

Richard A. Hollins* and Angelo C. Pinto (1)

Instituto Militar de Engenharia Praia Vermelha, Rio de Janeiro ZC-82, RJ, Brasil

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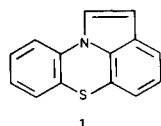
A synthesis of pyrrolo[3,2,1-*kl*]phenothiazine (**1**) is described. Electrophilic substitution of **1** leads to functionalization at the 2 position.

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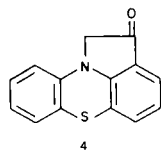
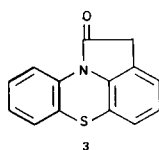
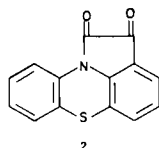
The interest in phenothiazine chemistry is evidenced by the thousands of articles pertaining to the subject and the large number of derivatives presently employed as medicinal agents (2-5).

There has been considerable interest regarding the structure-activity relationships of phenothiazines (**2**), dealing principally with steric effects in the *N*-side chain and electronic effects of ring substituents. There appears to be little interest, however, in exploring the effects of fusing additional ring systems to the phenothiazine nucleus.

An example of a 1,9-bridged phenothiazine has been synthesized (**6**) and several derivatives incorporating the 1,10 positions into six-membered rings have been reported (5,7-11), but pyrrolo[3,2,1-*kl*]phenothiazine (**1**) has not yet been reported despite its interesting structure of combined phenothiazine and indole moieties.



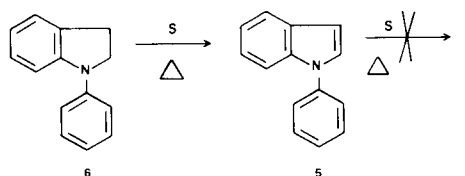
Two oxodihydro derivatives of this system are known, **2** (**6**) and **3** (**12**), and the attempted synthesis of a third (**4**) has been reported (13).



Our initial efforts to synthesize **1** were directed toward the reduction of **2**. Isatin derivatives are reduced with lithium aluminum hydride (14) or diborane (15) giving the corresponding indoles, but under the same conditions, **2** led to complex mixtures of products without the detectable formation of **1**.

The classical synthesis of phenothiazines of heating diphenylamines with sulfur was applied to *N*-phenylindole (**5**), but only resulted in recovery of starting material. Utilizing the same reaction conditions with *N*-phenylindoline (**6**) only led in aromatization to **5**. (Scheme I).

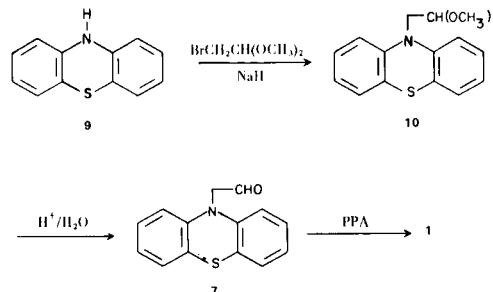
Scheme I



Despite the reported failure to cyclize phenothiazine-10-acetic acid and the corresponding acid chloride (**13**), we decided to study the possible cyclizations of the corresponding aldehyde (**7**) and nitrile (**8**).

The synthesis of **7** was readily accomplished by alkylation of phenothiazine (**9**) with bromoacetaldehyde dimethylacetal and sodium hydride in dioxane at reflux, followed by hydrolysis of the obtained acetal (**10**) in aqueous acetone. Treatment of a chloroform solution of **7** with polyphosphoric acid (PPA) at room temperature resulted in cyclization to **1** in 84% yield (Scheme II).

