HETEROCYCLES, Vol. 53, No.10, 2000, pp. 2151-2162, Received, 29th May, 2000

# SYNTHESIS OF PHENAZINE 5,10-DIOXIDES FROM BENZOFUROXAN CATALYZED BY MOLECULAR SIEVES

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**Abstract** - The synthesis of substituted phenazines was carried out. Phenazine 5,10-dioxides (**3**) were obtained from benzofuroxan (**1**) with dihydroxybenzene derivatives (**2**) catalyzed by molecular sieves at room temperature.

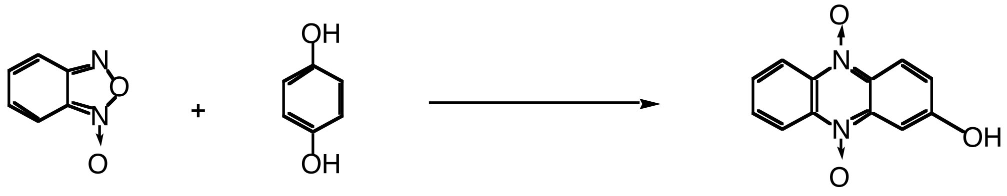
## INTRODUCTION

Benzofuroxan (**1**) has been shown to have numerous pharmacological and industrial applications.[1a-c] Reactions of benzofuroxan with phenolic compounds in basic medium provide the corresponding phenazine 5,10-dioxide derivatives.[2] Certain phenazine derivatives are known to have antibacterial activity and two of which, iodinin and myxin, are microbial metabolites.[3, 4] As a part of benzofurazan chemistry, reactions of benzofuroxans with active methylene compounds lead to the corresponding quinoxaline 1,4-dioxides catalyzed by silica gel[5] or molecular sieves[6, 7] and the antibacterial activity of quinoxaline 1,4-dioxides has been reported.[8] Pyrido[2,3-*b*]pyrazine 1,4-dioxides and pyrido[2,3-*b*]pyrazine 1-oxides have been obtained from pyrido[2,3-*c*]furoxan catalyzed by silica gel, alumina, or molecular sieves[9] and the antibacterial activity of pyrido[2,3-*b*]pyrazine 1,4-dioxides and pyrido[2,3-*b*]pyrazine 1-oxides has been reported.[10] In this study, phenazine 5,10-dioxide derivatives were obtained from benzofuroxan and dihydroxybenzene derivatives catalyzed by molecular sieves or silica gel or alumina at room temperature.

## RESULTS AND DISCUSSION

Phenazine 5,10-dioxide derivatives were synthesized as follows. A solution of compound (**1**) and 1,4-dihydroxybenzene derivatives (**2**) in methanol was evaporated in the presence of molecular sieves 4A, aluminum oxide, or silica gel. Both starting materials were adsorbed on the molecular sieves or other catalysts followed by standing at room temperature, 40 °C or 90 °C. The reaction mixture was chromatographed on silica gel to give the corresponding phenazine 5,10-dioxide derivatives (**3**).

