UTILITY OF HETEROCYCLIC DIAZO COMPOUNDS IN ORGANIC SYNTHESIS

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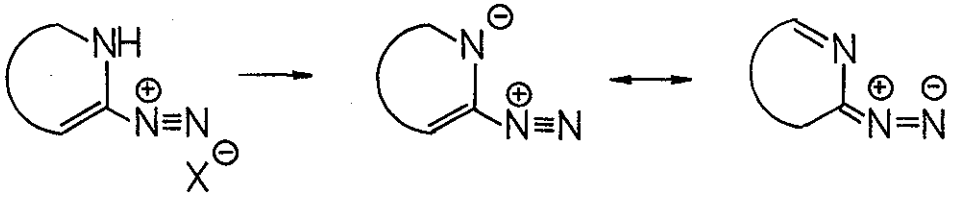
This review summarizes various transformations of heterocyclic diazo compounds and diazonium salts, in particular cyclizations, condensations, additions to multiple bonds, transformations involving elimination of the diazo group, rearrangements and reactivity of some heterocyclic systems as masked diazonium compounds.

1. Introduction

The chemistry of aliphatic and aromatic diazo and diazonium compounds has been presented in several review articles, but there are only two reviews concerning the synthesis and properties of heterocyclic diazo compounds[1] or diazotization of heterocyclic amines.[2] The aim of the present review is to present some aspects of the utility of heterocyclic diazo and diazonium compounds in organic synthesis. However, it is not intended to discuss some general transformations which are well documented and established for aromatic diazonium salts and are valid also for the heterocyclic series, i.e. substitutions of the diazonium group, reduction, addition reactions with the formation of pyrazoles, etc.

The earliest example of a heterocyclic diazo compound appears to be the diazotetrazole, prepared by Thiele in 1892.[3] Heterocyclic diazo compounds, generated from the corresponding diazonium salts having an endocyclic imino group, are similar to those aliphatic diazonium ions which can be in equilibrium with the diazoalkanes through loss of proton (1,2).[4] In a conjugated heterocyclic diazo compound structures (3a-3d) contribute to its stability and reactivity. Electron withdrawing substituents in



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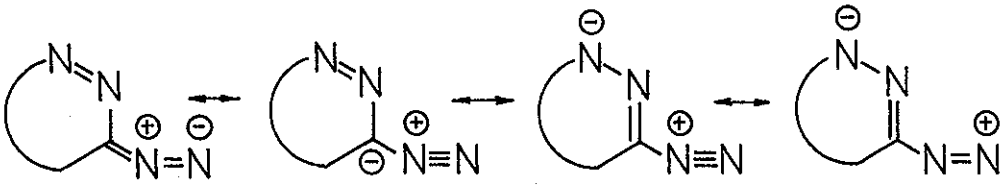
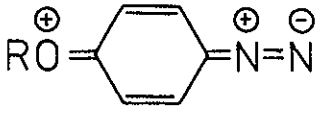


(3a) (3b) (3c) (3d)

the ring (or additional ring nitrogen) may be expected to lead to relatively greater contribution of forms (3c) and (3d), whereas electron-donating substituents will in turn favour the contributions from (3a). Thus, the contributing form (3a) may be comparable to some para substituted benzenediazonium salts where certain substituents (OMe, Ph) are known to retard the decomposition of these salts in water and where structures like (4) are important contributors.[5] The heterocyclic diazo compounds can be compared to diazo-oxides (also called diazoanhydrides or quinonediazides) and their behaviour



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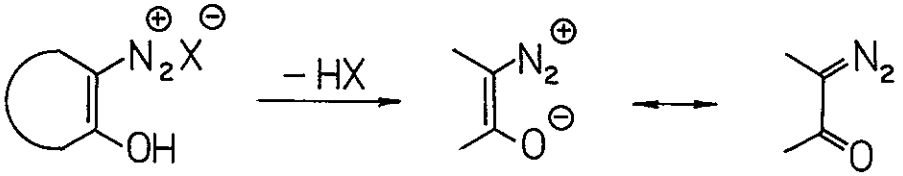
is between that of the aliphatic and aromatic diazo and diazonium compounds.

In addition to heterocyclic diazo-ketones (5), diazotization of aminoazinones affords the diazonium salts (6) which upon neutralization are converted into diazonium azinolates (7). On structural grounds these can exists only in the dipolar form. Some heterocyclic diazo compounds and diazo-oxides do not undergo coupling to phenols



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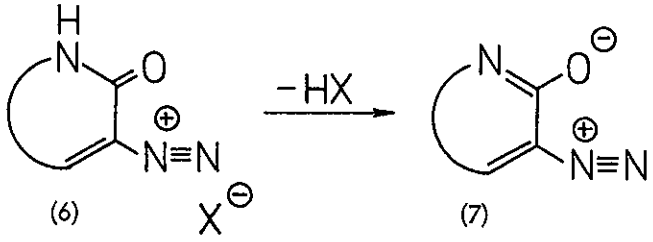


(6) (7)

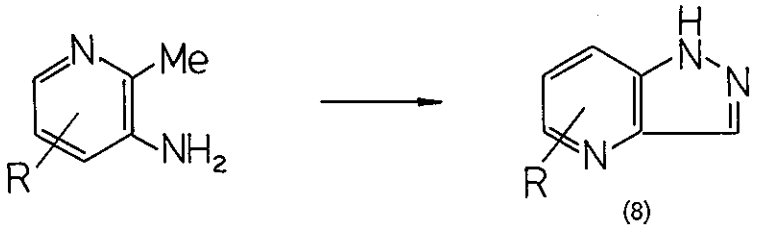
and this is explainable on ground of electron distribution with low positive charge on the end nitrogen of the diazo group.

2. Cyclizations of heterocyclic diazonium compounds

Syntheses of many heterocyclic compounds from heterocyclic precursors with an appropriate functional group ortho to the diazo or diazonium group are well established. In these reactions new bonds are formed between nitrogen and carbon, sulfur or nitrogen atom, the last type of reactions having a broad application in the field of 1,2,3-triazoles and 1,2,3-triazines.

2.1. Formation of a N-C bond

There are several examples of formation of a fused pyrazole ring involving the reaction between a diazonium group and an activated methyl or methylene group or even ethylene group. o-Methyl primary heteroaromatic amines when diazotized undergo internal coupling to give the corresponding pyrazolo heterocycles. In this manner were prepared pyrazolo(4,3-b)pyridazines (8)[6] (by direct diazotization of the corresponding amine, or better via N-nitroso derivatives), pyrazolo (3,4-c)pyridines (9),[7] pyrazolo (4,3-d)pyrimidines (10),[8-11], pyrazolo(3,4-c)quinolines (11),[12], pyrazolo(5,4-a) quinolizin-6-ium salts (12),[13], or pyrazolo(4,3-c)pyrazoles (13).[14,15] The last system



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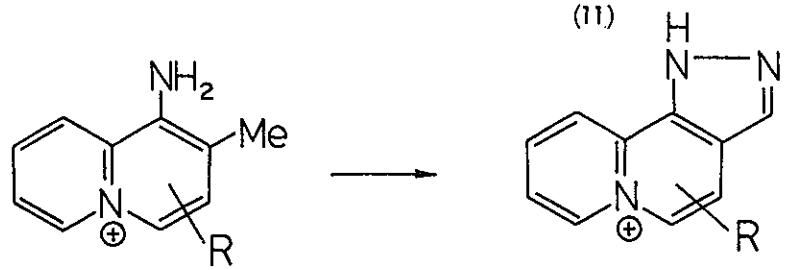

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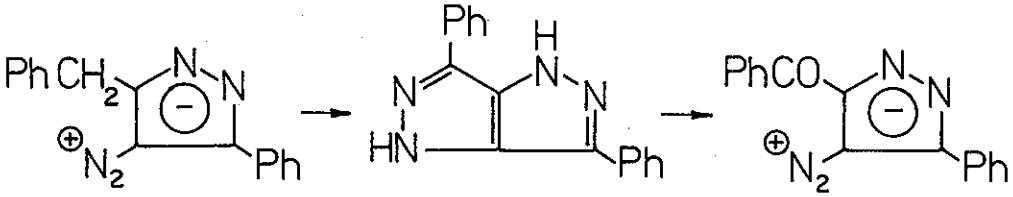
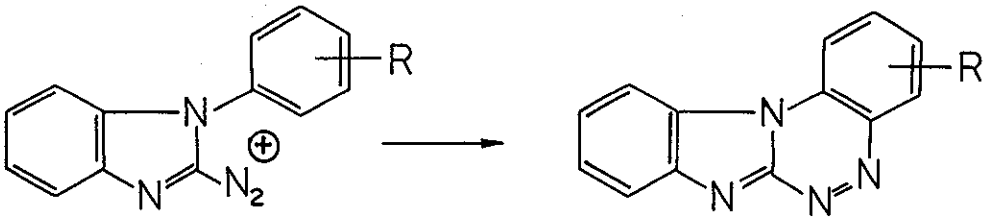
was also obtained from cyclization involving a benzyl group, i.e. 3-benzyl-4-diazo-5-phenylpyrazole is thermally isomerized in acetic acid into the bicycle (14).[16] Interestingly, the latter, upon oxidation with chromic acid in acetic acid is converted into another diazopyrazole (15). In some cases, even an ortho-phenyl ring may be



(14) (15)

involved in such cyclization. For example, the formation of dibenz(a,g)-imidazo(2,1-c)-1,2,4-triazines (16)[17] or internal coupling of triphenylpyrrole diazonium salt with the formation of the tricycle (17).[18]



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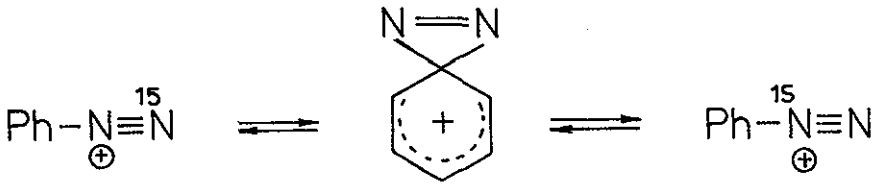
2.2. Formation of a N-N bond

This is a widely used method for the synthesis of polyazaheterocycles, i.e. of fused 1,2,3-triazoles and 1,2,3-triazines. However, before discussing the synthetic utility of this reaction, some particulars concerning the structure and reactivity of the diazo group should be mentioned.

Of particular interest is the stability of heterocyclic diazo compounds in view of an eventual nitrogen rearrangement. It has been first observed that during preparation of labeled phenyl azide with $H^{15}NO_2$ not only the last nitrogen in the azide group was labeled but the ^{15}N-incorporation took place also in β-position.[19,20] No such scrambling of label could be observed when preparing the labeled azide from 2,4-dinitrophenylhydrazine.[21] Such scrambling of the label, although to a minor extent was later observed when preparing diazoacetic ester from α-aminoacetic ester and $H^{15}NO_2$.[19] An exchange of α- and β-N has been observed during the solvolysis of benzenediazonium ion[22,23] and for the postulated rearrangement of (18) into (20) an intermediate spirodiazirine (19) was first postulated. Although later, on the basis

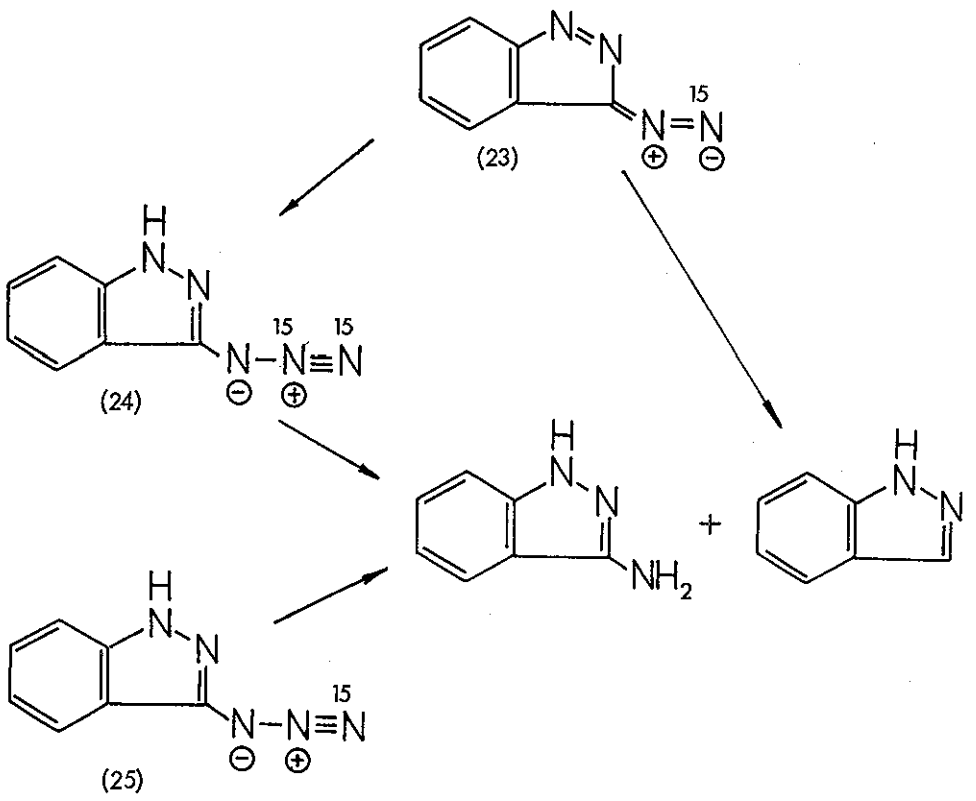


(18) (19) (20)

of nmr evidence the above isotope rearrangement was disputed,[24] recent nmr evidence confirmed the migration of labeled nitrogen.[25] The spirodiazirine intermediate has been later abandoned[26] and for aryldiazonium salts it is now postulated that the rearrangement of nitrogens, although occuring in a small proportion, takes place via a phenyl cation.[27-29] However, recently the first spirodiazirine (22), a valence isomer of a photochromic heterocyclic diazo compound (21) could be isolated and identified.[30,31] It should be mentioned that such photochemical conversion has been observed earlier with diazoamides which were transformed into the isomeric diazirines.[32]

Experiments with labeled 3-diazoindazole (23)and labeled 3-azidoindazoles (24,25) showed that these compounds upon photochemical elimination of nitrogen

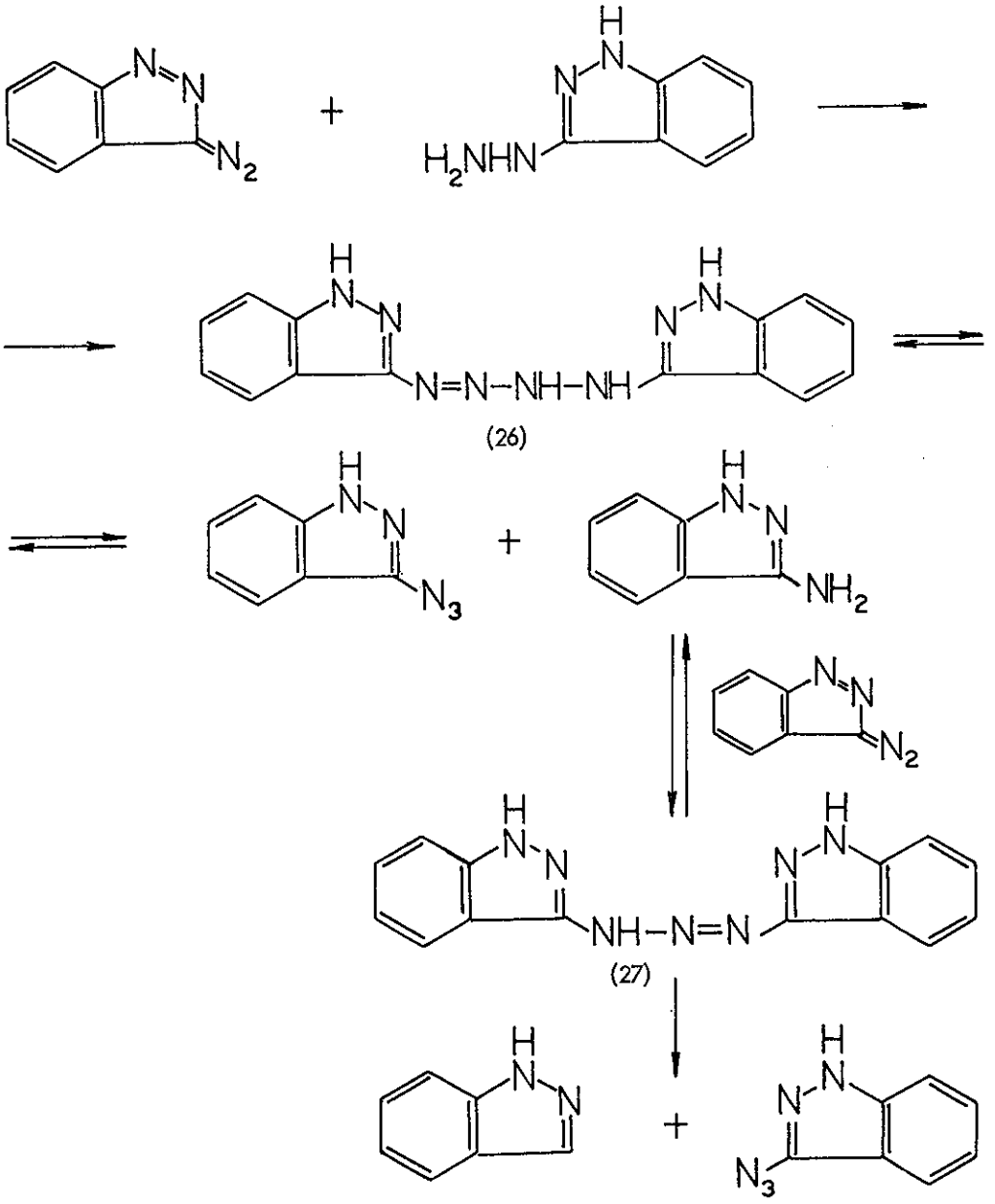
(21) (22)



