

CHEMISTRY OF HETEROCYCLIC DIAZO COMPOUNDS

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Abstract - The preparation, chemical properties and synthetic utility of nitrogen heterocyclic diazo compounds are reviewed.

INTRODUCTION:

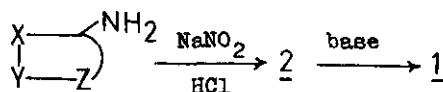
Heterocyclic diazo compounds (1) and their diazonium salts (2) are versatile reagents and their chemistry has received a considerable recent attention.^{1,2} However, in spite of their interesting synthetic potentialities, the chemistry of this class of compounds has been ignored in available organic chemistry books. Moreover, with exception of Tedder's chapter in "Advances in Heterocyclic Chemistry"³ which is now obsolete, no trials to review the chemistry of this class of compounds has been made. In the following we report the literature in this area which we hope will be



of value for both researchers and instructors of organic chemistry.

PREPARATION:

The common method for the synthesis of heterocyclic diazo compounds or diazonium salts is the diazotization of heteroaromatic primary amines in which the amino group is bonded directly to the ring (cf. Eq. 1). Butler⁴ has covered in details this subject. Stadtler et al⁵ reviewed the other methods for the synthesis of this class of compounds, but these methods are of minor importance.



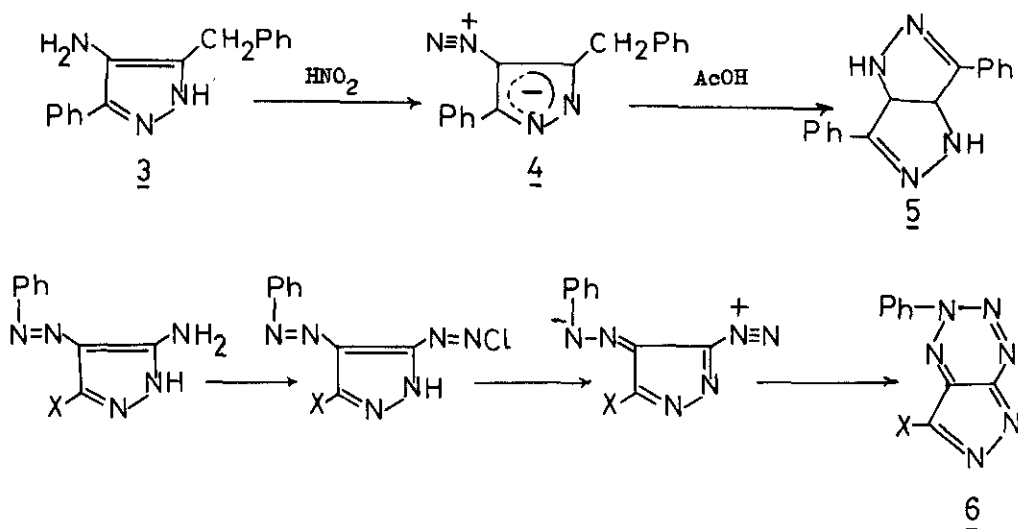
Eq. 1

CHEMICAL PROPERTIES:

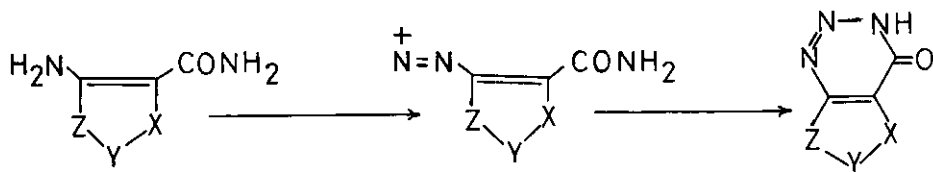
The diazo compounds can be converted into other derivatives. The reactivity and types of reactions undergone by these compounds are summarised in this review.

1. Intramolecular cyclization:

Heterocyclic diazo compounds are considered as dipolar compounds. Thus, interaction between the positive and negative ends of the molecule leads to the formation of fused heterocycles.⁶⁻⁸ Diazotization of 4-amino-3-phenyl-5-benzylpyrazole (**3**) has afforded the corresponding diazopyrazole derivative (**4**). Compound **4** when heated in acetic acid has afforded the pyrazolo 3,4-c pyrazole derivative (**5**).⁸ Similarly, the pyrazolo 3,4-e -1,2,3,4-tetrazine (**6**) has been formed when a solution of diazotized 5-amino-4-phenylazopyrazole was left to stand at room temperature in protic media.



One of the most efficient routes for the synthesis of azopurines is the self coupling of diazotized aminoimidazole derivatives via amide or amidic nitrogen at 5-position.¹⁰ Recently a survey of this synthetic route for obtaining derivatives of these ring systems has been reviewed.¹¹ 3-Amino-4-methylquinoline (**7**) reacts with two molecules of nitrous acid to form the quinolino-0-triazine derivative (**8**) and 3-azidoquinolino-4-carboxaldehyde (**9**).^{12,13} On the other hand, when the reaction was carried out in the presence of sulphuric acid, compound **10** was formed. 6-Methyluracil (**11**) behaves similarly on diazotization¹³ (cf. Chart 1).



Diazotization of 8-aminoquinoline (12) leads to the formation of the diazonium salt which undergoes internal coupling to give the fused 1,2,3-triazole derivative (13).¹⁴

