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Synthesis of Tetracyclic Phenazine Derivatives by Reactions of Lawsone with Diamines

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The reaction of lawsone (**1**) with 1,2-diaminobenzene (**2**) gave the tetracyclic phenazine derivatives (**4**) while with 2,3-diaminotoluene (**5**) a mixture of the phenazine regioisomers (**8**) and (**9**) were obtained, on simple grinding as also on heating. No reaction was observed with 1,2-diaminoethane (**10**) under similar conditions.

Key Words: Lawsone, 1,2-Diaminobenzene, 2,3-Diaminotoluene, 1,2-Diaminoethane, Regioisomers.

INTRODUCTION

Quinones bearing hydroxy groups on the quinone ring represent an interesting class within the quinone family and almost all exhibit some kind of biological activity[1,2]. A great variety of these hydroxyquinones are found in nature[3]. These vary in structural complexity from the simple hydroxynapthoquinone, lawsone, the main component of a natural dye[4], to complex structures such as the trimeric hydroxynapthoquinone conocurvone, a potential anti-HIV agent[5].

Lawsone (2-hydroxy-1,4-napthoquinone), also known as hennotannic acid, is present in the leaves of *Lawsonia inermis* (henna plant)[6] as well as root cultures of *Impatiens balsamina* (jewel weed)[7]. Lawsone reacts chemically with the protein keratin in skin and hair by Michael addition, resulting in a strong permanent stain that lasts until the skin or hair is shed. Synthesis and reaction patterns of hydroxyquinones have been reviewed[8]. In this communication, we report the reactions of lawsone with different 1,2-diamines using conventional heating and mortar-pestle grinding, a green synthesis approach.

EXPERIMENTAL

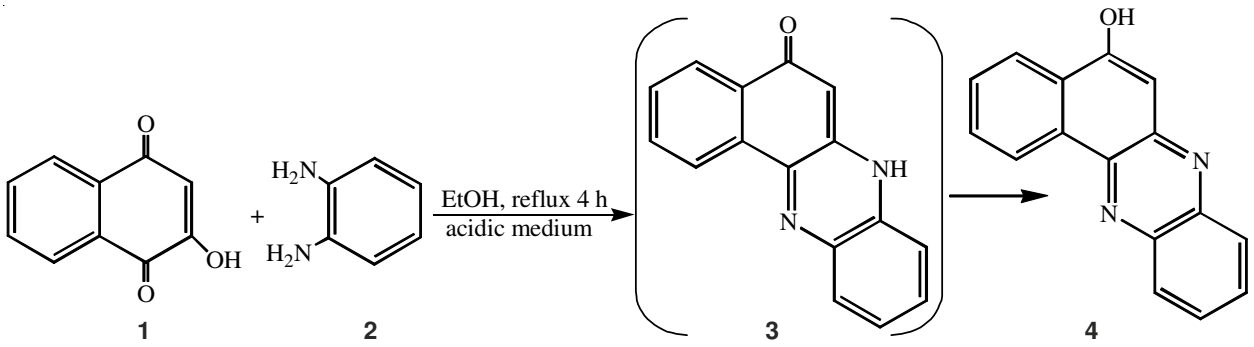
All chemicals used in the present investigation were of analytical grade and their purity was checked by TLC. The melting points of newly synthesized compounds were determined in open capillary tubes using Perfit model and are uncorrected. The spectral studies were carried out for their characterization using FT IR spectrophotometer (model 8400S, Shimadzu), 300 MHz NMR spectrometer (model Jeol AL-300) and mass spectrometer (model Jeol SX-102). Column chromatography was carried out using Merck Kielselgel 60 (60-120 mesh), while precoated silica gel 60, F254 (Merck, Germany) plates were used for thin layer chromatography. visualization was achieved by using UV light or iodine chamber.

Reaction of lawsone with 1,2-diaminobenzene (2): (A) Lawsone 0.522 g (3 mmol) in 10 mL of ethanol containing 2-3 drops acetic acid was treated with equal equivalent of 1,2-diaminobenzene (0.324 g). The reaction mixture was heated under reflux and the course of the reaction was monitored by TLC until disappearance of the starting napthoquinone (4 h). The reaction mixture was then cooled and ethanol removed under reduced pressure. The crude product was purified by silica gel column chromatography with petroleum ether/benzene (3:1) as solvent. Yield (82 %).

