# 7,8-Dioxochlorpromazine, Synthesis and Properties

*A. Zirnis (I) and J. K. Suzuki*

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

and

*J. W. Daly*

National Institute of Arthritis, Metabolism and Digestive Diseases, National Institutes of Health, Bethesda, Maryland 20014

and

*A. A. Manian*

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

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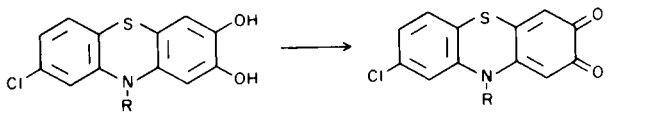
7,8-Dihydroxychlorpromazine and 2-chloro-7,8-dihydroxyphenothiazine were converted to the corresponding 7,8-dioxo compounds by oxidation with tetrachloro-*o*-quinone. Spectral properties indicate that the 7,8-dioxo compounds exist in zwitterionic forms reminiscent of aminochromes. The 7,8-dioxochlorpromazine is proposed as a possible metabolite of chlorpromazine.

The recent identification of 7,8-dihydroxychlorpromazine as a metabolite in schizophrenic patients on long term chlorpromazine therapy (2), utilizing a standard prepared at this laboratory (3), demonstrates another step in the hydroxylation pathways for this psychotropic drug. The major route for biological ring hydroxylation of chlorpromazine, as well as for promazine, appears to be initiated by oxidation at the 7-position (4,5), *para* to the ring nitrogen of the phenothiazine moiety. The corresponding monohydroxylated metabolite of chlorpromazine, with the hydroxy group in the 3-position has been reported to be present, in trace amounts, in human urine (6). Another minor hydroxylation pathway is indicated by isolation of 8-hydroxychlorpromazine (7). Further hydroxylation of the monohydroxychlorpromazine metabolites occurs in humans with the formation of isomeric dihydroxychlorpromazines. In addition to 7,8-dihydroxychlorpromazine (**1a**), the 3,7-dihydroxy metabolite has been identified (2), and the 3,8-dihydroxy analog has been suggested as a metabolite (8).

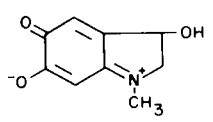
In a recent *in vitro* study utilizing mushroom tyrosinase Grover *et al.* (9), have demonstrated enzyme-catalyzed conversion of 7-hydroxychlorpromazine to 7,8-dihydroxychlorpromazine and 3-hydroxypromazine to 2,3-dihydroxypromazine. In addition, these investigators have demonstrated that all of the phenothiazine derivatives are easily oxidized to their stable semiquinone free radical form in 50% hydrochloric acid or sulfuric acid solutions. They proposed that the 7,8-dihydroxychlorpromazine is oxidized to its quinone, which in the manner of dopaquinone could be expected to form "melanin-like" polymers or copolymers with dopaquinone. This would provide a plausible explanation for the significant hyperpigmentation in patients on prolonged, high dose chlorpromazine therapy. We have undertaken the synthesis of the quinone

Scheme I

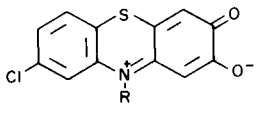


**1a**, R=$CH_2CH_2CH_2NMe_2$·HCl
**1b**, R=H

**2a**, R=$CH_2CH_2CH_2NMe_2$·HCl
**2b**, R=H



**3**



**4a**, R=$CH_2CH_2CH_2NMe_2$·HCl
**4b**, R=H

of 7,8-dihydroxychlorpromazine to provide a standard for further evaluation and biological studies.

7,8-Dioxochlorpromazine hydrochloride (**2a**) was obtained by the oxidation of 7,8-dihydroxychlorpromazine hydrochloride (**1a**). Initially, silver oxide was used. This oxidant has been successfully employed by Heacock (10, 11) for the oxidation of catechol amines to aminochromes (**3**,12). However, inconsistent results and difficulties in isolation caused us to turn to another oxidant, tetrachloro-*o*-quinone (13) whose use provided a convenient synthesis of the desired product. Similar oxidation of 2-chloro-7,8-dihydroxyphenothiazine (**1b**) provided 2-chloro-7,8-dioxophenothiazine (**2b**). A monosemicarbazone of each of the quinones was prepared.

