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F U R A Z A N S

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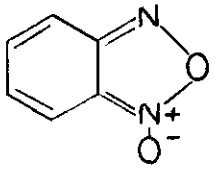
The Chemistry and uses of furazans (1,2,5-oxadiazoles) and furoxans (furazan-2-oxides) are reviewed.

1. INTRODUCTION

In 1962, Behr reviewed the chemistry of this area of heterocyclic chemistry and indicated that there still were conspicuous gaps to be filled in our knowledge of these compounds.[1] Kaufman and Picard in 1959 reviewed the furoxans[2], while Boulton and Ghosh selectively considered benzofuroxans (1)[3]. A limited review by Scrowston dealing with the preparation, properties and reactions of some of these compounds

has also appeared[4]. The historical aspects which have led up to the present accepted structures for furazans (2) and furoxans (3) have been dealt with in detail by earlier reviews[1,2], and will not be repeated here. Recent crystallographic studies have shed further light on the detailed



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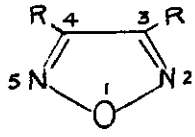

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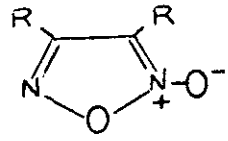


(3)

structure of certain derivatives. In the case of 3-methyl-4-phenylsulfonyl furoxan it was shown that the phenyl ring is planar, whereas the furoxan nucleus is non-planar, while the configuration of the sulfonyl group is that of a slightly distorted tetrahedron[5]. In the case of 3-methyl-4-furoxan hydrazide, non-hydrogen atoms deviate significantly from planarity and the furoxan ring is not strictly planar[6]. UV data for the 2500 - 2300 Å region have been compiled along with microwave spectroscopic studies for furazan. A planar molecule of C_{2v} symmetry with some aromatic character has been observed, but in the $\pi - \pi^*$ excited state, non-planarity indicated that the charge in electronic structure is sufficient to destroy the aromatic π-bonding of this cyclic compound[7]. Further structural support has come from heat capacity calculations on furazan[8], as well as MO data[9] and MO calculations[10]. Using improved LCAO (linear combination of AO/method) bond lengths and bond angles have been established[11]. The areas

of IR and Raman spectra have not been neglected. The IR (5000 - 400 cm^{-1}) and Raman spectra of mono- and dideuterated 1,2,5-oxadiazoles were determined. A complete assignment of the fundamental vibrations of the deuterated 1,2,5-oxadiazoles, fulfilling the Teller-Redlich product rule and the complete isotope rule was made[12]. Earlier IR studies on several mono- and disubstituted furazans indicated that the high intensity band at 917 - 878 cm^{-1} was the best for establishing correlations, because it showed small variations with substitution[13]. Chemical Abstracts coverage from 1962 to issue No.9, 1975 delineates the period under review. It should be emphasised that for the sake of presenting a balanced view of the field some material which appeared in earlier reviews is included, but this is kept to a minimum.

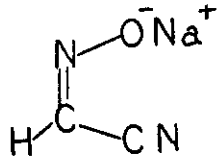
Whereas the literature search has been comprehensive, of necessity this review is selective and should by no means be regarded as a compilation of all the reports published in this rapidly expanding field. For convenience a division has been made between preparations and reactions of furazans and furoxans, but as will be discussed later, furoxans can be converted by several methods into furazans, but not vice-versa. Where preparations have led to compounds of biological or commercial interest these have been considered in the section dealing with uses.

2. FURAZAN PREPARATIONS

(a) Synthesis of unsubstituted furazan.

This synthesis was only accomplished as recently as

1965. Furazan, b.p. 98° is a stable liquid which can be produced by dehydrating glyoxime with succinic anhydride at 150 - 170°, followed by distillation, in a 51% yield[14]. Treatment with NaOH yields a crystalline, pyrophoric and otherwise unstable salt (4). MS showed ions at m/e 43 ($HCNO^+$),

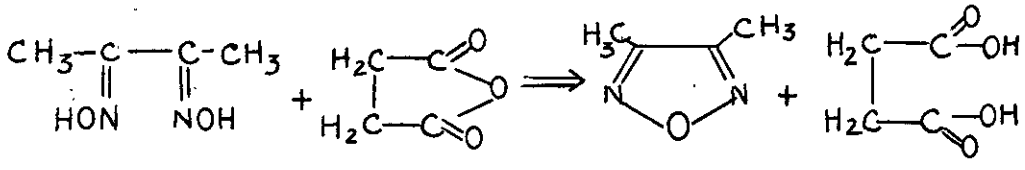


(4)

m/e 27 ($H\overset{+}{C}N$), m/e 40 ($C_2H_2N^+$) and m/e 30 ($\overset{+}{N}O$)[14].

(b) Cyclization of glyoximes.

Furazans are most often prepared by dehydration of the appropriately substituted glyoximes. In the case of monosubstituted furazans, irrespective of the nature of the substituent group, are readily isomerised by alkali to oximes of α-ketonitriles, whereas disubstituted furazans are usually very stable to both heat and chemical attack. For example, 3,4-dimethylfurazan (6) has been prepared from dimethylglyoxime (5) using succinic anhydride[15].

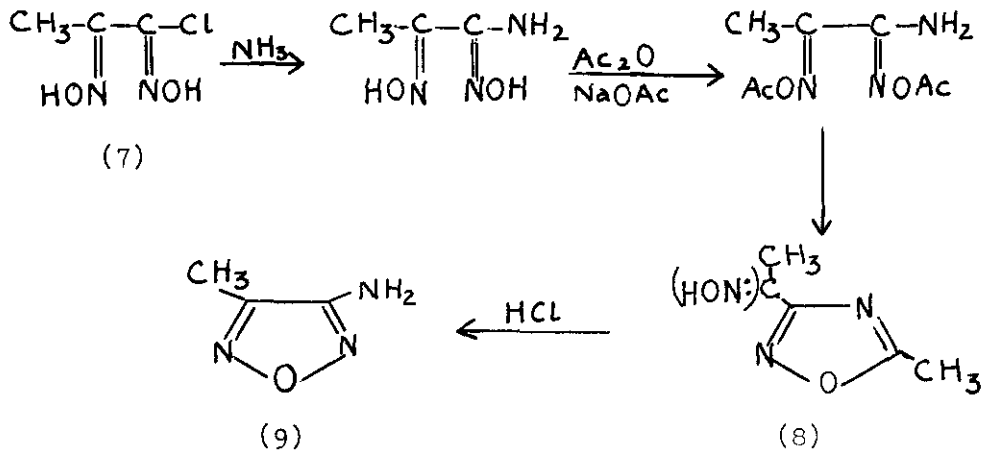


(5) (6)

(c) Synthesis from 1,2,4-oxadiazoles.

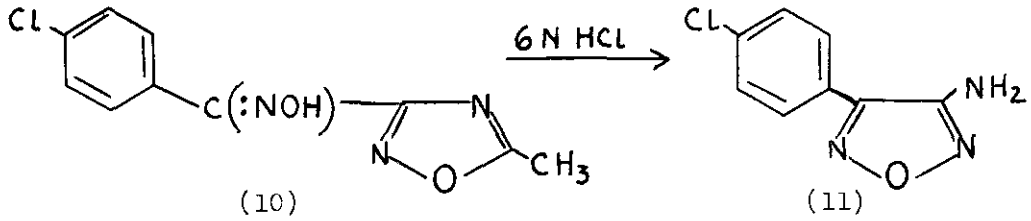
The synthesis of amino furazans has utilized this

method. 3-Methyl-4-aminofurazan (9) was prepared by Scheme I shown below by starting with chloroglyoxime (7) and involved the intermediate formation of 1,2,4-oxadiazole (8)[1].



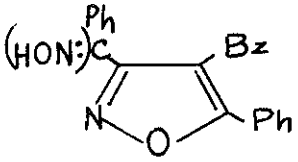
Scheme 1.

