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The Action of Organolithium Compounds on

Phthalazine and 1(2*H*)-Phthalazinone(I)

A. Hirsch and D. G. Orphanos

Phthalazine and 1(2*H*)-phthalazinone undergo 1,2-addition of organolithium compounds to C = N to give, following hydrolysis, 1-substituted - 1,2-dihydrophthalazines and 4-substituted - 3,4-dihydro-1(2*H*)-phthalazinones respectively. These dihydro-derivatives may be easily autoxidized to the corresponding 1-substituted phthalazines and 4-substituted-1(2*H*)-phthalazinones.

Although phthalazine and 1(2*H*)-phthalazinone are known to give with phenylmagnesium bromide 1-phenylphthalazine and 1,4-diphenylphthalazine (2), respectively, the corresponding reactions with organolithium compounds have not been investigated. Therefore, the study of the action of organolithium compounds on phthalazine was undertaken. The object of this investigation was limited to the preparation of select phthalazine derivatives which have either not been previously described or which are obtained with difficulty via known synthetic methods. For much the same reasons, the aforementioned study was also extended to 1(2*H*)-phthalazinone.

Thus, when phthalazine (I) was properly treated with an organolithium compound (II), and the resulting adduct hydrolyzed, 1-substituted-1,2-dihydrophthalazine (IV) was obtained. Similarly, by the same reaction, 1(2*H*)-phthalazinone (V) gave 4-substituted-3,4-dihydro-1(2*H*)-phthalazinone (VII).

The addition of organolithium compounds to the carbon-nitrogen double bond in the phthalazine as well as in 1(2*H*)-phthalazinone should apparently proceed by a mechanism similar to that of the addition of the same reagents to the carbon-nitrogen double bond in pyridine (3).

Dihydro-derivatives IV and VII are relatively stable, particularly in an inert atmosphere. With the exception of IVa and VIIa, they have been successfully isolated from the reaction mixture. Although IVa and VIIa could not be isolated in a pure state, evidence for their existence in the crude reaction mixture has been provided by infrared spectra (strong NH absorptions) and by the fact that on treatment with air, they afforded the expected known 1-methylphthalazine (VIIIa) and 4-methylphthalazinone (IXa), respectively.

It was anticipated that reaction of excess of organolithium compounds with phthalazine could reasonably provide 1,4-disubstituted-1,2,3,4-tetrahydrophthalazines. However, in no case was there obtained a disubstituted derivative despite many attempts. 1-Substituted phthalazine was constantly isolated

along with yellow oily unidentifiable materials.

This lack of success in the preparation of 1,4-disubstituted phthalazines, is not well understood, and a reasonable explanation is difficult to find.

Compounds IV and VII, except for IVc and VIIc, on contact with air are slowly dehydrogenated to the corresponding 1-substituted phthalazines (VIII), and 4-substituted phthalazinones (IX). This autoxidation is greatly accelerated in solution, especially in a polar solvent. The crude reaction mixture, resulting from this transformation, was always found to give a positive peroxidic test to potassium iodide-acetic acid. This latter fact is in accordance with the studies of several workers (4,5,6) who have clearly shown that oxidative dehydrogenations proceed via intermediate hydroperoxides or peroxides.

Isolation of peroxy compounds from a variety of nitrogen heterocyclic compounds has been described in several instances (7). Thus, the autoxidative dehydrogenation of IV and VII to the corresponding VIII and IX presumably proceeds by a mechanism involving the intermediates illustrated in Schemes A and B (8).

