SYNTHESIS OF HETEROCYCLIC SYSTEMS ON THE BASIS OF INTRAMOLECULAR NUCLEOPHILIC SUBSTITUTION OF A NITRO GROUP (REVIEW)

G. I. Migachev and V. A. Danilenko

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Literature data on reactions involving intramolecular nucleophilic substitution of nitro groups that lead to new five-, six-, and seven-membered heterorings in various di-, tri-, and polycyclic systems are systematized and correlated. The effect of the conformational structures of the reacting molecules and dipolar aprotic solvents on the reaction and the yields of cyclization products is demonstrated.

The aim of the present review was to examine and systematize condensed heterocyclic systems synthesized on the basis of intramolecular nucleophilic substitution of a nitro group. Studies that examine the data from this point of view have not been made. A number of examples of the synthesis of heterocyclic compounds by means of this reaction have been examined in monographs [1-3] and review papers [4-7]. Insufficient study has been devoted to the reaction, and the results of investigations have not been correlated, although the reaction may be an effective method for the synthesis of many heterocyclic systems.

Reaction Conditions and Factors That Affect Intramolecular Substitution of a Nitro Group

Intramolecular nucleophilic substitution of a nitro group is generally the final step in the preparation of new five-, six-, or seven-membered heterorings in various di-, tri, and polycyclic systems. The nitro group is the most favorable substitutable group in intramolecular nucleophilic substitution as compared with other substituents in the aromatic ring (F, Cl, Br, OCH_3) both because of the accessibility of the corresponding starting nitro compounds and because of the high sensitivity of the nitro group to attack by nucleophiles. The latter may include OH, SH, NH_2, NHAlk, NHAr, COOH, and other groups.

Despite the diversity of the heterocyclic systems obtained and the conditions of their synthesis, there are common principles and factors that affect the reaction.

Inasmuch as it is a bulky substituent, the nitro group is very susceptible to the effect of steric factors. Nitro groups in the ortho position to bulky substituents that deflect them from the plane of the aromatic ring are most readily replaced. Thus in the case of 6,6'-dinitrobiphenyl-2,2'-dicarboxylic acid the nitro group deviates 30.4° from the plane of the benzene ring [8]. Disruption of the conjugation of the nitro group with the aromatic ring evidently facilitates its replacement.

Nucleophilic substitution of a nitro group is facilitated by the activating effect of substituents (most often other nitro groups).

For the successful occurrence of the reaction it is necessary for the molecule of the nitro compound to have (or sufficiently readily assume) a structure with close reaction centers. In the overwhelming majority of known examples the nitro group and the nucleophile are in the ortho position of the aromatic ring or in ortho,ortho' positions of biphenyl derivatives; an intramolecular hydrogen bond that stabilizes the favorable conformation can be formed between the nucleophile and the nitro group in this case [8-10]. On the other hand, intramolecular hydrogen bonds that stabilize conformations with remote reaction centers inhibit and often exclude the reaction. In the latter cases one resorts to changing the solvent and acylation or alkylation of the proton-donor groups in order to carry out the reaction.

Dipolar aprotic solvents ensure higher yields and shorter reaction times for intramolecular substitution of a nitro group than other solvents. Their effect is explained by many

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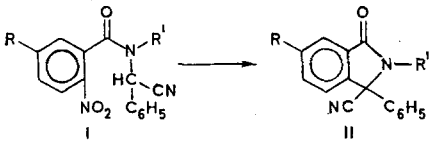
reasons. First, these solvents destroy the intramolecular hydrogen bond that stabilizes the unfavorable conformation with remote reaction centers [11]. Second, even in the absence of bases, they ionize the nucleophilic groups [9]. Third, because of poor solvation in dipolar aprotic solvents, the reactivities of the anions increase. In these solvents the anions act as "true" nucleophiles, whereas in protic solvents their nucleophilicity is markedly reduced because of solvation [12]. Even a weak nucleophile therefore displaces the nitro group vigorously in dipolar aprotic solvents. Fourth, they thoroughly solvate and to an even greater extent polarize the dipolar activated complex [12]. As a result of this, S_NAr reactions, which pass through a strongly polarized transition state, proceed considerably faster than in protic solvents. The subsequent decomposition of the transition state is facilitated by the formation of an energetically more favorable aromatic system.

The number of communications regarding new examples of the synthesis of heterocyclic systems on the basis of intramolecular nucleophilic substitution of a nitro group has increased markedly in connection with the increased use of dipolar aprotic solvents in organic chemistry.

Two-Ring Heterocycles

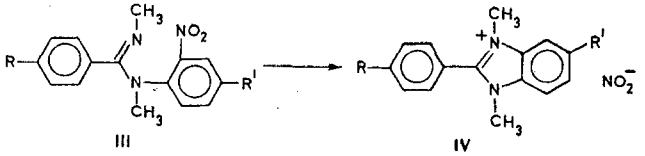
Isoindolines. Isoindolines II were obtained in high yields by treatment of o-nitrobenzamides I with sodium carbonate in alcohol [13, 14]. Cyclization does not take place when Br or CH_3O is present instead of an o-nitro group in starting I.



I II

R = H, CH_3, NO_2; R' = CH_3, $CH_2C_6H_5$, C_6H_5

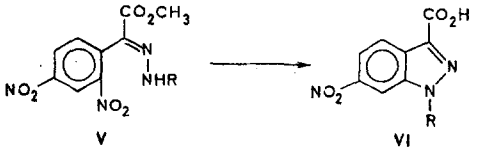
Benzimidazolium Salts. When o-nitrobenzamidines III are refluxed in bromobenzene, the process is accompanied by replacement of the nitro group and the formation of benzimidazolium salts IV. The introduction of a second nitro group in the meta position to the displaceable nitro group significantly facilitates the reaction and increases the yields of salts IV to 100% [15]. The corresponding o-chlorobenzamidines give salts IV in 25% yields in the case of very prolonged refluxing in bromobenzene.



III IV

R = H, NO_2, OCH_3; R' = H, NO_2

Indazoles. 6-Nitro-1-phenylindazole-3-carboxylic acid (VI, R = C_6H_5) was obtained in 96% yield in 1889 by cyclization of hydrazone V (R = C_6H_5) in an alkaline medium [16]. The reaction proceeds more smoothly in the presence of alkali in CH_3OH—DMSO at 70°C [17].

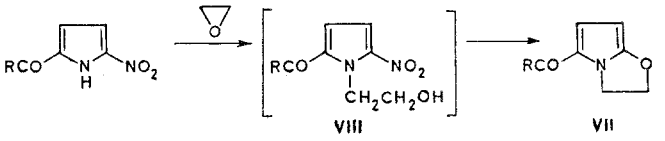


V VI

R = C_6H_5, o-$HO_2CC_6H_5$

Substitution of the bromine atom in the synthesis of indazoles via a similar scheme takes place under more severe conditions [18].

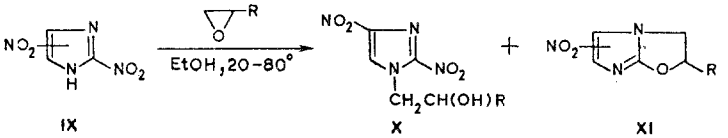
Dihydropyrrolooxazoles. 5-Acyl-2,3-dihydropyrrolo[2,1-b]oxazoles (VII) were isolated in the thermolysis of 2-acyl-5-nitropyrroles and ethylene oxide at 120°C [19]. The reaction proceeds through the intermediate formation of N-(hydroxyethyl) derivatives VIII.