(23) (24) (25)

afforded indazole and 3-aminoindazole without isotope rearrangement.[33] If 3-diazoindazole was reduced, besides the anticipated 3-hydrazinoindazole, also indazole, accompanied with 3-aminoindazole and 3-azidoindazole were isolated and identified. The

formation of these products proceeds via an intermediate tetrazene (26) and further via a triazene (27).[33] Similar conversions have been observed also in the pyrazole,



imidazole and 1,2,3-triazole series and the reaction is similar to the formation of arylazides from aryldiazonium salts and hydrazine.[34] For example, 5-diazoimidazole-4-carboxamide afforded in this manner the 5-azido compound[35] and recently tetrazene itself could be isolated.[36] The latter compound is thermally either decomposed to give nitrogen and hydrazine or isomerized into ammonium azide. Finally, it should be mentioned that particular tetrazenes may cyclize into the corresponding tetrazolo compounds in the presence of a nucleophile.[37] Similar experiments with the purpose to establish eventual isotope scrambling have been performed also with a diazo-ketone. A s-triazolo(4,3-b)pyridazine diazo-ketone with ^{15}N-label in the diazo group revealed after thermolysis or photolysis no ^{15}N-rearrangement.[38]

There are many examples of synthesis of 1,2,3-triazoloazines from o-diamino-heterocycles and nitrous acid. In this manner, the parent heterocycles and derivatives of 1,2,3-triazolo(4,5-d)pyridine (28),[39-41] 1,2,3-triazolo(4,5-c)pyridine (29),[39-45] 1,2,3-triazolo(4,5-c)pyridazine (30),[46] 1,2,3-triazolo(4,5-d)pyridazine (31),[47-50] 1,2,3-triazolo(4,5-d)pyrimidine (32),[9,51-58] 1,2,3-triazolo(4,5-c)quinoline (33)[41] and 1,2,3-triazolo(4,5-b)quinoline (34)[41] have been prepared.

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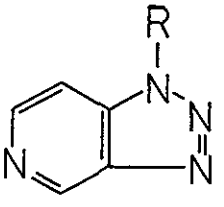

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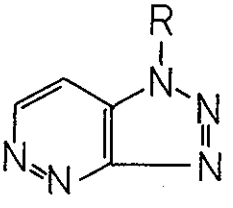

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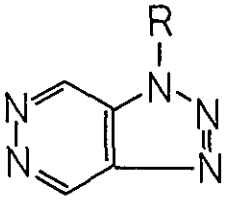

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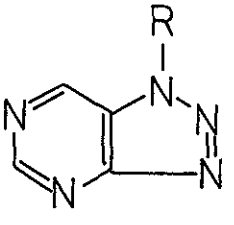

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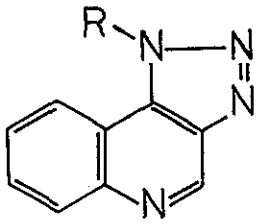

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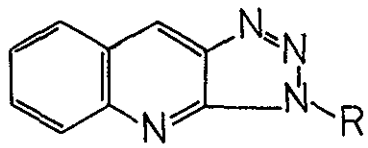

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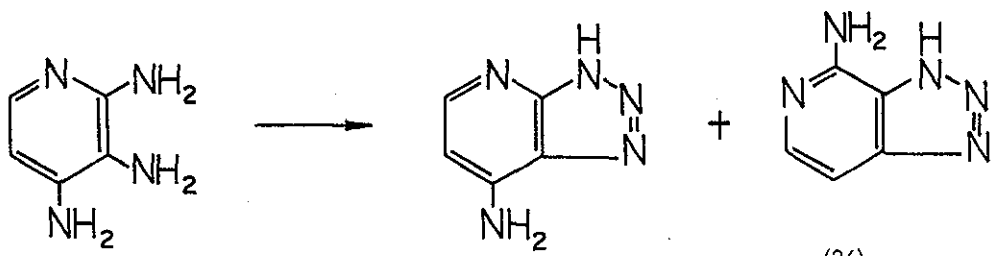
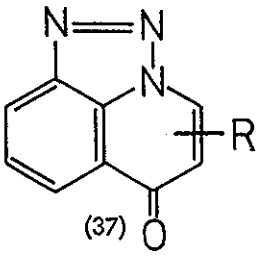
Although 2,3-diaminopyridine is readily converted with nitrous acid into the corresponding triazolopyridine,[59] 6-chloro-3,4-diaminopyridine afforded only the corresponding 3-diazonium salt.[60] Moreover, the use of isopentyl nitrite or aqueous nitrous acid on 4-amino-5-methylaminopyridine gave only the corresponding 5-N-nitroso derivative.[52] Diazotization of 2,3,4-triaminopyridine afforded a mixture of (35) and (36), the latter being the major product,[61] indicating the preferential attack of the diazo group on the neighbouring amino group at position 4.



(35) (36)

A fused triazolo ring can be formed also from heterocycles with an amino group peri to a ring NH group. Such examples include the formation of triazoloquinolines from 8-aminoquinolines (37)[62-64] triazolobenzoxazine (38),[65], triazolocinnolinone (39)[66] triazoloacridones (40),[67,68] triazolophenoxazines (41, X = O)[69-71] and azaanalogs,[72] triazolophenothiazines (41, X = S)[71] and analogs,[73] or triazolobenzacridone (42).[74]

A more detailed investigation on diazotization of 8-aminoquinolines revealed that upon diazotization and neutralization compounds of the type (44) are formed.[75] Dehydration of (44) gives back the diazo compound (43) and permanganate oxidation gives compound (45). A structure, similar to (44), has been proposed for the cyclic product (47) abtained from diazotization of (46) and subsequent heating of the acidic



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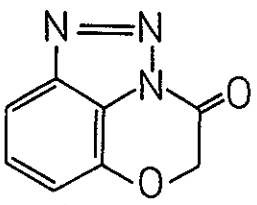

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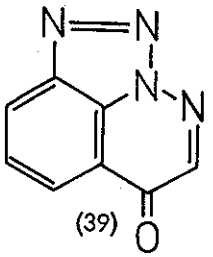

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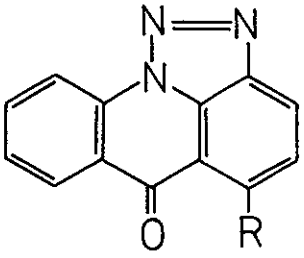

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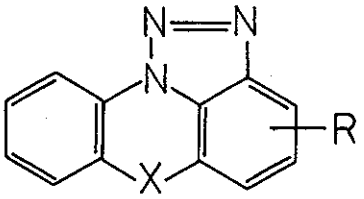

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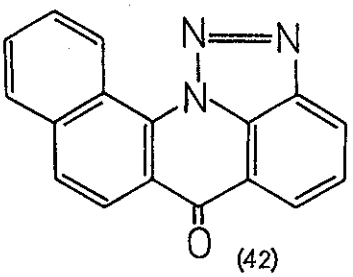

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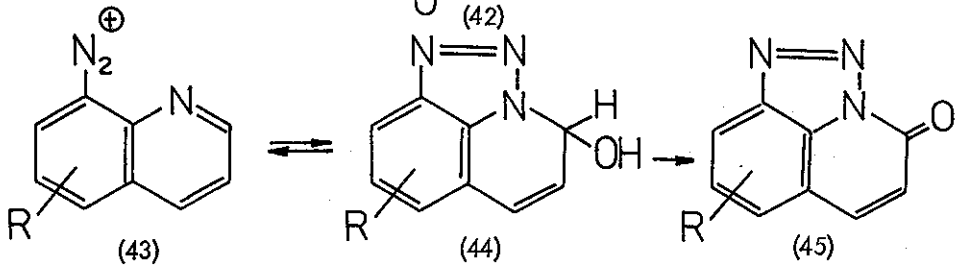
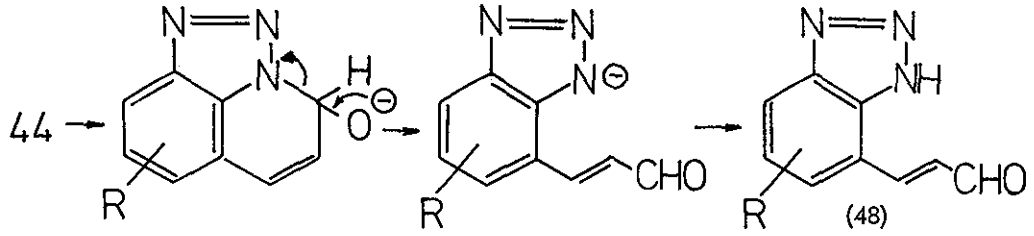


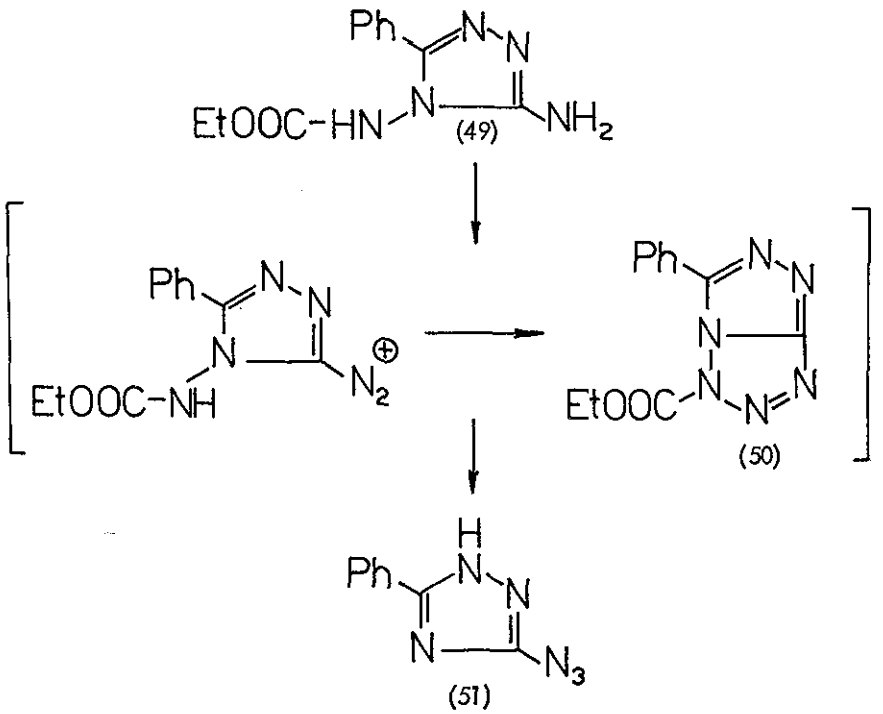
(43) (44) (45)

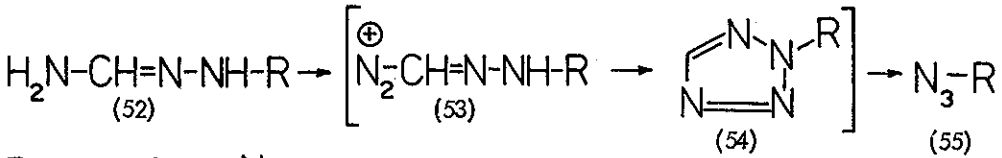
(46) (47)

diazo solution.[76] In an alkaline solution, compounds of the type (44) undergo ring opening to benzotriazolylacrylic aldehyde (48).[75]



A particular case represents the following transformation. Diazotization of 3-amino-4-carbethoxyamino-5-phenyl-1,2,4-triazole (49) afforded 3-azido-5-phenyl-1,2,4-triazole (51). This transformation has been explained in terms of an intermediate *s-triazolo*(4,3-d)*tetrazole* (50) which was, however, not isolated.[77] A related reaction is the transformation of (52) into (55) upon diazotization.[78] The reaction proceeds via an intermediate diazonium salt (53) which cyclizes into a tetrazole derivative (54) and this, upon elimination of hydrogen cyanide, gives the product (55).





(52) (53) (54) (55)

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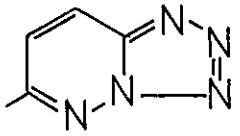
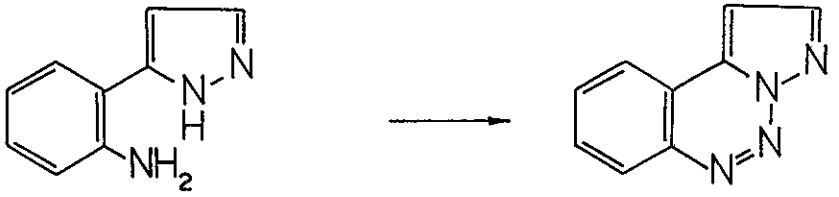


Another possibility of N-N bond formation is the attack of an o-diazophenyl group on the adjacent ring nitrogen of a five- or six-mebered heterocycle. Examples of such heterocyclic ring formation include the synthesis of pyrazolobenzotriazines (56)[79,80] benzimidazolobenzotriazines (57),[81] or 1,3,5-triazino(1,2-c)-1,2,3-benzotriazines (58).[82]



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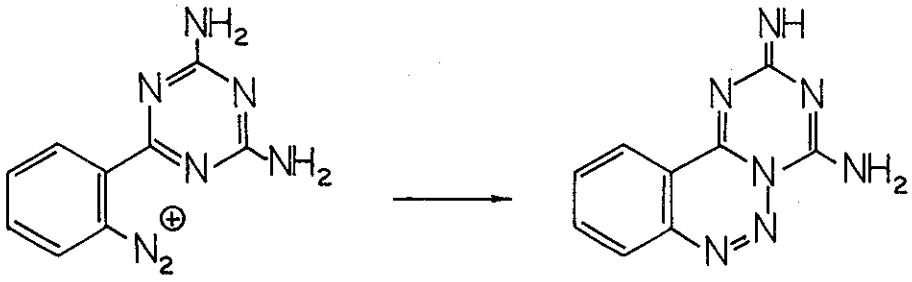

