# Synthesis of Possible Metabolites of Chlorpromazine. II. (1) 3-, 8- and 9-Hydroxychlorpromazine (2a, 3)

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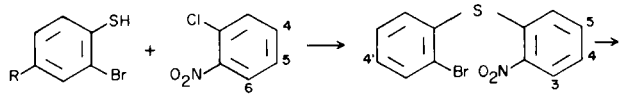
The title compounds have been prepared as analytical standards for the identification of chlorpromazine metabolites in biological materials. Unequivocal structural proof of key compounds was accomplished by using at least two unrelated syntheses for each one. Resistance of some phenothiazines to preparation via classic Smiles rearrangement is discussed. More examples are offered of halogen-induced Smiles rearrangement. A rare example of phenothiazine polymorphism is presented.

The 3-, 8- and 9-hydroxychlorpromazines have been prepared as part of a continuing program for the synthesis of possible metabolites of chlorpromazine.

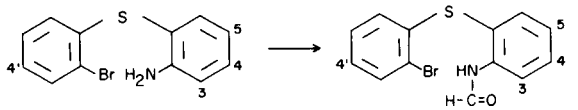
Most of the phenothiazine nuclei described herein were constructed by adaptations of the Bernthsen and Ullmann approaches (1, 4-7) (Schemes 1 and 2, Tables I-V).

Ring closure, in the usual manner (1, 4, 6), of the 2-amino-2′-bromodiphenylsulfides (**24**, **26** and **27**) gave the corresponding phenothiazines (**41**, **43** and **45**). Cyclization of the formyl derivatives of **24** and **26** (**33** and **35**) provided isomeric phenothiazines which were most probably the rearranged products (**42** and **44**) (1,4). Lack of material precluded ring-closure of the formyl derivative (**36**) of **27**.

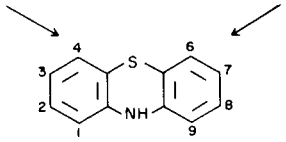
SCHEME I



| | | | | |
|---|---|---|---|---|
| 1 | R = H | 3 | 5-Cl, 4-$OCH_2C_6H_5$ | 12 | 4-Cl, 5-$OCH_2C_6H_5$ |
| | | 4 | 5-Cl, 4-$OCH_3$ | 13 | 4-Cl, 5-$OCH_3$ |
| | | 5 | 5-Cl, 4-OH | 14 | 4-Cl, 5-OH |
| | | 6 | 5-Cl, 4-$OCH(CH_3)_2$ | 15 | 4-Cl, 5-$OCH(CH_3)_2$ |
| 2 | R = Cl | 7 | 5-$OCH_3$ | 16 | 4′-Cl, 4-$OCH_3$ |
| | | 8 | 5-OH | 17 | 4′-Cl, 4-OH |
| | | 9 | 5-$OCH(CH_3)_2$ | 18 | 4′-Cl, 4-$OCH(CH_3)_2$ |
| | | 10 | 6-$OCH(CH_3)_2$ | 19 | 4′-Cl, 3-$OCH(CH_3)_2$ |
| | | 11 | 6-OH | 20 | 4′-Cl, 3-OH |



| | | | |
|---|---|---|---|
| 21 | 4-Cl, 5-$OCH_2C_6H_5$ (a) | 29 | 4-Cl, 5-$OCH_2C_6H_5$ |
| 22 | 4-Cl, 5-$OCH_3$ (a) | 30 | 4-Cl, 5-OH (a) |
| 23 | 4-Cl, 5-$OCH(CH_3)_2$ (a) | 31 | 4-Cl, 5-$OCH_3$ |
| 24 | 4′-Cl, 4-$OCH_3$ | 32 | 4-Cl, 5-$OCH(CH_3)_2$ |
| 25 | 4′-Cl, 4-OH (a) | 33 | 4′-Cl, 4-$OCH_3$ |
| 26 | 4′-Cl, 4-$OCH(CH_3)_2$ | 34 | 4′-Cl, 4-OH (b) |
| 27 | 4′-Cl, 3-$OCH(CH_3)_2$ | 35 | 4′-Cl, 4-$OCH(CH_3)_2$ |
| 28 | 4′-Cl, 3-OH (a) | 36 | 4′-Cl, 3-$OCH(CH_3)_2$ (a) |
| | | 37 | 4′-Cl, 3-OH (b) |

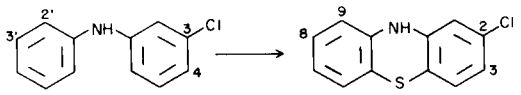


| | | |
|---|---|---|
| 38 | 2-Cl, 3-$OCH_2C_6H_5$ | (From 29) |
| 39 | 2-Cl, 3-$OCH_3$ | (From 31) |
| 40 | 2-Cl, 3-$OCH(CH_3)_2$ | (From 32) |
| 41 | 2-Cl, 8-$OCH_3$ | (From 24) |
| 42 | 3-Cl, 8-$OCH_3$ | (From 33) |
| 43 | 2-Cl, 8-$OCH(CH_3)_2$ | (From 26) |
| 44 | 3-Cl, 8-$OCH(CH_3)_2$ | (From 35) |
| 45 | 2-Cl, 9-$OCH(CH_3)_2$ | (From 27) |

(a) Cyclization not attempted. (b) Cyclization unsuccessful.

The amines **21-23** were automatically formylated before cyclization because this step usually improves the yield of phenothiazine (6) and because the desired phenothiazine would be obtained regardless of whether rearrangement

SCHEME 2



| | | | |
|---|---|---|---|
| 46 | 4-$OCH_3$ | 39 | 3-$OCH_3$ |
| 46A | 3'-$OCH_3$ | 41 | 8-$OCH_3$ |
| 47 | 3'-$OCH(CH_3)_2$ | 43 | 8-$OCH(CH_3)_2$ |
| 48 | 2'-$OCH(CH_3)_2$ | 45 | 9-$OCH(CH_3)_2$ |
| 58 | 2'-OH | 55 | 9-OH |

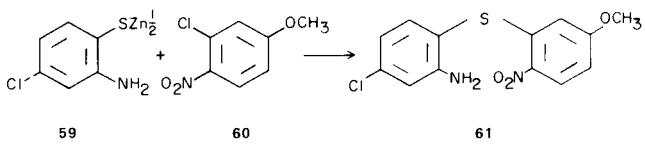
occurred. The latter is true whenever there is no other substituent on the bromine-containing ring.

