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A new Route for the Synthesis of Phenazine Di-N-Oxides

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Summary. Several phenazine 5,10-dioxides (**7a–d**) were prepared by the reaction of 2-methyl-3-acetylquinoxaline 1,4-dioxide (**2**) with different aromatic aldehydes or by direct cyclization of the quinoxaline cinnamoyl derivatives **3** in basic medium. In addition, the phenazine derivatives **8** and **9–12** were synthesized by a one-pot reaction of substituted *o*-nitroanilines with different hydroxy compounds in the presence of sodium hypochlorite solution.

Keywords. 2-Methyl-3-acetylquinoxaline-1,4-dioxide. Cinnamoylquinoxaline 1,4-dioxide; Phenazine 5,10-dioxide.

Ein neuer Syntheseweg für Phenazin-di-N-oxide

Zusammenfassung. Mehrere Phenazin-5,10-dioxide (**7a–d**) wurden durch Reaktion von 2-Methyl-3-acetylchinoxalin-1,4-dioxid (**2**) mit verschiedenen aromatischen Aldehyden oder durch direkte Cyclisierung der Chinoxalinderivate **3** in basischem Milieuhergestellt. Zusätzlich wurden die Phenazinderivate **8** und **9–12** in einer Eintopfreaktion von substituierten *o*-Nitroanilinen mit verschiedenen Hydroxyverbindungen in Gegenwart von Natriumhypochloritlösung synthetisiert.

Introduction

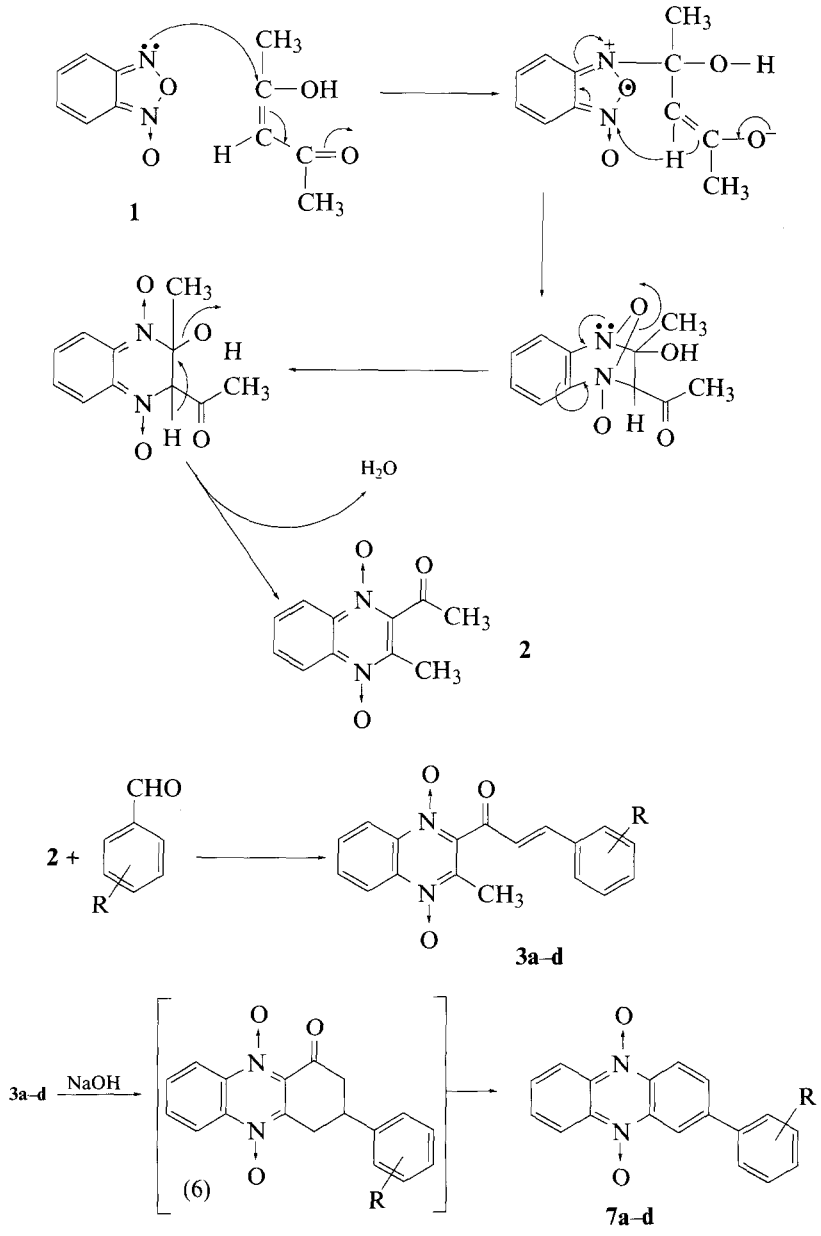
Many phenazine 5,10-dioxides are known to have antibacterial activity [1]. They are also useful as internal germicids and fungicides [2]. In the light of these considerations, and in continuation of our work on the synthesis of biological active heterocyclic compounds [3–5], the present work deals with the synthesis of some new functionalized quinoxaline 1,4-dioxides (**2**) and phenazine 5,10-dioxides (**7**) *via* the reaction of benzofurazan 1-oxide (**1**) with 2,4-diketone.

