APPLICATION OF BENZOFURAZAN OXIDE TO THE SYNTHESIS OF HETERO-AROMATIC N-OXIDES

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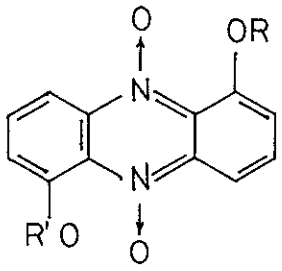
Benzofurazan oxide (BFO) reacts with enamines, enolate anions, phenolate anions, and related species to give a variety of heteroaromatic N-oxides, hitherto difficult to prepare.

CONTENTS

A. INTRODUCTION

The salient feature of heteroaromatic N-oxides is the dipolar $=\underset{|}{N}\rightarrow O$ function which, incorporated in an aromatic ring system through the nitrogen atom, can serve both as an electron

donor and an electron acceptor. Interest in these compounds was spurred by the isolation of the antibiotic iodinin (1, R=R'=H)[1] from chromobacterium iodinum in 1938, and of the bacteriostatic aspergillic acid (2) from the mold aspergillus flavus in 1943[2]. Myxin (1, R=H, R'=CH_3)[3,4], quinoxaline di-N-oxides (3)[5,6,7], and derivatives of 1-hydroxybenzimidazole-3-oxide (4)[8,9] also possess antibacterial activity.



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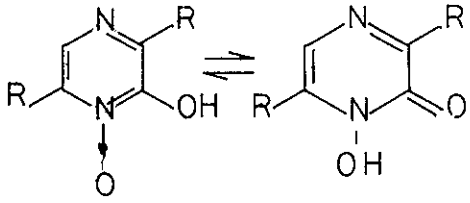
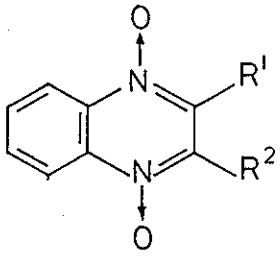


2 (R = $CH_2CH(CH_3)_2$)



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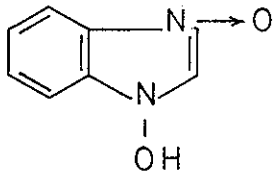

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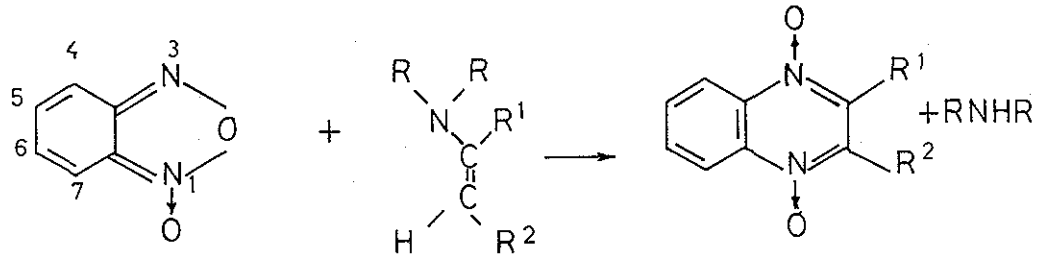
The chemistry of heteroaromatic N-oxides has been reviewed recently[10,11] and offers special challenge because of a virtually stunning array of reactions: in the pyridine and related series, both electrophiles and nucleophiles can attack the oxygen atom or the alpha and gamma carbon atoms; electrophiles can attack the

beta position as well, either directly or following transitory nucleophilic attack at the gamma position[12].

Early preparative methods usually followed one of two routes: (i) cyclization of a suitable precursor to give the desired heteroaromatic N-oxide ring, or (ii) direct N-oxidation of the parent heterocyclic base[13,14]. Of these routes, the former requires precursors that may not be easily available, whereas the latter is too drastic for labile substituents, and may give impure products, particularly in the diazine series, where mixtures of mono- and di-N-oxides often result[15,16]. The setting changed in 1965 with the finding that quinoxaline di-N-oxides (3) could be synthesized in one step from benzofurazan oxide (5, hereinafter referred to as BFO) and enamines (6, Chart 1)[17]. Within a decade this method, referred to as the "Beirut Reaction" in two recent reviews[18], has encompassed the synthesis of an impressive list of biologically active compounds including phenazine di-N-oxides (1), hydroxamic acids (2), quinoxaline di-N-oxides (3), substituted 1-hydroxybenzimidazole-3-oxides (4), and benzo-1,2,4-triazine-1,4-dioxides.

Chart 1



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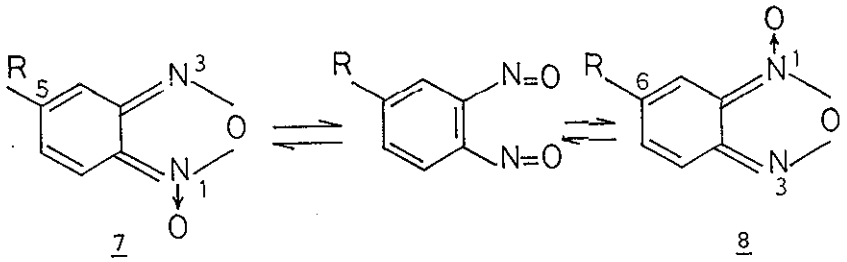
This review presents work done in our laboratory during the past ten years, together with work done elsewhere. Although the main emphasis is on synthetic applications of BFO, some reactions of the N-oxide products are discussed in the hope that they may point out directions for future work.

B. THE REAGENT: BENZOFURAZAN OXIDE

Benzofurazan oxide (5, benzofuroxan) and congeners are prepared by hypochlorite oxidation of o-nitroanilines or by pyrolysis of o-nitrophenyl azides[19]. With certain substituted BFOs, such as 7 and 8, the possibility of tautomerism in solution (possibly via an elusive o-dinitroso intermediate)[20] leads to ambiguities in nomenclature. For example, the names 5-methyl and 6-methylbenzofurazan oxide (7 and 8, R=Me) denote two different molecules which, because of ready interconversion, cannot be isolated at room temperature[21]. To avoid ambiguity, such compounds



7 8

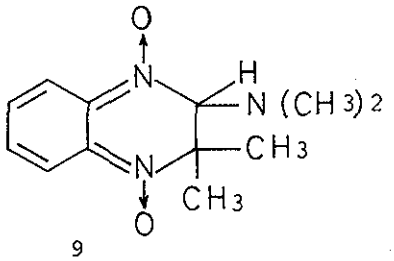
are sometimes referred to with both numbers, the larger of which is placed in parentheses, e.g. 5(6)methylbenzofurazan-1-oxide for the tautomeric system 7 ⇌ 8 (R=Me). The tautomerism of substituted BFOs has been studied by nmr at low temperature[22]. Of the two

tautomeric forms, 7 is more stable when R = Cl, MeO, OAc but less stable when R = COOH, COOEt. When R = Me, the two forms appear to be of equal stability. The chemistry of BFO has been reviewed[23].

C. REACTION OF BFO'S WITH ENAMINES - THE BEIRUT REACTION

Addition of an enamine (6, Chart 1) to BFO[24] or substituted BFO produces a deep red coloration and a rise in temperature of the mixture. Soon, yellow quinoxaline di-N-oxides (3) precipitate in yields ranging from 27% to 90%[25,17]. The method not only eliminates cumbersome steps of earlier methods but also makes possible preparation of compounds previously inaccessible.

The reaction resembles a 1,4-cycloaddition, but the possibility that the initial step is a Diels-Alder addition is ruled out by the observation that BFO does not react with tetracyanoethylene or other Diels-Alder dienophiles. The fully aromatic final product arises by elimination of the amine component of the enamine participant. This elimination requires that the enamine possess a hydrogen atom at the beta carbon, as in 6. In the absence of such hydrogen, β -elimination cannot occur and intermediate products may be isolated, such as 9 from the reaction of BFO with N,N-dimethylisobutenylamine[26]. The reaction of BFO with ynamines[27] to give amino-substituted quinoxaline di-N-oxides is analogous to that with enamines but does not require the elimination step.



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Whereas BFO and its 5(6)-monosubstituted or 5,6-disubstituted congeners react rapidly at room temperature with many enamines, the 4(7)-monosubstituted and 4,7-disubstituted derivatives react much more sluggishly, if at all. The greatly reduced reactivity of these derivatives probably results from repulsive interactions between the 1- (or 4-) oxide and the 8- (or 5-) substituent on the developing quinoxaline system[25].

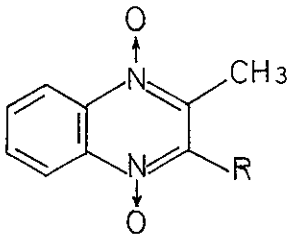
A possible mechanism for the reaction of BFO with enamines is discussed in Section E.

D. VARIANTS OF THE BEIRUT REACTION

Several variants of the reaction between BFO and enamines have been developed over the past ten years. All have a common feature: reaction of BFO with enamines prepared in situ, or with species electronically related to enamines.

D-1. BFO with enamines in situ: BFO and congeners react with aldehydes and ketones in the presence of a suitable base (pyrrolidine, morpholine, ammonia, diethylamine) to give substituted quinoxaline di-N-oxides[9,27,28] such as 10 from 3-pentanone, and 11 from

4-hydroxy-2-butanone. For the reaction between BFO and

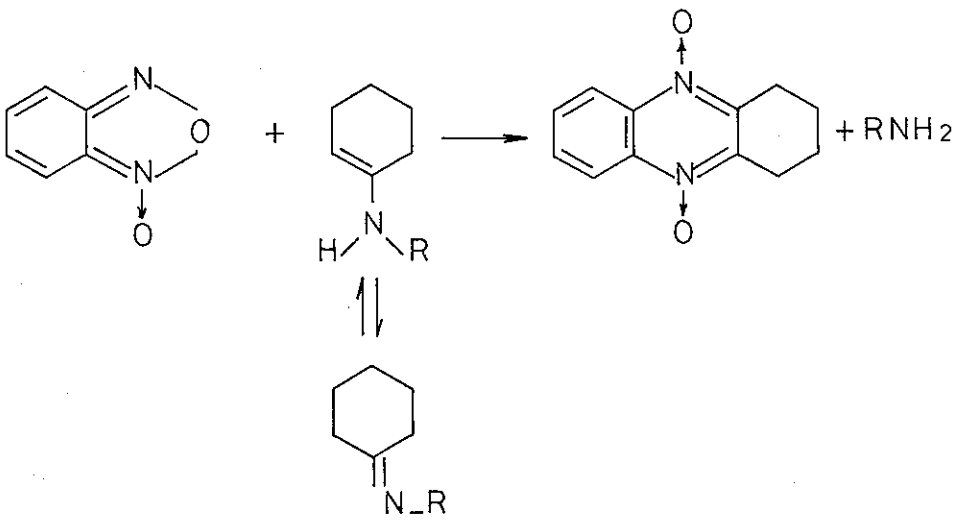


10 R = Et
11 R = CH_2OH

cyclohexanone in morpholine we have observed that the nmr signal of the vinylic proton of the (in situ formed) 1-morpholino-1-cyclohexene appears faster than the signal of the aromatic protons of the quinoxalino product and that, furthermore, the intensity of the vinylic signal decreases as the intensity of the aromatic signal increases[29]. This observation suggests that reaction occurs via the enamine.

