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REACTIONS OF BENZOFURAZAN OXIDE WITH AMINES—I

REDUCTION WITH DIETHYLAMINE

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Abstract—The reactions of benzofurazan oxide with diethylamine gave a complex mixture from which quinoxaline-1,4-dioxide (10–15%), *o*-benzoquinone dioxime (5%), benzofurazan (5–10%), 1-hydroxy-2-methyl-benzimidazole-3-oxide (3%), *o*-nitrosoaniline (5%), *o*-nitroaniline (<3%), 3-methylbenzotriazine (5%), 3-methyl-benzotriazine-4-oxide (10%), and *o*-nitrophenyl-N,N-diethyl hydrazine (10%) were isolated.

The formation of these products seems to have a common pathway that involves the reduction of benzofurazan oxide and the oxidation of diethylamine.

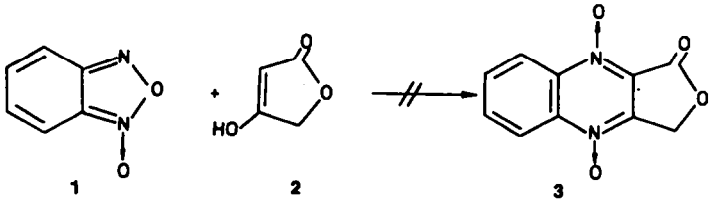
Diethylamine was found to be a convenient medium for the reaction of benzofurazan oxide (1) with enolate anions to give quinoxaline-1,4-dioxides.[1] It was also used with α-methylene aldehydes or ketones to generate enamines *in situ* that eventually reacted with benzofurazan oxide to produce quinoxaline-1,4-dioxides.[2] These reactions proceed with the development of a deep red color which turns reddish-brown. Previously, the desired products, quinoxaline-1,4-dioxides, were isolated and no effort was made to look into the side products of these reactions. In an attempt to synthesize quinoxaline-1,4-dioxide 3, tetronic acid 2[3] was treated with benzofurazan oxide (1) in diethylamine for one week at room temperature. However, the work-up of the deep red mixture failed to yield the expected product 3, and only part of benzofurazan oxide was recovered. Examination of the red solution by TLC revealed the presence of more than ten products. The same products were obtained in the absence of tetronic acid, and therefore, directed our attention to the reaction of benzofurazan oxide and diethylamine. Diethylamine was reported to add to benzofurazan oxide at 0° to give *o*-nitrophenyl-N,N-dialkyl hydrazine.[4] No additional products were described from this reaction. However, electron-rich reagents such as alkoxides, hydroxides, hydroxylamines, thiols, triphenylphosphine, hydrides as well as electrolysis are known to reduce benzofurazan oxide to *o*-benzoquinone dioxime (5) and benzofurazan.[5,6] Consequently, it is expected that the reaction of diethylamine with benzofurazan oxide should yield *o*-nitrophenyl-N,N-diethyl hydrazine (4), *o*-benzoquinone dioxime (5), and benzofurazan. In the present work, these compounds were isolated along with seven additional products. The formation and possible pathways to this surprisingly large number of products are described below.

Treatment of benzofurazan oxide with diethylamine for one week at room temperature resulted in the precipitation of a flaky yellow solid (10–15% yield) which was shown to be quinoxaline-1,4-dioxide by comparison with an authentic sample. Evaporation of the clear dark red solution at room temperature yielded a thick oily residue which was extracted several times with benzene. The remaining benzene-insoluble, water-soluble residue was acidified with acetic acid to give 1-hydroxy-2-methyl-benzimidazole-3-oxide (10), the identity of which was established by mixture m.p. and identical spectra data with an authentic sample.[7]

Concentration of the benzene layer caused the precipitation of the known *o*-benzoquinone dioxime (5).[8] Repeated chromatography of the benzene solution led to the separation of the following products arranged in the order of their elution from the chromatography column: *o*-nitrophenyl-N,N-diethyl hydrazine (4) benzofurazan (8), *o*-nitroaniline, *o*-nitrosoaniline (9), 3-methylbenzotriazine (11) and 3-methylbenzotriazine-4-oxide (12). Several unstable intermediates and traces of unidentified products were also observed.

