

PENTACYCLIC PHENOTHIAZINES I. CONSTRUCTION OF THE PYRIDO[3',4':4,5]PYRROLO[3,2,1-kl]PHENOTHIAZINE RING SYSTEM VIA SELECTIVE METALLATION OF A 2-SUBSTITUTED-PYRROLO[3,2,1-kl]PHENOTHIAZINE

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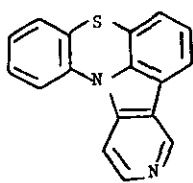
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Abstract - A new pentacyclic heterocycle, 3-benzyl-1,2,3,4-tetrahydro-4H-pyrido[3',4':4,5]pyrrolo[3,2,1-kl]phenothiazin-4-one (2), the first known example of the pyrido[3',4':4,5]pyrrolo[3,2,1-kl]phenothiazine ring system (1) has been prepared in seven steps beginning with pyrrolo[3,2,1-kl]phenothiazine (3). Key to the success of the synthesis is the selective metallation, and subsequent alkylation with ethylene oxide, of 2-[2-pyrrolo[3,2,1-kl]phenothiazinyl]-4,4-dimethyl-2-oxazoline (10).

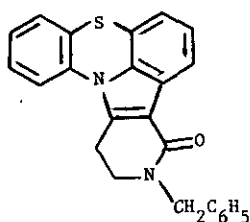
As part of our ongoing program directed toward the synthesis of analogues of the phenothiazine antipsychotic drugs containing conformational restriction in the side chain^{1,2}, we have sought to prepare hexahydro derivatives of the pyrido[3',4':4,5]pyrrolo[3,2,1-kl]phenothiazine ring system (1). This report describes the synthesis of the first representative of this pentacyclic system, namely, 1-benzyl-1,2,3,4-tetrahydro-4H-pyrido[3',4':4,5]pyrrolo[3,2,1-kl]phenothiazin-4-one (2).

The general strategy selected for the synthesis of 2 involved fusion of the 2-pyrido ring system onto the 1,2-positions of the readily available^{3,4} pyrrolo[3,2,1-kl]phenothiazine (3). The choice of a protected 2-carboxyl derivative, of 3 (the oxazoline derivative 10) served a dual purpose; i.e., (1) to direct selective metallation and subsequent alkylation (with ethylene oxide) at the 1-position to form 12 and (2) to provide a functional group for cyclization to the lactone 13, the immediate precursor to 2. This synthesis is patterned after the one recently employed by Ellefson and Prodan⁵ for the preparation of 1,2,3,4-tetrahydro-1-benzothieno[2,3-h]isoquinoline.

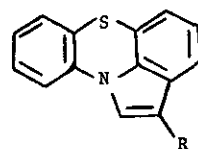
We have recently shown that pyrrolo[3,2,1-kl]phenothiazine (3) metallates with approximately equal facility at the 1- and 10-positions⁶. Thus, a mixture containing the 1- and 10-formyl- and the 1,10-diformyl-derivatives (6,7 and 8) was obtained on treatment of 3 with a three-fold excess of n-butyl lithium in ether, followed by reaction with N,N-dimethylformamide. Treatment of 3 with four equivalents of n-butyl lithium in ether, followed by quenching with deuterium oxide gave 1,10-dideuteropyrrolo[3,2,1-kl]phenothiazine 9. The structure of 9, and hence the sites of metallation of 3, was confirmed by comparison of the ¹H and ¹³C nmr spectra of 3 and 9.⁶⁻⁸



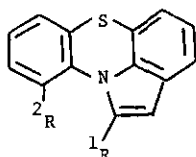
1



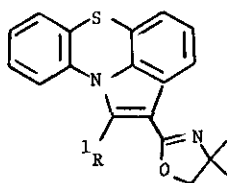
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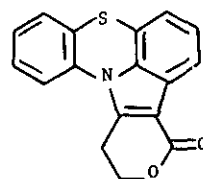
3 R = H
 4 R = COCF₃
 5 R = CO₂H



