[Contribution from the Cobb Chemical Laboratory, University of Virginia]

SOME DERIVATIVES OF PHENOTHIAZINE[1]

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In the course of synthetic experiments in the phenothiazine series, whose primary object was the designing of potential antioxidants,[3] a number of new derivatives were obtained which are reported in this article.

The Friedel and Crafts reaction with phenothiazine has been studied by Sholl and Seer (1) and by Baltzly, Harfenist, and Webb (2), who also determined the orientation in this reaction. We have chloroacetylated 10-acetylphenothiazine and have found that the chloroacetyl group enters the expected 2-position, as shown by degradation to phenothiazine-2-carboxylic acid. This compound was prepared for comparison by a simplified method. 2-Chloroacetylphenothiazine served us in the preparation of 2-dialkylaminoacetylphenothiazine derivatives and also as a starting material in the reduction to 2-chloro-1-(phenothiazinyl)-ethanol. A similar reduction of methyl phenothiazinyl-2-carboxylate furnished phenothiazinyl-2-methanol.

Wolff-Kishner reduction of 2-acetylphenothiazine gave 2-ethylphenothiazine in good yields. Additional reactions with 2-acetylphenothiazine, such as a Mannich reaction and a Willgerodt reaction are described in the experimental part.

In connection with this work 7-acetyl-7-benzo[c]phenothiazine was subjected to a Friedel-Crafts reaction with acetyl chloride and the N-acetyl group was removed by acid hydrolysis. The position of the acetyl group in the resulting *x*-acetyl-7-benzo[*c*]phenothiazine has not yet been established.

EXPERIMENTAL[4]

2-Chloroacetyl-10-acetylphenothiazine. To a suspension of 24.1 g. (0.1 mole) of 10-acetylphenothiazine in a stirred solution of 11.2 g. (0.1 mole) of chloroacetyl chloride in 400 ml. of carbon disulfide was added 40 g. (0.3 mole) of aluminum chloride over a period of 30 minutes at 25°. After stirring for another four hours the mixture was refluxed for 2.5 hours, cooled, the solvent was decanted, and the gummy residue was decomposed with *ca.* 300 g. of ice and 10 ml. of concentrated hydrochloric acid. The light brown chloroketone was filtered, washed, and recrystallized from ethanol. The yield of colorless crystals melting at 171–172.5° (dec.), was 18.9 g. (64%).

Anal. Calc'd for $C_{16}H_{12}ClNO_2S$: C, 60.47; H, 3.81.

Found: C, 60.32; H, 3.92.

2-Chloroacetylphenothiazine. A solution of 10 g. (0.0315 mole) of 2-chloroacetyl-10-acetylphenothiazine in 100 ml. of glacial acetic acid and 25 ml. of 20% hydrochloric acid

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[2] From a Masters' degree thesis, University of Virginia, 1954.

[3] An evaluation of compounds reported here will be published by J. W. Cole.

[4] All melting points are corrected. Microanalyses by Miss Patricia L. Paynter.

was refluxed for ten minutes, cooled, and allowed to crystallize. Recrystallization of the chloroketone from benzene gave 8.0 g. (92%) of red needles melting at 198–199° (dec.).

Anal. Calc'd for $C_{14}H_{10}ClNOS$: C, 60.98; H, 3.66.

Found: C, 61.04; H, 3.65.

Phenothiazine-2-carboxylic acid. This compound had been prepared previously (2). The following modification by the Kröhnke-King method (3, 4) proved to be more advantageous in our hands.

A solution of 28.3 g. (0.1 mole) of 2, 10-diacetylphenothiazine and 25.4 g. (0.1 mole) of iodine in 50 ml. of dry pyridine was heated to 90° for one hour and then allowed to stand at 25° overnight. The dark-brown gelatinous mixture was triturated with 500 ml. of ethanol, and the yellow crystals of 2-pyridiniumacetyl-10-acetylphenothiazine iodide were filtered and washed with ether. The material was then heated at 90° with 300 ml. of 5% sodium hydroxide solution for one hour; the alkaline solution was cleared with Darco, and acidified. The yellow crystalline acid was filtered and dried in a vacuum at 60°. It melted at 270–274° (dec.). [Literature melting point, 276–277° (dec.) (2).] The yield was 12.1 g. (50%).

The *methyl ester* (m.p. 166–167°) was prepared with diazomethane. A mixture melting point with a sample of methyl phenothiazinyl-2-carboxylate prepared by an authentic method (2) showed no depression.