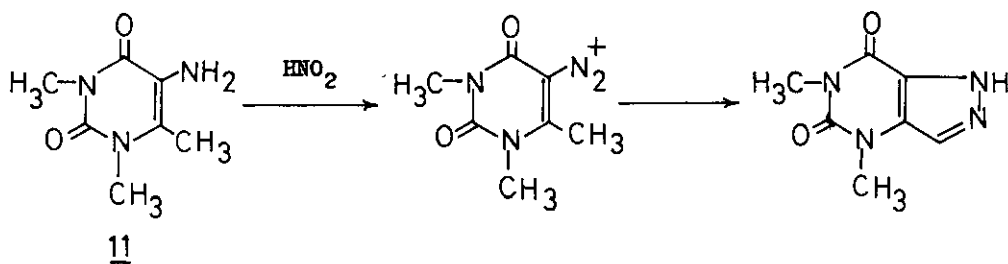
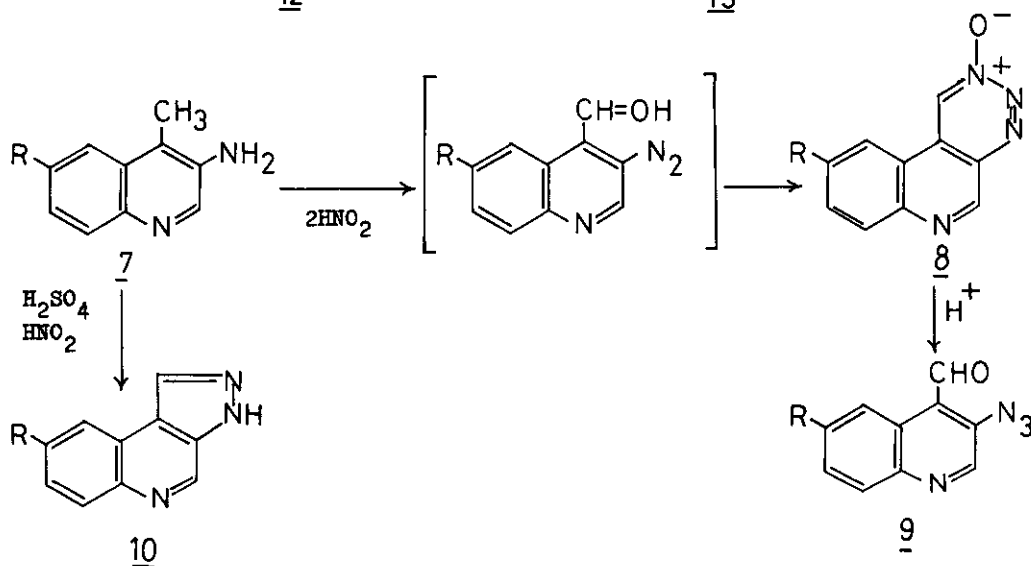
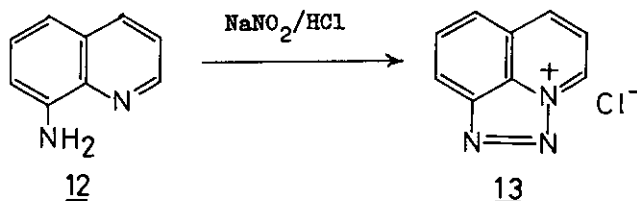
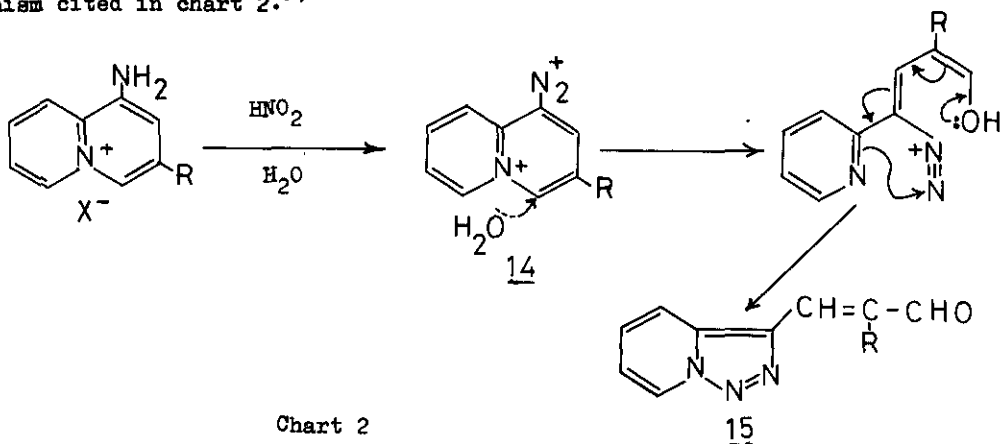


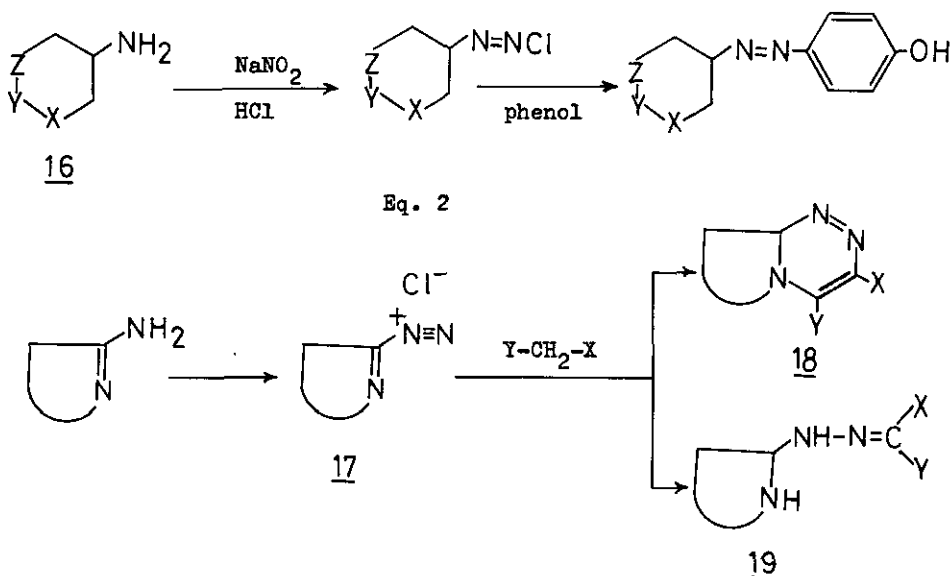
Chart 1

When aminoquinoline was diazotized, the produced diazonium salt (14) rearranges to 1,2,3-triazolo 1,5-a pyridine (15). The reaction is considered to proceed via the mechanism cited in chart 2!^{5,16}

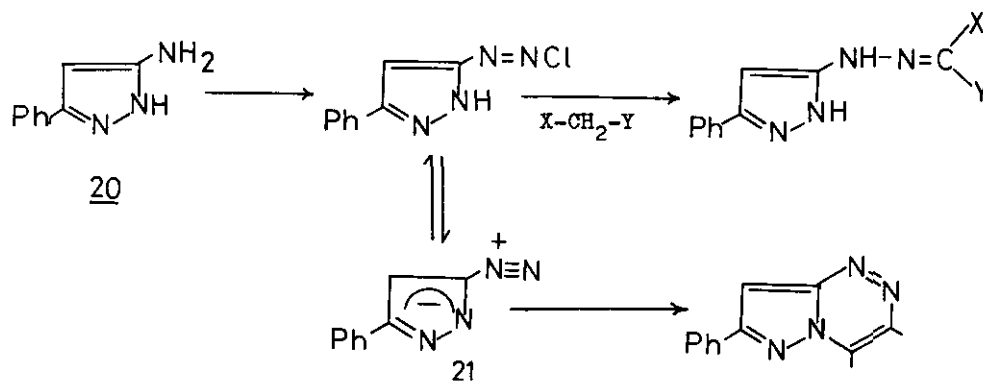


2. Coupling with phenols and active methylene reagents:

Amino heterocycles of the type 16, when treated with sodium nitrite in acid medium, readily yield the diazo derivative. These diazonium salts readily couple with phenols and active methylene compounds to yield the corresponding arylazo derivatives (cf. Eq. 2)^{5,17-23} On the other hand, the diazonium salts of the type 17 couple with active methylene reagents to yield either fused triazines 18 or the corresponding hydrazones 19 which readily cyclized into fused triazines by an intermolecular condensation reaction which occurred under coupling conditions.^{6,7,9,24-44}



Recently the diazotization of 5-amino-3-phenylpyrazole (20) and the reaction of this diazonium salt with a variety of active methylene reagents has been reported.¹¹ For example, as-triazines were the only product that isolated when the diazonium salt of (20) was reacted with ethyl acetoacetate or 3-aminocrotonitrile. On the other hand, the reaction with ethyl cyanoacetate and benzoylacetonitrile afforded, in acidic pH, hydrazones which readily cyclized into pyrazolo [1,5-c] as-triazines. The pyrazolo-[1,5-c] as-triazines were the only reaction products that formed in alkaline medium. The formation of cyclic or acyclic products from the coupling of active methylene compounds with the diazotized aminopyrazole (20) was explained by the mechanistic pathway for the reactions. Coupling with reagents which leads to the direct formation of cyclic products can take place with diazonium salts which exist in equilibrium with the diazobetaine (21) via a 1,4-dipolar cycloaddition. When a usual coupling took place, hydrazones were formed.⁶



