CYCLOADDITION TO sym-TETRAZINES (THE CARBONI–LINDSEY REACTION) (REVIEW)

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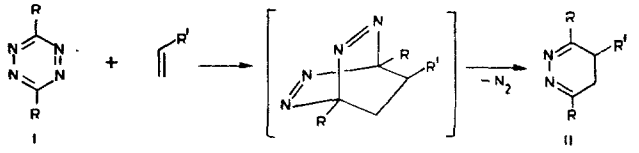
The available data on the reaction of sym-tetrazines with various unsaturated compounds from 1958 to 1980 are systematized. The reaction of sym-tetrazines with alkenes, alkadienes, alkynes, and unsaturated carbocycles and heterocycles are presented.

The relatively recently discovered one-step method for the synthesis of pyridazines and their dihydro derivatives from readily accessible sym-tetrazines and unsaturated compounds has rather rapidly acquired the status of a name reaction (the Carboni–Lindsey reaction [1]) after the establishment of its great synthetic possibilities and the preparation of not only hydrazines but also many other heterocyclic systems. The possiblity of the use of the most nitrogen-rich monocyclic tetrazine system as a source for the preparation of complex (including skeletal) carbocylic compounds was extremely unexpected.

The ability of tetrazines to react with unsaturated compounds (an allene) was first mentioned casually in 1957 by Carboni in a patent [2] that establishes the priority of a method for the synthesis of tetrazines with fluoroalkyl substituents. This reaction is a diene synthesis with "inverse electronic character" of the addends (with the diene as the acceptor and the dienophile as the donor). The s-cis-fastened azadiene system of one of the most π-deficient and most active π-acceptor heterocycles [3], viz., 1,2,4,5- or sym-tetrazines, acts as the diene, while the most diverse compounds with multiple bonds act as the dienophiles:



I II

It is apparent from this scheme that the Carboni–Lindsey reaction includes a direct Diels–Alder reaction and retrodiene decomposition. The reaction is irreversible in connection with the fact that the pronounced localization of the N=N bond in the highly strained adduct favors extrusion of molecular nitrogen. A lower orientation of the lower unoccupied molecular orbitals (LUMO) and higher occupied molecular orbitals (HOMO) of the diene as compared with the corresponding orbitals of the dienophile is characteristic for the inverse synthesis [4], and the interaction of the HOMO of the dienophile with the IUMO of the diene, which leads to acceleration of the reaction by electron-donor substituents in the dienophile and by electron-acceptor substituents in the diene (tetrazine), turns out to be the determining factor.

The Carboni–Lindsey reaction is very convenient in a preparative respect owing to visual monitoring of its course from the evolution of nitrogen gas and the disappearance of the red color of the tetrazine.

This review should be regarded as the first attempt to summarize and systematize data on the reaction of tetrazines with compounds that contain multiple bonds that have been accumulated in the last two decades. The systematization was accomplished by affiliation of the dienophile fragment that participates directly in the reaction with one or another class of organic compounds. In bridged systems, in which this sort of assignment can only be provisional, we will arbitrarily give priority to the smaller ring.

Reactions with Acyclic Unsaturated Compounds

Alkenes. In the case of alkenes Carboni and Lindsey were the first to make a detailed examination of the reaction with tetrazines [5, 6]. They did not investigate the mechanism

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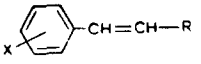
TABLE 1. Rate Constants for the Reaction of 3,6-Bis(carbomethoxy)tetrazine (I, R = CO_2CH_3) with Dienophiles (30°C, dioxane) [8, 12]

Substituted styrenes	$10^5 \cdot k_2$	Substituted styrenes	$10^5 \cdot k_2$
α-Morpholinostyrene	470 000	Ethylene	36 300
p-Methoxystyrene	25 000	Ethyl vinyl ether	21 600
Styrene	6 550	1-Hexene	5 560
p-Nitrostyrene	872	trans-4-Octene	330
α-Methylstyrene	600	Methyl acrylate	117
trans-β-Methylstyrene	145	cis-4-Octene	48
α-Phenylstyrene	3	Acrylonitrile	0,93

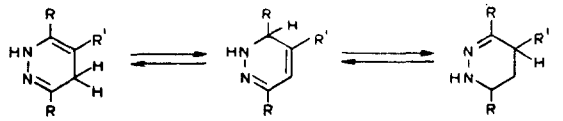
of the reaction but noted that electron-donor substituents in the dienophile and electron-acceptor substituents in the tetrazine facilitate the reaction. In this connection, they expressed the assumption that the olefin initially attacks the tetrazine at the C_3 and C_6 atoms. The products of the reaction are dihydropyridazines II, which are capable of prototropic transitions. Carboni and Lindsey demonstrated that acceptor olefins such as maleic acid, tetracyanoethylene, azodicarboxylic ester, and maleic anhydride, which are powerful dienophiles in the Diels–Alder reaction, do not react with tetrazines. They also pointed out that alkenes of the R'–CH=CH_2 type are more active with respect to tetrazines than alkenes of the R'–CH=CH–R' type. Thus acrolein reacts with tetrazine I (R = $CHFCF_3$) more rapidly than crotonaldehyde, while the sterically hindered tetramethylethylene adds to this tetrazine only with great difficulty, despite the high degree of electron enrichment of the double bond. The first semiquantitative data of Carboni and Lindsey on the relative reactivities of styrenes III in this reaction also illustrate the noted principle – styrene derivatives with a terminal methylene group are more reactive than any of the β-substituted styrenes.



