REACTIONS OF BENZOFURAZAN OXIDES WITH ENAMINES

BY

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ABSTRACT

Quinoxaline-di-N-oxides were prepared from the reaction of substituted benzofurazan oxides with enamines derived from five-, six-, seven-, eight-membered ring ketones and from acetophenone. The reaction is general for benzofurazan oxides with alkyl, alkoxy, trifluoromethyl, and halogen substituents in position 5(6) and for dialkyl and dihalogen substituted benzofurazan oxides in positions 5 and 6.

This route has advantages over the classical method of preparation of quinoxaline-di-N-oxides because it is simple and direct.

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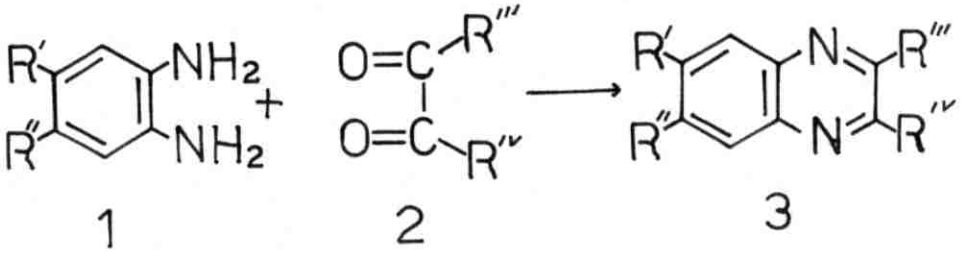
INTRODUCTION

Quinoxaline-di-N-oxides are compounds possessing the general structure (4). The classical method of preparation of these compounds involves condensation of an orthophenylenediamine (1) with a 1,2-dicarbonyl compound (2)[1], followed by oxidation of the resulting quinoxaline (3) by hydrogen peroxide in glacial acetic acid at 50 - 60°C[2].



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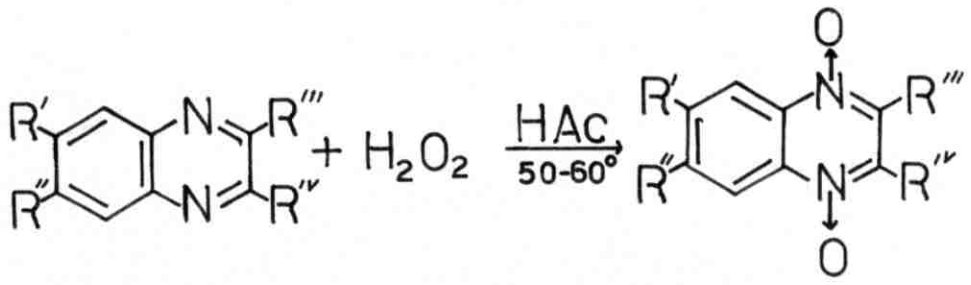


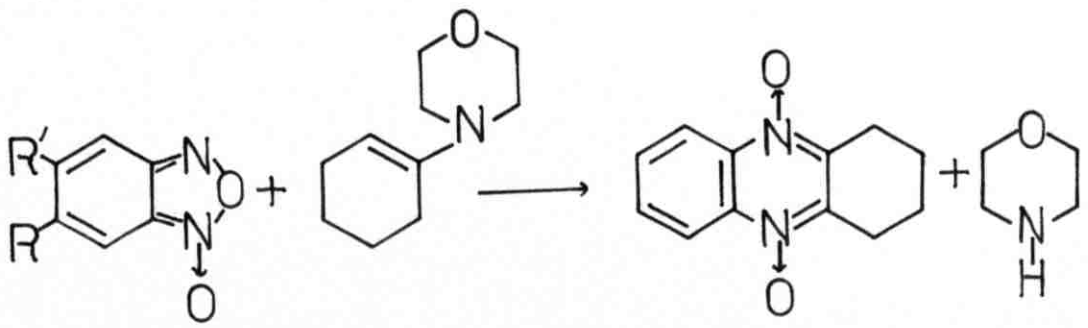
3 4

This method, however, has several shortcomings. In the first place, the starting materials for the condensation reaction are not easily available, and cases are on record where the condensation either fails or follows a different course; moreover, the oxidation step

is sometimes unpredictable and leads only to mono-N-oxides or to degradation products[3].

Quinoxaline-di-N-oxides have become important in recent years because they display antibiotic activity[4]. Certain compounds in this class are effective against amoebic infections in rats, cats, dogs and monkeys and against lymphogranuloma in both mice and eggs. Although the order of activity is comparable to that of chlorotetracycline, clinical studies showed toxic reactions precluding, for the time being, use of these compounds for therapeutic purposes.

A new route to quinoxaline-di-N-oxides, from the reaction of benzofurazan oxides with enamines, was reported by Haddadin and Issidorides in 1965[5]. This route is exemplified by the reaction of benzofurazan oxide [(5) R=R'=H] with 1-morpholino-1-cyclohexene (6) to give 1,2,3,4-tetrahydrophenazine-5,10-di-N-oxide (7). Other enamines used were derived from cyclopentanone, acetophenone and 3-cholestanone.



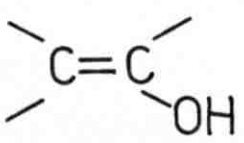
5 6 7

The purpose of this investigation was to test the generality of this reaction with substituted benzofurazan oxides [(5) R and/or R' ≠ H] and enamines derived from cyclic ketones and acetophenone.

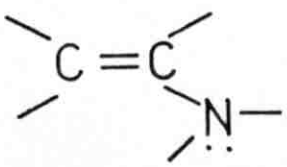
STARTING MATERIALS

Benzofurazan oxides and enamines, the starting materials in this investigation, have been generally known since the beginning of the century. It was only during the last decade, however, that these compounds assumed special importance in theoretical and preparative organic chemistry. Benzofurazan oxides, first prepared by Koreff and Ilinski in 1886[6], attracted attention as a result of the controversy regarding their structure. Enamines became versatile synthetic intermediates after Stork introduced them in 1954 as effective reagents in the alkylation of ketones[7].

The term enamine was coined by Wittig and Blumenthal in 1927[8] in analogy with enols (α,β-unsaturated alcohols), to denote compounds where the oxygen atom is replaced by a nitrogen (α,β-unsaturated amines).

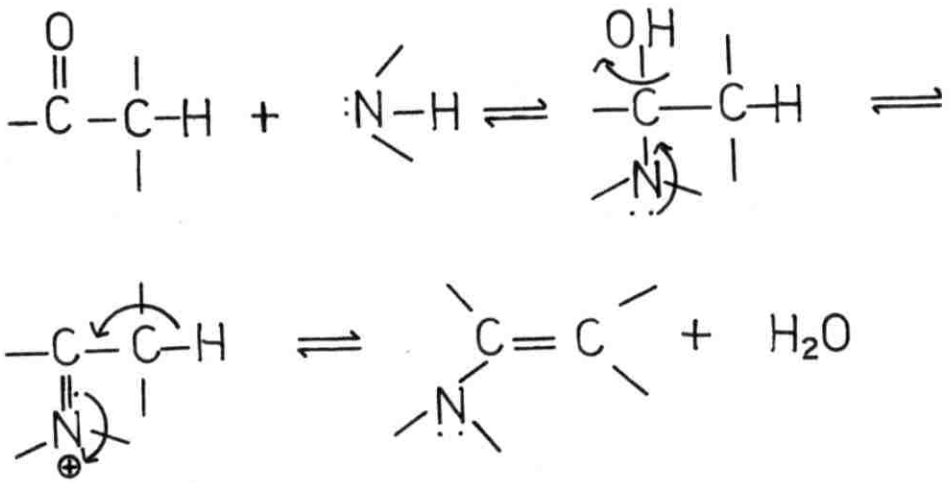


enol

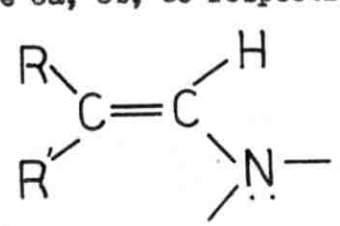


enamine

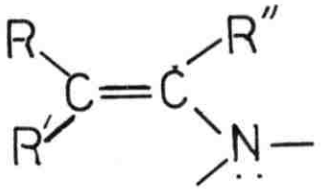
Enamines are usually prepared by the condensation of a secondary amine, (morpholine, piperidine, pyrrolidine, dimethyl amine), with a carbonyl compound[9].



The common enamines are derived from carbonyl compounds: aldehydes, acyclic ketones and cyclic ketones lead to enamines of the type 8a, 8b, 8c respectively.



8 a



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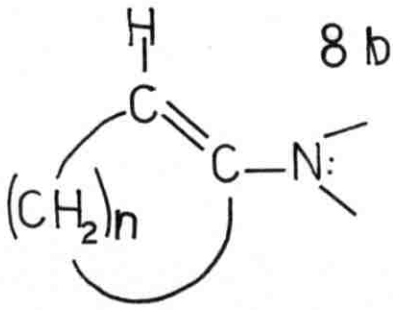


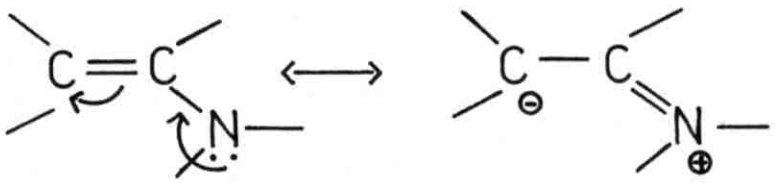
8c

The condensation reaction is reversible and is driven towards enamine-formation by the continuous removal of the water formed. Owing to the reversibility of the reaction enamines are either used immediately after their preparation or flushed with nitrogen and stored in the refrigerator, to prevent hydrolysis

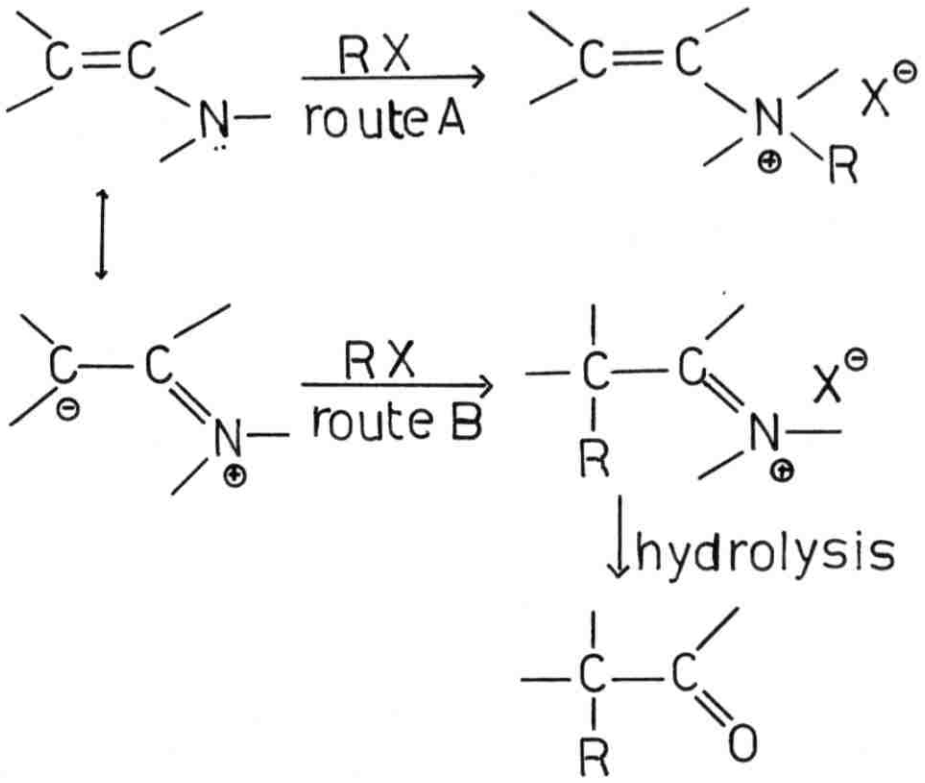
to the carbonyl compound and the secondary amine.

Other methods of preparation of enamines are known but the condensation reaction is the simplest, and, by small variations in the reaction conditions, a large variety of enamines can be prepared in high yields.

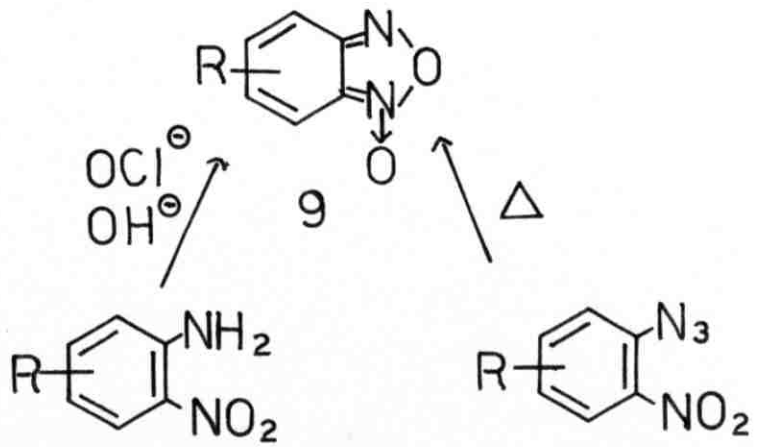
The conjugation of the free electron pair of the nitrogen with the π electrons of the double bond in enamines, generates a reactive moiety possessing two electron rich centers, namely the beta-carbon and the nitrogen.



