

THE CHEMISTRY OF DIAZAQUINONES

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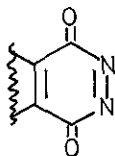
This article presents a survey of the synthesis, properties and reactions of 3,6-pyridazinedione, 1,4-phthalazinedione and related compounds.

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1.- INTRODUCTION

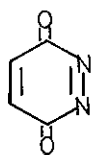
Since Clement in 1960¹ and Kealy in 1962² first prepared compounds of type I, for which the generic term diazaquinones was proposed, the study of the properties and reactions of these compounds has given rise to an increasing interest and has generated a good number of papers during the past few years.



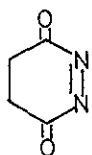
I

The main significance of these compounds lies in their intense dienophilic character due to the -N=N- double bond, which allows them to undergo cycloaddition reactions that may be applied to the synthesis of heterocyclic compounds. Some of the products thus obtained are useful as plant growth regulants and control agents for noxious weeds³. Other such products have shown cytotoxic activity⁴. The role of diazaquinones in the chemiluminescence of some cyclic hydrazides has been reviewed⁵.

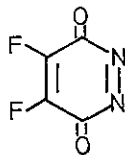
In addition to the simplest diazaquinone, 3,6-pyridazinedione (II), prepared by Kealy², its derivatives 4,5-dihydro-3,6-pyridazinedione (III)⁶, 4,5-difluoro-3,6-pyridazinedione (IV)², 4-chloro-3,6-pyridazinedione (Va) and 4-bromo-3,6-pyridazinedione (Vb)⁷ as well as its benzo-analog 1,4-phthalazinedione and derivatives (VI) are known.



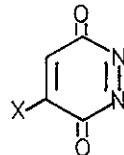
II



III



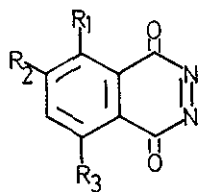
IV



V

a; X=Cl

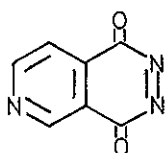
b; X=Br



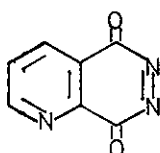
VI

- | | |
|--|-----------|
| a: R ₁ =R ₂ =R ₃ =H | (Ref. 1) |
| b: R ₁ =NH ₂ ; R ₂ =R ₃ =H | (Ref. 8) |
| c: R ₁ =R ₃ =H; R ₂ =(CH ₃ -CH ₂) ₂ N | (Ref. 8) |
| d: R ₁ =NO ₂ ; R ₂ =R ₃ =H | (Ref. 9) |
| e: R ₁ =R ₃ =H; R ₂ =NO ₂ | (Ref. 9) |
| f: R ₁ =CH ₃ -CO-NH; R ₂ =R ₃ =H | (Ref. 9) |
| g: R ₁ =Cl; R ₂ =R ₃ =H | (Ref. 10) |
| h: R ₁ =OH; R ₂ =R ₃ =H | (Ref. 10) |
| i: R ₁ =R ₃ =Cl; R ₂ =H | (Ref. 10) |

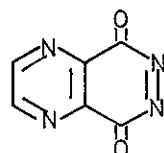
Diazaquinones in which an heterocyclic ring is fused with the diazaquinone ring, such as VII-XI¹¹, XII¹² and XIII-XVI¹³, as well as polycyclic diazaquinones XVII and XVIII⁸ have also been described.



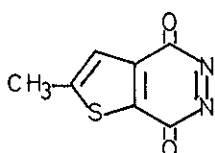
VII



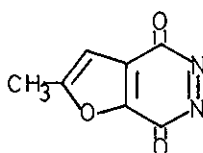
VIII



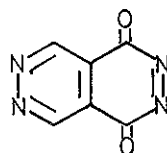
IX



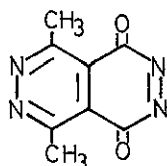
X



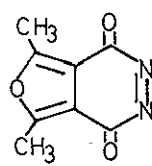
XI



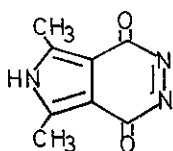
XII



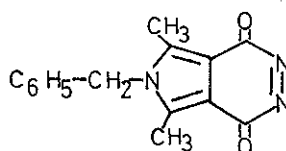
XIII



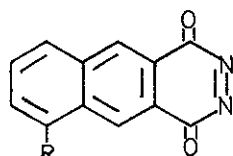
XIV



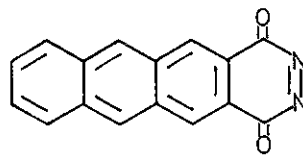
XV



XVI



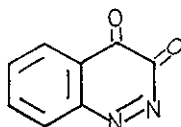
XVII



XVIII

a: R=H (Ref. 14)
 b: R=NO₂ (Ref. 10)

The synthesis of diazaorthoquinones such as 3,4-diketocinnoline (XIX) has been unsuccessfully attempted^{15, 16}.



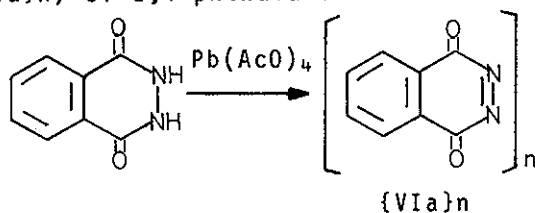
XIX

2.- SYNTHESIS AND STABILITY OF DIAZAQUINONES

2.1.- Preparation of diazaquinones

The preparation of diazaquinones is accomplished through the oxidation of cyclic hydrazides.

