[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

The Direct Preparation of Some Dihydro and Other Phenazine Derivatives

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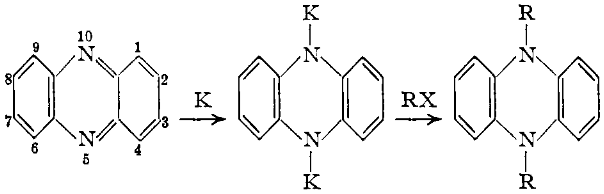
Lithium does not add directly to phenazine in tetrahydrofuran. An improved yield of 5-methyl-10-phenyl-5,10-dihydrophenazine was obtained when tetrahydrofuran was used in place of ethylene glycol dimethyl ether. 5,10-Diphenyl-5,10-dihydrophenazine has been prepared and its structure conclusively established by stepwise degradation to known compounds. A tetrabromophenazine is reported along with an attempt at direct acylation.

Although lithium, sodium and potassium do not add directly to phenazine in diethyl ether, Mikhailov and Blokhina[1] have found that the direct addition is possible in ethylene glycol dimethyl ether. The addition of the appropriate alkyl halide then produces the corresponding 5,10-dialkyl-5,10-dihydrophenazine as shown.



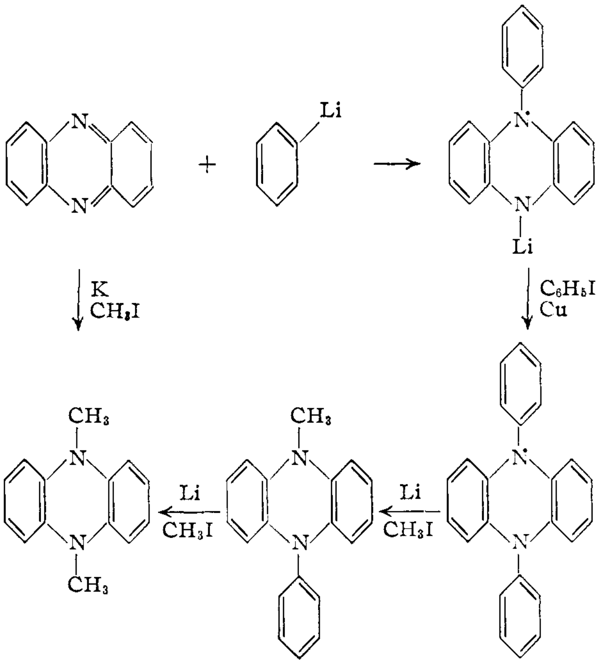
By adding phenyllithium to phenazine in ethylene glycol dimethyl ether, they were able to obtain, after derivatizing it with methyl iodide, 5-methyl-10-phenyl-5,10-dihydrophenazine. The phenyllithium, therefore, must add 1,4 across the nitrogens.

Attempts to add lithium directly to phenazine in tetrahydrofuran have up to this time not been successful. However, an improved yield of 5-methyl-10-phenyl-5,10-dihydrophenazine was obtained when tetrahydrofuran was used as the solvent. It was not possible, however, to add methyllithium to phenazine and thus obtain more than a trace of 5,10-dimethylphenazine after derivatizing with methyl iodide.

After addition of phenyllithium to phenazine, there was added an excess of iodobenzene, a catalytic amount of copper powder and some kerosene. The tetrahydrofuran was distilled off and the reaction mixture raised to reflux. In this manner there was formed a compound which analyzed correctly as a diphenylphenazine, but which melted 113° above a compound reported to be 5,10-diphenyl-5,10-dihydrophenazine. This compound was produced by the thermal decomposition of tetraphenylhydrazine in toluene.[2,3]

Using a lithium cleavage in tetrahydrofuran,[4] it was possible to determine that our compound is 5,10-diphenyl-5,10-dihydrophenazine. This proof was accomplished by cleaving the phenyl groups off in a stepwise manner and replacing them by methyl groups to produce successively 5-methyl-10-phenyl-5,10-dihydrophenazine and 5,10-dimethyl-5,10-dihydrophenazine, both known compounds,[1] as shown.

Phenylmagnesium bromide, when treated with phenazine in tetrahydrofuran and derivatized with methyl iodide, did not produce any of the expected 5-methyl-10-phenyl-5,10-dihydrophenazine. Instead a dark colored material was obtained which was presumably a mixture of phenazine and dihydrophenazine.