The progress of the reactions of benzofurazan oxide with diethylamine was monitored by tlc. Hydrazine 4 was, apparently, the first product to be formed. This result is not surprising since the formation of hydrazine 4 can be realized through a simple addition of diethylamine to benzofurazan oxide (Scheme 1, route a) whereas an addition of diethylamine via route b results in the formation of *o*-benzoquinone dioxime (5) and imine-enamine 6a, b. Although the dehydration of dioxime 5 is known to yield benzofurazan (8), other pathways (route c) cannot be excluded. The production of enamine 6b in the presence of benzofurazan oxide explains the formation of quinoxaline-1,4-dioxide.[9]

By far the most interesting product of the reactions of



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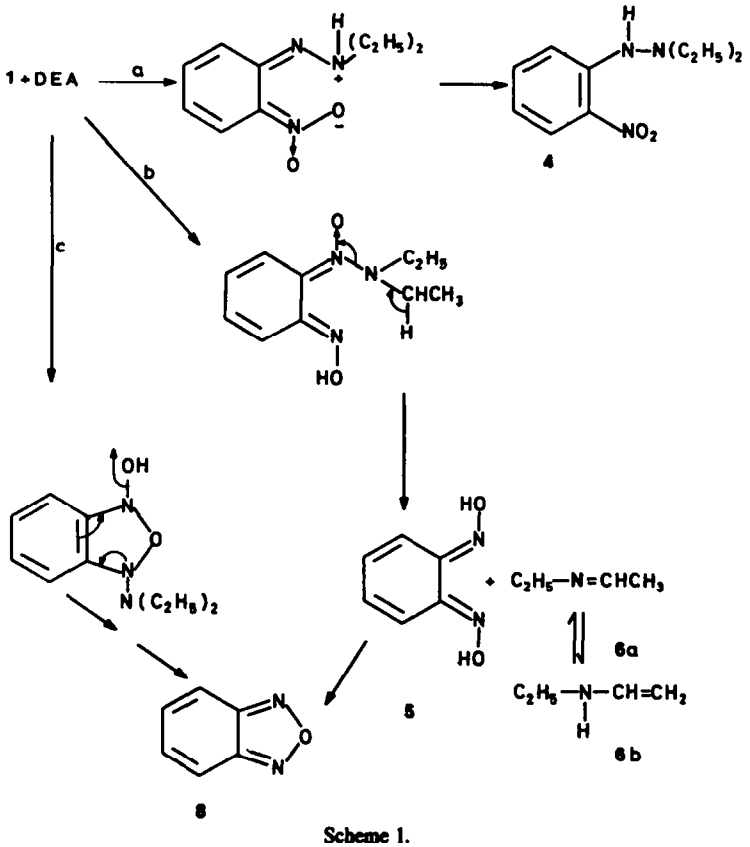
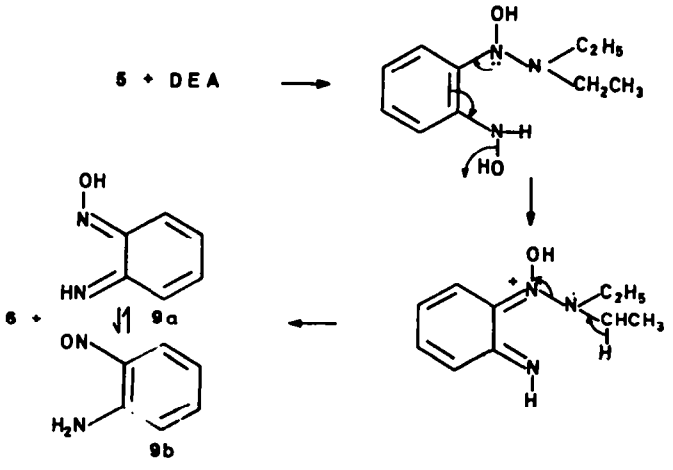


