SOME ASPECTS OF THE CHEMISTRY OF 1,2,3-TRIAZOLES

Thesis submitted to the University of Stirling

for the degree of

Doctor of Philosophy

by

Sean Patrick Lennon

Department of Chemistry
University of Stirling

April 1987

DECLARATION

I hereby declare that this thesis is my own unaided work based on research carried out in the Department of Chemistry, The University of Stirling between October 1981 and October 1985. The work it embodies has not been included in another thesis.

SEAN PATRICK LENNON

Dedication

This piece of work is dedicated to my family for their support and encouragement. It is also dedicated to my "wee friend" Allison for all the laughter and happiness she gave me in my last year at Stirling.

ACKNOWLEDGEMENTS

I wish to express sincere thanks to my supervisor, Dr. A. E. A. Porter, under whose direction and guidance this research was carried out, for his advice and encouragement throughout the period at Stirling. I would also like to acknowledge Ted's own unique sense of humour which kept me going.

I thank Dr. B. G. Cox for his assistance with kinetics investigations and for the useful discussions from these investigations.

To Gerry Castle, I say a big thank you for giving me an insight into Aberdonian generosity, and Mr. Graham Reed for making many pieces of useful (and sometimes interesting) glassware. I also have to mention John and Campbell for all the "crack" when Gerry wasn't in the stores.

I wish to go on record as acknowledging the valuable help that Mrs. Greta Berry rendered when I had my accident in 1984 for which I am grateful.

I also thank Mrs. Muriel McLeod for ordering the chemicals used in my research.

Thanks to the "team" for their friendship and laughter during the years 1981-86. This team consists of Hugh Hunter, Norman Govan, Ian Conner, Jebsen Wu, Senga Martin, Stevie Cree, Paul Millican and of course Stewart Gillespie and Alec MacKenzie.

Special/

Special mentions must go to my best friend, George Cameron, for his loyalty and to Carole Peasgood for her support and generosity during 1982-85.

I acknowledge constructive discussions with academic staff of the Chemistry and Biological Science Departments.

I am most indebted to the Cancer Research Campaign for the tenure of a research studentship. Finally, my sincere thanks go to Sylvia Maudsley for the excellent typing.

Abstract

In a wide ranging reaction dimethyl diazomalonate reacted with primary amines to yield the corresponding ammonium salts of 5-hydroxy-1,2,3- triazoles in high yields. On acidification of these salts the free 5-hydroxy-1,2,3-triazoles were obtained quantitatively.

When the 5-hydroxy-1,2,3-triazoles were isolated, they were found to be contaminated with α-diazoamides. These diazoamides arise from Dimroth Rearrangement of the 5-hydroxy-triazoles. This Rearrangement was thoroughly investigated and mechanisms were suggested for the base induced cyclisation of diazoamides ⟶ salts of 5-hydroxy-triazoles, and for the thermally promoted decomposition of 5-hydroxy-triazoles ⟶ α - diazoamides.

The hydroxy-triazoles were converted to 5-chloro-derivatives, under mild conditions, in good yields, using phosphorus pentachloride. These 5-chloro-triazoles proved to be very inert to a variety of nitrogen nucleophiles. When 5-chloro-4-methoxycarbonyl-1,2,3-triazoles were reacted with ammonia, ammonolysis of the 4-ester function results. The 5-azido-triazoles resulted from reaction of 5-chloro-derivative with sodium azide in moderate yields. Catalytic hydrogenation of 5-azido-1,2,3-triazole furnished excellent yields of 5-amino-1,2,3-triazoles.

Attempted preparation of 8-azapurines from 5-hydroxy- and 5-chloro-triazoles with amidines or amides proved fruitless.

9-p-Methoxybenzyl-8-azapurin-6-one was prepared from formamide and 1-p-methoxybenzyl-4-carboxamido-5-amino-1,2,3-triazole in a moderate yield. When the 5-amino function was methylated the pyrimidine ring formation is effected with acidified triethyl orthoformate. 9-p-Methoxybenzyl-8-azaadenine was prepared by chlorination of 9-p-methoxybenzyl-8-azapurine-6-one followed by reaction with ethanolic ammonia.

Attempted formation of the pyrimidine ring using imidates failed.

5-Diazo-1,2,3-triazoles were prepared and cycloaddition reactions were carried out on these compounds. The 5-diazo-triazoles proved unreactive and only decomposition was observed.

4-Aminomethyl-5-amino-1,2,3-triazoles were obtained by reduction of the 4-carboxamido-triazoles with diborane. A convenient preparation of 9-p-methoxybenzyl-1,6-dihydro-8-azapurine was described.

A fully protected 1,6-dihydro-8-azapurine ribonucleoside is prepared using this methodology in a 10% yield. The deprotected form was not isolated.

In an effort to synthesise truncated 8-azapurine ribonucleosides, allylic triazoles were prepared. After extensive investigations these triazoles were shown to be of no apparent use in the preparation of the target compound.

C O N T E N T S

APPENDICES

A river always
Flows over rocks and twigs, yet
It always gets there

Anon. Japanese Haiku

CHAPTER 1

Chapter 1

Introduction

A nucleoside consists of a purine or pyrimidine base linked to a pentose sugar. The pentose is D- ribose or 2- deoxy - D ribose. In a nucleoside the glycosidic C-1 atom of the pentose is bonded to N-1 of the pyrimidine or N-9 of the purine base. The configuration of this N- glycosidic linkage is β - in all naturally occurring nucleosides.

In a ribonucleoside the pentose is ribose, and the structures of the two major purine ribonucleosides are given in Fig. 1. These ribonucleosides are important constituents of ribonucleic acids, some

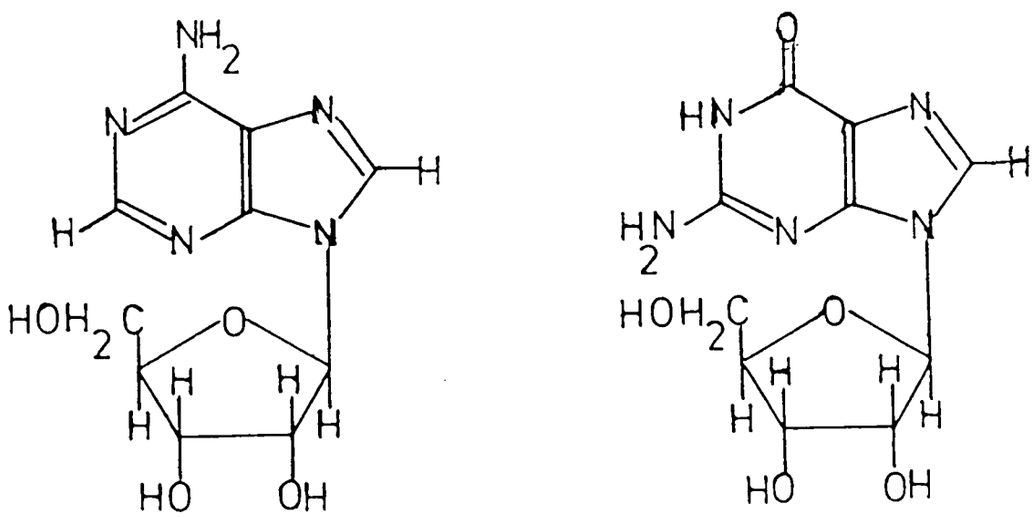


Fig. 1

of which act as templates for protein synthesis in cells. There are three kinds of R.N.A. Messenger R.N.A. (m R.N.A.) is the template for/

for protein synthesis, transfer R.N.A. (t R.N.A.) carries amino acids in an activated form to the ribosome for peptide bond formation in a sequence determined by the m R.N.A. template. There is at least one kind of t R.N.A. for each of the amino acids. The synthesis of R.N.A. is determined genetically by D.N.A., which is found in the nucleus of the cell, whereas most of the R.N.A. is found in the cytoplasm. Furthermore R.N.A. in the cytoplasmic fraction is located in small particles, in association with protein. These particles were shown to be sites of protein synthesis and are called ribosomes. This third kind of R.N.A. is ribosomal R.N.A. which is the major component of ribosomes but its precise role in protein synthesis is not yet known.

m R.N.A. is regarded as the information carrying intermediate between the gene and its polypeptide, and this information is carried in the following manner by the sequence of bases in m R.N.A. which is related to the sequence of amino acids in a protein. The relationship between the sequence of bases in m R.N.A. and the sequence of amino acids is the genetic code. The code is the same in all organisms and is quite simple. Three bases in m R.N.A., called a codon, specify an amino acid. Codons are recognised by the complimentary anti-codon triplet contained in t R.N.A., and peptide bond formation between the growing polypeptide chain and incoming activated amino-acids is carried out on the ribosomes.

If this process of protein synthesis can be interrupted in tumour cells, then the spread of cancers can be arrested. One of the methods used to antagonise protein synthesis in tumours is to treat these cells/

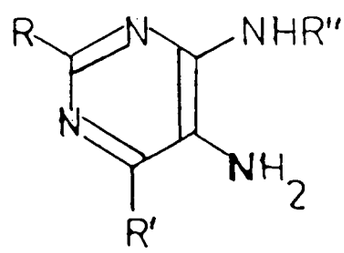
cells with modified ribonucleosides. When structural analogues of natural purine ribonucleosides, such as those shown on Fig. 1, are supplied exogenously to a cell, they can undergo a variety of transformations along numerous metabolic paths, and can thereby effect the synthesis of nucleic acids and/or proteins.

The aza-analogues of purine bases are an important group of anti-metabolites which are derived by the replacement of the methine group in the imidazole or pyrimidine ring with a nitrogen atom. This replacement represents a relatively minor alteration of these substances as it does not change the functional groups usually found in the purine ring and practically the same molecular weight is maintained. When the methine group in the imidazole portion of a purine nucleoside is replaced by nitrogen an 8-azapurine nucleoside is obtained.

1.1. 8-Azapurine Ribonucleosides

8-Azaadenosine has attracted considerable attention as a purine antagonist in the treatment of several metabolic disorders. Since azapurines appear to function by incorporation as ribosyl derivatives into nucleosides, the synthesis of these compounds was undertaken. In 1958 Davoll[1] became the first worker to prepare 8-azaadenosine, 8-azaguanosine, 8-azainosine, and 8-azaxanthosine analogues. Two methods were used. The first of these, treatment of 5-amino -4-glycosylaminopyrimidines (1) with nitrous acid, was

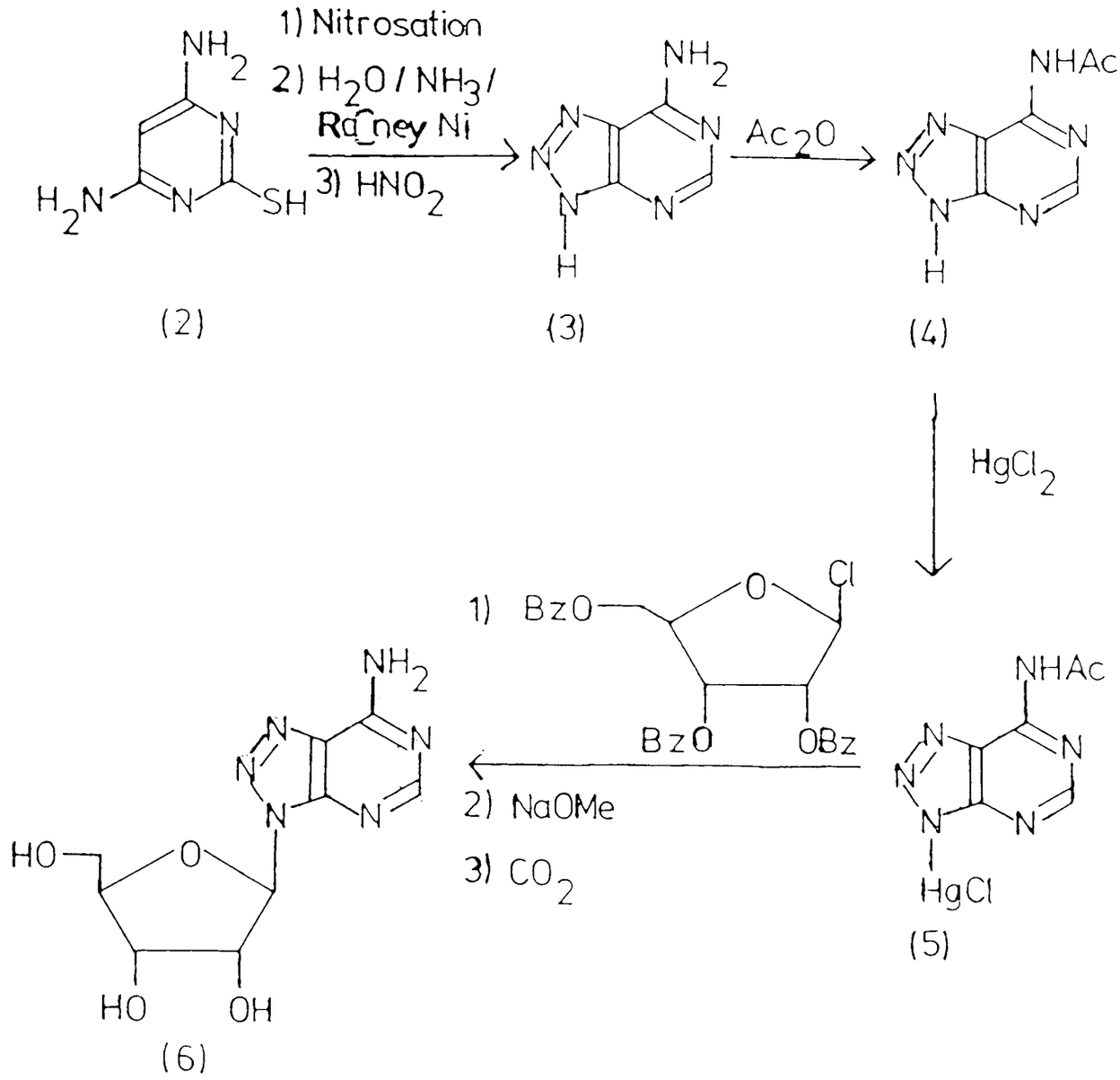
of/



(1)

R'' =Ribosyl

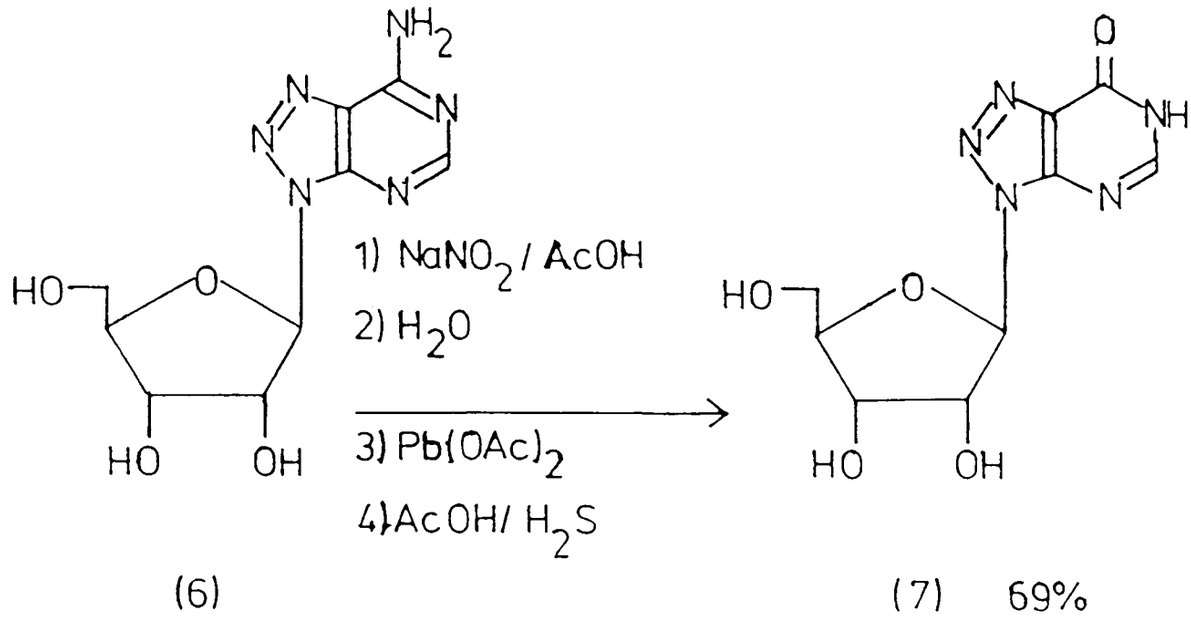
of little preparative value for furanose derivatives. The second synthetic method involved the reaction of chloromercuri-derivatives of the appropriate 8-azapurines with acylglycosyl halides. The overall yields of these reactions were only moderate, because the isomeric 7-, and 8-glycosyl -8-azapurines were formed in addition to the required analogue. The preparation of 8-azaadenosine is shown in Scheme 1.



16% + 7 + 8 isomers + $HgCl_2$

Scheme 1: Preparation of 7-Amino-3-β-D-Riboturanosyl-1,2,3-Triazolo [4,5d] pyrimidine (8-Azaadenosine).

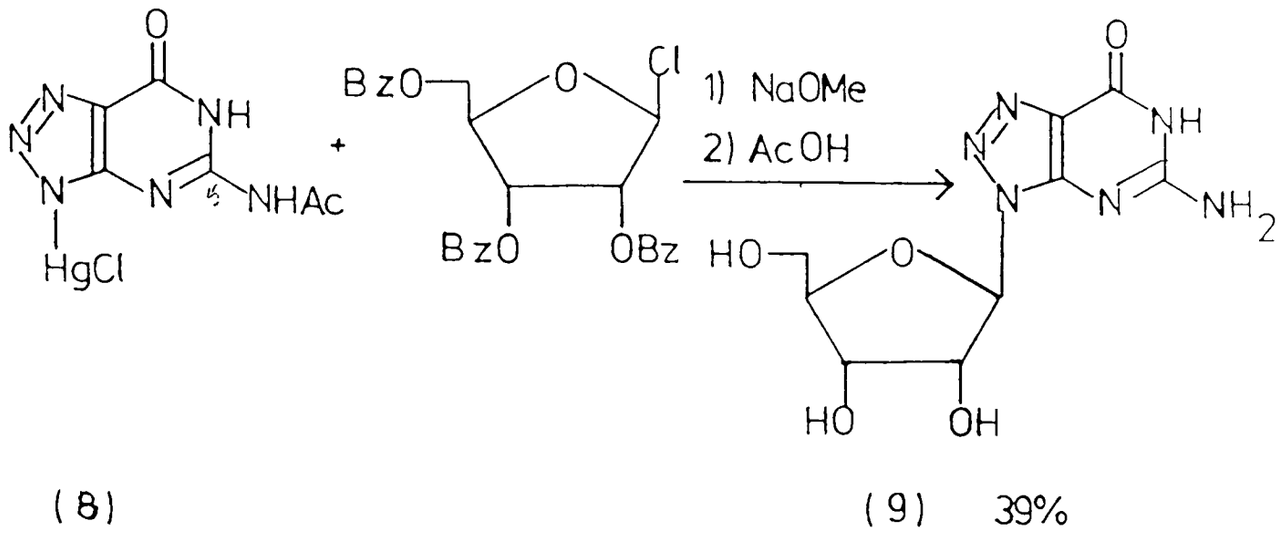
On deamination, 8-azaadenosine was converted to 8-azainosine (Scheme 2).



(6) (7) 69%

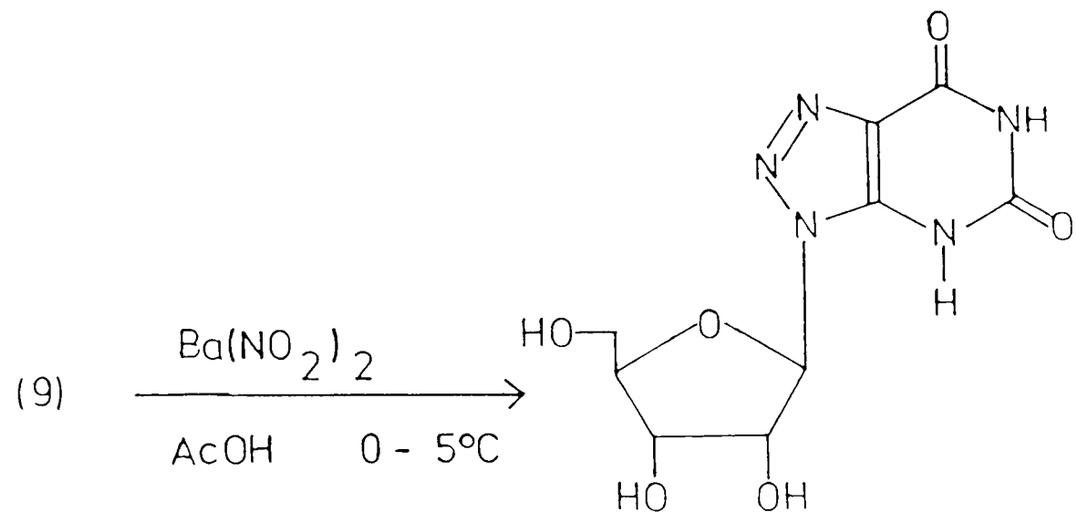
Scheme 2: Preparation of 3-β-D-ribofuranosyl-1,2,3-triazolo [4,5d] pyrimidin-7-one (8-Azainosine)

The preparation of 8-azaguanosine proved more difficult, but eventually deacylation of the condensation product of 5-acetamido-χ-chloromercuri-1,2,3-triazolo[4,5d] pyrimidine-7-one with 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl chloride gave the required analogue of guanosine in a 39% yield (Scheme 3). 8-Azaxanthosine was prepared by deamination of 9. (scheme 4)



(8) (9) 39%

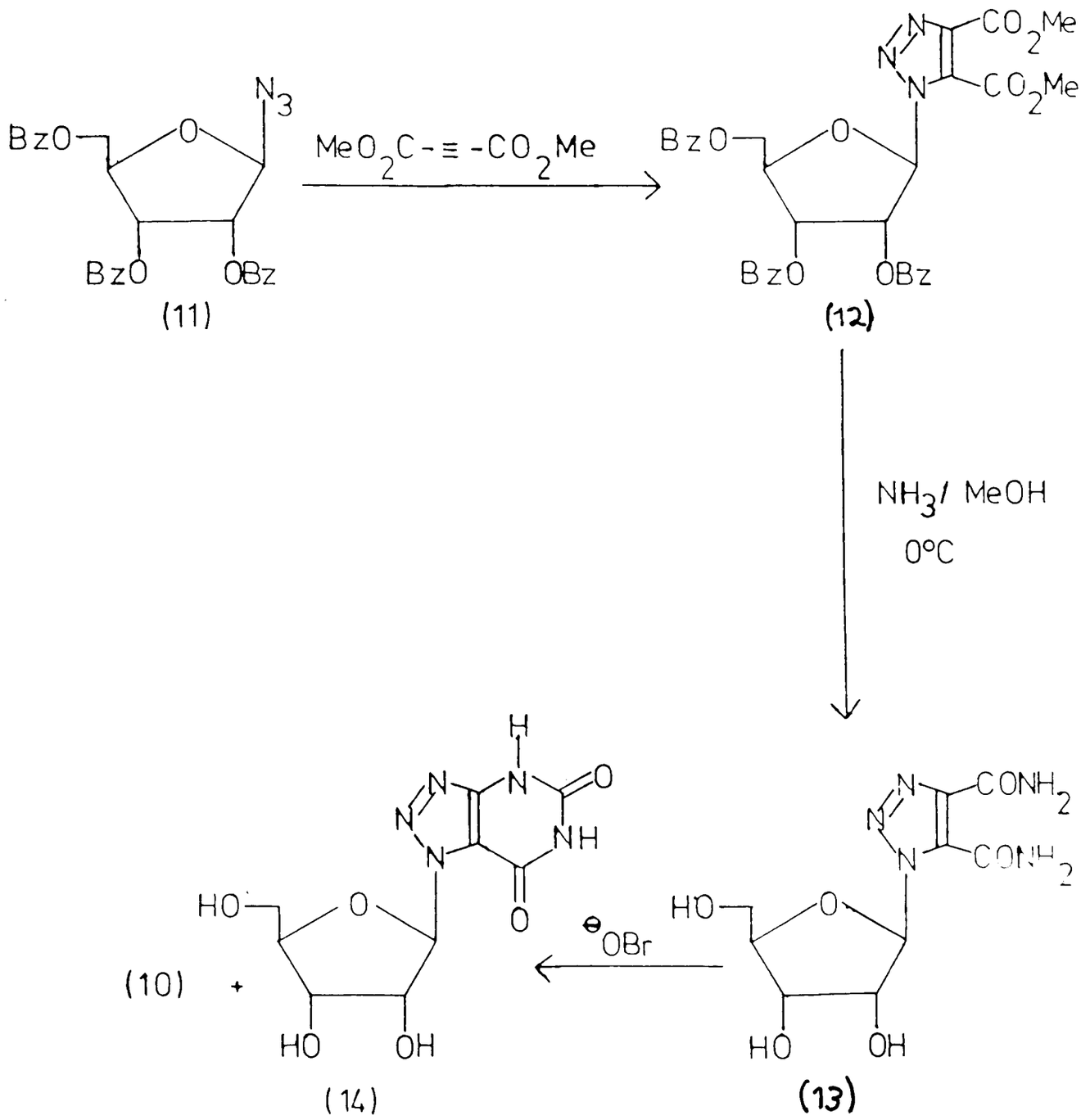
Scheme 3: Preparation of 5-amino-3-β-D-ribofuranosyl-1,2,3-triazolo[4,5d]pyrimidin-7-one (8-Azaguanosine).



(10) 47%

Scheme 4: Preparation of 3-β-D-ribofuranosyl-1,2,3-triazolo-[4,5d]pyrimidin-5,7-dione (8-Azaxanthosine).

At the same time Baddiley,[2] working independently of Davoll, also recognised the potential of azapurine nucleosides and embarked on a different approach to these compounds. The research group at Durham University were experimenting with glycosyl azides and particularly β-D-ribofuranosyl azide as an intermediate for the chemical synthesis of certain nucleotide precursors. In a subsequent publication Baddiley et al prepared (10) and isolated the 7-ribofuranosyl derivative of 8-azaxanthine[3] (Scheme 5).



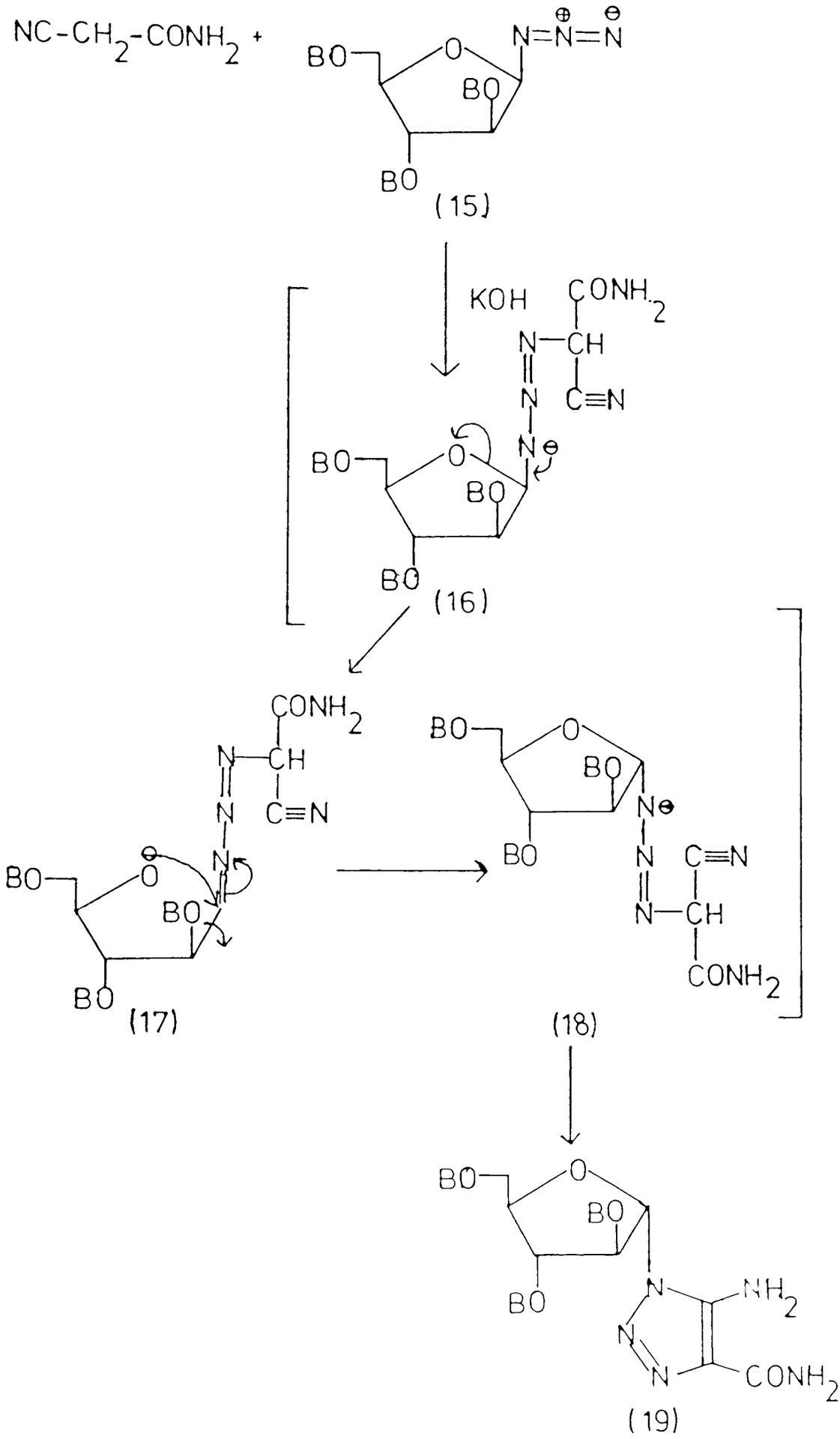
Scheme 5: Preparation of 8-azaxanthosine.

In the scheme shown, 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl azide was reacted with dimethyl acetylenedicarboxylate to yield the triazole (12). This type of 1,3-dipolar cycloaddition was first described by Curtius and Raschig.[4]

Debenzoylation and ammonolysis of (12) with methanolic ammonia gave 1-β-D-ribofuranosyl-1,2,3-triazole-4,5 -dicarboxamide (13). A Hofmann reaction was carried out on (13) with excess potassium hypobromite and the 9- and 7-β-D-ribofuranosyl derivates of 8-azaxanthine [(10) and (14) respectively] were formed.

In the early 1970s more attention was focussed on the reactions between glycosyl azides and substituted acetylenes. Huisgen suggested that the 1,3-dipolar cycloadditions took place by a concerted mechanism.[5] The suggestion was confirmed by Harmon et al who investigated reactions between various glycosyl azides and acetylenes with various functional groups.[6,7]. They observed that these reactions proceeded without inversion of anomeric centre.

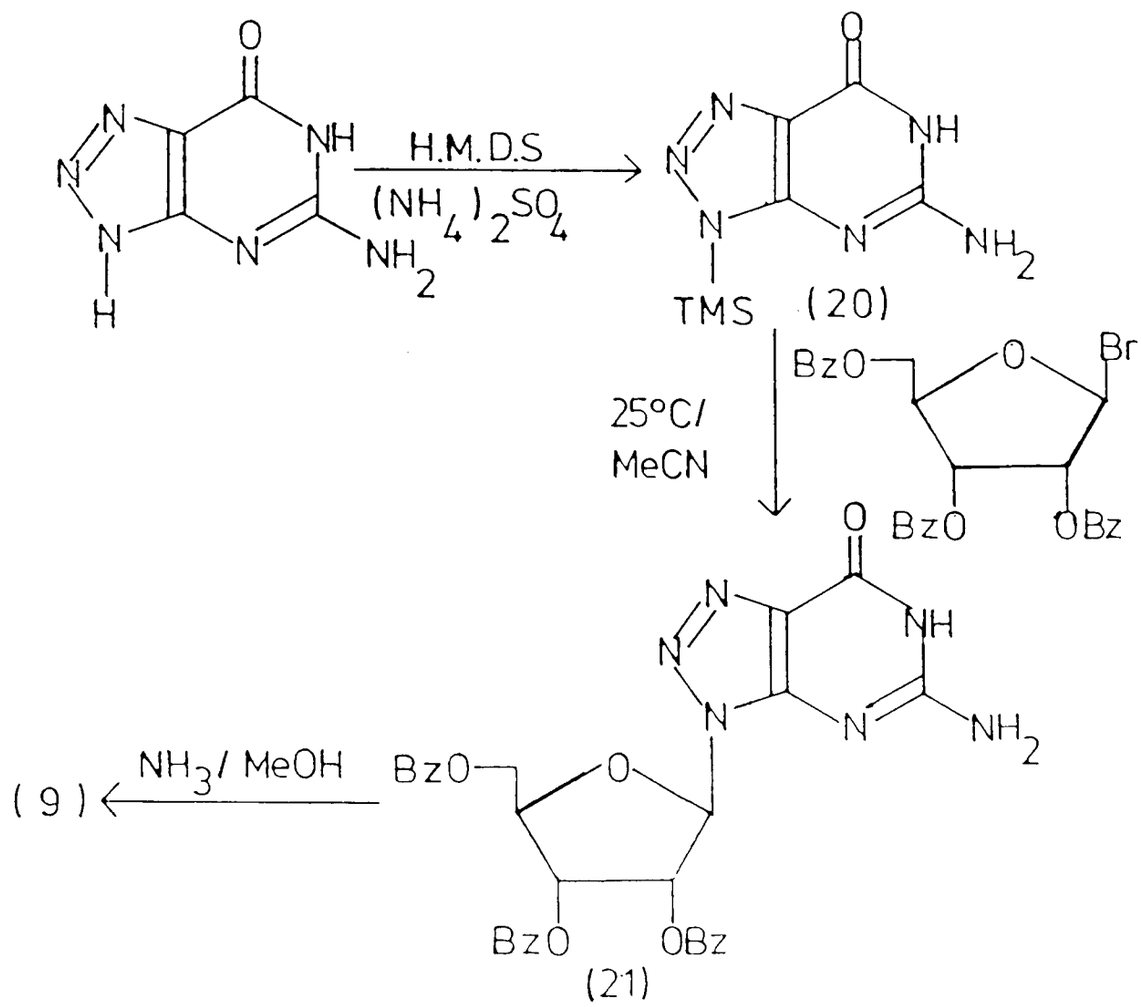
Tolman et al[8] investigated the base promoted 1,3-cycloaddition between 2,3,5-tri-O-benzyl-D-arabinosyl azide (α - and β -anomers) with cyanoacetamide and found that both anomers yielded the α - aminotriazole carboxamide (Scheme 6). It was suggested that the first step was attack by the carbanion generated from cyanoacetamide on the terminal nitrogen of the glycosyl azide followed by attack of the azide nitrogen adjacent to the sugar on the carbon of the nitrile/



Scheme 6: Mechanism of anomeric inversion.

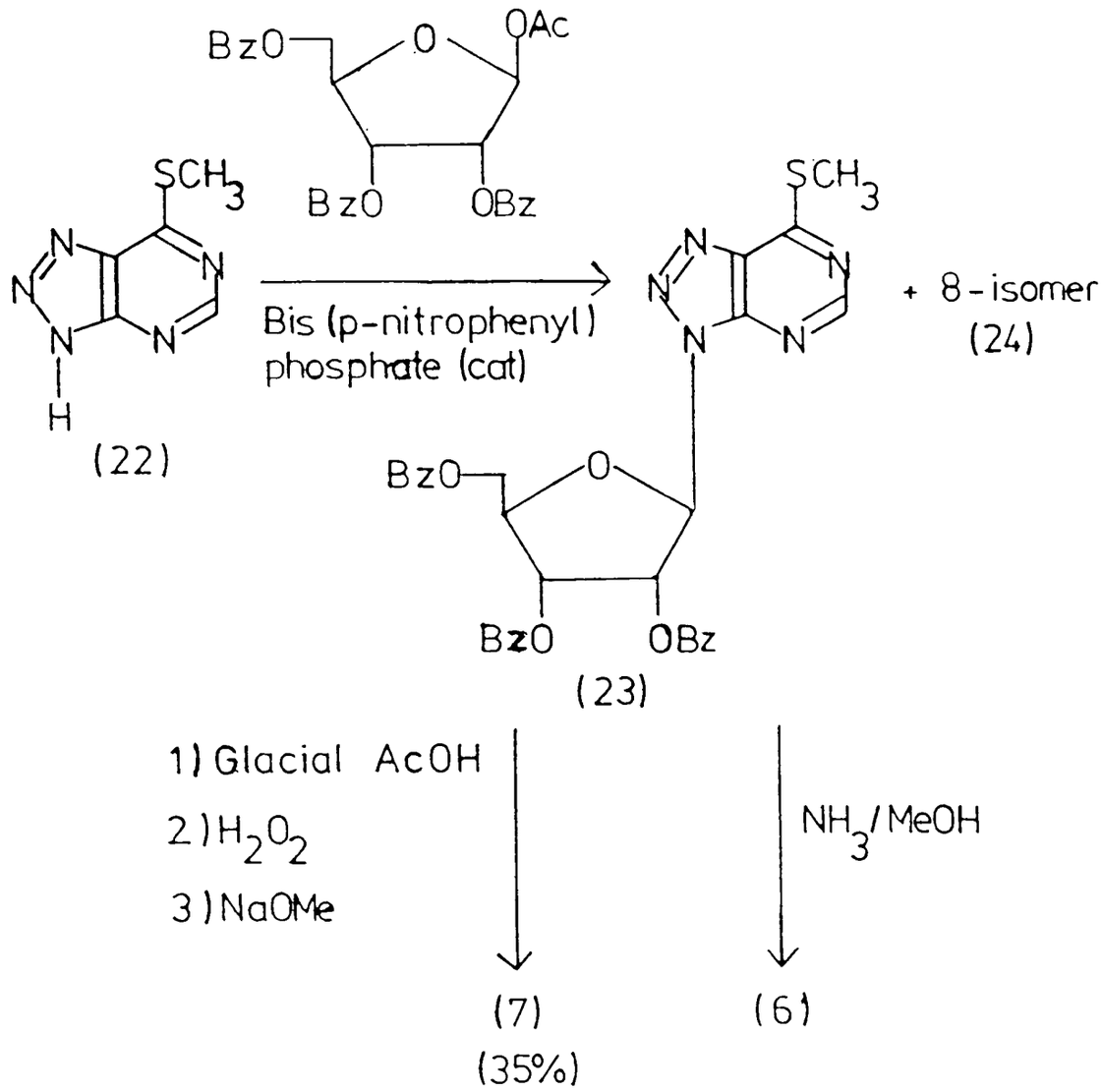
nitrile group. Rearrangement of the intermediate formed after initial attack of the cyanoacetamide carbanion could occur by delocalisation of the negative charge from the carbon adjacent nitrogen to the furanose ring oxygen. The C-N bond of the glycosyl azide would possess some double bond character, thereby permitting anomerisation of C-1.

The same group[9] synthesised 8-azaguanosine by direct glycosylation of the silylated derivative of 8-azaguanine with 2,3,5-tri-O-benzoyl-β-D-ribofuranosyl bromide (Scheme 7).



Scheme 7: Preparation of 8-Azaguanosine by glycosylation of the T.M.S. derivative of 8-azaguanine.

8-Azainosine (7) was prepared by the acid catalysed fusion of 7-methylthio-1,2,3-triazolo[4,5d]pyrimidine (22) with 1-O-acetyl-2,3,5-tri-O-benzoyl-ribofuranose at 210°C, followed by reaction with glacial acetic acid and hydrogen peroxide with subsequent deprotection (Scheme 8). A by-product of the first step was the

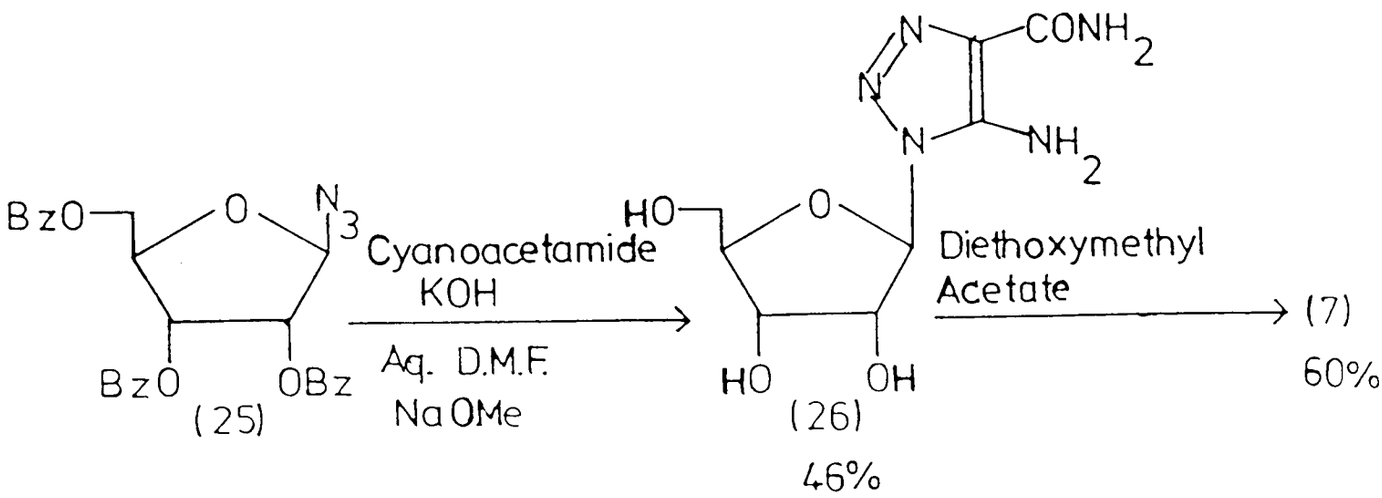


Scheme 8: Preparation of 8-azainosine and 8-azaadenosine by glycosylation of 7-methylthio-1,2,3-triazolo[4,5d] pyrimidine.

2-/

2-ribofuranosyl-1,2,3-triazolopyrimidine (24). Treatment of (23) with methanolic ammonia yielded 8-azaadenosine (6).

These syntheses are examples of glycosylation of the appropriate azapurine bases, but two other potential routes exist to 8-azapurines. Firstly, there is the triazole ring closure on a preformed pyrimidine nucleus, which in the case of azapurine ribonucleoside synthesis was of limited use. The second route is the pyrimidine cyclisation on a preformed triazole and this was successfully carried out in the synthesis of (7). 2,3,5-Tri-O-benzoyl-β-D-ribofuranosylazide (25) was cyclised with cyanoacetamide in aqueous D.M.F. containing KOH to give a reasonable yield of 5-amino-4-carboxamido-1-β-D-ribofuranosyl-1,2,3,-triazole (26) (Scheme 9). Treatment of (26)



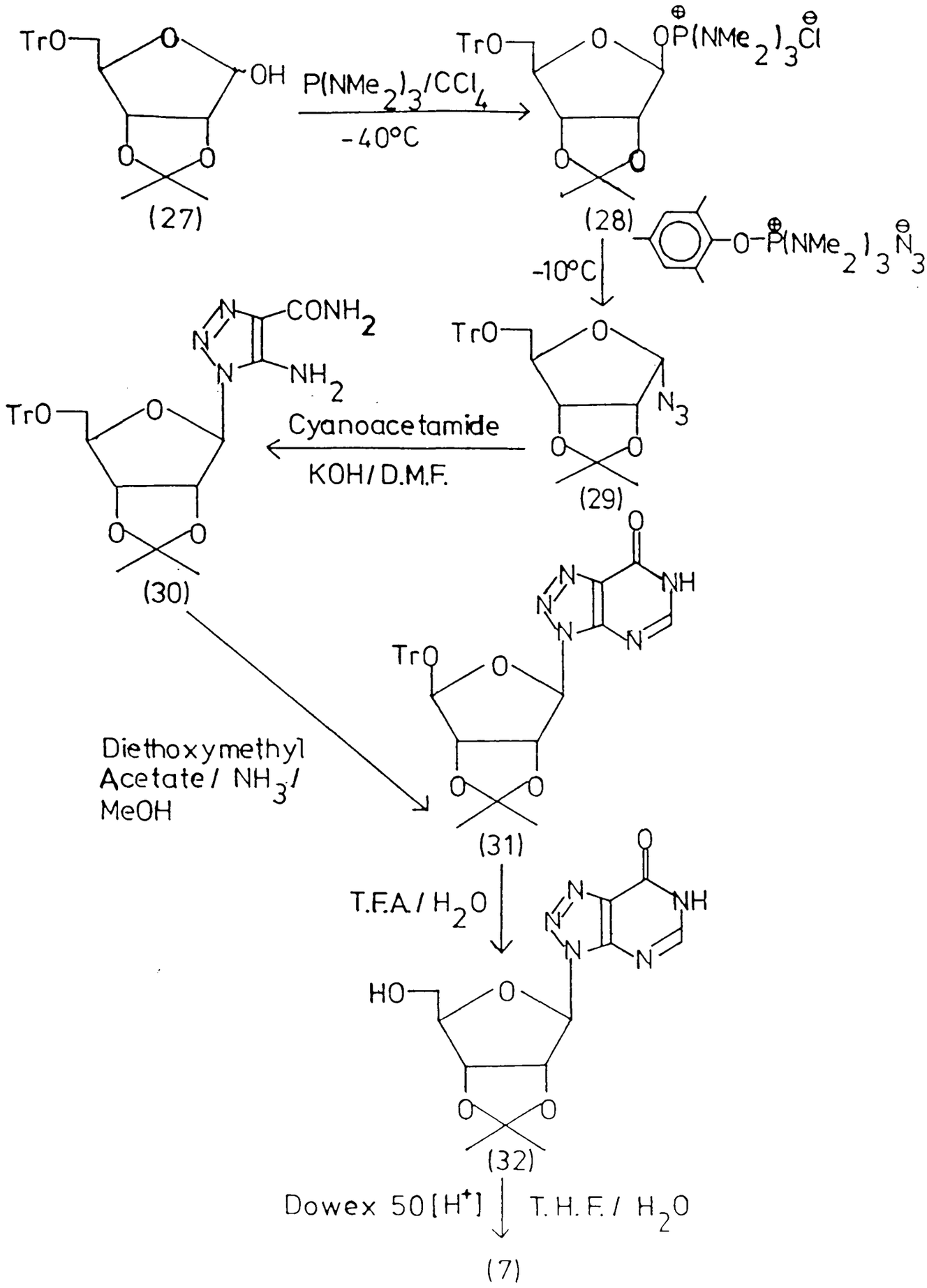
Scheme 9: Preparation of 8-azainosine from 2,3,5 tri-O-benzoyl ribofuranosylazide.

with/

with diethoxymethyl acetate furnished 8-azainosine (7) identical in every respect with (7) prepared by direct glycosylation method. This work confirmed the anomeric linkage as β - and N-3 as the site for (7) and other nucleosides derived from (23). In this work the nature of the sugar was such that the β -configuration was assured by the trans rule.[10]

Recently Gross et al[11] described an improved preparation of 8-azainosine from 5-O-trityl-2,3-O-isopropylidene-D-ribofuranose (27) (Scheme 10). The protected ribofuranose was converted to the 1-azidoglycoside (29) via the phosphonium salt (28). The advantage of this method was that one could avoid having to prepare unstable glycosyl halides.[12] The triazole ring was formed by using the previously described procedure of Tolman. With the azide (29) which was of α -configuration, anomeric inversion was observed to furnish the β -1,2,3-triazole-ribonucleoside (30). The azapurine nucleoside was prepared by the action of diethoxymethyl acetate on (30) followed by treatment with methanolic ammonia. Detritylation of (31) yielded 2',3'-O-isopropylidene 8-azainosine (32). The desired product was obtained when (32) was treated with Dowex 50[H^+] resin. There are two distinct advantages of this method over the best one previously reported.[9] Firstly, the synthetic route provided a particularly efficient means of converting sugar with a free hemiacetal hydroxyl group to 8-azapurine nucleosides, and, secondly, in this particular case, the yield was increased, i.e., an overall yield of 30% with six steps against 13% with seven steps.

Scheme 10:/



Scheme 10: Preparation of 8-azainosine from 5-O-trityl-2,3-O-isopropylidene-D-riboturanose.

1.2. 8-Azapurines

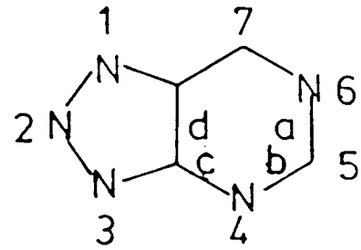
8-Azapurine ribonucleosides appear to function by incorporating themselves into m R.N.A., therefore disrupting the codons, and thus preventing the synthesis of proteins in tumour cells. These 8-azapurine ribonucleosides can be regarded as intermediates between the modified R.N.A. and 8-azapurines. It is usual to use 9-alkylated 8-azapurines in vivo which are a source of the 8-azapurine. These N-9 alkylated 8-azapurines appear to function by the enzyme mediated dealkylation at N-9 followed by incorporation into R.N.A. or the intermediate ribonucleoside.

8-Azapurines are the nitrogen analogues of naturally occurring purine bases where the methine group in the 2- position of the imidazole ring is replaced by nitrogen. The first recorded preparation of an 8-azapurine was in 1901[13] but it was only in 1945 that the importance of 8-azapurines to chemotherapy was realised.[14] Since then, most of the synthetic work has been carried out by the two particular research groups, J. A. Montgomery and A. Albert. The biochemistry of several types of 8-azapurines has been reviewed.[15]

STRUCTURE AND NOMENCLATURE

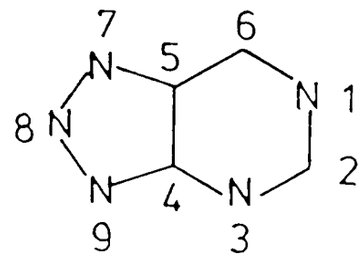
The use of the name "8-azapurine" is contrary to present I.U.P.A.C. nomenclature, but because of its widespread use in biological and biochemical literature, it has been permitted as a trivial name./

name. During the 1960s the term used systematically was "1,2,3,4,6-penta-azaindenes". In 1971 the systematic name became "1,2,3-triazolo-[4,5-d]pyrimidine", thus indicating the two constituent components, and the bonding in the molecule as shown below.



1,2,3-Triazolo-[4,5-d]pyrimidine (fusion numbering)

In some literature where "8-azapurine" trivial nomenclature is used the method of numbering is shown below.



8-Azapurine (trivial numbering)

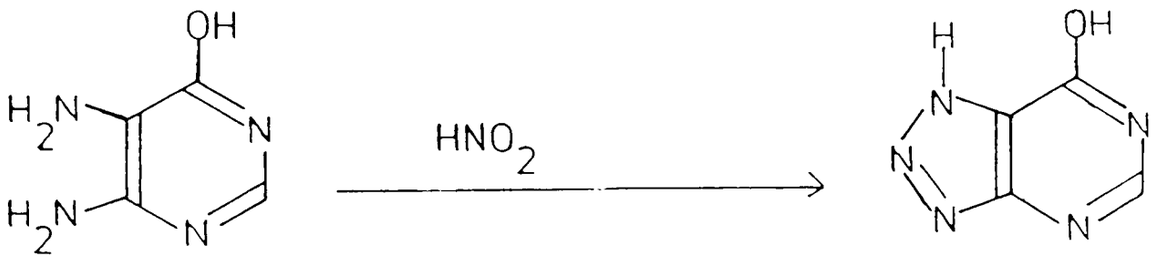
METHODS OF SYNTHESIS OF 1,2,3-TRIAZOLO-[4,5-d]PYRIMIDINES

A considerable amount of research effort has been devoted to the synthesis of 8-azapurine derivatives and two approaches are evident, that/

that based on the construction of the 8-azapurine ring system from a preformed pyrimidine ring, and that based on the utilisation of a preformed 1,2,3-triazole.

1,2,3-Triazolo-[4,5-*d*]pyrimidines from pyrimidine precursors

The above mentioned method was most commonly employed by the earlier workers in this area. In 1945 during a study into methionine and purine antagonists in relationship to sulphonamides Roblin *et al* diazotised various 4,5-diaminopyrimidines to obtain the appropriate 1-substituted-1,2,3-triazolo-[4,5-*d*]pyrimidines[14] (Scheme 11).



(33) (34)

Scheme 11: Preparation of 8-azahypoxanthine by diazotisation of 4,5-diamino-6-hydroxypyrimidine

The analogues of guanine, adenine, and xanthine were also prepared by this method and the new compounds were useful as purine antagonists of the metabolites which acted as sulphonamide inhibitors.

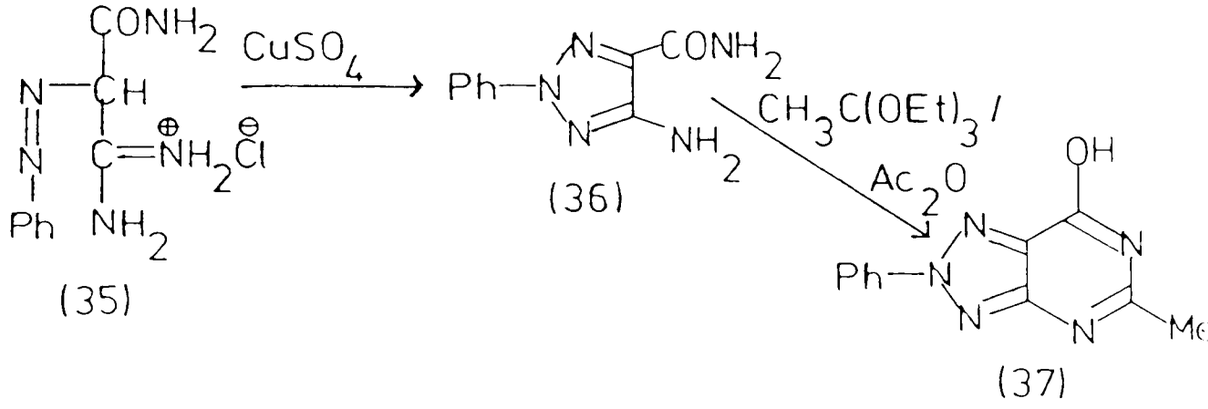
By using appropriate substituents on position -2 and -6 of the 4,5-diaminopyrimidines it was possible to functionalise the 1,2,3-triazolo-[4,5*d*]pyrimidines at positions -5 and -7 respectively.

None/

None of the derivatives prepared contained any substituents on the triazole ring nitrogens until Benson, Hartzel, and Savell prepared samples with aryl groups on the 2- position of the triazole by oxidation of the corresponding 4-amino-5-arylazopyrimidines.[16]

1,2,3-Triazolo-[4,5-*d*]pyrimidines from 1,2,3-triazole precursors

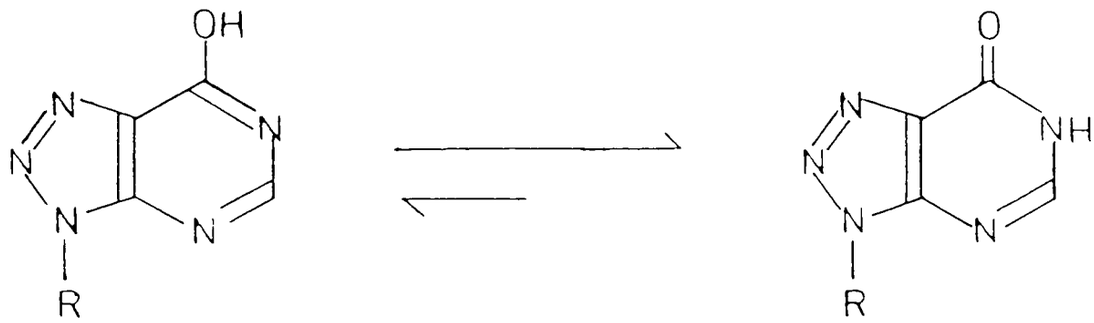
The second, and more widely accepted route to the 8-azapurines is a pyrimidine ring closure on an appropriate 1,2,3-triazole. This method is preferable because it generally permits greater flexibility both in the variation of the substituents and in altering the oxidation state of the pyrimidine ring. In 1956, Richter and Taylor[17] prepared 7-hydroxy-5-methyl-2-phenyl-1,2,3-triazolo-[4,5-*d*]pyrimidine (37) by oxidizing phenylazomalonamide amidine (35) with ammoniacal copper sulphate to the triazole (36), followed by cyclisation with triethyl orthoacetate and acetic anhydride (Scheme 12).



Scheme 12: Preparation of 7-hydroxy-5-methyl-2-phenyl-1,2,3-triazolo-[4,5-*d*]pyrimidine

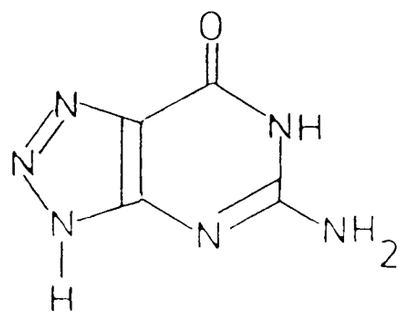
The/

The utility of 1-alkyl or 1-aryl-5-amino-4-carboxamido-1,2,3-triazoles was realised[2, 3, 18] and Dornow and Hellberg[18] condensed these triazoles with formamide to furnish the expected 8-azapurines with various substituents in the 9-position. Another cyclising reagent was triethyl orthoformate, although formamide appears to be preferred. During this work, the tautomerism that exists between hydroxy-azapurines and azapurinones was noted (Scheme 13).



Scheme 13: Tautomerism in hydroxy-8-azapurines

Between 1966 and 1981, Adrien Albert made a significant contribution to the chemical literature on 8-azapurine chemistry. His original interest was stimulated by a desire to synthesise a more effective form of "8-azaguanine" [ ]. This compound was found to inhibit



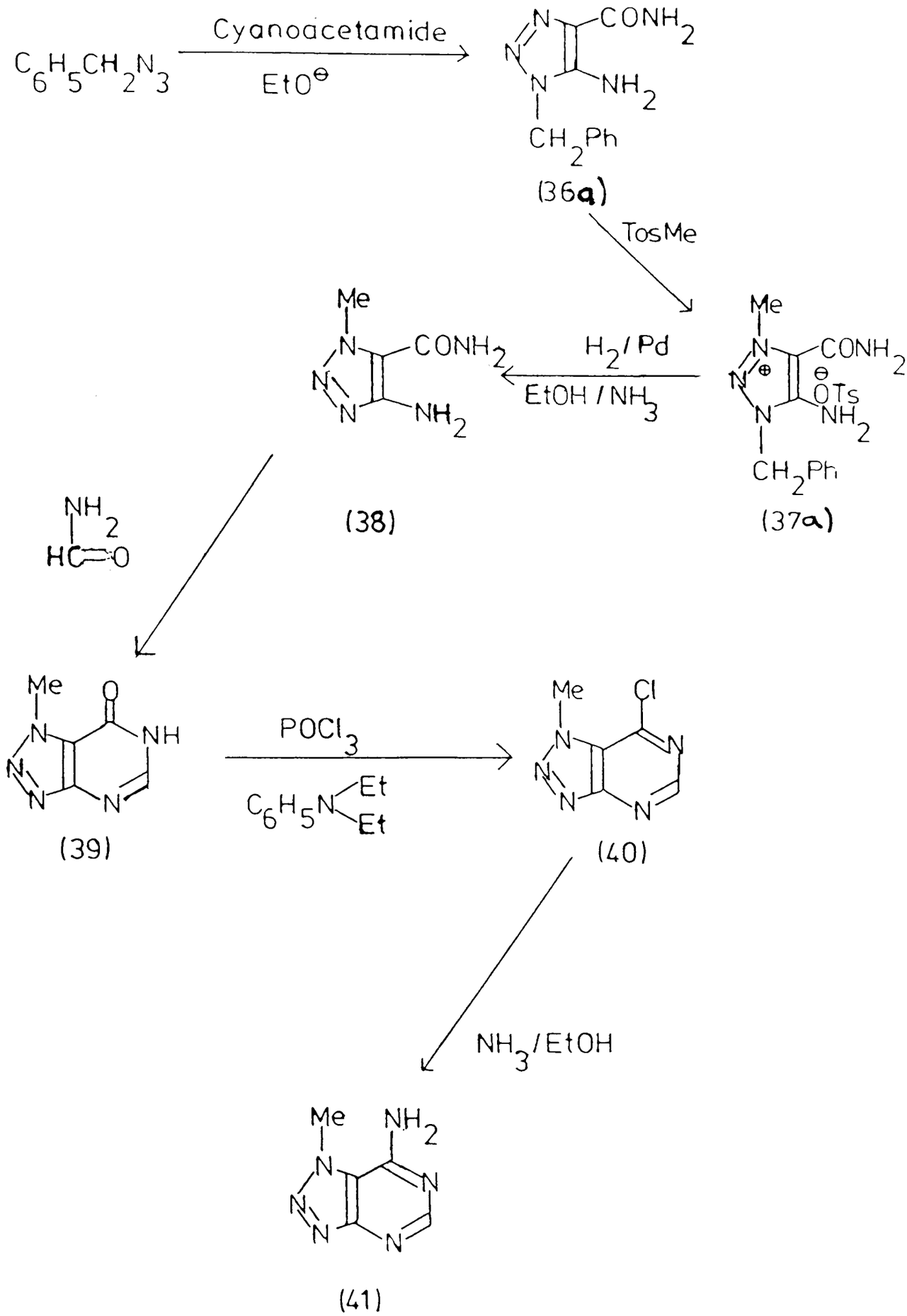
8-azaguanine

experimentally induced cancer in mice and rats without harm to the/

the host.[19] However it proved inactive against various types of cancer in hospital patients and its failure was attributed to rapid metabolism of the substance by guanylase.