Table 1

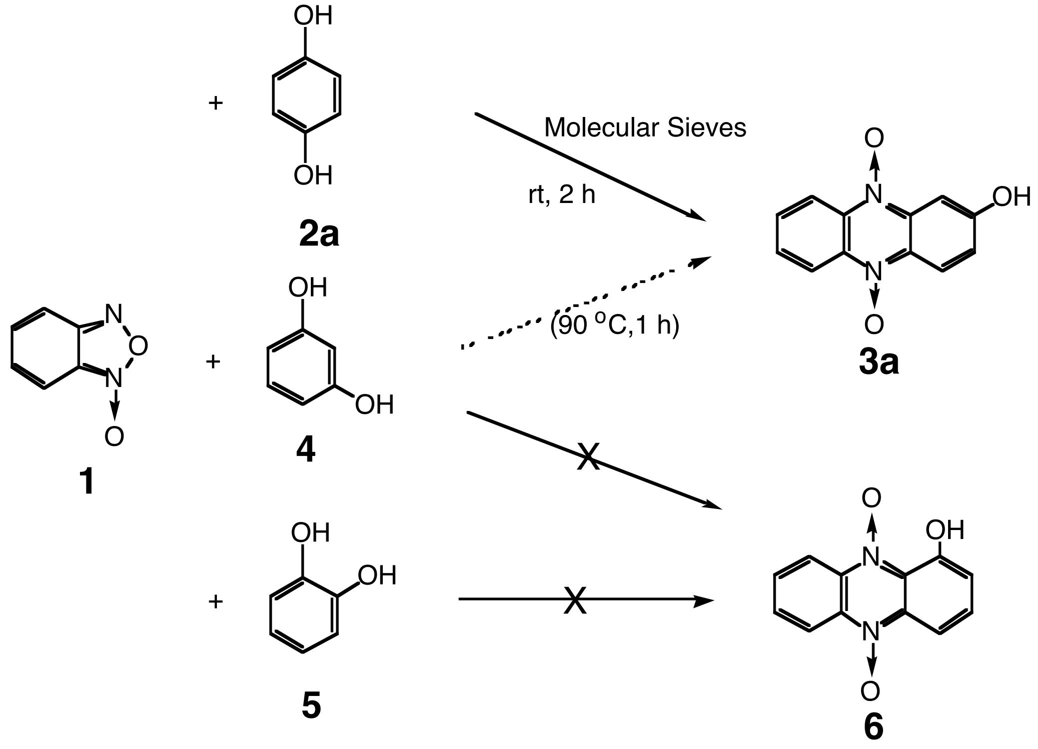


**1** **2a** **3a**

| Catalysts | **3a**[11](%) | **1** (%, recovery) | Reaction condition |
|---|---|---|---|
| Molecular sieves 4A | 87 | 0 | rt, 2 h |
| Aluminum oxide, basic | 37 | 0 | 90 °C,1 h |
| | 56 | 8 | 40 °C, 2 h |
| acidic | 21 | 7 | 40 °C, 2 h |
| neutral | 29 | 0 | 40 °C, 2 h |
| Silica gel C-200 | 16 | 39 | 90 °C, 2 h |
| None | 0 | 97 | rt, 2 h |

Various catalysts and temperature in the reaction of compound (**1**) with 1,4-dihydroxybenzene (**2a**) were examined (Table 1). In using catalysts, reaction efficacy varied considerably with the catalyst used. Phenazine 5,10-dioxide derivatives were obtained in good yield using molecular sieves 4A as catalyst at room temperature. The most suitable catalyst was molecular sieves 4A.

Table 2



| Compound No. | Yield (%) of Phenazine |
|---|---|
| **2a** | 87 (**3a**) |
| **4** | 0 (**3a, 6**) |
|  | 1.1* (**3a**) |
| **5** | 0 (**6**) |
|  | 0* (**6**) |

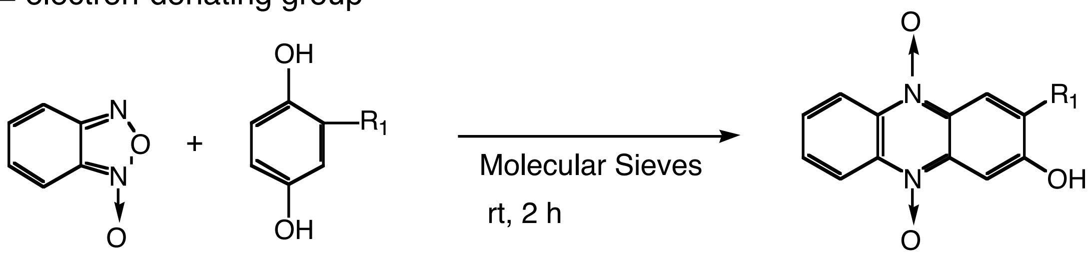
* 90 °C,1 h

1,4-Dihydroxybenzene reacted with compound (**1**) to give 2-hydroxyphenazine 5,10-dioxide (**3a**) in good yield but 1,2-dihydroxybenzene (**5**) did not and the reactivity of 1,3-dihydroxybenzene (**4**) was less. No 1-hydroxyphenazine 5,10-dioxide (**6**) was obtained (Table 2).