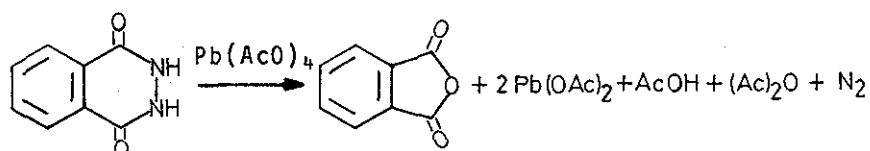
The first diazaquinone was prepared by Clement¹ by oxidizing phthalic hydrazide. When the oxidation with lead tetraacetate is carried out in acetonitrile, a green solution is obtained which very rapidly deposits a white, amorphous solid, formulated as a polymer ($\{VIa\}_n$) of 1,4-phthalazinedione.



The diazaquinone is the initial product of oxidation and is responsible for the colour but, due to its instability, it decomposes in short time. Clement showed the formation of 1,4-phthalazinedione (VIa) as an unstable compound by oxidizing phthalic hydrazide in the presence of butadiene. The cycloaddition reaction allows the interception of the diazaquinone as a Diels-Alder adduct.

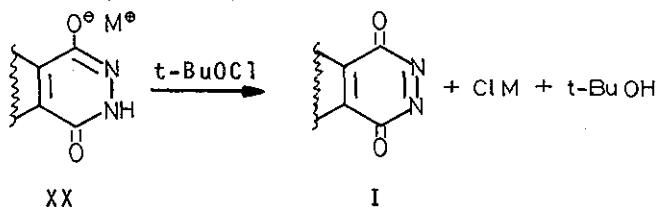
The oxidation of cyclic hydrazides to diazaquinones may also be accomplished in other solvents⁶. Acetone like acetonitrile provides reasonably stable solutions with the colour of the diazaquinone, such as 3,6-pyridazinedione (II) , 4,5-dihydro-3,6-

pyridazinedione (III) and 1,4-phthalazinedione (VIa), lasting a fairly long time. On the other hand, in methylene chloride the solutions of diazaquinones are very unstable but, in this chlorinated solvent, both the oxidation and the reaction with dienes go much quicker. The preparation of 1,4-phthalazinedione (VIa) and 3,6-pyridazinedione (II) was also achieved by employing lead tetraacetate in benzene¹⁷. The use of lead tetraacetate as the oxidizing agent results in undesirable side-reactions such as formation of cyclic anhydride from the hydrazide¹ as well as the previously mentioned polymerization of the diazaquinone.



Nevertheless, when the objective is the *in situ* preparation of adducts with reactive dienes, this procedure may be used with good results.

The second procedure for the synthesis of diazaquinones, reported by Kealy², is to oxidize the potassium or sodium salts of the cyclic hydrazides (XX) with *t*-butyl hypochlorite in acetone solution at -77°C .



In this way 3,6-pyridazinedione (II), 4,5-difluoro-3,6-pyridazinedione (IV) and 1,4-phthalazinedione (VIa) were prepared and under these conditions may be obtained as emerald-green solutions after filtration of the inorganic salts under nitrogen at -77°C . This method of preparing diazaquinones is preferred to the Clement's method because almost no inorganic by-products are obtained and the unreacted hydrazide may be removed by the

Vic can even be isolated as a deep violet crystalline solid⁸.

On the other hand, the diazaquinones with a fused heterocyclic ring are very unstable. Compounds VII-XI¹¹ and XII¹² cannot be isolated and they decompose when their solutions are warmed. In the decomposition of VIII a bishydrazide XXIII has been isolated¹¹. The diazaquinones XIII-XVI are neither stable in solution nor can they be isolated from their solutions. These solutions range in colour from orange (XIII), to yellow (XIV) and red (XV and XVI)¹³.

Polycyclic diazaquinones are much more stable. Compound XVIII can be isolated as violet crystals⁸ and XVIIa is isolated as maroon crystals so stable that its analysis and spectroscopic study have been carried out¹⁴. It shows a carbonyl band at 1715 cm^{-1} in the infrared and three maxima in the UV: 425 nm ($\log\epsilon$ 3.5), 296 (4.0) and 242 (4.8).

3.- REACTIONS OF DIAZAQUINONES

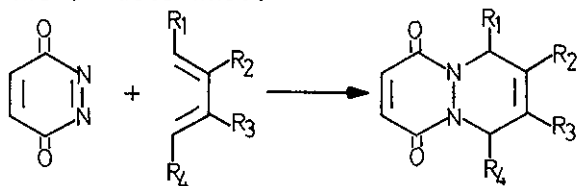
Due to instability of the diazaquinones, their reactions must be carried out, without previous isolation, in the reaction medium where they are prepared by oxidation of cyclic hydrazides, although in some instances they have been isolated prior to the reaction¹⁹. When Kealy's procedure² is employed, the diazaquinone is first prepared and then the other reactant is added to the filtered solution at -77°C . When Clement's procedure¹ is used, the oxidation of the cyclic hydrazide is performed at 0°C with the other reactant present.

3.1.- {4+2} Cycloaddition reactions

The most characteristic reactions of diazaquinones are the Diels-Alder cycloadditions. The diazaquinones are, together with 1,2,4-triazolin-3,5-diones²⁰⁻²², among the most potent dienophiles known. They undergo cycloaddition reactions even at -77°C with a great variety of dienes. Use of the diazaquinones in the Diels-Alder reaction has made some otherwise difficultly accessible ring systems readily available.

