FUSED FURAZANS

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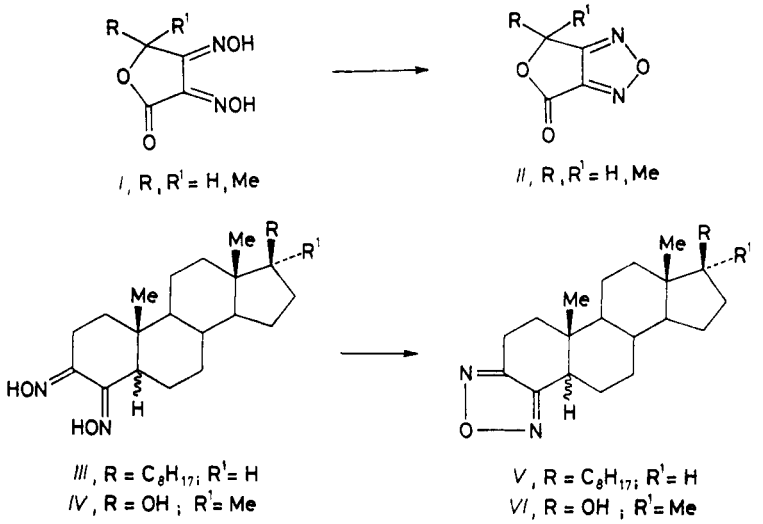
1. INTRODUCTION

As a continuation of our work concerning 1,2,5-heteradiazoles (refs[1-6]), the present paper deals with fused furazans – their syntheses, chemical reactivity and properties.

2. SYNTHESES

Among a great variety of synthetic approaches to fused furazans (refs[7-11]) there ought to be described the reaction of dioximes *I* with thionyl chloride affording furo[3,4-*c*]furazan *II* (ref.[12]).



I, R, R¹ = H, Me

II, R, R¹ = H, Me

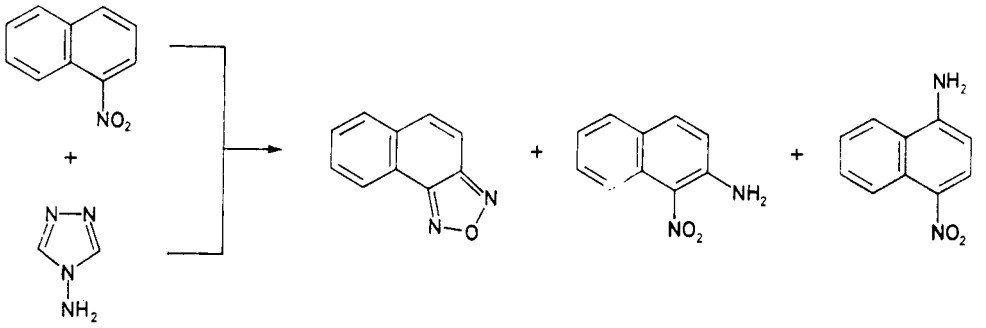
III, R = C_8H_{17}; R¹ = H
IV, R = OH ; R¹ = Me

V, R = C_8H_{17}; R¹ = H
VI, R = OH ; R¹ = Me

SCHEME 1

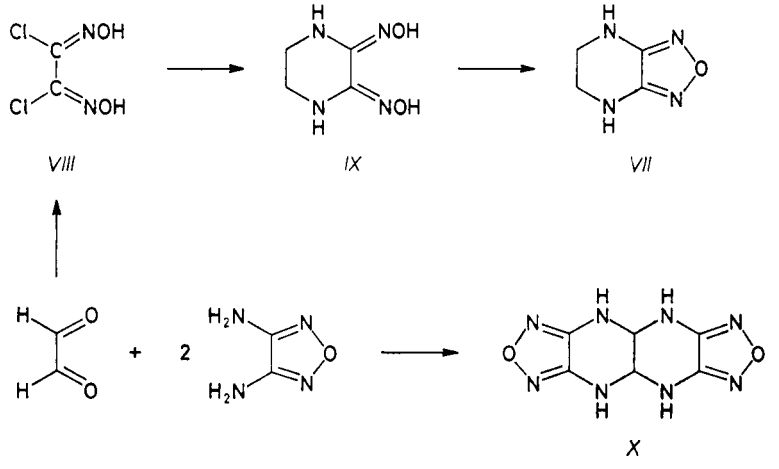
Also from dioximes *III* and *IV* upon heating with potassium hydroxide in ethylene glycol steroidal furazans *V* and *VI* were obtained (refs[13–15]) (Scheme 1).

The reaction of 1-nitronaphthalene with 4-amino-1,2,4-triazole, in the presence of potassium tert-butoxide leads to 1,2-naphthofurazan along with 1-nitro-2--naphthaleneamine and 4-nitro-1-naphthaleneamine (ref.[16]) (Scheme 2).



SCHEME 2

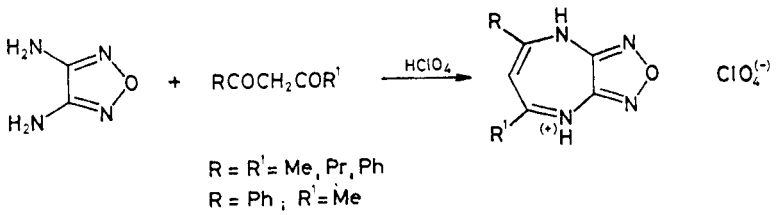
To furazan systems fused with saturated nitrogen heterocycles belongs *VII*. In the synthesis of this compound, the starting glyoxal was oximated and chlorinated to give dichloroglyoxime *VIII* converted by treatment with ethylenediamine into 2,3--piperazinedione oxime *IX*, which underwent cyclodehydratation to *VII* (ref.[17]). In this reaction also N,N'-disubstituted ethylenediamines can be used (ref.[18]).