Marchetti and Tosi reported[30] that azomethine derivatives of cyclohexanone (12) and acetophenone react with BFO to give quinoxaline-di-N-oxides. The yields are low in neutral medium but rise to 90% in triethylamine. The authors postulated preliminary isomerization of the azomethine to an enamine (Chart 2).

Chart 2



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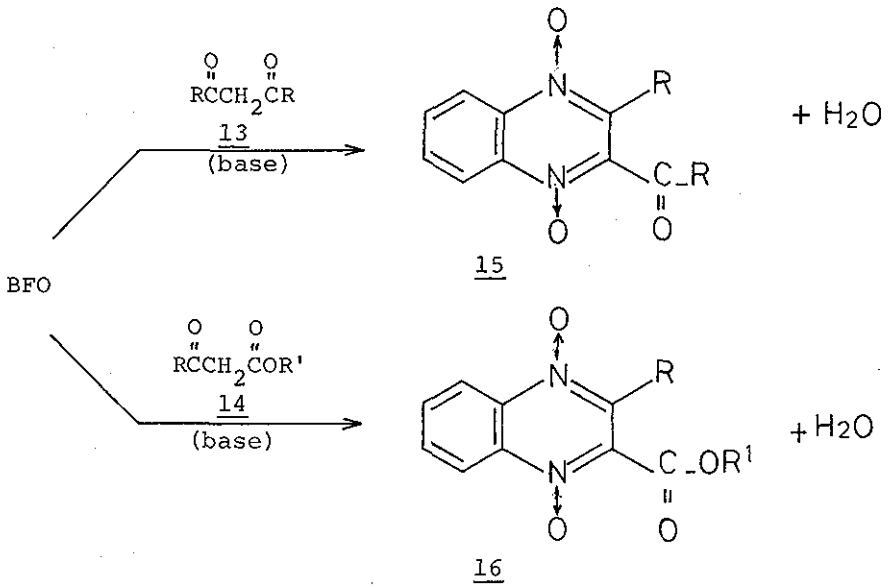
D-2. BFO with β-diketones, β-ketoesters, and other enolate anions: Enolate anions derived from β-diketones (13) and β-ketoesters (14) are electronically similar to enamines and react with BFO to give quinoxaline di-N-oxides of a substitution pattern (15, 16) difficult to arrive at by other methods (Chart 3)[31]. With symmetrical 1,3-diketones, such as 13, only one quinoxaline di-N-oxide can result. With unsymmetrical 1,3-diketones, however, the reaction could possibly give two

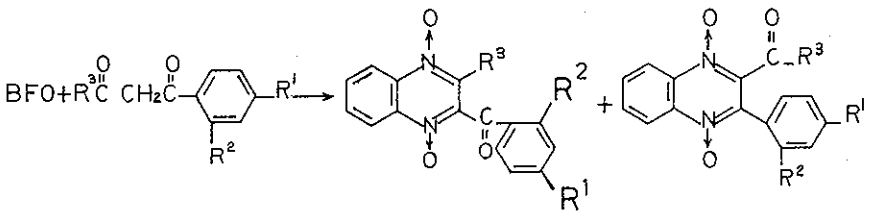
Chart 3



isomeric di-N-oxides. The effects of polar and steric factors on the regiospecificity of this reaction have been assessed for several unsymmetrical diketones of the substitution type shown in Chart 4[32]. The results in four typical cases (a to d, Chart 4) show that for the sterically demanding tertiary butyl group (R^3 = tBu) only isomer II forms, in which the t-butyl group is part of an acyl substituent of the quinoxalino system (case c),

whereas for the small methyl group (R^3 = Me) only isomer I forms, in which the methyl group is directly attached to the heterocyclic ring, regardless of the nature of R^1 and R^2 (cases a and d); case b (R^3 = isopropyl, R^1 = R^2 = H) represents an intermediate situation leading to both isomers. The original paper gives more details and a mechanistic interpretation.

Chart 4



Isomer I Isomer II

	Starting Diketone			Isomer obtained
	R^1	R^2	R^3	
a	X	H	CH_3	I only
b	H	H	$(CH_3)_2CH$	I:II (1:2)
c	H	H	$(CH_3)_3C$	II only
d	H	Y	CH_3	I only

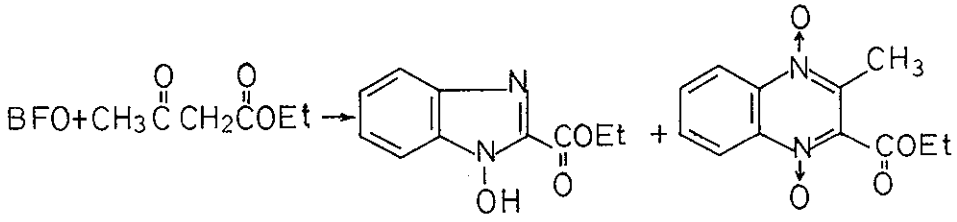
X = H, CH_3O, CH_3, Br, NO_2

Y = CH_3O, CH_3, NO_2

Quinoxaline di-N-oxides carrying substituents such as alkyl, aryl, amide, cyano, thioalkyl, and thioaryl are readily obtained from the reaction of BFO with enolate anions derived from ketones[33], β-ketoamides, β-cyanoketones[34], acetonylalkylsulfides[35], acetonylarylsulfides[35,36], and related species[27]. Of particular interest is the reaction of malononitrile with BFO to give 2-amino-3-cyanoquinoxaline di-N-oxide.

The reactions described here are sensitive to experimental conditions. Durckheimer obtained 2-carbethoxy-1-hydroxybenzimidazole (17, 29%) along with the expected 2-methyl-3-carbethoxyquinoxaline di-N-oxide (18, 55%) from the reaction of BFO with ethylacetoacetate in EtOH-EtONa. When potassium hydroxide was substituted for sodium ethoxide, the yield of 17 was raised to 62%[37] (Chart 5).

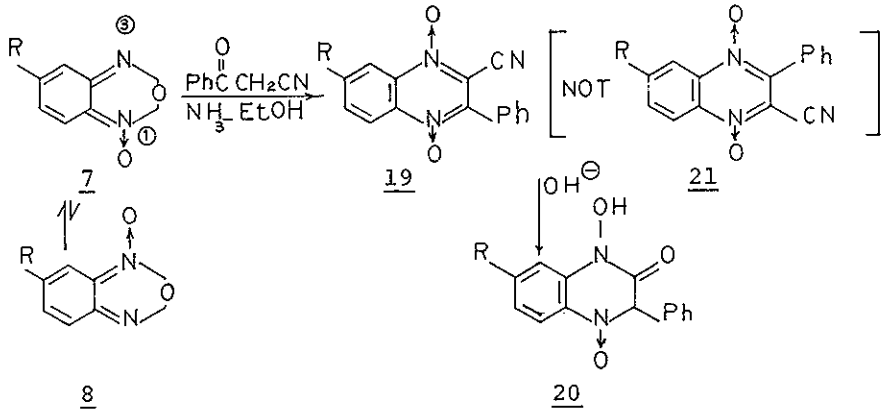
Chart 5



17 18

Mason and Tennant[34] reported that benzoylacetonitrile reacts with 5(6)-substituted BFO's to give only one isomer (19), whose cyano group may be readily replaced by hydroxide to give 1-hydroxyquinoxalin-2(1H)-one-4-oxides (20) (Chart 6). The authors account for the preferential formation of 19 by a mechanism involving attack of the enolate anion of benzoylacetonitrile at N-3 of the 5(6)-substituted BFO in its stabler tautomeric form 7 (Cf Sections B and E).

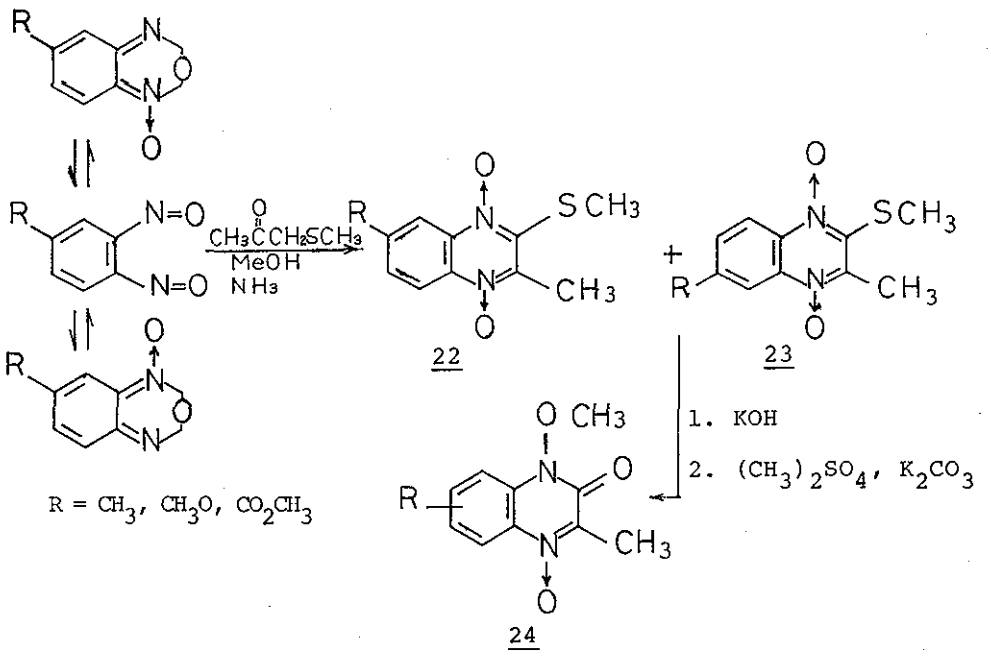
Chart 6



R = MeO, Cl, Br

In contrast to the findings of Mason and Tennant, Abushanab and Alteri[38] found that two isomeric thioalkylquinoxaline di-N-oxides (22 and 23) result from the reaction of 5(6)-substituted BFO's with acetonylmethylsulfide. The isomeric ratio of the products was determined by converting 22 and 23 to the corresponding hydroxamic acid esters (24), whose chemical shifts for the H-5 and H-8 protons are readily assignable, unlike those for H-5 and H-8 of 22 and 23 (Chart 7). The authors find their results partly incompatible with the Mason-Tennant mechanism and suggest that BFO reacts in its o-dinitrosobenzene form (see Section E on mechanism).

Chart 7



Two further variants of the reaction are outlined in Charts 8 and 9. The former uses diketene and an amine to generate a β-ketoamide in situ[39]; the latter leads to 3-amino substituted 1,4-dioxides in the 1,2,4-benzotriazine series (25)[40].