3.1.1.- Cycloadditions with open chain dienes

3,6-Pyridazinedione (II) reacts with butadiene and its derivatives to give the adducts XXIV.



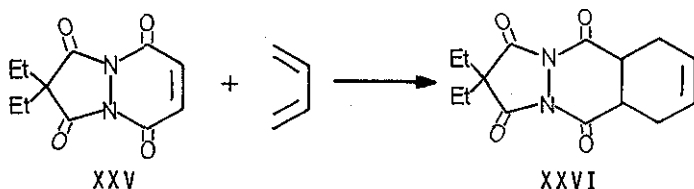
II

XXIV

a: R₁=R₂=R₃=R₄=H (Ref. 2,3,6)b: R₁=R₃=R₄=H; R₂=CH₃ (Ref. 23)c: R₁=R₄=H; R₂=R₃=CH₃ (Ref. 2,3)d: R₁=R₃=R₄=H; R₂=Cl (Ref. 23)e: R₁=R₄=H; R₂=R₃=Cl (Ref. 23)f: R₁=R₄=Ph; R₂=R₃=H (Ref. 18)

4,5-Dihydro-3,6-pyridazinedione (III) and 4,5-difluoro-3,6-pyridazinedione (IV) behave in analogous fashion when they react with butadiene and its derivatives^{2,6}.

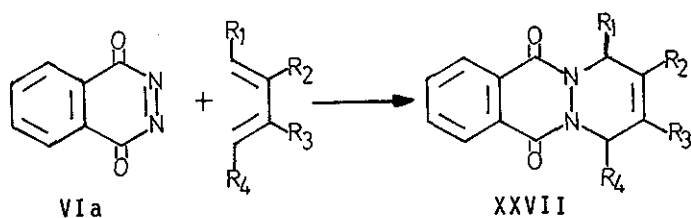
It must be pointed out that, of the two potentially dienophilic double bonds of II, only the -N=N- double bond reacts and no reactions involving the -C=C- double bond are known. Attempts to bring the -C=C- double bond into reaction by treating the adducts XXIV with excess diene have been unsuccessful²⁴. However, some compounds related to II, such as XXV, form adducts (XXVI) with the -C=C- double bond²⁵.



XXV

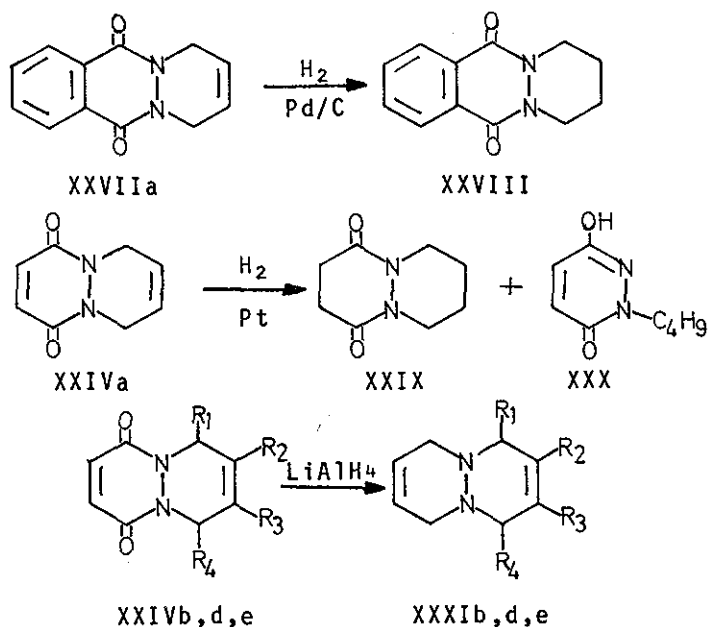
XXVI

The reactions of 1,4-phthalazinedione (VIa) with butadiene and derivatives follow the same pattern as II and made it possible to obtain the adducts XXVII, representatives of the pyridazino[1,2-b]-phthalazine heterocyclic system not previously known.

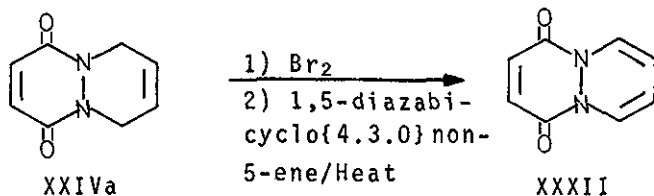


- a: $R_1=R_2=R_3=R_4=H$ (Ref. 1,2)
 b: $R_1=R_3=R_4=H$; $R_2=CH_3$ (Ref. 18,26)
 c: $R_1=R_4=H$; $R_2=R_3=CH_3$ (Ref. 2,3)
 d: $R_1=R_3=CH_3$; $R_2=R_4=H$ (Ref. 26)
 e: $R_1=OAc$; $R_2=R_3=R_4=H$ (Ref. 26)
 f: $R_1=R_4=OAc$; $R_2=R_3=H$ (Ref. 26)
 g: $R_1=R_4=Ph$; $R_2=R_3=H$ (Ref.18)