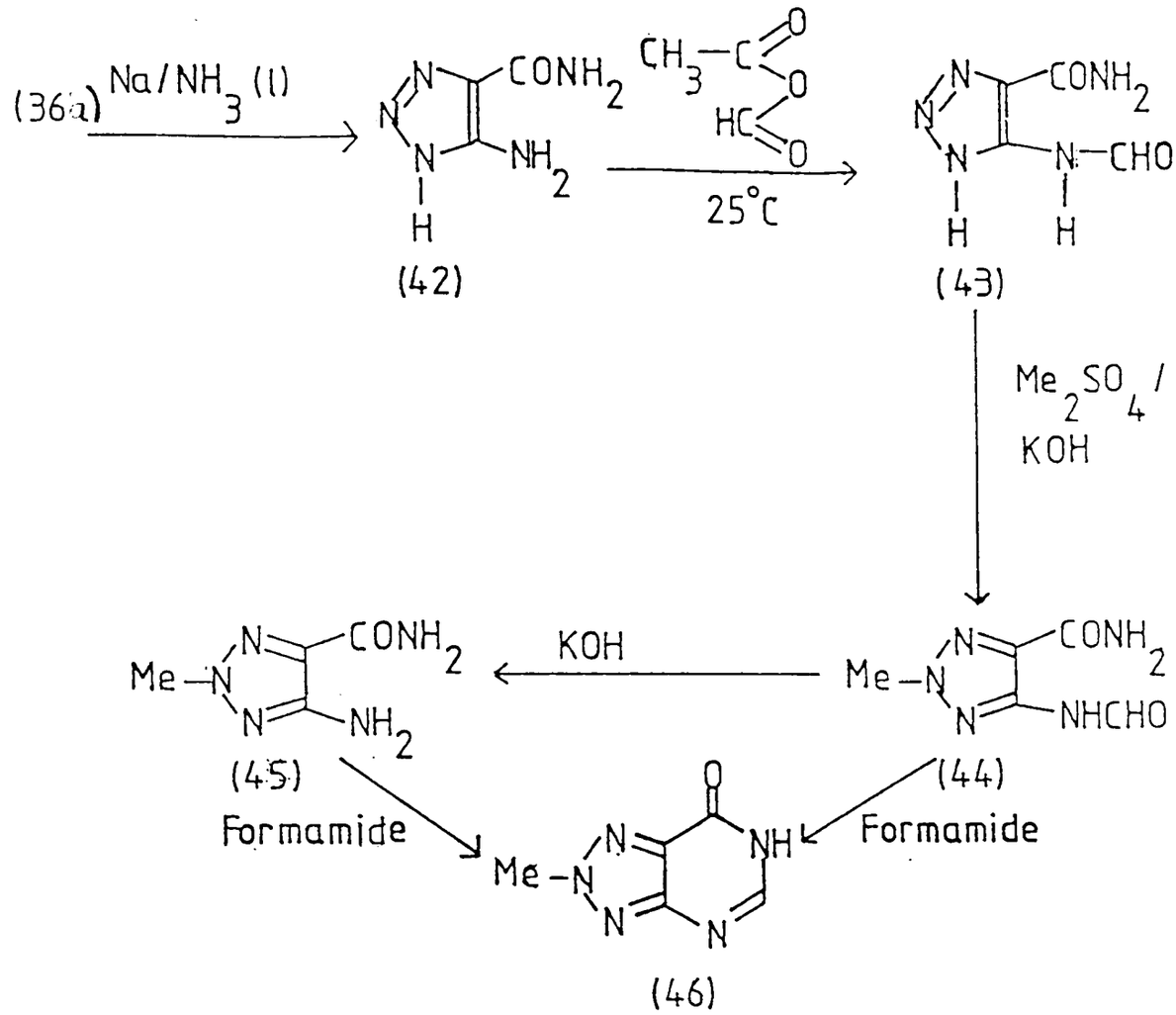
Albert decided that it would be interesting to examine 8-azapurines alkylated in the 7- or 8- positions because he thought that these new compounds would throw fresh light on purine metabolism, and even provide drugs free from the defects of 8-azaguanine.[20] The preparation of 7-methyl-8-azaadenine is outlined in Scheme 14. The initial triazole (36a) was prepared readily from the base induced cycloaddition of cyanoacetamide to benzyl azide.[21] Brief heating of this triazole with methyl toluene-p-sulphonate quaternised (36a) to the 1,2,3-triazolium tosylate (37a). Debenzylation was accomplished by catalytic hydrogenolysis over palladium and this salt was converted to 5-amino-4-carboxamido-3-methyl-1,2,3-triazole (38), which, when heated with formamide, cyclised to the 8-azapurin-6-one (39) in an excellent yield. Treatment of (39) with phosphorous-oxychloride and diethylaniline readily yielded 6-chloro-7-methyl-8-azapurine (40). On gentle heating with ethanolic ammonia (40) gave the 8-azaadenine derivative (41).

Scheme 14:/



Scheme 14: Preparation of 7-methyl-8-azaadenine

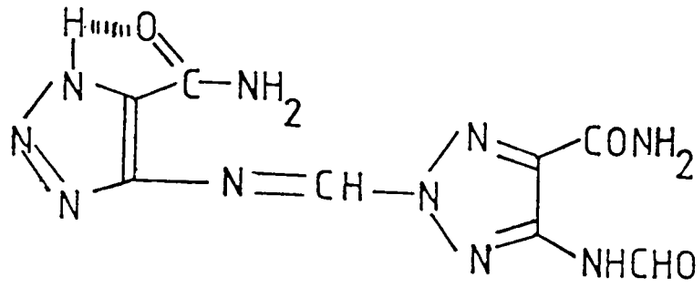
8-Methyl-8-azapurines were obtained by the method indicated in Scheme 15.[22] Debenzylation of (36a) furnished 5-amino-1,2,3-triazole -4-carboxamide (42). (43) was methylated with methyl sulphate



Scheme 15: Preparation of 8-methyl-8-azahypoxanthine

in aqueous alkali to give a 1:1 mixture of the 2-methyl and 1-methyl derivatives. The complete absence of the 3-methyl derivative indicated that the 4-carboxamido group strongly hindered methylation of the 3- position. This suggested that a small increase in size of the 5- substituent could generate enough/

enough steric hindrance to suppress methylation in the 1- position. Accordingly (42) was formylated to an anhydro-dimer (47) of 5-formamido-1,2,3-triazole-4-carboxamide (43) which was instantly



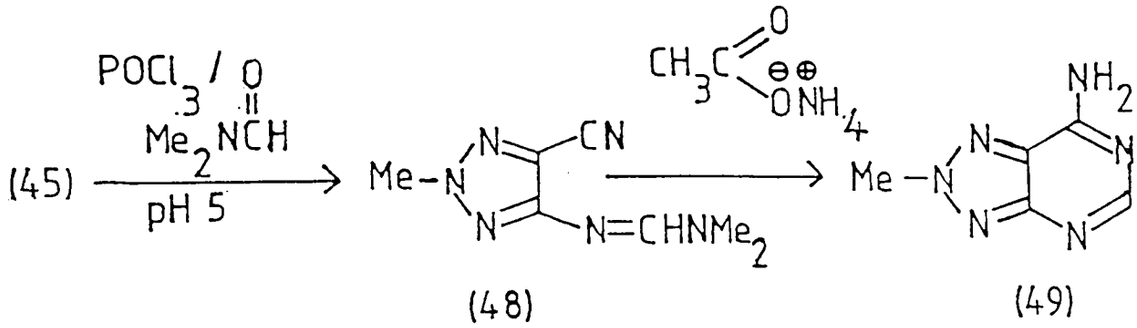
(47)

converted to the monomeric anion by aqueous potassium hydroxide. Methylation of (43) took place exclusively in the 2- position to give 5-formamido-2-methyl-1,2,3-triazole-4-carboxamide (44). This formyl triazole (44) was deformylated to the corresponding amine (45), and both substances were cyclised by boiling in formamide, to 8-methyl-8-azahypoxanthine (46) in yields of 94 and 85% yields respectively.

Albert also compared the relative usefulness of pyrimidine and 1,2,3-triazole intermediates for making 8-azapurines, with or without an alkyl group in the 9- position.[23] 5-Amino, 5-amino-1-benzyl, and 5-amino-1-methyl-1,2,3-triazole 4-carboxamides when condensed with formamide gave 8-azapurin-6-one, 9-benzyl, and 9-methyl-8-azapurin-6-one. Of these three reactions the first was not as useful for preparing 6- substituted -8-azapurines, as/

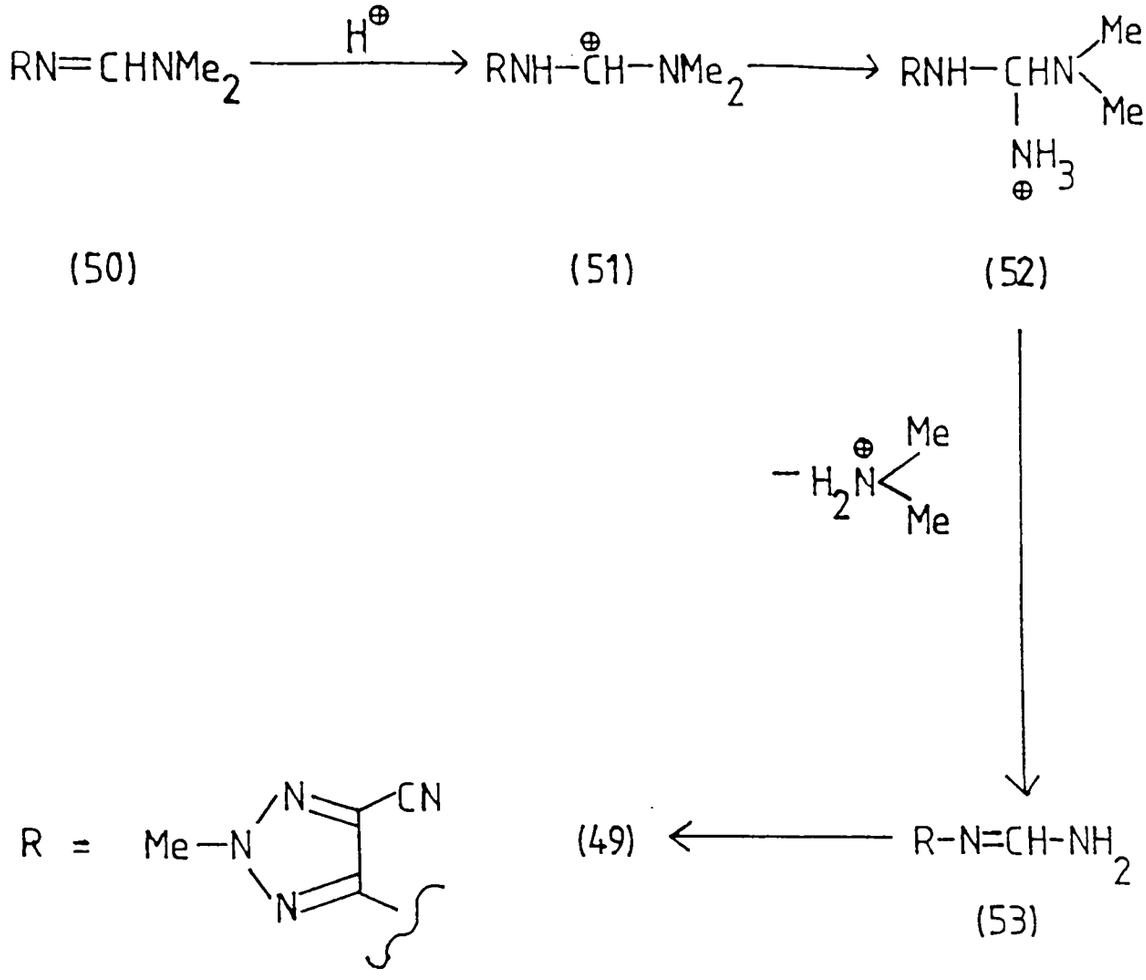
as were the 6- substituted 4,5-diaminopyrimidines.

In a search for new routes, cyano-amidines of the 1,2,3-triazole series were studied because of the facility of addition across the triple bond of a cyano- group.[24] For example, (45) was reacted with phosphoryl chloride and N,N[1]-dimethylformamide to form the cyano-amidine-triazole (48) in an almost quantitative yield (Scheme 16). Cyclising of (48) with ammonium acetate provided



Scheme 16: Preparation of 8-methyl-8-azaadenine from a cyano-amidine-triazole

a high yield of the 8-azaadenine (49). The following mechanism was suggested (Scheme 17).

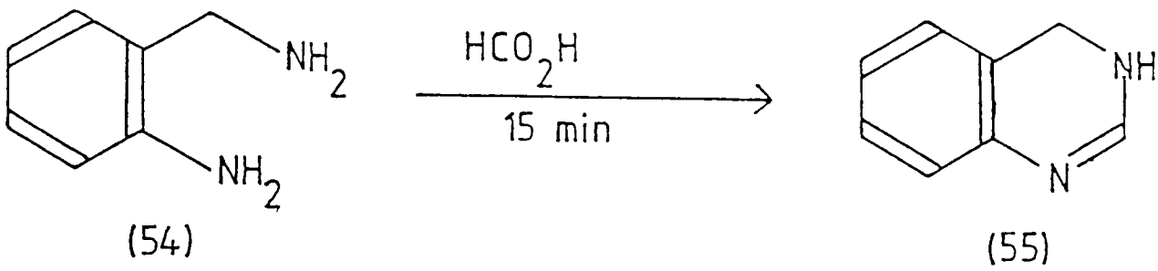


Scheme 17: Mechanism of formation of 8-methyl-8-azaadenine from 5-Dimethylaminomethyleneamino-2-methyl-1,2,3-triazole-4-carbonitrile

In the scheme illustrated the amidine group in (50) forms a carbocation, the delocalised charge of which resides partly on the carbon atom as in (51). This electrophilic reagent attacks ammonia to give (52). The species (52) undergoes fission to dimethyl ammonium and the primary amidine. This primary amidine cyclises/

cyclises with the nitrile group to yield the title product. The process of ring closure is independent of pH.

Albert turned his attention to 1,6-dihydro-8-azapurines for a number of reasons. These compounds were little explored and only indirectly accessible. It was also observed that these reduced 8-azapurines were stable to atmospheric oxidation unlike 1,6-dihydropurines.[25] Previously, all the known examples had been prepared by reduction of the corresponding 8-azapurines.[26] It was envisaged that 1,6-dihydro-8-azapurines were to be prepared from suitable 1,2,3-triazoles.[27] A precedent for a similar type of reaction lay in the Gabriel-Colman synthesis of 3,4-dihydroquinazoline (55) from 2-aminobenzylamine (54)[28] (Scheme 18). The appropriate



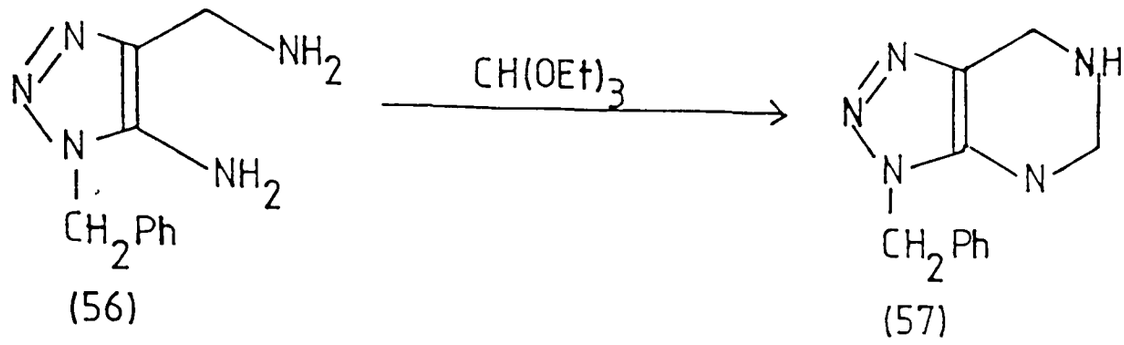
(54) (55)

Scheme 18: The Gabriel-Colman preparation of 3,4-dihydroquinazoline

route lay in cyclising 1,2,3-triazoles with an amino-group in position 5- of the triazole ring and an aminomethyl-group in position-4.

Preliminary work centred around using triethyl orthoesters to provide the final carbon atom, however only a trace of 9-benzyl -1,6-dihydro-8-azapurine (57) was obtained from 5-amino-4-aminomethyl-1-benzyl-1,2,3-triazole (56) with triethyl orthoformate in boiling ethanol/

ethanol[29] (Scheme 19). A dramatic increase in reactivity occurred

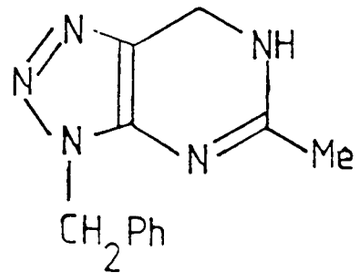


(56) (57)

Scheme 19: Preparation of 9-benzyl-1,6-dihydro-8-azapurine

when the triazole (56) was replaced by one of its salts. Thus triethyl orthoformate and the hydrochloride of (56) gave the required product in a 76% yield. Use of the acetate salt led to a bis-triazole.

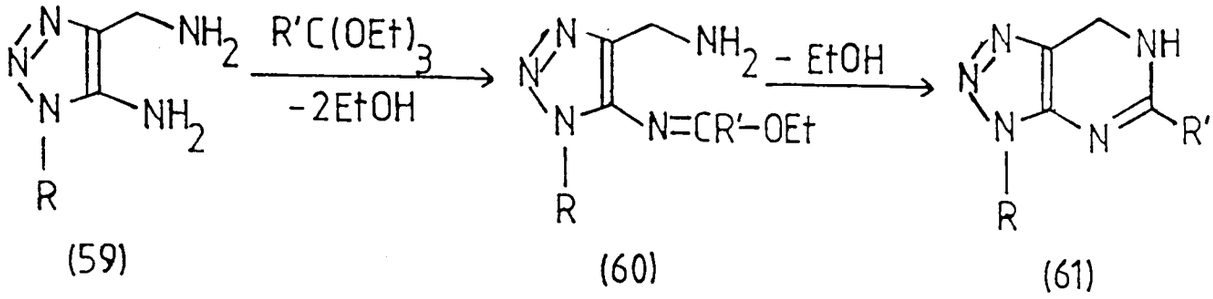
Paradoxically, the hydrochloride of (56) proved useless but the acetate highly suitable for condensing with triethyl orthoacetate to give 9-benzyl-1,6-dihydro-2-methyl-8-azapurine (58) in a 65% yield. The results can be explained by looking at the proposed



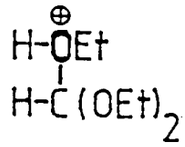
(58)

mechanism of the reaction. Orthoesters prefer reacting with aromatic rather than aliphatic primary amino groups because of extended/

extended conjugation stabilizing the intermediate (60) (Scheme 20).



Scheme 20: Reaction of orthoesters with 5-amino-4-aminomethyl triazoles

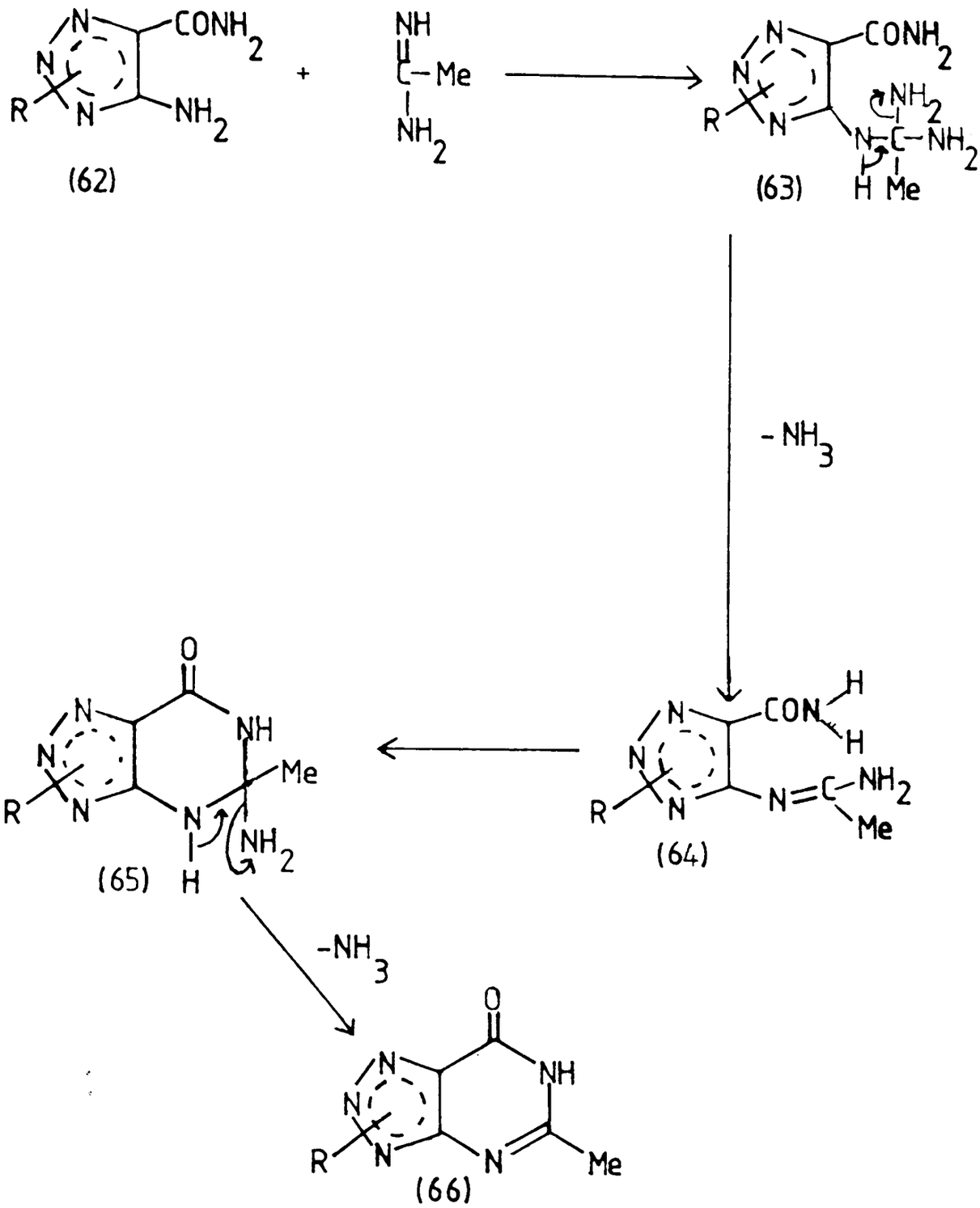
The beneficial effects of using a salt of the starting material may be due to the fact that the salt would be a proton source which would provide the orthoester with a better leaving group (i.e., ). The difference between the results of using salts of strong and of weak acids (taken in conjunction with electronic differences between the methylene and ethylidene groups) is seen as regulating the ionization of the aminomethyl group and so (in a favourable combination) facilitating ring closure before a side reaction can occur.

In developing this work it was found that amidines could replace the orthoesters. The best yields were obtained when the acetates of amidines were condensed with the free triazoles (59).

The utility of amidines as ring closure reagents was thus realised and/

and Albert, who wished to obtain 2- substituted 8-azapurin-6-ones, decided to react 5-amino-1,2,3-triazole-4-carboxamides with amidines.[30] The synthetic problem being solved here was the poor reactivity of acetamide and its homologues and the failure of benzamide to react with the 5-amino-1,2,3-triazole-4-carboxamides to give the appropriate 2- substituted 8-azapurin-6-one. The reaction of formamide with the triazoles to the 2- unsubstituted 8-azapurin-6-ones is well documented.[20, 22, 24, 25] It was proposed that amidines would react with the triazoles according to Scheme 21. Initial attack of the amidine on the aromatic amino group would lead to the tetrahedral intermediate (63) which would lose ammonia in consecutive steps to yield the desired product substituted in the 2- position with the characteristic group of the amidine. The reactivity of the amidines was as follows: trichloroacetamidine $\simeq$ benzamidine $>$ formamidine $>$ acetamidine. Generally good yields were recorded when the triazole component was varied except in the 1-methyl and 1-benzyl triazoles. It was not clear why this should be the case, but Albert suggested that the electron donating 1-alkyl substituents may have impeded the splitting off of a proton from the 5-amino group. In the examples where these triazoles were reacted with formamide and the expected products were obtained readily, then it was suggested that the larger positive charge on the reactive carbon atom in formamide, compared with that on acetamidine, may overcome this difficulty.

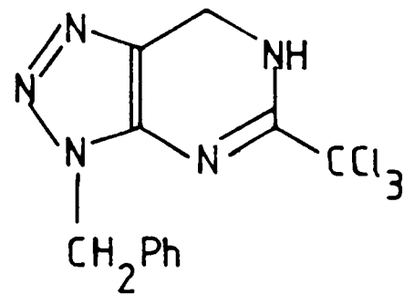
Scheme 21:/



Scheme 21: Reaction of acetamidine with a 5-amino-1,2,3-triazole-4-carboxamide

The synthesis of 1,6-dihydro-8-azapurines has been discussed previously and one of the compounds prepared was highly active against/

against colon and mammary cancers. This compound was 9-benzyl-1,6-dihydro-2- trichloromethyl-8-azapurine (67) which was also the most polar. The desirability of preparing other analogues



(67)

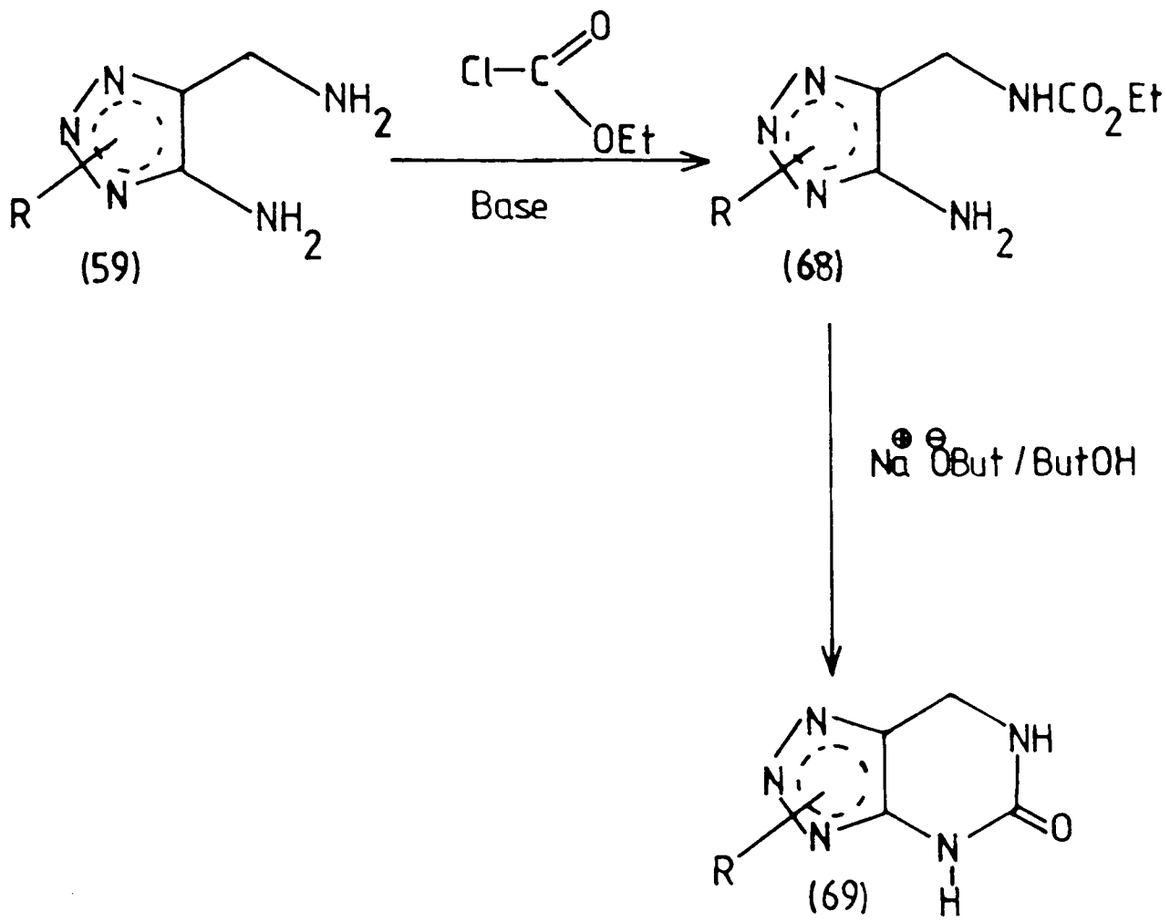
with varying polar groups in the 2- position was suggested.[31] Initial investigations were performed to yield the 2-oxo and 2-amino substituents. The latter compounds were derived from the reaction of suitable 5-amino-4-aminomethyl-1,2,3-triazoles with cyanogen bromide. The various yields of N-alkyl-8-azapurines are shown in Table I. The fully aromatic 8-azapurines were obtained smoothly by oxidation with potassium permanganate at room temperature.

R	Yield (%)
7 - Me	75
9 - Me	55
9 - CH_2Ph	40

Table I: Yields of 2-amino-N-alkyl-1,6-dihydro-8-azapurines

The/

The 2-oxo-derivatives were obtained in 2 steps from the aminomethyl-amino-triazoles (Scheme 22) via the 4-ethoxycarbonylaminomethyl-1,2,3-triazoles (68). The overall



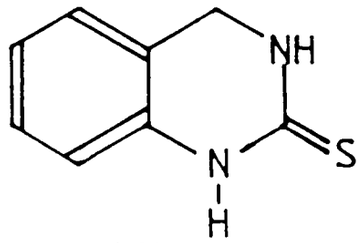
Scheme 22: Preparation of 2-oxo-1,6-dihydro-8-azapurines

yields were good especially in the 9-benzyl example (85%).

In a similar preparation of the 2-thione derivatives an interesting reaction was observed.[32] It had been long known that when

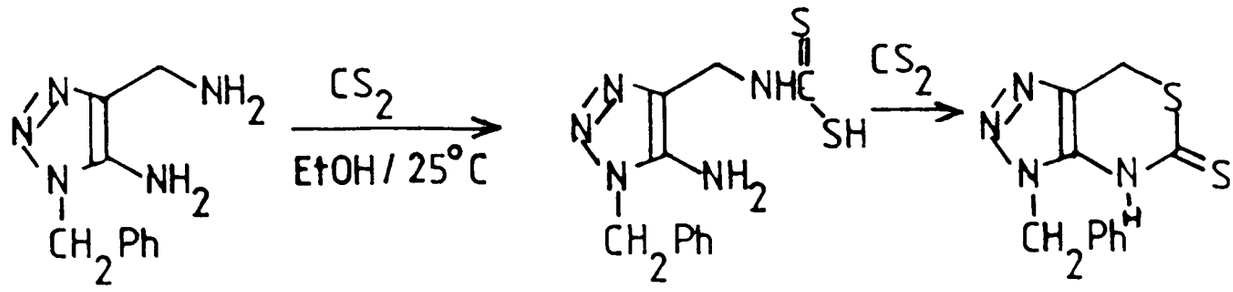
2-/

2-aminobenzylamine was heated with carbon disulphide, good yields of 3,4-dihydroquinazoline-2-[1H]-thione (70) were obtained.[33] Similarly 5-amino-4-aminomethyl-2-(and-3-)methyl-1,2,3-triazole gave quantitative yields of the corresponding N-methyl-1,6-dihydro-8-azapurin-2-thione when heated with carbon disulphide and triethylamine in pyridine.[34] The 1-methyl and the 1-benzyl analogues gave unexpected products (Scheme 23) in that one nitrogen



(70)

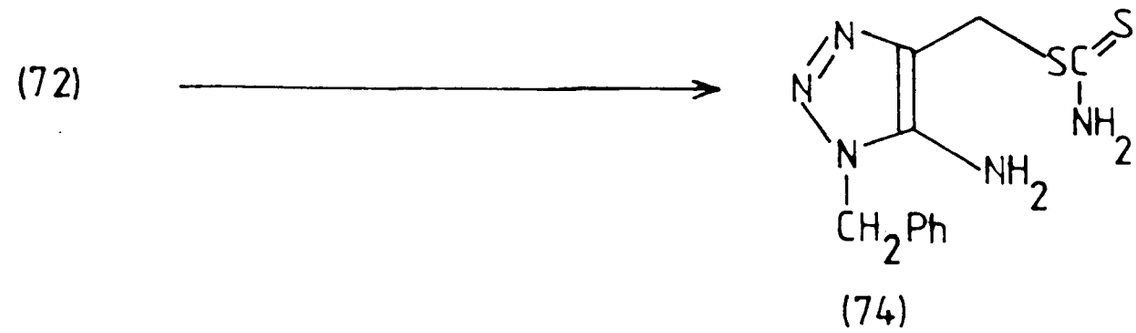
atom was lost and one sulphur atom was gained.



Scheme 23: Unexpected preparation of a triazolothiazine

The nucleus of this compound was hitherto unknown. Albert suggested that (73) was formed when there was a methylene shift in (72) from nitrogen to sulphur to yield the non-acidic compound (74)/

(74) (Scheme 24). This unprecedented shift was observed by changes in the N.M.R. spectra of (72), and it was explained that

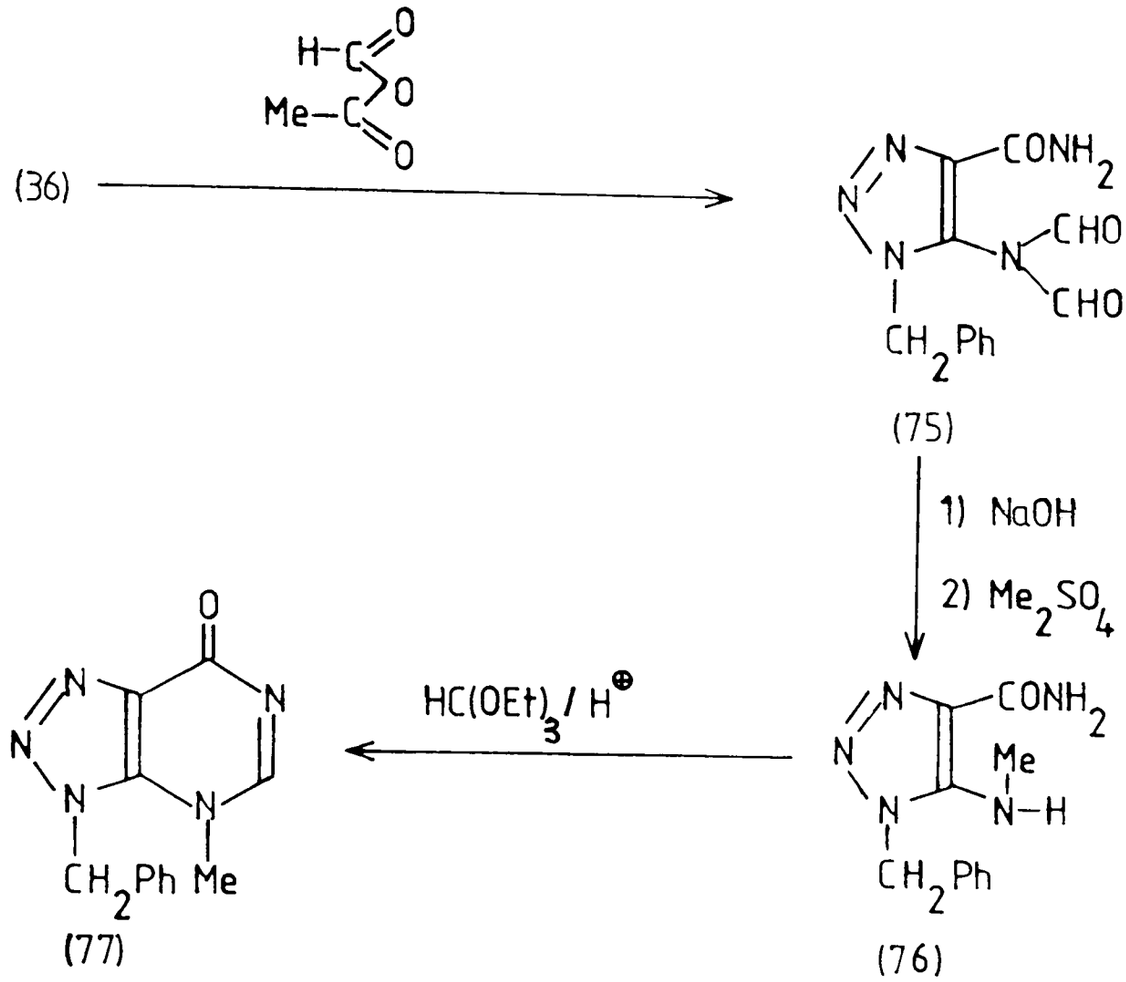


(74)

Scheme 24: N ⟶ S methylene shift

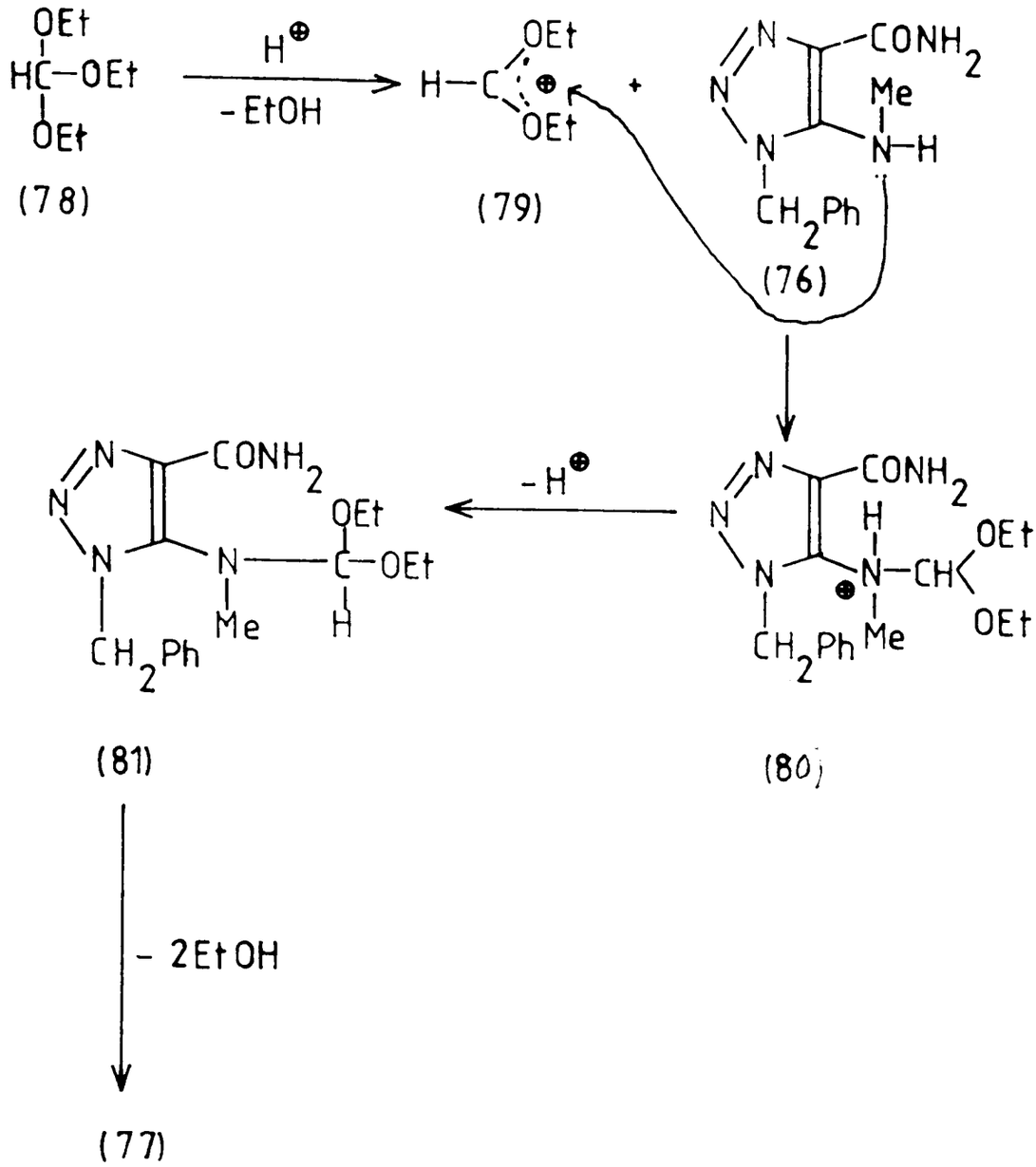
in this case an electron rich carbon bound sulphur atom attacked the electron depleted 4-methylene group simultaneously breaking the CH_2-NH_2 bond.

Following the common practise of N-alkylating heterocyclic drugs to obtain a depot effect, many 8-azapurines have been methylated in the 1-, 7-, 8-, and 9- positions. The synthesis of 3-methylated 8-azapurines proved more difficult, and two reasons were suggested for this observation: (i) the 3-alkyl series had less stabilizing conjugation than any isomeric N-alkyl series, and (ii) a transfer of alkyl groups from the 3- to the 9- position could have taken place if instability led to opening of the pyrimidine ring and then the triazole ring. Accordingly, 5-amino-1-benzyl-1,2,3-triazole-4-carboxamide (36) was converted to 1-benzyl-5-methylamino-1,2,3-triazole-4-carboxamide (76) via the N-diformyl triazole (75) (Scheme 25). The desired product (77) was produced in excellent yield by stirring the methylamino-triazole (76) with triethyl orthoformate/



Scheme 25: Preparation of 9-benzyl-3-methyl-8-azapurin -6-(3H)-one

orthoformate and concentrated hydrochloric acid at ambient temperature. The following mechanism for the cyclisation was suggested (Scheme 26):

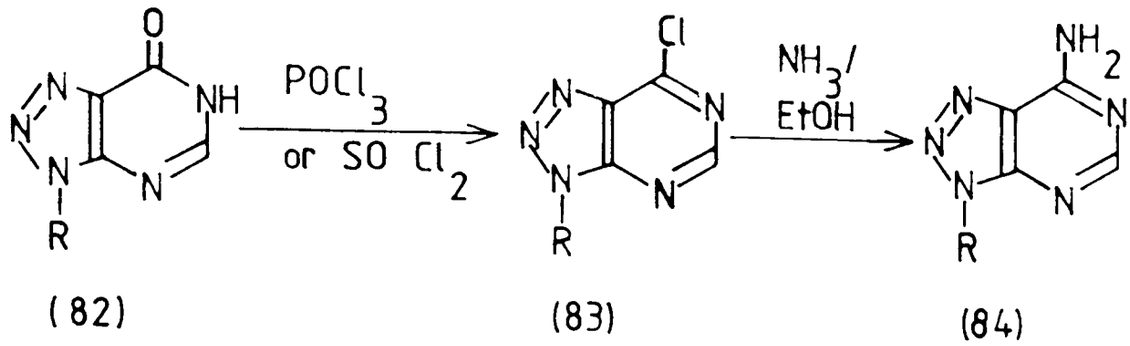


Scheme 26: Mechanism of formation of (77)

Electrophilic attack by the diethoxycarbenium ion (79) which is known to be stabilized by strong acids during the hydrolysis of orthoformate on the 5-methylamino should yield the acetal (81). Subsequent loss of two molecules of ethanol would yield the isolated product (77).[35]

Following/

Following on from some of Albert's earlier work, Da Settimo et al investigated the synthesis of 8-azaadenine derivatives from 8-azapurin-6-ones.[36] The 8-azahypoxanthine derivatives (82) were chlorinated to the 6-chloro-8-azapurines (83) and the reaction of (83) with ethanolic ammonia led to the 8-azaadenine derivatives (84), usually in good yields (Scheme 27).

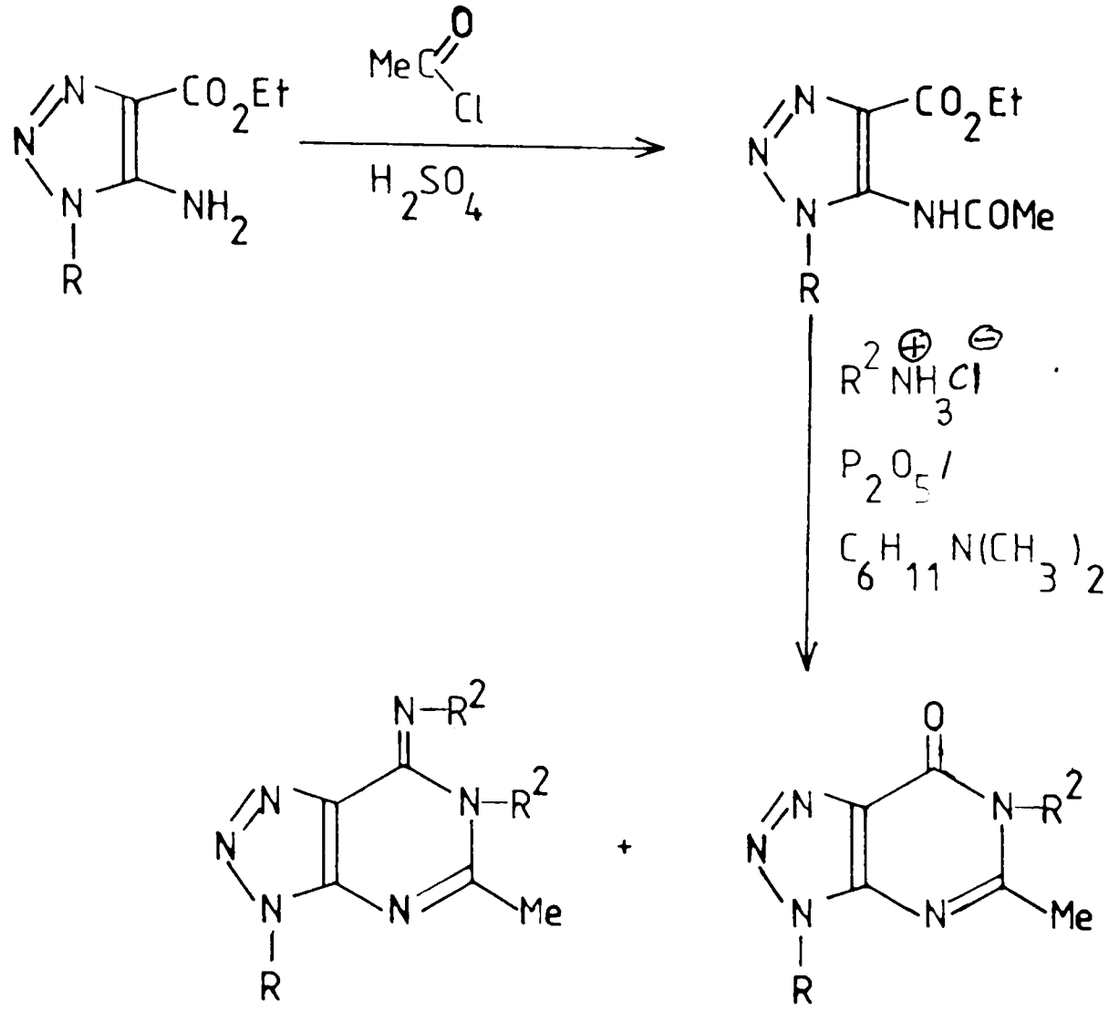


(82) (83) (84)

Scheme 27: Preparation of 8-azaadenine derivatives

Recently Nielsen et al have described the preparation of 8-azapurin--6-ones and 8-azapurin-6-imines from the cyclocondensation of ethyl 5-acetylamino-[1H]-1,2,3-triazole-4-carboxylates with amine hydrochlorides in the presence of phosphorus pentoxide and N,N-dimethylcyclohexylamine (Scheme 28).[37]

Scheme 28:/



Scheme 28: Preparation of 8-azapurin-6-ones and 8-azapurin-6-imines from 5-amino-4-ethoxycarbonyl-triazoles

The yields of the azapurines were low to fair, and the 8-azapurin-6-ones were used for antifungal testing.

BIOLOGICAL ACTIVITY OF 8-AZAGUANINE

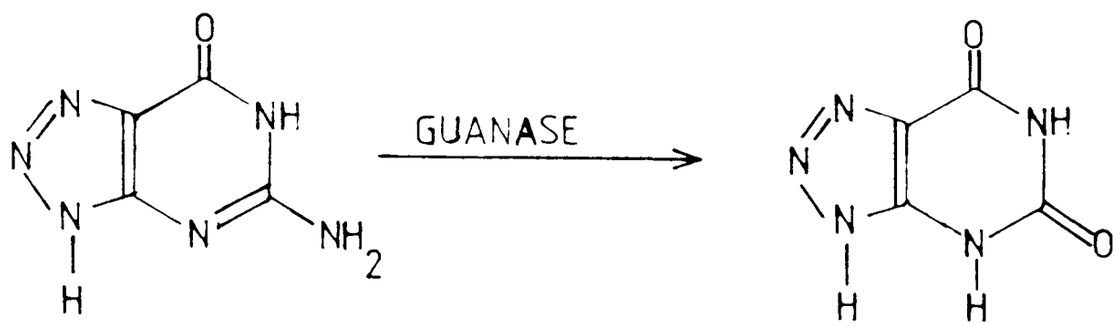
At the biochemical level, 8-azaguanine was shown to exert a strong action on isolated human cells, but proved to be inactive against various/

various types of cancer in hospital patients. Its failure was attributed to rapid metabolism of the substance by guanylase.[38] The biological activity of this compound is quite adequately covered by Mandel.[15] It seems important to relate the biological activity of the drug to metabolism in the tissue or cells.

METABOLISM

(i) Catabolism

In man and in several other living organisms 8-azaguanine was deaminated to 8-azaxanthine, a compound of little biological activity, by the action of guanase (Scheme 29). Tumours with high deaminase



Scheme 29: Decimination of 8-azaguanine

activity would not be expected to be sensitive to the drug, but when 8-azaguanine is administered with 5-amino-imidazole-4-carboxamide, itself without antineoplastic effect, the deamination enzyme was inhibited. The resultant increase in anabolism led to an increase in survival time in tumour bearing animals associated with an increase in toxicity.[39]

Anabolism/

Anabolism

After treatment of mice with 8-azaguanine, 8-azaguanosine and 8-azaguanosine monophosphate were isolated from liver, spleen and L1210 leukaemic cells. It was found that incorporation of 8-azaguanine into nucleic acids took place mainly into the R.N.A. although the isolation of deoxyazaguanosine from digested D.N.A. indicated that some of the analogue had been taken up into D.N.A.

Protein Synthesis

The requirement of guanosine di- or tri-phosphate for protein synthesis suggested another site of action of 8-azaguanine. The inhibition by 8-azaguanine of the inducible enzymes, β -galactosidase and catalase in Staphylococcus aureus, of amylase in a strain of Bacillus subtilis and of induced penicillinase in B. cerius indicated a drug effect on protein biosynthesis.

Summary

The relatively greater anabolic capacity of tumour cells would explain the predominant carcinostatic action of 8-azaguanine. Whether the actions of 8-azaguanine were related to the formation of fraudulent nucleotide derivatives or rather the nucleic acids containing the analogue was difficult to assess. However the incorporation of a small amount of 8-azaguanine into a particularly sensitive portion of R.N.A. may well be responsible for the drug's inhibitory/

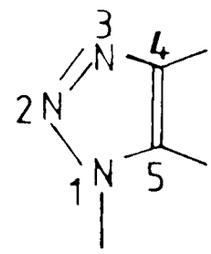
inhibitory effects, as for example messenger R.N.A.

Intermediates such as 8-azaguanosine diphosphate could play a major role in drug action by serving as direct nucleic acid precursors and also by antagonising the functions of guanosine diphosphate as co-factor for protein synthesis. Whether the drug effect on protein synthesis or some other disturbance evoked by a similar co-factor function is responsible for growth inhibition has not been decided.

1.3. 1,2,3-Triazoles

Of the two approaches available for the preparation of 8-azapurines, that indicated by the cyclisation of a 1,2,3-triazole has now gained the widest acceptance because it generally permits greater flexibility both in the variation of the substituents and in altering the oxidation of the pyrimidine ring. 1,2,3-Triazoles are also precursors for similar heterocyclic systems which are potential carcinostatic agents.

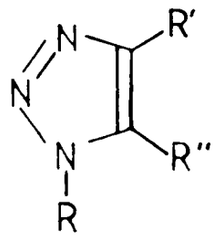
A 1,2,3-triazole consists of three nitrogen atoms and two carbon atoms as shown in the skeletal structure (85).



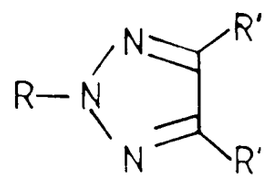
(85)

Three/

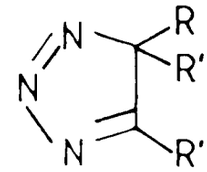
Three classes of 1,2,3-triazoles can be recognised and they are named [1H]-, [2H]-, and [4H]-, 1,2,3-triazoles in "Chemical Abstracts" (Scheme 30).



[1H]-1,2,3-triazole



[2H]-1,2,3-triazole



[4H]-1,2,3-triazole

Scheme 30: Various 1,2,3-triazoles

The chemistry of 1,2,3-triazoles has been reviewed previously,[40-43] the last review surveying the literature in the period 1961-72. In the intervening period several new syntheses of triazoles were introduced, and established routes were greatly extended. The importance of 1,2,3-triazoles is based in this instance, on their use as precursors for azapurines and similar heterocyclic systems.

Synthesis of the Triazole Ring

Most of the important general methods of forming triazoles involve azides. These methods include:

A)/

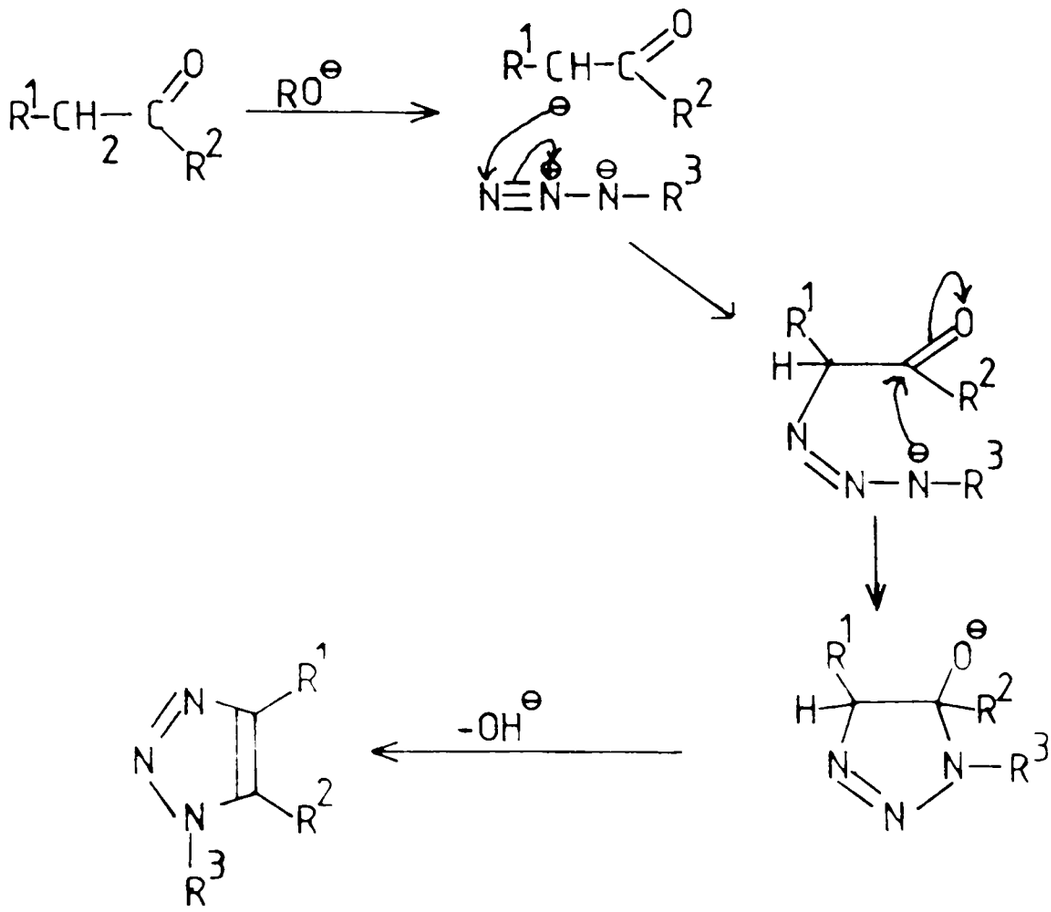
A) Triazoles from azides and acetylenes

B) Triazoles from azides and active methylene compounds

C) From azides and enamines or enol ethers

D) From azides and olefins with electron-withdrawing substituents.