Forced bromination of phenazine has produced a compound which contains four equivalents of bromine and is therefore designated as a tetrabromophenazine. Several attempts to directly acylate phenazine have so far met with no success.

Experimental[5]

The tetrahydrofuran used in all of the experiments was purified by shaking with sodium hydroxide pellets, drying over sodium metal and, finally, distilling from lithium aluminum hydride prior to every reaction. An oxygen-free, dry nitrogen atmosphere was used in all reactions employing organometallic compounds.

5,10-Dimethyl-5,10-dihydrophenazine.—A mixture of 3.6 g. (0.02 mole) of phenazine, 1.7 g. (0.4 g. atom) of potassium and 25 ml. of ethylene glycol dimethyl ether was stirred for 10.5 hr. An excess of methyl iodide was added which was followed by absolute ethanol to destroy the excess potassium. The reaction mixture was hydrolyzed with a saturated ammonium chloride solution. Distillation of the solvent left a residue which was recrystallized from ethanol to yield 2.5 g. (62%) of white needles, m.p. 153–155° (lit.[1] value 151–152°).

Direct Addition of Lithium to Phenazine (Attempted).—A mixture of 9 g. (0.05 mole) of phenazine, 1 g. (0.15 g.

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[1] B. M. Mikhailov and A. N. Blokhina, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, 304 (1950) [*C. A.*, **44**, 9452 (1950)].

[2] H. Wieland, *Ann.*, **381**, 200 (1911).

[3] K. Grebber and J. Karabinos, *J. Research Natl. Bur. Standards*, **49**, 163 (1952) [*C. A.*, **47**, 2087 (1953)].

[4] H. Gilman and J. J. Dietrich, *J. Org. Chem.*, **22**, 851 (1957).

[5] All melting points are uncorrected.

atom) of lithium and 50 ml. of tetrahydrofuran was refluxed for 4.5 hr. An excess of methyl iodide was then added, but only phenazine (62%) was recovered from the reaction mixture.

5-Methyl-10-phenyl-5,10-dihydrophenazine.—A solution of 0.06 mole of phenyllithium in 60 ml. of diethyl ether was added to 9 g. (0.05 mole) of phenazine in 60 ml. of tetrahydrofuran over a period of 15 min. at room temperature. Stirring was continued for 0.5 hr. before 8.5 g. (0.06 mole) of methyl iodide was added. The brown mixture was stirred for 2 hr. at room temperature and then hydrolyzed with dilute hydrochloric acid. An oil was obtained which solidified and was crystallized from ethanol to yield 7.3 g. of material melting 109–113°. This solid was dissolved in benzene, chromatographed on alumina and recrystallized from ethanol to yield 5 g. (37%) of material, m.p. 116–117° (lit.[1] value 116.5–117.5°).

5,10-Diphenyl-5,10-dihydrophenazine.—A solution of 0.06 mole of phenyllithium in 65 ml. of diethyl ether was added to 9 g. (0.05 mole) of phenazine in 65 ml. of tetrahydrofuran over a period of 15 min. Stirring was continued for 3.5 hr. at room temperature before 15.3 g. (0.075 mole) of iodobenzene, 1 g. of copper powder, and 70 ml. of kerosene were added. The other solvents were distilled off, and the temperature was maintained at 210° for 12 hr. The bulk of kerosene was distilled off and the residue dissolved in benzene and chromatographed on alumina to yield, after evaporation of the eluate, 4.2 g. of material, m.p. 280–283°. Two additional recrystallizations from benzene–petroleum ether (b.p. 60–70°) resulted in the isolation of 2.7 g. (16%) of pale yellow needles, m.p. 283–285°.

Anal. Calcd. for $C_{24}H_{18}N_2$: N, 8.28. Found: N, 8.15, 8.24.

Lithium Cleavage of 5,10-Diphenyl-5,10-dihydrophenazine.—A mixture of 2 g. (0.006 mole) of 5,10-diphenyl-5,10-dihydrophenazine, 0.33 g. (0.05 g. atom) of lithium and 10 ml. of tetrahydrofuran was refluxed for 3 days. Then 14.2 g. (0.1 mole) of methyl iodide was added and the solution filtered through glass wool to remove any unused lithium. The solvent was evaporated and the residue dissolved in benzene and chromatographed on alumina. The eluate was evaporated and the residue recrystallized from ethanol to produce 0.3 g. of yellow needles, m.p. 116–118°. Infrared spectra and mixture melting point proved the material to be 5-methyl-10-phenyl-5,10-dihydrophenazine.