Table 1

Absorption Spectra of Phenothiazine Derivatives

| Compound | λ max (ε) in ethanol |
|---|---|
| 7,8-Dihydroxychlorpromazine hydrochloride | 215 mμ (19300), 237 mμ (24000), 259 mμ (17100), 318 mμ (6470). |
| 7,8-Dioxochlorpromazine hydrochloride | 215 mμ (14000), 229 mμ (16600), 266 mμ (30400), 495 mμ (15100). |
| 7,8-Dioxochlorpromazine 7-semicarbazone hydrochloride | 218 mμ (7170), 270 mμ (9620), 307 mμ (7075), 482 mμ (7550). |
| 2-Chloro-7,8-dihydroxyphenothiazine | 238 mμ (19100), 264 mμ (19600), 328 mμ (4900). |
| 2-Chloro-7,8-dioxophenothiazine | 217 mμ (11800), 251 mμ (28300), 272 mμ (23800), 287 mμ (20500), 420 mμ (13440), 488 mμ (10610). |
| 2-Chloro-7,8-dioxophenothiazine -7-semicarbazone | Insoluble |

Spectral data favor the zwitterionic structures, (**4a**) and (**4b**) rather than the quinone structures, (**2a**) and (**2b**). These would make these dioxo compounds, thio analogs of aminochromes, for which the structure (**3**,12) has been established (10,14). The infrared spectra of the 7,8-dioxophenothiazines exhibit strong carbonyl absorption at 1600-1610 $cm^{-1}$ which is characteristic of the aminochromes (10). Ultraviolet and visible spectra of the quinones, semicarbazones, and the parent dihydroxy compounds have the absorption maxima shown in Table 1. The aminochromes are reported to have a characteristic absorption in the region 470-490 mμ (10) with a progressive shift towards lower frequency with increasing size of a *N*-alkyl group. The dioxophenothiazines exhibit absorption peaks in the same area.

The nuclear magnetic resonance spectral data for these compounds are presented in Table 2. The chemical shifts of the oxo-compounds are compatible with a significant contribution of the zwitterionic structure, which would be expected to have a deshielding effect on $H_a$, $H_b$ and $H_c$. Such zwitterionic contributions are reminiscent of the aminochromes, where the resonances of the protons corresponding to $H_d$ and $H_e$, however, appear at much higher field, 6.42 and 5.39, respectively (11).

Mass spectral data are given in Table 3. The *m/e* of ions corresponding to $^{35}Cl$ containing fragments are tabulated followed by their intensity relative to the base peak, which is set equal to 100. The mass spectral data of **2a** at first appears inexplicable since it corresponds to 7,8-dihydroxychlorpromazine rather than to a 7,8-dioxo analog. However, the literature contains many examples of the reduction of quinones to hydroquinones prior to fragmentation (15). The spectra of **2b** is that of the quinone. Attempts to obtain satisfactory nonpyrolitic mass spectra of the semicarbazones of **2a** or **2b** were unsuccessful. The semicarbazone of adrenochrome did afford a small molecular ion at *m/e* 235.

## 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 spectrophotometer Model 202. The nmr data were obtained on a Varian HA-100 spectrometer and are reported in ppm from the TMS internal standard. 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.

7,8-Dioxochlorpromazine Hydrochloride Monohydrate.

To a stirred solution of 1.00 g. (0.00258 mole) of 7,8-dihydroxychlorpromazine hydrochloride (3) in 16 ml. of methanol under nitrogen was added a solution of 0.634 g. (0.00258 mole) of tetrachloro-*o*-quinone in 3 ml. of methanol. The resulting suspension was stirred for 0.5 hour and filtered to give a dark red solid which was washed with methanol and with ether and dried *in vacuo* at 110° to give 0.751 g. (70%) product, melting at 207-208°.

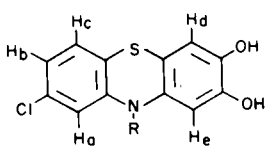
*Anal.* Calcd. for $C_{17}H_{17}ClN_2O_2S \cdot HCl \cdot H_2O$: C, 50.62; H, 5.00; N, 6.95. Found: C, 50.41; H, 4.90; N, 6.84.

7,8-Dioxochlorpromazine-7-semicarbazone Hydrochloride Hydrate.