III

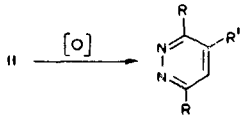
X=*p*-OCH_3, R=H>X=H, R=H≫X=*p*-OCH_3, R=CH_3>X=*o*-CH_3, R=CH_3>X=H, R=CH_3)))X=*p*-OCH_3, R=$CO_2C_2H_5$ or X=H, R=C_6H_5

In their analysis of the NH absorption in the IR spectra of dihydropyridazines Carboni and Lindsey postulated the existence of various tautomers IIa-IIc and gave preference to 1,4-dihydro form IIc:

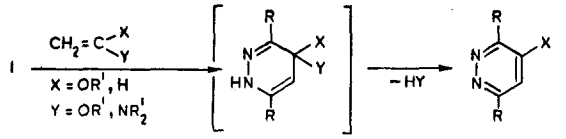


IIa IIb IIc

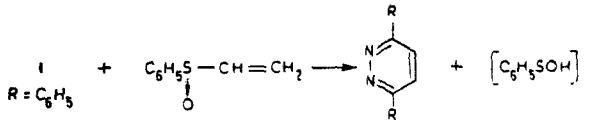
The dihydropyridazines that are formed in the reaction of tetrazines with olefins usually undergo smooth oxidation either in the course of reaction by excess tetrazine or air oxygen or after isolation – by means of various oxidizing agents – to the corresponding aromatic pyrazines:



However, pyridazines are formed without the participation of an oxidizing agent when vinyl ethers, enamines, and acetals are used as the olefins [7-13]:

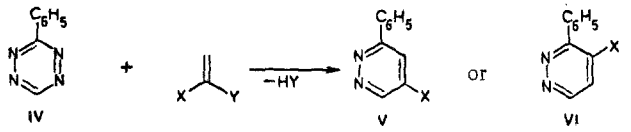


The quest to avoid working with acetylene at high temperatures and pressures led to the creation of an original synthetic reagent, viz., phenyl vinyl sulfoxide, which eliminates benzenesulfonic acid during the cycloaddition [14]:



The product of the reaction of tetrazine with ethylene was initially incorrectly assigned a 1,2-dihydro structure, despite the quite purposeful use of IR spectroscopy [15]. The definitive 1,4-dihydro structure IIc (R = CO_2CH_3, R' = H) was proved shortly thereafter by PMR spectroscopy [16]. In the overwhelming majority of cases the R' substituent attached to the double bond of the alkene is attached to the tetrahedral carbon atom in the resulting dihydropyridazine (structure IIc) [5, 15]. However, when the substituent is a nitrile group (acrylonitrile), the resulting dihydropyridazine also has a 1,4-dihydro structure, but in this case the nitrile group is attached to the trigonal carbon atom (structure IIa) [5, 7].

The reaction of 3-phenyltetrazine (IV) with ketene acetals is highly regioselective, regardless of variations in the temperature and the solvent [9]:

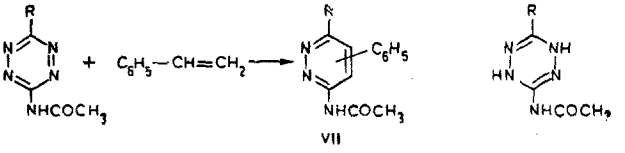


IV V VI

$X=Y=OC_2H_5$; $X=N(CH_3)_2$, $Y=OC_2H_5$ or $X=N(CH_3)_2$, $Y=SC_2H_5 \rightarrow$ VI, but $X=Y=N(CH_3)_2 \rightarrow$ V

It is also apparent that a good leaving group (Y = OC_2H_5, SC_2H_5) is split out exclusively from the "meta" position relative to the phenyl ring to give pyridazines VI, whereas in the case of a poorer and more bulky group [Y = $N(CH_3)_2$] splitting out occurs only from the "ortho" position to give pyridazine V.

The presence in the tetrazine ring of a powerful electron-donor substituent, viz., an amino group, completely suppresses the Carboni—Lindsey reaction with styrene or cyclohexene, but simple acetylation of this amino group makes it possible for the reaction to proceed with great ease. The reaction products are aromatized pyridazines VII (and the corresponding dihydrotetrazines), but the regioselectivity of the reaction was not established [17]:



VII

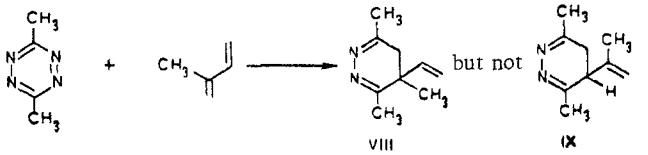
Kinetic studies [8, 12, 18] of the Carboni—Lindsey reaction make it possible to give the quantitative characteristics of the effects of steric and electronic factors (Table 1).

With styrene as the partner (50°C in dioxane) the reactivities of 3,6-disubstituted tetrazines I decrease in the order CO_2CH_3 > p-$NO_2C_6H_4$ > $CH_3 \approx C_6H_5$ [18]. In the same studies [8, 18] it is noted that there is a slight dependence of the rate of the reaction of tetrazine I (R = C_6H_5) with styrene on the nature of the solvent [dimethylformamide (DMF), nitrobenzene, ethyl benzoate, dioxane, and toluene at 90°C]; this is characteristic for the diene synthesis. Similar results were obtained for the reaction of various diaryltetrazines with styrene in the case of another set of solvents, viz., dioxane, acetonitrile, benzonitrile, and toluene [19]. In addition, the small values of the activation enthalpies and, on the other hand, the high absolute values of the activation entropies [19] indicate the ease with which the reaction occurs and the high degree of orderliness of the transition state, and this may serve as a satisfactory argument in favor of a concerted mechanism for the cycloaddition.

