Kurze Mitteilungen

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Some Reactions on 2-Chloroacethylphenothiazine *

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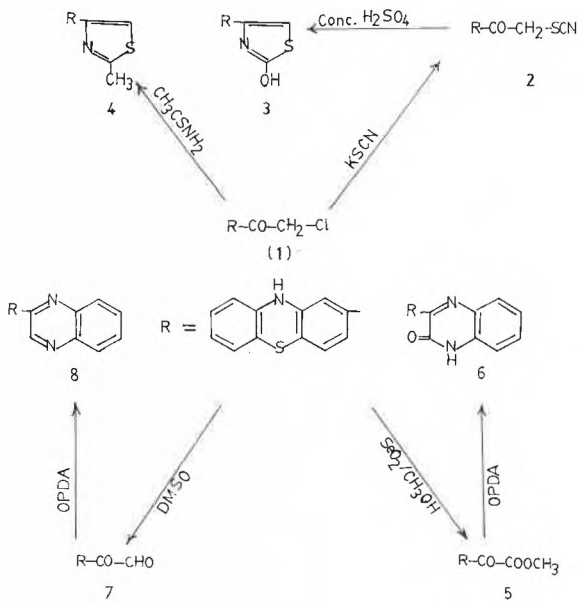
Abstract:

The possibility of using 2-chloroacetylphenothiazine (**1**) for the synthesis of thiazole moieties has been studied. In addition, we have investigated the convertion of **1** to methyl phenothiazine-2-glyoxylate (**5**) and phenothiazine-2-glyoxaldehyde (**7**) by the action of SeO_2/CH_3OH and dimethylsulphoxide respectively.

The interesting pharmacological properties of phenothiazine prompted us to introduce new substituents into this molecule. One of these variations is the introduction of heterocyclic moieties in the 2-position of the phenothiazine [1]. Therefore, we studied the possibility of using 2-chloroacetylphenothiazine (**1**) to synthesize a thiazole system containing in the 4-position a phenothiazin-2-yl group.

Thus, 2-chloroacetylphenothiazine (**1**), prepared according to methode of *Burger & Clements* [2], readily condenses with potassium thiocyanate in ethanol to give 2-(thiocyanato-acetyl)-phenothiazine (**2**). Treat-



Scheme 1

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ment of 2 with concentrated sulphuric acid gave 2-(2-hydroxy-4-thiazolyl)-phenothiazine (**3**). The IR spectrum of **3** showed absorption bands at 3100 (OH), 3310 (NH) and at 1590 cm^{-1} (thiazole moiety).

Compound **1** reacts readily with thioacetamide in boiling alcohol to give 2-(2-methyl-4-thiazolyl)-phenothiazine (**4**). It may be mentioned its isomer, 2-(4-methyl-2-thiazolyl)-phenothiazine, was synthesized by Rhône-Poulenc [3]. Structure **4** was established through its analysis and IR spectrum, which showed peaks at 1590 (thiazole moiety), 3360 (NH) and at 1480, 1360 cm^{-1} (CH_3).

Methylphenothiazine-2-glyoxylate (**5**) was synthesized by oxidation of 2-chloroacetylphenothiazine (**1**) with selenium dioxide in absolute methanol according to the synthesis of ethyl phenylglyoxylate [4]. Compound **5** was not obtained in crystalline form and was therefore characterized as its quinoxalinone derivative **6**, the 2-(2-oxo-1,2-dihydro-3-quinoxalinyl)-phenothiazine (**6**), made by condensation of o-phenylenediamine (OPDA) with **5**. The IR spectrum of the quinoxalinone derivative **6** showed absorptions at 1615 (C=O amide) and at 3360 cm^{-1} (NH), any signal of the starting ester is absent. Its mass spectrum shows the molecular ion M^+ at m/e 343 which is in good agreement with the proposed structure.

The use of 2-chloroacetylphenothiazine (**1**) for the synthesis of phenothiazine-2-glyoxylaldehyde (**7**) was studied. This glyoxylaldehyde **7** was obtained in crystalline form by the action of dimethylsulphoxide on **1**, according to *Saikachi*'s procedure [5]. Treatment of **7** with o-phenylenediamine afforded 2-(2-quinoxalinyl)-phenothiazine (**8**). The thiosemicarbazone derivative of **7** was prepared by reacting it with thiosemicarbazide. The IR spectrum of **7** shows at 1580 (aldehydic group) and at 1610 cm^{-1} (C=O), while in **8** these signals could not be seen.