SCHEME 3

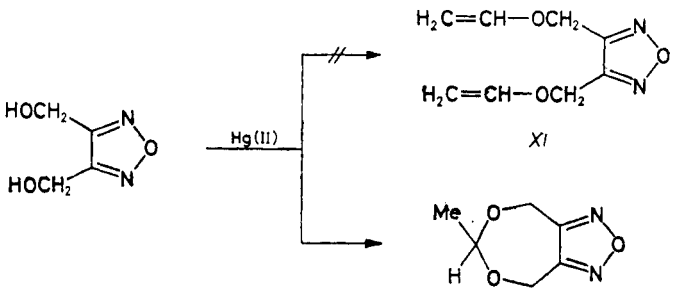
The treatment of glyoxal with 3,4-diaminofurazan gave rise to 1 : 2 condensation product *X* (ref.[12]) (Scheme 3).

An example of the synthesis of fused furazan systems from diaminofurazan and 1,3-diketones is the following process (ref.[19]) (Scheme 4).



SCHEME 4

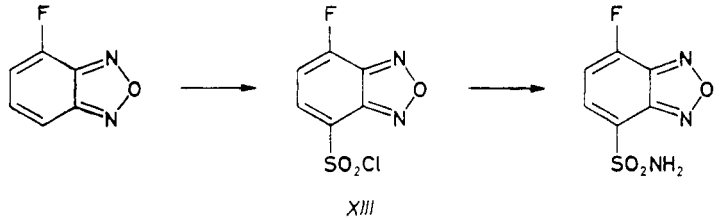
In the reaction of 2,3-dihydroxymethylfurazan with vinyl acetate, in the presence of mercury(II) instead of the expected diether *XI*, the furazanodioxepane *XII* was formed (ref.[20]). An attempted synthesis of *XII* from the same starting material, by an alternative route, using acetylene and cadmium diacetate, failed (ref.[21]) (Scheme 5).



SCHEME 5

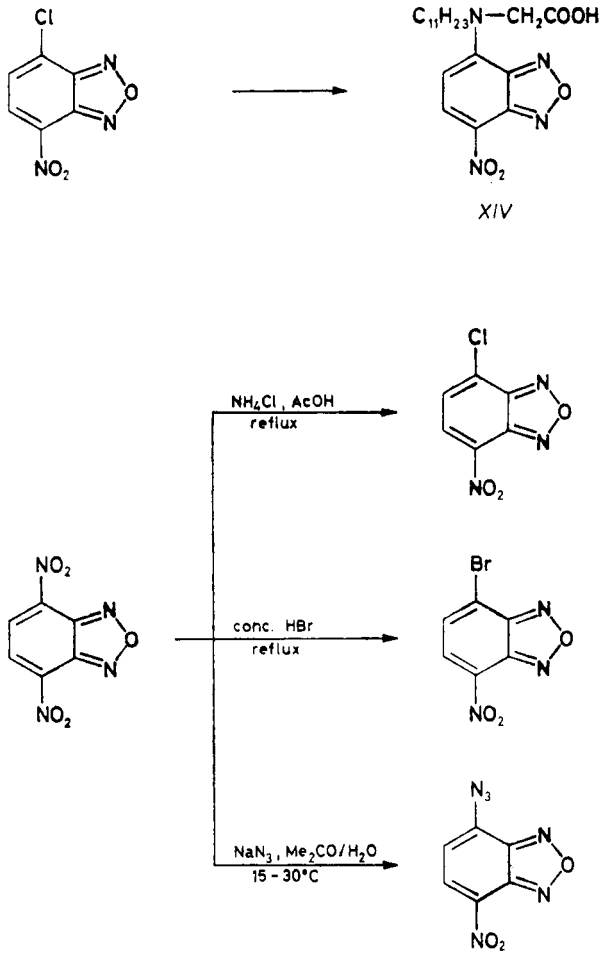
3. CHEMICAL REACTIVITY

In the study of chemical properties of benzo-fused furazans (refs[22-24]), as an example of electrophilic substitution can serve the reaction of 4-fluorobenzofurazan with chlorosulfonic acid, affording sulfochloride *XIII*, which was converted by aqueous ammonia into the corresponding sulfonamide (ref.[25]) (Scheme 6).



SCHEME 6

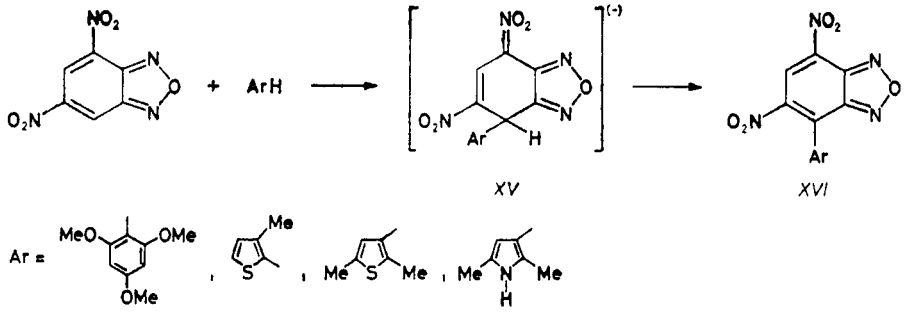
The treatment of 4-chloro-7-nitrobenzofurazan with N-undecylglycine, carried out in ethanol gives rise to *XIV*, (ref.[26]). In investigation of chemical properties of 4,7-dinitrobenzofurazan replacement of one of nitro groups have been performed (refs[27-30]) (Scheme 7).



XIV

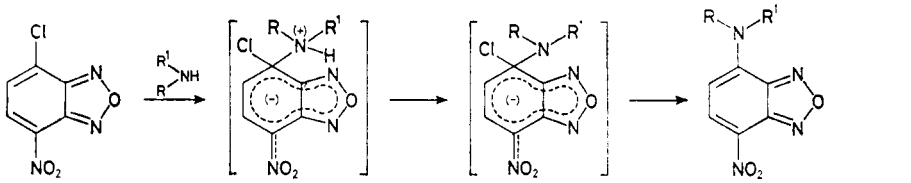
SCHEME 7

4,6-Dinitrobenzofurazan as a strong electrophile reacts with numerous nucleophiles, even weakly basic ones, for instance with 1,3,5-trimethoxybenzene to give σ-adducts *XV* undergoing a smooth oxidation to 7-arylfurazans *XVI* (refs[31-38]) (Scheme 8).