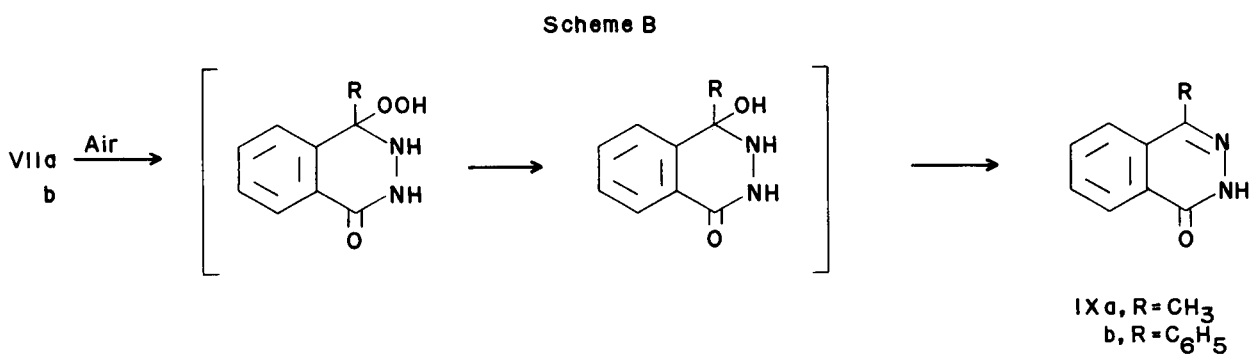
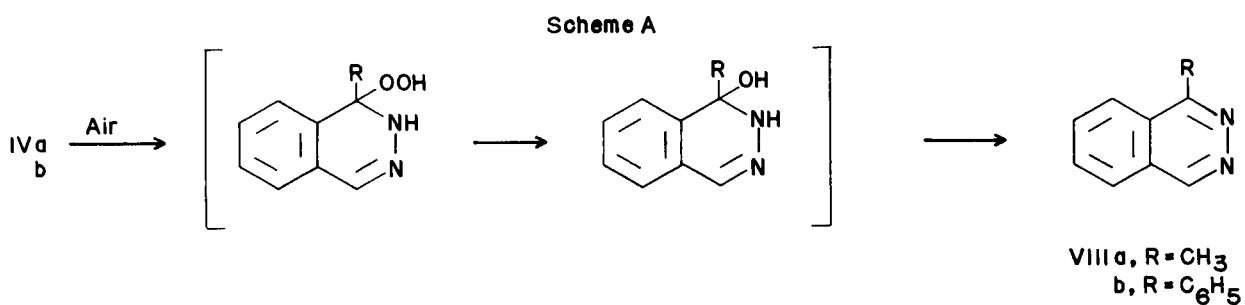
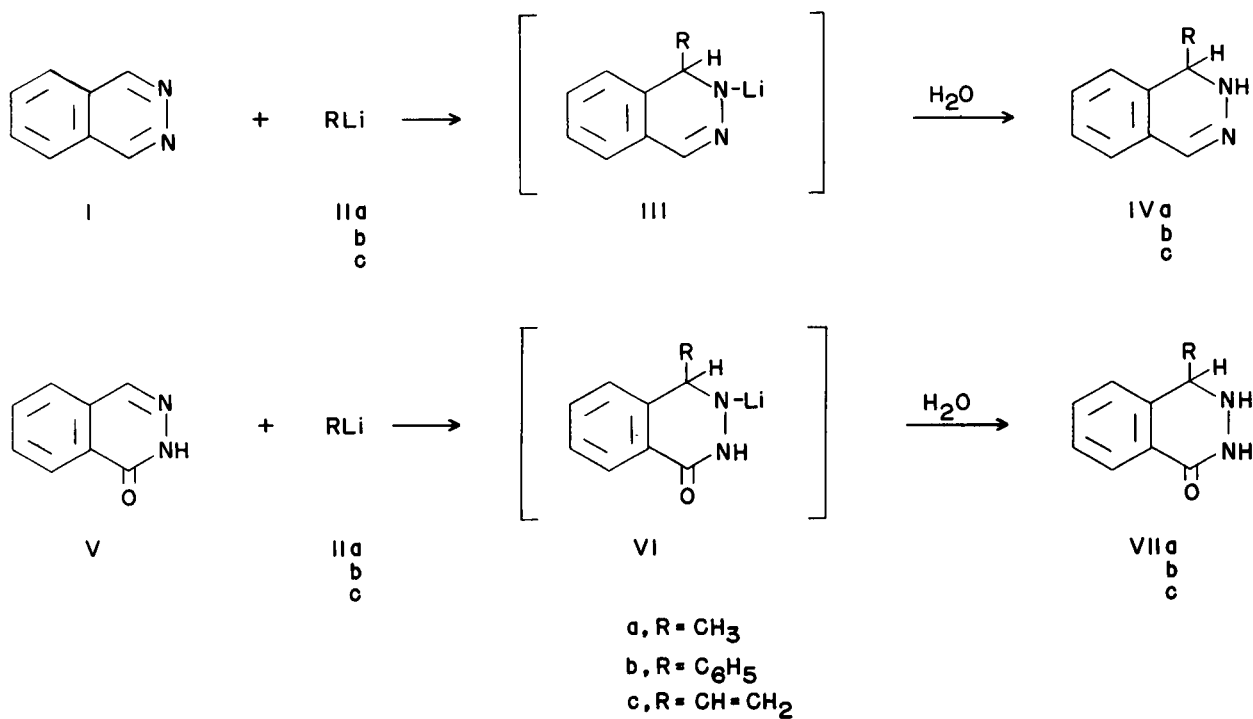
The mixture of autoxidation products from which 1-methylphthalazine was anticipated, afforded a white crystalline material melting at about 95°. It reacted strongly peroxidic to potassium iodide - acetic acid and a TLC showed the presence of a mixture of at least two compounds, one of which was an organic peroxide. Separation of this mixture was effected through a silica gel column using as eluent a mixture of ethanol-benzene (1:4). 1-Methylphthalazine was isolated as a white crystalline product melting at 71-72° (reported m.p. 70-74°). Correct analytical results on its picrate m.p. 204° (reported m.p. 203-205°) confirmed the identity of the compound.