Chart 8

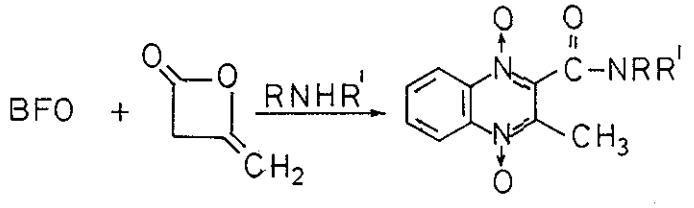
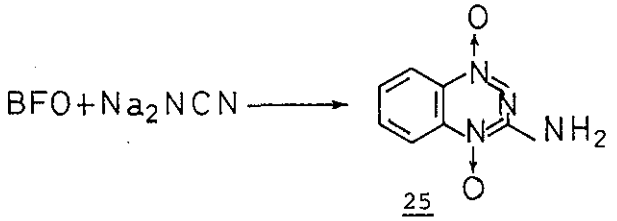


Chart 9



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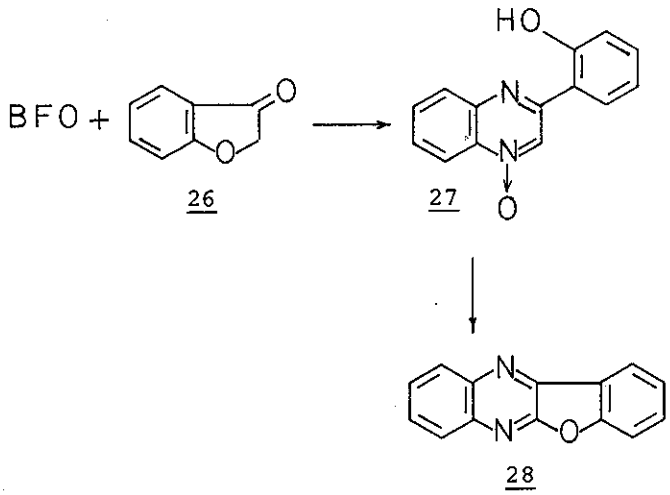
Most surprisingly BFO reacts with benzofuran-3(2H)-one (26) to give a product (27, Chart 10) at an oxidation state two levels lower than expected (di-N-oxide of 28). There is evidence that 26 plays the dual role of substrate as well as reductant during this reaction. The method is quite general, and the resulting monoxides may be readily cyclized[41] in refluxing acetic anhydride to the corresponding benzofuro[2,3-b]quinoxalines (28), thereby providing a practical route to a heterocyclic system for which no

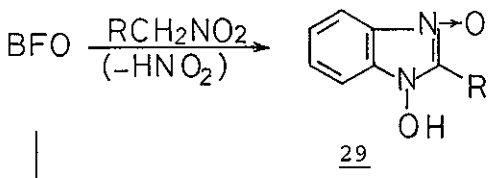
other convenient routes were available until recently[42].

Chart 10



The readily enolizable primary and secondary nitroalkanes (Chart 11) react with BFO to give 1-hydroxybenzimidazole-3-oxides (29) and 2,2-dialkylisobenzimidazole-1,3-dioxides (30) respectively. The reactions of Chart 11 are promoted by amines, which appear in the products as salts of nitrous acid[43,44,45,9]. Closely related is the reaction of BFO with cyanoacetamides[46] and with benzenesulfonylacetamides[36] to give 1-hydroxy-2-carboxylamidobenzimidazole-3-oxides (31, Chart 12). The different course followed by the reactions of Chart 6 (cyanoacetophenone) and Chart 12 (cyanoacetamide) should be noted.

Chart 11



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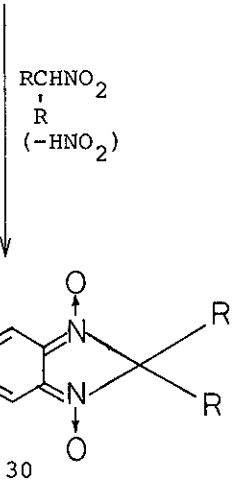
R = H, Alkyl, Aryl, $CH_2CH_2CONH_2$, CO_2Et



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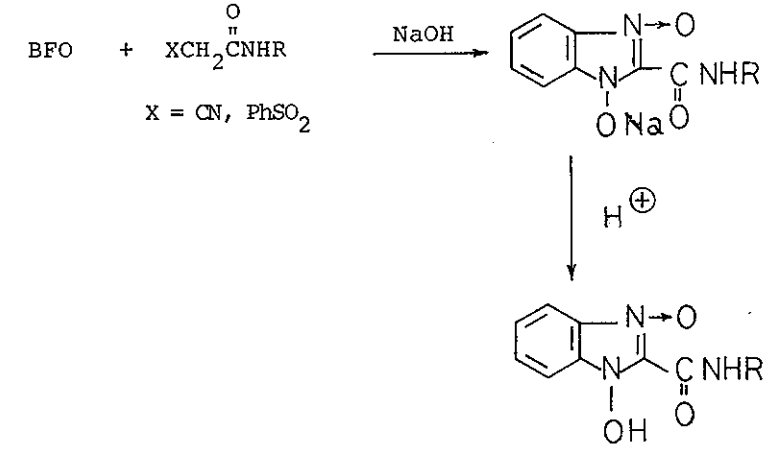
R = Alkyl; R-R = $(CH_2)_4$ and $(CH_2)_5$

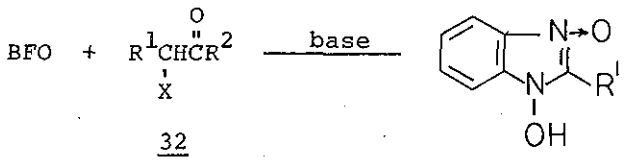
Chart 12



31

The reaction of Chart 13 is mechanistically related to the reactions of Charts 11 and 12 but requires an additional deacylation step to give the final product[47,36] (see Section E). Interestingly, from BFO and 32 (X = SR or SPh, R^1 = H, R^2 = CH_3 or Ph), quinoxaline di-N-oxides result rather than 1-hydroxybenzimidazole-3-oxides[36,35,38].

Chart 13



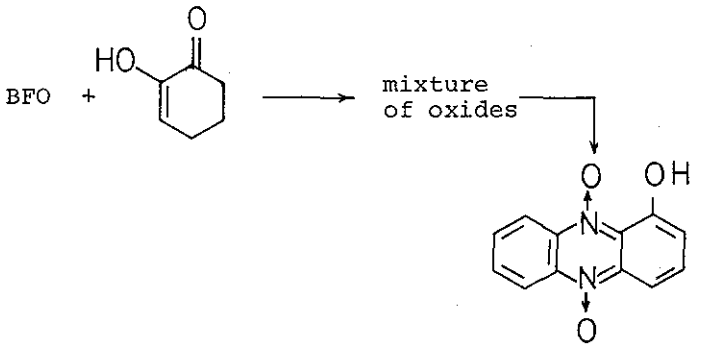
32

X = NO_2[47], SO_2Ph[36]

R^2 = alkyl or aryl

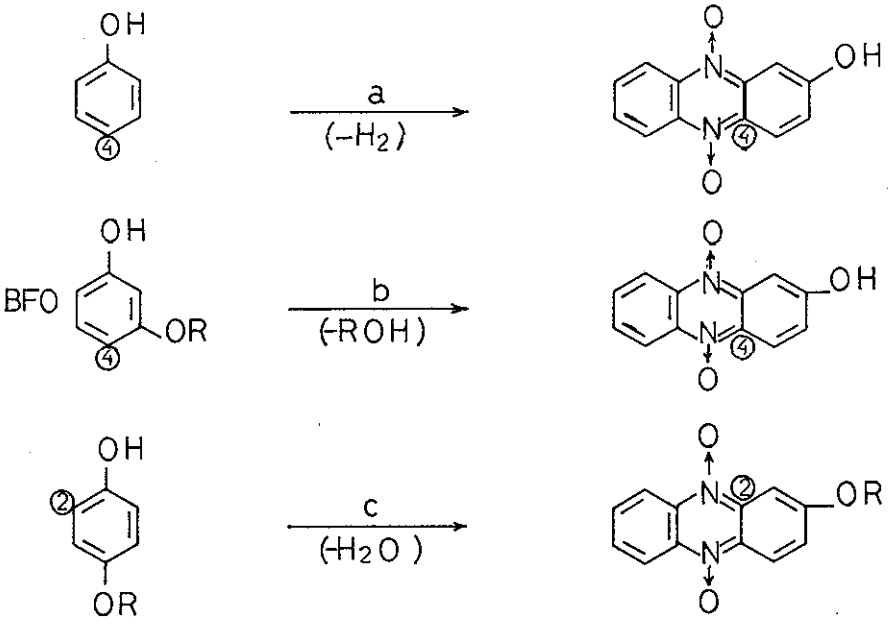
In basic solution, BFO and the highly enolic 1,2-cyclohexanedione react to give a mixture (mono- and di-N-oxides of 1-hydroxyphenazine) that can be oxidized further by m-chloroperbenzoic acid to give 1-hydroxyphenazine-5,10-dioxide (Chart 14)[48].

Chart 14



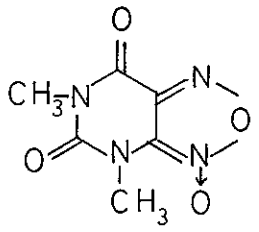
D-3. BFO with phenolate anions and related species: Many phenolate anions react smoothly with BFOs[9,49,27] to give phenazine di-N-oxide derivatives. Depending on the substitution pattern of the phenolate anion, the reaction usually follows one of three typical courses (Chart 15): If the para position of the phenolate anion carries no substituent, C-4 of the anion appears at the ring junction of the resulting phenazine system (cases a and b); if the para position of the phenolate anion carries a substituent, C-2 of the anion appears at the ring junction (case c). It should be

Chart 15



noted that formation of the fully aromatic final product requires an elimination step in b and c, but a dehydrogenation step in a. The original article presents further details[49].

The reaction of 33 with anilines to give 1,3-dimethylalloxazine 5-oxides[50] is analogous to that of BFO with phenols and with enamines.