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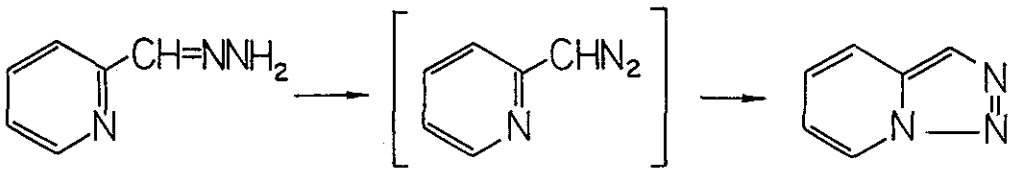
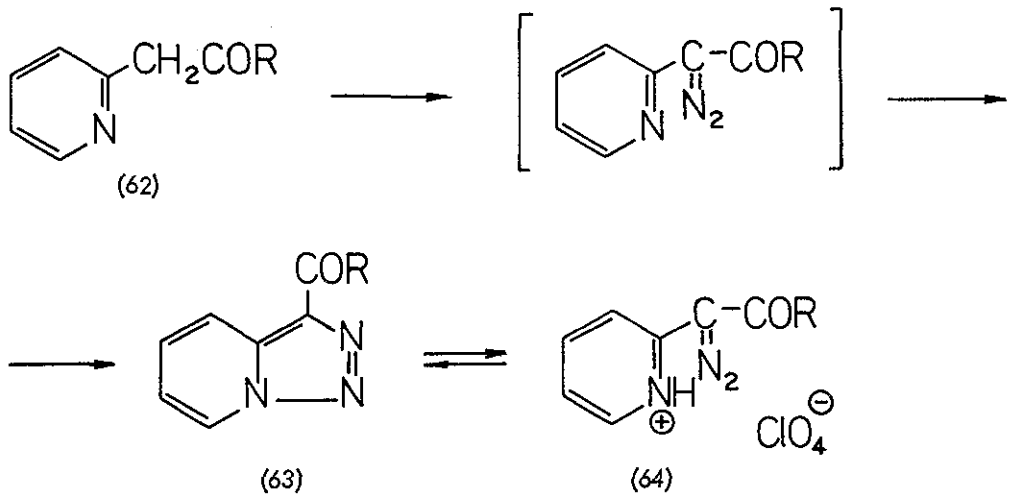
An attack of a side chain diazo group on an azine nitrogen is also possible. The hydrazone of 2-pyridylaldehyde (59), when oxidized with silver oxide afforded a diazo compound (60) which cyclized spontaneously into 1,2,3-triazolo(3,4-a)pyridine (61).[83] In a similar manner the fused triazole ring has been formed in the quinoline[83] or isoquinoline[84] series. An attempt to prepare the bicycle (61) by diazotization of



(59) (60) (61)

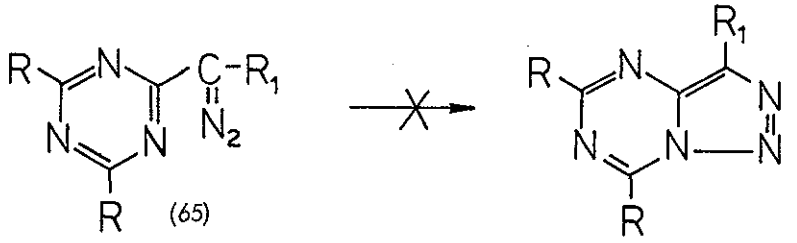
2-aminomethylpyridine failed. So far, no equilibrium could be established between (60) and (61) and only the bicyclic form is present in neutral solutions. Similar cyclization occurred when the diazo-transfer reaction was applied to acyl-pyridyl-2-methanes (62 to 63)[85] or to the corresponding quinolines. However, if these triazolopyridines were treated with perchloric acid in dioxane, protonation caused ring opening to give the corresponding diazo compound (64). These salts are sensitive to solvolysis and in the



(62) (63) (64)

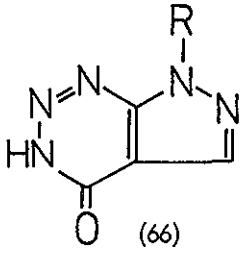
presence of ethanol or water they are converted back to the bicyclic system (63).[85]

On the other hand, it could be observed that the related diazoalkyl-1,3,5-triazines (65, R_1 = alkyl)[86] do not form the fused triazoles and also the carbethoxy analog (65, R_1 = COOEt) has been found to exist mainly in the open chain form.[87] This parallels the azido-tetrazolo isomerization where in the triazine series only the azide group is present and is not converted into a fused tetrazole ring.[88]



(65)

A large number of syntheses involves the generation of a 1,2,3-triazine ring by diazotization of o-aminoheterocyclic carboxamides, a well established transformation of o-aminobenzamides into benzo-1,2,3-triazinones.[89] In this manner representatives of pyrazolo(3,4-d)-1,2,3-triazinone (66),[90] pyrazolo(4,3-d)-1,2,3-triazinone (67),[91] imidazo(4,5-d)-1,2,3-triazinone (68)[92-95] 1,2,3-triazolo(4,5-d)-1,2,3-triazinones (69),[93,96] thieno(2,3-d)-1,2,3-triazinone (70),[97] thieno(3,2-d)-1,2,3-triazinone (71),[98]



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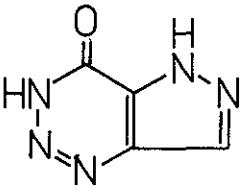

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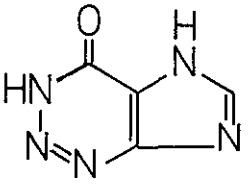
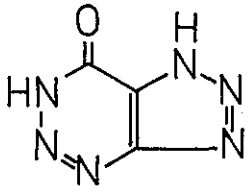


(68)

thiazolo(5,4-d)-1,2,3-triazinone (72)[99] or pyrido(3,2-d)-1,2,3-triazinone (73)[100] have been prepared. It is interesting to mention that with 4-diazoimidazole-5-carboxamide



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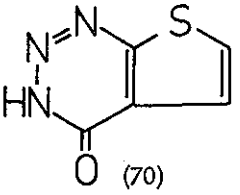

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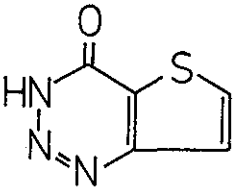
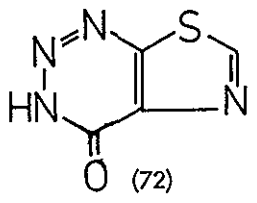


(71)

the cyclization to (68) is faster than the attempted photofluorination involving of the diazo group.[101] Instead of a side chain carboxamido group, an imidine function can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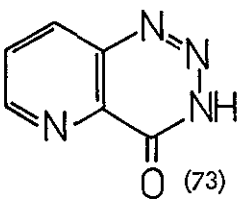
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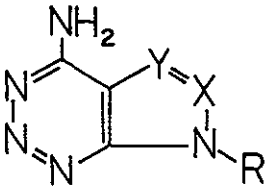
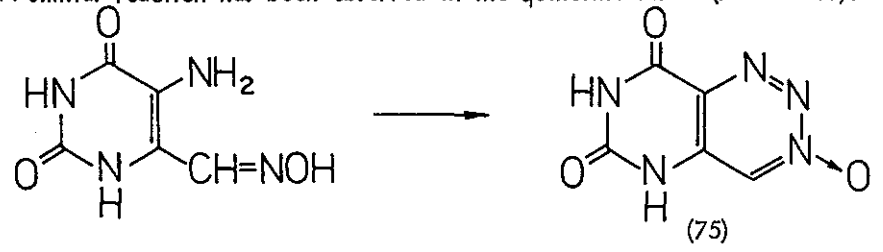

(74)

also be used and the corresponding condensed aminotriazines are then obtained. In this manner derivatives of imidazo(4,5-d)-1,2,3-triazine (74, X = CH, Y = N), pyrazolo-(3,4-d)-1,2,3-triazine (74, X = N, Y = CH) or 1,2,3-triazolo(4,5-d)-1,2,3-triazine (74, X = Y = N) were prepared.[102]

A related cyclization, leading to the corresponding triazine-N-oxides involves an attack of the diazo group on an ortho-aldoxime function, for example the formation of a derivative of pyrimido(5,4-d)-1,2,3-triazine (75).[103] An oxime function can be generated also from a methyl group during nitrosation of an adjacent amino group as shown in some cases. In this manner, the pyrimidine derivative (76) when treated with excess of nitrous acid, afforded the fused triazine (78) via an intermediate oxime (77).[104] A similar reaction has been observed in the quinoline series (79 into 80).[12] The same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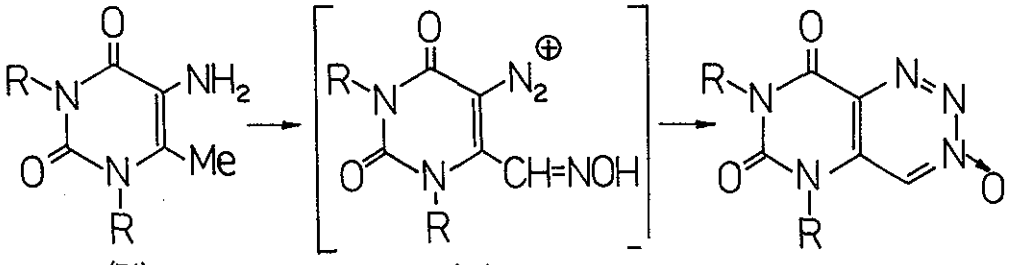
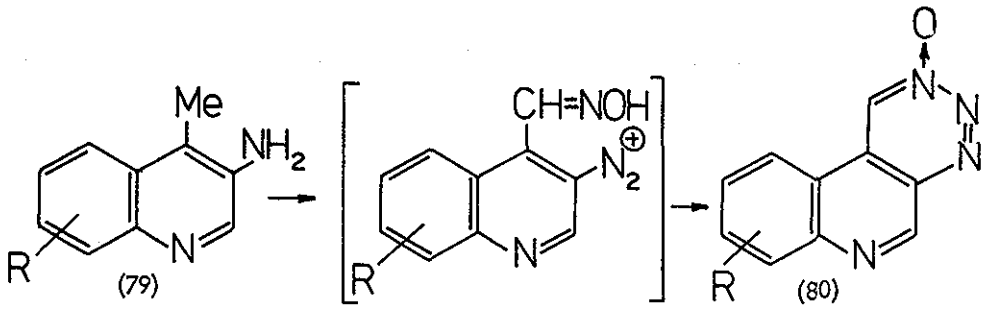
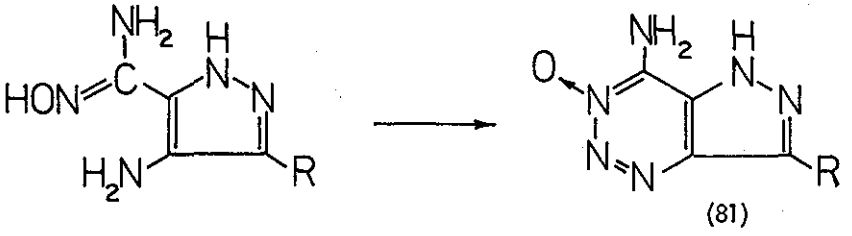
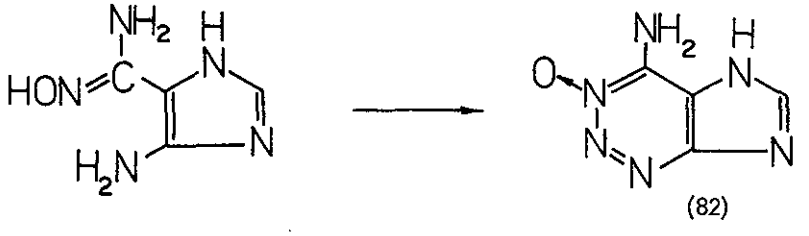
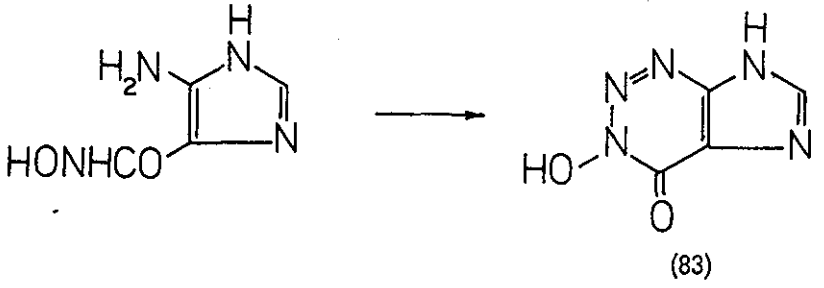

(76) (77) (78)



reaction occurs with α-aminooximes,which enables the introduction of an o-amino group to the N-oxide group. Such examples are in the pyrazole (81)[91] or imidazole (82)[105] series. In another approach, an o-amino hydroxamic acid afforded upon diazotization the corresponding triazine derivative (83).[106]

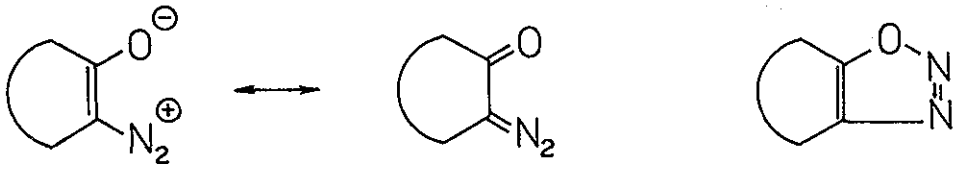






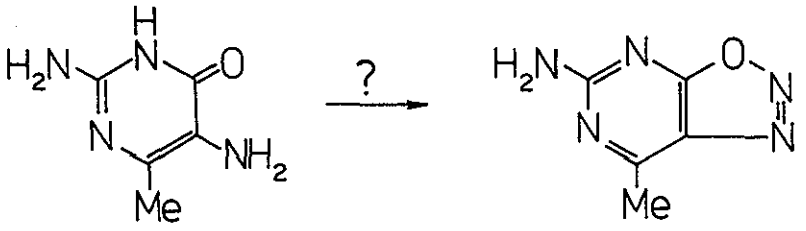
2.3. Formation of N-O bond

o-Amino hydroxyheterocycles are an exception from the so far discussed cyclizations, since upon diazotization they form diazo-oxides (84) rather than the corresponding fused 1,2,3-oxadiazoles (85). In some cases it was claimed that the prepared

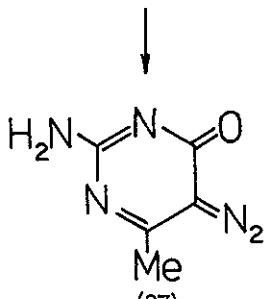


(84) (85)

compounds have an oxadiazole structure. For example, diazotization of 2,5-diamino-4-oxo-6-methylpyrimidine was reported to give the bicycle (86).[9] However, the properties of this compound seem to be more in agreement with the diazooxide structure (87).

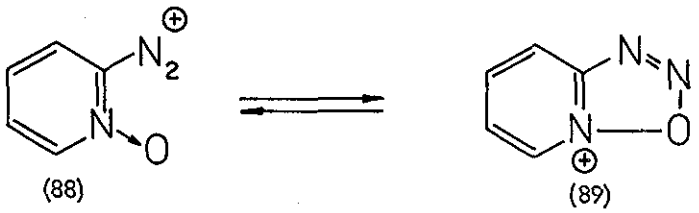


(86)

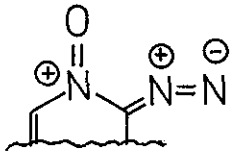


(87)

A related problem is the possibility of an oxatriazole ring formation from diazo N-oxides. Pyridine N-oxide 2-diazonium salts and other azine N-oxides or their benzo-analogs with an ortho standing diazo group exist in general in the open-chain form (88).[107,108] Moreover, the 2- or 4-diazonium salts of azine N-oxides are generally more stable than those of azines, which is attributed to the contribution of the canonical form (90).



(88) (89)

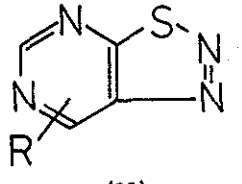


(90)

However, according to a report[109] it is claimed that diazonium tetrafluoroborates, prepared from 2-aminopyridine N-oxide, 2-aminoquinoline N-oxide and 1-aminoisoquinoline N-oxide, exist in the cyclic form, as (89), on hand of UV and IR data. These compounds undergo immediate coupling in an alkaline solution of β-naphthol.