3. Dipolar cycloaddition reactions:

Diazoheterocyclic compounds were found to be active intermediates for the synthesis of fused rings through [4+2] dipolar cycloaddition reactions. Thus, fused triazines were formed by the addition of 3-diazopyrazoles to a variety of dipolarophils under mild conditions (cf. chart 3).^{6,9,45-48}

Recently it has been reported that pyrazolo [1,5-c]-1,2,4-triazoles were formed when 5-diazo-3-methyl-4-phenylpyrazole (A) reacts with diazoalkanes. Also the same pyrazolo [1,5-c]-1,2,4-triazoles were obtained from diazo free ylides, for example, pyridium ylides, thus confirming the two steps cycloaddition mechanism suggested in chart 4.^{6,9,45-48}

In an attempt to use phosphanimines (22) as ylides in the reaction with diazopyrazoles, the expected 3H-pyrazolo [1,5-d] tetrazoles (23) were not obtained, but instead

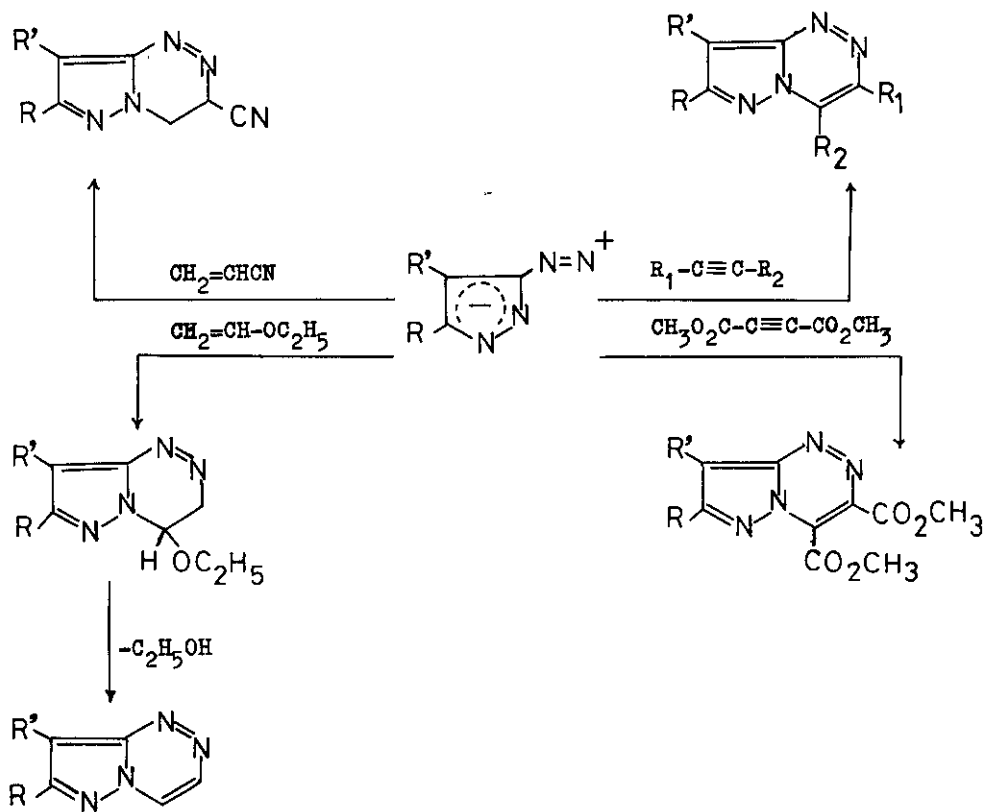
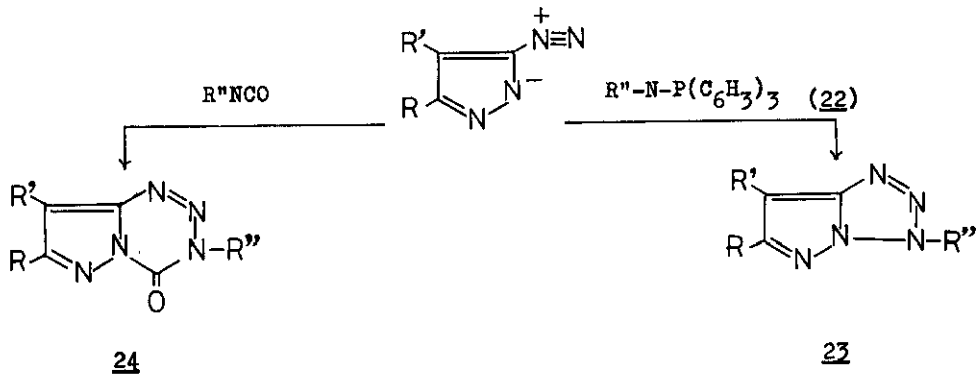
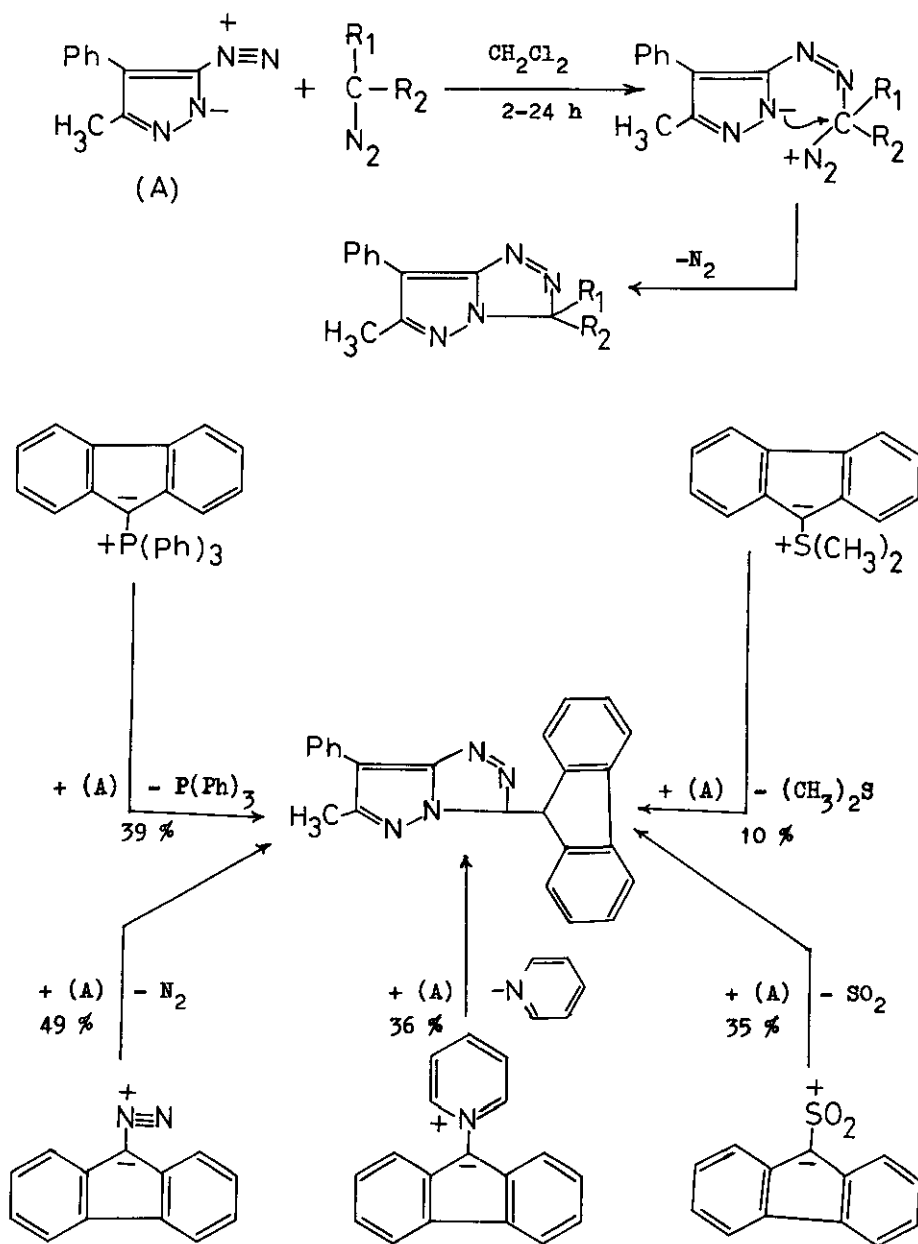