R = H, CH_3, C_3H_7, $C_{17}H_{35}$, C_6H_5

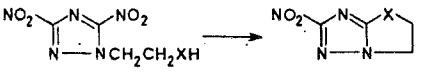
5-Acyl-2,3-hydropyrrolo[2,1-b]oxazole was obtained in high yield from the previously isolated N-(hydroxyethyl) derivative VIII (R = CH_3) with an equimolar amount of NaH in tetrahydrofuran (THF).

Dihydroimidazooxazoles. 2,4-Dinitroimidazoles X and 2,3-dihydroimidazo[2,1-b]oxazoles XI were obtained by condensation of 2,4(5)-dinitroimidazole (IX) with oxiranes (R = H, CH_3, CH_2Cl, CH_2OCH_3, CH_2OH) [20, 21].



IX X XI

Condensed 1,2,4-Triazoles. When a group that is capable of functioning as a nucleophile is present in N-substituted 3,5-dinitro-1,2,4-triazoles XII, the 3-nitro group undergoes intramolecular nucleophilic substitution, and condensed XIII systems are formed [22, 23].



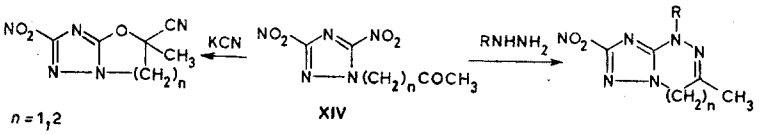
XII XIII

X = O, NH

Compounds of the XII type (X = O) are intermediates in the reaction of 3,5-dinitro-1,2,4-triazoles with alkene oxides in aprotic solvents [24].

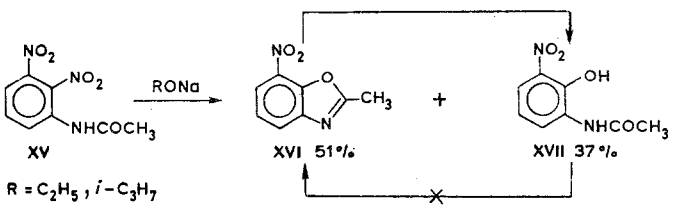
The reaction of 1-methyl-3-nitro-1,2,4-triazol-5-one with epichlorohydrin to give 6-methyl-2-(chloromethyl)oxazolo[2,3-b][1,2,4]triazol-5-one proceeds similarly [25].

The reaction of dinitrotriazolyl ketones XIV with potassium cyanide and hydrazines proceeds through intermediate adducts involving the keto group with subsequent intramolecular attack of the o-nitro group by the hydroxy and hydrazo groups to give five-, six-, and seven-membered condensed systems [22].



n = 1,2 XIV

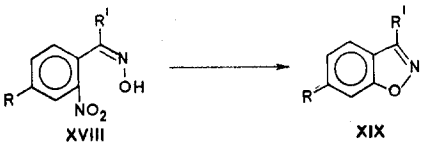
Benzoxazole. The reaction of 2,3-dinitroacetanilide (XV) with sodium alkoxides in anhydrous dimethylformamide (DMF) at 140°C gives 2-methyl-7-nitrobenzoxazole (XVI) in up to 50% yield, along with 2-nitro-6-acetamidophenol (XVII) [26]. Compound XVII remains unchanged when it is heated in anhydrous DMF in the presence of sodium alkoxides, while benzoxazole XVI forms phenol XVII under the same conditions.



XV XVI 51% XVII 37%

R = C_2H_5, i-C_3H_7

On the basis of the data in [26] it may be assumed that the formation of XVI is the result of intramolecular nucleophilic substitution of the o-nitro group and is an intermediate step in the replacement of the nitro group by a hydroxy group. This is one of the few examples that make it possible to observe an intramolecular transformation that appears to be an intermolecular reaction involving nucleophilic substitution of a nitro group.

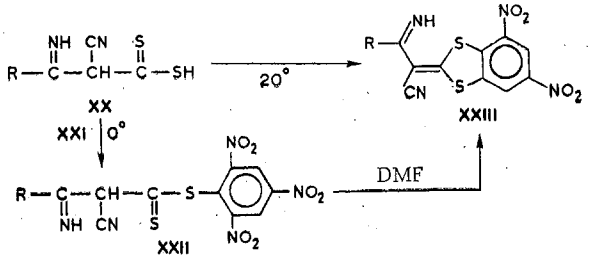


XVIII XIX

R = H, Cl, Br, J, NO_2, OCH_3, $SO_2C_6H_5$, $SO_2N(CH_3)_2$, $SO_2N(C_2H_5)_2$, piperidinosulfonyl, morpholinosulfonyl;
R' = CH_3, C_6H_5, $COCH_3$, COC_6H_5, CO_2CH_3

Benzisoxazoles. Cyclization of oxime XVIII leads to the corresponding benzisoxazoles XIX. In the overwhelming majority of described cases another nitro group [3, 27-31] or another substituent [3, 32] is present in the meta position to the nitro group undergoing substitution.

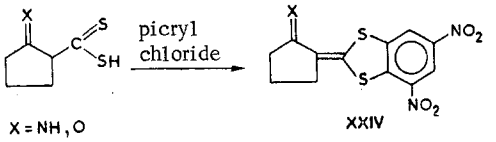
Benzodithioles. The reaction of 2-cyano-3-iminodithiocarboxylic acids XX with picryl chloride (XXI) in ethanol at 0°C yields intermediate esters XXII, which readily lose a nitro group in DMF to give benzodithioles XXIII. The latter are formed immediately when the reaction is carried out in ethanol at 20°C [33].



XX XXIII XXII

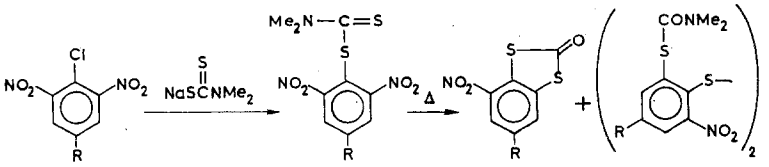
R = CH_3, C_6H_5, m- and p-$CH_3C_6H_5$, p-$CH_3OC_6H_5$, β-$C_{10}H_7$

2-Imino- and 2-oxocyclopentanedithiocarboxylic acids react with picryl chloride to give benzodithioles XXIV [34, 35].



X = NH, O XXIV

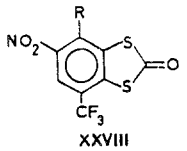
Benzodithiolones. Dithiocarbamates XXVI are obtained by reaction of 3,5-dinitrochlorobenzenes XXV with sodium N,N-dimethyldithiocarbamate in DMSO at room temperature. Displacement of the nitro group to give 1,3-benzodithiol-2-ones XXVII is observed when XXVI is subsequently heated in DMSO. In a number of cases linear disulfides are formed as side products [36].



XXV XXVI XXVII

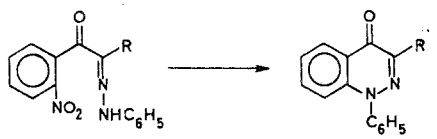
R = H, F, NO_2, CH_3, CF_3, CN

Benzodithiolones XXVIII were similarly obtained in 11% (R = H) and 77% [R = $N(CH_3)_2$] yields [36].



