

# New Tetracyclic Ring Systems. Synthesis of 1*H*-Oxazolo[5,4,3-*kl*]phenothiazines and [1,4]Oxazino[2,3,4-*kl*]phenothiazines

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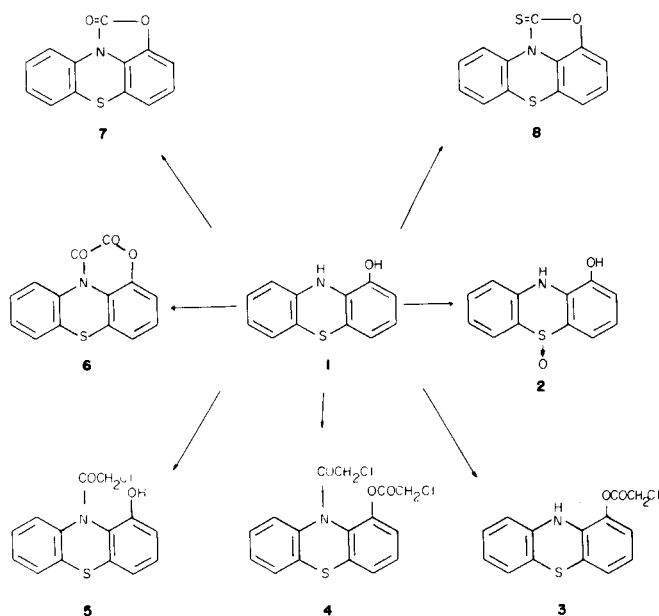
1-Hydroxyphenothiazine was converted to 1*H*-oxazolo[5,4,3-*kl*]phenothiazin-1-one, 1*H*-oxazolo[5,4,3-*kl*]phenothiazine-1-thione, [1,4]oxazino[2,3,4-*kl*]phenothiazin-1(2*H*)-one and [1,4]oxazino[2,3,4-*kl*]phenothiazine-1,2-dione. Also prepared from 1-hydroxyphenothiazine were the *N*-chloroacetyl derivative, the *O*-chloroacetyl derivative, the *N,O*-di(chloroacetyl) derivative and the sulfoxide.

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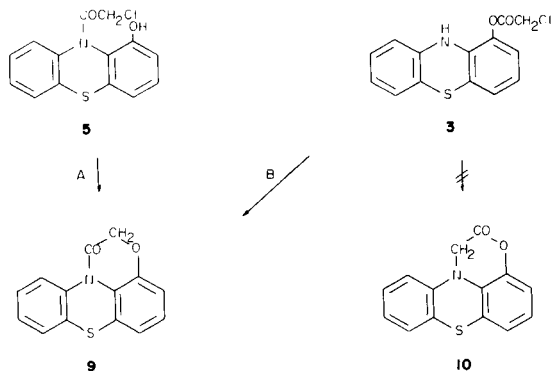
As part of an investigation of the hydroxyphenothiazines (1,2) we have prepared various derivatives of 1-hydroxyphenothiazine (1) (3), as indicated in Schemes 1 and 2.

The sulfoxide 2 was prepared by refluxing 1 with 30% hydrogen peroxide in ethanol-acetone. Treatment of 1

Scheme 1



Scheme 2



with chloroacetyl chloride, using the three procedures described in the experimental provided 3, 4 and 5. The reactions of 1 with oxalyl chloride, phosgene and thio-phosgene produced, respectively, 6, 7 and 8. Ring closure of 5 with sodium hydride-dimethylformamide gave 9 (Scheme 2). Identical treatment of 3 also gave 9 rather than the anticipated lactone 10 suggesting an *O*-*N* chloroacetyl shift prior to cyclization.

## EXPERIMENTAL

Melting points were determined in capillary tubes in an electrically heated Thiele-Dennis apparatus. Elemental analyses were performed by Micro-Analysis, Inc., Wilmington, Delaware. Infrared spectra were taken on a Perkin-Elmer 137 B Infracord spectrophotometer as Nujol mulls.

### 1-Hydroxyphenothiazine 5-Oxide (2).

A mixture of 30 g (0.14 mole) of 1-hydroxyphenothiazine (1) (1), 630 ml of acetone, 270 ml of ethanol and 43.2 ml of 30% hydrogen peroxide was heated under reflux for 30 minutes, allowed to cool to room temperature and diluted with 2 liters of water. After standing at room temperature overnight, the mixture was filtered and the resulting solid was extracted with boiling chloroform. The chloroform-insoluble, dark brown sulfoxide 2 was dissolved in 3.6 liters of boiling methanol, treated with carbon and filtered. Concentration of the filtrate to 400 ml, under reduced pressure, provided 10.3 g (32%) of 2 as off-white solid, mp 195-197°. An additional crystallization from methanol gave the analytical sample, mp 196-197°.

