*Tetrahedron* Vol. 47, Nos. 18/19, pp. 2925–2945, 1991
Printed in Great Britain.

0040–4020/91 $5.00+.00


# TETRAHEDRON REPORT NUMBER 289

# 1,3-DIPOLAR CYCLOADDITIONS OF DIAZOALKANES TO SOME NITROGEN CONTAINING HETEROAROMATIC SYSTEMS

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(*Received* 24 *November* 1990)

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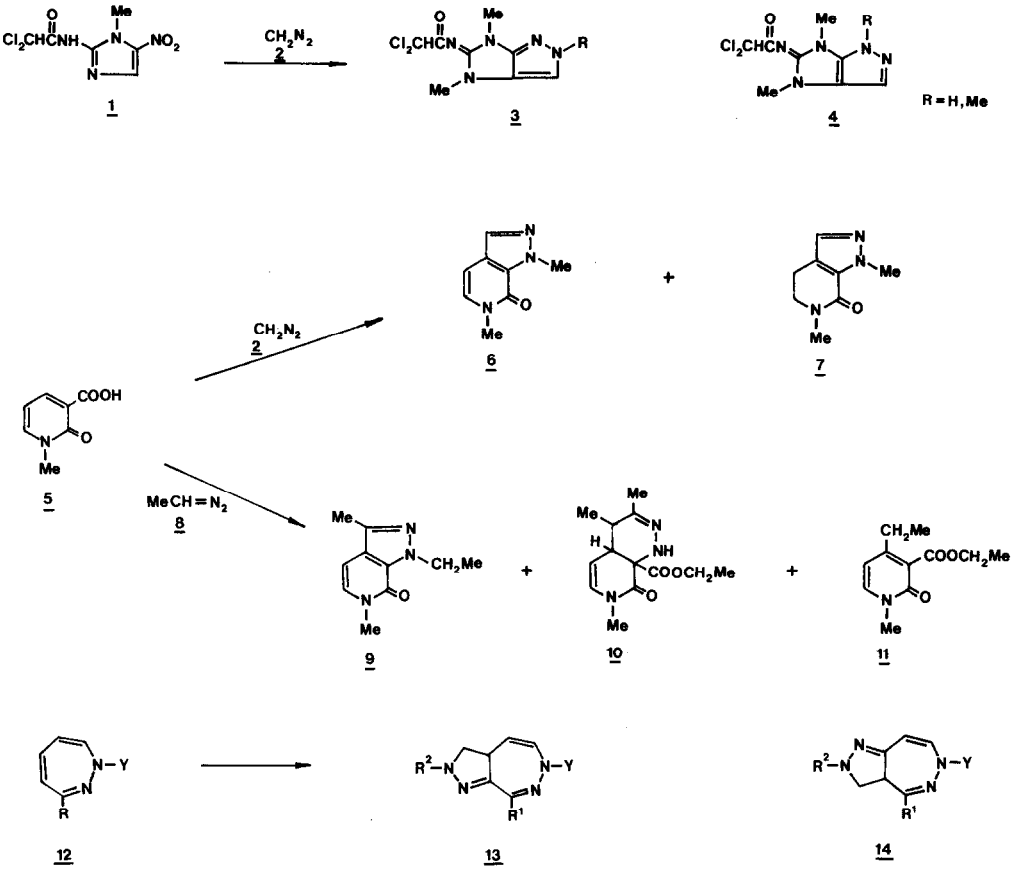
## INTRODUCTION

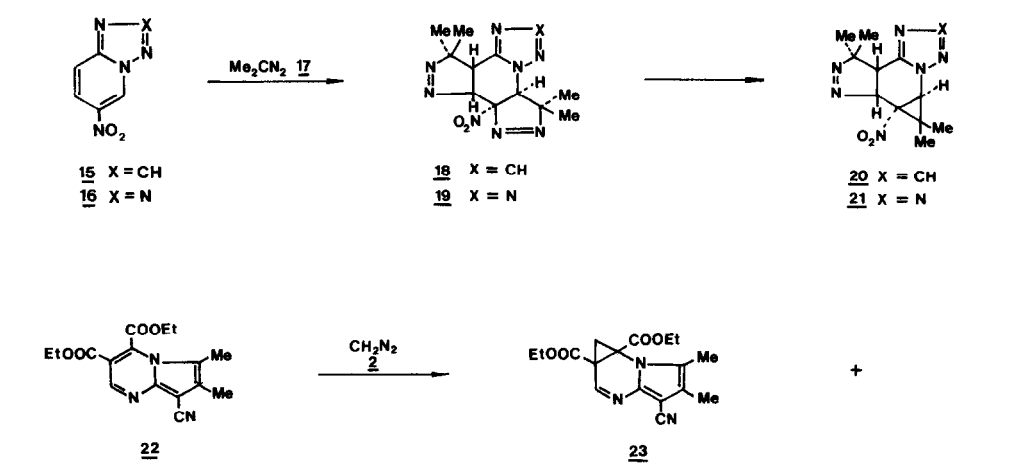
The aliphatic diazo compounds were found to undergo cycloadditions with C–C multiple bonded systems about 100 years ago.[1–3] Since then they have played a dominant role in cycloaddition chemistry and several reviews and monographs have been written recently.[4] There are numerous examples of cycloadditions of diazoalkanes to the systems with double and triple bonds, hetero-multiple bonds and heterocumulenes to form various five-membered heterocycles[5] including natural products.[6]

In aromatic and heteroaromatic series diazo compounds have been frequently used as a source for carbenes in cyclopropenation reactions affording cycloheptatrienes and norcaradienes and their aza analogs.[6a]

On the other hand, there are only sporadic examples of cycloadditions of diazoalkanes to five- and six-membered nitrogen containing heteroaromatic systems reported in the literature. In this connection, a regiospecific reaction of 1-methyl-2-dichloroacetamido-5-nitro-imidazole (**1**) with diazomethane (**2**) gives imidazo[4,5-*c*]pyrazole derivatives **3** and **4**.[7] 3-Carboxypyridone derivative **5** affords with diazomethane (**2**) two products **6** and **7** and with diazoethane (**8**) three compounds **9–11**.[8] 1H-1,2-Diazepines **12** react regioselectively at the 4-double bond to form isomeric pyrazolinodiazepine derivatives **13** and **14** and some other products formed from these primary cyclo-



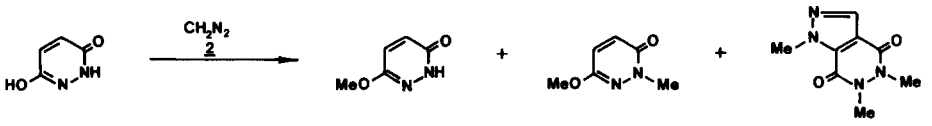
adducts.[9] In the azolo[1,5-*a*]pyridine series the corresponding 6-nitro derivatives **15** and **16** have been found to be reactive as 1,3-dipolarophiles. The nitro group activates both the $C_5$–$C_6$ and $C_7$–$C_8$ double bond of the pyridine part of the bicyclic system producing the bis-cycloadducts **18** and **19** as intermediates. The subsequent elimination of one molecule of nitrogen yields the final products **20** and **21**.[10] The pyrrolo[1,2-*a*]pyrimidine derivative **22** gives with an excess of diazomethane (**2**), the three products **23**–**25**.[11]



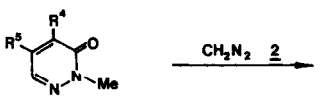
24 25

## CYCLOADDITIONS TO MONOCYCLIC PYRIDAZINES

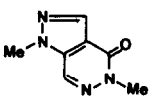
Systematic studies have been carried out in pyridazine series in recent years. The cycloaddition of diazoalkanes to pyridazin-3(2H)-ones has been found to be regioselective and, in many cases, regiospecific. For example, the cycloaddition of diazomethane to pyridazine derivatives has been first observed as a side reaction by methylation of 6-hydroxypyridazin-3(2H)-one (**26**), in which besides O-methyl **27**, and O,N-dimethyl **28** derivatives also the corresponding pyrazolo[3,4-*d*] pyridazine derivative **29** has been formed in 9% yield.[12,13] N-Methylpyridazin-3(2H)-ones **30**–**32** give with diazomethane (**2**) the isomeric N-methyl pyrazolo[3,4-*d*]pyridazin-4(5H)-ones **34** and **35**, while from 4-bromo derivative **33** the isomeric -7(6H)-one derivative **36** is obtained.[14]



26 27 28 29



30 $R^4 = R^5 = H$
31 $R^4 = H$, $R^5 = Br$
32 $R^4 = H$, $R^5 = Cl$
33 $R^4 = Br$, $R^5 = H$



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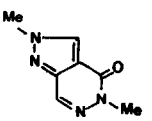

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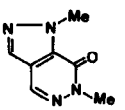

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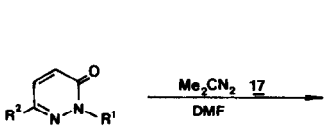
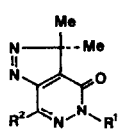
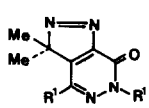
2-Substituted pyridazin-3(2H)-ones **37**–**41** when they are treated with 2-diazopropane (**17**) in DMF in the presence of oxygen from the air, give the corresponding 3H-pyrazolo[3,4-*d*]pyridazin-4(5H)-ones **42**–**46** as the major or as the only products in high yields. Only in the cases of **37** and **40** minor amounts of the regioisomers which are derivatives of the isomeric 3H-pyrazolo-[3,4-*d*]pyridazin-7(6H)-one, **47** and **50** were formed in 1.1% and 5.5% yield, respectively.