XXVIII

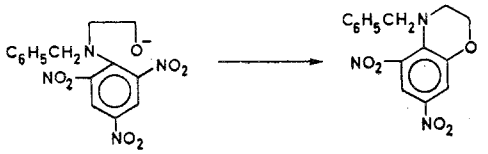
Cinnolinones. 1-Phenylcinnolin-4(1H)-ones XXX were obtained in 71-98% yields by heating hydrazone XXIX in alcohol with the addition of an aqueous solution of sodium carbonate [37].



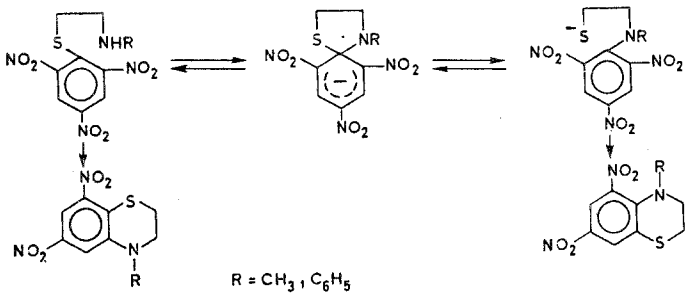
XXIX XXX

R = CN, $CONH_2$, $COCH_3$, COC_6H_5, $CO_2C_2H_5$

Dihydrobenzoxazine. The cyclization of N-benzyl-N-(2-hydroxyethyl)picramide proceeds without prior Smiles rearrangement to give 5,7-dinitro-4-benzyl-2,3-dihydro-1,4-benzoxazine [38].



Dihydrobenzothiazines. Depending on the base and solvent used, 1-[2-(N-methylamino)ethylthio]-2,4,6-trinitrobenzene undergoes cyclization both without and with prior Smiles rearrangement [39, 40]. The two reaction pathways are due to the close nucleophilicities of the dialkylamino group and the thiolate anion.

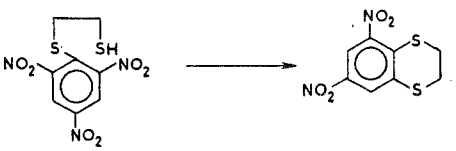


R = CH_3, C_6H_5

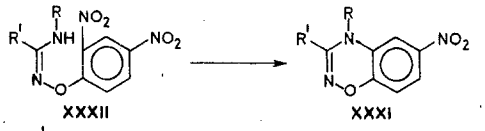
The formation of the rearrangement product — 5,7-dinitro-4-methyl-2,3-dihydro-1,4-benzothiazine — is promoted by the use of strong bases and a solvent that solvates the anionic spiro complex well. On the other hand, the use of a weak base and solvents that solvate the spiro complex weakly leads to unrearranged 6,8-dinitro-4-methyl-2,3-dihydro-1,4-benzothiazine.

A decrease in the nucleophilicity of the amino group (R = C_6H_5) hinders cyclization with participation of this nucleophile, and 1-(2-anilinoethylthio)-2,4,6-trinitrobenzene is converted primarily to rearranged 5,7-dinitro-4-phenyl-2,3-dihydro-1,4-benzothiazine [40].

Benzodithiane. 5,7-Dinitro-1,4-benzodithiane was obtained in 20% yield from 1-(2-mercaptoethylthio)-2,4,6-trinitrobenzene by heating with triethylamine in DMSO [41].



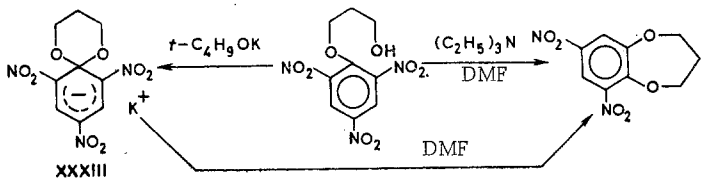
Benzoxadiazines. Benzoxadiazines XXXI are obtained by heating dinitrophenyl ethers of benzylamidoxime (XXXII) in alcoholic alkali [42].



XXXII XXXI

R = H, R' = C_6H_5, p-$CH_3C_6H_4$, m- and p-$NO_2C_6H_4$; R = C_6H_5, R' = C_6H_5, m- and p-$NO_2C_6H_4$; R = $CH_2C_6H_5$, R' = C_6H_5

Benzodioxepanes. Heating 1-(3-hydroxypropoxy)-2,4,6-trinitrobenzene with triethylamine in DMF leads to 6,8-dinitro-1,5-benzodioxepane in 15% yield [41].

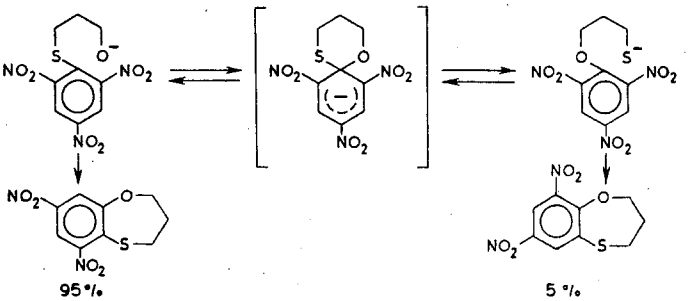


XXXIII

The same compound is obtained when spiro complex XXXIII, which is isolated when a solution of 1-(3-hydroxypropoxy)-2,4,6-trinitrobenzene is treated with potassium tert-butoxide, is heated in DMF [41].

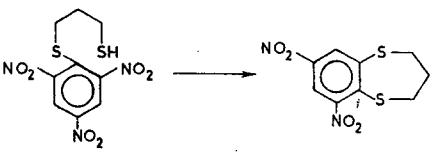
The introduction of gem-dimethyl groups in the β position of XXXIII decreases the stability of the spiro complex, which gives 6,8-dinitro-3,3-dimethyl-1,5-benzodioxepane in 10% yield when it is refluxed in DMF for 6 h [43].

Benzoxathiepanes. The intramolecular nucleophilic cyclization of 1-(3-hydroxypropylthio)-2,4,6-trinitrobenzene proceeds in part with Smiles rearrangement to give isomeric 6,8- and 7,9-dinitro-1,5-benzoxathiepanes in a ratio of 95:5 [43].



95% 5%

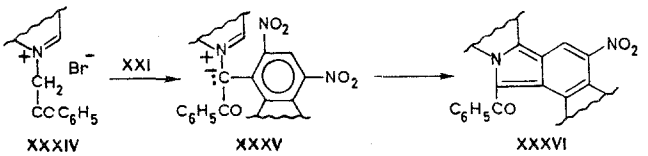
Benzodithiepane. 1-(3-Mercaptopropylthio)-2,4,6-trinitrobenzene in benzene in the presence of triethylamine gives 6,8-dinitro-1,5-benzodithiepane in 80% yield [41]. This compound was previously obtained via a similar scheme in low yield [44].



Tri- and Polycyclic Systems

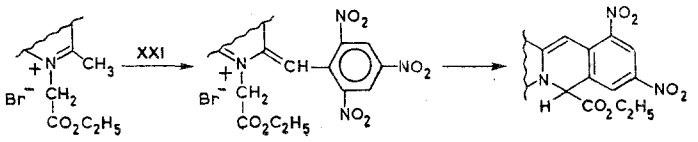
Condensed Pyrrole, Imidazole, Thiazole, and Pyridine Rings. Quaternary pyridinium, quinolinium, and isoquinolinium salts XXXIV are readily arylated by picryl chloride and 2,4-dinitrochloronaphthalene in the presence of triethylamine. Arylation products XXXV are treated with piperidine in DMSO, during which the nitro group in the ortho position to the chlorine

atom undergoes intramolecular substitution as a result of nucleophilic attack by the carbanionoid carbon atom to give condensed tri-, tetra-, and pentacyclic systems XXXVI, which contain a pyrrole ring [45, 46].



