Fused furoxans

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

Описаны методы синтеза и реакционная способность, а также физические и биологические свойства конденсированных фуроксанов.

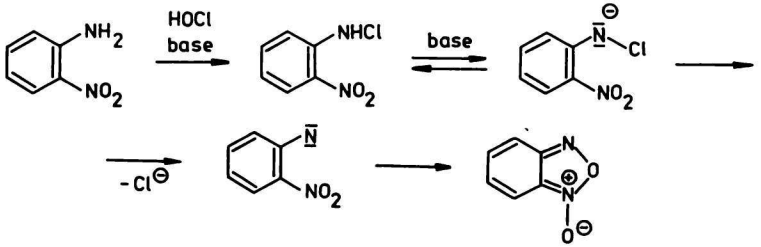
Fused furoxans are interesting from the theoretical point of view, as well as when taking into account their biological activities [1, 2]. Some derivatives of benzofuroxans were found to inhibit the nucleic acid synthesis, which offers new possibilities of their applications [3, 4].

A special attention ought to be paid to benzofuroxans as synthons of quinoxaline 1,4-dioxides [5—8], exhibiting a variety of interesting biological properties [9—11].

The present paper is a continuation of our former reviews dealing with 1,2,5-heterodiazoles — furazans [12, 13] and furoxans [14], as well as thia- and selenadiazoles [15, 16], along with the research work concerning pyridothia- and -selenadiazoles [17].

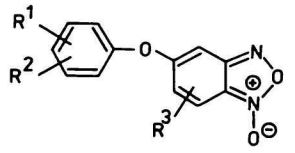
Syntheses

One of often used synthetic approaches to benzofuroxan *I* and its derivatives is the cyclization of 2-nitroanilines *via* oxidation in alkaline solution [18—20]. The mechanism of this reaction involves as the first step the *N*-chlorination of 2-nitroaniline, followed by the loss of chloride ion and the singlet nitrene *II* formation.



II *I*

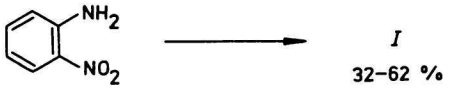
In this way compounds of the type *III* have been obtained [1].



III

R^1 and R^2 = alkyl, haloalkyl, halo
R^3 = H, halo

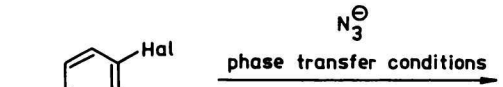
Intramolecular cyclization of *o*-nitroaniline to benzofuroxan can be performed by the electrochemical route by the electrolysis on a graphite electrode in the presence of KI; the electrogenerated iodonium ion acts here as a catalytic electron carrier [21].



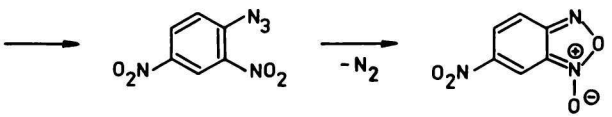
I

32–62 %

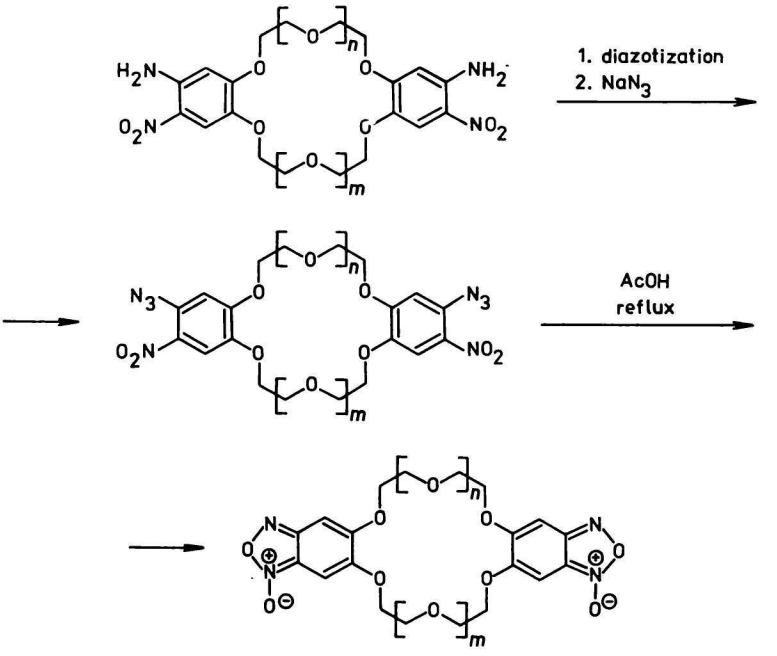
In the nucleophilic substitution of halo-2,4-dinitrobenzenes with $N_3^{\ominus}$ carried out under phase transfer conditions, the mixture of 2,4-dinitrophenylazide and 6-nitrobenzofuroxan has been obtained. The ratio of products depends on the nature of starting material, and on the reaction time [22].



Hal = F, Cl, Br, I

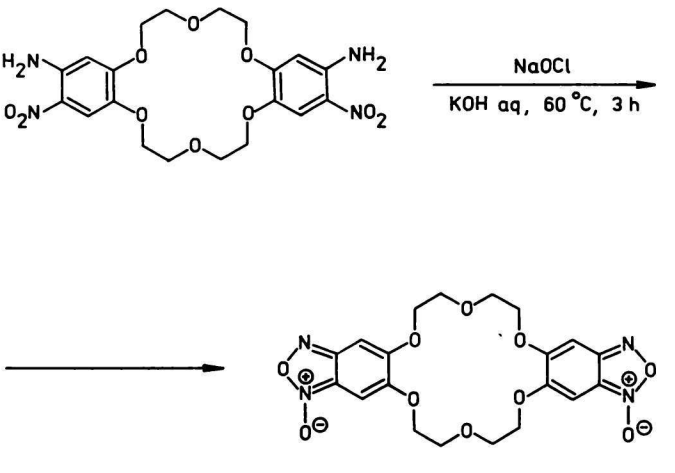


Crown ether annellated benzofuroxans *IV* have been obtained in the following reactions [23].