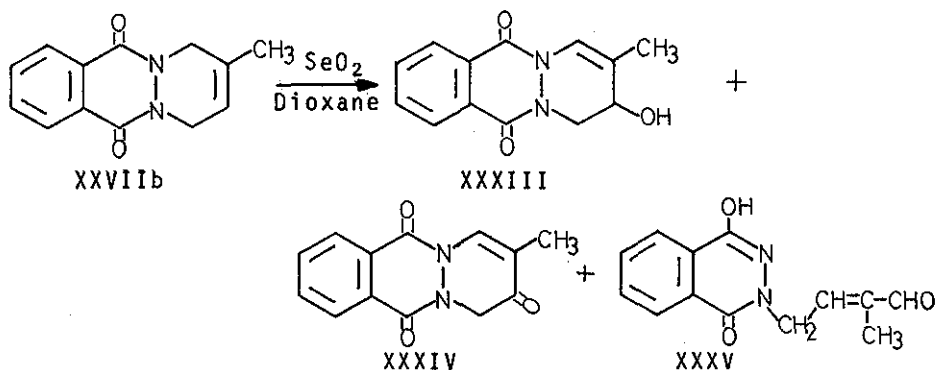
Some chemical transformations of adducts XXIV and XXVII have been studied. Hydrogenation of adduct XXVIIa affords 1,2,3,4-tetrahydropyridazino{1,2-b} phthalazine-6,11-dione (XXVIII)¹ and hydrogenation of XXIVa gives 1,2-succinylhexahydropyridazine (XXIX) as well as 2-butyl-6-hydroxy-3(2H)-pyridazinone (XXX)². Reduction of XXIV b,d,e with lithium aluminium hydride gives XXXI b,d,e^{2,3}.



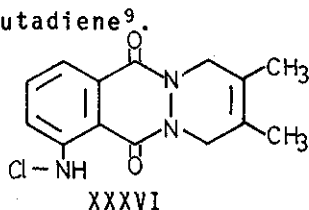
Diazanaphthoquinone XXXII, whose UV spectrum indicates the presence of the aromatic ten π -electron ring system, was prepared by bromination of the adduct XXIVa followed by treatment with 1,5-diazabicyclo{4.3.0}non-5-ene²⁷.



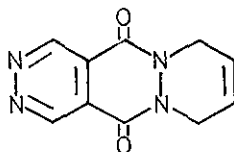
The oxidation of the adducts XXIV and XXVII with selenium dioxide in dioxane leads to the hydroxy- and keto-derivatives, with rearrangement of a double bond, together with α,β -unsaturated aldehydes formed through ring opening. Thus, XXVIIb leads to XXXIII, XXXIV and XXXV²⁶.



The substituted derivatives of 1,4-phthalazinedione (VI) show also a strong dienophilic character. VIc, VIId and VIe form Diels Alder adducts with butadiene, 2,3-dimethylbutadiene or 1,4-diphenylbutadiene^{9,28} and VIf, VIg, VIh and VIi behave in the same manner with 2,3-dimethylbutadiene^{9,10}. Diazaquinone VIb, when prepared by Kealy's method, affords the compound XXXVI by reaction with 2,3-dimethylbutadiene⁹.



The presence of heteroatoms in the ring fused to the diazaquinone ring does not appreciably modify its dienophilic character and thus butadiene or 2,3-dimethylbutadiene undergo cycloaddition with diazaquinones VII-XI¹¹ and XII¹². The adduct of XII with butadiene is of some interest since it is representative of the novel 2,3,5a,9a-tetraazaanthracene heterocyclic system.

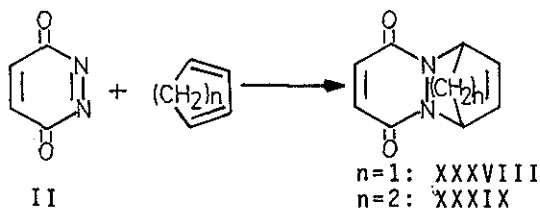


XXXVII

Butadiene, 2-methylbutadiene and 2,3-dimethylbutadiene react also with polycyclic diazaquinones XVIIa and XVIIb^{10,29}. The reaction of *N*-bromosuccinimide with adducts obtained from XVIIa has been reported to yield different addition or substitution products depending on the solvent and the reaction conditions²⁹.

3.1.2.- Cycloadditions with cyclic dienes

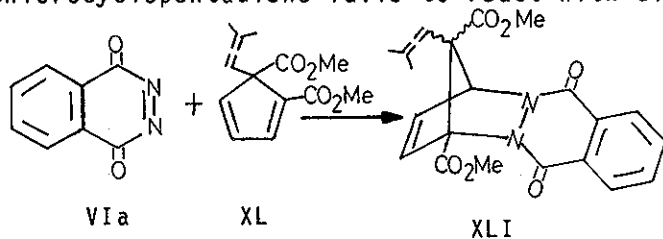
3,6-Pyridazinedione (II) also forms adducts with cyclic dienes such as cyclopentadiene (XXXVIII) and cyclohexadiene (XXXIX)^{2,3} and the same was observed with 1,4-phthalazinedione (VIa) and its derivatives VIb, VIc and VIf, in which the substituents do not prevent the reaction^{9,30}.



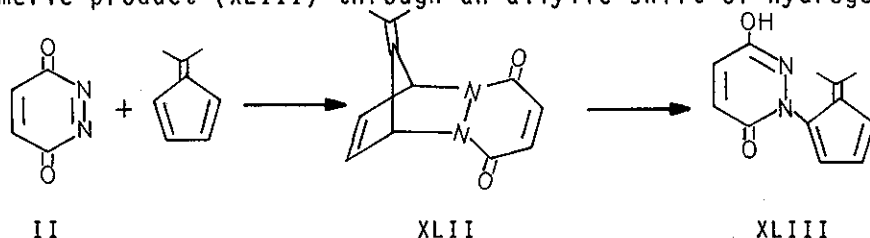
Polyheterocyclic diazaquinones VII, VIII, XIII, XIV and XVI react also with cyclopentadiene or cyclohexadiene to yield the corresponding Diels-Alder adducts^{11,13}, but XV fails to do so¹³.