Various 1,4-dihydroxybenzene derivatives (**2a~2g**) in reactions with compound (**1**) were examined. The influence of electron-withdrawing and electron-donating groups in the reactions was examined using dihydroxybenzene derivatives.

Table 3

$R_1$ = electron-donating group



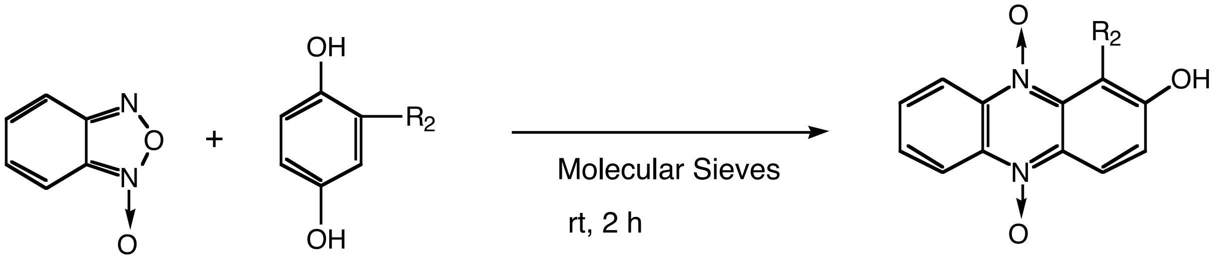
**1** **2** **3**

| Compound No. | $R_1$ | Yield (%) | **1** (Recovery) |
|---|---|---|---|
| **3a** | H | 87 | 0 |
| **3b** | $CH_3$ | 80 | 0 |
| **3c** | $OCH_3$ | 91 | 0 |

As evident from Table 3, the electron-donating group on 1,4-dihydroxybenzene made possible phenazine synthesis in good yield but comparison of yields of various phenazines as products indicated the electron-withdrawing group on 1,4-dihydroxybenzene not to lead to good yield (See Table 4). Phenazines (**3a~3f**), the assignments were made based on the following; When $^1$H-NMR signals of phenazines were compared, $^1$H-NMR spectrum of compound (**3d**) showed two doublet signals (δ 7.45 and 8.91 ppm) and the coupling constant was 10.27 Hz. These signals may possible consist of protons 3 and 4. Phenazines including the electron-donating group have two singlet signals consisting of protons 1 and 4.

Table 4

$R_2$ = electron-withdrawing group



**1** **2** **3**

| Compound No. | $R_2$ | Yield (%) | **1** (Recovery) |
|---|---|---|---|
| **3d** | CHO | 52 | 29 |
| **3e** | $COCH_3$ | 26 | 44 |
| **3f** | $COCH_2CH_3$ | 34 | 47 |
| **3g** | COOH | 0 | 90 |

The ethyl 2-hydroxyphenazine-1-yl ketone 5,10-dioxide (**3f**) has interesting $^1$H-NMR spectrum which showed two quartets at δ 2.63 and 2.99 ppm with each 1H integration for protons at the methylene of **3f** at 25 °C. The methylene group may thus rotate slowly enough to show different chemical shifts of two kinds of protons. The temperaturedependent $^1$H-NMR spectra for compound (**3f**) are shown in Figure 1. The two quartet signals broadened slightly at 80 °C and then changed to one signal (δ 2.82 ppm) at 140 °C.