Results and Discussion

Quinoxaline 1,4-dioxides (**2**) were obtained by the reaction of benzofurazan 1-oxide (**1**) and acetylacetone in the presence of base [6]. Quinoxaline 1,4-dioxide formation formally involves loss of water when an active methylene compound is used as substrate. This reaction is now commonly referred to as the *Beirut* reaction.

α-Methylquinoxalines exhibit the typical reactivity of active methylene compounds. Condensation with aldehydes [7] proceeds readily; thus, treatment of 2-methyl-3-acetylquinoxaline 1,4-dioxide (**2**) with different aromatic aldehydes in basic medium at room temperature for a few minutes yields the cinnamoyl quinoxaline 1,4-dioxide derivatives (**3a–d**) in good yield. The 2-styryl derivative (**4**) or the dicondensation product (**5**) were not detected in the reaction mixture, even in the presence of excess aldehyde, under these reaction conditions.

The structures of **3a–d** were elucidated from their spectral and elemental analyses. The ^{1}H NMR spectra of **3c** show two multiplets at $\delta = 8.62$ (H_6 and H_7)



7a: R = H; **b**: R = *p*-NO_2; **c**: R = *p*-Cl; **d**: R = *p*-Br

Scheme 1

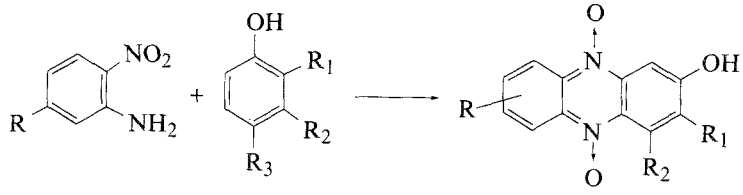
and 7.9 (H_5 and H_8), two doublets at $\delta = 7.37$ (2H, CH=CH), and a singlet at $\delta = 2.61$ (3H, CH_3) ppm.

Compounds **3a–d**, when stirred in alcoholic sodium hydroxide solution, afforded the corresponding phenazine 5,10-dioxide derivatives **7a–d** *via* the intermediate **6** which aromatize by loss of hydrogen to give **7**.

The intermediate **6** is difficult to isolate, even when the reaction is carried out under a nitrogen atmosphere. The structures of compounds **7a–d** were found to be in agreement with spectral data. The ^1H NMR spectrum of **7c** shows signals at $\delta = 8.6$ (m, 2H, H_6 and H_9), 7.9 (m, 2H, H_7 and H_8), and 7.6 (m, 2H, H_1 and H_3) ppm.

The absence of a methyl signals in the ^1H NMR spectrum indicates that the methyl group was involved in the *Michael* type reaction leading to intermediate **6**. The N→O functions of quinoxaline dioxide may be regarded as nitrone functions which resemble the C=O group in facilitating the removal of a proton from an α-carbon atom. Therefore, the methyl hydrogens at position 2 in the quinoxaline derivative **3** are expected to show enhanced activity and behave as good *Michael* donors [8].