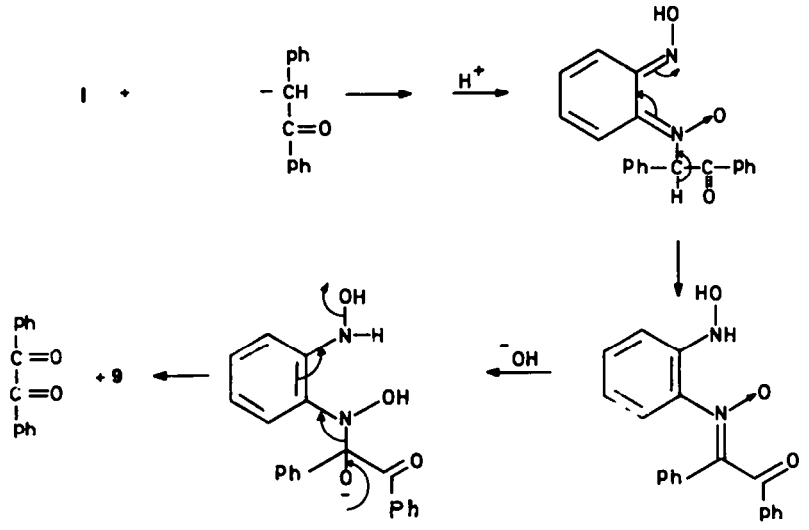
Scheme 1.

benzofurazan oxide with diethylamine is *o*-nitrosoaniline (**9**) which remained unknown until 1969 when it was encountered as a minor by-product from the action of triphenylphosphine on benzofurazan oxide.[10] *o*-Nitrosoaniline (**9**) was isolated at that time in minute quantities enough for a m.p., mass spectrum, and IR determinations. In the present study, *o*-nitrosoaniline (**9**) was obtained in gram-quantities. The oxidation level of **9** is two stages below that of benzofurazan oxide and one stage below *o*-benzoquinone dioxime (**5**). Thus, it is reasonable to assume that **5** is reduced further by diethylamine to give **9** (Scheme 2). This assumption is supported by the fact that treatement of **5** with diethylamine produced **9** in a better yield than that obtained from the reaction of benzofurazan oxide and diethylamine.[11]

The previous finding that led to the preparation of the elusive **9** in sufficient quantities for further study,[11] prompted us to examine the reactions of electron-rich reagents with benzofurazan oxide as an alternative route to **9**. Mechanistic considerations suggested that desoxybenzoin should be a suitable reagent. Indeed, the reaction of benzofurazan oxide with desoxybenzoin in methanolic potassium hydroxide gave, among other products, benzil and **9** (Scheme 3). It was observed that *o*-nitrosoaniline possesses a green color in aprotic solvents whereas it acquires a brown-red color in protic solvents. It is believed that the compound exists in the



Scheme 2.