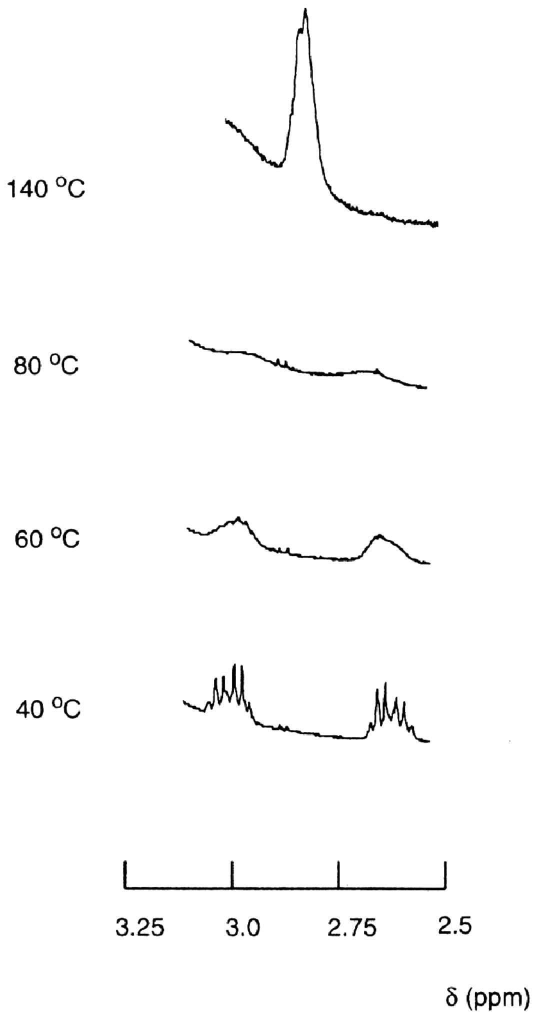
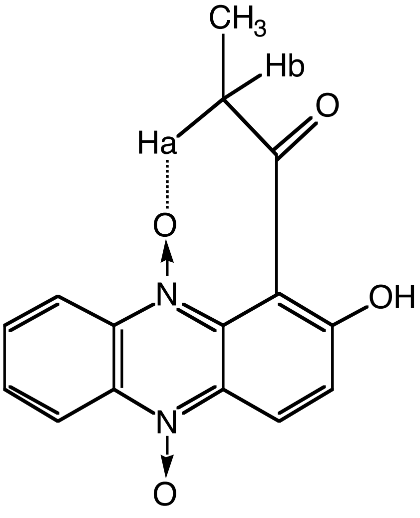


Figure 1

Scheme 1 shows the positions of protons at the methylene of **3f** to be close to oxygen at *N*-oxide, and consequently oxygen affects the rotation of the two protons at methylene. The oxygen may possibly function as a barrier against conformation of methylene and so methylene group rotation is slow enough that different chemical shifts are apparent.

Molecular sieves 4A or other catalysts would thus appear to affect dehydration in the reaction mechanism and the reaction proceed not in but on molecular sieves in that the



