Synthesis of 7,8-Dihydroxychlorpromazine and Analogs (1)

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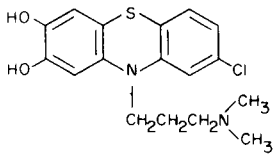
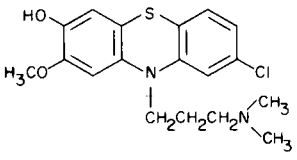
7,8-Dihydroxy derivatives of chlorpromazine, promazine, phenothiazine, and 7-methoxy-8-hydroxychlorpromazine and its nor$_1$ analog were prepared through multi-step syntheses. Structures were confirmed by chemical and spectroscopic evidence. The unusual nmr spectral shifts in several of these compounds are discussed.

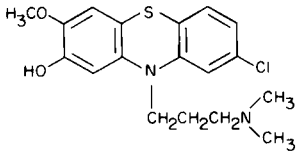
From *in vitro* studies on the metabolism of monohydroxychlorpromazines (3), Daly and Manian (4,5) demonstrated and confirmed a new pathway *via* the formation of *o*-dihydroxychlorpromazines, which are then mono-*O*-methylated. 7-Hydroxychlorpromazine, a major hydroxylated metabolite of chlorpromazine in man (6-8), and 8-hydroxychlorpromazine, a suggested metabolite (9), were converted in their systems (4,5) through an extremely labile 7,8-dihydroxychlorpromazine (I) to a mixture of 7-hydroxy-8-methoxychlorpromazine (II) (10) (7 parts) and 8-hydroxy-7-methoxychlorpromazine (III) (3 parts). Since this new metabolic pathway was solely based on token chemical evidence such as color reactions and thin layer chromatography (only one (II) (10) of these three proposed compounds is known in the literature), the final proof of structure of these two new metabolites by synthesis is necessary to confirm the correctness of the present proposal. We would like to report our successful synthesis of I and III.



I



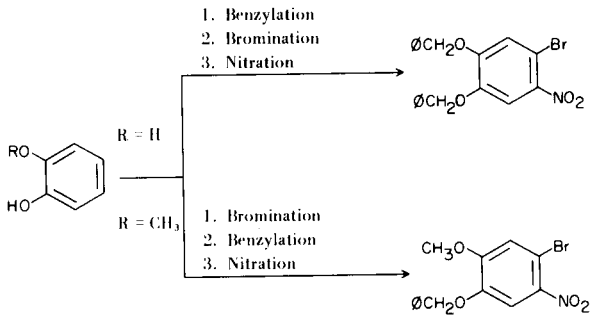
II



III

The scheme for the synthesis of these 7,8-disubstituted chlorpromazines is an adaptation of the Ullmann approach (11). The synthesis was begun by treating 3,4-dibenzyloxybromobenzene in glacial acetic acid with 70% nitric acid to form 4,5-dibenzyloxy-2-nitrobromobenzene in high yield. Similarly, the other intermediate, 4-benzyloxy-5-methoxy-2-nitrobromobenzene, was obtained by nitration of the appropriate bromo derivative of guaiacol (Scheme I). The structures of these two intermediates were confirmed by a combination of chemical and nmr evidence.

SCHEME I



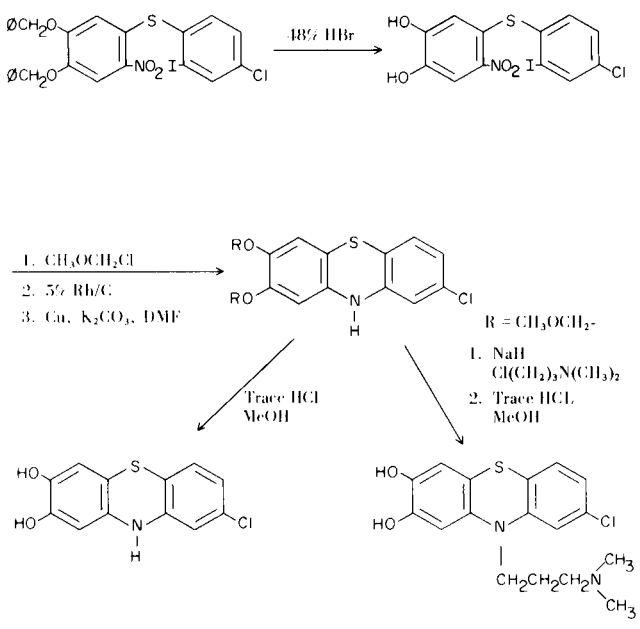
Condensation of these 4,5-disubstituted-2-nitrobromobenzenes with 2-bromo-4-chlorobenzenethiol gave the expected 4,5-disubstituted-2′-bromo-4′-chloro-2-nitrophenylsulfide intermediates. Reduction of the nitro group to an amine, followed by intramolecular cyclization afforded the disubstituted phenothiazines. The resulting phenothiazines were subsequently *N*-alkylated.