Deactivated cyclopentadiene derivatives, such as 5-(3',3'-dimethylallyl)-1,5-bis(carbomethoxy)cyclopentadiene (XL) forms the cycloadducts XLI with 1,4-phthalazinedione (VIa)³¹, but hexa

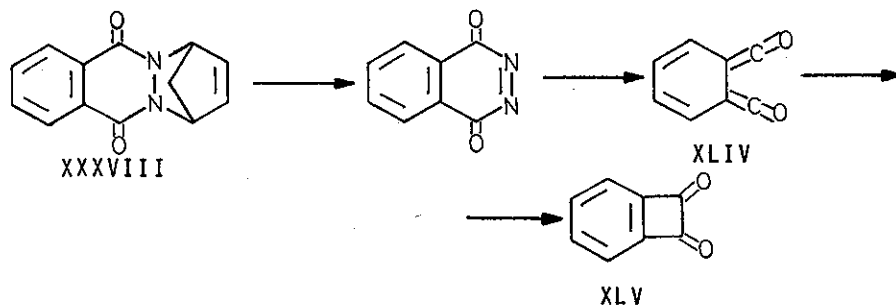
chlorocyclopentadiene fails to react with diazaquinones¹¹.



3,6-Pyridazinedione and 6,6-dimethylfulvene give an adduct (XLII) which undergo rearrangement in the solid state to an isomeric product (XLIII) through an allylic shift of hydrogen².

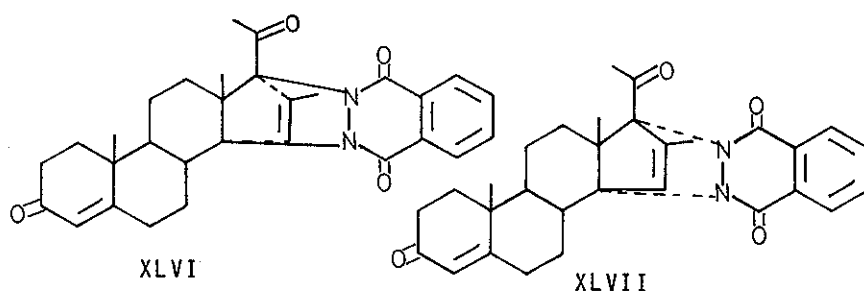


Vapour phase pyrolysis of cyclopentadiene adduct XXXVIII affords benzocyclobutenedione (XLV)³². This process represents a useful synthetic route to benzocyclobutenedione and can be rationalised as a retro-Diels-Alder reaction followed by nitrogen extrusion from 1,4-phthalazinedione. The bis-ketene XLIV could then close to give benzocyclobutenedione.

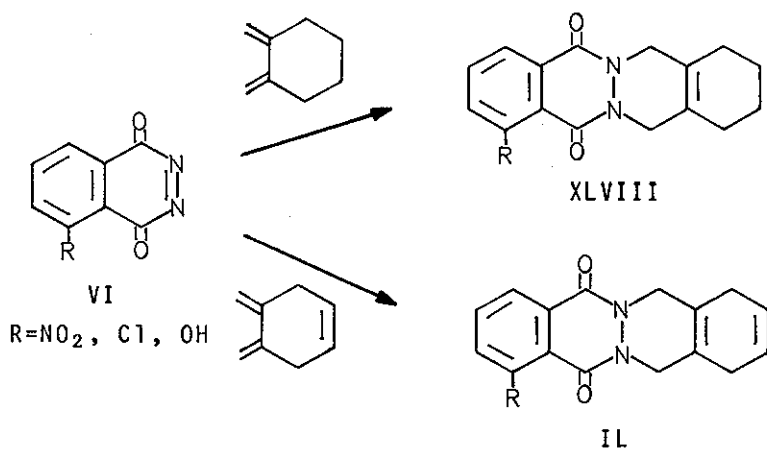


Diels-Alder cycloadditions of 3,6-pyridazinedione (II) and 1,4-phthalazinedione (VIa) to steroidal dienes have been studied³³⁻³⁵. Thus, 1,4-phthalazinedione (VIa) reacts with 16-methylpregna-4,14,16-triene-3,20-dione to give the two possible adducts XLVI and XLVII, to which the 14 β ,17 β and 14 α , 17 α con-

figurations were assigned.