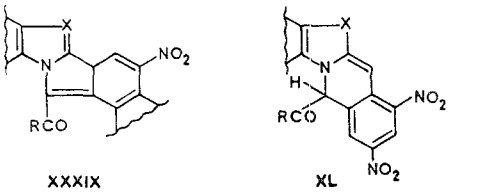
XXXIV XXXV XXXVI

Quaternary ammonium salts of quinoline homologs XXXVII are arylated by picryl chloride at the α-methyl group. In this case substitution of the nitro group takes place under the same conditions to give six-membered polycyclic systems XXXVIII [47].



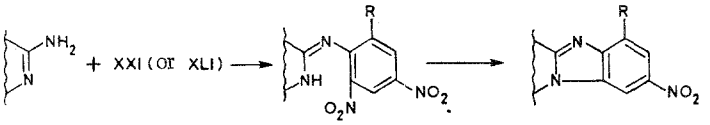
XXXVII XXXVIII

Three-, four-, and five-ring compounds of the XXXIX and XL type were similarly obtained from thiazole, benzothiazole, and benzimidazole betaines [46, 47].



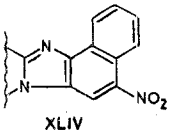
XXXIX X = S, NCH_3 XL X = S, R = OC_2H_5, C_6H_5

The condensation of picryl chloride or 2,4-dinitrochlorobenzene (XLI) with 2-aminopyridine, 2-aminoquinoline, and 9-aminophenanthridine in benzene at 20°C leads to XLII, which undergo cyclization to give polycyclic systems of the XLIII type when they are refluxed in N,N-dimethylaniline (for 2.5 h in a nitrogen atmosphere) [48-50].



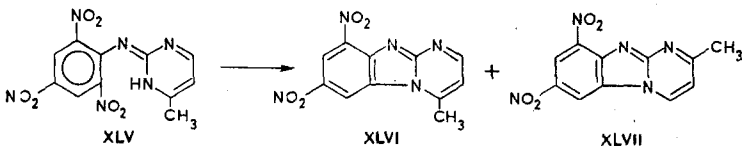
R = H, NO_2 XLII XLIII

The use of 2,4-dinitrochloronaphthalene as the polynitrohaloaryl compound make it possible to synthesize a number of XLIV polycycles [49].



XLIV

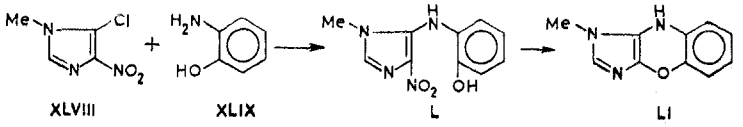
The heterocyclic imino group acts as the nucleophile in substitution of the nitro group in these reactions. Pyrimido[1,2-a]benzimidazoles XLVI and XLVII were similarly obtained in the condensation of 2-aminopyrimidine XLV with picryl chloride [2].



XLV XLVI XLVII

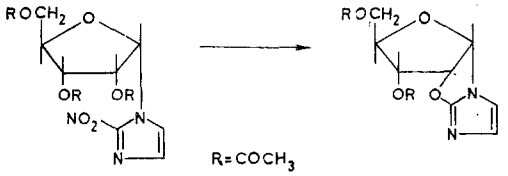
Cyclization with splitting out of the nitro group was not observed when picryl chloride was replaced by 2,4-dinitrobromobenzene or XLV was replaced by 2-aminothiazole in the latter reaction [51].

The condensation of nitroimidazole XLVIII with o-aminophenol (XLIX) in ethanol in the presence of sodium acetate leads to L. Heterocycle LI was obtained when L was heated to 120°C in diethylamine in a sealed tube [51].



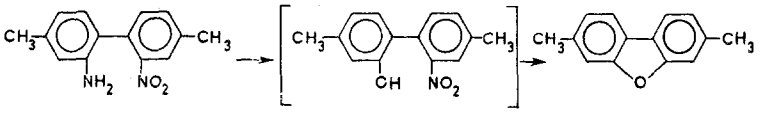
XLVIII XLIX L LI

Intramolecular substitution of the nitro group was observed in 1-(α-D-ribofuranosyl)-2-nitroimidazole when it was treated with sodium methoxide in methanol [52]. The hydroxy group formed during saponification acts as the nucleophile.

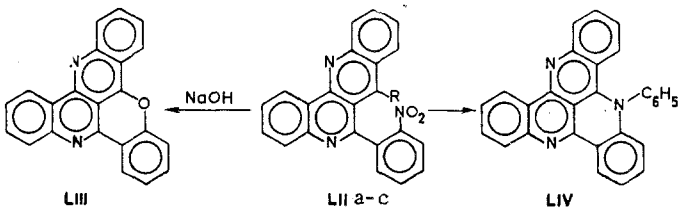


R=COCH$_3$

Condensed Furan and Pyran Rings. Substitution of the nitro group in the ortho' position to give 3,7-dimethyldibenzofuran was observed in the diazotization of 2-amino-2'-nitro-4,4'-dimethylbiphenyl with subsequent exchange of the diazo group [53].



Substitution of the nitro group by the phenoxide anion also occurred when phenol LIIa (R = OH) was treated with a solution of alkali, and LIII was formed. Compound LIV, which is evidently the product of intramolecular conversion of the intermediately formed amine LIIc (R = NHC$_6$H$_5$), was obtained when chloro derivative LIIb (R = Cl) was refluxed in aniline [54].

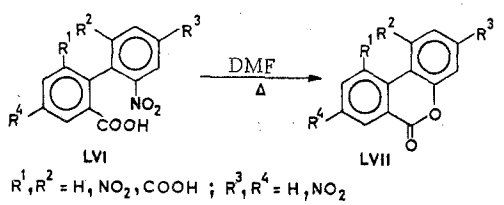


LIII LII a-c LIV

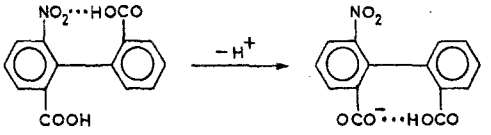
Intramolecular substitution of the nitro group has frequently been observed under the standard conditions of decarboxylation of o-nitrobiphenylcarboxylic acids [55-58]. Thus substitution of the o-nitro group was observed in the decarboxylation of 2'-nitrobiphenyl-2-carboxylic acid and 2,4-dinitrobiphenyl-2,4'-dicarboxylic acid in refluxing quinoline in the presence of copper chromite, and 9-fluorenone and 2-nitro-9-fluorenone structures were initially erroneously assigned to the cyclic products [55, 56]. It was subsequently shown [57] that the products of this reaction are, respectively, 6H-dibenzo[b,d]pyran-6-one (LV) and its

8-nitro derivative. Compound LV was obtained by heating the potassium salts of 2'-X-biphenyl-2-carboxylic acids (X = F, Br, NO_2) in vacuo at 220°C (in 13, 20, and 89% yields, respectively) [59].