Addition of electrophiles to enamines, such as in the alkylation of unactivated carbonyl compounds (Stork reaction)[7], may be in one of two ways. Addition may occur either at the nitrogen atom (Route A) leading to N-alkylated products (soluble quaternary ammonium salts), or at the beta-carbon atom (Route B) leading to immonium salts which, upon hydrolysis, yield the monoalkylated carbonyl compound. Whether nitrogen or beta-carbon-alkylation occurs depends on the reactivity of the alkylating reagent, the structure of the alkylated enamine and the polarity of the solvent[10].



Benzofurazan oxides* (benzofuroxans) (9) are usually prepared by oxidation of o-nitroanilines[11] or by pyrolysis of o-nitrophenylazides[12].



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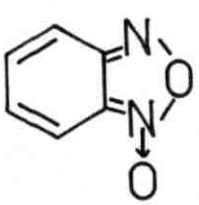
*Chemical Abstracts preferred name.

The oxidation of o-nitroanilines to benzofurazan oxides was discovered by Green and Rowe[6], who used alkaline hypochlorite as an oxidizing agent; phenyliodosodiacetate in benzene has also been used for the oxidation, but in this case the yields vary considerably with the nature and position of substituents on the aromatic ring of the substrate[6]. Occasionally the oxidation of the o-nitroanilines fails to give the desired product (e.g. 2,4-dinitroaniline[13], 4-amino-3-nitrophenol[14]) and, therefore, recourse must be made to the more reliable method of preparing benzofurazan oxides via decomposition of the o-nitrophenylazide.

The structure of benzofurazan oxide remained uncertain until 1960 when it was assigned structure (10).



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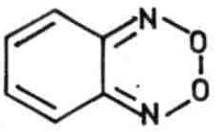

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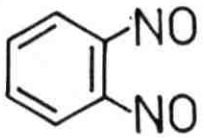

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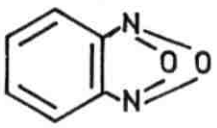
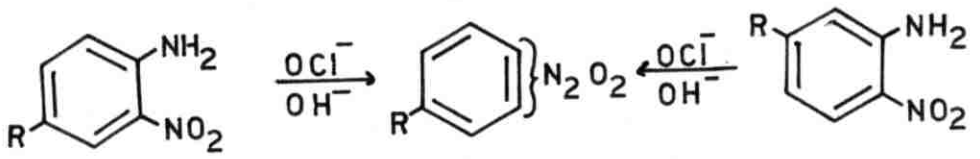


12 a

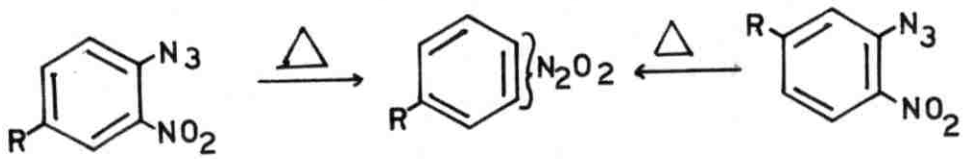
The earliest formulae to be suggested, (11) and (12), have been dismissed either because they are inconsistent with the fact that benzofurazan oxide shows no peroxide properties (11) or because benzofurazan oxide does not show the optical and chemical properties commonly associated with C-nitroso compounds (12)[6].

The structure accepted today (10) was first suggested by Green

and Rowe in 1912 but later abandoned in favour of (12a) because the unsymmetrical structure of (10) dictated two isomers for 4- and 5-substituted benzofurazan oxides when it was known that the same benzofurazan oxide is obtained from isomeric starting materials such as (13) and (14), (hypochlorite oxidation of o-nitroanilines), and (15) and (16), (o-nitrophenyl azide pyrolysis)[6].

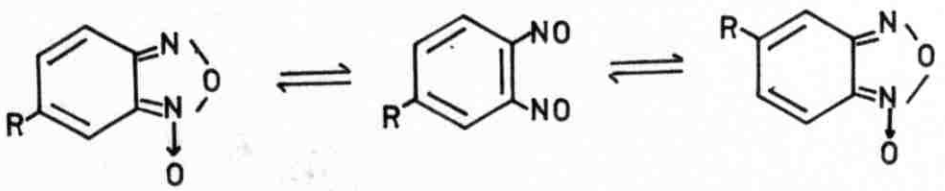


13 14



15 16

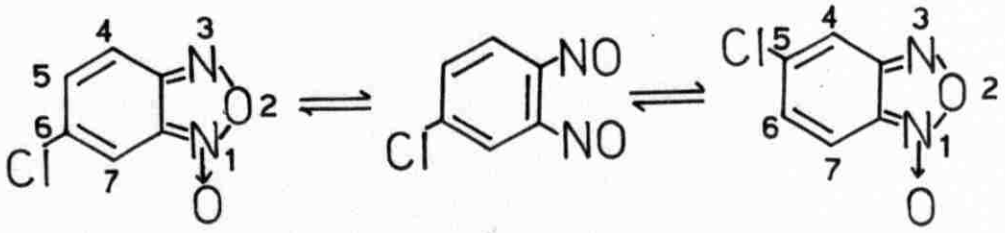
In 1931 Hammick and his coworkers suggested a rapid interconversion of stable into unstable isomers, probably via the o-dinitroso form, to account for the formation of one compound when pairs of isomers are expected[15].



17 18

Hammick's interpretation differs slightly from the present day picture in that both isomers (17) and (18) are now known, from nmr studies, to be present in solutions of most benzofurazan oxides, although usually one is detected when the substituent is in the 4- or 7- positions[16]. Evidence that the interconversion of isomers is via the o-dinitroso form has also been presented[17].

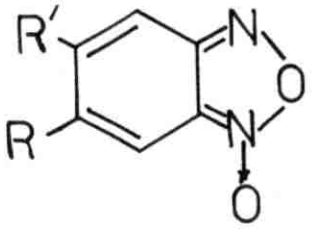
The possibility of tautomerism leads to ambiguities in the nomenclature of compounds in the series. Thus 5-chlorobenzofurazan oxide and 6-chlorobenzofurazan oxide denote two different molecules which cannot be isolated separately at room temperature because of their interconversion. In order to avoid ambiguity, benzofurazan oxides with such substituents will be referred to with both numbers, the larger number between brackets. The above chloro derivative, for example, will be described as 5(6)-chlorobenzofurazan oxide, regardless of the form adopted in the crystal.



5(6)-chlorobenzofurazan oxide.

DISCUSSION

Seven benzofurazan oxides were prepared in the course of this investigation (structures 19 - 25).



19 R = R' = H

20 R = H R' = Me

21 R = H R' = Cl

22 R = H R' = MeO

23 R = H R' = CF_3

24 R = R' = Me

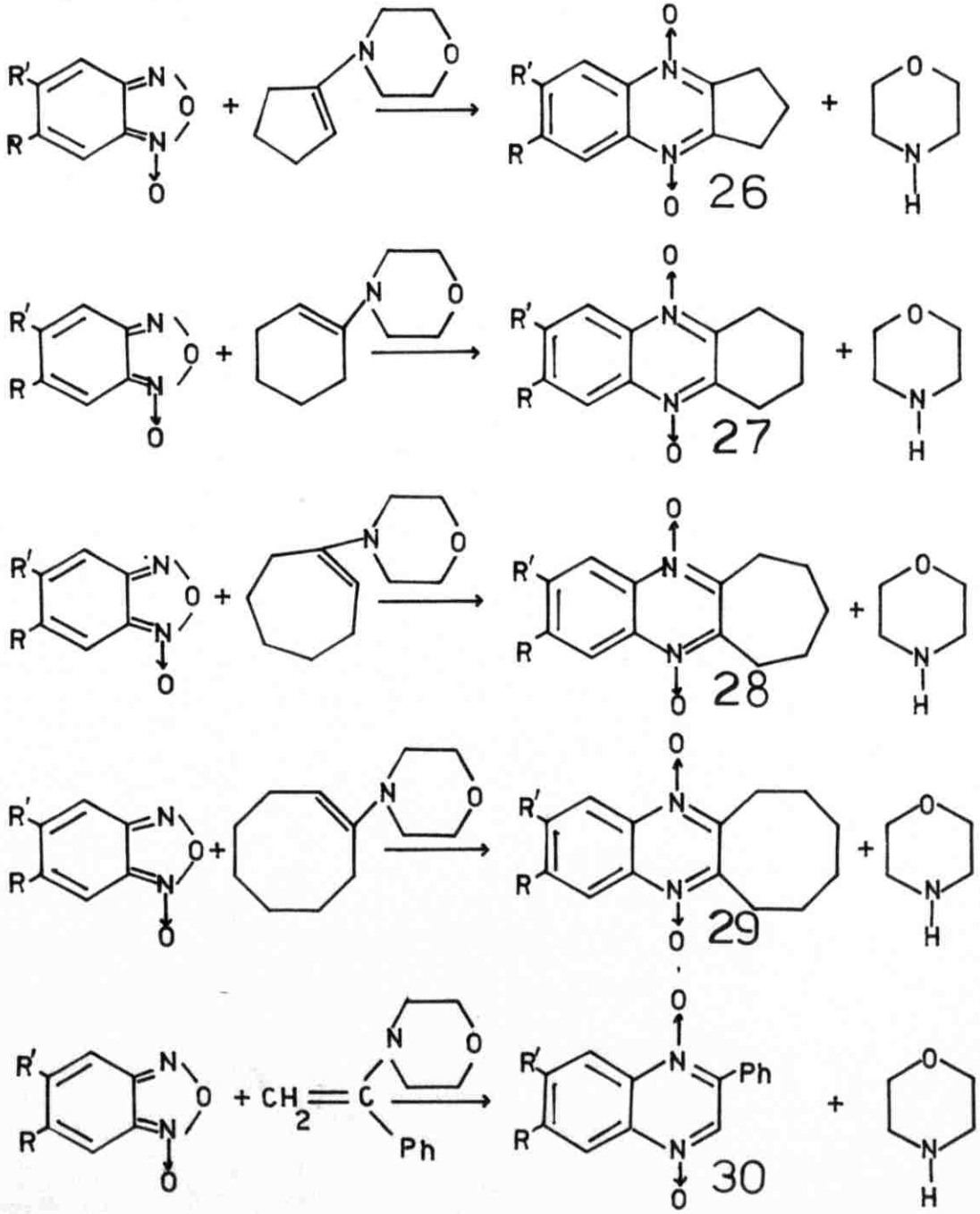
25 R = R' = Cl

With the exception of 5(6)-trifluoromethylbenzofurazan oxide (23), which was prepared by pyrolysis of the nitrophenyl azide[18], all other benzofurazan oxides were prepared by the hypochlorite oxidation, of the appropriate o-nitroaniline.

The enamines used were derived from cyclopentanone, cyclohexanone, cycloheptanone, cyclooctanone, and acetophenone. All were prepared by the condensation of the ketone with morpholine[9]. In some cases prolonged heating was necessary as, for example, in the case of acetophenone where the reflux period was six days.

The reaction between the benzofurazan oxides and the enamines was carried out by dissolving the benzofurazan oxide in warm methanol and adding the enamine in small portions and with constant shaking.

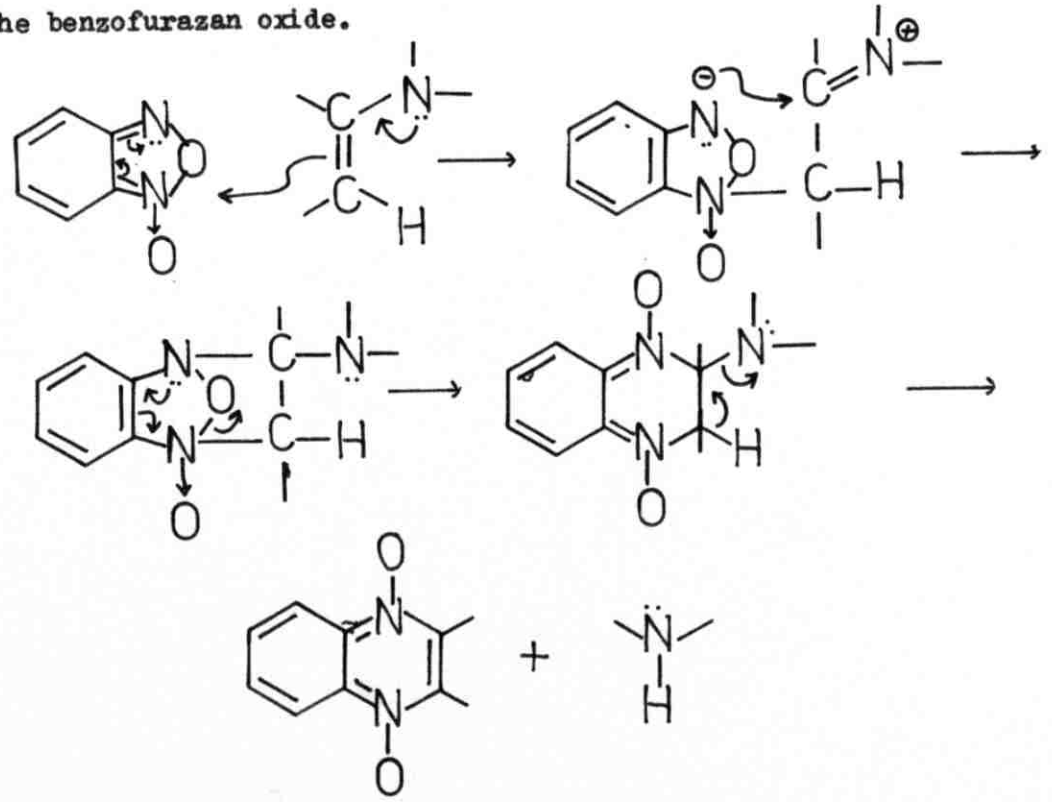
A deep red colouration ensued with a rise in temperature. The quinoxaline-di-N-oxides, which in some cases precipitated within minutes after the addition of the enamine, were obtained after cooling the reaction mixture overnight in the refrigerator. Twenty-two different quinoxaline-di-N-oxides of the general structures shown (26 - 30) were obtained in yields ranging from 39% to 90%.