Attempts to cyclize the unprotected phenolic compounds, **34** and **37**, were unsuccessful. No effort was made to ring close **25**, **28** and **30**.

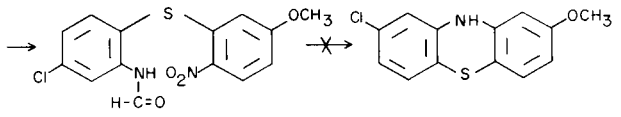
Preparation of each of the phenothiazines, **39**, **41**, **43** and **45** by both the Ullmann (Scheme 1) and Bernthsen (Scheme 2) routes provided structural proof for these compounds.

A simple synthesis for some hydroxyphenothiazines, which utilized the reaction between the zinc salt of an *o*-aminothiophenol and chlorohydroquinone, was reported earlier (8). The use of 2,5-dichlorohydroquinone (**52**) in an attempted adaptation of this method to the synthesis of 2-chloro-3-hydroxyphenothiazine (**53**) was unsuccessful.

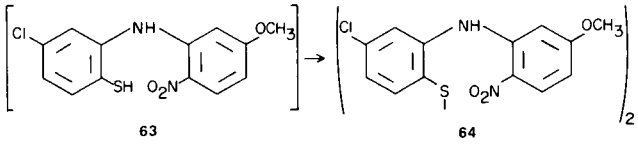
SCHEME 4



59 60 61

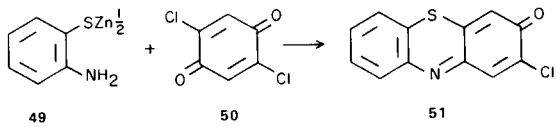


62 41

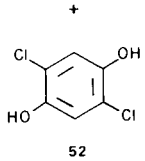


63 64

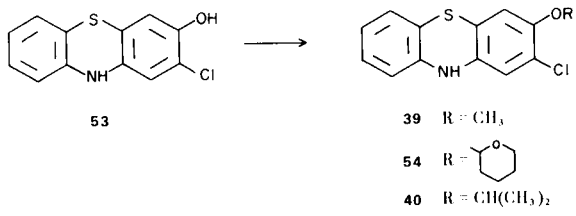
SCHEME 3



49 50 51



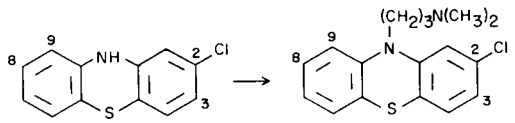
52



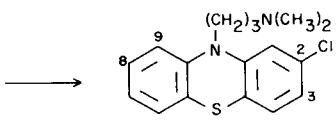
53

| | | | |
|---|---|---|---|
| 39 | R = $CH_3$ | | |
| 54 | R = | | |
| 40 | R = $CH(CH_3)_2$ | | |

SCHEME 5



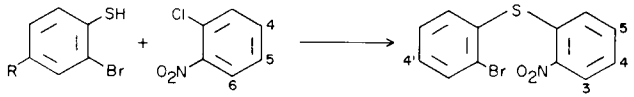
| | | | |
|---|---|---|---|
| 39 | 3-$OCH_3$ | 65 | 3-$OCH_3$ |
| 54 | 3-O- | 66 | 3-O- |
| 40 | 3-$OCH(CH_3)_2$ | 67 | 3-$OCH(CH_3)_2$ |
| 43 | 8-$OCH(CH_3)_2$ | 68 | 8-$OCH(CH_3)_2$ |
| 45 | 9-$OCH(CH_3)_2$ | 69 | 9-$OCH(CH_3)_2$ |



| | |
|---|---|
| 70 | 3-OH |
| 71 | 8-OH |
| 72 | 9-OH |

TABLE I

2′-Bromo-2-nitrodiphenylsulfides

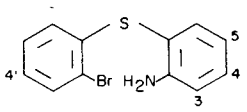



| No. | Diphenylsulfide | 2-Bromo-thiophenol R | 2-Chloro-nitrobenzene | Reflux Time hour | Mp, °C (f) | Yield % | Analyses C Calcd. | C Found | H Calcd. | H Found | N Calcd. | N Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **12** | 4-Cl, 5-$OCH_2C_6H_5$ | H (b) | 5-Cl, 4-$OCH_2C_6H_5$ (c) | 2 | 137-138 | 86 | 50.61 | 50.89 | 2.91 | 3.07 | 3.19 | 3.38 |
| **13** | 4-Cl, 5-$OCH_3$ | H | 5-Cl, 4-$OCH_3$ (c) | 2 | 129.5-130.5 | 94 | 41.65 | 41.50 | 2.42 | 2.48 | 3.74 | 3.97 |
| **14** | 4-Cl, 5-OH | H | 5-Cl, 4-OH (d) | 2 | 184-185 | 1 | 39.95 | 39.96 | 1.96 | 2.25 | 3.89 | 4.18 |
| **15** | 4-Cl, 5-$OCH(CH_3)_2$ | H | 5-Cl, 4-$OCH(CH_3)_2$ (c) | 2.5 | 131.5-132.5 | 82 | 44.72 | 44.53 | 3.25 | 3.29 | 3.48 | 3.60 |
| **16** | 4′-Cl, 4-$OCH_3$ | Cl (b) | 5-$OCH_3$ (e) | 2.5 | 117-118 | 62 | 41.65 | 41.57 | 2.42 | 2.18 | 3.74 | 3.60 |
| **17** | 4′-Cl, 4-OH | Cl | 5-OH (c) | 24 | 176-177 | 51 | 39.95 | 39.75 | 1.96 | 2.12 | 3.89 | 3.53 |
| **18** | 4′-Cl, 4-$OCH(CH_3)_2$ | Cl | 5-$OCH(CH_3)_2$ (c) | 20 | 77-78 | 67 | 44.73 | 44.34 | 3.25 | 3.22 | 3.48 | 3.41 |
| **19** | 4′-Cl, 3-$OCH(CH_3)_2$ (a) | Cl | 6-$OCH(CH_3)_2$ (c) | 24 | 78-80 | 42(g) | 44.73 | 44.18 | 3.25 | 3.34 | 3.48 | 3.82 |
| **20** | 4′-Cl, 3-OH | Cl | 6-OH (c) | 24 | 115.5-117 | 46 | 39.95 | 40.42 | 1.96 | 2.41 | 3.89 | 3.89 |

(a) This compound was also prepared by treating **20** (7.2 g.) with 2-iodopropane (5.1 g.) in refluxing (2 hours) DMF (30 ml.), in the presence of anhydrous potassium carbonate (3.2 g.), yield 80%. (b) A. J. Saggiomo, P. N. Craig and M. Gordon, *J. Org. Chem.*, 23, 1906 (1958). (c) Experimental section. (d) K. Fries and W. Buchler, *Ann. Chem.*, 454, 247 (1927). (e) Commercial. (f) All of these compounds were crystallized from ethanol; **14** was given an additional crystallization from benzene. (g) The yields in this synthesis were erratic. Also isolated were bis(2-bromo-4-chlorophenyl)-disulfide (1) (oxidation of **2**) and 2,7-dichlorothianthrene (reaction of **2** with itself).