6 1R = CHO, 2R = H
 7 1R = H, 2R = CHO
 8 1R = 2R = CHO
 9 1R = 2R = D



10 1R = H
 11 1R = D
 12 1R = CH₂CH₂OH



13

The 4,4-dimethyl- Δ^2 -oxazoline functionality has been effectively utilized for the regioselective ortho lithiation and subsequent substitution of benzenes^{9,10} and pyridines¹¹. It was reasoned that the powerful ortho directing influence of this heterocycle could also be employed to effect selective lithiation of the pyrrolo[3,2,1-k]phenothiazine system. Indeed, treatment of the aryloxazoline 10 with an excess of n-butyl lithium in ether at 25°C followed by quenching with deuterium oxide gave exclusively the 1-deutero-derivative 11, as was confirmed by comparison of the 250 MHz ¹H nmr spectra of 10 and 11. The spectra were identical with the exception that, the signal for the 1-proton (a broadened singlet at 8.05 ppm) of 10 and the broadening of the signal observed for the 10-proton (a doublet of doublets at 7.19 ppm) in 10, disappeared in 11. Presumably the broadening of these signals is due, at least in part, to long range coupling between the 1- and 10-protons in 10, which disappears in the 1-deutero-derivative. As expected, irradiation of the resonance for the 1-proton of 10 caused the broadening of the signal at 10-position to disappear. Assignment of the entire ¹H nmr spectrum of 10, determined with the aid of selective decoupling experiments and comparison to the known spectra of 3 and 9^{6,7}, appears in the Experimental. Reaction of the 1-lithio-derivative of 10 with ethylene oxide gave the 2-hydroxyethyl compound 12. The latter compound was cyclized to the lactone 13 in routine fashion. When heated with benzylamine, 13 was converted

directly to the title compound 2. The oxazoline 10 was obtained from the corresponding acid 5 according to established procedures. Compound 5 was prepared by alkaline hydrolysis of the 2-trifluoroacetyl derivative (4) which, in turn, was obtained by a Friedel-Crafts type of acylation of 3. Hollins and Pinto³ had previously shown that electrophilic reagents (e.g., Vilsmeier and Mannich) preferentially attack the 2-position of 3 as expected.

EXPERIMENTAL

Infrared spectra were obtained on a Beckman IR-33 spectrophotometer. Nuclear magnetic resonance spectra were recorded on an EM-360 Varian 60 MHz or, in the case of compounds 10 and 11, on a Bruker WM 250 MHz spectrometer using tetramethylsilane as an internal standard.

2-Trifluoroacetylpyrrolo[3,2,1-kl]phenothiazine (4). To a solution of 2.23 g (10 mmol) of pyrrolo[3,2,1-kl]phenothiazine (3) in 40 ml of dry dimethylformamide was added 4.20 g (20 mmol) of trifluoroacetic anhydride at 0°C. The solution darkened, and after approximately 2 hours a yellow solid began to precipitate. The reaction mixture was allowed to warm, and after it stood 2 additional hours at 25°C, water (100 ml) was added. The solid was collected on a filter, washed several times with cold water and then dried *in vacuo* at 100°C for 10 hours. Recrystallization of the dried yellow solid from toluene gave 2.3 g (72%) of 4 as thin yellow needles; m.p. 198–199°C; ir (KBr): ν 1660 cm⁻¹ (C=O); nmr (CDCl₃): δ 8.25 (s, 1H, C-1 aromatic proton), 6.84–7.88 (m, 7H, remaining aromatic protons). Anal. calcd. for C₁₆H₈F₃NOS: C, 60.19; H, 2.53; N, 4.39. Found: C, 60.45; H, 2.47; N, 4.41.

Pyrrolo[3,2,1-kl]phenothiazine-2-carboxylic Acid (5). Compound 4 (2.3 g, 7.2 mole) was suspended in a solution containing 20 ml of methanol and 20 ml of 20% aqueous sodium hydroxide solution and the mixture was refluxed for 6 hours. The clear solution was then cooled to 0–5°C and acidified with conc. hydrochloric acid. The solid which formed was collected on a filter, washed several times with cold water and dried for 12 hours *in vacuo* at 100°C to give 1.8 g (94% crude yield) of 5 as a pale green amorphous powder; m.p. 300–301°C; ir (KBr): ν 2400–3315 cm⁻¹ (broad series, CO₂H), 1657 cm⁻¹ (C=O). It was not possible to obtain an nmr spectrum of 5 in deuteriochloroform, or a satisfactory elemental analysis of it, due to poor solubility in organic solvents.

