THE CHEMISTRY OF FUROXANS

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Abstract – Syntheses, chemical reactivity, as well as physical and biological properties of furoxans are presented.

I. INTRODUCTION

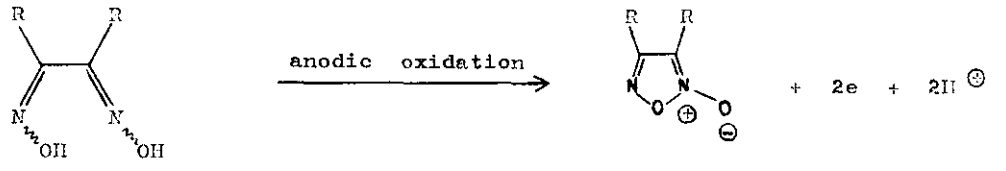
The present review, dealing with 1,2,5-oxadiazole-1-oxides, i.e. furoxans is a continuation of our former papers concerning oxa-, thia- and selenadiazoles[1-4]. The chemistry of furoxans is intensively developing[5-7]; because of the big amount of papers concerning benzofuroxans, useful synthons of biologically active quinoxaline-di-N-oxides[8,9], this topic is not included here.

Presenting syntheses and properties of furoxans, we divide them into two groups - symmetrically and unsymmetrically 3,4-disubstituted.

II. SYNTHESES

SYMMETRICALLY 3,4-DISUBSTITUTED FUROXANS

Among numerous syntheses of furoxans there ought to be mentioned chemical oxidation reactions of dioximes[10-13]; the anodic oxidation being a convenient modification of this method[14].

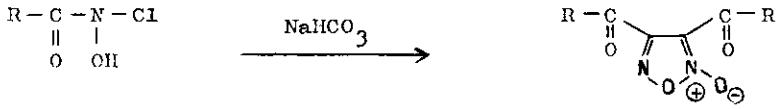


R = Me 30%

R = C_6H_5 68%

[x] Deceased

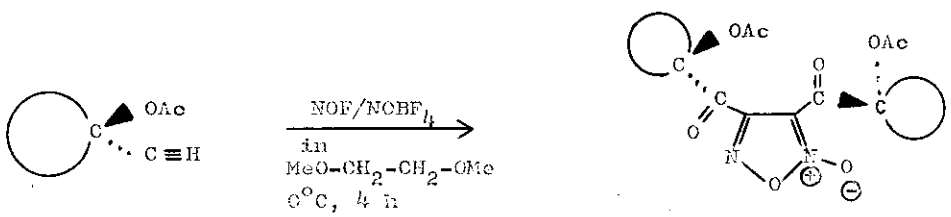
The following procedure also results in furoxans[15]:

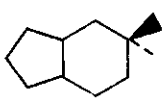


R = NHR^1 , R^1 = C_{1-6} alkyl , C_{4-7} cycloalkyl

R = NR^2R^3 , R^2 , R^3 = C_{1-4} alkyl , and other

The furoxan ring can be formed in the reaction of terminal acetylenes with NOF[16]:





1

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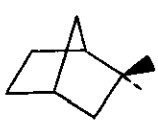
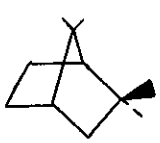


2

39%



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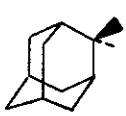


4

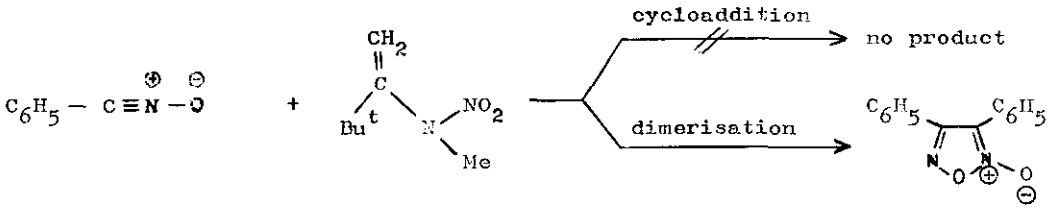
78%

The presence of α-acetoxy group in the starting acetylene is necessary for the reaction to proceed. The process begins with the attack of nitronium ion, present in the reaction mixture, on the acetylenic moiety. The dimerisation of the formed nitroacetylene and the subsequent rearrangement gives way to 1 - 4.

Structures of 1 - 4 can be confirmed by their thermal reversion into two molecules of β-acetoxy-α-oxonitrile oxide, reacting as 1,3-dipole with dipolarophiles[17] /described in the following part, dealing with the chemical reactivity of furoxans/

For the synthesis of isoxazoles and dihydroisoxazoles often the cycloaddition of nitrile oxides to substituted alkenes or alkynes is used. In this procedure, as the side reaction, the dimerisation of $RC\overset{\oplus}{N}-\overset{\ominus}{O}$, resulting in furoxan, takes place; for this purpose the use of certain nitrile oxides in cycloaddition reactions is limited[18].