**3f**

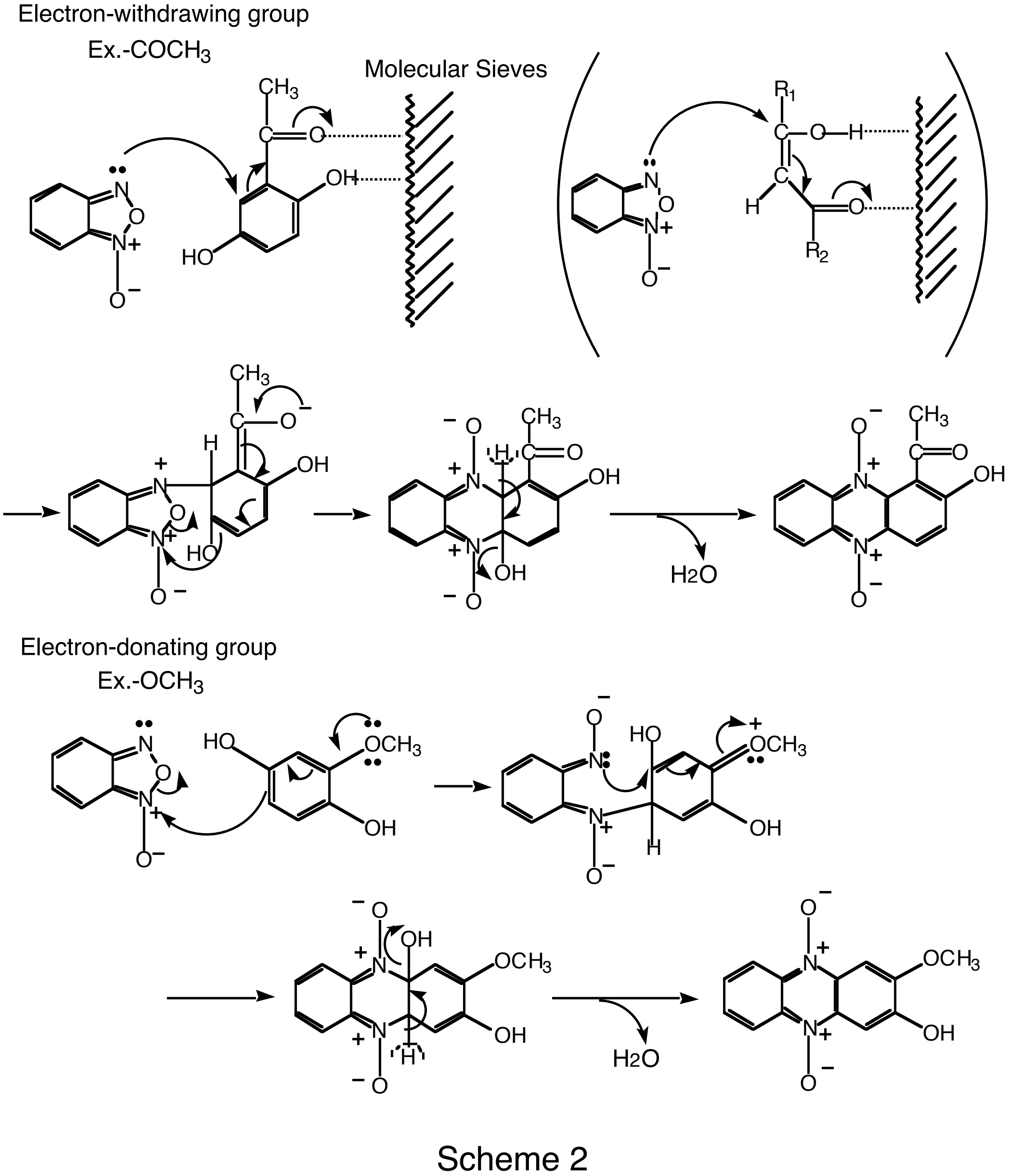
Scheme 1

pore diameter of molecular sieves 4A is approximately 0.4 nm. Windows to the cages are too small to allow the organic molecules access to cages.

The enol form of carbonyl compounds was previously shown necessary for the formation of quinoxalines or pyridopyrazines, whose yields depends on enol content in 1,3-diketones.[7, 9] Molecular sieves or other catalysts may serve to enhance the stability of the enol form of carbonyl compound and the dehydration capacity of catalysts may determine significantly the possibility of synthesis.

Molecular sieves may have similar effect as electron-withdrawing groups on dihydroxybenzenes (see Scheme 2). Electron-withdrawing groups and molecular sieves surface force dihydroxybenzenes to couple at the ortho position followed by cyclization and elimination of water to yield phenazines. The different attacking positions in the reaction on molecular sieves may lead to different structures of phenazines as products. In the case of reaction with 2,5-dihydroxybenzoic acid, no product was obtained, possibly owing to steric hindrance.

The present method is simple and efficient for the preparation of phenazine 5,10-dioxide derivatives under mild conditions.