| | $R^1$ | $R^2$ |
|---|---|---|
| 37 | Me | H |
| 38 | Me | Me |
| 39 | $CH_2Ph$ | Ph |
| 40 | Me | OMe |
| 41 | Me | Cl |

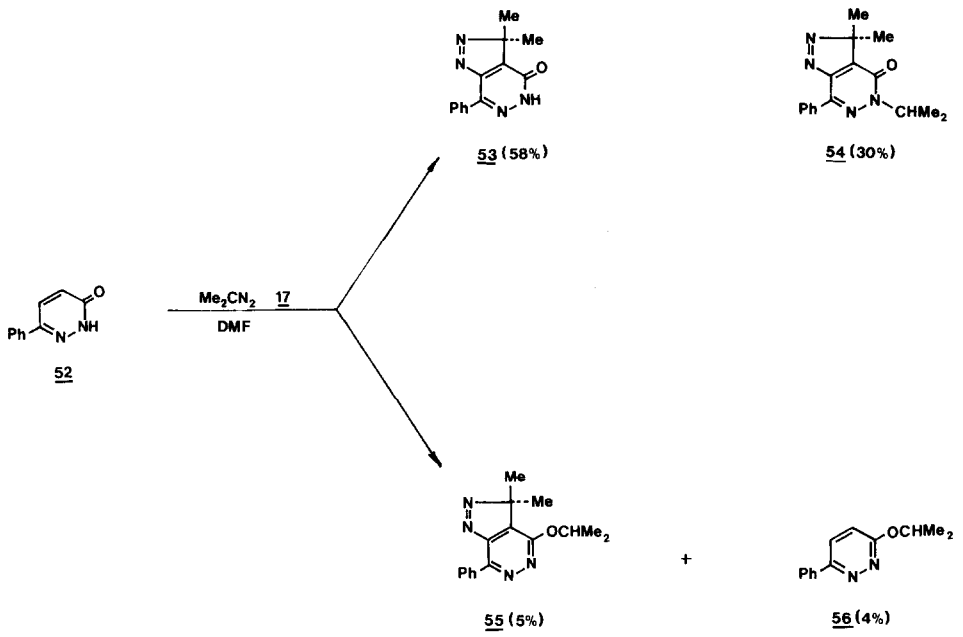


| | $R^1$ | $R^2$ | yield(%) |
|---|---|---|---|
| 42 | Me | H | 61,5 |
| 43 | Me | Me | 83 |
| 44 | $CH_2Ph$ | P | quant. |
| 45 | Me | OMe | 82 |
| 46 | Me | Cl | quant. |



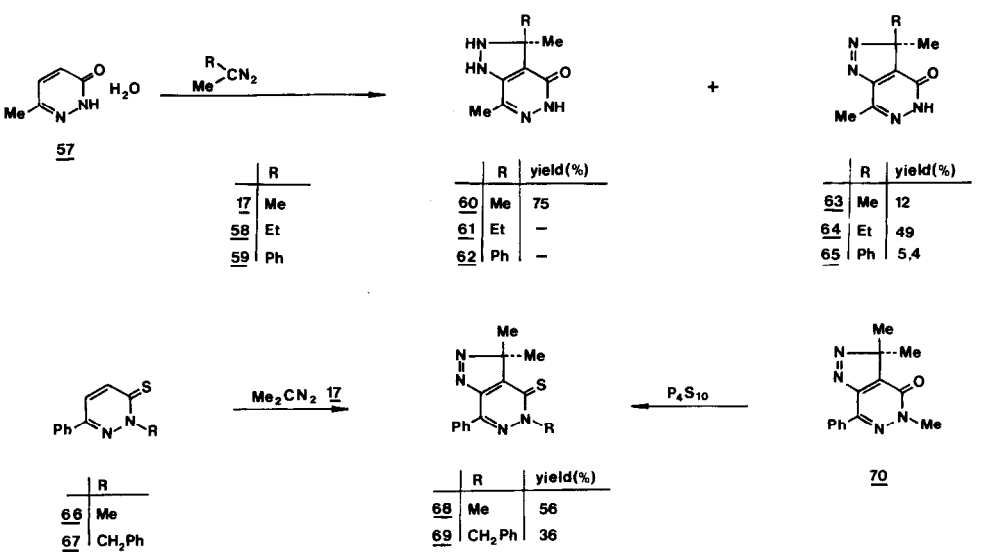
| | $R^1$ | $R^2$ | yield(%) |
|---|---|---|---|
| 47 | Me | H | 1,1 |
| 48 | Me | Me | – |
| 49 | $CH_2Ph$ | Ph | – |
| 50 | Me | OMe | 5,3 |
| 51 | Me | Cl | – |

The cycloaddition of diazoalkanes to 6-substituted pyridazin-3(2H)-ones is more complicated. **52** gave a mixture of four products **53**–**56**.[15]




The compound **57** gives two products with **17**. One product is the 1,2-dihydro-3H-pyrazolo-[3,4-*d*]pyridazine derivative **60**, which in spite of its instability, is isolable, due to its insolubility in the reaction mixture. The second product is the corresponding dehydrogenated product (**63**). With 2-diazobutane (**58**) and 1-phenyldiazoethane (**59**) only dehydrogenated cycloadducts **64** and **65** have been isolated.

Pyridazine-3(2H)-thiones **66** and **67** are the most reactive dipolarophiles in this series. Cycloaddition with **17** is completed in several minutes at room temperature giving the cycloadducts **68** and **69**, respectively. The structure of **68** was confirmed by transformation of the compound **70**.[15]




| | R |
|---|---|
| 17 | Me |
| 58 | Et |
| 59 | Ph |

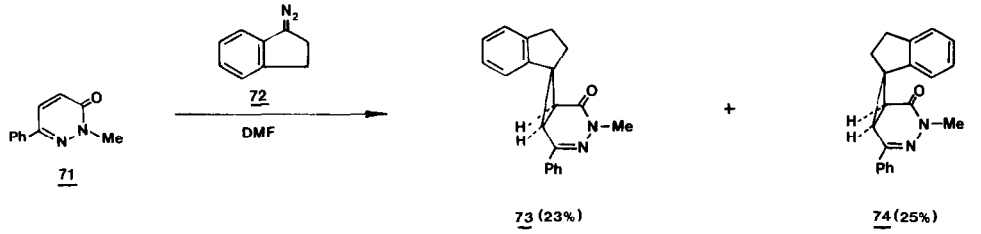
| | R | yield(%) |
|---|---|---|
| 60 | Me | 75 |
| 61 | Et | – |
| 62 | Ph | – |

| | R | yield(%) |
|---|---|---|
| 63 | Me | 12 |
| 64 | Et | 49 |
| 65 | Ph | 5,4 |

| | R |
|---|---|
| 66 | Me |
| 67 | $CH_2Ph$ |

| | R | yield(%) |
|---|---|---|
| 68 | Me | 56 |
| 69 | $CH_2Ph$ | 36 |

In the reaction of **71** with 1-diazoindane (**72**) in DMF in a molar ratio 1:2.5 the primary cycloadduct could be detected only by tlc. It was extremely unstable and elimination of nitrogen produced a mixture of *exo*- and *endo*-spiro compounds **73** and **74**.[15]



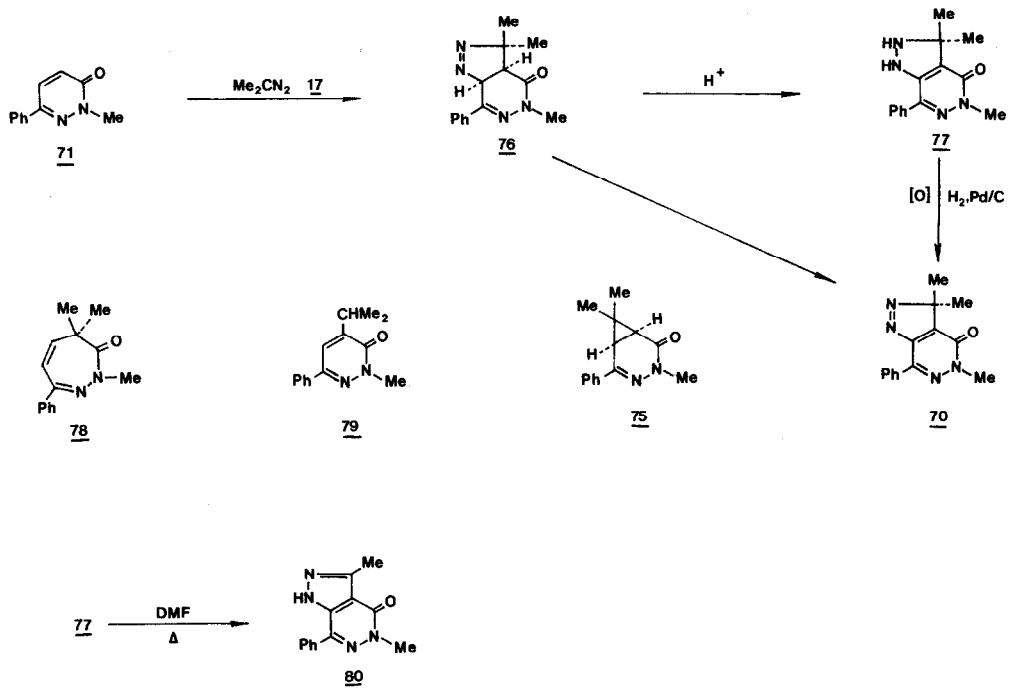

Regiospecific 1,3-dipolar cycloaddition of 2-diazopropane (**17**) to 2-methyl-6-phenylpyridazin-3(2H)-one **71** in diethyl ether gives a mixture of three products: 1,2-diazepine derivative **78**, 4-isopropylpyridazine derivative **79** and diazabicyclo[4.1.0]heptenone derivative **75**, presumably formed from the primary CH,CH-dihydro cycloadduct **76**.[16] The reaction is strongly dependent upon the solvent and upon the temperature. The primary cycloadduct **76** could be isolated in analytically pure form at temperature below 0°C due to its relatively low solubility in diethyl ether. At room temperature, the secondary reactions were observed, in which the dihydro-intermediate **76** is transformed in three different ways. In the presence of acid, the isomerization into NH,NH-dihydro species **77** takes place. In the presence of oxygen from the air dehydrogenation is the main reaction producing the 3H-pyrazolo[3,4-*d*]pyridazine derivative **70**. Elimination of a molecule of nitrogen from the pyrazole part of the molecule followed by rearrangement, gives a mixture of **75**, **78** and **79**. The relative proportions of these three products is strongly dependent upon the solvent used in the reaction. In more polar solvents, such as DMF, methanol and ethanol, in the presence of air, **76** is dehydrogenated quantitatively yielding **70**, in propanol a mixture of **77** and **70** is formed, while in less polar solvents, such as acetonitrile, dioxane, ethyl acetate, benzene and others, the compounds **75**, **78** and **79** are formed in the relative proportions summarized in Table 1.

