positive charge on the ring nitrogen atom. Canonical forms can be drawn with separation of charge on the nitrogen and oxygen atoms. Also, *ortho*- and *meta*-coupling is not observed, and H_3 and H_4 as well as H_7 and H_8 appear as 2-proton singlets and have thus become essentially equivalent.

The assignment of the methoxy groups is based primarily on the effect of the *N*-substituted side chain. The possibility of hydrogen-bonding is removed between the *N*-hydrogen atom and the neighboring C_9-methoxy group and the latter would be more affected than either the C_6 or C_7-methoxy groups by *N*-substitution. In **11a**, two resolved 3-proton singlets are observed at δ 3.78 and 3.72. In **11b**, the two signals coincide and appear at δ 3.79 as a 6-proton singlet. Thus the higher field signal of **11a** has been assigned to the C_9-methoxy group. Similarly, the high field methoxy signals in **12a** and **12b** have been assigned to the C_9-methoxy group which exhibits a small but perceptible downfield shift with the addition of the side chain.

Mass spectral data for **1**, **2**, and **3** are satisfactory for our structures. Molecular ion peaks occur at m/e 350 (M) for **1** and **3** and at m/e 350 (M + 2) for **2**. This is in agreement with previously reported data for 7,8-dihydroxy- and 7,8-dioxochlorpromazine (8).

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover melting point apparatus in open capillaries and are uncorrected. Electron-impact mass spectra were obtained on a Hewlett-Packard 5985 quadrupole spectrometer. Nuclear magnetic resonance spectra were obtained on a JEOL FX-100 FT-NMR spectrometer. Elemental analysis were performed by Micro-Tech Laboratories, Skokie, Illinois. SB/CD chambers (17) are from Regis Chemical Company, Morton, Brove, Illinois.

2,5-Dimethoxythiophenol.

In a manner described previously (25), 2,5-dimethoxythiophenol was prepared from 2,5-dimethoxyaniline in 42% yield, b.p. 88-92°/0.26 mm (lit. b.p. 131°/8 mm) (26).

3,5-Dimethoxythiophenol.

By the precedure of Newman and Angier (27), 3,5-dimethoxythiophenol was obtained from 3,5-dimethoxyaniline in 30% yield, b.p. 98°/0.2 mm, 102°/0.35 mm (lit. b.p. 111°/0.1 mm).

2,4-Dimethoxythiophenol.

In a similar manner, 2-4-dimethoxyaniline was converted to 2,4-dimethoxythiophenol in 78% yield, b.p. 118-122°/2 mm (lit. b.p. 142°/8 mm) (26).

4′-Chloro-2,5-dimethoxy-2′-nitrodiphenyl Sulfide (**10**).

The procedure of Galt and London (28) was used to prepare **10** from 2,5-dimethoxythiophenol and 2,5-dichloronitrobenzene. Crude product (93%), m.p. 117.5-119°, was obtained. An analytical sample was crystallized from ethanol, m.p. 117-119°.

Anal. Calcd. for $C_{14}H_{17}ClNO_4S$: C, 51.62; H, 3.71; N, 4.30. Found: C, 51.44; H, 3.49; N, 4.13.

4′-Chloro-3,5-dimethoxy-2′-nitrodiphenyl Sulfide (**16**).

In the above manner, **16**, m.p. 95.5-97° was obtained (99%) from the condensation of 3,5-dimethoxythiophenol and 2,5-dichloronitrobenzene. A sample was crystallized from ethanol for analysis, m.p. 96-98°.

Anal. Calcd. for $C_{14}H_{17}ClNO_4S$: C, 51.62; H, 3.71; N, 4.30. Found: C, 51.68; H, 3.60; N, 4.33.

4′-Chloro-2,4-dimethoxy-2′-nitrodiphenyl Sulfide (**17**).

In like manner, **17**, m.p. 113-135°, was obtained (91%) from 2,4-dimethoxythiophenol and 2,5-dichloronitrobenzene. An analytical sample from ethanol melted at 134-135°.

Anal. Calcd. for $C_{14}C_{17}ClNO_4S$: C, 51.62; H, 3.71; N, 4.30. Found: C, 51.42; H, 3.60; N, 4.29.

Ring Closure of Nitrodiphenyl Sulfides **10**, **17**, and **18**.

4′-Chloro-2,5-dimethoxy-2′-nitrodiphenyl Sulfide (**10**).

Method I.