*Anal.* Calcd. for  $C_{12}H_9NO_2S$ : C, 62.33; H, 3.89; O, 13.85. Found: C, 62.49; H, 3.67; O, 14.04.

The infrared spectrum of 2 showed a prominent band at 10.5  $\mu$ . Strong absorption in this region is characteristic of the phenothiazine sulfoxides.

### 1-Chloroacetoxyphenothiazine (3).

To a solution of 0.4 g (0.01 mole) of sodium hydroxide in 35 ml of water, at room temperature, was added 2.15 g (0.01 mole) of 1. The dark brown solution was filtered and cooled to 0° by addition of crushed ice. To this stirred mixture, maintained at 0° was added, dropwise, 1.13 g (0.01 mole) of chloroacetyl chloride. Stirring was continued for 10 minutes and the resulting solid was filtered and dried *in vacuo* to give 1.5 g (52%) of 3. Crystallization from ether (carbon) gave the analytical sample, mp 145-146°; ir, needle-like peaks at 2.9  $\mu$  (-NH-) and 5.7  $\mu$  (ester C=O).

*Anal.* Calcd. for  $C_{14}H_{10}ClNO_2S$ : C, 57.63; H, 3.43; N, 4.80. Found: C, 57.84; H, 3.27; N, 4.72.

### 10-Chloroacetyl-1-chloroacetoxyphenothiazine (4).

To a solution of 5.38 g (0.025 mole) of 1 in 60 ml of boiling benzene, under nitrogen, was added, dropwise, 8.5 g (0.075 mole) of chloroacetyl chloride. The mixture was allowed to reflux for 3 hours and concen-

trated, *in vacuo*, to give 8.5 g (92%) of **4**, mp 195-199°. An analytical sample, mp 199-200°, was obtained by recrystallization from benzene (carbon).

*Anal.* Calcd. for  $C_{16}H_{11}Cl_2NO_3S$ : C, 52.17; H, 2.98; N, 3.80. Found: C, 52.39; H, 3.12; N, 3.80.

The ir spectrum of **4** was devoid of an -NH- peak but did have the expected strong, sharp ester carbonyl (5.6  $\mu$ ) and amide carbonyl (6.0  $\mu$ ) peaks.

#### 10-Chloroacetyl-1-hydroxyphenothiazine (**5**).

A mixture of 21.5 g (0.1 mole) of **1**, 14 g (0.12 mole) of chloroacetyl chloride and 360 ml of benzene was heated under reflux, in a nitrogen atmosphere, for 30 minutes. The mixture was allowed to cool and concentrated under reduced pressure to give 23g of crude **5**, mp 128-131°. This material was dissolved in acetone, at room temperature, treated with carbon, diluted with ligroine (bp 90-120°) and concentrated to give 21.5 g (74%) of **5** as a white solid, mp 150-151°.

*Anal.* Calcd. for  $C_{14}H_{10}ClNO_2S$ : C, 57.63; H, 3.43; N, 4.80. Found: C, 57.87; H, 3.34; N, 4.95.

The ir spectrum of **5** contained no -NH- peak but did have a very strong amide carbonyl peak (6.1  $\mu$ ).

#### [1,4]Oxazino[2,3,4-kl]phenothiazine-1,2-dione (**6**).

To a stirred solution of 8.89 g (0.07 mole) of oxalyl chloride in 350 ml of benzene was added, at room temperature, a solution of 15.1 g (0.07 mole) of **1** in 350 ml of benzene. The mixture was heated under reflux, in a nitrogen atmosphere, for 2 hours, allowed to cool and concentrated *in vacuo*. The resulting crude **6** (15.5 g) was dissolved in 2 liters of boiling carbon tetrachloride, treated with carbon and concentrated to give 13 g (69%) of **6**, mp 172-174°.

*Anal.* Calcd. for  $C_{14}H_8NO_4S$ : C, 62.45; H, 2.60; O, 17.84. Found: C, 62.15; H, 2.60; O, 17.55.