Table 1. The formation of products in the reaction of **71** with **17** in various solvents

| Solvent | Products /%/[a] | | | | | |
|---|---|---|---|---|---|---|
| | 71 | 77 | 78 | 79 | 75 | 70 |
| DMF | - | - | - | - | - | 100 |
| MeOH[b] | 65 | - | - | - | - | 35 |
| EtOH | 14 | - | - | - | - | 86 |
| 1-propanol | 10 | 13 | - | - | - | 77 |
| 2-propanol | 7 | 16 | - | - | - | 62 |
| acetone | - | 60 | - | 15 | - | 34 |
| acetonitrile | - | - | 13 | 17 | 8 | 62 |
| dioxane | - | - | 45 | 31 | 12 | 11 |
| dioxane/water (4:1) | 20 | 24 | 13 | 7 | 2 | 35 |
| ethyl acetate | - | - | 48 | 35 | 12 | 6 |
| methylene chloride | - | - | 69 | 22 | 9 | - |
| benzene | - | - | 61 | 27 | 12 | - |

[a] determined by $^1$H nmr technique

[b] decomposition of 17 in MeOH is very fast (∿ 10 min).



The dihydro-intermediate **76** was found to be thermally unstable. In most cases a mixture of **75**, **78** and **79** is formed, while in hydroxylic solvents **77** and **70** are also produced. Transformation of **76** in the solid state by heating above its melting point takes place vigorously giving **75**, **78** and **79** in approximately equimolar amounts. In nonpolar solvents, such as benzene, toluene and dioxane, **78** is the main product. In more polar solvents, such as DMF and DMSO, **79** is the major product, while **75** is always the minor product (Table 2). The dihydro-derivative **77** is thermally more stable. By heating in DMF elimination of methane is observed giving 1H-pyrazolo[3,4-*d*]pyridazine derivative **80**.

Table 2. The formation of products by thermal decomposition of **76**

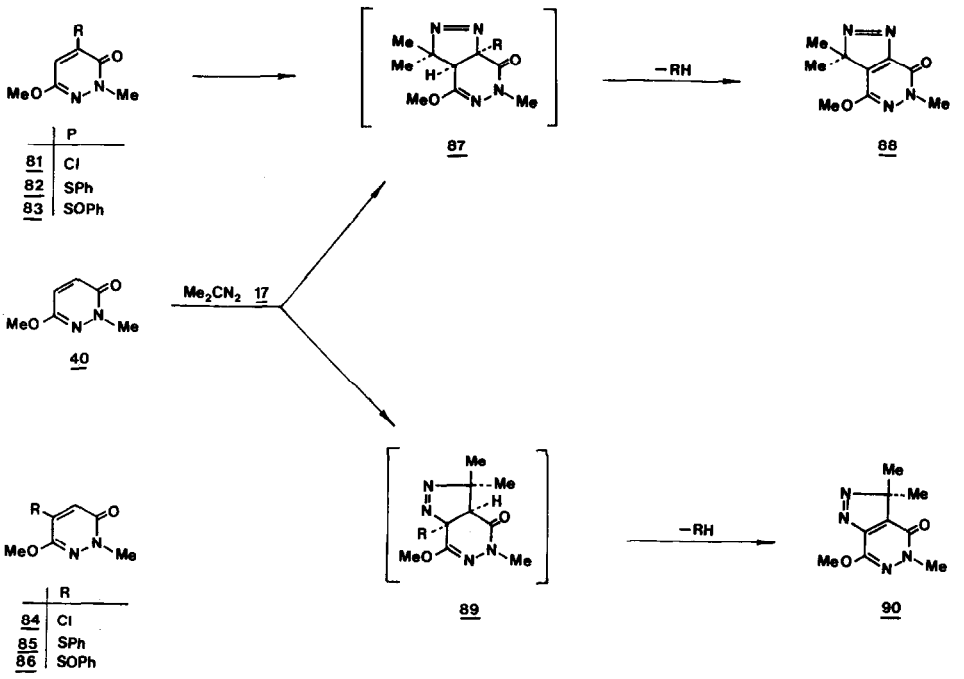
| Solvent | Reaction conditions | Products[a] | | | | |
|---|---|---|---|---|---|---|
| | | 77 | 78 | 79 | 75 | 70 |
| - | Δ (∿ 90°C) | | 37 | 35 | 28 | - |
| benzene | reflux, 30 min. | - | 58 | 24 | 18 | - |
| toluene | reflux, 10 min. | - | 52 | 27 | 21 | - |
| dioxane | reflux, 10 min. | - | 52 | 32 | 16 | - |
| DMF | reflux, 15 min. | - | 26 | 62 | 12 | - |
| DMSO | 115°C, 5 min. | 0 | 17 | 68 | 6 | - |
| DMF/$H_2O$ (1:1) | reflux, 5 min. | 31 | 25 | 35 | 6 | 3 |
| MeOH | reflux, 30 min. | 36 | 21 | 23 | 6 | 13 |

[a] determined by $^1H$ nmr technique

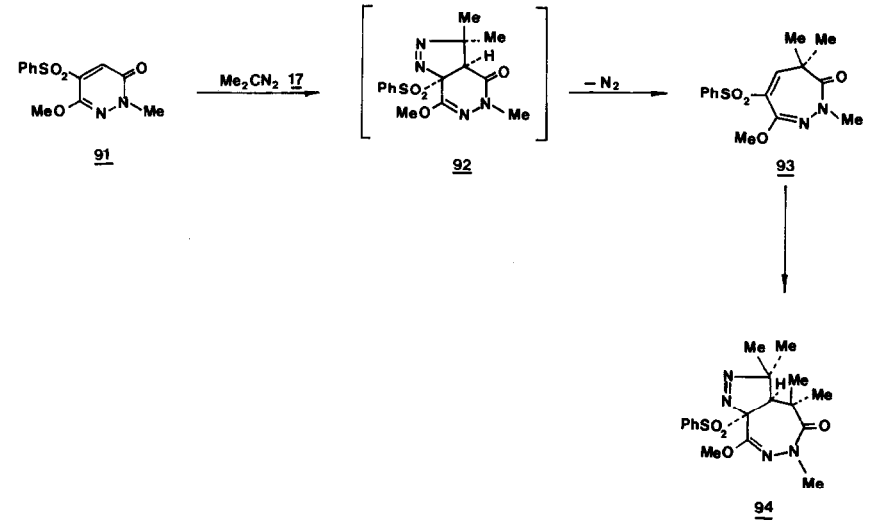
Oxidation of **76** and **77** could be achieved with a variety of oxidizing agents, such as oxygen or bromine. The simplest method is oxidation by air in the presence of a base. Under these conditions the transformation is practically quantitative to give **70** as the only product. Catalytic hydrogenation of **70** over Pd/C produced **77** as the only product.[17]

*Directed regiospecificity*

1,3-Dipolar cycloaddition of diazoalkanes to 4- and 5-unsubstituted pyridazin-3(2H)-ones is regiospecific producing in most cases pyrazolo[3,4-*d*]pyridazin-4(5H)-ones as the major products, and in some cases the corresponding -7(6H)-ones as minor products. The regiospecificity in the cycloadditions of 4- and 5-substituted derivatives is strongly dependent on structure. When 4-substituted 6-methoxy-2-methylpyridazin-3(2H)-ones **81**–**83** are treated with 2-diazopropane **17** in a mixture of chloroform and diethyl ether in the presence of triethylamine then the corresponding 3H-pyrazolo[3,4-*d*]pyridazin-7(6H)-one derivative **88** is formed as the only product. However, the 5-substituted derivatives **84**–**86** afford the isomeric -4(5H)-one **90** as the only product. These examples show that cycloadditions are regiospecifically controlled by the position of substituents. In contrast 6-methoxy-2-methylpyridazin-3(2H)-one (**40**) gives a mixture of **90** (82%) as the major product and **88** (5%).[18]