Following the conditions of Cadogen and Kulik (12), a mixture of 5 g. (0.015 mole) of **10**, 10.2 g. (0.062 mole) of triethyl phosphite, and 12.5 ml. of cumene was refluxed under nitrogen for 18 hours. The resulting dark reaction mixture was filtered through silica gel, washing with benzene-hexane (2:1). The filtrate was stripped and the resulting oil filtered through silica gel, washing with benzene-hexane (1:2). The filtrate was stripped at aspirator and vacuum pump pressures to a red oil weighing 4.7 g. Trituration of this oil with 8 ml. of benzene-hexane (1:2) gave a solid weighing 2.3 g. The mother liquor was saved for later work-up. The solid on crystallization from ethanol gave 0.66 g. (14%) 2-chloro-6,9-dimethoxyphenothiazine **11a**, m.p. 137-138°.

Anal. Calcd. for $C_{14}H_{12}ClNO_2S$: C, 57.23; H, 4.12; N, 4.77. Found: C, 57.12; H, 4.24; N, 4.67.

Fremy's salt oxidation (19) of **11a** gave 2-chloro-6,9-dimethoxyphenothiazin-7-one **14**, m.p. 266-267.5 dec.

Anal. Calcd. for $C_{14}H_{10}ClNO_3S$: C, 54.63; H, 3.28; N, 4.55. Found: C, 54.25; H, 3.21; N, 4.43.

From the ethanol mother liquor 0.39 g. of a white solid, m.p. 110-113°, was isolated which analyzed for diethyl *N*-ethyl-*N*-[*o*-(2,5-dimethoxyphenylthio)-4′-chlorophenyl]phosphoramidate **13**.

Anal. Calcd. for $C_{20}H_{27}ClNO_5PS$: C, 52.22; H, 5.92; N, 3.05. Found: C, 52.23; H, 6.16; N, 3.05.

The benzene-hexane mother liquor was stripped to an oil which was chromatographed through a 125 g. alumina column (neutral Brockman, + 10% water), eluting with benzene-hexane (1:2). Like fractions were stripped to an oil which readily solidified. Crystallization from ethanol gave a mixture of 2-chlorodimethoxyphenothiazines, m.p. 104-123°, weighing 0.57 g. (13%). A second crystallization gave a m.p. of 105-106°. Nmr showed the presence of the 6,9-isomer **11a** and a second dimethoxy isomer in roughly a 1:1 ratio. A *meta*-coupling was observed (J m = 3 Hz) from the spectrum of the latter superimposed on that of **11a**. After further column chromatography and crystallization, a pure sample was obtained, m.p. 134-135° and was assigned the structure of 2-chloro-7,9-dimethoxyphenothiazine **12a**.

Anal. Calcd. for $C_{14}H_{12}ClNO_2S$: C, 57.23; H, 4.12; N, 4.77. Found: C, 57.08; H, 4.02; N, 4.67.

Fremy's salt oxidation of **12a** gave 2-chloro-9-methoxyphenothiazin-7-one **15**, m.p. 240° dec.

Anal. Calcd. for $C_{13}H_8ClNO_2S$: C, 56.22; H, 2.90; N, 5.04. Found: C, 56.25; H, 3.02; N, 4.90.

Method II (High Dilution).

A mixture of 50 g. (0.15 mole) of **10**, 102 g. (0.62 mole) of triethyl phosphite, and 1500 ml. of cumene was refluxed under nitrogen for 18 hours. It was stripped to an oil weighing 96 g., which on stirring with 100 ml. of chloroform-hexane (1:3) for one hour gave 15.8 g. (35%) **11a**, m.p. 137.5-139° after filtration and drying. The mother liquor was stripped to an oil which was applied onto 250 g. of silica gel and eluted with chloroform-hexane (1:2) to give another oil weighing 39 g., containing phenothiazines **11a** and **12a**. The oil was again chromatographed through 250 g. of silica with chloroform-hexane (1:3). Product fractions were stripped to a solid weighing 5.2 g. (11%), which showed the presence of both isomers by thin layer chromatography.

4′-Chloro-3,5-dimethoxy-2′-nitrodiphenyl Sulfide (**17**).

Under the conditions of Method II, 17.5 g. (0.054 mole) of **17** was ring closed to give an initial crop of 2.58 g. (16%) of **12a**, m.p. 131.5-133°. The mother liquor was chromatographed to give a further 2.21 g. (13%) of **12a**, m.p. 133-135°.