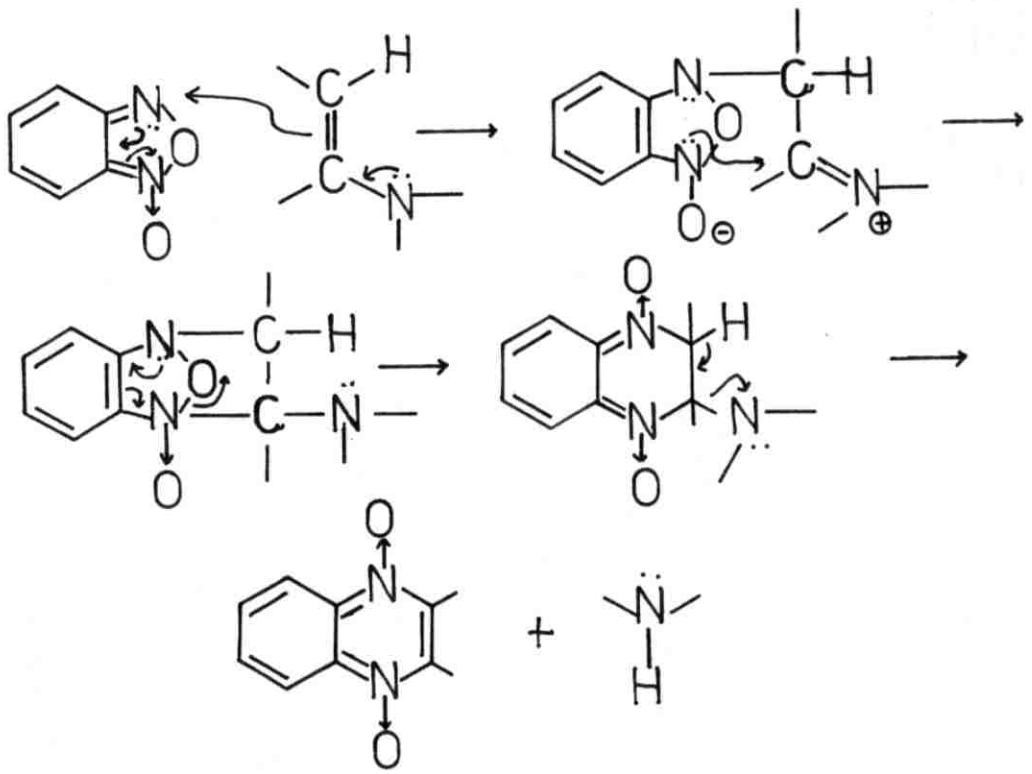
The yellow quinoxaline-di-N-oxides were characterized by their infrared spectra (N-O absorption at approx. 1320 cm^{-1}.), their melting points (approx. 100 °C higher than that of the respective benzofurazan oxide) and their elemental analyses.

The mechanism postulated for this reaction involves a 1,4-addition of the enamine to the hetero-ring of the benzofurazan oxide, followed by elimination of the secondary amine. A similar mechanism has been postulated for the reaction of benzofurazan oxide with 1,3-diketones to give quinoxaline-di-N-oxides[19].

The beta-carbon in the enamine, electron rich by its conjugation with the lone electron pair of the nitrogen, can attack either the 1-nitrogen (Scheme I) or the 3-nitrogen (Scheme II) in the benzofurazan oxide.

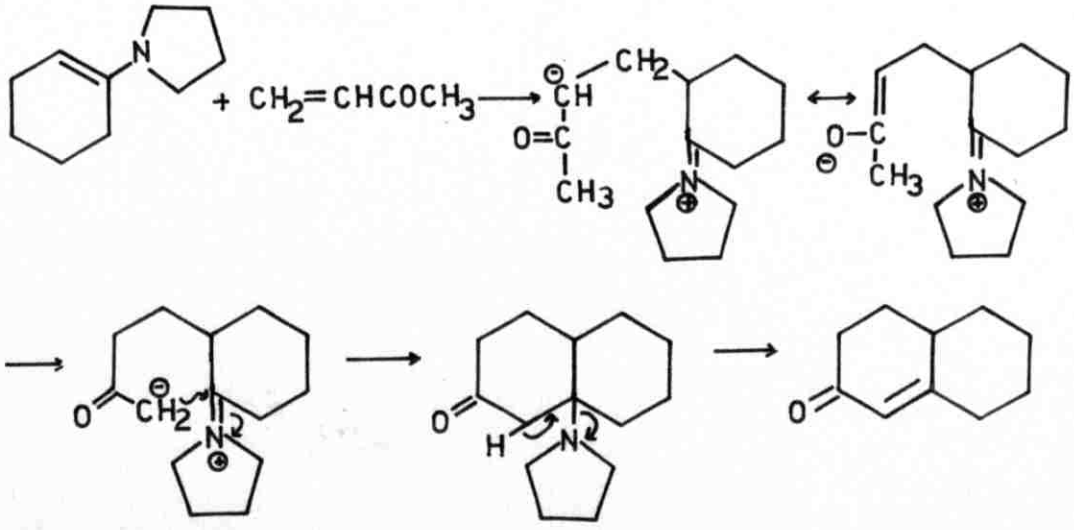


Scheme I



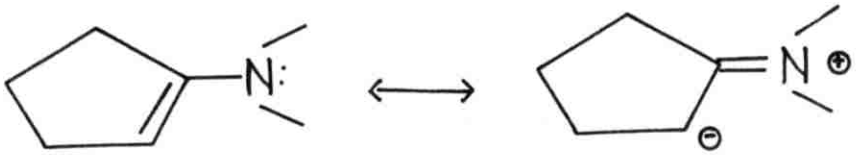
Scheme II

Although the same product is obtained from either Scheme I or Scheme II, the latter may be more plausible by analogy with the attack of enamines on the beta-carbon of α,β-unsaturated carbonyl compounds (Scheme III)[20].



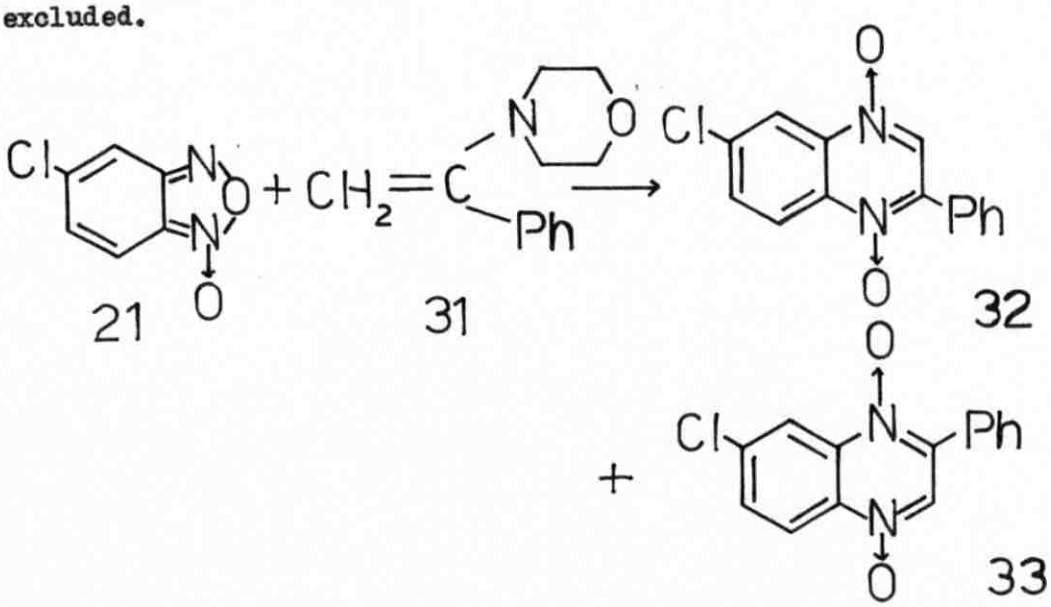
Scheme III

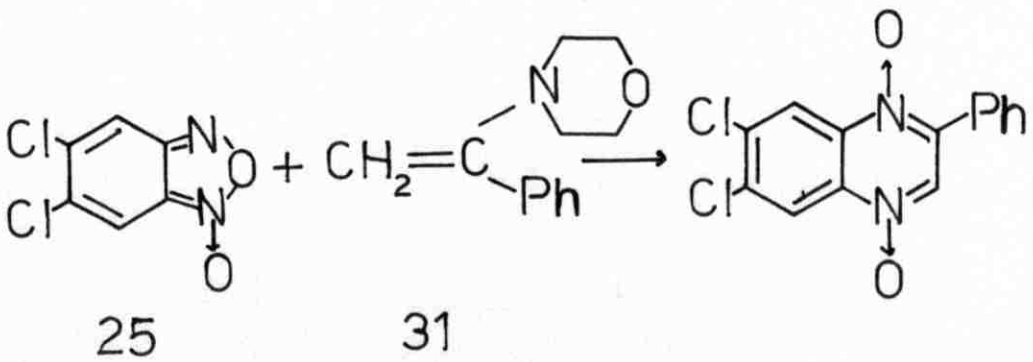
Of the enamines used, 1-morpholino-1-cyclopentene appeared to be the most reactive and 1-morpholino-1-phenylethylene the least reactive. The observed order of reactivity may be explained on the basis of steric and electronic factors affecting the overlap between the nitrogen lone electron pair and the double bond of the enamine. In the case of the cyclopentanone enamine this overlap is favoured because of the increase in exo double bond character to the five-membered homocyclic ring.



In reactions of benzofurazan oxides with this enamine special care was taken with temperature control to obtain pure products and better yields; in the case of the highly reactive 5(6)-chlorobenzofurazan oxide and 5,6-dichlorobenzofurazan oxide, the reaction with this enamine could not be sufficiently controlled even at temperatures of -5°C, and tars were obtained, from which no definite product could be isolated. The low reactivity of the acetophenone enamine (31) may be attributed to the steric factor of the phenyl ring; of all the substituted benzofurazan oxide only 5(6)-chlorobenzofurazan oxide (21) and 5,6-dichlorobenzofurazan oxide (25) reacted with this enamine to give the expected di-N-oxides. In the reaction of 5(6)-chlorobenzofurazan oxide (21) with this enamine two isomeric

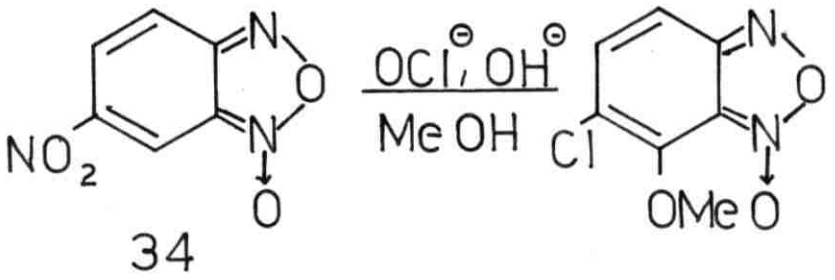
quinoxaline-di-N-oxides, 32 and 33, may conceivably result. Although thin-layer chromatography of the crude product in ethyl acetate: chloroform showed it to be chromatographically homogenous, the possibility of a mixture of the two products cannot as yet be excluded.





5(6)-Nitrobenzofurazan oxide (34) and 4(7)-nitrobenzofurazan oxide were also prepared, but reactions with the enamines yielded intractable tars. The reaction was highly exothermic despite temperature control and dilution of the reactants. Mallory has

reported[21] that nitrobenzofurazan oxides when placed in methanolic solutions of alkaline hypochlorite undergo ring substitution reactions, as outlined below for the reaction of 5(6)-nitrobenzofurazan oxide.



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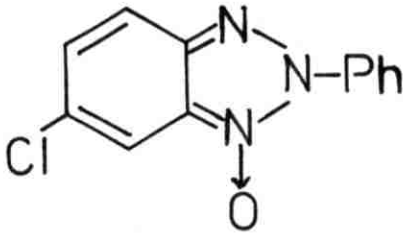
It is quite probable, therefore, that the reaction of enamines with nitrobenzofurazan oxides follows a course other than the one leading to quinoxaline-di-N-oxides.