The most common method of triazole formation, relevant to this project was (B). In this method the base catalysed condensation of azides with active methylene compounds has been well established. With appropriate starting materials it is the best route to triazole bearing a 5-amino group, and one of the best to triazoles bearing a 5-hydroxy substituent, and an aryl or carbonyl function in the 4- position. A general example of this reaction is shown in Scheme 31. In this mechanism the carbanion attacks the terminal

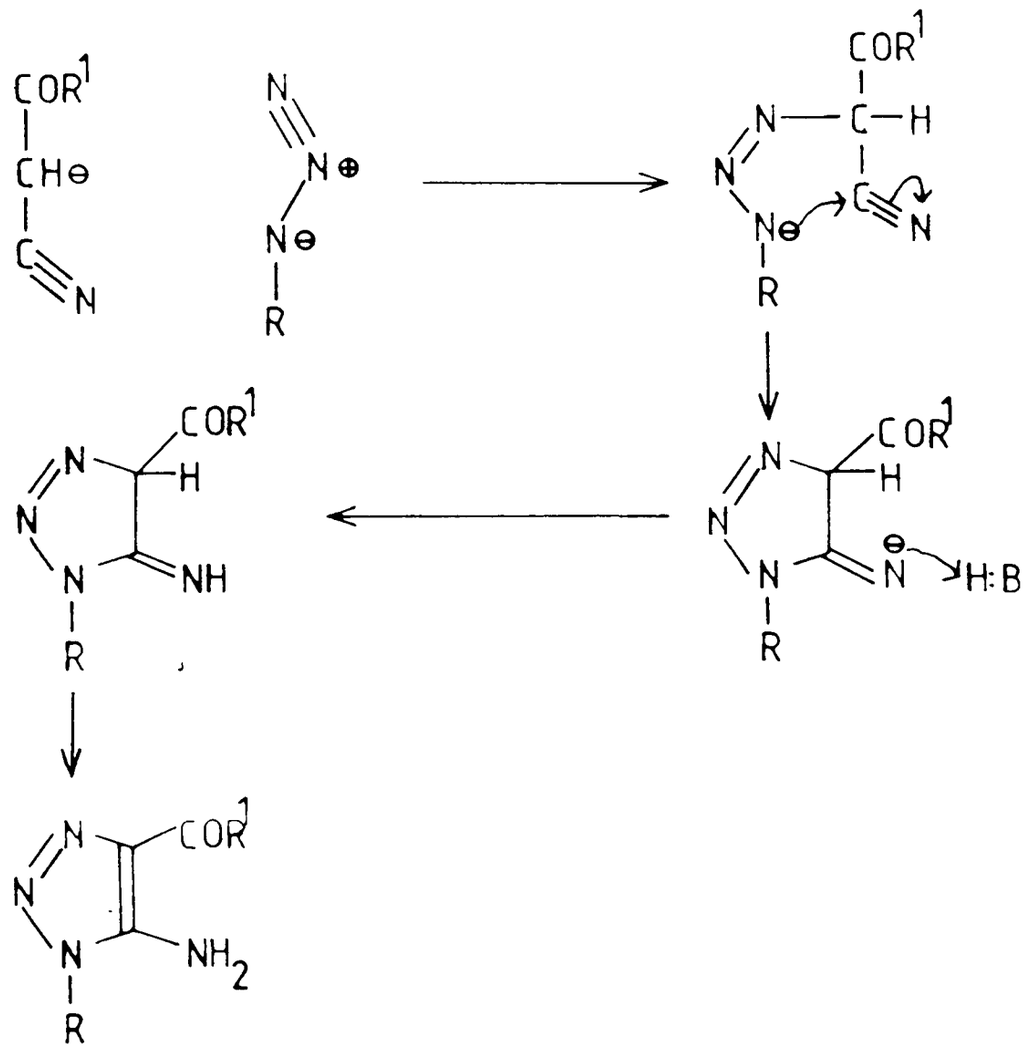


Scheme 31: General mechanism for triazole formation from azides

nitrogen/

nitrogen of the azide, followed by cyclisation and aromatisation to a triazole. In most cases, the activated methylene group is flanked on both sides by electron-withdrawing substituents. Thus cyclisation could conceivably take place in two different ways, in practice however, the reaction is in almost all cases regiospecific.

One of the most important reactions was that observed when one of the activating groups was a nitrile; cyclisation takes place onto the nitrile carbon leading to the formation of 5-amino-1,2,3 -triazoles (Scheme 32). The reaction was utilised and developed by Hoover

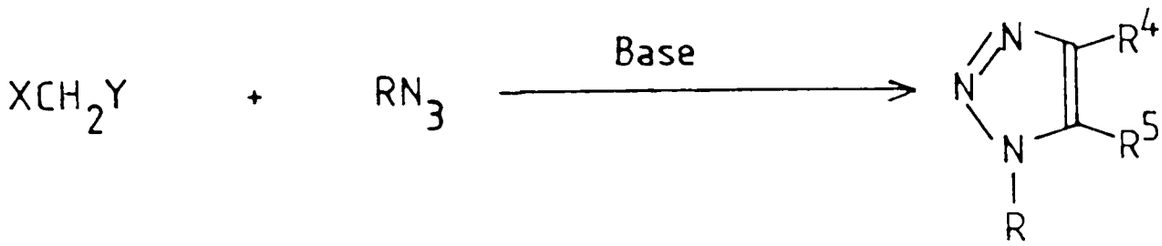


Scheme 32: Preparation of a 5-amino-1,2,3 -triazole

and Day who made such a valuable contribution to triazole chemistry.[21] Some of their results are shown on Table 2. An exception to the reaction in Scheme 32 was the cycloaddition of azides to α-cyanoacetophenone which gave 4-cyano-5-phenyl-1,2,3-triazoles.[44]

X	Y	R	R^4	R^5	Yield(%)
$CONH_2$	CN	$PhCH_2$	$CONH_2$	NH_2	81
CO_2Et	CO_2Et	$PhCH_2$	CO_2Et	OH	48
CO_2Et	CN	$PhCH_2$	CO_2Et	NH_2	25

Table 2: Azide addition to active methylene compounds according to the equation



OTHER TRIAZOLE SYNTHESES

Other methods of triazole syntheses are listed below and will not be dealt with in detail.

Triazoles A)/

Triazoles A) From azides and acylphosphorus ylides

B) By oxidation of triazolines

C) From ∝-diketone derivatives

D) By degradation of fused triazoles

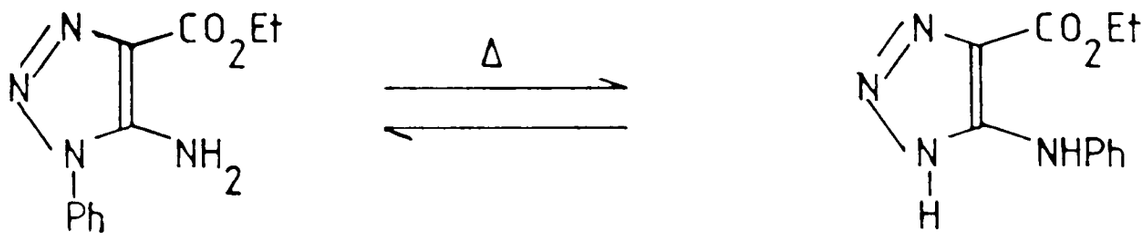
E) From diazoalkanes and imines or nitriles

F) By rearrangement or degradation of other heterocyclic systems

G) From linear triazenes

REARRANGEMENTS OF 1,2,3-TRIAZOLES

Dimroth discovered a thermal isomerization of 5-amino-1-aryl-1,2,3-triazoles.[45] At 150°C in ethanol an equilibrium mixture of 5-anilino-4-ethoxycarbonyl-1,2,3-triazole and 5-amino-4-ethoxycarbonyl-1-phenyl-1,2,3-triazole was obtained (Scheme 33). The forward reaction is based catalysed with almost quantitative

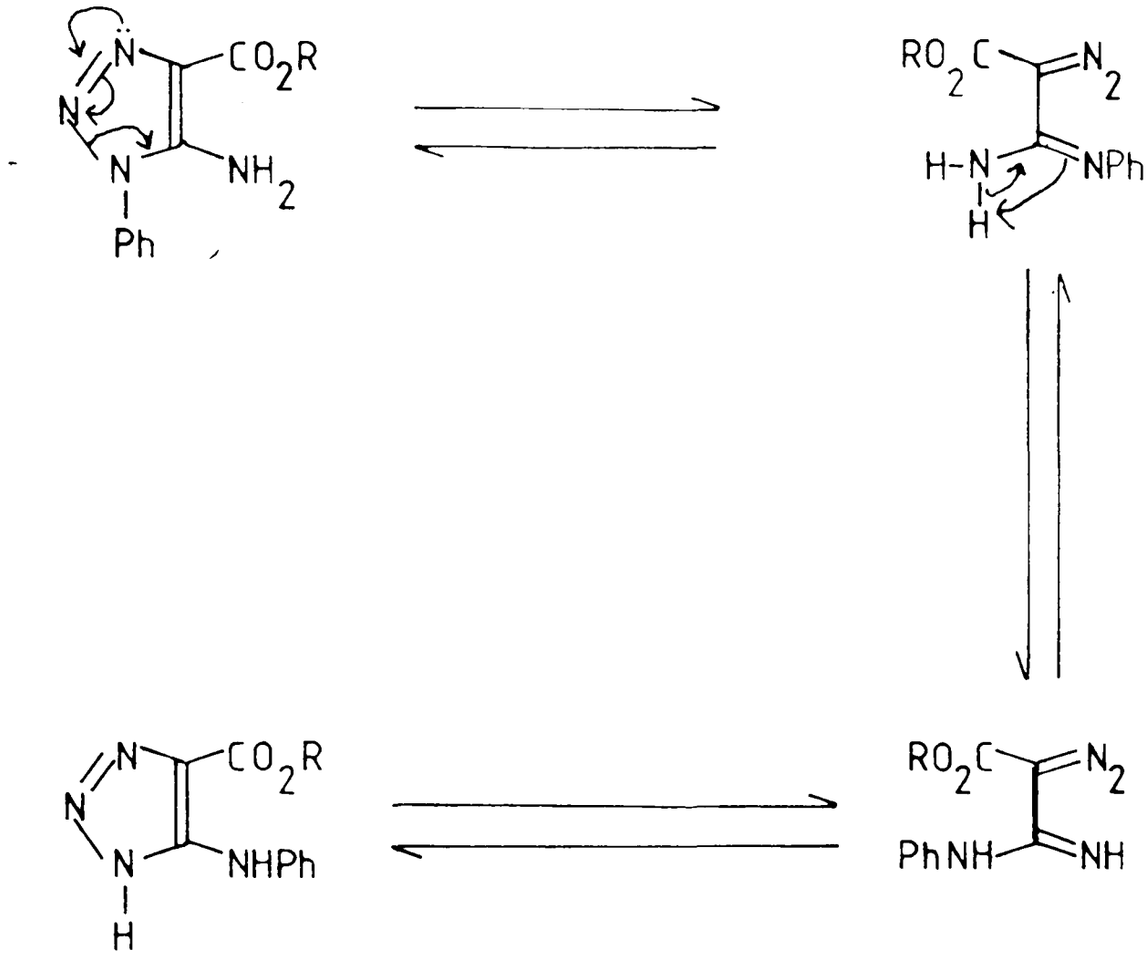


(86) (87)

Scheme 33: Dimroth rearrangement of 5-amino triazoles to 5-anilino triazoles

conversion to the N-1 unsubstituted triazole when the reaction was carried out in the presence of pyridine and sodium ethoxide. This/

This reaction was studied by Albert who suggested that the reaction involved a diazoimine intermediate[46] (Scheme 34).

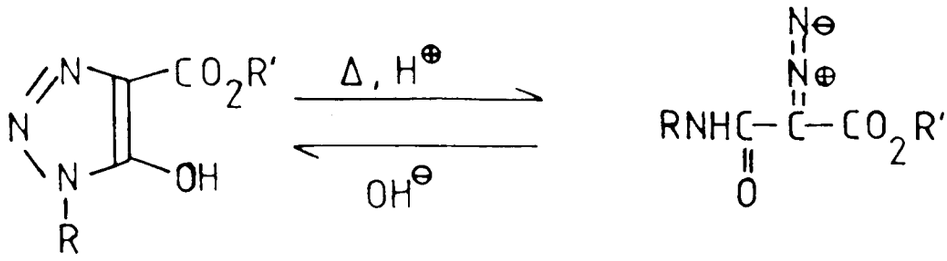


Scheme 34: Mechanism of Dimroth Rearrangement

Electron-withdrawing groups and large rigid groups tend to favour the isomer in which they are on the exocyclic nitrogen; alkyl groups tend to favour the cyclic nitrogen.

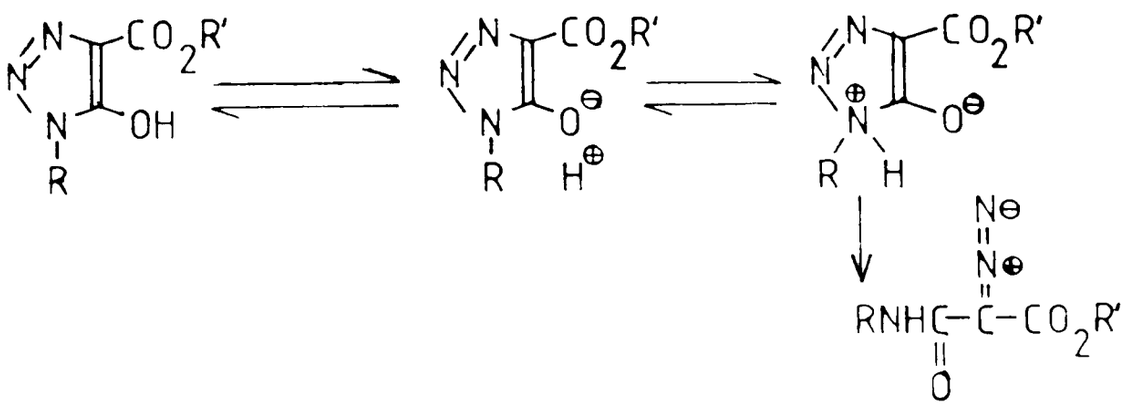
Dimroth also noted another interesting isomerization which was to prove of great importance in the development of the subject of/

of tautomerism.[47,48] In this event 5-hydroxy-triazoles were isomerised under acidic conditions to ∝-diazoamides. The reaction under consideration is shown in Scheme 35. Dimroth suggested that



Scheme 35: The Dimroth Rearrangement of 5-hydroxy-1,2,3-triazoles ⟶ ∝-diazoamides

the rearrangement occurred in the unionized hydroxy-triazole, a suggestion that was later reconsidered by Brown and Hammick who indicated that the change was bimolecular involving a proton and an enolate ion.[49] The tautomeric change that was suggested is shown in Scheme 36.



Scheme 36: Brown and Hammick's suggested mechanism for the Dimroth Rearrangement

The/

The nature of R was important and ring-opening rates increased as R- became more electron-withdrawing. In a later investigation Leffler and Liu noted the effect of R being electron-withdrawing.[50] They also investigated solvent and structural effects. In their paper, Brown and Hammick's suggestion that the reaction was bimolecular was refuted. The difference in interpretation can be accounted for by the fact that in both cases different types of solvents were used. Brown and Hammick carried out their measurements in water where significant dissociation of the hydroxy-triazole took place. Leffler and Liu carried out their measurements in acetonitrile and dimethylformamide and showed that the hydroxy-triazole did not dissociate extensively. Hence adding strong acids should not and did not affect the rate by changing the proportion of triazole in the associated form.

This lack of effect was consistent with the first order kinetics in the solvents used, however no mechanism for ring opening was suggested.

It is surprising to note that neither Dimroth, nor the later workers, investigated the base induced ring closure of α-diazoamides, to salts of hydroxy-triazoles, except to observe that this reaction actually occurs.

BIOLOGICAL PROPERTIES OF 1,2,3 -TRIAZOLES

Certain 1,2,3-triazole analogues of histamine have shown anti-histaminic and anti-acetylcholine activity. The 1,2,3-triazole ring is antagonistic to the imidazole ring in the triazole analogues of guanine and adenine.[51,52]

REFERENCES

1. J. Davoll, J.Chem.Soc., (1958), 1593.
2. J. Baddiley, J. G. Buchanan, and G. O. Osborne, J.Chem.Soc., (1958), 1651.
3. J. Baddiley, J. G. Buchanan, and G. O. Osborne, J.Chem.Soc., (1958), 3606.
4. Curtius and Raschig, J.Prakt.Chem., (1930), 125, 466.
5. R. Huisgen, J.Org.Chem., (1968), 33, 2291.
6. R. E. Harmon, R. A. Earl, and S. K. Gupta, J.Chem.Soc., (Chem.Comm.), (1971), 296.
7. R. E. Harmon, R. A. Earl, and S. K. Gupta, J.Org.Chem., (1971), 36, 2553.
8. R. L. Tolman, C. W. Smith, R. K. Robins, J.Amer.Chem.Soc., (1972), 94, 2531.
9. W. Hutzenlaub, R. L. Tolman, and R. K. Robins, J.Med.Chem., (1972), 15, 879.
10. R. S. Tipson, J.Biol.Chem., (1939), 130, 55.
11. F. Chretien, and B. Gross, Tetrahedron, (1982), 38, 103.
12. F. Chretien, B. Castro and B. Gross, Synthesis, (1979), 937.
13. S. Gabriel and J. Colman, Ber., (1901), 34, 1234.
14. R. O. Roblin, J. O. Lampen, J. P. English, Q. P. Cole and J. R. Vaughan, J.Amer.Chem.Soc., (1945), 67, 290.
15. H. G. Mandel, Pharmacol.Rev., (1959), 11, 743.
16. F. R. Benson, L. W. Hartzel, and W. L. Savell, J.Amer.Chem.Soc., (1950), 72, 1816.
17. E. Richter and E. C. Taylor, J.Amer.Chem.Soc., (1956), 78, 5848.

18./

18. A. Dornow and J. Hellberg, Chem.Ber., (1960), 93, 2001.

19. G. W. Kidder, V. C. Dewey, R. E. Parks and G. L. Woodside, Science, (1949), 109, 511.

A. Gellhorn, H. Engelman, D. Shapiro, S. Graff and H. Gillespie, Cancer Res., (1950), 10, 170.

K. Sugura, G. H. Hitchings, L. F. Cavalieri, and C. C. Stock, ibid, 178.

J. A. Montgomery, ibid, (1959) 19, 447.

20. A. Albert and K. Tratt, J.Chem.Soc. (C), (1968), 344.

21. J. R. E. Hoover and A. R. Day, J.Amer.Chem.Soc., (1956), 78, 5832.

22. A. Albert, J.Chem.Soc.(C), (1968), 2076.

23. A. Albert, J.Chem.Soc.(C), (1969), 152.

24. A. Albert, J.Chem.Soc., Perkin Trans. I, (1972), 461.

25. J. H. Lister, "The Purines", (1971), New York, Wiley Interscience, 433.

26. A. Albert, J. Chem.Soc., Perkin Trans. I, (1972), 457.

A. Albert, J.Chem.Soc. (B), (1966), 427.

27. A. Albert, J.Chem.Soc., Perkin Trans. I, (1976), 291.

28. J. Colman and S. Gabriel, Ber., (1904), 37, 3643.

29. A. Albert, J.Chem.Soc., Perkin Trans. I, (1973), 1634.

30. A. Albert and A. M. Trotter, J.Chem.Soc., Perkin Trans. I, (1979), 922.

31. A. Albert, J.Chem.Soc., Perkin Trans. I, (1980), 2918.

32. A. Albert, J.Chem.Soc., Perkin Trans. I, (1980), 2009.

33. M. Busch, Ber., (1892), 25, 2853.

W. L. F. Amarego, "The Quinazolines" (1967), Wiley Interscience, New York, p276.

34. A. Albert, J.Chem.Soc., Perkin Trans. I, (1981), 887.

35./

35. A. Albert, J.Chem.Soc., Perkin Trans. I, (1981), 2344.

36. A. Da. Settimo, O. Livi, P. L. Ferrarini and G. Biagi, Il Farmaco Ed.Sci., (1980), 35, 308.

37. F. Nielsen, E. B. Pedersen, and M. Begtrup, Liebigs Ann.Chem., (1984), 1848.

38. A. Gellhorn, Cancer, (1953), 6, 1030.

39. P. E. Carlo and H. G. Mandel, Cancer Res., (1954), 14, 459.

40. F. R. Benson and W. L. Savell, Chem.Rev., (1950), 46, 1.

41. E. Hoggarth in "Chemistry of Carbon Compounds", (E. H. Rodd, ed.), Vol. 4A, Elsevier, Amsterdam, (1957), 439.

42. J. H. Boyer in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 7, Wiley, New York, (1961), 434.

43. T. L. Gilchrist, and G. E. Gymer, Adv.Heterocyclic.Chem., (1974), 16, 33.

44. S. Maurona, Ann.Chim. (Rome), (1966), 56, 1531.

45. O. Dimroth, Ann., (1909), 364, 183, 212.

46. A. Albert, J.Chem.Soc.(C), (1970), 230.

47. O. Dimroth, Ann.,(1910), 377, 127.

48. O. Dimroth, Ann., (1910), 373, 349.

49. B. R. Brown, and D. LL. Hammick, J.Chem.Soc., (1947), 1384.

50. J. E. Leffler and S. K. Liu, J.Amer.Chem.Soc., (1956), 78, 1949.

51. J. C. Sheehan and C. A. Robinson, J.Amer.Chem.Soc., (1951), 73 1207.

52. J. C. Sheehan and C. A. Robinson, J.Amer.Chem.Soc., (1949), 71. 1436.

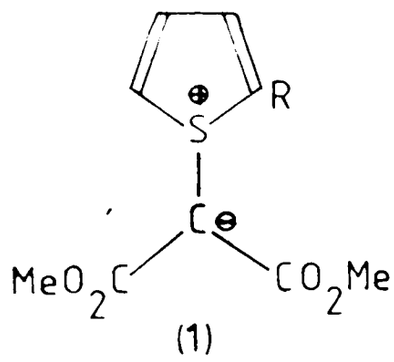
CHAPTER 2

Chapter 2

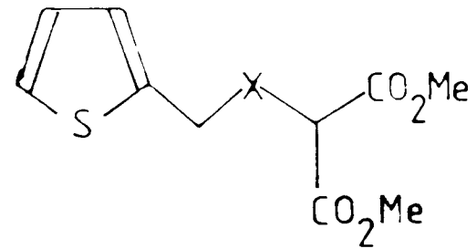
2.1. REACTIONS BETWEEN PRIMARY AMINES AND DIAZOMALONIC ESTERS

It has been shown[1-3] that diazomalonic esters react with thiophene and its derivatives to yield thiophenium ylides (1) in high yields and as a part of Porter's research group's continuing interest in this area of chemistry, it was decided to investigate the generality of this reaction, particularly in systems where competing side reactions might be expected.

In the case of thiophene derivatives containing OH or NH_2 groups competing carbene insertion reactions might be expected to yield the malonate derivatives (2). Porter found that 2-hydroxymethylthiophene gave rise to the ylide (1; R = CH_2OH), although others[4] have been unable to obtain the ylide and reported the formation of the carbene insertion product (2; X = O). Reaction of dimethyl diazomalonate with an excess of 2-thienylamine in the presence of $Rh_2(OAc)_4$ at room temperature resulted in the slow deposition of a colourless crystalline solid and after 3 days the reaction was complete as evidenced by the disappearance of the diazo-stretching vibration in the i.r spectrum.[5]



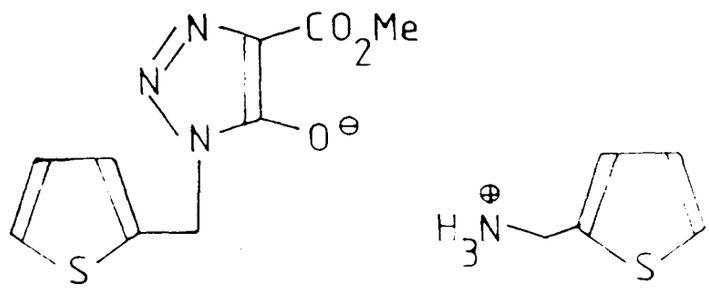
(1)



(2)

The/

The structure of the product proved difficult to elucidate particularly since the mass spectrum indicated a molecular formula of $C_9H_8N_3O_3S$ whereas the microanalytical data were consistent with a molecular formula of $C_{14}H_{16}N_4O_3S_2$. The structure of this compound was confirmed by X-ray crystallography as the primary ammonium salt of 1-(2-thienyl)-5-hydroxy-4-methoxycarbonyl-1,2,3-triazole (3). The X-ray structure accounted for the discrepancy



(3)

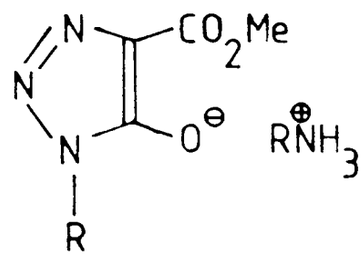
in the mass spectral/microanalytical date in that microanalysis clearly provided the empirical formula of the salts, whereas in the mass spectrum the highest mass is that due to the anion of the salt.

Recognising the synthetic potential of this reaction it was decided to investigate whether or not further triazoles could be prepared by using various primary amines with dimethyl diazomalonate. This was indeed the case and the results are shown in Table 1.

The/

TABLE 1

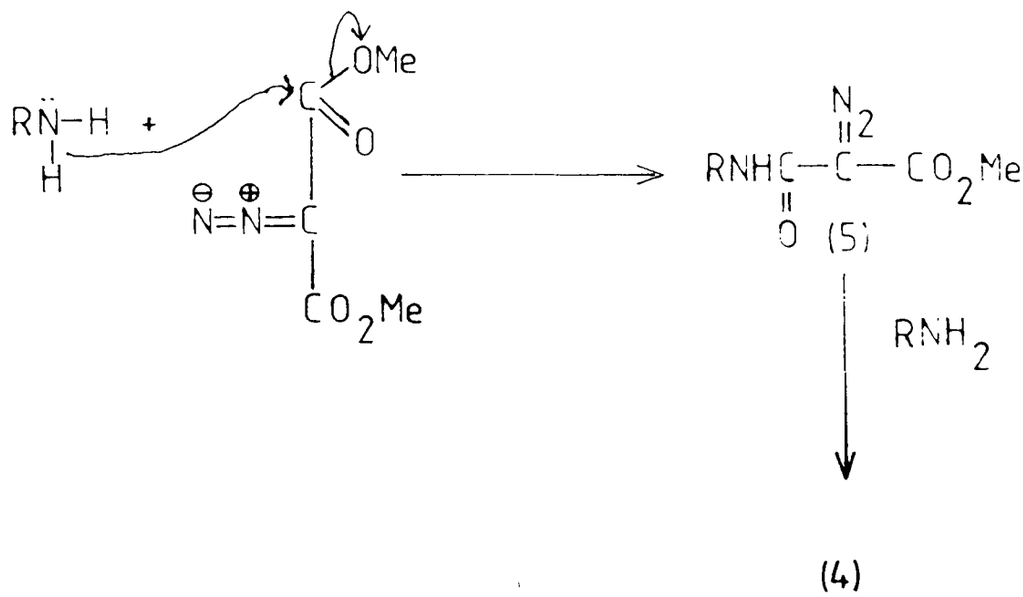
Amine	Reaction time (days)	Product(4)	Yield(%)
$n\text{-}BuNH_2$	3	$R = C_4H_9$	87
$n\text{-}C_5H_{11}NH_2$	5	$R = C_5H_{11}$	83
$n\text{-}C_6H_{13}NH_2$	3	$R = C_6H_{13}$	70
Cyclohexylamine	3	$R = C_6H_{11}$	66
$HO\text{-}CH_2\text{-}CH_2\text{-}NH_2$	3	$R = CH_2CH_2OH$	98
$PhCH_2$	3	$R = CH_2Ph$	84



(4)

The major limitation of this reaction appears to be that aromatic amines such as aniline fail to react, perhaps due to the reduced nucleophilicity of the nitrogen in aromatic amines.

Mechanistically it seems probable that the amine reacts with the diazomalonate to form the diazoamide (5) which then undergoes base catalysed cyclisation to the 1,2,3-triazole (4) (Scheme 1).



Scheme 1: Reaction of primary alkylamine with dimethyl diazomalonate to form 1-alkyl-5-hydroxy-4-methoxycarbonyl-1,2,3-triazole alkylammonium salts (4).

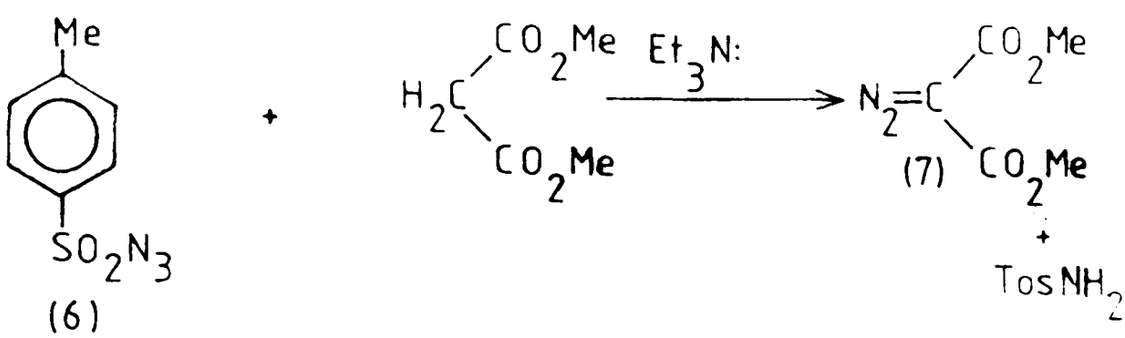
The/

The ring closure of diazoamides to 5-hydroxy-1,2,3-triazoles is a well studied reaction[6] first noted by Dimroth[7] and it has been established that under neutral or acidic conditions the open chain diazoamide (5) is stable but under basic conditions the rapid cyclisation to salts of the 5-hydroxy-1,2,3-triazoles occurs.

Although the cyclisation of diazoamides is well known, this simple "one pot" variant using dimethyl diazomalonate has not been previously reported. It does offer some advantages in that it appears to work well with primary aliphatic amines giving consistently high yields of (4). Low molecular weight amines of sufficient volatility serve as both solvent and substrate in the reaction, whereas with amines of higher molecular weight or low volatility the reaction is conveniently carried out in a suitable solvent (e.g., toluene) using a greater than two-fold excess of the amine to diazoester.

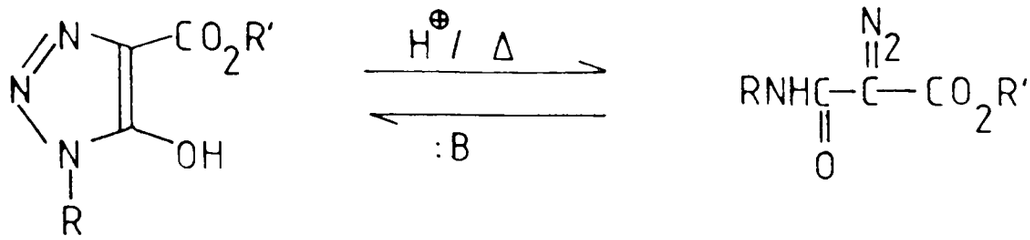
Another advantage of this method of triazole formation is that the use of sometimes hazardous azides is avoided.

The diazomalonic ester was formed in a moderate yield from the diazo-transfer reaction[8] to dimethyl malonate using tosyl azide in the presence of a base (Scheme 2).



Scheme 2: Preparation of dimethyl diazomalonate

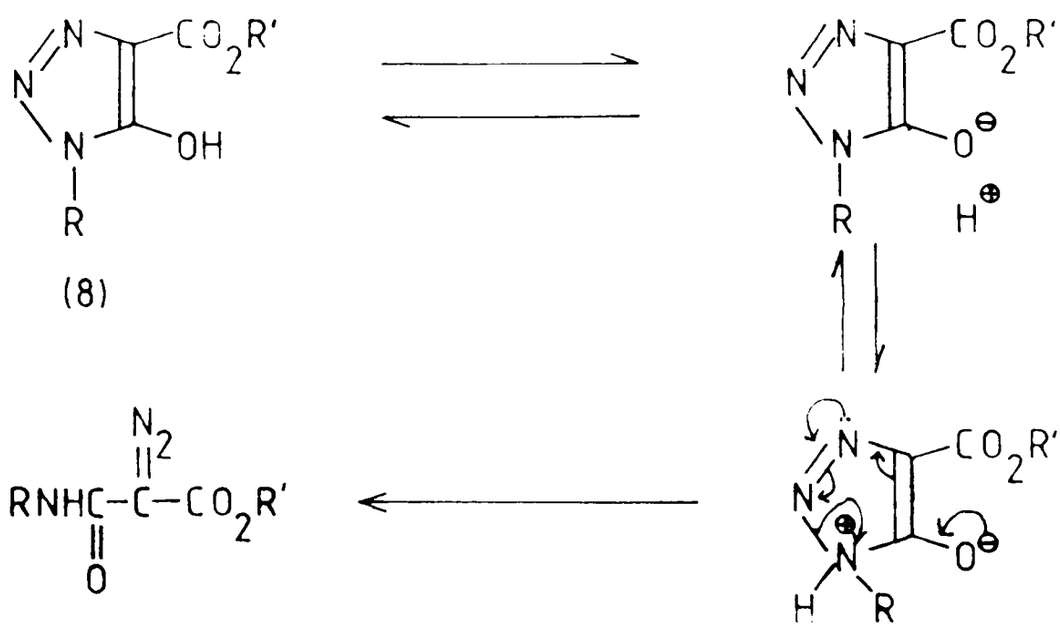
The following reaction was observed (Scheme 3). It was first



(8) (5)

Scheme 3: The Dimroth Rearrangement

established by Dimroth,[9,10,11] who suggested that the change occurred in the unionized enol molecule. Dimroth's data were reconsidered by Brown and Hammick,[6] and they suggested that the change was bimolecular involving a proton and an enol ion (Scheme 4). We became interested in this reaction for two reasons. Firstly,



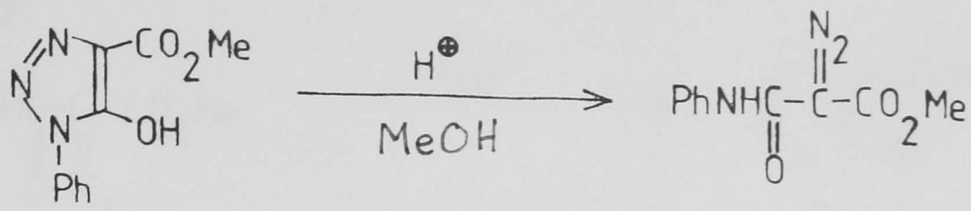
(8)

Scheme 4: Brown and Hammick's suggested mechanism for the Dimroth Rearrangement

in our work with dimethyl diazomalonate and primary alkylamines (Section 2.1.), it was suggested that the diazoamide (5) was an intermediate during the course of the reaction (Scheme 1). In one case, the ∝ -diazoamide was isolated and cyclised with the appropriate amine to the triazole salt. Secondly, when the triazole salts (4) were readily converted into the free hydroxy-triazoles by acidification of an aqueous solution, and were subsequently worked up, the residual hydroxy-triazoles often showed a diazo-stretching vibration in their i.r. spectra at 2140 cm^{-1}.

It was decided to investigate the base induced cyclisation, and the acid catalysed ring opening reaction. In the original work by Dimroth, and subsequent studies by Hammick and Brown, the reaction was followed by iodometry, however we found it convenient to monitor the reaction by u.v spectroscopy since the ring opening reaction and the ring closures give rise to clearly defined spectral changes with isobestic points (Figs. 1-4).

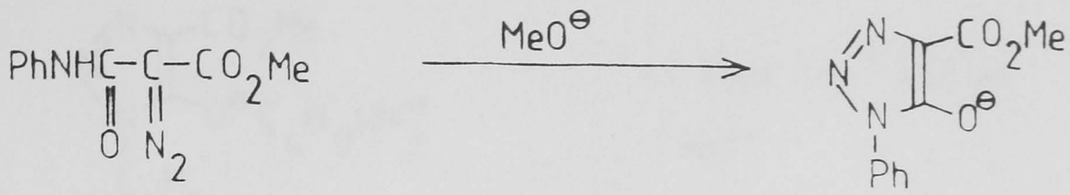
Since three of the reactions appeared to proceed at a measurable rate it was decided to monitor them by measuring changes in absorbance at fixed wavelengths over a period of time. The actual readings recorded for each investigation are shown in Appendix 1. The 1st-order rate constants were evaluated on a Commodore 64K microcomputer, using a programme devised to calculate Swinburne plots. These rate constants (1st Order) are shown on Tables 2-4 (Appendix 1). From Table 2 (ring-opening of N-phenyl-triazole) it is apparent that the 1st-order rate constants are independent of $[H^+]$. This observation contradicts the previous assertion that the/



$[H^{\oplus}] = 10^{-2}$ mol.dm^{-3}

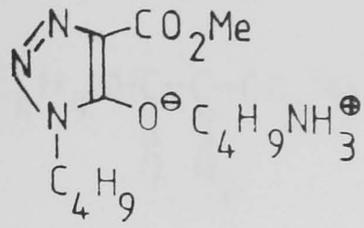
[hydroxy-triazole] $\simeq 10^{-4}$ mol.dm^{-3}

Fig 2



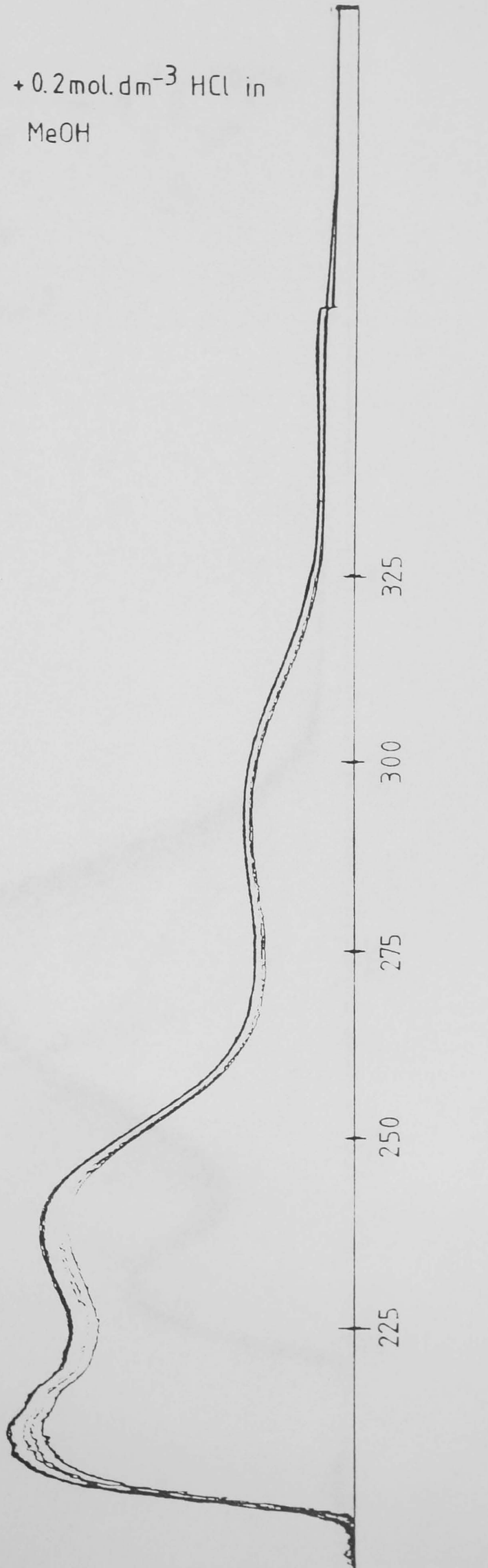
$[MeO^{\ominus}]$ = 3.5×10^{-4} mol.dm^{-3} in MeOH

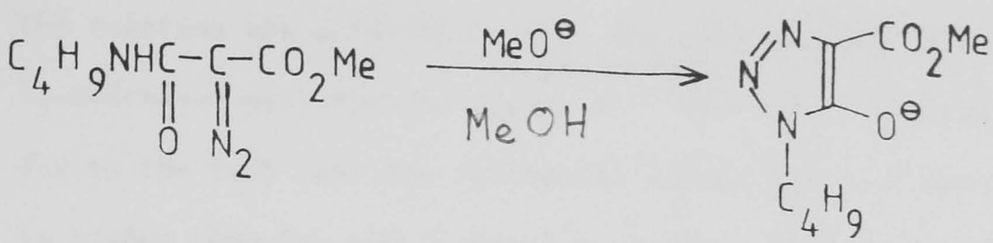
[diazoanilide] = 10^{-4} mol.dm^{-3}



[salt] ≈ 10^{-4} mol. dm^{-3}

+ 0.2 mol. dm^{-3} HCl in MeOH





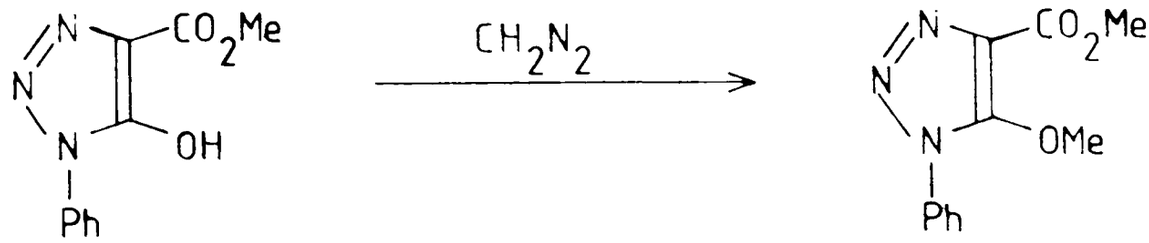
[diazoamide] ≈ 10^{-4} mol. dm^{-3}

[$MeO^{\ominus}$] = 2×10^{-2} mol. dm^{-3}

the reaction was acid-catalysed. The ring opening of 1-butyl -5-hydroxy-4-methoxycarbonyl-1,2,3-triazole was not observed. This could be due to the fact that the activation energy for this reaction is higher than for the N-phenyl triazole. Implicit in the above statement is the postulation that the reaction intermediate involved in this ring-opening reaction is stabilized by aryl groups but not by alkyl groups.

It would therefore appear that again Brown and Hammick's proposed mechanism (Scheme 4) is contradicted, since one would expect easier protonation of the N-1 position due to the greater basicity of the alkyl group.

Furthermore, it would also appear that N-1 is the least basic of the three triazole nitrogens, since its electrons participate in the aromatic system (6 π electrons). During the course of investigations we prepared a derivative of 8, where R = Ph (Scheme 5). The u.v spectra of 9 were recorded in, neutral, acidic, and basic



(8a) (9)

Scheme 5: Methylation of 5-hydroxy-4-methoxycarbonyl-1-phenyl-1,2,3-triazole

media/

media and as can be seen from the spectra (Fig. 5-7, Appendix I), there is very little spectral change between the sample in neutral. and in acidic solution.

It can be deduced here that either (a) no significant protonation occurs or (b) if protonation does occur, it occurs at N-2 or N-3 without changes in the u.v spectrum. The plot of ln k, versus 1/T was made (Fig. 8), and the following parameters were evaluated:

E_a = 97.08 kJ mol^{-1}

A = 9.26 x 10^{12} s^{-1}

$\Delta H^{\ddagger}$ = 94.6 kJ mol^{-1}

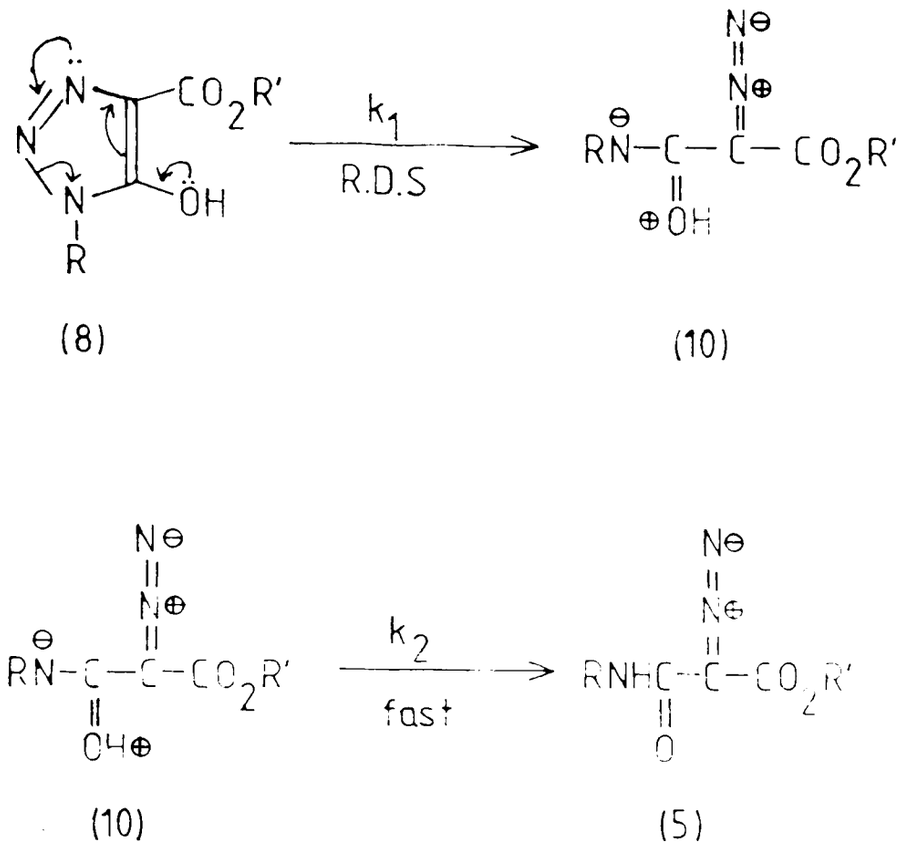
$\Delta S^{\ddagger}$ = -5.19 JK^{-1} mol^{-1}

Correlation Coefficient = 0.9969

The rate law for the reaction is Rate = k_1[hydroxy-triazole].

A consideration of the results would lead to the following mechanism being suggested (Scheme 6).

Scheme 6:/



Scheme 6: Proposed Mechanism for Ring Opening of Triazole Ring

This mechanism seems feasible since there is no dependence in the rate determining step on $[H^+]$. The reactive intermediate (10) would be stabilized by electron withdrawing R-substituents, and destabilized by electron donating R-substituents. This would account for the slow rate of ring opening in the case where R = nBu.

It/

It should also be pointed out that in the case of (8a) ring opening was observed to proceed under neutral conditions, and in aprotic solvents, where there was very little dissociation of the hydroxy-1,2,3-triazole.

The base induced cyclisation of ∝-diazoamides which had not been previously studied was investigated and the 1st order rate constants are shown in Table 3 (for N-phenyl ring closure) and Table 4 (for N-butyl cyclisation). Graphs of first order rate constants vs concentration of methoxide were plotted (Figs. 9-18).

Inspection of these plots show that the 1st order rate constants depend on [MeO^-], and that the rates of cyclisation of the methyl diazomalonanilide are approximately 10^3 faster than for the N-butyl diazoamide. An unfortunate feature in Figs. 14-18 is the curvature in the graphs. This indicates that some other process is taking place. It is quite possible that partial hydrolysis of the 4-ester function is taking place, due to moisture being present.

It was quite possible to evaluate the second order rate constants for the cyclisation of methyl diazomalonanilide because the curvature was insignificant in Figs. 9-13. These rate constants are shown on Table 5. The plot of $\ln \frac{(k_o.k_2)}{t}$ vs 1/T is shown on Fig. 19, and from this the activation parameters were evaluated.

$Ea = 67.86\ kJ\ mol^{-1}$

$\Delta H^{\ddagger} = 65.38\ kJ\ mol^{-1}$

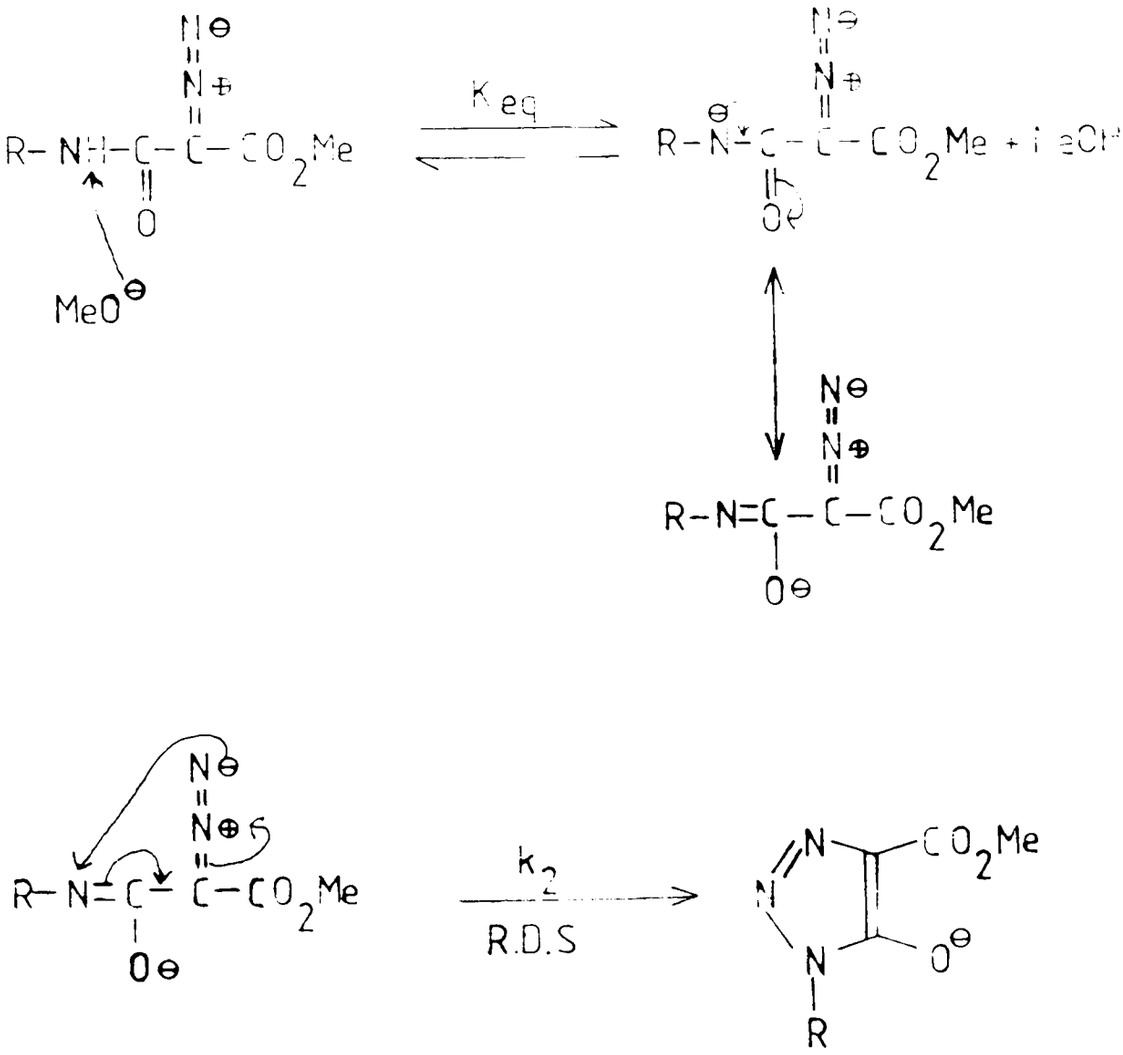
$A = 6.290 \times 10^{12}\ mol^{-1}.dm^3.s^{-1}$

$\Delta S^{\ddagger}$

$\Delta S^{\ominus\ddagger}$ = -6.49 $J.K^{-1}$ mol^{-1}

Correlation Coefficient = 0.99511

Because of the curvatures in Figs. 14-18, the activation parameters have not been evaluated. Aspects of this reaction will be discussed elsewhere in this section. The following mechanism is suggested (Scheme 7):



Scheme 7: Base induced cyclisation of ∝ -diazoamides

The first step is likely to be a fast pre-equilibration (diffusion controlled) proton extraction followed by rate determining cyclisation to the salt of the hydroxy-triazole. The equilibrium constant Keq would be directly proportional to the Ka (acidity) of the amide proton. The rate law is shown below:

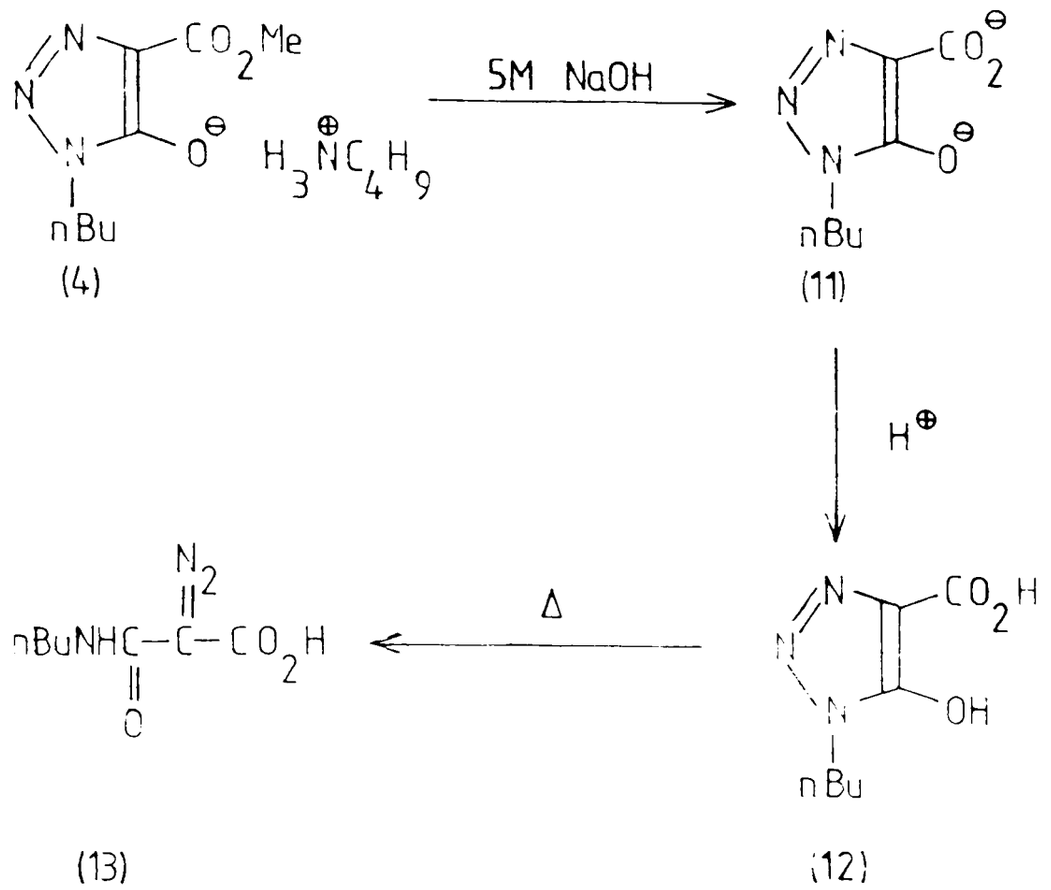
$$\text{Rate} = k_{1obs}[\text{diazoamide}] = k_2 Keq[MeO^-][\text{diazoamide}]$$

$$k_{1obs} = k_2 Keq[MeO^-]$$

Thus the 1st order rate constant is directly proportional to the methoxide concentration, and also to the acidity of the amide proton. The observation that the N-phenyl diazoamide cyclises by three orders of magnitude faster than the n-butyl diazoamide can be accounted for by noting that there is a difference of 3 in the pKa values between alkyl amides and anilides viz:

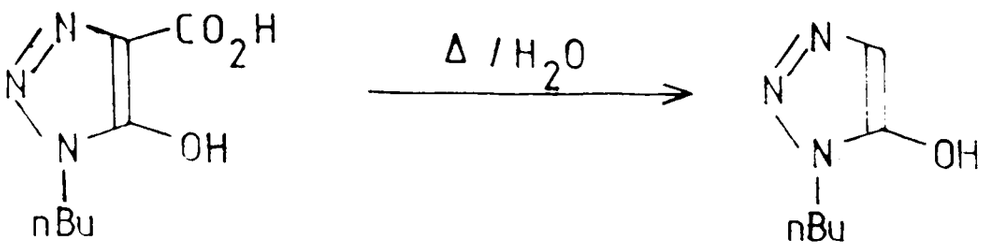
Amide	pKa
PhC(=O)-NHMe	>19.0
PhC(=O)-NHPh	16.53

It was decided to attempt to prepare the carboxylic acid (13) by the following route:



The preparation proceeded as expected until the attempted thermal ring opening ((12) ⟶ (13)). At this stage decarboxylation occurred, in fact attempted recrystallisation of (12) from water led to the 4-unsubstituted triazole (14). (Scheme 8).

Scheme 8:/



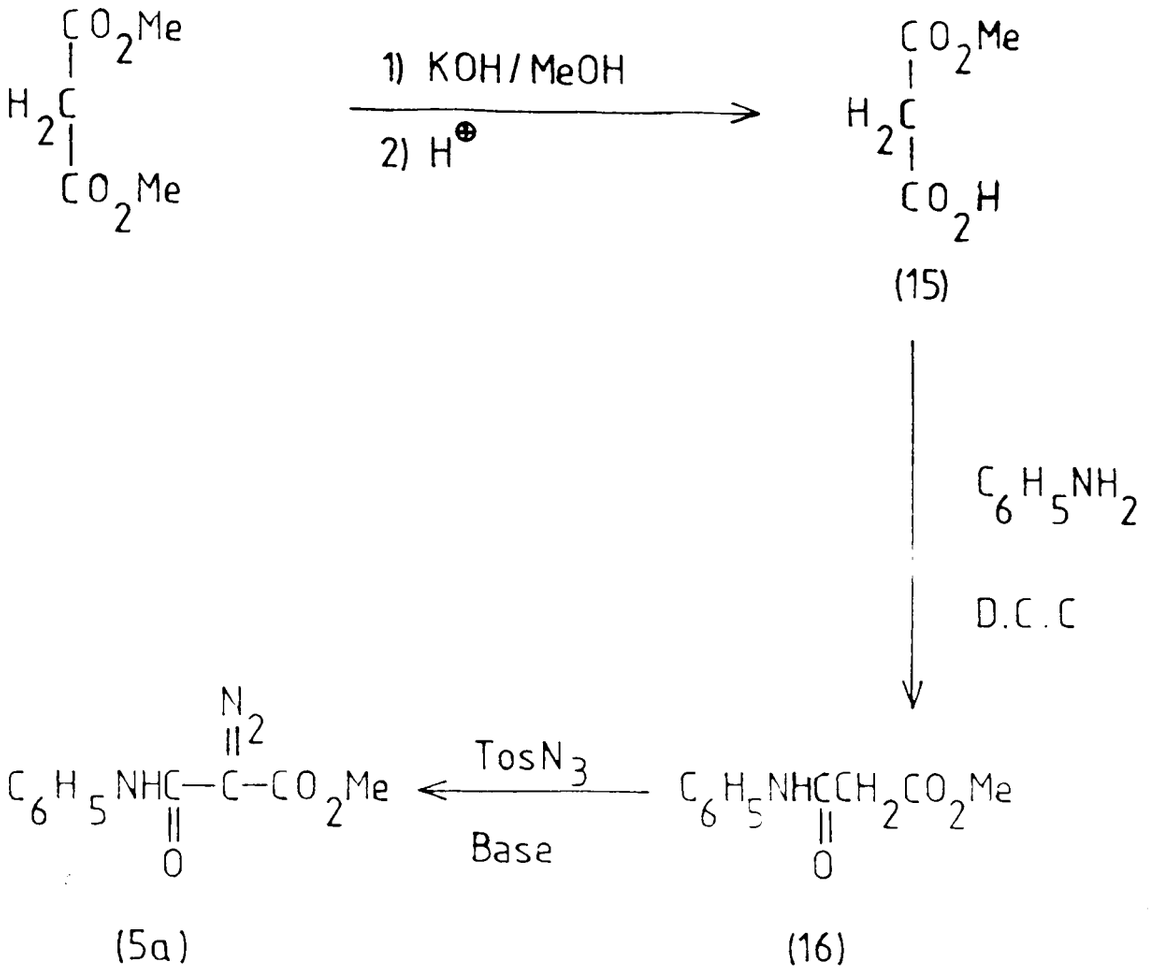
(12) (14)

Scheme 8: Decarboxylation of 1-butyl-5-hydroxy-1,2,3-triazole 4-carboxylic acid.

The u.v spectrum of the di-anion (11) was recorded in methanol and is shown in Fig. 20. λ max is at 267.5 nm (Cf Fig. 4; λ max of 4 (R = nBu) is at 274 nm). From this result, and the proximity of the two λ maxs, it is impossible to rule out hydrolysis as a side reaction.