Chart 3

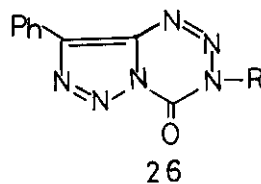
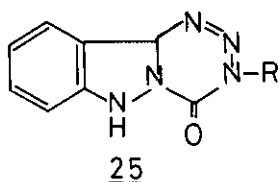
a carbonyl containing species with strong infrared carbonyl absorption was obtained. Suggesting how these compounds could have been formed, a reasonable reaction sequence seems to involve isocyanates resulting from reaction of (22) with carbon dioxide from the air. This view is supported by the report that the same compounds were



obtained from the reaction of diazopyrazoles with iso isocyanates. This reaction can be understood as a [7+2]cycloaddition of the diazopyrazole to the electron deficient hetero double bond of the isocyanate.⁴⁹ Alternative to the concerted [7+2] cycloaddition is the two steps mechanism consisting of a ring nitrogen acylation to a 1,9-dipole followed by intermolecular coupling leading to (24).⁴⁹

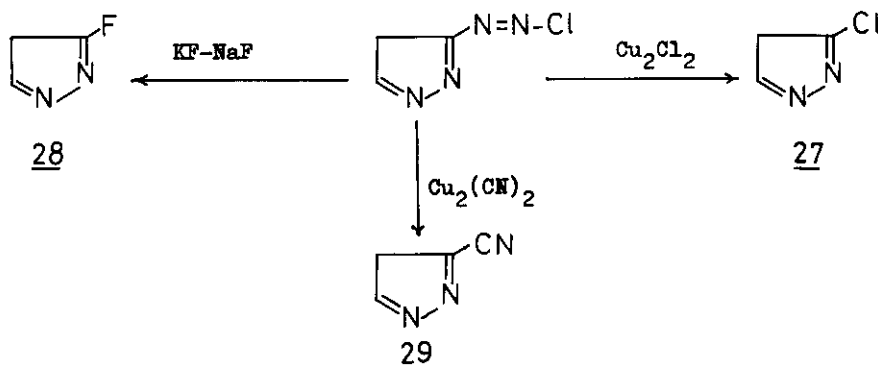


The reaction of diazoindazoles and 4-diazo-5-phenyl-1,2,4-triazole with isocyanate similarly yielded 1,2,3,5-tetrazin[5,4-b]indazol-4-ones (25) and 1,2,3-triazolo-[5,1-d]-1,2,3,5-tetrazin-4-one derivatives (26).⁴⁹

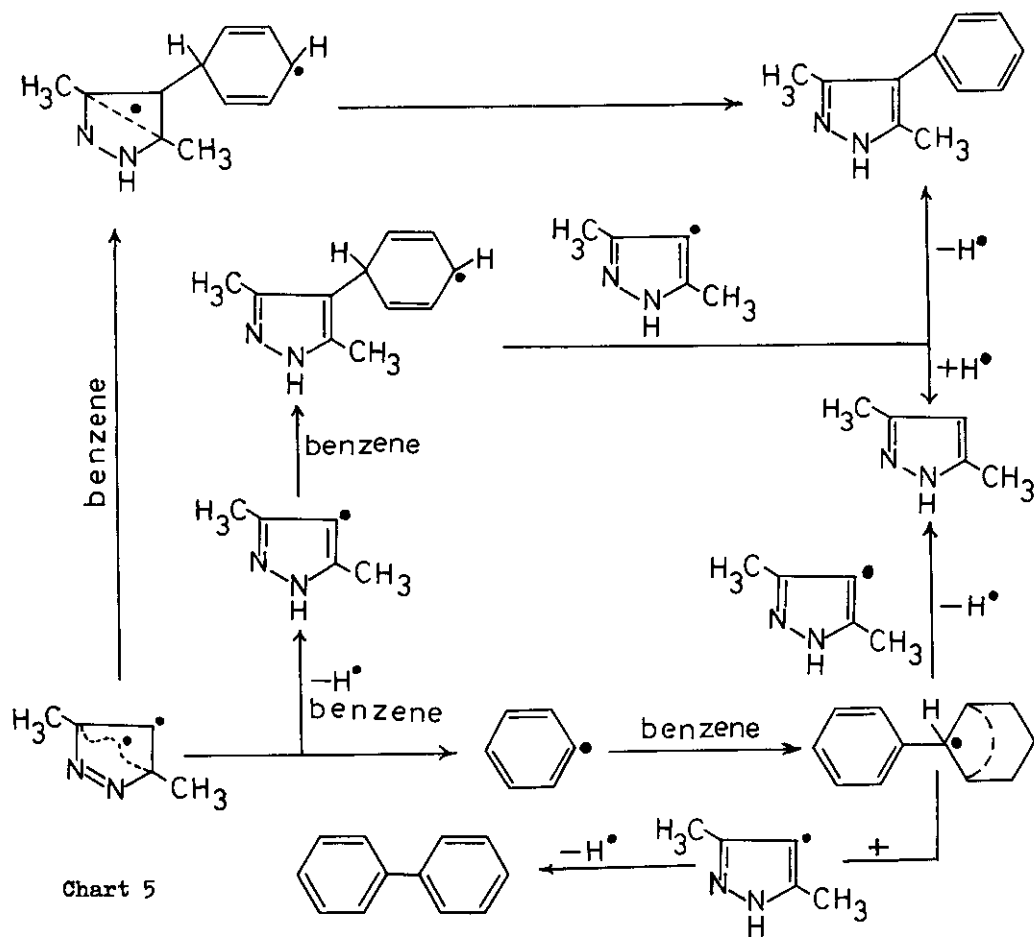
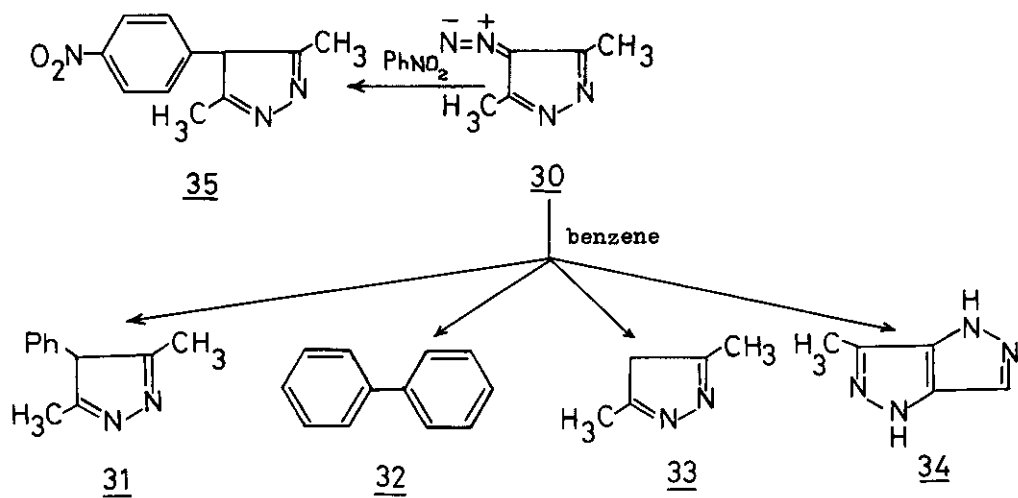