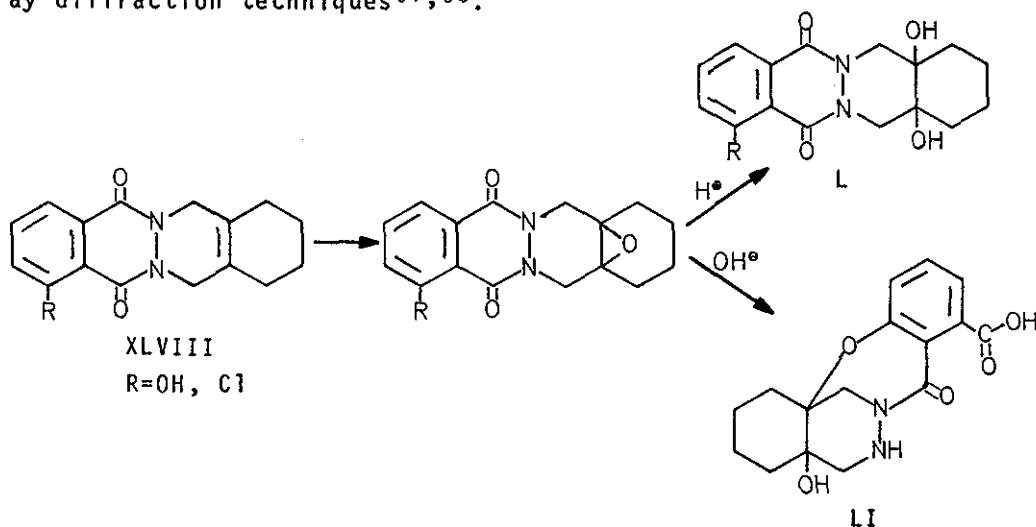


Substituted diazatetracyclic compounds referable to tetracyclines of known activity have been synthesized by Diels-Alder reaction of substituted phthalazinediones VI_{d,g,h} with 1,2-dimethylenecyclohexane (XLVIII) and 1,2-dimethylene- Δ^4 -cyclohexene (IL)¹⁰.

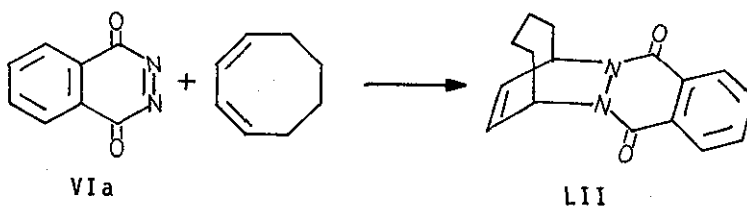


Epoxidation of adducts XLVIII from 5-hydroxy- and 5-chlorophthalazine-1,4-dione followed by solvolytic opening of the oxirane ring in acid medium has been carried out in order to modify their biological behaviour by introducing a 1,2-diol group at angular positions. Compounds L are thus obtained³⁶. Attempts to obtain the diol derivatives L by solvolytic opening of the oxirane ring when R=OH in alkaline medium afford a new condensed 1,4-oxazepine derivative, namely 4-carboxy-8,8a,9,10,11,12-hexahydro-5H,12H,12bH-8a-hydroxy-5-oxophthalazine{8a,2bc}benzo{f}{1,4}oxa-

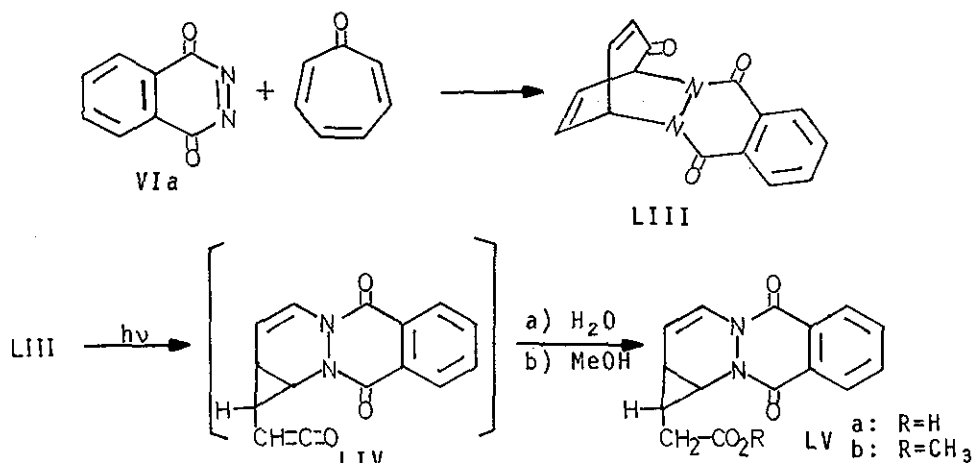
zepine (LI), whose structure was established by single crystal X-ray diffraction techniques^{37,38}.



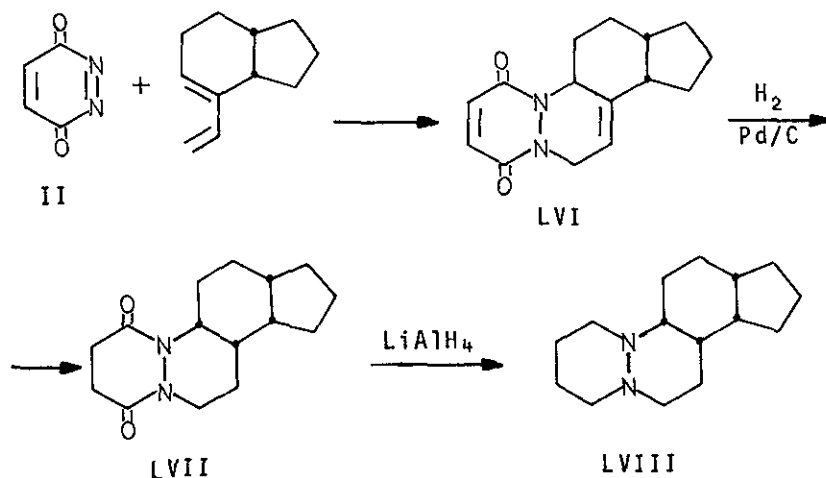
The dienophilic reactivity of diazaquinones allows them to undergo cycloaddition reactions with such unreactive dienes as 1,3-cyclooctadiene^{9,18,39}. The compound LII, formed with 1,4-phthalazinedione (VIa)³⁹, is the first reported Diels-Alder adduct of 1,3-cyclooctadiene and its formation at low temperature emphasizes the potent dienophilic character of diazaquinones.