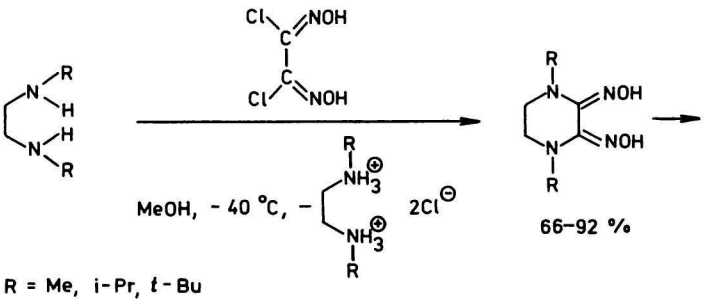
IV *m*, *n* = 1–8

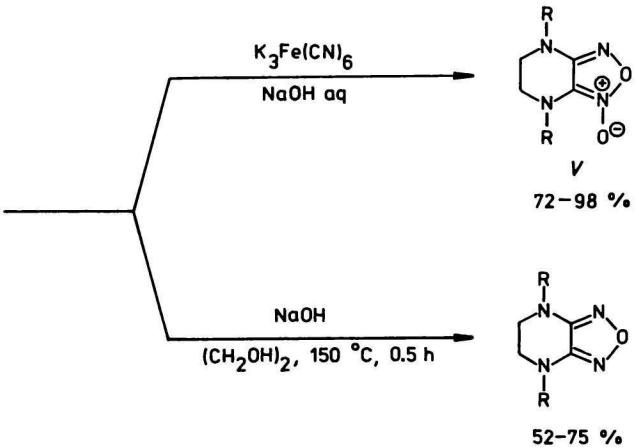
Synthesis of crown ether annellated benzofuroxans was also performed by oxidation of corresponding *o*-nitroanilines [24]; the nomenclature of these compounds is described in [25].



70 %

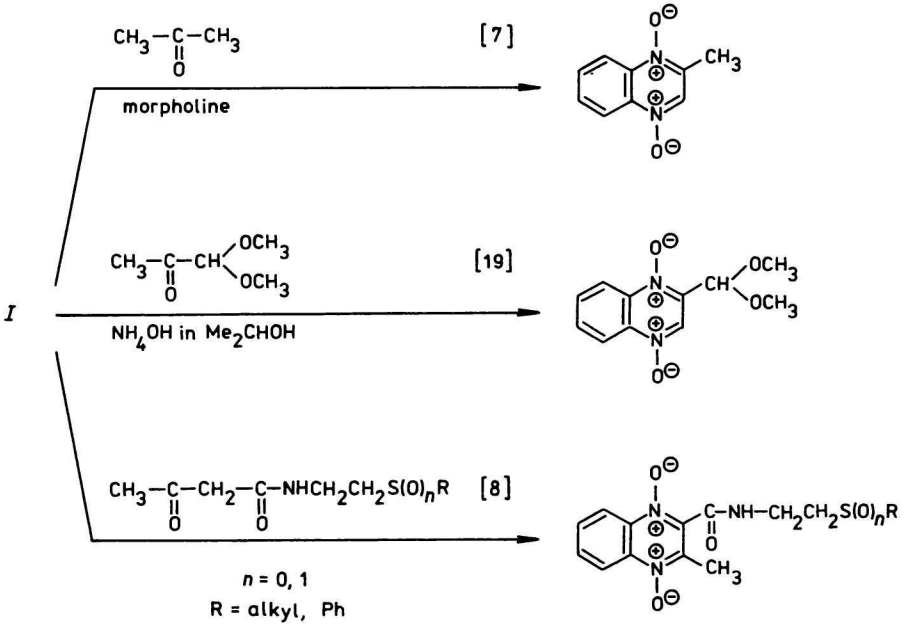
Another approach to fused furoxans is the oxidation of 1,2-dioximes; this procedure was applied in the synthesis of furoxanopiperazines *V*, while dehydration of dioximes led to corresponding furazans [26].



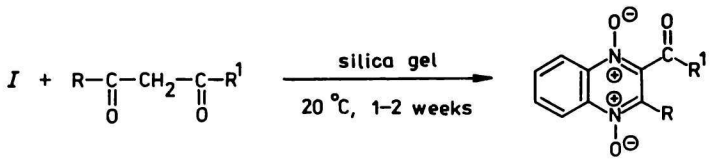


Chemical reactivity

Benzofuroxans are important synthons of quinoxaline-1,4-dioxides, interesting for their biological properties [9—11], some of these procedures will be presented here [7—10, 19, 27, 28].

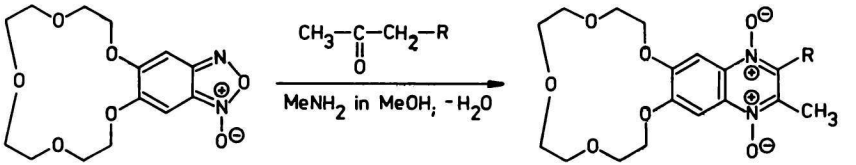


Such cyclocondensation reactions can be accomplished in the presence of silica gel instead of the base; in this case the components are adsorbed on silica gel. In the performed experiments alumina showed to be less convenient [29].



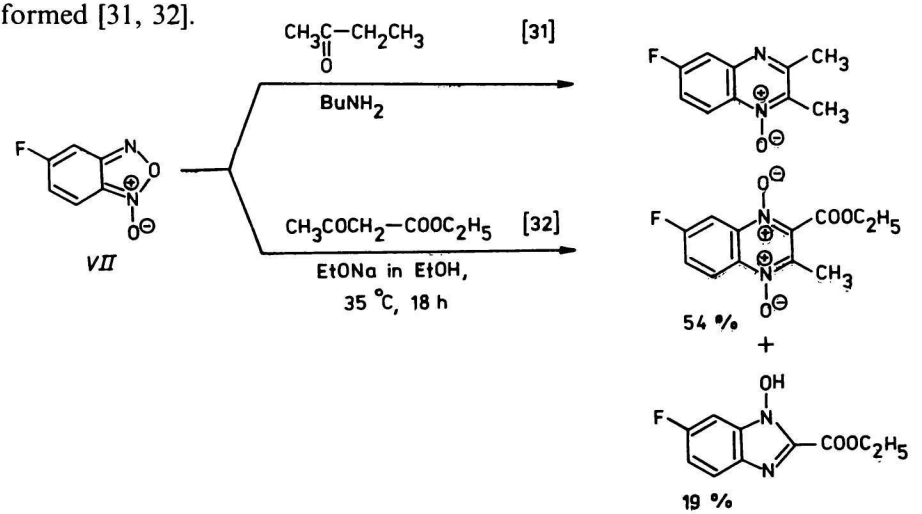
R	R^1	Yield
Ph	OEt	63 %
Ph	Ph	66 %
Ph	NH–Ph	90 %
Me	Ph	88 %