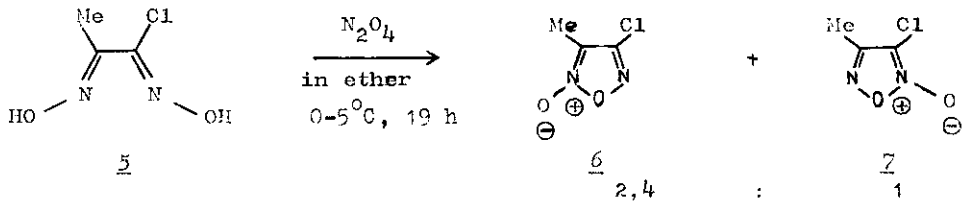
For instance, in the following reaction, instead of the expected 1,3-cycloadduct, only 3,4-diphenylfuroxan could be obtained[19].



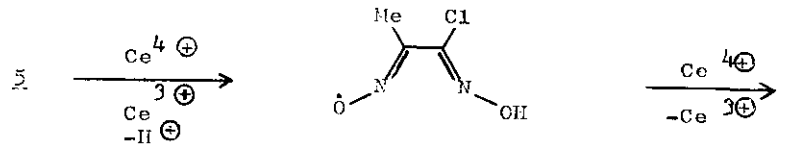
UNSYMMETRICALLY 3,4-DISUBSTITUTED FUROXANS

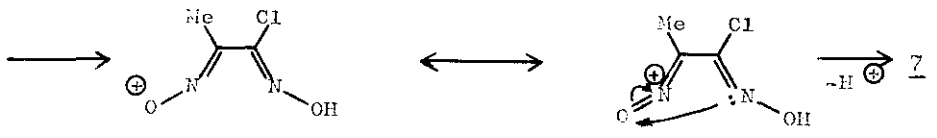
In the oxidation reaction of dioximes, the structure of the resulting furoxans depends on the configuration of dioximes, as well as on the nature of the oxidizing agent[20].

The oxidation of antichloromethylglyoxime 5 with dinitrogen tetraoxide gives way to the mixture of two isomers, 6 and 7, in the ratio of 2,4 : 1[21].

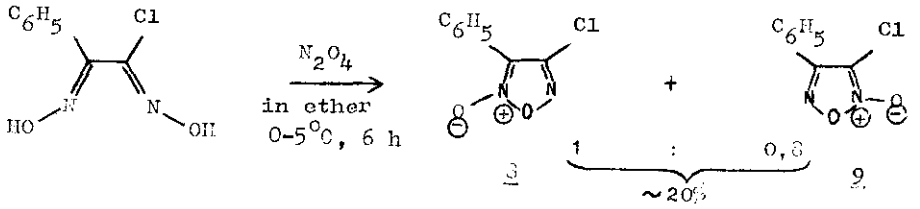


However, when ceric ion was used as the oxidizing agent, the major product was 7[21]. This fact can be explained by the following oxidation mechanism, where the attack of Ce^{4+} on the oxime group adjacent to the methyl is favoured.

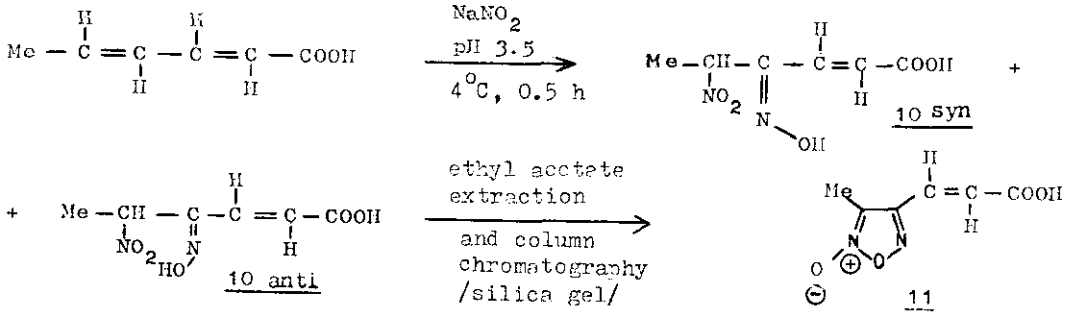




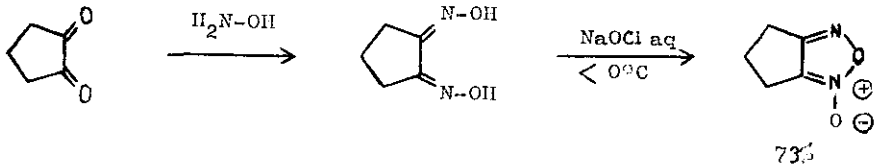
The oxidation reaction of anti - chlorophenylglyoxime results in the mixture of two isomeric furoxans 8 and 9, undergoing thermal isomerisation at the temperature of 100°C[22].