SCHEME 8

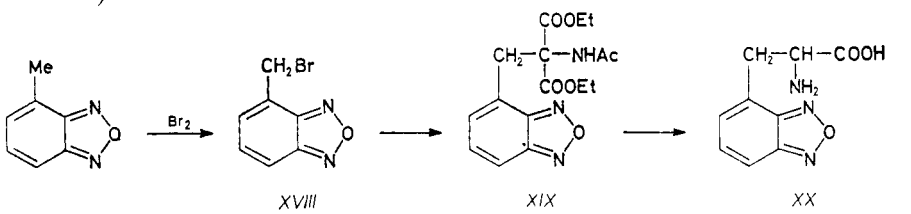
The reaction of 4-chloro-7-nitrobenzofurazan with amines proceeds by the addition-elimination mechanism, via a σ-adduct formed the primary σ'-adduct to afford *XVII* (ref.[39]). In the case of weakly nucleophilic amines, for instance nitroanilines, neither chloro- nor methoxynitrobenzofurazans give good results, and then a super-electrophilic 4-fluoro-7-nitrobenzofurazan must be used (ref.[39]) (Scheme 9).



XVII a, R = H ; R' = alkyl, allyl, aryl
XVII b, R, R' = alkyl, allyl

SCHEME 9

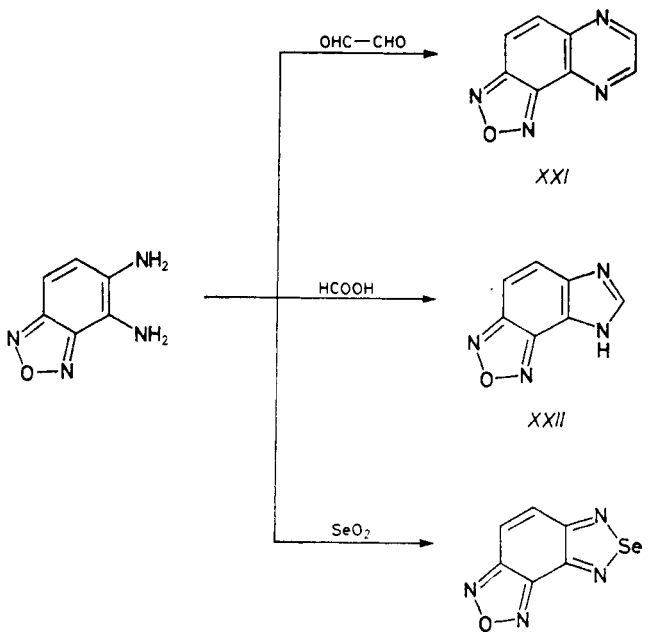
An example of the reactivity of the methyl substituent in benzofurazan system is the bromination of 4-methylbenzofurazan resulting in bromomethyl derivative *XVIII*; this undergoes substitution with diethyl acetamidomalonate to give *XIX*, which upon hydrolysis and decarboxylation leads to alanine derivative *XX* (ref.[40]) (Scheme 10.)



XVIII *XIX* *XX*

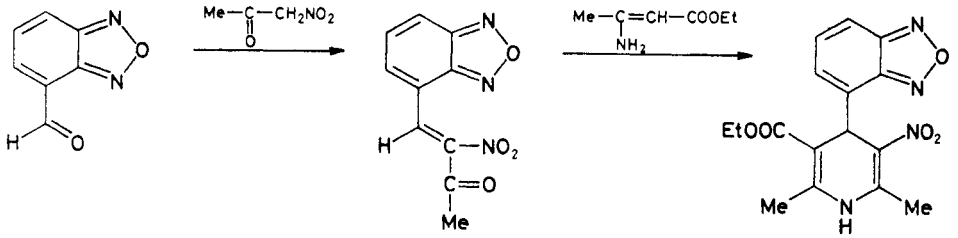
SCHEME 10

There ought also to be mentioned here the cyclocondensation of 4,5-diaminobenzofurazan with glyoxal, formic acid and selenium dioxide giving rise to tricyclic compounds *XXI*–*XXIII* (ref.[41]) (Scheme 11).

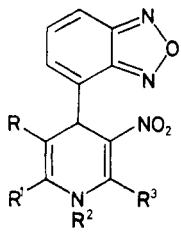


XXI XXII XXIII

SCHEME 11

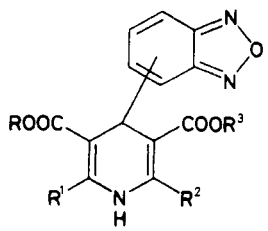


XXIV XXV



XXVI

R ◻ H, alkyl, CF_3, NO_2, COOH
R^1, R^3 = H, alkyl
R^2 = alkenyl, alkynyl, cycloalkyl, heteroaryl