Crown ether annellated benzofuroxans, for instance *VI* also undergo cyclocondensation reactions, for instance [30]

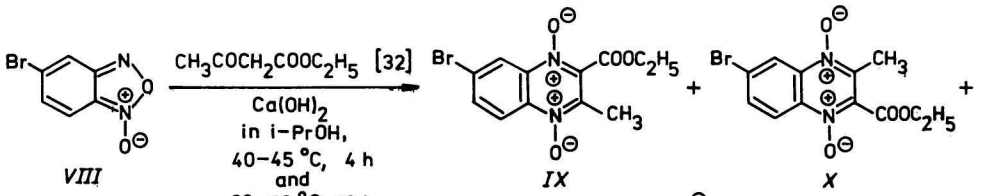


VI R = CH_3, $CONHCH_2CH_2OH$

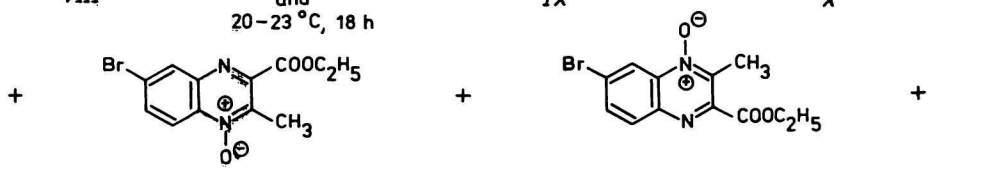
In the same manner react 5-halobenzofuroxans *VII* and *VIII*; in the case of *VIII*, along with isomeric *IX* and *X* also their deoxidation products *XI*—*XIV* are formed [31, 32].



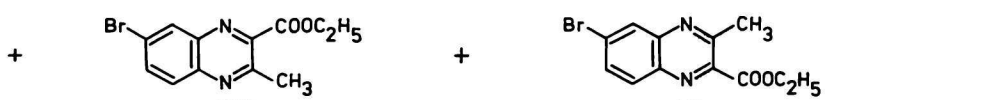
VII



VIII *IX* *X*

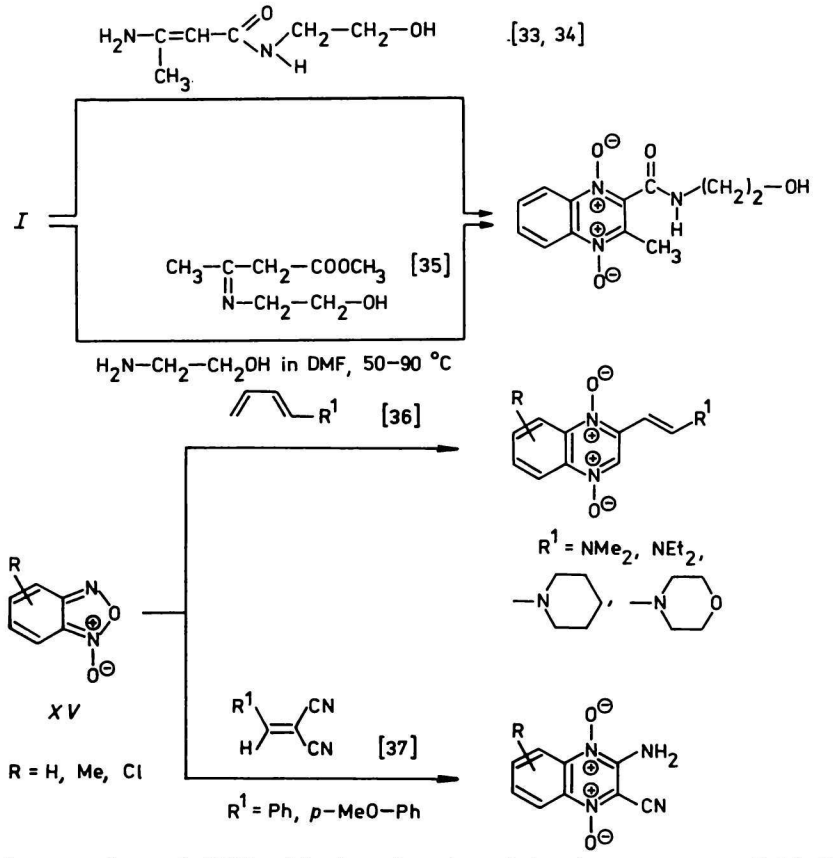


XI 0.6 % *XII* 1.4 %

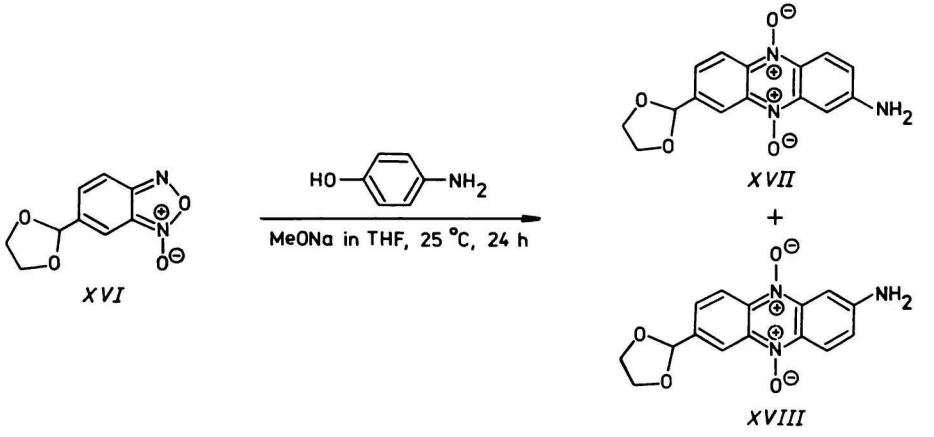


XIII 0.56 % *XIV* 0.84 %

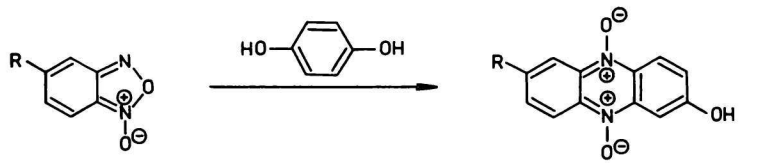
Other examples of syntheses of quinoxaline 1,4-dioxides are [33—37]