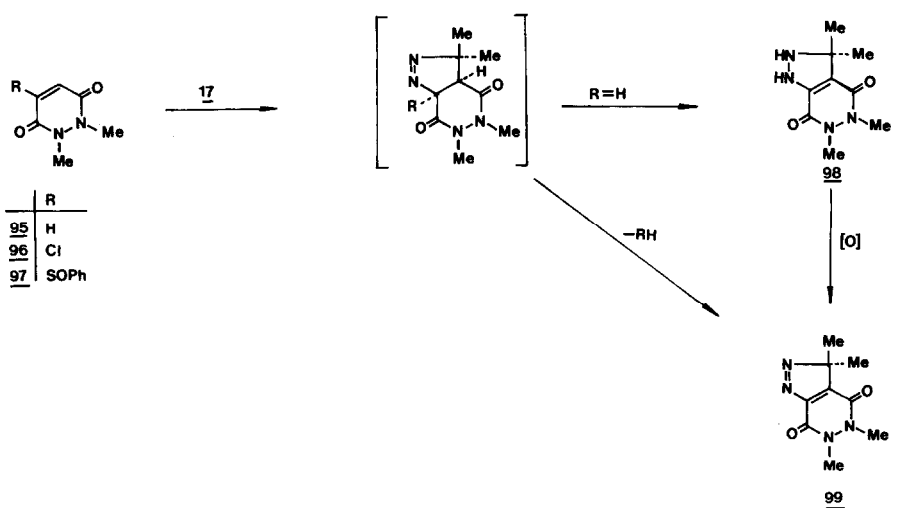

The cycloaddition of 5-phenylsulphonyl derivative **91** takes a different course. The corresponding primary cycloadduct **92** is not transformed into a pyrazolopyridazine derivative by elimination of phenylsulfinic acid, instead, a molecule of nitrogen is eliminated and the remaining molecule is rearranged into 1,2-diazepine derivative **93**, which reacts further, when an excess of **17** is used, to give **94**.[18]

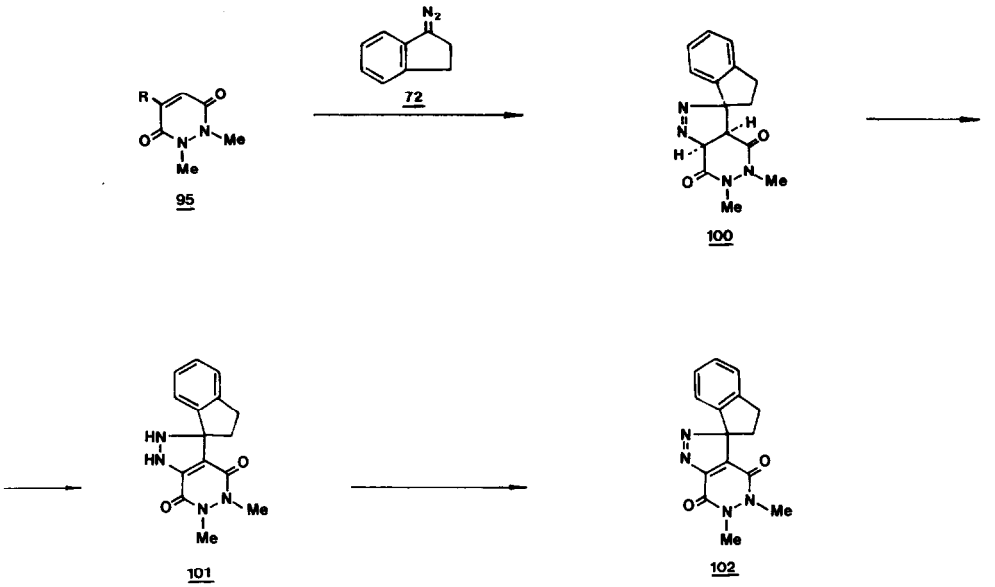


1,2-Dimethylpyridazine-3,6(1H,2H)-dione (**95**) and its 4-chloro- (**96**) and 4-phenylsulfinyl-derivatives (**97**) are more reactive. The compound **95** gives with **17** at 5°C the 1,2-dihydro derivative **98**, which is then dehydrogenated giving **99**. From **96** and **97** only **99** is formed in high yield. The high reactivity of **95** is also demonstrated in its reaction with 1-diazoindane (**72**). **95** Gives the primary 3a,7a-dihydro-cycloadduct **100** which is transformed in the presence of an acid into the 1,2-dihydro derivative **101** which finally dehydrogenates yielding **102**.[19]

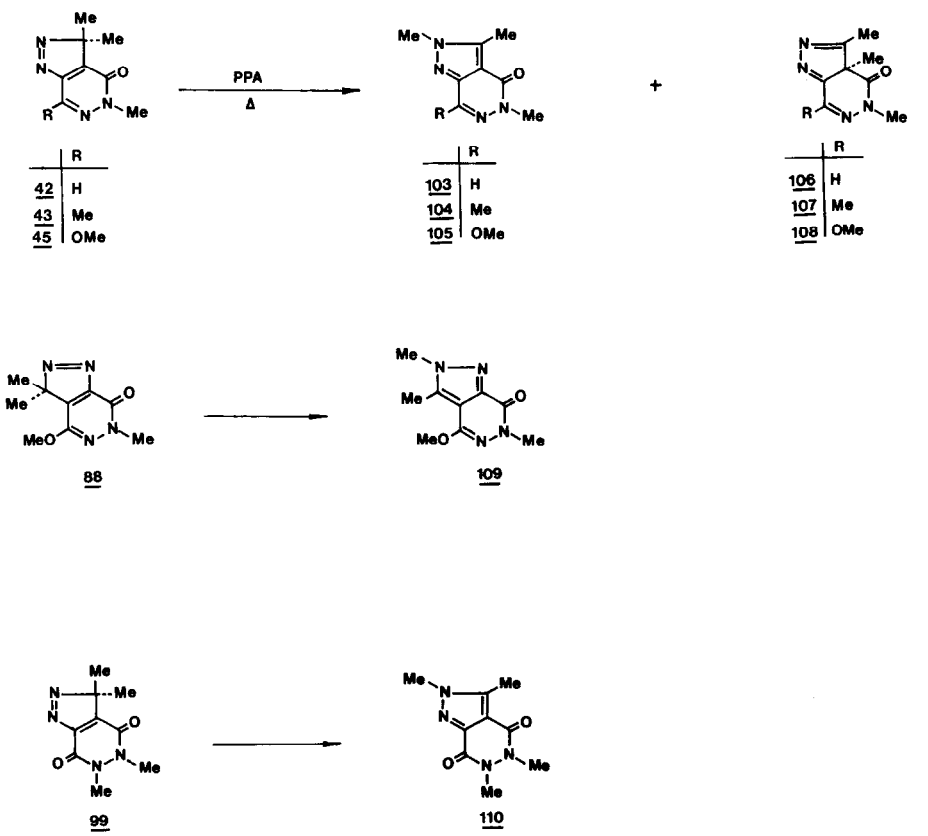
*Thermal*[1,5]*-sigmatropic rearrangements of methyl groups in* 3,3*-dimethyl-*3*H-pyrazolo*[3,4-d] *pyridazine derivatives*

3,3-Dimethyl-3H-pyrazolo[3,4-*d*]pyridazin-4(5H)-ones **42**, **43** and **45**, when heated in polyphosphoric acid at 120°C for 30 min give the isomeric $N_2$-methylated products **103–105** and

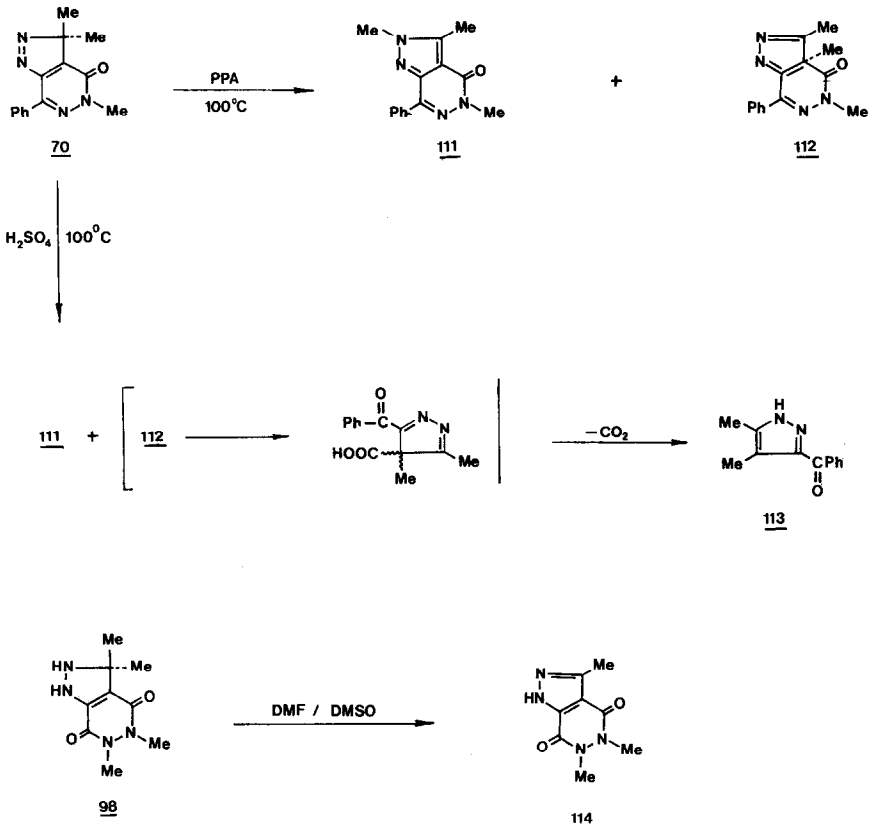





$C_{3a}$-methylated isomers **106–108**. The isomeric -7(6H)-one **88** and -4,7(5H,6H)-dione **99** give only the $N_2$-methylated products **109** and **110**, respectively.[19]