Proof of structure of 2-chloroacetyl-10-acetylphenothiazine. A solution of 2.93 g. (0.01 mole) of the chloroketone in 20 ml. of dry pyridine was warmed at 90° for ten minutes, cooled, and carefully treated with 75 ml. of ether. Yellow crystals of 2-pyridiniumacetyl-10-acetylphenothiazine chloride were filtered, washed with ether, and hydrolyzed with 5% sodium hydroxide solution as described above. The phenothiazine-2-carboxylic acid obtained from this reaction (yield, 1.26 g.) was esterified with diazomethane. The methyl ester (m.p. 166–167°) did not depress the melting point of a sample of methyl phenothiazinyl-2-carboxylate prepared by degradation of 2,10-diacetylphenothiazine.

Anal. Calc'd for $C_{14}H_{11}NO_2S$: C, 65.36; H, 4.31.

Found: C, 65.35; H, 4.43.

2-Chloro-1-(2-phenothiazinyl)ethanol. To a stirred suspension of 0.19 g. (0.005 mole) of lithium aluminum hydride in 100 ml. of dry ether was added portionwise 5.52 g. (0.02 mole) of 2-chloroacetylphenothiazine at 25°. After stirring for two hours the mixture was decomposed with 25 ml. of water, and the precipitated reduction product was filtered. The yield was 1.74 g. (31%). Recrystallization from benzene-ethanol furnished colorless flakes, m.p. 171–172°.

Anal. Calc'd for $C_{14}H_{12}ClNOS$: C, 60.53; H, 4.36.

Found: C, 60.59; H, 4.37.

2-Morpholinoacetylphenothiazine. A suspension of 2.75 g. (0.01 mole) of 2-chloroacetylphenothiazine, in a mixture of 2.18 g. (0.025 mole) of morpholine and 400 ml. of ethanol was shaken overnight. Filtration furnished 1.93 g. (59%) of a yellow solid which was recrystallized from ethyl acetate. It melted at 225–226° (dec.).

Anal. Calc'd for $C_{18}H_{18}N_2O_2S$: C, 66.23; H, 5.56.

Found: C, 66.02; H, 5.73.

2-Piperidinoacetylphenothiazine was prepared in an analogous manner. The yield of yellow crystals was 1.94 g. (60%). The material melted, after recrystallization from ethanol, at 190–191° (dec.).

Anal. Calc'd for $C_{19}H_{20}N_2OS$: C, 70.34; H, 6.21.

Found: C, 70.32; H, 6.15.

2-(3-Dimethylaminopropionyl)phenothiazine hydrochloride. A mixture of 7.22 g. (0.03 mole) of 2-acetylphenothiazine, 2.44 g. (0.03 mole) of dimethylamine hydrochloride, 1.80 g. (0.06 mole) of paraformaldehyde, and 50 ml. of isoamyl alcohol was refluxed for 15 minutes, allowed to cool, and the precipitated amino ketone hydrochloride was filtered. The greenish crystals weighed 6.40 g. (64%). Recrystallization from ethanol-ether gave a green material, m.p. 203–204° (dec.).

Anal. Calc'd for $C_{17}H_{19}ClN_2OS$: C, 60.97; H, 5.72.

Found: C, 60.40; H, 5.76.

Phenothiazinyl-2-methanol. To a stirred suspension of 0.38 g. (0.01 mole) of lithium aluminum hydride in 80 ml. of dry ether was added a solution of 2.57 g. (0.01 mole) of methyl phenothiazinyl-2-carboxylate in 250 ml. of dry ether. The mixture was stirred for one hour, and then cautiously decomposed with water and with 10 ml. of 10% hydrochloric acid. The ether layer was dried over sodium sulfate and evaporated leaving a residue (2.21 g., 96%) which melted at 165–175°. Several crystallizations from benzene raised the melting point to 202.5–203.5°. The yield of pure material was 0.76 g. (32%).

Anal. Calc'd for $C_{13}H_{11}NOS$: C, 68.09; H, 4.84.

Found: C, 68.00; H, 4.69.

2-Ethylphenothiazine. A mixture of 6.01 g. (0.025 mole) of 2-acetylphenothiazine, 4.15 g. (0.074 mole) of potassium hydroxide, 4.2 ml. of 64% hydrazine hydrate, and 33 ml. of ethylene glycol was refluxed for two hours. Water and ethylene glycol were distilled to b.p. 190–195° and the mixture was refluxed for four hours longer. Upon cooling a tan solid separated; ethanol (about 75 ml.) was added and the solid product was collected by filtration. Another batch of the same material was obtained from the filtrate by neutralization with hydrochloric acid. The precipitate was recrystallized from ethanol-water; it weighed 3.92 g. (69%) and melted at 128–131°. Several recrystallizations from ethanol-water mixtures raised the melting point to 135–136°.

Anal. Calc'd for $C_{14}H_{13}NS$: C, 73.97; H, 5.76.

Found: C, 73.95; H, 5.85.