A more recent example simply involved the treatment of the 1,2,4-oxadiazole (10) with 6N HCl under reflux conditions to yield the aminofurazan (11)[16].



(d) Using isoxazoles

In addition to the examples sited by Behr[1], 5-phenyl-3,4-dibenzoylisoxazole oxime (12) underwent transformation to 3-phenyl-4-dibenzoylmethylfurazan (13) on treatment with 20% KOH[17].



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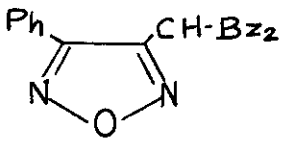

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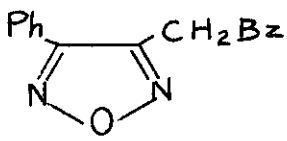
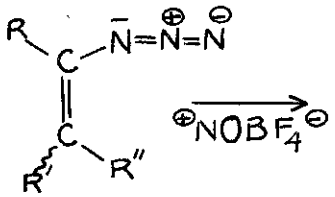


(14)

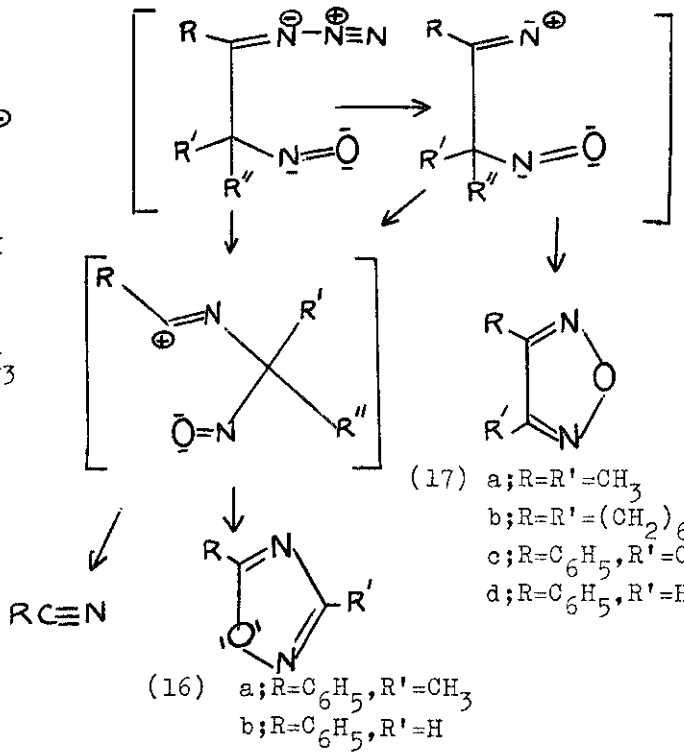
Further treatment of (13) with KOH or acid removes one benzyl group to produce (14).

(e) Preparation from vinyl azides.

Reaction of 1-aryl-2-alkylvinylazides with $NOBF_4$ gave moderate yields of 3-aryl-1,2,5-oxadiazoles along with 5-aryl-1,2,4-oxadiazoles. 1,2-Dialkylvinylazides with $NOBF_4$ however produced 2-oxo-1,2,5-oxadiazoles in high yields[18]. The authors



(15)
a;R=CH_3,R'=CH_3,R"=H
b;R=CH_3,R'=H,R"=CH_3
c;R=R'=$(CH_2)_6$,R"=H
d;R=C_6H_5,R'=H,R"=CH_3
e;R=H,R'=H,R"=C_4H_9
f;R=C_6H_5,R'=R"=H.



(17) a;R=R'=CH_3
b;R=R'=$(CH_2)_6$
c;R=C_6H_5,R'=CH_3
d;R=C_6H_5,R'=H.

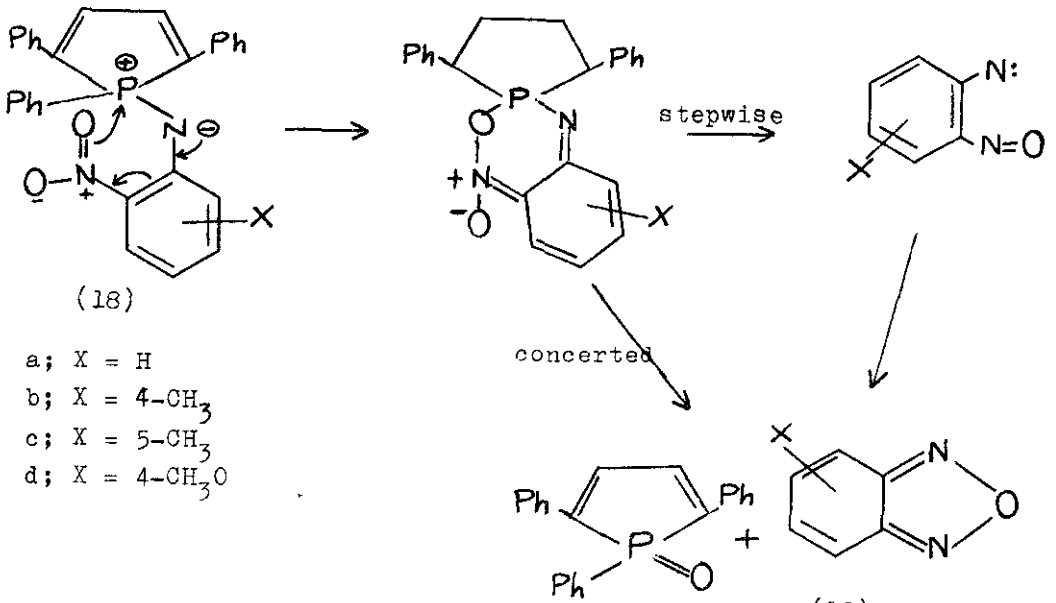
(16) a;R=C_6H_5,R'=CH_3
b;R=C_6H_5,R'=H

Scheme 2

with the aid of a number of models have proposed the mechanism shown in Scheme 2 to explain the formation of both 1,2,4-oxadiazoles and 1,2,5-oxadiazoles.

(f) Benzofurazans from triphenylphospholes by thermolysis.

Thermolysis of 1-O-(nitroarylimino)-1,2,5-triphenylphospholes at 150° gave 1,2,5-triphenylphosphole oxide and the corresponding benzofurazans. Two pathways were proposed, one concerted the other stepwise and are shown in Scheme 3[19].



(18)

a; X = H
b; X = 4-CH_3
c; X = 5-CH_3
d; X = 4-CH_3O

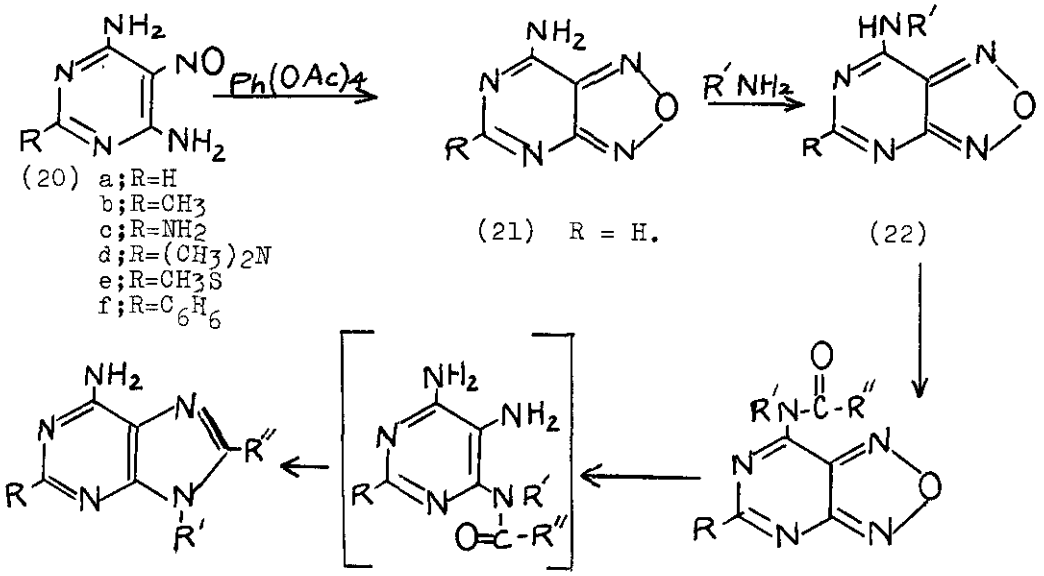
(19)

a; X = H
b; X = 4-CH_3
c; X = 5-CH_3
d; X = 5-CH_3O

Scheme 3.