Pyrrolo[3,2,1-kl]phenothiazine Carbonylchloride. The acid 5 (1.7 g, 6.4 mmol) was suspended in 25 ml of carbon tetrachloride and 1.27 g (10 mmol) of oxalyl chloride was added. The mixture was refluxed for 5 hours and then the excess oxalyl chloride and solvent were removed *in vacuo* (water aspirator), leaving 1.43 g (78%) crude yield) of the acid chloride as a pale green solid; m.p. 213–4°C; ir (KBr): ν 1714 cm⁻¹ (C=O). This compound was used, without further purification, in the next step.

2-[2-Pyrrolo[3,2,1-kl]phenothiazinyl]-4,4-dimethyl-2-oxazoline (10). To a suspension of 1.4 g (4.9 mmol) of pyrrolo[3,2,1-kl]phenothiazinecarbonyl chloride in 40 ml of methylene chloride was added 0.67 g (7.5 mmol) of 2-amino-2-methyl-1-propanol and the mixture was refluxed for 5 hours. During this time the acid chloride slowly dissolved and a white solid later began to precipitate. After the reaction mixture was cooled to 25°C,

it was filtered and the solid collected, washed with cold methylene chloride and dried *in vacuo* at 100°C to give 1.6 g (70% crude yield) of the intermediate hydroxy amide as an amorphous cream-colored powder; m.p. 192-194°C; ir (KBr): ν 3317 cm^{-1} (OH); 1607 cm^{-1} (C=O); nmr (CDCl₃): δ 8.03 (s, 1H, C-1 aromatic proton), 7.25-6.65 (m, 7H, remaining aromatic aromatic protons), 3.68 (s, 2H, CH₂), 1.42 (s, 6H, CH₃). The hydroxyamide derivative without further purification was refluxed with 4 ml of phosphorus oxychloride for 2 hours. The solution was cooled and 25 ml of ether was added causing precipitation of the hydrochloride of 10. The salt was collected (crude m.p. 250°C), suspended in water and the mixture basified with conc. ammonium hydroxide. The solid was then collected on a filter, dried in air at 25°C overnight and chromatographed on silica (3:1 toluene/ethyl acetate) to give 0.61g (58%) of the oxazoline 10 as rhombic yellow crystals; m.p. 151-153°C; ir (KBr): ν 1625 cm^{-1} (C=N), 1272 cm^{-1} (C-O); nmr (CDCl₃): δ 8.05 (s, aryl 1-H), 7.62 (dd, J_{3,4}=8.1 Hz, J_{3,5}=0.8 Hz, aryl 3-H), 7.19 (dd, J_{9,10}=7.9 Hz, J_{8,10}=1.2 Hz, aryl 10-H), 7.05 (dd, J_{7,8}=7.0 Hz, J_{7,9}=2.0 Hz, aryl 7-H), 6.98 (dd, J_{3,4}=8.1 Hz, J_{4,5}=7.0 Hz, aryl 4-H), 6.95 (dt, J_{9,10}=7.9 Hz, J_{8,9}=7.9 Hz, J_{7,9}=2.0 Hz, aryl 9-H), 6.89 (dq, J_{8,9}=7.9 Hz, J_{7,8}=7.0 Hz, J_{8,10}=1.2 Hz, aryl 8-H), 6.67 (dd, J_{4,5}=7.0 Hz, J_{3,5}=0.8 Hz, aryl 5-H), 4.07 (s, 2H, OCH₂), 1.40 (s, 6H, CH₃). Anal. calcd. for C₁₉H₁₆N₂OS: C, 71.22; H, 5.03; N, 8.74. Found: C, 71.22; H, 5.13; N, 8.62.

2-[1-Deutero-2-pyrrolo[3,2,1-k]phenothiazinyl]-4,4-dimethyl-2-oxazoline (11). To a solution of 0.16 g (0.5 mmol) of 10 in dry ether was added 4.5 ml of 1.65 N n-butyllithium (0.75 mmol) at room temperature under an argon atmosphere. After 5 hours excess deuterium oxide was added and the mixture was stirred an additional 4 hours. Dilute hydrochloric acid was then carefully added until the reaction was neutral and the ether phase was separated, washed with water and dried (anhydrous magnesium sulfate). Evaporation of the solvent left a crystalline residue which was chromatographed on silica (3:1 toluene/ethylacetate) to give 0.15 g of a 2:1 mixture of 10 and 11 according to nmr (ratio of C-1 to C-3 aryl protons). Repetition of the procedure using a 2 fold molar excess of n-butyllithium gave 11 uncontaminated with 10, m.p. 152-153°C. The ¹H nmr spectrum of 11 was virtually identical to that of 10 with the exception that the singlet for the C-1 aryl proton at 8.05 ppm in 10 was absent in 11.