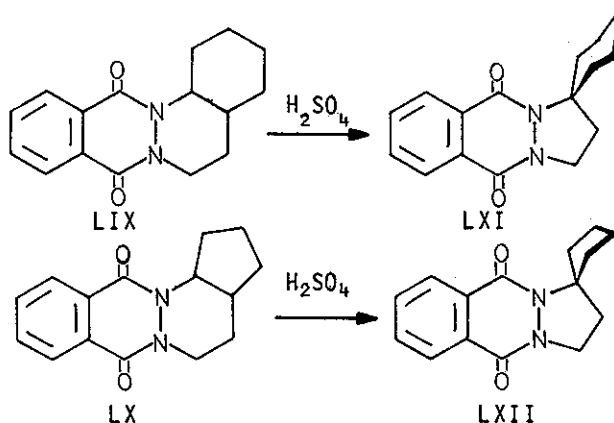
Treatment of tropone with 3,6-pyridazinedione (II) does not give any product, but 1,4-phthalazinedione (VIa) forms the adduct LIII with tropone⁴⁰. Irradiation of the compound LIII in methanol and in acetonitrile/water gave LVa and LVb respectively, formed by addition of water or methanol to the initially formed ketene LIV.



By taking advantage of the reactivity of diazaquinones towards 1-vinylcycloalkenes, the introduction of the 1,2-diazine group into the steroidal skeleton has been accomplished in a novel synthesis of bridgehead diazasteroids^{41,42}. Thus, Diels-Alder reaction of 3,6-pyridazinedione (II) with 2,3,3a,4,5,7a-hexahydro-7-vinylindene yielded LVI, which is easily hydrogenated to give LVII in which the B/C ring junction is *cis*. Reduction of LVII with lithium aluminium hydride afforded the tetrasubstituted hydrazine LVIII.

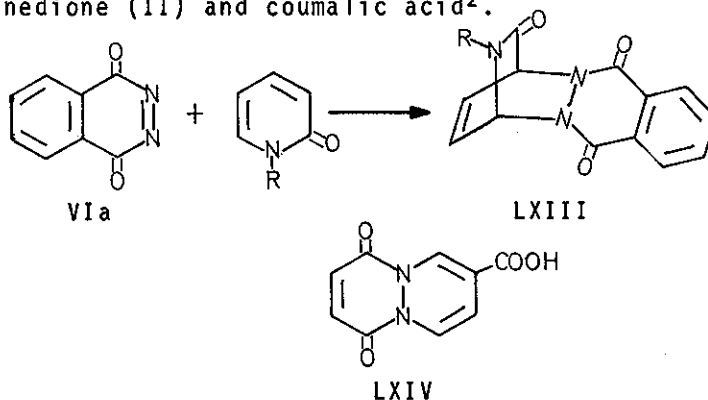


The reaction has been extended to other vinylcycloalkenes and diazaquinones^{41,42}. The hydrogenated adducts obtained from 1,4-phthalazinedione and 1-vinylcyclohexene (LIX) and 1-vinylcyclopentene (LX) were isomerized with concentrated sulfuric acid to give the spiro-compounds LXI and LXII, respectively, by ring contraction⁴³.



3.1.3.- Reactions with dienes containing heteroatoms

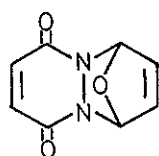
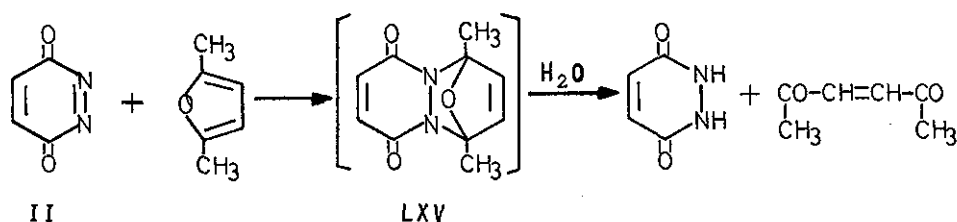
Diels-Alder reactions of diazaquinones have been extended to heterocyclic dienes. Cycloaddition of 1,4-phthalazinedione (VIa) with a variety of N-substituted pyridones afforded novel azabicyclic structures LXIII⁴⁴ and adduct LXIV is obtained from 3,6-pyridazinedione (II) and coumalic acid².



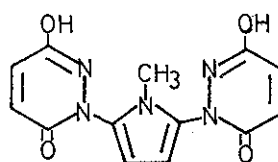
The reaction of diazaquinones with furans has been widely studied. Kealy reported² a rapid reaction of furan and 2,5-dimethylfuran with 3,6-pyridazinedione (II) but Diels-Alder adducts were not isolated. The product from furan precipitates from solution but decomposes exothermically on isolation. The adduct from 2,5-dimethylfuran (LXV) undergoes hydrolysis during isolation to give maleic hydrazide and 1,2-diacetylene. However, more recently, the isolation of the adduct LXVI from 3,6-pyridazinedione (II) and furan has been claimed^{2,3}.

Reaction of 1,4-phthalazinedione (VIa) with furan does not lead to the Diels-Alder adduct^{4,5}. The open conjugation of vinylfuran reacts with 1,4-phthalazinedione (VIa) but the adduct is too unstable to be isolated^{4,6}.

3,6-Pyridazinedione (II) has also been tested towards N-methylpyrrole². The Diels-Alder adduct was not isolated but instead a compound of structure LXVII was obtained.