Before these investigations could be carried out, it was necessary to prepare the compounds 5 a and b, and 8a and 8b. It is important to mention some of the synthetic problems encountered, especially in the preparation of (5a), i.e., methyl diazomalonanilide. The suggested route to (5a) is shown in Scheme 9.

Scheme 9:/



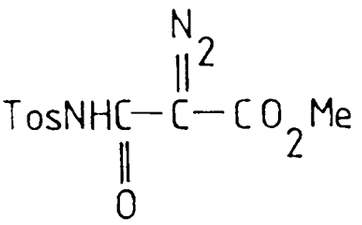
Scheme 9: Proposed preparation of methyl diazomalonanilide

The half acid (15), and the anilide (16) were prepared in good yields, but problems were encountered in the diazo-group transfer using recommended methods.[8,12]

When bases such as triethylamine were used no reaction was observed. A reaction was observed when sodium methoxide in methanol was employed. When worked up, this reaction yielded a compound which possessed/

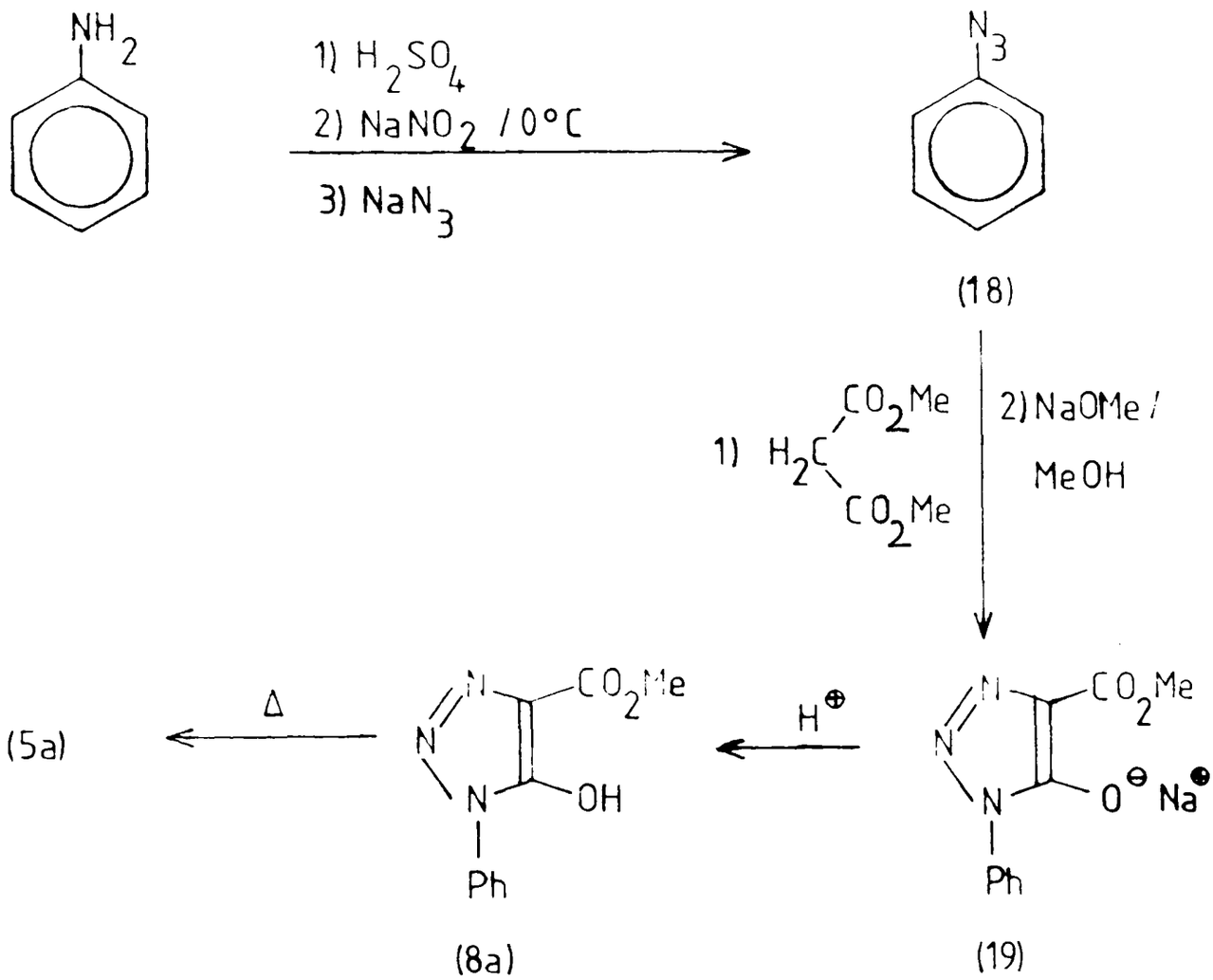
possessed the required diazo group, but N.M.R inspection of this compound also showed that the tosyl group was also present.

A tentative assignment for the compound is shown (17), but this compound was not fully characterised.



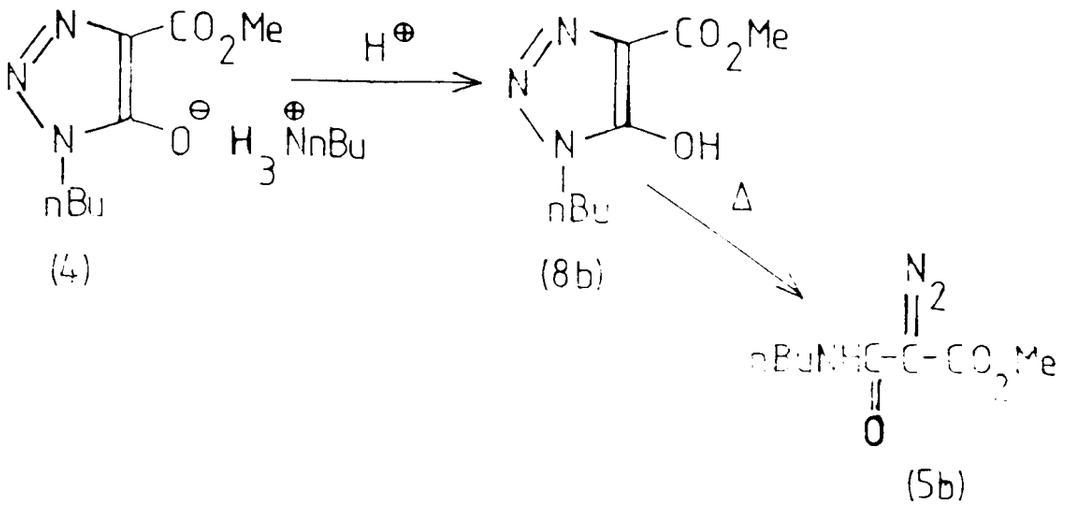
(17)

Compound (5a) was eventually prepared by a literature method,[13] which is summarised in Scheme 10. Phenyl azide (18) was prepared



Scheme10: Preparation of methyl diazomalonanilide

from the diazonium salt of aniline in a fair yield. The 1,3-cycloaddition of dimethyl malonate to phenyl azide furnished a good yield of the triazole salt (19). Acidification of (19) led to the free 5-hydroxy-1,2,3-triazole (8a). When (8a) was recrystallised yellow crystals of the required diazomalonanilide (5a) were obtained. The n-butyl-diazoamide (5b) was prepared as in Scheme 11.

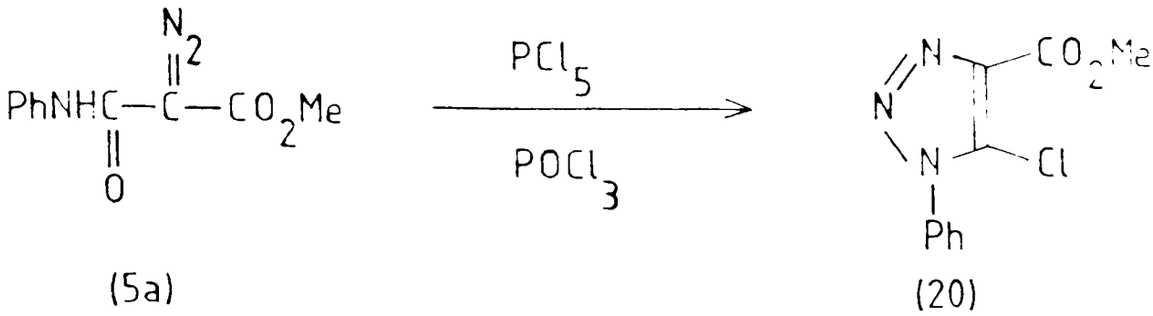


Scheme 11: Preparation of N-n-butyl-2-methoxycarbonyl-2-diazoacetamide

2.3. PREPARATION AND REACTIONS OF 5-CHLORO-1,2,3-TRIAZOLES

On heating methyl diazomalonanilide (5a) with phosphorus pentachloride in phosphorus oxychloride, 5-chloro-4-methoxycarbonyl-1-phenyl-1,2,3-triazole (20) was obtained.[14,15] (Scheme 12).

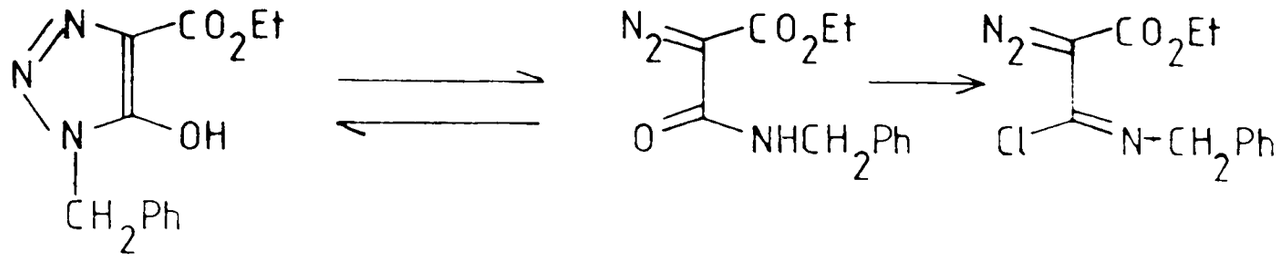
Scheme 12:/



(5a) (20)

Scheme 12: Preparation of 5-chloro-4-methoxycarbonyl-1-phenyl-1,2,3-triazole

Recently Buckle et al increased the yield of the above reaction by employing dry toluene as reaction solvent.[16] Under these conditions a side reaction which led to the chloro-diazoimine (23) was reduced (Scheme 13).

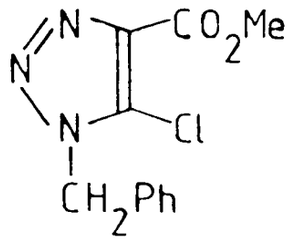


(21) (22) (23)

Scheme 13: Side reaction in preparation of 5-chloro-1,2,3-triazoles

It was decided to prepare a number of the 5-chloro-1,2,3-triazoles, and investigate their reactions with a variety of nucleophiles. Using Buckle's method[17,18] for the chlorination of 5-hydroxy-1,2,3-/

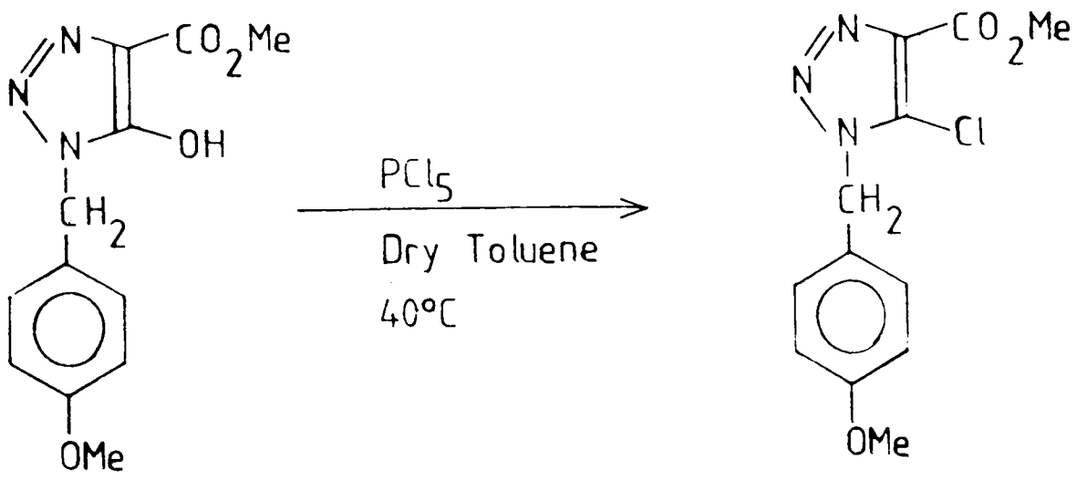
1,2,3-triazoles, 1-benzyl-5-chloro-4-methoxycarbonyl-1,2,3-triazole (24) was prepared in a very good (75%) yield by stirring the parent



(24)

5-hydroxy-1,2,3-triazole with phosphorus pentachloride in dry toluene at 40°C.

The other benzylic triazole that was prepared was 5-chloro-1-(4-methoxybenzyl)-4-methoxycarbonyl-1,2,3-triazole (26) from (25) (Scheme 14). The yield for this reaction was poor, but



(25) (26)

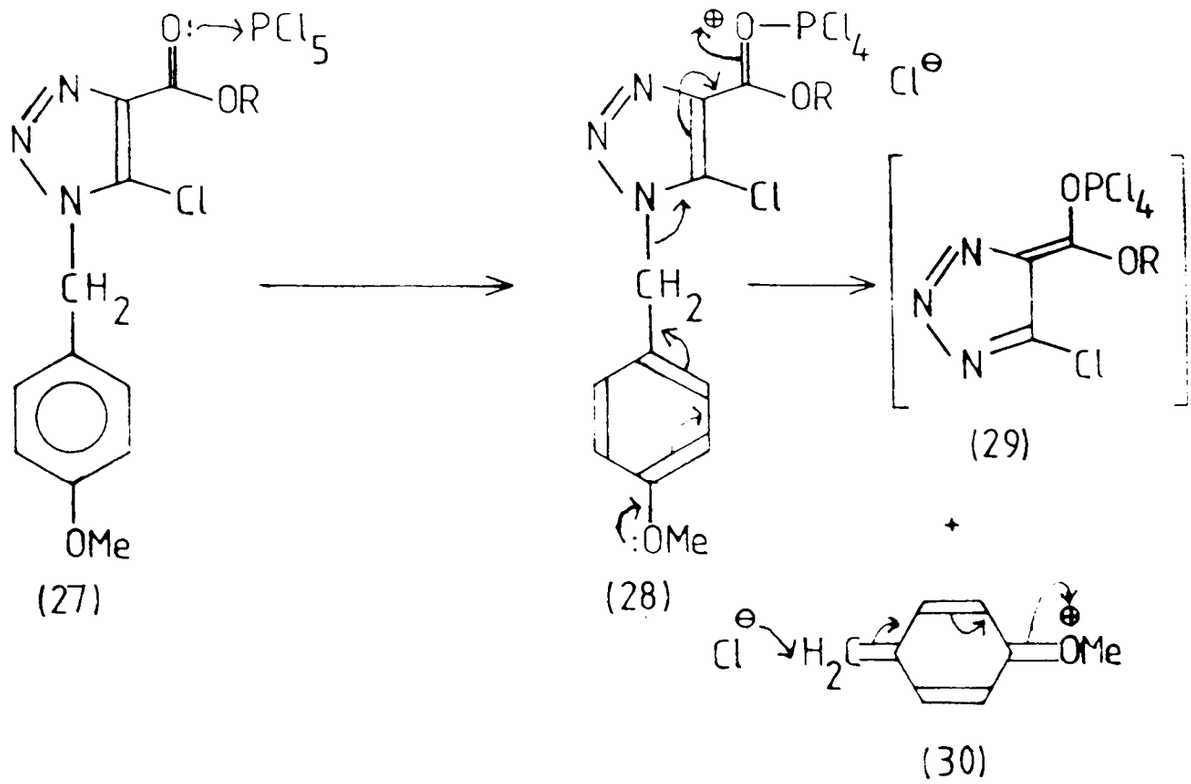
Scheme 14: Preparation of 5-chloro-1-(4-methoxybenzyl)-4-methoxycarbonyl-1,2,3-triazole

this/

this can be accounted for by Buckle's original observation that under these reaction conditions the p-methoxybenzyl group was rather labile, and the N-2 and N-3 derivatives are formed as by-products.

Studies by Buckle indicated that this rearrangement depended on the presence of phosphorus oxychloride and phosphorus pentachloride. The lability of the p-methoxybenzyl group had been observed previously under von Braun conditions[19].

By means of an explanation for this observation Buckle suggested the following mechanism (Scheme 15):



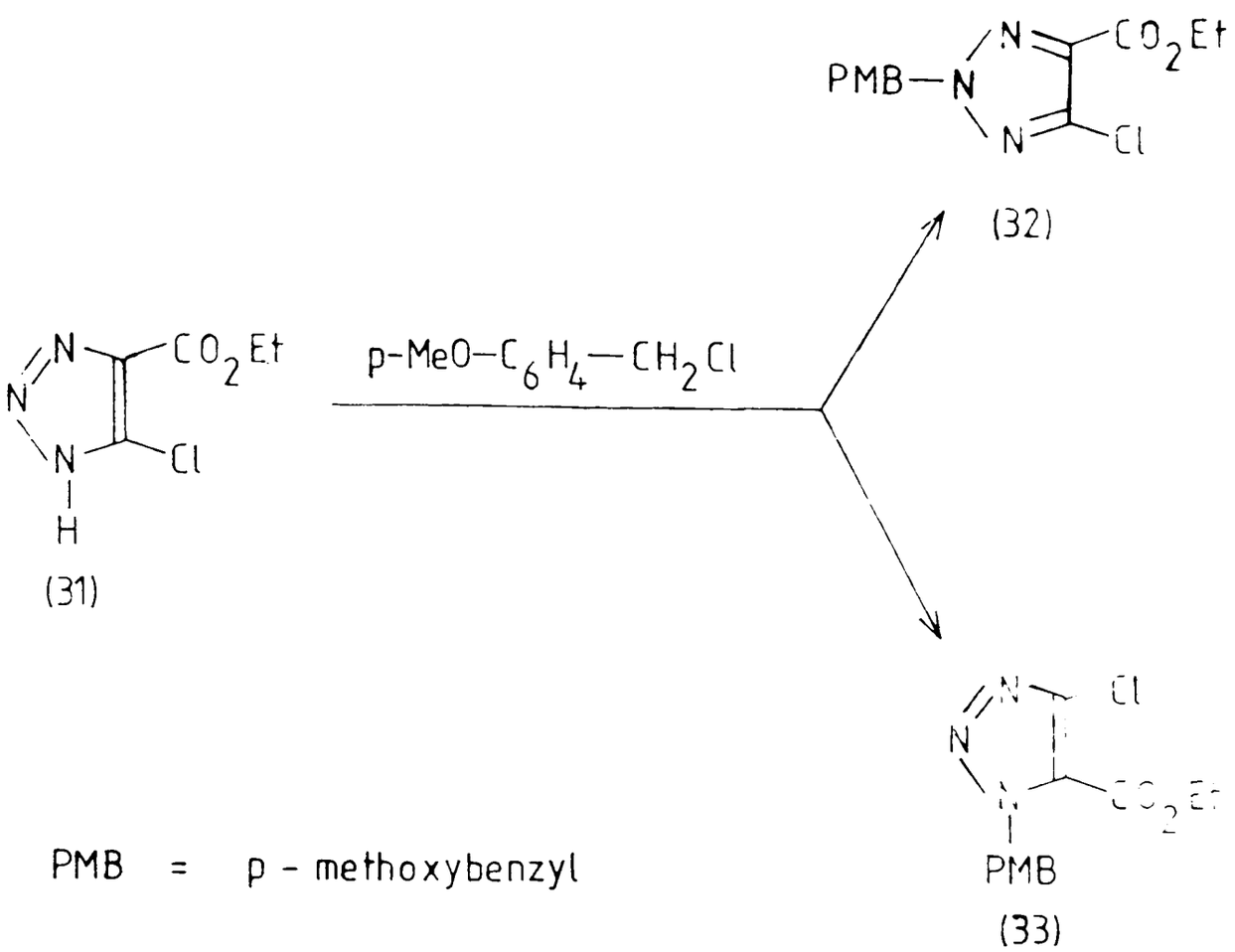
Scheme 15: Removal of p-methoxybenzyl group during preparation of chloro triazole

In/

In this scheme the activation for methoxybenzyl cleavage at N-1 is provided by the ability of the ester group and the cross conjugated azo-group to disperse negative charge in the transition state. Phosphorus pentachloride is thought to co-ordinate with the ester carbonyl group resulting in a reduction in activation energy. Realkylation of the proposed intermediate (29) with the reactive species (30), or with p-methoxybenzyl chloride then leads to the N-2 and N-3 isomers. Reduced stabilisation exists in the N-2 and N-3 isomers and they do not undergo this rearrangement.

Some support for this mechanism was obtained by observation of the products formed in the reaction between the N-unsubstituted triazole (31) with p-methoxybenzyl chloride in toluene at reflux temperature (Scheme 16). In the presence of catalytic amount of both phosphorus pentachloride and phosphorus oxychloride the N-2 and the N-3 compounds were exclusively formed in the ratio 3:2. The alkylation proceeded slowly in the absence of the two phosphorus reagents.

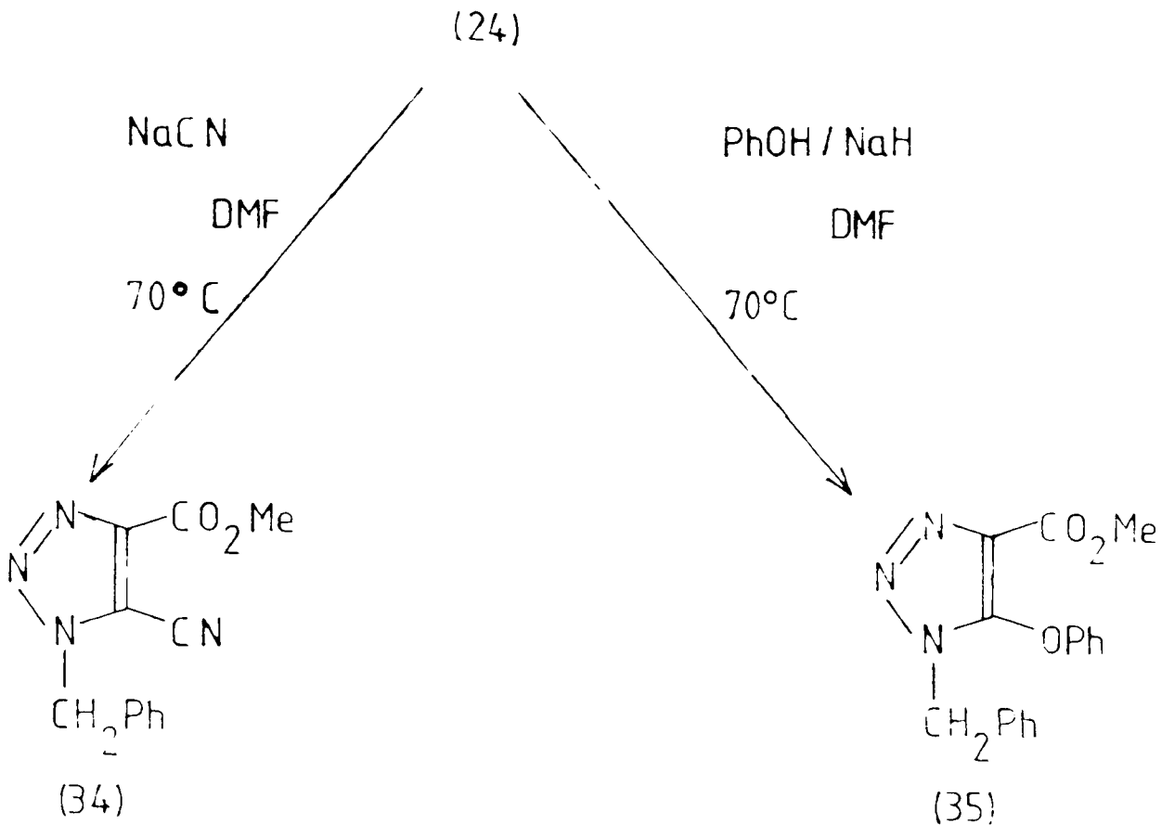
Scheme 16:/



Scheme 16: Realkylation of 5-chloro-4-ethoxycarbonyl-1,2,3-triazole with p-methoxybenzyl chloride

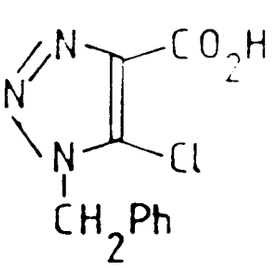
Having obtained these 5-chloro-1,2,3-triazoles, it was decided to attempt nucleophilic displacement of the 5-chloro group. The following reactions shown in Scheme 17 succeeded, in reasonable yields:

Scheme 17:/



Scheme 17: Reactions of 1-benzyl-5-chloro-4-methoxycarbonyl-1,2,3-triazole with various nucleophiles

Attempted displacement of the 5-chloro group was attempted with sodium methoxide in methanol failed to yield the desired product, but on work-up the 4-carboxylic acid (36) was formed. This product was formed possibly by hydrolysis of the ester function, due to

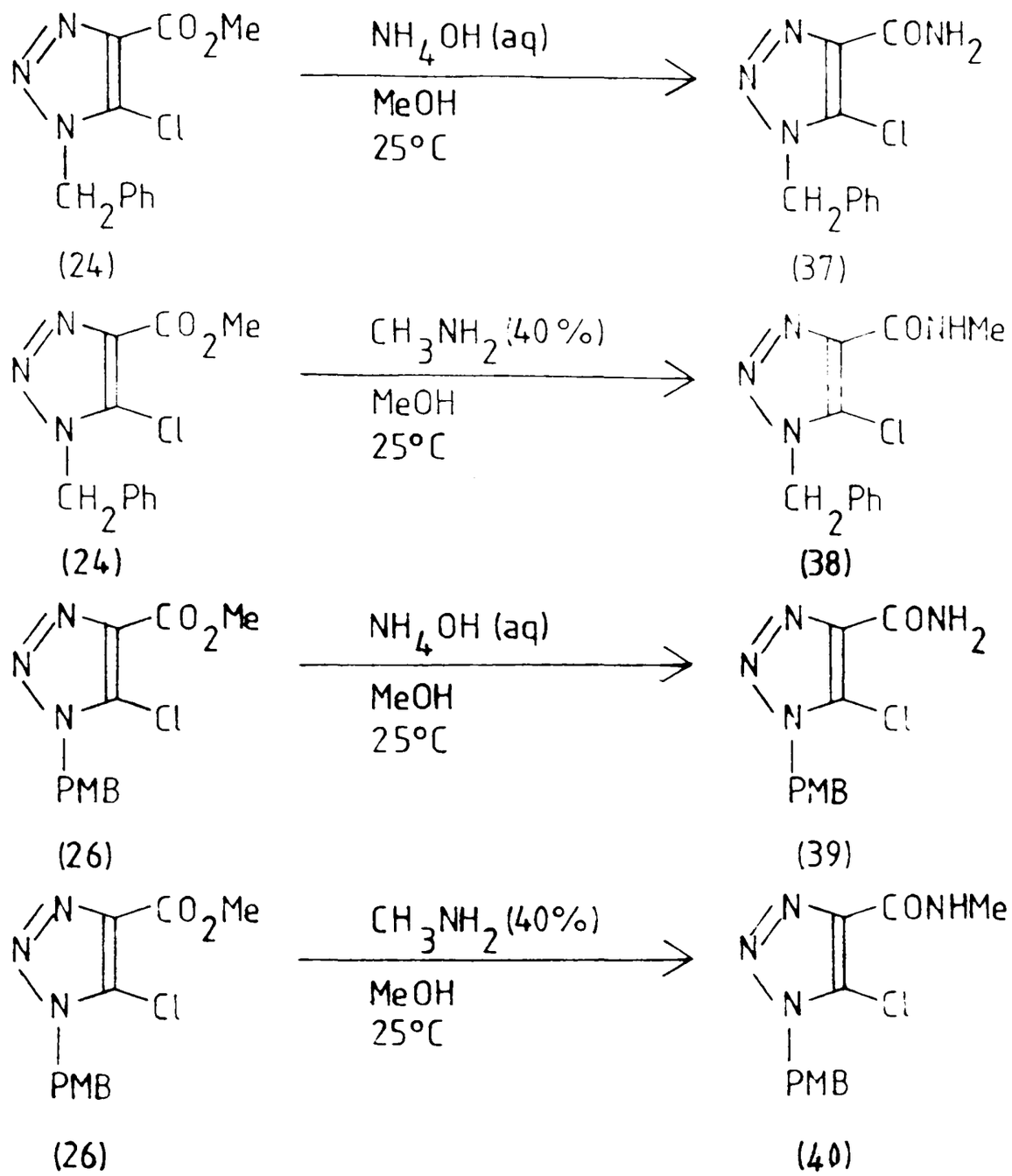


(36)

atmospheric/

atmospheric moisture being present during the course of the reaction.

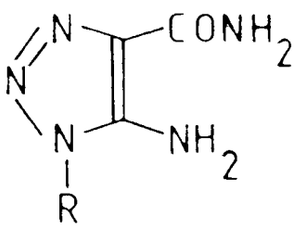
Most importantly we were interested in obtaining 4-carboxamido-5-amino-1,2,3-triazoles or 5-amino-1,2,3-triazoles by nucleophilic displacement with NH_3 The following initial reactions were carried out (Scheme 18):



Scheme 18: Reactions of 5-chloro-1,2,3-triazoles with ammonia and methylamine

The

The intention of the above reaction was to produce (41) which is a precursor of 8-azapurines. The next attempt to displace the chloro-group was to bubble dry ammonia through a solution of (24) or (26) in D.M.S.O. No reaction was observed, and the starting materials were retrieved.

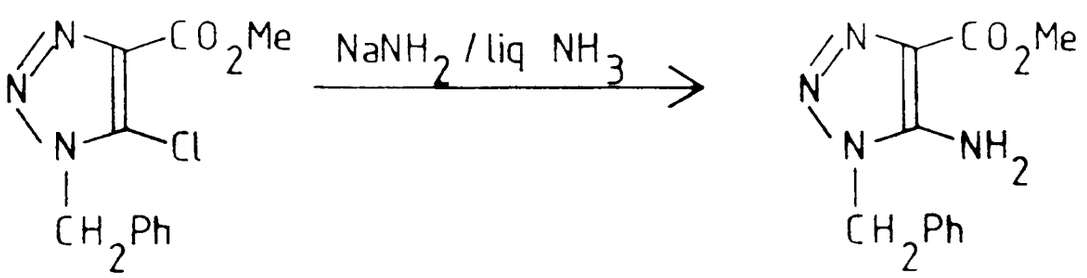


R = a) $PhCH_2$-

b) (p)-MeO-C_6H_4-CH_2-

(41)

The next attempt was to use more drastic conditions. The following reaction was attempted (Scheme 19):



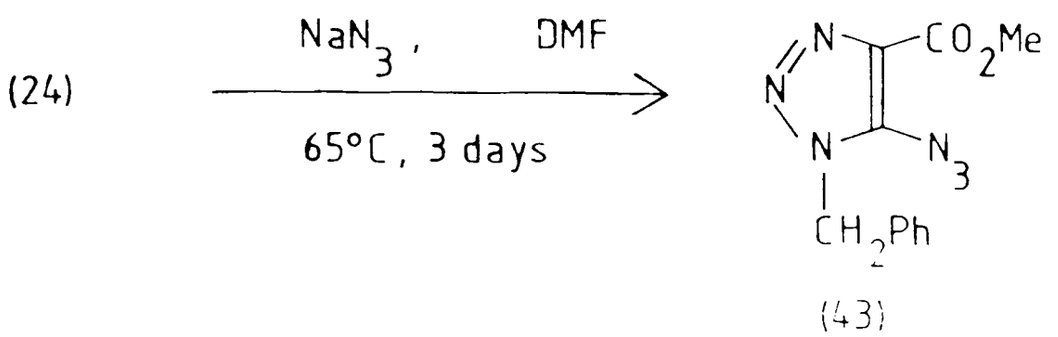
(24) (42)

Scheme 19:

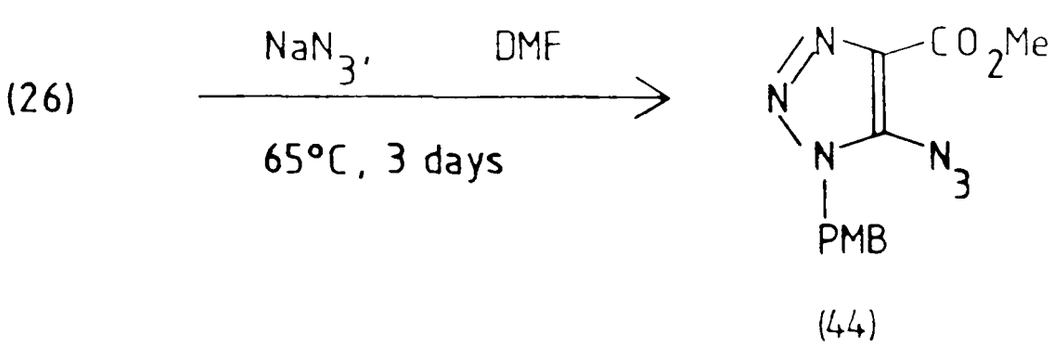
A reaction was observed, but no product was isolated, even by continual extraction with dichloromethane or ethyl acetate. It seems likely that the triazole has been destroyed during the course of this reaction.

The/

The chloro-triazoles (24) and (26) eventually underwent azidolysis reactions with sodium azide in D.M.F at 65°C (Scheme 20). These azido-triazoles were obtained in moderate yields because of side reactions (thermolysis of the 5-azido group).



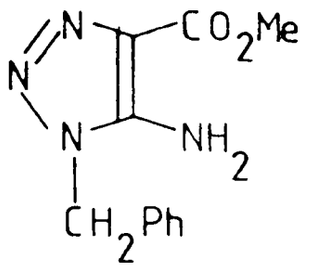
(43)



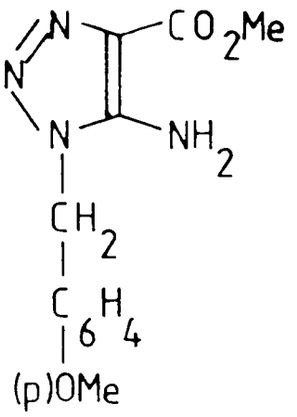
(44)

Scheme 20: Preparation of azido-triazoles

One of the impurities observed in these preparations was the 5-amino-triazole (45) or (46), which was probably formed when the 5-azido group, thermolysed to nitrogen, and a nitrene. This nitrene probably extracts hydrogen from the solvent to form the/



(45)

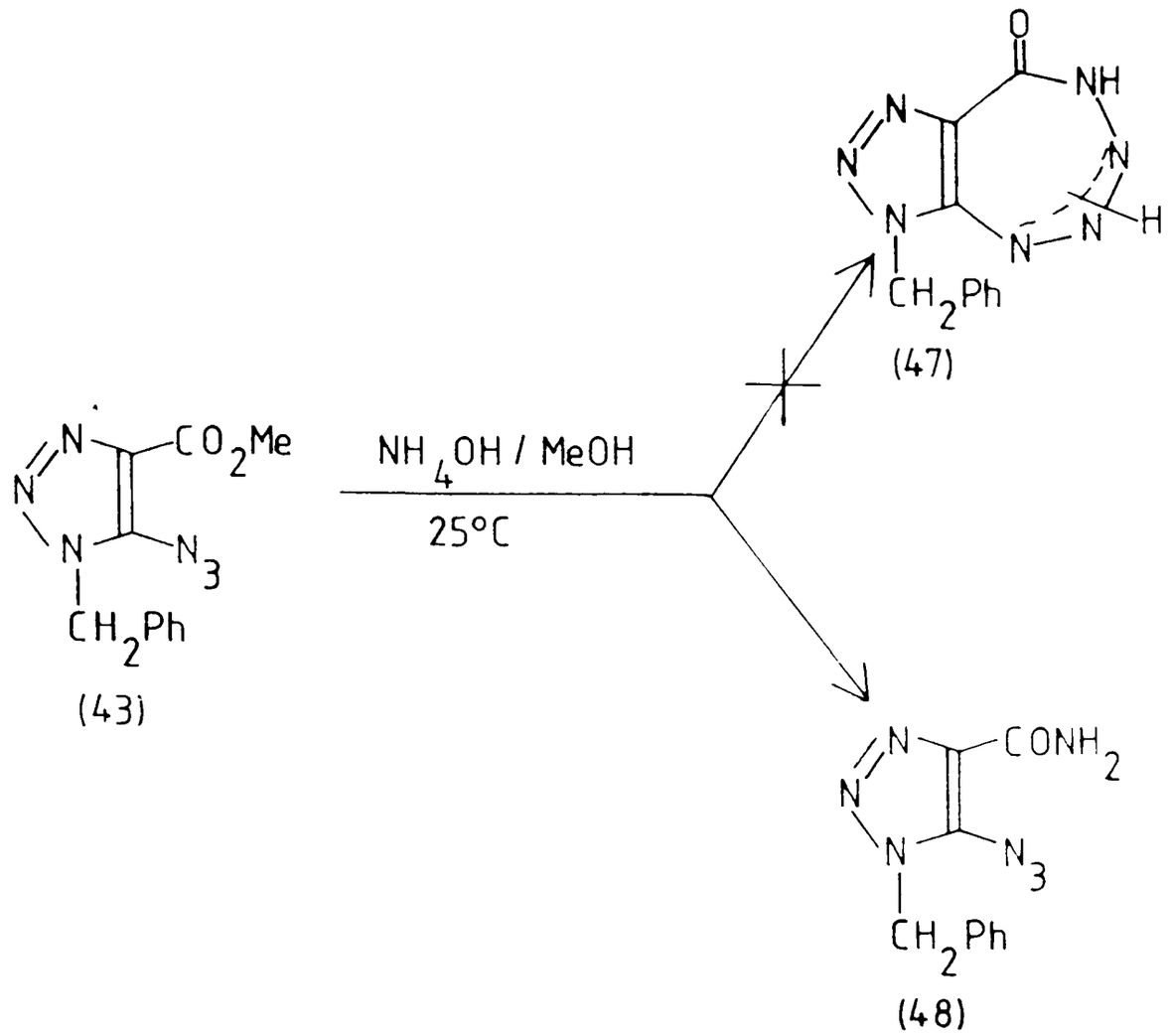


(46)

the 5-amino triazole.

The p-methoxybenzyl-amino triazole (46) and the benzyl analogue (45) were prepared in yields of 45% and 80% respectively from (44) and (43) by catalytic hydrogenation at 25°C and atmospheric pressure using 10% palladium on charcoal catalyst.

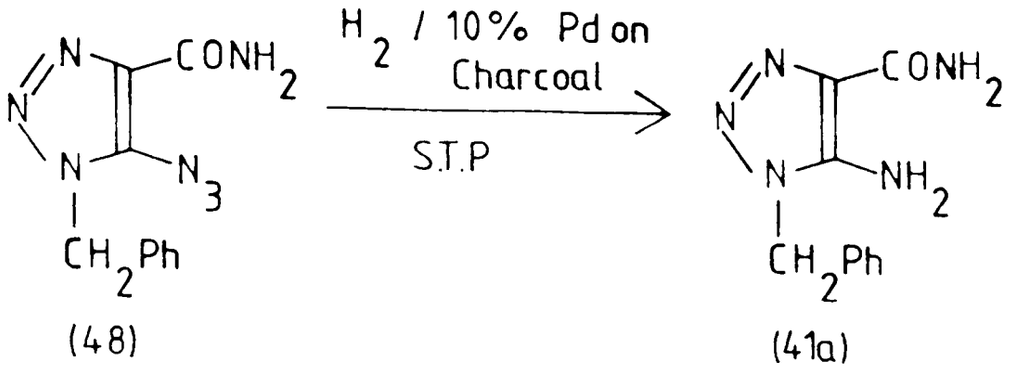
It was thought that ammonolysis of the ester function in (43) may have yielded the novel bicyclic compound (47) by an intramolecular cycloaddition of the azide group on the amide group. This novel compound was not observed and the sole product was the 5-azido-4-carboxamido triazole (48) (Scheme 21). This compound proved to be a/



Scheme 21: Ammonolysis of 5-azido-1-benzyl-4-methoxycarbonyl-1,2,3-triazole

be a convenient precursor for 5-amino-1-benzyl-1,2,3-triazole-4-carboxamide (41a). Catalytic hydrogenation of (48) furnished an excellent yield of (41a) (Scheme 22).

Scheme 22:/

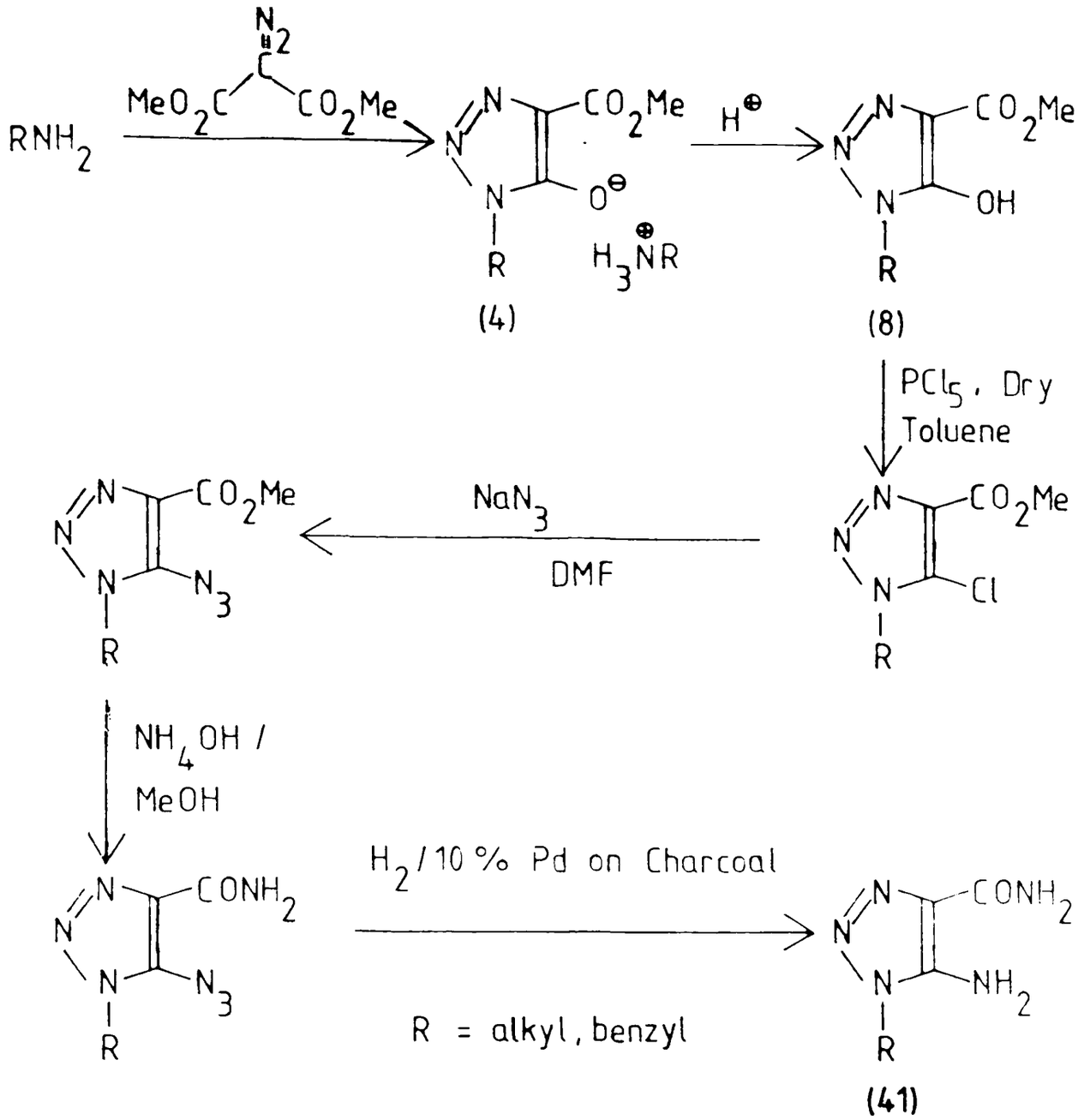


Scheme 22: Preparation of 5-amino-1-benzyl-1,2,3-triazole--4-carboxamide

The product (41a) is a very important precursor for the production of 8-azapurines. Thus a method has been devised wherein 5-chloro-1,2,3-triazoles can be utilized in the synthesis of 8-azapurines.

A summary of the synthesis is shown in Scheme 23.

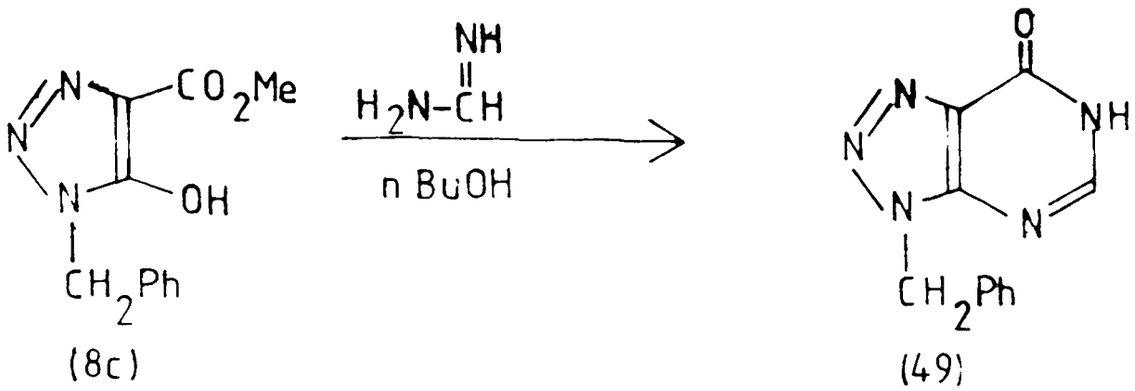
Scheme 23:/



Scheme 23: Preparation of 8-azapurine precursor from a primary alkyl amine.

2.4. ATTEMPTED PYRIMIDINE RING CLOSURES ON 5-HYDROXY AND 5-CHLORO-1,2,3-TRIAZOLES

The following reaction was attempted (Scheme 24) because of the desirability of making azapurines directly from the easily obtainable 5-hydroxy-1,2,3-triazoles. The reaction proved fruitless, in addition to attempts with several nucleophiles including guanidine and/

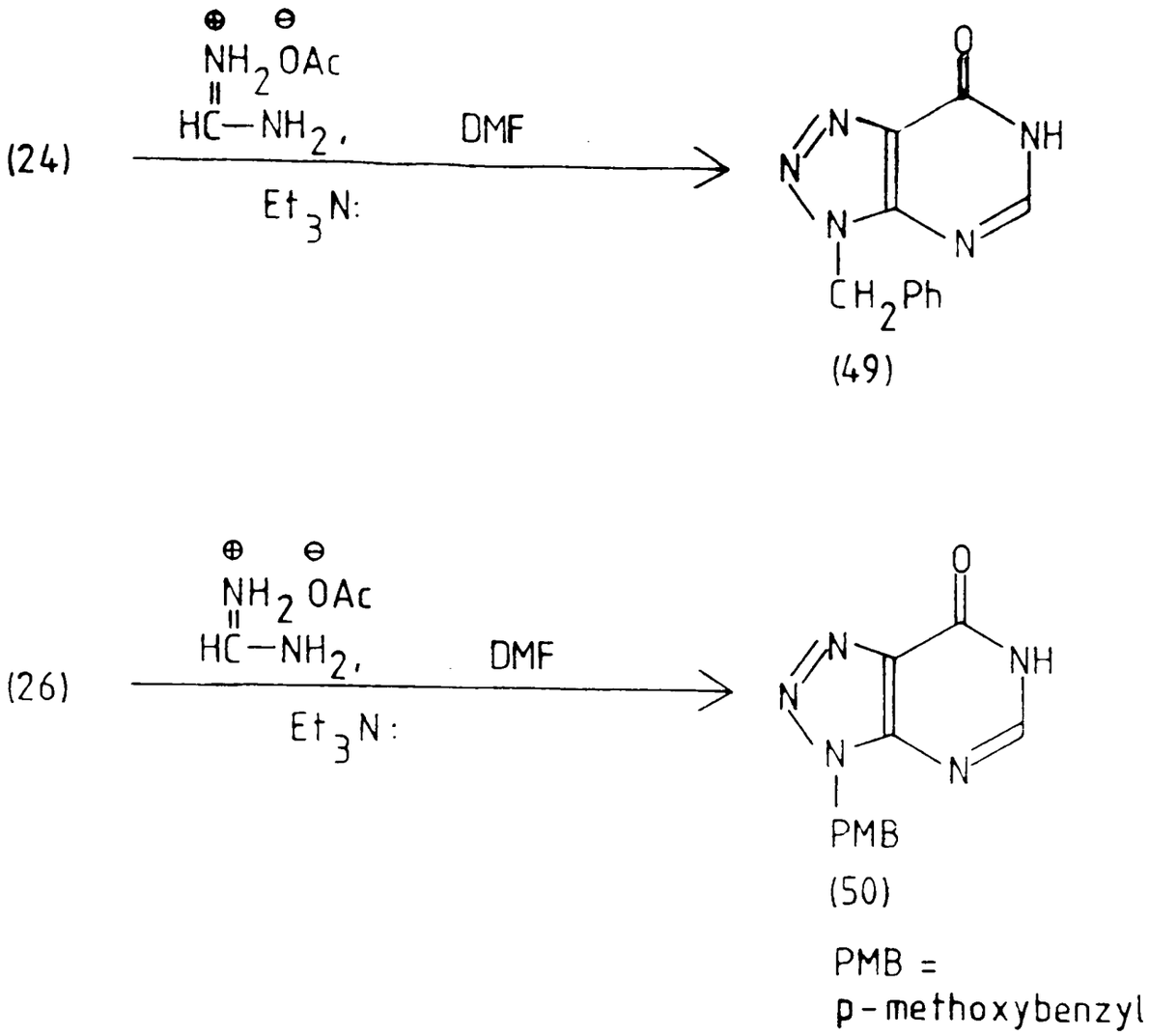


Scheme 24: Reaction of 1-benzyl-5-hydroxy-4-methoxycarbonyl--1,2,3-triazole with formamidine

and acetamidine. Thermal isomerisation of (8c) to the ∝ -diazoamide was observed and it would appear that the diazoamide thus formed fails to undergo the required reaction.

It was felt that since the chloro group is a better leaving group than hydroxy then perhaps it would be more useful to use the 5-chloro-1,2,3-triazoles (24) and (26) in conjunction with formamidinium acetate. The reaction conditions are outlined in Scheme 25.

Scheme 25:/



Scheme 25: Attempted use of 5-chloro-1,2,3-triazoles in 8-azapurine preparation

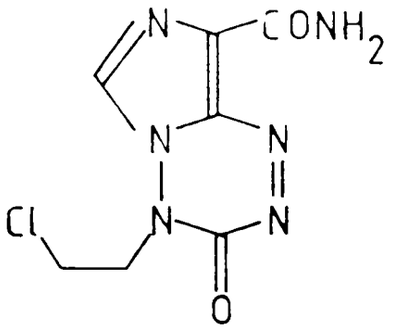
These two reactions were carried out at temperatures between 25° and 100°C. No reaction was observed, this being proven by t.l.c analysis, which indicated that the starting triazoles remained unchanged.

When one considers the results in 2.3. with respect to the inertness of/

of the 5-chloro group towards nitrogen nucleophiles then this observation is consistent with those results in 2.3.

2.5. SOME ATTEMPTED CYCLISATIONS ON 5-DIAZO-1,2,3-TRIAZOLES

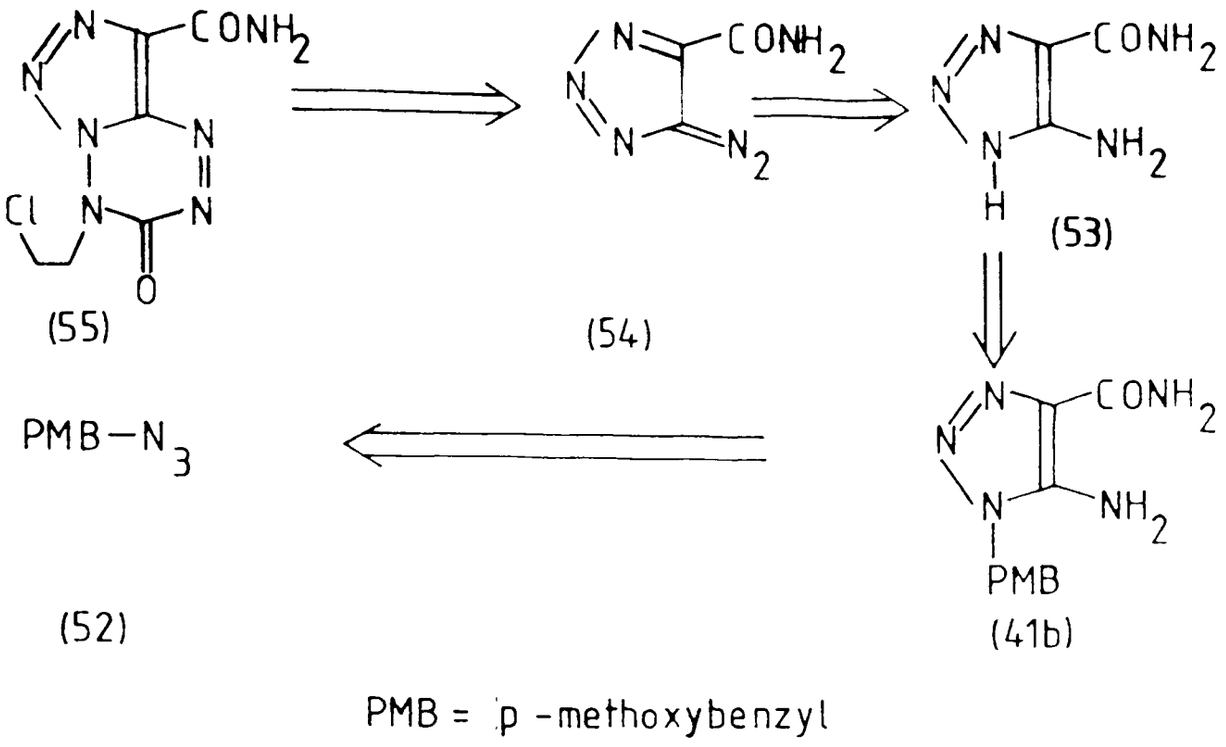
In 1982 at a meeting of the Pharmaceutical Society in Edinburgh, Malcolm Stevens of the University of Aston in Birmingham announced the discovery of a new and interesting compound which was then named AZLASTONE (51).[20] In preliminary trials azlastone had shown considerable promise as an anti-tumour agent.



(51)

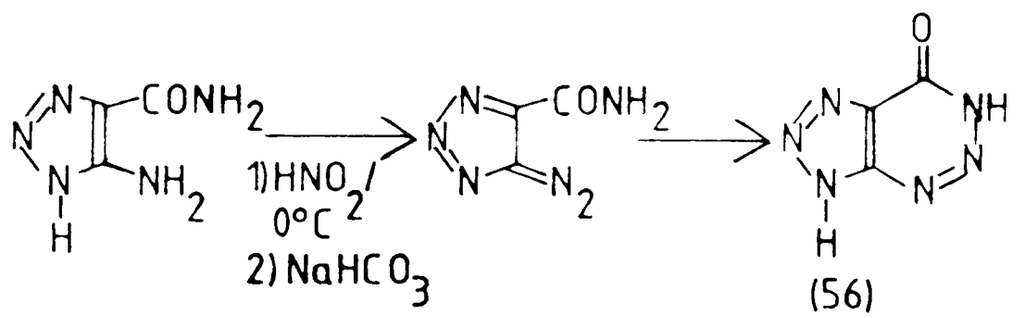
It was decided to investigate the possibility of azlastone analogue synthesis. The retrosynthetic route is shown in Scheme 26.

Scheme 26:/



Scheme 26: Proposed retrosynthesis of azlastone analogue

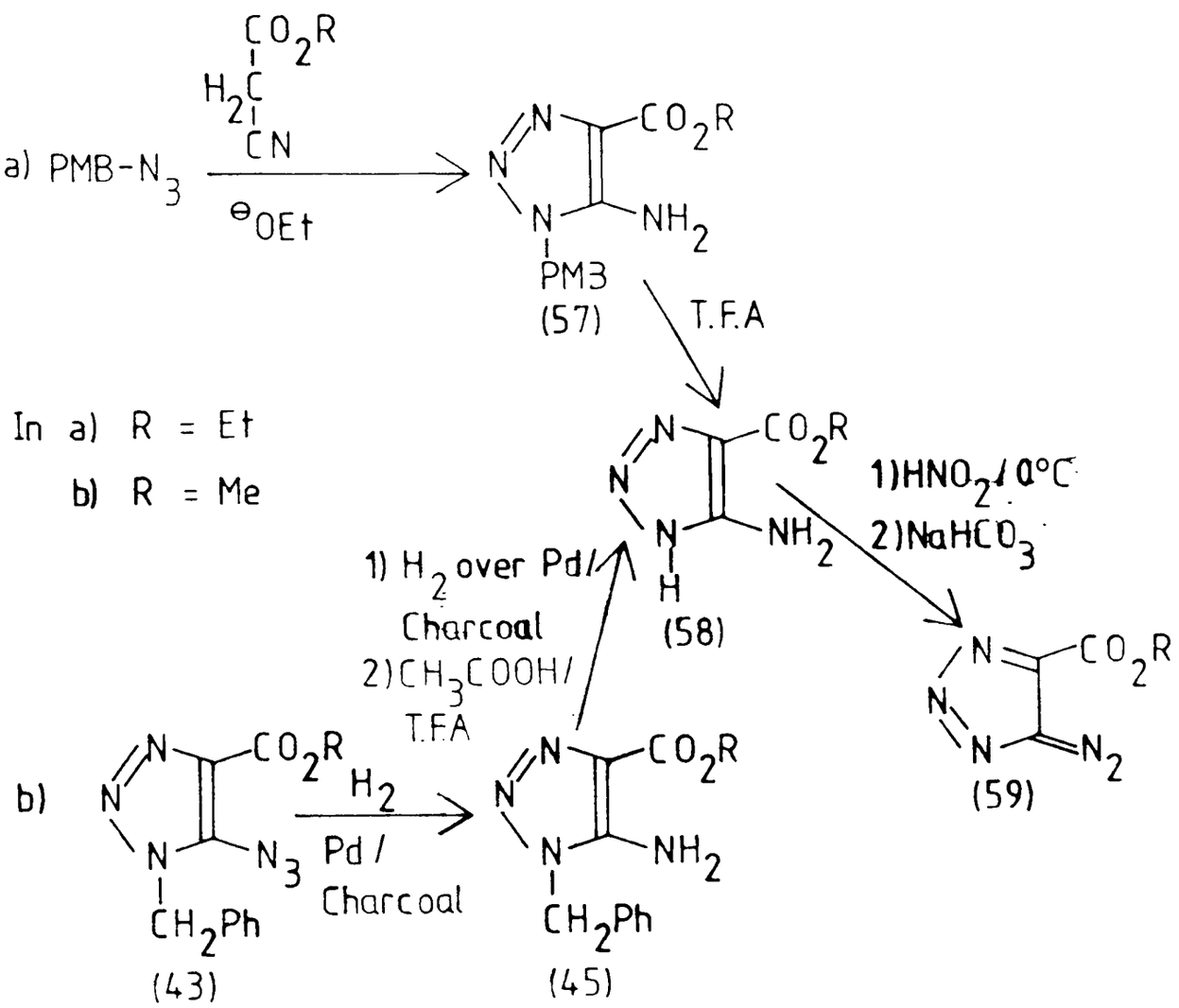
p-Methoxybenzyl azide was cyclised with cyanoacetamide in the presence of sodium ethoxide to yield the aminotriazole-carboxamide (41b) in a 69% yield. The compound was easily debenzylated with trifluoroacetic acid at 65°C to yield 5-amino-1,2,3-triazole-4-carboxamide (53). Attempted diazotisation of (53) ⟶ (54) failed because an unwanted side reaction appeared to lead to the cyclized product (56) (Scheme 27).