4. Replacement reactions for the diazo group:

Heterocyclic diazonium compounds undergo dediazotization reactions common for their benzenoid counter parts.^{26,50-53} Thus, the diazo group in many diazoheterocyclic compounds was replaced by substituents such as Cl, Br, I, F, N₃, CN, phenyl and pyridyl. As an example, when pyrazole-3-diazonium chloride reacted with either cuprous chloride, a mixture of potassium and sodium fluoride or cuprous cyanide, the 3-chloro- (27), 3-fluoro- (28) or the 3-cyanopyrazole (29) were obtained respectively.



The Gomberg-Buchman reaction of the heterocyclic diazo compounds has been investigated by Fukata et al.,⁵⁴ they have shown that when (30) was refluxed in benzene for 14 h 3,5-dimethyl-4-phenylpyrazole (31), biphenyl (32), 3,5-dimethylpyrazole (33) and the pyrazolo 3,4-c pyrazole (34) were obtained in 36, 17, 12 and 15% yields, respectively. On replacement of benzene by nitrobenzene, the reaction gave 4-nitrophenylpyrazole (35) in ratio of 10:3:3 for o, m and p-isomers, respectively. The



above mentioned results as well as the formation of biphenyl suggested that the reaction proceeded via free radical intermediates (cf. chart 5). This suggestion was supported by the observed catalytic effect of hydroquinone on the reaction and the increment in the yield of (36) by the latter catalyst (cf. chart 6).

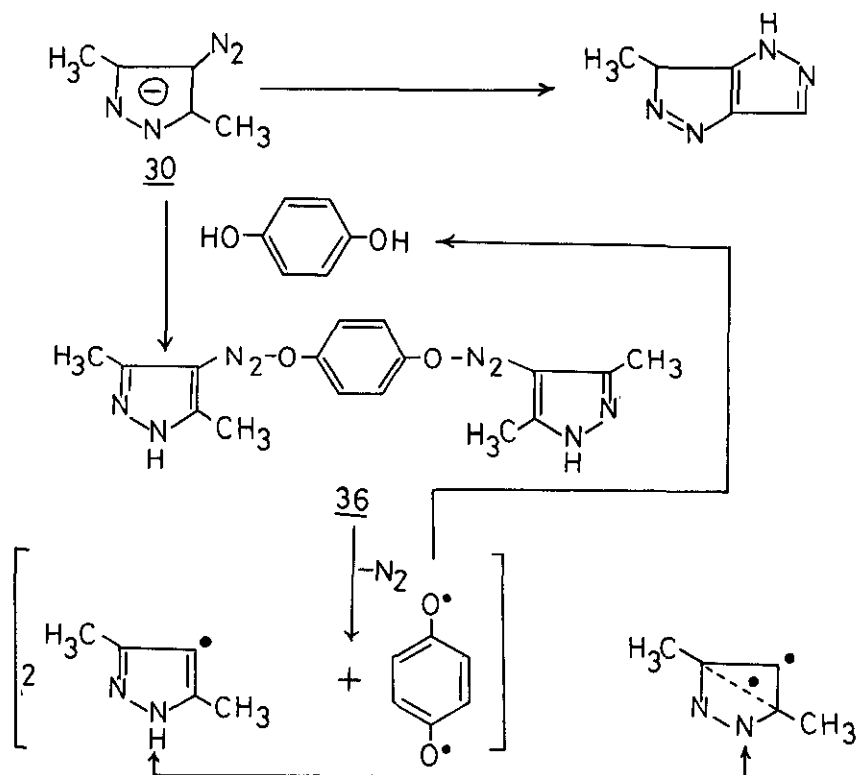
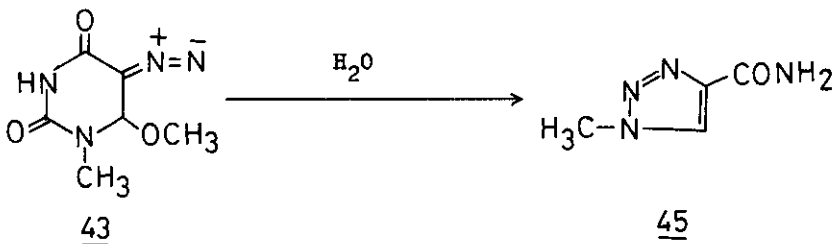
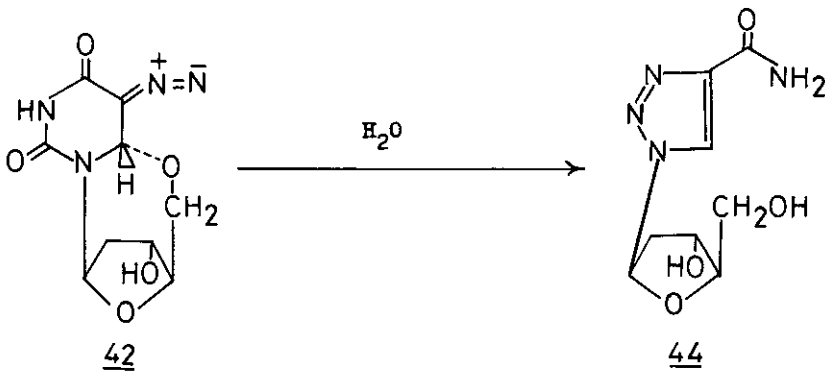
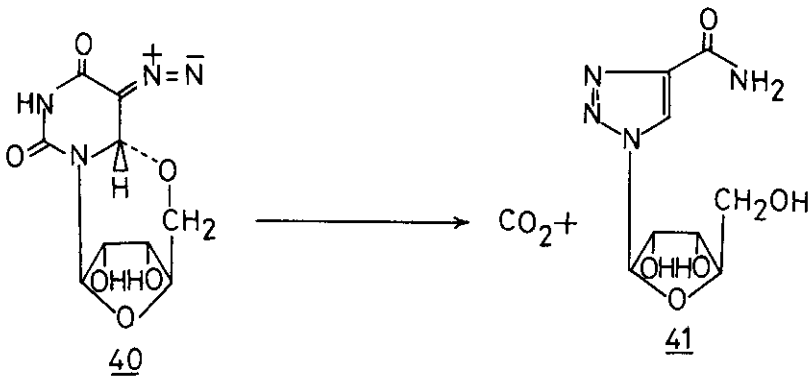
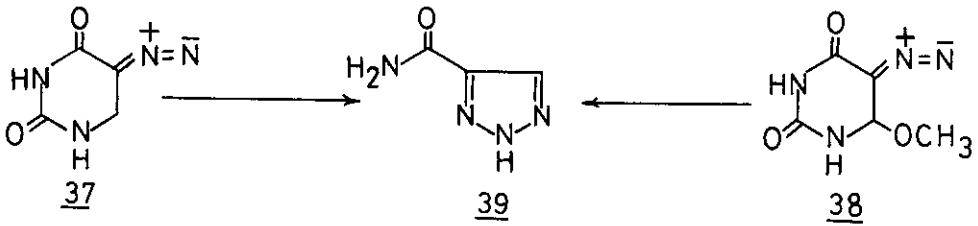