It is interesting to note that the rate of debenzylation to the formation of the final chlorpromazine depended on the substituent in the 7 or 8 position as well as alkylamine side chain. 8-Benzyloxy-7-methoxychlorpromazine was debenzylated with 10% palladium-charcoal at room temperature for 24 hours to yield the corresponding 8-hydroxy-7-methoxychlorpromazine. However, debenzylation of its nor$_1$ analog was only completed with palladium

black catalyst. Despite many attempts, debenzylation of 7,8-dibenzyloxychlorpromazine did not yield the desired product. The only isolated product obtained was confirmed by mass spectrometry (m/e 316) to be 2,3-dihydroxypromazine hydrochloride. The nmr spectrum in DMSO-d_6 at 100 mc. showed two singlets at 6.60 and 6.62 ppm corresponding to aromatic protons at C-9 and C-6 respectively. Signals for the remaining aromatic protons were exhibited at 6.92 to 7.18 ppm. The peaks at 8.82 and 9.08 ppm were assigned to the two phenolic protons.

A similar catalytic hydrogenation was made on 2-chloro-7,8-dibenzyloxyphenothiazine but here most of the starting material was recovered unchanged. Difficulties encountered in such a debenzylation caused us to seek another blocking group. The methoxymethyl group (CH_3OCH_2-) (12), easily removed by acid hydrolysis, was introduced to replace the benzyl group, following a similar approach (Scheme II).

SCHEME II



Both 2-chloro-7,8-dimethoxymethyleneoxyphenothiazine and 7,8-dimethoxymethyleneoxychlorpromazine were found to be more sensitive to light and air than their corresponding dibenzyloxy derivatives, and when subjected to acid hydrolysis rapidly yielded the desired products. The structures of products were confirmed by mass spectroscopy with the molecular ion peak at m/e 265 for 2-chloro-7,8-dihydroxyphenothiazine, and at m/e 350 for 7,8-dihydroxychlorpromazine. In the nmr spectrum at 60 mc. the resonances for the C-9 and C-6 protons in the 2-chloro-7,8-dihydroxyphenothiazine were centered at 6.23 and 6.35 ppm. The protons at C-1, -3, and -4 were more difficult to assign specifically but were in the region from 6.60 to 6.75 ppm. However, the hydrogens on C-9 and C-6 in 7,8-dihydroxychlorpromazine (at 100 mc.) were shifted to 6.62 and 6.65 ppm, and the hydrogens on C-1, -3, and -4 to 6.92-7.2 ppm. This agrees with the observation that the side chain of chlorpromazine acts to shift the entire phenothiazine ring resonance downfield by about 20 cps (13).

The two phenolic protons of 7,8-dihydroxychlorpromazine hydrochloride were at 8.95 ppm and 9.2 ppm. The proton from the salt N^+H was at 10.5 ppm. These peaks were verified by adding a drop of deuterium oxide to the DMSO solvent and causing broadening of these three peaks by exchange. Concurrently the protons on C-9 and C-6, which had exhibited slight differences in chemical shift (6.62 and 6.65 ppm respectively), coalesced to a single peak (6.64 ppm).

EXPERIMENTAL

Melting points are uncorrected. Spectral data were in agreement with assigned structures. Nmr data are reported in ppm from TMS internal standard in DMSO unless otherwise noted. Mass spectra were obtained with an AEI MS-9 mass spectrometer. Infrared spectra were recorded on a Perkin-Elmer Infracord Model 137.

4,5-Dibenzyloxy-2-nitrobromobenzene.