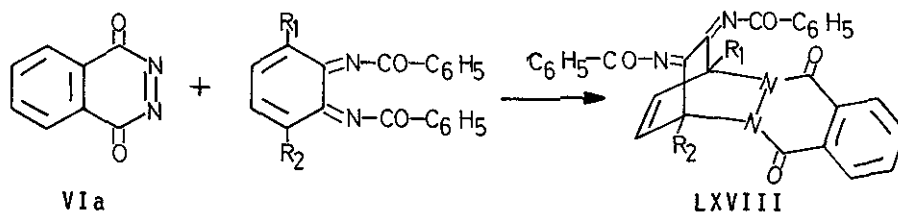
LXVI



LXVII

The reactivity of diazaquinones towards dienes containing heteroatoms in their conjugated systems was studied and the lack of reaction between 1,4-phthalazinedione (VIa) and dehydroindigo or dimethylfuran¹⁷, benzalazine, 2,5-dimethyl-1,3,4-oxadiazol and cinamalaniline^{4,6} nitrogenated heteroconjugations was found. When dienes such as o-quinonedibenzimides are used, the reaction

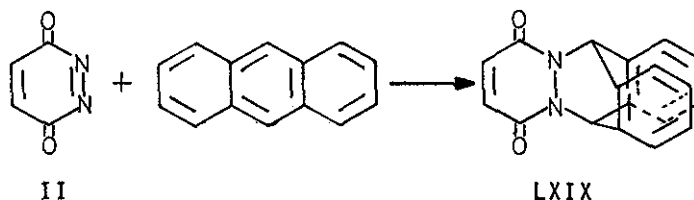
always takes place with the homoconjugation affording the adducts LXVIII, leaving the heteroconjugation unaffected¹⁷.



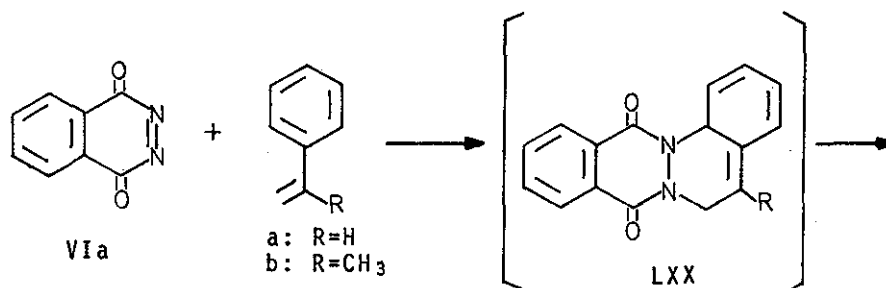
a: $R_1=R_2=H$; b: $R_1=CH_3, R_2=H$; c: $R_1=R_2=CH_3$

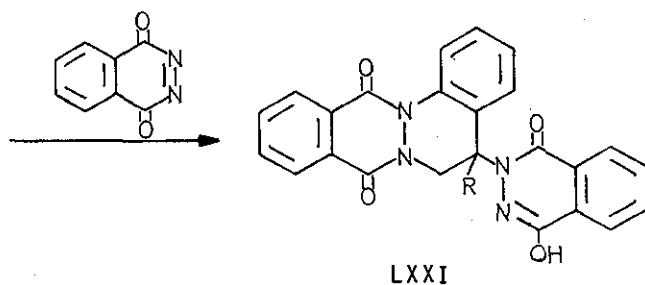
3.1.4.- Reactions with aromatic hydrocarbons

The extraordinary reactivity of diazaquinones as dienophiles allows them to react with aromatic hydrocarbons. With 3,6-pyridazine-dione (II) and anthracene, the adduct LXIX is formed⁶. This normal 9,10-anthracene addition is also observed with III and VIa⁶ and with polyheterocyclic diazaquinones such as XII¹².



Diazaquinones react as well with vinylaromatic compounds such as styrene, anethole, isosafrole⁴⁷ and α -methyl- and β -methylstyrene⁴⁸, but great difficulties are found in the isolation of the reaction products. When adducts LXX are formed, these undergo reaction with a second molecule of diazaquinone. According to the scheme below, 1,4-phthalazinedione(VIa) leads to LXXIa and

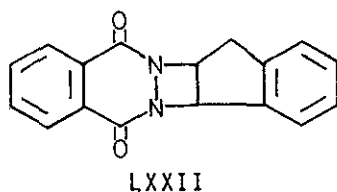




LXXIb by reaction with styrene and α -methylstyrene respectively. β -Methylstyrene fails to give an adduct with 1,4-phthalazinedione (VIa)⁴⁸.

3.2.- {2+2} Cycloaddition reactions

Although diazaquinones do not easily undergo {2+2} cycloaddition reactions, some cycloadditions of this kind have been reported. This process provides a one-step synthesis of derivatives of diazacyclobutane. The first example reported was the reaction of 1,4-phthalazinedione (VIa) with indene³⁹, which afforded LXXII. Similarly, phenanthrene seems to give an analogous adduct by cycloaddition involving the 9,10-bond³⁹. The vapour phase pyrolysis of LXXII affords benzocyclobutenedione and indene³².



In some reactions of diazaquinones with styrene {2+2} cycloaddition to the ethylenic double bond takes place. However, the product thus formed (LXXIII) undergoes addition of a molecule of water, *t*-butanol or acetic acid (originated as by-products in the preparation of the diazaquinone). Thus, the reaction of 3,6-pyridazinedione (II) with styrene affords the compounds LXXIVa, b, c depending upon the procedure used to generate the diazaquinone⁴⁷.

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