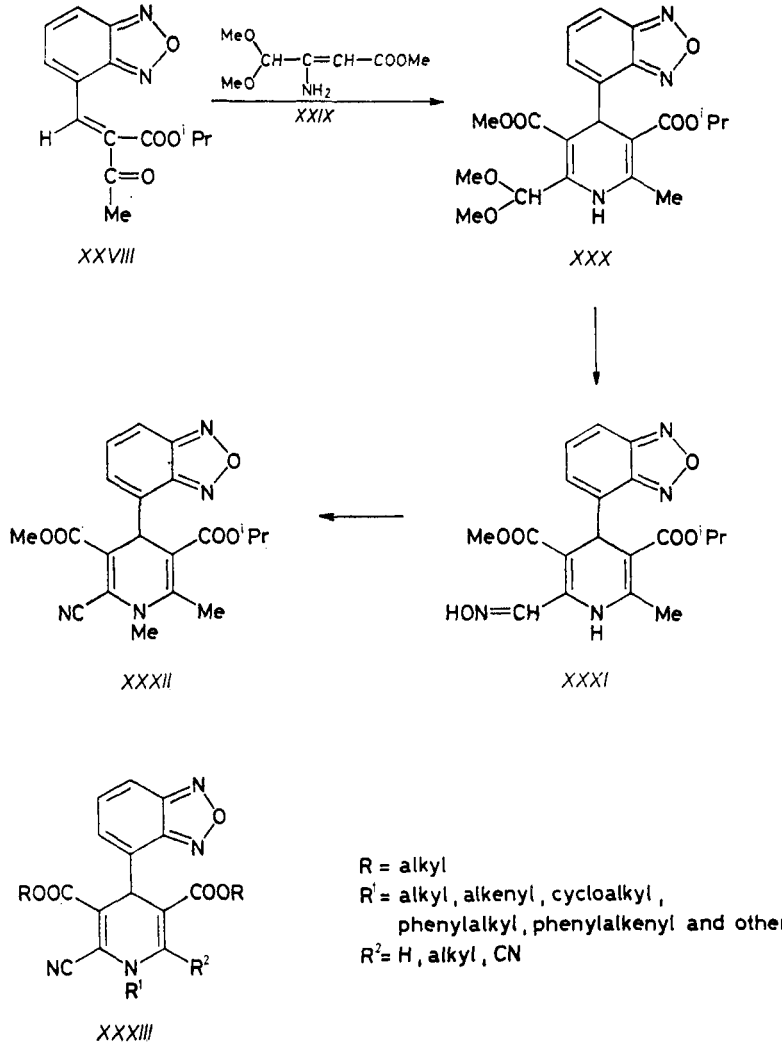
XXVII

R, R^1, R^3 = alkyl
R^2 = CH_2OH, CHO, CN, CF_3

SCHEME 12

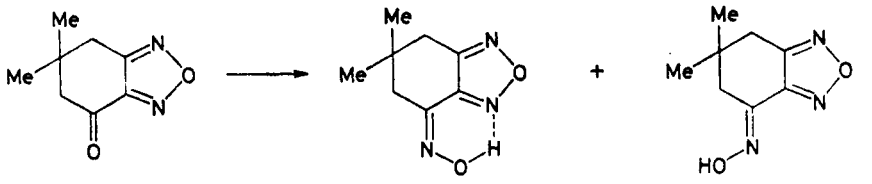
As an example of the reactivity of formylbenzofurazan can serve its reaction with acetylnitromethane leading to *XXIV*, converted by ethyl 3-aminocrotonate into 1,4-dihydropyridine *XXV*; on this way dihydropyridines *XXVI* were obtained (ref.[42]). Similar reaction afforded *XXVII* (ref.[43]) (Scheme 12).

The cyclocondensation of *XXVIII* with the ester *XXIX* gives *XXX*, which upon hydrolysis and oximation affords *XXXI*, converted by dehydratation and methylation into *XXXII*; by the same procedure a number of dihydropyridines *XXXIII* was synthesized (ref.[44]) (Scheme 13).



SCHEME 13

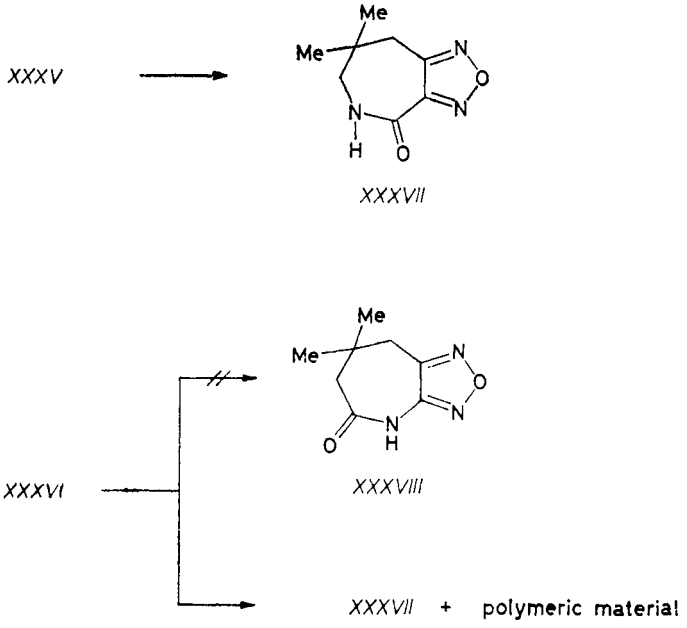
In the study of the reactivity of *XXXIV* its oximation leading to a mixture of (*Z*)- and (*E*)-oximes, *XXXV* and *XXXVI* respectively, was performed (ref.[45]) (Scheme 14).



XXXIV *XXXV* *XXXVI*

SCHEME 14

In order to corroborate structure of *XXXV* and *XXXVI*, their Beckmann rearrangement and characterization of the resulting amides was accomplished. The rearrangement was made with phosphorus pentachloride at room temperature in dry ether (ref.[46]). It was observed that (*Z*)-oxime *XXXV* was converted into the expected azepinone *XXXVII*, while the reaction of isomeric (*E*)-oxime *XXXVI* resulted only in a small amount of *XXXVII*, the main product being unidentified polymeric material (Scheme 15).