The second product, obviously being an organic peroxide, on passing through the silica gel column, was decomposed to an unidentifiable weak peroxidic oily material.

IVc and VIIc are extremely sensitive to air and

the products of the autoxidation are canary yellow materials of polymeric nature. The formation of such polymeric substances is not surprising and could be normally expected by considering the inter-

mediate hydroperoxides involved. It is well understood that the unusual occurrence of a vinyl group and peroxy group on the same molecule can rapidly give rise to autovinylpolymerization.



EXPERIMENTAL

Melting points (uncorrected) were determined on a Gallenkamp melting point apparatus. Infrared spectra were determined on a Perkin-Elmer Model 337 from Nujol mulls.

1-Vinyl-1,2-Dihydrophthalazine (IVc).

A solution of phthalazine (0.65 g.) (9) in dry ether (50 ml.) was cooled to 0°. To this solution, under a blanket of nitrogen and with vigorous stirring, 4 ml. of an 8% vinyl-lithium solution (10) was added dropwise in the course of 30 minutes. After the completion of the addition, stirring was continued for 30 minutes while the temperature was maintained at 0°. The light orange colored reaction solution was poured with vigorous stirring onto crushed ice. Ten minutes later the organic layer was separated, washed once with 5 ml. of water and dried over potassium carbonate. The ether was removed under reduced pressure, and the remaining oil was subjected to high vacuum until it solidified. This solid material on shaking with 80 ml. of pentane gave a light yellowish extract which on standing overnight in a refrigerator deposited pale yellow crystals melting at 63-64°, yield 0.43 g. (55%). IR spectrum displayed absorptions characteristic of NH (at 3250 cm⁻¹) and -CH = CH₂ at 1640, 982, and 907 cm⁻¹. 1-Vinyl-1,2-dihydrophthalazine (IVc) is sensitive to air and the product of autoxidation is a peroxidic high viscous yellow material of polymeric nature.

Anal. Calcd. for C₁₀H₁₀N₂: C, 75.93; H, 6.37; N, 17.70. Found: C, 76.01; H, 6.25; N, 17.89.

