Reissert Compound Studies. XIX. Reactions of Phthalazine (1)

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The use of a wide variety of quinolines (3) and isoquinolines (4) in Reissert compound formation has been reported and their value as synthetic intermediates has been demonstrated (5). A logical extension of this work on quinoline and isoquinoline would be in the area of azaquinolines or azaisoquinolines and in this line we now report on our work with phthalazine.

Reaction of phthalazine, benzoyl chloride, and potassium cyanide in methylene chloride-water gave the phthalazine Reissert compound (I). Use of an excess of benzoyl chloride and potassium cyanide did not lead to the formation of any material resulting from reaction at the second ring nitrogen.

Acid-catalyzed hydrolysis of the phthalazine Reissert compound proceeded in an analogous manner to the

hydrolysis of a normal Reissert compound (for example, II). Use of concentrated hydrochloric acid in the presence of 2,4-dinitrophenylhydrazine (6) with I gave a quantitative yield of benzaldehyde 2,4-dinitrophenylhydrazone while hydrolysis of I with hydrobromic acid in acetic acid (7) gave phthalazine-1-carboxylic acid as its hydrobromide.

Reaction of I with methyl iodide in the presence of sodium hydride in dimethylformamide proceeded as has been reported for II (5) to give III in quantitative yield. Hydrolysis in base converted III to 1-methylphthalazine in 76% yield. Condensation of I with benzaldehyde in the presence of sodium hydride in dimethylformamide at room temperature gave a quantitative yield of the carbinol (IV).

Reaction of phthalazine and potassium cyanide with

TABLE I
Phthalazine Reissert Analogues

X	M.p. (a)	Yield	Analyses					
			Calcd.			Found		
			C	Н	N	C	Н	N
$-CON(C_6H_5)_2$	206-208	72	74.98	4.58	15.90	75.01	4.59	15.76
$-CON(C_2H_5)_2$	136-138	11			21.86			22.08
$C_6H_5SO_2$ -	151-154	99	60.59	3.73	14.13			14.05
$-CO_2C_2H_5$	137-138 (b)	35	62.87	4.84	18.33	62.68	4.81	18.01
$-PS(OC_2H_5)_2$	83-86	74	50.47	5.21	13.59	50.56	5.25	13.69

(a) Recrystallized from ethanol unless otherwise noted. (b) Recrystallized from ethanol-water.

diphenylcarbamoyl chloride, diethylcarbamoyl chloride, benzenesulfonyl chloride, ethyl chloroformate, and diethyl chlorothiophosphate gave Reissert compound analogues of the type previously obtained from isoquinoline (5). These analogues are included in Table I.

EXPERIMENTAL (8)

1-Cyano-2-benzoyl-1,2-dihydrophthalazine (1).

To a mixture of 13.0 g. (0.2 mole) of potassium cyanide and 6.5 g. (0.05 mole) of phthalazine in 75 ml. of methylene chloride and 20 ml. of water was added 28.1 g. (0.2 mole) of benzoyl chloride. After stirring for several hours at room temperature, the mixture was washed with water, dilute hydrochloric acid, water, dilute sodium hydroxide, and water and dried over sodium sulfate. Concentration of the methylene chloride gave, after recrystallization from ethanol, 7.2 g. (55%) of I, m.p. 163-164°.

Anal. Calcd. for $C_{16}H_{11}N_3O$: C, 73.55; H, 4.24; N, 16.08; Mol. Wt., 261.3. Found: C, 73.44; H, 4.24; N, 16.04; Mol. Wt. (Rast), 263.

Hydrolysis of Reissert Compound (I).

Hydrolysis of I in glacial acetic acid-hydrobromic acid by the method of Davis (7) gave an 89% yield of phthalazine-1-carboxylic acid hydrobromide, m.p. 198-200°.

Anal. Calcd. for C₉H₇N₂O₂Br: C, 42.38; H, 2.77; N, 10.98; Br, 31.33. Found: C, 42.42; H, 2.91; N, 11.03; Br, 31.42.

Hydrolysis of I by concentrated hydrochloric acid in the presence of an equimolar quantity of 2,4-dinitrophenylhydrazone (6) gave a quantitative yield of benzaldehyde 2,4-dinitrophenylhydrazone.

$1-Methyl-1-cyano-2-benzoyl-1, 2-dihydrophthalazine\ (III).$

Treatment of compound I with methyl iodide and sodium hydride in dimethylformamide at room temperature by the

method of Popp and Wefer (9) gave a quantitative yield of III, m.p. 143-145° from ethanol.

Anal. Calcd. for $C_{17}H_{13}N_3O$: C, 74.16; H, 4.76; N, 15.27. Found: C, 74.03; H, 4.77; N, 15.16.

Hydrolysis of III.

Hydrolysis of III with warm alcoholic potassium hydroxide gave a 76% yield of 1-methylphthalazine, m.p. 70-71° (reported (10), m.p. 70-74°); picrate, m.p. 206-207° (reported (10), m.p. 203-205°).

Preparation of Carbinol (IV).

To a solution of 2.61 g. (0.01 mole) of I and 1.06 g. (0.01 mole) of benzaldehyde in 50 ml. of dimethylformamide was added 0.80 g. (0.01 mole) of 30% sodium hydride in oil. After formation of a red color, an additional quantity of benzaldehyde was added and the solution was stirred at room temperature for 1.5 hours and poured on ice. Extraction with chloroform and concentration of the chloroform gave a quantitative yield of IV, m.p. 172-175° from ethanol.

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.06; H, 5.18; N, 11.81.

Preparation of Phthalazine Reissert Compound Analogues.

The compounds shown in Table I were prepared from the appropriate reagent by a method similar to the preparation of I.

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