THE SYNTHESIS OF SOME IODOPHTHALAZINES AND PHTHALAZINECARBONITRILES

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ABSTRACT

1-Iodo- and 1,4-diiodo-phthalazines were obtained by treating the corresponding chloro compounds with a solution of sodium (or potassium) iodide in acetone containing hydrogen iodide. These iodophthalazines, on reaction with copper cyanide in pyridine, gave the relevant phthalazinecarbonitriles.

INTRODUCTION

The preparation of 1,4-diiodophthalazine (VI) has not been described in the literature. It was reported that 1-iodophthalazine (II) can be obtained, in unspecified yield, from the corresponding chloro compound I by the action of boiling hydriodic acid, either alone or in the presence of red phosphorus. However, in our hands, these procedures gave unsatisfactory results.

Attempts to prepare the iodophthalazines II and VI by (*a*) treating the corresponding phthalazinones with phosphorus triiodide or (*b*) the action of sodium (or potassium) iodide on the relevant chloro compounds in acetone were not successful. However, halogen exchange occurred readily when a significant quantity of hydrogen iodide was present in the latter reaction mixture. Attempts to effect the same reaction by merely using a solution of hydrogen iodide in acetone proved to be fruitless.

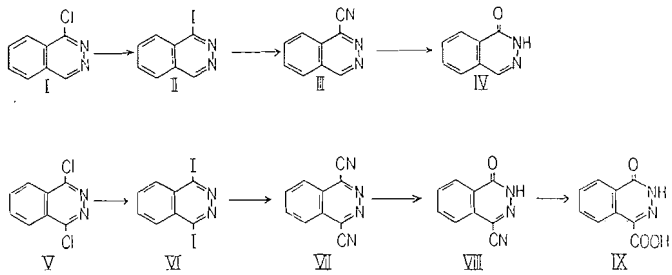
A survey of the literature reveals no previous preparation of phthalazinecarbonitriles. Earlier attempts[1] to obtain these substances from the chloro- or bromo-phthalazines via the halogen–nitrile exchange method were unsuccessful.

It has now been possible to prepare 1-phthalazinecarbonitrile (III) and 1,4-phthalazinedicarbonitrile (VII) by heating the corresponding iodo compounds with copper cyanide in pyridine for a few minutes.

The infrared spectrum of III showed a very weak nitrile absorption at 2 240 cm^{-1}, whereas such an absorption was not present in the infrared spectrum of VII. It has been shown that this band is not always evident in the infrared spectra of a variety of nitrogen heterocyclic compounds (2, 3) or in aromatic nitriles with ortho and para electron-withdrawing groups (4).

Anomalous results were obtained on the attempted hydrolysis of the nitriles III and VII. When III was refluxed in 10% sodium hydroxide solution, ammonia was constantly evolved for 5 h. This observation suggested that normal hydrolysis of III to the corresponding 1-phthalazinecarboxylic acid was taking place. However, all attempts to isolate the suspected carboxylic acid were unsuccessful and no evidence for its presence could be found. In all cases, 1(2*H*)-phthalazinone (IV) and a viscous unidentifiable oily material were isolated. Since it was found that IV is quite stable under similar alkaline reaction conditions, it appears to be more likely that the 1-phthalazinecarboxylic acid decomposes as fast as it forms, thereby giving rise to oily products.

[1]*In those attempts a wide variation of solvents (pyridine, quinoline, all three picolines, dimethylformamide, dimethyl sulfoxide, and glycol) and cyanidation agents (potassium cyanide, sodium cyanide, silver cyanide, and copper cyanide) were used to no avail.*



On the other hand, alkaline treatment of the dicarbonitrile VII, at room temperature for 15 min, resulted in a quantitative yield of 4-cyano-1(2*H*)-phthalazinone (VIII). The resulting cyanophthalazinone, on further alkaline treatment, under heating, was quantitatively hydrolyzed to the corresponding 1(2*H*)-phthalazinone-4-carboxylic acid (IX), which had previously been prepared by a direct route (5–8). The cyanophthalazinone VIII, aside from its conversion into the known IX, was also confirmed by elemental analysis and its infrared spectrum (absorption at 2 240 cm^{-1}).