In the reaction of *XVI* with 4-aminophenol in the presence of MeONa, isomeric phenazine-5,10-dioxides *XVII* and *XVIII* are formed [38].

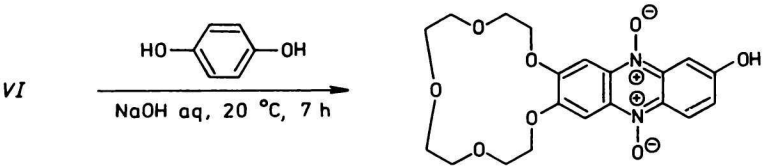


Phenazine-5,10-dioxides result also by cyclocondensation of benzofuroxans with hydroquinone [39].



R = Bu, hexyl, octyl

Similar reaction of crown ether annellated benzofuroxan *VI* gives rise to *XIX* [30].

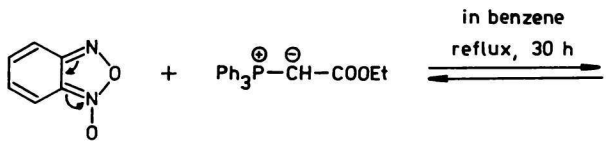


XIX

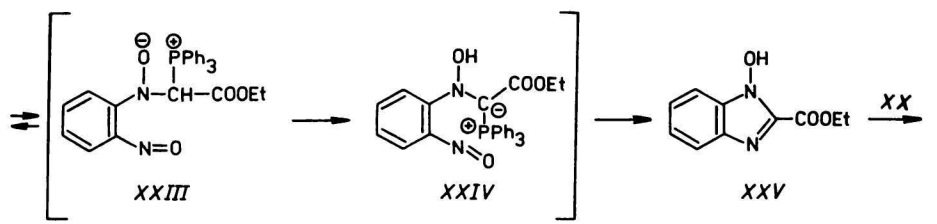
Among reactions of benzofuroxans, which do not lead to quinoxaline dioxides, the following ones will be presented.

In the treatment of benzofuroxan with the phosphorus ylide *XX*, products *XXI* and *XXII* have been obtained [40]. The mechanism involves nucleophilic attack of *XX* on benzofuroxan giving betaine *XXIII* which isomerizes to the ylide *XXIV*. This undergoes intramolecular Wittig reaction to give *XXV*, which with the second molecule of *XX* leads to intermediate *XXVI*, along with EtOH.

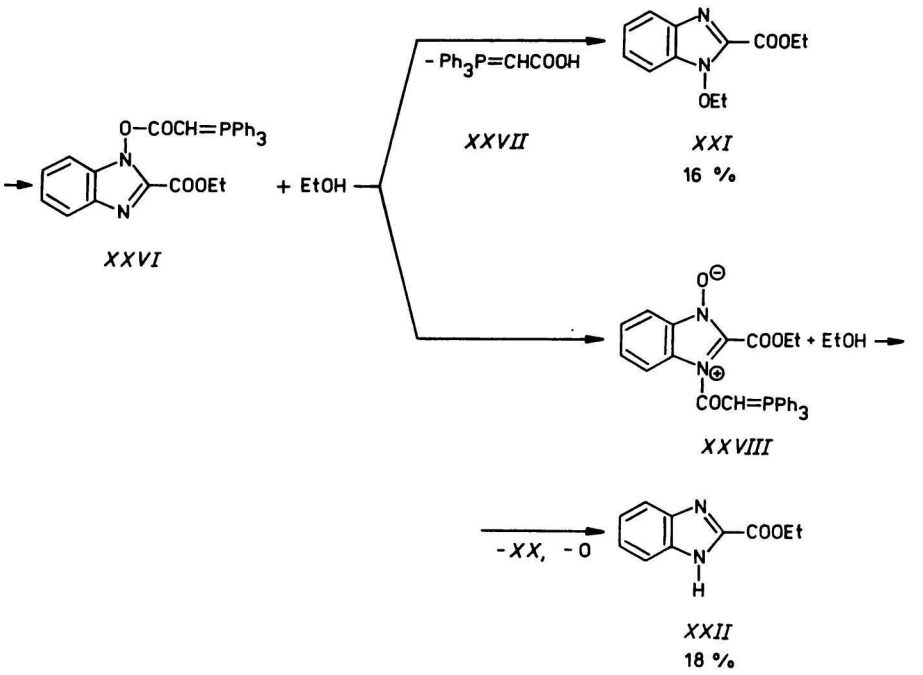
Direct attack of EtOH on *XXVI* furnishes *XXI* (with the loss of *XXVII*), whereas transformation of *XXVI* into *XXVIII* followed by ethanolysis of its amidic bond, and deoxygenation affords *XXII*.



