QUANTITATIVE PREPARATION OF CHLORO- AND BROMOPHTHALAZINES

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## ABSTRACT

A new improved synthesis of 1,4-dichloro- and 1,4-dibromophthalazine has been effected by reaction of 1,4-dioxophthalazine with  $PX_5$  (X = Cl, Br) in a sealed reaction flask. Halogenation of the dioxophthalazine has also been accomplished at atmospheric pressure in a halogenated solvent. The synthesis of 1-bromophthalazine is reported.

## INTRODUCTION

1,4-Dichlorophthalazine has been synthesized by the reaction of 1,4-dioxophthalazine with either  $POCl_3$  (1, 2) or  $PCl_5$  (3-6). Repetition of the  $POCl_3$  method gave unsatisfactory results. The use of  $PCl_5$  gave rise to an impure product in 55% yield. The purification of the reaction mixture was quite laborious, and always accompanied by considerable amounts of 1-chloro-4-oxophthalazine, which could only be removed with difficulty.

A modification of this latter method has now been developed in which heating of 1,4-dioxophthalazine with  $PCl_5$  in a sealed reaction vessel results in a quantitative yield of almost pure 1,4-dichlorophthalazine, without the need for further purification.

It has been earlier reported (3) that reaction of 1,4-dioxophthalazine with PBr<sub>5</sub> always affords a mixture of 1,4-dibromophthalazine and 1-oxo-4-bromophthalazine. No yields were mentioned. 1,4-Dibromophthalazine has now been readily obtained in a nearly quantitative yield by applying the modified procedure for the preparation of the analogous dichlorophthalazine.

It was later found that the preparation of 1,4-dibromophthalazine could also be achieved under atmospheric conditions by using  $CBr_4$  as a solvent. In this alternative modification, the obtained yield was 78% and the  $CBr_4$  solvent was easily recovered. No reference to the preparation of 1-bromophthalazine is available.

#### 1,4-Dichlorophthalazine

# EXPERIMENTAL

In a closed pressure bottle, a mixture of 1,4-dioxophthalazine (16.2 g, 0.1 mole and an excess of phosphorous pentachloride (85 g) was heated at  $140-150^{\circ}$  in an oil bath for 4 h. During the heating period the reaction mixture was agitated with the aid of a magnetic stirrer. After cooling to room temperature, the pressure bottle was placed in a refrigerator for a few hours and then carefully opened in a hood. HCl gas escaped vigorously. The solid orange-colored mass was crushed with a spatula and poured into 1 l of ice water. The whole mixture was stirred until all lumps were disintegrated. Then ammonium hydroxide was added to a basic reaction; care being taken to maintain the temperature below 10 °C. The solid was collected on a filter paper, washed with water, and dried. This crude material was redissolved in methylene chloride, shaken with charcoal, and filtered. The colorless filtrate was subjected to partial concentration until a thick paste was obtained. Upon addition of 100 ml diethyl ether, a white crystalline material melting at 161–162° separated. The yield was 19.2 g (96.5%).

1,4-Dichlorophthalazine was recrystallized from tetrahydrofuran in colorless long needles m.p. 164° (lit. m.p. 161–162°, 164°, 164–165°); see Fig. 1.

Infrared spectra were determined on Perkin-Elmer model 337 from Nujol mulls.

# 1,4-Dibromophthalazine

This compound was prepared in 97% yield by applying the reaction conditions for the preparation of the analogous 1,4-dichlorophthalazine. In this preparation, the halogenating agent was phosphorous pentabromide and a reaction temperature of 140° was more effective.

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1,4-Dibromophthalazine was crystallized from tetrahydrofuran in colorless long needles m.p. 160-161° (lit. m.p. 162°); see Fig. 2.

# Preparation of 1,4-Dibromophthalazine in an Open Flask

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A mixture of 1,4-dioxophthalazine (1.62 g, 0.01 mole), phosphorous pentabronide (9.5 g, 0.02 mole plus 10% excess), and carbon tetrabromide (50 g) were heated at 130° (temperature of oil bath) for 6 h. After cooling, the solid mass was treated with methylene chloride (25 ml) until all lumps had been disintegrated. This mixture, under vigorous stirring, was poured into ice water (100 ml) and stirring was continued for an additional 2 h. The yellow solid material was collected on a filter paper and washed thoroughly with water followed by petroleum ether. 1,4-Dibromophthalazine was crystallized from tetrahydrofuran in long pale-yellow needles melting at 160°, yield 2.2 g (78%).

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## 1-Bromophthalazine

A mixture of phosphorous oxybromide (12 g), diethyl ether (25 ml), 2H-1-phthalazinone (2 g), and tetrahydrofuran (80 ml) was stirred at room temperature for 15 min. Then, under vigorous stirring, the mixture was heated for 3 h in an oil bath maintained at a temperature of 55-60°. After cooling, a paleyellowish solid was collected on a filter paper, washed with diethyl ether, and dried in a vacuum desiccator. The product reacted acidic, and obviously was the hydrobromide salt of 1-bromophthalazine. On heating over 210°, it acquired a grey color and at 245° melted with decomposition, yield 3.5 g. This product was taken in water (no solution was achieved) and under vigorous stirring was carefully neutralized to a weakly basic reaction with ammonium hydroxide. The pale-yellow solid was collected on a filter paper, washed with distilled water until the washings were neutral, and finally washed with petroleum ether. It was dried in the dark in a vacuum desiccator. On heating, it became orange colored at about 100°, and at 175° melted

with foaming; yield 2.52 g (88%); see Fig. 3. Anal. Calcd. for C<sub>8</sub>H<sub>5</sub>BrN<sub>2</sub>: C, 45.95; H, 2.41; N, 13.40; Br, 38.22. Found: C, 45.82; H, 2.55; N, 13.10; Br, 38.51.

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