1-Phenyl-1,2-Dihydrophthalazine (IVb).

A solution of phthalazine (0.65 g.) in dry ether (50 ml.) was cooled to 0°. To this solution in a nitrogen atmosphere and under vigorous stirrings, 10 ml. of a 10% phenyllithium solution (11) was added dropwise in the course of 30 minutes while the temperature was kept at 0°. The light orange colored solution was poured under stirring onto crushed ice and the organic layer was separated, washed once with water, and dried over potassium carbonate. The ether was removed under reduced pressure, and the oily residue was subjected to high vacuum until it solidified (about 4 hours). The solid material on treatment at room temperature with a mixture of petroleum ether-diethylether (4:1) separated white crystals melting at 80-86°. This crystalline product on shaking with pentane (40 ml.), gave a solution from which some insoluble oily material was separated. The colorless solution upon removal of the solvent under reduced pressure, followed by high vacuum, led to a crystalline product melting at 74-75°. It weighed 0.19 g. The infrared spectrum showed strong NH absorption at 3290 cm⁻¹ and elemental analyses were consistent with the molecular formula C₁₄H₁₂N₂ which fits for 1-phenyl-1,2-dihydrophthalazine.

Anal. Calcd. for C₁₄H₁₂N₂: C, 80.74; H, 5.80. Found: C, 80.57; H, 5.55.

4-Vinyl-3,4-Dihydro-1(2H)-Phthalazinone (VIIc).

A solution of 1(2H)-phthalazinone (0.73 g.) in tetrahydrofuran (50 ml.) was cooled to 5-7°. To this solution, in a nitrogen atmosphere, with vigorous stirring, 4 ml. of an 8% vinylolithium solution was added dropwise in the course of 20 minutes. Stirring was continued for 20 minutes and the resulting reaction solution was poured onto crushed ice. The organic layer was separated and the aqueous layer extracted with ether. The organic layer was washed once with water and dried over potassium carbonate. Removal of the solvent under reduced pressure, followed by high vacuum led to a pale yellow solid product.

4-Vinyl-3,4-dihydro-1(2H)-phthalazinone was crystallized from petroleum ether in pale yellow hard prisms melting at 138-140° to an orange colored liquid, yield 0.12 g. The IR spectrum showed characteristic absorptions at 3175 cm⁻¹ (NH), 3120 cm⁻¹ (NHCO), and 1670 cm⁻¹ (-CONH), and 1620, 990, 932 cm⁻¹ (-CH = CH₂).

Anal. Calcd. for C₁₀H₁₀N₂O: C, 68.94; H, 5.78; N, 16.07. Found: C, 69.39; H, 5.44; N, 15.89.

4-Phenyl-3,4-Dihydro-1(2H)-Phthalazinone (VIIb).

A solution of 1(2H)-phthalazinone (0.73 g.) in tetrahydrofuran (50 ml.) was cooled to 5-7°. To this solution, in a nitrogen atmosphere and under vigorous stirring, 10 ml. of a 10% phenyllithium solution was added dropwise in the course of 20 minutes. After the completion of the addition, stirring was continued for 10 additional minutes, and the resulting reaction solution was poured, while stirring, onto crushed ice. The organic layer was separated and the aqueous layer extracted with ether. Both organic layer and ether extracts were combined, washed once with water and dried over potassium carbonate. Removal of the solvent under reduced pressure followed by high vacuum, gave a semi-solid material, which on treatment with a mixture of ether-pentane (1:1) separated a white crystalline product melting at 165-166°

(yield 0.13 g.). The IR spectrum showed strong characteristic absorptions at 3215 cm⁻¹ (NH) and 1660 cm⁻¹ (CONH).

Anal. Calcd. for C₁₄H₁₂N₂O: C, 74.97; H, 5.38; N, 12.49. Found: C, 75.12; H, 5.25; N, 13.11.