Scheme 2

**EXPERIMENTAL**

Melting points were determined with a Yanagimoto micromelting point apparatus and are uncorrected. The IR spectra were recorded on a JASCO IR-810 spectrophotometer. The $^1$H-NMR spectra were recorded on a JNM-GSX 400 FT NMR System with TMS as the internal standard. The MS spectra were recorded on a Hitachi M-2000 and JEOL JMS-GCmate spectrometers with an electron beam energy of 70 eV. Microanalysis was performed at the microanalytical laboratory of the Center for Instrumental Analysis in College of Science & Technology, Nihon University.

General Procedure (Table 1 ).

To a solution of **1** (34.5 mg, 0.25 mmol) and dihydroxybenzene (**2a**) (30.3 mg, 0.275 mmol) in methanol (5 mL) was added silica gel [Wako Pure Chemical Industries, Wakogel C-200, 1 g] or aluminium oxide [Merck, Aluminium oxide 90 active basic for column chromatography (Art. 1076), Aluminium oxide 90 active neutral for column chromatography (Art. 1077), Aluminium oxide 90 active acidic for column chromatography (Art. 1078), 1 g] or molecular sieves [4A powder, Union Showa, 1 g]. The mixture was evaporated in an evaporator at 30 °C. The adsorbent containing the adsorbed reagents was allowed to stand for 2 h at rt and then introduced onto the silica gel column (Wako Pure Chemical Industries, Wakogel C-200). The product 2-Hydroxyphenazine 5,10-dioxide (**3a**) was eluted with dichloromethane/methanol (95:5) and purified by preparative TLC (Merck, Silica gel plate 60 $F_{254}$ Art. 5717) with dichloromethane/methanol (95:5). Yield 49.8 mg (87 %).

2-Hydroxyphenazine 5,10-dioxide (**3a**)

Deep red powder, mp 243-245 °C(decomp) (lit.,[11] mp 234 °C(decomp)). IR (KBr) $cm^{-1}$: 1615, 1595, 1353, 1238, 1078, 837, 762. $^1H$- NMR (DMSO-$d_6$) δ : 7.49 (dd, 1H, $J_{1,3}$ = 2.2 Hz, $J_{3,4}$ = 9.5 Hz, C3-H), 7.77 (d, 1H, $J_{1,3}$ = 2.2 Hz, C1-H), 7.84-7.93 (m, 2H, C7-H, C8-H), 8.48 (d, 1H, $J_{3,4}$ = 9.5 Hz, C4-H), 8.52-8.56 (m, 2H, C6-H, C9-H), 11.33 (br s, 1H, OH, deuterium oxide-exchangeable). EI-MS m/z: 228.0502 (Calcd for $C_{12}H_8N_2O_3$: 228.0534). **3a** was characterized by comparison of IR spectra with an authentic sample. [11]

2-Hydroxy-3-methylphenazine 5,10-dioxide (**3b**)

Deep red powder, mp 223-225 °C. IR (KBr) $cm^{-1}$: 1620, 1457, 1346, 1254,1076, 830, 760. $^1H$-NMR (DMSO-$d_6$) δ : 2.41 (s, 3H, $CH_3$), 7.78 (s, 1H, C1-H), 7.78-7.90 (m, 2H, C7-H, C8-H), 8.33 (s, 1H, C4-H), 8.46-8.55 (m, 2H, C6-H, C9-H), 11.28 (br s, 1H, OH, deuterium oxide-exchangeable). EI-MS m/z: 242.0672 (Calcd for $C_{13}H_{10}N_2O_3$ :

242.0690). *Anal.* Calcd for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16; N, 11.56. Found: C, 64.46; H, 4.19; N, 11.57.