Scheme 27: Attempted preparation of 5-diazo-1,2,3-triazole -4-carboxamide.

This unfortunate side reaction has been noted previously to proceed in either acidic or alkaline media.[21] It therefore was deemed desirable to generate the 4-carboxamido group at a later stage in the sequence or if necessary left out from the reaction product completely.

Two different synthetic routes were attempted, and these are summarised in Scheme 28.



Scheme 28: Preparation of 4-alkoxycarbonyl-5-diazo-1,2,3-triazole

In route (a) the alkali-induced cyclization of p-methoxybenzyl azide with/

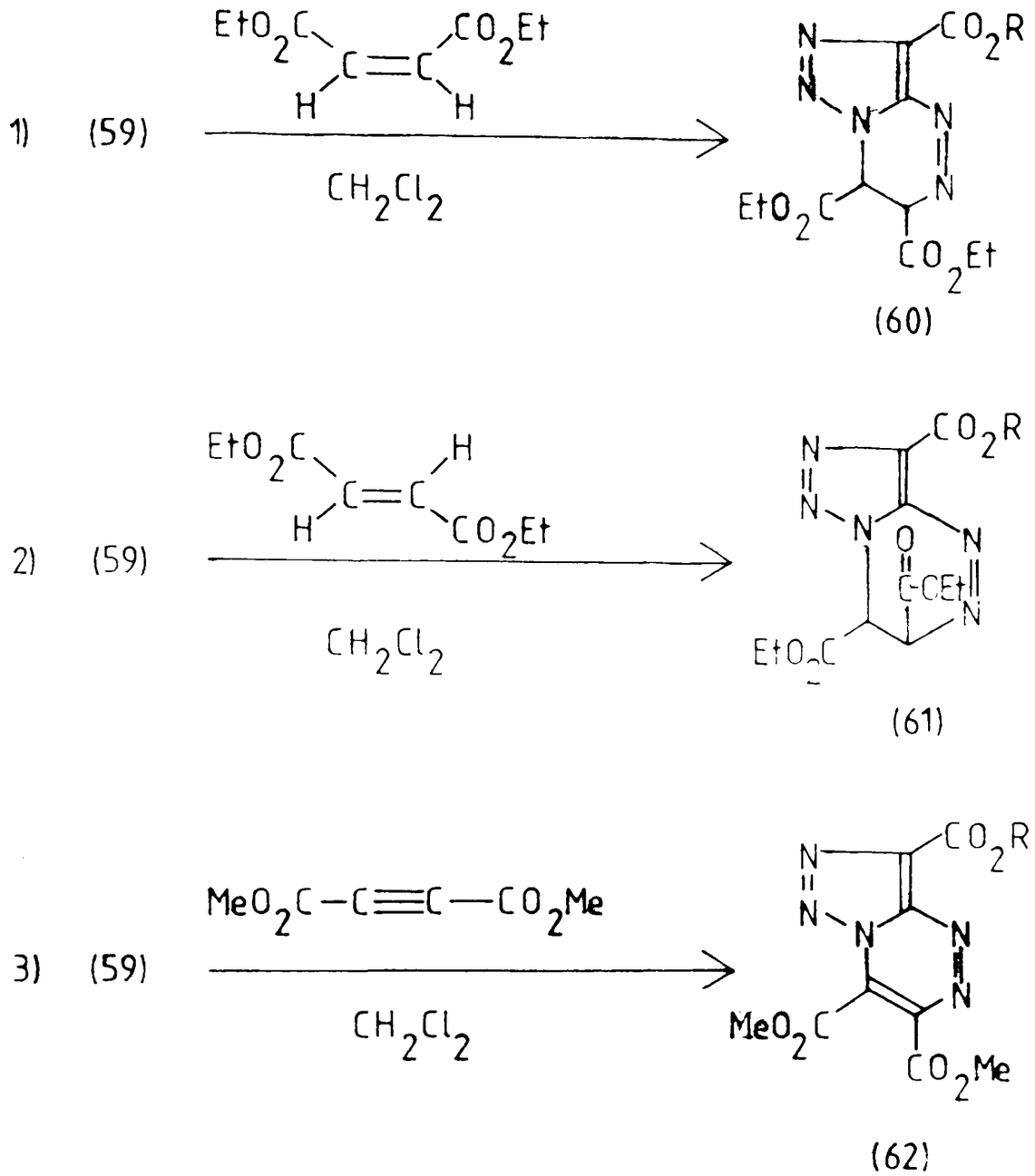
with ethyl cyanoacetate led to a poor yield (~ 15%) of the triazole (57) (R = Et). This compound was easily debenzylated with trifluoroacetic acid to yield (58a) in a 64% yield. This compound was diazotized, utilizing a literature procedure[22] wherein the starting 5-amino-1,2,3-triazole was stirred with a nitrous acid mixture for 2 hours at 0°C. This reaction mixture was neutralized with sodium bicarbonate and the 5-diazo-1,2,3-triazole was extracted into dichloromethane. In the interests of safety it was thought advisable to store these yellow compounds as concentrated dichloromethane solutions in the dark at 5°C.

The 5-diazo-1,2,3-triazole (59a) was characterized by I.R. spectroscopy with a strong stretch of 2180 cm^{-1}.

Route (b) proved more satisfactory in terms of the yields in each step. Debenzylation of (45)was accomplished by catalytic hydrogenolysis to yield (58b) (R = Me) in a 70% yield. This 5-amino-1,2,3-triazole was diazotised in a similar manner to (58a).

The following cycloadditions were attempted (Scheme 29):

Scheme 29:/



Scheme 29: Attempted cyclisation of 4-alkoxycarbonyl-5-diazo -1,2,3-triazoles

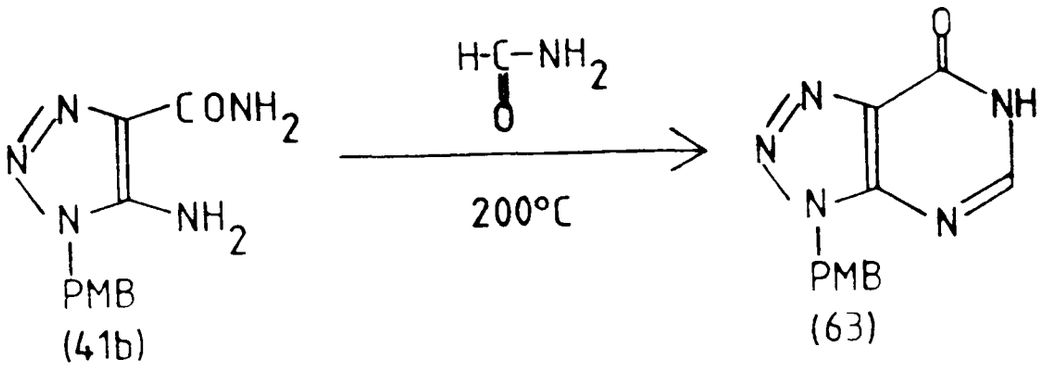
No reactions were observed in the above reactions, using (59a) or (59b) even after stirring in the dark at 25°C for 3 weeks. When (59a)/

(59a) was refluxed with diethyl maleate (Reaction 1), there did appear to be some decomposition of (59a).

No reaction was carried out with 2-chloroethyl isocyanate and (59a) and (59b), although it is felt that this reaction should be investigated.

2.6. PREPARATION OF 8-AZAPURINES

During the course of research, no new methods of synthesising 8-azapurin-6-ones were uncovered, so it was decided to prepare new benzylic analogues, using existing methodology. Utilizing 5-amino-1- (4-methoxybenzyl)-1,2,3-triazole-4-carboxamide (41b), with formamide the following 8-azapurin-6-one was prepared in a 75% yield (Scheme 30).

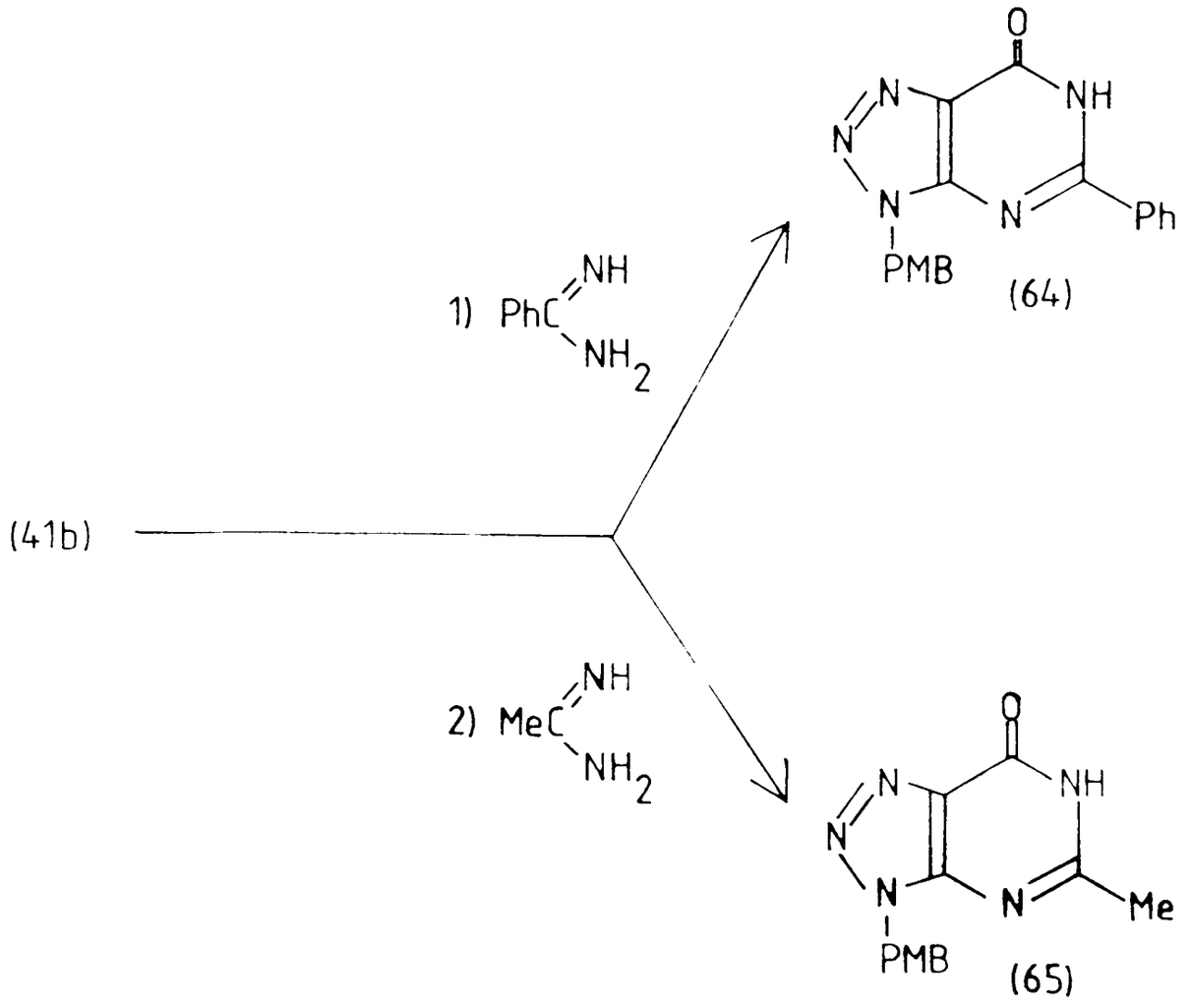


PMB = p-methoxybenzyl

Scheme 30: Preparation of 3-(4-methoxybenzyl)-[3H]-1,2,3-triazolo-[4,5-*d*]pyrimidin-7-one.

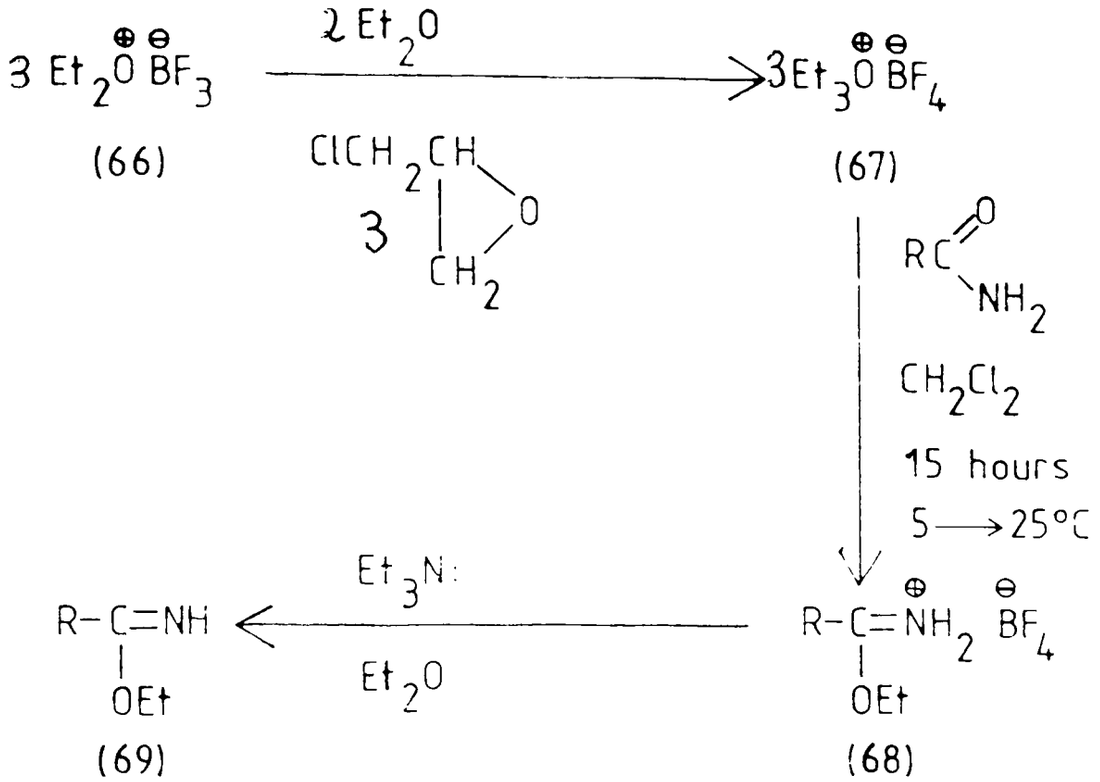
From this point, it was thought that perhaps if (41b) were condensed with acetamidine or benzamidine then the appropriate 2-substituted analogue/

analogue would be prepared (Scheme 31). These reactions proved fruitless and only the starting triazole was recovered from the



Scheme 31: Attempted preparations of 2-substituted 8-azapurin-6-ones

reactions. It was then decided to investigate the reactions of imidates with (41b). The imidates were prepared from the corresponding amides (where R = Ph, or Me) (Scheme 32). A literature precedent exists for a reaction between ethyl acetimidate acetate/



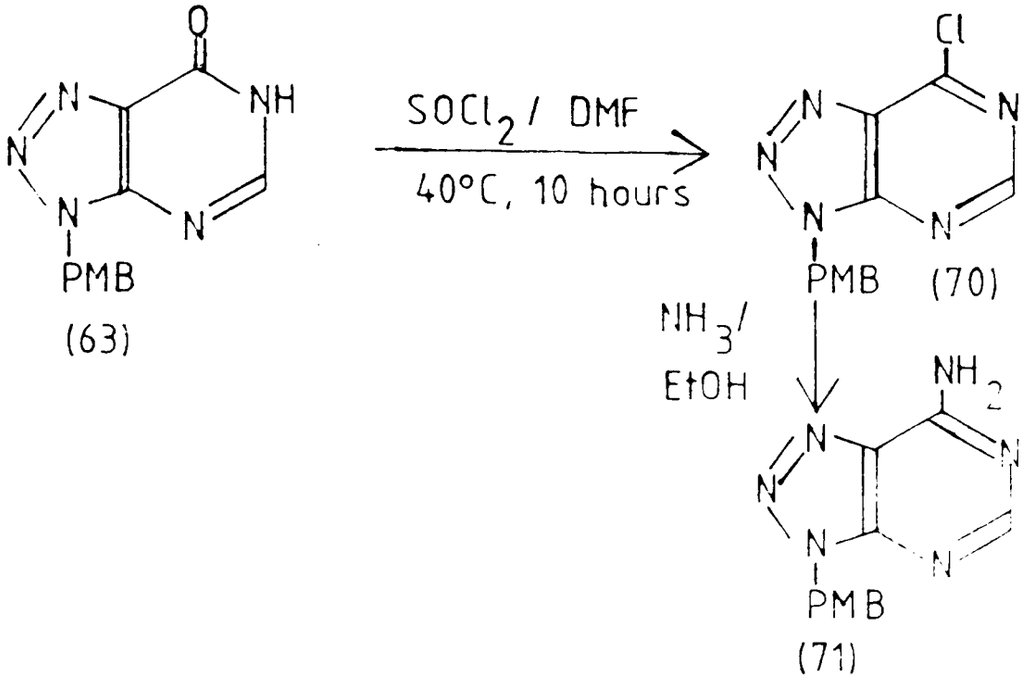
Scheme 32: Preparation of imidates

acetate and an amino-triazole-carboxamide.[23] A product was obtained in a low yield and it was difficult to purify.

In the reactions between ethyl acetimidate and ethyl benzimidate with (41b) in octanol at 120°C only the starting materials were recovered. Albert noted similar results, and suggested that the electron-donating 1-alkyl substituents may have impeded the splitting off/

off of a proton from the 5-amino groups.[23]

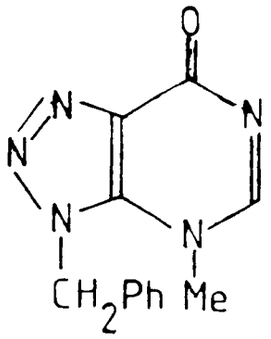
The 8-azapurin-6-one (63) was utilized in the preparation of the 8-azaadenine derivative (71) (Scheme 33).



Scheme 33: Preparation of 7-amino-3-(4-methoxybenzyl)-[3H]-1,2,3-triazolo-[4,5-d]pyrimidine (71)

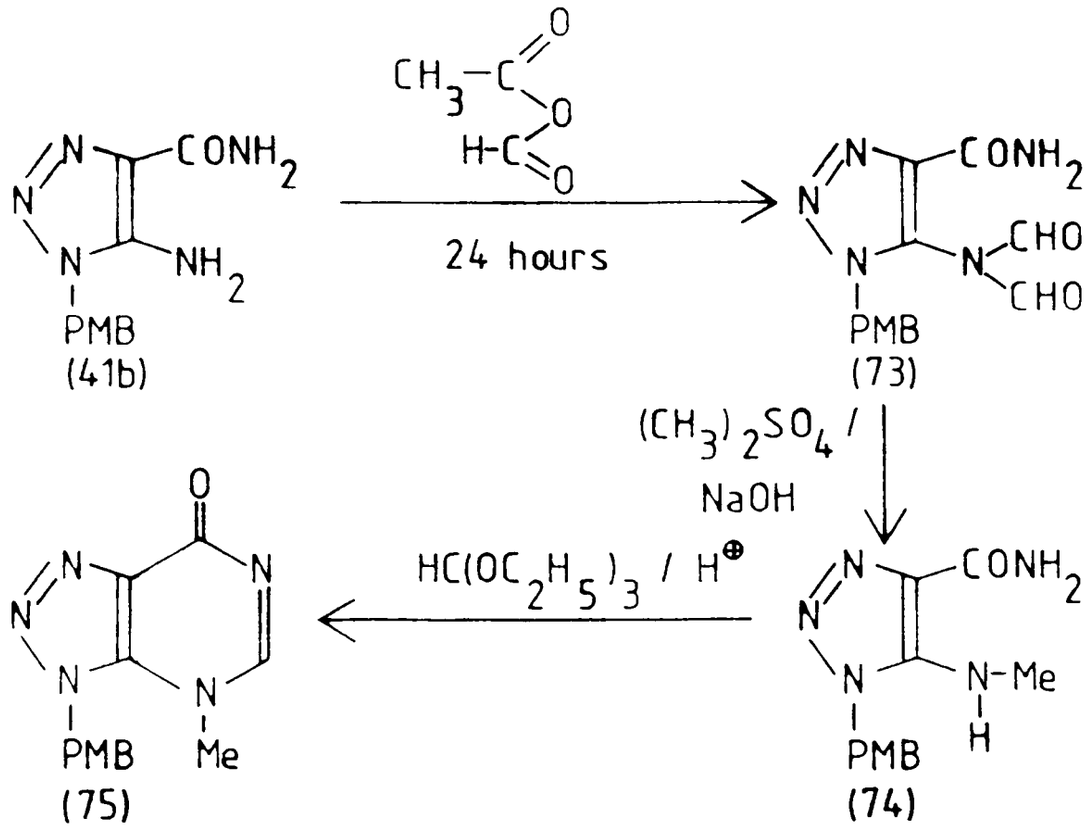
This reaction was accomplished via the chloro-azapurine intermediate (70). Compound (70) had to be reacted quickly with ethanolic ammonia, as (70) was rapidly hydrolysed in humid laboratory conditions to (63). The yield of the 8-azaadenine derivative (71) was good (79%).

Albert has synthesised the following compound because he was interested/



(72)

interested in investigating the properties of 3-substituted 8-azapurines.[24] His work was duplicated in Scheme 34 to prepare the p-methoxybenzyl analogue of (72), and also to prepare the 2,3-disubstituted 8-azapurines.



Scheme 34: Preparation of 3-(4-methoxybenzyl)-4-methyl[3H]-1,2,3-triazolo-[4,5d]pyrimidin-7[4H]-one (75)

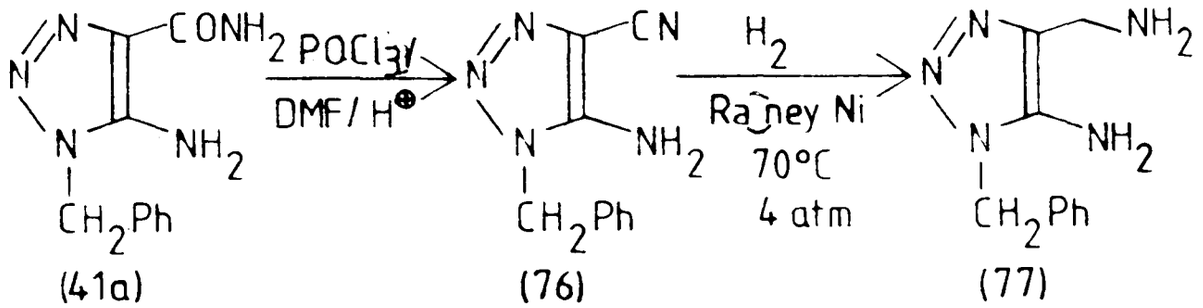
(41b)/

(41b) was diformylated with acetic formyl anhydride in a 54% yield. The anhydride was prepared using the recommended literature procedure.[25] The N-diformyl-1,2,3-triazole was stirred at ambient temperature with dimethyl sulphate and 1M sodium hydroxide to yield the N-methylamino-triazole (74) in an excellent (84%) yield. The next step, the pyrimidine ring closure was achieved in a 70% yield using triethyl orthoformate and concentrated hydrochloric acid.

When portions of (74) were reacted with triethyl orthoacetate and triethyl orthobenzoate to add methyl and phenyl in the 2-position no products were observed.

2.7. PREPARATION OF 4-AMINOMETHYL-1,2,3-TRIAZOLES FROM 4-CARBOXAMIDO-1,2,3-TRIAZOLES

5-Amino-4-aminomethyl- 1,2,3-triazoles are important precursors to 1,6-dihydro-8-azapurines. These triazoles were prepared by Albert[26] in two steps from 5-amino-4-carboxamido-1,2,3-triazoles (Scheme 35). The 1-benzyl derivative (76) was obtained by the



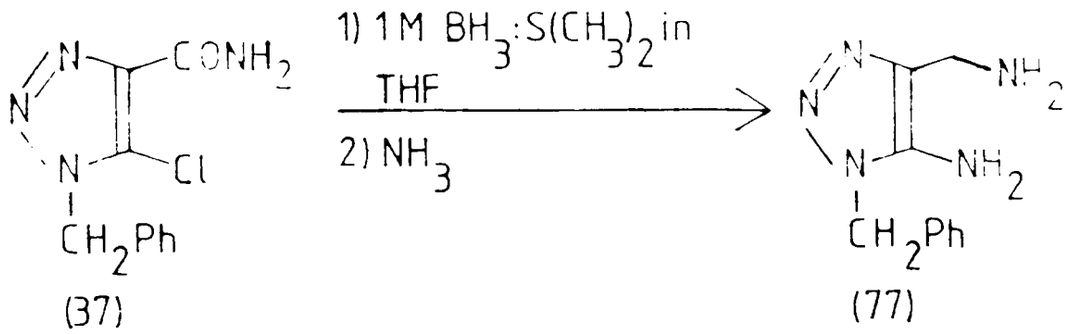
(41a) (76) (77)

Scheme 35: Two-step preparation of 5-amino-4-aminomethyl-1-benzyl-1,2,3-triazole (77)

combined/

combined action of phosphoryl chloride and dimethylformamide on (41a), followed by acidic hydrolysis without isolation of the resulting amidine. Hydrogenation of the amino-nitrile (76) gave a good yield of the required 1-benzyl derivative of 5-amino-4-aminomethyl-1,2,3-triazole (77).

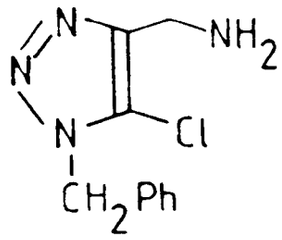
In an attempt to find a more convenient preparation of compounds such as (77), it was felt that a direct reduction of (41a) with diborane would be a useful method. The following reaction was attempted (Scheme 36). (37) was refluxed for 2 days with



Scheme 36: Attempted preparation of 5-amino-4-aminomethyl-1-benzyl-1,2,3-triazole

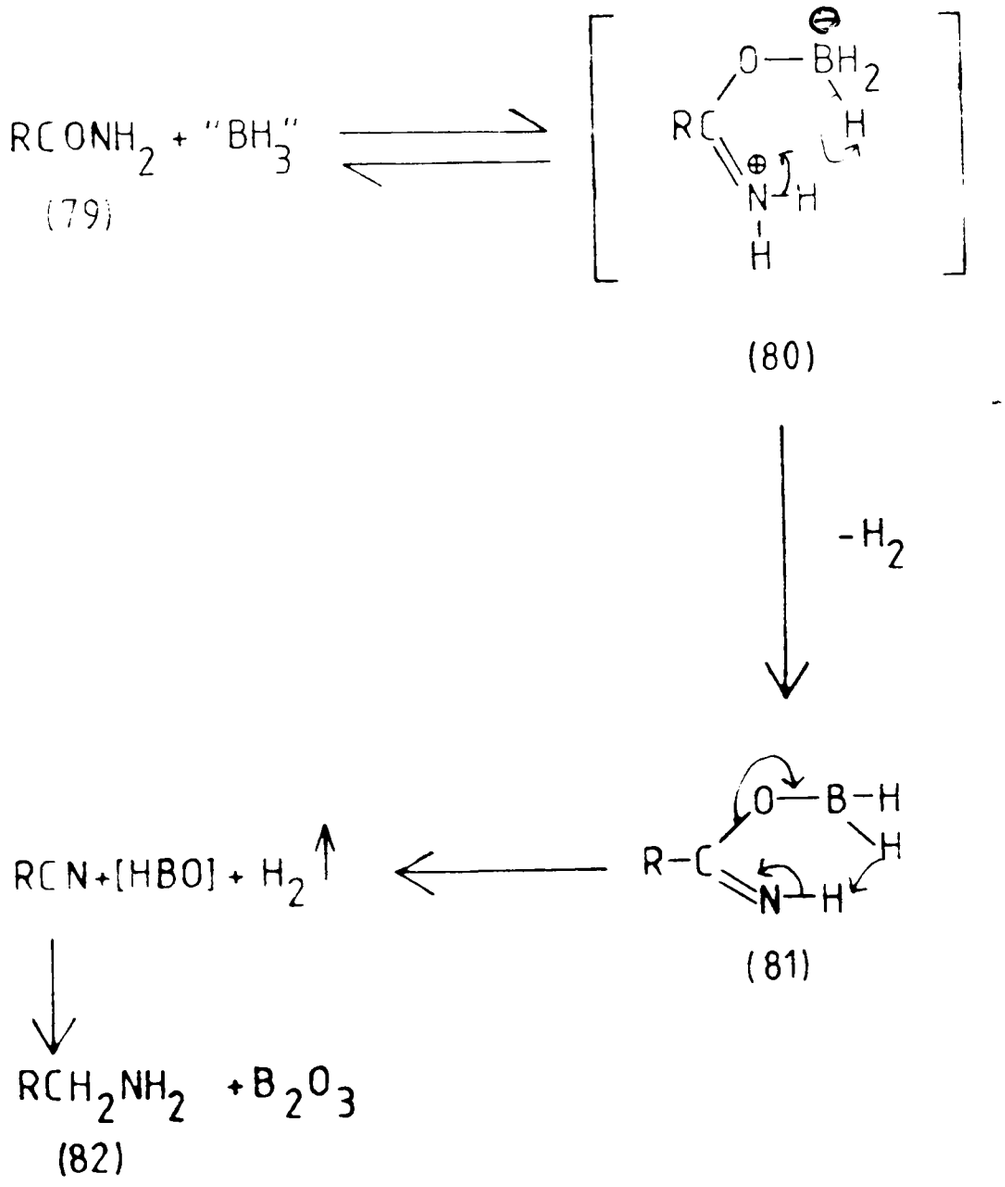
borane dimethyl sulphide (1M solution in THF) to reduce the carboxamide function. At the end of this period dry ammonia was bubbled through the reaction mixture to attempt to displace the 5-chloro function. The product that was isolated was 4-aminomethyl-1-benzyl-5-chloro-1,2,3-triazole (78) which was purified as its hydrochloride in a 65% yield.

Thus/



(78)

Thus it appears that the amide function has been reduced successfully. The following mechanism is suggested[27] (Scheme 37):



Scheme 37: Mechanism of amide reduction by diborane

(77)

(77) was conveniently prepared in a 46% yield from (41a) by refluxing (41a) with borane dimethyl sulphide. The product was isolated and purified as its hydrochloride salt, and was identical in all respects to the material prepared by Albert.[26]

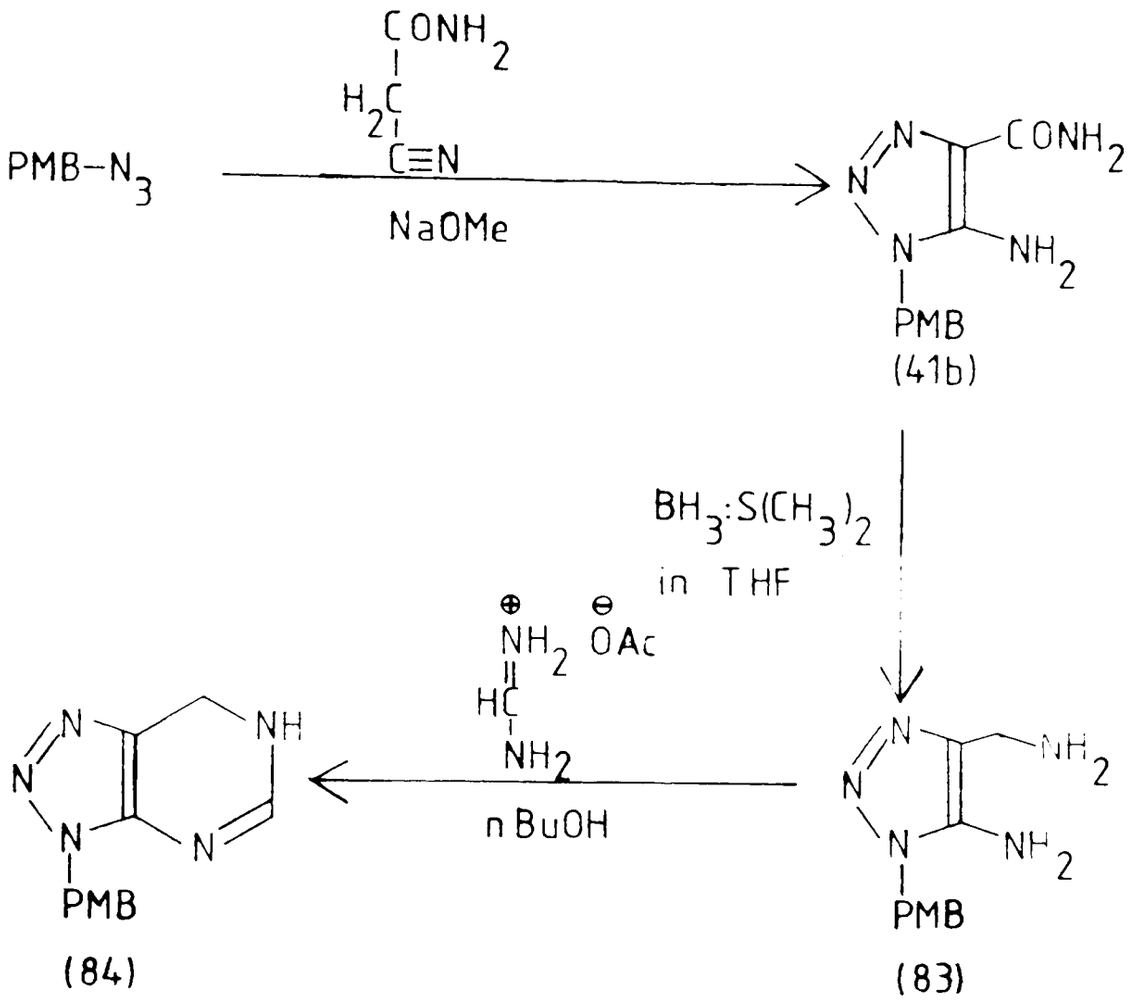
The advantages of this method above the previous one are (1) higher yield in one fewer step and (2) the avoidance of acidic conditions during the reduction stage which would be useful in the preparation of aminomethyl protected ribonucleoside-1,2,3-triazoles.

2.8. A CONVENIENT 3 STEP PREPARATION OF A BENZYLIC-1,6-DIHYDRO-8-AZAPURINE

1,6-Dihydro-8-azapurines, stable to atmospheric oxidation (unlike 1,6-dihydropurines), are candidate drugs in the chemotherapy of cancer. The most attractive route lay in condensing 5-amino-4-aminomethyl-1,2,3-triazoles with amidines.

A convenient synthesis of a 1,6-dihydro-8-azapurine from p-methoxybenzyl azide will be reported in this section. This synthesis is summarised in Scheme 38.

Scheme 38:/



Scheme 38: Synthesis of 3-(4-methoxybenzyl)-6,7-dihydro[3H]-1,2,3-triazolo-[4,5d]pyrimidine

(41b) was prepared in the usual manner from p-methoxybenzyl azide and cyanoacetamide. Reduction of (41b) with borane dimethyl sulphide/

sulphide complex yielded the 4-aminomethyl-1,2,3-triazole (83) in a 60% yield. This compound proved very difficult to purify and recrystallisation led to a waxy material which did not exhibit a well defined melting point.

The waxy material was likely to be a mixture of the expected product and the amine carbamate that these 4-aminomethyl-1,2,3-triazoles sometimes form in the presence of air.[26]

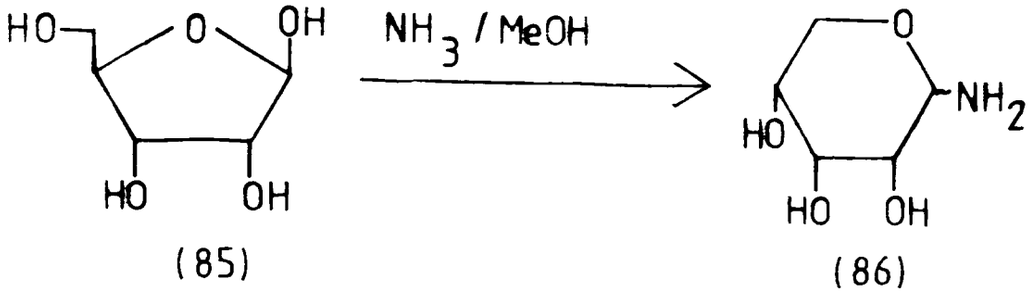
All spectral characteristics were recorded, and these were consistent with the structure of (83). When (83) was refluxed with formamidinium acetate in n-butanol, a good yield of the 1,6-dihydro-8-azapurine (84) (70%) was obtained. In this case the product was fully characterised.

By using this method it was therefore possible to increase the yield by using fewer steps than Albert's original method.

2.9. STUDIES ON THE PREPARATION OF 1,2,3-TRIAZOLE AND 8-AZAPURINE NUCLEOSIDES

Because of the proposed mode of action of 8-azapurines *via* their nucleosides it was felt that direct synthesis of these nucleosides would prove desirable.

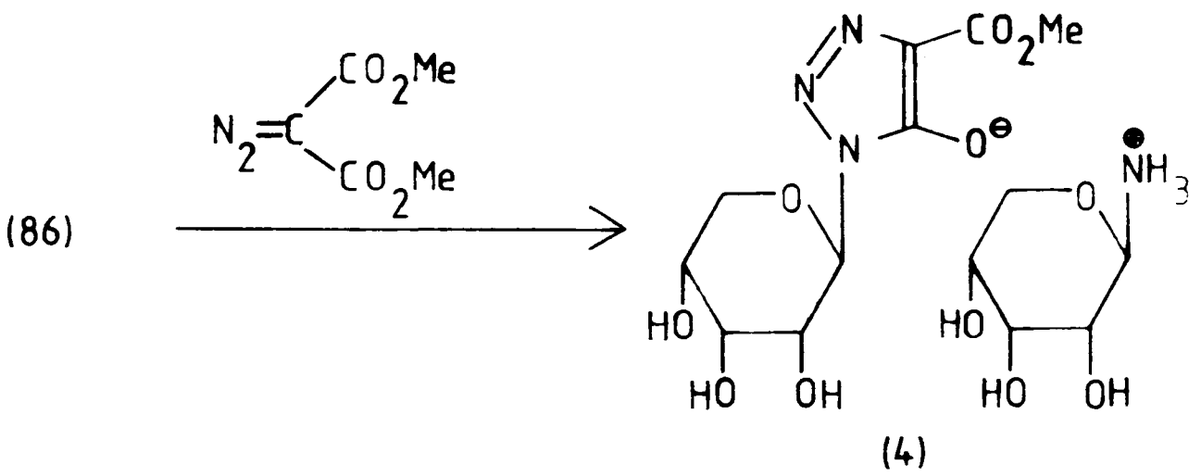
Initial work centred on attempts to synthesise triazoles of the type (4) by reacting ribosamines with dimethyldiazomalonate. D-Ribosylamine was prepared by a literature reaction from D-ribose and ammonia (Scheme 39).[28] The structure of the ring as being pyranose/



(85) (86)

Scheme 39: Preparation of D-ribopyranosylamine

pyranose has been well established.[29,30] It is believed that a furanose structure would lead to instability in the ribosamine.[31] It was hoped that (86), when stirred with dimethyl diázomalonate would furnish the triazole salt (4) (Scheme 40).



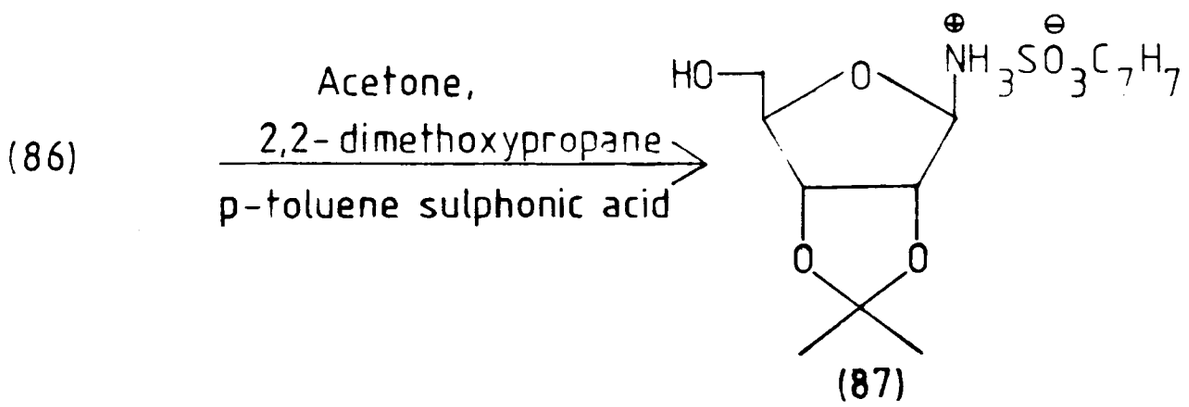
(4)

Scheme 40: Attempted preparation of the ribosylammonium salt of 5-hydroxy-4-methoxycarbonyl-1-ribopyranosyl-1,2,3-triazole

This/

This reaction was carried out using dry tetrahydrofuran as solvent, at room temperature. The course of the reaction was monitored by infra-red spectroscopy and it was apparent that there was no reaction because there was no disappearance of the strong peak at 2140 cm^{-1}, indicative of the diazo group.

The next stage consisted of protecting the ribosamine (86). This was undertaken by acetonation of the 2,3-hydroxy groups, using acetone, 2,2-dimethoxy-propane and p-toluene sulphonic acid (Scheme 41).[28] A good yield of the salt (87) was recorded and



Scheme 41: Preparation of 2,3-O-isopropylidene-D-ribofuranosylamine (toluene-p-sulphonate salt)

N.M.R. spectroscopsy proved that the β-anomeric form was predominant.

The furanose nature of the ribose ring was established by Levene who proved the structure by chemical means.[32] He rationalised this observation by stating that in a three dimensional model of the substance, it is shown that for a 2,3-monoacetone ribose the

5-/

5-membered ring is more stable.

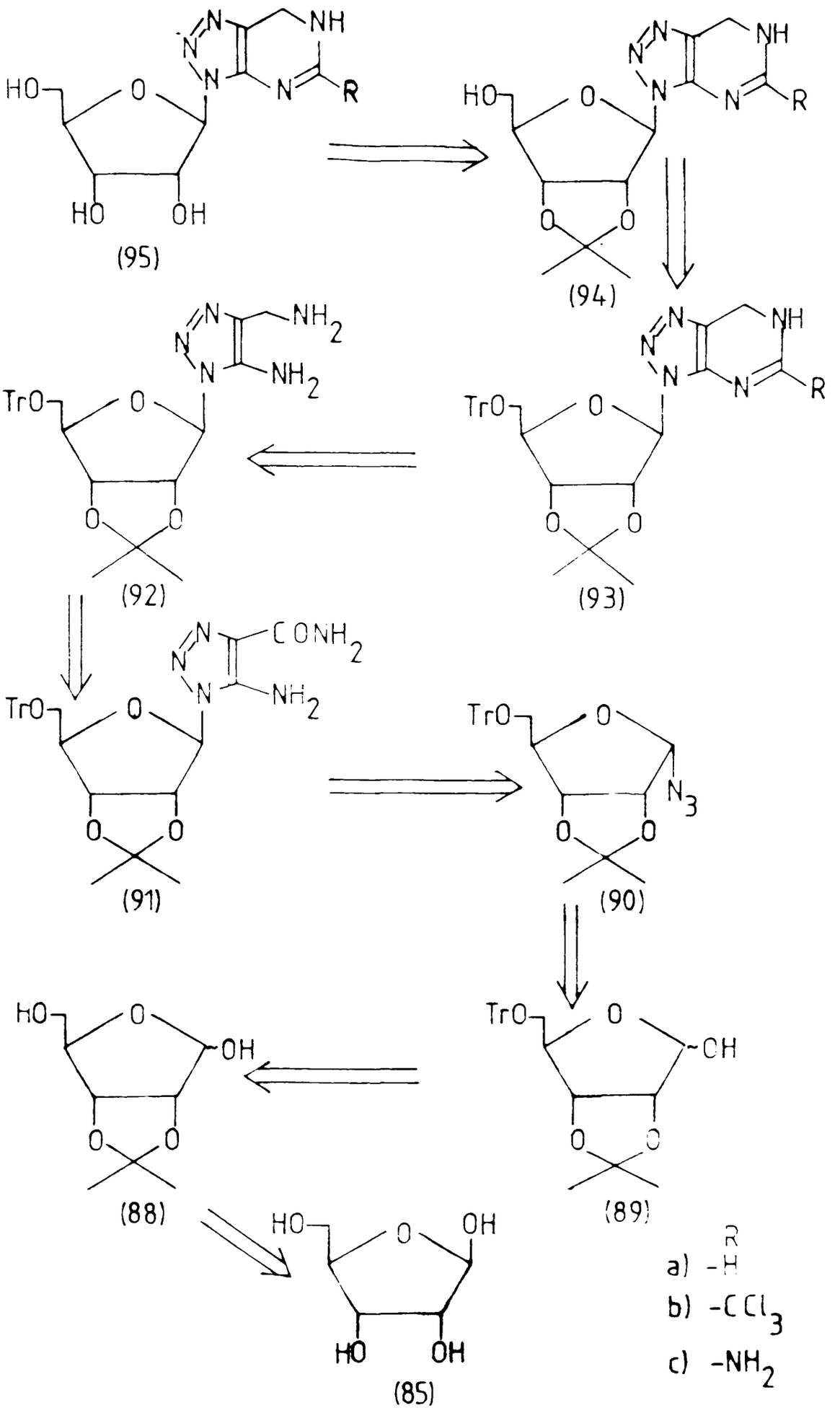
(87) was similarly stirred with dimethyldiazomalonate in dry T.H.F., this time in the presence of triethylamine. In addition to the difficulty of dissolving (87), no reaction was observed.

This reaction may have failed for a number of reasons. Firstly the ribosylamines (86) and (87) were not completely protected and this may be an important factor in hindering the course of the reaction. Secondly in the reaction between (87) and dimethyldiazomalonate it may have been the case that the free amine was not liberated. Thirdly (86) and (87) only dissolved with difficulty in the solvents used.

At this point, a suitable target was established and, considering the interest stimulated in 1,6-dihydro-8-azapurines, a synthesis of a 1,6-dihydro-8-azapurine ribonucleoside was devised. The retrosynthetic route is shown in Scheme 42.

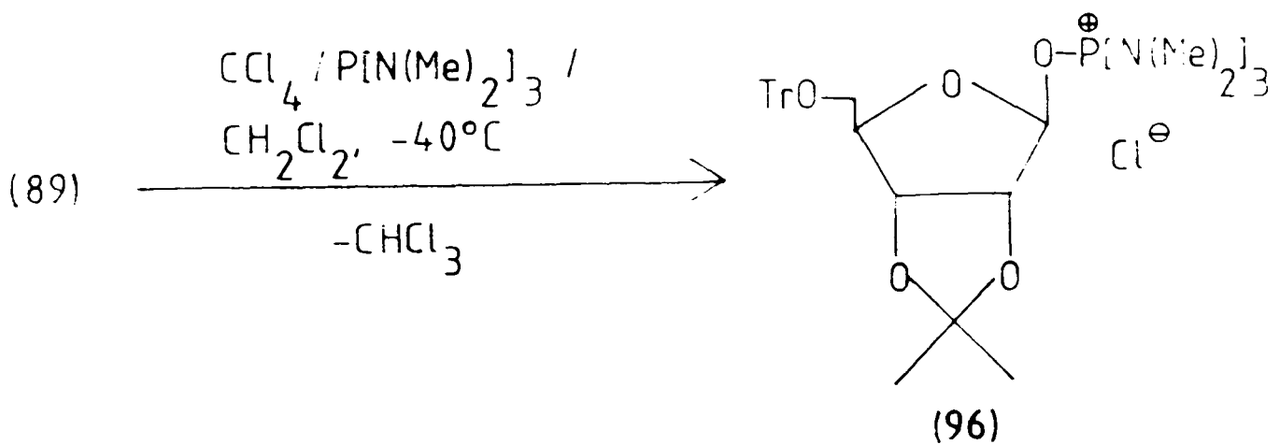
D-Ribose (85) was converted to the acetonide (88) in a moderate (50%) yield by reaction of the sugar with acetone in the presence of concentrated sulphuric acid.[33] (88) was tritylated with triphenylmethyl chloride and pyridine to (89).[34] The proportion of β to α-anomers in this step is approximately 3:1. The yield of product was 80%. It is important to use dry, freshly distilled pyridine and purified starting materials, because the reaction sometimes did not proceed unless these conditions were adhered to.

Scheme 42:/



Scheme 42: Retrosynthesis of a 1,6-dihydro-8-azapurine ribonucleoside

Some attractive chemistry was employed to convert the anomeric mixture of (89) to the glycosyl azide (90). This step was conveniently carried out without the use of glycosyl halides. Firstly, the ribofuranose (89) was activated to the corresponding alkoxytris [dimethylamino] phosphonium (ATDP) chloride (96) by means of the tris [dimethylamino]-phosphine/carbon tetrachloride reagent at -40°C under an inert gas, in dry dichloromethane as solvent[35] (Scheme 43). It is known that the anomeric configuration

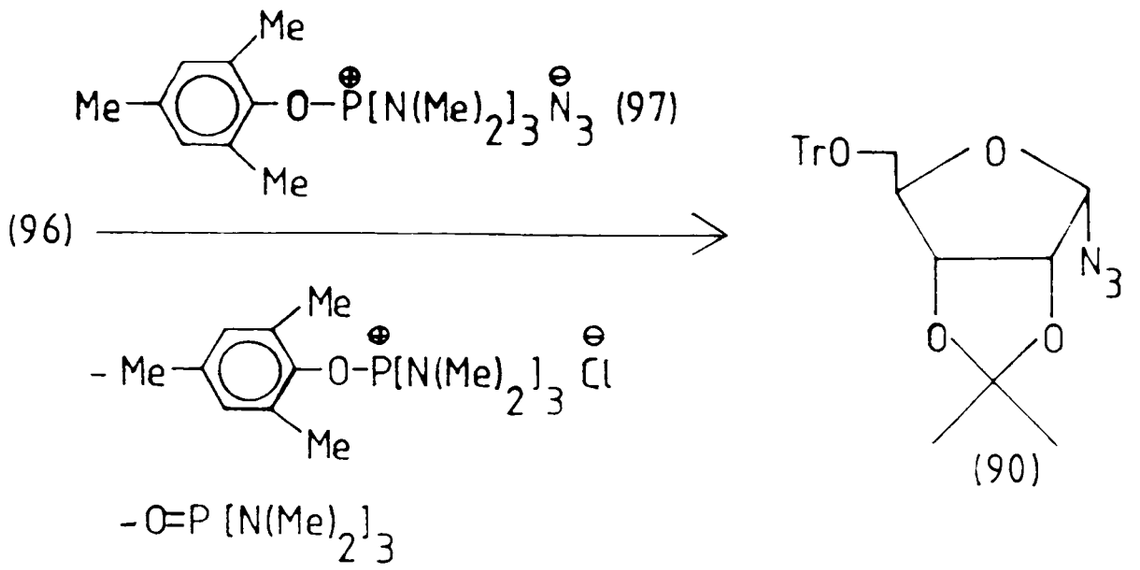


(96)

Scheme 43: Activation of free ribofuranose

of these salts is exclusively trans with respect to the substituent at C-2. The solution of the ATDP was treated with mesityloxytris-[dimethylamino]phosphonium azide (97) which was used as a source of azide ion (Scheme 44).

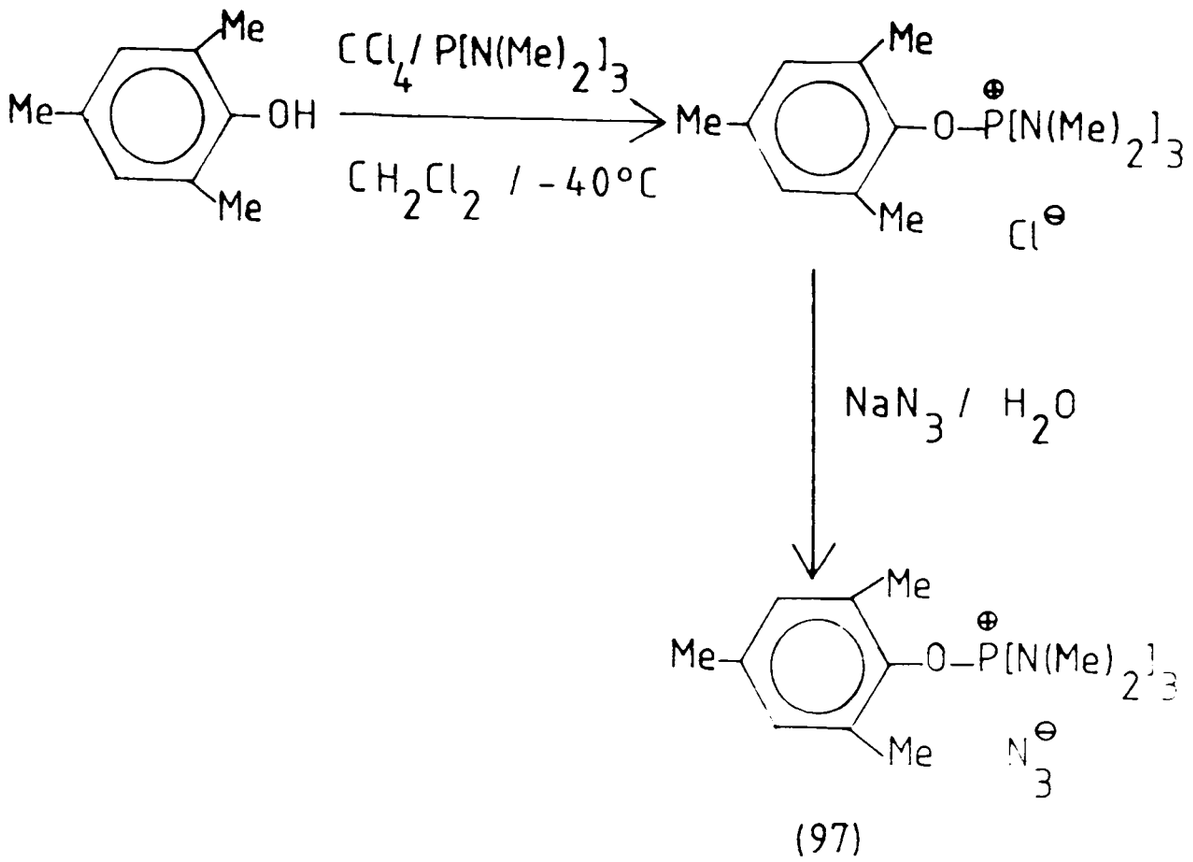
Scheme 44:/



Scheme 44: Preparation of 2,3-O-Isopropylidene-5-O-trityl-∝-D-ribofuranosyl azide

The reaction was complete with in 2-3 hours at -10°C, and afforded the azide in a 70 % yield, mainly in the 1,2-cis configuration. The azide reagent (97) was prepared from 2,4,6-trimethylphenol as indicated in Scheme 45.

Scheme 45:/



(97)

Scheme 45: Preparation of mesityloxy-tris[dimethylamino] phosphonium azide

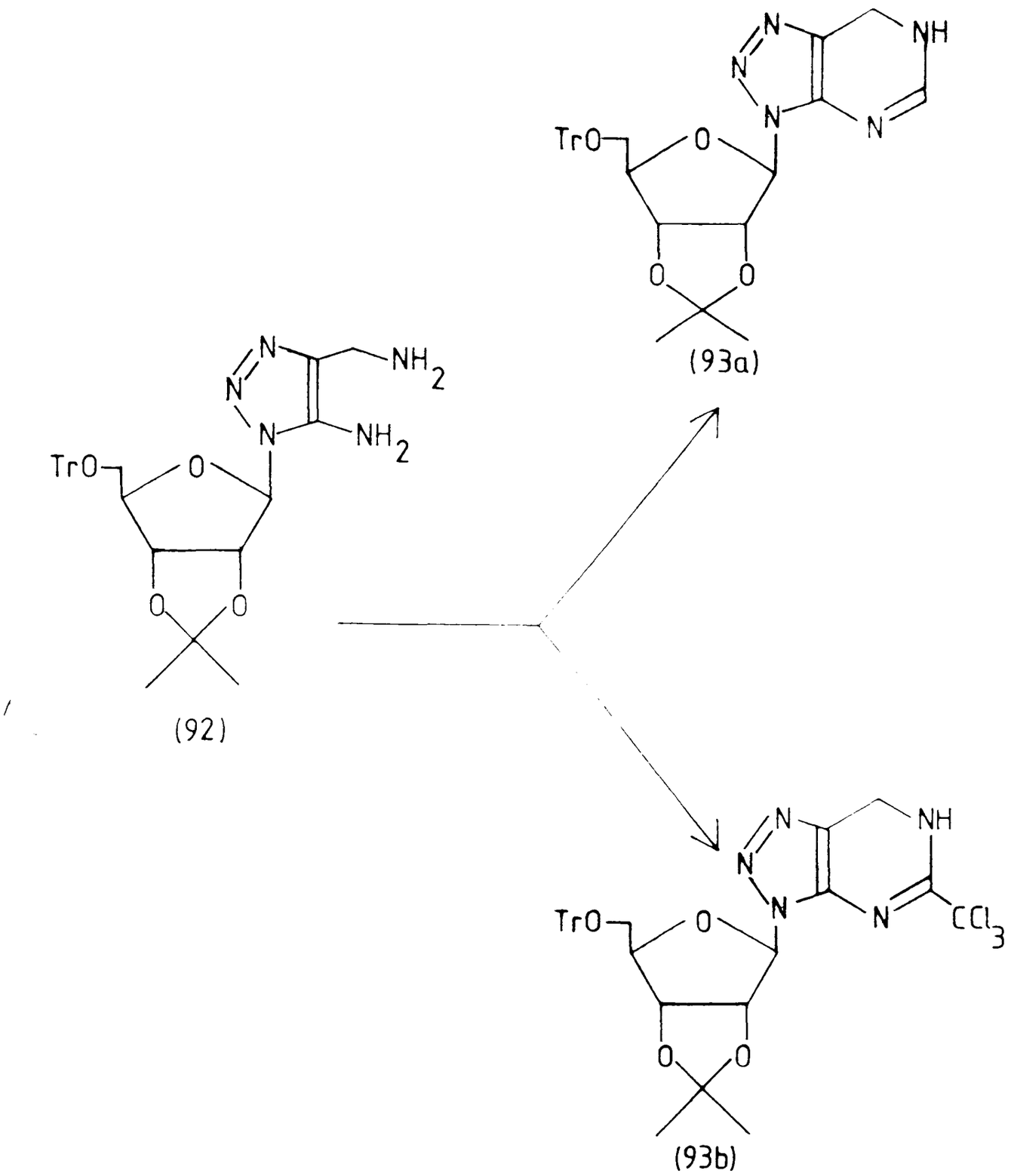
The 1,2,3-triazole (91) was formed by using Tolman's procedure[36] based on the action of powdered potassium hydroxide on a solution of (90) and cyanoacetamide in aqueous dimethylformamide at room temperature for 3 hours. A good yield of (91) was obtained which was of β-(1,2-trans) configuration.