1-Phenylphthalazine (VIIIb).

A solution of 1-phenyl-1,2-dihydrophthalazine (IVb) (0.05 g.) in methanol (5 ml.) was stirred for 4 hours in an open flask. Removal of the methanol under reduced pressure led to a gummy residue, from which on trituration with 3 ml. of ether, separated a pale yellow crystalline material melting at 140-141°. It was dissolved in ether and filtered through charcoal. Removal of the solvent afforded a white, faint yellow-tinged crystalline product melting at 144° (reported m.p. 142-143°), (11) (yield 0.045 g.).

Anal. Calcd. for C₁₄H₁₀N₂: C, 81.52; H, 4.89; N, 13.58. Found: C, 81.48; H, 5.05; N, 13.65.

4-Phenyl-1(2H)-Phthalazinone (IXb).

4-Phenyl-3,4-dihydro-1(2H)-phthalazinone (VIIb) was autoxidized to the corresponding 4-phenyl-1(2H)-phthalazinone (IXb) by a procedure similar to that applied for the conversion of IVb to VIIIb. The product obtained showed a m.p. 235° (reported m.p. 236°) (12,13). The yield was almost quantitative.

Anal. Calcd. for C₁₄H₁₀N₂O: C, 75.65; H, 4.53. Found: C, 75.88; H, 4.56.

1-Methylphthalazine (VIIIa).

Phthalazine (0.65 g.) was dissolved in ether (60 ml.) and the resulting solution cooled to 0°. Under a blanket of nitrogen and with vigorous stirring, 4 ml. of a 6% methylolithium solution was added dropwise to the former solution in the course of 15 minutes. Then, stirring was continued for 10 more minutes. The reaction mixture was poured onto crushed ice and stirred for a few minutes. The organic layer was separated, washed with water, and dried over potassium carbonate.

Removal of the solvent under reduced pressure afforded a yellowish oil. Its IR spectrum showed strong absorption at 2290 cm⁻¹ (NH). It was presumed to be 1-methyl-1,2-dihydrophthalazine. In no case, however, has any attempt been made to isolate this substance because of experimental difficulties. Thus, the crude oily reaction product was dissolved in ethanol and at room temperature, was stirred in an open flask for 4 hours. Removal of the ethanol under reduced pressure followed by high vacuum resulted in a yellow oil which on scratching with a spatula, was solidified to a yellow material of low melting point. This product, on trituration with a few ml. of a mixture of hexane-diethylether (1:1) gave a pale yellow solid melting at 95-98°. It was further dissolved in ether, shaken with charcoal, and filtered through a funnel packed with a thin layer of magnesium sulfate. The colorless filtrate, after removal of the ether, afforded a white crystalline product, melting at 100-102°, yield 0.34 g. It reacted strongly peroxidic to potassium iodide - acetic acid, and had an active oxygen of 4.4%. A TLC taken of this material showed the presence of three different compounds. The percentage of each compound was estimated from the intensity of its R_f to be approximately R_f: 0.00, 20%; 0.50, 80%; 0.60, traces. The compound with R_f 0.50 was found to be an organic peroxide when a second chromatogram was sprayed with a mixture of hydrogen iodide-glacial acetic acid as the detecting agent. Considerable difficulty was experienced in the separation of this mixture. This mixture, on passing through a column packed with silica gel, using as eluent a mixture of ethanol-benzene (1:4) led to the isolation of 1-methylphthalazine as a white crystalline compound melting at 71-72° (reported m.p. 70-74°) (14), yield 0.06 g. Correct analytical results on its picrate m.p. 204° (reported m.p. 203-205°) (14,15) confirmed the identity of the substance. The second compound in the mixture, being an organic peroxide; could not be isolated. On passing through the silica gel column, it was decomposed to an unidentifiable oily, weak peroxidic material.

Anal. Calcd. for C₁₁H₁₁N₂O₇: C, 48.26; H, 2.97; N, 18.76. Found: C, 48.40; H, 2.71; N, 18.66.