A mixture of 100.9 g. (0.273 mole) of 3,4-dibenzyloxybromobenzene (14) in 1.0 l. of glacial acetic acid was warmed to 35° to effect complete dissolution. Maintaining the temperature at 35°, 80 ml. of 70% nitric acid was added dropwise over 25 minutes. At the end of the nitric acid addition the temperature rose to 42° and a yellow solid precipitated. The mixture was cooled and stirred an additional 2.5 hours. The mixture was diluted with 900 ml. of water, and the crude yellow powder collected and washed well with water. Recrystallization from 2 l. ethanol gave 90.5 g. (80%) of very pale yellow needles, m.p. 105-107°; ir (chloroform): 1530 and 1345 cm^{-1} (NO_2); nmr: -CH_2-, 5.11 ppm (singlet, 4H); C-6, 7.16 ppm (singlet, 1H); phenyl protons, 7.38 ppm (singlet, 10H); C-3, 7.60 ppm (singlet, 1H).

Anal. Calcd. for $C_{20}H_{16}BrNO_4$: C, 57.98; H, 3.89; N, 3.38; Br, 19.29. Found: C, 57.92; H, 3.96; N, 3.52; Br, 19.17.

2′-Bromo-4′-chloro-4,5-dibenzyloxy-2-nitrodiphenyl Sulfide.

To a suspension of 82.9 g. (0.20 mole) of 4,5-dibenzyloxy-2-nitrobromobenzene in 300 ml. of ethanol was added a solution of 44.8 g. (0.20 mole) of 2-bromo-4-chlorobenzenethiol (15), 8.0 g. (0.20 mole) of sodium hydroxide, and 300 ml. of 50% ethanol. After refluxing this mixture for 5 hours, it was cooled and the supernatant decanted from a yellow gum. An additional 700 ml. of ethanol was placed over this gum and the mixture heated to reflux with good stirring for 3 hours. After cooling overnight, 99.2 g. (89%) of a bright yellow solid, m.p. 106-109° were collected. A small amount was recrystallized from ethanol to give an analytical sample as bright yellow needles, m.p. 108-110°.

Anal. Calcd. for $C_{26}H_{19}BrClNO_4S$: C, 56.08; H, 3.44; N, 2.52; S, 5.76. Found: C, 56.03; H, 3.56; N, 2.73; S, 5.60.

2-Amino-2′-bromo-4′-chloro-4,5-dibenzyloxydiphenyl Sulfide.

To a Parr shaker were charged 15.0 g. (0.027 mole) of 2′-bromo-4′-chloro-4,5-dibenzyloxy-2-nitrodiphenyl sulfide, 250 ml. of benzene, 3.7 g. of platinum oxide and 60 psi of hydrogen. The mixture was shaken 16 hours, the catalyst filtered, and concentrated to dryness. The resulting oil was dissolved in a minimum amount of benzene and hexane was added to the cloud point. After cooling, the product was filtered and dried to yield 11.0 g. (78%), m.p. 85-87°.

Anal. Calcd. for $C_{26}H_{21}BrClNO_2S$: C, 59.27; H, 4.02; N, 2.66. Found: C, 59.33; H, 4.21; N, 2.67.

A small portion was converted to the hydrochloride salt with ethereal hydrogen chloride and crystallized from methanol to a constant, m.p. 193-196°.

Anal. Calcd. for $C_{26}H_{21}BrClNO_2S$·HCl: C, 55.44; H, 3.94; N, 2.49. Found: C, 55.77; H, 3.98; N, 2.60.

2-Chloro-7,8-dibenzyloxyphenothiazine.

A mixture of 500 ml. of dimethylformamide, 0.40 g. of copper-bronze, 5.0 g. of potassium carbonate and 10.0 g. (0.0188 mole) of 2-amino-2′-bromo-4′-chloro-4,5-dibenzyloxydiphenyl sulfide were heated to a gentle reflux and stirred under nitrogen for 4½ hours. The reaction mixture was filtered hot, and the filtrate taken to dryness. Soluble impurities were extracted for 10 minutes with 50 ml. of hot high boiling petroleum ether (b.p. 110°) at reflux, and the extract discarded. The product was then extracted with 5 x 400 ml. portions of petroleum ether (b.p. 110°) for 5 hours each. The combined extracts were cooled slowly to room temperature and filtered to yield 1.4 g. of product, m.p. 167-170°. Recrystallization from benzene-hexane yielded 1.10 g. (13%), m.p. 170-172°.

Anal. Calcd. for $C_{26}H_{20}ClNO_2S$: C, 70.02; H, 4.52; N, 3.14. Found: C, 69.83; H, 4.58; N, 3.07.

7,8-Dibenzyloxychlorpromazine.