The/

The next step, the reduction of the 4-carboxamido function proved very difficult, mainly because it was not possible to purify the product in the usual manner. The usual method of isolation and purification of 4-aminomethyl-1,2,3-triazoles is by preparation of their hydrochloride salts. Because of the presence of acid sensitive protecting groups, it was deemed undesirable to bubble hydrogen chloride through a solution of (92).

The crude 1,2,3-triazole (92) was reacted with formamidinium acetate and trichloroacetamidinium acetate (Scheme 46). In the reaction between (92) and trichloroacetamidine, a reaction did occur and the reaction mixture darkened quite considerably. No product was isolated from this reaction. The reaction between (92) and formamidine proceeded successfully although (93a) was only obtained in a poor yield (19%). (93a) was characterized by its p.m.r spectrum, recorded at 360 MHz. A singlet at 6.2 δ indicated that the product was of the β-configuration. P.M.R. also indicated the presence of an impurity. This impurity was present in the product to the extent of 20%. It was felt in discussions that this impurity may have been the α-anomer. This seems unlikely because the triazole (91) was of the β-configuration and anomeric inversion at this stage should not occur, because the reduction of the amide group, and the pyrimidine ring closure do not permit epimerisation. From the high field P.M.R, the isoproplylidene peaks of the major compound appear at 1.35 δ , and 1.56 δ , for the minor compound the isopropylidene peaks occur at 1.39 and 1.61 δ .

Scheme 46:/



Scheme 46: Attempted preparations of 1,6-dihydro-8-azapurine ribonucleosides

If/

If the difference between the two isopropylidene signals is more than 0.18 δ , then this is characteristic of a β-configuration according to the rule proposed by Imbach[37] and clearly the products must both be of the β-configuration. The minor product is possibly an unreacted intermediate species, which unfortunately was very difficult to separate from the desired product.

A well defined singlet occurred at 4.8 δ with an integration of 2 protons. This can be assigned as the 7-CH_2 group in the reduced pyrimidine ring. An octet was distinguished at 3.2 δ and this was due to the diastereotopic protons on C_5 of the ribose portion.

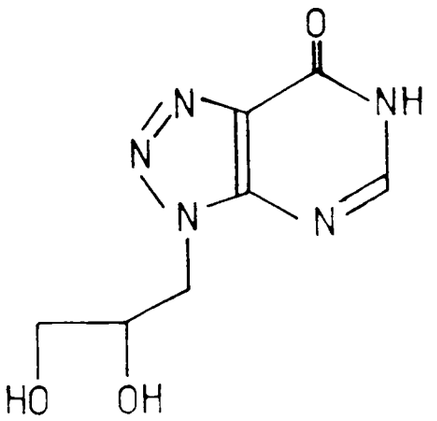
The C_{13} N.M.R spectrum was also recorded and important peaks were noted at 41.1 ppm due to 7-CH_2, 64.2 ppm due to C_5 of the ribose portion and 150.2 ppm due to the methine group in the pyrimidine group. Peaks which can be accounted for as being caused by impurities occurred at 63.83 ppm (CH_2) and 91.07 ppm (due to a CH).

(93a) was completely deprotected in one step by using trifluoroacetic acid. No (95) was isolated because of the small amounts of material used, but the disappearance of the isopropylidene peaks in the N.M.R. spectrum was noted. The reaction conditions will have to be optimized but it does appear that the first 1,6-dihydro-8-azapurine ribonucleoside has been prepared.

2.10. INVESTIGATION OF ALLYLIC TRIAZOLES/

2.10. INVESTIGATION OF ALLYLIC TRIAZOLES

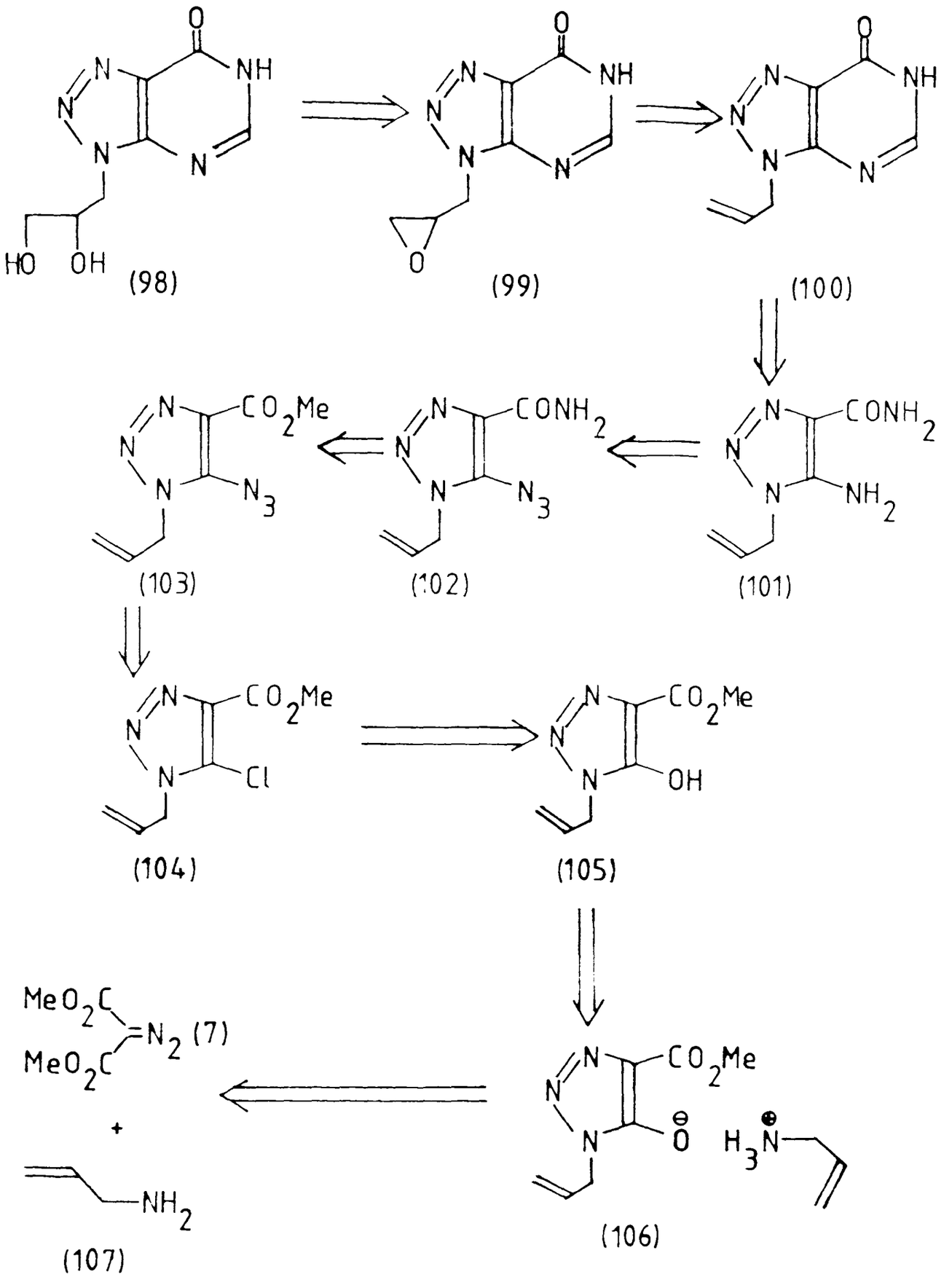
Recently, considerable interest has been directed towards the syntheses of analogues of normal nucleosides. An example of this is a compound where the ribose unit has been replaced by a truncated acyclic analogue. An example of a truncated analogue is shown below (98).



(98)

It seemed that (98) could be prepared by utilizing allylic precursors. This rationale is shown in the retrosynthetic inspection (Scheme 47).

Scheme 47:/

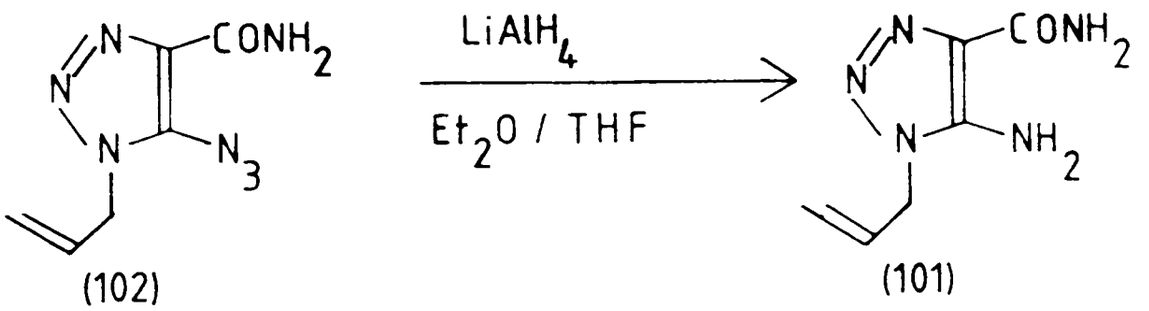


Scheme 47: Retrosynthesis of (98)

When/

When allylamine (107) was stirred with the diazomalonic ester (7) a good yield of the 1,2,3-triazole salt (106) was afforded. The 5-hydroxy-1,2,3-triazole (105) was yielded quantitatively after acidification of (106), followed by extraction into dichloromethane. (105) was chlorinated to (104) in a 45% yield by the action of phosphorous pentachloride in dry toluene. The 5-azido derivative (103) was prepared by azidolysis of the 5-chloro-1,2,3-triazole (104). Ammonolysis of (103) furnished a quantitative yield of the 5-azido-4-carboxamido-1,2,3-triazole (102).

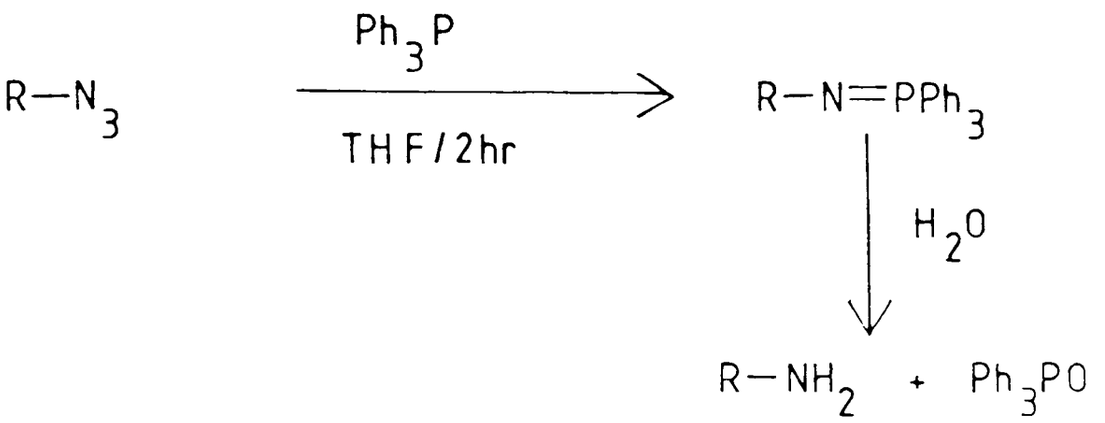
It was at this point difficulties were realized because catalytic hydrogenation of (102) would also reduce the allylic double bond. To overcome this problem (102) was reacted with lithium aluminium hydride (Scheme 48).



Scheme 48: Attempted reduction of 1-allyl-5-azido-4-carboxamido-1,2,3-triazole

A/

A low yield (15%) of (101) was obtained, and it was difficult to purify. Attention was drawn to an attractive variation of the Staudinger Reaction.[38] In this reaction sensitive azides are reacted with triphenylphosphine in T.H.F to form an iminophosphorane, which is hydrolysed to the primary amine and triphenylphosphine oxide (Scheme 49).

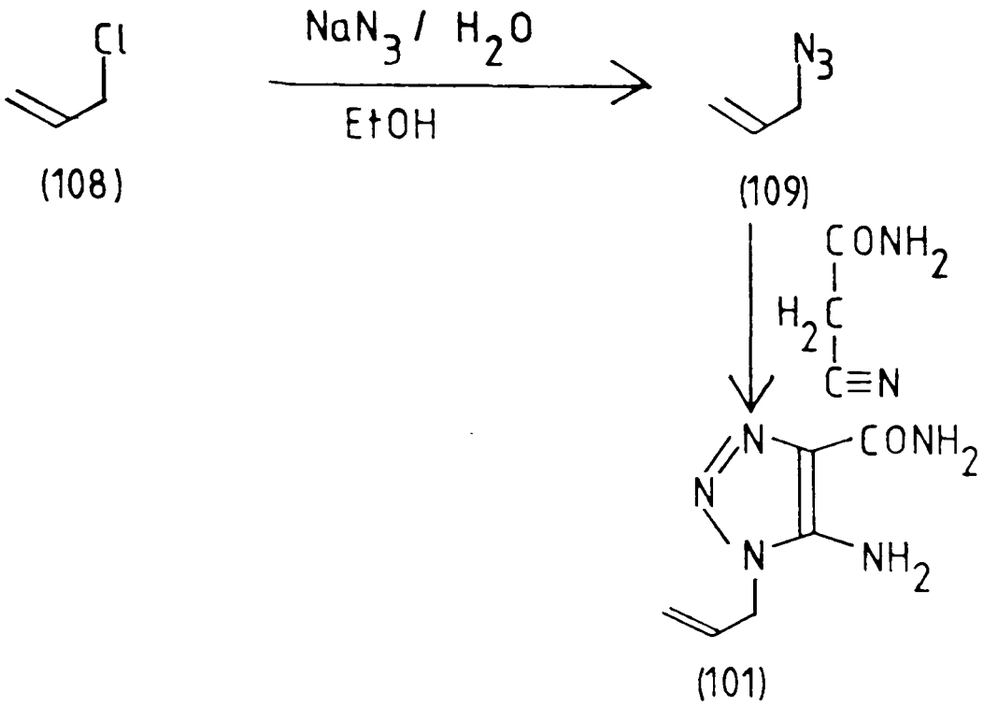


Scheme 49: Reduction of azides by triphenylphosphine

This methodology was applied to (102) and (103), but although the azide functions reacted completely, no amines were isolated following hydrolysis. It would appear from N.M.R evidence that the iminophosphorane did not undergo hydrolysis.

This approach to prepare (101) was abandoned when it was felt that a more convenient route existed in the base promoted reaction between allyl azide (109) and cyanoacetamide. The allyl azide was in its turn prepared from allyl chloride[39] (108) (Scheme 50).

Scheme 50:/



(101)

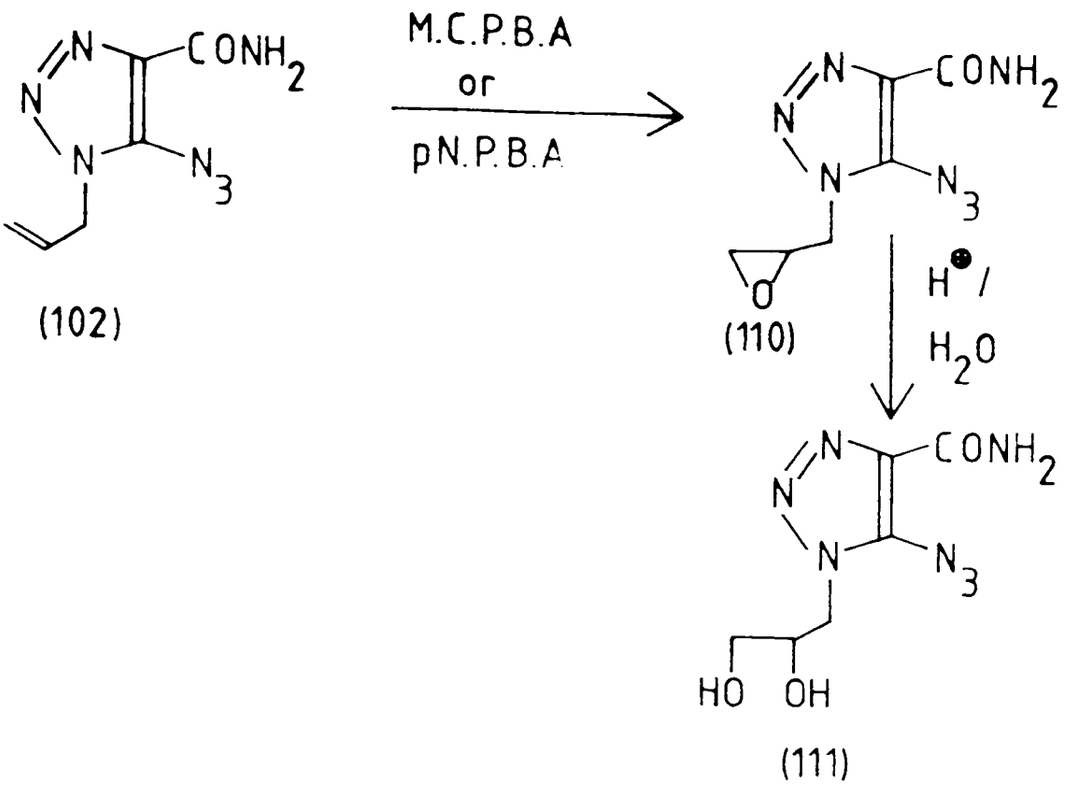
Scheme 50: Preparation of 1-allyl-5-amino-4-carboxamido-1,2,3-triazole

(109) was obtained in a 17% yield and proved very hazardous when distilled. It exhibited a tendency to explode. When (109) was reacted with cyanoacetamide in the presence of sodium ethoxide, a 42% yield of (101) was obtained. This compound was quite impure and was also water soluble.

Due to the inherent health hazards and low yields encountered, it was decided to discontinue this particular line of approach.

The final approach involved backtracking to (102) and attempting to prepare the diol (111) by epoxidation to (110) and hydrolysis to (111) (Scheme 51). The epoxidation step failed to yield (110), regardless of whatever epoxidation reagent was used, and only the starting materials were retrieved.

Scheme 51:/



Scheme 51: Attempted preparation of 5-azido-4-carboxamido-1-(1,2-dihydroxy propyl)-1,2,3-triazole

2.11.CONCLUSIONS

Broadly speaking, we had three main objectives in this project:

(a) To develop a suitable synthesis of 1-substituted triazoles.

(b) To develop new methods of producing 9-substituted-8-azapurines.

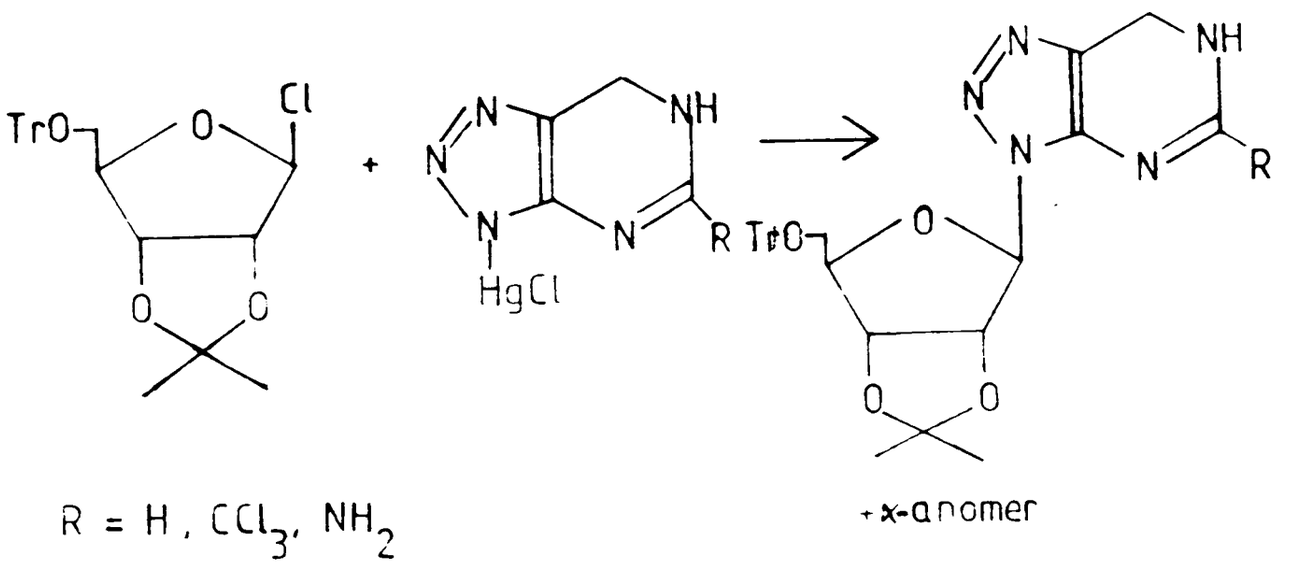
(c) To synthesise the corresponding ribonucleosides of the 8-azapurines.

During the course of the work all these areas were investigated and the first area yielded fruitful results. The second object was partially accomplished, but no novel methods were uncovered. However,/

However, a new route has become apparent from modification of the 5-chloro-1,2,3-triazoles.

This new route is only advantageous in that the use of hazardous azides at an early stage is avoided. It suffers from the disadvantage that too many steps are involved in the synthesis.

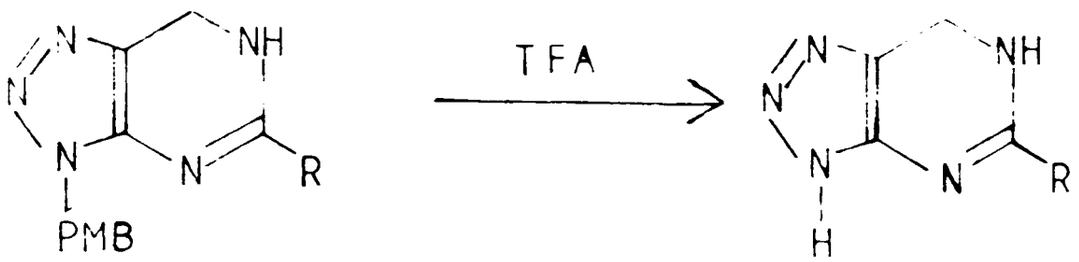
The third objective was accomplished, although the route suffers from a low yield in one of its later steps. Interesting work could be carried out in future to obtain these seemingly illusive 1,6-dihydro-8-azapurine ribonucleosides. A suggested route would be by direct glycosylation of the unsubstituted 1,6-dihydro-8-azapurines (Scheme 52). These 1,6-dihydro-8-azapurines could be obtained from



Scheme 52: Proposed preparation of 1,6-dihydro-8-azapurine ribonucleoside

9-p-methoxybenzyl-1,6-dihydro-8-azapurines as shown in Scheme 53.

Scheme 53:/

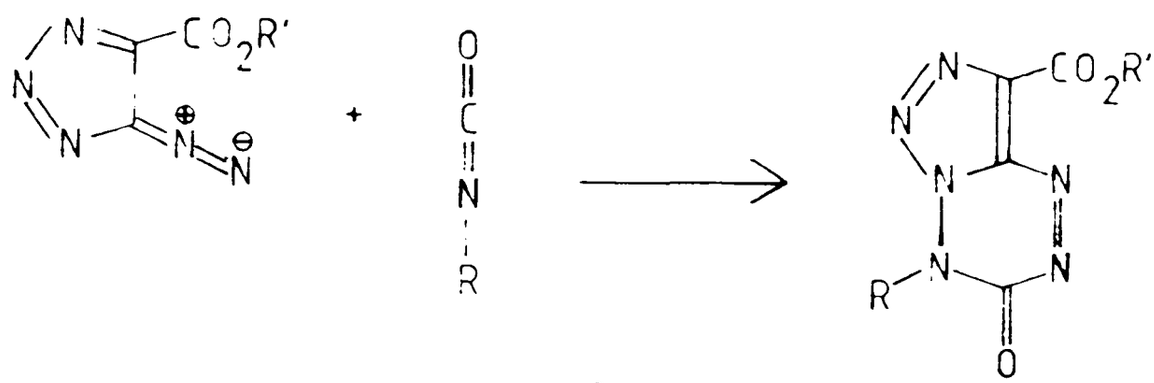


Scheme 53: Preparation of 1,6-dihydro-8-azapurine

In this method the available p-methoxybenzyl-1,6-dihydro-8-azapurine would be of potential use.

The reaction in Scheme 52 may be unsatisfactory since it would be difficult to control the relative proportions of the anomeric products.

The other reaction to be investigated thoroughly should be the reaction between 5-diazo-1,2,3-triazoles and isocyanates (Scheme 54).



Scheme 54: Cyclisation of 5-diazo-1,2,3-triazoles with isocyanates

REFERENCES

1. R. J. Gillespie, J. Murray-Rust, P. Murray-Rust and A. E. A. Porter, J.Chem.Soc., Chem.Commun., (1978), 83.
2. R. J. Gillespie, A. E. A. Porter and W. E. Willmott, J.Chem.Soc., Chem.Commun., (1978), 85.
3. R. J. Gillespie and A. E. A. Porter, J.Chem.Soc., Perkin Trans I, (1979), 2624.
4. A. W. Taylor, Beecham Pharmaceuticals, Brockham Park, personal communication to A. E. A. Porter.
5. P. Murray-Rust, J. McManus, Seán P. Lennon, A. E. A. Porter and J. A. Rechka, J.Chem.Soc., Perkin Trans I, (1984), 713.
6. B. R. Brown and D. LL Hammick, J.Chem.Soc., (1947), 2624.
7. O. Dimroth, Ann, (1910), 377, 127.
8. M. Regitz, Chem.Ber., (1966), 99, 3128.
9. O. Dimroth, Ann., (1904), 335, 1.
10. O. Dimroth, Ann., (1905), 338, 143.
11. O. Dimroth, Ann., (1910), 375, 336.
12. M. Regitz, personal communication to Seán P. Lennon.
13. J. E. Leffler and S. K. Liu., J.Amer.Chem.Soc., (1956), 78, 1949.
14. J. R. E. Hoover and A. R. Day, J.Amer.Chem.Soc., (1956), 78, 5832.
15. O. Dimroth, Ann., (1909), 364, 183, 212.
16. D. R. Buckle, D. J. Outred and C. J. H. Rockell, J.Heterocyclic Chem., (1981), 18, 1117.
17. D. R. Buckle and C. J. M. Rockell, J.Chem.Res., (S), (1982), 292.
18. D. R. Buckle and C. J. M. Rockell, J.Chem.Soc., Perkin Trans I, (1982), 627.
19. J. E. Baldwin, L. I. Kruse and J. K. Cha, J.Amer.Chem.Soc., (1981), 103, 942.

20./

20. M. F. G. Stevens, J. A. Hickman, N. W. Gibson, R. Stone and E. Lunt, British Pharmaceutical Conference, Edinburgh, 1982.

21. Y. F. Shealy, R. F. Struck, L. B. Holum and J. A. Montgomery, J.Org.Chem., (1961), 26, 2396.

22. H. K-W. Hui and H. Shechter, Tetrahedron Letters, (1982), 23, 5115.

23. A. Albert and A. M. Trotter, J.Chem.Soc., Perkin Trans I, (1979), 922.

24. A. Albert, J.Chem.Soc., Perkin Trans I, (1981), 2344.

25. Reagents for Organic Synthesis, Fieser and Fieser, Vol. 2, p10.

26. A. Albert, J.Chem.Soc., Perkin Trans I, (1973), 1634.

27. The Chemistry of Amides, J. Zabicky (Ed.), (1970), Interscience, p797.

28. N. G. Cusack, B. J. Hildick, D. H. Robinson, P. W. Rugg and G. Shaw, J.Chem.Soc., Perkin Trans I, (1973), 1720.

29. R. K. Ralph and G. Shaw, J.Chem.Soc., (1956), 1877.

30. R. S. Tipson, J.Org.Chem., (1961), 26, 2462.

31. J. Baddiley, J. G. Buchanan, R. Hodges and J. F. Prescott, J.Chem. Soc., (1957), 4769.

32. P. A. Levene and E. T. Stiller, J.Biol.Chem.,(1933), 102, 187.

33. M. A. Hughes and P. R. H. Speakman, Carbohydrate Res., (1965), 1, 171.

34. R. S. Klein, H. Ohriu and G. G. Fox, J. Carbohydrates, Nucleosides, Nucleotides, (1974), 1, 265.

35. F. Chretien, B. Castro and B. Gross, Synthesis, (1979), 937.

36. C. W. Smith, R. W. Sidwell, R. K. Robins and R. L. Tolman, J.Med. Chem., (1972), 15, 883.

37. G-L. Imbach, G-L. Barascut, B. L. Kam and C. Tapiero, Tetrahedron Letters, (1974), 129.

38./

38. M. Vaultier, N. Knouzi and R. Carrie, Tetrahedron Letters, (1983), 24, 763.

39. M. O. Forster and H. E. Fierz, J.Chem.Soc., (1908), 1174.

CHAPTER 3

Chapter 3

Experimental

Melting points were determined on a Kofler block and are uncorrected. I.R spectra were recorded on a Perkin-Elmer 577 instrument as KBr discs or solution spectra, as indicated. N.M.R spectra were recorded on a Perkin-Elmer R24, R.32 or Bruker W.P 80 instrument and mass spectra on a Jeol J.M.S D100. U.V spectra were recorded on a Pye Unicam S.P 800A uv/visible spectrophotometer. Kinetics were observed on a Gilford 2000S.

T.L.C was carried out on Kieselgel $60F_{254}$ silica plates from Merck and column chromatography was on Merck Kieselgel Art 7730.

1-Butyl-5-hydroxy-4-methoxycarbonyl-1,2,3-triazole butylammonium salt (4; R = Bu^n)

Dimethyl diazomalonate (1.58 g, 10 m moles) was added to a large excess of butylamine and the reaction was stirred at room temperature for 3 days. At this point the resultant salt had precipitated from solution and was isolated by filtration.

Yield 2.2 g (87%)

M.Pt/

M.Pt (ethyl acetate) 111 - 113°C

$\tilde{\nu}_{max}^{KBr}$ 3200-2400, 1690, 1570, 1460 and 1415 cm^{-1}

N.M.R ($CDCl_3$, 60 MHz) δ 8.4 (3H, brs) 3.9 (2H,m) 3.65 (3H,s), 3.0 (2H,t) 2-1.2 (8H,m) 1.1-0.8 (6H,m)

(Found: C, 52.9; H, 9.05; N, 20.9. $C_{12}H_{24}N_4O_3$ requires C, 52.95; H, 8.82; N, 20.59%).

5-Hydroxy-4-Methoxycarbonyl-1-pentyl-1,2,3-triazole pentylammonium salt (4; R = n-C_5H_{11})

Dimethyl diazomalonate (1.58 g, 10 m moles) was added to a solution of n-pentylamine (2.18 g, 25 m moles) in toluene (10 ml) and the reaction was stirred for 3 days at room temperature. The product was isolated by filtration.

Yield 2.55 g (85%)

M.Pt (CH_3CN) 110-113°C

ν_{max}^{KBr} 3200-2400, 1690, 1550 and 1460 cm^{-1}

N.M.R δ (D.M.S.O_{d_6},60 MHz) 8.0 (3H, br s), 3.55 (3H,s) and 2.5-1.0 (22H,m)

(Found: C, 56.2; H, 9.3; N, 18.45. $C_{14}H_{28}N_4O_3$ requires C, 56.0; H, 9.33; N, 18.66%)

1-Hexyl-5-hydroxy-4-methoxycarbonyl-1,2,3-triazole n-hexylammonium salt (4; R = n-C_6H_{13})

Dimethyl diazomalonate (1.58 g, 10 m moles) was added to a solution of n-hexylamine (2.53 g, 25 m moles) in toluene (10 ml) and the reaction mixture/

mixture was stirred for 3 days at room temperature. The product was isolated by filtration.

Yield 2.3 g (70%)

M.Pt (MeOH/MeCN) 120-122°C

ν_{max}^{KBr} (KBr) 3200-2400, 1690, 1575, 1460 and 1160 cm^{-1}

N.M.R δ(D.M.S.O$_{d_6}$,60 MHz) 8.0 (3H, brs), 4.0 (3H,s) 3.0-1.0 (26H,m)

(Found: C, 58.6; H, 9.7; N, 16.95, $C_{16}H_{32}N_4O_3$ requires C, 58.54; H, 9.76; N, 17.07%)

1-Cyclohexyl-5-hydroxy-4-methoxycarbonyl-1,2,3-triazole cyclohexylammonium salt (4, R = C_6H_{11})

Dimethyl diazomalonate (1.58 g, 10 m moles) was stirred with cyclohexylamine (2.38 g, 25 m moles) in toluene (10 ml) for 3 days at room temperature. The product was isolated by filtration.

Yield 2.16 g (66%)

M.Pt (CH_3CN/MeOH) 154-157°C

ν_{max}^{Nujol} 3200-2400, 1690, 1575, 1450, 1410, 1325, 1165, and 1050 cm^{-1}

N.M.R. δ(D.M.S.O$_{d_6}$,60 MHz) 7.0 (3H, brs), 3.6 (3H,s) and 3-1.0 (22H,m)

(Found: C, 59.3; H, 8.7; N, 17.3. $C_{16}H_{28}N_4O_3$ requires C, 59.26; H, 8.64; N, 17.28%).

5-Hydroxy-1-(2-hydroxyethyl)-4-methoxycarbonyl-1,2,3-triazole 2-hydroxyethylammonium salt (4; R = CH_2CH_2OH)

Dimethyl/

Dimethyl diazomalonate (1.58 g, 10 m moles) was added to a solution of ethanolamine (1.53 g, 25 m moles) in toluene (10 mls) and the reaction was stirred for 3 days at room temperature. The product was isolated by filtration.

Yield 2.45 g (98%)

M.Pt (ethanol) 99-104°C (decomp.)

ν_{max}^{KBr} 3500-2500, 1700, 1630, 1580, 1530, and 1450 cm^{-1}

N.M.R. δ(D.M.S.O$_{d_6}$, 60 MHz) 5.5 (3H, brs) and 3.7-3.2 (11H,m)

(Found: C, 38.65; H, 6.65; N, 22.85. $C_8H_{16}N_4O_5$ requires C, 38.71; H, 6.45; N, 22.58%).

1-Benzyl-5-hydroxy-4-methoxycarbonyl-1,2,3-triazole benzylammonium salt (4; R = CH_2Ph)

Dimethyl diazomalonate (1.58 g, 10 m moles) was added to a solution of benzylamine (3.21 g, 30 m moles) in toluene (10 mls). The reaction was stirred for 3 days at room temperature and at the end of the period the product was isolated by filtration.

Yield 2.68 g (84%)

M.Pt (ethanol) 153-156°C (decomp.)

ν_{max}^{KBr} 3200-2500, 1960, 1690, 1580, 1520, 1460 and 1410 cm^{-1}

N.M.R. δ($CDCl_3$, 60 MHz) 7.2 (5H,s), 7.1 (5H,s), 5.05 (2H,s) 3.95 (2H,s) and 3.7 (3H,s).

(Found: C, 63.5; H, 5.9; N, 16.65. $C_{18}H_{20}N_4O_3$ requires C, 63.53; H, 5.88; N, 16.47%).

Tosyl/

Tosyl Azide (6)[1]

Sodium azide (71.5 g) in water (300 ml) and acetone (500 ml) was added rapidly to a solution of tosyl chloride (190.7 g) in 500 ml of acetone. The reaction mixture was stirred at room temperature for two hours. The acetone was removed by rotary evaporation under reduced pressure at a temperature less than 35°C. Dichloromethane (200 ml) was added and the resultant mixture was washed with water (2 x 200 ml). The organic layer was separated, dried (sodium sulphate), filtered and evaporated under reduced pressure to yield 170 g (~85%) of tosyl azide.

N.M.R $\delta(CDCl_3$, 60 MHz) 7.5 (4H,q), 3.5 (4H,s)

ν^{Film}_{max} @ 2140 cm^{-1}

Dimethyl diazomalonate (7)[2]

Triethylamine (60 g) was added to a solution of dimethyl malonate (70 g) and tosyl azide (98.5 g) in dry toluene (400 ml). After 18 hours tosyl amide was filtered off and the solution was concentrated under reduced pressure. The orange residue was extracted repeatedly with petrol (40/60) until it solidified. The petrol extracts were combined and evaporated under reduced pressure to yield a yellow oil. This yellow oil was distilled in vacuo to yield 32 g (40%) of product.

B.Pt 65-70°C (2.5-3.0 m m Hg)

N.M.R $\delta(CDCl_3$, 60 MHz) 3.75 (s)

ν^{Film}_{max} @ 2140 cm^{-1}

5-/

5-Hydroxy-4-methoxycarbonyl-1-phenyl-1,2,3-triazole (8a)[3]

Phenyl azide (4.76 g, 0.04 moles) dissolved in dry methanol (15 ml) was added to an equimolar amount of sodium (0.92 g, 0.04 moles) and dimethyl malonate (5.28 g, 0.04 moles) in methanol (40 ml). This reaction mixture was refluxed for 2 hours. After this time the reaction mixture was cooled. The sodium salt of the triazole was isolated by adding ether to the cold reaction mixture. The salt was then dissolved in the minimum amount of water and chilled in an ice-bath. The cold salt solution was added dropwise with constant agitation to cold dilute hydrochloric acid. The free hydroxy-triazole thus formed was extracted into dichloromethane (3 x 50 ml). The organic solution was dried (sodium sulphate) and evaporated <u>in vacuo</u> to yield 5.8 g (66%) of crude product. A portion (2 g) of this product was dissolved in hot methanol and this solution was rapidly chilled in an ice bath. A solution of sodium methoxide in methanol was added to this solution, followed by ether at 0°C to precipitate the sodium salt of the triazole. The salt was filtered off and dissolved in water. This solution was added to cold dilute hydrochloric acid at 0°C dropwise. The free hydroxy-triazole was filtered off, dried <u>in vacuo</u> and stored at -5°C.

$\nu_{max}^{CHCl_3}$ 3250 (br), 2140, 1690 and 1595 cm^{-1}

N.M.R δ(D.M.S.Od_6) 7.5 (5H,m), 3.75 (3H,s)

Methyl diazomalonanilide[3]

The 5-hydroxy triazole (8a) prepared above (2 g) was recrystallised from hot/

hot methanol as pale yellow crystals.

$\nu_{max}^{CHCl_3}$ 3310, 2130, 1685, 1650 and 1595 cm^{-1}

N.M.R $\delta(CDCl_3$, 60 MHz) 9.5 (1H, brs), 7.5 (5H,m), 3.8 (3H,s)

Phenyl azide (18)[3]

To a solution of aniline (9.3 g) and concentrated sulphuric acid (33.4 g) in water was added a concentrated solution of sodium nitrite (containing 6.9 g of sodium nitrite) at 0°C.

An aqueous solution of sodium azide (containing 6.5 g of sodium azide) was added with stirring, the reaction vessel being kept in the ice bath until nitrogen evolution ceased ($\sim$ 3 hours). The phenyl azide was extracted into ether (3 x 50 ml) and washed with dilute sodium hydroxide until free from acid. The ether layer was dried (magnesium sulphate), filtered and evaporated under reduced pressure.

Yield 6.2 g (52%)

N.M.R. $\delta(CDCl_3$, 60 MHz) 7.2 (m)

ν_{max}^{Film} 2100 and 1590 cm^{-1}

5-Methoxy-4-methoxycarbonyl-1-phenyl-1,2,3-triazole (9)

5-Hydroxy-4-methoxycarbonyl-1-phenyl-1,2,3 triazole (8a) (0.44 g) was suspended in ether (20 ml). To this suspension ethereal diazomethane was added until the yellow colour persisted. The suspension was stirred at/

at room temperature until a homogenous solution was obtained (10 min), stirring was continued for another 1 hour until all the 5-hydroxy-1,2,3-triazole had reacted. Excess diazomethane was blown off using a stream of nitrogen, the solvent was then evaporated under reduced pressure and the residue was purified by chromatography on silica gel (Elutant Pet 40/60 0.75 : EtOAc 0.25) to yield 0.26 g (55%) of product.

M.Pt (Et_2O-petrol) 81-83°C

$\nu_{max}^{CHCl_3}$ 2940, 1715, 1595, 1575, 1470, 1095, and 985 cm^{-1}.

U.V.(MeOH) λ_{max} @ 222.5 nm (ε = 9500)

N.M.R $\delta(CDCl_3$, 60 MHz) 7.5 (5H,m), 4.2 (3H,s) 3.95 (3H,s)

Mass Spec M^+ @ 233.

Acc. Mass Spec: $C_{11}H_{11}N_3O_3$ requires 233.0800; found 233.0788 (Error -5.1 ppm)

1-Butyl-5-hydroxy-4-methoxycarbonyl-1,2,3-triazole (8b)

The butylammonium triazole salt (4-R = n Bu) (1 g) was stirred in 1 M hydrochloric acid (5 ml) for 15 minutes, followed by extraction into dichloromethane (2 x 10 ml). The extracts were dried over magnesium sulphate, filtered, and evaporated under reduced pressure to furnish a quantitative yield of the product as a viscous oil which isomerised on attempted distillation.

$\nu_{max}^{CHCl_3}$ 3300 br, 2980, 2140 w, 1720, 1590, 1550 and 1460 cm^{-1}

N.M.R. $\delta(CDCl_3$, 60 MHz) 4.2 (3H,m), 3.65 (3H,s) 3.4 (2H,q) and 2.0-0.7 (5H,m).

(Found:/

(Found: M^+, 199.0953. $C_8H_{13}N_3O_3$ requires M^+, 199.0957)

N-Butyl-2-methoxycarbonyl-2-diazoacetamide (5b)

The 5-hydroxy-1,2,3-triazole (8b) (0.5 g) was heated briefly at 100°C (2-3 min) followed by high vacuum distillation of the resultant oil at 0.1-0.05 Torr in a Kugelrohr distillation apparatus with a pre-set oven temperature of 150-180°C. There was some decomposition of the starting material, but the product was chromatographically homogenous.

Yield 0.35 g (70%)

ν_{max}^{Film} 3360, 2960, 2140, 1700, 1660, 1540, and 1440 cm^{-1}

N.M.R $\delta(CDCl_3$, 60MHz) 7.6 (1H, brs), 4.15 (1H,t), 3.8 (3H,s), 3.3 (2H,m), 1.5 (4H,m) and 0.9 (3H,m)

(Found: M^+, 199.0950. $C_8H_{13}N_3O_3$ requires M^+ = 199.0952).

1-Butyl-5-hydroxy-1,2,3-triazole-4-carboxylic acid (12)

The butylammonium triazole salt (4) (2.72 g) was stirred in 5 M sodium hydroxide solution (10 ml) for 24 hours at room temperature. At the end of this period the reaction mixture was chilled to 0°C and concentrated hydrochloric acid was added slowly until a white crystalline precipitate was noted. This precipitate was filtered off and dried in vacuo.

Yield 1.8 g (90%)

ν_{max}^{KBr} 3600-2200, 2000-1800, 1600(v br) cm^{-1}.

N.M.R δ(D.M.S.O d_6, 90 MHz) 6.9 (2H, br), 3.8 2H,t) 1.8-0.5 (7H,m)

u.v/

u.v (MeOH) λ_{max} @ 271 nm (ε = 9500), and 225 (ε = 5000)

u.v. (MeOH/$H^{\oplus}$) λ_{max} @ 290 nm (v br) (ε = 1500) and 240 nm (ε = 5000)

Mass Spectrum : No molecular ion was observed. Peaks @ 141 (1.0) (M-44) and 44 (100), indicating a loss of CO_2.

1-Butyl-5-hydroxy-1,2,3-triazole (14)

When recrystallisation of (12) was attempted in water, decarboxylation occurred and the title product was formed as white needles.

ν_{max}^{KBr} 3000, 2700-2000, 1630-1470, 1320, 1240, 1100, 1070, 780- cm^{-1}

N.M.R δ(D.M.S.O$_{d_6}$, 90 MHz) 10.4 (1H, br), 6.9 (1H,s) 4.13 (2H, t), 1.8 (2H,m), 1.35 (2H,m) 0.95 (3H,t).

Mass Spec $M^{\oplus}$ @ 141 (9.2)

Acc. Mass Spec. (Found: 141.0894. $C_6H_{11}N_3O$ requires 141.0902 (Error -5.7 ppm)).

Microanalysis (Found: C. 51.02, H. 7.82, and N. 29.71. $C_6H_{11}N_3O$ requires C. 51.06, H. 7.80, and N. 29.79%).

M.Pt (Water) 135-136.5°C

Methyl hydrogen malonate (15)[4]

Dimethyl malonate (132 g) was dissolved in absolute methanol (300 ml) and stirred during the addition of potassium hydroxide (60 g) in absolute methanol. The reaction mixture was stirred overnight, and at the end of this period the precipitate of potassium methyl malonate was filtered off. More of the salt was isolated by addition of diethyl ether to the filtrate.

The/

The potassium salt was dissolved in water (150 ml) and this solution was cooled to 5°C using an ice bath. Concentrated hydrochloric acid (150 ml) was added slowly to this solution ensuring that the temperature did not exceed 10°C. This solution was stirred for 1 hour. Excess potassium chloride was filtered off and washed with diethyl ether. The aqueous solution was extracted with diethyl ether (10 x 50 ml). These ether extracts were combined and dried over anhydrous magnesium sulphate, filtered and evaporated under reduced pressure to give an oil which was distilled in vacuo.

Wt of product = 35 g (~ 30%)

B.Pt (1.5 mm Hg) - 99-101°C

N.M.R, $\delta(CDCl_3$, 60 MHz) 3.9 (3H,s), 3.6 (2H,s)

ν_{max}^{Film} 3500 cm^{-1} (v br), 1760 cm^{-1}

Methyl malonanilide (16)[5]

To a solution of aniline (2.5 g) and the half ester of dimethyl malonate (15) (3.3 g) in dichloromethane (40 ml) was added dicyclohexylcarbodiimide (6 g), slowly. The precipitate of dicyclohexylurea was filtered off and the filtrate was stirred for 90 minutes.

At the end of this period saturated sodium bicarbonate was added to the reaction mixture. The resultant precipitate was filtered off, washed with a little dichloromethane and discarded. The organic layer was separated and to it a fresh solution of citric acid was added. The organic layer was again separated and finally washed with sodium bicarbonate solution. The organic layer was separated, dried over sodium sulphate, filtered and evaporated under/

under reduced pressure to yield an oil. This oil was chromatographed on silica (diethyl ether) to furnish the expected product (3 g ~ 58%).

N.M.R $\delta(CDCl_3$, 60 MHz) 9.25 (1H, br), 7.6-7.0 (5H,m), 3.7 (3H,s), 3.4 (2H,s)

$\nu_{max}^{CHCl_3}$ 3400, 3000, 1720, 1685, 1600, 1540, 1440 cm^{-1}

M.Pt (ether/petrol) 44-45°C Lit M.Pt - 42-43°C[5]

1-Benzyl-5-chloro-4-methoxycarbonyl-1,2,3-triazole (24)

A suspension of 1-benzyl-5-hydroxy-4-methoxycarbonyl-1,2,3-triazole (8c) (1 g) was stirred at 40°C for 90 minutes, in dry toluene (40 ml) with phosphorus pentachloride (0.94 g). At the end of this period, the solvent was removed, under reduced pressure, and the resultant residue was dissolved in diethyl ether (30 ml). This ethereal solution was washed well with saturated sodium bicarbonate solution (3 x 20 ml) and then with water (3 x 20 ml). The organic solution was separated and dried with magnesium sulphate (anhyd.) filtered and evaporated under reduced pressure to yield a pinkish oil which later solidified. The crude product was recrystallised from ether/pet ether to yield white needles (0.803 g, 75%).

M.Pt 77-79°C

$\nu_{max}^{CHCl_3}$ 3000, 1725, and 1450 cm^{-1}

N.M.R, $\delta(CDCl_3$, 60 MHz) 7.2 (5H,s), 5.45 (2H,s), 3.85 (3H,s)

Mass Spec. M^+ @ 251 (1.0) M + 2 (0.3)

Microanalysis (Found: C. 52.71, H. 4.20, N. 16.83. $C_{11}H_{10}N_3O_2Cl$ requires C. 52.49, H. 3.98, N. 16.73%).

5-/

5-Hydroxy-1-(4-methoxybenzyl)-4-methoxycarbonyl-1,2,3-triazole (25)

To a stirred solution of sodium methoxide (from sodium (1.508 g, 0.065 mole)) in methanol (120 ml) was added dimethyl malonate (8.58 g, 0.065 mole). After 30 minutes a solution of 4-methoxybenzyl azide (52) (10.63 g, 0.065 moles) in methanol (20 ml) was added dropwise with stirring and the mixture was refluxed for 18 hours. After cooling, the bulk of the methanol was removed and water (300 ml) was added. Acidification to pH 1 with dilute hydrochloric acid gave an oil which on cooling solidified. This solid was extracted into dichloromethane. The dichloromethane solution was separated and dried (sodium sulphate), filtered and evaporated under reduced pressure to give the expected product (13 g, 76%).

N.M.R δ(D.M.S.O$_{d_6}$,60 MHz) 7.0 (4H,AA'BB'q), 5.25 (2H,s) 3.95 (6H,s)

$\nu_{max}^{CHCl_3}$ 3250 (br), 2095 (w), 1600 cm^{-1}

Mass Spec M^+ @ 263

Acc. Mass Spec $C_{12}H_{13}N_3O_4$ requires 263.0907. Found: 263.0894 (Error -4.6 ppm)

M.Pt ($CHCl_3$/Petrol 60/80) 109-111.5°C

5-Chloro-1-(4-methoxybenzyl)-4-methoxycarbonyl-1,2,3-triazole (26)

The hydroxy-1,2,3-triazole (25), (2.63 g, 10 m moles) was stirred with phosphorus pentachloride (2.1 g, 12 m moles) in 60 ml of dry toluene at 40°C for 90 minutes. The toluene was removed by evaporation under reduced pressure and the residue was dissolved in diethyl ether. The organic layer was washed well with aqueous sodium bicarbonate (sat) (3 x 25 ml) and then with water. Evaporation of the dried ($MgSO_4$), filtered, organic/

organic phase gave an oil from which the chloro compound (0.7 g. 25%) was isolated by chromatography on silica (EtOAc/Pet 40/60. 0.3/0.7).

M.Pt (diethyl ether/petrol 40/60) 93-95°C

$\nu_{max}^{CHCl_3}$ 1725, 1610, 1580, 1535, 1510 cm^{-1}

N.M.R. $\delta(CDCl_3$, 60 MHz) 7.0 (4H,AA'BB'q), 5.45 (2H,s) 3.9 (3H,s), 3.75 (3H,s)

Mass Spec. M^+ @ 281 (3.0) M + 2 @ 283 (0.9)

Acc. Mass Spec. $C_{12}H_{12}N_3O_3Cl$ requires 281.0565. Found: 281.0567 (Error 0.7 ppm).

1-Benzyl-5-cyano-4-methoxycarbonyl-1,2,3-triazole (34)

Sodium cyanide (196 mg, 0.004 moles) was added to a solution of the chlorotriazole (24) (0.75 g, ~ 0.003 moles) in dry dimethylformamide (5 ml) and the mixture was stirred at 80°C for 36 hours. At the end of this time the reaction mixture was cooled, and the solvent evaporated in vacuo. The residue was partitioned between water and ethyl acetate. The organic layer was separated and washed several times with water. The ethyl acetate layer was dried with magnesium sulphate, filtered and evaporated under reduced pressure to yield 0.43 g (60%) of an oil.

$\nu_{max}^{CHCl_3}$ 2240 (w), 1725, 1760, 1540, 1460, 1200 cm^{-1}

N.M.R. $\delta(CDCl_3$, 90 MHz) 7.4 (5H,s), 5.7(2H,s), 4.1 (3H,s)

Mass Spec. M^+ @ 242 (1.6)

Acc. Mass Spec. $C_{12}H_{10}N_4O_2$ requires 242.0804. Found: 242.0894 (Error -4.1 ppm)

1-/

1-Benzyl-4-methoxycarbonyl-5-phenoxy-1,2,3-triazole (35)

Sodium phenoxide was prepared by stirring sodium hydride (2 equiv) (60% oil dispersion) with phenol (2 equiv) in D.M.F. Stirring was continued for 30 minutes until the formation of the sodium salt was complete. To this mixture the chlorotriazole (24) (0.75 g, ~0.003 moles) was added. The reaction mixture was stirred at 70°C for 3 days. At the end of this period the solvent was removed in vacuo and the residue was partitioned between ethyl acetate and water. The organic layer was separated and washed several times with 5% sodium hydroxide solution and then with water. The organic phase was dried over magnesium sulphate, filtered and evaporated under reduced pressure to yield an oil which was crystallised with aqueous alcohol to furnish 0.7 g (72%) of product.

N.M.R. $\delta(CDCl_3$, 90 MHz) 7.5-6.8 (10H,m), 5.4 (2H,s), 3.7 (3H,s).

$\nu_{max}^{CHCl_3}$ 1725, 1570, 1485, 1200 cm^{-1}

Mass Spec. M^+ @ 209

Acc. Mass Spec. $C_{17}H_{15}N_3O_3$ requires 309.1113. Found: 309.1107 (Error -1.8 ppm)

M.Pt ($MeOH/H_2O$) 82-83°C

1-Benzyl-5-chloro-1,2,3-triazole-4-carboxylic acid (36)

A solution of sodium methoxide was prepared by dissolving sodium (0.17 g) in methanol (30 ml). This solution was stirred for 30 minutes, until all the sodium salt was formed. The chlorotriazole (24) (0.9 g) was added and stirring was continued at ambient temperature for 5 days. The methanol was removed in vacuo and the residue was dissolved in a little/

little water. This solution was acidified with dilute hydrochloric acid and the resultant white suspension was extracted into dichloromethane (3 x 50 ml). The organic layer was dried (sodium sulphate) and evaporated to yield 0.75 g of product.

ν_{max}^{KBr} 2950 (br) 1670 br, 1530, 1450 cm^{-1}

N.M.R $\delta(CDCl_3/D.M.S.O_{d_6}$, 60 MHz) 8.4 (1H,br), 7.3 (5H,s), 5.6 (2H,s)

Mass Spec. M^+ @ 237 (1.5) M + 2 @ 239 (0.4)

Acc. Mass Spec. Found: 237.0298. $C_{10}H_8N_3O_2Cl$ requires 237.0305 (Error -3.9 ppm)

M.Pt ($CHCl_3$/Petrol) Prisms - 133-135°C

1-Benzyl-4-carboxamido-5-chloro-1,2,3-triazole (37)

To a solution of (24) (0.5 g) in methanol (10 ml) was added an excess of aqueous ammonia (d = 0.880) and the resultant mixture was stirred for 48 hours. The white solid which formed during the reaction was isolated by filtration and was dried in vacuo to yield 0.31 g (63%) of (37).

M.Pt (MeOH/Et_2O) 164-166°C

$\nu_{max}^{CHCl_3}$ 3400, 1665, and 1565 cm^{-1}

N.M.R. $\delta(CDCl_3/D.M.S.O_{d_6}$, 60 MHz) 7.3 (5H,s) and 5.5 (2H,s)

Mass Spec. M^+ @ 236

Acc. Mass Spec. (Found: 236.0456. $C_{10}H_9N_4OCl$ requires M^+ 236.0465. (Error -3.8 ppm).

1-Benzyl-5-chloro-4-N-methylcarboxamido-1,2,3-triazole (38)

The/

The chloro-triazole (24) (0.25 g) was stirred at room temperature with 40% aqueous methylamine (5 ml) for 2 hours. After this time the solvent was removed under reduced pressure to yield 0.15 g (60%) of (38).

M.Pt (MeOH-Et_2O) 149-150.5°C

$\nu_{max}^{CHCl_3}$ 3410, 1665, and 1565 cm^{-1}

N.M.R. $\delta(CDCl_3$, 60 MHz) 7.3 (5H,s), 5.5 (2H,s) and 3.05 (3H,d)

(Found: M^+, 250.0626. $C_{11}H_{11}N_4OCl$ requires M, 250.0622).

4-Carboxamido-5-chloro-1-(4-methoxybenzyl)-1,2,3-triazole (39)

Aqueous ammonia (d = 0.85) (10 ml) was added to a solution of the chloro-triazole (26) (1.5 g) in methanol. The resulting solution was stirred for 48 hours at room temperature. The white product which precipitated during the course of the reaction was filtered off, and the filtrate was evaporated to dryness in vacuo to yield more product.

Yield 1.3 g (92%)

M.Pt (MeOH) 167-170°C

$\nu_{max}^{CH_2Cl_2}$ 3500, 3395, 1695, 1615, 1585, 1515 cm^{-1}

N.M.R $\delta(CDCl_3$, 90 MHz) 7.05 (4H,AA'BB'q), 5.45 (2H,s), 3.8 (3H,s)

Mass Spec. M^+ 266 (9.0) /268 (2.6)

Acc. Mass Spec. (Found: 266.0566 : $C_{11}H_{11}N_4O_2Cl$ requires 266.0570 (Error -1.5 ppm)).

5-Chloro-1-(4-methoxybenzyl)-4-N-methylcarboxamido-1,2,3-triazole (40)

Aqueous methylamine (40%) (20 ml) was added to a solution of (26) (1.5 g) in/

in methanol (50 ml). This solution was stirred for 48 hours at room temperature. A little of the product had precipitated, and was filtered off. The remainder of the product was obtained by evaporating the filtrate to dryness in vacuo.

Yield = 1.35g (~ 93%)

M.Pt ($MeOH/Et_2O$) 109-110.5°C

$\nu_{max}^{CHCl_3}$ Peaks @ 3430, 1675, 1615, 1570 and 1510 cm^{-1}

N.M.R $\delta(CDCl_3$, 90 MHz) 7.05 (4H,AA'BB'q), 5.45 (2H,s) 3.8 (3H,s), 2.95 (3H,d).

Mass Spec. 280 (9.4), 282 (3.6)

Acc. Mass Spec. (Found: 280.0720 $C_{12}H_{13}N_4O_2Cl$ requires 280.0727 (Error -2.5 ppm)).

5-Azido-1-benzyl-4-methoxycarbonyl-1,2,3-triazole (43)

The chloro-triazole (24) (1.26 g, 0.00501 moles) was stirred with sodium azide (0.651 g, 0.01 moles) in dry dimethyl formamide (20 ml) for 3 days at 70°C. At the end of this period the solvent was removed in vacuo and the residue was partitioned between dichloromethane and water. The organic layer was washed several times with water, dried (sodium sulphate), filtered and evaporated to yield a crude brown oil. This oil was purified by column chromatography on silica using petrol (40/60) : ethyl acetate (0.65 : 0.35) as solvent to yield 0.66 g (51%) of the product as an oil.

$\nu_{max}^{CHCl_3}$ 2110, and 1700 cm^{-1}

N.M.R./

N.M.R. $\delta(CDCl_3$, 60 MHz) 7.31 (5H,s), 5.37 (2H,s) 3.95 (3H,s)

Mass Spec. M^+ @ 258 (6%)

Acc. Mass Spec. (Measured value 258.0861. $C_{11}H_{10}N_6O_2$ requires 258.0865 (Error 0.15 ppm)).

5-Azido-1-(4-methoxybenzyl)-4-methoxycarbonyl-1,2,3-triazole (44)

The chloro-triazole (26) (1 g, 0.0036 moles) was stirred with sodium azide (0.65 g, 0.01 moles) in dry dimethylformamide for 3 days in the dark at 65°C. After this period the solvent was removed in vacuo. The residue was partitioned between dichloromethane and water. The organic layer was separated and washed several times with water, dried (sodium sulphate), filtered, and evaporated to yield a brown oil. This oil was purified by chromatography on silica to yield 0.5 g (~49%) of an oil.

$\nu_{max}^{CHCl_3}$ 2145, 1725, 1610, 1560, 1250 cm^{-1}

N.M.R $\delta(CDCl_3$, 60 MHz) 7.1 (4H,AA'BB'q), 5.3 (2H,s), 3.95 (3H,s), 3.8 (3H,s)

Mass Spec. M^+ @ 288 (4.4)

Acc. Mass Spec. (Found: 288.0952. $C_{12}H_{12}N_6O_3$ requires 288.0971. (Error -6.6 ppm)).

