

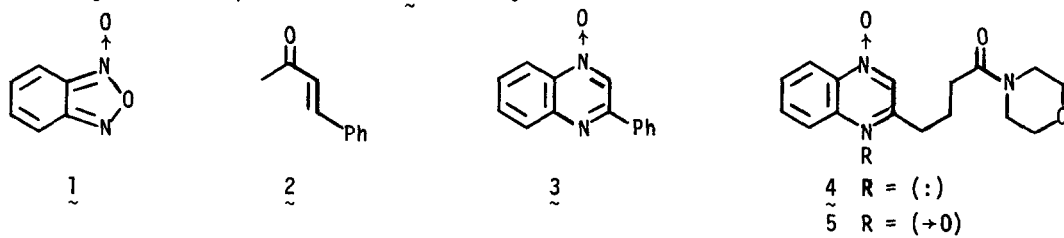
BENZOFURAZAN OXIDE CHEMISTRY: A NOVEL REACTION
FOR THE SYNTHESIS OF QUINOXALINE MONOXIDES¹

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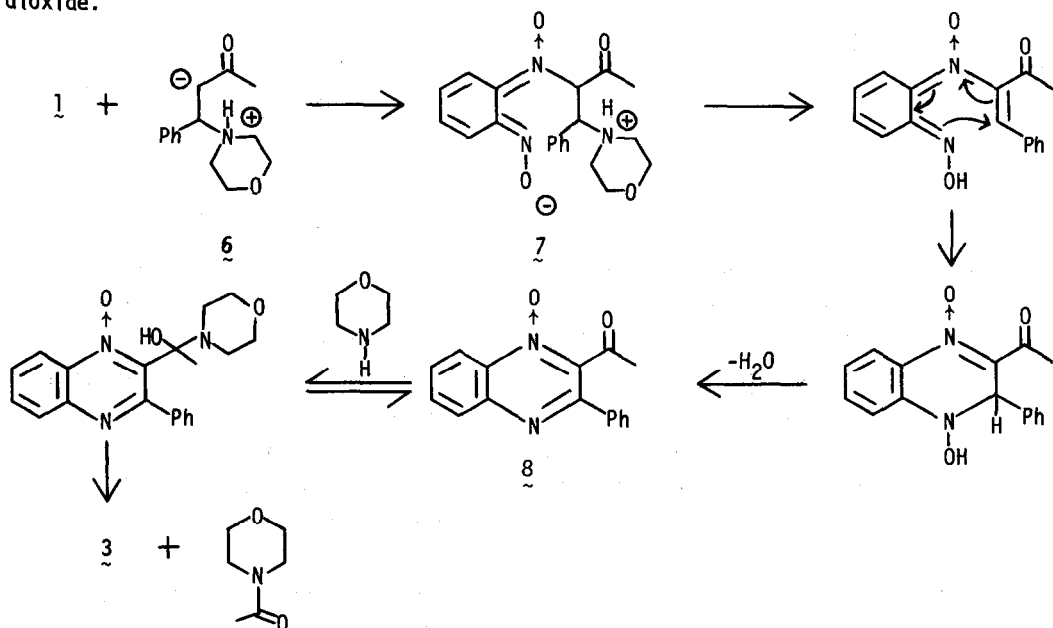
We report a transformation of benzofurazan oxide (BFO) (1) into 3-substituted quinoxaline-1-N-oxides by reaction with various α,β -unsaturated aldehydes and ketones in the presence of morpholine. Reaction of 1 eq. BFO, 1.1 eq. trans-4-phenyl-3-buten-2-one (2), and 1.1 eq. morpholine in either acetonitrile or benzene at reflux for 24 hr gave 3-phenylquinoxaline-1-oxide (3) in 22% yield.² Substitution of cinnamaldehyde for 2 under the same conditions gave 3 in 54% yield, and the use of 2-cyclohexen-1-one as the enone component under the same conditions gave the morpholine amide 4 in 13% yield.