(g) Oxidation of amino pyrimidine

This transformation is of value in the synthesis of adenine derivatives. For example 4,6-diamino-5-nitrosopyrimidine (20a) was converted to 7-aminofurazano [3,4-d] pyrimidine (21) by lead tetraacetate oxidation. The introduction of the eventual adenine C_8 and C_9 substituents was achieved by reacting the furazan with alkylamine to give (22) followed by acylation to (23) and then reductive cleavage of the furazan ring gave the intermediate (24) which was recyclised to the desired adenine derivative (25). Scheme 4 summarises the reaction pathway and indicates the different models used.[20]



(20) a;R=H
b;R=CH_3
c;R=NH_2
d;R=$(CH_3)_2N$
e;R=CH_3S
f;R=C_6H_6

(21) R = H.

(22)

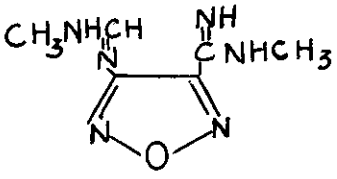
(23)

(24)
R'=H,CH_3,C_6H_{11},C_2H_5
R"=H,CH_3,C_6H_5

(25)

Scheme 4.

Treatment of (21) with 40% aq.CH_3NH_2 yielded (26), which on dilution gave (27).



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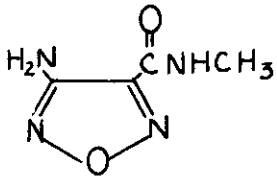

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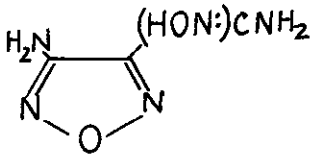


(28)

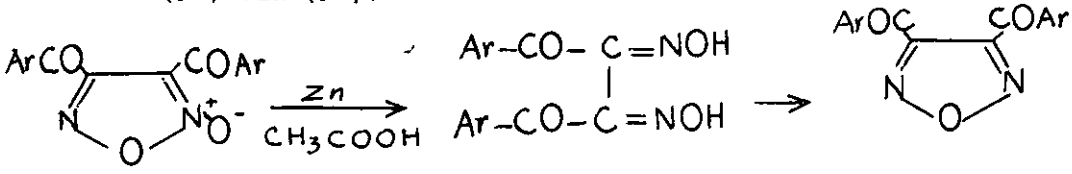
Of related interest is the approach used by Ichikawa and co-workers to produce adenine[21]. The furazan intermediate (28) was treated with HCO_2H and Raney nickel followed by H_2S to produce adenine.

(h) Reduction of furoxans.

Several reagents have been utilized;

i) Na_2CO_3 followed by acid: The unique compound, phenyl-hydroxyfurazan was prepared by this route[1].

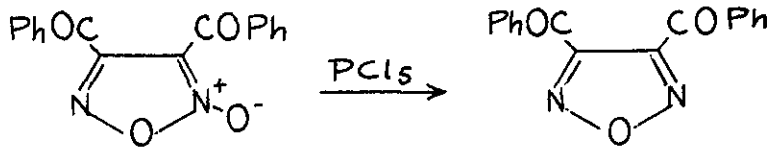
ii) Zn/CH_3COOH[1] : Ring opening occurs, i.e. (29) goes to (31) via (30).



(29) (30) (31)

iii) Trialkyl and triarylphosphines and phosphites: Reduction occurred without ring opening.[22,23]

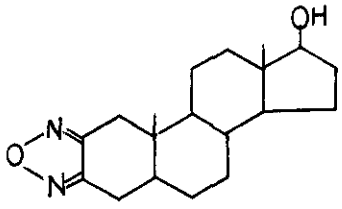
iv) PCl_5 or stannous chloride in acetic acid: Compound (32) was converted to compound (33).



(32) (33)

(i) Preparation of some special molecules.

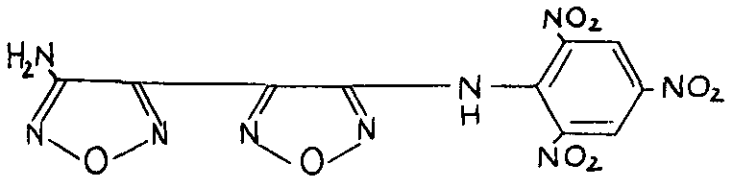
i) Furazan derivatives of steroids[24]. Treatment of 2,3-bis(hydroximino) steroids were converted to furazan derivatives by heating with KOH in ethylene glycol at 170 - 190°. For example 2,3-bis(hydroxyimino)androstan-17β -ol yielded 17β-hydroxyandrostano[2,3c]furazan (34).



(34)

In the case of compounds which are unstable to alkali, ring closure was brought about by $SOCl_2$ in SO_2 or with succinic anhydride at 180 - 190°.

ii) Bifurazanyls. These are mainly obtained by condensing the appropriate aminofurazans with picrylfluoride in the presence of Et_2N. Compound (35) was prepared by this technique.[25]



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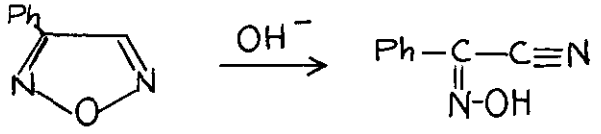
3. REACTIONS OF FURAZANS

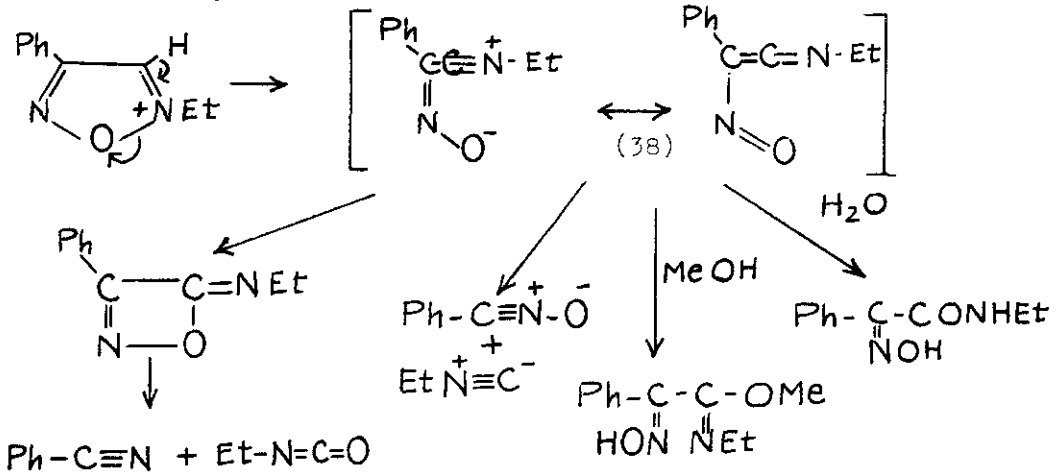
(a) Behaviour towards acids and bases.