The preparative and analytical significance of the Carboni—Lindsey reaction was revealed in a study by Nenitzescu and co-workers [15]. Thus 3,6-bis(carbomethoxy)tetrazine was recommended as a reagent for the titrimetric determination of olefins; the end of the reaction is noted from the abrupt disappearance of the red color of tetrazine at the titration point. The use of alkenes for the synthesis of pyridazine was also described in [20-22].

Alkadienes. In conformity with the principle of retention of orbital symmetry, butadiene and its derivatives react with tetrazines at one double bond [5, 6]. The reactions of

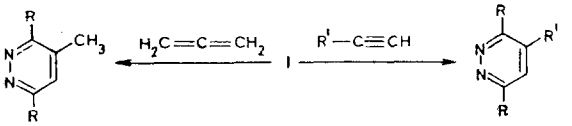
tetrazine I (R = $CHFCH_3$) with butadiene, 2,3-dimethylbutadiene, and isoprene have been studied; the unsymmetrical character of the latter made it possible to obtain additional information from a structural investigation of the product of its reaction with 3,6-dimethyltetrazine (I, R = CH_3). It was shown that this product is a vinyl (VIII) rather than an isopropenyl (IX) derivative of dihydropyridazine (VIII is not oxidized to the corresponding pyridazine), which in this case constitutes evidence in favor of the determining role of electronic factors in the dienophile.



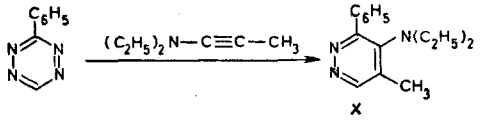
VIII IX

The cumulated alkadine allene is the only dienophile claimed in Carboni's first patent [2]. In its reactions with tetrazines it behaves like a latent alkyne, and methylpyridazines are formed directly [2, 5, 6].

Alkynes. Acetylenic hydrocarbons, like alkadienes, react with tetrazines to give immediately aromatic pyridazines [5, 6, 11, 18, 20-22]; they react under considerably more severe conditions than olefins, which is readily explained by the increased electron-acceptor character of the triple bond:

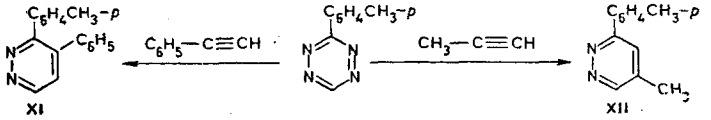


The problem of the regioselectivity of the reaction of tetrazines with alkynes was posed, although not explicitly, in [24], which was devoted to a study of the Carboni—Lindsey reaction with enamines. It was found that the reaction of 3-phenyltetrazine with 1-diethylaminopropyne is highly regioselective — 3-phenyl-4-diethylamino-2-methylpyridazine (X) was obtained in quantitative yield:



X

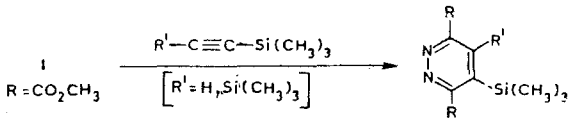
This problem was dealt with in somewhat greater detail but still schematically in [25], in which unsymmetrical 3-(p-tolyl)tetrazine was subjected to reaction with phenylacetylene and methylacetylene. High regioselectivity was again noted: 3,4- and 3,5-disubstituted pyridazines XI and XII, respectively, were obtained:



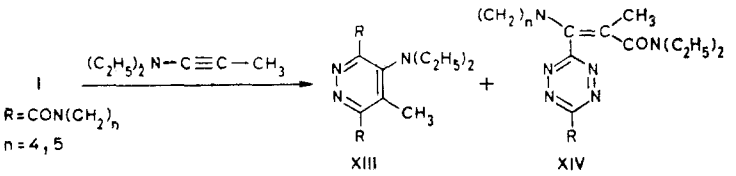
XI XII

Using the concept of the retention of orbital symmetry and calculations by the extended Huckel method (EHM) (which are not presented in the paper), Meresz and Foster-Verner [25] assume that the total change in the orientation in this reaction may be due to a considerable extent to the effects of secondary orbital overlapping.

In 1974 Birkofer and Stilke [21] synthesized mono- and disilylated pyridazines by subjecting the corresponding acetylenes to the reaction:

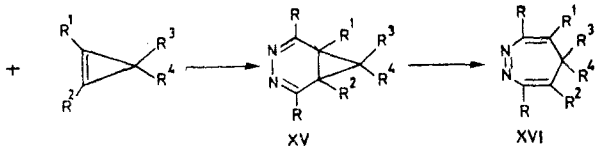


It was observed that in addition to the product of normal [4 + 2] cycloaddition (XIII) of 1-diethylaminopropyne to 3,6-dicarboxamide derivatives of tetrazine, one observes the formation of XIV, which can be conceived of as being the result of [2 + 2] cycloaddition to the substituent [27]:

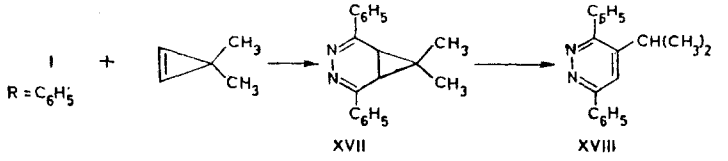


Reactions with Alicyclic Unsaturated Compounds

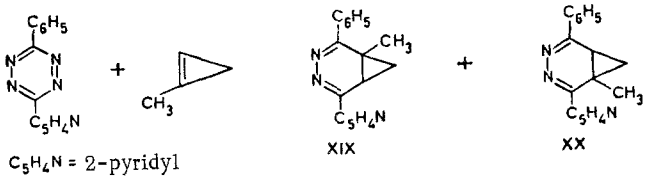
Cyclopropene and Its Derivatives. The problem of the mutual valence isomerizations of 1,2-diazepines XVI and diazanorcaradienes XV underwent new development after the discovery of extremely mild and one-step methods for the synthesis of these compounds. Cyclopropene and its numerous derivatives react with tetrazines to give initially bicyclic compounds XV with a diazanorcaradiene structure, which, depending on the nature of the substituents and the conditions under which the reactions were carried out, are capable of undergoing "expansion" to 1,2-diazepines XVI [12, 28-30].