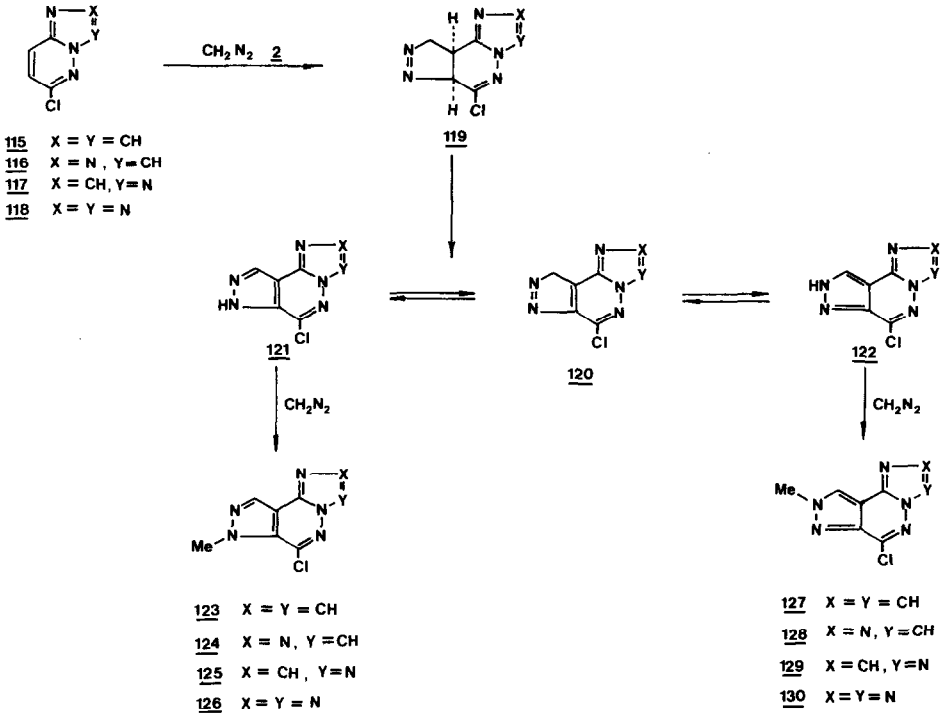
When **70** is heated in PPA at 100°C, a 1,5-sigmatropic rearrangement of one of the methyl groups is taking place either in clock-wise or anticlock-wise direction around the pyrazole part of the molecule giving two isomeric products **111** and **112**. In concentrated sulfuric acid **111** and **113** are formed. The compound **113** is formed from **112** by hydrolysis and decarboxylation.[17] When **98** is heated in a mixture of DMF/DMSO, elimination of methane takes place producing **114**.




## CYCLOADDITIONS TO BICYCLIC AND POLYCYCLIC AZOLO- AND -AZINOPYRIDAZINES WITH A BRIDGEHEAD NITROGEN ATOM

Cycloaddition of diazoalkanes to bicyclic heteroaromatic 10$\pi$-electron systems with a bridgehead nitrogen atom such as imidazo[1,2-*b*]pyridazine (**115**), *s*-triazolo[4,3-*b*]pyridazine (**116**), *s*-triazolo[1,5-*b*] pyridazine (**117**) and tetrazolo[1,5-*b*]pyridazine (**118**) and their derivatives has been observed. The reaction proceeds by a regiospecific 1,3-dipolar cycloaddition of diazoalkane to partially localized and polarized $C_7$–$C_8$ double bond followed by loss of a molecule of hydrogen from the primary cycloadducts giving the stable pyrazolo[4,3-*d*]azolopyridazines, which may react further.

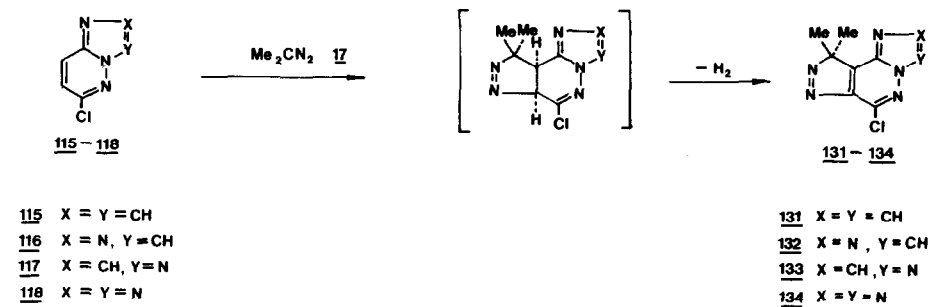
Cycloaddition of diazomethane to the systems **115–118** gives the primary cycloadducts of the type **119**, and this is followed by oxidative transformation giving the intermediate **120**. [1,3]- or [1,5]-Sigmatropic rearrangement of one of the hydrogen atoms of the methylene group giving the tautomeric intermediates **121** and **122**, and N-methylation with an excess of diazomethane yields mixtures of the corresponding isomeric pairs of 7-methyl-7H- **123–126** and 8-methyl-8H-pyrazolo-[4,3-*d*]azolopyridazines **127–130**.[20]

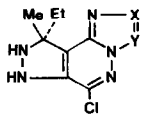



The isomeric 9H-pyrazolo[4,3-*d*]pyridazines are formed when 2-diazopropane (**17**) is used instead of diazomethane. In this way derivatives of 9,9-dimethyl-9H-imidazo[1,2-*b*]pyrazolo[4,3-*d*]-pyridazine (**131**),[21-22] 9,9-dimethyl-9H-pyrazolo[4,3-*d*]-*s*-triazolo[4,3-*b*]pyridazine (**132**),[23] 9,9-dimethyl-9H-pyrazolo[4,3-*d*]-*s*-triazolo[1,5-*b*]pyridazine (**133**)[23] and 9,9-dimethyl-9H-pyrazolo [4,3-*d*]tetrazolo[1,5-*b*]pyridazine (**134**)[24] were prepared.

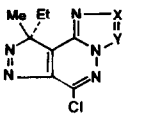
When less reactive diazoalkanes, such as 2-diazobutane (**58**), phenyldiazomethane (**149**) and 1-diazo-1-phenylethane (**59**) are employed in these cycloadditions, the primary CH,CH-dihydro-cycloadducts as well CH,NH- and NH,NH-dihydro-cycloadducts, which are produced by rearrangement, can be isolated in some instances. For example, in the reaction of **115–118** with 2-diazobutane (**58**) the mixture of the corresponding NH,NH-dihydro-cycloadducts **135–138** are isolated,[75] and with 1-diazo-1-phenylethane (**59**) 6a,9a-dihydro- **143** and **144** which are stable in nonpolar solvents, while in DMSO they rearrange into 8,9a-dihydro-tautomeric forms **145** and **146** and 7,8-dihydro-tautomeric forms **147** and **148**.

The compounds **113–115** react with phenyldiazomethane (**149**) to give intermediates which further alkylate giving mixtures of isomeric products benzylated at $N_7$ **150–152** or $N_8$ **153–155**.[25]



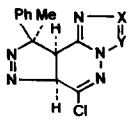


135–138

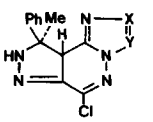


139–142

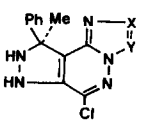
135 139 X = Y = CH
136 140 X = N, Y = CH
137 141 X = CH, Y = N
138 142 X = Y = N



143, 144

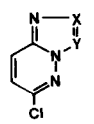


145, 146



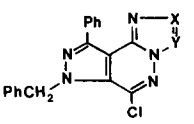
147, 148

143 145 147 X = N, Y = CH
144 146 148 X = Y = N



113–115





150–152

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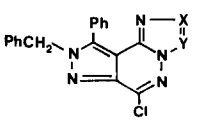
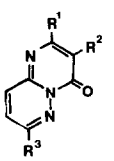


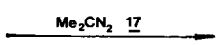
153–155

113 150 153 X = N, Y = CH
114 151 154 X = CH, Y = N
115 152 155 X = Y = N

Similarly in the azinopyridazine series the 1,3-dipolar cycloaddition of 2-diazopropane takes place to the partially localized and polarized double bond $C_8$–$C_9$ in pyrimido[1,2-*b*]pyridazin-4-ones **156–159** giving pyrazolo[4,3-*d*]pyrimido[1,2-*b*]pyridazin-4(10H)-one derivatives **160–163**.[26]



156–159



160–163

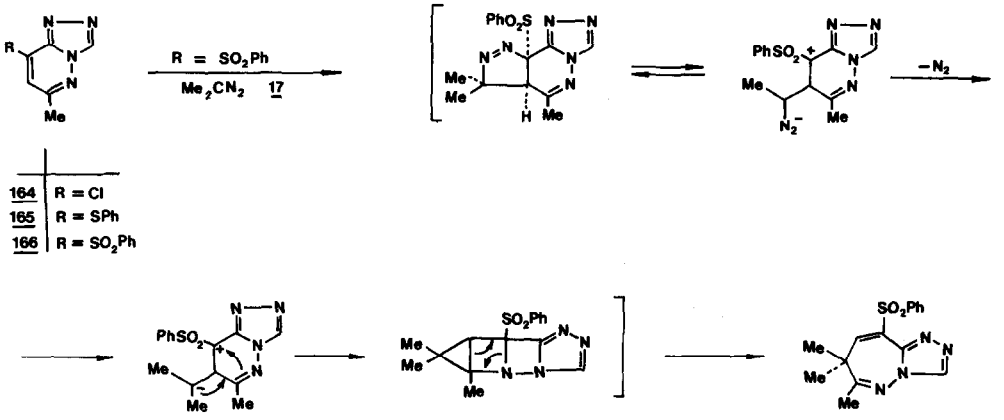
156 160 $R^1 = R^2 = H$, $R^3 = Cl$
157 161 $R^1 = Ph$, $R^2 = R^3 = H$
158 162 $R^1 = Ph$, $R^2 = H$, $R^3 = Cl$
159 163 $R^1 = Ph$, $R^2 = Br$, $R^3 = H$

## THE SYNTHESIS OF ISOMERIC PYRAZOLO[3,4-*d*]AZOLOPYRIDAZINES

Since the cycloaddition of diazoalkanes to azolopyridazines is regiospecific affording only pyrazolo[4,3-*d*] fused systems, an attempt to prepare the isomeric pyrazolo[3,4-*d*]fused systems has been carried out, starting from 8-substituted *s*-triazolo[4,3-*b*]pyridazine derivatives.