5-Amino-1-benzyl-4-methoxycarbonyl-1,2,3-triazole (45)

The azido-triazole (43) (0.2 g) was dissolved in dry methanol (20 ml). A catalytic amount of 10% palladium on charcoal was added to this solution. The solution was hydrogenated at S.T.P for 3 days. The charcoal was filtered/

filtered off and the filtrate was evaporated under reduced pressure to dryness. The residue was dried <u>in vacuo</u> for another hour. The weight of product was 0.15 g (80%).

ν_{max}^{KBr} 3400, 3280, 3215, 3150, 1675, 1615, 1550, 1500, and 1440 cm^{-1}

N.M.R. δ(D.M.S.O$_{d_6}$,60 MHz) 7.3 (5H,s), 6.65 (2H, br), 5.48 (2H,s), 3.8 (3H,s).

Mass Spec. M^+ @ 232 (19.1)

Acc. Mass Spec. (Found: 232.0946. $C_{11}H_{12}N_4O_2$ requires 232.0960 (Error -6.0 ppm)).

M.Pt ($CHCl_3$/Petrol) 183-184°C

5-Amino-1-(4-methoxybenzyl)-4-methoxycarbonyl-1,2,3-triazole (46)

The azido-triazole (44) (240 mg) was dissolved in ethyl acetate (20 ml). The resulting solution was hydrogenated at room temperature and atmospheric pressure using 10% palladium on charcoal catalyst for 2 days. The charcoal was filtered off and at this stage white crystals were observed, recrystallising from the filtrate. The filtrate was evaporated to dryness and the residue was collected and washed with a little diethyl ether.

Yield of product 145 mg (66%)

ν_{max}^{KBr} 3450, 3280, 3220, 3160, 1680, 1635, 1570, 1510, 1440, and 1380 cm^{-1}

N.M.R δ($CDCl_3$/D.M.S.O$_{d_6}$,60 MHz). 7.05 (4H,AA'BB'q) 6.35 (2H, br), 5.35 (2H,s), 4.85 + 4.77 (2 x 3H, 2 x s)

Mass Spec. M^+ @ 262 (12)

Acc. Mass Spec. (Found: 262.1043. $C_{12}H_{14}N_4O_3$ requires 262.1066 (Error -8.8 ppm)).

M.Pt/

M.Pt ($CHCl_3$/Petrol) prisms 190-192°C

5-Azido-1-benzyl-4-carboxamido-1,2,3-triazole (48)

The azido-triazole (43) (0.5 g) was dissolved in methanol (7 ml). To this solution ammonia (S.G = 0.88) was added until a turbidity was observed. More methanol (10 ml) was added to homogenise the reaction mixture. A little more ammonia was added (1 ml) to ensure an excess of reactant. Stirring was continued overnight in a tightly stoppered round bottomed flask. At the end of this period a precipitate was noted and filtered off. More ammonia (5 ml) was added to the filtrate and stirring was continued for another 14 hours. The methanol was removed in vacuo and the resultant precipitate was filtered from its aqueous environment.

Yield = 0.28 (60%)

ν_{max}^{KBr} 3325, 3150, 2120, 1655, 1540, and 1460 cm^{-1}

N.M.R δ(D.M.S.O_{d_6}, 60 MHz) 7.9 + 7.55 (2 x 1H, 2 br), 7.3 (5H,s), 5.45 (2H,s)

Mass Spec. M^+ @ 243 (9%)

Acc. Mass Spec. (Found: 243.0857. $C_{10}H_9N_7O$ requires 243.0868 (Error -4.5 ppm)

M.Pt ($MeOH/Et_2O$) needles. Change shape @ 140°. 159-161°C decompose violently.

5-Amino-1-benzyl-4-carboxamido-1,2,3-triazole[6] (41a)

The azido-triazole (48) (0.36 g, 0.0015 mole) was dissolved in methanol (40/

(40 ml). This solution was hydrogenated at room temperature and at atmospheric pressure in the presence of a palladium on charcoal catalyst for 3 days. At the end of this period, the reaction mixture was boiled and the charcoal was filtered off quickly. A precipitate was noted immediately in the filtrate. The filtrate was evaporated to dryness to yield 0.3 g of a solid. This residue was washed with a little diethyl ether (5 ml). The insoluble product was filtered off (0.19 g ~ 60%) as a white solid.

ν_{max}^{KBr} 3400, 3290, 3120, 1660, 1630 and 1240 cm^{-1}

N.M.R, δ(D.M.S.O$_{d_6}$,60 MHz) 7.2 (5H,s), 6.2 (2H,br) 5.4 (2H,s)

Mass Spec. M^+ @ 217 (70%)

M.Pt (ethanol) 233-234°C Lit[6] 233-235°C

1-Benzyl-5-hydroxy-4-methoxycarbonyl-1,2,3-triazole (8c)

The benzylammonium salt (4, R = $PhCH_2$) (1 g) was stirred in 1 M hydrochloric acid (5 ml) for 15 minutes, followed by extraction into dichloromethane (3 x 10 ml). The extracts were dried over magnesium sulphate, filtered, and evaporated under reduced pressure to produce a quantitative yield of the product.

M.Pt (CH_2Cl_2) 109-111°C

ν_{max}^{KBr} 3010, 1690, 1600, 1530, 1450, and 1290 cm^{-1}

N.M.R $\delta(CDCl_3)$ 7.2 (5H,s), 5.25 (2H,s) and 3.8 (3H,s)

Acc. Mass Spec. (Found: M^+, 233.0791. $C_{11}H_{11}N_3O_3$ requires M, 233.0800.

4-/

4-Methoxybenzyl Azide[7] (52)

Sodium azide (6.5 g, 0.1 mole) was stirred for 24 hours at ambient temperature with a solution of 4-methoxybenzyl chloride (15.65 g, 0.1 mole) in dry dimethylformamide (50 ml) and the mixture was diluted with water (200 ml). The organic azide was extracted into ether and the extracts were washed well with water and dried (sodium sulphate). Filtration then evaporation under reduced pressure at a temperature less than 20°C yielded the azide as a colourless oil.

Yield 15.4 g ~95%

ν_{max}^{Film} @ 2090 cm^{-1}

N.M.R $\delta(CDCl_3$, 60 MHz) 7.2 (4H,AA'BB'q), 4.2 (2H,s), 3.7 (3H,s)

5-Amino-4-carboxamido-1-(4-methoxybenzyl)-1,2,3-triazole (41b)

4-Methoxybenzyl azide (52) (10 g) and cyanoacetamide (5.2 g) were refluxed in dry ethanol in the presence of sodium ethoxide (2.8 g of sodium in 150 ml of ethanol) for 1 hour. After this time the reaction mixture was cooled. The product was isolated by filtration, washed with a little ethanol and then with ether. The product was dried <u>in vacuo</u>.

Yield 10.5 g (69.3%)

ν_{max}^{Nujol} 3400, 3305, 3710, 1670, 1635, and 1585 cm^{-1}

N.M.R $\delta(D.M.S.O_{d_6}$,90 MHz) 7.0 (4H,AA'BB'q), 6.35 (2H,br), 5.33 (2H.s), 3.72 (3H,s)

Mass Spec. M^+ @ 247

Acc. Mass Spec. (Found: 247.1066. $C_{11}H_{13}N_5O_2$ requires 247.1069 (Error -1.2 ppm)).

M.Pt/

M.Pt (Methanol) 207.5-209.5°C

5-Amino-4-carboxamido-1,2,3-triazole (53)

5-Amino-4-carboxamido-1-(4-methoxybenzyl)-1,2,3-triazole (41b) (4 g) was stirred for 12 hours with trifluoroacetic acid (25 ml) at 65°C. The reaction mixture was evaporated and the residue was dissolved in water. The water insoluble material was soluble in dichloromethane and evaporation of the aqueous solution in vacuo yielded a product.

ν_{max}^{Nujol} 3370, 3210, 1740, 1680, 1640, and 1600 cm^{-1}

N.M.R δ(D.M.S.O_{d_6}, 90 MHz) 8.0 and 7.7 (br)

Mass Spec. $M^+ - H_2O$ @ 223

5-Amino-4-ethoxycarbonyl-1-(4-methoxybenzyl)-1,2,3-triazole (57)[6]

4-Methoxybenzyl azide (52) (50 g) was refluxed with ethyl cyanoacetate (34.7 g) and sodium ethoxide (from 7.1 g of sodium) in ethanol for 18 hours. 5 volumes of water were added, and this solution was extracted into dichloromethane (5 x 400 ml). The dichloromethane layer was separated, dried (sodium sulphate), filtered, and concentrated under reduced pressure. This concentrated solution was chromatographed on silica (ethyl acetate : petrol (40/60); 0.5 : 0.5) to yield some starting material and some product. The product was recrystallised from chloroform/petrol (40/60) to yield 8.5 g ($\sim$ 10%) of the expected product.

$\nu_{max}^{CHCl_3}$ 3490, 3440, 3010, 1685, 1625, 1515, and 1200 cm^{-1}

N.M.R/

N.M.R $\delta(CDCl_3$, 90 MHz) 7.05 (4H,AA'BB'q), 5.4 (2H,s), 5.05 (2H,br), 4.5 (2H,q), 3.82 (3H,s) and 1.45 (3H,t)

Mass Spec. M^+ @ 276

Acc. Mass Spec. (Found: 276.1204, $C_{13}H_{16}N_4O_3$ requires 276.1224 (Error -6.5 ppm)).

M.Pt 160-161.5°C

5-Amino-4-ethoxycarbonyl-1,2,3-triazole (58a)

(57) (2.76 g) was stirred with trifluoroacetic acid at 65°C for 15 hours.

At the end of this time the solvent was removed in vacuo. The residue was dissolved in water and this mixture was filtered off and the aqueous filtrate was evaporated in vacuo to yield a solid. This solid was stirred with a saturated solution of sodium bicarbonate until effervescence ceased. The aqueous solution was evaporated to dryness and subjected to Soxhlet extraction with ethyl acetate for 3 days.

Yield 1.56 g (64%)

ν_{max}^{Nujol} 3460, 3325, 1695, 1640 cm^{-1}

N.M.R. $\delta(D.M.S.O_{d_6}$, 90 MHz) 5.7 (2H,br), 4.2 (2H,q), 1.2 (3H,t)

Mass Spec. M^+ @ 156

Acc. Mass Spec. (Found: 156.0653. $C_5H_8N_4O_2$ requires 156.0648 (Error 3.2 ppm)).

M.Pt (Ethanol/Ether) 190-191°C

5-Amino-4-methoxycarbonyl-1,2,3-triazole (58b)

5-Amino-1-benzyl-4-methoxycarbonyl-1,2,3-triazole (45) (1.2 g) was dissolved/

dissolved in glacial acetic acid (20 ml) and to this solution trifluoroacetic acid (1 ml) was added. This solution was subjected to catalytic hydrogenation for 1 day at standard temperature and pressure using a 10% palladium on charcoal catalyst. The charcoal was filtered off, and the filtrate was evaporated in vacuo to yield 0.5 g (70%) of product.

N.M.R δ(D.M.S.O$_{d_6}$,60 MHz) 7.0 (3H,br), 3.6 (3H,s)

Mass Spec. M^+ @ 142 (100)

Acc. Mass Spec. $C_4H_6N_4O_2$ requires 142.0491. Found: 142.0494 (Error 2.1 ppm)

M.Pt (Ethanol/ether) 184-185°C

5-Diazo-4-ethoxycarbonyl-1,2,3-triazole (59a)

The deprotected amino-triazole (58a) (1.0 g) was stirred at 2°C for 90 minutes in 40 ml of 1 M hydrochloric acid and sodium nitrite solution (3 g in 10 ml water). After this time the reaction mixture was neutralised with sodium bicarbonate and the aqueous solution was subjected to continuous extraction for 3 days in the dark with dichloromethane. The dichloromethane layer was dried over magnesium sulphate and was concentrated in vacuo.

$\nu_{max}^{CH_2Cl_2}$ 2180, 1755, 1715 and 1510 cm^{-1}

T.L.C (EtOAc) R_F = 0.4

These were the only characteristics recorded because the products were/

were kept in dichloromethane solutions in the interest of safety.

5-Diazo-4-methoxycarbonyl-1,2,3-triazole (59b)

To a stirred solution containing 50 mg of 5-amino-4-methoxycarbonyl-1,2,3-triazole (58b) in 1.5 ml of concentrated hydrochloric acid was added a solution containing 50 mg of sodium nitrite in 0.5 ml water over a ten minute period, keeping the temperature under 5°C. The mixture was allowed to stir for twenty minutes at 0°C and then 1.7 ml of ice-water was added. The solution was neutralized with sodium bicarbonate (sat) and extracted with dichloromethane (3 x 50 ml). The dichloromethane layer was dried over magnesium sulphate, filtered, and concentrated to 10 ml in the dark at 0°C.

$\nu_{max}^{CH_2Cl_2}$ @ 2150 and 1700 cm^{-1}

T.L.C (EtOAc) $R_F = 0.3$

As in (59a), the product was not isolated, but retained as a dichloromethane solution and therefore no other characteristics were recorded.

3-(4-Methoxybenzyl)-[3H]-1,2,3-triazolo-[4,5d] pyrimidin-7-one (63)

The aminotriazole carboxamide (41b) (0.99 g) was heated at 190-220°C for two hours in formamide (5 ml). After this period the reaction mixture was diluted with water (75 ml) and a product precipitated. The product was filtered off, washed with water and dried in vacuo.

Yield 0.51 g (~ 48%)

V/

ν_{max}^{Nujol} 3200, 1735, 1680, 1590, 1555, 1520 cm^{-1}

N.M.R, δ(D.M.S.Od_6, 90 MHz) 8.27 (1H,s), 7.15 (4H,AA'BB'q), 5.7 (2H,s) and 3.75 (3H,s)

Mass Spec. M^+ @ 257

Acc. Mass Spec. (Found: 257.0899. $C_{12}H_{11}N_5O_2$ requires 257.0913 (Error -5.4 ppm)).

M.Pt (Ethanol/decolourising charcoal) 223-225°C (dec)

Triethyl oxonium tetrafluoroborate (67)[8]

Boron trifluoride diethyl etherate was distilled (B.Pt 116°C @ 30 mm Hg) from calcium hydride. This purified dietherate (ca 10 g) was dissolved in diethyl ether and to this solution, a solution of epichlorohydrin (5 g in 20 ml of diethyl ether) was added dropwise under reflux. The mixture was stirred at room temperature for 2 hours and left to stand for 60 hours. The gelatinous solid which had formed during the reaction was washed several times with ether (this salt is very hygroscopic, and eventually liquifies in air). The product was stored in a vacuum desiccator to be carried on to the next step without analysis.

Ethyl acetimidate (69a)[9]

A solution of triethyloxonium tetrafluoroborate (8.4 g, 0.04 moles) in dry dichloromethane was added over 5 minutes at room temperature to a suspension of acetamide (1.18 g, 0.02 mole) in dry dichloromethane (40 ml). A clear solution resulted immediately. The solution was stirred overnight at room temperature. The solution was then concentrated to a small volume. To this solution triethylamine (5 g, $\sim$ 0.049 moles) was/

was added. The reaction mixture was shaken for one minute. To the reaction mixture dry ether (200 ml) was added. The tetrafluoroborate salt was filtered off and the ether filtrate was evaporated in vacuo down to an oil which by N.M.R inspection consisted of the product and triethylamine.

ν_{max}^{Film} 3300, 3000-2800, 1655 (strong), 1500 cm^{-1}

Ethyl benzimidate (69b)[9]

A solution of triethyloxonium fluoroborate (5 g, 0.026 mole) in dry dichloromethane (15 ml) was added over five minutes at room temperature to a suspension of benzamide (2.42 g, 0.02 mole) in dry dichloromethane (40 ml) was added. After this period a white product was filtered off and the filtrate was concentrated to one third of its original volume. To this concentrated solution dry diethyl ether (40 ml) and more of the ethyl benzimidate fluoroborate (68b) precipitated. To the salt triethylamine (5 g, 0.049 moles) was added. Ether (200 ml) was added to this mixture and the resultant precipitate was filtered off and discarded. The ether extract was evaporated under reduced pressure to yield an oil which contained triethylamine.

N.M.R (68b) δ(D.M.S.O_{d_6}, 90 MHz) 7.9 (5H,m), 4.55 (2H,q), 1.5 (3H,t)

ν_{max}^{Film} of (68b) 3305, 3000-2800, 1680, 1635 (strong), 1600, and 1580 (sharp) cm^{-1}

7-Chloro-3-(4-methoxybenzyl)-[3H]-1,2,3-triazolo-[4,5-d]-pyrimidine (70)

The/

The 8-azapurin-6-one (63) (1.028 g, 0.004 moles) was stirred with dry D.M.F (0.55 ml, 0.008 mole) in dry dichloromethane (20 ml) at 40°C. To this suspension redistilled thionyl chloride (2.0 ml, 0.026 moles) was added until a solution was obtained. Stirring was continued overnight. The solvent and volatiles were removed in vacuo and the residue was redissolved in dichloromethane (40 ml). This layer was washed well with saturated sodium bicarbonate solution until effervescence ceased. The dichloromethane layer was dried with magnesium sulphate, filtered and evaporated to yield a solid (0.91 g ~ 84%).

N.M.R δ(D.M.S.O$_{d_6}$, 90 MHz) 8.25 (1H,s), 7.1 (4H,AA'BB'q), 5.65 (2H,s), 3.72 (3H,s)

Mass Spec. M^+ @ 275 (6.8), 277 (2.3)

It was important to use this product as soon as possible because analysis indicated that it reverted to the 8-azapurin-6-one within 2 days due to the ongoing humid laboratory conditions.

7-Amino-3-(4-methoxybenzyl)-[3H]-1,2,3-triazolo-[4,5-d]-pyrimidine (71)

To a solution of the chloro-azapurine (70) (1.3 g) in an ethanol/dichloromethane solution (2 : 1) (45 ml) was added a solution of ammonia in ethanol (20 ml). Stirring was continued for 2 hours. The reaction mixture was left to stand at room temperature overnight. The resultant precipitate was filtered off and more product was recovered by concentrating the filtrate and adding chloroform to the concentrate. The precipitates were combined and washed well with water and dried in vacuo at 25°C.

Yield/

Yield 0.95 g (79%)

ν_{max}^{KBr} 3120 (v br), 1700, 1685, 1610, 1580, 1510, 1400, 1320, 1250, and 1175 cm^{-1}

N.M.R δ(T.F.A., 90 MHz) 8.7 (1H,s), 7.25 (4H,AA'BB'q), 5.9 (2H,s), 3.95 (3H,s)

Mass Spec. M^+ @ 256 (26)

Acc. Mass Spec. (Found: 256.1088. $C_{12}H_{12}N_6O$ requires 256.1073. (Error 5.9 ppm)).

M.Pt (Methanol) 253-255°C (Crystal shape changes @ 200°C).

Acetic formic anhydride[10]

A 500 ml three neck flask equipped with stirrer, thermometer, and dropping funnel was charged with sodium formate (60 g, 0.822 moles) and diethyl ether (50 ml). The dropping funnel was charged with acetyl chloride (58.8 g, 0.75 moles), a cooling bath was put in place to control the mildly exothermic reaction and the acetyl chloride was added in a period of ten minutes at a temperature controlled to 13-18°C. The mixture was stirred overnight at room temperature to ensure complete reaction. After this time the ether was removed under reduced pressure and the residue was distilled under reduced pressure to yield the product.

Yield 42 g ($\sim$ 65%)

B.Pt 24-27°C (30 mm Hg)

N.M.R, $\delta(CDCl_3$, 60 MHz) 9.0 (1H,s), 2.35 (3H,s)

I.R ($CHCl_3$) 1795, 1770, 1260, and 1050 cm^{-1}

4-/

4-Carboxamido-5-diformylamino-1-(4-methoxybenzyl)-1,2,3-triazole (73)[11]

The amino-triazole (41b) (2.47 g, 0.01 moles) and freshly distilled acetic formic anhydride (17 ml) were stirred at room temperature for 24 hours. The volatile components were removed in vacuo at 50°C. The residue was stirred with a little ethanol and filtered off.

Yield 1.63 g (54%)

N.M.R δ(D.M.S.O$_{d_6}$, 90 MHz) 9.38 (2H,s), 7.05 (4H,AA'BB'q), 5.4 (2H,s), 3.75 (3H,s)

ν_{max}^{KBr} 3395, 3150, 1680 (v br), 1610, 1510, 1480, 1315, and 1160 cm^{-1}

Mass Spec. M^+ @ 303 (4.2)

Acc. Mass Spec. (Found: 303.0947. $C_{13}H_{13}N_5O_4$ requires 303.0968 (Error -6.9 ppm)).

M.Pt (crude) 148-150°C dec

M.Pt (EtOH) 160-196°C - due to the fact that during recrystallisation there is conversion of (73) to the monoformyl derivative.

4-Carboxamido-1-(4-methoxybenzyl)-5-methylamino-1,2,3-triazole (74)

Dimethyl sulphate (1.5 g) was added during 20 minutes to (73) (1.01 g) in 1 M sodium hydroxide (30 ml) with rapid stirring and the temperature was maintained at 20°C. Stirring was continued for 30 minutes and the resultant suspension was refrigerated overnight. The product was isolated by filtration.

Yield 0.73 g (84%)

N.M.R δ(D.M.S.O$_{d_6}$, 90 MHz) 7.5 (1H,br), 7.0 (4H,AA'BB'q), 5.5 (2H,s), 3.7/

3.7 (3H,s), 2.95 (3H,d)

ν_{max}^{KBr} 3300 br, 2930, 1650 (br), 1595, 1505, 1350, and 1250 cm^{-1}

Mass Spec. M^+ @ 261 (13.3)

Acc. Mass Spec. (Found: 261.1215. $C_{12}H_{15}N_5O_2$ requires 261.1226 (Error -4.2 ppm)).

M.Pt (Ethanol) 157-158.5°C

3-(4-Methoxybenzyl)-4-methyl-[3H]-1,2,3-triazolo-[4,5-d]-pyrimidin-7-[4H]-one (75)

5-Methylamino-1-(4-methoxybenzyl)-1,2,3-triazole-4-carboxamide (74) (0.261 g, 0.001 mole), triethyl orthoformate (2 ml), and 10 M hydrochloric acid (0.13 ml) were stirred together at room temperature for 24 hours. The resultant precipitate was filtered off, washed with acetone and [illegible] with 3 M sodium acetate. The product was isolated by filtration.

Yield 0.19 g (70%)

ν_{max}^{KBr} 1660 (br), 1545, 1340, 1245, 1150, and 1060 cm^{-1}

N.M.R δ(D.M.S.O$_{d_6}$, 90 MHz) 8.23 (1H,s), 7.05 (4H,AA'BB'q), 5.97 (2H,s) 3.85 (3H,s), 3.77 (3H,s)

Mass Spec. M^+ @ 271 (11.5)

Acc. Mass Spec. (Found: 271.1071. $C_{13}H_{13}N_5O_2$ requires 271.1070 (Error 0.4 ppm)).

Microanalysis (Found: C. 57.38, H. 4.89, N. 25.66. $C_{13}H_{13}N_5O_2$ requires C. 57.57, H. 4.80, N. 25.83%).

M.Pt (Ethanol) 222-224°C

4-/

4-Aminomethyl-1-benzyl-5-chloro-1,2,3-triazole (78)

To a solution of 2 M borane (dimethyl sulphide complex) in tetrahydrofuran (15 ml, 0.03 moles) was added 0.94 g (0.004 moles) of 1-benzyl-4-carboxamido-5-chloro-1,2,3-triazole (37) in dry T.H.F (20 ml) over a period of 15 minutes at 0°C under a nitrogen atmosphere. The reaction mixture was then refluxed for 36 hours. After this time the solution was filtered, and the filtrate was evaporated to dryness in vacuo. The residue was dried for a further 1 hour in vacuo at room temperature to remove any remaining T.H.F. To the glassy residue water (5 ml) was carefully added to hydrolyse any excess borane. Then sodium hydroxide solution (4 ml, 5 M) was added to isolate the amine. The resulting two phase mixture was extracted with dichloromethane (4 x 50 ml). The organic extracts were combined, dried (sodium sulphate) and evaporated under reduced pressure to yield a viscous oil. This oil was dried in vacuo for a further 1 hour. After this time the residue was redissolved in dichloromethane/ether and dry hydrogen chloride was bubbled through the solution. When more ether was added the hydrochloride salt precipitated as a white solid (0.62 g ~ 60%). The free chloro-aminomethyl triazole was liberated by dissolving the hydrochloride in water, adding sodium hydroxide pellets until the solution was basic, and the liberated amine was extracted into dichloromethane (5 x 50 ml). The organic extracts were dried (sodium sulphate), filtered and evaporated in vacuo to yield 0.53 g of the product as an oil (Yield ~ 60%).

N.M.R $\delta(CDCl_3, 60MHz)$ 7.2 (5H,s), 5.4 (2H,s), 3.8 (2H,br)

M^+ @ 222 (4%)

Acc. Mass Spec. (Found: 222.0665. $C_{10}H_{11}N_4Cl$ requires 222.0672 (Error -3.2 ppm)).

5-/

5-Amino-4-aminomethyl-1-benzyl-1,2,3-triazole (77)[12]

To a suspension of 5-amino-1-benzyl-4-carboxamido-1,2,3-triazole (41a) (0.434 g, 0.002 moles) under nitrogen in dry T.H.F (15 ml), was added borane (dimethyl sulphide complex in T.H.F (2 M)), (10 ml, 0.02 moles). The resulting solution was refluxed for 48 hours. At the end of this time the reaction mixture was evaporated to dryness in vacuo. The residue was subsequently dried for 1 hour at room temperature in vacuo. To this residue water (5 ml) was added carefully to destroy excess borane. 20% w/v sodium hydroxide solution (5 ml) was added to this aqueous solution. This mixture was extracted with dichloromethane (3 x 50 ml). The extracts were combined, dried (sodium sulphate), filtered and evaporated under reduced pressure to yield 0.4 g of a crude solid. This crude solid was dissolved in dichloromethane (30 ml). Any insoluble material was filtered off. Ether (60 ml) was added until the solution became slightly turbid. This mixture was chilled to 0°C and dry hydrogen chloride gas was bubbled through the mixture. The resultant precipitate was filtered off and washed with a little ether. This salt was redissolved in water (2 ml) and 20% sodium hydroxide solution was added to liberate the free amine. The product was extracted into dichloromethane (3 x 10 ml). The organic extracts were combined, dried (Na_2SO_4), filtered and evaporated by passing a stream of nitrogen over the solution to yield 0.27 g (66%) of a solid product.

N.M.R. δ(D.M.S.O$_{d_6}$, 60 MHz) 7.3 (5H,s), 5.4 (4H,brs), 3.7 (2H,brs), 2.5 (2H,br)

N.M.R. δ(D.M.S.O$_{d_6}$ + D_2O, 60 MHz) 7.3 (5H,s), 5.4 (2H,s) and 3.7 (2H,s)

ν_{max}^{Nujol} 3320, 3140, 1655, 1590, 1300, 1240, 920 and 725 cm^{-1}

Mass Spec. M^+ @ 203 (26.8)

Acc./

Acc. Mass Spec. $C_{10}H_{13}N_5$ requires 203.1171. Found: 203.1169 (Error -1.0 ppm).

M.Pt (uncorrected) (benzene) 103-104°C (needles)

Lit M.Pt 105°C[12]

5-Amino-4-aminomethyl-1-(4-methoxybenzyl)-1,2,3-triazole (§ 3)

A suspension of 5-amino-4-carboxamido-1-(4-methoxybenzyl)-1,2,3-triazole (41b) (1.85 g) in dry T.H.F (50 ml) was added to a solution of borane (dimethyl sulphide complex in T.H.F (2 M)) (50 ml). The resultant solution was refluxed for 48 hours. At the end of this time, the reaction mixture was evaporated to dryness in vacuo. The residue was subsequently dried for 45 minutes at room temperature in vacuo. The residue was treated with water (25 ml) to hydrolyse any remaining borane. This mixture was basified to pH 12 with 20% sodium hydroxide solution. The insoluble amine was extracted with dichloromethane (3 x 80 ml). The organic extracts were combined, dried (sodium sulphate), filtered, and evaporated under reduced pressure to yield 2.0 g of a residue. The residue was redissolved in dry dichloromethane, and dry ether was added to this solution until a slight turbidity was observed. This solution was chilled to 3°C and dry hydrogen chloride gas was passed through it. A gelatinous precipitate formed and was isolated by filtration with great difficulty. The precipitate was added to sodium hydroxide solution (20%, 25 ml), and this mixture was extracted into dichloromethane (2 x 50 ml). The organic extracts were combined, dried (sodium sulphate), filtered, and evaporated under reduced pressure to yield 1.07 g (60%) of product as a white solid.

N.M.R/

N.M.R δ(D.M.S.O$_{d_6}$, 60 MHz) 7.1 (4H,AA'BB'q), 6.0 (1H,br), 5.4 (2H,s), 5.31 (2H,s), 3.8 (5H, s + br)

$\nu_{max}^{CHCl_3}$ 3250, 3150, 1610, 1575, 1500, 1260, 1190, 1000, and 690 cm^{-1}

Mass Spec. M^+ @ 233 (11.3)

Acc. Mass Spec. (Found: 233.1282. $C_{11}H_{15}N_5O$ requires 233.1277. (Error 2.1 ppm)).

M.Pt (crude product) 93-96°C incomplete melting.

Attempts at recrystallisation using a variety of solvents failed due to the waxiness of the product. The product is probably a mixture of the free amine and the amine carbamate which it might form in the presence of air.

3-(4-Methoxybenzyl)-6,7-dihydro-[3H]-1,2,3-triazolo-[4,5-d]-pyrimidine (84)

The aminomethyl triazole (83), (0.3 g) was refluxed for 4 hours with formamidinium acetate (0.41 g) in dry n-butanol. At the end of this period the solvent was evaporated at 90°C under water pump pressure. To the residue warm water was added, and this mixture was chilled for five hours. At the end of this period a white solid was noted and this was recrystallised from benzene/petrol (60/80) to give 0.22 g (70%) of product.

N.M.R. δ(D.M.S.O$_{d_6}$, 90 MHz) *8.0 (1H,br), 7.3-6.8 (5H,AA'BB'q + d**), 5.25 (2H,s), 4.75 (2H,s), 3.73 (3H,s)

* collapses when D_2O is added.

** becomes a singlet when D_2O is added.

V/

ν_{max}^{KBr} 3320, 1640, 1603, 1570, 1520, 1250, 1100 and 750 cm^{-1}

Mass Spec. M^+ @ 243 (13.2)

Acc. Mass Spec. (Found: 243.1124. $C_{12}H_{13}N_5O$ requires 243.1121 (Error 1.2 ppm)).

M.Pt (Benzene/Petrol (60/80)) 124-126°C (very fine needles)

D-Ribopyranosylamine (86)[13]

D-Ribose (50 g) was added to a stirred cooled solution of ammonia in methanol (75 ml). During the addition ammonia was bubbled through the mixture which was then transferred to a refrigerator and stored at 5°C for 2 weeks. After this period the product was broken up, washed with methanol and dried in vacuo.

Yield 45 g (~90%)

M.Pt 126-127°C

Lit 128-129°C[13]

2,3-O-Isopropylidene-D-ribofuranosylamine (Toluene-p-sulphonate salt) (87)[13]

Powdered D-ribopyranosylamine (20.4 g, 0.138 mole) was added to a vigorously stirred solution of dry p-toluene-sulphonic acid monohydrate (53 g ~0.28 mole) in 2,2-dimethoxypropane (143 ml, 1.1 mole) and dry acetone (1000 ml). At this point the formation of a white precipitate was noted. The mixture was left to stir overnight, during which time the solid precipitate had dissolved. After this time dry ether (450 ml) was added, and within a period of 1 hour crystallisation commenced. The mixture was stored overnight at 4°C and the product was collected, and/

and washed with dry ether.

Yield 39 g (80%)

N.M.R. δ(D.M.S.O$_{d_6}$, 90 MHz) 8.0 (1H,br), 7.15 (4H,AA'BB'q), 5.15 (d), 5.03 (s), 4.3-3.5 (3H,m), 3.4 (2H,s), 2.3 (3H,s), 1.5, 1.4, 1.3 and 1.27 (anomeric isopropylidene peaks)

M.Pt 125-127°C

Lit M.Pt 128-129°C[13]

2-3-Isopropylidene-D-ribofuranose (88)[14]

D-Ribose (5 g, 0.033 moles) was added with stirring to acetone (100 ml) containing concentrated sulphuric acid (1.5 ml). Within 5 minutes the ribose had dissolved and after 1 hour the solution was neutralised with an excess of solid sodium bicarbonate (8 g). The solids were filtered off and washed with a little dry acetone. The solution was evaporated under reduced pressure to a syrup (6.8 g) which was used directly without further purification for the next step. From previous preparations it was expected that the overall yield for this preparation was 50-60%.

N.M.R. δ($CDCl_3$, 60 MHz) 5.3 (1H,s), 1.47 + 1.3 (6H, 2 x s)

5-O-Trityl-2,3-O-isopropylidene-D-ribofuranose (89)[15]

The crude product from the previous preparation above (19 g) in dry pyridine (40 ml) was treated with trityl chloride (33.5 g, 0.12 moles) at room temperature. After 24 hours the mixture was poured into 500 ml of water with rapid stirring. The supernatant aqueous extract was decanted/

decanted and the precipitated syrup was washed with water, dissolved in 300 ml of dichloromethane and shaken with a solution of 40 g of cadmium chloride in 400 ml of water. After filtration of the insoluble material, the organic layer was separated and dried over anhydrous sodium sulphate. Filtration then evaporation under reduced pressure yielded a syrup which was purified by column chromatography (Pet : EtOAc 0.85 : 0.15 ⟶ 0.7 : 0.3) to yield 18.2 g of product.

N.M.R. $\delta(CDCl_3$, 90 MHz) 7.35 (15H,m), 5.35 (d,1H), 4.75 (2H,m), 4.35 (1H,m), 3.85 (1H,d), 3.4 (2H,m), 1.47 and 1.33 (6H,2 x s)

5-O-Trityl-2,3-O-isopropylidene-D-α-ribofuranosyl azide (90)[16]

A solution of the protected ribofuranose (89) (1.1 g) in dry dichloromethane (38 ml) containing carbon tetrachloride (0.8 g) was cooled to -40°C under an inert atmosphere. The mixture was stirred and a solution of hexamethylphosphorous triamide (0.51 g) in dry dichloromethane (13 ml) was added dropwise during 1 hour. The phosphonium azide (97) was then added to the cold solution and the mixture was stirred at -10°C for 3 hours. The solvent was evaporated and the residue was dissolved in hexane (500 ml). The solution was washed with water (3 x 50 ml), dried with magnesium sulphate, filtered, and evaporated under reduced pressure. The resultant syrup was chromatographed on silica (elute ether/petrol 0.2 : 0.8).

Yield 0.81 g (70%)

$\nu_{max}^{CHCl_3}$ @ 2120 cm^{-1}

N.M.R/

N.M.R $\delta(CDCl_3$, 90 MHz) 7.35 (15H,m), 5.3 (1H,d), 4.95-4.3 (3H,m), 3.3 (2H,octet) 1.58 and 1.35 (6H,2 x s)

5-Amino-4-carboxamido-1-(5'-O-trityl-2',3'-O-isopropylidene-D-β-ribofuranosyl)-1,2,3-triazole (91)[17]

The glycosyl azide (90) (350 mg) was added to a cooled solution of potassium hydroxide (64 mg) and cyanoacetamide (96 mg) in water (0.5 ml) and D M F (5 ml). The yellow solution was allowed to warm up slowly to room temperature. After 3 hours all the starting material had disappeared and the reaction mixture was evaporated to dryness in vacuo. The residue was partitioned between water and ethyl acetate. The organic layer was separated, dried over magnesium sulphate, filtered, and evaporated to dryness. The residual syrup was chromatographed on silica with ethyl acetate as eluant to yield 270 mg ($\sim$65%) yield of the product.

N.M.R $\delta(CDCl_3$, 250 MHz) 7.27 (17H,m), 5.93 (1H,s), 5.68 (1H,d), 5.43 (2H,s), 4.82 (1H,q), 4.50 (1H,m), 3.04 (2H,octet), 1.57 and 1.38 (6H,2 x s)

$\nu_{max}^{CHCl_3}$ 3400, 1670, 1625, 1585, 1450, 1385 and 1075 cm^{-1}

M.Pt (ethyl acetate/petrol) 220-222°C

Microanalysis (Found: %C. 66.56, %H. 5.71, %N. 12.92. $C_{30}H_{31}N_5O_5$ requires %C. 66.54, %H. 5.73, %N. 12.94).

5-Amino-4-aminomethyl-1-(5'-O-trityl-2',3'-O-isopropylidene-β-D-ribofuranosyl)-1,2,3-triazole (92)

To/

To a solution of borane (dimethyl sulphide complex in T.H.F. (2 M, 20 ml)) under a nitrogen atmosphere at 0°C was added the protected triazole nucleoside (2.16 g ~ 0.004 mole) in dry T.H.F (25 ml). The resultant solution was refluxed for 48 hours. After this period the solution was evaporated to dryness under reduced pressure ensuring that bumping was kept to a minimum. The residue was dried further in vacuo for $1\frac{1}{2}$ hours at room temperature. Water (25 ml) was added carefully to hydrolyse residual borane. To this mixture sodium hydroxide solution (20%, 20 ml) was added. The aqueous mixture was extracted with dichloromethane (3 x 100 ml). The organic extracts were combined, dried (sodium sulphate), filtered, and evaporated under reduced pressure to yield a syrup. This syrup was shaken with ether (25 ml) and petrol (25 ml) to remove any non-polar material. The syrup solidified to an amorphous solid (1.1 g) which proved difficult to purify by crystallisation, and therefore was used directly for the next step.

N.M.R $\delta(CDCl_3$, 90 MHz) 7.2 (15H,m), 5.9 (1H,s), 5.6 (1H,d), 5.3 (8H,m), 1.53 and 1.31 (6H,2 x s)

$\nu_{max}^{CHCl_3}$ 3600-3000, 1625, 1485, 1445, and 1075 cm^{-1}

3-(5'-O-Trityl-2'-3'-O-isopropylidene-β-D-ribofuranosyl)-6,7-dihydro-1,2,3-triazolo-[4,5-d]-pyrimidine (93a)

The crude aminomethyl triazole (0.67 g) was refluxed with formamidinium acetate (0.45 g) in n-butanol (5 ml) for 4 hours. At the end of this period the solution was cooled and the solvent was removed in vacuo at 70°C. The residue was partitioned between ethyl acetate (20 ml) and water (5 ml). The organic layer was subsequently dried (magnesium sulphate)/

filtered,
sulphate) and evaporated in vacuo to yield 0.75 g of a viscous brown oil. This oil was purified by chromatography on silica (EtOAc/Pet 0.8 : 0.2 → EtOAc → EtOAc/MeOH 0.9 : 0.1) to yield 0.13 g of product (19%). T.L.C also indicated the presence of an impurity.

N.M.R δ($CDCl_3$ 360 MHz) 7.3 (16H,m), 6.9 (1H,brs), 6.2 (1H,s), 5.45 (1H,d), 4.9 (1H,q), 4.71 (2H,s), 4.3 (1H,m), 3.2 (2H,octet), 1.57 and 1.35 (6H, 2 x s)

N.M.R also indicated the presence of the impurity mentioned above. Comparison of the integrations of the isopropylidene peaks showed that the sample was 20% impure (4: 1 desired product/impurity).

^{13}C spectrum ($CDCl_3$, 90 MHz) ppm: 25.3, 26.9, (isopropylidene) 41.1 (NCH_2), 64.18 (OCH_2), 82.39, 83.51, 87.37 and 89.57 (ribose carbons) 126.77-128.53 (trityl carbons) and 150.20 $N=\overset{1}{C}H$

The impurity displayed peaks at 63.83, 82.24, 83.51, 87.37, and 91.07 ppm

$\nu_{max}^{CHCl_3}$ 3440, 1610, 1580, 1490, 1200 and 905 cm^{-1}

Mesityloxy-tris [dimethylamino] phosphonium azide (97)[16]

A solution of 2,4,6-trimethylphenol (13.6 g, 0.1 moles) in dry dichloromethane (500 ml), containing carbon tetrachloride (20 g, 0.13 mole) was cooled to -40°C under an inert atmosphere. The mixture was stirred and an excess solution of hexamethylphosphorous triamide (19.56 g, 0.12 mole) in dry dichloromethane (20 ml) was added dropwise during 3 hours. The mixture was allowed to warm to room temperature and a solution of sodium azide (21 g) in water (20 ml) was added with stirring. The organic layer was separated, dried with magnesium sulphate, filtered, and evaporated/

evaporated under reduced pressure to give a yellow syrup. The syrup was dissolved in water (70 ml) and washed with ether (3 x 100 ml) in order to remove hexamethylphosphoric triamide. The aqueous layer was extracted with dichloromethane (3 x 200 ml). The organic extracts were dried with magnesium sulphate, filtered, and evaporated to give the product as a gum. The crude compound was dissolved in acetone (20 ml), and precipitated by the addition of dry ether and isolated by filtration.

Yield 27.2 g (80%)

$\nu_{max}^{CHCl_3}$ @ 2030 cm^{-1}

N.M.R $\delta(CDCl_3$, 90 MHz) 6.95 (2H,s), 2.98 and 2.87 (18H,2 x s), 2.32 (9H,s)

1-Allyl-5-hydroxy-4-methoxycarbonyl-1,2,3-triazole (allylammonium salt) (106)

Dimethyldiazomalonate (45 g) was stirred at ambient temperature with allylamine (50 g) for 3 days. At the end of this time the precipitated triazole salt (26 g) was filtered off. Inspection of the filtrate by i.r spectroscopy indicated the presence of a diazo compound. More allylamine (20 ml) was added to the reaction mixture and stirring was continued for another 3 days. After this time a further 14 g of product was isolated.

Yield 40 g (60%)

N.M.R $\delta(D.M.S.O_{d_6}$/T.F.A) 8.1 (3H,br), 6.2-5.8 (2H,m), 5.7-5.2 (4H,m), 5.0 (2H,d), 3.85 (3H,s), 3.5 (2H,m).

ν_{max}^{KBr} 3200-2300, 1700, 1650, 1570, 1460, and 1420 cm^{-1}

Mass Spec. M^+ @ 183 (17%)

Microanalysis/

Microanalysis (Found: C. 50.01, H. 6.78, N. 23.13. $C_{10}H_{16}N_4O_3$ requires C. 50.00, H. 6.67, N. 23.33%).

M.Pt ($MeOH/Et_2O$) 168-170°C prisms

1-Allyl-5-hydroxy-4-methoxycarbonyl-1,2,3-triazole (105)

The allylammonium triazole salt (106) (24 g) was stirred for 30 minutes with 5 M hydrochloric acid (50 ml). After this period the aqueous solution was extracted with dichloromethane (10 x 100 ml). The dichloromethane extracts were combined, dried (sodium sulphate), filtered, and evaporated under reduced pressure to yield 18.1 g (99%) of product.

N.M.R δ(D.M.S.O_{d_6}, 60 MHz) 11.28 (1H,s), 6.25-5.63 (1H,m), 5.15 (2H,d), 4.7 (2H,d), 3.8 (3H,s)

ν_{max}^{KBr} 2400 (br), 1920 (br), 1705 cm^{-1}

Mass Spec. M^+ @ 183 (10.7)

Acc. Mass Spec. (Found: M^+ 183.0650. $C_7H_9N_3O_3$ requires 183.0645 (Error 2.7 ppm)).

M.Pt ($CHCl_3$/Petrol 60 : 80) 99-100°C (Prisms)

1-Allyl-5-chloro-4-methoxycarbonyl-1,2,3-triazole (104)

The hydroxy-triazole (105) (1.83 g, 0.01 mole) was stirred with phosphorus pentachloride (3.12 g, 0.015 moles) at 45°C in dry toluene for 15 hours. The toluene was removed in vacuo, and the orange-red residue was redissolved in diethyl ether. This solution was washed well with saturated sodium bicarbonate solution, and then with water. The organic layer was separated, dried (magnesium sulphate), filtered, and evaporated to give 1.55 g/

1.55 g of an oil. This oil was chromatographed on silica using petrol (40/60) : ethyl acetate 0.75 : 0.25 as eluant

Yield 0.9 g (45%) oil

$\nu_{max}^{CHCl_3}$ 3000, 2950, 1730, 1650, 1540, 1460, 1250-1200, 1050, and 820 cm^{-1}

N.M.R. $\delta(CDCl_3$, 60 MHz) 6.3-5.7 (1H,m), 5.35 (2H,d), 5.0 (2H,d), 3.93 (3H,s)

Mass Spec. M^+ @ 201 (0.8)

Acc. Mass Spec. (Found: 201.0307. $C_7H_8N_3O_2Cl$ requires 201.0306 (Error 0.5 ppm)).

1-Allyl-5-azido-4-methoxycarbonyl-1,2,3-triazole (103)

The allylic chloro-triazole (104) (1.01 g, 0.005 moles) was stirred for 15 hours at 65°C, in the dark, with sodium azide (0.65 g, 0.01 mole) in dry D.M.F (10 ml). At the end of this time the solvent was removed in vacuo and the residue was partitioned between water (10 ml) and dichloromethane (50 ml). The dichloromethane layer was separated and washed with water (5 x 10 ml), and dried over sodium sulphate. This solution was evaporated in vacuo to yield 0.96 g of an oil. This oil was chromatographed on silica gel (petrol : ethyl acetate 0.7 : 0.3) to afford 0.66 g (65%) of the title product as an oil.

N.M.R. $\delta(CDCl_3$, 60 MHz) 6.2-5.6 (1H,m), 5.4-4.6 (4H,m), 3.95 (3H,s)

$\nu_{max}^{CHCl_3}$ 3000, 2140 (S), 1710 (S), 1550, 1530 cm^{-1}

Mass Spec. M^+ @ 208 (10%)

Acc. Mass Spec. (Found: 208.0710. $C_7H_8N_6O_2$ requires 208.0709 (Error 0.5 ppm)).

1-/

1-Allyl-5-azido-4-carboxamido-1,2,3-triazole (102)

1-Allyl-5-azido-4-methoxycarbonyl-1,2,3-triazole (103) (0.208 g, 0.001 mole) was dissolved in methanol (3 ml). Concentrated ammonia (SG - 0.88) was added to this solution until a turbidity was observed. More methanol was added to homogenise the reaction mixture. This solution was stirred for 18 hours. At the end of this period the solvent was evaporated off in vacuo, and the residue was taken up in ether (0.5 ml). Filtration yielded the product as a white crystalline material.

Yield 0.135 g (~ 70%)

$\nu_{max}^{CHCl_3}$ 3330, 3140, 2125, 1660, and 1540 cm^{-1}

N.M.R $\delta(CDCl_3$, 60 MHz) 7.3 (2H,br), 5.3 (3H,m), 4.5 (2H,d)

Mass Spec. M^+ @ 193 (8)

Acc. Mass Spec. (Found: 193.0720. $C_6H_7N_7O$ requires 193.0713 (Error 3.6 ppm)).

M.Pt ($CHCl_3$/Petrol) 146-148°C

Allyl azide (109)[18]

Allyl chloride (25 g) and ethanol (50 ml) were refluxed with sodium azide (25 g) in water (75 ml) over two hours. After this time the reaction mixture was poured into water (400 ml) and the resultant oil was extracted into diethyl ether (2 x 150 ml). The organic layer was separated, washed once with dilute sulphuric acid and then several times with water. The organic layer was separated, dried (calcium chloride), filtered and evaporated down to yield a sweet smelling product. Distillation of this material yielded 4.6 g (17%) of material (B.Pt = 77°C)./

77°C). After the completion of the distillation the residue exploded violently.

ν_{max}^{Film} 2100 cm^{-1}

N.M.R. $\delta(CDCl_3$, 60 MHz) 5.9 (1H,m), 5.2 (2H,d), 3.65 (2H,d)

1-Allyl-5-amino-4-carboxamido-1,2,3-triazole (101)

Allyl azide (109) (1.66 g, 0.02 moles) was refluxed with cyanoacetamide (1.8 g, 0.02 moles) in sodium ethoxide solution (0.5 g of sodium in 40 ml of ethanol). The reaction mixture was cooled and the product was filtered off and washed with a little ethanol. The product was subsequently dried in vacuo.

Yield 1.4 g (42%)

N.M.R (T.F.A, 60 MHz) 6.2-5.5 (1H,m), 5.3 (2H,d), 4.7 (2H,d)

ν_{max}^{Nujol} 3400, 3300, 3150, 1630 cm^{-1}

Mass Spec. M^+ = 167 (16%)

Acc. Mass Spec. (Found: 167.0808. $C_6H_9N_5O$ requires 167.0808).

REFERENCES

1. W. von E. Doering and C. H. De Puy. J.Amer.Chem.Soc. (1953), 75, 5955.
2. M. Regitz. Chem.Ber. (1966), 99, 3128.
3. J. E. Leffler and S. K. Liu. J.Amer.Chem.Soc. (1956), 78, 1949.
4. A. Galat. J.Amer.Chem.Soc. (1946), 68, 376.
5. H. Staudinger and H. Becker. Chem.Ber. (1917), 50, 1016.
6. J. R. E. Hoover and A. R. Day. J.Amer.Chem.Soc. (1956), 78, 5832.
7. D. R. Buckle and C. J. M. Rockell. J.Chem.Soc. Perkin Trans I (1982), 627.
8. Fieser and Fieser. "Reagents for Organic Synthesis" (1967), 1, 1210.
9. Z. Weintaub, S. R. Oles and N. Kalish. J. Org.Chem. (1968), 33, 1679.
10. Fieser and Fieser. "Reagents for Organic Synthesis" (1969), 2, 10.
11. A. Albert. J.Chem.Soc. (C), (1969), 152.
12. A. Albert. J.Chem.Soc. Perkin Trans I (1973), 1634.
13. N. G. Cusack, B. J. Hildick, D. H. Robinson, P. W. Rugg and G. Shaw. J.Chem.Soc. Perkin Trans I (1973), 1720.
14. N. A. Hughes and P. R. H. Speakman. Carbohydrate Res (1965), 1, 171.
15. R. S. Klein, H. Ohrui and G. G. Fox. J.Carbohydrates, Nucleosides, Nucleotides (1974), 1, 265.
16. F. Chretien, B. Castro and B. Gross. Synthesis (1979), 937.
17. F. Chretien and B. Gross. Tetrahedron (1982), 38, 103.
18. M.O. Forster and H. E. Fierz. J.Chem.Soc. (1908), 1174.

APPENDIX 1

APPENDIX 1

Calculation of First Order Rate Constants by the Kezdy-Swinbourne Method

For a first order reaction of A, the rate law may be represented by equation 1 where $C_{A,O}$ and C_A are concentrations of A species at

$$C_A = C_{A,O} \exp(-kt) \qquad (1)$$

time $t = 0$ and t respectively, k is the first order rate constant. The observations of concentration change (x_0, x_1 x_2 ..... x_∞) are made at times 0, t_1, t_2, ... t_∞. For a reading (x_n taken at t_n) we can write

$$(x_\infty - x_n) = (x_\infty - x_o) \exp(-kt_n) \qquad (2)$$

For a reading (x^1n) taken at Δt seconds later

$$(x_\infty - x^1_n) = (x_\infty - x_o) \exp[-k(t_n + \Delta t)] \qquad (3)$$

Dividing (2) by (3) gives

$$(x_\infty - x_n) \exp(kt_n) = (x_\infty - x^1_n) \exp[k(t_n + \Delta t)]$$

$$x_n = x_\infty [1 - \exp(k\Delta t)] + x^1_n \exp(k\Delta t) \qquad (4)$$

Thus from a plot of x_n against x^1_n with Δt constant we have

$$\text{slope} = \exp(k\Delta t)$$

$$\text{i.e., } k = \ln(\text{slope})/\Delta t \qquad (5)$$

when $x_n = x^1_n$ the value of x is x_∞. In practice a value of Δt = 0.5 to 1.0 of the reaction half life was used.

A/

A Basic programme based on equation 4, was written for a Commodore PET microcomputer to calculate k values of first order reactions according to equation 5.

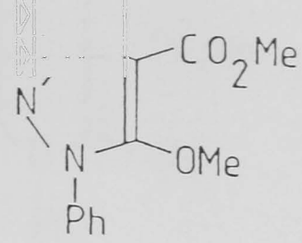
The readings x_0, x_1, x_2 ..... x_n at Δt constant were entered into the microcomputer, then x^1_n was chosen according to the above condition and the value k is given by equation 5.

References: F. J. Kezdy, J. Jaz and A. Bruylants: Bull. Soc. Chim. Belg., (1958), 67, 687.

E. S. Swinbourne, J. Chem. Soc., (1960), 2371.

E. S. Swinbourne, Analysis of Kinetic Data, Nelson, 1971.

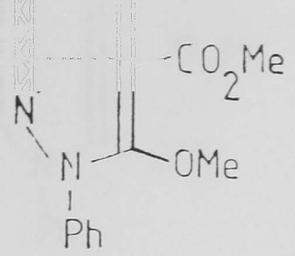
Fig.5:



in MeOH

[triazole] ≃ 2×10^{-4} mol dm^{-3}

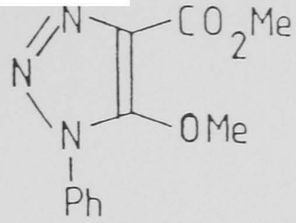
Fig.6 :



in 0.1 mol dm^{-3} methanolic hydrochloric acid

[triazole] = 2×10^{-4} mol dm^{-3}

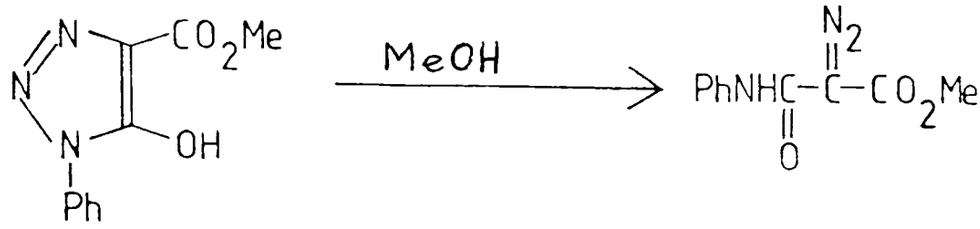
Fig. 7 :



in 0.1 mol dm^{-3} methanolic sodium methoxide

[triazole] = 2×10^{-4} mol dm^{-3}

Reaction:



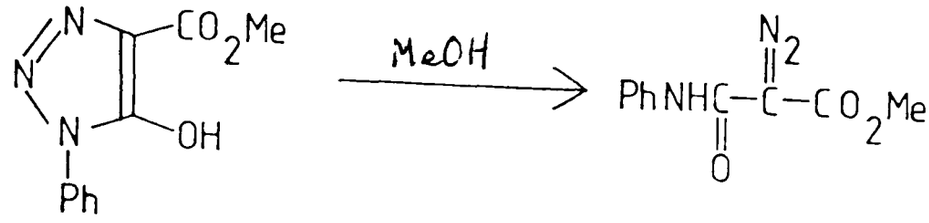
T = 25°C

Measure-ment	$[H^+]$ = 10^{-3} mol dm^{-3} A	$[H^+]$ = 4×10^{-3} mol dm^{-3} A	$[H^+]$ = 10^{-2} mol dm^{-3} A
1	6.5	7.2	11.5
2	13.1	15.0	19.3
3	19.7	22.4	26.5
4	25.5	29.0	33.0
5	30.5	35.4	39.5
6	35.5	41.4	45.5
7	40.5	47.0	51.0
8	45.0	52.0	56.0
9	48.8	56.7	60.6
10	52.5	61.4	65.0
11	56.0	65.3	69.1
12	59.4	69.5	73.0
13	62.0	72.7	76.4
14	65.0	76.4	79.5
15	67.5	78.6	81.7
16	70.0	81.5	84.6
17	72.1	83.8	87.0
18	74.1	86.3	89.1
19	75.5	88.0	90.8
20	77.1	90.3	92.7

Time interval between measurements = 900 seconds

(A = Absorbance)

Reaction:

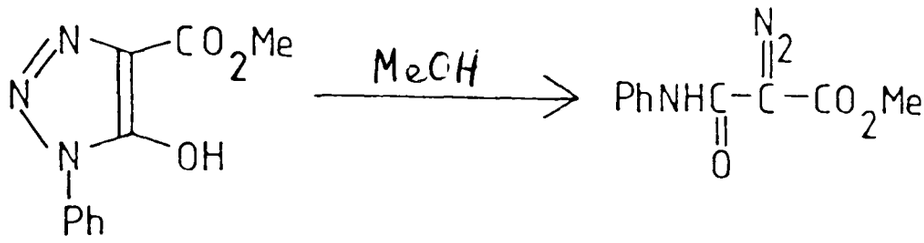


T = 29.7°C

Measure-ment	$[H^+]$ $= 10^{-3}$ mol dm^{-3}	$[H^+]$ $= 4 \times 10^{-3}$ mol dm^{-3}	$[H^+]$ $= 10^{-2}$ mol dm^{-3}
	A	A	A
1	8.8	14.2	18.9
2	15.8	22.5	27.4
3	22.6	30.5	35.0
4	28.5	37.3	41.8
5	33.9	43.7	48.6
6	38.9	49.7	54.4
7	43.9	55.2	60.0
8	48.3	60.0	64.2
9	52.2	64.5	68.0
10	55.5	68.5	71.4
11	58.6	72.3	74.7
12	61.6	75.9	77.8
13	64.0	78.5	80.0
14	66.7	81.0	82.5
15	68.8	83.7	85.0
16	70.5	85.0	86.6
17	72.5	87.3	89.0
18	74.7	89.9	91.1
19	76.0	91.1	92.5
20	76.9	92.5	93.7

Time interval between measurements = 600 seconds

Reaction:



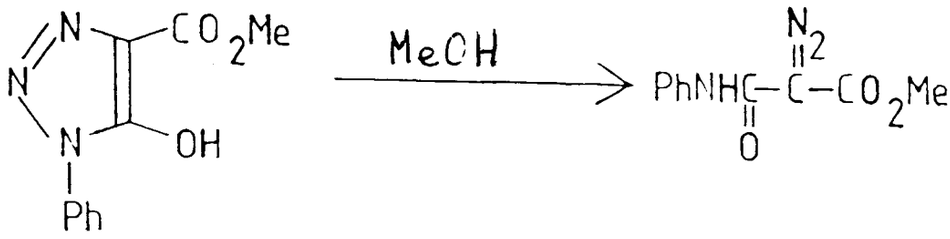
T = 34.7°C

Measurement	$[H^+]$ = 10^{-3} mol dm^{-3} A	$[H^+]$ = 4 x 10^{-3} mol dm^{-3} A	$[H^+]$ = 10^{-2} mol dm^{-3} A
1	15.5	23.7	25.4
2	20.9	29.1	31.8
3	26.0	34.0	37.4
4	30.7	38.7	42.8
5	35.3	43.2	48.0
6	39.5	47.6	52.5
7	43.0	52.7	57.0
8	46.3	55.8	61.0
9	49.5	59.0	63.5
10	52.0	62.5	66.0
11	54.7	66.0	69.6
12	57.0	68.7	72.0
13	59.5	71.2	74.5
14	61.4	73.7	76.5
15	63.2	75.9	78.4
16	64.9	78.0	80.5
17	66.2	80.1	81.5
18	67.4	82.0	83.0
19	68.6	84.0	84.2
20	69.8	85.9	85.6

When $[H^+]$ = 10^{-3} and 10^{-2} mol dm^{-3} time interval between measurements = 300 seconds.

When $[H^+]$ = 4 x 10^{-3} mol dm^{-3} time interval between measurements = 180 seconds.