As mentioned for furazan itself, substituted furazans are also fairly stable to acids, but alkalie, even in the cold readily causes isomerisation (36→37).[1]



(36) (37)

Olofson and Michelman, who were the first to prepare furazan itself[14], have detailed the base decomposition and rearrangement, and Scheme 5 invokes nitrosoketenimine (38) as an intermediate.[26]



Scheme 5.

(b) Photolysis.

Irradiation of 3,4-diphenyl-1,2,5-oxadiazole in benzene gave a mixture of PhCN (50%), 3,5-diphenyl-1,2,4-oxadiazole (10%) and diphenylfuroxan (14%). Irradiation in excess PhCN resulted in double fragmentation and large amounts of the 1,2,4-oxadiazole derivative, whereas MeOH as solvent produced BzOMe, benzamide, and PhCN[27]. This study has more recently been extended, and it was shown that polycyclic oxadiazoles such as benzo-, naphtho- and phenanthrofurazan upon irradiation afforded a complex mixture of products in the presence of triethylphosphite or Ph_3P, in that the corresponding 1,4-dinitriles were obtained in good yields[28].

(c) Polarography.

1,2-Naphthofurazan and 1,2-naphthofurazan-4-sulfonic acid exhibited one polarographic wave corresponding to a 6-electron reduction in the pH region 1.6 to 12. For benzofurazan, 6 and 4 electron waves were recorded in acidic and alkali solution respectively. The furoxans, which correspond to the above furazans , however, exhibited 2 or 3 reduction waves, depending on pH. The first-wave corresponded to the reduction to quinone dioxime and the second and third waves to the reduction of the protonated and non-protonated forms of the latter.[29]

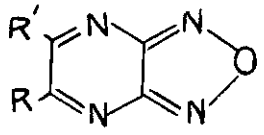
(d) Hydrogenation.

Aspects of this area have been reviewed by Boulton and Ghosh[3]. V. Cere et al. have shown that hydrogenation of benzofurazan and its chloroderivative gave 4,5,6,7-tetrahydrobenzo [2.1.3] oxadiazole and a small amount of 1,2-phenylenedi-

amine, while benzo [2.1.3]- oxadiazoles substituted with no reduction sensitive groups were hydrogenated to 1,2-phenylenediamines or to mixtures containing the 4,5,6,7- tetrahydro-derivative[30].

(e) Condensation reactions to yield pyrazines.

When 3,4-diaminofurazan was condensed with α-dicarbonyl compounds such as benzil, oxalic acid, 9,10-phenanthraquinone and acenaphthoquinone , 5,6-disubstituted furazan [3,4-b] pyrazines (38A) were formed.[31]



(38A) R = R' = Ph, OH
RR' = 9,10-phenanthro, or 1,2-acenaphthol

(f) Lithiation reaction.

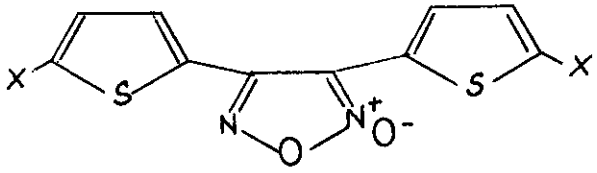
Recently three types of reactions, namely, laterial lithiation, ring cleavage and addition of BuLi to the furazan ring were observed. In the case of 3,4-dimethyl-1,2,5-oxadiazole, laterial lithiation gave the respective acetic acid after carboxylation[32].

4. PREPARATION OF FUROXANS

There are three routes to the formation of furoxans, namely intramolecular cyclization, intermolecular condensation or rearrangement reactions. In the case of unsymmetrically substituted furoxans, it should be remembered that it is possible for an equilibrium to exist between the furazan-2-and -5-oxides. A study of 4(3) and 3(4)-methyl derivatives by Gasco and Boulton in relation to activation energies and equili-

brium constants showed that the equilibrium constants were nearly unity, except for the ether and amine derivatives, in which cases the isomerisation was more rapid and the 3-methyl isomers were preferred.[33]

It is also important to re-emphasise the importance of reaction conditions. For example when thiophene-2-carbonitrile N-oxide and 5-chlorothiophene-2-carbonitrile N-oxide, which were synthesised by chlorination of corresponding aldoxime with NOCl, reacted with compounds having C=C and C≡C bonds they produced 2-isoxazoline and isoxazoles through 1,3-dipolar cyclo-addition. However, in the absence of such dipolarophiles, the furoxans (39), which are the dimers of the nitrile N-oxide were formed from these 1,3-dipoles.[33A]



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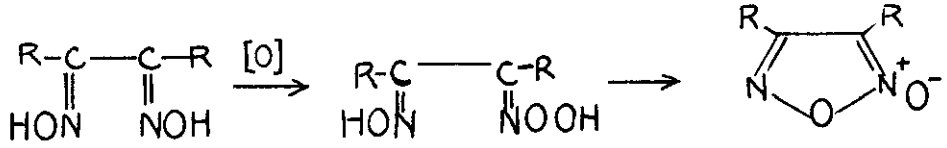
(a) Oxidation of appropriately substituted glyoximes (α-dioximes),

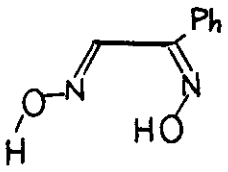
Several oxidising reagents have been utilized and include alkaline ferricyanide, sodium hypochlorite in ether, nitric acid, chlorine or bromine water[1]. Scheme 6 summarises the reaction pathway.



Scheme 6.

A recent report mentions the use of $K_3Fe(CN)_6$ and NH_3 for the preparation of 3-amino-4-phenylfuroxan in a single operation from amphi-phenylglyoxime[34]. Quantitative rearrangement into 3-phenyl-4-aminofuroxan is possible by heat treatment in excess of 80°.

When the three isomers of phenylglyoxime (40,41,42) were oxidised, the same 4-phenylfurazan oxide (43) was produced, and it was found that isomerization into 3-phenylfurazan-2-oxide was not observed, although an equilibrium between the two is possible[35].



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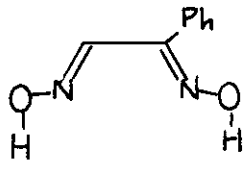

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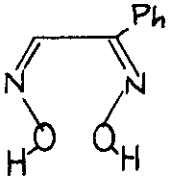

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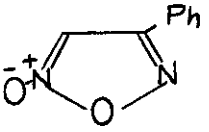
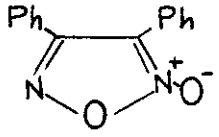


(43)

Compounds (44) and (45) were obtained by the oxidation of benzildioxime and phenanthrenequinone dioxime respectively[36].



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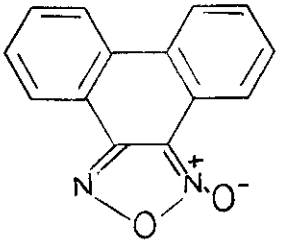
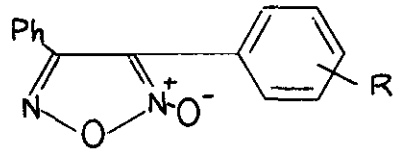


(45)

(b) Oxidation of compounds other than α-dioximes.

i) Oxidation of mono oximes: Oxidation of PhCH=NO C_6H_4R (R = H, 2-Cl, 4-Cl) with MnO_4 gave the corresponding furoxan (46)[37].

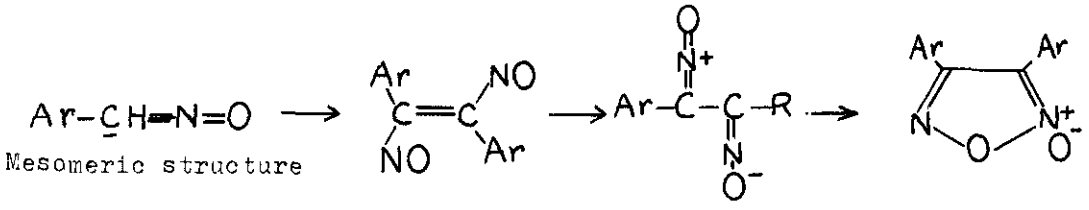


(46)

ii) Oxidation of α-oximinoacetoacetarylamides: This produced 3,4-bis(arylcarboxamido)-furoxans[38].