I *XX*

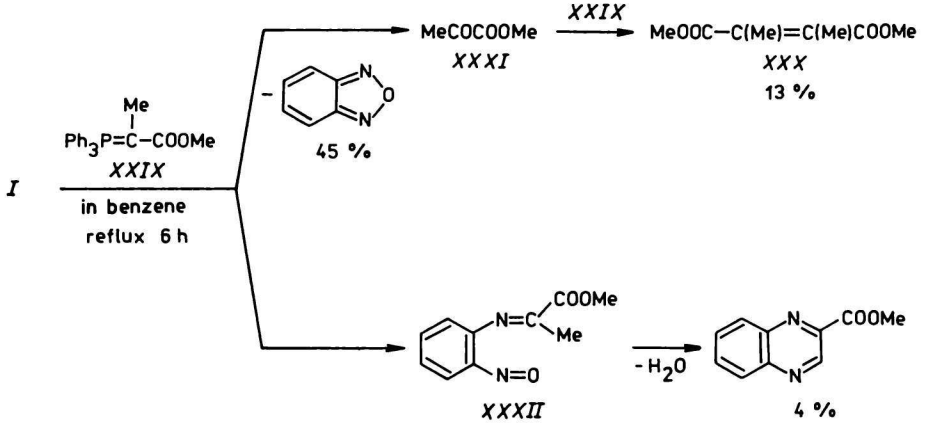


XXIII *XXIV* *XXV*

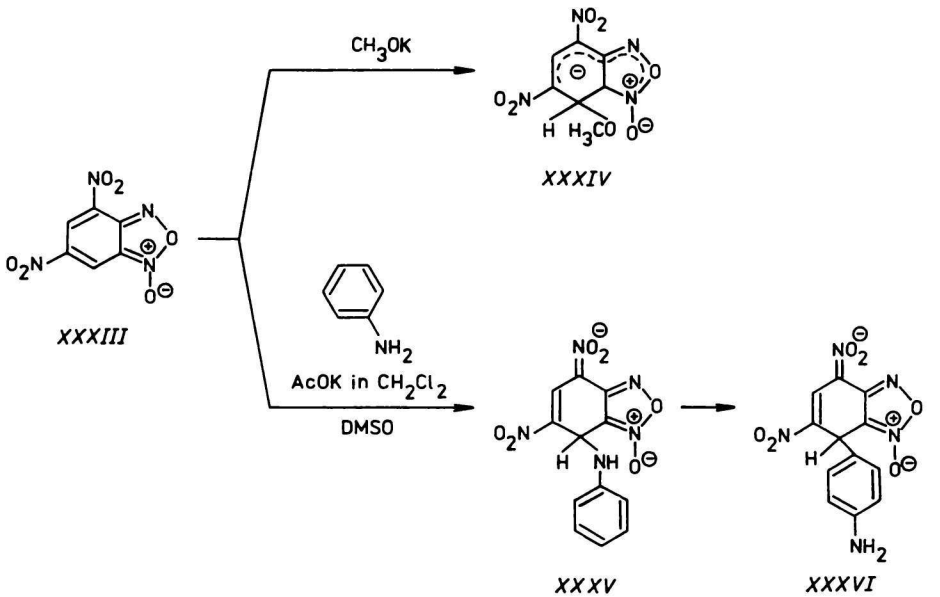


Reaction of benzofuroxan with the ylide *XXIX* gave rise to three products: benzofurazan, diester *XXX* and methyl 2-quinoxalinecarboxylate.

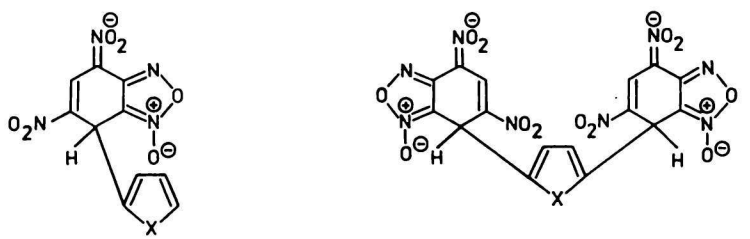
The oxidation of the ylide *XXIX* by benzofuroxan to *XXXI* and further Wittig reaction of *XXXI* with the unreacted ylide *XXIX* gave as the predominant products benzofurazan and *XXX*, while the Wittig reaction of benzofuroxan and *XXIX* led to intermediate *XXXII* undergoing the intramolecular dehydration to methyl 2-quinoxalinecarboxylate.



4,6-Dinitrobenzofuroxan *XXXIII* possesses a superelectrophilic character, even stronger than 1,3,5-trinitrobenzene, which can be seen in easy formation of σ (or Meisenheimer) complexes with a series of nucleophiles; *e.g.* with potassium methoxide a highly explosive *XXXIV* was obtained [41]. *XXXIII* can react with aniline to give *N*-bonded adduct *XXXV*, which undergoes a rapid rearrangement to C-bonded adduct *XXXVI* [42]; similar complexes are produced with *N*-methylaniline and *N*, *N*-dimethylaniline [43].

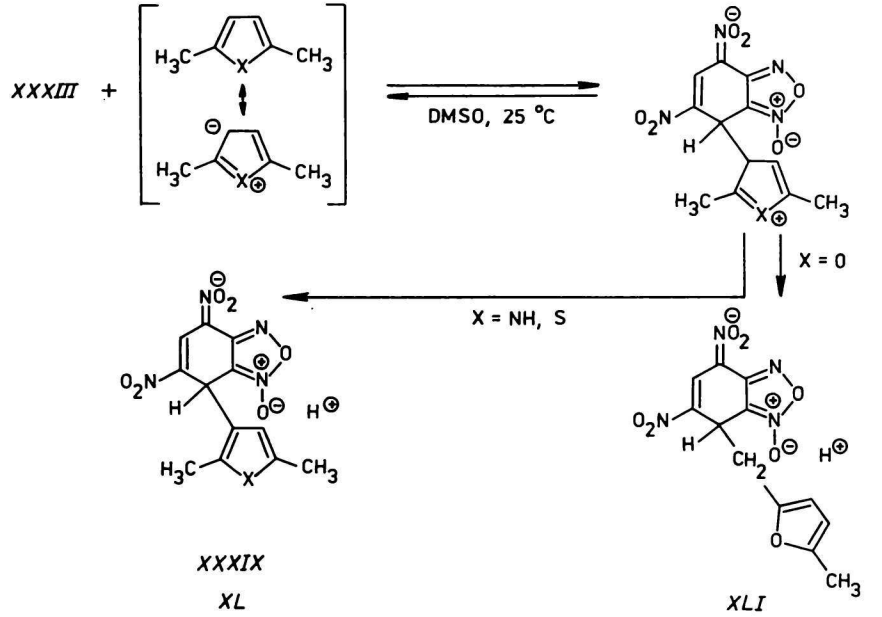


When *XXXIII* reacts with electron excessive heterocycles like pyrrole, thiophene or furan, C-bonded adducts *XXXVII* and *XXXVIII* are formed [42].