A mixture of 12.3 g. (0.0277 mole) of 2-chloro-7,8-dibenzyloxyphenothiazine, 4.11 g. (0.97 mole) of 57% sodium hydride and 410 ml. of dimethylsulfoxide were stirred at 40° for 2 hours. To the stirred solution was added dropwise over 10 minutes a solution of 16.9 g. (0.136 mole) of 3-*N,N*-dimethylaminopropyl chloride in 100 ml. of dimethylsulfoxide. The mixture was stirred under nitrogen and heated at 70° for 4 hours, then stirred overnight at room temperature.

The mixture was poured into 4 l. of water and the product extracted with 3 x 1.5 l. of ether, the ether washed with 5 x 2 l. of water, the ether layer dried (sodium sulfate) and removed under vacuum to leave a solid. Crystallization from petroleum ether (b.p. 66-70°) (Darco) yielded in 2 crops 7.50 g. (57%) of product, m.p. 91-92°.

Anal. Calcd. for $C_{31}H_{31}ClN_2O_2S$: C, 70.11; H, 5.89; N, 5.27. Found: C, 70.26; H, 6.15; N, 5.31.

2,3-Dihydroxypromazine Hydrochloride.

A mixture of 2.70 g. (0.0051 mole) of 7,8-dibenzyloxychlorpromazine, 250 ml. of methanol and 2.0 g. of palladium black were shaken under 55 psi for 16 hours at room temperature, then 24 hours under the heat lamp. The catalyst was filtered in a nitrogen tent, the solvent removed at reduced pressure below 55° to leave a semisolid, which was crystallized from 7 ml. of ethanol to yield a solid. Solution in 60 ml. of ethanol, concentration to 12 ml. and cooling yielded 0.45 g. (25%) of product, m.p. 236-238° dec.

Anal. Calcd. for $C_{17}H_{20}N_2O_2S$·HCl: C, 57.86; H, 6.00; N, 7.92. Found: C, 57.69; H, 6.13; N, 7.99.

2-Iodo-4-chlorothiophenol.

A. Diazotization.

A mixture of 1271 g. (5.02 moles) of 2-iodo-4-chloroaniline, 940 ml. of concentrated hydrochloric acid and 2600 ml. of water was stirred at -2° to 2° and a solution of 455 g. (6.75 moles) of sodium nitrite in 800 ml. of water was added beneath the surface in 1¼ hours. A 10% excess (45.5 g. sodium nitrite in 100 ml. of water) was added, and the mixture filtered before use in the next step.

B. Substitution.

A solution of 1320 g. (8.25 moles) of potassium ethylxanthate in 2540 ml. of water was heated and maintained at 72-78° as the above diazonium salt solution was added rapidly in 15 minutes. After the addition, the mixture was stirred at 78° for 20 minutes and at room temperature for 2 hours. The heavy oily layer was separated from the aqueous supernate which was extracted 3 times with 2.5 l. of benzene. The oil and the benzene extracts were combined and washed 3 times with 2.5 l. of 5% aqueous sodium hydroxide solution.

C. Hydrolysis.

The benzene solution was added to a solution of 1775 g. (28.6 moles) of 90% potassium hydroxide in 1180 ml. of water and 3560 ml. of ethanol and the resulting mixture refluxed and stirred under nitrogen for 15 hours. It was then added to 25 l. of ice and water, acidified with 2.5 l. of concentrated hydrochloric acid and stirred for 30 minutes. The organic layer was separated and the aqueous layer extracted 3 times with 5 l. of ether. The combined organic solutions were washed with 4 x 1 l. of water to a neutral *p*H, dried over sodium sulfate and stripped to a crude oil which was distilled under reduced pressure. The yellow distillate weighed 364 g. (27%) and boiled over a range of 88°/0.025 mm to 124°/0.7 mm (253 g.). The residue, after treatment with aqueous sodium hydroxide solution and sodium dithionite, gave another 97.5 g. (7%) boiling at 92-102°/0.1 mm.

2′-Iodo-4′-chloro-2-nitro-4,5-dibenzyloxydiphenyl Sulfide.

To a suspension of 560 g. (1.35 moles) of 4,5-dibenzyloxy-2-nitrobromobenzene in 4.4 l. of ethanol was added a near complete solution of 364 g. (1.35 moles) of 2-iodo-4-chlorothiophenol, 54 g. (1.35 moles) of sodium hydroxide, 1.1 l. of ethanol and 1.1 l. of water. The resulting mixture was stirred and refluxed under nitrogen for 8 hours. After standing at room temperature, the aqueous ethanolic supernate was separated from a heavy, residual gummy material which was stirred and refluxed with 5.5 l. of ethanol for 2 hours. It was stirred at room temperature for 2 hours, and in an ice bath for one hour. The yellow solid which formed was collected and washed with ethanol. Drying yielded 570 g. (77%) of product melting at 105-111°. An analytical sample was obtained by crystallizing from ethanol and chloroform, m.p. 111.5-113.5°.