In conclusion, the preparation of quinoxaline-di-N-oxides from enamines and benzofurazan oxides appears to be quite general for 5(6)-monosubstituted and 5,6-disubstituted benzofurazan oxides. Electron-withdrawing substituents on the benzofurazan oxide (chloro, trifluoromethyl) facilitate the reaction, and in some cases (nitro) diversion from the usual path may occur as a result of this increased reactivity. This new route to quinoxaline-di-N-oxides offers numerous advantages over the classical method of preparation from 1,2-dicarbonyl compounds and o-phenylenediamines in that it is direct, uses readily available starting materials, and yields reasonably pure products in satisfactory yields.

6-Chloro-2-phenylbenzotriazole oxide (35), the N-phenyl analogue of 5(6)-chlorobenzofurazan oxide, failed to react with

both 1-morpholino-1-cyclopentene and 1-morpholino-1-cyclohexene. The failure of these reactions may be due to the fact that the benzotriazole oxide, unlike the benzofurazan oxide, cannot undergo ring opening after initial attack by the nucleophilic carbon of the enamine.



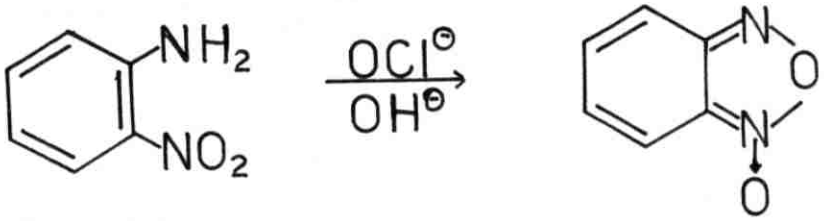
35

EXPERIMENTAL*

Part I

PREPARATION OF BENZOFURAZAN OXIDES

A- Benzofurazan Oxide[11]:



A solution of o-nitroaniline (40 g.) and potassium hydroxide (21 g.) in 95% ethanol (250 ml.) was cooled to 0°C in an ice-salt bath. Commercial sodium hypochlorite (Clorox) was then added in portions** over a period of 10 minutes until the colour of the solution remained unchanged (approximately 800 ml.). The flocculent

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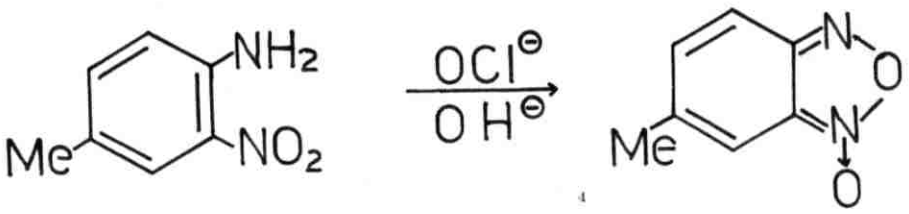
* Melting points are uncorrected. Elemental analyses were performed by Dr. F. Pascher, Bonn, Germany. Infrared spectra were determined in nujol using a Perkin-Elmer grating infrared spectrophotometer Model 257.

** Upon addition of sodium hypochlorite, the initial red solution turns a deeper colour which becomes paler with shaking until a new portion of Clorox is added.

yellow precipitate was filtered by suction, dried in air, and recrystallized from a mixture of 95% ethanol (45 ml.) and water (15 ml.). The yield of benzofurazan oxide melting at 72 - 73°C (lit: 72 - 73° [11]) was 31.3 g. (81%).

B- 5(6)-Methylbenzofurazan Oxide:

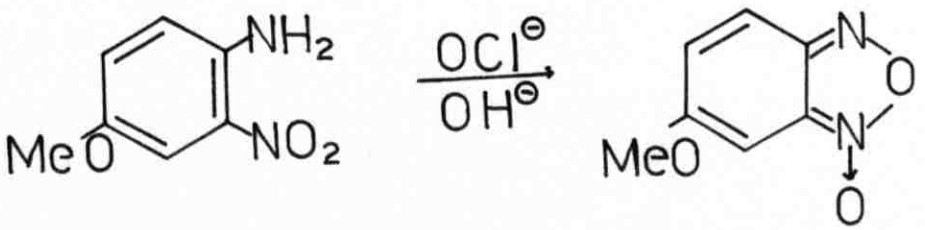


The procedure was essentially that described for the preparation of benzofurazan oxide.

A solution of 4-methyl-2-nitroaniline (44 g.) and potassium hydroxide (21 g.) in 95% ethanol (300 ml.) and methoxyethanol (200 ml.) was treated with sodium hypochlorite solution (Clorox, 800 ml.) at 0°C.

The yellow precipitate was collected by suction filtration, dried in air, and recrystallized from methanol. The yield of 5(6)-methylbenzofurazan oxide melting at 96 - 97°C (lit: 96° [22], 98° [23]) was 29 g. (69%).

C- 5(6)-Methoxybenzofurazan Oxide:

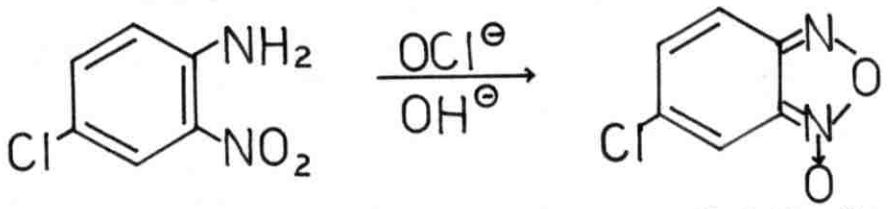


The procedure was essentially that described for the preparation of benzofurazan oxide.

A solution of 4-methoxy-2-nitroaniline (49 g.) in 2-(2-ethoxyethoxy)ethanol (600 ml.) was added to a solution of potassium hydroxide (21 g.) in 95% ethanol (15 ml.). The resulting solution was cooled to 0°C in an ice-salt bath and treated with a solution of sodium hypochlorite (Clorox, 800 ml.).

After recrystallization from methanol, the product (38.1 g., 80%) melted at 114 - 115°C (lit: 115° [22], 118° [23]).

D- 5(6)-Chlorobenzofurazan Oxide:

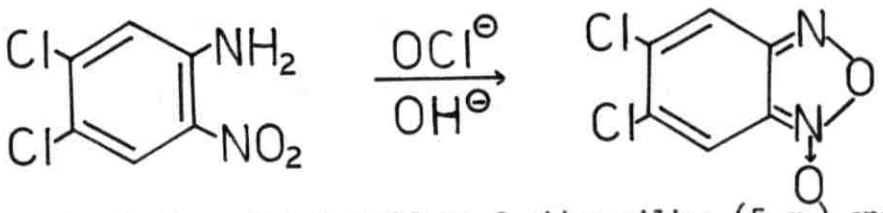


The procedure is essentially that described for the preparation of benzofurazan oxide.

A solution of 4-chloro-2-nitroaniline (51 g.) in 2-(2-ethoxyethoxy)ethanol (400 ml.) was added to a solution of potassium hydroxide (21 g.) in 95% ethanol (15 ml.). The resulting solution was cooled to 0°C and treated with sodium hypochlorite solution (Clorox, 800 ml.).

Recrystallization from methanol yielded 42 g. (84%) of product melting at 46 - 47°C (lit: 48° [22,23]).

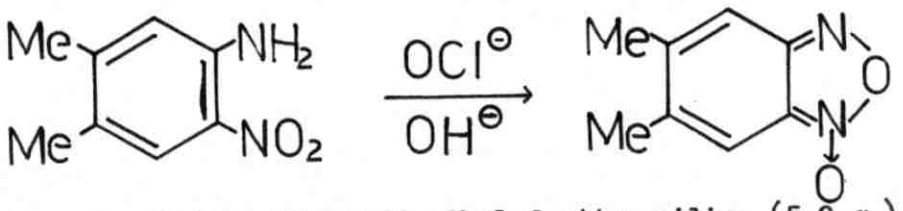
E- 5,6-Dichlorobenzofurazan Oxide[24]:



A solution of 4,5-dichloro-2-nitroaniline (5 g.) and potassium hydroxide (16 g.) in 95% ethanol (200 ml.) was stirred magnetically while maintained at 6-10°C. Commercial sodium hypochlorite solution (Clorox, 370 ml.) was added dropwise and the precipitated material was collected, dried in air, and recrystallized from 95% ethanol.

The yield of 5,6-dichlorobenzofurazan oxide melting at 129 - 131°C (lit: 130.8 - 131.2° [24]) was 4.2 g. (64%).

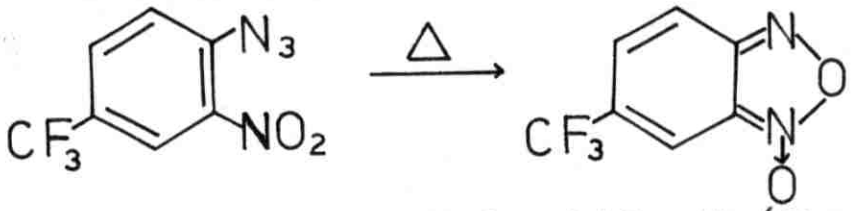
F- 5,6-Dimethylbenzofurazan Oxide[24]:



A solution of 4,5-dimethyl-2-nitroaniline (5.0 g.) and potassium hydroxide (2.2 g.) in 95% ethanol (300 ml.) was treated, at room temperature and over a period of 45 minutes, with a solution of sodium hypochlorite (Clorox, 440 ml.). After cooling the reaction mixture in an ice-bath, the precipitate was collected by suction filtration, dried in air, and recrystallized from 95% ethanol.

The yield of 5,6-dimethylbenzofurazan oxide melting at 138 - 140°C (lit: 139.4 - 139.7° [24]) was 4.3 g. (88%).

G- 5(6)-Trifluoromethylbenzofurazan Oxide*:



A solution of 4-amino-3-nitrobenzotrifluoride (20 g.) in acetic acid (150 ml.) and concentrated sulfuric acid (77 ml.) was maintained below 5°C and vigorously stirred during the addition, in portions, of sodium nitrite (8 g.). Urea (8 g.) was then added, followed by sodium azide (6.5 g.), and vigorous stirring was continued for 20 minutes. The reaction mixture was then poured onto 800 g. of ice and the crude azido product was extracted with chloroform. The extract was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The oily residue was refluxed in toluene (160 ml.) for 18 hours behind a shatterproof shield. After cooling to room temperature, the toluene was evaporated and the residue was distilled under reduced pressure.

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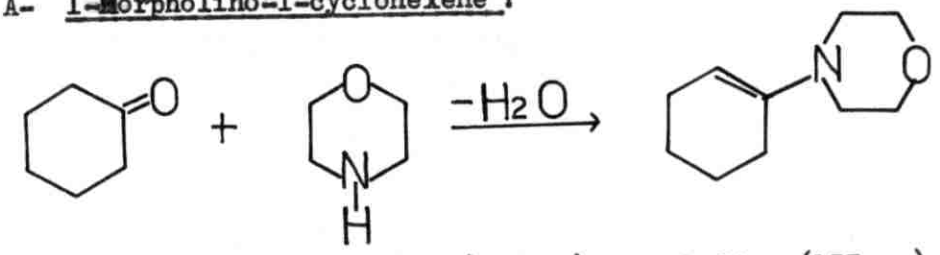
* Private communication from Dr. J. David Johnston, to whom we express our thanks.

Part II

PREPARATION OF ENAMINES

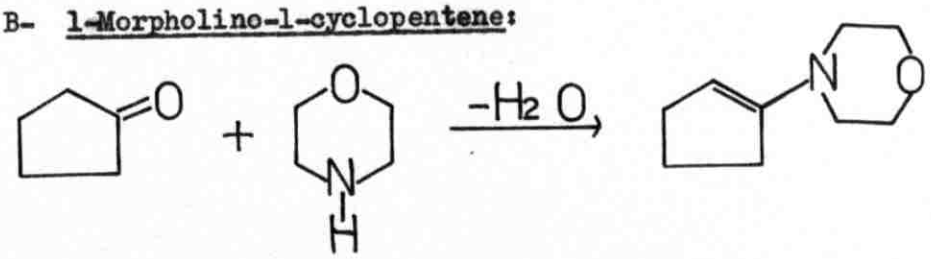
A- 1-Morpholino-1-cyclohexene[9]:



A solution of cyclohexanone (147 g.), morpholine (157 g.), and p-toluenesulfonic acid (1.5 g.) in toluene (300 ml.) was placed in a one-litre round-bottomed flask equipped with a reflux condenser and a Dean-Stark water separator. The solution was refluxed for 16 hours, the water being removed at regular intervals. After removal of the toluene at atmospheric pressure (b.p. 111°C), boiling chips and wooden splinters were introduced into the flask in order to minimize bumping and foaming. The product was isolated by distillation under reduced pressure.

The boiling point of the pure, colourless 1-morpholino-1-cyclohexene was 125 - 127°C/ca. 15 mm. Yield: 191 g. (76%).