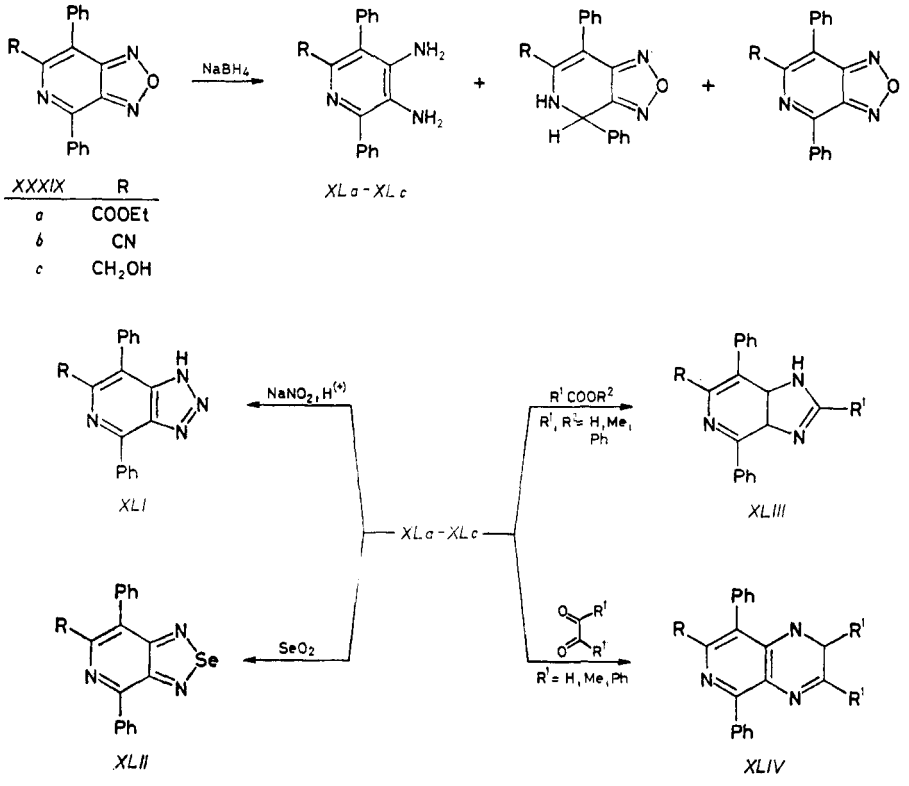


SCHEME 15

The formation of the azepinone *XXXVII* from the (*E*)-oxime *XXXVI* is due to a partial *E* to *Z* isomerization of starting oximes. The CNDO/2 calculations of

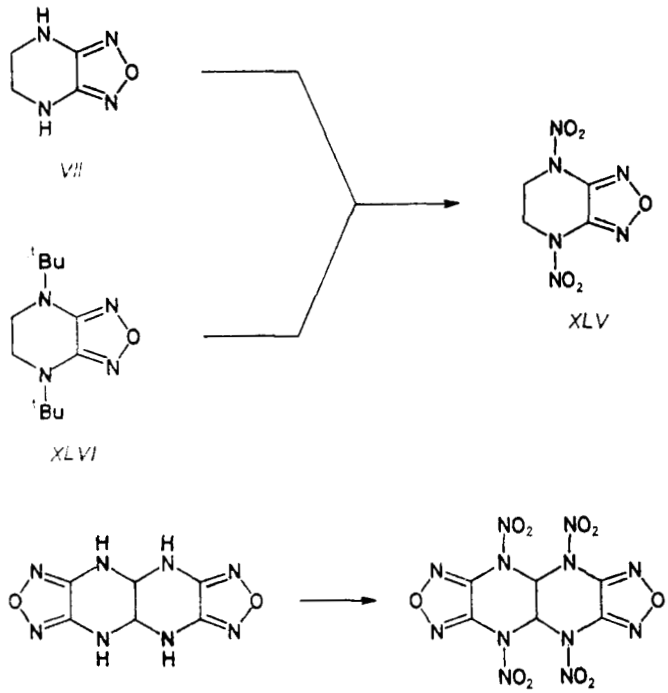
oximes *XXXV* and *XXXVI* have shown that *XXXV* is more stable than *XXXVI*, this fact being probably due to its intramolecular hydrogen bond (ref.[47]).

Investigating heterocycle-fused furazans, the reduction of 4,7-diphenylfurazano-[3,4-*c*]pyridines *XXXIXa*–*XXXIXc* was performed; the results are dependent on reaction conditions (ref.[48]). Obtained 3,4-diamino-2,5-diphenylpyridines *XLa*–*XLc* were converted into the fluorescent pyridine-fused heterocycles *XLI*–*XLIV* (Scheme 16).



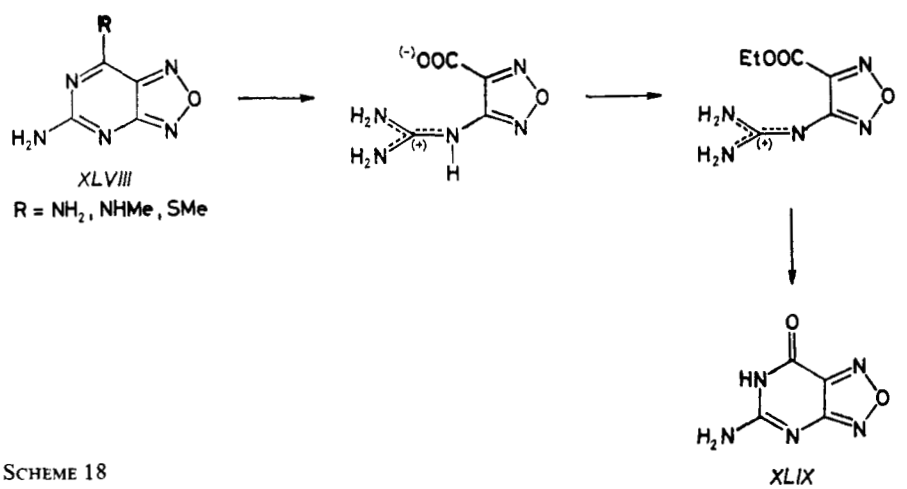
SCHEME 16

The nitration of *VII*, performed with nitrogen pentoxide in nitric acid or with nitric acid in trifluoroacetic anhydride results in N,N'-dinitro derivative *XLV* which can be also obtained from N,N'-ditert-butyl derivative *XLVI* by nitrolysis of tert-butyl groups with nitrogen pentoxide in nitric acid; similar nitration of *X* affords tetranitro derivative *XLVII* (refs[18,49,50]) (Scheme 17).