The enhanced susceptibility of a cyano group to displacement by nucleophiles has been described in many instances (9–11), and the conversion of III and VII into IV and VIII, respectively, should not be altogether unexpected.

The rapid displacement of the 1- (or 4-) cyano group in 1,4-phthalazinedicarbonitrile (VII) is explicable only by assuming that the intermediate in this nucleophilic aromatic substitution would derive stabilization from the electron-withdrawing benzene ring and the 4- (or 1-) cyano group, in addition to stabilization attributable to the azine group.

Carbonitriles III and VII, on treatment with concentrated sulfuric acid or 36% hydrochloric acid at 25° for 24 h, remained unaffected. Extensive decomposition of the starting material occurred after 2 h if temperatures of over 60 °C were applied.

For identification purposes, the infrared spectra of II and VI are presented in Figs. 1 and 2, respectively.

EXPERIMENTAL

Melting points are uncorrected. Analyses were carried out by Dr. C. Daessle, Montreal, Quebec. Infrared absorption spectra were determined with a Perkin–Elmer model 337 spectrophotometer from Nujol mulls.

1,4-Dichlorophthalazine (V)

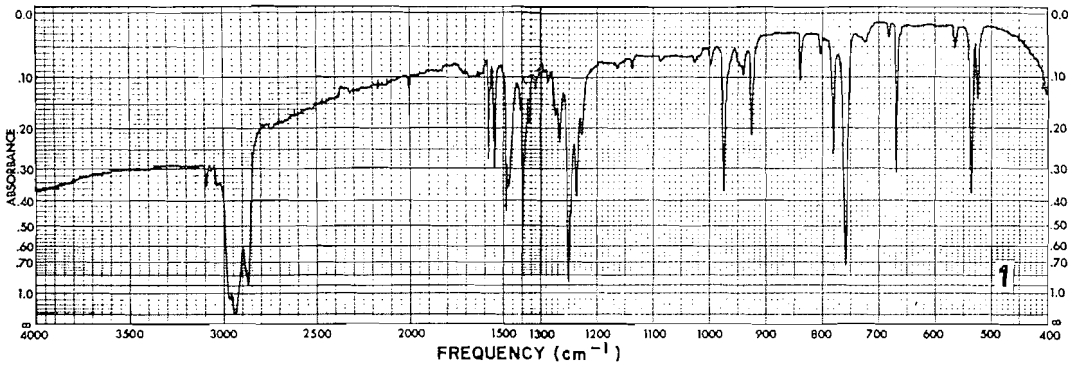
The procedure described previously by this laboratory was slightly modified (12). 2,3-Dihydro-1,4-phthalazinedione (16.2 g, 0.1 mole) and phosphorus pentachloride (85 g) were thoroughly mixed in an ordinary 6 fl. oz carbonated beverage bottle equipped with a magnetic stirring bar. The bottle was sealed with the appropriate metallic cap and placed in a cool oil bath. The temperature of the bath[2] was gradually brought up to about 180°. At this temperature the solid reaction mixture was slowly liquefied, and as soon as agitation became effective, the temperature of the oil bath was lowered to 140–150° and maintained there for 4 h. After the reaction bottle was cooled to room temperature,[3] it was refrigerated for a few hours and then carefully opened in a hood. The product was isolated as described in the original procedure (12). The yield and melting point were the same.

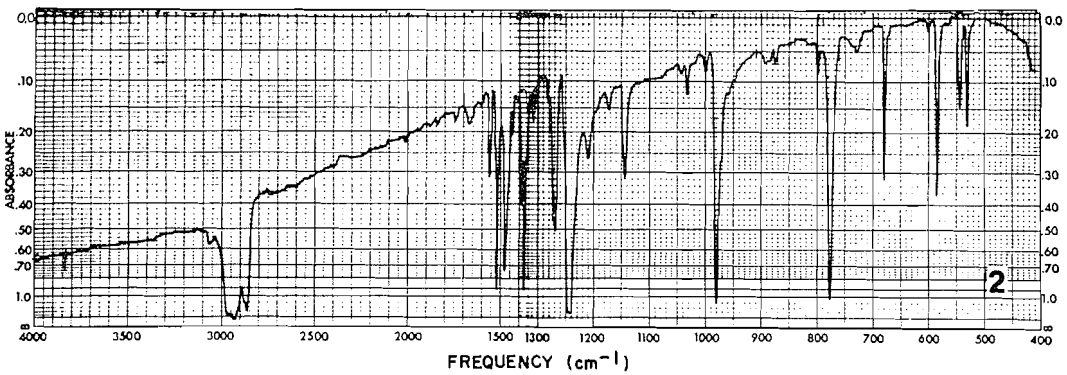
1-Iodophthalazine (II)