B- 1-Morpholino-1-cyclopentene:

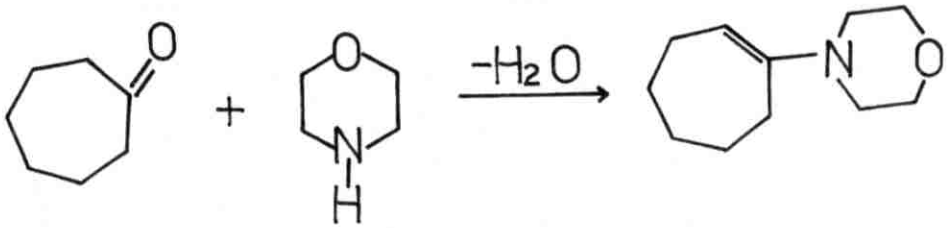


The procedure was essentially that described for the preparation of 1-morpholino-1-cyclohexene.

A solution of cyclopentanone (63 g.), morpholine (80 g.),

and p-toluenesulfonic acid (0.75 g.) in 150 ml. of toluene was refluxed in a one-litre flask, the water being separated by means of a Dean-Stark water separator. After refluxing for about 14 hours, the toluene was removed by distillation at atmospheric pressure (b.p. 111°C). The product, 1-morpholino-1-cyclopentene, was then distilled as a colourless liquid, b.p. 110°C/4 mm.; yield: 81 g. (72%).

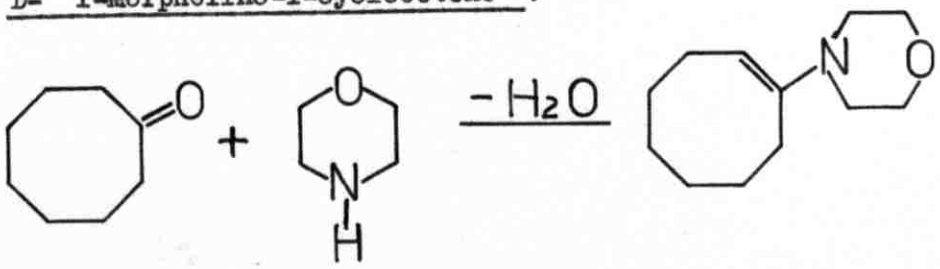
C- 1-Morpholino-1-cycloheptene[25]:



The procedure was essentially that described for the preparation of 1-morpholino-1-cyclohexene.

A solution of cycloheptanone (22.4 g.), morpholine (30 g.), and p-toluenesulfonic acid (0.5 g.) in toluene (200 ml.) was refluxed for 48 hr. with regular separation of the water formed. After removal of the toluene at atmospheric pressure, the product, 1-morpholino-1-cycloheptene, was distilled as a colourless liquid, b.p. 127 - 128/6 mm.; yield: 30 g. (83%).

D- 1-Morpholino-1-cyclooctene[26]:

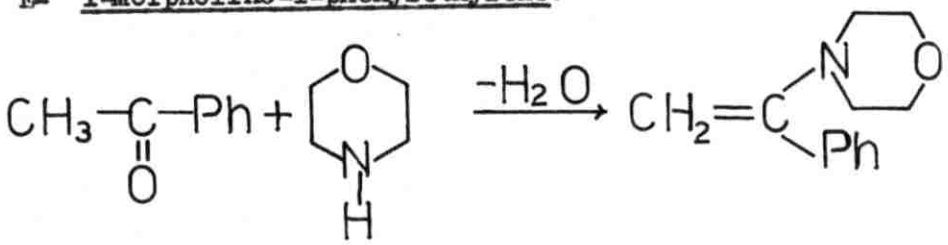


The procedure was essentially that described for the

preparation of 1-morpholino-1-cyclohexene.

A solution of cyclooctanone (25 g.), morpholine (25 g.), and p-toluenesulfonic acid (0.5 g.) in toluene (100 ml.) was refluxed for 18 hours with regular separation of the water formed. After removal of the toluene at atmospheric pressure, the product, 1-morpholino-1-cyclooctene, was distilled. The boiling point of the colourless product was 178 - 180°C/ca. 20 mm.; yield: 33 g. (85%).

E- <u>1-Morpholino-1-phenylethylene</u>:



The procedure was essentially that described for the preparation of 1-morpholino-1-cyclohexene.

A solution of acetophenone (60 g.), morpholine (60 g.), and p-toluenesulfonic acid (0.8 g.) in toluene was refluxed for six days with regular separation of the water formed. After removal of the toluene at atmospheric pressure, the product, 1-morpholino-1-phenylethylene was distilled under reduced pressure.

Part III

PREPARATION OF QUINOXALINE-DI-N-OXIDES

General Procedure:

A warm methanolic solution of the benzofurazan oxide was treated with the enamine (15% in excess of the stoichiometric amount), in small portions and with constant shaking. A deep red colouration ensued with a rise in temperature*. The reaction mixture was cooled overnight in the refrigerator and the precipitated product was collected by suction filtration, dried in air, and recrystallized. In certain cases the yield was improved by concentration of the methanolic reaction mixture prior to isolation of the product**.

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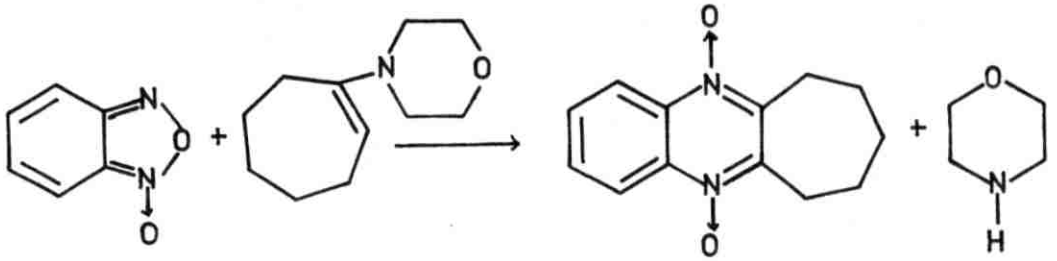
* The reaction between benzofurazan oxides and enamines is highly exothermic and control of the temperature during addition of the enamine is necessary to prevent decomposition products and low yields.

** Many of the quinoxaline-di-N-oxides melt with decomposition over a wide range even when analytically pure. In certain cases the melting point of a given sample varies depending on the rate of heating, the amount of material present, and the manner of packing in the capillary tube.

A- 7,8,9,10-Tetrahydro-6H-cyclohepta [b] quinoxaline-5,11-di-N-oxide:



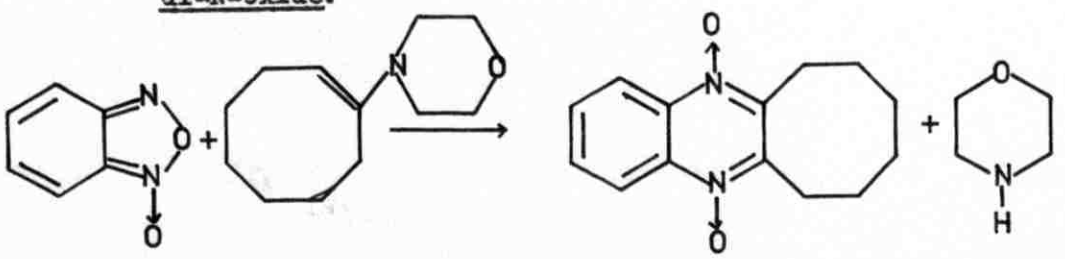
To a warm solution of benzofurazan oxide (2.7 g., 0.02 mole) in methanol (25 ml.) was added, in small portions and with constant shaking, 1-morpholino-1-cycloheptene (4.2 g., 0.023 mole). The reaction mixture was cooled overnight in the refrigerator and the precipitated product was collected by suction filtration and recrystallized from methanol/benzene.

The yield of 7,8,9,10-tetrahydro-6H-cyclohepta [b] - quinoxaline-5,11-di-N-oxide melting at 173 - 175°C was 3.0 g. (65%). The analytical sample, obtained after three recrystallizations from methanol/benzene, melted at 172 - 174°C.

IR (cm^{-1}): 1345, 1312, 1042, 962, 914, 860, 770.

Analysis: Calculated for $C_{13}H_{14}N_2O_2$; C 67.81%, H 6.13%, N 12.17%. Found; C 67.65%, H 5.97%, N 12.32%.

B- 6,7,8,9,10,11-Hexahydrocycloocta [b] -quinoxaline-5,12-di-N-oxide:



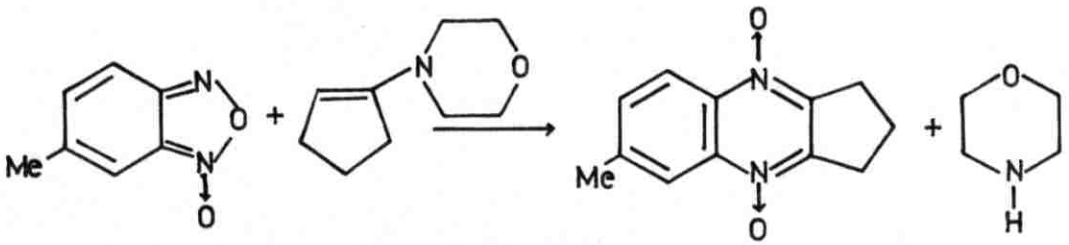
This compound was obtained by treating a warm solution of benzofurazan oxide (2.7 g., 0.02 mole) in methanol (25 ml.) with 1-morpholino-1-cyclooctene (4.5 g., 0.023 mole).

The yield of di-N-oxide melting at 170 - 172°C was 4.0 g. (80%). The analytical sample, obtained after three recrystallizations from trifluoroacetic acid: methanol: benzene, melted at 169.5 - 170.5°C.

IR (cm^{-1}): 1350, 1323, 1309, 1205, 1098, 1050, 1035, 982, 854, 771.

Analysis: Calculated for $C_{14}H_{16}N_2O_2$; C 68.83%, H 6.60%, N 11.47%. Found: C 68.91%, H 6.66%, N 11.33%.

C- <u>6-Methyl-2,3-dihydro-1H-cyclopenta [b] quinoxaline-4,9-di-N-oxide</u>:



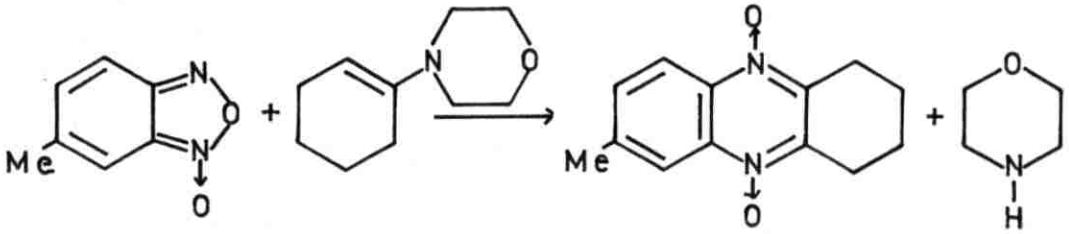
Addition of 1-morpholino-1-cyclopentene (3.5 g., 0.023 mole) to a warm solution of 5(6)-methylbenzofurazan oxide (3.0 g., 0.02 mole) in methanol (40 ml.) yielded the expected 6-methyl-2,3-dihydro-1H-cyclopenta [b] quinoxaline-4,9-di-N-oxide.

The yield of product melting at 168-173°C (dec.) was 2.2 g. (52%). The analytical sample, obtained after three recrystallizations from methanol/benzene, melted with decomposition at 168 - 171°C.

IR (cm^{-1}): 1340, 1299, 1205, 1110, 829, 679.

Analysis: Calculated for $C_{12}H_{12}N_2O_2$; C 66.65%, H 5.59%, N 12.96%. Found; C 66.68%, H 5.67%, N 12.79%.

D- 7-Methyl-1,2,3,4-tetrahydrophenazine-5,10-di-N-oxide:



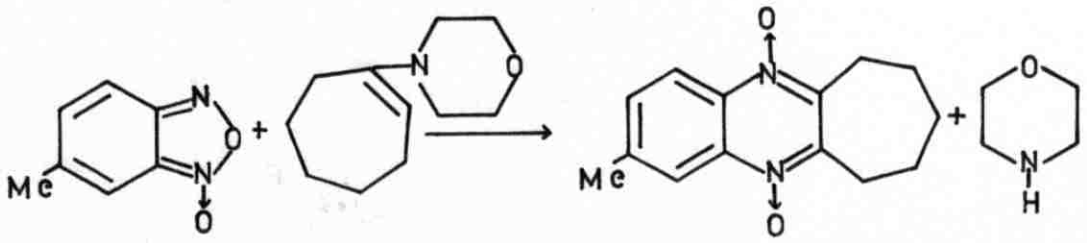
Addition of 1-morpholino-1-cyclohexene (4.0 g., 0.023 mole) to a warm solution of 5(6)-methylbenzofurazan oxide (3.0 g., 0.02 mole) in methanol (40 ml.) yielded the expected 7-methyl-1,2,3,4-tetrahydrophenazine-5,10-di-N-oxide.

The yield of product melting at 207 - 209°C (dec.) was 3.6 g. (79%). The analytical sample, obtained after three recrystallizations from methanol/benzene, melted with decomposition at 212 - 214°C (evacuated capillary).