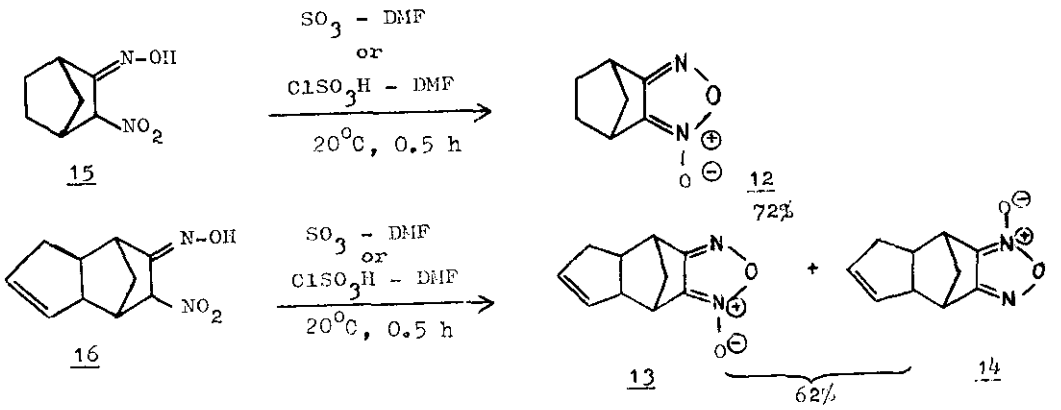
The mixture of syn- and anti-oximes 10, formed in the reaction of sorbic acid with sodium nitrite yields furoxan 11 in the following procedure[23]:



Among bicyclic furoxans, trimethylenefuroxan ought to be mentioned; this compound is obtained by oximation of cyclopentene-1,2-dione and subsequent treatment of dioxime with sodium hypochlorite[24]:

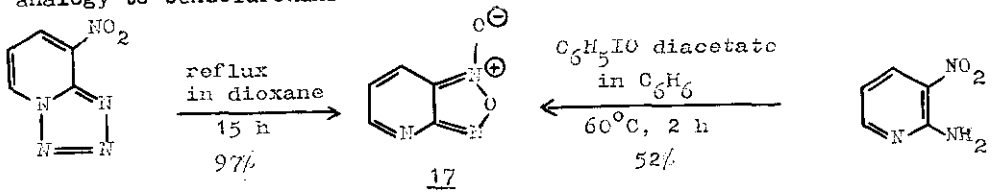


The strained furoxans 12 - 14 can be synthesized from nitrooximes 15 and 16 in the following procedure[25]:



In the case of 16, the mixture of isomers 13 and 14, decomposing explosively when heated to 80°C, is formed.

Pyrido[2,3-c]furoxan 17 can be obtained in following procedures, the aim of these reactions being the use of 17 as the synthon of pyridopyrazine-1,4-dioxides, in the analogy to benzofuroxans[26,27].



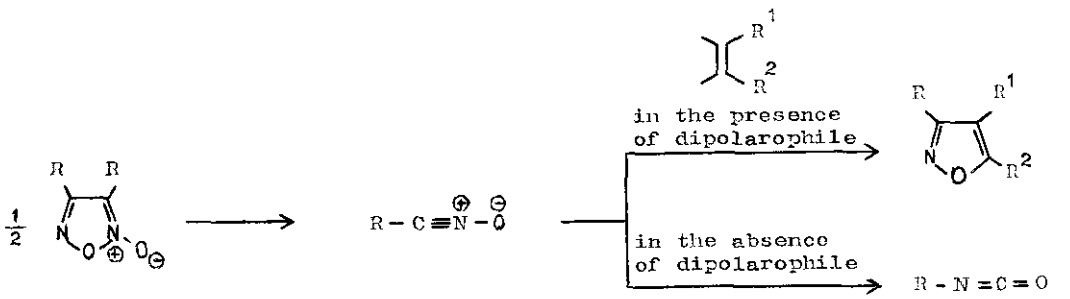
III. CHEMICAL REACTIVITY

SYMMETRICALLY 3,4-DISUBSTITUTED FUROXANS

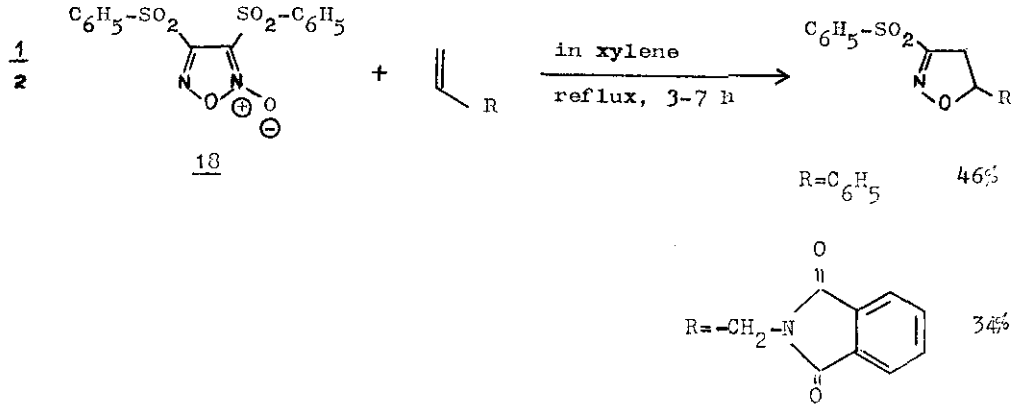
In numerous studies of the thermolysis of alkyl- and arylfuroxans there was found, that at the lower temperature range /100 to 300°C, depending on the substituent/, the ring cleavage leading to nitrile oxides, takes place.

Nitrile oxides in the presence of dipolarophiles give 1,3-dipolar cycloadducts and in the absence of dipolarophiles rearrange to isocyanates[28].