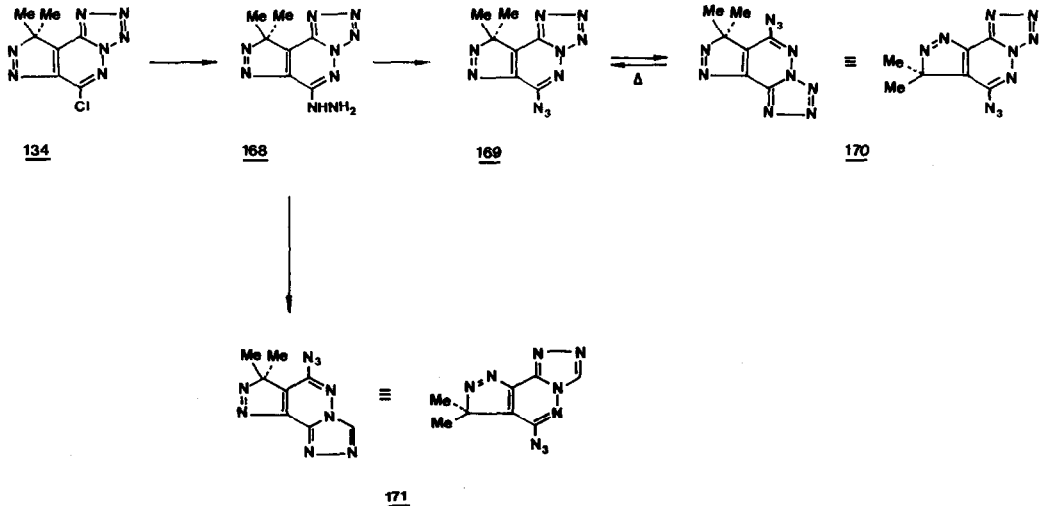
8-Chloro- (**164**), 8-phenylthio- (**165**) and 8-phenylsulphonyl- (**166**) derivatives have been prepared. However, the compounds **164** and **165** do not react with 2-diazopropane (**17**), whereas

**166** reacts vigorously at room temperature giving fused 1,2-diazepine derivative **167**, the structure of which has been confirmed by X-ray analysis, suggesting thus that the addition is taking place in the opposite direction in comparison to that observed in derivatives unsubstituted at position 8. However, the primary cycloadduct is unstable, a molecule of nitrogen is eliminated followed by rearrangement giving the final product according to the Scheme below.[10] An alternative mechanism, i.e. addition of diazoalkane to the carbonyl group, analogous to the known ring-expansion of ketones by diazoalkanes, is less probable, since in this case the carbonyl group is a part of the cyclic amide structure.




167

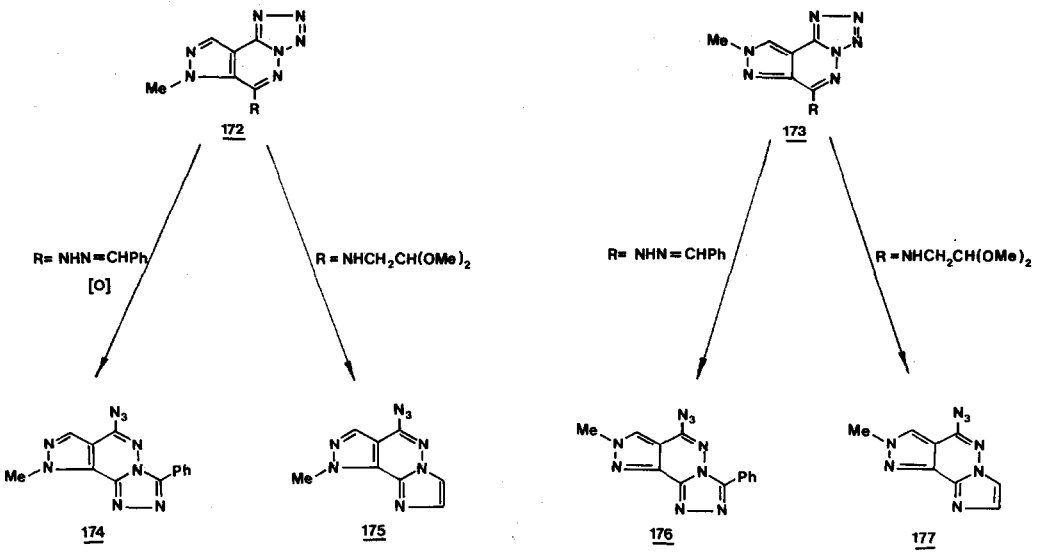
Derivatives of pyrazolo[3,4-*d*] fused systems can be prepared by azido-tetrazolo valence isomerization, observed previously in tetrazolo[1,5-*b*]pyridazine system,[27] from the corresponding pyrazolo[4,3-*d*]tetrazolo[1,5-*b*]pyridazines. The compound **134** is treated with hydrazine hydrate giving the hydrazino derivative **168**, which was converted with nitrous acid into the corresponding azido derivative **169**. When this is heated in an NMR tube in DMSO-$d_6$ solution at 110°C, the azido-tetrazolo isomerization produced a mixture of **169** and the isomeric 7H-pyrazolo[3,4-*d*]tetrazolo[1,5-*b*]-pyridazine derivative **170** in the ratio 4 : 1. When **168** reacts with a mixture of triethyl orthoformate and acetic anhydride the hydrazino group cyclizes into a triazole ring and this is followed by opening of the tetrazole ring giving 7H-pyrazolo[3,4-*d*]-*s*-triazolo[4,3-*b*]pyridazine derivative **171**.[23]




134 168 169 170

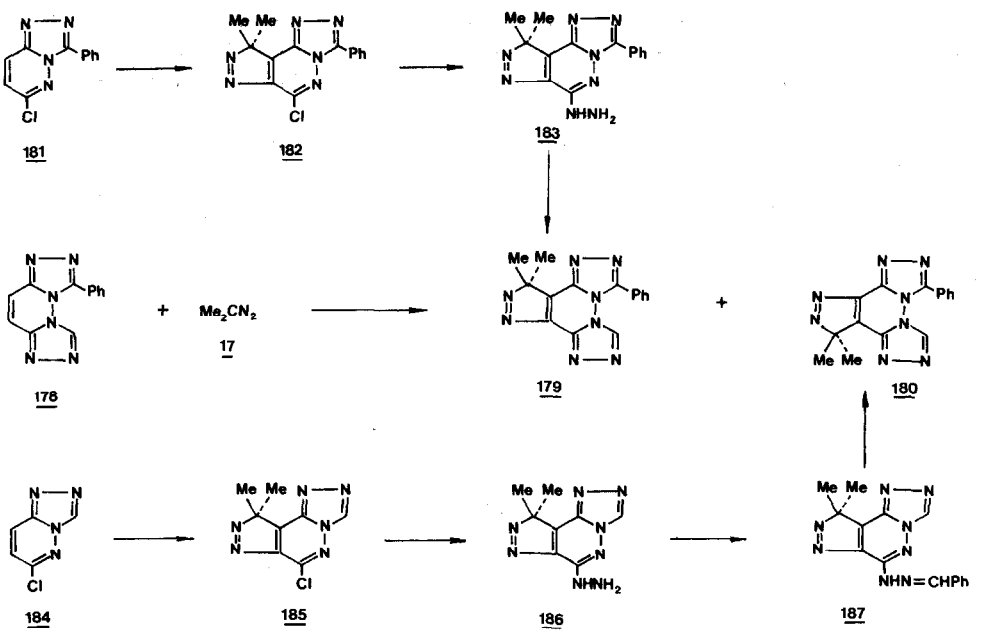
171

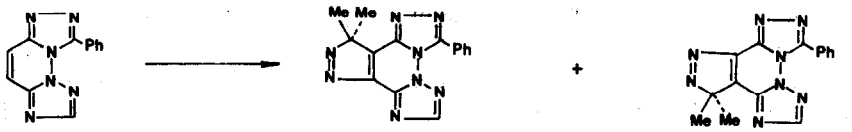
Similarly, the corresponding 8-methyl-8H- **176** and 9-methyl-9H-pyrazolo[3,4-*d*]-*s*-triazolo[4,3-*b*]-pyridazines **174** and 1-methyl-1H- **175** and 2-methyl-2H-imidazo[1,2-*b*]pyrazolo[3,4-*d*]pyridazine **177** are obtained from **172** and **173**, respectively.[28,29]




Cycloaddition of 2-diazopropane (**17**) to derivatives of the tricyclic heteroaromatic 14$\pi$-electron system **178** occurs across the 4,5-double bond producing a mixture of the isomeric derivatives **179** and **180** of the tetracyclic system 11H-pyrazolo[3,4-*d*]bis-*s*-triazolo[4,3-*b*:3′,4′-*f*]pyridazine in the ratio 1 : 1. The structures **179** and **180** have been determined by independent syntheses starting from **181** by the reaction sequence **181** → **182** → **183** → **179** and from **184** by an analogous sequence **184** → **185** → **186** → **187** → **180**.[30]

Similarly, the tricyclic system **188** gives derivatives of two isomeric tetracyclic systems **189** and **190**.