TABLE II

2-Amino-2'-Bromodiphenylsulfides

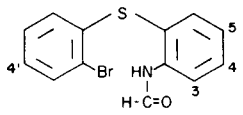



| No. | Diphenylsulfide | Method | Mp., °C (a) | Yield % | Analyses C Calcd. | C Found | H Calcd. | H Found | N Calcd. | N Found |
|---|---|---|---|---|---|---|---|---|---|---|
| **21** | 4-Cl, 5-$OCH_2C_6H_5$ | A | 94-95 | 62 | 54.22 | 54.43 | 3.56 | 3.70 | | |
| **22** | 4-Cl, 5-$OCH_3$ | B | 125.5-127 | 96 | 45.28 | 45.54 | 3.22 | 3.10 | 4.07 | 4.17 |
| **23** | 4-Cl, 5-$OCH(CH_3)_2$ | A | 99-100 | 96 | 48.32 | 48.38 | 4.03 | 4.09 | 3.73 | 3.89 |
| **24** | 4'-Cl, 4-$OCH_3$ | B | 83.5-84.5 (b) | 88 | 45.28 | 45.39 | 3.22 | 3.44 | 4.07 | 4.29 |
| **25** | 4'-Cl, 4-OH | B | 156-157 | 79 | 43.57 | 43.34 | 2.74 | 3.04 | 4.24 | 4.32 |
| **26** | 4'-Cl, 4-$OCH(CH_3)_2$ | C | 122 | 87 | 48.32 | 48.48 | 4.03 | 4.18 | 3.73 | 4.00 |
| **27** | 4'-Cl, 3-$OCH(CH_3)_2$ | C | b.p. 181 (0.1 mm) | 69 | 48.32 | 48.32 | 4.03 | 3.98 | 3.73 | 3.90 |
| **28** | 4'-Cl, 3-OH | B | 133-134 | 86 | 43.57 | 43.41 | 2.74 | 2.59 | 4.24 | 4.37 |

(a) All crystallizations were from ethanol except for that of **28** which was from ether-petroleum ether (1:1). (b) Treatment of **24** with saturated ethanolic hydrogen chloride provided the hydrochloride, m.p. 170-173°, *Anal.* Calcd. for $C_{13}H_{11}BrClNOS\cdot HCl$: C, 40.96; H, 3.17; N, 3.68. Found: C, 40.74; H, 3.05; N, 3.97.

TABLE III

2′-Bromo-2-formamidodiphenylsulfides

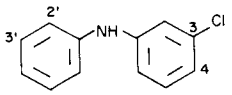



| No. | Diphenylsulfide | Method | Reflux Time hour | Mp., °C (Solvent) | Yield % | Analyses C Calcd. | C Found | H Calcd. | H Found | N Calcd. | N Found |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **29** | 4-Cl, 5-$OCH_2C_6H_5$ (a) | A | 4.5 | 145.5-146.5 (MeOH) | 90 | 53.51 | 53.64 | 3.34 | 3.25 | 3.12 | 2.94 |
| **30** | 4-Cl, 5-OH | (b) | 17 | 198-199 ($C_6H_6$-EtOH) | 87 | 43.51 | 43.62 | 2.51 | 2.72 | 3.95 | 3.61 |
| **31** | 4-Cl, 5-$OCH_3$ | B | 10 | 134.5-135.5 (EtOH) | 79 | 45.10 | 45.36 | 2.98 | 2.94 | 3.76 | 4.03 |
| **32** | 4-Cl, 5-$OCH(CH_3)_2$ | A | 4.5 | 88-92 (ligroine) | 98 | 47.94 | 47.83 | 3.74 | 3.57 | 3.50 | 3.80 |
| **33** | 4′-Cl, 4-$OCH_3$ | B | 10 | 146-147 (EtOH) | 78 | 45.10 | 45.55 | 2.98 | 3.10 | 3.76 | 4.23 |
| **34** | 4′-Cl, 4-OH | B | 2.5 | 231.5-232.5 (EtOH) | 90 | 43.51 | 43.70 | 2.51 | 2.59 | 3.95 | 3.78 |
| **35** | 4′-Cl, 4-$OCH(CH_3)_2$ | C | 25 | 103-104 (MeOH) | 91 | 47.94 | 48.09 | 3.74 | 3.83 | 3.50 | 3.57 |
| **36** | 4′-Cl, 3-$OCH(CH_3)_2$ | C | 25 | 126-127.5 (EtOH) | 93 | 47.94 | 47.80 | 3.74 | 3.79 | 3.50 | 3.81 |
| **37** | 4′-Cl, 3-OH | B | 2.5 | 167-168.5 (MeOH) | 91 | 43.51 | 43.80 | 2.51 | 3.01 | 3.95 | 4.21 |

(a) This compound was also prepared by heating **30** (1 g.) with benzyl chloride (0.4 ml.) in refluxing acetone (15 ml.) for 4 hours in the presence of anhydrous potassium carbonate (0.4 g.). (b) An attempt to prepare **29** using method B on **21** resulted in concomitant debenzylation and formation of **30**.