Anal. Calcd. for $C_{26}H_{19}ClINO_4S$: C, 51.71; H, 3.17; N, 2.32. Found: C, 51.92; H, 3.24; N, 2.40.

2′-Iodo-4′-chloro-2-nitro-4,5-dihydroxydiphenyl Sulfide.

A mixture of 570 g. (0.945 mole) of 2′-iodo-4′-chloro-2-nitro-4,5-dibenzyloxydiphenyl sulfide, 5.7 l. of glacial acetic acid, and 2.8 l. of 48% hydrobromic acid was stirred and refluxed for 30 minutes. The hot mixture was then poured into 20 l. of ice and water and stirred for 2 hours. The supernate was removed and the residual solid washed thoroughly with water, taken up in ether, dried over sodium sulfate and stripped to a dark oil. The latter was stripped with benzene, triturated with hexane, col-

lected and washed with petroleum ether. The solid was crystallized by taking up in benzene-ethanol and concentrating to a mull which on filtration, washing with benzene and petroleum ether and drying yielded 201 g. (50%) of product melting at 184.5-187°. A second crop weighed 91 g. (22%) and melted at 183.5-185.51°. An analytical sample from benzene melted at 186-187.5°.

Anal. Calcd. for $C_{12}H_7ClINO_4S$: C, 34.02; H, 1.67; N, 3.31. Found: C, 34.22; H, 1.63; N, 3.35.

2′-Iodo-4′-chloro-2-nitro-4,5-dimethoxymethyleneoxydiphenyl Sulfide.

A mixture of 355 g. (0.84 mole) of 2′-iodo-4′-chloro-2-nitro-4,5-dihydroxydiphenyl sulfide, 254 g. (1.84 moles) of anhydrous potassium carbonate, and 2.6 l. of DMF was stirred under nitrogen in an ice bath for 2 hours. A solution of 148 g. (1.84 moles) of chloromethyl methyl ether in 300 ml. of DMF was then added dropwise in 35 minutes at 3 to 8°. In a similar manner, 222.0 g. (1.61 moles) of potassium carbonate, and 129 g. (1.61 moles) of chloromethyl methyl ether in 220 ml. of DMF was added in mole proportion periodically over a space of 6 hours. The resulting mixture was stirred at room temperature for 1 hour and then poured into 13 l. of water containing 100 g. of sodium hydroxide. The mixture was diluted further to 21 l. with ice and water, stirred for 30 minutes, and then let stand for 1 hour. The red supernate was separated from a tacky yellow precipitate which was taken up in ether and washed with 2 l. of 5% aqueous sodium hydroxide and with water several times to neutral *p*H. The ether solution was dried over sodium sulfate, and stripped to a yellow solid which was crystallized from ethanol to give 238 g. of (66%) product, m.p. 78.5-81.5°. An analytical sample from ethanol melted at 78-80°.

Anal. Calcd. for $C_{16}H_{15}ClINO_6S$: C, 37.55; H, 2.96; N, 2.74. Found: C, 37.32; H, 2.94; N, 2.91.

2′-Iodo-4′-chloro-2-amino-4,5-dimethoxymethyleneoxydiphenyl Sulfide.

A mixture of 100 g. (0.196 mole) of 2′-iodo-4′-chloro-2-nitro-4,5-dimethoxymethyleneoxydiphenyl sulfide, 40 g. of 5% rhenium-charcoal, and 1 l. of ethyl acetate was shaken under hydrogen at 100 psi for 3 hours. The catalyst was filtered and the filtrate stripped to a brown oil which weighed 90.8 g. and used as such in the next reaction.

2-Chloro-7,8-dimethoxymethyleneoxyphenothiazine.