Anal. Calcd. for $C_{13}H_8ClNO_2S$: C, 56.22; H, 2.90; N, 5.04. Found: C, 56.45; H, 2.96; N, 4.97.

4′-Chloro-2,4-dimethoxy-2′-nitrodiphenyl Sulfide (**18**).

Under conditions of Method II, 17.5 g. (0.054 mole) of **18**, was ring closed to yield an initial crop of 6.60 g. (41%) of **12a**, m.p. 132-134°. Chromatography of the mother liquor followed by crystallization gave 0.08 g. of **11a**, m.p. 137-138° a mixture of **11a** and **12a** weighing 4.0 g. (25%), and 0.80 g. (5%) of pure **12a**, m.p. 134-135°.

Anal. Calcd. for $C_{14}H_{12}ClNO_2S$: C, 57.23; H, 4.12; N, 4.77. Found: (**12a**): C, 57.13; H, 4.12; N, 4.71; (**11a**): C, 57.07; H, 4.19; N, 4.75.

6,9-Dimethoxychlorpromazine (**11b**).

In a manner described previously (19), 0.55 g. (0.0019 mole) of **11a** was converted to 0.14 g. (20%) of **11b**. An analytical sample was obtained from petroleum ether, m.p. 87-88°.

Anal. Calcd. for $C_{19}H_{23}ClN_2O_2S$: C, 60.22; H, 6.12; N, 7.50. Found: C, 60.14; H, 6.19; N, 7.39.

7,9-Dimethoxychlorpromazine Hydrochloride **12b** as obtained with **11b** Hydrochloride.

In the above manner, a mixture of 0.5 g. (0.0015 mole) of isomers **11a** and **12a** were converted to a mixture of **11b** and **12b**, isolated as hydrochlorides weighing 0.067 g., m.p. 167-168°. Crystallization from acetone-ether gave a sample weighing 0.028 g., m.p. 180-190°. Nmr indicated a mixture of **11b** and **12b** in a 1:2 ratio.

Anal. Calcd. for $C_{19}H_{23}ClN_2O_2S \cdot HCl$: C, 54.94; H, 5.82. N, 6.74. Found: C, 54.70; H, 5.79; N, 6.60.

2-Chloro-6,9-dihydroxyphenothiazine (**19**).

A mixture of 10 g. (0.034 mole) of 2-chloro-6,9-dimethoxyphenothiazine **11a** and 50 g. (0.43 mole) of pyridine hydrochloride was heated and stirred under nitrogen in an oil bath maintained at 195-205° for 0.5 hour. The hot reaction mixture was added to 350 ml. of ice cold water containing 2 g. of sodium bisulfite. The resulting green suspension was filtered and the solid washed wtih aqueous bisulfite and with water. After drying at room temperature and then at 78° for 3 hours, the product weighed 7.5 g. (83%), m.p. 190-196° dec. An analytical sample from chloroform-ether did not melt $>$ 260°.

Anal. Calcd. for $C_{12}H_8ClNO_2S$: C, 54.24; H, 3.03; N, 5.27. Found: C, 54.22; H, 3.10; N, 5.33.

2-Chloro-7,9-dihydroxyphenothiazine.

In a similar manner as above, 1 g. (0.0034 mole) of 2-chloro-7,9-dimethoxyphenothiazine **12a** gave 0.86 g. (96%) of 2-chloro-7,9-dihydroxyphenothiazine, m.p. 213-216° dec. An analyzed sample melted at 199-201° dec.

Anal. Calcd. for $C_{12}H_8ClNO_2S$: C, 54.24; H, 3.03; N, 5.27. Found: C, 54.27; H, 3.12; N, 5.27.

2-Chloro-6,9-dimethoxymethyleneoxyphenothiazine (**20**).

In a manner similar to that described previously (19), 7.5 g. (0.028 mole) of **19** was converted to 5.4 g. (54%) of **20**, m.p. 72-74°. An analytical sample from petroleum ether melted at 73-74°.

Anal. Calcd. for $C_{16}H_{16}ClNO_4S$: C, 54.31; H, 4.56; N, 3.96. Found: C, 54.15; H, 4.59; N, 3.96.

2-Chloro-7,9-dimethoxymethyleneoxyphenothiazine.

In the above manner, 0.85 g. (0.0032 mole) of 2-chloro-7,9-dihydroxyphenothiazine yielded 0.31 g. (28%) of product, m.p. 75.5-77.5°. An analytical sample obtained from petroleum ether melted at 74-75°.