6H-Dibenzo[b,d]pyran-6-ones LVII are formed when acids LVI are refluxed in dipolar aprotic solvents [60, 61].



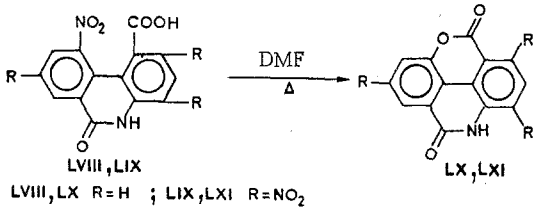
o,o'-Disubstituted biphenyls generally have a cis conformation, and an intramolecular hydrogen bond may be formed between the substituents [8-10, 62]. Substitution of the nitro group by the carboxylate anion proceeds readily in these cases. The introduction of a third and fourth substituent in the ortho position of biphenyl may have a substantial effect on the mutual orientation of the reacting groups, particularly in the case of ionization of the COOH group. Thus substitution of a nitro group is hindered in the case of LVI ($R^1 = R^3 = R^4 = H$, R^2 = COOH), evidently because of the existence of a conformation with remote reaction centers.



The introduction of electron-acceptor substituents in the 4 and 4' positions of biphenyl leads to an increase in the yields of dibenzopyranones.

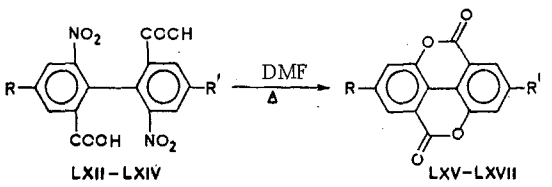
The introduction of a bridged X group in the biphenylcarboxylic acid molecule excludes substitution of the nitro group [59], evidently because of the formation of chelates [63].

The corresponding 5,10-dioxo-4,5,9,10-tetrahydro-9-oxa-4-azapyrenes are readily formed when 10-nitrophenanthridonecarboxylic acids LVII and LIX are refluxed in quinoline or in dipolar aprotic solvents [64, 65].



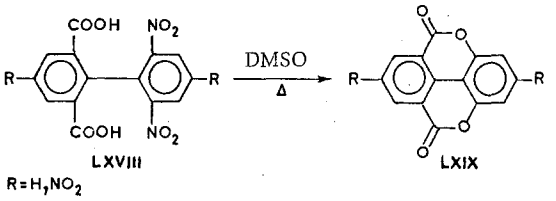
The NO_2 and COOH groups in LVIII and LIX have a favorable mutual orientation. In contrast to them, 6,6'-dinitrobiphenyl-2,2'-dicarboxylic acids LXII-LXIV, owing to the possibility of rotation of the benzene rings about the C—C bond, can, by ionization of the COOH group, form unreactive conformations that are stabilized by an intramolecular hydrogen bond [9, 10] between the carboxy group and the carboxylate anion. For this reason, the nitro groups in 6,6'-dinitrobiphenyl-2,2'-dicarboxylic acid (LXII) are evidently substituted with greater difficulty. The introduction of substituents in the 4 and 4' positions (particularly NO_2 groups) facilitates the reaction [66] and increases the yields of 4,9-dioxapyrenes LXV-

LXVII. Substitution of the nitro group is facilitated by the energic favorability of the formation of an aromatic system from compounds with unconjugated chromophores.

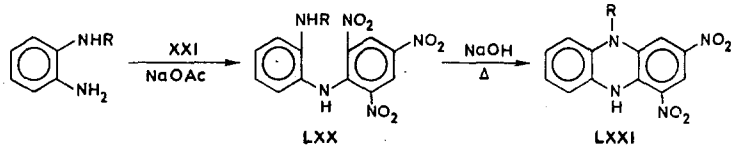


LXII, LXV R=R'=H ; LXIII, LXVI R=H, R'=NO_2 ; LXIV, LXVII R=R'=NO_2

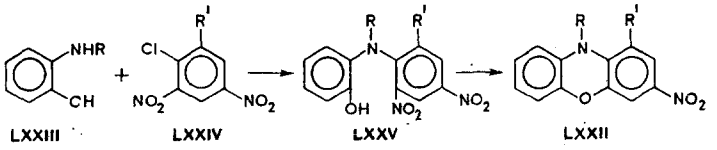
Substitution of two nitro groups in one benzene ring occurs when 2',6'-dinitrobiphenyl-2,6-dicarboxylic acids LXVIII are heated in dipolar aprotic solvents; 4,10-dioxapyrenes LXIX are formed in high yields [67].



Dihydrophenazines. The corresponding N-substituted dihydrophenazines LXXI were obtained by condensation of picryl chloride with N-monosubstituted phenylenediamines (R = Alk, Ar) [68-72] and subsequent treatment of the resulting diarylamines LXX with alkali. 4-Chloro-3,5-dinitropyridine was used for the synthesis of dihydrophenazine analog LXXI with two six-membered nitrogen-containing heterorings [73].

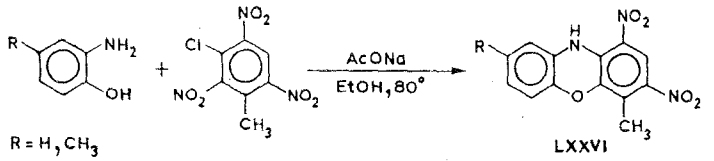


Phenoxazines. A number of phenoxazines LXXII were synthesized by reaction of o-aminophenols LXXIII with halonitrobenzenes LXXIV. The reaction proceeds through intermediate 2-nitro-2'-hydroxydiphenylamines LXXV, which undergo intramolecular cyclization with substitution of the nitro group under the influence of alkali [42, 74-80].



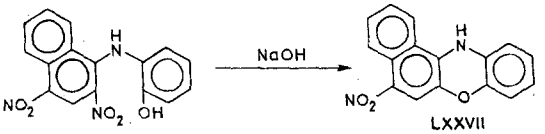
When R = R' = H, cyclization of hydroxydiphenylamine LXXV is hindered [76, 78] because of the formation of an intramolecular hydrogen bond between the amino and o-nitro groups [77, 80], which stabilizes the conformation with remote reaction centers. When R = H and R' = NO_2, CO_2H, SO_3H, and CH_3 and if the hydrogen atom attached to the nitrogen atom is replaced by an alkyl, aryl, or acyl group, phenoxazines can be obtained under milder conditions [1, 80-83]. The effect of the nature of substituent R' on the cyclization and the spatial orientation of the reacting groups is discussed in [1].

Only the most sterically hindered 2-nitro group is substituted when a methyl group is introduced in the 3 position of picryl chloride. Phenoxazines LXXVI are obtained in 50-67% yields [84].

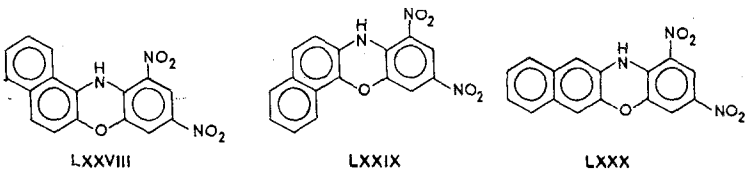


The introduction of a nitro group in the o-aminophenol molecule decreases the yield markedly. Thus the reaction of 2-amino-5-nitrophenol with picryl chloride in DMF in the presence of triethylamine at 80°C gives 1,3,7-trinitrophenoxazine in 17% yield [84]. Phenoxazines can also be obtained from o-aminodiaryl ethers [82, 84, 85].