2.4. Formation of N-S bond

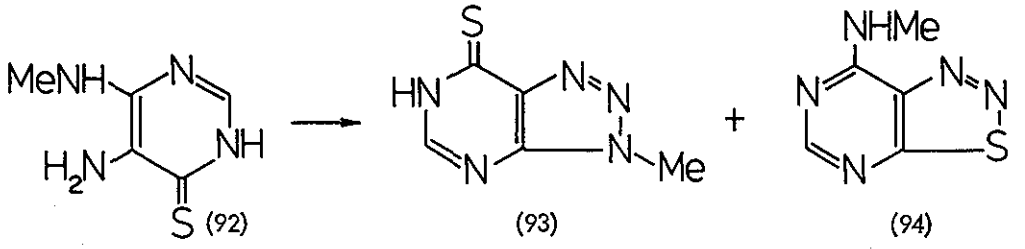
Contrary to diazo-ketones the corresponding sulfur analogs are nonexistent and o-amino mercaptoheterocycles are upon diazotization transformed into the corresponding thiadiazolo compounds. In this manner 1,2,3-thiadiazolo(5,4-d)pyrimidines (91) were

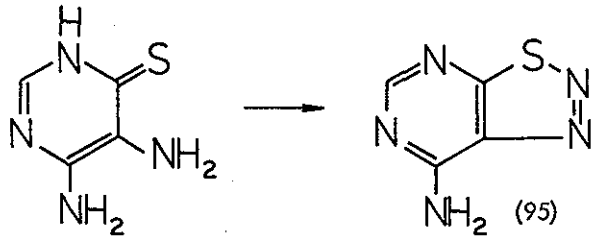


(91)

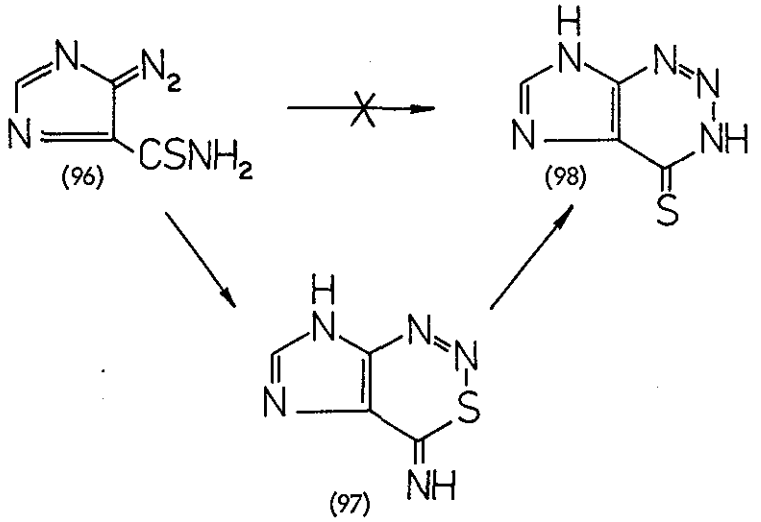
prepared.[9,110] When diazotizing 5-amino-6-methylamino-4-thioxopyrimidine (92) an equilibrium mixture of the triazolopyrimidine (93) and thiadiazolopyrimidine (94) was obtained.[51] The same mixture was obtained when the 6-oxo analog of (93) was treated with P_4S_{10} in boiling pyridine. The diazonium group in the above reaction evidently at-

tacks the methylamino group, as well as the thioxo group. It is, however, interesting to note that diazotization of 4,5-diamino-6-thioxopyrimidine afforded only the corresponding thiadiazolopyrimidine (95).[111]





An interesting case represents 4-diazo-5-thiocarboxamidoimidazole (96). By analogy with the corresponding carboxamido derivative one would anticipate that cyclization would afford imidazo(4,5-d)-1,2,3-triazine-4-thione (98). However, it was established that the first cyclic product is imidazo(4,5-d)-1,2,3-thiadiazin-4-imine (97)[112,113] and this is in the presence of ammonia converted into (98).

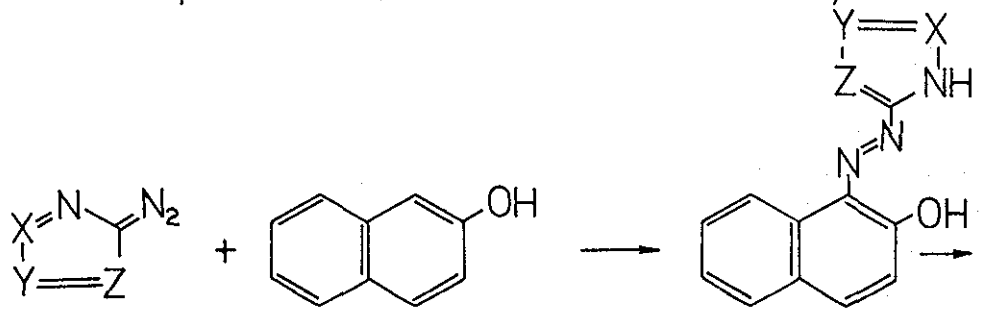


3. Condensation of heterocyclic diazo compounds and additions to multiple bonds to form new heterocycles

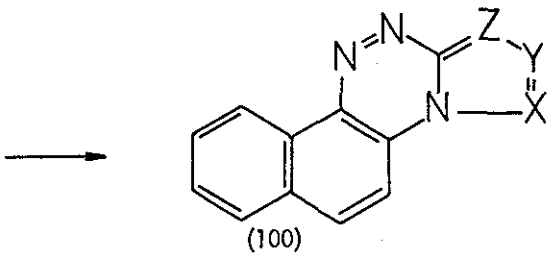
Heterocyclic diazo compounds and diazonium salts undergo coupling to phenolic compounds with subsequent cyclization. They also react with reactive methylene compounds and the intermediate hydrazones may be cyclized to new azaheterocycles. In the case of α-methylene carbonyl compounds the reaction can be regarded as addition of the diazo compound to an enolic double bond.

3.1. Heterocycles from coupling reactions

It has been reported that 3-diazopyrazoles undergo cyclizative coupling to β-naphthol to form naphthopyrazolo-1,2,4-triazines (100, X = N, Y = Z = CH).[114-116] It is also possible to isolate the intermediate azo compounds (99) formed from diazoimidazole, diazopyrazole, diazo-1,2,3-triazole, diazo-1,2,4-triazole or diazotetrazole.[112] From experimental evidence it was concluded that the ease of cyclization of



(99)

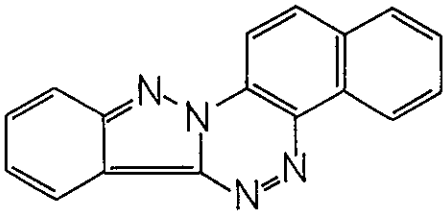


(100)

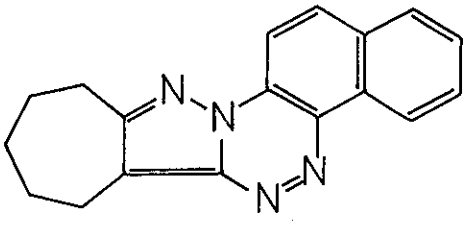
the azo compounds (99) into the naphthazolo-1,2,4-triazines (100) depends upon the relative basicity of the heterocycle and the order being imidazole $\gg$ pyrazole $>$ $>$ 1,2,4-triazole $>$ 1,2,3-triazole $>$ tetrazole.[117] The cyclizative coupling has been used for the synthesis of several polycyclic 1,2,4-triazines, for example indazolonaphtho-

triazine (101),[118] its tetrahydro derivative[119] and (102).[120]

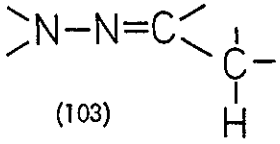
Heterocyclic diazo compounds and diazonium salts react with compounds with reactive methylene groups and the primary reaction products can exist either as hydrazones (103) or as enehydrazines (104). With enolizable 1,3-dicarbonyl compounds



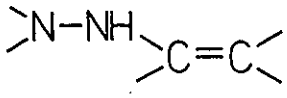
(101)



(102)



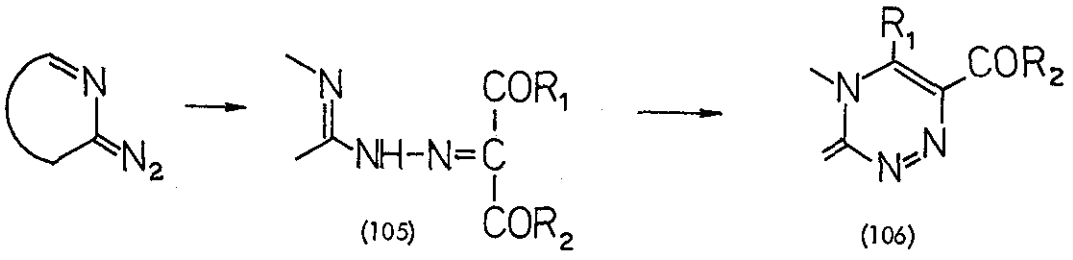
(103)



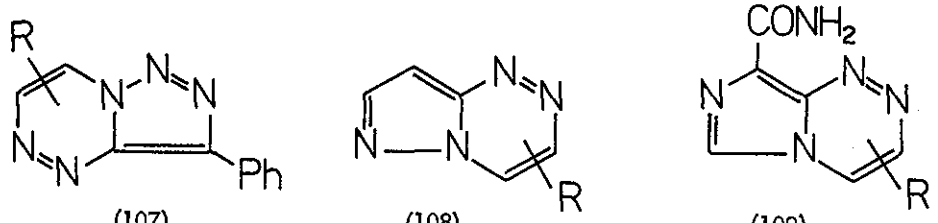
(104)

several E or Z isomers or intramolecular hydrogen bonded structures are possible. The stabilization of the hydrazone form against the enamine is understandable if we consider hydrazones as azaenamines. For related products, obtained from aromatic diazonium salts and reactive methylene compounds, the hydrazone structure is preferred.[121] Equilibria have been examined spectroscopically.[122,123]

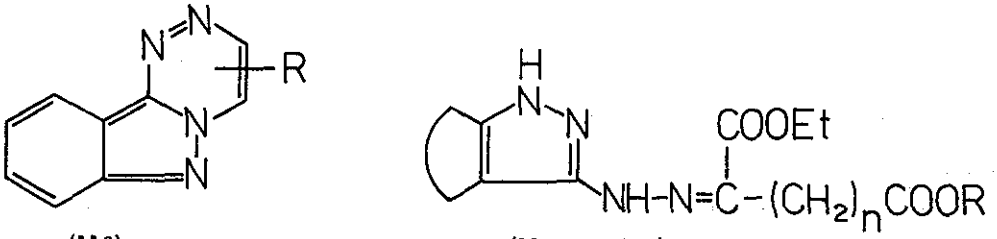
Reactions of several diazoheterocycles with 1,3-dicarbonyl compounds, malonic esters and other compounds with reactive methylene groups have been described. The initially formed hydrazones (105) were sometimes isolated and upon heating or by acid catalysis they are easily converted into fused 1,2,4-triazine derivatives (106). In this manner, from 5-phenyl-1,2,3-triazole-4-diazonium salt derivatives of 1,2,3-triazolo-(5,1-c)-1,2,4-triazine (107), the open-chain hydrazones or mixtures of both were obtained.[124] From pyrazole-3-diazonium salt derivatives of pyrazolo(5,1-c)-1,2,4-triazine (108)[33,125] were prepared and 4-diazo-5-carboxamidoimidazole yielded derivatives of imidazo(1,5-c)-1,2,4-triazine (109).[33] In a similar way from 3-diazoindazole derivatives of indazolo(3,2-c)-1,2,4-triazine (110) were prepared.[123,126,127]



(105) (106)



(107) (108) (109)

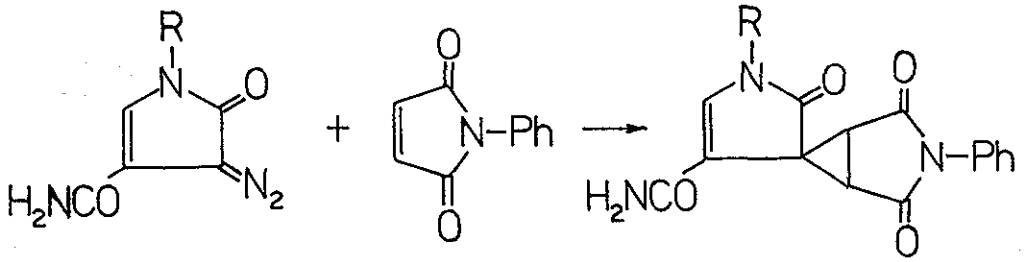


(110) (111, n= 3,4)

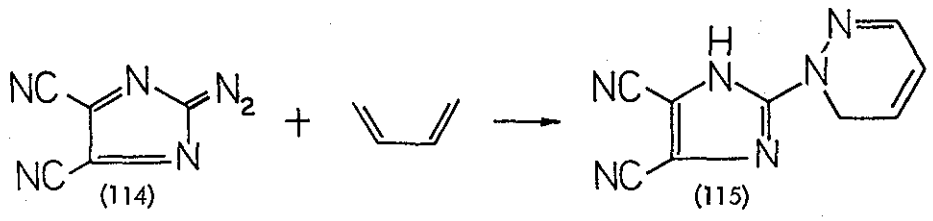
However, some cyclic dicarbonyl compounds (2-carbethoxycyclohexanone or -pentanone) reacted in a reaction sequence similar to the Japp-Klingemann reaction[128] to give the open-chain products (111).[33,126] Similar transformation could be observed also in the case of methylacetoacetic acid,[127] to give the decarboxylated product.

3.2. Addition reactions of diazo heterocycles to multiple bonds

Some reactions of heterocyclic diazo compounds with ethylenes, acetylenes or conjugated dienes have been described. The diazopyrrolinones (112) reacted with N-phenylmaleimide and the intermediate pyrazoline eliminated nitrogen to yield the cyclopropane derivative (113).[129] 3-Diazo-4,5-dicyanoimidazole (114) reacted with butadiene in a 1,3-dipolar cycloaddition reaction to give the pyridazine derivative (115).[130] With the electron-rich cis-1,2-dimethoxyethylene only the corresponding azoolefin was formed.

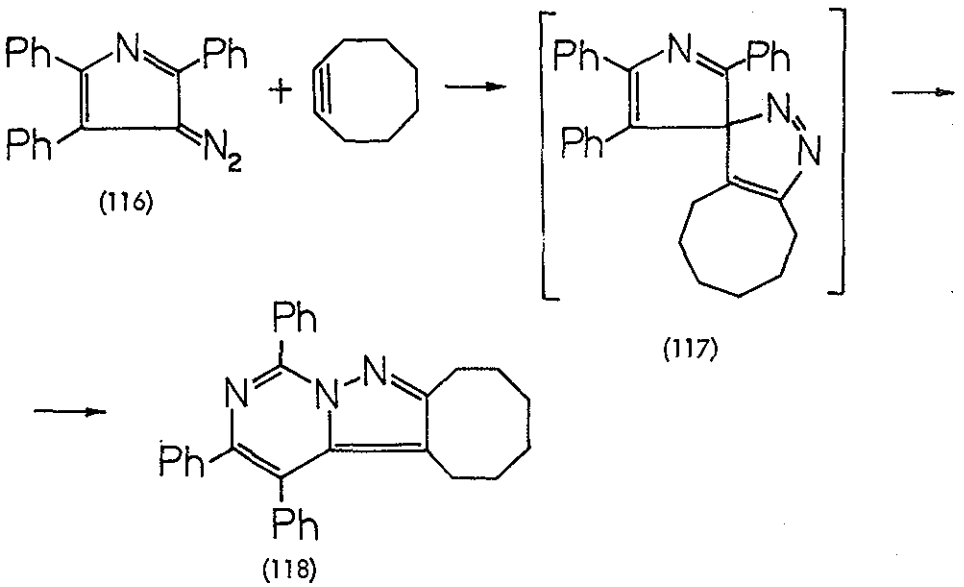


(112) (113)



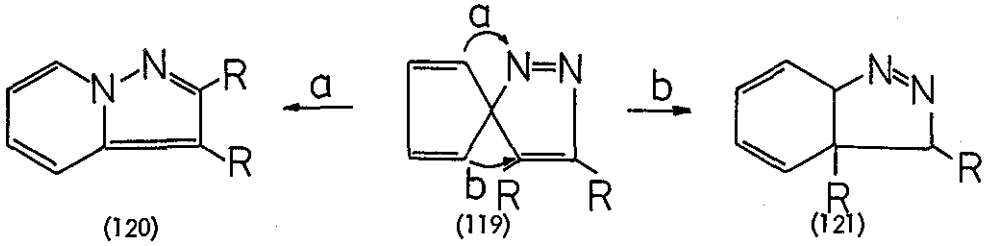
(114) (115)

There are some examples of reaction with compounds with triple bonds. 3-Diazo-2,4,5-triphenylpyrrole (116) reacted with cyclooctyne in a 1,3-dipolar cycloaddition to give the pyrazolopyrimidine derivative (118).[131] The primary addition product, the spiro compound (117), could not be isolated as, for example, in the related reaction with diazocyclopentadiene. The spiro compound (117) undergoes quickly a sigmatropic rearrangement(1,5-shift) to (118). The rearrangement proceeds only in one