IR (cm^{-1}): 1340, 1312, 1200, 1116, 1087, 829, 670.

Analysis: Calculated for $C_{13}H_{14}N_2O_2$; C 67.81, H 6.13%, N 12.17%, O 13.90%. Found; C 67.71%, H 6.06%, N 12.34%, O 13.91%.

E- 2-Methyl-7,8,9,10-tetrahydro-6H-cyclohepta [b] - quinoxaline-5,11-di-N-oxide:



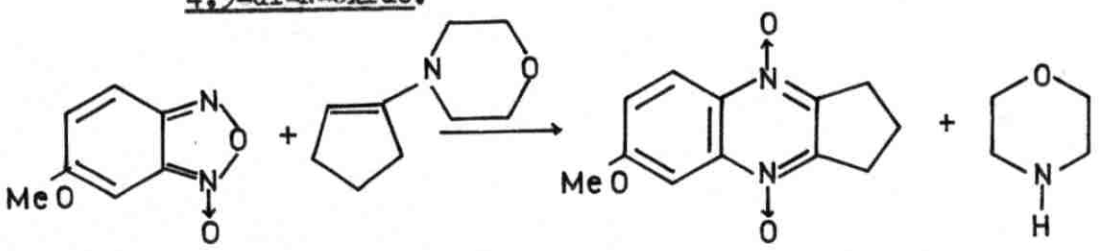
When a warm solution of 5(6)-methylbenzofurazan oxide (3.0 g., 0.02 mole) in methanol (40 ml.) was treated with 1-morpholino-1-cycloheptene (4.2 g., 0.023 mole), 2-methyl-7,8,9,10-tetrahydro-6H-cyclohepta [b] quinoxaline-5,11-di-N-oxide was obtained.

The yield of di-N-oxide melting at 161-163°C was 4.0 g. (82%). The analytical sample, obtained after three recrystallizations from methanol, melted at 163 - 164°C.

IR (cm^{-1}): 1340, 1312, 1200, 1040, 820.

Analysis: Calculated for $C_{14}H_{16}N_2O_2$; C 68.83%, H 6.60%, N 11.47%. Found; C 68.89%, H 6.55%, N 11.48%.

F- <u>6-Methoxy-2,3-dihydro-1H-cyclopenta [b] quinoxaline-4,9-di-N-oxide</u>:



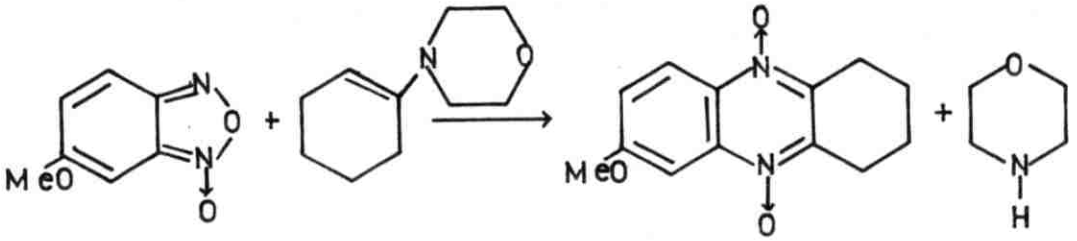
When a warm solution of 5(6)-methoxybenzofurazan oxide (3.3 g., 0.02 mole) in methanol (40 ml.) was treated with 1- morpholino-1-cyclopentene (3.5 g., 0.023 mole), 3.0 g. (65%) of 6-methoxy-2,3-dihydro-1H-cyclopenta [b] quinoxaline-4,9-di-N-oxide, melting at 182 - 186°C (dec.), was obtained.

The analytical sample, melting with decomposition at 183 - 185°C, was obtained after three recrystallizations from methanol/benzene.

IR (cm^{-1}): 1620, 1340, 1300, 1125, 1106, 1038, 1020, 841, 699.

Analysis: Calculated for $C_{12}H_{12}N_2O_3$; C 62.06%, H 5.21%, N 12.06%. Found; C 62.08%, H 5.32%, N 12.02%.

G- 7-Methoxy-1,2,3,4-tetrahydrophenazine-5,10-di-N-oxide:



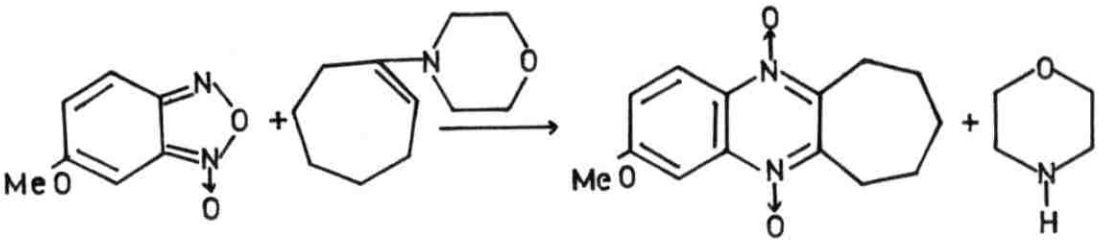
When a warm solution of 5(6)-methoxybenzofurazan oxide (3.3 g., 0.02 mole) in methanol (40 ml.) was treated with 1-morpholino-1-cyclohexene (4.0 g., 0.023 mole), 7-methoxy-1,2,3,4-tetrahydrophenazine-5,10-di-N-oxide was obtained.

The yield of di-N-oxide melting at 202 - 204°C (dec.) was 2.4 g. (49%). The analytical sample, obtained after three recrystallizations from methanol/benzene, melted with decomposition at 205 - 208°C (evacuated capillary).

IR (cm^{-1}): 1618, 1346, 1335, 1325, 1312, 1228, 1079, 1011, 845, 830, 760, 690.

Analysis: Calculated for $C_{13}H_{14}N_2O_3$; C 63.40%, H 5.73%, N 11.38%, O 19.49%, Found; C 63.41%, H 5.73%, N 11.28%, O 19.37%.

H- 2-Methoxy-7,8,9,10-tetrahydro-6H-cyclohepta[b]-quinoxaline-5,11-di-N-oxide:



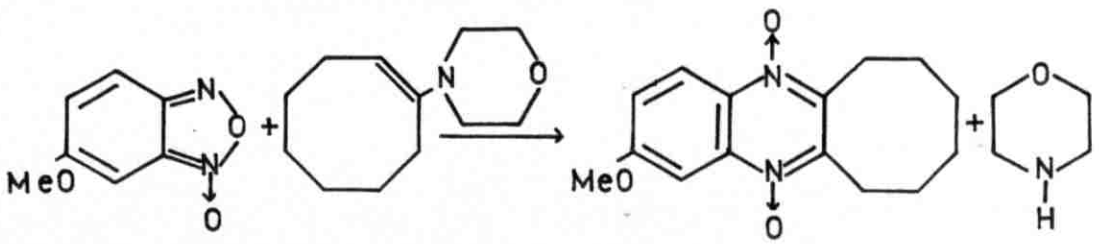
Treatment of a warm solution of 5(6)-methoxybenzofurazan oxide (3.3 g., 0.02 mole) in methanol (40 ml.) with 1-morpholino-1-cycloheptene (4.2 g., 0.023 mole), gave 2-methoxy-7,8,9,10-tetrahydro-6H-cyclohepta [b] quinoxaline -5,11-di-N-oxide (4.0 g., 77% yield), melting at 173 - 175°C.

The analytical sample, obtained after three recrystallizations from methanol/benzene, melted at 174 - 176°C.

IR (cm^{-1}): 1615, 1518, 1399, 1344, 1332, 1312, 1273, 1200, 1128, 1034, 848, 835, 732.

Analysis: Calculated for $C_{14}H_{16}N_2O_3$; C 64.60%, H 6.20%, N 10.76%, Found; C 64.73%, H 6.15%, N 10.84%.

I- <u>2-Methoxy-6,7,8,9,10,11-hexahydrocycloocta [b] - quinoxaline-5,12-di-N-oxide</u>:



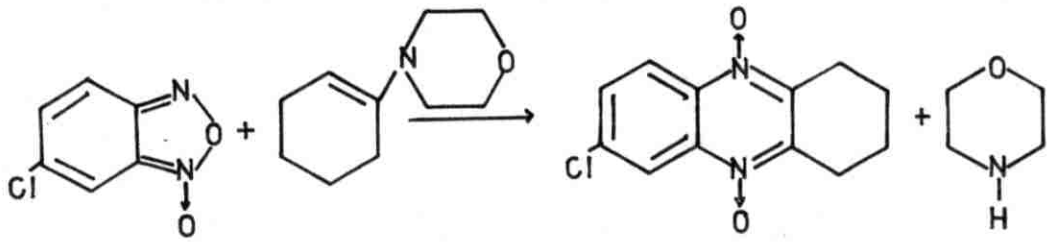
Treatment of a warm solution of 5(6)-methoxybenzofurazan oxide (3.3 g., 0.02 mole) in methanol (40 ml.) with 1-morpholino-1-cyclooctene (4.5 g., 0.023 mole), yielded the expected di-N-oxide in 90% yield (4.9 g. m.p. 203 - 209°C (dec.)).

The analytical sample, obtained after three recrystallizations from trifluoroacetic acid: benzene: methanol, melted with decomposition at 206 - 207°C.

IR (cm^{-1}): 1620, 1515, 1350, 1341, 1330, 1310, 1265, 1231, 1212, 1100, 1020, 920, 842, 823, 770, 745, 730, 662.

Analysis: Calculated for $C_{15}H_{18}N_2O_3$; C 65.67%, H 6.61%, N 10.21%. Found; C 65.72%, H 6.71%, N 10.21%.

J- 7-Chloro-1,2,3,4-tetrahydrophenazine-5,10-di-N-oxide:



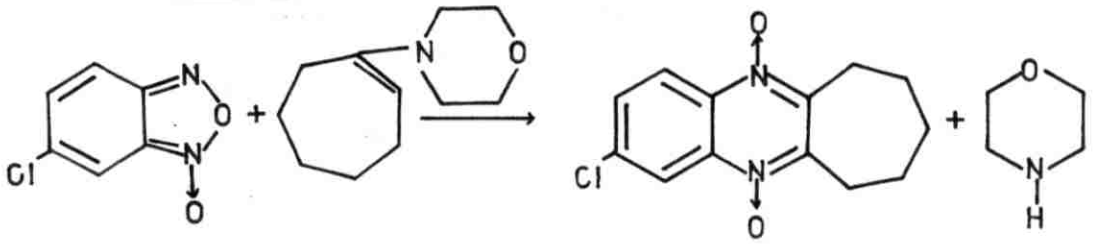
This compound was obtained upon treating a warm solution of 5(6)-chlorobenzofurazan oxide (3.4 g., 0.02 mole) in methanol (40 ml.) with 1-morpholino-1-cyclohexene (4.0 g., 0.023 mole).

The di-N-oxide melting at 188 - 191°C (dec.) weighed 2.60 g. (52%). The analytical sample, obtained after three recrystallizations from methanol/benzene, melted with decomposition at 188° - 192°C (evacuated capillary).

IR (cm^{-1}): 3100, 3060, 1600, 1510, 1350, 1335, 1330, 1310, 945, 836, 720, 660.

Analysis: Calculated for $C_{12}H_{11}N_2O_2Cl$; C 57.49%, H 4.42%, N 11.18%, O 12.77%, Cl 14.14%. Found; C 57.54%, H 4.40%, N 11.04%, O 12.70%, Cl 13.98%.

K- 2-Chloro-7,8,9,10-tetrahydro-6H-cyclohepta[b]-quinoxaline-5,11-di-N-oxide:



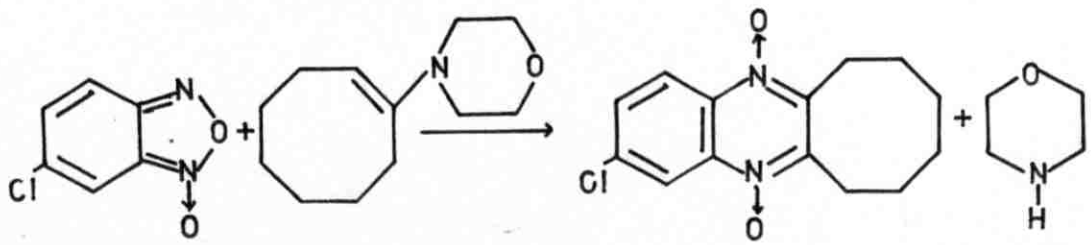
This compound was obtained by treating a warm solution of 5(6)-chlorobenzofurazan oxide (3.4 g., 0.02 mole) in methanol (40 ml.) with 1-morpholino-1-cycloheptene (4.2 g., 0.023 mole).

The yield of di-N-oxide melting at 175-176°C was 4.4 g. (84%). The analytical sample, obtained after three recrystallizations from methanol/benzene, melted at 175 - 176°C.

IR (cm^{-1}): 3102, 1600, 1500, 1340, 1315, 1200, 1151, 1142, 1069, 1040, 922, 872, 868, 831, 684, 655.

Analysis: Calculated for $C_{13}H_{13}N_2O_2Cl$; C 58.98%, H 4.95%, N 10.59%, Cl 13.40%. Found; C 59.05%, H 4.94%, N 10.56%, Cl 13.42%.