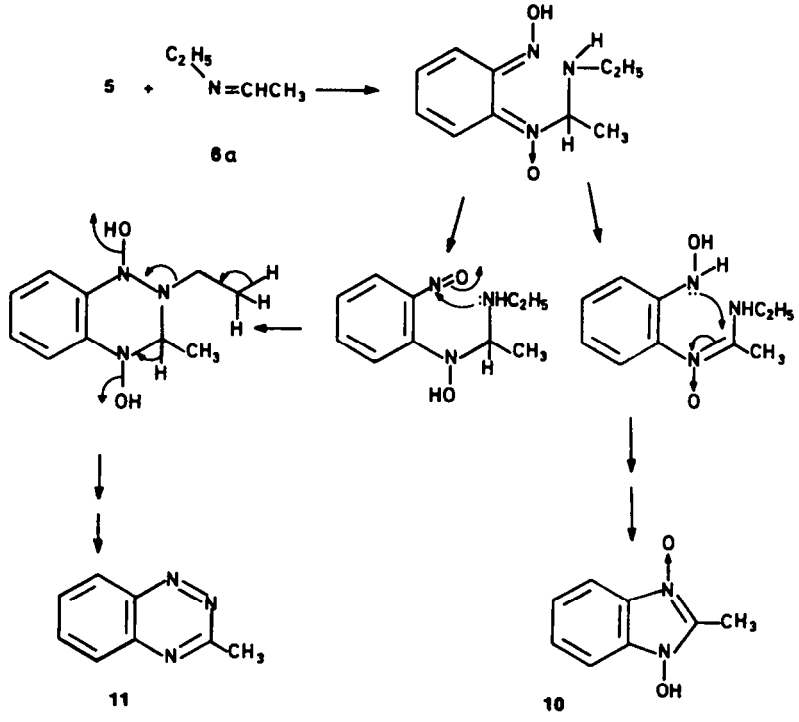


Scheme 3.

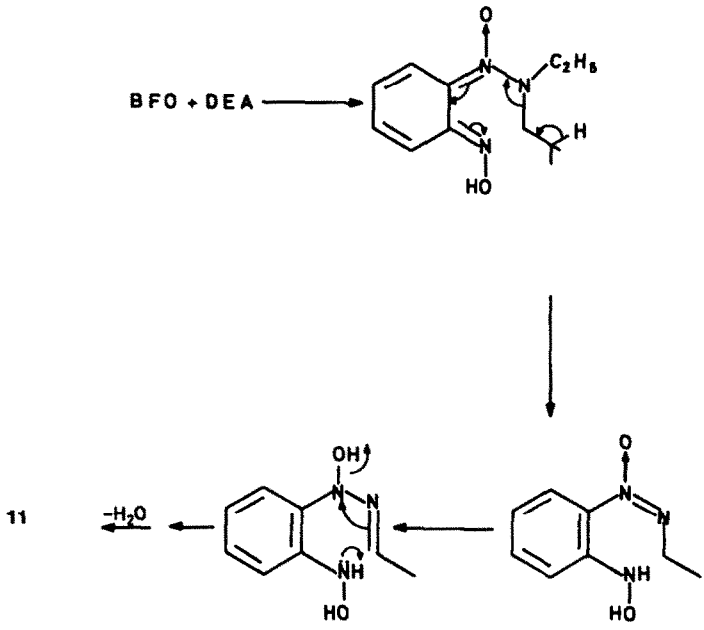
two tautomeric forms **9a** ⇌ **9b**. Although *o*-nitrosoaniline is indefinitely stable in pure crystalline form and in aprotic solvents, it is oxidized to *o*-nitroaniline in the presence of base. Such ease of oxidation would explain the formation of *o*-nitroaniline in the reaction of benzofurazan oxide with diethylamine.

Another interesting aspect of the reactions of benzofurazan oxide and diethylamine is the formation of 1-hydroxy-2-methyl benzimidazole-3-oxide (**10**) and 3-methylbenzotriazine (**11**). These two products, which were identified by comparison with authentic samples,[7,12] could arise from the reaction of dioxime **5** with imine **6a** (Scheme 4). Scheme 4 draws support from the fact that treatment of dioxime **5** with diethylamine gave both **10** and **11** together with *o*-nitrosoaniline and other products. However, the formation of **11** (Scheme 5) and **10**[13] via other paths is possible.

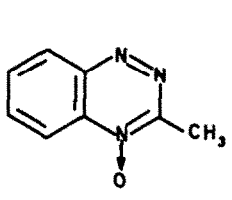
A mechanism analogous to that of Scheme 4 where benzofurazan oxide is involved instead of dioxime **5** explains the formation of either 3-methylbenzotriazine-4-oxide (**12**) and/or 3-methylbenzotriazine-1-oxide (**13**). The 3-methylbenzotriazine oxide isolated is tentatively assigned structure **12**. Reduction of **12** with sodium dithionite gave **11**. Oxidation of either **12** or **11** with *m*-chloroperbenzoic acid gave the same di-N-oxide, which in turn was reduced to **11** with sodium dithionite. Furthermore the synthesis of 3-methylbenzotriazine-1-oxide (**13**) has been reported, although no evidence was advanced in support of its structure.[14] The reported m.p. of **13** (92–93°) is different from that of the presumed **12**



Scheme 4.