To refluxing DMF (3.8 l.) was added 52.5 g. (0.38 mole) of anhydrous potassium carbonate and 3.0 g. of copper-bronze catalyst. These were followed by a solution of 90.8 g. (0.188 mole) of 2′-iodo-4′-chloro-2-amino-4,5-dimethoxymethyleneoxydiphenyl sulfide in 500 ml. of DMF. The resulting mixture was refluxed and stirred under nitrogen for 2 hours, filtered hot through a celite pad and stripped to a dark oil. The latter was taken up in chloroform, which was filtered and stripped to another oil that was crystallized from hexane-benzene with charcoal treatment. This yielded 39.0 g. (59%) of product, m.p. 103.5-104.5°. An analytical sample, crystallized from hexane, melted at 106-106.5°.

Anal. Calcd. for $C_{16}H_{16}ClNO_4S$: C, 54.31; H, 4.56; N, 3.96. Found: C, 54.40; H, 4.54; N, 4.06.

7,8-Dimethoxymethyleneoxychlorpromazine.

A mixture of 5 g. (0.0141 mole) of 2-chloro-7,8-dimethoxymethyleneoxyphenothiazine, 2.38 g. (0.0496 mole) of 57% sodium hydride in mineral oil, and 160 ml. of DMSO was stirred at room temperature under nitrogen for 2½ hours. A solution of 8.49 g. (0.0695 mole) of 3-*N,N*-dimethylaminopropyl chloride in 40 ml. of DMSO was added in 8 minutes and the resulting mixture stirred and maintained at 75-85° for 3 hours. After reaching room temperature, the reaction mixture was poured into 1.5 l. of ice and water containing 5 g. of sodium hydroxide. The resulting suspension was extracted 3 times with 400 ml. of ether, the combined ether extracts washed to neutral *p*H with water and dried over sodium sulfate. The filtered ether solution was applied to 60 g. of silica gel and the mixture stripped to dryness. The silica gel was then treated with 250 ml. of chloroform and 25 g. more of silica gel and the mixture stripped to dryness. The silica gel was then thoroughly washed with chloroform until no material was eluted. It was then treated 3 times with methanol-ammonium hydroxide, and the extracts were concentrated. The residue was taken up in ether, separated from a little water and dried over sodium sulfate. The ether solution was stripped to a brown oil which after drying under vacuum at room temperature weighed 3.26 g. (54%). Thin layer chromatography indicated one major spot and a trace of impurity. Distillation resulted in considerable decomposition and was, therefore, abandoned.

7,8-Dihydroxychlorpromazine Hydrochloride.

A solution of 2.17 g. (0.0051 mole) of 7,8-dimethoxymethyleneoxychlorpromazine in 50 ml. of methanol was refluxed under nitrogen as a total of 1.5 ml. of methanolic hydrogen chloride was added in portions until a strong acid *p*H was obtained. After refluxing for 30 minutes, the reaction mixture was treated with sulfur dioxide and stripped to a gummy blue residue which was dried in vacuum at room temperature for 2 hours. It was crystallized two times by dissolving in hot sulfur dioxide-ethanol with charcoal treatment and concentrating in vacuum. After drying, the pink product weighed 0.916 g. (47%) and melted at 213-214.5°.

Anal. Calcd. for $C_{17}H_{19}ClN_2O_2S{\cdot}HCl$: C, 52.71; H, 5.20; N, 7.23. Found: C, 52.87; H, 5.32; N, 7.16.

2-Chloro-7,8-dihydroxyphenothiazine.

A solution of 0.5 g. (0.00141 mole) of 2-chloro-7,8-dimethoxymethyleneoxyphenothiazine in 50 ml. of 10% acetic acid in methanol was refluxed under nitrogen. After 1 ml. of ethanolic hydrogen chloride was added, the resulting reaction mixture was refluxed for 1 hour. It was cooled in an ice bath, treated with sulfur dioxide and stripped to a pale blue green solid which after drying *in vacuo* at room temperature for 0.5 hour weighed 0.4 g. A small sample weighing about 60 mg. was crystallized from sulfur dioxide-water-ethanol to give 18 mg. of product which melted at 257-260°.

Anal. Calcd. for $C_{12}H_8ClNO_2S$: C, 54.24; H, 3.03; N, 5.27. Found: C, 54.09; H, 3.11; N, 5.13.

4-Benzyloxy-5-methoxy-2-nitrobromobenzene.