To a stirred mixture of potassium or sodium iodide (30 g), 1-chlorophthalazine (16.5 g) (13), and acetone (300 ml), a 50% aqueous solution of hydroiodic acid (20 ml) was added. The resulting yellow mixture was stirred at room temperature for 18 h. The canary-yellow precipitate was obtained by filtration, washed with diethyl ether, and dried *in vacuo*. This acidic product was apparently the hydroiodide salt. It was dissolved in ice-cold water (1 l), stirred for 15 min, and then neutralized carefully with dilute ammonium hydroxide. The faint-yellowish solid was collected, washed with cold water followed by petroleum ether,

[2]*The temperature of the oil bath should not be permitted to rise over 190° because of the explosion hazard. In any event, it should be recognized that any sealed glass vessel of this type constitutes a potential bomb and must be handled with extreme caution.*

[3]*The reaction bottle is removed from the oil bath when the latter has reached room temperature.*





FIGS. 1 and 2.

and dried *in vacuo*. It weighed 22.5 g (88%) and melted at 78° with decomposition (reported (1) m.p. 78°) 1-Iodophthalazine undergoes slow decomposition at room temperature to an amorphous yellow powder. This decomposition can be retarded by storing the substance in a freezer.

1,4-Diiodophthalazine (VI)

To a stirred mixture of potassium or sodium iodide (25 g), 1,4-dichlorophthalazine (9.95 g, 0.05 mole), and acetone (300 ml), a 50% aqueous solution of hydroiodic acid (20 ml) was added. The resulting yellow mixture was stirred at room temperature for 18 h. The canary-yellow solid was collected, washed with a little acetone followed by diethyl ether, and dried *in vacuo*. This acidic product was apparently the hydroiodide salt. It was dissolved in distilled water (2 l) and stirred until the initial yellow color of the solid had been discharged (about 1 h). The white solid was collected, washed with distilled water until the washing was no longer acidic, and dried *in vacuo*.

It melted at 156–157° with decomposition and was pure enough to be used for the next step, yield 14.5 g (76%). 1,4-Diiodophthalazine was crystallized from methylene chloride as hard white prisms melting at 161° with decomposition.

Anal. Calcd. for $C_8H_4I_2N_2$: C, 25.16; H, 1.05; N, 7.33; I, 66.45. Found: C, 25.35; H, 0.98; N, 7.53; I, 66.61.

1-Phthalazinecarbonitrile (III)

1-Iodophthalazine (12.8 g, 0.05 mole) was thoroughly mixed with copper cyanide (4.48 g, 0.05 mole). To this mixture was added dry pyridine (75 ml), and the resulting greenish suspension was placed in a preheated (110–120°) oil bath and kept there for 10 min under vigorous stirring. The black-colored reaction mixture was poured into chilled water (500 ml) and stirred for a few minutes.

Diethyl ether (500 ml) and some ice were added to lower the temperature to about 5–10°. To this chilled mixture, with vigorous stirring, dilute hydrochloric acid was added slowly until a pH of 2 was attained. Stirring was continued for an additional 20 min. (The aqueous layer must be maintained at all times at a pH of 2.)

The clear yellowish ether layer was separated and the aqueous layer extracted twice with 300 ml of diethyl ether each. The combined ether extracts were washed with water until neutral, dried over $MgSO_4$, shaken

with charcoal, and filtered. The colorless filtrate, upon removal of the solvent under reduced pressure, left a white crystalline product melting at 148–149° and weighing 1.35 g (17.3%).

1-Phthalazinecarbonitrile was recrystallized from diethyl ether as fine white needles melting at 156–157°. The infrared spectrum showed a very weak, but sharp absorption at 2 240 cm^{-1} (C≡N).