(c) Nitrile oxide.

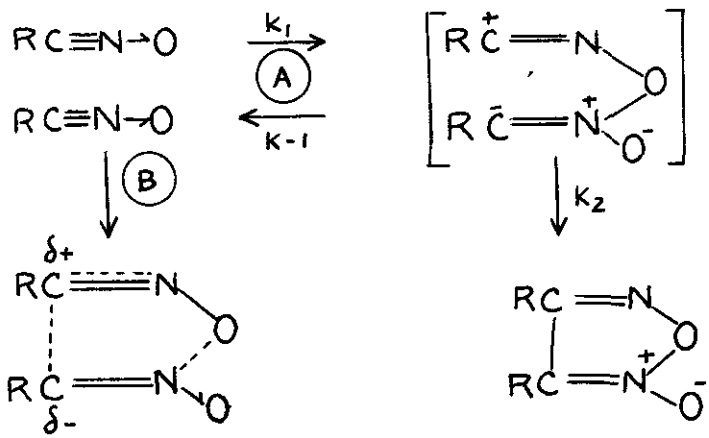
Although furazan oxide formation from nitrile oxides is probably the longest known reaction of this class of compounds, it is the least understood mechanistically. The following Scheme 7 was suggested in view of the fact that 1,3-dipolar cycloaddition is not likely[39].



Scheme 7.

In a more recent study involving the dimerization rates of benzonitrite N-oxide and some m- and p- substituted derivatives, the rate order was found to be m- Cl > p-Cl > H > p-Me > p-OMe and

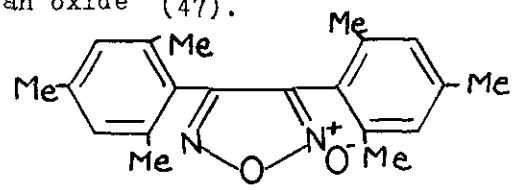
a one step concerted mechanism has been suggested[40]. This is shown in Scheme 8.



Scheme 8.

Path B was preferred since path A, which includes a Zwitter ion intermediate, would be expected to be solvent dependent.

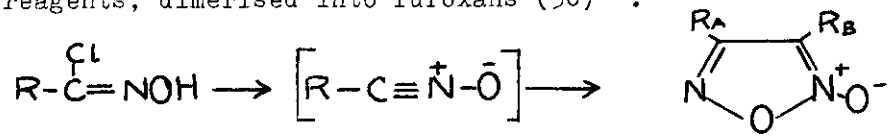
Sterically hindered nitrile oxides, under special conditions can in fact dimerise as was shown for the production of dimesityl furazan oxide (47).[39]



(47)

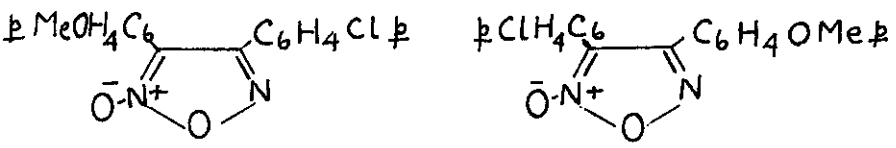
One very interesting study in this area was the one by Wakefield and Wright which showed that pentaflurobenzonitrile N-oxide dimerised to 3,4-bis-(pentafluorophenyl)furoxan whereas pentachlorobenzonitrile N-oxide was stable[41]. Consideration can also be given here to the treatment of sugar hydroximoyl chlorides (48).

Base treatment lead to the corresponding unstable nitrile oxides (49), which in the absence of nucleophilic or dipolarophilic reagents, dimerised into furoxans (50)[42].



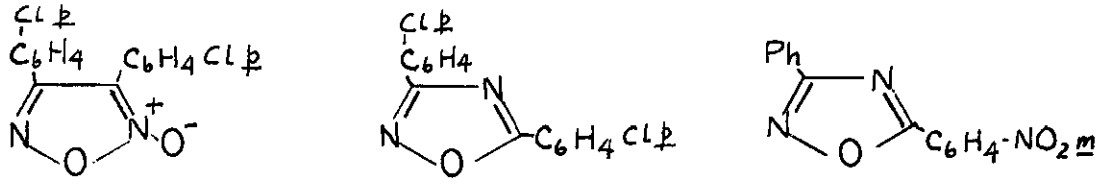
(48) (49) (50)

Mixed dimerisations have also been undertaken. When equimolar amounts of p-chloro-, p-methoxybenzonitrile N-oxide were mixed in CCl_4 at 40°, 3,4-bis(p-chlorophenyl)-furazan N-oxide (24%), 3,4-bis(p-methoxylphenyl)-furazan N-oxide (24%) and a mixture of (51) and (52) were produced[43].



(51) (52)

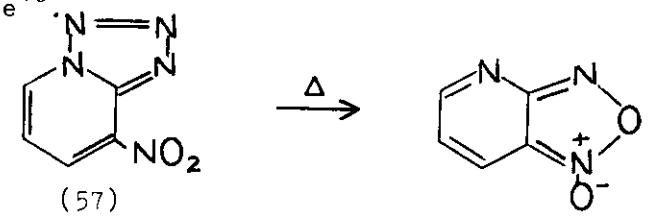
However, dimerisation of p-chlorobenzonitrile alone lead to (53) as well as (54)[44], and mixtures of PhC-Cl: NOH and m-$NO_2C_6H_4CH$:NOH in toluene yielded (55) in 30% after refluxing until the evaluation of HCl ceased. Treatment of Ph C≡NO (56) and m-$NO_2C_6H_4CH$ = NOH gave the furoxan (44) in 35%. The same treatment in the presence BF_3 - Et_2O gave 15% (55) and 40% (44)[45].



(53) (54) (55)

(d) Pyrolysis of nitropyridotetrazole (57).

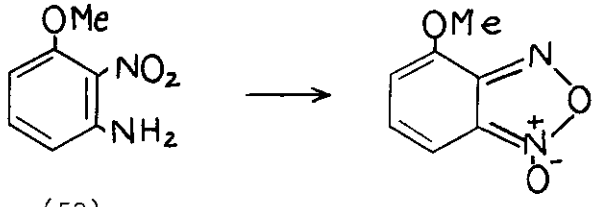
The production of (58) from (57) probably goes via the azide[46].



(57) (58)

(e) Use of O-nitroanilines.

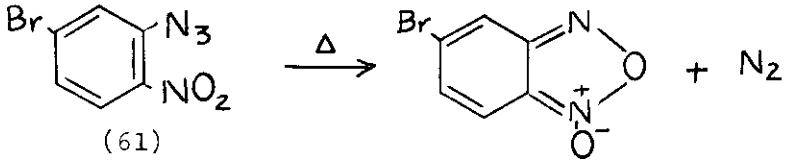
Cyclisation to (60) was achieved by using sodium hypochlorite on the o-nitroaniline (59)[47].



(59) (60)

(f) Phenylazides.

Thermal decomposition of the bromo-nitrophenylazide (61) produced the benzofuroxan (62)[48], and 5-methyl-6-nitrobenzofuroxan was prepared by treating 5-chloro-2,4-dinitrotoluene with NaN_3 then heating the azide thus formed[49].