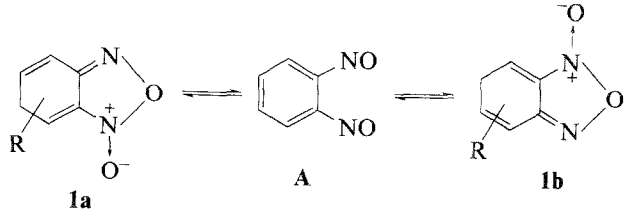
Phenazine 5,10-dioxide derivatives (**7a–f**) could also be synthesized in a one-pot reaction in excellent yield (over 80%), when a mixture of *o*-nitroaniline derivatives and different aromatic hydroxy compounds were treated with sodium hypochlorite solution at room temperature. Thus, treatment of *o*-nitroaniline derivatives with catechol ($R_1 = OH$, $R_2 = R_3 = H$), resorcenol ($R_2 = OH$, $R_1 = R_3 = H$), and/or hydroquinone ($R_3 = OH$, $R_1 = R_2 = H$) in the presence of sodium hydroxide and sodium hypochlorite at room temperature for extended periods afforded the corresponding phenazine 5,10-dioxides derivatives **8a–f**.



Scheme 2

These results indicate that the first step in the above reaction is the formation of benzofurazan 1-oxide by the action of sodium hypochlorite on the *o*-nitroaniline derivative which in turn reacts directly with phenols to give the corresponding 7- or 8-methyl phenazine derivatives **8a–f** (*cf.* Table 2).

Mixtures of isomeric di-N-oxides are generally obtained when 5 or 6-substituted benzofurazan 1-oxide are used in the *Beirut* reaction [9]. This can be ascribed to