To a solution of 105 g. (0.38 mole) of 4-benzyloxy-3-methoxybromobenzene (15) in 900 ml. of glacial acetic acid was added 105 ml. of 70% nitric acid dropwise in 10 minutes. The reaction was slightly exothermic and was not allowed to get warmer than 40°. In approximately 30 minutes a bright yellow solid precipitated. It was allowed to stand overnight and then poured into 2.0 l. of cold water. The crude yellow solid was collected and washed with water. Trituration with 1.0 l. of ethanol gave 104.8 g. (86.5%) of yellow powder, m.p. 146-148°. An analytical sample was obtained as yellow needles, m.p. 147-148°, from methanol; ir (chloroform): 1525 and 1345 cm^{-1} ($-NO_2$ absorptions); nmr: $-CH_3$, 3.92 ppm (singlet, 3H); $-CH_2-$, 5.13 ppm (singlet, 2H); C-6, 7.07 ppm (singlet, 1H); phenyl protons, 7.35 ppm (singlet,

5H); C-3, 7.56 ppm (singlet, 1H).

Anal. Calcd. for $C_{14}H_{12}BrNO_4$: C, 49.72; H, 3.58; N, 4.14; Br, 23.63. Found: C, 49.91; H, 3.67; N, 4.11; Br, 23.58.

4-Benzyloxy-2′-bromo-4′-chloro-5-methoxy-2-nitrodiphenyl Sulfide.

To a suspension of 47.2 g. (0.140 mole) of 4-benzyloxy-5-methoxy-2-nitrobromobenzene in 175 ml. of ethanol was added a solution of 31.3 g. (0.1395 mole) of 2-bromo-4-chlorobenzenethiol (15), 5.6 g. (0.1395 mole) of sodium hydroxide and 175 ml. of 50% ethanol. After refluxing for 6 hours, the mixture was allowed to stand overnight. The yellow solid was collected, washed well with ethanol and dried to give 63.4 g. (95%) of yellow powder, m.p. 163-165°.

Anal. Calcd. for $C_{20}H_{15}BrClNO_4S$: C, 49.96; H, 3.15; N, 2.91; S, 6.67. Found: C, 50.23; H, 3.17; N, 3.07; S, 6.96.

2-Amino-4-benzyloxy-2′-bromo-4′-chloro-5-methoxydiphenyl Sulfide.

A mixture of 15.0 g. (0.0312 mole) of 4-benzyloxy-2′-bromo-4′-chloro-5-methoxy-2-nitrodiphenyl sulfide, 4.0 g. of platinum oxide catalyst, and 250 ml. of benzene was shaken (under 60 psi of hydrogen) for 21 hours in a Parr apparatus. After filtering the catalyst and distilling the benzene, the crude solid was recrystallized from benzene-hexane to give 11.9 g. (85%) of fluffy white solid, m.p. 154-155°.

Anal. Calcd. for $C_{20}H_{17}BrClNO_2S$: C, 53.29; H, 3.80; N, 3.11. Found: C, 53.72; H, 3.96; N, 3.19.

8-Benzyloxy-2-chloro-7-methoxyphenothiazine.

A mixture of 56.7 g. (0.126 mole) of 2-amino-4-benzyloxy-2′-bromo-4′-chloro-5-methoxydiphenyl sulfide, 3.0 l. of *N,N*-dimethylformamide, 31.2 g. (0.225 mole) of anhydrous potassium carbonate, and 2.5 g. of copper-bronze catalyst was heated at reflux under nitrogen for 24 hours. After cooling to room temperature, the reaction mixture was filtered and the DMF distilled at 60°, under reduced pressure. The dark residue was then crystallized from 500 ml. of toluene (Darco G-60). After refrigerating overnight, the product was collected, washed with cold toluene until all the purple color was removed. The yield was 19.9 g. (43.8%) of grey crystals, m.p. 199-201°. The mother liquor was evaporated to near dryness and crystallized from 75 ml. of toluene to give an additional 5.5 g. (12%), m.p. 198-200°.

Anal. Calcd. for $C_{20}H_{17}ClNO_2S$: C, 64.95; H, 4.36; N, 3.79. Found: C, 65.46; H, 4.42; N, 3.97.

8-Benzyloxy-7-methoxychlorpromazine.

A mixture of 28.8 g. (0.0778 mole) of 8-benzyloxy-2-chloro-7-methoxyphenothiazine, 12.0 g. (0.250 mole) of 57% sodium hydride dispersion, and 1440 ml. of freshly distilled dimethyl sulfoxide was stirred for 2 hours under nitrogen. A solution of freshly distilled 3-*N,N*-dimethylaminopropyl chloride in 300 ml. of freshly distilled dimethyl sulfoxide was then added all at once and the reaction mixture heated at 70° for 2 hours. The mixture was stirred overnight under nitrogen and then poured into 8.0 l. of cold water which contained 95 g. of ammonium chloride. The product was extracted with a total of 2.5 l. of ether, washed with 3 x 1 l. of water, dried with sodium sulfate and the ether distilled to give a crude solid which was recrystallized from 2.0 l. of low boiling petroleum ether (Darco G-60). After refrigerating for 20 hours, the solid was collected to give 19.2 g. (54.2%) of beige crystals, m.p. 86-88°. One more recrystallization from 1.0 l. of low boiling petroleum ether yielded 16.0 g. (45%) of white crystals, m.p. 88-89°.