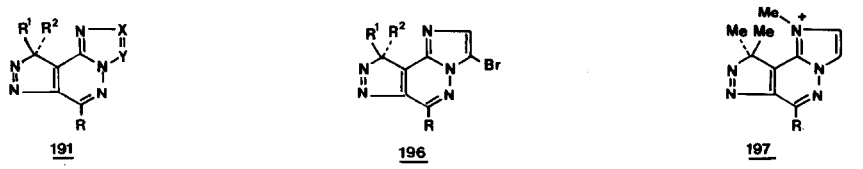
188 189 190

## REACTIONS OF PYRAZOLOAZOLOPYRIDAZINES (191)

*Nucleophilic and electrophilic substitutions*

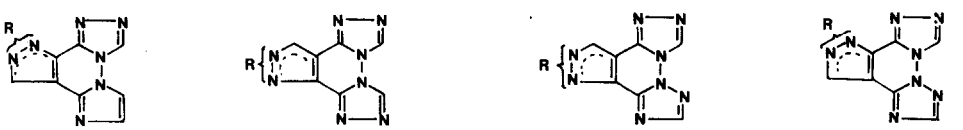
Since pyrazoloazolopyridazines and pyrazoloazinopyridazines are new heterocyclic systems their chemical behaviour under the conditions for nucleophilic and electrophilic substitutions has been studied. All these systems undergo an easy nucleophilic substitution of chlorine at position 6 with alkoxy, amino and substituted amino, hydrazino and substituted hydrazino, azido, and other groups, such as **191**, affording the intermediates suitable for further cyclizations taking place at position 5 to give derivatives of new tetracyclic systems, such as **192–195** and their stable tautomers.

Electrophilic reactions, such as bromination, are taking place at position 3 in imidazo[1,2-*b*] pyrazolo[4,3-*d*]pyridazine to give **196**, and quaternization with methyl iodide in methanol at nitrogen at position 1 to give **197**.[22]



191 196 197

R = H, Cl, RO, $NH_2$ NHR, $NHNH_2$, NHN=CHR, $N_3$, etc.

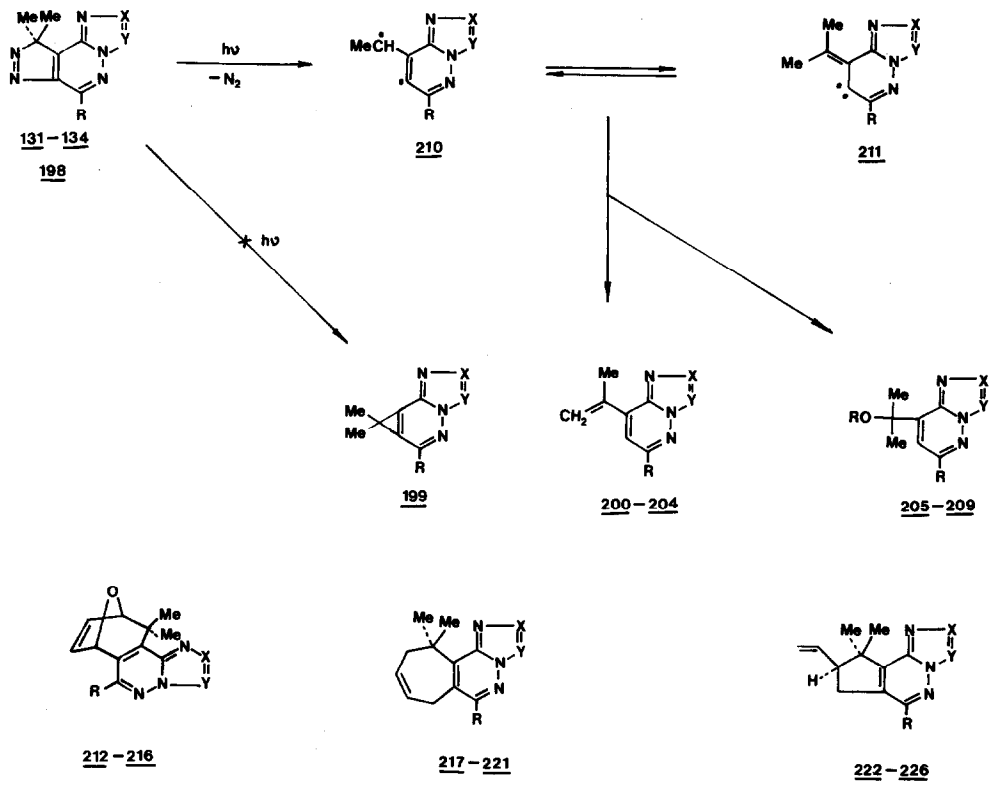


192 193 194 195

*Photochemical transformations of 3H-pyrazolo*[4,3-d]*azolopyridazine derivatives*

Although the chemistry of cycloproparenes is well established,[31] there is presently known only one example of such a molecule which contains a heteroatom in the aromatic skeleton.[32] On this basis, it seems therefore possible that each of the pyrazoloazolopyridazine and pyrazoloazinopyridazines could lose molecular nitrogen and cyclize to the corresponding cyclopropa[*d*]pyridazine (**199**). The irradiation of compounds **131–134** and **198** leads to the loss of molecular nitrogen in the first step, however, in the second step, when the reactions are carried out in a mixture of tetrahydrofuran and pentane 8-isopropenylazolopyridazines **200–204** are obtained in 7–29% yield. The presence of the pyrazole ring cleaved product is evident from the appearance of a new aromatic proton (6.96–7.33 ppm) corresponding to $H_7$ in the azolopyridazine system. Irradiation in methanol provides mixture of products, from which olefins **200–204** are isolated as the minor components

(5–30%) and methyl ethers **205–209** as the major components (36–67%). The formation of ethers reflects facile trapping of the diradical form of the intermediate **210**. The carbene form **211** is less probable, because its presence would cause the disruption of the $10\pi$-electron system. Photoaddition of an alcohol to olefins **200–204** does not provide a route to ethers **205–209**: **200–204** are stable to the reaction conditions and are recovered unchanged. When the reactions are performed in furan, the diradicals **210** react with the solvent to form 1 : 1 adducts **212–216** in 56–70% yields, accompanied by small amounts of the alkenes **200–204** (8–12%). Similarly photodecomposition in the presence of buta-1,3-diene results in the formation of two types of addition products. The major components are 7H-dihydrocyclohepta[*d*]pyridazines **217–221** corresponding to 1,4-cycloaddition of the diradicals **210**. The minor components (3–16%) correspond to 1,2-addition of diradicals **210** to form cyclopenta[*d*]pyridazines **222–226**.[23,26,33–35]



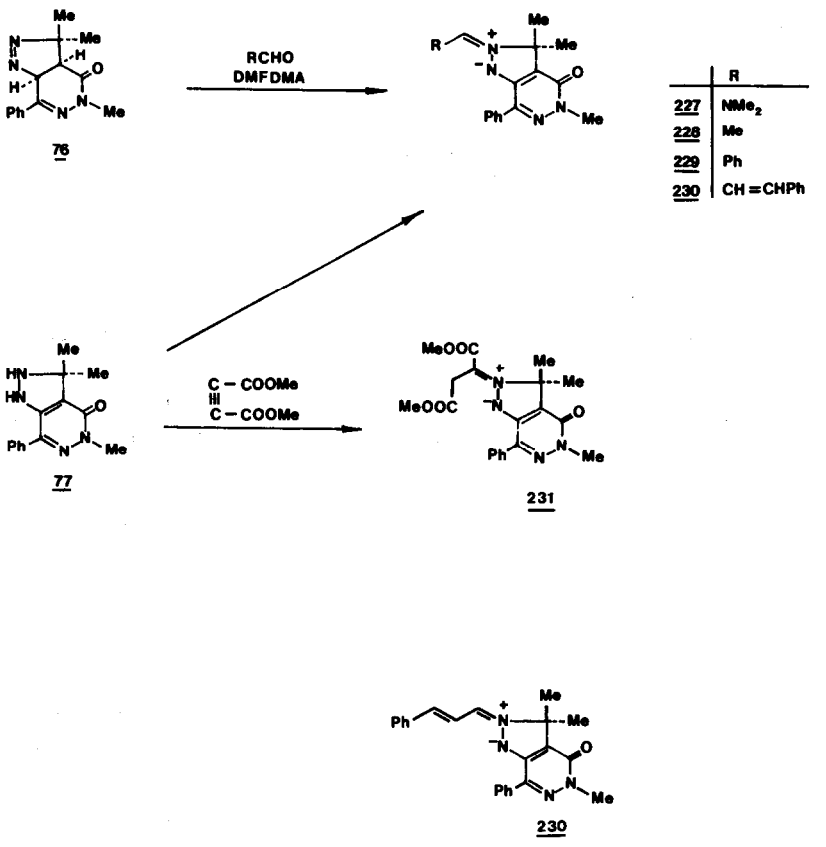

| | | | | | | X | Y | R |
|---|---|---|---|---|---|---|---|---|
| 131 | 200 | 205 | 212 | 217 | 222 | CH | CH | Cl |
| 132 | 201 | 206 | 213 | 218 | 223 | N | CH | Cl |
| 133 | 202 | 207 | 214 | 219 | 224 | CH | N | Cl |
| 134 | 203 | 208 | 215 | 220 | 225 | N | N | Cl |
| 198 | 204 | 209 | 216 | 221 | 226 | N | N | OMe |