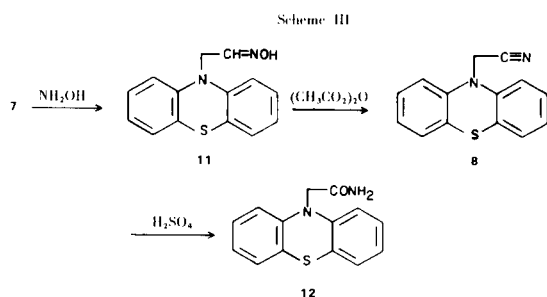
Scheme II



The spectral properties of **1** are clearly in accord with its assigned structure. The pmr spectrum of **1** presents a complex multiplet from δ 6.40 to δ 7.15 and a pair of doublets (AX pattern) at δ 7.3 ($J = 3$ Hz) and δ 6.35 ($J = 3$ Hz) corresponding to the two protons of the pyrrole ring, positions 1 and 2 respectively.

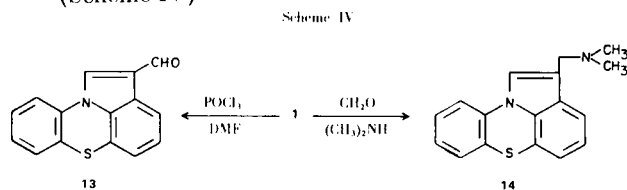
Transformation of aldehyde **7** into its oxime derivative (**11**) followed by dehydration with acetic anhydride gave nitrile **8**. Attempts to cyclize **8** with sulfuric acid only resulted in its hydrolysis to amide **12**, which failed to react further. (Scheme III).

Formylation of **1** with phosphorus oxychloride and dimethylformamide resulted in the formation of the 2-carboxaldehyde **13** in 72% yield. In the pmr spectrum of **13**, the AX quartet of **1** is replaced by a singlet (1 proton)



at δ 8.28, and that substitution occurred in the 2-position, as predicted, was readily confirmed by comparison with the pmr spectra of **1**, **5**, and *N*-phenylindole-3-carboxaldehyde. (Scheme IV).

The Mannich condensation of **1** with formaldehyde and dimethylamine afforded **14** in 78% yield. Substitution was again assigned to the 2-position, with the proton at C-1 presenting a singlet at δ 7.14 in the pmr spectrum of **14**. (Scheme IV)



The facile synthesis of **1** and its ready electrophillic substitution in the 2-position should allow easy access to many derivatives of this interesting new heterocyclic system.

EXPERIMENTAL

The ir spectra were obtained on a Perkin-Elmer model PE 137 spectrophotometer and the high resolution mass spectra on a Varian MAT CH-5 mass spectrometer. The pmr spectra were recorded on a Hitachi Perkin-Elmer R-20B nuclear magnetic resonance spectrometer. All melting points are uncorrected. Phenothiazine-10-acetaldehyde Dimethylacetal (**10**).

A stirred mixture of 30 g. of phenothiazine and 10 g. of sodium hydride (59% dispersion in oil) in 400 ml. of dry dioxane was heated at reflux until it took on a deep yellow coloration (ca. 2 hours). With continued heating, 50 ml. of bromoacetaldehyde dimethylacetal was added dropwise over a period of 2 hours, and the mixture was maintained at reflux for an additional 6 hours before destroying the excess sodium hydride with methanol. After removal of solid material by filtration, the mixture was concentrated at reduced pressure to a dark oil which was crystallized from 50 ml. of methanol giving 35 g. (82%) of yellow crystals, m.p. 62-64°. A sample recrystallized again from methanol afforded colorless crystals, m.p. 63.5-64.5° (lit. (16) 63-64°).

Phenothiazine-10-acetaldehyde (**7**).

A solution of 10 g. of **10**, 2.5 g. of *p*-toluenesulfonic acid and 5 ml. of water in 80 ml. of acetone was heated at reflux for 2 hours. After cooling, the mixture was extracted with chloroform (2 x 100 ml.). The combined chloroform extracts were washed

with a saturated solution of sodium carbonate (100 ml.) and distilled water (2 x 100 ml.), dried over magnesium sulfate and evaporated at reduced pressure. The yellow crystalline mass obtained (8.0 g., 95%) was recrystallized from ether giving yellow needles, m.p. 115-116°; ir (potassium bromide): 1720 cm^{-1} (C=O); pmr (deuteriochloroform): δ 9.75 (t, 1, CHO, $J = 1$ Hz), 6.50-7.26 (m, 8, ArH), 4.45 (d, 2, CH_2 , $J = \text{Hz}$).