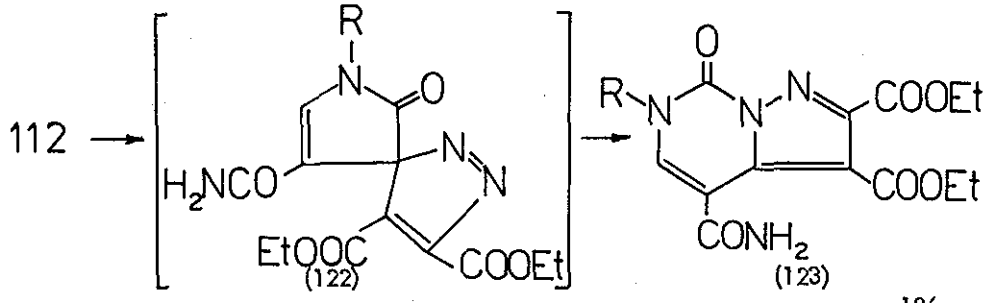
(116) (117) (118)

direction to give only one product (118). This differs from a similar cycloaddition involving diazocyclopentadiene, where the intermediate diazaspirene (119) underwent a 1,5-sigmatropic shift to give either a pyrazolo(1,5-a)pyridine (120) or the indazole (121).[132,133] The driving force for the conversion of the above mentioned spiro compounds to the final products is undoubtedly the formation of stable aromatic 10-π

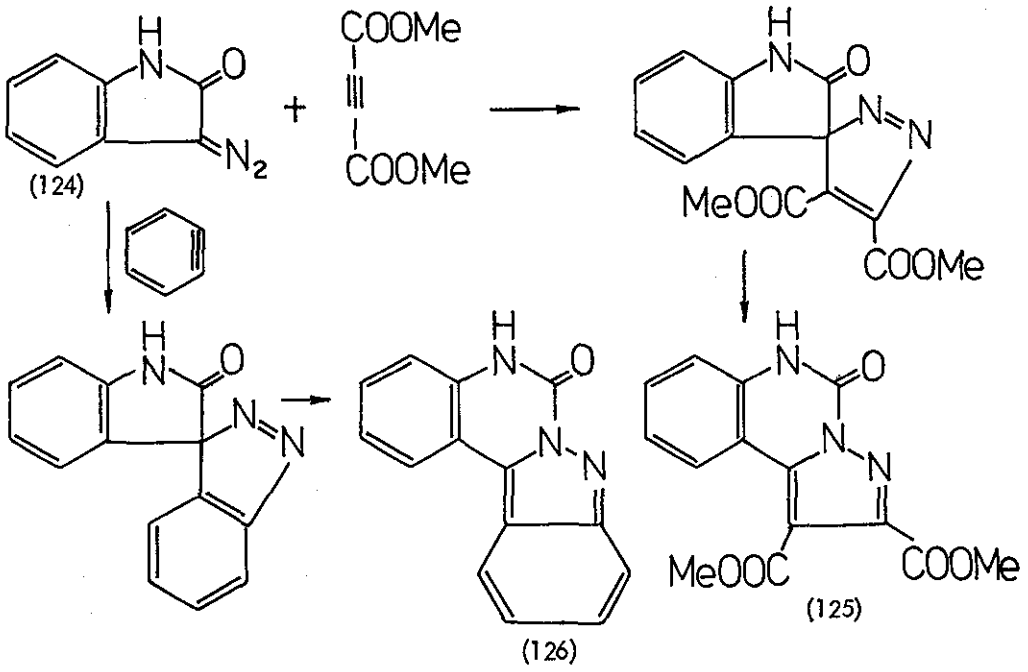


electron compounds. This rearrangement is sometimes referred to as Alphen-rearrangement.[134,135]

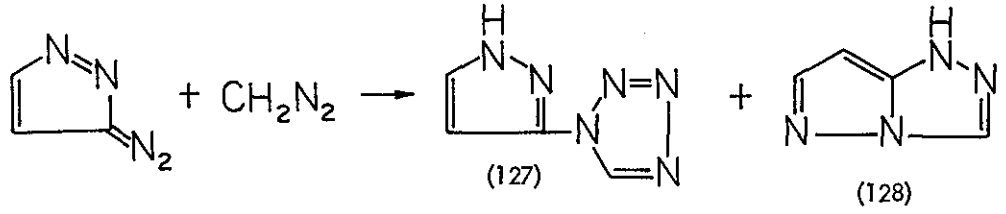
With diethyl acetylenedicarboxylate the diazopyrrolinones afforded the corresponding pyrazolo(1,5-c)pyrimidines (123), again via the spiro intermediate (122).[129]



In a similar manner reacted 3-diazooxindole (124) to give the tricycle (125).[136] The addition to dehydrobenzene apparently involves the primary formation of the spiro compound which gave (126) as end product.[136] Finally, 3-diazopyrazole reacted also with diazomethane in a 1,3-dipolar cycloaddition to give pyrazolyl-tetrazole (127),[137] the structure being established by X-ray analysis. Besides, as established later, a small amount of pyrazolo(5,1-c)triazole (128) was formed.[138]



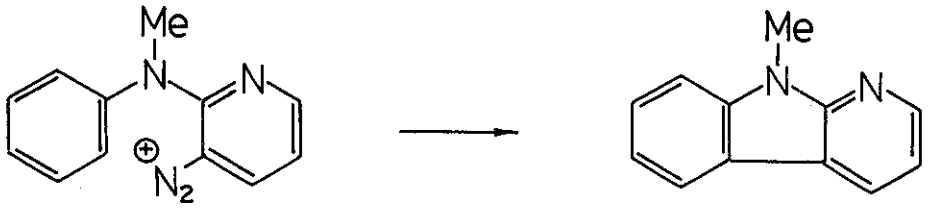
(124) (125) (126)



(127) (128)

4. *Transformations involving elimination of the diazo group*

Heterocyclic diazonium salts have been decomposed thermally or catalytically with simultaneous elimination of the diazo group and cyclization into a new heterocyclic system. As an extension of similar examples in the carbocyclic series, these transformations are sometimes referred to as Graebe-Ullmann and Pschorr reaction. There are review articles on these reactions. Many polycyclic five- and six-membered heterocycles have been synthesized in this manner,[139] for example, carbazoles, carbolines (129),[140,141] dibenzofurans, dibenzothiophenes, phenanthridines, azaphenanthrenes (130),[142] etc. On the other hand, decomposition of heterocyclic diazo compounds may also lead to hetarynes and these reactions are also reviewed.[143] In an attempt to



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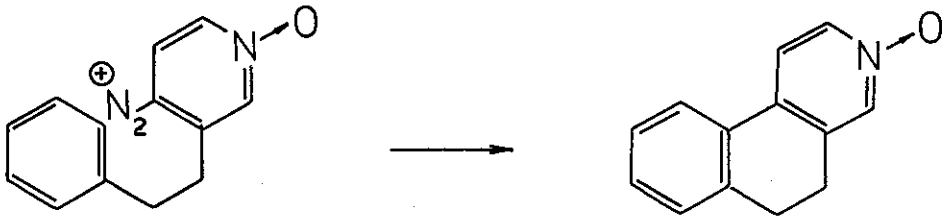
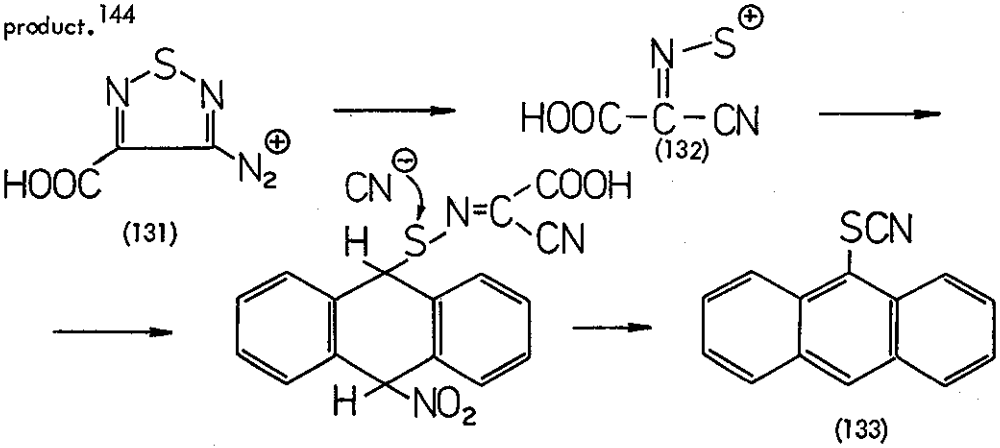


(130)

generate the dehydroheterocycle, 3-amino-1,2,5-thiadiazole-4-carboxylic acid was diazotized in the presence of anthracene. One of the products was 9-thiocyanatoanthracene (133), formed by the collapse of the diazonium ion (131) into the electrophilic intermediate (132) which adds to anthracene and further elimination afforded the product.[144]

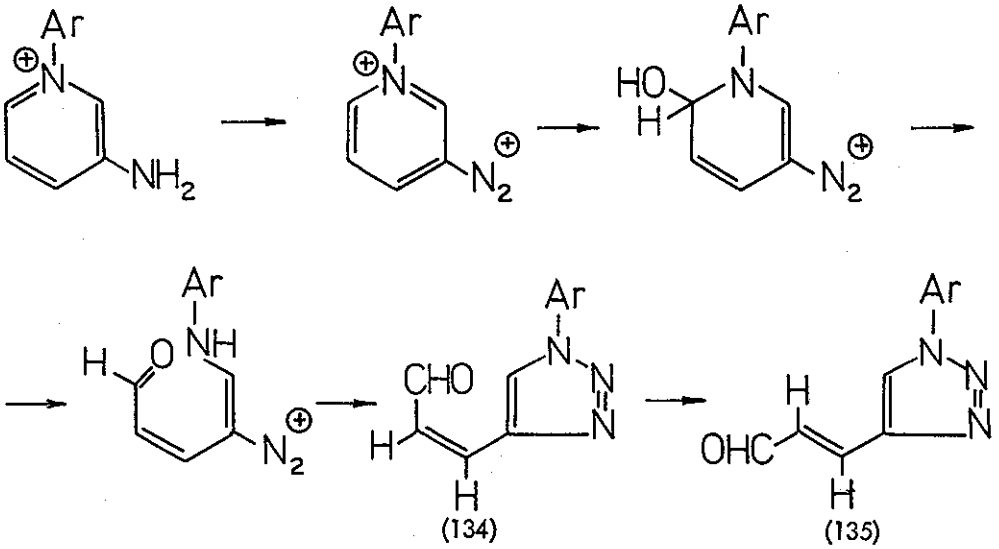


(131) (132) (133)

5. Rearrangements of heterocyclic diazo compounds and diazonium salts

There are several types of rearrangement of diazoheterocycles which have been studied. One group of compounds involves quaternized diazoheterocycles which undergo ready ring opening and recyclization to another system. N-aryl-3-aminopyridinium

salts, when diazotized, are transformed into the corresponding 1,2,3-triazolyl acrylaldehydes (134,135).[145,146] The initially formed cis-compounds (134) are easily isomerized into the more stable trans-isomers (135). Similar behaviour was encountered

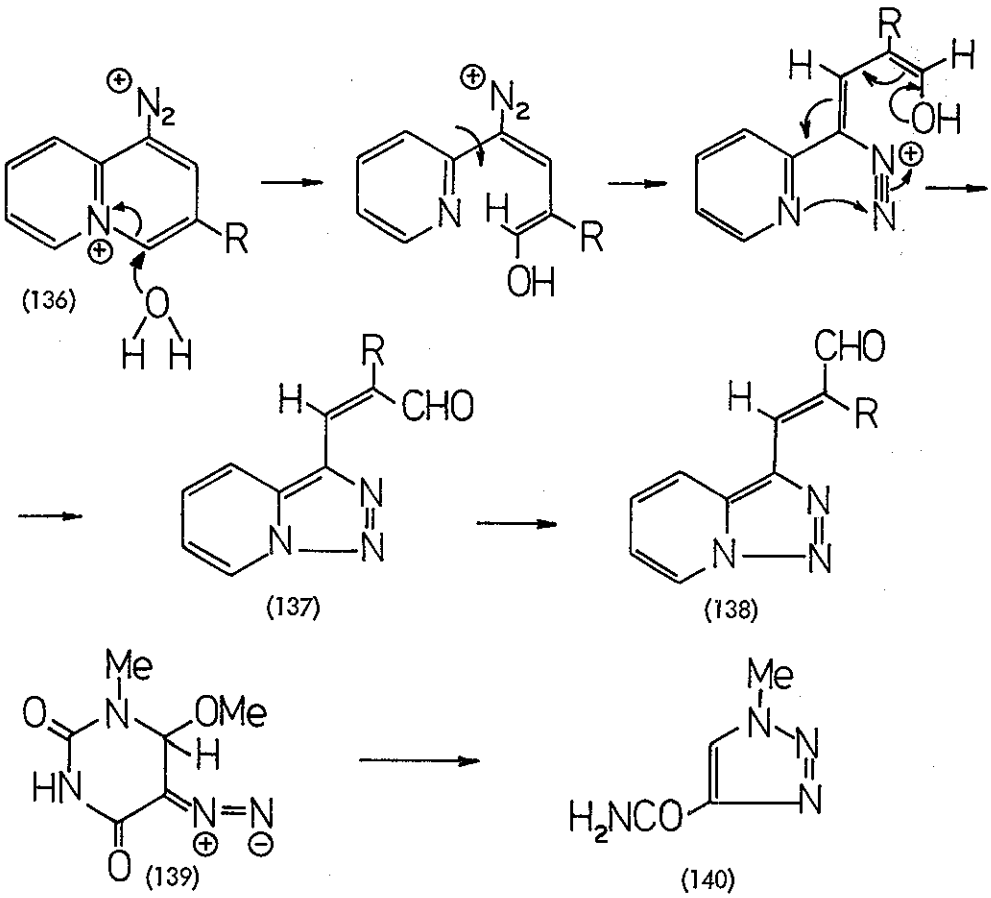


(134) (135)

with diazotized 1-aminoquinolizinium chloride (136). The diazonium salt was obtained only with nitrosylsulfuric acid or pentyl nitrite.[147] With nitrous acid in dilute aqueous solution a neutral compound was obtained and to it tentatively a furazan structure was assigned.[147] Later, evidence was presented[148] that the product is actually a 1,2,3-triazolo(1,5-a)pyridine (137) and that this kind of reaction takes place also with other analogs of (136).[149] Under the influence of traces of acid the cis-isomer (137) is rapidly converted into the more stable trans-isomer (138).[148,149] It should be noted that retention of cis-configuration is always observed under conditions which do not promote isomerization and the cis-aldehyde (137) was always obtained first.

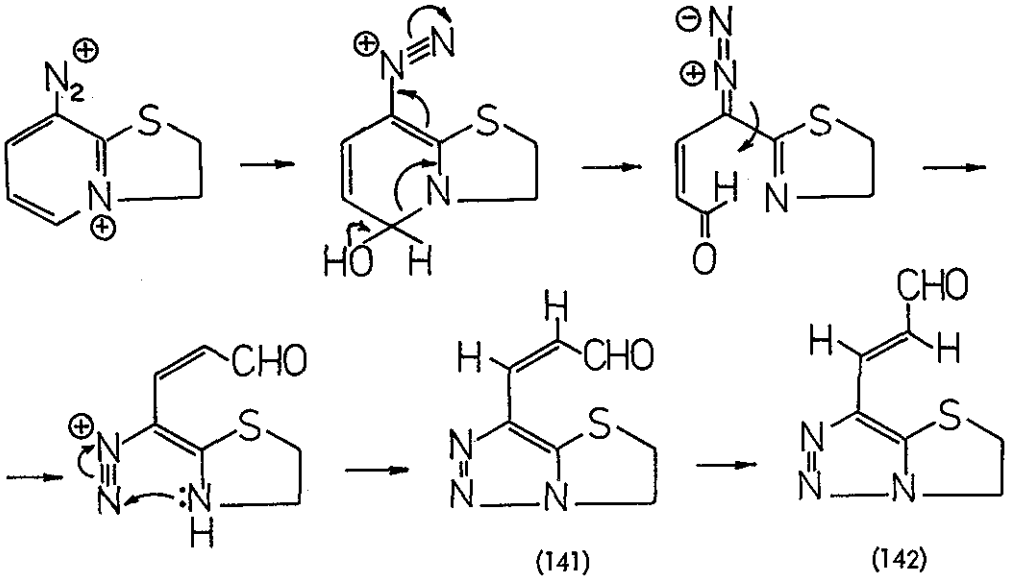
A different, thermally induced type of rearrangement has been observed with a diazouracil derivative (139)[150] or cyclo-5-diazouridine[151] where a triazole ring is formed (140). It is anticipated that the 2-CO group is eliminated from the pyrimidine ring and subsequent bond formation between N_1 and the diazo group gives the triazole compound.