Lithium Cleavage of 5-Methyl-10-phenyl-5,10-dihydrophenazine.—A mixture of 1.5 g. (0.0055 mole) of 5-methyl-10-phenyl-5,10-dihydrophenazine, 0.33 g. (0.05 g. atom) of lithium and 10 ml. of tetrahydrofuran was stirred for 3 days at reflux. Then 14.2 g. (0.1 mole) of methyl iodide was added and the solvent distilled off. The residue was dissolved in benzene and chromatographed on alumina. Evaporation of the eluate followed by two recrystallizations of the residue from ethanol produced 0.4 g. of white needles, m.p. 154–156°. This compound, from infrared data and mixture melting point, proved to be 5,10-dimethyl-5,10-dihydrophenazine.

Decomposition of Tetraphenylhydrazine.—A mixture of 5.5 g. (0.016 mole) of tetraphenylhydrazine and 25 ml. of sodium-dried toluene was refluxed under nitrogen for 0.5 hr. The resulting solution was chromatographed on alumina and the eluate distilled to yield a yellow oil. This oil solidified when boiled with ethanol–acetone, but efforts to recrystallize the solid from ethanol, ethanol–benzene, benzene–petroleum ether (b.p. 60–71°), and other solvent systems have so far been unsuccessful. Several other runs also produced oils which behaved in a similar manner.

Addition of Methyllithium to Phenazine (Attempted).—A solution of 0.053 mole of methyllithium in 60 ml. of diethyl ether was added to 9 g. (0.05 mole) of phenazine in 60 ml. of tetrahydrofuran over a period of 15 min. at room temperature. After 15 min. of stirring, 11 g. (0.08 mole) of methyl iodide was added and the reaction mixture hydrolyzed with water. The residue from evaporation of the ether layer was recrystallized twice from ethanol to produce 0.2 g. of white needles, m.p. 152–155°. A mixture melting point proved this material to be 5,10-dimethyl-5,10-dihydrophenazine. The mother liquor was concentrated to yield 0.4 g. of white needles, m.p. 125–127°. This material was not identified.

Addition of Phenylmagnesium Bromide to Phenazine (Attempted).—A solution of 0.06 mole of phenylmagnesium bromide in 60 ml. of diethyl ether was added to 9 g. (0.05 mole) of phenazine in 80 ml. of tetrahydrofuran and stirred for 1.75 hr. at room temperature. The reaction was terminated by the addition of an excess of methyl iodide and hydrolyzed with dilute hydrochloric acid. After distillation of the solvent, the residue was dissolved in benzene and chromatographed on alumina. No 5-methyl-10-phenyl-5,10-dihydrophenazine was obtained, but a small amount (2 g.) of starting material was recovered. From the dark color of the material, remaining on the column, it was supposed that this material was in the form of a phenazine–dihydrophenazine complex.[6]

Tetrabromophenazine.—A mixture of 9 g. (0.05 mole) of phenazine, 32 g. (0.2 mole) of bromine and 100 ml. of glacial acetic acid was refluxed and stirred for 13 hr. in a flask equipped with a hydrogen bromide trap. The reaction mixture was diluted with ammonium hydroxide solution and filtered. The crude solid was recrystallized four times from pyridine to yield 0.4 g. of green-yellow needles, m.p. 340–341°.

Anal. Calcd. for $C_{12}H_4N_2Br_4$: N, 5.64. Found: N, 5.59, 5.71.

Numerous attempts to produce other bromo derivatives of phenazine have not succeeded up to this time.

Acylation of Phenazine (Attempted).—A mixture of 9 g. (0.05 mole) of phenazine, 10.4 g. (0.1 mole) of acetic anhydride, 20 g. (0.15 mole) of aluminum chloride and 75 ml. of 1,1,2,2-tetrachloroethane was stirred at 140° for 5.25 hr. The reaction mixture was hydrolyzed with dilute hydrochloric acid, and the 1,1,2,2-tetrachloroethane layer washed with a dilute sodium carbonate solution. Evaporation of the solvent yielded 6.2 g. (69%) of pure phenazine after recrystallizing it from benzene.

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[6] F. Bohlmann, *Ber.*, **85**, 390 (1952).