Scheme 5.



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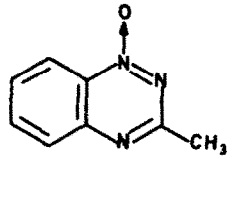

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(130°). In view of the above uncertainty about the structures of the 3-substituted benzotriazine oxides, a systematic study of all the benzotriazine oxides has been initiated the results of which will be reported separately.

EXPERIMENTAL

M.ps were determined on a Mel-Temp. apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer model 257 spectrophotometer, and UV spectra on a Carey–17B spectrophotometer. NMR spectra were taken on a Varian A-60D spectrometer in $CDCl_3$ with TMS as an internal reference. Elemental analyses were performed by Pascher Laboratories, Bonn, Germany. Mass spectra were determined on a Varian-MAT CH 5 mass spectrometer at 70 eV, 100 uA, 200°.

The reaction of benzofurazan oxide with diethylamine

A mixture of benzofurazan oxide[15] (10 g) and diethylamine (100 ml) was refluxed for 15 hr. After cooling (ice), the clear dark-red soln was decanted and the deposited yellow flaky crystals were washed with diethylamine. The solid (1.25 g), m.p. 235–237°) was found to be identical with quinoxaline1,4-dioxide[16] (m.p., IR, NMR).

The diethylamine soln and washings were evaporated at room temp. (reduced pressure) to a thick dark oily residue. The residue was stirred with benzene (25 ml) and the benzene soln was decanted. The process was repeated with two portions (10 ml) each) of benzene. The residue, after these extractions, was allowed to dry from benzene wetting; then water (5 ml) was added. The resulting red aqueous soln was filtered from any suspended material and carefully acidified with AcOH until precipitation of a whitish solid occurred. This solid was purified by dissolution in a soln of ammonia and acidification with AcOH, yield: 0.3 g, m.p. 205–207°, identical with an authentic sample of 1-hydroxy-2-methyl-benzimidazole-3-oxide[7] (m.m.p., NMR ($CD_3)_2SO$), IR). Mass: 164 (M^+), 148 ($M^+ - 16$, most intense).

The benzene soln was concentrated to about half its volume and upon cooling for overnight in the refrigerator deposited crystals of *o*-benzoquinone dioxime[8] (0.3–0.5 g; m.p. 145–147°).

Further concentration of the benzene soln and repeated chromatography (alumina activity II or silica gel; elution with petroleum ether and gradually increasing polarity of eluent with benzene) gave the following products, arranged in order of elution from the column:

1. *o-Nitrophenyl-N,N-diethyl hydrazine.*[4] Red oil, yield 1–1.2 g; NMR: τ 2.3 (1H, two doublets), 2.8 (2H, multiplet), 3.7 (1H, multiplet), 7.4 (4H, broad quartet), 9.0 (6H, triplet). IR (neat): 3310 cm^{-1} (N–H), 1610, 1570, 1500, 1440, 1415, 1340, 1320, 1260, 1220, 750. Mass: 209 (M^+, most intense), 192 (M^+–OH), 180 (M^+–C_2H_5), 176 (M^+–OH–O), 161 (3-methylbenzotriazine oxide$^+$), 147 (2-methylbenzimidazole-1-oxide$^+$), 146, 138, 133, 132, 120 (benzofurazan$^+$), 118 (benzotriazole$^+$).

2. *Benzofurazan.* Sublimable solid, m.p. 55–57°, identical with authentic sample,[8] (m.m.p., IR, NMR), yield: 0.3–0.8 g.

3. *o-Nitroaniline.* Sublimable solid, m.p. 68–69°, identical with authentic sample, (m.m.p., IR), yield: 0.05–0.3 g.

4. *o-Nitrosoaniline.* Green hairy needles (from hexane), yield: 0.3–0.5 g, m.p. 78–79°, identical with authentic sample[10] (m.m.p., IR, NMR: several signals between τ 3 and 4 (5H), a pair of doublets centered at τ 1.9 (1H)).