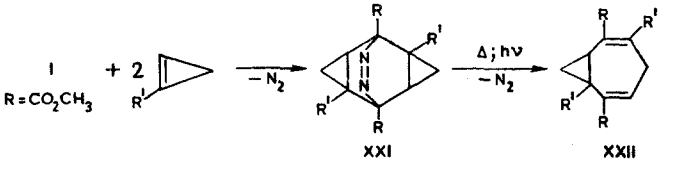
However, heating the product (XVII) of the reaction of 3,6-diphenyltetrazine with 3,3-dimethylcyclopropene in DMSO at 160°C does not lead to a diazepine but rather to isopropylpyridazine XVIII [31].



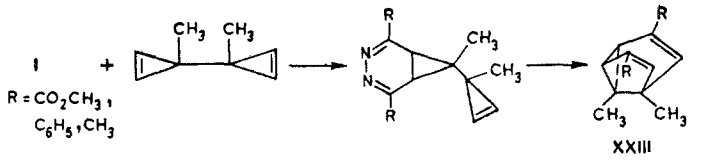
The increased reactivity of cyclopropenes leads to a decrease in the selectivity of their reactions with tetrazines [31] — the XIX:XX isomer ratio is 3:1.



If the cyclopropene dienophile is used in excess amounts, the resulting diazanorcaradiene XV adds yet another molecule of cyclopropene, and adduct XXI upon photolysis or thermolysis loses yet another nitrogen molecule retained from the starting tetrazine to give homotropylidene XXII [32]:

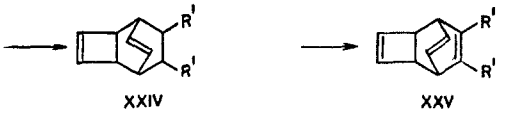


There is no doubt that precisely this reaction served as the prototype of a rare (with respect to its beauty) molecular design — the one-step synthesis of semibulvalene XXIII [33], in which intramolecular cycloaddition of cyclopropene to diazanorcaradiene culminates in retrodegradation:



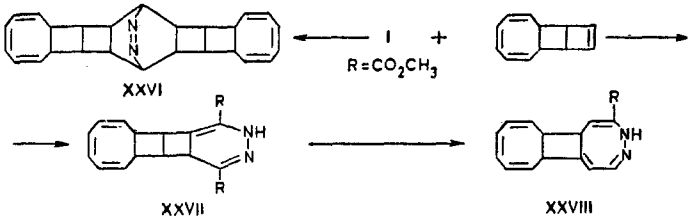
When the methyl groups in the biscyclopropene are replaced by phenyl groups, the reaction with tetrazines proceeds in accordance with the normal scheme — bisdiaznorcaradienes are formed [33].

Four-Membered Unsaturated Carbocycles. Cyclobutene [15] and its condensed derivatives [34-42] react with tetrazines via the standard scheme; the double bond of cyclobutene, which is included in the composition of polycyclic systems, is more dienophilic than the double bond in adjacent or remote rings with large dimensions, such as XXIV and XXV (the arrows indicate the site of addition of tetrazine).



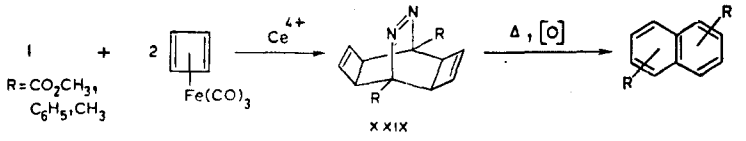
XXIV XXV

The very strained structure of two condensed four-membered rings makes, on the one hand, the double bond of cyclobutene very reactive [two molecules of the dienophile react with tetrazine under mild conditions (XXVI)] and, on the other, promotes valence isomerization of adduct XXVII to diazocine derivative XXVIII [34].



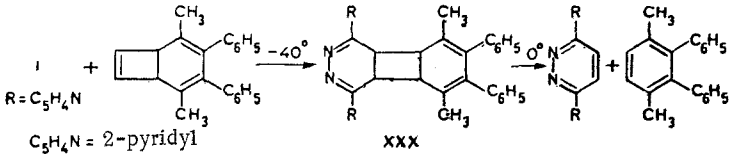
XXVI XXVII XXVIII

The reactivities of cyclobutadiene [38, 43-45] and benzocyclobutadiene [44] are so high that products of double addition of the dienophiles are formed regardless of the reagent ratio. The exo,exo-adducts XXIX that are obtained in conformity with control by secondary orbital interactions are converted by thermolysis to 2,6- (R = CO_2CH_3) [44, 45] or 1,5-substituted (R = CH_3) dihydronaphthalenes, which undergo aromatization as a result of oxidation:



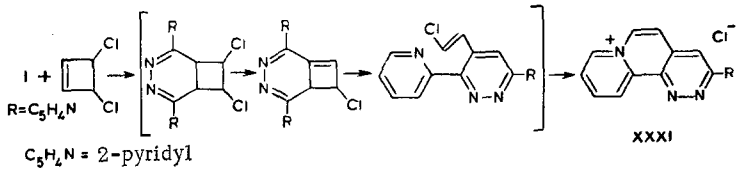
XXIX

Three-ring compound XXX, which is stable at −20°C but undergoes symmetry-prohibited secondary retrodegradation at 0°C, has been obtained [39]:



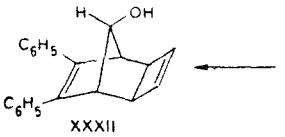
C_5H_4N = 2-pyridyl XXX

3,6-Diphenyltetrazine does not react with cis-3,4-dichlorocyclobutene; however, when the latter was refluxed in chlorobenzene with 3,6-di(2-pyridyl)tetrazine [37, 38], 8a-azonia-3,4-diazaphenanthrene salts XXXI, the structure of which was proven by means of x-ray diffraction analysis, were isolated for the first time. Thus the reaction includes cycloaddition to the tetrazine and electrocyclization at the substituent with prior conrotatory opening of the cyclobutene ring:



C_5H_4N = 2-pyridyl XXXI

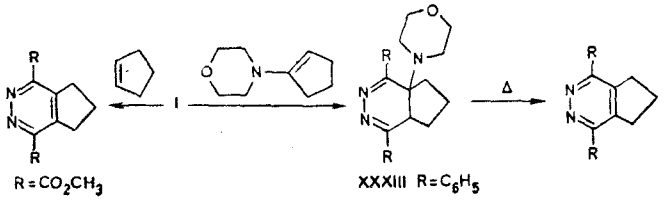
In a study of the kinetics of the reaction of alcohol XXXII with 3,6-di(2-pyridyl-tetrazine, McCay and co-workers [40] directed their attention to the sharp increase in the rate when chloroform was replaced by DMSO as the solvent. They explained this phenomenon by a



XXXII

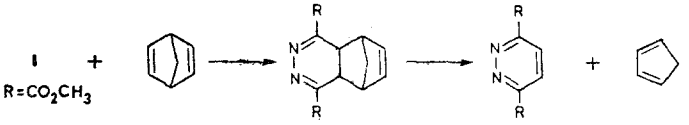
change in the ratio of rotamers of XXXII with intra- and intermolecular bonds in media with different polarities. The participation of the oxygen and hydrogen atoms of the hydroxy group of alcohol XXXII, as well as the unshared pairs and vacant oribtals of the atoms of the other groupings in the same position, was analyzed by means of perturbation theory in terms of orbital interaction through space [41, 42].

Five-Membered Unsaturated Carbocycles. Cyclopentene has been subjected to reaction with tetrazines more than once [5, 7, 15, 18]; however, in contrast to other carbocycles, it does not form a dihydropyridazine, but an aromatic compound is obtained immediately [15]. On the other hand, contrary to expectations, it is difficult to split out an amine residue from enamine derivative XXXIII [7]:



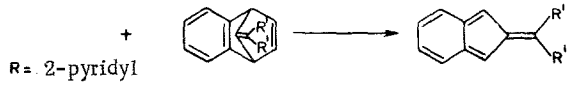
R=CO_2CH_3 XXXIII R=C_6H_5

Norbornene [12] and benzvalene [46, 47] readily form the corresponding dihydropyridazines; benzvalene, like cyclopropenes and cyclobutadienes, is capable of undergoing double addition [47]. The addition of norbornadiene to tetrazines makes it possible to realize retrodiene synthesis under mild conditions [5, 6, 12, 48]:



R=CO_2CH_3

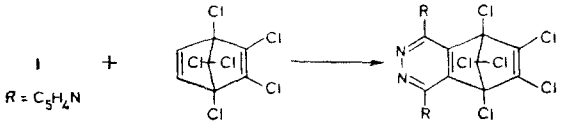
The use of this reaction has led to the production of the difficult-to-obtain isobenzofulvenes [48-52]:



R= 2-pyridyl

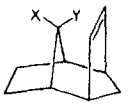
Sasaki and co-workers [53] regard the formation of diazafluoranthene derivatives as an example of molecular design:

Despite the presence of a large number of acceptor atoms, highly chlorinated bicyclo[2.2.1]hepta-2,5-diene nevertheless undergoes "condensation" with tetrazine under severe conditions [36]:



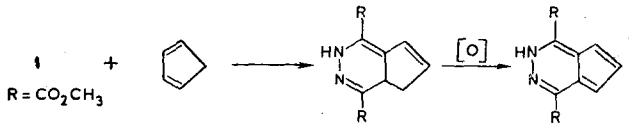
C_5H_4N = 2-pyridyl

An extremely convenient subject for the investigation of interactions through space is presented in [54]. An investigation of the kinetics of the reactions of XXXIV with 3,6-di-(2-pyridyl)tetrazine and a determination of the activation parameters make it possible to draw conclusions that are in agreement with the conclusions in [19]: A synchronous mechanism for cycloaddition is extremely likely for the Carboni–Lindsey reaction.

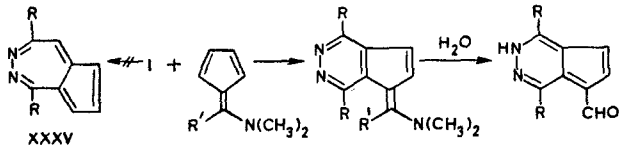


XXXIV

Cyclopentadiene reacts readily with tetrazine to give a dihydro derivative, which is oxidized to the electronic azulene analog [12].