Anal. Calcd. for $C_{16}H_{16}ClNO_4S$: C, 54.31; H, 4.56; N, 3.96. Found: C, 54.24; H, 4.50; N, 3.85.

6,9-Dimethoxymethyleneoxychlorpromazine Hydrogen Oxalate Hydrate (**21**).

Using a procedure similar to that described previously (19), 5 g. (0.014 mole) of **20** yielded 4.9 g. (63%) of **21**, m.p. 119-120°. An analytical sample melted at 120-121°

Anal. Calcd. for $C_{21}H_{27}ClN_2O_4S \cdot C_2H_2O_4 \cdot H_2O$: C, 50.50; H, 5.71; N, 5.12. Found: C, 50.34; H, 5.34; N, 4.93.

7,9-Dimethoxymethyleneoxychlorpromazine Hydrogen Oxalate Hydrate.

In the above manner, 0.30 g. (0.00085 mole) of 2-chloro-7,9-dimethoxymethyleneoxyphenothiazine yielded 0.22 g. (48%) of product, m.p. 128-128.5°.

Anal. Calcd. for $C_{21}H_{27}ClN_2O_4S \cdot C_2H_2O_4 \cdot H_2O$: C, 50.50; H, 5.71; N, 5.12. Found: C, 50.38; H, 5.37; N, 4.96.

6,9-Dihydroxychlorpromazine (**1**).

A solution of 3 g. (0.0058 mole) of 6,9-dimethoxymethyleneoxychlorpromazine hydrogen oxalate monohydrate **20**, 45 ml. of methanol, and 7.2 ml. of 9.2% methanolic hydrogen chloride was refluxed under nitrogen for 1.5 hours. The reaction mixture was stripped to an oil which was dissolved in 30 ml. of distilled water. The aqueous solution was stirred under nitrogen as 25 ml. of 0.6*M* ammonium hydroxide solution was added to give a suspension. The solid was collected under nitrogen and washed with 25 ml. of water. After drying *in vacuo* at room temperature for 35 hours at 100°, and at 110° for 16 hours, an anhydrous product was obtained as a grey solid weighing 1.71 g. (83%), m.p. 168-170° dec; ms: (70 eV) m/e 350 (M).

Anal. Calcd. for $C_{17}H_{19}ClN_2O_2S$: C, 58.19; H, 5.46; N, 7.98. Found: C, 57.94; H, 5.46; N, 7.89.

7,9-Dihydroxychlorpromazine (**3**).

In a similar manner, **3** was obtained from 7,9-dimethoxymethyleneoxychlorpromazine hydrogen oxalate hydrate in 41% yield, m.p. 153-157° dec; ms: (70 eV) m/e 350 (M).

Anal. Calcd. for $C_{17}H_{19}ClN_2O_2S$: C, 58.19; H, 5.46; N, 7.98. Found: C, 58.37; H, 5.55; N, 7.68.

6,9-Dixochlorpromazine Hydrochloride (**2**).

To a solution of 0.20 g. (0.00057 mole) of **1**, 10 ml. of methanol, and 0.092 g. (0.00082 mole) of 90% perchloric acid, was added 0.21 g. (0.00085 mole) of *p*-chloranil and 10 ml. of methanol. The resulting mixture was stirred at room temperature for 2.5 hours and stripped to a blue-green solid. The latter was washed with 25 ml. of methanol, dried *in vacuo* at room temperature and extracted exhaustively with ethyl ether. The resulting hydroperchlorate salt weighted 0.125 g., m.p. 189-90° dec. It was stirred with 25 ml. of Dowex 1-X8 (chloride form) into 50 ml. of methanol for 3 hours. The resin was filtered and washed well with methanol and the methanol filtrate stripped to a blue film which was dried *in vacuo* over phorphorus pentoxide. The residue was taken up in isopropanol, filtered, and concentrated slowly to 3 ml. as a dark solid formed. The latter was collected, washed with isopropanol and with ether, and dried *in vacuo* at 100° for 30 hours to weigh 0.066 g. (30%), m.p. 154-160° dec. Nmr indicated the presence of 15-20% of **1**; ms: (70 eV) m/e 350 (M + 2).

Anal. Calcd. for $C_{17}H_{17}ClN_2O_2S \cdot HCl$: C, 52.99; H, 4.71; N, 7.27. Found: C, 52.76; H, 4.70; N, 7.21.

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REFERENCES AND NOTES

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(2) Author to whom correspondence should be addressed.

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

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