There are some cases where a endocyclic nitrogen or sulfur atom is attacked by a diazonium group with the formation of a new cycle. 8-Aminodihydrothiazolo(3,2-a)

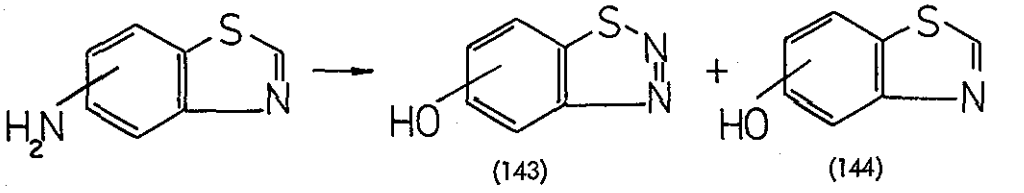


pyridinium bromide, when diazotized with isoamyl nitrite in aqueous acetic acid was transformed into an almost equimolar mixture of cis- (141) and trans-thiazolo(2,3-e)-1,2,3-triazolyl acrylaldehyde(142).[152] The transformation involves addition of the hydroxyl ion to the highly electron deficient pyridinium system, with subsequent ring opening and attack of the diazo group to the endocyclic nitrogen atom with simultaneous formation of the bicycle. The cis-isomer (141) is converted in weak acid into the trans-isomer (142).

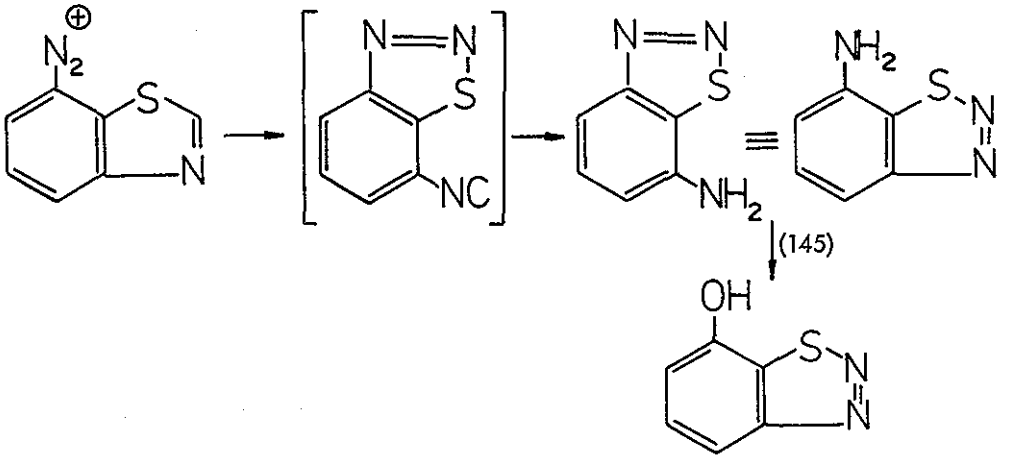
Studies on diazotization and hydrolysis of 5- and 6-aminobenzothiazoles revealed that, depending on the ratio of nitrous acid to aminobenzothiazole, either the corresponding hydroxybenzothiazoles (144) or hydroxy-1,2,3-benzothiadiazoles (143) are formed.[153] The latter are formed in particular when excess of nitrous acid was employed. Although the mechanism of this rearrangement is not established, it must undoubtedly



(141) (142)

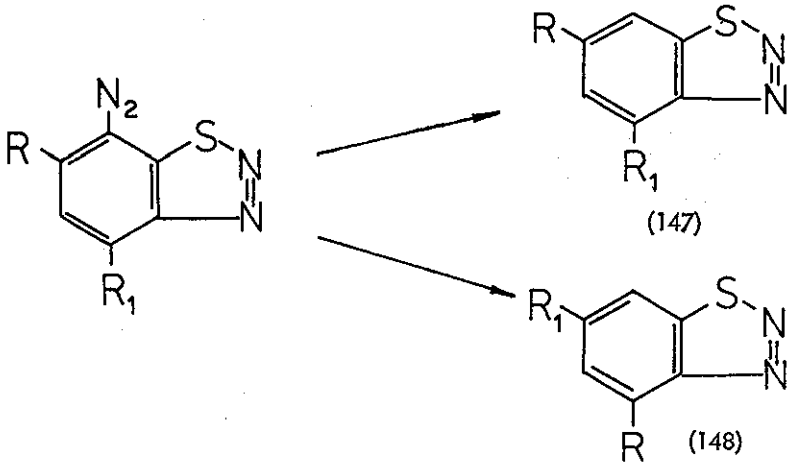


(143) (144)



(145) (146)

involve opening of the thiazole ring with subsequent formation of the fused thiadiazole part. 7-Aminobenzothiazole behaves differently and with one equivalent of nitrous acid 7-aminobenzothiadiazole (145) is obtained. With excess of nitrous acid the amino group is converted into the hydroxy group to give (146).[153] In this rearrangement, electrophilic attack of the diazonium group on the endocyclic sulfur is followed by ring opening of the thiazole ring. In a further study of this rearrangement a novel transformation of diazonium salts, derived from 7-amino-1,2,3-benzothiadiazoles has been discovered.[154] Diazotization of substituted 7-amino-1,2,3-benzothiadiazoles, followed by removal of the diazonium group with hypophosphorus acid or through Sandmeyer reaction, may lead to the expected normal products (147) or to the rearranged products (148).[154] Moreover, it was found that substituents have an important role in this rearrangement. With position 4 unsubstituted, any substituent, other than hydrogen, at position 6 caused rearrangement and the effect must be largely steric.



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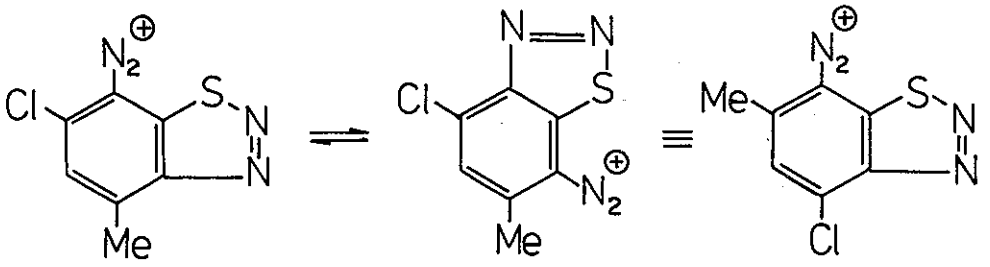
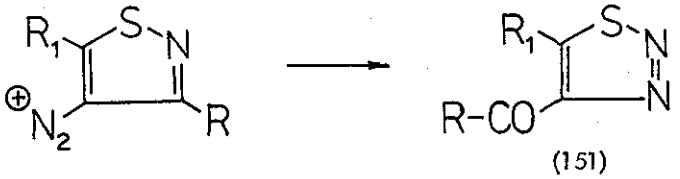
(148)



(149) (150)

This brings the diazonium group close enough to the endocyclic sulfur to bring about the rearrangement (149,150).

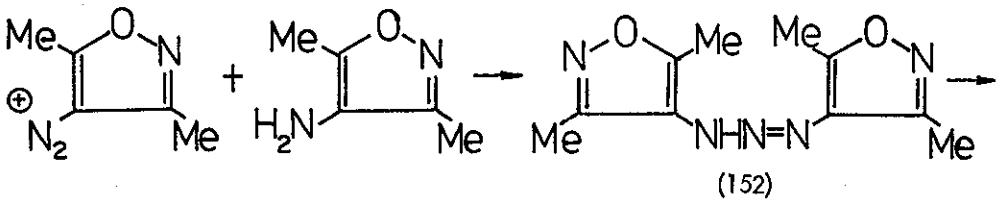
Another rearrangement with no definite evidence for the mechanism, although several have been proposed, has been observed with a diazoisothiazole. Whereas diazotized 5-amino-3-methylisothiazole reacts with thiourea in a normal manner to give the corresponding thio compound which is further transformed into disulfide, 4-amino-3-methylisothiazole behaved differently and the product was identified as 4-acetyl-1,2,3-thiadiazole (151).[155] Similar transformation could be observed with 4-aminoisothiazole and its 5-methyl analog.



(151)

An interesting transformation was observed when 4-amino-3,5-dimethylisoxazole was diazotized and subsequently treated with potassium cyanide and cupric sulfate. Instead of the expected cyano compound an isoxazolyl-1,2,3-triazole (153) was obtained.[156] The formation of the latter is explained to proceed via an intermediate triazene (152). A similar conversion has been observed with 3,5-dimethyl-isoxazole-4-diazonium salt which upon heating in the presence of cupric sulfate and sulfuric acid afforded the triazole (154).[157] Also 5-methyl-3-aminoisoxazole, when diazotized with one half equivalent amount of sodium nitrite in 10% hydrochloric acid did not afford the diazonium salt, but the corresponding triazene (155). The latter, when dissolved in warm alkaline solution, afforded the isoxazolyl-tetrazole (156).[158]

There are some interesting rearrangements in the benzoazepine series. 3-Amino-2,5H-4-methyl-6,7-benzoazepine-2,5-dione (157), when treated with nitrous acid, afforded as the major product the azepine (158). This is rearranged into the quinoline derivative (159), which was also the minor product in the above diazotization reaction.[159] If diazotization was performed in a mixture of methanol and acetic acid, the diazo compound (160) was isolated. On the other hand, hydrogenation of compound (159) afforded the tricycle (161), apparently by reduction of the diazo into hydrazino group



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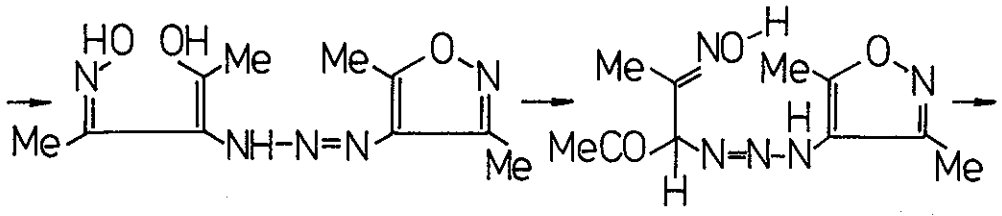

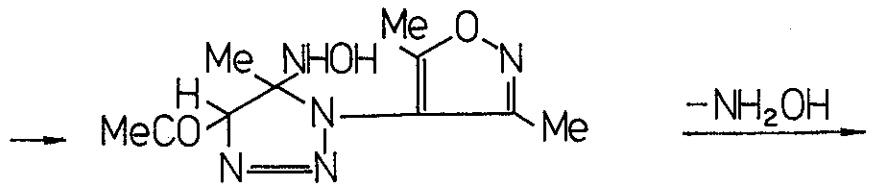

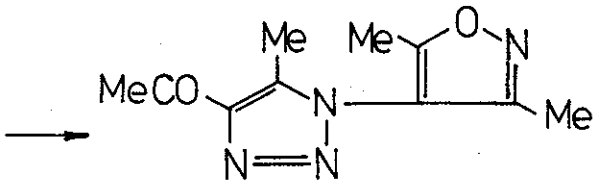

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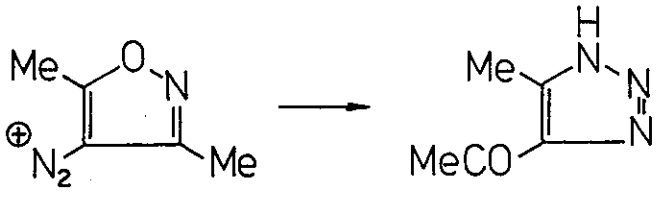

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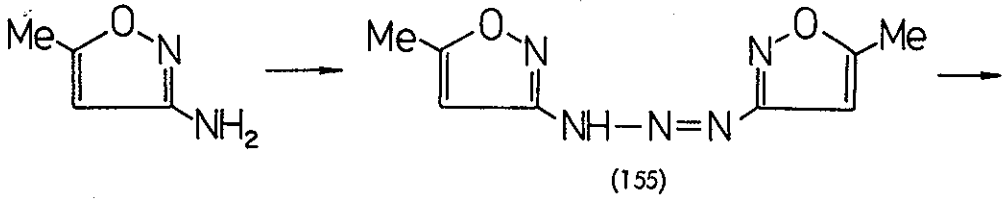

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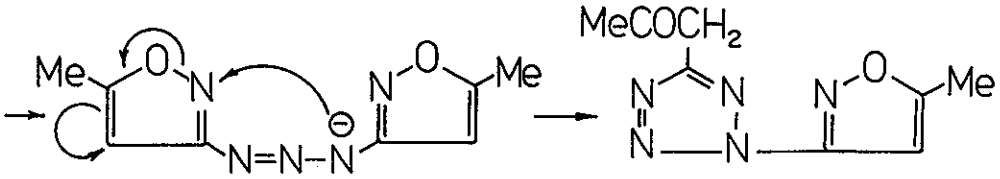

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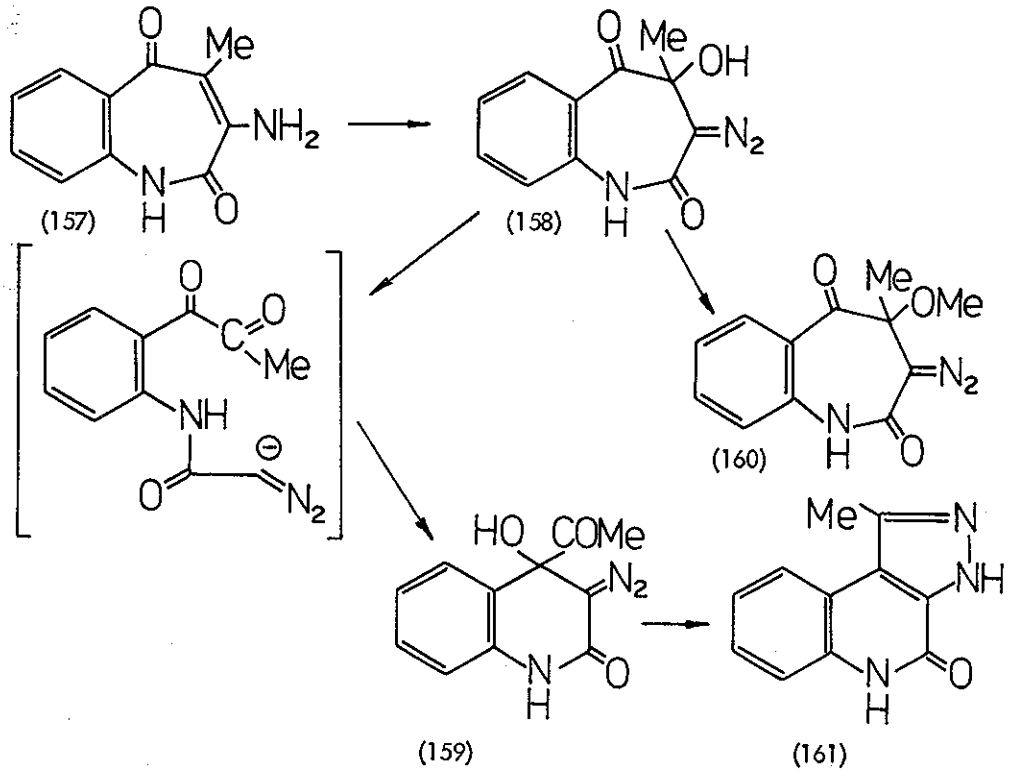
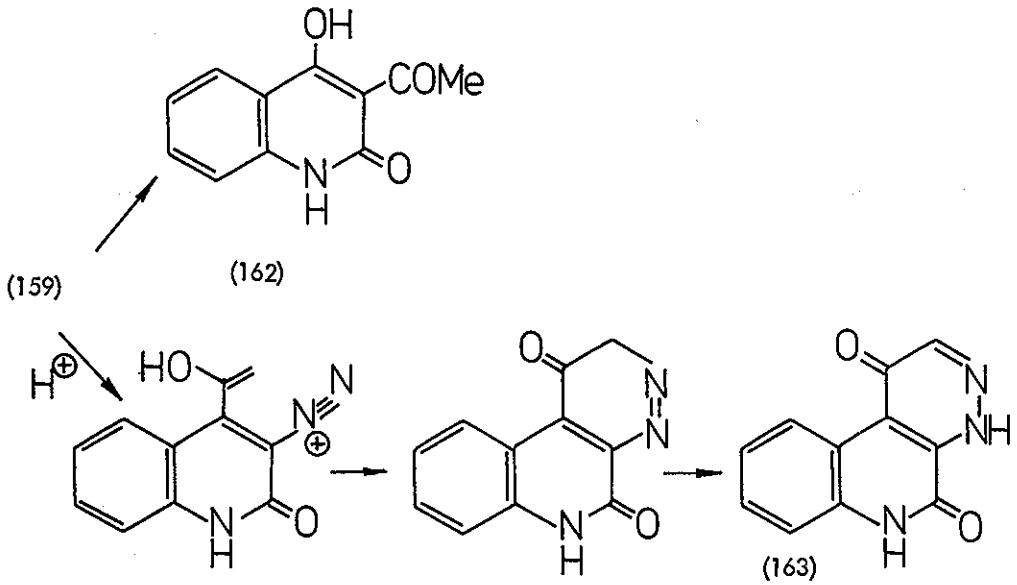
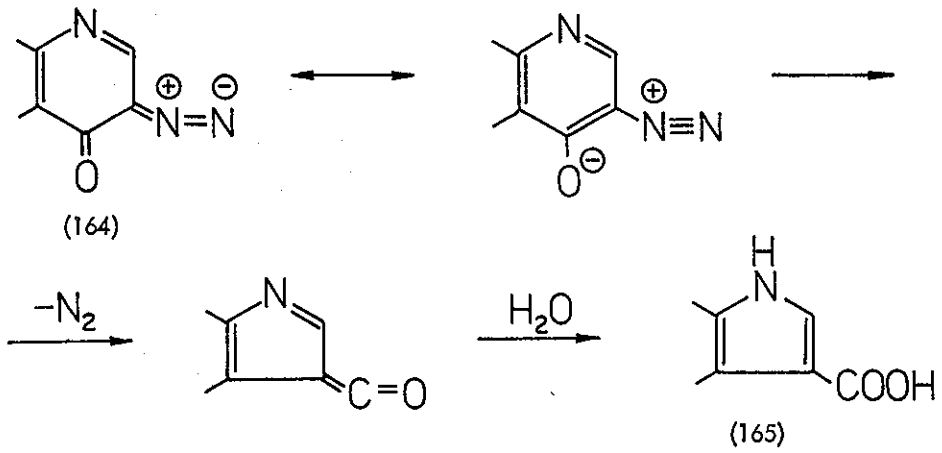