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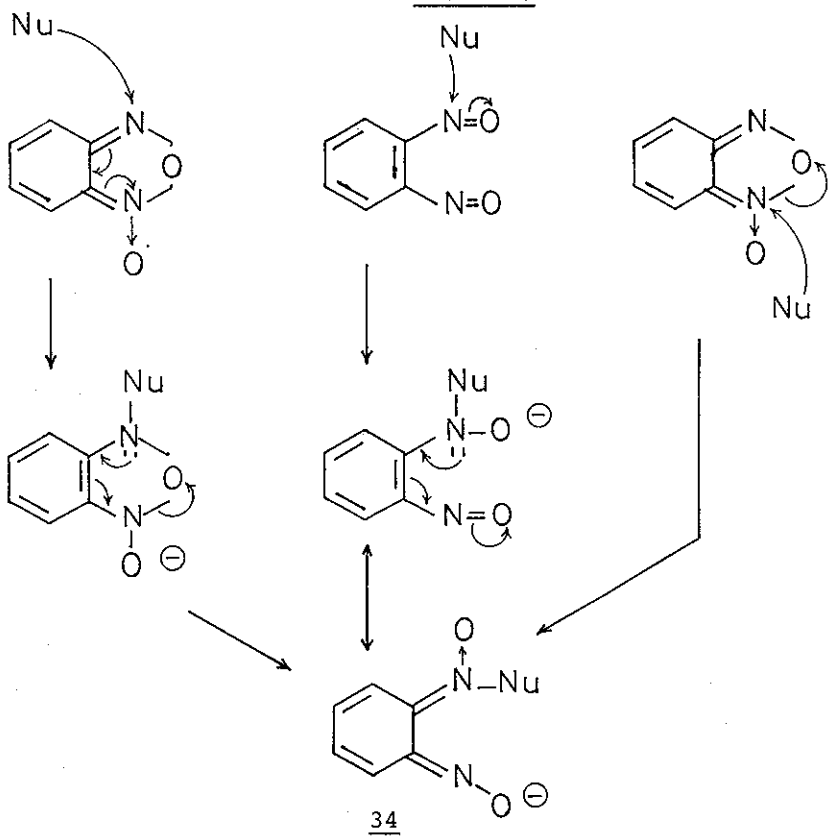
E. MECHANISM

Toward electron-donors, BFO behaves like an electrophile. Nucleophilic attack may be postulated to occur at either N-3 or N-1 of the bicyclic form, or at either nitrogen atom of an elusive o-dinitrosobenzene. For BFO (and for BFO's containing identical substituents at C-5 and C-6 or at C-4 and C-7) the same intermediate results (34 or its conjugate acid*, Chart 16), regardless of the mode of attack. With unsymmetrically

* In the following discussion the intermediates are usually depicted as conjugate acids, even though in basic conditions they may exist as anions.

Chart 16



34

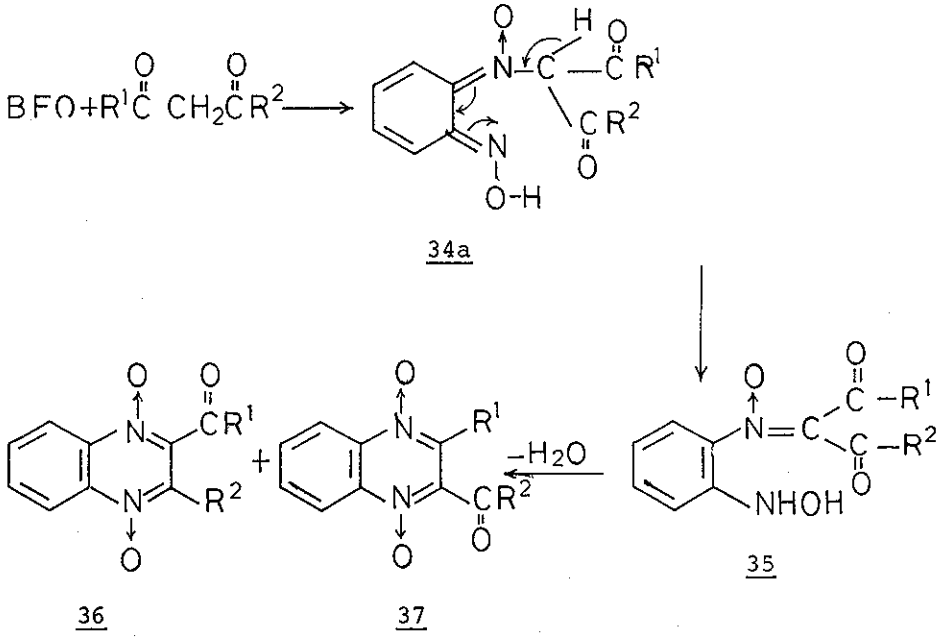
substituted benzofurazan oxides, however, two intermediates of type 34 may result, depending on whether one or the other of the nitrogen atom of the reactant is attacked. Mason and Tennant[34] have interpreted the reaction of 5(6)-substituted BFOs with

benzoylacetonitrile in terms of attack by the enolate anion at N-3 of the bicyclic form of BFO in its most stable tautomeric form. On the other hand, Abushanab and Alteri have reported[38] that the isomeric ratio of the products resulting from 5(6)-substituted BFOs and acetonyl methyl sulfide can be rationalized best by nucleophilic attack on BFO in its o-dinitrosobenzene form (refer to discussion on Charts 6 and 7, Section D-2). To date no unequivocal proof exists for the intermediacy of o-dinitrosobenzene in the isomerization of benzofurazan oxides, and although Abushanab and Alteri make cogent arguments to support their case, the matter cannot yet be considered settled.

The postulated intermediate (34) accounts for most of the observed products, as outlined in the cases that follow.

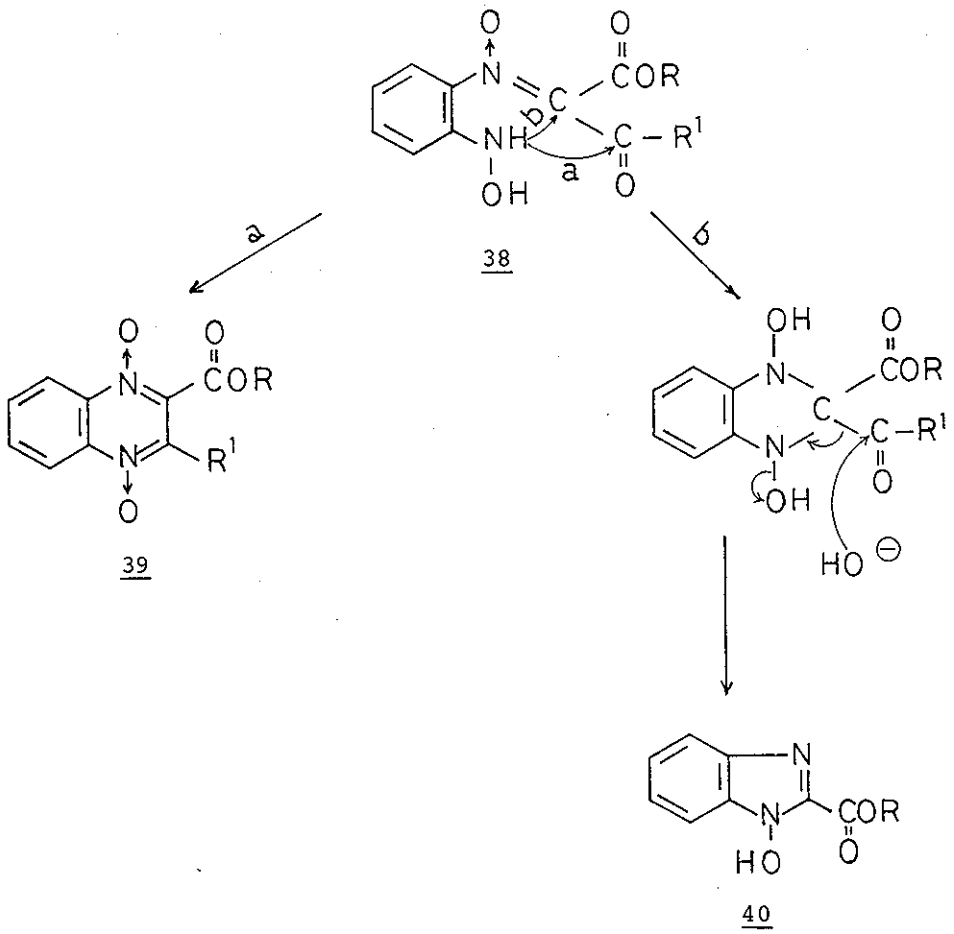
(a) With 1,3-diketones such as $R^1\overset{O}{\overset{\|}{C}}CH_2\overset{O}{\overset{\|}{C}}R^2$, intermediate 34a isomerizes to the hydroxylamino-nitrone (35), as originally proposed by Mason and Tennant[34]. The latter, then, undergoes cyclization in the expected manner[51] to give the final products. With symmetrical 1,3-diketones ($R^1 = R^2$) there is only one product (36 = 37), but with unsymmetrical 1,3-diketones ($R^1 \neq R^2$) the reaction may give two isomeric di-N-oxides by attack of the hydroxylamino nitrogen on one or the other of the carbonyl groups of 35[32] (Chart 17). With enamines the reaction follows a similar path, with elimination of an amine rather than of water taking place in the last step.

Chart 17



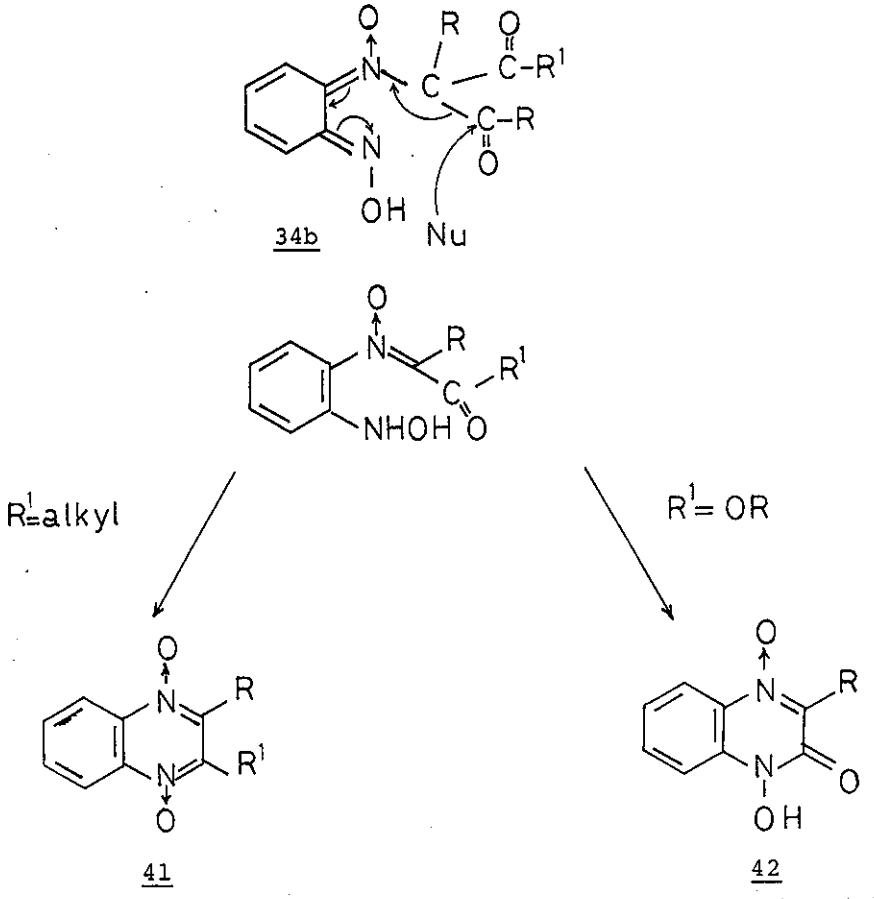
(b) With β-ketoesters, R^1COCH_2COR, intermediate 34a (R^2 = OR) rearranges to the hydroxylamino-nitrone 38, which then gives the normal product (39) by attack of the hydroxylamino nitrogen at the (more reactive) keto carbonyl group. In some cases attack may occur on the carbon atom of the nitrone function (a site known to be prone to nucleophilic attack[51]), ultimately leading to the observed 1-hydroxy-2-carbalkoxy benzimidazole derivative[37] (40, Chart 18) via a deacylation step.