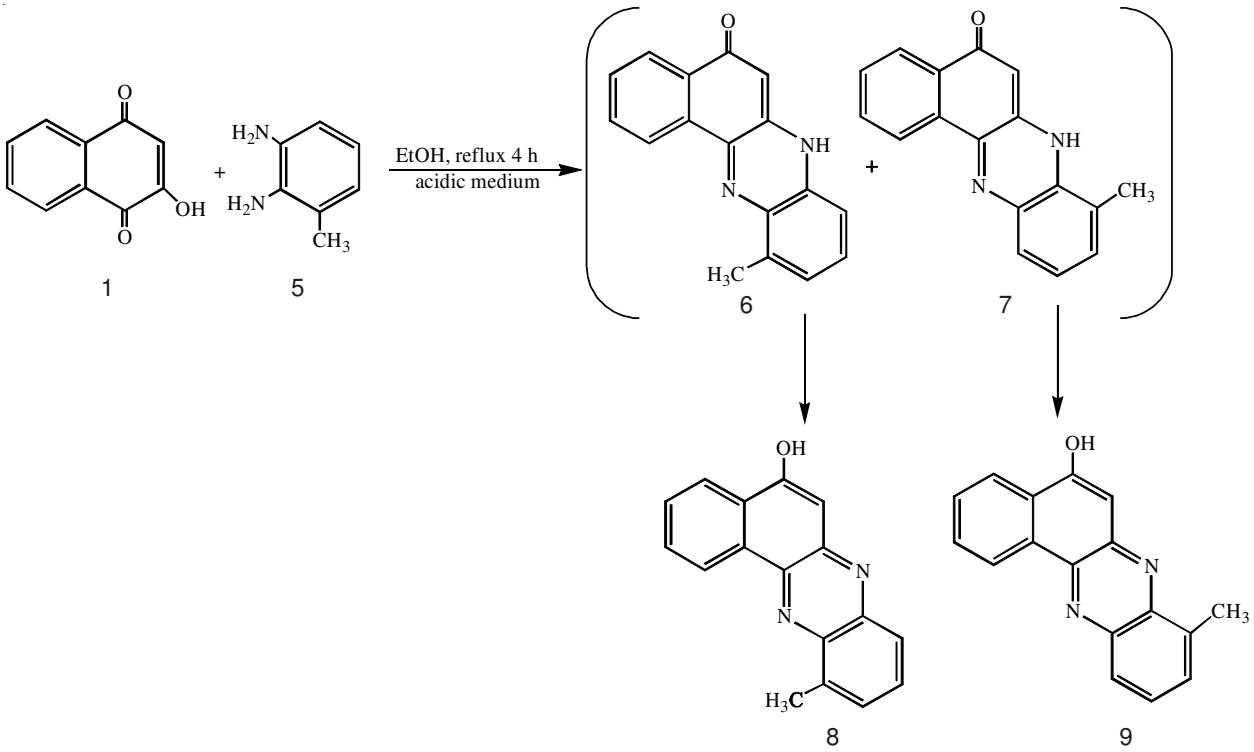
(B) Lawsone (0.522 g, 3 mmol) and 1,2-diaminobenzene (0.324 g, 3 mmol) were placed in a mortar and ground by hand with the pestle. Few drops of acetone were added to ease grinding. Grinding was continued until the mixture appeared homogeneous and the reaction was complete (TLC), which took 0.5 h. The solvent was evaporated and the purification of crude product was carried out by column chromatography (silica gel) with pet. ether/benzene (3:1) as solvent. The product was obtained in enhanced yield (97 %).

Benzo[a]phenazin-5-ol (4)

Physical properties: Yellow powder, m.p. 92 ºC; IR (KBr, λ_{max}, cm^{-1}); 3250 (O-H), 3090 (Aromatic C-H), 1610 (C=N), 1480 (Aromatic C=C), ^1H NMR (300 MHz; $CDCl_3$; Me_4Si) 7.40 (1H, s, 6-H), 7.80-8.30 (8H, m, Arom-H), 12.30 (1H, s, O-H); MS (*m/z*; rel. int. %) $[M]^+$ ($C_{16}H_{10}N_2O$) (72), 229 $[M-OH]^+$ (36); Anal. calcd. for $C_{16}H_{10}N_2O$: C, 78.04; H, 4.06; N, 11.38. Found: C, 77.86; H, 4.15; N, 11.28 %.