SCHEME 17

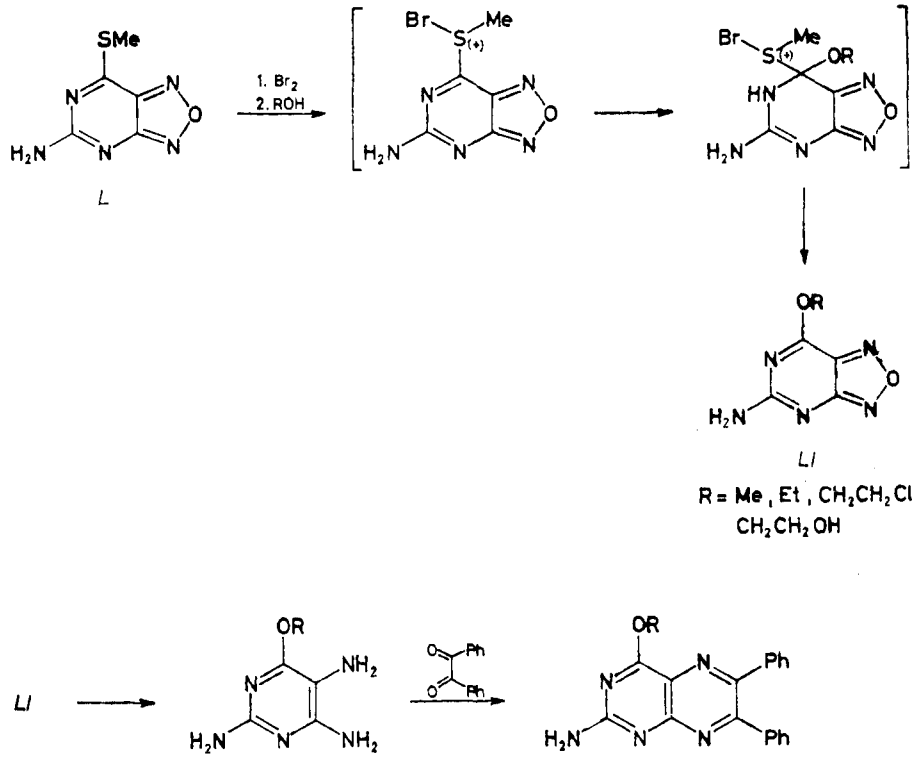
It was observed that the treatment of 5-aminofurazano[3,4-*d*]pyrimidines *XLVIII* with either acid or base led to the ring opening of the pyrimidine moiety with the formation of 4-guanidino-3-furazanocarboxylic acid, the esters of which could be recyclized into *XLIX* by aqueous base (ref.[51]) (Scheme 18).



SCHEME 18

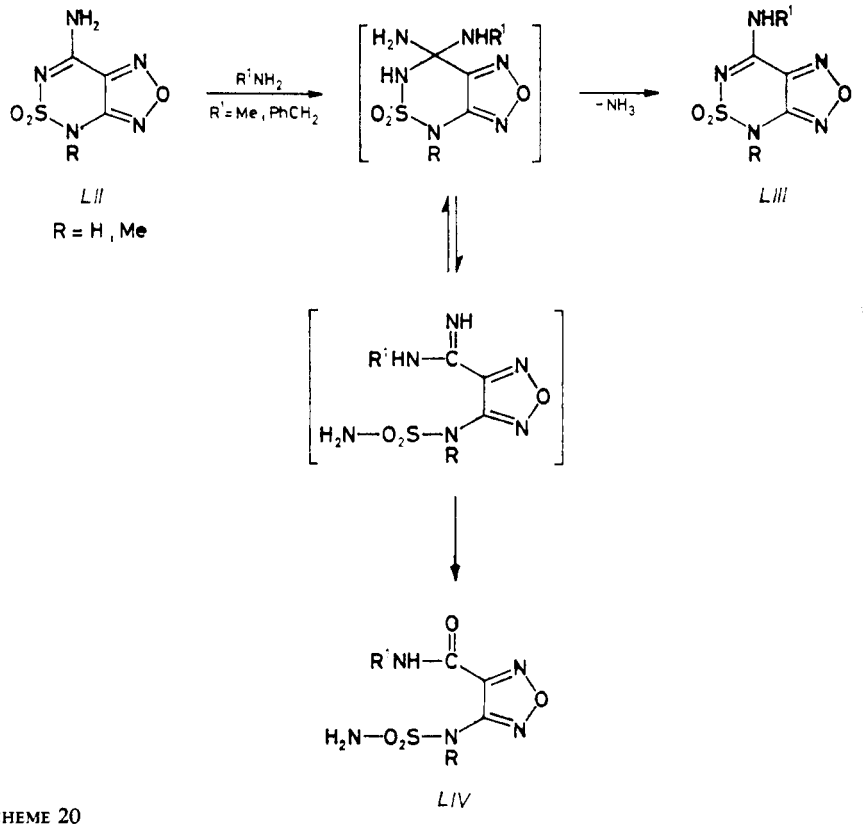
Among pyrimidine-fused furazans, methylthio derivative *L* showed to be a convenient substrate for the introduction of alkoxy groups into the 7 position of furazanopyrimidines; for this purpose *L* was treated with bromine in the appropriate alcohol to give *LI* in yields up to 90%. The proposed mechanism involves addition--elimination sequence (refs[51,52]).

Resulting *LI* treated with hydrogen, suffered a hydrogenolysis of the furazan ring, leading to 6-alkoxy-2,4,5-triaminopyrimidines, which could be condensed in situ with benzil to give 2-amino-4-alkoxypteridines (ref.[52]) (Scheme 19).