(157) (158) (159) (160) (161)



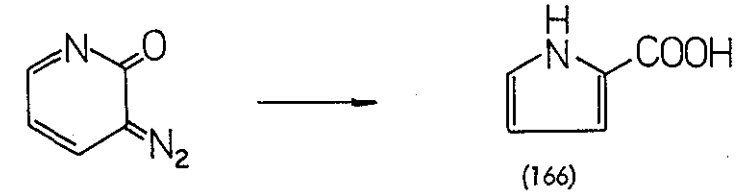
with subsequent cyclization. Thermal rearrangement of (159) afforded the carbostyril (162), whereas acid-catalyzed treatment transformed (159) almost quantitatively into (163).[159]

Heterocyclic compounds which upon diazotization assume a diazo-oxide structure, are in general photochemically isomerized in a Wolff like rearrangement of diazo-ketones (164-165). The reaction proceeds with ring contraction and a competitive reaction can



be the generation of a singlet α-ketocarbene which undergoes addition of nucleophiles at a greater rate than the rearrangement takes place.[30,31,160,161] Thus, it is possible to prepare substituted indoles, azaindoles and pyrrole derivatives by photochemical rearrangement of diazo-ketones.

3-Diazo-2-pyridone, was isomerized into pyrrole-2-carboxylic acid (166)[162] and 3-diazo-4-pyridone gave pyrrole-3-carboxylic acid.[163] However, the 2,6-dimethyl analog of the latter diazo-ketone coupled to the rearranged pyrrole to give the azo-compound (167).[164] Further examples of this rearrangement are in the quinoline series (168),[162-164] (169)[162,163] in the case of naphthyridines (170),[162] (171),[165,166] (172),[167] (173),[167] benzimidazoles (174),[163] benzothiazoles (175),[162] benzotriazoles (176,177),[163,168] s-triazolo(4,3-b)pyridazines (179),[169] and others (180).[158]



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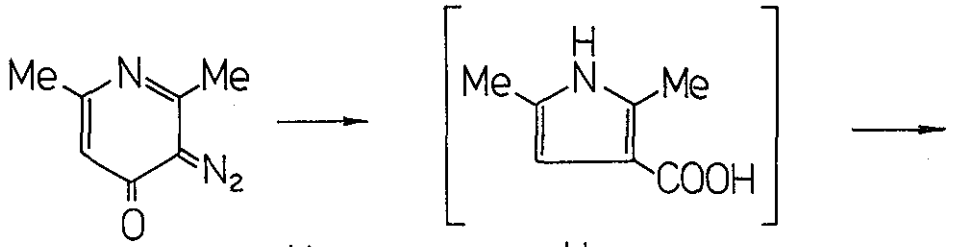

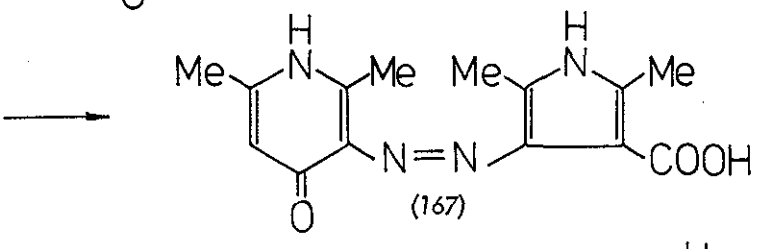

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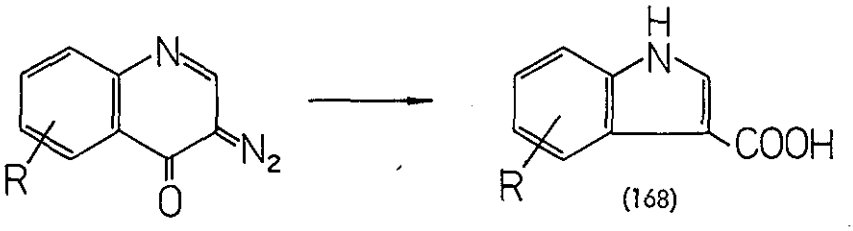

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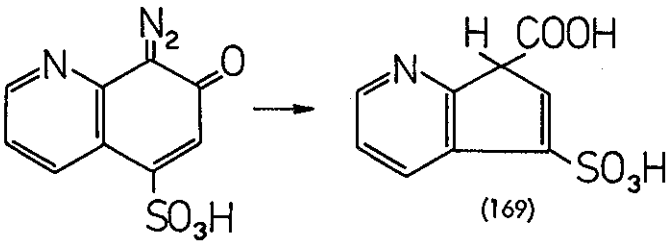

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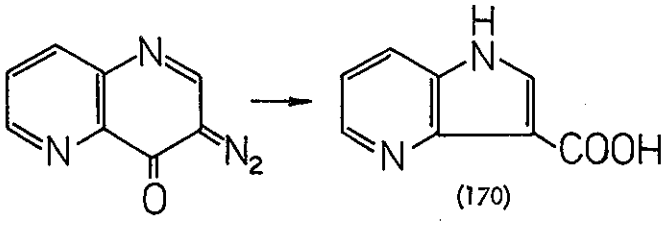

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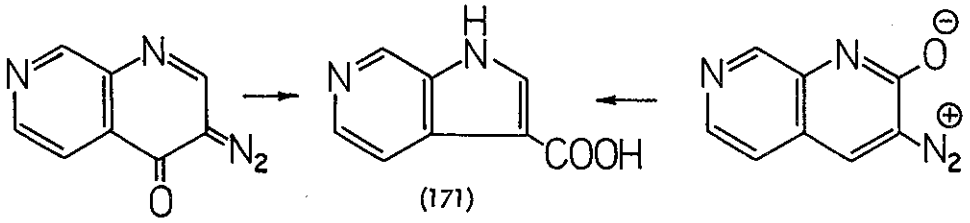

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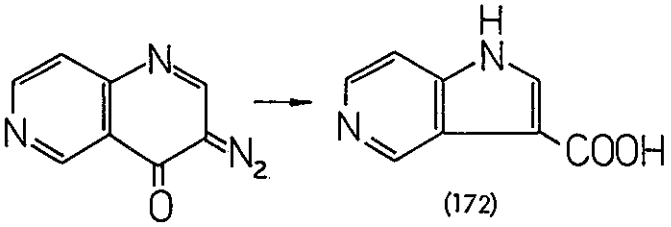

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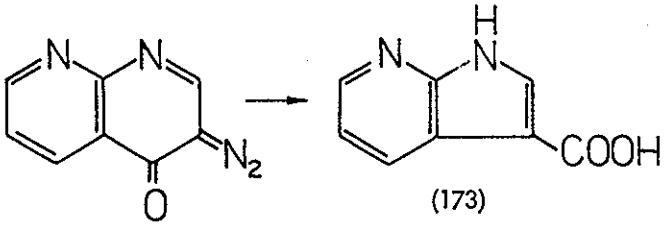

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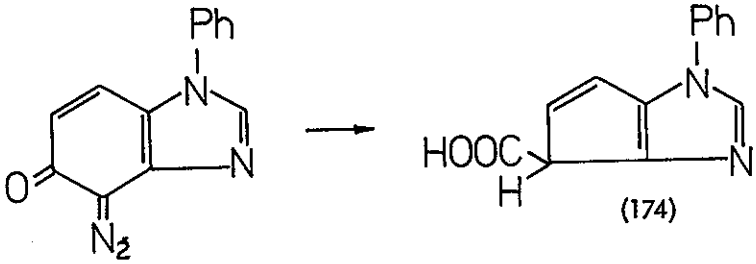

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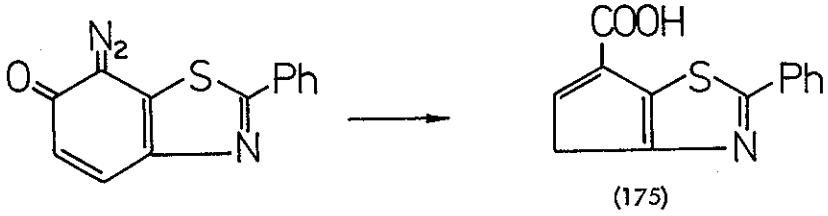

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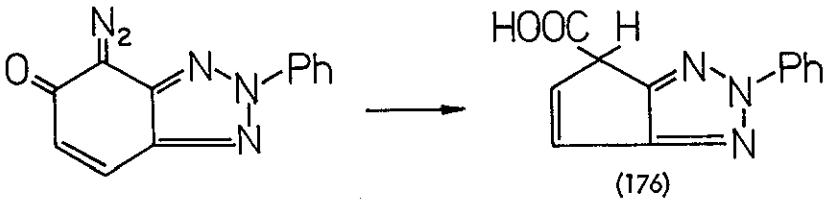

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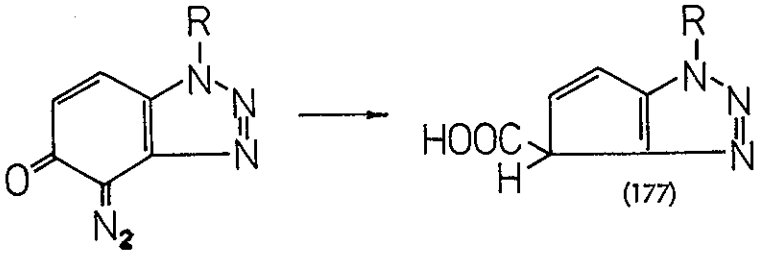

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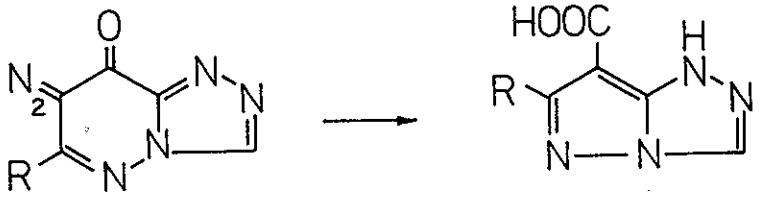

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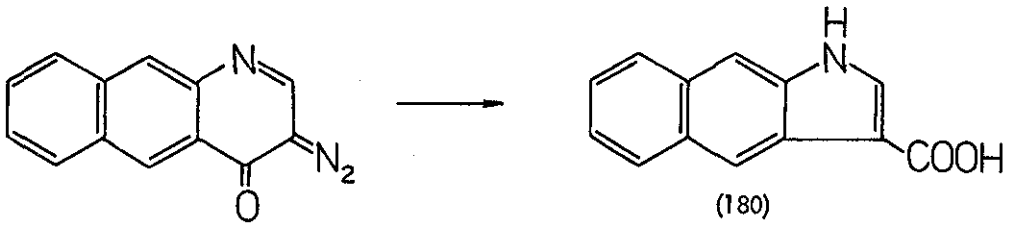
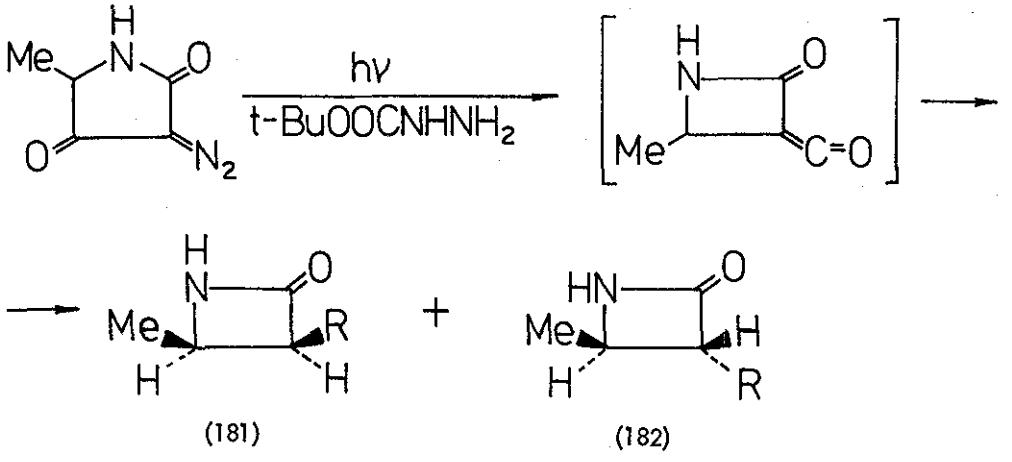


(180)

In a similar manner, 3-diazo-5-methylpyrrolidine-2,4-dione when photolyzed in the presence of t-butyl-carbazate afforded a mixture of cis-and trans-β-lactam (181,182).[170] The rearrangement presents a new method for the synthesis of β-lactams.

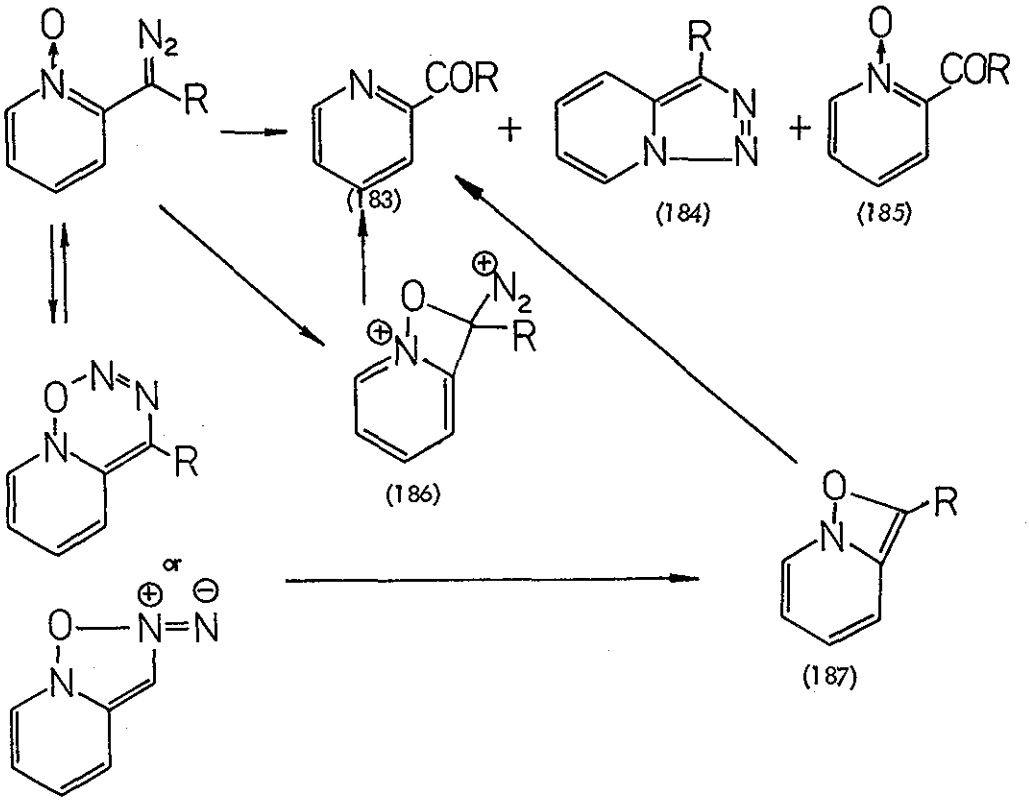


(181) (182)

R= CONHNHCOO-Bu-t

Studies on attempted photorearrangement of some diazo-oxides in the presence of sensitizers have shown that in this case the triplet carbene reacts preferentially by hydrogen abstraction. In this manner, an unsensitized photoreaction of (178) produced (179), whereas in the presence of a sensitizer (178) is transformed into 6-methyl-8-hydroxy-s-triazolo(4,3-b)pyridazine.[171]

An interesting case represents the decomposition of 2-pyridyldiazomethane 1-oxides.[172] These, when decomposed thermally or photochemically, are transformed into 2-acylpyridines (183) as the main product, accompanied sometimes with small quantities of triazolopyridines (184) and 2-acylpyridine 1-oxides (185). The formation

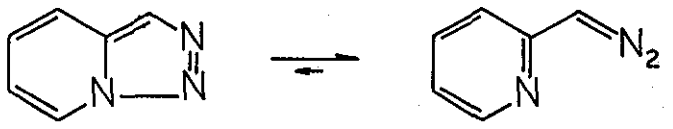


of the latter two products is proposed to occur through a bimolecular process, whereas the formation of (183) may proceed either via (186) or (187).