L- 2-Chloro-6,7,8,9,10,11-hexahydrocycloocta[b] quinoxaline-5,12-di-N-oxide:



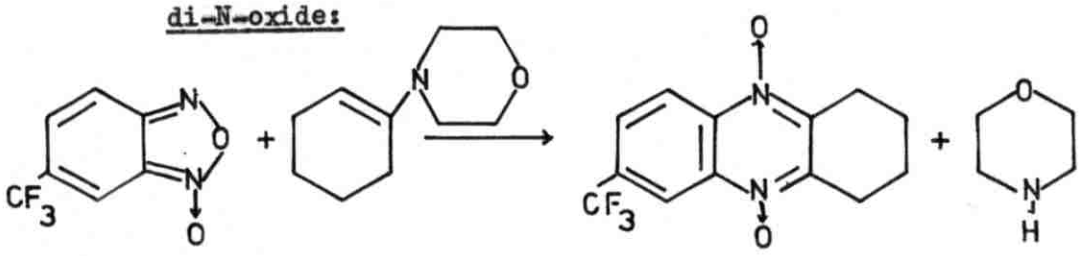
Addition of 1-morpholino-1-cyclooctene (4.5 g., 0.023 mole) to a warm solution of 5(6)-chlorobenzofurazan oxide (3.4 g., 0.02 mole) in methanol (40 ml.) yielded the expected di-N-oxide.

The yield of product melting at 145 - 150°C was 4.0 g. (71%). The analytical sample, obtained after three recrystallizations from methanol/benzene, melted at 142 - 146°C.

IR (cm^{-1}): 1600, 1500, 1350, 1335, 1320, 1309, 1210, 1205, 1152, 1102, 1068, 1038, 982, 880, 840, 709, 670.

Analysis: Calculated for $C_{14}H_{15}N_2O_2Cl$; C 60.33%, H 5.45%, N 10.05%, Cl 12.72%. Found; C 60.47%, H 5.48%, N 10.11%, Cl 12.79%.

M- <u>7-Trifluoromethyl-1,2,3,4-tetrahydrophenazine-5,10-di-N-oxide:</u>



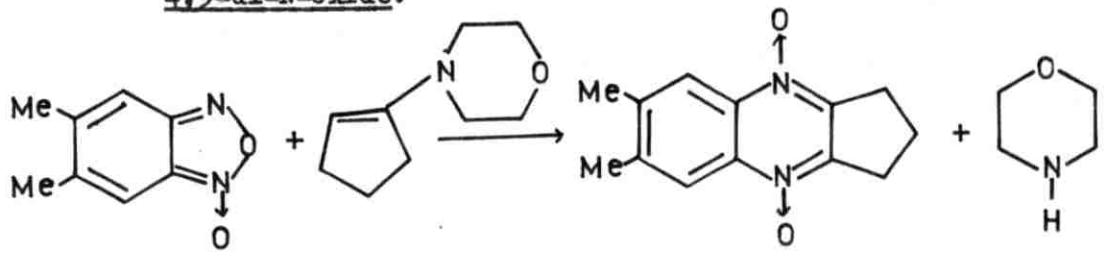
7-Trifluoromethyl-1,2,3,4-tetrahydrophenazine-5,10-di-N-oxide precipitated as yellow plates upon treatment of a warm methanolic solution of 5(6)-trifluoromethylbenzofurazan oxide with 1-morpholino-1-cyclohexene.

The crude di-N-oxide melted at 177 - 179°C (dec.). The analytical sample, obtained after three recrystallizations from methanol, melted with decomposition at 183.5 - 185°C.

IR (cm^{-1}): 1355, 1345, 1320, 1300, 1240, 1180, 1125, 1092, 980, 945, 905, 870, 847, 700, 653.

Analysis: Calculated for $C_{13}H_{11}F_3O_2N_2$; C 54.93%, H 3.90%, N 9.86%, F 20.05%. Found; C 55.08%, H 3.88%, N 9.95%, F 20.15%.

N- 6,7-Dimethyl-2,3-dihydro-1H-cyclopenta [b] quinoxaline-4,9-di-N-oxide:



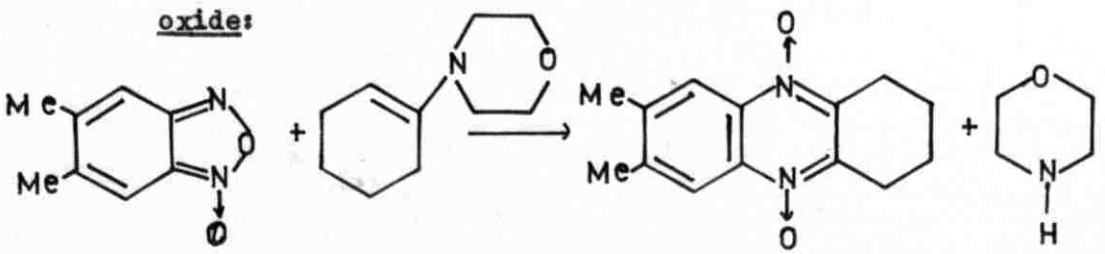
This di-N-oxide, melting at 198 - 200°C (dec.), was obtained in 78% yield (3.6 g.) by treating a warm solution of 5,6-dimethyl-benzofurazan oxide (3.3 g., 0.02 mole), in methyl sulfoxide (10 ml.) and methanol (35 ml.), with 1-morpholino-1-cyclopentene (3.5 g., 0.023 mole).

The analytical sample, melting with decomposition at 198 - 202°C, was obtained after three recrystallizations from benzene.

IR (cm^{-1}): 3040, 1550, 1500, 1340, 1292, 1119, 1038, 912, 885, 682.

Analysis: Calculated for $C_{13}H_{14}N_2O_2$; C 67.81%, H 6.13%, N 12.17%. Found; C 67.72%, H 6.20%, N 12.15%.

O- 7,8-Dimethyl-1,2,3,4-tetrahydrophenazine-5,10-di-N-oxide:



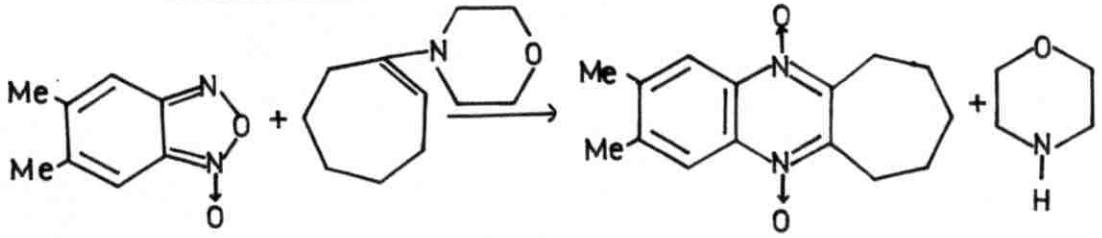
7,8-Dimethyl-1,2,3,4-tetrahydrophenazine-5,10-di-N-oxide, melting at 214 - 218°C (dec.), was obtained in 70% yield (3.4 g.) upon treatment of a solution of 5,6-dimethylbenzofurazan oxide (3.3 g. 0.02 mole) in warm methanol (70 ml.) with 1-morpholino-1-cyclohexene (4.0 g., 0.023 mole).

The analytical sample, obtained after three recrystallizations from methanol/benzene, melted with decomposition at 215 - 216°C.

IR (cm^{-1}): 1340, 1327, 1308, 1131, 1070, 970, 911, 878, 675.

Analysis: Calculated for $C_{14}H_{16}N_2O_2$; C 68.83%, H 6.60%, N 11.47%, Found; C 68.98%, H 6.62%, N 11.23%.

P- 2,3-Dimethyl-7,8,9,10-tetrahydro-6H-cyclohepta [b] - quinoxaline-5,11-di-N-oxide:



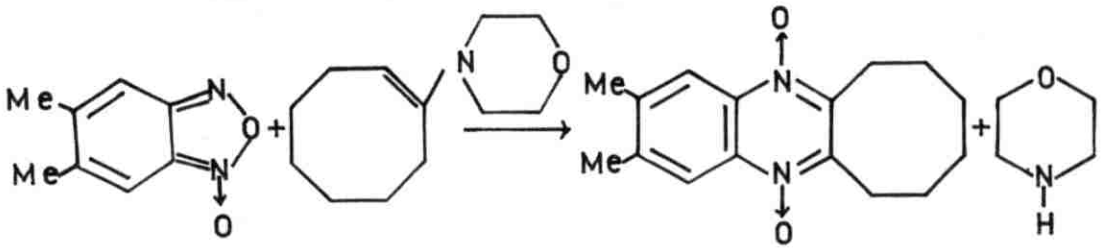
2,3-Dimethyl-7,8,9,10-tetrahydro-6H-cyclohepta [b] - quinoxaline-5,11-di-N-oxide melting at 215 - 216°C (dec.) was obtained in 75% yield (3.9 g.) upon addition of 1-morpholino-1-cycloheptene (4.2 g., 0.023 mole) to a warm solution of 5,6-dimethylbenzofurazan oxide (3.3 g., 0.02 mole) in methanol (70 ml.).

The analytical sample, obtained after three recrystallizations from methanol/benzene, melted with decomposition at 215 - 217°C.

IR (cm^{-1}): 1340, 1310, 1020, 962, 881, 723, 650.

Analysis: Calculated for $C_{15}H_{18}N_2O_2$; C 69.74%, H 7.02%, N 10.58%, Found; C 69.65%, H 7.04%, N 10.46%.

Q- 2,3-Dimethyl-6,7,8,9,10,11-hexahydrocycloocta [b] - quinoxaline-5,12-di-N-oxide:



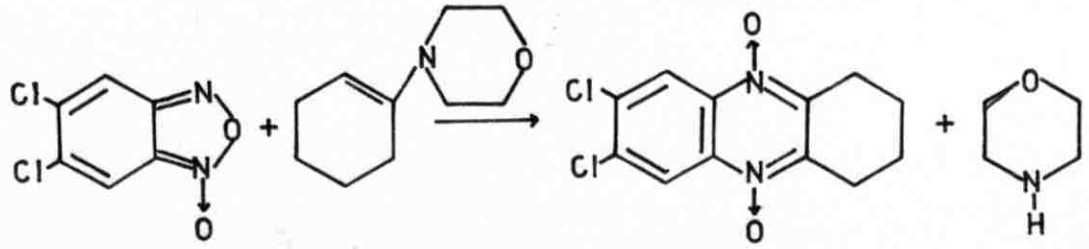
When a warm solution of 5,6-dimethylbenzofurazan oxide (3.3 g., 0.02 mole) in methanol (70 ml.) was treated with 1-morpholino-1-cyclooctene (4.5 g., 0.023 mole), 4.8 g. (90%) of the expected di-N-oxide was obtained, melting at 195 - 199°C.

The analytical sample, melting at 197.5 - 199°C, was obtained after three recrystallizations from methanol/benzene.

IR (cm^{-1}): 1510, 1344, 1330, 1313, 1204, 1101, 1030, 950, 880, 873, 725, 685, 645.

Analysis: Calculated for $C_{16}H_{20}N_2O_2$; C 70.56%, H 7.40%, N 10.29%. Found; C 70.53%, H 7.50%, N 10.26%.

R- 7,8-Dichloro-1,2,3,4-tetrahydrophenazine-5,10-di-N-oxide:



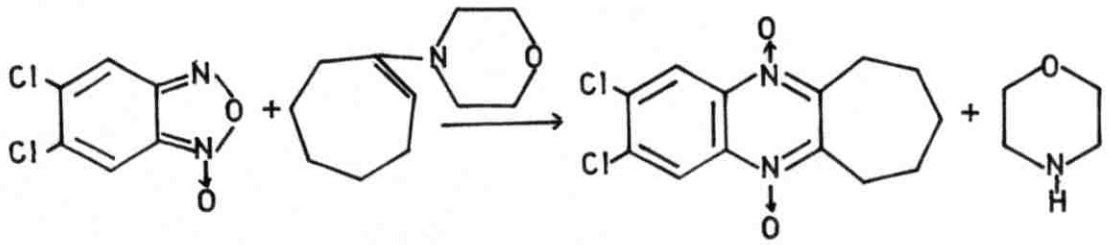
When a warm solution of 5,6-dichlorobenzofurazan oxide (4.1 g., 0.02 mole) in methanol (110 ml.) was treated with 1-morpholino-1-cyclohexene (4.0 g., 0.023 mole), 7,8-dichloro-1,2,3,4-tetrahydrophenazine-5,10-di-N-oxide was obtained in 48% yield (2.7 g., m.p. 200 - 205°C (dec.)).

The analytical sample, obtained after three recrystallizations from methanol/benzene, melted with decomposition at 203 - 205°C.

IR (cm^{-1}): 1600, 1500, 1400, 1340, 1328, 1170, 1095, 965, 890, 860, 730, 680, 669.

Analysis: Calculated for $C_{12}H_{10}N_2O_2Cl_2$; C 50.55%, H 3.53%, N 9.83%, Cl 24.87%. Found; C 50.63%, H 3.59%, N 9.69%, Cl 24.76%.