β-(2-Phenothiazinyl)thioacetomorpholide. A mixture of 12.0 g. (0.05 mole) of 2-acetylphenothiazine, 2.56 g. (0.08 mole) of sulfur, and 20 ml. of morpholine was refluxed for 11 hours. The hot melt was poured into 300 ml. of ethanol, the solvent was evaporated until crystals appeared, and the thiomorpholide was allowed to crystallize at 4°. Several crystallizations from ethanol gave a yellow-orange solid, m.p. 193.5–194°. The yield was 14.3 g. (43%).

Anal. Calc'd for $C_{18}H_{18}N_2OS_2$: C, 63.13; H, 5.29.

Found: C, 62.95; H, 5.02.

Tetrachlorophenothiazine-2-carboxamide. Phenothiazine-2-carboxylic acid (18.3 g.) was added portionwise to 180 ml. of technical thionyl chloride. The mixture was allowed to stand for 45 minutes at 25° and then warmed on a steam-bath for two hours. Excess thionyl chloride was removed and the black residue was extracted continually with 500 ml. of ether. A green solid weighing 12.4 g. (41%) was filtered from the ether extract, dissolved in 170 ml. of dry dioxane, and added to 135 ml. of 28% ammonium hydroxide. After standing for two hours 12.4 g. of a light brown precipitate was collected. After several recrystallizations from ethanol it melted at 266–267° (dec.).

Anal. Calc'd for $C_{13}H_6Cl_4N_2OS$: C, 41.08; H, 1.59.

Found: C, 40.98; H, 1.64.

Tetrachloro-2-cyanophenothiazine. A mixture of 10 g. (0.026 mole) of tetrachlorophenothiazine-2-carboxamide in 100 ml. of freshly distilled phosphorus oxychloride and 10 ml. of dry pyridine was refluxed for four hours. Upon cooling a yellow solid precipitated out which was filtered and decomposed with ice. The mixture was made strongly basic with solid sodium carbonate and 7.7 g. (82%) of a solid was collected. Several recrystallizations from benzene-ethanol led to a melting point of 225.5–227.5° (dec.).

Anal. Calc'd for $C_{13}H_4Cl_4N_2S$: C, 43.12; H, 1.11.

Found: C, 42.98; H, 1.22.

7-Acetyl-7-benzo[c]phenothiazine. This compound was prepared in 98% yield by refluxing 100 g. of 7-benzo[*c*]phenothiazine and 50 g. of sodium acetate with 500 ml. of acetic anhydride and decomposition with ice. Recrystallization from a 1:8 mixture of acetone-isopropyl ether gave colorless crystals, m.p. 134–135°. The literature (5) reports m.p. 126°.

Anal. Calc'd for $C_{18}H_{13}NOS$: C, 74.20; H, 4.49; N, 4.81.

Found: C, 74.06; H, 4.27; N, 4.82.

7,x-Diacetyl-7-benzo[c]phenothiazine. To a mechanically stirred mixture of 44 g. (0.151 mole) of 7-acetyl-7-benzo[*c*]phenothiazine, 11.9 g. (0.151 mole) of acetyl chloride, and 500 ml. of carbon disulfide was added 60.5 g. (0.453 mole) of aluminum chloride over a period of 45 minutes. The mixture was refluxed and stirred for ten hours and the solvent was decanted from a dark, gummy residue which was hydrolyzed by adding it to 500 g. of cracked ice. A tan solid separated which was washed with water and air-dried. The yield of crude product, melting at 190–194°, in several runs varied from 35.2 g. (69.5%) to 36.5 g. (72.5%). Several recrystallizations from ethanol raised the melting point to 203–204°.

Anal. Calc'd for $C_{20}H_{15}NO_2S$: C, 72.05; H, 4.53; N, 4.20.

Found: C, 71.90; H, 4.46; N, 4.28.

x-Acetyl-7-benzo[c]phenothiazine. A solution of 20 g. (0.06 mole) of 7, x-diacetyl-7-benzo[c]phenothiazine, 20 ml. of 20% hydrochloric acid, and 50 ml. of glacial acetic acid was refluxed for four hours. Upon cooling 15.7 g. (89%) of glistening red platelets precipitated from the solution. Recrystallization from ethanol gave a material of m.p. 195–196°.

Anal. Calc'd for $C_{18}H_{13}NOS$: C, 74.20; H, 4.49.

Found: C, 73.98; H, 4.33.

The *oxime* was prepared by refluxing with alcoholic hydroxylamine for three hours. It melted at 190–190.5°.

Anal. Calc'd for $C_{18}H_{14}N_2OS$; C, 70.56; H, 4.61.

Found: C, 70.53; H, 4.92.

SUMMARY

Several reactions of methyl ketone derivatives of phenothiazine and 7-benzo[*c*]phenothiazine have been reported.

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