However at very high temperatures /500 - 600°C, under flash vacuum pyrolysis conditions/ the formed nitrile oxides can be isolated and characterized[18].

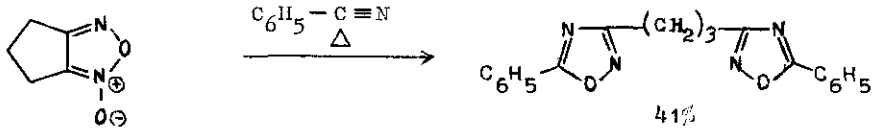


Furoxans generally are readily available, therefore their use as nitrile oxides precursors is of interest in the synthesis of heterocycles. In this regard the reaction of 18 with a series of dipolarophiles, giving rise to isoxarolines, was studied[18].

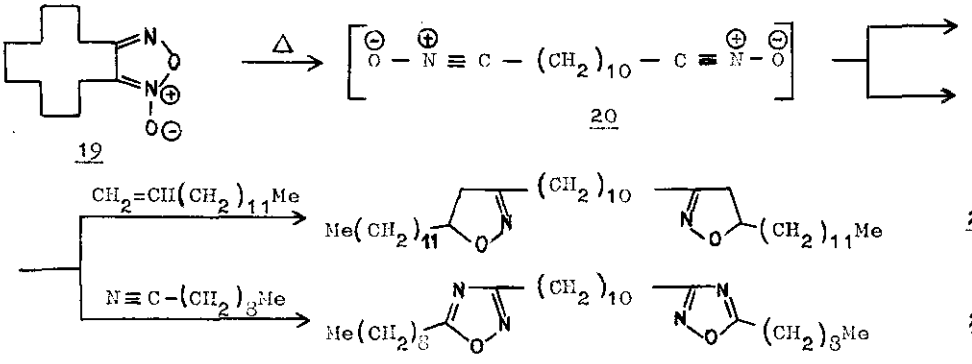


18

In a similar way, fused furoxans heated with dipolarophiles yield bicycloadducts, for instance[24]:



Readily accessible bicyclic furoxans, e.g. 19 give rise to bis-nitrile oxides and di-isocyanates, difficult to obtain on other routes. Thus, thermolysis of 19 in the presence of tetradec-1-ene and decanonitrile, used as dipolarophiles, resulted in cycloadducts 21 and 22, respectively[28].



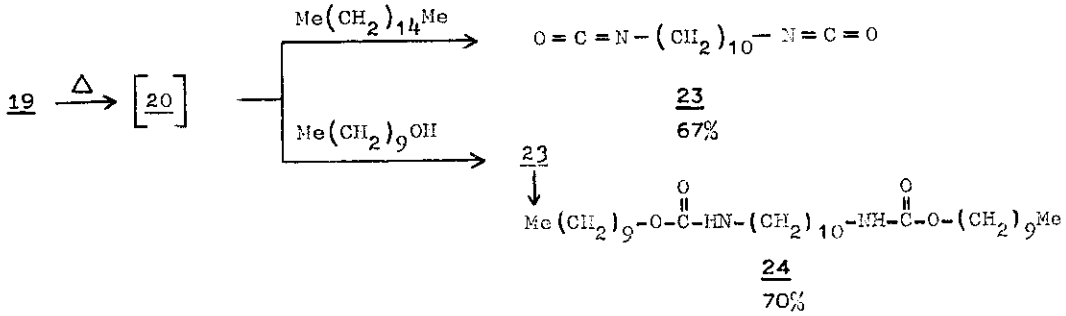
19

20

21

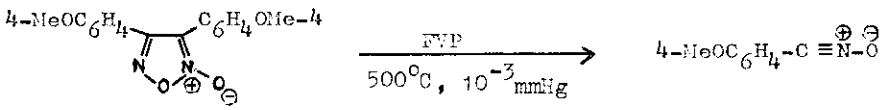
22

Thermolysis of 19 in the absence of dipolarophiles, with hexadecane yielded diisocyanate 23, and with decan-1-ol 23 was isolated as the carbamate 24[28].

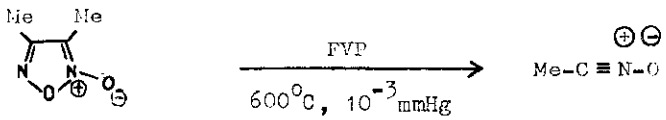


Similar results were obtained in the case of 3,4-diphenylfuroxan[28].

When furoxans are thermolyzed under flash vacuum pyrolysis conditions nitrile oxides can be isolated and identified, for instance dianisylfuroxan gives way to anisonitrile oxide[29]:

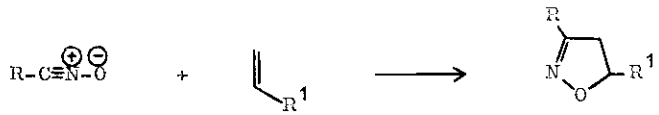


On this way 3,4-dimethylfuroxan yields the unstable acetonitrile oxide.