Chart 6

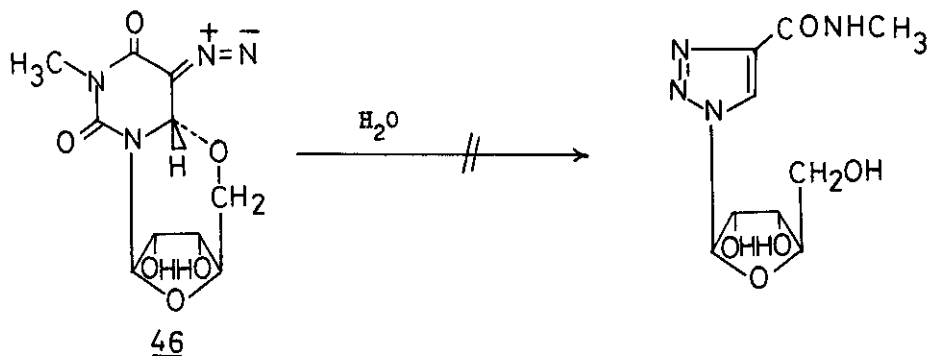
5. Molecular rearrangement and ring contraction:

Heterocyclic diazo compounds undergo a variety of interesting molecular rearrangements to afford products which are difficult to access by other procedures. For example, ring contraction of 5-diazouracil (**37**) or its methanolate (**38**) into the corresponding 1,2,3-triazolecarboxamide (**39**) has been reported recently.^{48,49,55}

Also similar rearrangement takes place in case of $\text{O}^5\text{-6(5)-cyclo-5-diazouridine}$ (**40**) to give 1-($\beta\text{-D-ribofuranosyl}$)-1,2,3-triazol-4-carboxamide (**41**). The mechanism of this rearrangement was investigated using O^{18} -labeled diazouracils and diazouridines. It was shown that the rearrangement of (**40**) into (**41**) proceeds via initial attack at C-2 by using labeled O^{18} at 4-position. In the same manner $\text{O}^{5'}\text{-6(5)-cyclo-5-diazo-2'-deoxyuridine}$ (**42**) and 5-diazo-1-methyluracil-6-methanolate (**43**)



gave the expected triazole derivatives **44** and **45**, respectively. Trials of rearrangement of 0^5 -6(5)-cyclo-5-diazo-3-methyluridine (**46**) were unsuccessful and this might be due to the absence of an initial attack by water. An evidence that the ring contractions proceed via N-1, C-2 and bond cleavage was given by the methan-



olysis of (40) to give (41), methyl 1-(B-D-ribofuranosyl)-1,2,3-triazolecarboxylate (47) and methyl carbamate (48). Methanolysis of 43 gave 1-methyl-1,2,3-triazole-4-carboxamide (45), 48 and methyl 1-methyl-1,2,3-triazole-4-carboxylate (49). Methanolysis of (38) gave methyl N-(1,2,3-triazole-4-yl-carbonyl)-carbamate (50) (cf. chart 7).

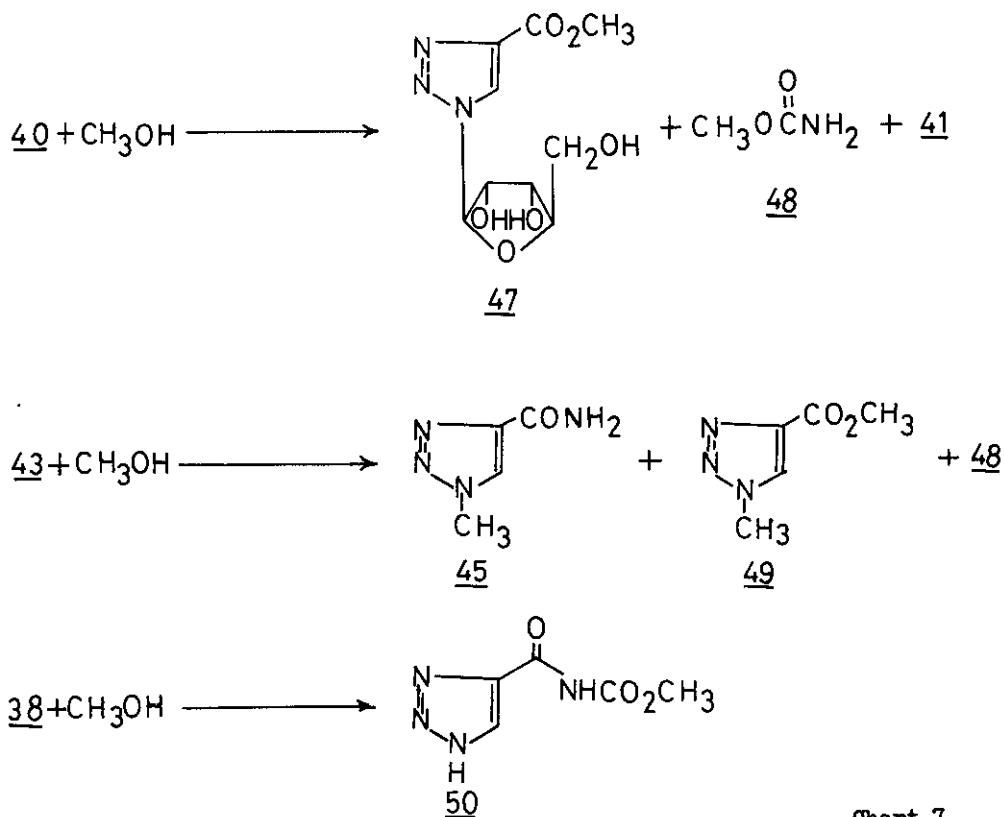
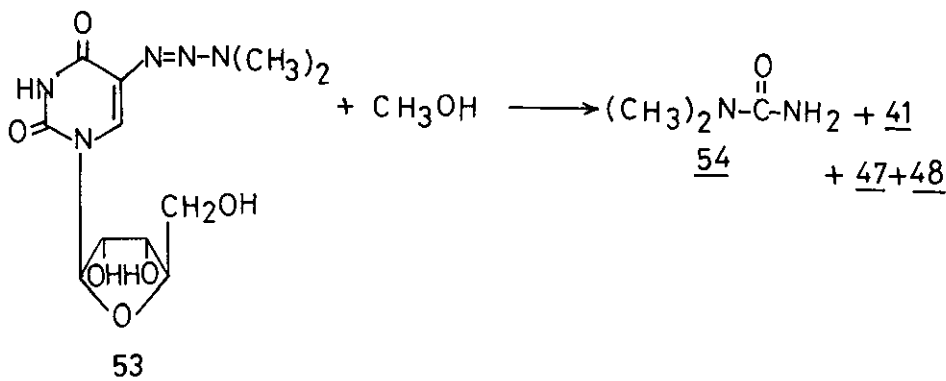
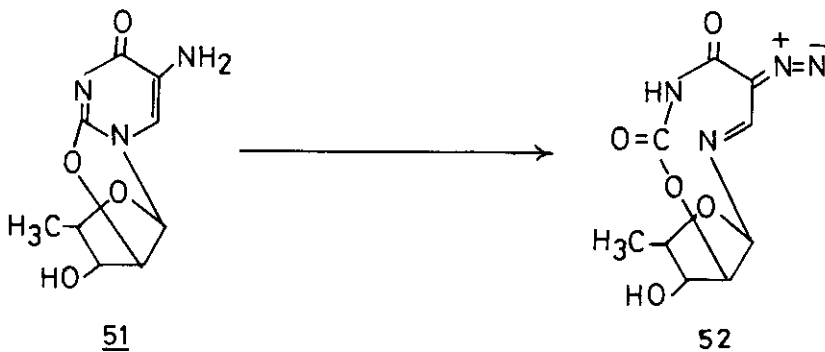