TABLE IV

Diphenylamines

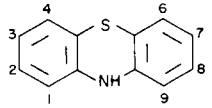


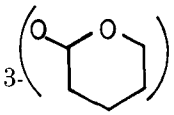

| No. | Diphenylamine | Starting Materials | | Method | B.P., °C (mm.) M.P., °C (solvent) | Yield % | Analyses C Calcd. | C Found | H Calcd. | H Found | N Calcd. | N Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **46** | 4-$OCH_3$ | acetanilide | 4-Br, 2-Cl anisole (a) | A | 146-153 (0.3) 100.5-101 (EtOH) | 31 | 66.79 | 66.63 | 5.18 | 5.21 | 6.00 | 6.06 |
| **46A** | 3'-$OCH_3$ | | **57** | (d) | 167-172 (0.1) (e) | 78 | – | – | – | – | – | – |
| **57** | 3'-OH | 3-Cl aniline | resorcinol | B | 190-200 (0.5) (b) 34-37 (c) | 64 | – | – | – | – | – | – |
| **47** | 3'-$OCH(CH_3)_2$ | | **57** | C | 140-143 (0.1) 53-53.5 (c) | 88 | 68.81 | 68.65 | 6.16 | 6.17 | 5.35 | 5.44 |
| **58** | 2'-OH | 3-Cl aniline | catechol | B | 168-175 (0.2) 55-57 (ligroine) | 33 | 65.60 | 65.76 | 4.56 | 4.67 | 6.38 | 6.07 |
| **48** | 2'-$OCH(CH_3)_2$ | | **58** | C | 162-168 (l) | 84 | 68.81 | 68.61 | 6.16 | 6.11 | 5.35 | 5.44 |

(a) Experimental section. (b) Lit. (16) 180-195° (0.4). (c) Distillate crystallized on cooling and was used without recrystallization. (d) Routine methylation with dimethylsulfate in methanolic sodium hydroxide. (e) Lit. (16) b.p. 153-156° (0.2).

TABLE V

Phenothiazines

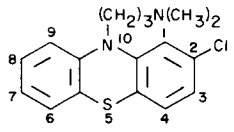


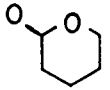
| No. | Phenothiazine (a) | Method | Starting Material | Reflux Time hour | Mp., °C (solvent) | Yield % | Analyses C Calcd. | C Found | H Calcd. | H Found | N Calcd. | N Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **38** | 2-Cl, 3-$OCH_2C_6H_5$ | A | 29 | 4 | 178.5-179 (pet. ether-$C_6H_6$) | 53 | 67.16 | 66.73 | 4.12 | 3.99 | 4.12 | 4.21 |
| **53** | 2-Cl, 3-OH (b) | D | 51 | – | 189.5-191 (EtOH) | – | (g) | – | – | – | – | – |
| **39** | 2-Cl, 3-$OCH_3$ | A | 31 | 2 | 197.5-198.5 (ligroine-$C_6H_6$) | 50 | 59.18 | 59.08 | 3.82 | 3.81 | 5.31 | 5.57 |
| | | B | 46 | 1 | | 17 | | | | | | |
| | | C | 53 | (d) | | 50 | | | | | | |
| **54** | 2-Cl, 3-  | C | 53 | – | 190-191 (EtOH) | 47 | 61.17 | 61.34 | 4.80 | 4.96 | 4.20 | 4.03 |
| **40** | 2-Cl, 3-$OCH(CH_3)_2$ | A | 32 | 4 | 151-151.5 ($C_6H_6$) | 82 | 61.75 | 61.40 | 4.80 | 4.72 | 4.80 | 4.70 |
| | | C | 53 | 2 | | 76 | | | | | | |
| **41** | 2-Cl, 8-$OCH_3$ | A | 24 | 30 | 207-208 ($C_6H_6$) (i) | 40 | 59.18 | 59.00 | 3.82 | 4.11 | 5.31 | 5.36 |
| | | B | 46A | (e) | | 43 | | | | | | |
| **42** | 3-Cl, 8-$OCH_3$ | A | 33 | 3 | 178-178.5 (toluene-ligroine) | 53 | 59.18 | 58.98 | 3.82 | 3.99 | 5.31 | 5.41 |
| **43** | 2-Cl, 8-$OCH(CH_3)_2$ | A | 26 | 10 | 175-176 ($Et_2O$) | 37 | 61.75 | 62.25 | 4.80 | 5.21 | 4.80 | 4.59 |
| | | B (c) | 47 | 2 | | 25 | | | | | | |
| | | C (h) | 56 (h) | 18 | | 43 | | | | | | |
| **44** | 3-Cl, 8-$OCH(CH_3)_2$ | A | 35 | 3 | 182-184 ($Et_2O$) | 90 | 61.75 | 62.27 | 4.80 | 4.88 | 4.80 | 4.77 |
| **45** | 2-Cl, 9-$OCH(CH_3)_2$ | A | 27 | 10 | b.p. 190 (0.2 mm.) | 40 | 61.75 | 61.69 | 4.80 | 4.62 | 4.80 | 5.23 |
| | | B | 48 | 2 | | 13 (f) | | | | | | |
| | | C | 55 | 2 | | 58 | | | | | | |
| **55** | 2-Cl, 9-OH (b) | B | 58 | 1 | 173-176 ($C_6H_6$) | 29 | 57.69 | 58.16 | 3.23 | 3.37 | 5.60 | 6.04 |

(a) These compounds were all white or off-white. (b) A single attempt to synthesize **53** by demethylation of **39** with pyridine hydrochloride at 200° was unsuccessful. Application of the same method to **45** provided 32% of 2-chloro-9-hydroxyphenothiazine (**55**). (c) Xylene was substituted for *o*-dichlorobenzene as solvent. Thionation in a concentrated solution (1.3 g./5 ml.) of the latter gave a compound identical with that obtained on demethylation of 2-chloro-8-methoxyphenothiazine (**41**) (footnote h). In more dilute solution (104 g./960 ml.) 17% of **43** was obtained. Also isolated was 2% of an unidentified isomeric chloroisopropoxyphenothiazine, m.p. 137.5-139° (crystallized 3x from ethanol). *Anal.* Calcd. for $C_{15}H_{14}ClNOS$: C, 61.75; H, 4.80; N, 4.80. Found: C, 61.77; H, 4.96; N, 5.38. (d) Fifteen minutes at room temperature. (e) Solvent eliminated, reaction maintained at 170-180° for 50 minutes and extracted with benzene. (f) Attempts to improve this yield by using xylene as solvent (instead of *o*-dichlorobenzene), or by eliminating solvent, were unsuccessful. (g) Identified by conversion to the authenticated methyl and isopropyl ethers (**39** and **40**). (h) The starting material, 2-chloro-8-hydroxyphenothiazine (**56**) was prepared by demethylating (note b) **41**. It was difficult to purify (indefinite m.p. at about 260° and was not submitted for analysis. (i) Lit. (16) m.p. 204-205°.