2-Hydroxy-3-methoxyphenazine 5,10-dioxide (**3c**)

Deep red powder, mp 248-250 °C. IR (KBr) $cm^{-1}$: 1620, 1524, 1470, 1347, 1223, 1185, 1082, 852, 763. $^1H$-NMR (DMSO-$d_6$) δ : 4.06 (s, 3H, $OCH_3$), 7.80 (s, 1H, C1-H), 7.81 (s, 1H, C4-H), 7.84-7.89 (m, 2H, C7-H, C8-H), 8.52-8.57 (m, 2H, C6-H, C9-H), 11.47 (br s, 1H, OH, deuterium oxide-exchangeable). EI-MS m/z: 258.0639 (Calcd for $C_{13}H_{10}N_2O_4$ : 258.0639). *Anal.* Calcd for $C_{13}H_{10}N_2O_4$: C, 60.47; H, 3.90; N, 10.85. Found: C, 60.42; H, 4.01; N, 10.80.

2-Hydroxy-1-phenazinecarboxaldehyde 5,10-dioxide (**3d**)

Orange powder, mp 221-224 °C. IR (KBr) $cm^{-1}$: 1630, 1583, 1472, 1355, 1290, 1170, 1104, 832, 776. $^1H$-NMR (DMSO-$d_6$) δ : 7.45 (d, 1H, $J_{3,4}$ = 10.2 Hz, C3-H), 7.85-7.96 (m, 2H, C7-H, C8-H), 8.68-8.77 (m, 2H, C6-H, C9-H), 8.91 (d, 1H, $J_{3,4}$ = 10.2 Hz, C4-H), 11.99 (s, 1H, CHO), 15.23 (s, 1H, OH, deuterium oxide-exchangeable). EI-MS m/z: 256.0489 (Calcd for $C_{13}H_8N_2O_4$ : 256.0483). *Anal.* Calcd for $C_{13}H_8N_2O_4$: C, 60.94; H, 3.15; N, 10.93. Found: C, 60.85; H, 3.29; N, 10.73.

2-Hydroxyphenazine-1-yl methyl ketone 5,10-dioxide (**3e**)

Deep red powder, mp 182-183 °C (mp. 180-181 °C).[11] IR (KBr) $cm^{-1}$: 1706, 1555, 1415, 1337, 1278, 1173, 816, 768. $^1H$-NMR (DMSO-$d_6$) δ : 2.56 (s, 3H, $CH_3$), 7.61 (d, 1H, $J_{3,4}$ = 9.5 Hz, C3-H), 7.83-7.88 (m, 2H, C7-H, C8-H), 8.40 (d, 1H, $J_{3,4}$ = 9.5 Hz, C4-H), 8.45-8.51 (m, 2H, C6-H, C9-H), 11.45 (s, 1H, OH, deuterium oxide-exchangeable). EI-MS m/z: 270.0686 (Calcd for $C_{14}H_{10}N_2O_4$ : 270.0640). **3e** was characterized by comparison of IR spectra with an authentic sample.[11]

Ethyl 2-hydroxyphenazine-1-yl ketone 5,10-dioxide (**3f**)

Deep red powder, mp 180-182 °C. IR (KBr) cm$^{-1}$: 1675, 1590, 1555, 1420, 1348, 1285, 1180, 1113, 831, 763. $^1$H-NMR (DMSO-$d_6$) $\delta$ : 1.17 (t, 3H, $J$ = 6.8 Hz, $C\underline{H_3}$-$CH_2$), 2.63 (q, 1H, $J$ = 6.8 Hz, $CH_3$-$CHa\underline{Hb}$), 2.99 (q, 1H, $J$ = 6.8 Hz, $CH_3$-$C\underline{Ha}Hb$), 7.56 (d, 1H, $J_{3,4}$ = 9.7 Hz, C3-H), 7.87 (m, 1H, C7-H, C8-H), 8.40 (m, 1H, C9-H), 8.50 (d, 1H, $J_{3,4}$ = 9.7 Hz, C4-H), 8.52 (m, 1H, C6-H, C9-H), 11.36 (s, 1H, OH, deuterium oxide-exchangeable). EI-MS m/z: 284.0804 (Calcd for $C_{15}H_{12}N_2O_4$ : 284.0796). *Anal.* Calcd for $C_{15}H_{12}N_2O_4$: C, 63.38; H,4.25 ; N, 9.85. Found: C, 63.22; H, 4.38; N, 9.86.

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