Anal. Calcd. for $C_9H_5N_3$: C, 69.67; H, 3.25; N, 27.08. Found: C, 69.94; H, 3.43; N, 27.03.

1,4-Phthalazinedicarbonitrile (VII)

This substance was prepared by a procedure similar to that applied above for the preparation of 1-phthalazinecarbonitrile. Thus, from the reaction of 1,4-diiodophthalazine (19.1 g, 0.05 mole) and copper cyanide (9 g, 0.1 mole) in pyridine (80 ml) was obtained 3.2 g of 1,4-phthalazinedicarbonitrile. It melted at 201–204°, and recrystallization from diethyl ether gave yellowish shiny crystals melting at 204–205°. The infrared spectrum showed no evidence of the C≡N stretching frequency.

Anal. Calcd. for $C_{10}H_4N_4$: C, 66.66; H, 2.23; N, 31.10. Found: C, 66.87; H, 2.32; N, 31.39.

4-Cyano-1(2H)-phthalazinone (VIII)

To a solution of 1,4-phthalazinedicarbonitrile (1.8 g) in dioxane (5 ml), 10 ml of a 20% sodium hydroxide solution was added. The resulting orange-colored solution was stirred for 15 min at room temperature. The yellow suspension was dissolved in 80 ml of water. The clear yellow solution was extracted with diethyl ether to remove ether-soluble impurities. The alkaline layer was weakly acidified with dilute hydrochloric acid. The yellowish precipitate was collected on filter paper, washed with water, and dried. It melted at 269–270° and weighed 1.49 g. This material was dissolved in tetrahydrofuran, shaken with charcoal, and filtered. Removal of the solvent under reduced pressure left a white solid melting at 270°. The infrared spectrum showed characteristic bands at 3 175, 3 100, 2 240, 1 715, and 1 645 cm^{-1}.

Anal. Calcd. for $C_9H_5N_3O$: C, 63.16; H, 2.95; N, 24.55. Found: C, 63.46; H, 3.21; N, 24.46.

1(2H)-Phthalazinone-4-carboxylic Acid (IX) from 4-Cyano-1(2H)-phthalazinone (VIII)

A mixture of 4-cyano-1(2*H*)-phthalazinone (0.5 g), 4% sodium hydroxide solution (8 ml), and methanol (25 ml) was refluxed until evolution of ammonia ceased (tested with wet red litmus paper) (about 7 days). The yellowish solution was filtered and the filtrate concentrated to about 10 ml under reduced pressure. The remaining alkaline solution was cautiously acidified with dilute hydrochloric acid, and the precipitated white solid was collected, washed with diethyl ether, and dried. It melted at 234° with foaming, and weighed 0.51 g. 1(2*H*)-Phthalazinone-4-carboxylic acid was recrystallized from a mixture of methanol and dioxane (3:1) as hard white crystals melting at 236° with foaming (reported (5) m.p. 232°).

Alternatively, the substance can be prepared directly from 1,4-phthalazinedicarbonitrile under conditions identical with those described above. The time for the hydrolysis can be reduced to a few hours if a more concentrated sodium hydroxide solution is used and no methanol is present. In the latter case, the yield of pure product is much lower and its purification is achieved with difficulty. The infrared spectrum displayed characteristic absorptions at 3 250, 3 170, 1 680, and 1 640 cm^{-1}.

Anal. Calcd. for $C_9H_6O_3N_2$: C, 56.84; H, 3.18; N, 14.73. Found: C, 56.92; H, 3.01; N, 14.76.

1(2H)-Phthalazinone (IV) from 1-Phthalazinecarbonitrile (III)

1-Phthalazinecarbonitrile (0.2 g) in 10% sodium hydroxide solution (25 ml) was refluxed for 5 h. During this time ammonia was constantly evolved. The alkaline reaction solution was weakly acidified with dilute hydrochloric acid and then extracted with methylene chloride. The extract was dried over $MgSO_4$, decolorized with charcoal, and filtered. The colorless filtrate, upon removal of the solvent, left a semisolid material which, on trituration with a few milliliters of diethyl ether, separated out as a white crystalline material melting at 184–185°, yield 0.052 g. Its infrared spectrum was identical with that displayed by an authentic sample of 1(2*H*)-phthalazinone, and a mixed melting point with the latter compound showed no depression.

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