Chart 7

Compound (52) was obtained on diazotization of O²-2'-cyclo-5-amino-5'-deoxyuridine (51) which suggested that these ring contractions require the formation of a tautomeric carbinol-amidine prior to nucleophilic attack. On the other hand, methanolysis of 5-(3,3-dimethyl-1-triazino)-uridine (53) leads to the formation of compounds 54, 41, 47 and 48. This reaction was probably the result of a direct nucleophilic attack on 53 rather than a prior decomposition of the triazino group since 5-(3,3-dimethyl-1-triazino)-1,3-dimethyluracil (55) was recovered quantitatively unchanged under similar conditions. A partial hydrolysis of 43 labeled with oxygen-18 at C-2 showed a retention of isotopic label and suggested that the transition state for ring opening involved a partial C-N bond cleavage rather than the formation of a tetrahedral intermediate. The results suggested that the proton at N-3 of the uracil ring must tautomerise to the O-2 position and the diazo derivative of this tautomer must be formed prior to ring opening.⁵⁶⁻⁵⁸ From these data the mechanism demonstrated in chart 8 was suggested.



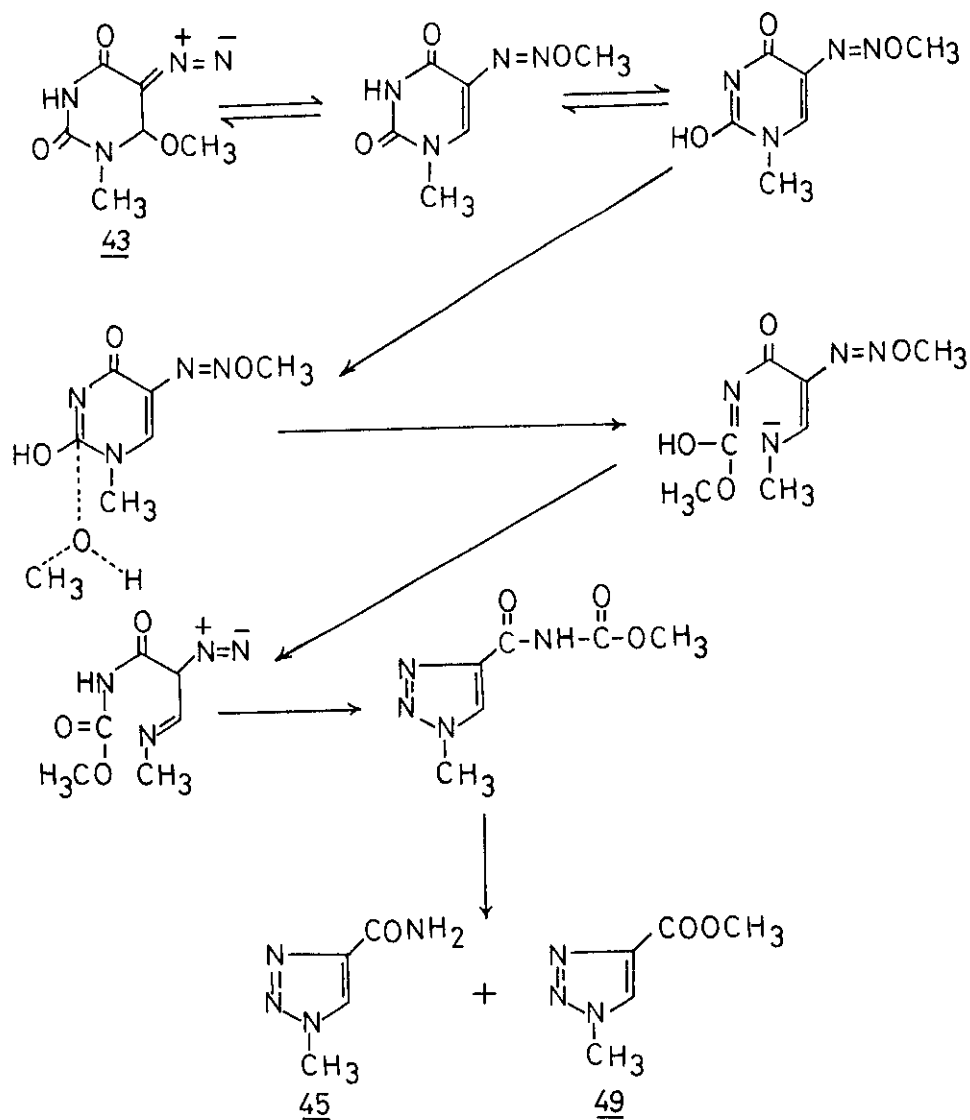
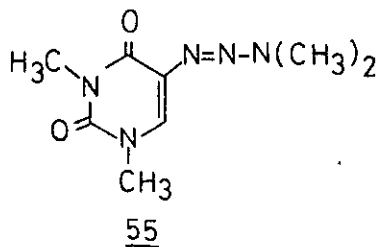


Chart 8

6. Pyrolysis:

Recently it has been reported that the pyrolysis of 3-phenyl-4-methyl-5-diazopyrazole (56) gave 2-cyano-2-methyl-3-phenyl-2H-aziridine (57, 60%), benzonitrile (58, 10%) and acrylonitrile (59, 1%). On the other hand, photolysis of 56 in cyclohexane yields 57 (15%) and 3(5)-cyclohexyl-4-methyl-5(3)-phenylpyrazole (60, 60%)⁴⁵ (cf. chart 9).