Anal. Calcd. for $\text{C}_{14}\text{H}_{11}\text{NOS}$: C, 69.71; H, 4.56; N, 5.81. Found: C, 69.52; H, 4.78; N, 5.88.

Pyrrolo [3,2,1-*kl*]phenothiazine (**1**).

To a solution of 2 g. of **7** in 100 ml. of chloroform was added 30 g. of polyphosphoric acid and the two-phase system stirred at room temperature for 4 hours. The chloroform layer was separated, washed with water (2 x 100 ml.) and dried over magnesium sulfate. After evaporation at reduced pressure, the residual solid was chromatographed over silica gel with petroleum ether (30-60°) giving 1.60 g. (87%) of colorless crystals, m.p. 115-117°. A sample recrystallized from hexane gave colorless platelets, m.p. 117-118°; uv (95% ethanol): 226 nm (ϵ 30,800), 253 (30,360), 268 (12,050), 277 (10,270), 299 (4,240), 311 (5,450), 342 (9,290); pmr (deuteriochloroform): δ 7.30 (d, 1, H-1, $J = 3.0$ Hz), 6.40-7.15 (m, 7, ArH), and 6.35 (d, 1, H-2, $J = 3.0$ Hz).

Anal. Molecular Weight Calcd. for $\text{C}_{14}\text{H}_9\text{NS}$: 223.0456. Found (high resolution mass spectrum): 223.0463.

Anal. Calcd. for $\text{C}_{14}\text{H}_9\text{NS}$: C, 75.30; H, 4.06; N, 6.27. Found: C, 75.08; H, 4.17; N, 6.16.

Oxime of Phenothiazine-10-acetaldehyde (**11**).

A mixture of 4 g. of **7**, 3 g. of hydroxylamine hydrochloride, 3 g. of potassium carbonate, 10 ml. of water and 65 ml. of 95% ethanol was heated at reflux for 2 hours, then cooled and extracted with ether (2 x 75 ml.). The combined extracts were dried over magnesium sulfate and evaporated giving 3.2 g. (75%) of colorless crystals. Recrystallization from chloroform-carbon tetrachloride (1:1) gave colorless needles, m.p. 173-174°; ir (potassium bromide): 3200 cm^{-1} (OH); pmr (deuteriochloroform-DMSO- d_6): δ 11.3 (s, 1, NOH), 6.62-7.30 (m, 9, ArH + $\text{C/H} = \text{N}$), 4.69 (d, 2, CH_2 , $J = 4.0$ Hz).

Anal. Calcd. for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{OS}$: C, 65.60; H, 4.72; N, 10.93. Found: C, 65.70; H, 4.66; N, 10.87.

Phenothiazine-10-acetonitrile (**8**).

A solution of 2 g. of **11** in 30 ml. of acetic anhydride was heated at reflux for 20 minutes. After cooling, the mixture was poured over 25 g. of crushed ice. The precipitate was filtered, washed with water and air dried giving 1.49 g. (80%) of off-white solid. Recrystallization from hexane gave colorless needles, m.p. 116-117°; ir (potassium bromide): 2240 cm^{-1} (C \equiv N); pmr (deuteriochloroform): δ 6.72-7.30 (m, 8, ArH) and 4.48 (s, 2, CH_2).

Anal. Calcd. for $\text{C}_{14}\text{H}_{10}\text{N}_2\text{S}$: C, 70.56; H, 4.23; N, 11.76. Found: C, 70.61; H, 4.33; N, 11.81.

Phenothiazine-10-acetamide (**12**).