Scheme-I: Reaction of lawsone with 1,2-diaminobenzene



Scheme-2: Reaction of lawsone with 1,2-diaminototuene

Reaction of lawsone with 2,3-diaminotoluene (5): Following the procedures described above, 0.522 g (3 mmol) of **1** was treated with 0.366 g (3 mmol) of **5**, in ethanol. The progress of the reaction was examined on TLC plate, which indicated the formation of two products. The products were separated by column chromatography with petroleum ether/ benzene (1:3) as solvent and characterized as the regioisomers, **8** and **9** on the basis of spectral studies. Yield: 41 % of (**8**), 52 % of (**9**). The same products were obtained from mortar-pestle grinding method. Yield 38 % of (**8**), 56 % of (**9**).

11-Methylbenzo[a]phenazin-5-ol (8)

Physical properties: Yellow powder, m.p. 108 ºC; IR (KBr, ν_{max}, cm^{-1}); 3370 (O-H), 3080 (aromatic C-H), 1595 (C=N), 1490 (aromatic C=C), ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) 2.40 (3H, br s, Ar-CH_3), 7.30 (1H, s, 6-H), 7.80-8.10 (7H, m, Arom-H), 12.10 (1H, s, O-H); MS (*m/z*; rel. int. %) $[M]^+$ ($C_{17}H_{12}N_2O$) (78), 243 $[M\text{-}OH]^+$ (42), 227 $[243\text{-}CH_2]^+$; Anal. calcd for $C_{17}H_{12}N_2O$: C, 78.46; H, 4.62; N, 10.77. Found: C, 78.32; H, 4.70; N, 10.82 %.

8-Methylbenzo[a]phenazin-5-ol (9)

Physical properties: yellow powder, m.p. 112 ºC; IR (KBr, ν_{max}, cm^{-1}); 3320 (O-H), 3070 (aromatic C-H), 1620 (C=N), 1495 (aromatic C=C), ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si) 2.40 (3H, br s, Ar-CH_3), 7.25 (1H, s, 6H), 7.70-8.30 (7H, m, Arom-H), 12.20 (1H, s, O-H); MS (*m/z*; rel. int. %) $[M]^+$ ($C_{17}H_{12}N_2O$) (80), 243 $[M\text{-}OH]^+$ (36), 227 $[243 - CH_2]^+$; Anal. calcd. for $C_{17}H_{12}N_2O$: C, 78.46; H, 4.62; N, 10.77. Found: C, 78.38; H, 4.68; N, 10.72 %.

Reaction of Lawsone with 1,2-diaminoethane: No reaction was observed when lawsone was treated with 1,2-diaminoethane under similar reaction conditions. It appears that the aromatic stabilization of the phenazine moiety is the driving force in the reaction.

RESULTS AND DISCUSSION

The reaction of lawsone (**1**) with 1,2-diaminobenzene (**2**) gave the corresponding tetracyclic phenazine derivative **4** (**Scheme-I**) while refluxing with 2,3-diaminotoluene (**5**) gave the mixture of the regioisomers, **8** and **9** (**Scheme-II**).

These reactions were also carried out under mortar-pestle grinding technique, where the reaction was complete in lesser time and in enhanced yield.

The structure of all the condensation products have been assigned on the basis of the spectral (FT IR, ^{1}H NMR and mass) data and other analytical techniques. In the IR spectrum of **4**, **8** and **9** a broad absorption peak between 3100-3400 cm^{-1} due to the -OH stretching vibrations was obtained. In the ^{1}H NMR spectra of **4**, **8** and **9** the aromatic ring protons are manifested as a multiplet at 7.70-8.30 ppm, the hydroxyl proton gives a signal about 12.10-12.30 ppm for one proton in **4**, **8** and **9**. Products **8** and **9** also exhibited a well defined single peak at 2.40 ppm assigned to three CH_3 protons.

The final products **4**, **8** and **9** are probably obtained through the intermediates **3**, **6** and **7**.

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