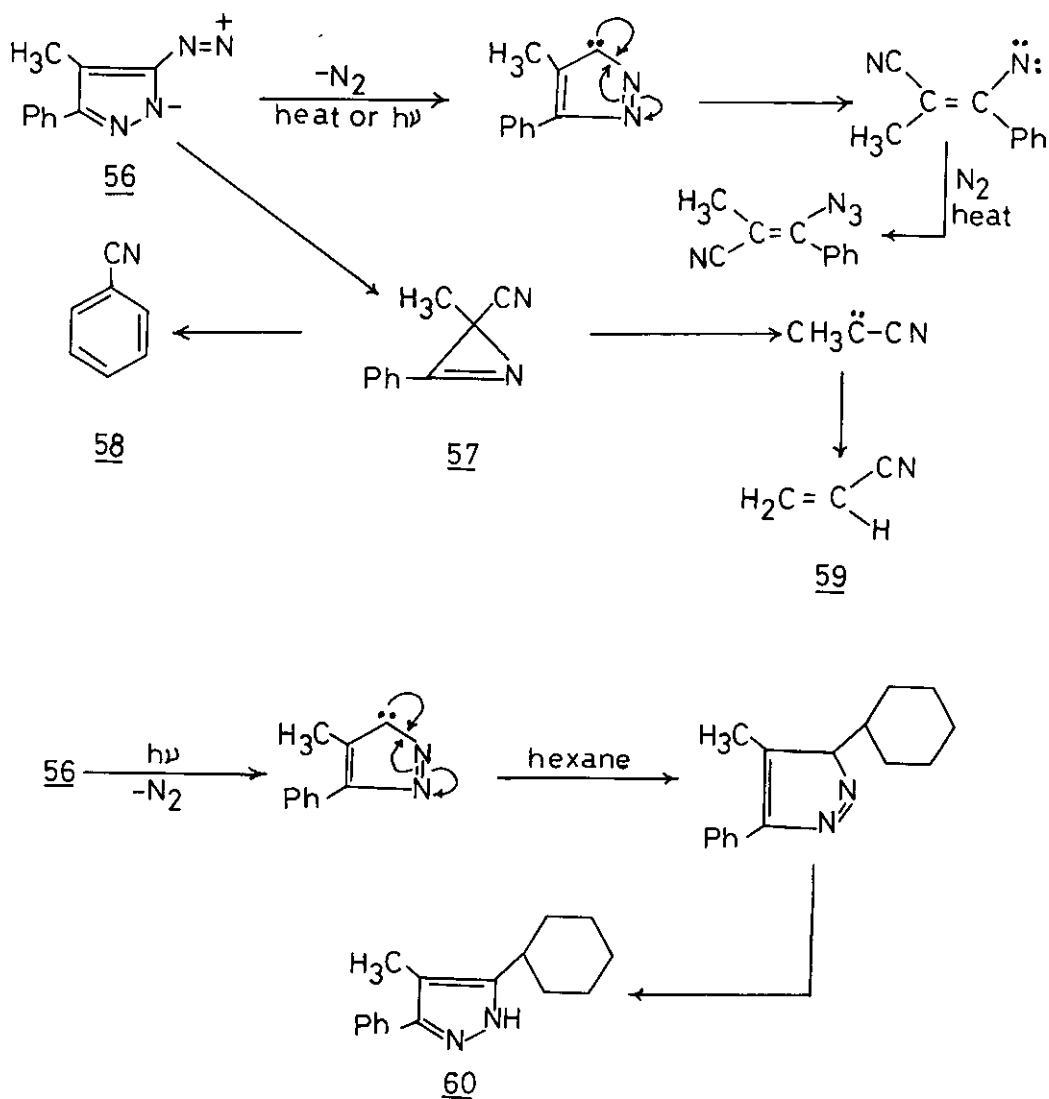
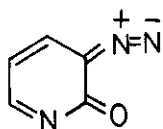


Chart 9

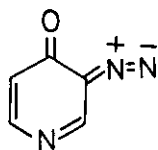
MASS SPECTRA OF HETEROCYCLIC DIAZO COMPOUNDS:

Up to our knowledges, few investigations have dealt with the mass spectra of heterocyclic diazo compounds.⁵⁹⁻⁶¹ The unstability of these compounds under the conditions of measurement might be the reason for the lack of data on this subject.

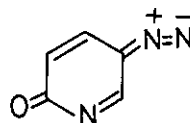
Thorsted and Undheim⁶¹ have recently discussed the mass spectra of the diazopyridones 61, 62 and 63. The authors have shown that these compounds are characterized by a signal due to the $M - N_2$ ions which arise both by pyrolysis followed by ionization and by electron induced fragmentation of the diazo oxides.



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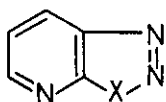


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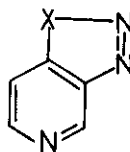


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The authors⁶¹ have compared the mass spectra pattern of these compounds with that of the model compounds 64 and 65. They have concluded the following fragmentation patterns for these compounds (cf. chart 10).



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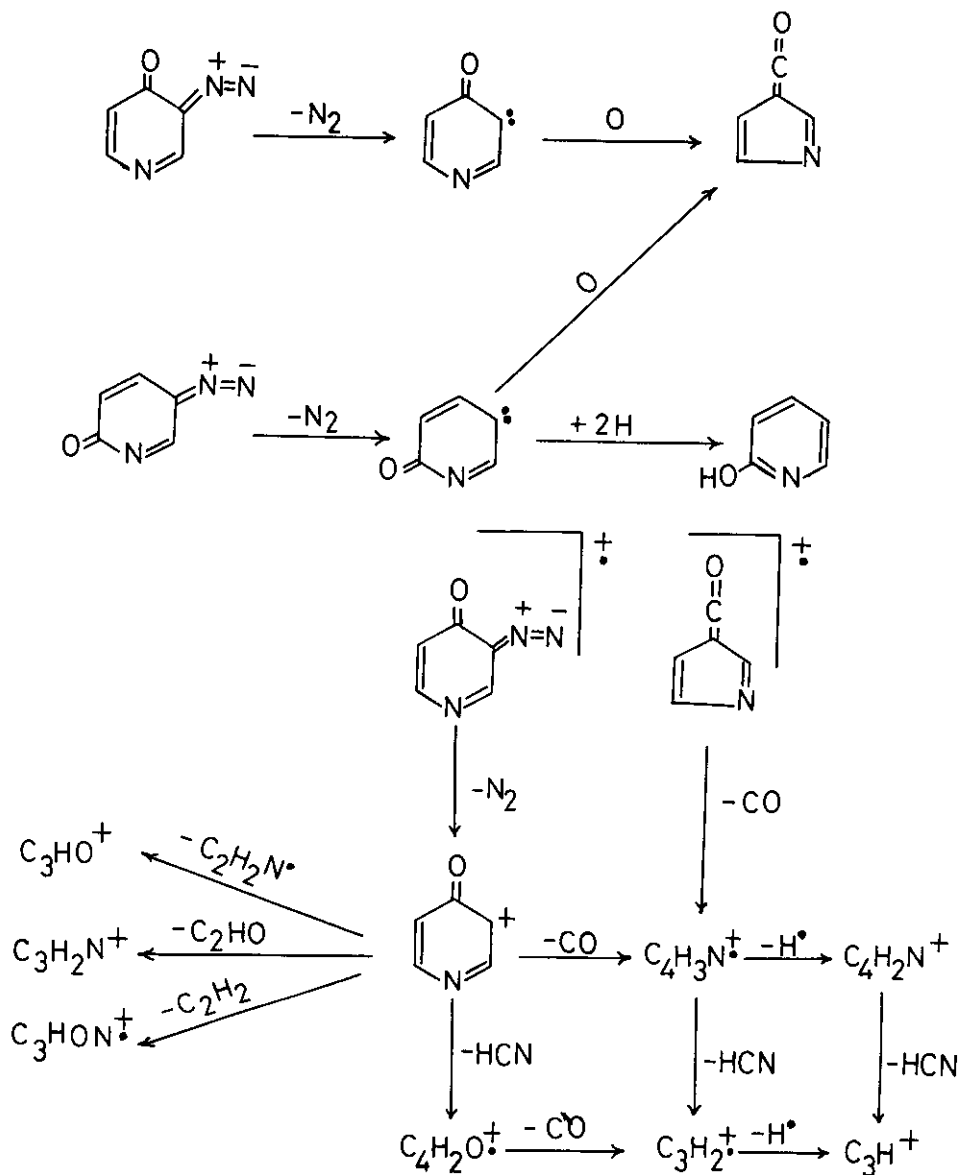


Chart 10

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