Chart 18



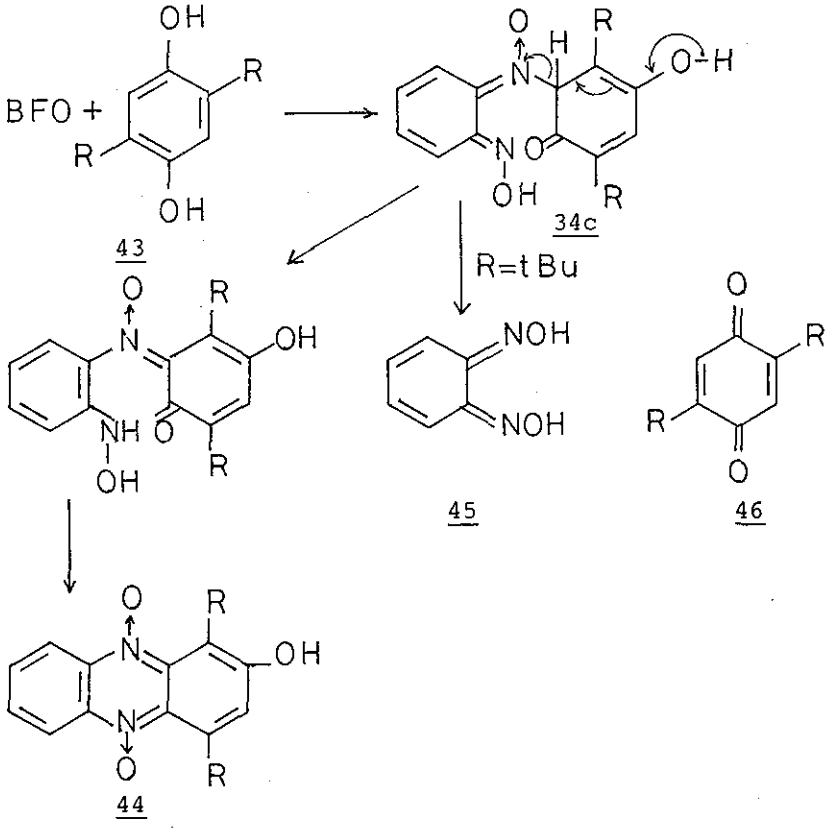
(c) With 1,3-diketones and β-ketoesters of the substitution type shown in Chart 19 (R^1 = alkyl or alkoxyl), intermediate 34b cannot isomerize to a hydroxylamino-nitrone, for it lacks the necessary hydrogen atom; nevertheless, in this case hydroxylamino-nitrones arise indirectly via a fragmentation reaction[32]. The final products are quinoxaline di-N-oxides (41) or 1-hydroxyquinoxalin-2(1H)-one-4-oxides (42).

Chart 19



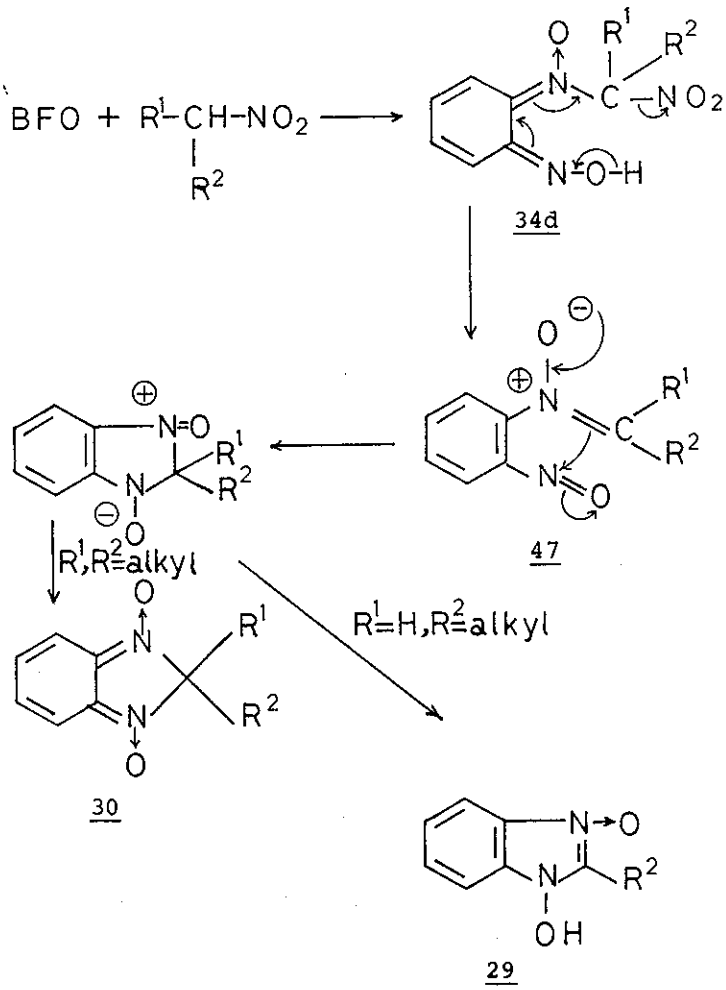
(d) With phenols such as 43, intermediate 34c, resulting from attack by the phenolate anion, normally gives rise to the hydroxyl-amino-nitrone and thence to product 44. If particular circumstances militate against this course (as when R = tert. butyl[49]), an oxidation-reduction may occur to give o-quinone dioxime (45) and a quinone (46) (arrows, Chart 20). The ability of BFO to oxidize hydroquinones to quinones may suggest alternate mechanistic possibilities (such as reaction via o-quinone dioximes and p-benzoquinones) leading to the observed phenazine di-N-oxide products[49].

Chart 20



(e) With nitroalkanes, intermediate 34d (Chart 21) follows a path strikingly different from that of previous cases: it eliminates a readily displaceable function (nitrite) to give a nitroso-nitrone (47) which, unlike hydroxylamino-nitrones, leads not to quinoxaline di-N-oxide derivatives but to 1-hydroxybenzimidazole-3-oxides (29) or to 2,2-dialkylisobenzimidazole-1,3-dioxides (30), as outlined in Chart 21[43,44,45,9]. A similar mechanism via nitroso-nitrones

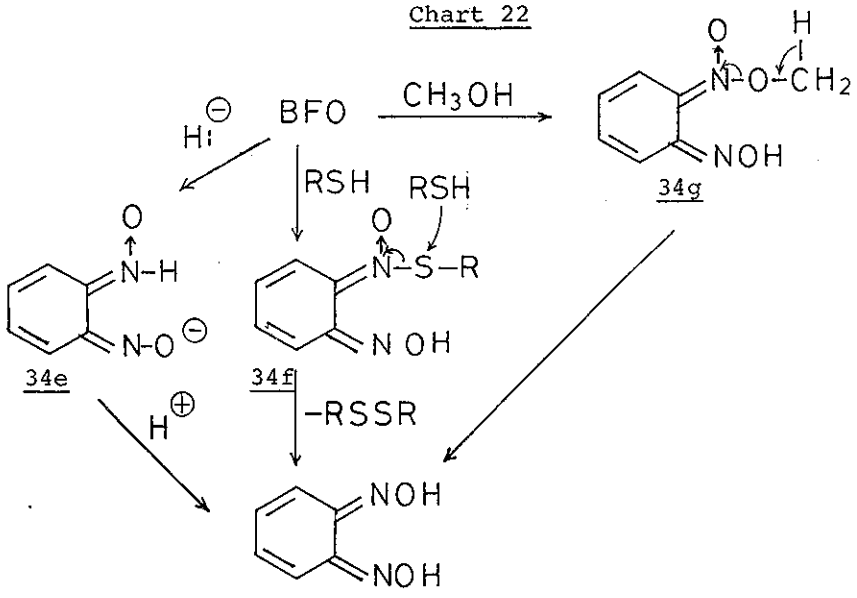
Chart 21



accounts for the products obtained in Section D-2 Chart 12 (elimination of cyanide or sulfinate from the key intermediate) and Chart 13 (elimination of nitrite or sulfinate, coupled with a base-induced deacylation step). Lending further credence to the intermediacy of nitroso-nitrones in these reactions is the observation that 1-hydroxybenzimidazole-3-oxides also result, most plausibly via nitroso-nitrones[52], when aldehydes react with o-quinone dioxime. A nitroso-nitrone is probably also implicated in the abnormal reaction of BFO with benzofuran-3(2H)-ones to give quinoxaline mono-N-oxides[41].

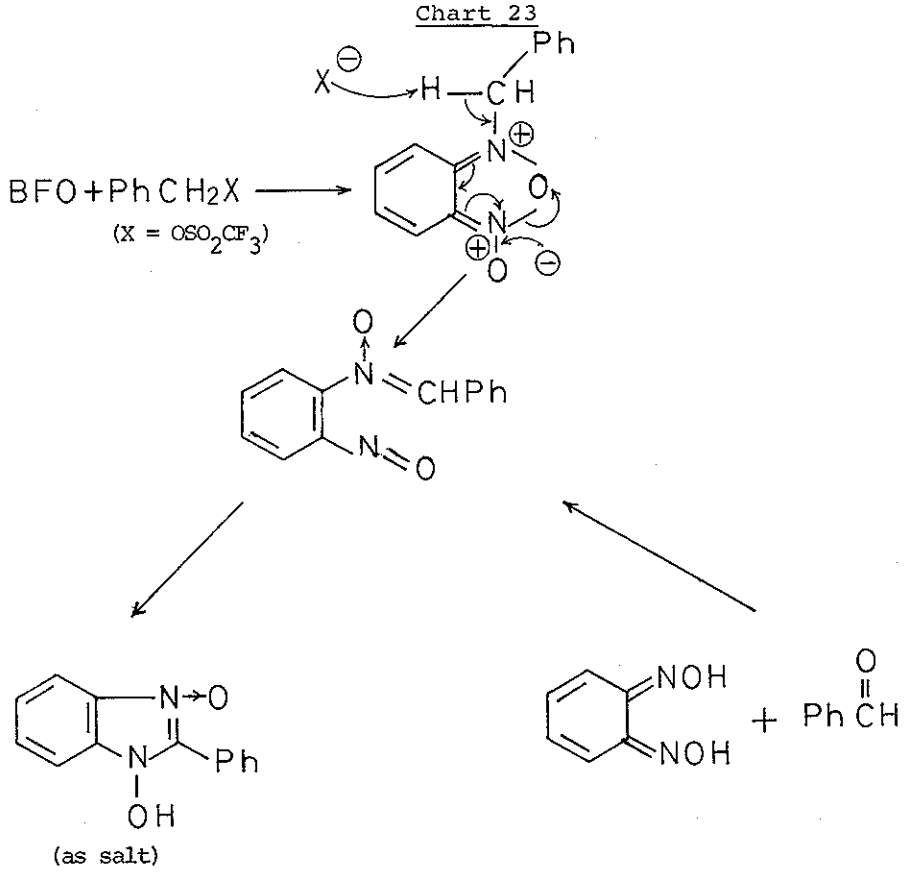
The reduction of BFO to o-quinone dioxime by sodium borohydride as well as by reagents such as hydroxylamine[53,54], methanol, and thiols[49] probably involves intermediates analogous to 34 (34e to g, Chart 22).