Benzophenoxazines. The cyclization of 2,4-dinitro-1-naphthyl(2-hydroxyphenyl)amine in aqueous alkali by heating on a water bath leads to benzophenoxazine LXXVII [86, 87].



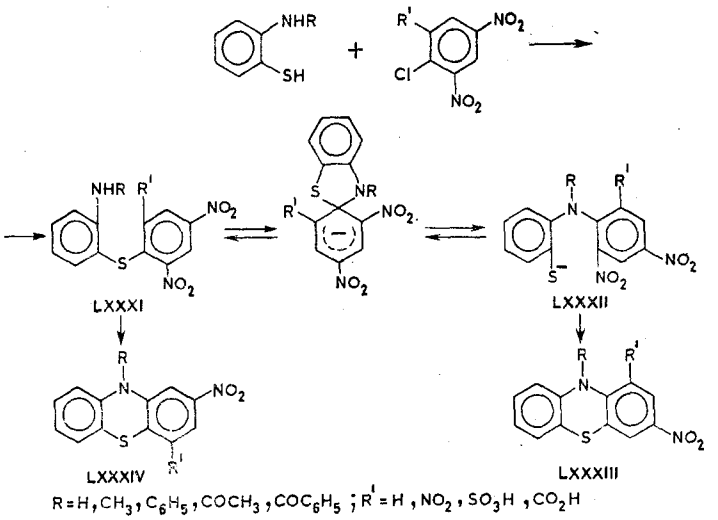
Benzophenoxazines LXXVIII-LXXX were obtained by condensation of picryl chloride with 1-amino-2-naphthol, 2-amino-1-naphthol, and 2-amino-3-naphthol in the presence of potassium alkoxides [88].



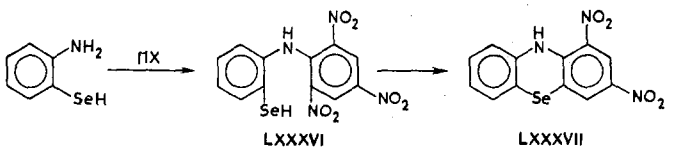
Phenothiazines. These compounds are obtained by the reaction of o-mercaptoanilines with halonitrobenzenes. o-Aminodiaryl sulfides LXXXI are formed in the first step. In contrast to phenoxazines, the establishment of the position of the substituents in substituted phenothiazines presents certain difficulties, since the Smiles rearrangement generally precedes substitution of the nitro group [89-92]; in this case o-aminodiphenyl sulfides LXXXI undergo partial or complete rearrangement to o-mercaptodiphenylamines LXXXII, and both the amino group and the thiophenoxide anion may act as the nucleophile in displacement of the nitro group [4, 93]. (Formula, top, following page.)

When R = H, C_6H_5, acyl, and benzoyl and R' = NO_2 [93-105] and when R = CH_3, C_6H_5 and R' = H [93], the reaction proceeds with prior Smiles rearrangement, and phenothiazines LXXXIII are formed. When R = CH_3 and R' = NO_2, condensation takes place simultaneously both without and with prior Smiles rearrangement, i.e., with the formation of isomeric phenothiazines LXXXIII and LXXXIV [93]. The reaction of 2,4,6-trinitro-3-chlorotoluene with o-aminothiophenol (LXXXV) also gives two isomeric phenothiazines [106]. The ratio of phenothiazines LXXXIII and LXXXIV may change substantially as a function of the reaction conditions [93].

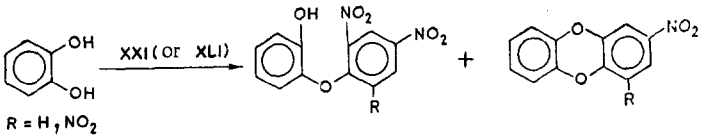
The effect of steric factors and the conformational structure of LXXXI on their ability to undergo cyclization is examined in [4].



Phenoselenazine. The reaction of picryl chloride with o-aminoselenophenol gave picrylaminoselenophenol LXXXVI, which undergoes cyclization to 1,3-dinitrophenoselenazine (LXXXVII) in alcoholic alkali [107].

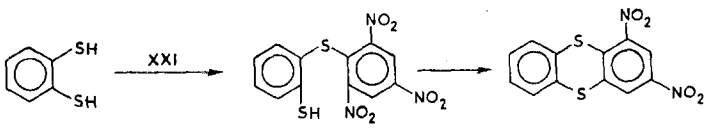


Diphenylenedioxides. 2,4,6-Trinitrophenyl or 2,4-dinitrophenyl ethers of pyrocatechol were obtained in 15 and 10% yields, respectively, in the reaction of pyrocatechol with picryl chloride (XXI) or 2,4-dinitrochlorobenzene (XLI) in benzene in the presence of sodium methoxide. In addition to these principal products, 1,3-dinitrodiphenylenedioxide and 2-nitrodiphenylenedioxide were isolated [41]. The yields of cyclization products increase substantially as the temperature is raised.

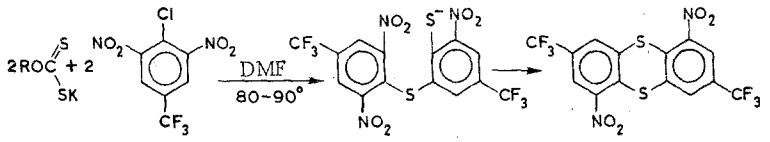


An interesting case of intramolecular nucleophilic substitution of a nitro group that is accompanied by a Smiles rearrangement is observed in the formation of 1,2,3,7,8,9- and 1,2,3,6,7,9-hexachlorodiphenylenedioxides [108].

Thianthrenes. 1-(o-Mercaptophenylthio)-2,4,6-trinitrobenzene was obtained by reaction of dithiopyrocatechol with picryl chloride in the presence of sodium methoxide. Treatment of this product with yet another equivalent of sodium methoxide leads to 1,3-dinitrothianthrene [109].

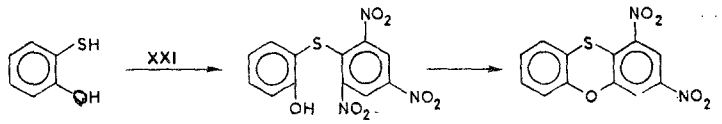


An original method for the preparation of a substituted thianthrene was based on the reaction of the potassium salt of ethyl or isopropyl dithiocarbonate with 4-chloro-3,5-dinitrotrifluoromethylbenzene [110]. As a result of substitution of the nitro group, the intermediately formed o-mercaptodiaryl sulfide LXXXVIII undergoes cyclization to 1,6-dinitro-3,8-bis(trifluoromethyl)thianthrene.