TABLE VI

Chlorpromazine Ethers

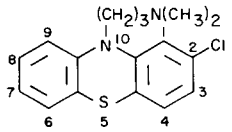



| No. | Chlorpromazine Ether | Solvent | Base | Temp °C | Time hour | B.P., °C (mm.) | Yield % | Analyses C Calcd. | C Found | H Calcd. | H Found | N Calcd. | N Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **65** | 3-$OCH_3$ (a,d) | xylene | $NaNH_2$ | reflux | 3 | 184-186 (0.04) | 26 | 61.94 | 62.15 | 6.07 | 6.06 | 8.04 | 8.19 |
| **66** | 3-  | DMSO | $NaNH_2$ | 60-70 | 3 | m.p. 73-75($Et_2O$) | 86 | 63.06 | 62.44 | 6.50 | 6.54 | 6.69 | 6.81 |
| **67** | 3-$OCH(CH_3)_2$ (b) | xylene | NaH | reflux | 3 | 200-204 (0.1) | 66 | 63.75 | 64.08 | 6.68 | 6.66 | 7.44 | 7.33 |
| **68** | 8-$OCH(CH_3)_2$ (e) | xylene | NaH | reflux | 10 | 186-188 (0.005) | 80 | 63.75 | 64.43 | 6.68 | 6.68 | 7.44 | 7.27 |
| **69** | 9-$OCH(CH_3)_2$ | xylene | NaH | reflux | 10 | 170-173 (0.002) | 60 | (c) | – | – | – | – | – |

(a) Picrate, m.p. 175-176°, *Anal.* Calcd. for $C_{24}H_{24}ClN_5O_8S$: C, 49.85; H, 4.19; N, 12.12. Found: C, 50.14; H, 4.25; N, 11.91; hygroscopic hydrochloride; hydroiodide, m.p. 196°, *Anal.* Calcd. for $C_{18}H_{22}ClIN_2OS$: C, 45.34; H, 4.62; N, 5.88. Found: C, 45.85; H, 5.00; N, 5.82. (b) Hydrochloride, m.p. 193-194°, *Anal.* Calcd. for $C_{20}H_{26}Cl_2N_2OS$: C, 58.11; H, 6.30; N, 6.78. Found: C, 58.01; H, 5.85; N, 7.04; hydrobromide, m.p. 195-196°, *Anal.* Calcd. for $C_{20}H_{26}BrClN_2OS$: C, 52.46; H, 5.68; N, 6.12. Found: C, 52.54; H, 5.52; N, 6.08. (c) Hydrochloride, m.p. 169-170°, *Anal.* Calcd. for $C_{20}H_{26}Cl_2N_2OS$: C, 58.11; H, 6.30; N, 6.78. Found: C, 58.62; H, 6.65; N, 6.79. (d) Also formed by treating 3-Hydroxychlorpromazine (**70**), in THF, with ethereal diazomethane, yield 53%. (e) Single attempts to prepare **67** and **68** in xylene sodium amide and in toluene sodium amide gave low yields of these compounds.

TABLE VII

Hydroxychlorpromazines




| No | Hydroxychlorpromazine | M.P. °C (Solvent) | Yield % | Analyses C Calcd. | C Found | H Calcd. | H Found | N Calcd. | N Found | Cl Calcd. | Cl Found |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **70** | 3-OH | 140-142 (pet. ether, b.p. 20-40°-$Et_2O$, 9:1) | 33 | 60.98 | 61.03 | 5.68 | 5.75 | 8.36 | 8.10 | 10.61 | 10.48 |
| **71** | 8-OH (A) (a) | 75 (foaming) (pet. ether, 20-40°) | 19 | 60.98 | 61.19 | 5.68 | 5.93 | 8.36 | 8.11 | 10.61 | 10.46 |
| | 8-OH (B) (a) | 126-127 (pet. ether-$Et_2O$ 19:1) | | 60.98 | 60.74 | 5.68 | 5.76 | 8.36 | 7.69 | 10.61 | 10.46 |
| | 8-OH (C) (a) | 128-130 (pet. ether-$Et_2O$ 19:1) | | 60.98 | 61.34 | 5.68 | 5.94 | 8.36 | 7.91 | 10.61 | 10.34 |
| | 8-OH (D) (a) | 168-169 (EtOH) | | 60.98 | 60.43 | 5.68 | 6.01 | 8.36 | 8.59 | 10.61 | 10.63 |
| **72** | 9-OH | 149-150 (pet. ether-$Et_2O$, 2:1) | 21 | 60.98 | 60.95 | 5.68 | 5.74 | 8.36 | 7.87 | 10.61 | 10.24 |

(a) Polymorphs of **71** (see discussion section).

An alternate preparation of **53** (Scheme 3) was begun with the reaction between the zinc mercaptide (**49**) (8) and commercial 2,5-dichloro-*p*-benzoquinone (**50**) in refluxing ethanol (9). Subsequent reduction of the resulting phenothiazone (**51**) with sodium hydrosulfite produced the desired compound.

An attempt to prepare 2-chloro-8-methoxyphenothiazine (**41**) via Smiles rearrangement and subsequent ring closure is outline in Scheme 4.

Although rearrangement of **62** occurred, ring closure of the resulting thiol (**63**) did not follow (10a). Only the oxidation product (**64**) of **63** was isolated.

This outcome is the same as that recorded in an identical effort to prepare 2-methoxy-8-trifluoromethylphenothiazine (5).

Conversion of the phenothiazine ethers (**39**, **54**, **40**, **43** and **45**) to chloropromazine ethers (**65-69**) and subsequent hydrolysis to 3-, 8- and 9-hydroxychlorpromazine (**70-72**) are outlined in Scheme 5 and detailed in Tables VI and VII.

The isopropyl group, used successfully for phenolic protection in the synthesis of the 8- and 9- derivatives (**71** and **72**) (10), failed in the preparation of 3-hydroxychlorpromazine (**70**). The rather vigorous conditions (reflux with concentrated hydrochloric acid) necessary for cleavage of the 3-isopropoxy compound (**67**) decomposed the relatively unstable product (**70**).

This problem was overcome by substituting tetrahydropyranyl (removable on short exposure to weak acid at room temperature) for the isopropyl group.

Although polymorphism is little known among the phenothiazines (11), 8-hydroxychlorpromazine (**71**) was isolated as four distinct forms. Three of these forms were white and melted at 75° (A), 126-127° (B) and 168-169° (D). The fourth form was yellow and melted at 128-130° (C). As Nujol mulls the polymorphs provided infrared spectra which were all different from one another. In chloroform solution all four spectra were identical. Elemental analyses (C, H, N, Cl) for each of the forms were in excellent agreement with the values calculated for 8-hydroxychlorpromazine (Table VII). Thin-layer chromatography (12) indicated that each sample was homogeneous and identical in $R_f$. Finally, the following interconversions were effected by pumping at appropriate temperatures or by varying crystallization solvent ratios. The lowest melting form (A) was obtained by crystallization of the crude **71** from petroleum ether (b.p. 20-40°).