S- 2,3-Dichloro-7,8,9,10-tetrahydro-6H-cyclohepta [b] - quinoxaline-5,11-di-N-oxide:



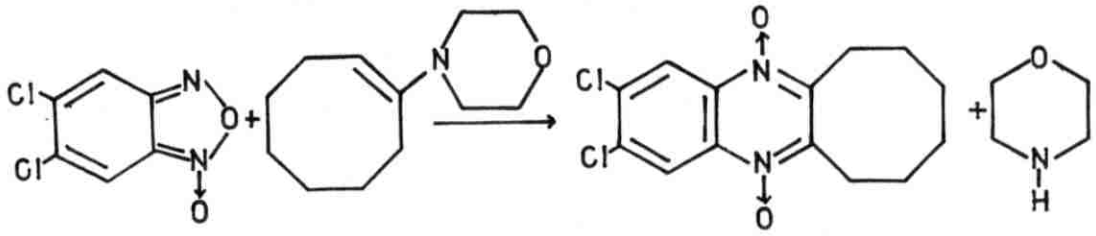
Addition of 1-morpholino-1-cycloheptene (4.2 g., 0.023 mole) to a warm solution of 5,6-dichlorobenzofurazan oxide (4.1 g., 0.02 mole) in methanol (110 ml.) yielded the expected quinoxaline-di-N-oxide.

The yield of product, melting at 195 - 196°C (dec.), was 5.2 g. (87%). The analytical sample, melting with decomposition at 197 - 198°C, was obtained after three recrystallizations of the crude product from chloroform.

IR (cm^{-1}): 1342, 1325, 1309, 1205, 1165, 1045, 965, 900, 878, 699, 684, 654.

Analysis: Calculated for $C_{13}H_{12}N_2O_2Cl_2$; C 52.19%, H 4.04%, N 9.36%, Cl 23.70%. Found; C 52.18%, H 4.09%, N 9.42%, Cl 23.86%.

T- 2,3-Dichloro-6,7,8,9,10,11-hexahydrocycloocta [b] - quinoxaline-5,12-di-N-oxide:



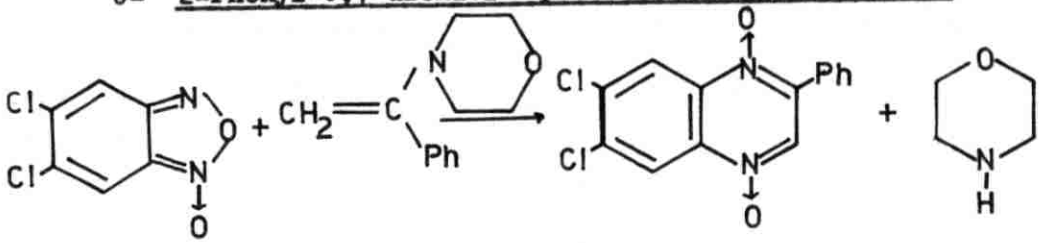
2,3-Dichloro-6,7,8,9,10,11-hexahydro-cycloocta [b] - quinoxaline-5,12-di-N-oxide, melting at 196 - 201°C, was obtained in 71% yield (4.4 g.) by treating a warm solution of 5,6-dichloro-benzofurazan oxide (4.1 g., 0.02 mole) in methanol (110 ml.) with 1-morpholino-1-cyclooctene (4.5 g., 0.023 mole).

The analytical sample, melting with decomposition at 201 - 203°C, was obtained after three recrystallizations from trifluoroacetic acid/methanol.

IR (cm^{-1}): 3070, 1500, 1336, 1325, 1310, 1214, 1208, 1100, 1060, 1035, 1004, 860, 710, 929, 650.

Analysis: Calculated for $C_{14}H_{14}N_2O_2Cl_2$; C 53.69%, H 4.51%, N 8.95%, Cl 22.64%. Found; C 53.75%, H 4.67%, N 8.80%, Cl 22.46%.

U- 2-Phenyl-6,7-dichloro-quinoxaline-1,4-di-N-oxide:



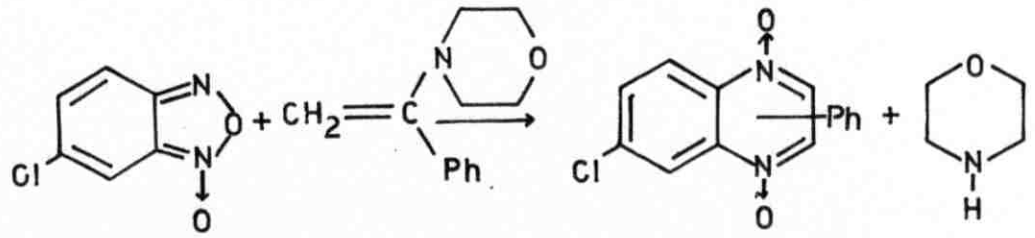
When a warm solution of 5,6-dichlorobenzofurazan oxide (4.1 g., 0.02 mole) in methanol (110 ml.) was treated with 1-morpholino-1-phenylethylene (4.3 g., 0.023 mole), 3.0 g. (50%) of the expected di-N-oxide was obtained, m.p. 249 - 251°C (dec.).

The analytical sample, obtained after three recrystallizations from trifluoroacetic acid: methanol, melted with decomposition at 245 - 246°C.

IR (cm^{-1}): 3100, 1350, 1323, 1308, 1232, 1142, 1095, 945, 890, 869, 840, 780, 759, 700, 690.

Analysis: Calculated for $C_{14}H_8N_2O_2Cl_2$; C 54.74%, H 2.63%, N 0.12%, Cl 23.09%. Found; C 54.59%, H 2.75%, N 8.98%, Cl 23.20%.

V- The reaction of 5(6)-chlorobenzofurazan oxide with 1-morpholino-1-phenylethylene:



The product was obtained in 39% yield (2.1 g.), m.p. 210 - 225°C (dec.), by treating a warm solution of 5(6)-chlorobenzofurazan oxide (3.4 g., 0.02 mole) in methanol (40 ml.) with 1-morpholino-1-phenylethylene (4.3 g., 0.023 mole).

The analytical sample, obtained after three recrystallizations from trifluoroacetic acid/methanol, melted with decomposition at 216 - 220°C.

Thin-layer chromatography of the crude product in ethyl acetate: chloroform showed it to be chromatographically homogenous.

IR (cm^{-1}): 3100, 1600, 1530, 1500, 1355, 1310, 1285, 1230-40, 1110, 888, 880, 860, 835, 770, 759, 685.

Analysis: Calculated for $C_{14}H_9N_2O_2Cl$; C 61.66%, H 3.33%, N 10.27%, Cl 13.03%. Found; C 61.79%, H 3.48%, N 10.32%, Cl 13.19%.

PART IV

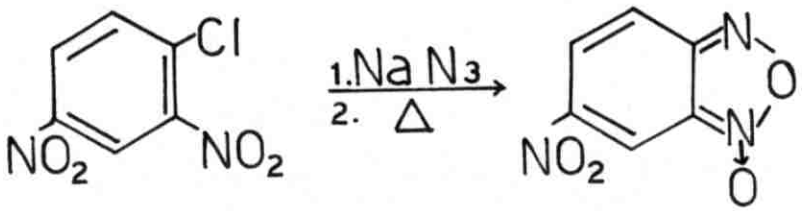
SOME ATTEMPTED REACTIONS

A- The reaction of 5(6)-nitrobenzofurazan oxide with enamines:

Treatment of warm or cold (-5°C) solutions of 5(6)-nitrobenzofurazan oxide (3.6 g., 0.02 mole) in methanol (50 ml.) with several enamines yielded intractable tars.

This reaction was attempted with the morpholino enamines of cyclopentanone, cyclooctanone, cyclohexanone, and cycloheptanone.

Preparation of 5(6)-nitrobenzofurazan oxide:



The procedure was essentially that described by Boulton, Gripper Gray and Katritzky for the preparation of 4-azido-7-nitrobenzofurazan oxide from 4-chloro-7-nitrobenzofurazan oxide[27].

2,4-Dinitrochlorobenzene (10 g., 0.05 mole) in acetone-methanol (1:1; 22 ml.) was treated with a solution of sodium azide (3.2 g., 0.05 mole) in acetone-methanol-water (1:2:2; 25 ml.). After 1 hr. at 20°C the mixture was diluted with water. An oil separated which, after decantation of the upper aqueous layer, was heated with 50 ml. of water on a water bath for 2 hr.. The mixture was then cooled and the precipitated solid was collected

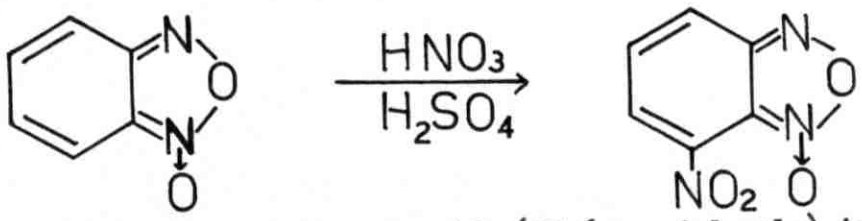
by suction filtration and recrystallized from ethanol to give 3.4 g., (76%) of 5(6)-nitrobenzofurazan oxide melting at 67 - 69°C (lit: 72° [23], 68 - 69° [16], 68.8 - 70.6° [21]).

B- The reaction of 4(7)-nitrobenzofurazan oxide with enamines:

The procedure was that described for the reaction of 5(6)-nitrobenzofurazan oxide with enamines.

The reaction was attempted with the morpholino enamines of cyclopentanone, cyclohexanone and cycloheptanone, all of which yielded intractable tars.

Preparation of 4(7)-Nitrobenzofurazan oxide:



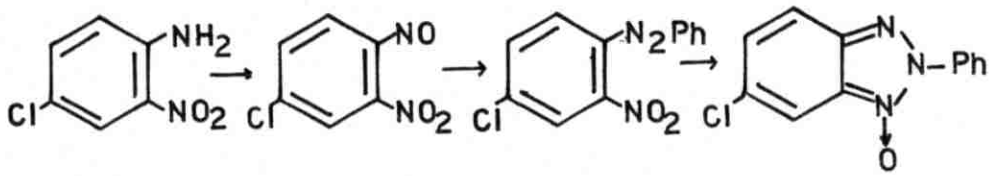
A solution of benzofurazan oxide (13.6 g., 0.1 mole) in concentrated sulfuric acid (44.5 ml.) was stirred magnetically. The solution was maintained at 5 - 12°C. during the addition over a period of 45 min. of a mixture of fuming nitric acid (5 ml.) and concentrated sulfuric acid (20 ml.). The reaction mixture was stirred for an additional 1.5 hr. in an ice bath and then poured into ice-water. The solid was collected by suction filtration, washed with water, and recrystallized from glacial acetic acid (Norit) to give 8.0 g. (44%) of product melting at 141 - 143°C (lit: 141.6 - 143.2° [21], 143° [23]).

C- The reaction of 6-chloro-2-phenylbenzotriazole oxide with enamines:

When a warm solution of 6-chloro-2-phenylbenzotriazole oxide (1.3 g.,0.005 mole) in methanol (70 ml.) was treated with either 1-morpholino-1-cyclopentene or 1-morpholino-1-cyclohexene no reaction occured and the starting material was recovered in 85% yield, (1.1 g., m.p. 138 - 142°C), after evaporation of the methanol.

Refluxing of the reactants in methanol for 30 min. gave the same results as above.

Preparation of 6-chloro-2-phenylbenzotriazole oxide[17]:



i) 2-Nitro-4-chloronitrosobenzene[28]:

A clear solution of Caro's acid* was added to a suspension of 2-nitro-4-chloroaniline (40 g., 0.23 mole) in ice-cold concentrated sulfuric acid (60 ml.) and water (10 ml.) which had been previously stirred mechanically for 1 hr.. The mixture was stirred for 17 hrs. and the yellow solid was collected by suction filtration, dried in air and recrystallized from

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*Prepared by slowly adding ammonium persulfate (145 g., 0.64 mole) to cold concentrated sulfuric acid (54 ml.), allowing this mixture to stand for 1 hr., and pouring onto crushed ice (355 g.).

methanol/benzene to give 26.0 g. (61%) of 2-nitro-4-chloronitroso-benzene melting at 123 - 125°C (dec.), (lit: m.p. 125 - 128° [28]).

ii) 4-Chloro-2-nitroazobenzene[17]:

A solution of 2-nitro-4-chloronitrosobenzene (9.5 g., 0.05 mole), and 5 ml. of freshly distilled aniline in glacial acetic acid (250 ml.) was stirred magnetically at room temperature in the dark for 5 hr.. After dilution of the solution with 500 ml. of water and cooling in an ice bath, the crude brown product of 2-nitro-4-chloroazobenzene was collected by suction filtration, washed with 500 ml. of water, and air-dried.

iii) 6-Chloro-2-phenylbenzotriazole Oxide[17]:

A stirred solution of the crude 4-chloro-2-nitro-azobenzene (7 g.) in warm 95% ethanol (25 ml.) was treated with a solution of sodium sulfide nonahydrate (24 g.) in 30 ml. of water; and the resulting mixture was stirred at room temperature for 17 hr.. After cooling the mixture in an ice bath, the light-tan solid was collected by suction filtration and recrystallized three times from 95% ethanol (Norit) to give 5.2 g. (79%) of white needles melting at 141 - 143°C (lit: 142.2 - 142.8° [17]).

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