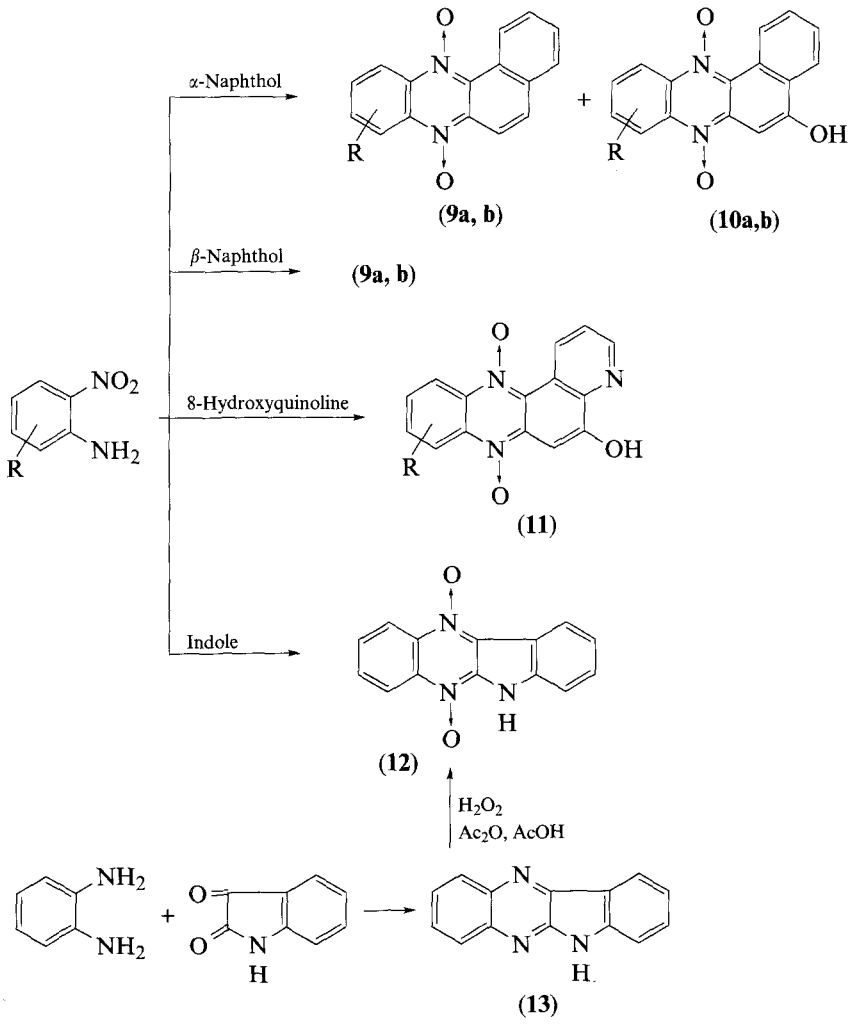


1a **A** **1b**

Scheme 3

the fact that benzofurazan 1-oxides react in their *o*-dinitrosobenzene form (**A**), which is an intermediate between the rapidly interconverting tautomers **1a** and **1b**.

Similarly, *o*-nitroaniline derivatives were subjected to react with α-naphthol to afford a mixture of the phenazine derivatives **9** and **10**, whereas the reaction with β-naphthol lead to the formation of **9** only and, when reacted with 8-hydroxyquinoline, gave pyrido[2,3-*a*]phenazinol-7,12-dioxides (**11**). In addition, *o*-nitroanilines were reacted with indole to give the indoloquinoxaline derivative **12**. Its structure was confirmed by an independent synthesis *via* the condensation of isatin derivatives with *o*-phenylenediamine to give the corresponding quinoxaline derivative **13** which on oxidation with peracetic acid gave compound 12.



Scheme 4

Experimental

Melting points were recorded on a Gollen Kamp apparatus and are uncorrected. IR spectra (KBr disc, ν in cm^{-1}) were recorded on a Perkin Elmer 838 spectrophotometer. ^1H NMR spectra were obtained

with a Varian 200 MHz spectrometer using *TMS* as internal standard (δ in ppm). Mass spectra were obtained on a Hewlett Packard 5970 mass spectrometer.

Benzofurazan 1-oxide (**1**)

1 was prepared according to a procedure reported previously [10].

2-Methyl-3-acetylquinoxaline 1,4-dioxide (**2**)

To a mixture of benzofurazan 1-oxide (**1**, 3 mmol) and acetylacetone (3 mmol) in ethanol (20 ml), a catalytic amount of triethyl amine was added. The reaction mixture was left to stand at room temperature for 3 hours. The obtained precipitate was filtered, dried, and crystallized from ethanol to give the quinoxaline derivative **2** (Table 1).

Phenazine 5,10-dioxide derivatives (**7a–d**)

Method 1

a) Synthesis of 2-methyl-3-cinnamoyl-quinoxaline 1,4-dioxides (**3a–d**)

A mixture of 2-methyl-3-acetyl-quinoxaline 1,4-dioxide (**2**, 3 mmol) and the appropriate aromatic aldehyde (3 mmol) in methanolic sodium hydroxide solution (10 ml, 5%) was stirred for 5–10 minutes at room temperature. The formed yellow to orange precipitate was filtered off, washed with water, and recrystallized from the appropriate solvent to give the cinnamoyl derivatives **3a–d**. The results are listed in Table 1.

3c: IR 1680 (C=O), 1585 (C=C) 1330 (N→O); ^{1}H NMR: 8.62 (m, H_6, H_7), 7.9 (m, H_5, H_8), 7.75, 7.37 (d, 2H, CH=CH–), 2.61 (s, 3H, CH_3); MS: (*m/z*): 340 (12%), 325 (26%).

b) Synthesis of phenazine 5,10-dioxide derivatives (**7a–d**)

A solution of **3a–d** (3 mmol) in methanolic sodium hydroxide solution (10 ml, 10%) was stirred for 2–3 hours at ambient temperature. The reaction mixture was turned deep green to violet in colour. The reaction mixture was poured into water and acidified with diluted hydrochloric acid (*pH* 2); the formed precipitate was filtered off, washed with water, and recrystallized from ethanol to give the phenazine derivatives **7a–d** (Table 1).