Experimental

Melting points (uncorrected) were taken in open capillary tubes by the use of *Gallenkamp* electric melting point apparatus. Infrared spectra were performed on Pye Unicam Infracord Spectrophotometer model SP 2000 using KBr. The mass spectrum was taken on an A.E.I. MS 9 instrument.

*2-(Thiocyanato-acetyl)-phenothiazine (**2**):*

A solution of 2-chloroacetylphenothiazine (**1**) (2.75 g, 10 mmole) in ethanol (40 ml) was added to a solution of potassium thiocynate (1.54 g; 14 mmole) in ethanol (5 ml). The mixture was heated for an hour with stirring on a boiling steam bath. The precipitate was isolated by filtration and recrystallized from benzene to give **2** as orange crystals, m.p. 215–216 °C (quantitative yield).

Analysis: $C_{15}H_{10}N_2OS_2$ (298.39)
required: C: 60.38; H: 3.38; S: 21.49
found: C: 60.64; H: 3.48; S: 21.67.

*Cyclization of **2**: 2-(2-hydroxy-4-thiazolyl)-phenothiazine (**3**):*

A mixture of **2** (2.09 g; 7 mmole) in glacial acetic acid (40 ml) and concentrated sulphuric acid (0.3 ml) was heated with stirring for 30 minutes on a steam bath and then cooled. The precipitate was recrystallized from isopropanol-benzene mixture (1:1) to give **3** as yellow-brown crystals, m.p. 300 °C (90% yield).

Analysis: $C_{15}H_{10}N_2OS_2$ (298.39)
required: C: 60.38; H: 3.38; S: 21.49
found: C: 60.72; H: 3.13; S: 20.99.

*2-(2-Methyl-4-thiazolyl)-phenothiazine (**4**):*

A solution of 2-chloroacetylphenothiazine (**1**) (0.83 g; 3 mmole) and thioacetamide (0.23 g; 3 mmole) in ethanol (20 ml) was heated with stirring on a steam bath for an hour, and then cooled. The precipitate formed was recrystallized from ethanol to give **4** as yellow crystals, m.p. 183 °C (quantitative yield).

Analysis: $C_{16}H_{12}N_2S_2$ (296.42)
required: C: 64.83; H: 4.08; S: 21.64
found: C: 64.62; H: 4.28; S: 21.33.

*2-(2-Oxo-1,2-dihydro-3-quinoxalinyl)-phenothiazine (**6**):*

A mixture of 2-chloroacetylphenothiazine (**1**) (13.7 g; 50 mmole), selenium dioxide (5.85 g; 50 mmole) and absolute methanol (50 ml) was stirred and refluxed for 10 hours. The selenium was removed and the filtrate was evaporated, leaving methyl phenothiazine-2-glyoxylate (**5**) as an oil.

A solution of o-phenylenediamine (1 g; 10 mmole) in ethanol (20 ml) was added to one tenth of the volume of the crude glyoxylate **5** and the mixture was heated on a steam bath for 30 minutes. After dilution with water the precipitate formed was crystallized from benzene to give **6** as brown-red crystals, m.p. 206 °C (60% yield).

Analysis: $C_{20}H_{13}N_3OS$ (343.41)
required: C: 69.95; H: 3.82; N: 12.24
found: C: 70.25; H: 3.65; N: 12.47.

*Phenothiazine-2-glyoxylaldehyde (**7**):*

A solution of 2-chloroacetylphenothiazine (**1**) (0.826 g; 3 mmole) in dimethylsulphoxide (7 ml) was heated for 4 hours on a steam bath and allowed to stand overnight. After the addition of water (50 ml) the precipitate formed was recrystallized from benzene and gave red crystals, m.p. 194 °C (70% yield). Its thiosemicarbazone derivative was crystallized from alcohol, yellow crystals, m.p. 182 °C.

Analysis: $C_{14}H_9NO_2S$ (255.30)
required: C: 65.87; H: 3.55
found: C: 65.49; H: 3.73

*2-(2-Quinoxalinyl)phenothiazine (**8**):*

A solution of o-phenylenediamine (1.08 g; 0.01 mole) in ethanol (20 ml) was added to glyoxylaldehyde derivative **7** (2.55 g; 0.01 mole) in ethanol (5 ml). The mixture was heated on a steam bath for 30 minutes and then diluted with water. The crystalline mass separating was filtered off and recrystallized from ethanol to give **8** as yellow crystals, m.p. 230 °C (77% yield).

Analysis: $C_{20}H_{13}N_3S$ (327.41)
required: C: 73.37; H: 4.00; N: 12.84
found: C: 73.66; H: 4.32; N: 12.59.

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