Chart 22



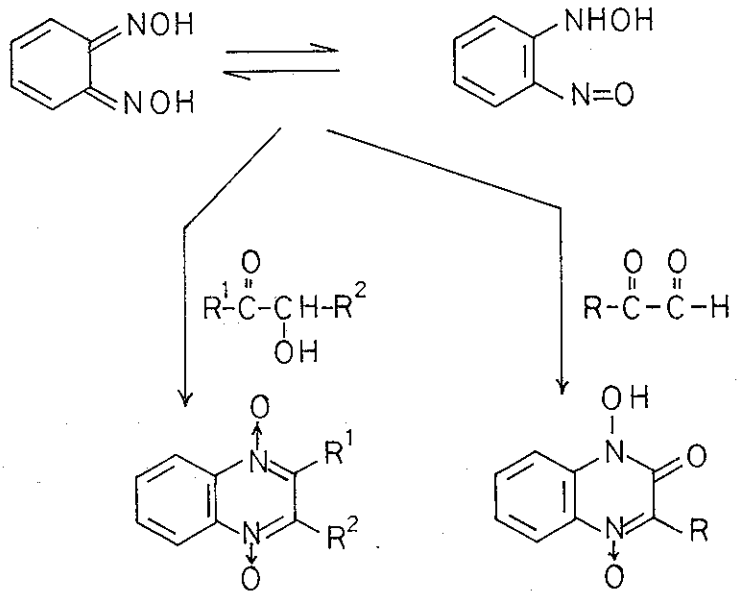
In all the above reactions, BFO behaves like an electrophile. There are, however, cases in which the role is dramatically reversed. Notable among these is the reaction of BFO with alkyl trifluoromethane-sulfonates to give 1-hydroxybenzimidazole 3-oxides[52]. The electrophile here, being a powerful alkylating agent, is attacked by N-3 of BFO to give the final product via a nitroso-nitrone intermediate (Chart 23). The reaction of BFO (nucleophilic N-3) with formaldehyde (electrophilic carbon) in alkali to give the hitherto unknown 1,3-dihydroxybenzimidazolin-2-one[40] evidently follows a similar mechanism.

Chart 23



Abushanab has described a preparation of quinoxaline di-N-oxides from o-quinone dioxime (one oxidation level below that of BFO) and alpha-hydroxyaldehydes or alpha-hydroxyketones (one oxidation level above that of simple aldehydes and ketones). Extension of this reaction to alpha-ketoaldehydes gives 3-substituted-1-hydroxyquinoxaline-2-one-4-oxides in good yield[55]. These reactions possibly involve participation of the dioxime in its tautomeric o-hydroxylaminonitrosobenzene form (Chart 24).

Chart 24

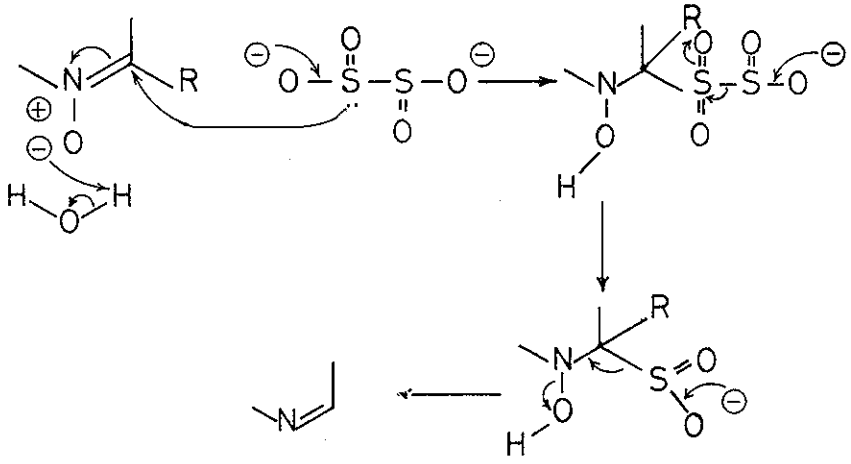


F. SOME CHEMICAL TRANSFORMATIONS

Since the chemistry of N-oxides has been reviewed elsewhere[11,10,56], the present discussion deals only with a few reactions, selected because of their synthetic potential or novelty.

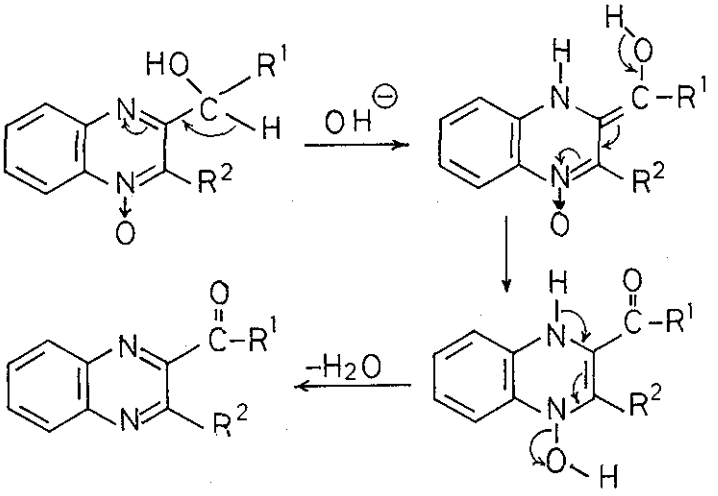
F-1. Deoxygenations: Quinoxaline di-N-oxides can be deoxygenated smoothly by phosphorus trichloride or by sodium dithionite. In our laboratory we have found reactions with phosphorus trichloride to be somewhat faster, but yields with dithionite to be considerably higher[57]. Attack occurs at different sites: at oxygen with phosphorus trichloride[58], at alpha carbon with sodium dithionite[57] (Chart 25, partial structures).

Chart 25



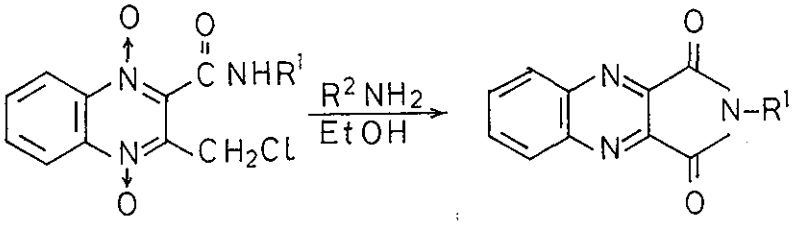
In appropriately substituted quinoxaline N-oxides, deoxygenation sometimes may occur even in the absence of reducing agents, through a remarkable base-induced intramolecular oxidation-reduction comprising successive prototropic shifts followed by an elimination (Chart 26)[57]. The recently reported

Chart 26



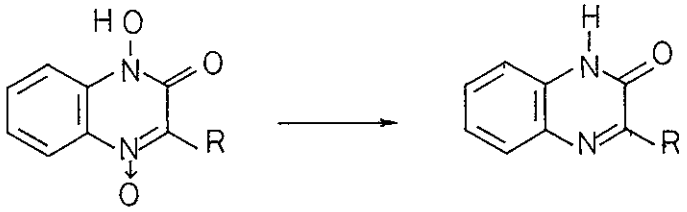
transformation[59] shown in Chart 27 involves, among other steps, analogous prototropic shifts and eliminations.

Chart 27



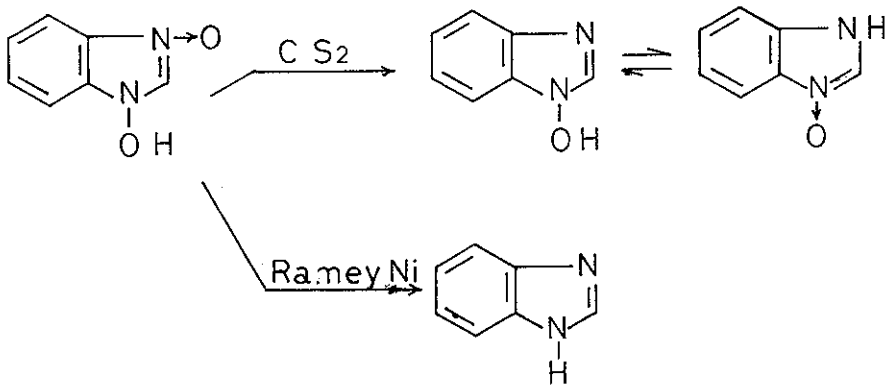
In the hydroxamic acid series, sodium dithionite deoxygenates 1-hydroxyquinoxaline-2(1H)-one-4-oxides to the corresponding quinoxalones (Chart 28)[34].

Chart 28



Selective deoxygenations have been reported in the benzimidazole series[36], as outlined in Chart 29 for 1-hydroxybenzimidazole-3-oxide. In the 2,2-dialkylisobenzimidazole 1,3-dioxide

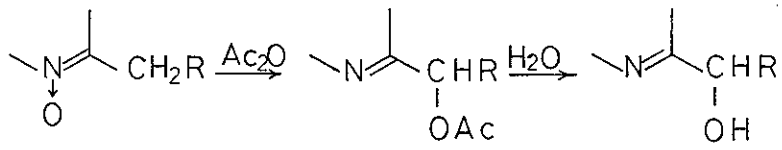
Chart 29



series (30, Chart 11), stepwise reduction is possible with sodium borohydride[44]. The same reagent reduces 2,3-disubstituted quinoxaline di-N-oxides to give predominantly cis 1,2,3,4-tetrahydroquinoxalines in good yield[60].

F-2. Deoxygenative side-chain acetoxylation: Acetic anhydride converts alpha or gamma alkyl substituted heteroaromatic-N-oxides to the corresponding deoxygenated acetoxy derivatives (Chart 30, partial structures). This valuable reaction[11,10] has been the

Chart 30



subject of several mechanistic studies[61]. Applications have been reported in the quinoxaline series[62,57].

F-3. Miscellaneous transformations: Easy access to aromatic N-oxides by the Beirut Reaction has spurred a great deal of work aimed at transforming these products into derivatives with enhanced biological activity. Table I gives some recent examples.