Method 2

A mixture of 2-methyl-3-acetylquinoxaline 1,4-dioxide (**2**, 3 mmol) and the appropriate aromatic aldehyde derivative (3 mmol) was stirred in methanolic sodium hydroxide solution (10 ml, 5%). After 5–10 minutes a yellow to orange precipitate of **3a–d** was formed. Stirring was continued for further 6 hours during which the solution turned green to violet in colour. The reaction mixture was then quenched with diluted hydrochloric acid (*pH* 2–3). The separated product was filtered off, washed with water, and recrystallized from ethanol to give the corresponding phenazine derivatives **7a–d**. The results are listed in Table 1.

7c: IR: 3335 (OH stretching); ^{1}H NMR: 8.6 (m, 2H, H_6, H_9), 7.9 (m, 2H, H_7, H_8), 7.6 (m, 2H, H_1, H_3), 7.5, 7.35 (d, 4H, $2H_a$, $2H_b$); MS: (*m/z*): 302 (12%), 226 (100%).

Reaction of different aromatic hydroxy compounds and indole phenols with benzofurazan 1-oxide (**1**)

General procedure

A solution of sodium hypochlorite (1 *M*) was added in portions with stirring into a mixture of the appropriate phenol (0.0657 mol) and *o*-nitroaniline derivative (0.0657 mol) in methanolic sodium hydroxide (10 ml, 5%). The reaction mixture was stirred overnight at room temperature and then poured into water and acidified with dilute hydrochloric acid to give the corresponding phenazine derivatives **9**–**11** (Table 2).

6H-Indolo[2,3-b]quinoxaline 5,11-dioxide (**12**)

A mixture of glacial acetic acid (8.5 ml), acetic anhydride (3.6 ml), and hydrogen peroxide (30%, 3.8 ml) was heated for 6 hours at 40 °C. 6*H*-Indolo[2,3-*b*]quinoxaline was added and the reaction mixture

Table 1. Characterization of the newly prepared compounds **2**, **3a–d**, **7a–d**

	R	Yield (%)	m.p. (°C)	Molecular formula[a]
2	–	86	152	$C_{11}H_{10}N_2O_3$
3a	H	85	154	$C_{18}H_{14}N_2O_3$
3b	*p*-NO_2	90	232	$C_{18}H_{13}N_3O_5$
3c	*p*-Cl	90	190	$C_{18}H_{13}N_2O_3Cl$
3d	*p*-Br	83	212	$C_{18}H_{13}N_2O_3Br$
7a	H	60	220	$C_{18}H_{12}N_2O_3$
7b	*p*-NO_2	62	245	$C_{18}H_{11}N_3O_5$
7c	*p*-Cl	65	208	$C_{18}H_{11}N_2O_3Cl$
7d	*p*-Br	68	225	$C_{18}H_{11}N_2O_3Br$

[a] All elemental analyses (C, H) are in agreement with calculated values

Table 2. Characterization of the newly prepared compounds **8a–f**, **9**, **10**, **11a, b**, **12**

	R	R^1	R^2	R^3	Yield (%)	m.p. (°C)	Molecular formula[a]
8a	H	OH	H	H	60	250	$C_{12}H_8N_2O_4$
8b	H	H	OH	H	65	230	$C_{12}H_8N_2O_4$
8c	H	H	H	OH	63	185	$C_{12}H_8N_2O_3$
8d	CH_3-	OH	H	H	70	194	$C_{13}H_{10}N_2O_4$
8e	CH_3	H	OH	H	65	210	$C_{13}H_{10}N_2O_4$
8f	CH_3	H	H	OH	62	197	$C_{13}H_{10}N_2O_3$
9	H	–	–	–	80	180	$C_{16}H_{10}N_2O_2$
10	H	–	–	–	60	237	$C_{16}H_{10}N_2O_3$
11a	H	–	–	–	60	244	$C_{15}H_9N_3O_3$
11b	CH_3	–	–	–	60	217	$C_{16}H_{11}N_3O_3$
12	H	–	–	–	92	285	$C_{14}H_{19}N_3O_2$

[a] All elemental analyses (C, H) are in agreement with calculated values

was heated for 26 hours at 50 °C. The reaction mixture was poured into water and the crude product was recrystallized from glacial acetic acid.

IR: 756, 1336 (N → O); MS: (*m/z*): 251 (5.8%).

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