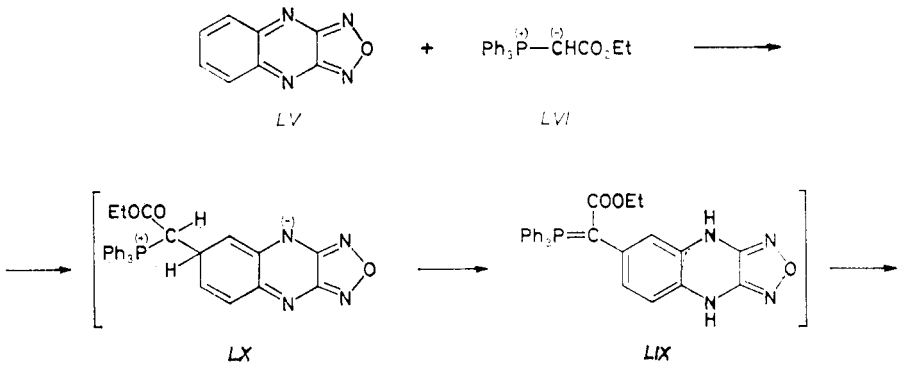
SCHEME 19

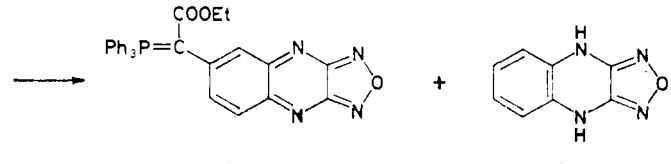
In the study of thiadiazinedioxide-fused furazans *LII*, their reactions with methylamine and benzylamine have been performed. At room temperature there was observed the nucleophilic displacement of the amino group, leading to alkylamino derivative *LIII*, while at 100°C (sealed tube), besides this reaction, also cleavage of the thiadiazine ring to *LIV* took place (ref.[53]) (Scheme 20).



SCHEME 20

It was established that the reaction of *LV* with phosphorus ylide *LVI* in CH_2Cl_2 at room temperature affords transylidation product *LVII* along with dihydro derivative *LVIII* (ref.[54]) (Scheme 21).



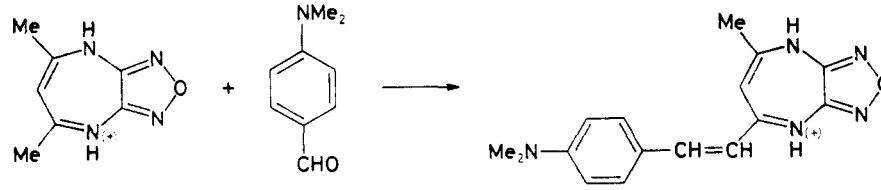


LVII *LVIII*

SCHEME 21

In this procedure *LV* undergoes a nucleophilic attack of the ylide *LVI* at the 6-position to give the unisolable ylide *LIX* via intermediate *LX*. The subsequent oxidation of *LIX* by atmospheric oxygen leads to the ylide *LVII*, very stable due to its long conjugated system (Scheme 21).

Methine dye *LXI* (ref.[19]) (Scheme 22) was prepared by condensation of *p*-dimethylaminobenzaldehyde with 5,7-dimethyl-1,4-diazepinofurazan in acidic media.

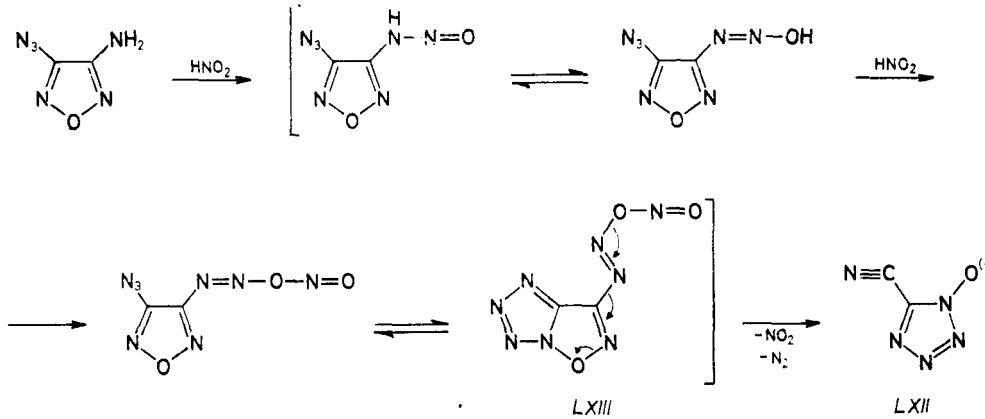


LXI

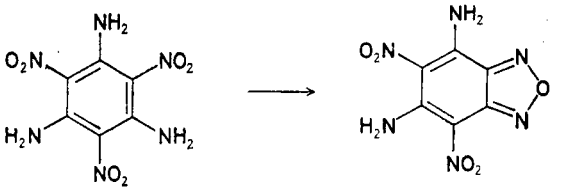
SCHEME 22

Describing fused furazans an attention ought to be paid to a rather complicated conversion of amidoazidofurazan by nitrous acid into the cyanotetrazole derivative *LXII* proceding via bicyclic intermediate *LXIII* (ref.[55]).

There may be also mentioned formation of benzofurazan derivative *LXIV* by decomposition of the strong explosive triaminotrinitrobenzene under controled conditions (ref.[56]) (Scheme 23).



LXIII *LXII*



LXIV

SCHEME 23

4. PHYSICAL PROPERTIES

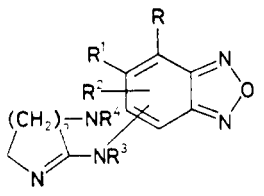
The UV-VIS and IR spectra (refs[57–59]) of a series of *XVIIa* and their electrochemical properties (refs[39,60,61]) were analysed. Magnetic circular dichroism spectra of benzofurazan (ref.[62]), as well as ^{1}H NMR spectra of σ-adducts of benzofurazan (ref.[33]), of furazanopiperazines (ref.[38]) and of steroidal furazans (ref.[13]) were discussed.