The infrared spectrum of **6** showed the lactone and lactam peaks at 5.6  $\mu$  and 5.9  $\mu$ , respectively.

#### 1H-Oxazolo[5,4,3-kl]phenothiazin-1-one (**7**).

To a stirred solution of 16 g (0.075 mole) of **1** in 1 liter of benzene, at room temperature, under nitrogen, was slowly added 600 ml of 12.5% phosgene in benzene. Stirring was continued at room temperature for 2 hours and the mixture was allowed to stand overnight. After low pressure solvent removal, the solid, mp 242-244°, was vacuum sublimed (2 hours at 190-200° and 0.1 mm/Hg) to give 14.7 g (81%) of **7**, mp 244-245°. Subsequent recrystallization from acetone removed a trace of color but did not raise the melting point.

*Anal.* Calcd. for  $C_{13}H_7NO_2S$ : C, 64.73; H, 2.90; N, 5.80; O, 13.27. Found: C, 64.61; H, 2.85; N, 5.89; O, 13.46.

The ir spectrum displayed a very strong doublet at 5.7  $\mu$ .

#### 1H-Oxazolo[5,4,3-kl]phenothiazine-1-thione (**8**).

To a mixture of 10.75 g (0.05 mole) of **1**, 15.10 g (0.12 mole) of triethylamine and 250 ml of toluene, at 0°, under nitrogen, was added 7.0 g (0.06 mole) of thiophosgene (Aldrich) in 100 ml of toluene. The dark mixture was stirred for 10 minutes at 0° and at 20° for 4 hours and then filtered. The filtrate was concentrated, *in vacuo*, and the resulting slurry was diluted with cyclohexane to give 8 g of solid, mp 175-180°. Extraction of the solid with boiling cyclohexane (5  $\times$  200 ml) and concentration of the extract gave 2.3 g of **8**, mp 190-192°. Recrystallization from cyclohexane raised the melting point to 191-192°, yield 2.1 g (16%). A trace of color was removed from this material by vacuum sublimation (6 hours,

175-180°, 0.1 mm/Hg) without changing the melting point.

*Anal.* Calcd. for  $C_{13}H_7NO_2S$ : C, 60.70; H, 2.72; S, 24.90. Found: C, 61.13; H, 2.56; S, 24.49.

#### [1,4]Oxazino[2,3,4-kl]phenothiazin-1(2H)-one (**9**).

##### Method A (Ring Closure of **5**).

A solution of 7.3 g (0.025 mole) of **5** in 25 ml of dimethylformamide was slowly added, under nitrogen, to a mixture of 1.2 g (0.025 mole) of sodium hydride (50% of dispersion in mineral oil) in 150 ml of dimethylformamide at room temperature. The mixture was heated under reflux for 4 hours, allowed to cool and filtered. The filtrate was poured into 2 liters of water and the resulting emulsion was stirred to facilitate agglomeration. The solid was dried, dissolved in boiling carbon tetrachloride (carbon) cooled and diluted with ether to give 2.1 g (33%) of **9** as white solid, mp 166-167°.

*Anal.* Calcd. for  $C_{14}H_9NO_2S$ : C, 65.88; H, 3.52; N, 5.49. Found: C, 66.00; H, 3.54; N, 5.50.

The ir spectrum of **9** displayed the anticipated very strong amide carbonyl at 5.9  $\mu$  and an absence of absorption in the -NH- region (3  $\mu$ ).

##### Method B. (Ring Closure of **3**).

A solution of 1.46 g (0.005 mole) of **3** in 8 ml of dimethylformamide was slowly added, under nitrogen, to a stirred mixture of 0.1 g of sodium hydride (50% dispersion in mineral oil) and 300 ml of dimethylformamide at 20°. The mixture was heated under reflux for 4 hours, allowed to cool and filtered. The filtrate was poured into 2 liters of water, allowed to stand overnight and filtered. The resulting solid was dissolved in 10 ml of hot carbon tetrachloride (carbon) and diluted with 30 ml of petroleum ether (bp 20-40°). A white solid was obtained which, on recrystallization from carbon tetrachloride-petroleum ether (20-40°) gave 70 mg of **9**, mp 166-167°.

*Anal.* Calcd. for  $C_{14}H_9NO_2S$ : C, 65.88; H, 3.52; N, 5.49. Found: C, 65.89; H, 3.74; N, 5.51.

Ir comparison of the products obtained *via* Methods A and B confirmed the identity of these products.

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