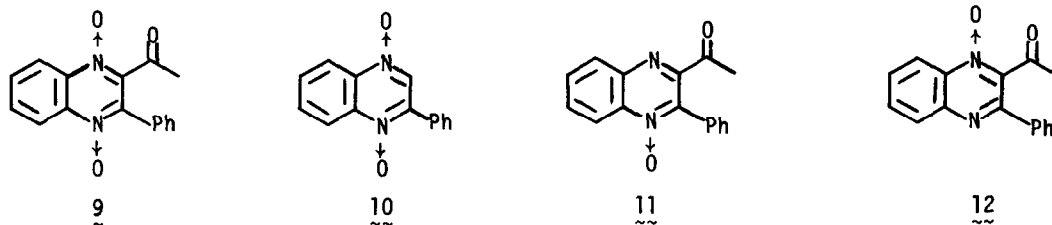
The structures assigned to 3 and 4 are based on a number of arguments. Compound 3, mp 134-135°, was identical to an independently prepared sample³ by tlc, ir, and mixture melting point comparison. Since 3 was prepared in the literature by selective oxidation of 2-phenylquinoxaline, we obtained a further proof of structure for 3 through its transformation into 2-chloro-3-phenylquinoxaline⁴ in 41% yield by reaction with phosphorus oxychloride. Such a transformation is easily explained if the starting material is 3, and it is difficult to rationalize mechanistically if the starting material were 2-phenylquinoxaline-1-oxide. The formula C₁₆H₁₁N₃O₃ for the amide 4, mp 110-112°, was established by combustion analysis and by mass spectrometry ($m/e = 285 (M^+ - 16)$).⁵ The nmr spectrum (CDCl₃: δ) consisted of the eight protons of the morpholine unit (2.3--3), six protons for the butyric side chain (1.8--2.6), the C-2 proton of the quinoxaline (8.63), and the four adjacent aromatic protons (7.6--8.4). The presence of an oxidizable ring nitrogen in 4 was shown by its transformation, with MCPBA in CHCl₃ to the dioxide 5, mp 155-157°, whose combustion analysis,⁵ mass spectrum ($m/e = 301 (M^+ - 16)$), ir and nmr spectra were in accord with the structure assignment. The assignment of the butyric amide side chain in 4 is based on analogy to 3 where the β -substituent of the starting enone ends up in the 3-position of the product. Reaction of 4 with phosphorus oxychloride gave an intractable mixture, so we were unable to infer the absence of a substituent α to the N-oxide by chemical degradation as we did with 3.

Any mechanism which is advanced to explain these reactions must account for the

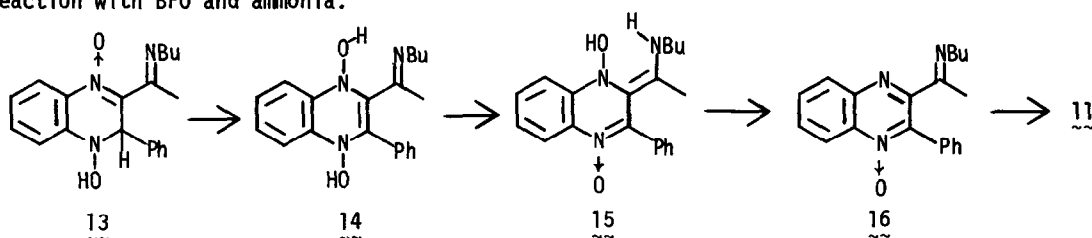
transformation of an enone and BFO into a product which has formally lost the elements of water and an acyl function. Some clue as to the disposition of the acyl function is provided by structure 4 where it is trapped by morpholine in the form of an amide. It was found that there was no reaction between BFO and 2 in the absence of morpholine. We suggest that the following mechanism is consistent with the experimental facts.⁶ Since the presence of morpholine was shown to be necessary, we suggest a Michael addition of morpholine to 2 to give a nucleophilic species 6. Condensation of 6 with BFO leads to intermediate 7 which then loses morpholine and water to give the 2-acyl intermediate 8. Condensation of 8 with morpholine, followed by fragmentation of N-acetylmorpholine, completes the reaction. The proposed deacetylation of 8 by morpholine is supported by the following observations: (1) The presence of N-acetylmorpholine in the reaction mixture was shown by glpc; (2) 2-acetyl-3-phenylquinoxaline-1,4-dioxide (9) was converted to 2-phenylquinoxaline-1,4-dioxide (10) and N-acetylmorpholine under normal reaction conditions; and (3) 2-formylquinoxaline-1,4-dioxide is readily deacylated by morpholine under our reaction conditions to give quinoxaline-1,4-dioxide.



