A Synthesis of 5-Oxo-1,2,3,4-Tetrahydro[1,4]azepino-[6,7,1-*kl*]phenothiazine

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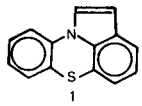
Received July 26, 1982

A synthesis of a new heterocyclic system (5) is described starting from 1-carbomethoxyphenothiazine

J. Heterocyclic Chem., **20**, 467 (1983).

In a previous paper (1) we described the synthesis of the heterocyclic system pyrrolo[3,2,1-*kl*]phenothiazine (**1**) by cyclization of phenothiazine-10-acetaldehyde with polyphosphoric acid (PPA) in chloroform.



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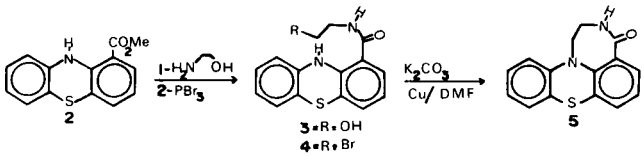
The classical approach to synthesis of phenothiazine derivatives with a ring between C-1 and C-10 is based on the alkylation of the nitrogen atom followed by ring closure under Friedel-Crafts conditions (2-4).

In this communication we wish to report the synthesis of a new heterocyclic system 5-oxo-1,2,3,4-tetrahydro[1,4]-azepino[6,7,1-*kl*]phenothiazine using a different approach to form the ring between carbons 1 and 10 of phenothiazine nucleus, starting from 1-carbomethoxyphenothiazine (**2**) (5) as shown in Scheme I.

Scheme 1



2 5

Condensation of **2** with ethanolamine in dry ethanol yielded, as the only product, amide **3** in 93% yield. The structure of this new product was confirmed by ^{1}H nmr and ir spectral data. The nmr spectrum of **3** shows the two methylene groups as a multiplet between δ 3.25 and 3.76. The ir spectrum displays absorptions at 3250 (OH) and 1630 (C=O) cm^{-1}.

Compound **3**, on reaction with phosphorus tribromide in refluxing benzene, afforded in 95% yield bromide **4**, which isolated without further purification was converted to **5** in 84% yield after treatment with copper dust in dimethylformamide in the presence of potassium carbonate.

The nmr spectrum of **5** presents a broad singlet at δ 3.4 exchangeable with deuterium oxide (1H, N-H), a pair of doublets at δ 7.40 (1H, J = 7.5 and 2.5 Hz, Ar-H), a complex multiplet from δ 6.43 to 7.02 (6H, Ar-H), and an A_2B_2 pattern between δ 3.98 and 4.42 corresponding to the two methylene groups of the azepin ring. The ir spectrum of **5** shows absorptions at 3450 (N-H) and 1650 cm^{-1} (C=O). The spectral properties of **5** are clearly in accord with its assigned structure.

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 nmr spectra were recorded on a Hitachi-Perkin-Elmer R-20B nuclear magnetic resonance spectrometer. All melting points are uncorrected.

2-Hydroxymethyl-1-phenothiazinecarboxyamide (**3**).

A solution of **2** (2.0 g, 7.78 mmoles) in ethanolamine (15 ml) and dry ethanol (80 ml) was heated at reflux for 5 hours. The solution was diluted with 15 ml of water and extracted with benzene (3 × 50 ml). The combined benzene extracts were washed with a saturated solution of sodium chloride (3 × 50 ml), water (2 × 50 ml) and then dried over magnesium sulfate and evaporated at reduced pressure giving 2.06 g (93%) of a yellow oil; ir (film): 3250 (OH), 1630 (C=O), 1280 (C-OH) and 1070 cm^{-1} (C-OH); ^{1}H nmr (deuteriochloroform): δ 3.12 (broad, s, 1, O*H*), 3.25-3.76 (m, 5, C*H*$_2$-C*H*$_2$ and CON-*H*), 6.30-7.08 (m, 7, Ar-*H*) and 9.74 (broad, s, 1, N-*H*).

Anal. Calcd. for $C_{15}H_{14}N_2O_2S$: C, 62.92; H, 4.93; N, 9.78. Found: C, 62.96; H, 4.86; N, 9.82.

2-Bromoethyl-1-phenothiazinecarboxyamide (**4**).

A solution of **3** (1.2 g, 4.2 mmoles) and phosphorus tribromide (3 ml) in benzene (100 ml) was boiled under reflux for 1 hour. After the solution has been cooled to 0°, water (50 ml) was added. The benzene layer was separated and the aqueous layer was extracted with benzene (2 × 50 ml). The combined benzene extracts were washed with water and then concentrated at reduced pressure to give 1.39 g (95%) of a yellow solid. This was satisfactory for use in the next step without further treatment. However, a sample was recrystallized from ethanol to give yellow crystals; mp 115-117°; ir (potassium bromide): 3450 (N-H) and 1650 cm^1 (C=O); ^{1}H nmr (deuteriochloroform): δ 3.35-3.57 (m, 5, CH$_2$-C*H*$_2$ and CON*H*) 6.58 (broad, s, 1, N-*H*) and 6.74-7.23 (m, 7, Ar-*H*).

Anal. Calcd. for $C_{15}H_{13}BrN_2OS$: C, 51.59; H, 3.75; N, 8.02. Found: C, 51.62; H, 3.79; N, 8.10.

5-Oxo-1,2,3,4-tetrahydro[1,4]azepin[6,7,1-*kl*]phenothiazine (**5**).

A mixture of **4** (0.8 g, 2.3 mmoles), potassium carbonate (0.6 g) and copper in dust (0.1 g) in dimethylformamide (100 ml) was refluxed for 12 hours. The cooled reaction mixture was filtered and a mixture of ethanol-ether (200 ml, 1:1) was added to the filtrate. The solution was concentrated to one third of the original volume and allowed to stand overnight in the refrigerator. The solid was collected and washed several times with a fresh cold mixture of hexane-ether (3:1). Recrystallization of the crude product from ethanol-ether (1:1) formed yellow crystals, mp 162-164° (0.52 g, 84%); ir (potassium bromide): 3450 (N-H) and 1650 cm^{-1} (C=O); ^1H nmr (deuteriochloroform + pyridine-d_5): δ 3.4 (1H, N-H, exchangeable with deuterium oxide), 8.98-4.42 (m, 4, CH_2-CH_2), 6.43-7.02 (m, 6, Ar-H) and 7.40 (dd, 1, J = 7.5 and 2.5 Hz, Ar-H).

Anal. molecular weight Calcd. for $C_{15}H_{12}N_2OS$: 268.0668. Found (high resolution mass spectrum): 268.0662.

Anal. Calcd. for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44. Found: C, 67.19; H, 4.62; N, 10.41.

Acknowledgment.

We thank the Secretary of Planning (FINEP), the National Council of Scientific and Technological Development (CNPq) and the Research Council of the Federal University of Rio de Janeiro for support of this work.

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