A → (5 hours at 95°) → B

A → (crystallization from ether-petroleum ether (1:19)) → B

A → (crystallization from ether-petroleum ether (1:19)) → C

A → (5 hours at 100°) → D

B → (ether solution allowed to concentrate in open beaker) → D

B → (5 hours at 140°) → D

C → (5 hours at 110°) → B

It is interesting that two apparently identical crystallizations of A produced different polymorphs (B and C).

## EXPERIMENTAL

Melting points were determined in capillary tubes in an electrically heated Thiele-Dennis apparatus and are uncorrected. All reactions were mechanically stirred under dry nitrogen and in the absence of strong, direct light. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Infrared spectra were taken as liquid films or Nujol mulls on a Perkin-Elmer Model 137B, Infracord Spectrophotometer. Organic solutions were dried with anhydrous magnesium sulfate and decolorized with Darco G-60. Concentration and complete solvent removal were carried out under reduced pressure.

2'-Bromo-2-Nitrodiphenylsulfides (Table I).

These compounds were prepared via the reaction between appropriately substituted *o*-bromothiophenols (**1** and **2**) and *o*-chloronitrobenzenes (**3** to **11**) (4) in ethanolic sodium ethoxide.

2,5-Dichloro-4-nitrophenyl Benzyl Ether (**3**).

Benzylation of **5** (Table I, note d) with benzyl bromide (anhydrous potassium carbonate, refluxing acetone, 5 hours) gave 86% of **3**, m.p. 109-110° (ethanol).

*Anal.* Calcd. for $C_{13}H_9Cl_2NO_3$: C, 52.35; H, 3.04; N, 4.69. Found: C, 52.36; H, 3.13; N, 4.67.

2,5-Dichloro-4-nitroanisole (**4**).

Treatment of **5** with dimethyl sulfate (potassium carbonate, toluene, 115°, 1 hour) provided 54% of **4**, m.p. 100-101° (ethanol); (lit. (13) m.p. 99°).

2,5-Dichloro-4-nitrophenyl Isopropyl Ether (**6**).

Isopropylation of **5** was effected with isopropyl iodide in refluxing (40 hours) acetone containing potassium carbonate; yield 43%, m.p. 56-57.5° (ligroine).

*Anal.* Calcd. for $C_9H_9Cl_2NO_3$: C, 43.20; H, 3.60. Found: C, 43.43; H, 3.62.

4-Chloro-3-nitrophenol (**8**).

This phenol (**8**) was obtained in 71% yield on cleavage of commercial 4-chloro-3-nitroanisole with pyridine hydrochloride (200°, 5 hours). Purification was effected by solution in a minimal amount of 5% sodium hydroxide, decolorization and acidification with hydrochloric acid; m.p. 120.5-121.5°; (lit. (14) 126-127°).

4-Chloro-3-nitrophenyl Isopropyl Ether (**9**).

Isopropylation of **8** with isopropyl iodide in refluxing (8.5 hours)

10% ethanolic potassium hydroxide afforded 84% of **9**; b.p. 118-120° (0.9 mm.), m.p. 46.5-47.4° (petroleum ether).

*Anal.* Calcd. for $C_9H_{10}ClNO_3$: C, 50.19; H, 4.69; N, 6.50. Found: C, 50.09; H, 4.70; N, 6.85.

3-Chloro-2-nitrophenol (**11**) (15).

3-Chlorophenol (128 g.) was added slowly, with cooling, to 750 g. of oleum (27% sulfur trioxide). The mixture was kept at 15° for 12 hours and then heated on a water-bath for 2 hours to complete disulfonation. Nitric acid (45 ml., d., 1.5), dissolved in 200 ml. of oleum (27% sulfur trioxide), was added to the cooled mixture during 30 minutes, the mixture was allowed to stand for 2 hours, diluted and distilled with superheated steam (inlet temperature, 200°, outlet temperature, 120°). A yellow oil distilled which solidified at room temperature, m.p., 44-45°, (lit. (15) m.p. 37.5°), yield 93 g. (54%).

*Anal.* Calcd. for $C_6H_4ClNO_3$: C, 41.52; H, 2.32; N, 8.07. Found: C, 41.75; H, 2.32; N, 7.99.

3-Chloro-2-nitrophenyl Isopropyl Ether (**10**).

Isopropylation of **11**, effected as described in the synthesis of **9**, gave 53% of **10**, b.p. 100-104° (0.9 mm), m.p. 45-45.5° (ethanol).

*Anal.* Calcd. for $C_9H_{10}ClNO_3$: C, 50.13; H, 4.68; N, 6.49. Found: C, 50.59; H, 4.95; N, 6.70.

2-Amino-2′-Bromodiphenylsulfides (Table II).

Reduction of the nitro compounds in Table I was effected with stannous chloride dihydrate and hydrochloric acid using one of the variations described below.

Method A.

To a suspension of 20 g. (0.05 mole) of 2′-bromo-4-chloro-5-isopropoxy-2-nitrodiphenylsulfide (**15**) in 200 ml. of ethanol at 55°, was added, in portions, a solution of 37.5 g. (0.17 mole) of stannous chloride dihydrate in 80 ml. of hydrochloric acid. The mixture was heated under reflux for 2 hours. Dilution of the clear, amber solution with 2 l. of cold water gave a cream-colored gum. The gum was dissolved in ether, washed with water, dried and evaporated to give the amine (**23**).

Method B.

A mixture of 55.5 g. (0.15 mole) of 2′-bromo-4′-chloro-4-hydroxy-2-nitrodiphenylsulfide (**17**), 267 g. (1.18 moles) of stannous chloride dihydrate and 230 ml. of hydrochloric acid was heated under reflux for 2 hours, basified with sodium hydroxide solution and worked up, as in method A, to provide **25**.

Method C.

To a solution of 90 g. of stannous chloride dihydrate in 120 ml. of hydrochloric acid was added, during 20 minutes, a solution of 30 g. of **18** in 600 ml. of ethanol. After 30 minutes at reflux, and workup as in method A, **26** was obtained.

2′-Bromo-2-Formamidodiphenylsulfides (Table III).