To a stirred suspension of 0.75 g. (0.00186 mole) of 7,8-dioxochlorpromazine hydrochloride monohydrate in 30 ml. of ethanol under nitrogen was added 0.208 g. (0.00186 mole) of semicarbazide hydrochloride in 7.5 ml. of water followed by another 7.5 ml. of

Table 2

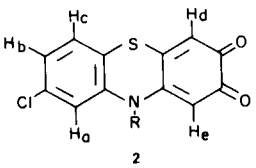
Nuclear Magnetic Resonance Spectra of Phenothiazine Derivatives



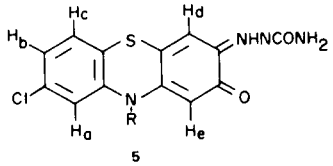
1

a, R = $-CH_2CH_2CH_2NMe_2$ ($H_f$ $H_g$ $H_h$ $H_i$)

b, R = H



2



5

| Proton(s) | Resonance Signal (number protons, type signal, coupling constant) | Chemical Shift (δ) in DMSO-$^2H_6$ 1a | 2a | 5 | 2b | 5 |
|---|---|---|---|---|---|---|
| $H_a$ | 1H, doublet, J=3 cps | 7.13 | 7.84 | 7.47 | 7.89 | 7.23 |
| $H_b$ | 1H, doublet, doublets, J=3,8 cps | 7.03 | 7.42 | 7.19 | 7.45 | 7.05 |
| $H_c$ | 1H, doublet, J=8 cps | 7.26 | 7.77 | 7.42 | 7.85 | 7.30 |
| $H_d$ | 1H, singlet | 6.72 | 6.97 | 7.05 | 7.08 | 6.95 |
| $H_e$ | 1H, singlet | 6.68 | 6.38 | 6.31 | 6.82 | 5.99 |
| $H_f$ | 2H, triplet, J=7 cps | 3.91 | 4.33 | 4.20 | - | - |
| $H_g$ | 2H, multiplet | 2.1-2.3 | 2.1-2.3 | 2.1-2.3 | - | - |
| $H_h$ | 2H, triplet, J=8 cps | 3.20 | 3.33 | 3.25 | - | - |
| $H_i$ | 6H, singlet | 2.77 | 2.82 | 2.79 | - | - |

Table 3

Mass Spectral Data for Phenothiazine Derivatives (Electron Impact, 70ev)

| Compound | *m/e* (Intensity) |
|---|---|
| **1a** | 350 (35), 304 (10), 278 (10), 264 (15) |
| **2a** (a) | 350 (35), 304 (10), 278 (10), 264 (20) |
| **2b** | 263 (100), 235 (65), 207 (20) |

(a) Chemical ionization mass spectrum with isobutane; 351 (100), 278 (85), 264 (55).

water. The resulting mixture was stirred for 5 hours, filtered and the dark solid washed with ethanol and with ether. The solid after drying *in vacuo* at 110° weighed 0.616 g. (72%) and melted at 204.5-205.5° dec.

*Anal.* Calcd. for $C_{18}H_{20}ClN_5O_2S \cdot HCl \cdot H_2O$: C, 46.95; H, 5.08; N, 15.21. Found: 46.80; H, 4.72; N, 14.97.

2-Chloro-7,8-dioxophenothiazine.

To a stirred solution of 0.376 g. (0.00141 mole) of 2-chloro-7,8-dihydroxyphenothiazine (3) in 5 ml. methanol under nitrogen was added a solution of 0.346 g. (0.00141 mole) of tetrachloro-*o*-quinone in 2 ml. of methanol. After stirring for 40 minutes, the suspension was filtered to give a red-brown solid which, after washing with methanol and drying *in vacuo* at room temperature overnight, weighed 0.347 g. (93%) and melted at 263-264° dec.

*Anal.* Calcd. for $C_{12}H_6ClNO_2S$: C, 54.65; H, 2.29; N, 5.31. Found: C, 54.64; H, 2.36; N, 5.26.

2-Chloro-7,8-dioxophenothiazine-7-semicarbazone.

A suspension of 0.050 g. (0.00019 mole) of 2-chloro-7,8-dioxophenothiazine and 0.021 g. (0.00019 mole) of semicarbazide hydrochloride in 2.5 ml. of pyridine was stirred at room temperature overnight. The solid was collected, washed with pyridine, water, and absolute ethanol and dried at 110° to weigh 0.032 g. (52%), m.p. 252-253° dec.

*Anal.* Calcd. for $C_{13}H_9ClN_4O_2S$: C, 48.67; H, 2.82; N, 17.46. Found; C, 49.03; H, 3.09; N, 17.32.

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