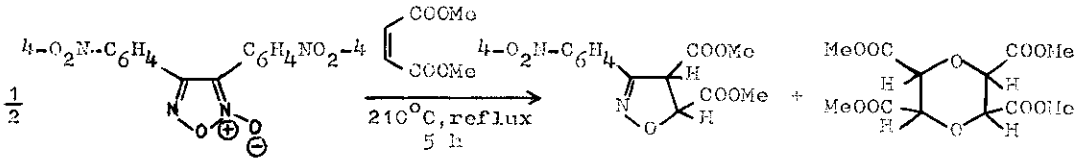
So, the FVP technique permits the spectroscopic examination and identification of shortlived nitrile oxides, and on the other hand, provides a convenient synthetic route from furoxans to isoxazolines.

The following cycloadducts of nitrile oxides, resulting in the FVP of furoxans with alkenes, were obtained[29]:



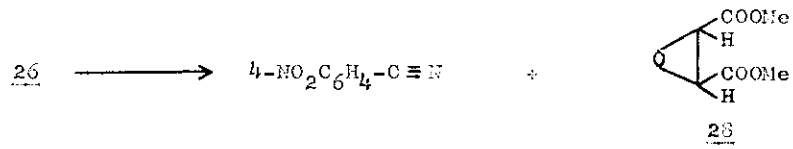
R	R^1	yield(%)
4-$MeOC_6H_4$	Bu	75
Me	Bu	79
Et	Bu	95
C_6H_5	Bu	97
4-MeC_6H_4	$C_{12}H_{25}$	86

Among other cycloaddition reactions of nitrile oxides, formed in situ from furoxans one can mention the thermolysis of 25 in the presence of dimethyl maleate[30,31]:



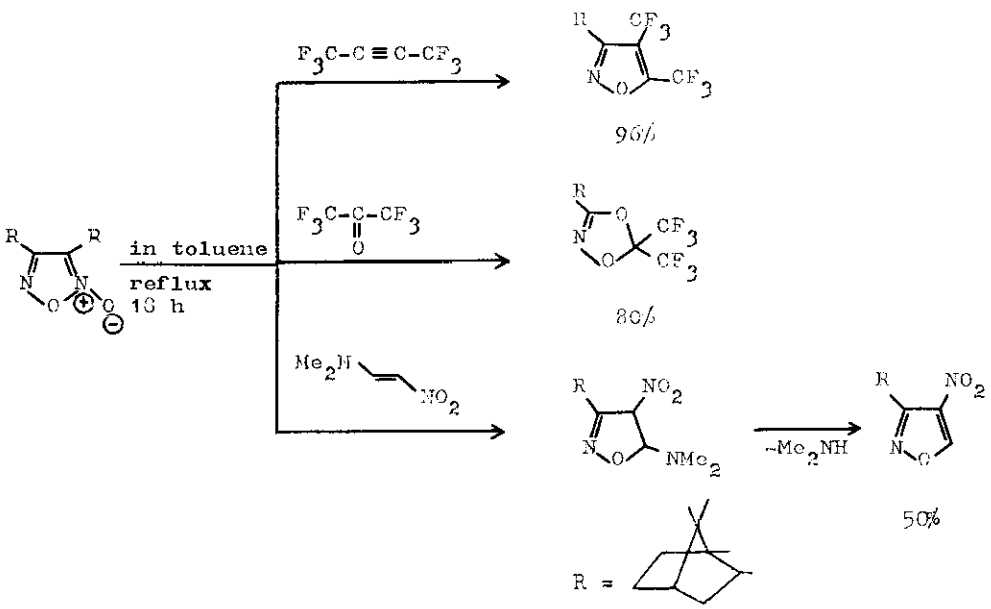
25 → 26 (19.8%) + 27 (12.4%)

The by-product 27 results from the dimerisation of the oxirane 28, formed by the decomposition of cycloadduct 26 taking place under the reaction conditions.



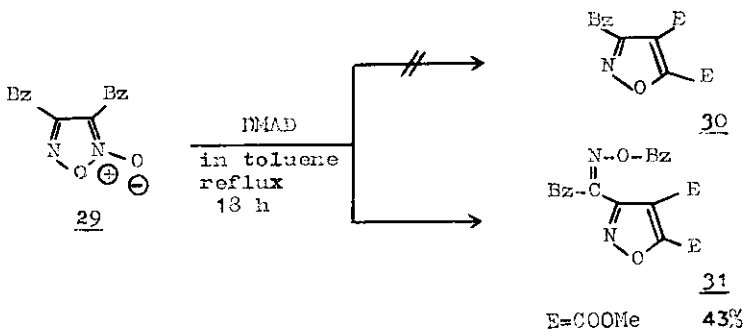
28

Also diacyl furoxans may serve as the source of nitrile oxides, trapped as 1,3-cycloadducts[17]:

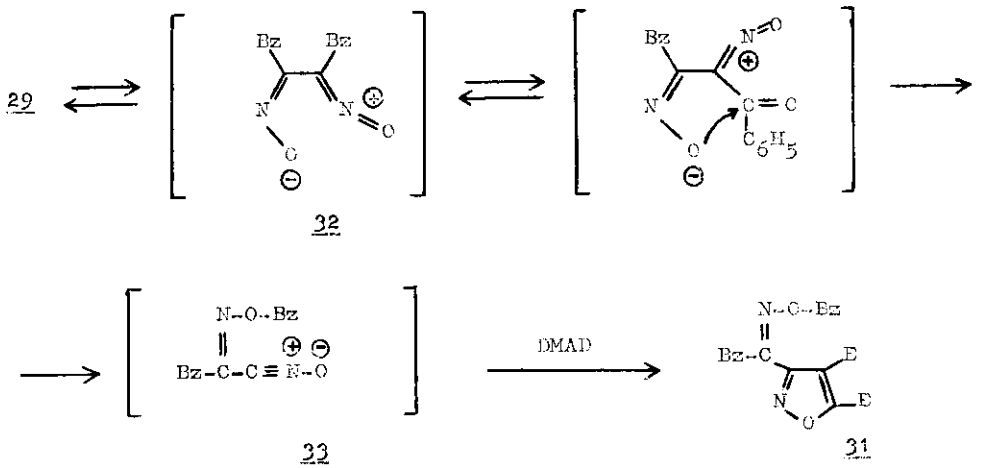


The reaction with nitroenamine provides a convenient route in the synthesis of 4-nitroisoxazoles[17].

However, in the treatment of 3,4-dibenzoylfuroxan 29 with DMAD, instead of the expected isoxazole 30 the adduct 31 is formed[17].

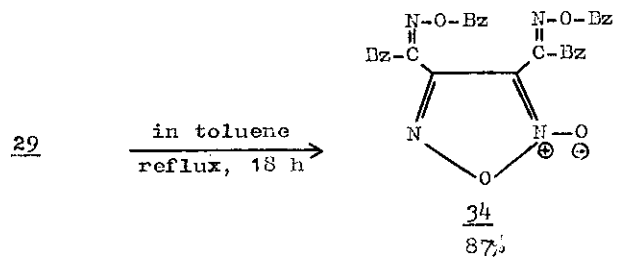


The mechanism of this reaction can be presented as follows:

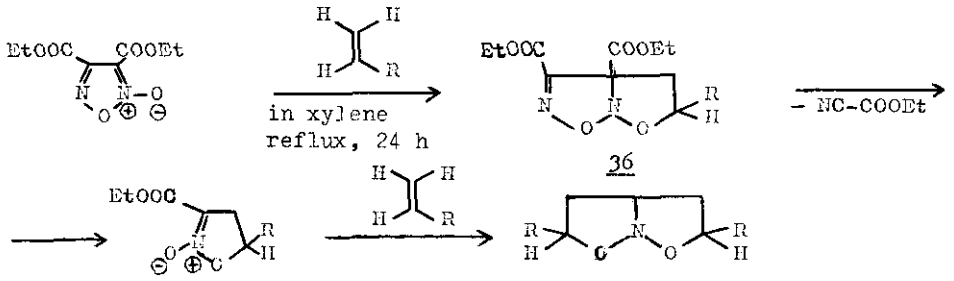


Furoxan 29 is in the thermal equilibrium with the ring - opened isomer 32. The intramolecular transfer of the benzoyl group in 32 gives rise to 33, which undergoes cycloaddition with dipolarophiles to yield 31.

Other mechanism, a nitrone - like addition is also possible[32], however a proof for the described mechanism was obtained by heating 29 in toluene in the absence of dipolarophile. Under these conditions 29 gives 34, resulting from the dimerisation of the nitrile oxide 33[17].



Furoxans can be considered as cyclic 1,3-dipolar nitrones, and as the first example of the nitrone - type 1,3-dipolar cycloaddition of these species the reaction of diethyl furoxandicarboxylate with olefins, giving way to bicyclic compounds 35, was reported [33]. In the first step the 1,3-dipolar cycloadduct 36 is formed, which eliminates ethyl cyanoformate by a retro-1,3-dipolar cycloaddition to give 37; the next 1,3-dipolar cycloaddition of 37 with another molecule of olefin results in the end product 35. The stereochemistry of this reaction is described.

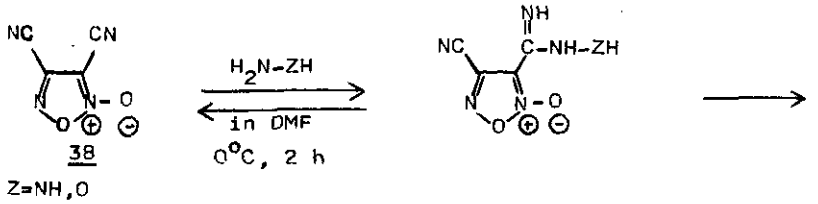


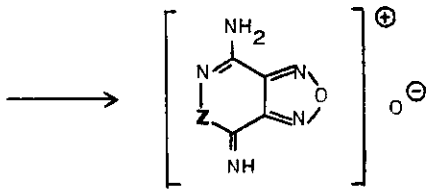
R
n-C_6H_{13}
n-C_7H_{15}
n-C_8H_{17}
n-$C_{10}H_{17}$
CH_2-C_6H_5 and other

Furoxans treated with reducing agents, e.g. triethyl phosphite, can be converted into the appropriate furazans [13,34].

3,4-Diphenylfuroxan was found to be inert towards nucleophiles; the reaction with piperidine, even under reflux, did not take place [35,36].