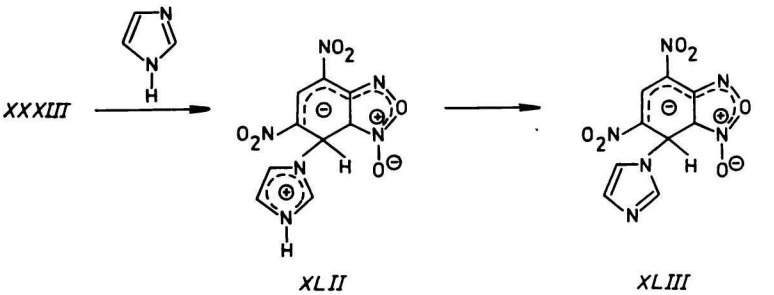


In order to investigate whether *XXXIII* will add to less nucleophilic β-positions of pyrrole, thiophene or furan, its reactions with these heterocycles having blocked α-positions have been accomplished.

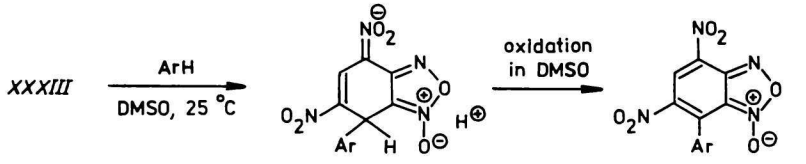
In the case of pyrrole and thiophene the expected products *XXXIX* and *XL* have been obtained, while in the case of 2,5-dimethylfuran the side-chain electrophilic substitution, giving rise to *XLI* took place [42].



Treatment of *XXXIII* with imidazole results in the σ complex *XLII*, which deprotonates to the anionic σ complex *XLIII* [44].

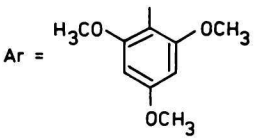


Among nucleophiles reacting with *XXXIII* are even weakly basic ones, *e.g.* 1,3,5-trimethoxybenzene; the formed σ adduct *XLIV* undergoes an oxidation to *XLV* [45].

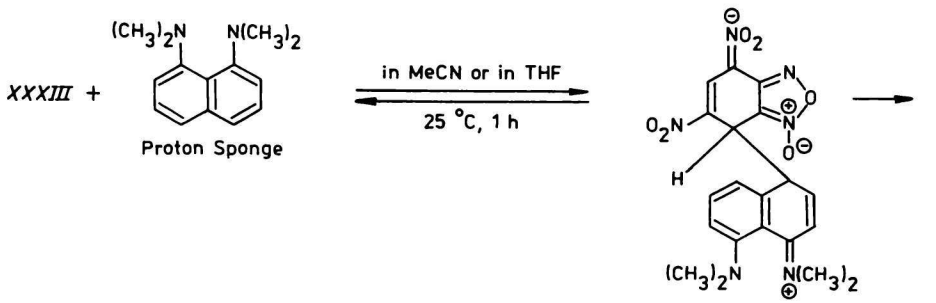


XLIV
100 %

XLV
ca. 50 %

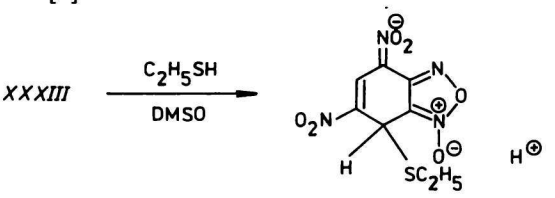


The electrophilic properties of *XXXIII* can be also seen in its reaction with 1,8-bis(dimethylamino)naphthalene (the Proton Sponge), leading to the C-bonded adduct *XLVI*. This experiment provides the first evidence of the nucleophilic character of the Proton Sponge [46].



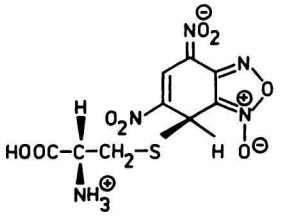
XLVI

XXXIII can also add sulfur bases, *e.g.* the addition of ethanethiol results in the complex *XLVII* [3].

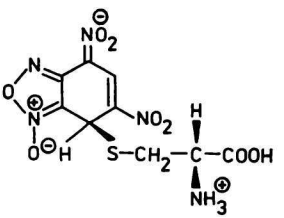


XLVII

In the reaction with L-cysteine two diastereomeric complexes *XLVIIIa* and *XLVIIIb* are formed [3].

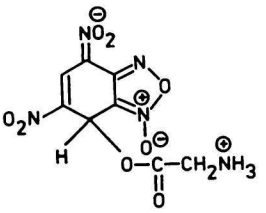


XLVIIIa

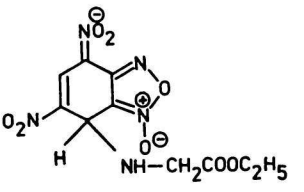


XLVIIIb

It is noteworthy that *XXXIII* adds glycine in DMSO solution to give the oxygen complex *XLIX*, while with glycine ethyl ester the nitrogen complex *L* is obtained [3].