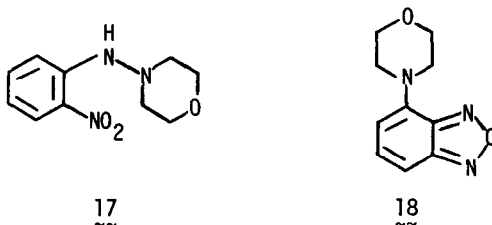
Preliminary experiments using BFO, 2, and bases other than morpholine gave rise to different products. Use of butylamine gave 3-acetyl-2-phenylquinoxaline-1-oxide (11), mp 126-127°, in 16% yield, while the use of ammonium hydroxide gave 2-acetyl-3-phenylquinoxaline-1,4-dioxide (9), mp 183-185°, in 10% yield. There was no 3 present in either case. The structure assignment for 11 is based on its combustion analysis, its spectral data, and its transformation to 9 by oxidation with MCPBA. The assignment of structure as 11 rather than the alternative 12 is based on the observation that there was no deacetylation of the reaction product by morpholine under normal reaction conditions. The structure assigned to 9 is supported by combustion analysis,⁵ spectral data, and by its chemical transformation by morpholine into the known 10.³



The dramatic shift in product that is observed with the use of butylamine may be explained by steps 13 through 16. The dioxide 9 which is formed in the reaction of BFO, 2, and ammonium hydroxide is the sort of product which would be normally encountered from the reaction of BFO and benzoylacetone in the presence of ammonium hydroxide (the "Beirut reaction").^{6,7} It is possible that 2 is oxidatively transformed into benzoylacetone in a side reaction with BFO and ammonia.



The low yields of these reactions are due in part to the occurrence of competing side reactions. The reaction of BFO with morpholine has been reported to give both 17 and 18.⁸ TLC comparison of a reaction mixture of BFO, 2, and morpholine with a reaction mixture of BFO and morpholine (both 24 hr reflux in benzene) showed that nearly all of the components other than 3 were side products from the reaction of BFO with morpholine.



References and Notes

1. Contribution No. 482 from the Institute of Organic Chemistry.
2. There has been reported a very interesting synthesis of 3-(2-hydroxyphenyl)quinoxaline-1-oxides by the reaction of benzofuroxans with benzofuranones: (a) M. J. Haddadin, J. J. Zamet, and C. H. Issidorides, Tetrahedron Lett., 3653 (1972); (b) J. J. Zamet, M. J. Haddadin, and C. H. Issidorides, J. Chem. Soc. Perkin I, 1687 (1974).
3. J. K. Lanquist and G. J. Stacey, J. Chem. Soc., 2822 (1953).
4. D. Shiho and S. Tagami, J. Amer. Chem. Soc., **82**, 4044 (1960).
5. Combustion analyses for C, H, and N within 0.4% of theory.
6. The subject of BFO transformations into heteroaromatic N-oxides has been critically reviewed: M. J. Haddadin and C. H. Issidorides, Heterocycles, **4**, 767 (1976).
7. K. Ley and F. Seng, Synthesis, 415 (1975).
8. D. W. S. Latham, O. Meth-Cohn, and H. Suschitsky, Tetrahedron Lett., 5635 (1972); J. Chem. Soc. Perkin I, 2216 (1976).