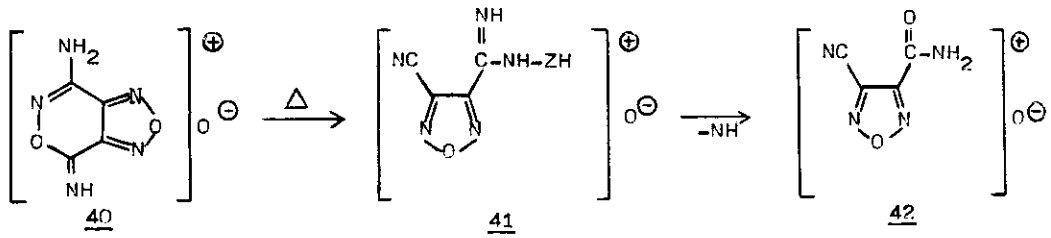
In the investigation of 3,4-dicyanofuroxan 38, the explosive properties of its mixtures with hydrazine have been observed. The reaction of 38 with hydrazine and hydroxylamine gives way to 39 and 40, respectively[37].





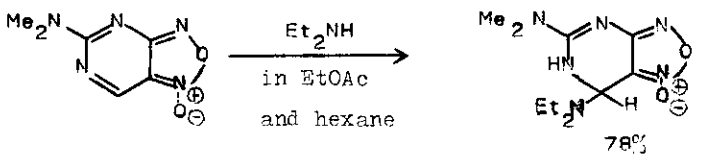
	Z	
39	NH	67%
40	O	78%

Moderate heat converted the oxazinofuroxan 40 into 42, via the tautomerisation of 40 to 41 and the subsequent elimination of imidogen [37].



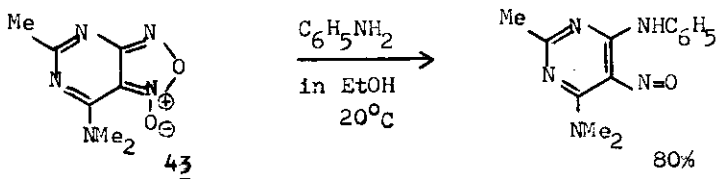
40 41 42

Pyrimidofuroxans undergo nucleophilic addition at C_7, for instance [38]:



78%

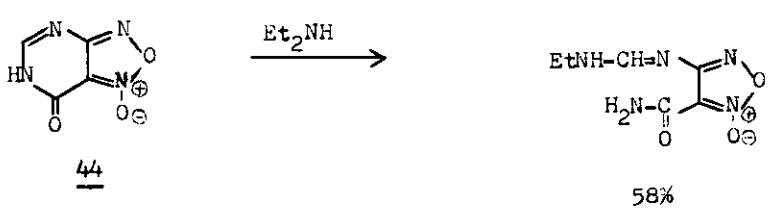
In the study of aminative ring opening reactions there was observed that pyrimidofuroxan 43 treated with primary or secondary amines yields aminonitroso-pyrimidines via furoxan ring opening [39]:



43

80%

On the other hand, in such reactions of 44 the pyrimidine ring opening takes place [39]:

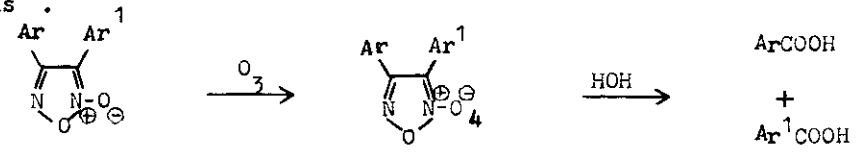


44

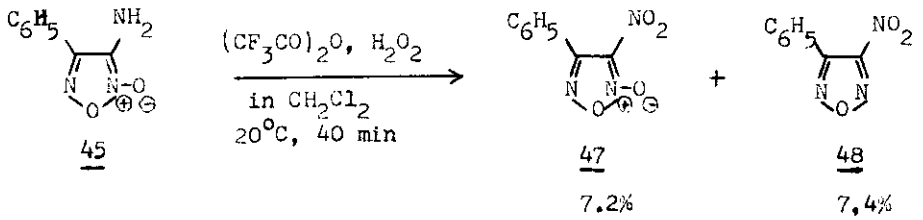
58%

UNSYMMETRICALLY 3,4-DISUBSTITUTED FUROXANS

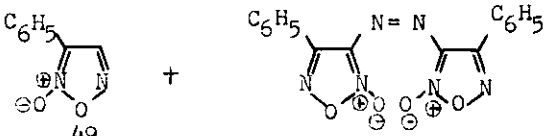
Unsymmetrical diarylfuroxans undergo oxidation with ozone to give aromatic acids[40].



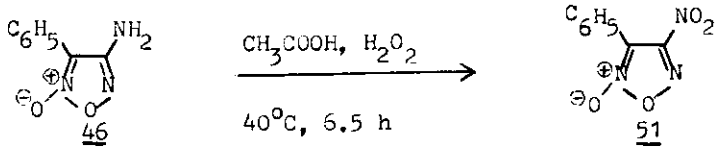
Studying the oxidation reaction of isomeric 45 and 46, the following results were obtained: in the oxidation of 45, besides the expected 47 also 48, 49 and 50 were formed, while in the case of 46 the sole product was 51 [41,42].