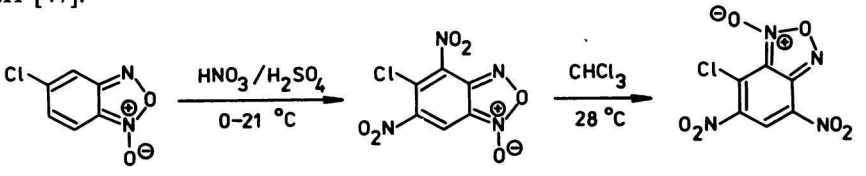


XLIX



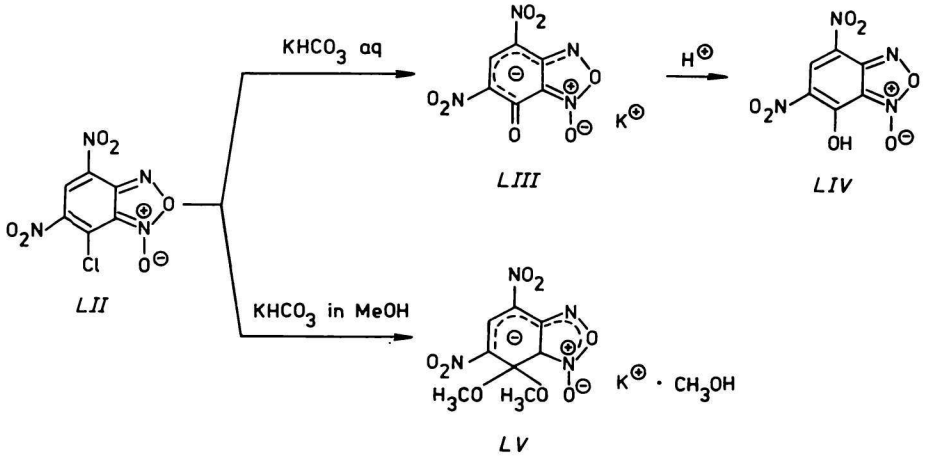
L

Among derivatives of 4,6-dinitrobenzofuroxan one ought to mention 5-chloro-4,6-dinitrobenzofuroxan *LI* resulting in the nitration of 5-chlorobenzofuroxan; *LI* must be stored below 0 °C in order to prevent its isomerization to *LII* [47].

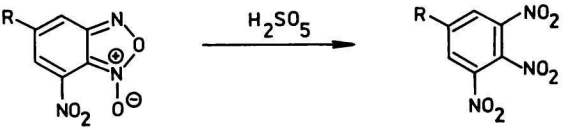


LI *LII*

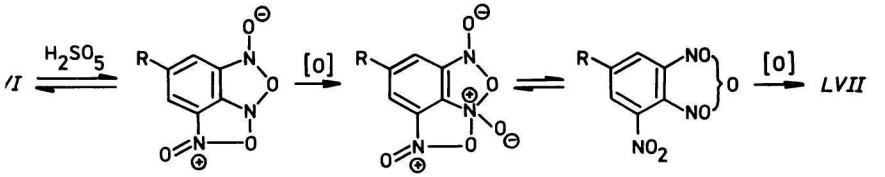
LII reacts with potassium bicarbonate in water to give *LIII*, which can be converted to *LIV*, while with methanol in the presence of potassium bicarbonate *LV* is formed [47].



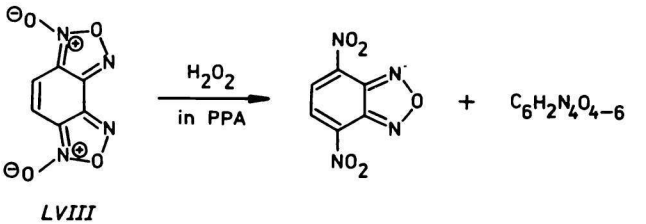
In the study of oxidation of benzofuroxans and their nitro derivatives, the following reaction has been performed [48].



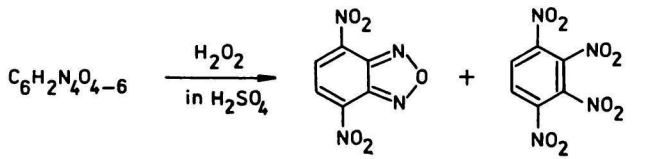
The proposed mechanism of the above oxidation involves separate steps of the oxygen introduction.



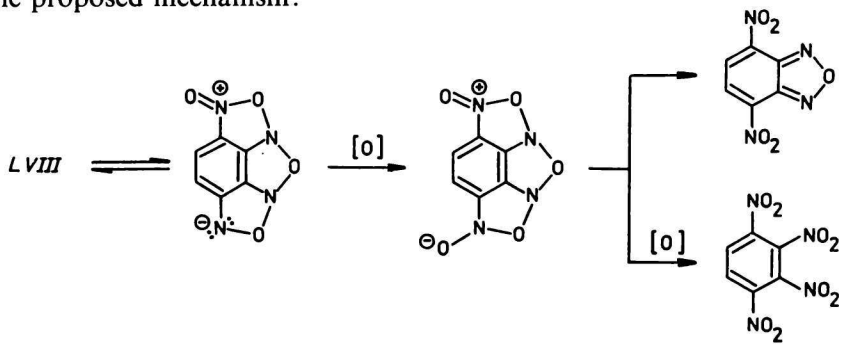
Benzodifuroxan *LVIII* underwent oxidation with H_2O_2 in PPA to give 4,7-dinitrobenzofurazan and unresolved mixture $C_6H_2N_4O_{4-6}$; the latter could be converted into 4,7-dinitrofurazan and 1,2,3,4-tetranitrobenzene by treatment with H_2O_2 in sulfuric acid [49].



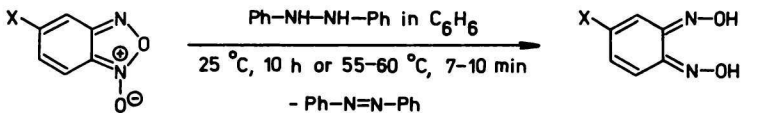
LVIII



The proposed mechanism:

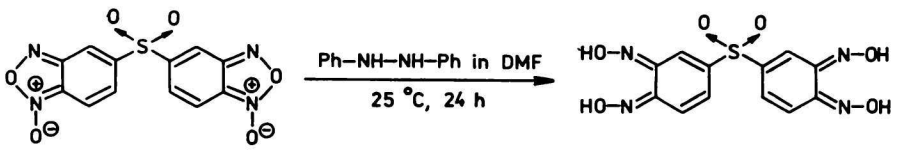


On the other hand, reduction of benzofuroxans gives rise to *o*-quinone dioximes; in these reactions hydrazobenzene showed to be a convenient reducing agent [50].