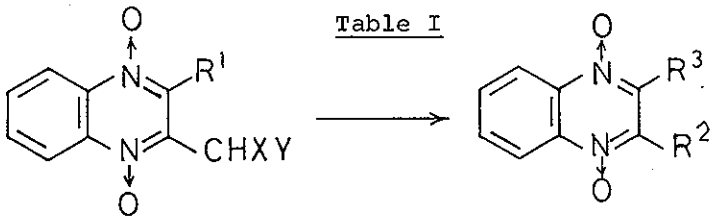


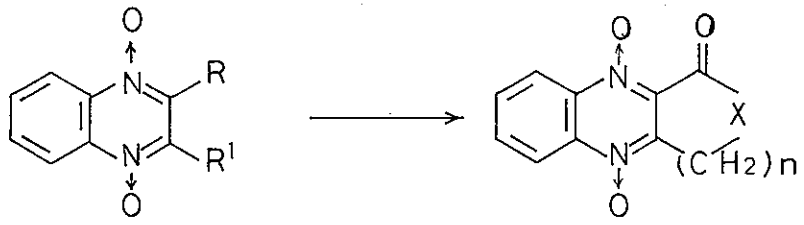
Table I

X	Y	R^1	Reagent	R^2	R^3	Ref.
Cl	H	CONRR	$PhCHCO_2^-$ (OH)	$CH_2O_2CCHOHPh$	CONRR	a)
Br	H	CONHR	RSH	CH_2SR	CONHR	b)
H	H	SOR	HCl or HBr	CH_3	Cl or Br	c)
H	H	SO_2R	HCl or HBr	CH_3	Cl or Br	d)
Br	H	SCH_3	CH_3SNa	CH_2SCH_3	SCH_3	e)
Br	H	CH_2Br	NaOAc	CH_2OAc	CH_2OAc	f)
H	H	H	SeO_2	CHO	H	g)
H	H	CONRR	$Cl_2/CHCl_3$	CH_2Cl	CONRR	h)
H	H	CONHR	Cl_2/HOAc	$CHCl_2$	CONHR	i)
H	H	$CO_2C_2H_5$	CH_2O/Triton B	CH_2CH_2OH	$CO_2C_2H_5$	j)
- O -		H	$NH_2NHCO_2CH_3$/HCl	$CH{=}NNHCO_2CH_3$	H	k)
Cl	Cl	CONHR	$NH_2NHCO_2CH_3$	$CH{=}NNHCO_2CH_3$	CONHR	l)
- O -		H	$HONHCH_2CH_2OH$	$CH{=}N(O)CH_2CH_2OH$	H	m)

a) R. Nast, K. Ley, U. Eholzer, S. African 6905,797/1970 (CA: 1970, 73, 120671y). b) M.J. Abu El-Haj Ger. Offen. 2, 120, 501/1971 (CA: 1972, 76, 77558e). c,d,e) E. Abushanab Brit. 1, 293, 850/1972 (CA: 1973, 78, 43518c), and ref. 35. f) A.S. Elina, L.G. Tsyrulinikova, O. Magidson, V.I. Fatneva, USSR 178, 382/1973 (CA: 1974, 80, 37163h). g) P. Benko, L. Buda, L. Pallos, I. Simonek, P. Foris, J. Kovacs, K. Magyar, G. Tokar, Hung. Teljes 8581/1974 (CA: 1975, 82, 57734g). h) K. Ley, U. Eholzer, K.G. Metzger, D. Fritsche, S. African 6806, 093/1969 (CA: 1970, 72, 3509p). i) F. Seng, K. Ley, K.G. Metzger Ger. Offen. 2, 122, 572/1972 (CA: 1973, 78, 43523a). j) H. Hartung, W. Durckheimer, W. Raetner, E. Schrinter, Ger. Offen. 2, 052, 279/1972 (CA: 1972, 77, 34572t). k) J.D. Johnston, Ger. Offen. 1, 927, 337/1970 (CA: 1970, 72, 100753c). l) F. Seng, K. Ley, K.G. Metzger, Ger. Offen. 2, 122, 572/1972 (CA: 1973, 78, 43523a). m) H.K. Kim, Ger. Offen. 2, 043, 532/1971 (CA: 1971, 74, 125729d).

Various standard reactions, such as those outlined in Table 2, have been used to introduce a heterocyclic ring at the 2,3-positions of quinoxaline di-N-oxides.

Table 2



R	R^1	Reagent	X	n	Ref.
CONRR	CH_2OH	morpholine	O	1	a)
CONRR	CH_2OAc	HCl	O	1	a)
$CO_2C_2H_5$	CH_2Br	CH_3NH_2	NCH_3	1	b)
CH_2CH_2OH	CO_2^-	HCl	O	2	c)

a) F. Seng, K. Ley, K. G. Metzger, Ger. Offen. 1,813,918/1970 and 1,807,735/1970 (CA: 1970, 73, 45539f, 56130s). b) Pfizer Inc., Brit. 1,303,372/1973 (CA: 1973, 78, 124629s). c) Table 1, ref. j.

Of particular interest is the preparation of pyrimidoquinoxalines[63,64] from starting materials readily available from BFO and malononitrile (Charts 31 and 32).

Chart 31

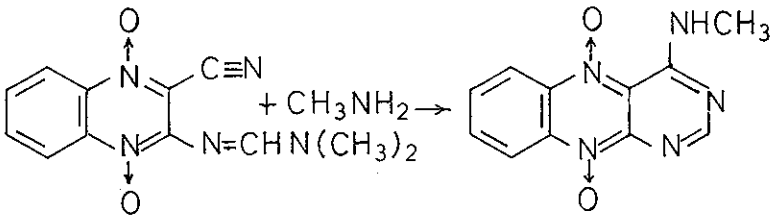
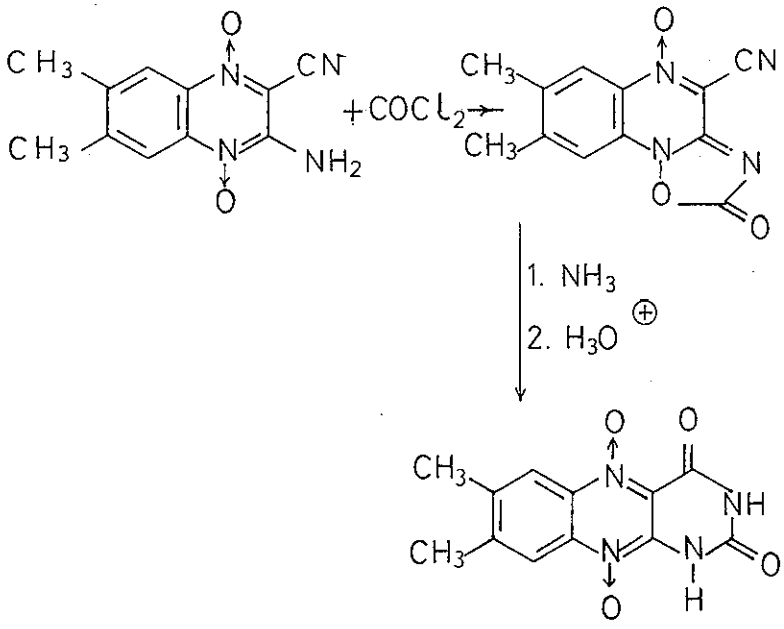
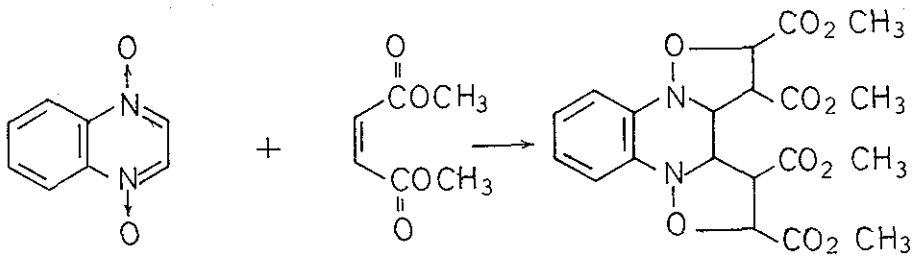


Chart 32



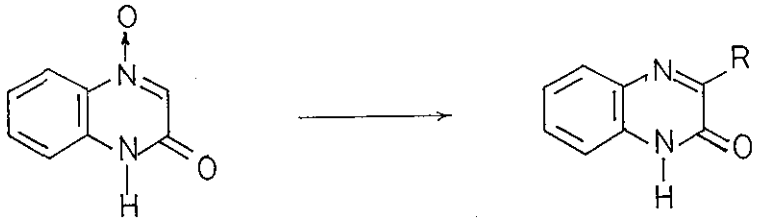
Quinoxaline di-N-oxide has been reported to undergo cycloaddition reactions with dimethyl maleate and with N-phenylmaleimide[65] (Chart 33).

Chart 33



Quinoxaline-2(1H)-one-4-oxide reacts with phenylisocyanate or with benzyne to give deoxygenated products substituted at position 3 (Chart 34)[66].

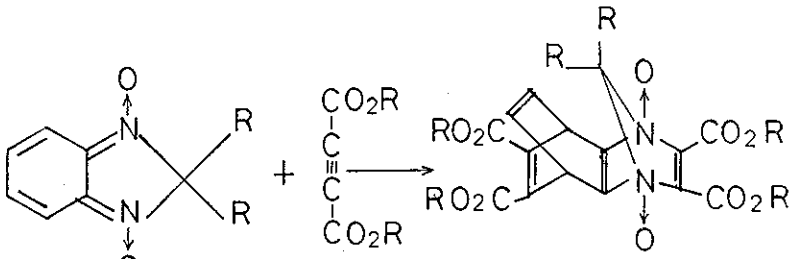
Chart 34



R = NHPh or o-C_6H_4OH

An adduct is readily formed between 2,2-dimethyliso-benzimidazole-1,3-dioxide (30, R = Me) and dimethylacetylene dicarboxylate[67] (Chart 35).

Chart 35

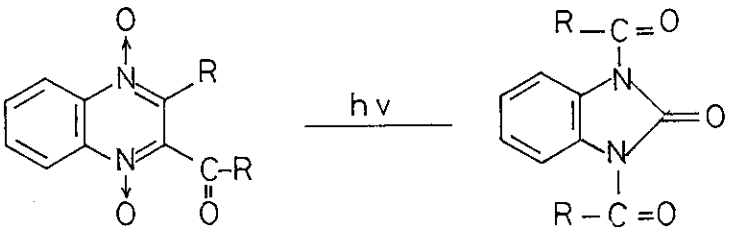


30

(R = Me)

F-4. Photochemical reactions: Although extensive photochemical work has been done on a variety of aromatic N-oxides[68] relatively little has been done on quinoxaline 1,4-dioxides. Landquist[69] irradiated quinoxaline 1,4-dioxide and isolated quinoxaline-3(4H)-one-1-oxide. We have shown that substituted quinoxaline 1,4-dioxides (15), upon irradiation, give 1,3-disubstituted benzimidazolones[70,71,72] (48, Chart 36). The oxaziranes 49 and 50 have been suggested as intermediates, but the possibility that the reaction goes via 51 cannot be ruled out (Chart 37).