A solution of 0.28 g. of **8** in 10 ml. of concentrated sulfuric acid (d 1.84) was allowed to stand at room temperature for 10 hours. The mixture was then diluted with 25 ml. of water and extracted with chloroform (3 x 30 ml.). The combined extracts were washed with a saturated solution of sodium carbonate (2 x 50 ml.), water (3 x 50 ml.) and then dried over magnesium sulfate. The chloroform was evaporated to a reddish solid which upon washing with ether gave 0.26 g. (88%) of a white solid. Recrystallization from methanol gave colorless needles, m.p. 237° sub.; ir

(potassium bromide): 3475 and 3190 cm^{-1} (NH_2) and 1660 cm^{-1} ($\text{C}=\text{O}$); pmr (DMSO- d_6): δ 6.60-7.30 (m, 10, ArH and NH_2) and 4.39 (s, 2, CH_2).

Anal. Calcd. for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{OS}$: C, 65.60; H, 4.72; N, 10.93. Found: C, 65.51; H, 4.98; N, 10.56.

Pyrrolo[3,2,1-*kl*]phenothiazine-2-carboxaldehyde (13).

To 1.53 g. of freshly distilled phosphorus oxychloride was slowly added (30 minutes) 5 g. of freshly distilled dimethyl formamide. To this mixture was slowly added (1 hour) with stirring a solution of 1.12 g. of **1** in 10 ml. of dimethylformamide. After stirring at room temperature for an additional 1.5 hours, 10 g. of crushed ice was added, the mixture stirred for 30 minutes, and then 10 ml. of water was added with rapid stirring. One third of a solution of 3.75 g. of sodium hydroxide in 10 ml. of water was added dropwise and then the remaining two thirds added rapidly. The resulting suspension was heated to boiling, cooled and then left overnight in a refrigerator. The precipitate was collected, resuspended in 35 ml. of water, filtered, washed with water (3 x 30 ml.) and air dried giving 1.25 g. (71%) of a yellow solid. Recrystallization of a sample from carbon tetrachloride gave yellow crystals, m.p. 193° dec.; uv (95% ethanol): 248 nm (ϵ 31,950) and 373 (10,770); ir (potassium bromide): 3100 cm^{-1} ($=\text{CH}$) and 1666 cm^{-1} ($\text{C}=\text{O}$); pmr (DMSO- d_6): δ 10.05 (s, 1, CHO), 8.28 (s, 1, H-1), 6.75-7.82 (m, 7, ArH).

Anal. Molecular Weight Calcd. for $\text{C}_{15}\text{H}_9\text{NOS}$: 251.0404. Found (high resolution mass spectrum): 251.0416.

Anal. Calcd. for $\text{C}_{15}\text{H}_9\text{NOS}$: C, 71.69; H, 3.61; N, 5.57. Found: C, 71.46; H, 3.61; N, 5.49.

2-Dimethylaminomethyl-pyrrolo[3,2,1-*kl*]phenothiazine (14).

A solution of 0.3 g. of **1**, 1 ml. of 40% aqueous dimethylamine, 0.15 ml. of 40% aqueous formaldehyde and 1.4 ml. of glacial acetic acid in 5 ml. of dioxane was heated at 80°. The addition of 1 drop of 40% aqueous formaldehyde at half hour intervals continued until the indicated the total consumption of **1** (ca. 3 hours). The solution was diluted with 10 ml. of water, 4 drops of concentrated hydrochloric acid added and the mixture extracted with ether (2 x 10 ml.). The aqueous phase was basified with solid sodium carbonate, extracted with ether (2 x 20 ml.) and the combined ether extracts dried over magnesium sulfate and evaporated at reduced pressure to an oil. Crystallization in heptane afforded 0.29 g. (78%) of colorless crystals, m.p. 66-67°; pmr (deuteriochloroform): δ 7.14 (s, 1, ArH), 7.1-6.3 (m, 7, ArH), 3.35 (s, 2, CH_2), 2.16 (s, 6, CH_3).

Anal. Molecular Weight Calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{S}$: 280.1034.

Found: (high resolution mass spectrum): 280.1028.

Anal. Calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{S}$: C, 72.82; H, 5.75; N, 9.99. Found: C, 72.48; H, 5.45; N, 9.93.

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