Describing fused furazans, one ought to notice the explosive properties of nitraminofurazans *XLV* and *XLVII* (refs[17,18,63]) which could be predicted by calculations (refs[64,65]). Similarly σ-adducts *XV* of 4,6-dinitrobenzofurazan (ref.[33]) as well as those formed with other nucleophiles are sensitive explosives, difficult to handle under normal conditions (refs[30,36,66,67]).

5. BIOLOGICAL ACTIVITIES

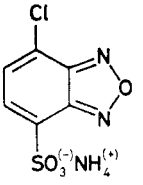
Fused furazans exhibit various biological activities, for instance species bearing benzofurazanyl system, e.g. *LXV* are cardiotonics (refs[68,69]). Chlorobenzofurazan *LXVI* is used to label glutathione as a model thiol peptide, and bovine serum albumin or other thiol containing proteins (ref.[7]). Glycine and serine derivatives *LXVII* serve as radiosensitizers (ref.[23]).

Compounds *LXVIII* possessing pyrimidine-fused furazan system are vasodilators applied in treatment of hypertension and angina pectoris as well as asthma and bronchitis (ref.[70]) (Scheme 24).

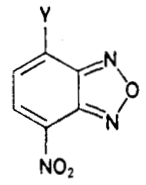


LXV

R, R^1, R^2 = H, alkyl, alkoxy, halo, OH, CN
R^3 = H, alkyl, cycloalkyl
R^4 = H, alkyl
n = 1, 2

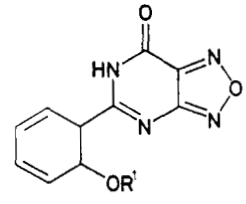


LXVI



LXVII

Y = NH—CH_2COOH, NHCH(—CH_2OH)—COOH



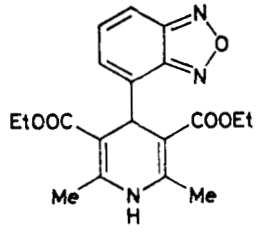
LXVIII

R^1 = C_{1-4}alkyl, C_{2-6}alkenyl, C_{4-5}cycloalkyl

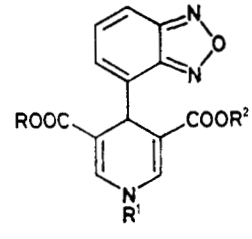
SCHEME 24

Benzofurazans bearing dihydropyridine moieties are useful drug intermediates (refs[71-73]) as well as therapeutics in circulatory system disorders (refs[8-10,74-76]).

In this connection should be mentioned a cardiac vasodilator *XXVI* (ref.[42]). Calcium antagonists *LXIX* (ref.[77]), as well as *XXXIII* (ref.[44]) and *LXX* (ref.[78])



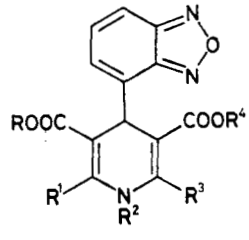
LXIX



LXX

R_1, R^2 = Me, ^{i}Pr, Bu, ^{i}Bu, cyclopentyl

R^1 = C_{1-6}alkyl



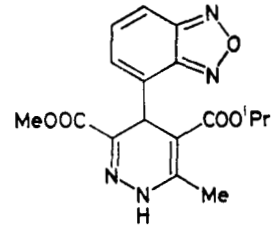
LXXI

R = (un) substituted alkyl

R^1, R^3 = H alkyl

R^2 = H, (un) substituted alkyl

R^4 = substituted alkyl



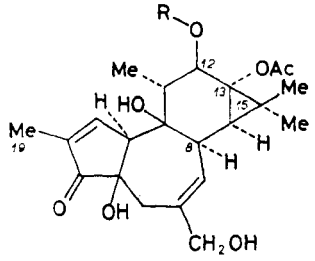
LXXII

SCHEME 25

show calcium channel blocking properties. Benzofurazanyldihydropyridines *LXXI* (ref.[79]) and *LXXII* (refs[80,81]) are useful coronary vasodilators and antihypersensitive agents (Scheme 25).

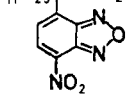
A derivative of phorbol esters *LXXIII* is equipotent with 12-O-tetradecanoyl phorbol 13-O-acetate (TPA) as activator of protein kinase C and phospholipid metabolism (refs[26,82,83]).

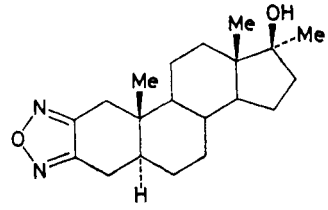
Administration of steroidal furazan *VI* (refs[13-15]) to rats shows its anabolic activity, however lower than that of furazabol *LXXIV* (ref.[13]) (Scheme 26).



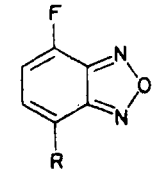
TPA, R = $C_{13}H_{27}$—CO

LXXIII, R = $C_{11}H_{23}N$—CH_2—CO





LXXIV



LXXV

R = SO_3Ph, SO_3CH_2Ph, SO_2Cl, $SO_2NR^1R^2$ (R^1, R^2 = H, alkyl)

SCHEME 26

6. APPLICATIONS

In the study of electrochemical properties of *XVIIa* was observed that the polarographic reduction waves are well reproducible, and can be of use in the qualitative and quantitative analysis of amines. In this procedure, amines were reacted with 4-chloro-7-nitrobenzofurazan to give aminofurazans *XVIIa*, which, after being separated, were determined by polarography (refs[60,84]).

Amines can also be determined by an alternative method, utilizing strong fluorescent properties of *XVIIa*, formed in their reaction with 4-chloro-7-nitrobenzofurazan or with more reactive 4-fluoro-7-nitrobenzofurazan (refs[39,85-90]). As fluorescent indicators of amines and thiols can also serve derivatives *LXXV* (ref.[25]) (Scheme 26).

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