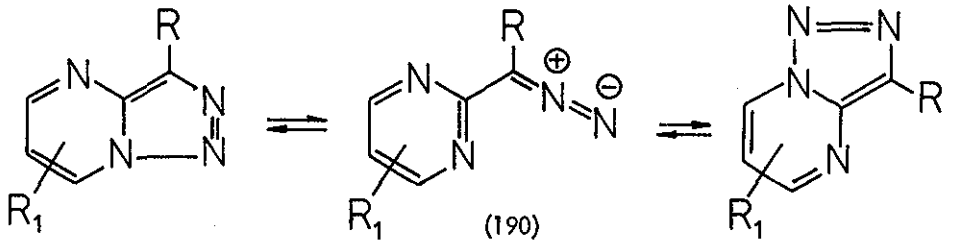
6. Derivatives of 1,2,3-triazole and 1,2,3-triazine as masked diazonium compounds

There are several chemical transformations involving a 1,2,3-triazole or 1,2,3-triazine ring fused to a heterocyclic ring, similar to those observed with some monocyclic compounds or benzo derivatives. These under the influence of heat or acid catalysis undergo rupture of the heterocyclic ring to give an intermediate diazo or diazonium compound.

For example, it has been suggested that ring-chain tautomerism precedes the thermolytic decomposition of fused 1,2,3-triazolo heterocycles, for example triazolopyridines (188,189).[173,174] The first example of a measurable diazoalkylideneamine 1,2,3-triazole tautomerism has been demonstrated with 1,2,3-triazolo(1,5-a)pyrimidines

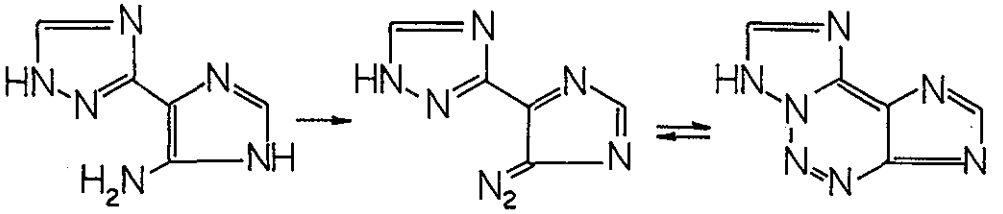


(188) (189)

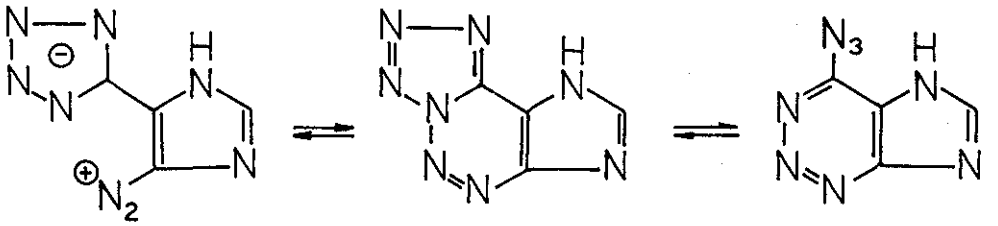


(190)

at higher temperatures and the intermediate diazo compound (190) could be detected.[175] A particular case represents the system (191) which upon diazotization afforded a mixture of the diazo compound (192) and the tricycle (193).[176] In a solution of trifluoroacetic acid only protonated (192) was present, but in DMSO or 2-methoxyethanol only (193) was present. If a solution in DMSO was treated with trifluoroacetic acid,



(191) (192) (193)

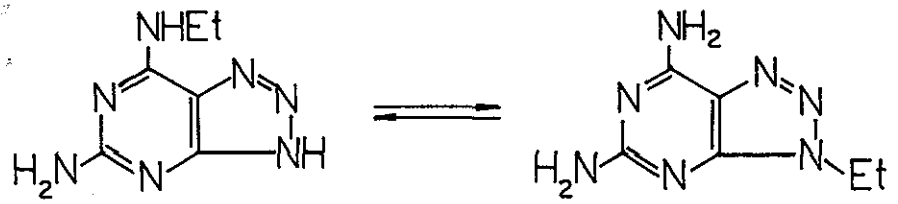


(194) (195) (196)

both forms, (192) and (193), were present.[176] With the related tetrazole analog, in addition to the mentioned equilibria, also azido-tetrazolo isomerization is possible (194-196). Another example of a labile triazine ring was demonstrated with imidazo-(4,5-d)-1,2,3-triazine (197), which upon heating in water, was transformed into the diazoimidazole (198).[177]

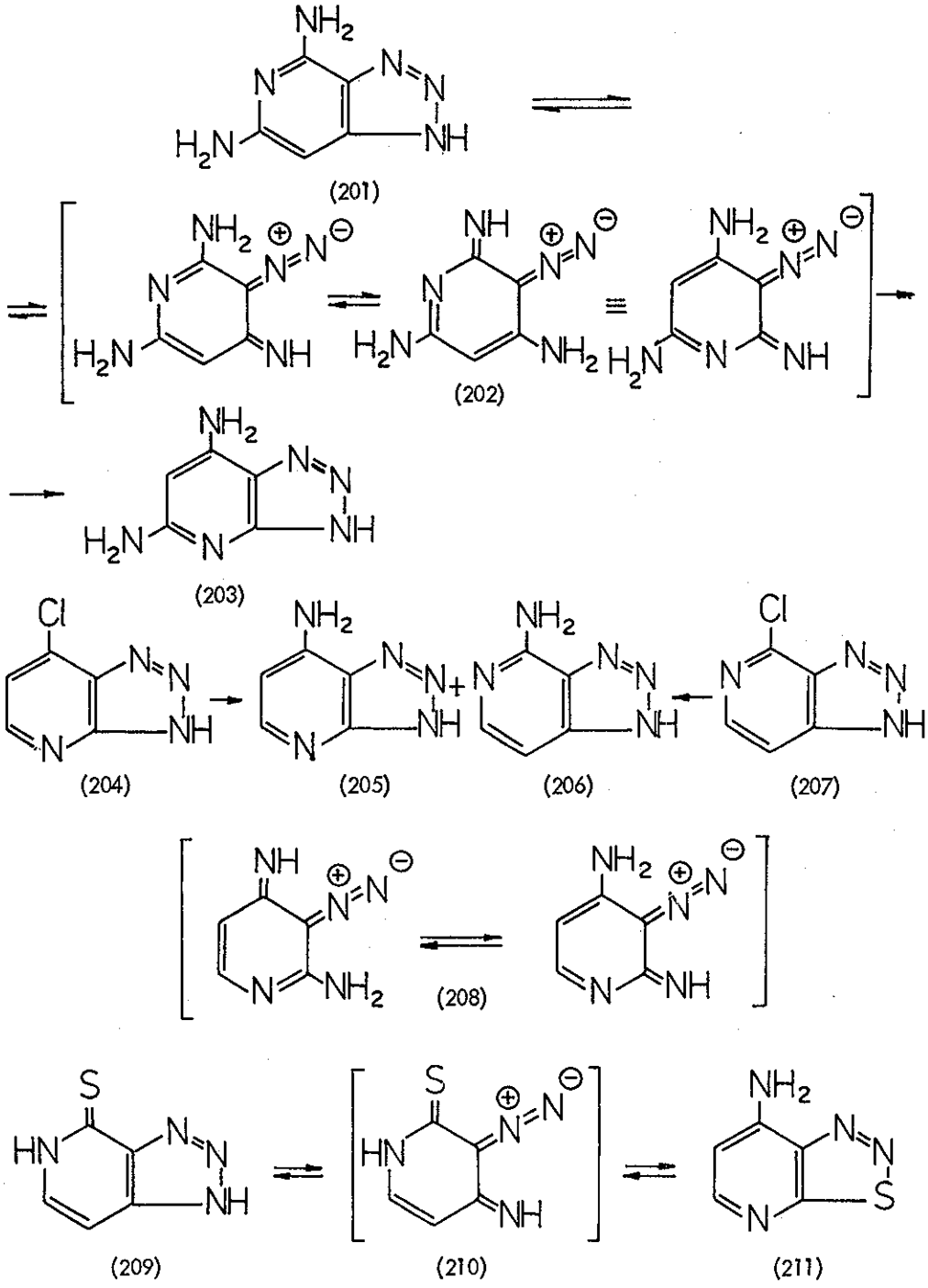
(197) (198)

It has been observed that compounds (199) and (200) are interconvertible.[178] Althogh this rearrangement is best envisaged as to proceed via an intermediate diazo



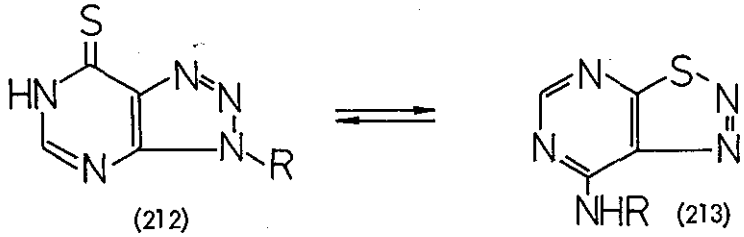
(199) (200)

compound, the latter could not be trapped. Similarly, the conversion of the triazolo-pyridine (201) into the isomeric triazolopyridine (203) was interpreted as to proceed via a diazo intermediate (202),[39] although the reaction conditions were quite severe. Also 7-chloro-1,2,3-triazolo(4,5-b)pyridine (204) when heated with ethanolic ammonia at 150° for 19 hr gave the corresponding amino derivative (205) and a small amount of the rearranged product (206).[179] On the other hand, also from the isomeric chloro compound (207) a mixture of (205) and (206) was obtained. It is anticipated that the rearrangement involves a diazo intermediate (208). Furthermore, during thionation of (204) a mixture of the expected compound and the rearranged product was obtained. In a separate experiment it could be shown that compound (209) is partly rearranged in boiling propanol into thiadiazolopyridine (211), or vice versa. The rearrangement is again explained as to proceed via an intermediate diazo compound (210).[179] Similar



(201) (202) (203) (204) (205) (206) (207) (208) (209) (210) (211)

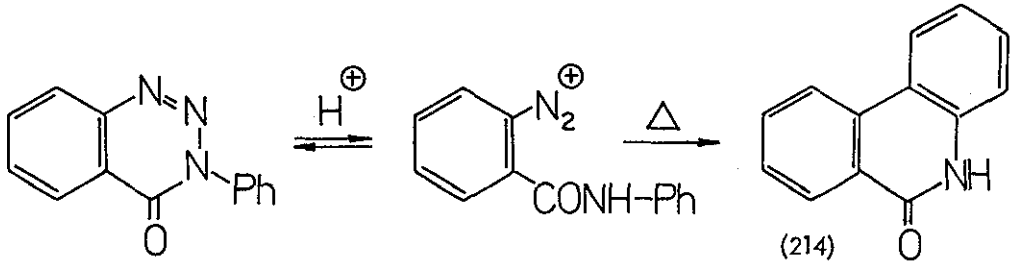
thermal rearrangement, leading to an equilibrium, has been observed with triazolopyrimidines (212), convertible into thiadiazolopyrimidines (213).[180,181]



(212) (213)

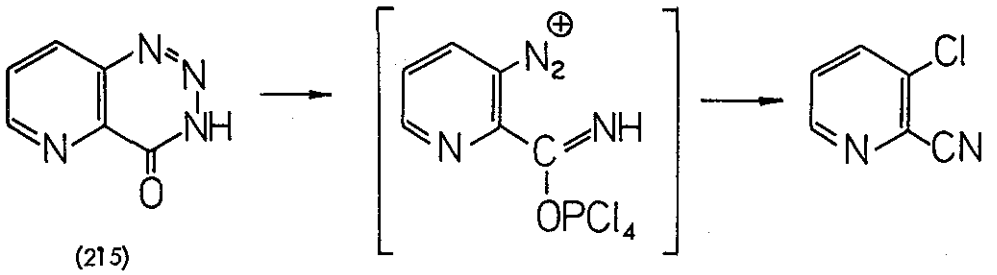
Breakdown of the triazole ring in fused triazoloheterocycles under the influence of acidic reagents is also explained by the formation of an intermediate diazonium ion, followed by attack of the solvent or other reagent on the derived carbonium ion.[182-188]

In strongly acid solution the diazonium ions may be formed from 1,2,3-triazine derivatives and coupling to phenols has been observed. Moreover, decomposition of some benzotriazinones in phosphoric acid has been used for the preparation of 6-phenanthridones (214)[189-191] or phenanthridines.[192] The decomposition reaction is mechanistically similar to the Pschorr reaction.[193] Similarly, the conversion of pyrido(3,2-d)-

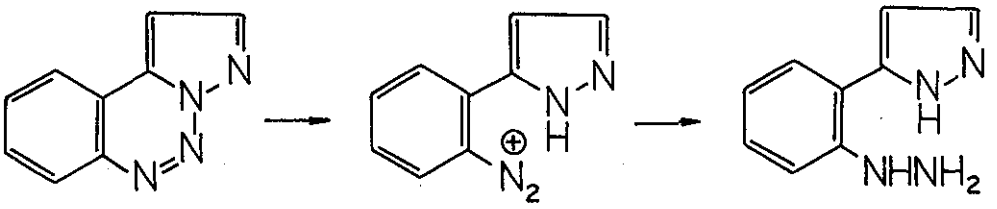


(214)

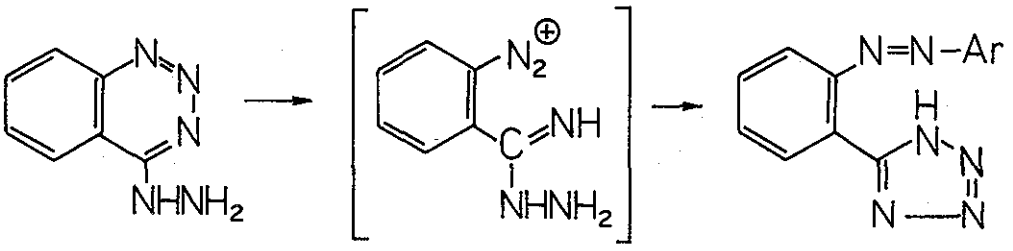
1,2,3-triazin-4-one (215) into 2-cyano-3-chloropyridine with phosphorus pentachloride can be explained as to proceed via an intermediate diazo compound.[100] Moreover, pyrazolobenzotriazine, when reduced with $SnCl_2$ in hydrochloric acid, is transformed to the hydrazino compound (216), evidently via the intermediate diazonium salt.[79] Finally, the attempted transformation of 4-hydrazinobenzo-1,2,3-triazine into the corresponding azide by nitrosation in aqueous solution, which instead generated a diazonium salt, falls into the same group. After ring opening, the diazo group underwent coupling to phenols and from the residual side chain upon nitrosation a tetrazole ring was formed to give (217).[194]



(215)



(216)



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