LXXXVIII

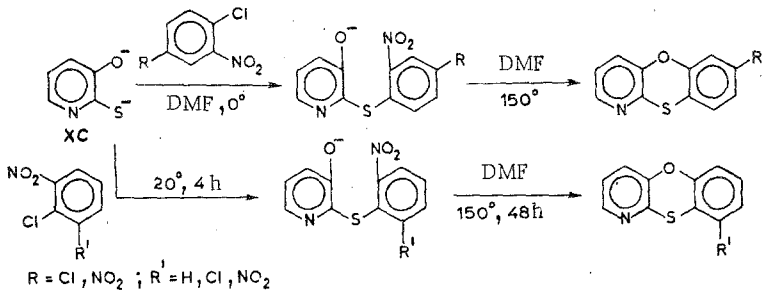
Phenoxathiins. Sulfide LXXXIX was obtained in 90% yield in the reaction of monothiopyrocatechol with picryl chloride in the presence of an equimolar amount of sodium methoxide. 1,3-Dinitrophenoxathiin was obtained in high yield when 2 moles of a base were added to the starting reaction mixture or from thioether LXXXIX by the addition of 1 mole of sodium methoxide [109].



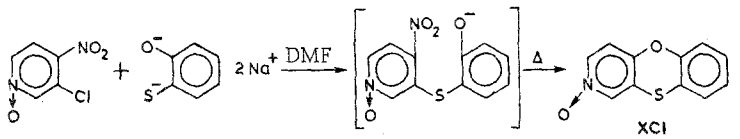
LXXXIX

Earlier reports regarding phenoxathiins obtained by a similar method are presented in [111,112].

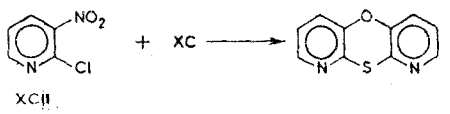
Azaphenoxathiins. 1-Azaphenoxathiins were obtained in 19-28% yields by condensation of the disodium salt of 2-mercapto-3-pyridinol (XC) with o-nitrohalobenzenes [113-115].



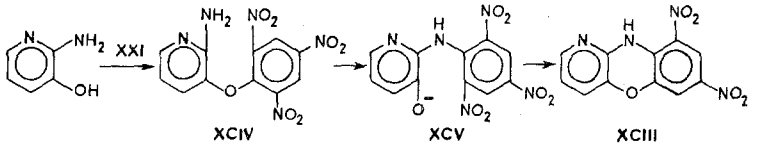
2-Azaphenoxathiin was obtained in the reaction of oxide XCI with phosphorus trichloride in chloroform [116].



1,8-Diazaphenoxathiin was obtained in 31% yield by heating 2-chloro-3-nitropyridine (XCII) with XC in DMSO for 48 h [117].

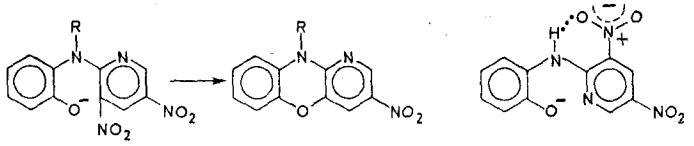


Azaphenoxazines. 7,9-Dinitro-1-azaphenoxazine (XCIII) was synthesized by condensation of 2-amino-3-hydroxypyridine with picryl chloride [118]. Intermediate pyridyl phenyl ether XCIV undergoes a Smiles rearrangement to the corresponding o-hydroxypyridylamine XCV, which in alcoholic alkali gives cyclization product XCIII.



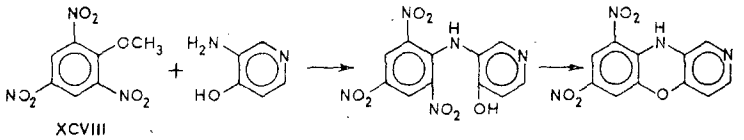
7,9-Dinitro-4-methyl-3-phenyl-1-azaphenoxazine was obtained by reaction of 2-amino-3-hydroxy-4-methyl-5-phenylpyridine with picryl chloride in alcohol in the presence of sodium ethoxide [119].

N-(3,5-Dinitro-2-pyridyl)-2-hydroxyanilines XCVI readily undergo cyclization in alcoholic alkali with displacement of a nitro group [120, 121].

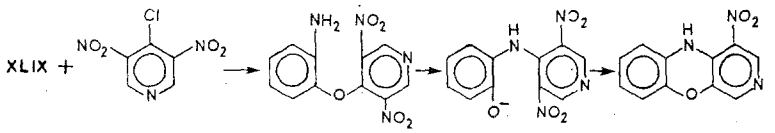


When R = H, cyclization does not occur in alcoholic media because of the formation of structure XCVII, which is stabilized by an intramolecular hydrogen bond [6]. However, replacement of alcoholic alkali by DMSO promotes the reaction [122].

An amine intermediate was isolated in 70% yield in the reaction of 3-amino-4-hydroxypyridine with 2,4,6-trinitroanisole (XCVIII); treatment of this intermediate with alcoholic alkali gives 7,9-dinitro-2-azaphenoxazine in good yield [6].

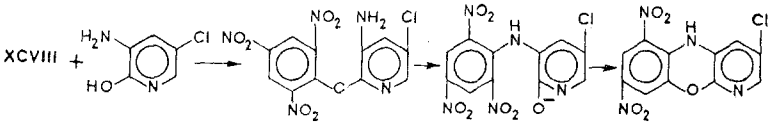


1-Nitro-3-azaphenoxazine, which is the first known compound from the azaphenoxazine series [123], was obtained in 70% yield by treatment of 3,5-dinitro-4-chloropyridine with o-aminophenol (XLIX) in ethanol in the presence of anhydrous sodium acetate.

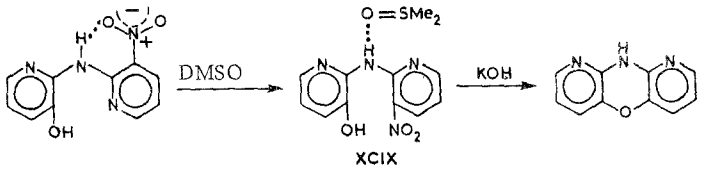


The condensation of N-benzyl-2-hydroxyaniline with 4-chloro-3-nitropyridine hydrochloride in aqueous alkali leads to 10-benzyl-3-azaphenoxazine [124].

The reaction of 3-amino-2-hydroxy-5-chloropyridine with 2,4,6-trinitroanisole (XCVIII) in the presence of a base gives 7,9-dinitro-2-chloro-4-azaphenoxazine [120].

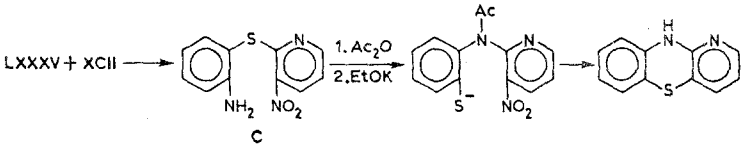


The reaction of 2-amino-3-hydroxypyridine with 2-chloro-3-nitropyridine gave 3-hydroxy-3'-nitro-2,2'-dipyridylamine (XCIX), which was cyclized to 1,9-diazaphenoxazine in low yield (31%) in refluxing DMSO in the presence of alkali [11, 125, 126]. The DMSO in this reaction blocks the hydrogen atom, as a result of which the amine molecule can take on a conformation that is favorable for the reaction.



XCIX

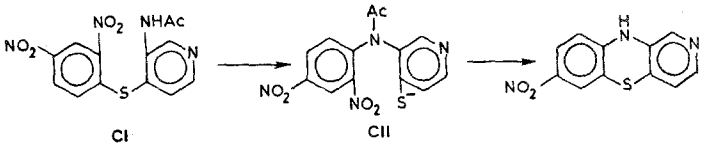
Azaphenothiazines. The corresponding sulfide C is obtained by condensation of o-aminothiophenol (LXXXV) with 2-chloro-3-nitropyridine (XCII). Treatment of its N-acetyl derivative with potassium ethoxide gives 1-azaphenothiazine as a result of the Smiles rearrangement and subsequent cyclization [127].