A mixture of 11.2 g. (0.027 mole) of 2-amino-5-benzyloxy-2′-bromo-4-chlorodiphenylsulfide (**21**), 224 ml. of ethanol and 112 g. of 90% formic acid was heated under reflux, cooled and diluted with water to give **29**.

Method B.

This method was identical with method A except for the elimination of ethanol as diluent.

Method C.

A mixture of 30 g. (0.08 mole) of 2-amino-2′-bromo-4′-chloro-4-isopropoxydiphenylsulfide (**26**), 90 ml. of formic acid (97-100%) and 3 g. of pyridine was heated under reflux. On cooling, **35** separated.

Diphenylamines (Table IV).

Method A.

The Goldberg Reaction between appropriately substituted acetanilides and bromobenzenes was carried out as described in references 5 and 6.

Method B.

A literature synthesis of **46A** (16) was adapted as follows to prepare **58**.

A mixture of 306 g. (2.4 moles) of 3-chloroaniline, 290.4 g. (2.6 moles) of catechol, 20 g. of zinc chloride and 90 ml. of xylene was stirred under reflux, for 30 hours, in a reactor equipped with a Barrett distilling receiver (for water separation). Xylene was removed from the mixture by steam distillation and the residue was extracted with ethyl acetate. The extract was washed with water, dried, distilled and crystallized to give **58**.

Method C.

Routine isopropylation of the appropriate hydroxydiphenylamines with 2-iodopropane in ethanolic potassium hydroxide.

4-Bromo-2-chloroanisole.

Routine methylation of commercial 4-bromo-2-chlorophenol with dimethyl sulfate gave 71% of the ether, m.p. 66-67° (ethanol).

*Anal.* Calcd. for $C_7H_6BrClO$: C, 37.94; H, 2.73: Found: C, 38.04; H, 2.79.

Phenothiazines (Table V).

Method A.

Ring-closure of the appropriate 2-amino-2′-bromodiphenylsulfides (Table II) and 2′-bromo-2-formamidodiphenylsulfides (Table III) was brought about as described in references 1,4 and 6.

Method B.

Except as noted, thionation of the diphenylamines in Table IV was carried out in *o*-dichlorobenzene as suggested by Massie and Kadaba (7).

Method C.

2-Chloro-3-hydroxyphenothiazine (**53**) was converted to its methyl and isopropyl ethers (**39** and **40**) in aqueous-ethanolic potassium hydroxide, containing sodium hydrosulfite, with dimethyl sulfate and 2-bromopropane respectively.

The isopropyl ethers (**43** and **45**) of 2-chloro-8-hydroxyphenothiazine and 2-chloro-9-hydroxyphenothiazine were prepared routinely with 2-iodopropane in acetone-potassium carbonate and *N,N*-dimethylformamide-potassium carbonate respectively.

2-Chloro-3-hydroxyphenothiazine (**53**) (24.9 g., 0.1 mole) in 300 ml. of dihydropyran containing 1 ml. of hydrochloric acid was stirred at room temperature for 3 hours. The dark mixture was allowed to stand at room temperature overnight, heated under reflux for 3 hours, cooled to room temperature and diluted with 2 l. of ether. The ether was washed with 10% sodium hydroxide (2 x 500 ml.) and water (2 x 1 l.), dried and decolorized (dark red to orange). After solvent stripping the residue was freed of volatiles by pumping at 120° for 3 hours. The remaining oil was dissolved in ethanol (Darco) and the ethanolic solution was allowed to concentrate in air for 3 days. The pyranyl compound (**54**) separated as tan solid.

Method D.

A mixture of 7.8 g. (0.025 mole) of the zinc salt of 2-aminobenzenethiol (**49**) (8), 10 g. (0.056 mole) of commercial 2,5-dichloro-*p*-benzoquinone (**50**) and 100 ml. of 95% ethanol was stirred at room temperature for 1 hour and heated at reflux for 8 hours. The mixture was allowed to cool and the dark brown solid was washed with 4% hydrochloric acid (2 x 200 ml.) and water and dried. The yield of 2-chlorophenothiazone-3 (**51**) was 10.5 g. (78%), m.p. 201-203°. Two crystallizations from benzene provided the analytical sample, m.p. 211-212°.

*Anal.* Calcd. for $C_{12}H_6ClNOS$: C, 58.18; H, 2.44; N, 5.66. Found: C, 57.99; H, 2.78; N, 5.99.

Reduction of **51** to 2-chloro-3-hydroxyphenothiazine (**53**) was effected by stirring (15 g., 0.06 mole) under reflux (0.5 hour) with 15 g. of sodium hydrosulfite in 750 ml. of acetone. The mixture was poured into a solution of 50 g. of sodium hydrosulfite in 2.5 l. of water and the resulting yellow solid was dried *in vacuo* to give 12.2 g. (81%) of **53**, m.p. 184-188°. Crystallization from ethanol-aqueous sodium hydrosulfite (Darco) gave off-white solid, m.p. 189.5-191°.

Routine conversion (Method C) of **53** to the authentic methyl and isopropyl ethers (**39** and **40**) afforded structural proof.

Attempted Preparation of 2-Chloro-8-methoxyphenothiazine (**41**) Via Smiles Rearrangement.

The zinc salt of 2-amino-4-chlorothiophenol (81 g., 0.21 mole) (8) in 1 l. of ethanol was mixed, at room temperature, with 470 ml. of ethanolic sodium ethoxide (9.7 g., 0.42 g. atom of sodium). 3-Chloro-4-nitroanisole (80 g., 0.42 mole) (17) was added in 1 l. of ethanol and the solution was heated under reflux overnight. The mixture was filtered and the filtrate was concentrated. Crystallization of the residue from ethanol gave 62 g. (47%) of 2-amino-4-chloro-5′-methoxy-2′nitrodiphenylsulfide (**61**) as yellow crystals, m.p. 132-134.5°. A second crystallization (ethanol) provided the analytical sample, m.p. 138.5-139.5°.

*Anal.* Calcd. for $C_{13}H_{11}ClN_2O_3S$: C, 50.24; H, 3.57; N, 9.02. Found: C, 50.19; H, 3.62; N, 9.30.

4-Chloro-2-formamido-5′-methoxy-2′-nitrodiphenylsulfide (**62**).

This compound was obtained by routine formylation of **61** with 90% formic acid (10 hours reflux); yield 69%, m.p. 144.5-145.5° (ethanol).

*Anal.* Calcd. for $C_{14}H_{11}ClN_2O_4S$: C, 49.61; H, 3.27; N, 8.27. Found: C, 49.50; H, 3.37; N, 8.55.