4-Methyl-1(2H)-Phthalazinone (IXa).

A solution of 1(2H)-phthalazinone (0.73 g.) in dry tetrahydrofuran was cooled to about 3-5°. To this solution, in a nitrogen atmosphere under vigorous stirring 4 ml. of a 6% methylolithium solution was added dropwise in the course of 20 minutes. After the completion of the addition, stirring was continued for one hour, the temperature being kept below 5°.

The resulting reaction solution was poured under vigorous stirring, onto crushed ice and a few minutes later the organic layer was separated, and the aqueous layer extracted with ether. Both organic layer and ether extract were combined, washed once with water and dried over magnesium sulfate. Removal of the solvent under reduced pressure followed by high vacuum led to a solid material melting

broadly at about 85°. The IR spectrum showed characteristic absorptions at 3200 cm^{-1} (NH), 3175 cm^{-1} (CONH), and 1665 cm^{-1} (CONH), and thus confirmed the presence of 4-methyl 3,4-dihydro-1(2H)-phthalazinone (VIIa) which was not isolated and characterized. The crude solid material was dissolved in 5 ml. of ethanol, stirred in an open flask for eight hours, shaken with charcoal, and filtered. The colorless ethanol solution on standing for a few hours in a freezer, deposited 4-methyl-1(2H)-phthalazinone (IXa) as white crystals melting at 222-223° (reported m.p. 222-224°) (16,17), yield 0.42 g.

Anal. Calcd. for $\text{C}_9\text{H}_9\text{N}_2\text{O}$: C, 67.48; H, 5.03; N, 17.48. Found: C, 67.28; H, 4.85; N, 17.34.

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REFERENCES

- (1) Presented in Part at the 48th Annual Conference of the Chemical Institute of Canada, Montreal, Quebec, June, 1965.
- (2) A. Mustafa, A. H. Harhash and A. A. S. Saleh, *J. Am. Chem. Soc.*, **82**, 2735 (1960).
- (3) K. Ziegler and H. Zeiser, *Ann.*, **485**, 174 (1931). K. Ziegler and H. Zeiser, *Ber.*, **63**, 1847 (1930).
- (4) A. Rieche, "Alkylperoxyde und Oxonide," Steinkopff, Dresden, 1931.
- (5) C. Walling, "Free Radicals in Solutions," John Wiley and Sons, New York, N. Y., 1957, pp. 398 et seq.
- (6) M. Viscontini and H. R. Weilenmann, *Helv. Chim. Acta.*, **42**, 1854 (1959).
- (7a) W. Metzger and H. Fischer, *Ann.*, **527**, 1 (1956). (b) G. O. Schenck, *Angew. Chem.*, **69**, 579 (1957).
- (8) E. G. E. Hawkins, "Organic Peroxides," D. Van Nostrand Company, Ltd., Princeton, New Jersey, 1961, p. 401.
- (9) A. Hirsch and D. G. Orphanos, *J. Heterocyclic Chem.*, **2**, 206 (1965).
- (10) Purchased from Metallomer Laboratories, Maynard, Mass.
- (11) "Organic Syntheses," Col. Vol. II., John Wiley and Sons, New York, N. Y., 1965, p. 518.
- (12) A. Lieck, *Ber.*, **38**, 3918 (1905).
- (13) R. Von Rothenburg, *J. Prakt. Chem.*, **51**, 140 (1895).
- (14) V. Mizuno, K. Adachi and K. Ikeda, *Pharm. Bull.*, (Tokyo), **2**, 225 (1954); *Chem. Abstr.*, **50**, 1035d (1956).
- (15) S. Gabriel and G. Eschenback, *Ber.*, **30**, 3022 (1897).
- (16) S. Gabriel and A. Neumann, *ibid.*, **26**, 521 (1893).
- (17) F. Rowe and A. Peters, *J. Chem. Soc.*, 1331 (1933).

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