X = H, Cl, Br

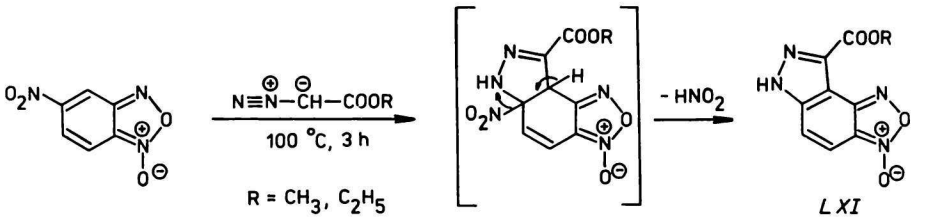
In the similar procedure from bis-benzofuroxan *LIX* tetraoxime *LX* was obtained.



LIX *LX*

65 %

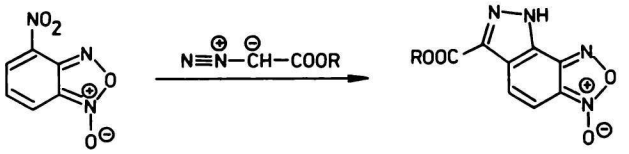
The reaction of 5-nitrobenzofuroxan with diazoacetates resulting in pyrazolobenzofuroxans *LXI* proceeds *via* 1,3-dipolar cycloaddition, followed by elimination of nitrous acid [51].



LXI

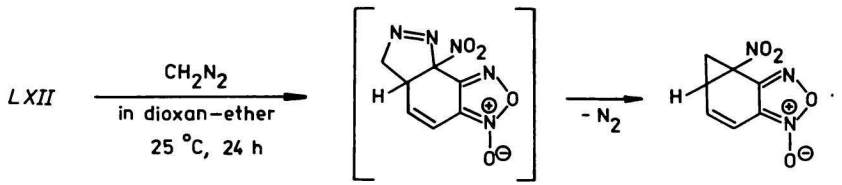
R: CH_3 (82 %), C_2H_5 (85 %)

Similar reaction of 4-nitrobenzofuroxan *LXII* affords pyrazolobenzofuroxans *LXIII* [51].



LXII *LXIII*

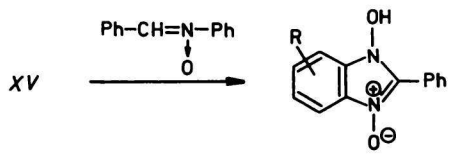
Treatment of 4-nitrobenzofuroxan with diazomethane gives rise to *LXIV* formed presumably *via* the 1,3-cycloadduct *LXV*, undergoing the loss of nitrogen [52].



LXV *LXIV*

20 %

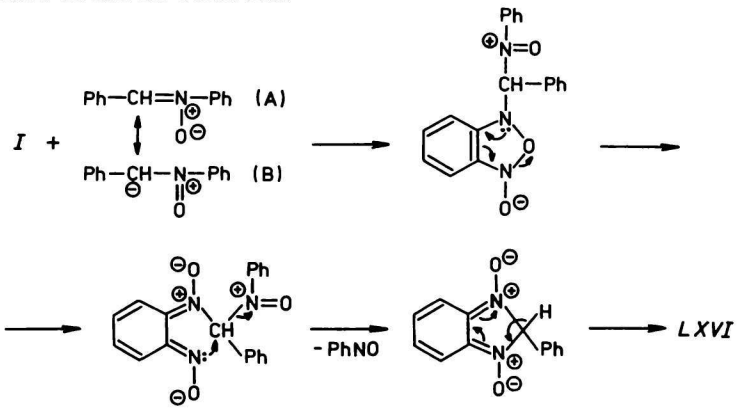
In the reaction of benzofuroxans *XV* with nitrones, a novel ring transformation to benzimidazoles *LXVI* takes place [53].



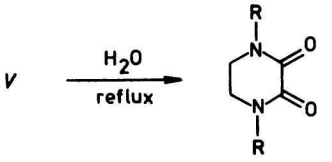
LXVI

The reaction proceeds probably through the initial attack of the carbanion atom of B on the nitrogen atom of A, followed by rearrangement and elimination of nitrosobenzene.

It is noteworthy that no 1,3-dipolar cycloaddition reaction of nitrones onto benzofuroxans could be observed.



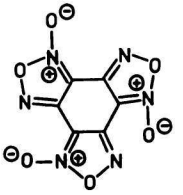
Studying the reactivity of furoxanopiperazines the hydrolysis of *V* resulting in piperazinediones *LXVII* was performed [26].



LXVII

Physical properties

In the investigation of physical properties of benzofuroxans and their derivatives, ^{1}H NMR data for *XXXIX*, *XL*, and *XLI* [42], *XLII* [44], *XLVII*, *XLVIIIa*, and *XLVIIIb* [3], *XXXIII*, *LIII*, *LIV*, and *LV* [47], as well as ^{1}H and ^{13}C NMR data for *V* [26], *LI* and *LII* [47], and ^{13}C NMR data for benzotrifuroxan *LXVIII* [54] are discussed.



LXVIII

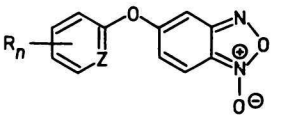
The electrochemical behaviour of benzofuroxan on bare platinum as well as on platinum surfaces covered by heavy metal monolayers deposited at underpotentials was studied. Thallium, lead, and bismuth adsorbates were found to markedly catalyze the reduction of benzofuroxan [55].

Fused furoxans are often explosive [56], *e.g. XXXIV* [41], *XXXV—XL* [42], *XLVIIIa* and *XLVIIIb* [3], *LVIII* [49] possess such properties; working up conditions for *I* [57] and *XXXV—XL* [42] are described.

Biological activity

In the study of inhibition of nucleic acid synthesis by nitrobenzofuroxans, complexes of 4,6-dinitrobenzofuroxan with thiols *XLVII*, cysteine *XLVIII* and amino acids have been obtained and their properties presented [3, 4].

Compounds *III* [1] and *LXIX* [2] exhibit herbicidal activity, whereas crown annellated benzofuroxans *IV* and *LXX* are complexing agents and intermediates for pharmaceuticals [23].

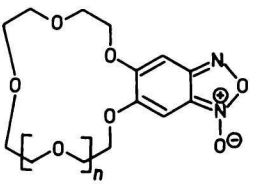


LXIX

Z = CH, CR, N

R = NO_2, halo, cyano, (halo)alkyl

n = 1, 2



LXX

n = 1–8

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