45 → 47 (7.2%) + 48 (7.4%)

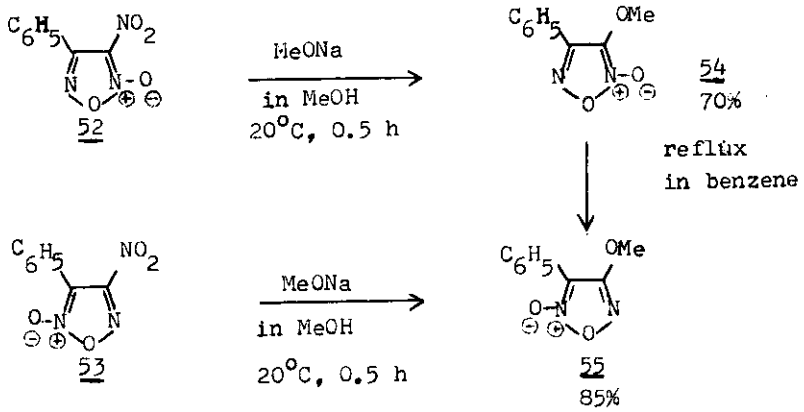


49 (20%) + 50 (2.6%)

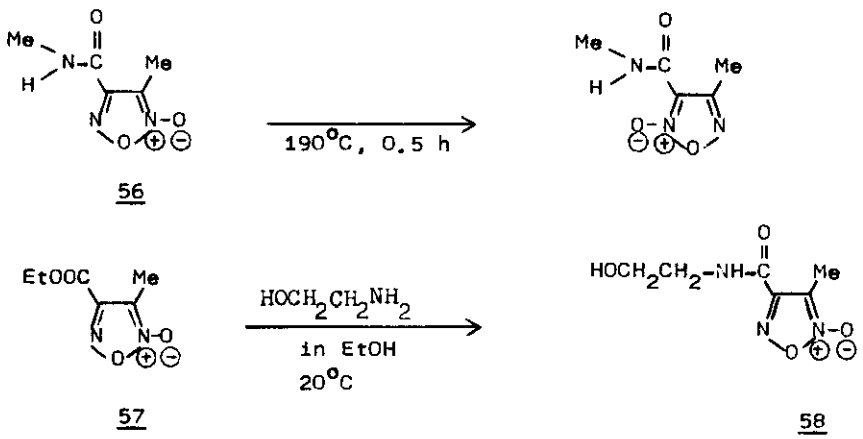


46 → 51

Furoxans 52 and 53 treated with sodium methoxide afford 54 and 55, respectively. The thermal isomerisation of 54 to 55 can be performed by its refluxing in benzene [42].

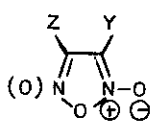


The reactivity of furoxans has been largely investigated having in view their biological activity. For instance, the thermolysis of 56 resulted in its isomerisation, and the aminolysis of 57 gave rise to 58 [43]:



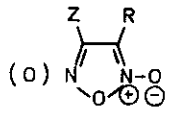
IV. PHYSICAL PROPERTIES

The ^{13}C NMR spectroscopy is often used in the structure elucidation, e.g. in the case of 3,4-dimethylfuroxan [44] or norbornene furoxans [25]. This technique is also very helpful in the identification of isomeric pairs of furoxans:



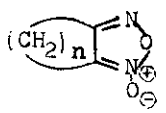
Z	Y	ref.
Me, Et	H	29
C_6H_5	H	20
Me	Cl	21
C_6H_5	Cl	22
C_6H_5	NO_2	41

Numerous papers are dealing with X-ray crystallographic analysis of furoxans:



Z	R	ref.
NO_2	H	45
HOOC-C(H)=C(H)-	H	23
C_6H_5	NO_2	42

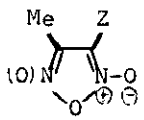
as well as of bicyclic systems:



	ref.
n = 3	24
n = 4	46
n = 6	47

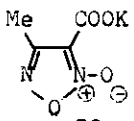
and of norbornene furoxans [25].

Among investigations of isomeric pairs of furoxans by X-ray crystallographic analysis the following ones ought to be presented:



Z	ref.
$-C(=O)-NH_2$	48
$-C(=O)-NMe_2$	49,50
$-NH-C(=O)-O-CHMe_2$	51
$-SO_2C_6H_5$	52

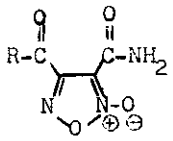
Some furoxans have explosive properties, e.g. dicyanofuroxans [37,53], potassium salt 59 [54], trimethylene furoxan [24] and dicyclopentadiene furoxan [25].



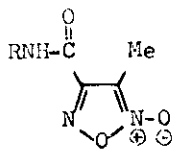
59

V BIOLOGICAL ACTIVITY

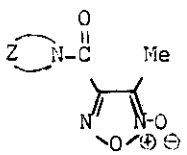
Among biologically active furoxans the following ones show antihypertensitive properties [15,34,43]:



R = OH, alkoxy, amino



R = C_{1-4} alkyl, C_{5-7} cycloalkyl



Z
$(CH_2)_4$
$(CH_2)_5$
$(CH_2)_2O(CH_2)_2$
$(CH_2)_2NMe(CH_2)_2$
and other

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Received, 31st July, 1984