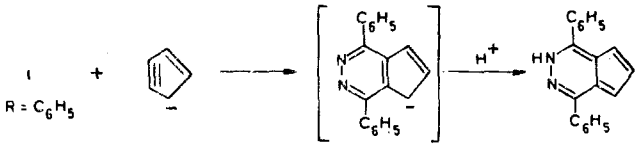


Fulvenes do not react with tetrazines at the exocyclic bond but rather at one or two of the side bonds [55, 56] to give pseudoazulenes. The opinion of Sasaki and co-workers [55] that when there is a dimethylamino group attached to the exocyclic double bond of fulvene, the process is "swayed" to favor [6 + 4] cycloaddition to give, ultimately, 3,6-diazaazulene XXXV, was proved to be correct in [13]:

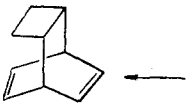


XXXV

3,6-Diphenyltetrazine has been used [57] as an interceptor of a five-membered aryne, viz., the dehydrocyclopentadienyl anion formed in the pyrolysis of the diazocyclopentadiene-2-carboxylate anion:



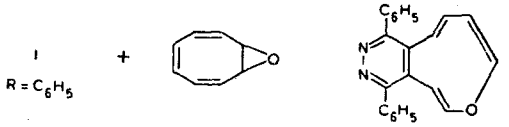
Six-, Seven-, and Eight-Membered Unsaturated Carbocycles. Cyclohexene [5, 6, 15, 17, 18], cycloheptene [6, 15], and cyclooctene [15] readily undergo the Carboni–Lindsey reaction via the normal scheme. It was recently shown that cis,cis-cycloocta-1,5-diene reacts autonomously with the double bonds with one and two tetrazine molecules, and the resulting dihydropyridazines are very much inclined to form hydroperoxides [58]. In decadiene XXXVI the sterically least hindered double bond is attacked by tetrazine [15]:



XXXVI

The reactions of tetrazines with dehydrobenzene ensure direct conversion to phthalazines [12, 36]:

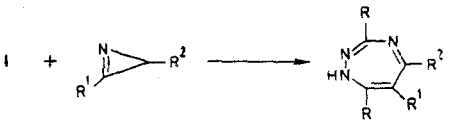
When cyclooctatriene α-oxide is heated with tetrazine with subsequent oxidation with chloranil, it undergoes "straightening" to give a nine-membered ring containing 10 π electrons; however, according to NMR data, the product does not display aromatic properties [59]:



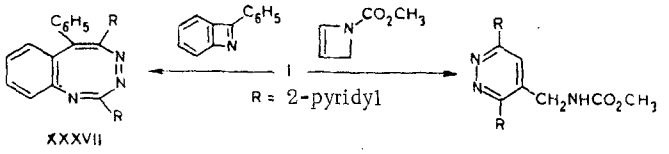
Other nonantriene mesobicyclic systems in which CH_2, CD_2, and NAc are present in the three-membered ring in place of oxygen behave similarly [60].

Reactions with Heterocyclic Compounds

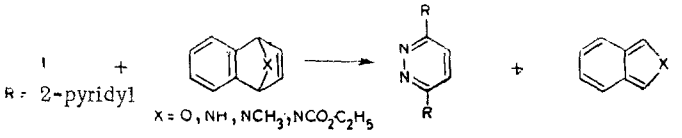
Three-Membered Heterorings. Replacement of the C=C bond in cyclopropene by a C=N bond (conversion to azirines) makes it possible in one step to make the transition to triazepines [61-65], which, depending on the substituting groups and the reaction conditions, are capable of undergoing decomposition or isomerization to pyrazoles [61, 63-65], 1,2,4-triazoles [61], and even pyrimidines [65].



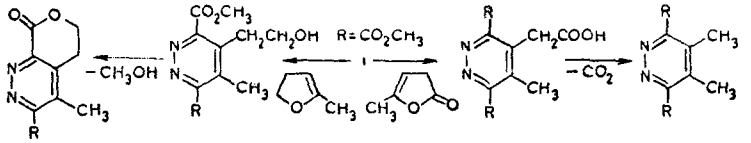
Four-Membered Heterorings. Such heterorings always undergo transformations upon reaction with tetrazine, regardless of whether a nitrogen atom does (2-phenylbenzazete [66]) or does not participate (N-methoxycarbonyl-Δ^2-azetine [67]) in the formation of a double bond. In both cases the heteroring of the dienophile is opened, but in the first case electrocyclic ring expansion leads to a triazacyclooctatetraene derivative, viz., triazocine XXXVII:



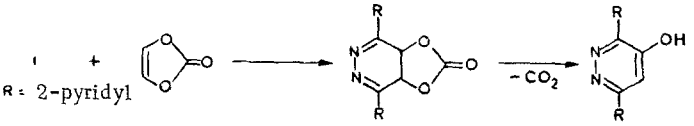
Five-Membered Heterorings. The exceptionally mild conditions in the reactions of tetrazines with endo compounds have permitted the synthesis of the very unstable isoindole and isobenzofuran [68, 69]:



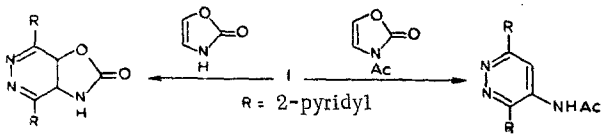
The first reactions with opening of the dienophile heteroring at the carbon–heteroatom bond were described in [11]:



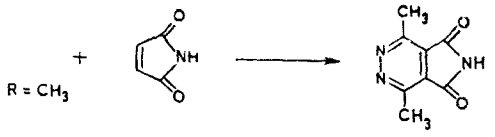
A similar reaction with vinylene carbonate gives a hydroxypyridazine [70]:



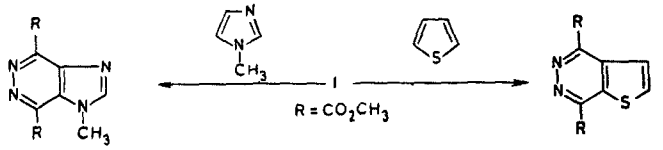
N-Acetyl-4-oxazolin-2-one has two alternative possibilities for ring opening, but cleavage only at the bond with the more electronegative oxygen atom is realized [70], and the product of the reaction with oxazolinone itself is more stable:



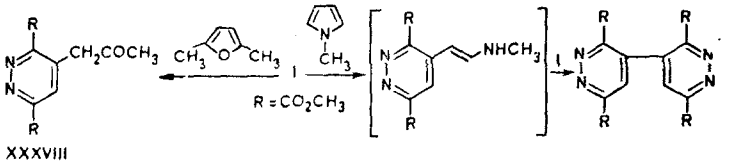
When donor substituents are present in the tetrazine, the reaction with maleinimide can be realized [20]:



A systematic study of the behavior of aromatic heterocycles in the Carboni—Linsey reaction was begun in 1975 [71, 72]. Naturally, only π-surplus heterocycles can be subjected to the reaction. The quite aromatic thiophene and N-methylimidazole do not undergo ring opening in the cycloaddition process [71, 72]:

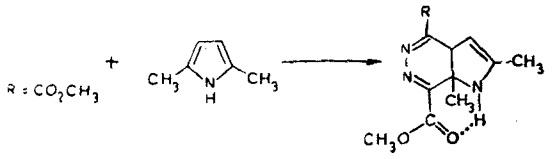


The less aromatic 2,5-dimethylfuran and N-methyl(or phenyl)pyrrole undergo ring opening at the carbon—heteroatom bond in the reaction with tetrazines; in the first case isomerization gives the stable ketone XXXVIII, while in the second case the enamine that is formed as a result of ring opening adds a second molecule of tetrazine:

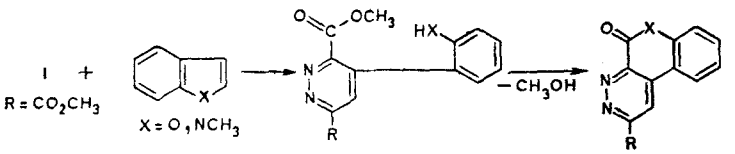


XXXVIII

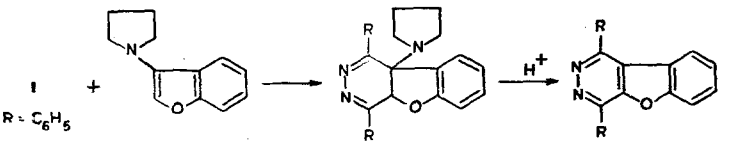
However, if the labile hydrogen atom in pyrrole is not substituted, the reaction proceeds as in the case of the more aromatic thiophene and imidazole. Seitz and Kaempchen [72] see hindrance to ring opening in stabilization of the adduct by an intramolecular hydrogen bond:



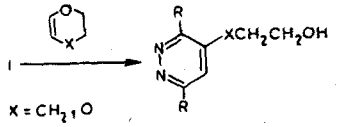
Azaindole and benzothiophene also do not undergo ring opening in reactions with tetrazines [73], whereas coumarone and N-methylindole react with 3,6-bis(carbomethoxy)tetrazine to give coumarin and quinolone derivatives of pyridazine owing to intramolecular condensation of the o,o'-oriented groupings:



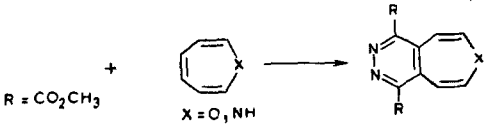
The anomaly previously noted in [7] for five-membered carbocycles is repeated in the reaction of tetrazine with 3-pyrrolidinobenzo[b]-furan [74]: Under mild conditions the pyrrolidine residue, which is removed by acid hydrolysis, is retained in the molecule with a dihydropyridazine structure:



Six-Membered Heterorings. Aromatic six-membered heterocycles, being π-deficient systems with respect to their electronic nature [3], cannot be dienophiles in the Carboni—Lindsey reaction. Dioxene and dihydropyran undergo ring opening during cycloaddition [11, 20]:



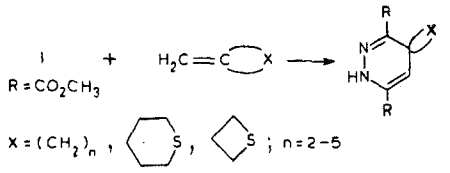
Seven-Membered Heterorings. The double bond lying opposite the donor heteroatom is attacked in the reactions of tetrazines with oxepines and azepines [75, 76]:



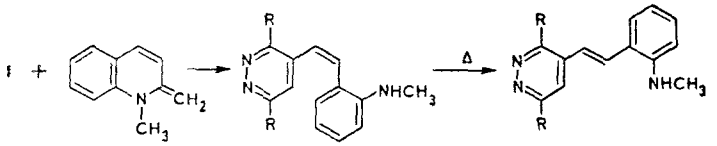
Reactions of tetrazine with 1-carbethoxy-1,2-diazepine, 2-diethylamino-3H-azepine, and 2,3-dihydro-1H-azepin-3-one have also been described [76].

Reactions of Exocyclic Double Bonds of Dienophiles

Carbocyclic hydrocarbons from cyclopropane to cyclohexane that contain exocyclic double bonds, as well as exo-methylene derivatives of thiacyclohexane and thietane, react with tetrazines to give spirodihydropyridazines that are incapable of oxidation [77]:

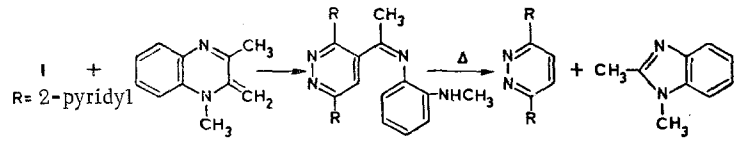


In [78-80] it was shown that tetrazines are such strong inverted dienes that they can serve as traps for *in situ* generated exo-methylene anhydro bases of azinium cations. The heteroring of the dienophile is opened in the reactions of anhydro bases of α-alkylazinium cations. A quinaldinium anhydro base undergoes ring opening to give cis-stilbenes XXXIX, which upon heating undergo isomerization to trans-stilbenes XL:



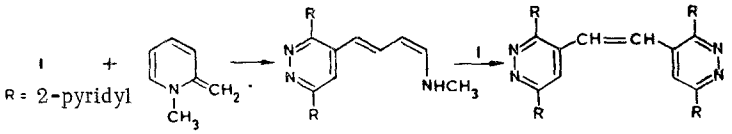
XXXIX XL

The anhydro base of the 1,2,3-trimethylquinoxalinium ion reacts with 3,6-di(2-pyridyl) tetrazine to give azomethine XLI, which upon heating undergoes disproportionation to 1,2-dimethylbenzimidazole and a pyridazine:



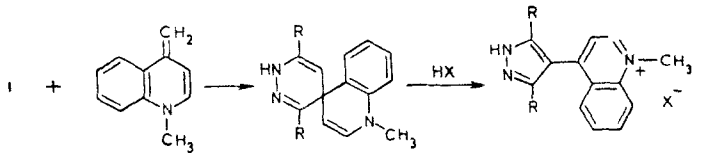
XLI

The anhydro base of the α-picolinium ion adds two molecules of tetrazine, since dienamine XLII formed after the first ring opening is quite electron-rich:



XLII

The possibility of stabilization through ring opening is excluded in the reaction of the anhydro bases of γ-alkylazinium cations (γ-picolinium, lepidinium, and acridinium), and the spirocyclic compounds are therefore completely stable. However, they undergo recyclization to pyrazoles under the influence of acids:

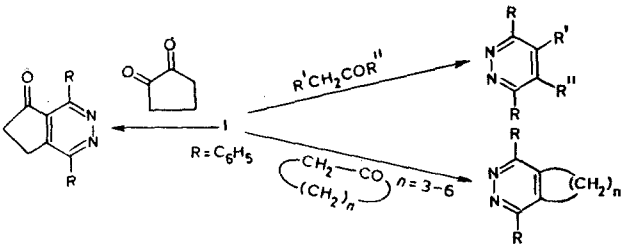


XLIII

Similar processes have been noted for the anhydro bases of pyrylium and thiapyrylium salts.

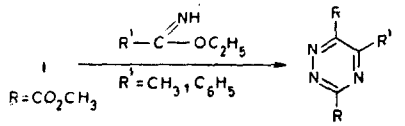
Other Reactions

Aldehydes and ketones that are capable of enolization react smoothly with 3,6-diphenyltetrazine in alkaline media to give substituted pyridazines [13, 81]:

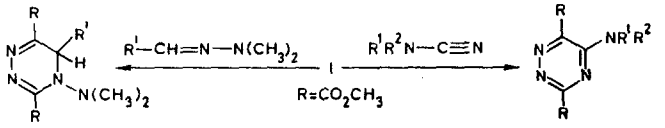


Haddadin and co-workers [81] propose a stepwise mechanism for this reaction without sufficiently weighty evidence.

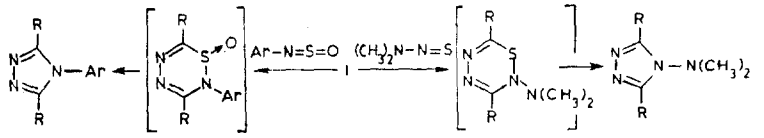
The reaction of tetrazines with imino esters serves as a new method for the synthesis of 1,2,4-triazines [11]:



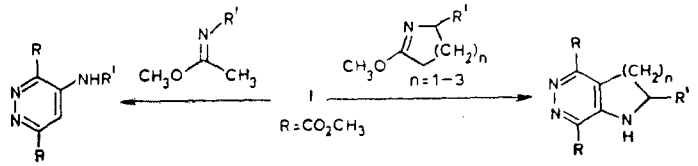
The reaction of tetrazine with N-substituted cyanamides [82] and hydrazones [83] also leads to triazines:



N-Thionitrosodimethylamine [82] and N-sulfinyl sulfonamides [84] behave rather peculiarly. Although these compounds do not contain active carbon–carbon or carbon–heteroatom bonds, the process can be conveniently regarded as a modification of Carboni–Lindsey cycloaddition. In both cases decomposition of the intermediately formed compounds leads to 1,2,4-triazole derivatives:



Attempts by Seitz and Overheu [85] to obtain physiologically active derivatives of 1,2,4-triazine from tetrazines and ethers of lactim forms led to unexpected isomerization (of the modified Dimroth-rearrangement type) with the formation of pyridazines:



Conclusion

Our review encompasses the literature data from 1958 through 1980. We did not set out to chronologically trace the development of the reaction; however, it is apparent from the data presented in the review that the possibilities of the Carboni–Lindsey reaction go far beyond the limits of a qualitative analysis of the unsaturated character and the synthesis of only some pyridazines [1]. In a reasonable approach (for example, see [33]) the reaction of unsaturated compounds with tetrazines is capable of enriching synthetic chemistry substantially and curtailing expenses in the construction of complex heterocyclic systems.

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DIFORMAZYL DERIVATIVES OF DIBENZO-18-CROWN-6

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New derivatives of the macrocyclic polyether dibenzo-18-crown-6 that contain formazyl groupings in the aromatic rings were synthesized. The complexing ability of the polyether ring and the formazyl groupings was studied. Complexes of two types, viz., those that contain a transition metal and those that simultaneously contain a transition metal and an alkali or alkaline earth metal, were isolated in crystalline form.

Macrocyclic polyethers occupy a special place among complexing compounds as a consequence of their ability to form ion–dipole complexes with salts of various metals, including alkali and alkaline earth metals. Representatives of this class of compounds have found ex-

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