(61) (62)

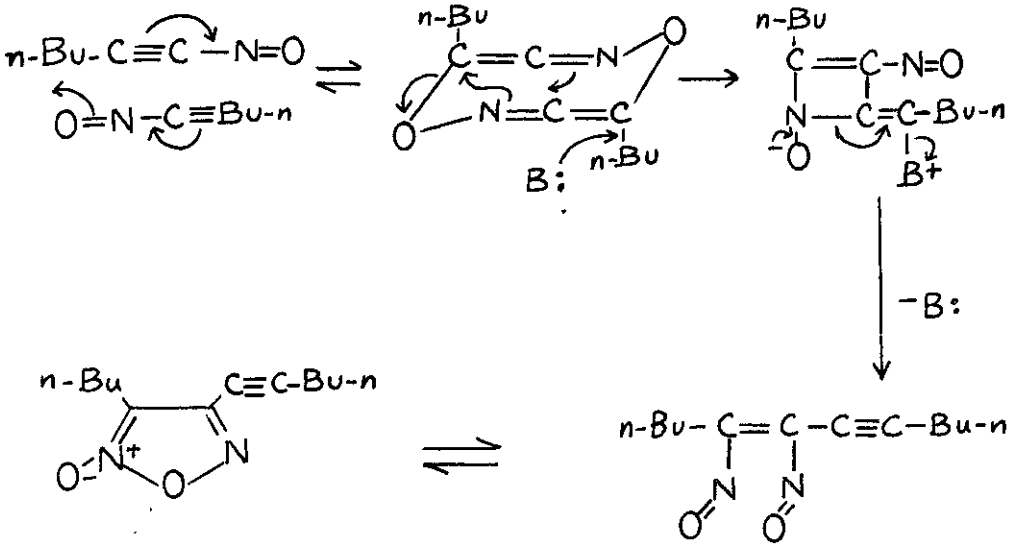
(g) Use of diazo compounds.

Treatment of α-diazosulfones, α-diazoketones and ethyl diazoacetate with N_2O_3 at 0-5° in CH_2Cl_2 gave 62-100% of 3,4-disubstituted furoxans[50]. This type of reaction has also been achieved on other diazocarbonyl compounds more recently by

treatment with HNO_2 at 0^o and pH 1-2.[51] Furoxan formation is similarly achieved when nitrodiazoketones were reacted with nitrogen tetroxide[52].

(h) Nitrosoacetylenes.

The nitrosoacetylenes were, firstly, prepared by reacting nitrosyl chloride with metal acetylides in solution at low temperatures. When the solution was allowed to warm up to room temperature, the nitrosoacetylenes underwent a complete rearrangement. The authors in a facinating study have elucidated these rearrangements, and their mechanistic proposals are shown in Scheme 9[53].

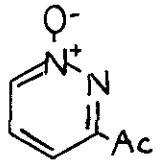


Scheme 9.

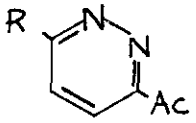
(i) Nitration of 1-oxo-pyridazine.

Nitration of (63) gave 3,4-bis(3'-pyridazinoyl)furoxan 1',1'-dioxide rather than a simple nitration produce. Compounds

(64) and (65) also gave furoxans upon nitration[54].



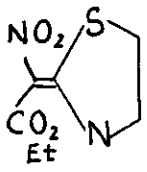
(63)



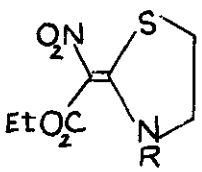
(64) R = H (65) R = OMe

(j) Thiazolidines.

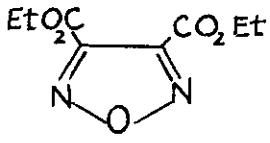
2-Substituted thiazolidines (66) were first prepared by the reaction of 2-alkylthiothiazoline and an active methylene compound. N-Halogenation of (66) was then effected by t-BuOCl or Br_2 in methanol-chloroform. BF_3 - etherate treatment of (67) in Ac_2O gave the products (68), (69) and (66)[55].



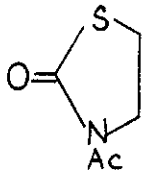
(66)



(67) R=Cl or Br



(68)

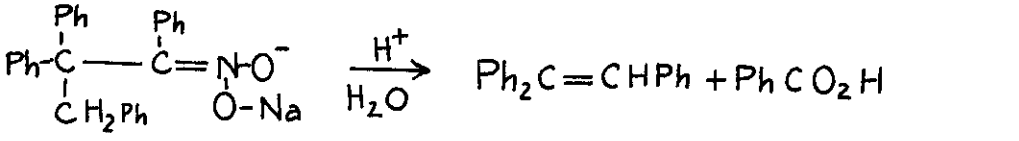


(69)

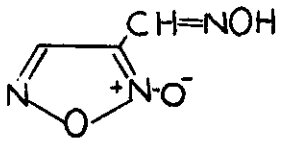
This new method of furoxan formation was also shown to be applicable to the conversion of ethyl nitroacetate to compound (68)[55].

(k) Hydrolysis of Na salt of 1-nitro-1,2,2,3-tetraphenylpropane (70).

When compound (70) was treated with aqueous acid one of the products formed was 3,4-diphenylfurazan-2-oxide (44)[56].



(70) (56) (44)



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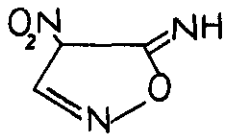


(73)

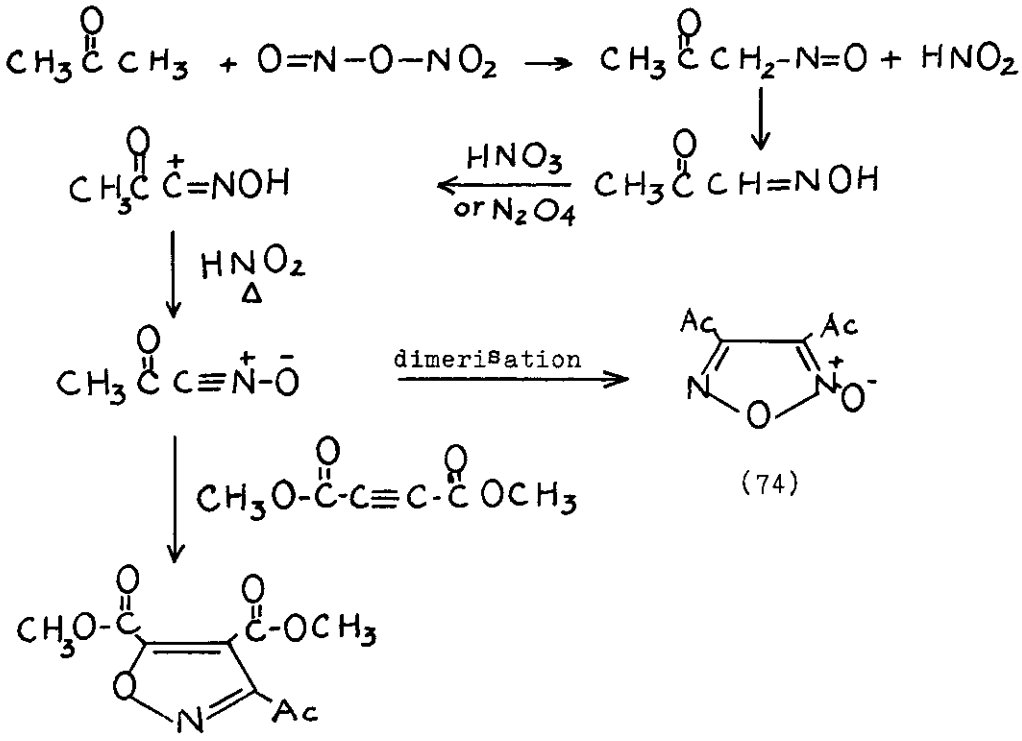
(1) Some special preparations of interest.

i) Use of fulminuric acid:

Dimerisation between fulminuric acid, NCCH—$(NO_2)CONH_2$ (71) and HON:CHCNO gave (72) and this underwent rearrangement to (73) with subsequent ring-cleavage back to (71).[56A]

ii) Acetone as the starting point for furoxan synthesis:

Acetone was first reacted with a 10-fold excess of anhydrous N_2O_4 at 0-5° to give an unstable intermediate which when it was heated at 50° decomposed slowly with evolution of NO. Distillation in vacuo of the mixture gave a 93% yield of diacetyl furoxan (74). The presence of the intermediate AcC≡NO was shown by trapping with $(:C\ CO_2Me)_2$ to give 3,4-dicarbomethoxy-5-acetylisoxazole (75). The authors have proposed a detailed mechanism for this transformation and this is shown in Scheme 10[57].