To a solution of 86 g. (0.27 mole) of **62** in 1 l. of acetone was added 544 ml. of 1 *N* ethanolic sodium hydroxide. Immediate precipitation occurred. The suspension was stirred under reflux for 2.5 hours and filtered. Concentration of the filtrate gave a dark brown solid (sodium salt of **63**) which was dissolved in water and acidified with hydrochloric acid. The red-brown color was replaced by yellow and an oily precipitate appeared. This material was extracted with ether and the solvent was stripped. On standing in air the residual oil solidified (yellow). Crystallization from ethanol-benzene (1:1) gave orange needles of the disulfide (**64**), m.p. 166-167°.

*Anal.* Calcd. for $C_{13}H_{10}ClN_2O_3S$: C, 50.39; H, 3.26; N, 9.05. Found: C, 50.63; H, 3.26; N, 9.35.

Chlorpromazine ethers (Table VI).

Various phenothiazine ethers (Table V) were alkylated with 3-dimethylaminopropyl chloride using methods described previously (1).

Hydroxychlorpromazines (Table VII).

8- and 9-Hydroxychlorpromazine (**71** and **72**).

These compounds were made by hydrolyzing the corresponding isopropyl ethers (**68** and **69**) with refluxing hydrochloric acid (0.5 and 3 hours respectively) (1).

3-Hydroxychlorpromazine (**70**).

Method A.

To a mixture of 13.2 g. (0.04 mole) of 2-chloro-3-tetrahydropyranyloxyphenothiazine (**54**) and 92 ml. of DMSO was added, at room temperature, 1.88 g. (0.048 mole) of sodium amide. The temperature was maintained at 60-70° for 1 hour, a solution of 5.2 g. (0.043 mole) of 3-dimethylaminopropyl chloride in 16 ml. of DMSO was added and the temperature was kept at 60-70° for 3 hours. After standing overnight at room temperature the mixture was poured into 600 ml. of water. The resulting gray emulsion was extracted with ether and the red ether solution was washed with water and extracted with a solution of 30 g. of tartaric acid in 200 ml. of water. The tartrate solution was treated with carbon and basified (*p*H 8) with 15% ammonium hydroxide. The resulting gray-pink solid was dried *in vacuo* at 100° for 6 hours (wt 4.5 g.) and extracted with 9:1 petroleum ether (20-40°)-ether in a Sohxlet extractor. On standing at room temperature overnight there separated from the extracts red-brown prisms, and clumps of very pale pink amorphous solid. Both solids melted 143-145° and their mixture melting point was not depressed. A mixture of both forms was crystallized from petroleum ether (20-40°)-ether (9:1) to give a pale pink solid, m.p. 84° (foaming). Heating this solid for 5 minutes at 115-120° raised its m.p. to 140-142°.

Method B.

Alkylation of **54** was carried out essentially as described in method A. However, the ether extract (instead of extraction with tartaric acid) was simply washed with water, dried, decolorized and evaporated. The residual oil was dissolved in the minimal amount of ether and allowed to stand for 2 days. 3-Tetrahydropyranyloxychlorpromazine (**66**) separated as white prisms (Table (VI).

A solution of 3.0 g. (0.0072 mole) of **66** in 70 ml. of ether was acidified at room temperature with a saturated ethereal solution of hydrogen chloride gas. The resulting solid was washed with ether and crystallized from ethanol-ether (1:5) to give 2.5 g. (93%) of 3-hydroxychlorpromazine hydrochloride (**73**), as a pale pink solid, m.p. 83-84° (foaming).

*Anal.* Calcd. for $C_{17}H_{20}Cl_2N_2OS$: C, 54.98; H, 5.43; N, 7.54. Found: C, 54.63; H, 5.98; N, 7.18.

On exposure to light and air, **73** turned to gum.

To a solution of 2.2 g. of **73** in 150 ml. of water was added solid sodium carbonate to *p*H 8. The solid was extracted with ether, washed with water, dried and decolorized. The ether was evaporated and the residual tan oil was treated with petroleum ether. The resulting solid was crystallized from ether-petroleum ether (1:5) to give 0.7 g. of 3-hydroxychlorpromazine (**70**) as white crystals, m.p. 139-140° dec.

The infrared spectrum of this material was identical with that prepared using method A.

Acknowledgment.

The authors gratefully acknowledge the assistance of Dr. Frederick Leonard (deceased), Klaus Herrle, Mary Schlauter, Adrienne Gould, K. Takeda and Andrew J. Saggiomo.

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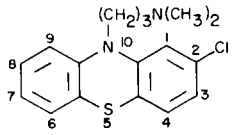
(2a) This investigation was supported by the Psychopharmacology Research Branch, National Institute of Mental Health, Contract SA-43-ph-3758; (b) Psychopharmacology Research Branch, National Institute of Mental Health, Chevy Chase, Md.

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

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(8) E. A. Nodiff and M. Hausman, *ibid.*, 31, 625 (1966).

(9) Adaptation of the method of T. Mine, *Kogyo Kagaku Zasshi*, 67, 149 (1964); *Index Chemicus*, 14, 41560 (1964).

(10) The isopropyl group was also employed in the preparation of 7-hydroxychlorpromazine and some of its derivatives (1).

(10a) Resistance to cyclization in a similar reaction (halogen not in the same ring as the nitro group) has been mentioned by S. P. Massie [*Chem. Rev.*, 54, 797 (1954)].

(11) D. F. Houston, E. B. Kester and F. DeEds [*J. Am. Chem. Soc.*, 71, 3819 (1949)] suggested the possibility of polymorphism for the octyl ether of 7-hydroxyphenothiazone-3.

(12) We are grateful to Dr. Harry Goldenberg for performing the thin-layer chromatographic analyses.

(13) Prepared via an alternative route by M. Goi and K. Konishi, *J. Soc. Org. Synthet. Chem. Japan*, 12, 189 (1954); *Chem. Abstr.*, 51, 1884d (1957).

(14) R. Meldola, G. H. Wolcott and E. Wray, *J. Chem. Soc.*, 69, 1322 (1896).

(15) Attempts to prepare **11** as suggested by H. Hodgson and F. H. Moore [*J. Chem. Soc.*, 1599 (1925)], using ordinary steam instead of superheated steam, gave erratic yields.

(16) French Patent No. 1,173,121 (February 20, 1959).

(17) H. H. Hodgson and F. H. Moore, *J. Chem. Soc.*, 157 (1926).

Received January 2, 1968 Philadelphia, Pa. 19144