Mass: 122 (M^+, most intense), 104 (M^+–H_2O). (Found: C, 59.36; H, 4.90; N, 23.12. Calc.: C, 59.01; H, 4.91; N, 22.95%).

Highly purified samples are indefinitely stable in the solid form or in a hydrocarbon solvent. In aqueous media, the slightly soluble product takes up a reddish color but when extracted from the medium by a hydrocarbon solvent the green color is

regenerated in the hydrocarbon solvent. Basification of the aqueous soln (or an alcoholic soln) results in the gradual transformation to *o*-nitroaniline.

5. *3-Methylbenzotriazine.* Yellow crystals (from hexane), m.p. 92–94°, identical with authentic sample[12] (m.m.p., IR, UV,[12] NMR: τ 2 (1H, multiplet), 2.5 (3H, multiplet), 7.0 (3H, singlet). Mass: 145 (M^+), 118 (benzotriazole$^+$), 117 (M^+-N_2, most intense), 90 ($C_6H_4N^+$).

6. *3-Methylbenzotriazine-4-oxide.* Yellow crystals (from petroleum ether-benzene) m.p. 130–131°. (Found: C, 60.04; H, 4.34; N, 25.79. Calc.: C, 59.62; H, 4.38; N, 26.07%). NMR: τ 2.5 (2H, multiplet), 1.85 (2H, multiplet), 7.1 (3H, singlet). Mass: 161 (M^+, most intense), 120 (benzofurazan$^+$), 117 (M^+-N_2), 116, 104 ($C_6H_4N_2^+$), 90 ($C_6H_4N^+$). IR (KBr): 1610 cm^{-1}, 1570, 1470 (–CH_3), 1350 (N–O), 780, 760.

Treatment of the oxide with sodium dithionite in water-ethanol[16] gave 3-methylbenzotriazine. Oxidation with m-chloroperbenzoic acid in benzene[17] gave a dioxide tentatively identified as 3-methylbenzotriazine-1,4-dioxide, m.p. 186–188° (from benzene). (Found: C, 54.33; H, 3.93; N, 23.35. Calc.: C, 54.23; H, 3.98; N, 23.72%). Mass: 177 (M^+, most intense), 161 (M^+-16), 160 (M^+-17), 136 (M^+-CH_3CN, $(BFO)^+$). NMR: τ 2 (2H, multiplet), 2.5 (2H, multiplet), 7.35 (3H, singlet). IR (KBr): 1490, 1460, 1405, 1350 (N–O), 1310 (N–O), 1095, 970, 780, 730. Reduction of the dioxide with sodium dithionite gave 3-methylbenzotriazine.

7. *Unidentified product.* Transparent plates (ligroin-benzene), m.p. 120–121°, yield is less than 3%. The identity of this and other minor products is under investigation.

The reaction of o-benzoquinone dioxime with diethylamine. A mixture of *o*-benzoquinone dioxime[8] (2 g) and diethylamine (100 ml) was refluxed for 12 hr. Work-up and repeated chromatography as previously described resulted in the isolation of the following: 1-hydroxy-2-methyl-benzimidazole-3-oxide (100 mg), benzofurazan (500 mg), *o*-nitrosoaniline (200 mg), *o*-nitroaniline (~50 mg), 3-methylbenzotriazine (*ca.* 100 mg). Tlc of the crude mixture showed the presence of few other products, but the absence of quinoxaline-1,4-dioxide, *o*-nitrophenyl-N,N-diethyl hydrazine and 3-methylbenzotriazine oxide was noticed.

The reaction of benzofurazan oxide with desoxybenzoin. To a soln of BFO (5 g) and desoxybenzoin (8 g) in MeOH (100 ml) is added 5% methanolic KOH (5 ml). An exothermic reaction ensued and a deep green color developed. After 5 min, water (50 ml) was added and the soln was extracted with benzene. The green benzene layer was dried, concentrated (5 ml) and separated from any deposited solid. Chromatography of the benzene concentrate gave, among other products, benzil and *o*-nitrosoaniline (0.4 g).

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