## TRANSFORMATIONS OF DIHYDRO CYCLOADDUCTS. THE FORMATION OF AZOMETHINE IMINES AND THEIR FURTHER REACTIONS

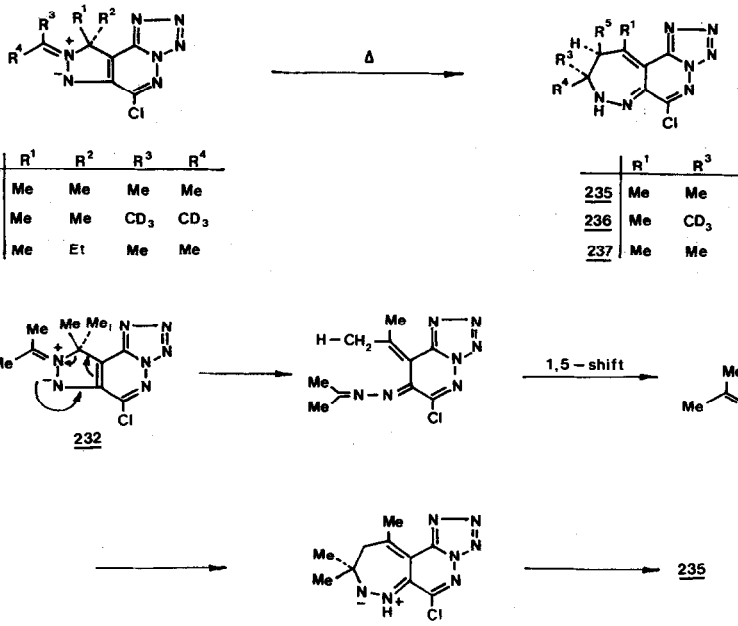
Azomethine imines are important intermediates as 1,3-dipoles in cycloadditions and electrocyclic reactions in which five, six, and seven-membered heterocyclic systems are formed.[36–39]

In this connection an interesting example has been reported of the transformation of 1,5-diazabicyclo[3.3.0]oct-2-ene derivatives, which undergo either an electrocyclic ring-opening or cycloreversion followed by cycloelimination, producing 1,2-diazepine or pyrazole derivatives. The corresponding azomethine imine has been proposed, but not isolated, as one of the intermediates.[40]

The dihydro-intermediates **76** and **77** react with aldehydes, dimethylformamide dimethyl acetal (DMFDMA) and dimethyl acetylenedicarboxylate to give the corresponding stable azomethine imines **227–231**. Since there are two possible isomeric structures, the structure of **230** has been determined by X-ray analysis showing that the product is (2*Z*,2′*E*)-2-cinnamylidene-7-phenyl-3,3,5-trimethyl-3H-pyrazolo[3,4-*d*]pyridazin-4(5H)-one 2-azomethine imine.[17]



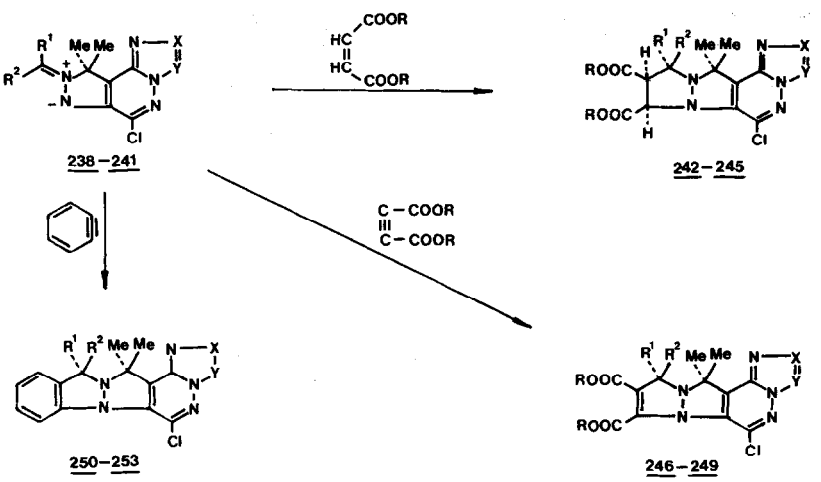

When studying the chemical properties of these types of intermediates, an interesting thermal rearrangement has been observed. The azomethine imine **232** obtained from the corresponding NH,NH-dihydro cycloadduct and acetone is transformed by heating in xylene, into the tetrazolo-pyridazinodiazepine derivative **235**. From the hexadeuterio-derivative **233** and the ethyl substituted derivative **234**, the corresponding fused 1,2-diazepine derivatives **236** and **237** are obtained. This shows that one of the methyl groups attached to the pyrazole ring at position 8, or the methylene group of the ethyl group attached at position 8 is incorporated into the seven-membered ring. The rearrangement can be considered as a thermal electrocyclic 6π-electron ring-opening of **232** followed by a 1,5-sigmatropic hydrogen shift and electrocyclization to give **235**.[41]



| | $R^1$ | $R^2$ | $R^3$ | $R^4$ |
|---|---|---|---|---|
| 232 | Me | Me | Me | Me |
| 233 | Me | Me | $CD_3$ | $CD_3$ |
| 234 | Me | Et | Me | Me |

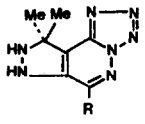
| | $R^1$ | $R^3$ | $R^4$ | $R^5$ |
|---|---|---|---|---|
| 235 | Me | Me | Me | H |
| 236 | Me | $CD_3$ | $CD_3$ | H |
| 237 | Me | Me | Me | Me |

Azomethine imines **238–241** react also as 1,3-dipoles with unsaturated compounds, such olefins, acetylenes and arynes forming new tetracyclic **242–249** and pentacyclic systems **250–253**.



| | | | | |
|---|---|---|---|---|
| 238 | 242 | 246 | 250 | X=Y=CH |
| 239 | 243 | 247 | 251 | X=N, Y=CH |
| 240 | 244 | 248 | 252 | X=CH, Y=N |
| 241 | 245 | 249 | 253 | X=Y=N |

This reaction sequence can be conveniently applied for the synthesis of α-heteroaryl-α-amino acids. The NH,NH-dihydro cycloadducts **254** are transformed with methyl 2-benzoylamino-3-dimethylaminopropenoate (**255**) into azomethine imines **256**. This reagent (**255**) has been introduced recently into organic synthesis, especially for preparation of amino acids and heterocyclic systems.[42] They react as 1,3-dipolar compounds with unsaturated compounds **258** giving fused heterocyclic systems attached at α-position in α-amino acid derivatives **259**.



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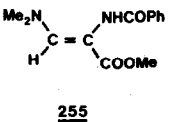

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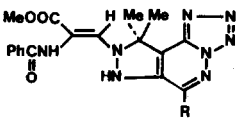

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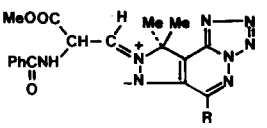

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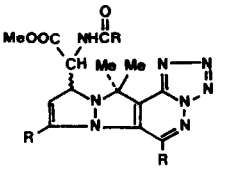
HC≡CR 258



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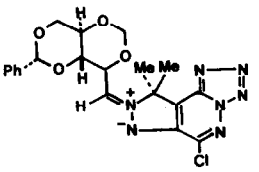

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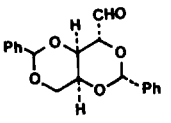

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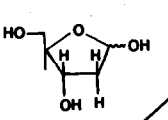

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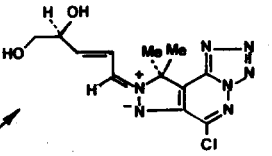

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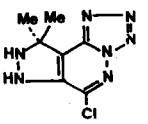

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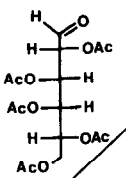

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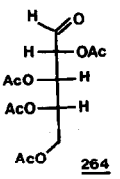

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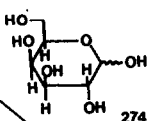
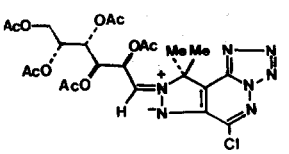


1.)

274

2.) $CH_2$=CH−COOMe

269



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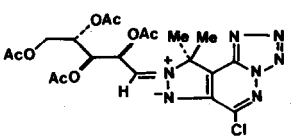
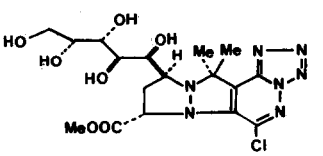


268



275

$CH_2$=CH−COOMe

269

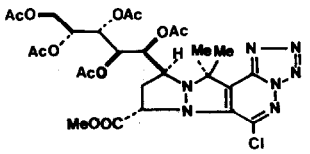
$CH_2$=CH−COOMe

269

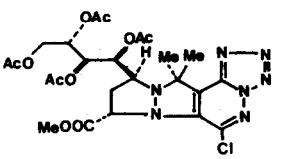
HC≡C−CPh

O

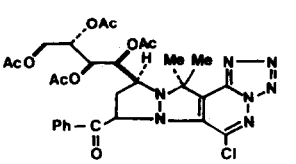
270



271



272



273

Analogously, the NH,NH-dihydro intermediates can be applied for the regioselective synthesis of C-nucleosides, when protected or unprotected sugars are employed as carbonyl reagents. For example, from **260** and 1.4: 3.5-dibenzylidene-D-ribose **261**, 2-deoxy-D-ribose, **262**, pentaacetyl-al-D-galactose **263**, and tetraacetyl-al-L-arabinose **264** the corresponding azomethine imines **265–268** are obtained. These are then converted with methyl acrylate **269** or benzoylacetylene **270** regiospecifically into chiral derivatives of tetracyclic systems **271–273**. Furthermore, the NH,NH-dihydro-cycloadduct **260**, can be in one-pot synthesis transformed into a derivative of the tetracyclic, system **275**. as exemplified with D-galactose **274** and methyl acrylate **269**.[43]

*Acknowledgement*—I am pleased to express my sincere gratitude to my research students and other coworkers for their enthusiasm; their names are mentioned in the list of references. My sincere appreciation is due also to Professor W. D. Ollis, Department of Chemistry, University of Sheffield, for his valuable comments and suggestions in preparation of this Report.

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