Anal. Calcd. for $C_{25}H_{27}ClN_2O_2S$: C, 65.99; H, 5.98; N, 6.16. Found: C, 66.10; H, 6.07; N, 6.06.

8-Hydroxy-7-methoxychlorpromazine.

A mixture of 3.0 g. (0.0066 mole) of 8-benzyloxy-7-methoxychlorpromazine, 3.0 g. of 10% palladium-charcoal, and 250 ml. of methanol was shaken under 50 psi of hydrogen in a Parr shaker for 29 hours. After distillation of the solvent, the residue was recrystallized from petroleum ether (b.p. 66-75°) to give 0.59 g. (24%) of a white powder, m.p. 182-184°.

Anal. Calcd. for $C_{18}H_{21}ClN_2O_2S$: C, 59.25; H, 5.80; N, 7.68. Found: C, 59.52; H, 5.77; N, 7.57.

8-Benzyloxy-7-methoxy-nor$_1$-chlorpromazine.

A mixture of 16.1 g. (0.0436 mole) of 8-benzyloxy-2-chloro-7-methoxyphenothiazine, 3.22 g. (0.070 mole) of 57% sodium hydride in mineral oil, and 260 ml. of freshly distilled dimethylsulfoxide was stirred for 2 hours at room temperature under nitrogen. A solution of 11.8 g. (0.0872 mole) of *N*-(3-chloropropyl)-*N*-methylformamide (16) in 50 ml. of dimethyl sulfoxide was added and the mixture refluxed for 8 hours (17). The cooled reaction mixture was poured into a solution of 33 g. of ammonium chloride in 1600 ml. of cold water, extracted with ether, the combined extracts washed five times with an equal volume of water, dried over sodium sulfate, and evaporated to a crude oil which was hydrolyzed by refluxing for 5 hours in a mixture of 100 ml. of 20% sodium hydroxide plus 700 ml. of ethanol. The cooled hydrolysis mixture was poured into 3.0 l. of cold water, extracted with ether, dried over sodium sulfate, and evaporated to a crude oil which was crystallized from 1200 ml. of petroleum ether (b.p. 66-75°) (Darco G-60) to give 9.3 g. (48%) white needles, m.p. 83-85°. Recrystallization of an analytical sample from petroleum ether (b.p. 30-60°) gave white needles, m.p. 86-88°.

Anal. Calcd. for $C_{24}H_{25}ClN_2O_2S$: C, 65.36; H, 5.71; N, 6.35. Found: C, 65.48; H, 5.80; N, 6.32.

8-Hydroxy-7-methoxy-nor$_1$-chlorpromazine.

A mixture of 1.4 g. (0.00318 mole) of 8-benzyloxy-7-methoxy-nor$_1$-chlorpromazine, 100 ml. of absolute ethanol, and 0.2 g. of palladium black catalyst was shaken in a Parr apparatus at 55 psi of hydrogen for 25 hours, then was added 0.2 g. of fresh catalyst and the mixture shaken for 17 hours more. Then, 0.4 g. of fresh catalyst was added and the mixture was shaken an additional 6 hours. The catalyst was filtered under a nitrogen atmosphere and the filtrate evaporated to a crude beige solid. This material is very hygroscopic and could not be handled in the atmosphere without becoming a dark gum almost immediately. A small amount of the solid was transferred under nitrogen for elemental analysis.

Anal. Calcd. for $C_{17}H_{19}ClN_2O_2S$: C, 58.19; H, 5.46; N, 7.99. Found: C, 57.96; H, 5.93; N, 7.56.

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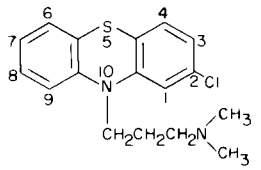
(2) Pharmacology Section, Psychopharmacology Research Branch, National Institute of Mental Health, Rockville, Maryland 20852.

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



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

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