2-[1-(2-Hydroxyethyl)-pyrrolo[3,2,1-k]phenothiazin-2-yl]-4,4-dimethyl-2-oxazoline (12). To a solution of 0.64 g (2 mmol) of 6 in 40 ml of dry ether was added 2.2 ml of 1.65 N n-butyllithium (3.5 mmol) at 25°C. After two hours, an excess (approximately 1 ml) of ethylene oxide (condensed in a vial cooled to -70°C in an acetone/dry ice bath) dissolved in 5 ml of ice cold dry ether was transferred to the reaction flask which had previously been cooled to 0°C in an ice/salt bath. The reaction mixture was allowed to warm to 25°C and stirred at that temperature for 8 hours. It was then quenched with 50 ml of water and the ether layer was separated, dried (anhydrous magnesium sulfate) and condensed *in vacuo* (rotary evaporator) to give a pale yellow oil. The oil was chromatographed on silica (4:1 toluene/ethyl acetate) to give 0.46 g (65%) of 12 as a pale yellow crystalline solid, m.p. 126-127°C; ir (KBr): ν 3250 cm^{-1} (broad, OH), 1625 cm^{-1} (C=N); nmr (CDCl₃): δ 6.60-7.50 (m, 7H, aromatic), 4.16 (t, 2H, J=4.8Hz, CH₂OH), 4.07 (s, 2H, ring CH₂), 3.53 (t, 2H, J=4.8 Hz, ArCH₂),

1.33 (s, 6H, CH₃). Anal calcd for C₂₁H₂₀N₂O₂S: C, 69.21; H, 5.53; N, 7.69. Found: C, 68.67; H, 5.64; N, 7.51.

1,2-Dihydro-4H-pyrano[3',4':4,5]pyrrolo[3,2,1-kl]phenothiazin-4-one (13). The alcohol 12 (0.2 g, 0.57 mmol) was heated to reflux temperature in 25 ml of 6 N hydrochloric acid solution and then allowed to cool to 25°C and stand for 2 hours. The reaction mixture became a deeply yellow colored solution on the addition of acid and then a white precipitate slowly formed. The precipitate was collected on a filter, washed with water and dried *in vacuo* at 100°C, to yield 0.14 g (84%) of 13 as a white crystalline solid, which was essentially insoluble in organic solvents; m.p. 255-257°C; ir (KBr): ν 1705 cm⁻¹ (C=O). Anal. calcd. for C₁₇H₁₁N₂O₂S: C, 69.61; H, 3.78; N, 4.77. Found: C, 69.10; H, 3.74; N, 4.70.

3-Benzyl-1,2,3,4-tetrahydro-4H-pyrido[3',4':4,5]pyrrolo[3,2,1-kl]phenothiazin-4-one (2). The lactone 13 (0.3 g, 1 mmol) was heated together with an excess of benzylamine (5 ml) at 100°C for 8 hours. The reaction mixture was then cooled and rapidly chromatographed on silica using 4:1 toluene/ethyl acetate as an eluent to remove the excess benzylamine. The somewhat crude material that remained after the solvents were removed (rotary evaporator) was rechromatographed on silica (10:1 toluene/ethyl acetate) to give 0.241 g (62%) of 2 as a white crystalline solid; m.p. 167-168°C; ir (KBr): ν 1625 cm⁻¹ (C=O); nmr (CDCl₃): δ 6.67-7.78 (m, 12H, aromatic, including 5H for benzyl at 7.30), 4.70 (s, 2H, CH₂); 3.42 (m, 4H, CH₂CH₂). Anal. Calcd. for C₂₄H₁₈N₂O₂S: C, 75.37; H, 4.74; N, 7.32. Found: C, 75.69; H, 4.78; N, 7.27.

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