(74)

(75)

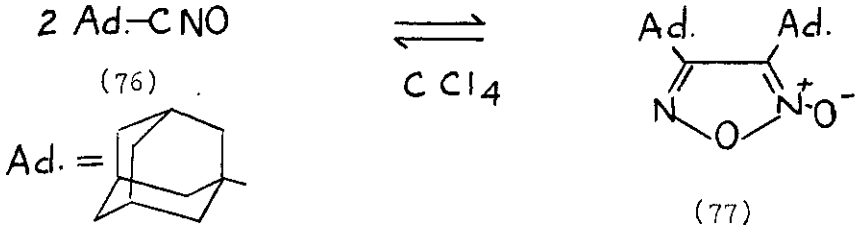
Scheme 10.

iii) Nitration reactions producing diacetylfurazan N-oxide as a by-product:

Acetophenones and acetylbenzothiophenes usually undergo nitration by displacement of the acetyl group, but diacetylfurazan N-oxides were also produced in cases in which the acetyl group was not displaced[58].

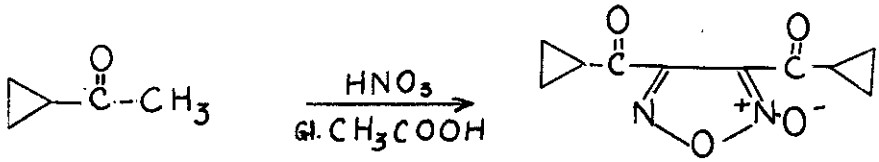
iv) Adamantane-furoxan derivative

Adamantane-1-carbonitrile N-oxide (76) was dimersed to (77) in CCl_4 [59].



(77)

v) Preparation of the first cycloalkylcarbonyl furoxan:

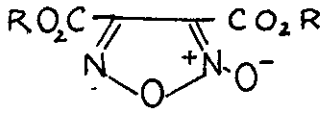


(78)

Bis(cyclopropane carbonyl)furoxan (78) was produced by the treatment of methylcyclopropylketone with a mixture of HNO_3 and AcOH [60].

vi) Synthesising alkyl esters of furoxan dicarboxylic acid:

H_2SO_4 was added to $O_2N\text{-}CH_2\text{-}CO_2\text{-}R$ (R = Me, Et, Pr, Bu) at such a rate as to keep the temperature at -5°. After 12 hours at -5° the mixture was poured into H_2O to yield (79)[61].



(79) R = Me, Et, Pr, Bu.

vii) Nitrosation of dimethylphenacylsulfonium bromide:

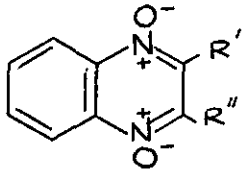
When dimethylphenacylsulfonium bromide was treated with $NaNO_2$ and HCl in H_2O, 3,4-dibenzoyl-1,2,5-oxadiazole-2-oxide was obtained in 70% yield. However, if nitrosation was carried out in 1:1 aqueous dioxane, ω-chloro-ω-isonitrosoacetophenone was formed in 80%[62].

5. REACTIONS OF FUROXANS

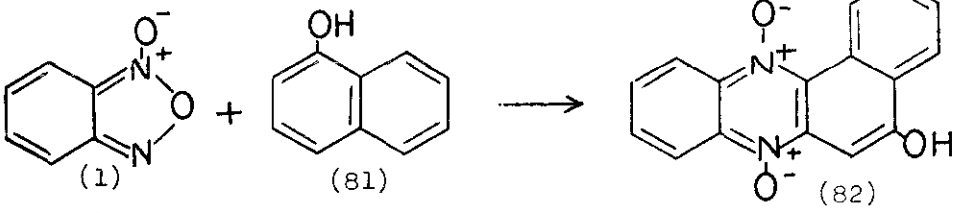
The review by Boulton and Ghosh[3] discussed the reaction of benzofuroxans in terms of electrophilic and nucleophilic attack, oxidation, reduction, rearrangement and some miscellaneous reactions. In view of the broad coverage of this earlier review, only limited space has been devoted in this review to this aspect, and has been confined to recent work.

(a) Conversion of furoxans to phenazines.

It was pointed out by Boulton and Gosh that a variety of enamines and enolate anions have been found to react with benzofuroxan, giving quinoxaline di-N-oxides (80) in moderate yields[3]. This type of addition has been recently repeated to produce 2-(p-methoxyphenyl)-3-methyl-quinoxaline 1,4-dioxide[63].

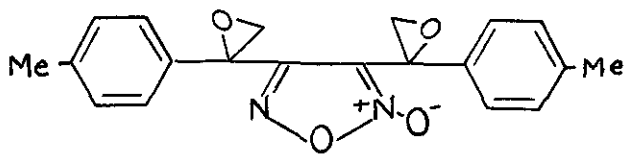

(80)

In a similar type of reaction, benzofuroxan (1) has been shown to react with phenolic compounds like 1-naphthol (81) to yield phenazine derivatives (82) in a one step reaction[64].


(1) (81) (82)

(b) Reduction with LAH.

When the furoxan (83) was treated with LAH, 1-amino-2-(p-chlorophenyl)-2-propanol HCl (84) was obtained[65].



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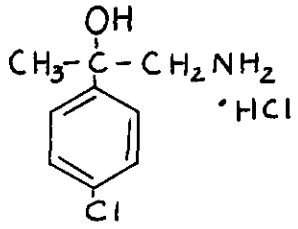


(84)

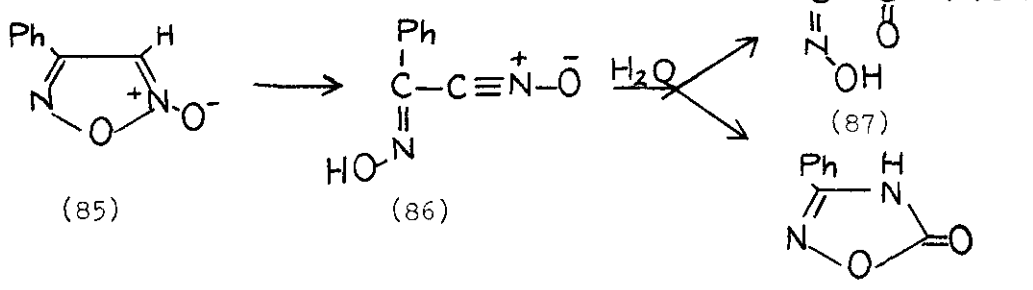
Similarly 3,4-diaroylfurazan oxide was reduced with LAH to give $ArCH(OH)CH_2NH_2$ [66].

(c) Reduction with triphenyl phosphate.

Both diphenyl substituted furoxan and furazan were converted to PhC≡N (88% and 79% respectively) when treated with triphenyl phosphate[67].

(d) Stepwise degradation of phenyl furoxan.

When 4-phenylfurazan-2-oxide (85) was treated in $CHCl_3$ and potassium phosphate-NaOH buffer (pH8), α-hydroxyimino-anti-phenylacetonitrile oxide (86), α-hydroxyiminophenylacetyl-hydroxamic acid (87) and 3-phenyl-1,2,4-oxadiazol-5-one (88) were produced. Scheme 11 summarises this reaction[68].

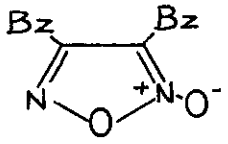


(85) (86) (87) (88)

Scheme 11.