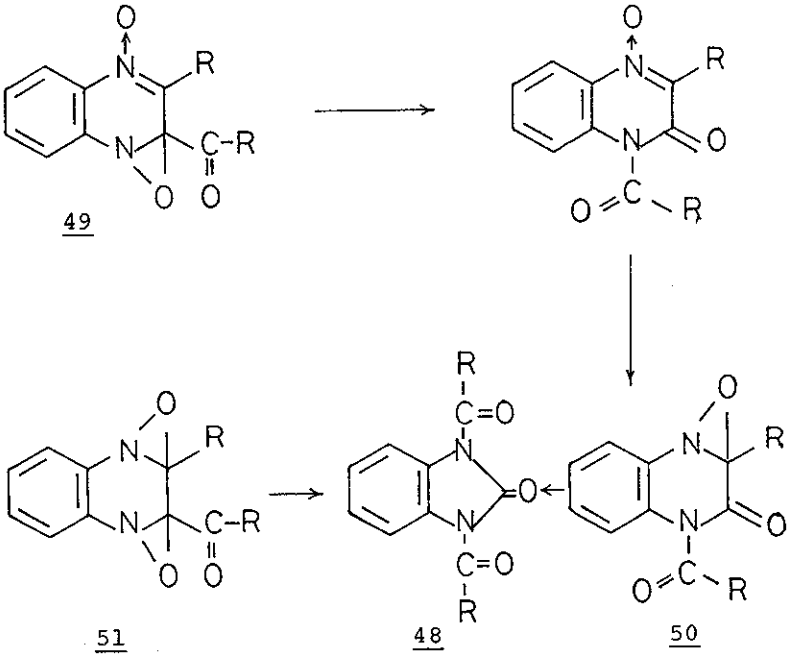
Chart 36



15 48

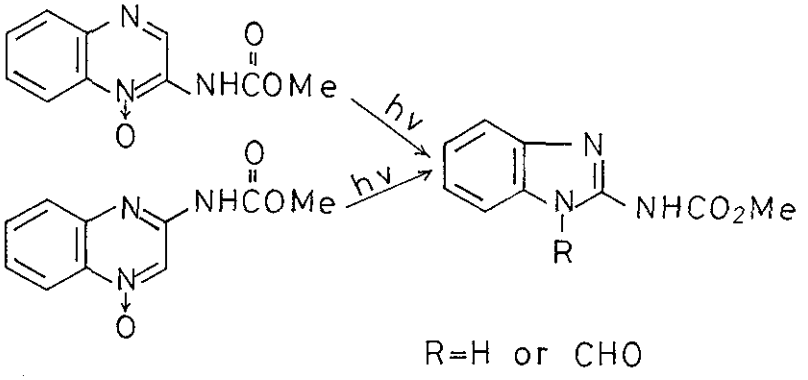
(R = Alkyl or Aryl)

Chart 37



An interesting example of ring contraction has been reported recently[15] (Chart 38).

Chart 38

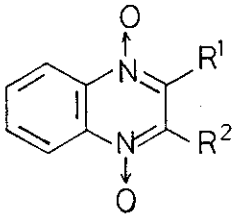


G. SPECTROSCOPIC PROPERTIES

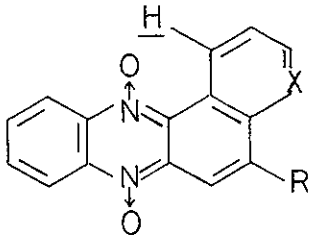
The types of compounds to be discussed in this section are shown in Chart 39. Infrared frequencies are reported in reciprocal centimeters, and nmr values in ppm (delta).

G-1. Quinoxaline and phenazine series: The infrared spectra of quinoxaline N-oxides and N,N'-dioxides show characteristic N→O stretching frequencies in the 1280-1380 region[73]. The band usually appears in the range 1320 to 1350 (nujol mulls or KBr)[36,31,71,25,32], but occasionally two bands may appear such as in 3 (R^1 = Ph, R^2 = SO_2Ph)[36] at 1340 and 1360. Isomers

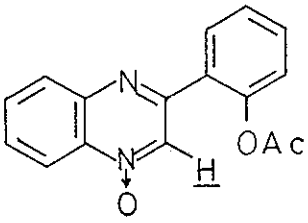
Chart 39



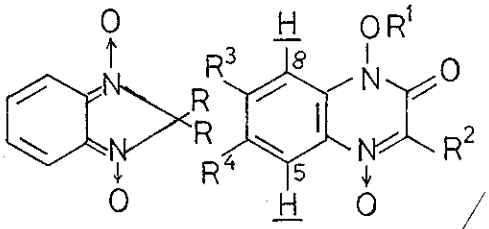
3



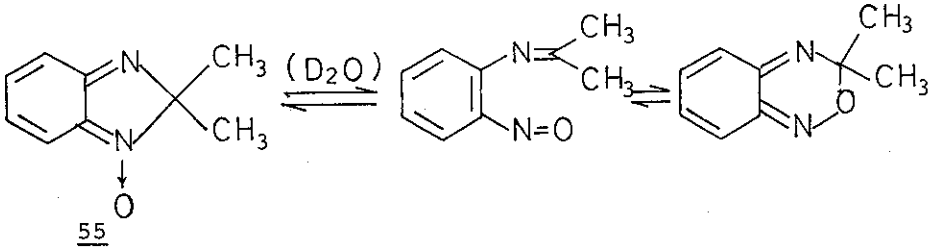
52



53



30 54



55

such as 3 (R^1 = COR, R^2 = R or Ar) and 3 (R^1 = COAr, R^2 = R or Ar) are readily distinguishable because the former absorbs around 1700-1710, whereas the latter around 1660-1680[32].

Quinoxaline di-N-oxides (3) show aromatic A_2B_2 multiplets in the range 8.30-8.70 (deshielded H-5 and H-8 protons) and 7.60-7.80 (H-6 and H-7 protons)[17,31,36,35].

In the benzo[∝]phenazine-7,12-dioxide series, a pronounced downfield shift is observed for H-1 because of its proximity to the 12-oxide. Typical examples are 52 (R = OH, X = CH), 52 (R = H, X = CH), and 52 (R = OH, X = N) with signals at 10.0, 10.65, and 11.6 respectively[49].

Deoxygenation of 3 (R^1 = CH_3; R^2 = Ph, $COCH_3$, COOEt) to the parent quinoxaline is attended with readily detectable downfield shifts for the R^1 methyl singlet (2.45 → 2.71 for R^2 = Ph, 2.49 → 2.92 for R^2 = COMe, 2.55 → 2.86 for R^2 = CO_2Et)[57]. A similar downfield shift is observed for the H-2 singlet upon deoxygenation of 53 (8.63 → 9.08)[41].

The ratio of isomers such as 3 (R^1 = Et, R^2 = COAr) and 3 (R^1 = COEt, R^2 = Ar) can be conveniently determined in a mixture from the intensity of the methyl triplets at 1.23-1.27 for the former and at 1.02-1.06 for the latter. The corresponding values for the methyl doublets in 3 (R^1 = $CH(CH_3)_2$, R^2 = COAr) and 3 (R^1 = $COCH(CH_3)_2$, R^2 = Ar) are 1.37-1.41 and 0.94-0.99 respectively[32].

Through-space hydrogen-fluorine long-range coupling has been observed in some 2-substituted-3-trifluoromethyl quinoxalines, their 1-oxides, and 1,4-dioxides. J_{H-F} is susceptible to changes in hydrogen-fluorine internuclear distances[74].

G-2. Benzimidazole series: The dialkylisobenzimidazole-1,3-dioxides (30) exhibit strong absorption bands for the N-oxide at 1307, 1361, and 1399. The uv spectra show λ_{max} at 510 nm (ϵ 7.25 x 10^3) and 245 nm (ϵ 2.34 x 10^4). The dimethyl compound (30, R = Me), a red crystalline solid readily soluble in both water and organic solvents, shows a singlet in the nmr at 1.7 for the gem dimethyl group, and a symmetrical AA'BB' multiplet for the vinylic protons at 6.9 (J = 3Hz) and 7.25 (J = 3Hz)[43,44].

The monoxide 55 presents an interesting case: its nmr spectrum, unchanged between -60° and +60°, consists of a methyl singlet at 1.54 and an unsymmetrical multiplet in the aromatic region. In D_2O solution, however, an additional small singlet appears in the methyl region which suggests the possibility of valence tautomerism via an intermediate nitroso structure[44]. The nmr spectrum of dimethyl isobenzimidazole (55 without the oxygen atom) shows a methyl singlet at 1.45 and a symmetrical AA'BB' multiplet in the aromatic region. Further spectral data on benzimidazoles are given in a recent review[75].

G-3. Hydroxamic acid series: Iron(III) chloride gives a deep red color with 1-hydroxy-3-phenylquinoxaline-2-one-4-oxide (54, $R^1 = R^3 = R^4 = H$, R^2 = Ph)[34]. The infrared spectrum of 54 ($R^1 = R^3 = R^4 = H$, R^2 = Ph) shows characteristic bands for the

carbonyl (1608) and the N-oxide (1350); the nmr spectrum shows a multiplet centered at 7.88 (8 aromatic protons) and a doublet at 8.40 (H-5 proton, J = 8 Hz). Interestingly, in these compounds (unlike in quinoxaline di-N-oxides), deshielding is reduced at position 8 and only the proton at position 5 absorbs downfield[36]. Warm acetic anhydride converts 54 ($R^1 = R^3 = R^4 = H$, $R^2 = Ph$) into an acetoxy derivative (54, $R^3 = R^4 = H$, $R^1 = Ac$, $R^2 = Ph$) with characteristic carbonyl infrared band at 1800[34]. A related acetoxy derivative, 54 ($R^1 = Ac$, $R^2 = CH_3$, $R^3 = R^4 = H$), shows infrared bands at 1818 and 1724 for the two carbonyl groups, and its nmr spectrum (unlike the usual A_2B_2 pattern of 3) shows two separate one-proton doublet of doublets (J = 7.5 and 2.0 Hz) at 7.7 (for the C-8 proton) and at 8.3 (for the C-5 proton); the two protons at C-6 and C-7 give a multiplet at 7.15-7.5[35]. The nmr spectra of a series of hydroxamic acid esters substituted on the homocyclic ring (54, $R^1 = R^2 = CH_3$) give signals in the range 6.98-8.4 (H-8 proton) and 7.9-9.17 (H-5 proton)[38].

H. CONCLUSION

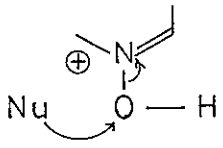
Although much progress has been made over the past decade in the synthesis of heterocyclic-N-oxides from BFO, a number of problems remain to be solved.

Perhaps the greatest endeavor during the next decade will be in arriving at a better understanding of the reaction. Although

most of the reported products may be accounted for in terms of hydroxylamino-nitrone or nitroso-nitrone intermediates, the mechanism of the reaction is not established. Unequivocal proof of the isomerization of BFO via o-dinitrosobenzene is as yet forthcoming, and there is still controversy regarding the site of attack by nucleophiles. Moreover, the possibility that certain reactions of BFO may be preceded by an oxidation-reduction step raises an uncertainty regarding the reactants in subsequent steps and, therefore, calls for the exercise of caution regarding mechanistic interpretations.

The synthetic possibilities of analogs of BFO are still to be explored, as are also new methods for functionalizing alkyl side chains in quinoxaline di-N-oxides so as to obtain products with enhanced biological activity[28].

The protonated N-oxide function contains an electrophilic oxygen that may be transferred to other biologically important receptors[76]. The detailed mode of action of heteroaromatic



N-oxides in modifying enzymes and biological oxidation-reduction systems, or in causing structural alteration of nucleic acids remains a challenging problem for the future.

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Note: A review, somewhat limited in scope, on synthetic applications of BFO was published after this work was completed. See K. Ley and F. Seng, Synthesis, 1975, 415.

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