C

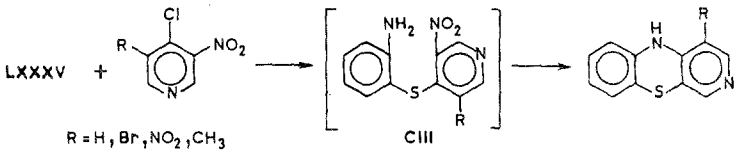
This method is also used in the synthesis of 1-azaphenothiazine derivatives [128-130].

The condensation of 3-amino-1H-pyridine-4-thione with 2,4-dinitrochlorobenzene with subsequent acetylation gave 2,4-dinitrophenyl 3-acetamido-4-pyridyl sulfide (CI), which upon refluxing with potassium methoxide in methanol undergoes the Smiles rearrangement; the resulting diarylamine CII undergoes cyclization to the deacylated 7-nitro-2-azaphenothiazine [131].



CI CII

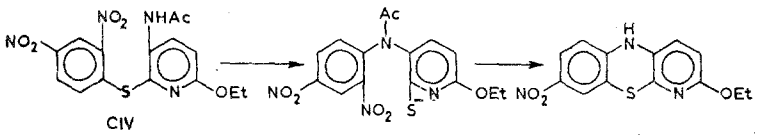
Diaryl sulfides CIII, which rapidly undergo rearrangement and cyclization to 3-azaphenothiazines, are formed when 5-substituted 3-nitro-4-chloropyridines are refluxed with o-aminothiophenol in an alcohol solution of sodium ethoxide in the presence of sodium acetate [132, 133].



CIII

3-Azaphenothiazine was obtained in 62% yield from 3-nitro-4-chloropyridine and o-aminothiophenol via this scheme. Intermediate sulfide CIII (R = H) is converted to 3-azaphenothiazine after acetylation in the presence of potassium hydroxide in acetone [134]. 3-Azaphenothiazine was previously synthesized via a similar scheme with prior formylation of sulfide CIII (R = H) [135].

The condensation of 2,4-dinitrochlorobenzene and 3-amino-6-ethoxy-1H-pyridine-2-thione with subsequent acylation gave sulfide CIV, which, under the influence of alkali, undergoes rearrangement to a diarylamide, which is readily cyclized to 3-ethoxy-7-nitro-4-azaphenothiazine [131].

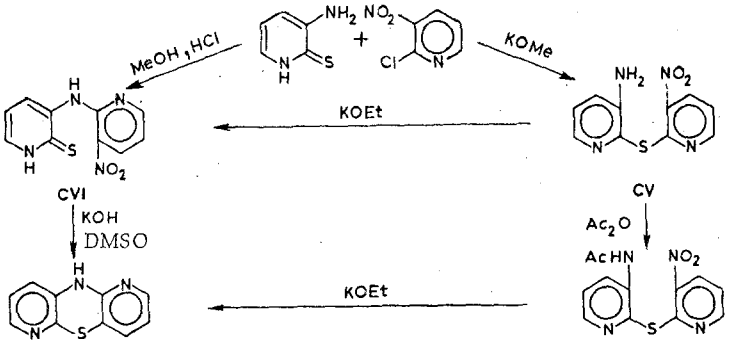


CIV

2-Chloro-7-nitro-4-azaphenothiazine was similarly obtained [136]. 3-Ethoxy-7,9-dinitro-4-azaphenothiazine is the product of the condensation of 2,4,6-trinitroanisole and 3-amino-6-ethoxy-1H-pyridine-2-thione in an alkaline medium [137, 138].

1,6-Diazaphenothiazine was obtained from 2-amino-1H-pyridine-2-thione and 2-chloro-3-nitropyridine by two methods [22]. In the presence of potassium methoxide the product is sulfide CV, which is then acetylated with acetic anhydride; after the Smiles rearrangement, the product undergoes cyclization in an alkaline medium to 1,6-diazaphenothiazine in 43% yield. 3-Methyl- and 3,8- and 3.7-dichloro-1,6-diazaphenothiazines have been prepared by the same method [122, 139, 140].

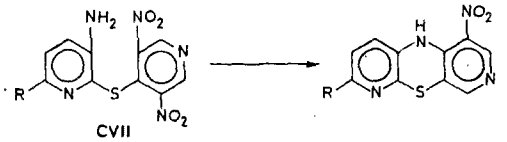
The Smiles rearrangement occurs when sulfide CV is refluxed in an alkaline medium, and thiolactam CVI can be isolated; this thiolactam is also formed in the condensation of the starting compounds in the presence of acid [7].



CVI CV

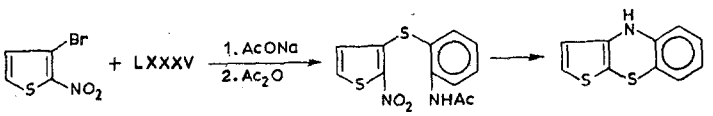
The cyclization of thiolactam CVI in alcoholic alkali is impossible because of intramolecular hydrogen bonding between the amino and 3-nitro groups. Dimethyl sulfoxide solvates CVI at the amino hydrogen atom, thereby freeing the nitro group for nucleophilic attack. 1,6-Diazaphenothiazine is obtained in 92% yield [122].

Dipyridyl sulfides CVII, which readily undergo rearrangement and subsequent cyclization to 1-nitro-3,6-diazaphenothiazines, were obtained in the reaction of 3-amino-1H-pyridine-2-thiones with 3,5-dinitro-4-chloropyridine in the presence of alcoholic potassium methoxide [141].



CVII
R = Cl, OCH_3

Thienobenzothiazines. The first thiophene analog of phenothiazine was synthesized in 1966 [142]. Condensation of 3-bromo-2-nitrothiophene with o-aminothiophenol gave the sulfide, which was then acetylated with acetic anhydride; the resulting sulfide CVIII was treated with powdered potassium carbonate in refluxing DMF. Under these conditions the Smiles rearrangement is followed by displacement of the nitro group by the thiophenoxide anion, and 4H-thieno[2,3-b][1,4]benzothiazine (CIX) is formed.

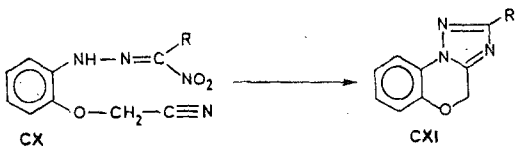


CVIII CIX

A similar method was used to obtain 6- and 7-bromo and 6-methylthio derivatives of thienobenzothiazine (CIX) [142].

9H-Thieno[3,2-b][1,4]benzothiazines are formed in the condensation of 2-bromo-3,5-dinitrothiophene with o-aminothiophenol and its derivatives [142, 143].

Triazolobenzoxazines. An interesting case of displacement of a nitro group attached to an unsaturated carbon atom with the simultaneous formation of two heterorings is observed when nitrohydrazones CX are refluxed in benzene with NaH; 4H-[1,2-4]triazolo[5,1-c][1,4]benzoxazines CXI are obtained in 41-59% yields [144]. (Formula, top, following page.)



CX

CXI

R = H, CH_3, C_2H_5, C_6H_5

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