(e) Reaction with certain electrophiles.

Dibenzoylfuroxan (89) reacted with PhC≡CH, PhCH=CH$_2$ or Ph-CH = CH-Ph to give the isoxazole (90) in 70%, the isoxazolines (91) and (92) in 35% and 25% respectively[69].



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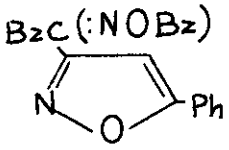

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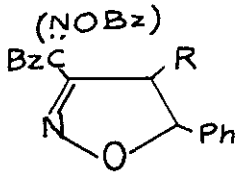


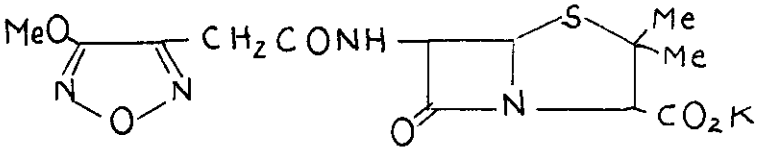
(91); R = H

(92); R = Ph

6. USES.

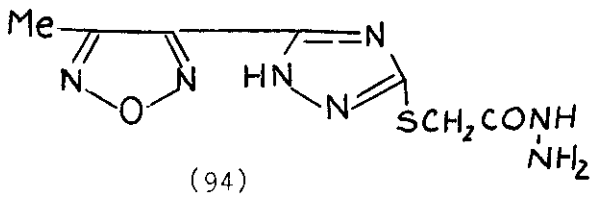
a) Bactericidal and bacterio-static activity.

Several of the furazan compounds which have been shown to possess antibacterial activity are in fact derivatives of known antibiotics, such as cephalosporanic acid and penicillanic acid[70→76]. Compound (93) is an example of such penicillanic acid derivatives, and some were shown to be effective against



(93)

both gram-positive and gram-negative bacteria. The furazan derivative (94) and its 2-and 5-oxides were prepared and shown to have tuberculostatic activity at the 100γ/ml level[77].



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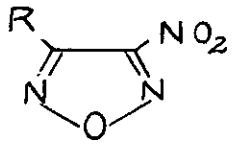


(95) R = Me

(96) R = Ph

In an extensive study, 31 furoxan and furazan derivatives were tested against 10 species of gram-negative and gram-positive bacteria and the only compounds with marked inhibiting action were 3-methyl-4-nitrofuroxan (95) and 3-phenyl-4-nitrofuroxan (96)[78]. Similar compounds have also been patented[79] and *in vitro* and *in vivo* antibacterial action are recorded for other furazan derivatives[80]. Other references are cited by Boulton and Ghosh[3].

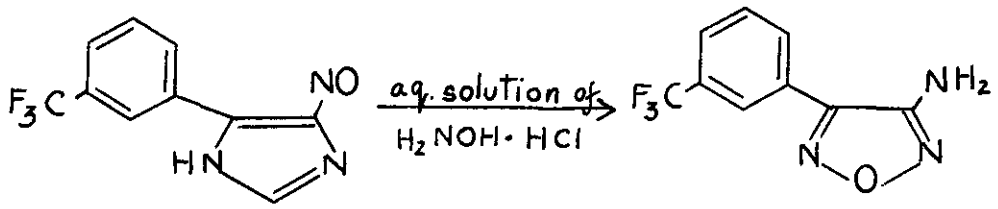
(b) Fungistatic activity.

Klamann and Koser indicated that some of the furoxans they showed to have bacteriostatic properties also have fungistatic action[79]. A number of other patents and papers make reference to this type of activity[3].

(c) Anticonvulsants and muscle relaxants.

Many recent patents have appeared which indicate the use of furazans and furoxans as anticonvulsants and muscle relaxants[81→96]. The methods which were utilized in the preparation of these compounds were not novel, but one of special

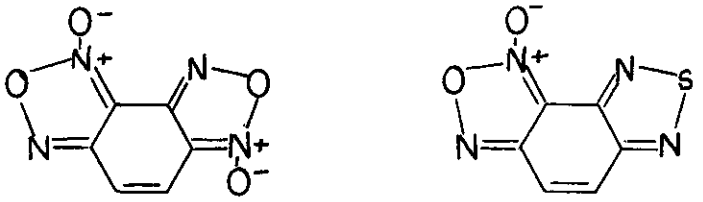
interest was the conversion of compound (97) to (98)[85].



(97) (98)

(d) Vasodilator drugs.

A new class of vasodilator drugs has recently been reported. These compounds were furazanobenzofuroxan, furoxanobenzofuroxan (99) and furoxanobenzothiadiazole (100). Structure activity relationships of these compounds were also surveyed.[97]



(99) (100)

(e) Anthelmintic activity.

It was shown that 3-alkyl-, aryl- aralkyl-and heterocylic substituted 1,2,5-oxadiazoles were effective anthelmintics for mice, sheep and dogs in doses of 50 - 1000 mg/kg of body weight when used as solids or in liquid suspensions given orally or injected subcutaneously[98].

(f) Anti-cancer.

It is not surprising that this group of compounds has been tested for anti-cancer activity. Some symmetrically substituted 3,4-furoxans showed neoplasma inhibition[99].

(g) Radioprotectant.

Two reports have appeared which cite the use of 3,4-diphenylfurazan-2-oxide as an active radioprotectant[100,101].

(h) Plant growth regulators.[102-104]

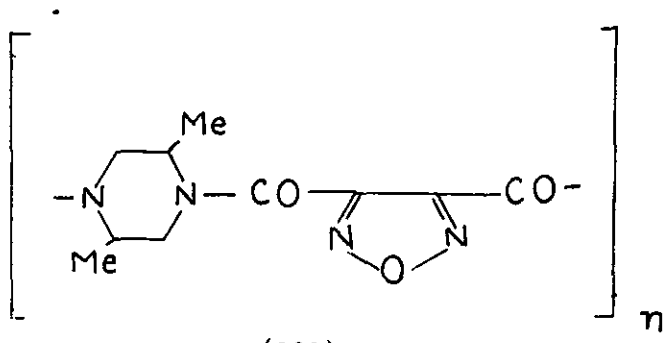
Phenylfurazan-2-oxide has been shown to promote early fruiting and increase the size of fruits in that if applied at an optimum growth stage it was an effective fruit thinner. It was also claimed to promote early break of bud dormancy[103,104]. These results were obtained using lima beans, tobacco, strawberry, tomato, apple and peach plants[104].

(i) Pesticides.

Several reports have appeared concerning the use of derivatives of furazans as insecticides[105-110]. Some of these, for example 1,2,5-oxadiazolylphosphorothioates, were effective against insects and mites.

(j) Polymers.

Certain polymers which contain the furazan moiety were shown to be heat and hydrolysis resistant[111]. Of importance also was the fact that they were extrudable, press moldable and had good solubility in many volatile solvents. Their use in the preparation of films, fibers and coating was also proposed[111]. On the qualitative side the thermal stability of some polymers containing 1,2,5-oxadiazole groups has been calculated[112]. Of special interest is the polymer (101), a trans-2,5-dimethylpiperazine-furazan-3,4-dicarboxylic acid polymer which has been used for water desalination by reverse osmosis. A membrane of this material had high water permeability and good NaCl rejection during extended use[113].



(101)

(k) Detonators.

Some study has been made of the detonation of 3-methyl-4-nitrofuroxan[114] and other furoxans[115]. Furazandicarbonitrile monoxide has recently been patented as a possible rocket propellant[116].

(l) Miscellaneous uses.

Other areas in which furazan compounds have been utilised include photographic desensitizing[117], the inclusion in photographic material of diphenylfuroxan in order to increase the speed in non-silver light-sensitive systems[118], as depolarisers in electric cells[119, 120] and finally as antiskinning agents in drying oils[121].

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