Reaction:

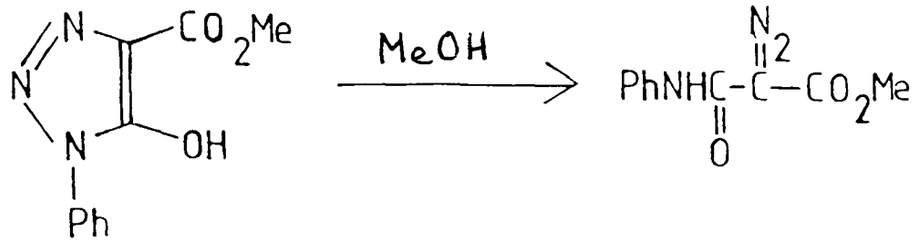


T = 40.7°C

Measure-ment	$[H^+]$ = 10^{-3} mol dm^{-3} A	$[H^+]$ = 4 x 10^{-3} mol dm^{-3} A	$[H^+]$ = 10^{-2} mol dm^{-3} A
1	15.9	20.9	26.9
2	22.2	27.5	34.4
3	28.6	33.7	41.0
4	33.8	38.7	46.1
5	38.1	43.2	51.7
6	42.6	47.6	56.5
7	46.3	51.7	61.1
8	49.8	55.1	64.5
9	52.4	57.5	67.2
10	55.0	60.0	69.8
11	57.2	62.1	72.5
12	59.7	64.8	75.2
13	61.6	67.0	77.9
14	62.5	68.0	79.2
15	63.9	69.5	80.5
16	65.2	70.7	81.9
17	66.6	72.1	83.2
18	67.7	73.2	84.2
19	68.3	74.1	85.1
20	69.1	74.9	85.9

Time interval between measurements = 180 seconds

Reaction:

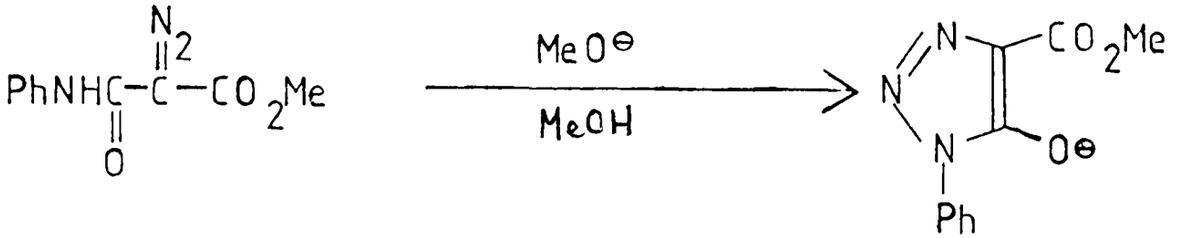


T = 45.8°C

Measure-ment	$[H^+]$ = 10^{-3} mol dm^{-3}	$[H^+]$ = 4 x 10^{-3} mol dm^{-3}	$[H^+]$ = 10^{-2} mol dm^{-3}
	A	A	A
1	18.8	22.1	27.2
2	24.6	27.6	34.4
3	30.0	32.0	40.9
4	34.6	35.9	46.5
5	39.0	40.2	51.8
6	43.2	43.5	57.0
7	47.0	46.9	61.3
8	50.5	49.4	65.2
9	53.7	52.2	69.2
10	56.7	55.0	73.2
11	59.0	56.9	76.0
12	61.2	58.9	78.7
13	63.4	60.8	81.1
14	65.2	62.2	83.4
15	66.9	63.7	85.4
16	68.5	65.0	87.1
17	69.9	66.0	88.6
18	71.1	67.0	90.0
19	72.2	68.0	91.3
20	72.9	68.8	92.4

Time interval between measurements = 90 seconds

Reaction:



T = 16.25°C

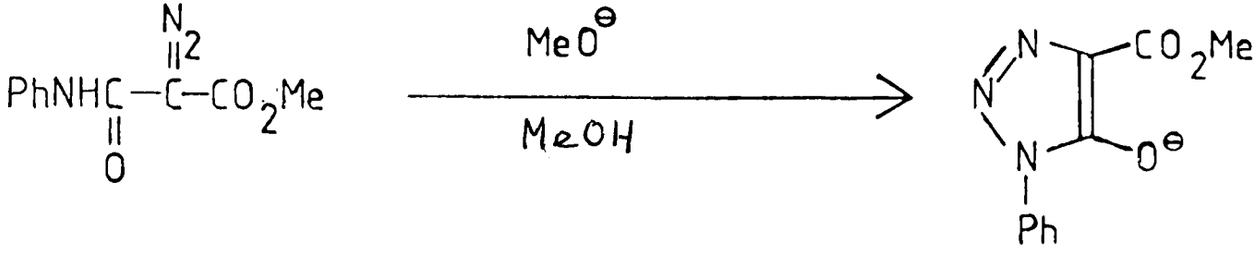
Measure-ment	$[MeO^{\ominus}]$ = 10^{-3} mol dm^3	$[MeO^{\ominus}]$ = 2 x 10^{-3} mol dm^{-3}	$[MeO^{\ominus}]$ = 3 x 10^{-3} mol dm^3	$[MeO^{\ominus}]$ = 4 x 10^{-3} mol dm^{-3}	$[MeO^{\ominus}]$ = 5 x 10^{-3} mol dm^{-3}
	A	A	A	A	A
1	83.5	77.0	91.3	91.0	75.4
2	72.6	68.0	83.0	81.9	68.0
3	63.5	60.3	75.1	73.1	63.1
4	55.6	53.8	68.3	65.6	57.8
5	48.7	47.7	62.2	58.8	53.5
6	42.8	42.5	57.2	53.4	49.6
7	87.2	38.2	52.4	48.3	45.7
8	32.9	34.4	48.4	44.0	42.4
9	28.8	31.2	44.7	40.2	39.5
10	25.4	28.3	41.2	36.8	36.9
11	22.6	25.8	38.3	34.0	34.7
12	20.0	23.7	35.6	31.7	32.8
13	17.7	21.8	33.5	29.3	30.7
14	15.8	20.3	31.6	27.3	29.2
15	14.1	19.0	29.8	25.8	27.3
16	12.6	17.7	28.3	24.4	25.5
17	11.1	16.7	26.8	23.2	23.9
18	9.9	15.7	25.7	22.2	22.7
19	9.0	14.8	24.7	21.3	21.8
20	8.0	14.2	23.7	20.3	20.9

Cont'd./

$[MeO^{\ominus}]_{-3}$ (mol dm^{-3})	t (interval between measurements) seconds	3t	C.C	4t	C.C	5t	C.C
10^{-3}	40	120	0.999950	160	0.999920	200	0.999910
2×10^{-3}	20	60	0.999947	80	0.999952	100	0.999961
3×10^{-3}	10	30	0.999920	40	0.999907	50	0.999899
4×10^{-3}	8	24	0.999917	32	0.999948	40	0.999879
5×10^{-3}	5	15	0.999412	20	0.999177	25	0.998869

C.C = Correlation Coefficient

Reaction:



T = 20.6°C

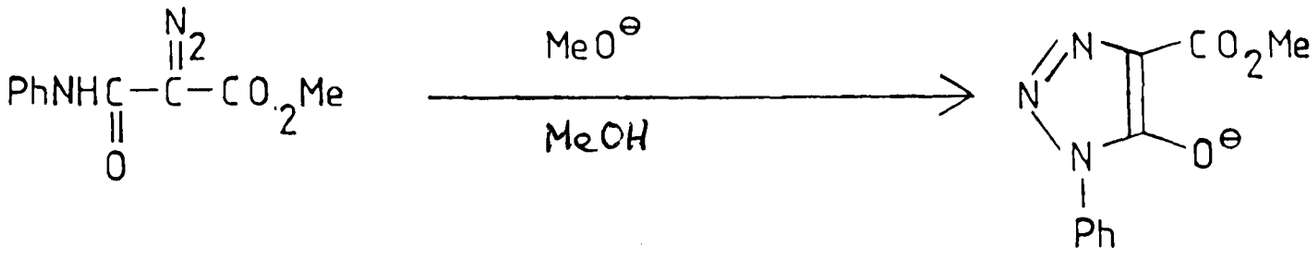
Measure-ment	$[MeO^{\ominus}]$ = 10^{-3} mol dm^{-3} A	$[MeO^{\ominus}]$ = 2×10^{-3} mol dm^{-3} A	$[MeO^{\ominus}]$ = 3×10^{-3} mol dm^{-3} A	$[MeO^{\ominus}]$ = 4×10^{-3} mol dm^{-3} A	$[MeO^{\ominus}]$ = 5×10^{-3} mol dm^{-3} A
1	82.8	77.3	89.4	93.7	82.7
2	74.4	68.3	77.5	84.5	74.7
3	66.9	59.9	67.1	76.5	67.2
4	60.0	53.0	58.7	69.6	60.7
5	54.4	46.8	51.6	63.3	55.2
6	49.3	41.0	45.6	57.7	50.1
7	45.1	35.9	40.7	52.9	45.7
8	41.3	32.4	36.4	48.7	41.8
9	38.2	30.4	33.1	45.3	38.5
10	35.3	28.7	30.1	42.2	35.3
11	33.0	27.1	27.4	39.7	32.9
12	30.8	25.2	25.7	37.3	30.4
13	28.9	23.6	24.0	35.4	28.4
14	27.3	22.0	22.6	33.8	26.6
15	25.9	21.0	21.5	32.2	25.0
16	24.7	19.6	20.5	31.1	23.7
17	23.7	18.9	19.7	29.8	22.6
18	22.8	18.0	19.0	28.8	21.6
19	22.0	17.2	18.4	27.9	20.7
20	21.5	16.6	17.9	27.2	19.9

Cont'd./

$[MeO^{\ominus}]$ (mol dm^{-3})	t (interval between measurements) seconds	3t	C.C	4t	C.C.	5t	C.C
10^{-3}	30	90	0.999963	120	0.999950	150	0.999940
2×10^{-3}	16	48	0.996220	64	-	80	-
3×10^{-3}	10	30	0.999966	40	0.999926	50	0.999920
4×10^{-3}	6	18	0.999843	24	0.999810	30	0.999841
5×10^{-3}	4	12	0.999956	16	0.999920	20	0.999896

C.C = Correlation Coefficient

Reaction:



T = 25.2°C

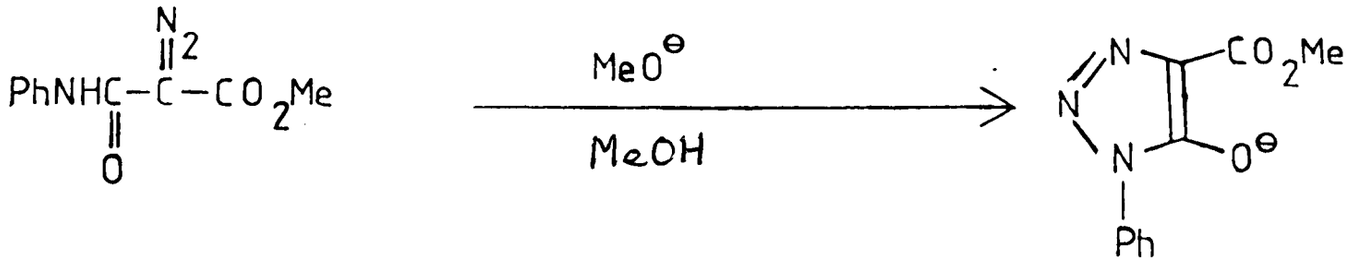
Measure-ment	$[MeO^{\ominus}]$ = 10^{-3} mol dm^{-3}	$[MeO^{\ominus}]$ = 2 x 10^{-3} mol dm^{-3}	$[MeO^{\ominus}]$ = 3 x 10^{-3} mol dm^{-3}	$[MeO^{\ominus}]$ = 4 x 10^{-3} mol dm^{-3}	$[MeO^{\ominus}]$ = 5 x 10^{-3} mol dm^{-3}
	A	A	A	A	A
1	80.6	81.9	83.7	81.3	73.1
2	69.8	76.2	75.7	74.3	66.4
3	60.0	70.1	69.3	67.0	60.3
4	51.9	65.0	62.9	61.6	55.1
5	45.1	59.9	57.9	56.3	50.4
6	39.1	55.7	53.7	51.7	46.6
7	34.5	52.0	50.0	47.8	43.0
8	30.0	48.7	46.8	44.3	39.9
9	26.4	46.2	44.0	41.2	37.1
10	23.2	43.6	41.2	38.2	34.8
11	20.8	41.5	38.8	35.6	32.7
12	18.8	39.6	37.1	33.3	30.9
13	16.8	37.4	35.3	31.2	29.2
14	15.2	35.7	33.8	29.2	27.8
15	14.0	34.5	32.4	27.4	26.5
16	12.7	33.4	31.3	26.0	25.3
17	11.5	32.2	30.2	24.8	24.3
18	10.7	31.0	29.3	23.8	23.6
19	10.0	29.9	28.5	22.9	22.8
20	9.4	29.1	27.8	21.8	22.2

Cont'd./

$[MeO^{\ominus}]$ (mol dm^{-3})	t (interval between measurements) seconds	3t	C.C	4t	C.C	5t	C.C
10^{-3}	20	60	0.999918	80	0.999881	100	0.999866
2×10^{-3}	6	18	0.999476	24	0.999459	30	0.999495
3×10^{-3}	5	15	0.999710	20	0.999640	25	0.999678
4×10^{-3}	3	9	0.999816	12	0.999707	15	0.999655
5×10^{-3}	2.5	7.5	0.999950	10	0.999958	12.5	0.999952

C.C = Correlation Coefficient

Reaction:



T = 30.5°C

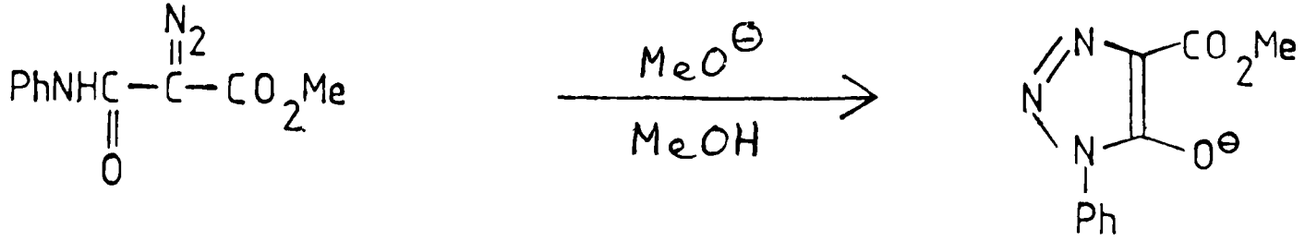
Measure-ment	$[MeO^{\ominus}]$ = 10^{-3} mol dm^{-3} A	$[MeO^{\ominus}]$ = 2 x 10^{-3} mol dm^{-3} A	$[MeO^{\ominus}]$ = 3 x 10^{-3} mol dm^{-3} A	$[MeO^{\ominus}]$ = 4 x 10^{-3} mol dm^{-3} A	$[MeO^{\ominus}]$ = 5 x 10^{-3} mol dm^{-3} A
1	93.8	88.0	69.8	64.0	75.0
2	84.5	79.8	66.4	55.9	68.5
3	75.5	72.6	63.2	48.8	62.5
4	67.8	66.3	60.3	43.0	57.5
5	61.1	61.3	57.8	37.3	52.8
6	54.9	56.4	55.5	33.2	48.8
7	49.6	52.5	53.3	29.5	45.3
8	44.5	48.9	51.4	25.8	42.6
9	39.8	46.1	49.7	22.9	40.4
10	35.5	43.6	48.1	20.3	38.7
11	31.7	41.2	47.1	18.1	36.7
12	27.8	39.4	46.1	16.2	34.9
13	24.7	37.7	45.2	14.3	33.5
14	22.1	36.2	44.2	12.9	32.1
15	19.7	34.9	43.2	11.4	30.8
16	17.3	33.9	42.3	10.1	29.9
17	15.3	33.1	41.7	9.1	28.8
18	13.7	32.0	41.1	8.2	27.7
19	12.0	31.3	40.5	7.4	26.7
20	10.4	30.7	39.9	6.7	25.9

Cont'd./

$[MeO^{\ominus}]$ (mol dm^{-3})	t (interval between measurements) seconds	3t	C.C	4t	C.C	5t	C.C
10^{-3}	10	30	0.999841	40	0.999781	50	0.999717
2×10^{-3}	5	15	0.999928	20	0.999934	25	0.999923
3×10^{-3}	2.5	7.5	0.999368	10	0.999076	12.5	0.998836
4×10^{-3}	2	6	0.999818	8	0.999634	10	0.999753
5×10^{-3}	1.5	4.5	0.998636	6	0.997700	7.5	0.996652

C.C = Correlation Coefficient

Reaction:



T = 35.8°C

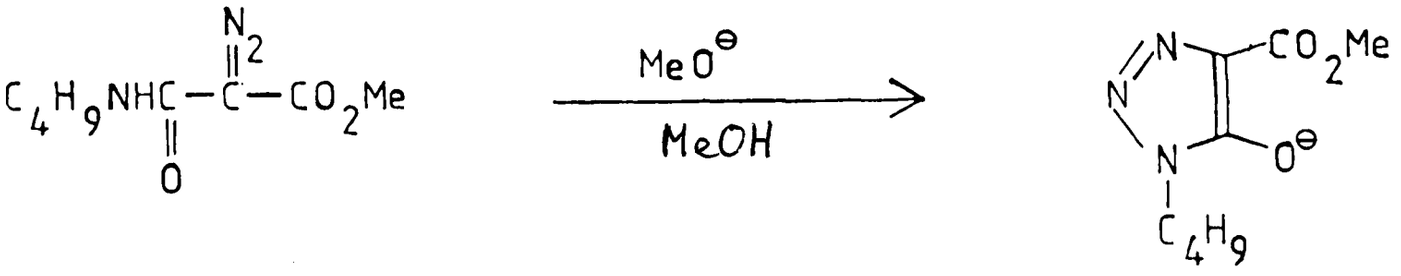
Measure-ment	$[MeO^{\ominus}]$ = 10^{-3} mol dm^{-3} A	$[MeO^{\ominus}]$ = 2×10^{-3} mol dm^{-3} A	$[MeO^{\ominus}]$ = 3×10^{-3} mol dm^{-3} A	$[MeO^{\ominus}]$ = 4×10^{-3} mol dm^{-3} A	$[MeO^{\ominus}]$ = 5×10^{-3} mol dm^{-3} A
1	70.3	87.2	73.8	79.4	82.0
2	66.3	82.3	68.7	75.1	75.3
3	62.9	78.2	64.6	71.7	69.5
4	59.7	74.3	61.2	68.6	64.6
5	56.2	70.8	57.8	65.7	60.0
6	53.0	67.9	54.9	63.6	56.0
7	50.4	65.2	52.3	61.6	52.6
8	48.3	62.7	49.9	59.8	49.5
9	46.2	60.7	47.8	58.5	46.6
10	44.4	58.9	46.3	57.3	44.3
11	42.8	57.6	44.7	56.2	42.1
12	41.3	56.3	43.3	55.3	40.2
13	39.8	54.9	42.0	54.6	38.3
14	38.4	53.9	41.0	53.8	36.6
15	37.3	52.9	40.1	53.2	35.1
16	36.4	52.2	39.2	52.7	33.9
17	35.7	51.6	38.6	52.1	32.8
18	34.8	50.7	38.0	51.7	31.7
19	34.2	50.2	37.5	51.3	30.8
20	33.7	49.7	36.9	51.0	29.9

Cont'd./

$[MeO^{\ominus}]$ (mol dm^{-3}	t (interval between measurements) seconds	3t	C.C	4t	C.C	5t	C.C
10^{-3}	6	18	0.999106	24	0.999295	30	0.999473
2×10^{-3}	3	9	0.999774	12	0.999712	15	0.999707
3×10^{-3}	2	6	0.999826	8	0.999793	10	0.999761
4×10^{-3}	1.5	4.5	0.998060	6	0.999505	7.5	0.999787
5×10^{-3}	1	3	0.999880	4	0.999790	5	0.999700

C.C = Correlation Coefficient

Reaction:



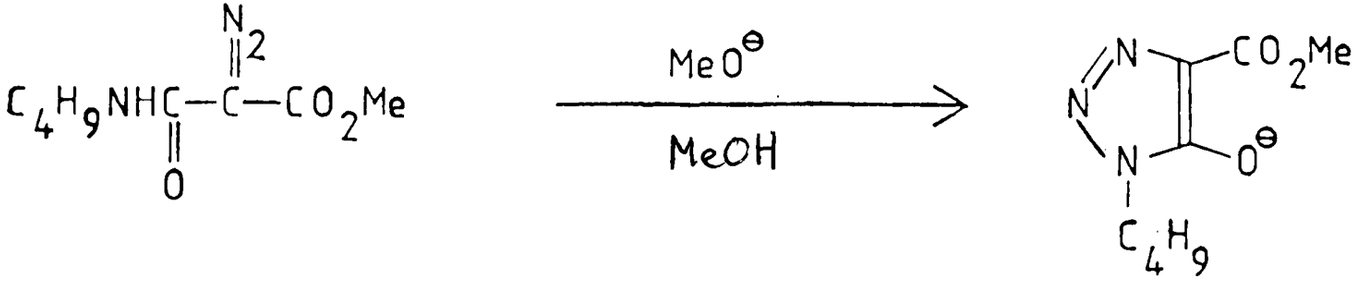
T = 19.5°C

Measure-ment	$[MeO^{\ominus}]$ = 8×10^{-2} mol dm^{-3}	$[MeO^{\ominus}]$ = 0.1 mol dm^{-3}	$[MeO^{\ominus}]$ = 0.2 mol dm^{-3}	$[MeO^{\ominus}]$ = 0.3 mol dm^{-3}	$[MeO^{\ominus}]$ = 0.4 mol dm^{-3}
	A	A	A	A	A
1	13.6	0.7	5.0	6.6	4.6
2	19.7	7.5	14.0	14.8	10.4
3	25.0	13.7	22.5	22.0	15.7
4	29.9	18.8	30.0	28.2	20.3
5	34.8	23.3	36.5	33.8	24.6
6	38.7	27.5	42.2	38.5	28.3
7	41.9	31.7	47.0	42.6	31.8
8	44.6	35.0	51.7	46.0	34.9
9	47.2	38.2	55.5	49.0	37.7
10	49.4	41.0	59.0	51.6	40.0
11	51.5	43.6	61.9	53.9	42.2
12	53.7	45.7	64.5	55.8	44.4
13	55.5	47.7	67.0	57.7	46.0
14	57.0	49.2	69.2	59.0	47.7
15	58.3	50.8	71.0	60.5	49.1
16	59.4	52.1	72.8	61.7	50.2
17	60.6	53.4	74.5	62.8	51.4
18	61.7	54.4	76.0	63.7	52.3
19	62.6	55.3	77.2	64.4	53.1
20	63.3	56.1	78.2	65.1	54.0

Continued/

[MeO] mol dm^{-3}	t (sec)	$\frac{3}{}$ t	C.C	$\frac{4}{}$ t	C.C	$\frac{5}{}$ t	C.C
8 x 10^{-2}	120	360	0.99943	480	0.99925	600	0.99918
0.1	90	270	0.99980	360	0.99975	450	0.99963
0.2	36	108	0.99987	144	0.99980	180	0.99973
0.3	20	60	0.99991	80	0.99985	100	0.99978
0.4	10	30	0.99994	40	0.99989	50	0.99986

Reaction:



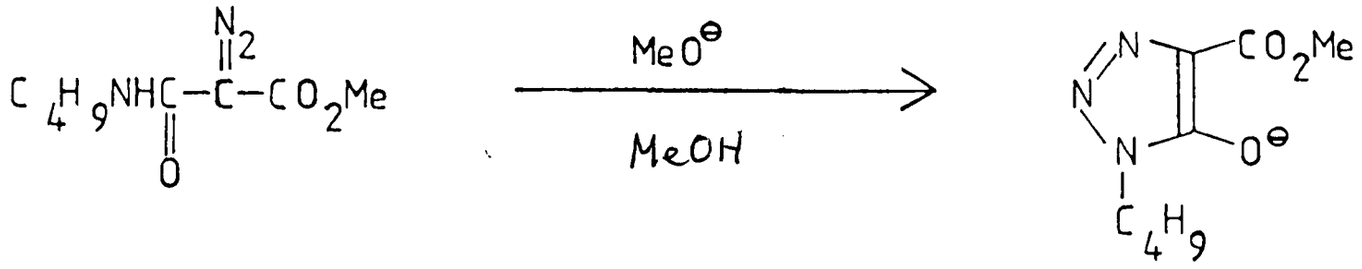
T = 25.2°C

Measure-ment	$[MeO^{\ominus}]$ = 8×10^{-2} mol dm^{-3}	$[MeO^{\ominus}]$ = 0.1 mol dm^{-3}	$[MeO^{\ominus}]$ = 0.2 mol dm^{-3}	$[MeO^{\ominus}]$ = 0.3 mol dm^{-3}	$[MeO^{\ominus}]$ = 0.4 mol dm^{-3}
	A	A	A	A	A
1	2.7	7.4	8.8	5.0	12.3
2	9.7	13.9	15.6	11.1	19.1
3	15.7	20.0	21.7	16.7	25.0
4	21.3	25.4	27.2	21.3	30.5
5	26.3	29.8	32.0	25.3	35.3
6	31.0	34.3	36.3	28.9	39.3
7	35.1	38.2	39.7	32.2	43.0
8	39.1	41.7	42.8	34.9	46.2
9	42.3	44.9	45.3	37.3	49.1
10	45.6	48.0	47.7	39.4	51.7
11	48.5	50.7	49.7	41.2	54.0
12	51.0	53.0	51.4	42.9	56.0
13	53.2	55.1	53.0	44.2	57.8
14	55.2	56.9	54.5	45.4	59.4
15	56.8	58.8	55.7	46.8	60.9
16	58.7	60.3	56.8	47.6	62.4
17	60.0	61.7	57.8	48.5	63.5
18	61.3	62.7	58.6	49.2	64.5
19	62.7	64.0	59.2	49.8	65.4
20	63.9	64.9	59.9	50.1	66.1

Continued/

$[MeO^{\ominus}]$ mol dm^{-3}	t (sec)	$\frac{3}{}$ t	C.C	$\frac{4}{}$ t	C.C	$\frac{5}{}$ t	C.C
8×10^{-2}	60	180	0.99990	240	0.99986	300	0.99979
0.1	44	132	0.99990	176	0.99989	220	0.99984
0.2	20	60	0.99985	80	0.99978	100	0.99971
0.3	10	30	0.99991	40	0.99989	50	0.99982
0.4	5.5	16.5	0.99992	22	0.99987	27.5	0.99988

Reaction:



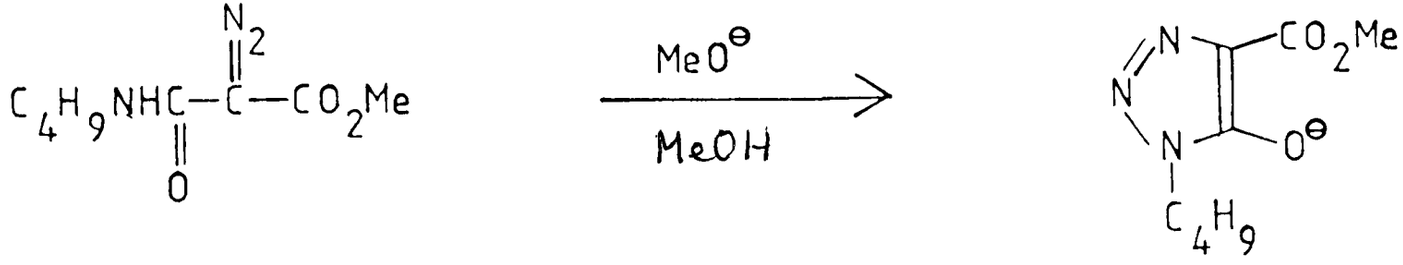
T = 31.3°C

Measurement	$[MeO^{\ominus}]$ = 8×10^{-2} mol dm^{-3} A	$[MeO^{\ominus}]$ = 0.1 mol dm^{-3} A	$[MeO^{\ominus}]$ = 0.2 mol dm^{-3} A	$[MeO^{\ominus}]$ = 0.3 mol dm^{-3} A	$[MeO^{\ominus}]$ = 0.4 mol dm^{-3} A
1	5.5	7.3	4.5	5.7	10.2
2	13.0	14.0	12.3	10.8	14.0
3	19.5	19.8	18.8	15.4	17.5
4	25.1	25.0	24.7	19.0	21.0
5	29.7	29.4	29.5	22.5	24.5
6	33.8	33.7	34.0	25.5	27.7
7	37.5	37.5	37.8	28.0	30.3
8	40.7	40.7	41.0	30.4	32.8
9	43.4	43.7	44.0	32.8	35.0
10	45.6	46.8	46.6	34.6	37.0
11	47.8	49.3	48.6	35.9	39.0
12	49.5	51.3	50.5	37.2	40.7
13	51.0	53.2	52.0	38.7	41.8
14	52.5	54.8	53.5	39.7	42.5
15	53.7	56.4	54.7	40.4	43.3
16	54.7	57.8	55.7	41.2	44.0
17	55.3	59.0	56.5	41.9	44.5
18	55.9	60.2	57.4	42.5	44.9
19	56.7	61.3	58.0	43.1	45.5
20	57.3	62.4	58.6	43.7	45.9

Continued/

$[MeO^{\ominus}]$ mol dm^{-3}	t (sec)	$\frac{3}{}$ t	C.C	$\frac{4}{}$ t	C.C	$\frac{5}{}$ t	C.C
8×10^{-2}	40	120	0.99988	160	0.99988	200	0.99987
0.1	20	60	0.99985	80	0.99984	100	0.99976
0.2	10	30	0.99995	40	0.99993	50	0.99991
0.3	5	15	0.99972	20	0.99969	25	0.99945
0.4	3	9	0.99667	12	0.99499	15	0.99285

Reaction:



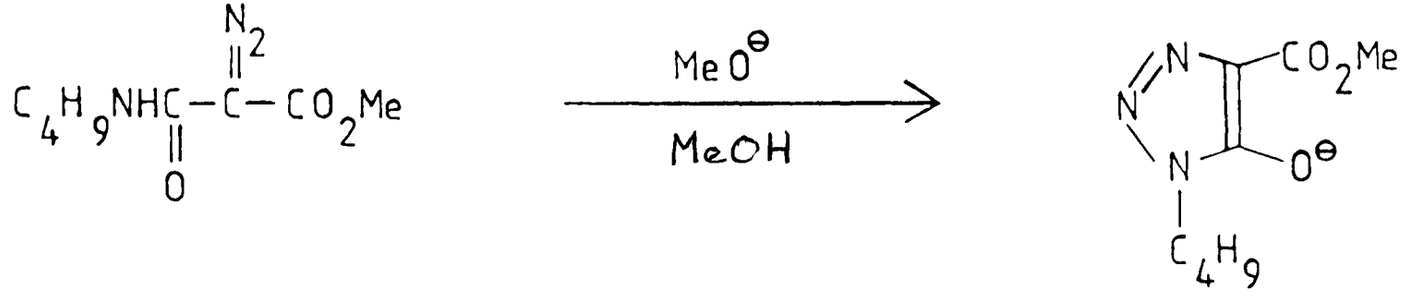
T = 36.0°C

Measurement	$[MeO^{\ominus}]$ = 8×10^{-2} mol dm^{-3}	$[MeO^{\ominus}]$ = 0.1 mol dm^{-3}	$[MeO^{\ominus}]$ = 0.2 mol dm^{-3}	$[MeO^{\ominus}]$ = 0.3 mol dm^{-3}	$[MeO^{\ominus}]$ = 0.4 mol dm^{-3}
	A	A	A	A	A
1	1.5	3.1	4.3	4.6	7.4
2	9.2	11.2	13.0	10.4	10.5
3	16.3	17.9	20.3	15.3	14.0
4	23.0	23.8	26.7	19.8	16.7
5	29.0	29.3	32.8	23.7	19.0
6	34.3	33.9	37.9	27.5	21.5
7	38.8	37.8	42.3	30.4	23.2
8	43.0	41.1	46.2	33.6	25.1
9	46.7	44.0	49.7	35.9	26.7
10	49.9	46.5	52.7	37.7	28.2
11	52.9	48.8	55.0	39.5	29.7
12	55.4	50.7	57.1	41.0	30.7
13	57.6	52.3	58.9	42.8	31.8
14	59.5	53.8	60.7	43.8	32.9
15	61.2	55.0	61.8	44.8	33.8
16	62.7	56.0	63.2	45.8	34.7
17	64.0	57.0	64.3	46.7	35.4
18	65.1	57.8	65.3	47.4	36.1
19	66.2	58.4	66.3	47.9	36.4
20	67.1	58.9	67.0	48.4	37.0

Continued/

$[MeO^{\ominus}]$ mol dm^{-3}	t (sec)	$\underline{3}$ t	C.C	$\underline{4}$ t	C.C.	$\underline{5}$ t	C.C
8×10^{-2}	30	90	0.99985	120	0.99982	150	0.99976
0.1	20	60	0.99993	80	0.99996	100	0.99997
0.2	6	18	0.99981	24	0.99979	30	0.99968
0.3	3	9	0.99962	12	0.99957	15	0.99962
0.4	1.5	4.5	0.99976	6	0.99954	7.5	0.99969

Reaction:



T = 42.0°C

Measurement	$[MeO^{\ominus}]$ = 8×10^{-2} mol dm^{-3}	$[MeO^{\ominus}]$ = 0.1 mol dm^{-3}	$[MeO^{\ominus}]$ = 0.2 mol dm^{-3}	$[MeO^{\ominus}]$ = 0.3 mol dm^{-3}	$[MeO^{\ominus}]$ = 0.4 mol dm^{-3}
	A	A	A	A	A
1	4.8	7.0	8.0	14.0	7.0
2	11.8	14.5	13.3	16.5	9.0
3	18.2	21.6	17.3	18.9	11.0
4	23.8	27.8	21.8	21.0	12.6
5	29.0	32.9	25.3	22.8	13.9
6	33.5	37.3	28.6	24.4	15.5
7	37.6	41.4	31.6	25.8	16.8
8	41.2	45.2	33.9	27.3	17.8
9	44.7	48.3	36.6	28.8	18.5
10	47.7	51.0	38.5	30.0	19.3
11	50.3	53.1	40.6	30.9	19.7
12	52.6	55.4	42.5	31.8	20.2
13	54.8	57.2	44.2	32.7	20.7
14	56.6	58.9	45.3	33.3	21.1
15	58.3	60.5	46.8	33.9	21.5
16	59.7	61.7	47.7	34.5	21.9
17	61.0	62.8	48.8	35.0	22.2
18	62.1	63.8	49.9	35.4	22.4
19	63.3	64.6	50.8	35.8	22.7
20	64.4	65.3	51.3	36.2	22.9

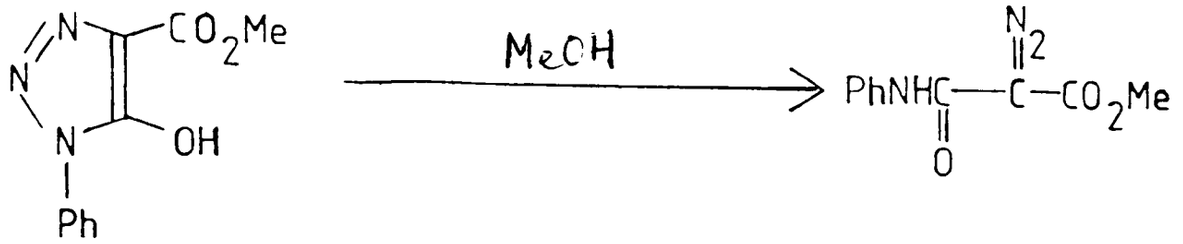
Continued/

$[MeO^{\ominus}]$ mol dm^{-3}	t (sec)	$\underline{3}$ t	C.C	$\underline{4}$ t	C.C	$\underline{5}$ t	C.C
8×10^{-2}	12	36	0.99995	48	0.99993	60	0.99989
0.1	10	30	0.99989	40	0.99992	50	0.99992
0.2	3.5	10.5	0.99978	14	0.99972	17.5	0.99972
0.3	1.5	4.5	0.99940	6	0.99916	7.5	0.99882
0.4	1	3	0.99824	4	0.99717	5	0.99707

TABLE 2

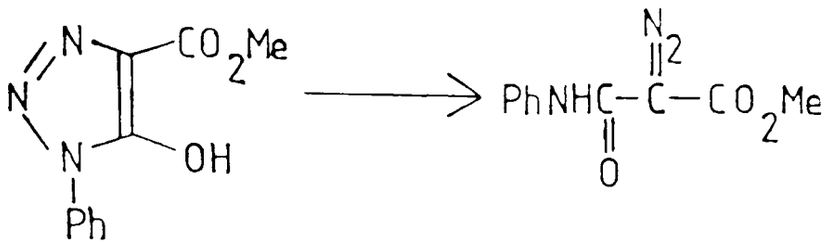
N-Phenyl triazole ring-opening

First-order rate constants and $[H^{\oplus}]$ at various temperatures for



	$[H^{\oplus}]$ (mol dm^{-3})	k (S^{-1})	Correlation Coefficient
25°C	10^{-3}	8.4234×10^{-5}	0.99985
	4×10^{-3}	8.4764×10^{-5}	0.99979
	10^{-2}	8.8254×10^{-5}	0.99977
29.7°C	10^{-3}	1.515×10^{-4}	0.99982
	4×10^{-3}	1.596×10^{-4}	0.99980
	10^{-2}	1.735×10^{-4}	0.99943
34.7°C	10^{-3}	2.977×10^{-4}	0.99980
	4×10^{-3}	3.686×10^{-4}	0.99954
	10^{-2}	3.169×10^{-4}	0.99939
40.7°C	10^{-3}	6.709×10^{-4}	0.99977
	4×10^{-3}	6.511×10^{-4}	0.999712
	10^{-2}	6.676×10^{-4}	0.99936
45.8°C	10^{-3}	1.053×10^{-3}	0.99975
	4×10^{-3}	1.086×10^{-3}	0.99977
	10^{-2}	1.076×10^{-3}	0.99965

Fig 8 : Plot of $\ln k_1$ vs 1/T for



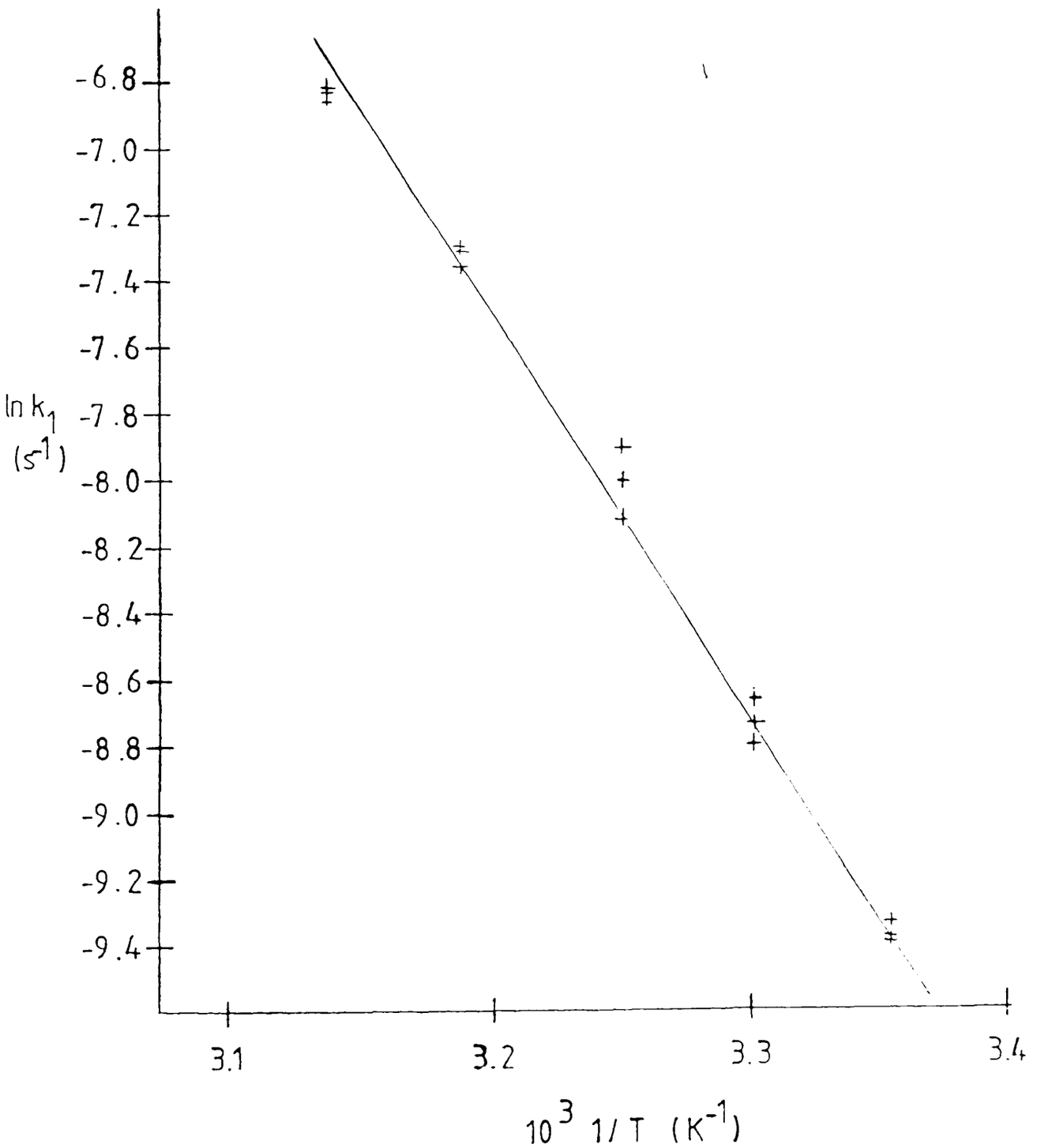
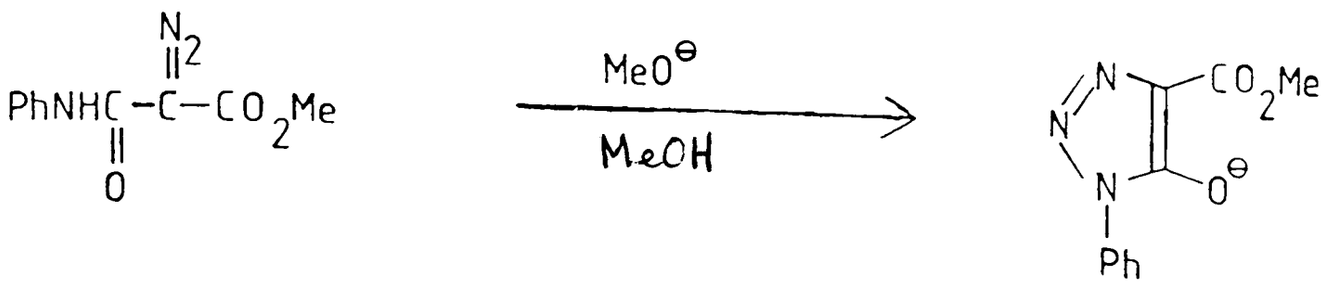


TABLE 3

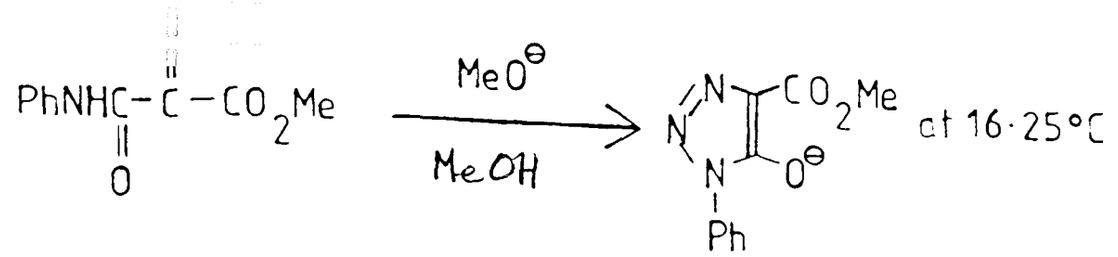
First-order rate constants for the reaction

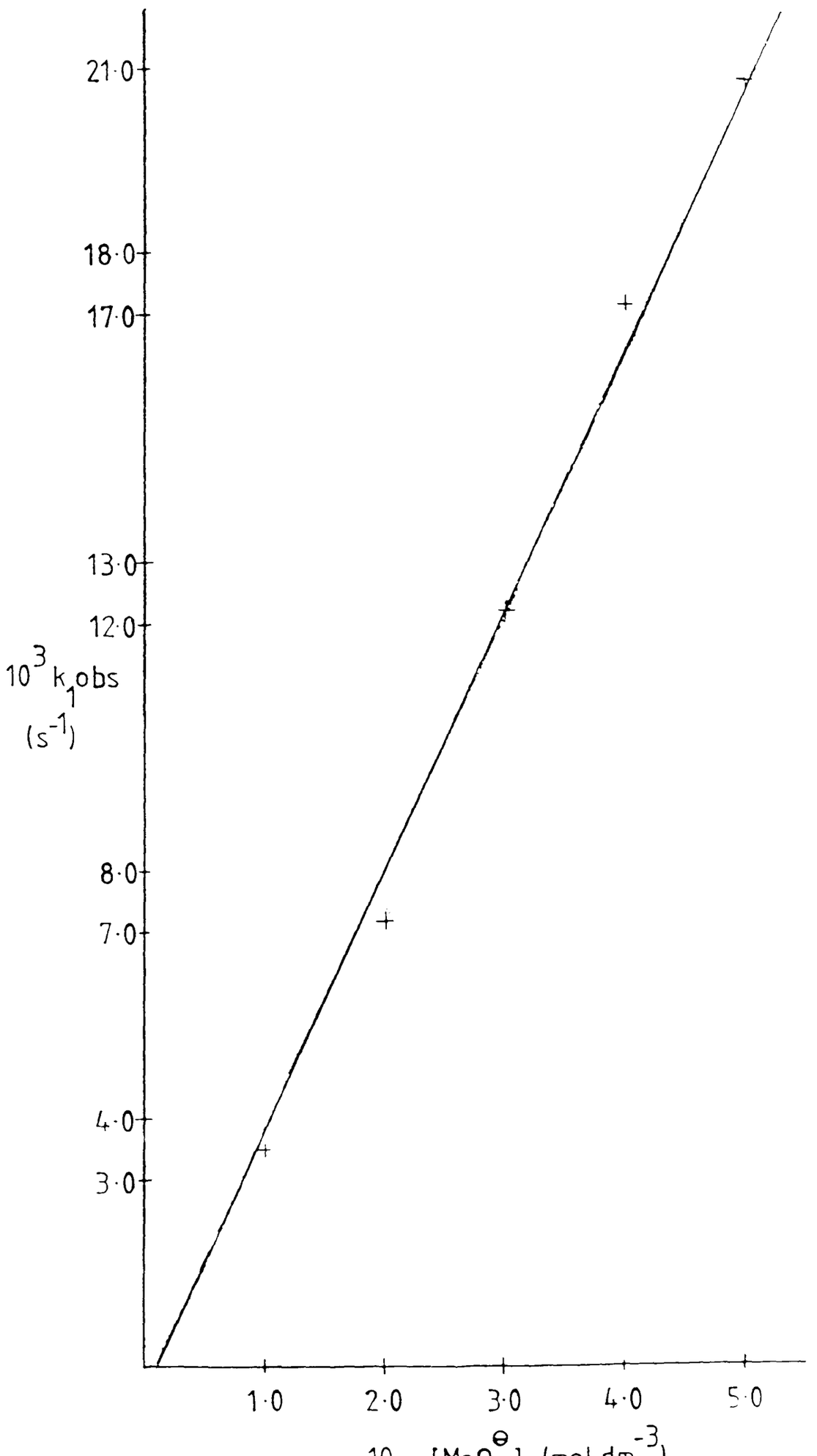


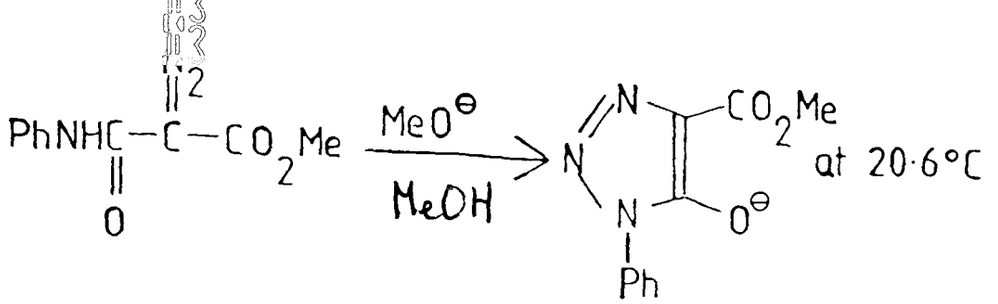
	$[MeO^{\ominus}]$ mol dm^{-3}	k_1 (obs)(s^{-1})	Correlation Coefficient
16.25°C	10^{-3}	3.484×10^{-3}	0.99995
	2×10^{-3}	7.206×10^{-3}	0.99996
	3×10^{-3}	1.226×10^{-2}	0.99992
	4×10^{-3}	1.726×10^{-2}	0.99995
	5×10^{-3}	2.100×10^{-2}	0.99941
20.6°C	10^{-3}	4.751×10^{-3}	0.99996
	2×10^{-3}	1.061×10^{-2}	0.99622
	3×10^{-3}	1.797×10^{-2}	0.99997
	4×10^{-3}	2.332×10^{-2}	0.99984
	5×10^{-3}	3.228×10^{-2}	0.99996
25.2°C	10^{-3}	8.105×10^{-3}	0.99992
	2×10^{-3}	1.984×10^{-2}	0.99949
	3×10^{-3}	2.749×10^{-2}	0.99971
	4×10^{-3}	3.869×10^{-2}	0.99982
	5×10^{-3}	5.191×10^{-2}	0.99996

Continued/

	$[MeO^{\ominus}]$ mol dm^{-3}	k_1 (obs) (s^{-1})	Correlation Coefficient
30.5°C	10^{-3}	1.016×10^{-2}	0.99984
	2×10^{-3}	2.887×10^{-2}	0.99993
	3×10^{-3}	4.421×10^{-2}	0.99937
	4×10^{-3}	6.874×10^{-2}	0.99982
	5×10^{-3}	8.933×10^{-2}	0.99864
35.8°C	10^{-3}	1.776×10^{-2}	0.99947
	2×10^{-3}	4.257×10^{-2}	0.99977
	3×10^{-3}	6.214×10^{-2}	0.99983
	4×10^{-3}	9.904×10^{-2}	0.99981
	5×10^{-3}	1.159×10^{-1}	0.99988


PhNHC
O
C
CO2Me
MeO⊖
MeOH
N
N
CO2Me
O⊖
N
Ph
at 16·25°C


21·0
18·0
17·0
13·0
12·0
8·0
7·0
4·0
3·0
10³ k₁obs
(s⁻¹)
1·0
2·0
3·0
4·0
5·0
10 [MeO⊖] (mol dm⁻³)


PhNHC
O
C
C
CO2Me
MeO⊖
MeOH
N
N
N
Ph
CO2Me
O⊖
at 20·6°C

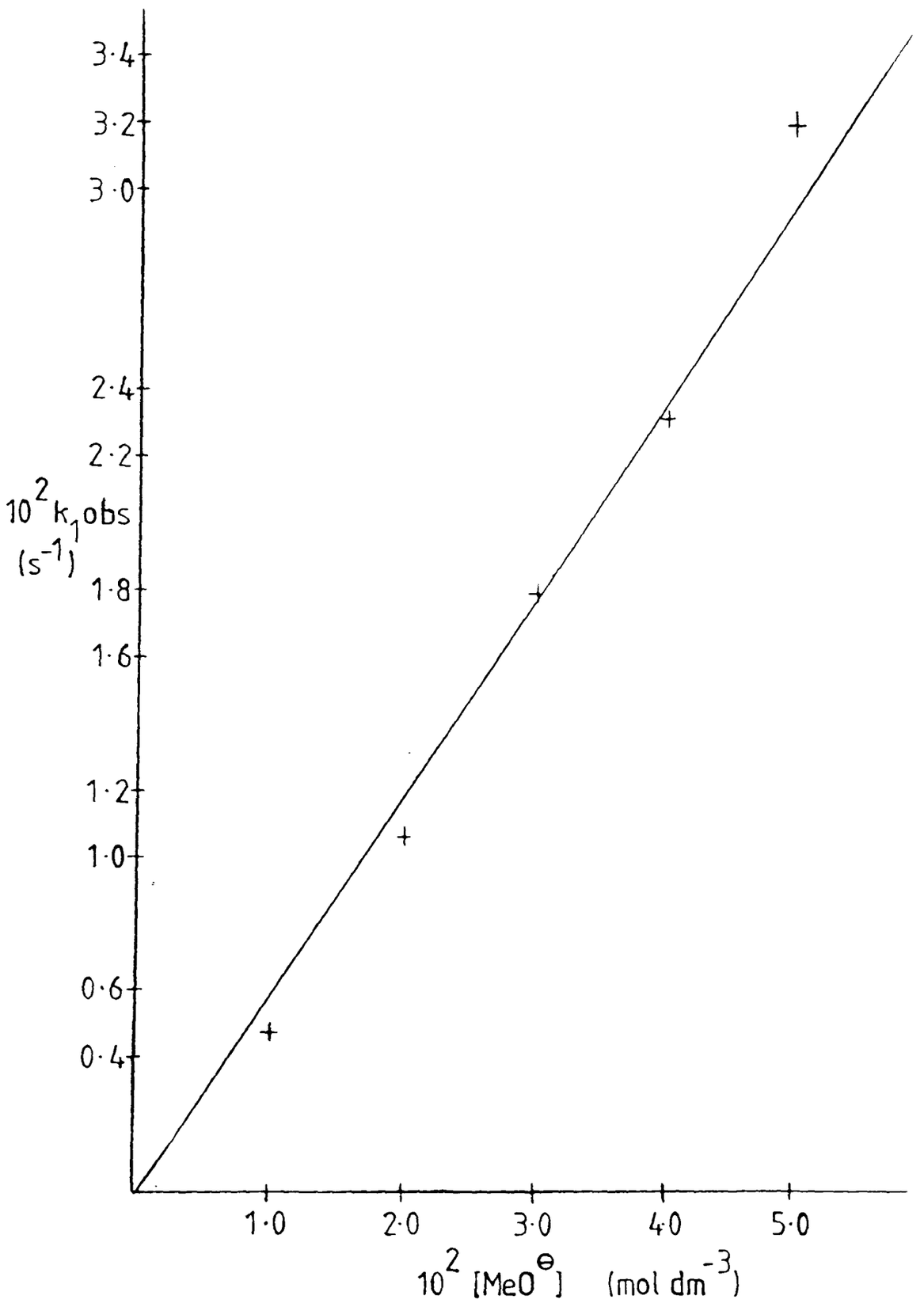
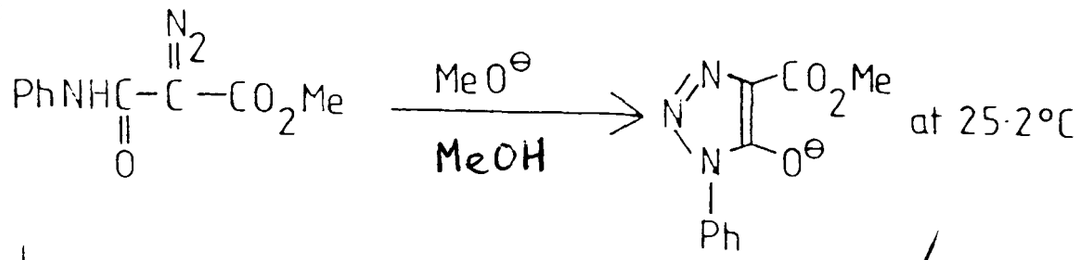

3·4
3·2
3·0
2·4
2·2
10² k₁obs
(s⁻¹)
1·8
1·6
1·2
1·0
0·6
0·4
1·0
2·0
3·0
4·0
5·0
10² [MeO⊖] (mol dm⁻³)

Fig 11:



at 25·2°C

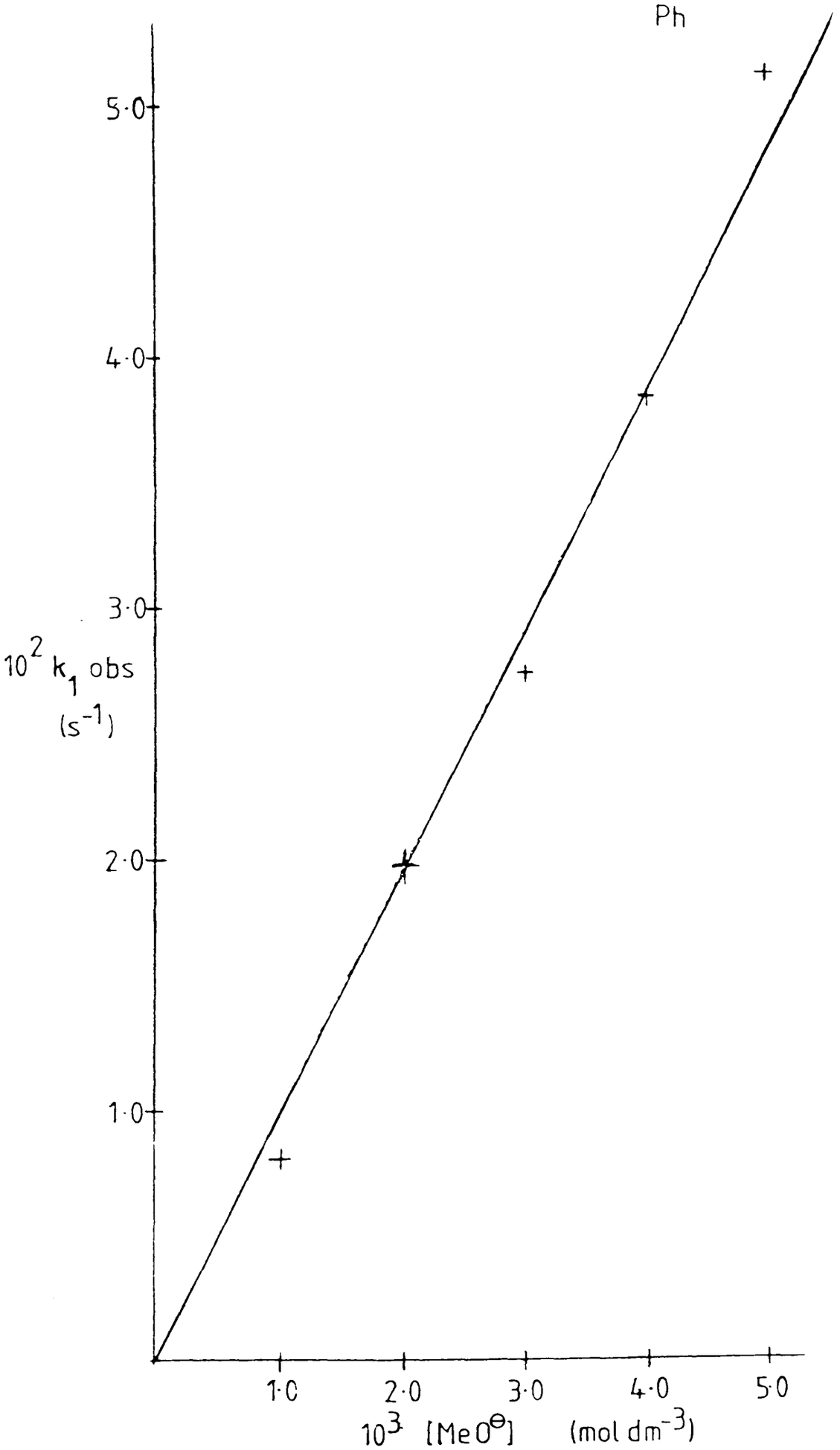
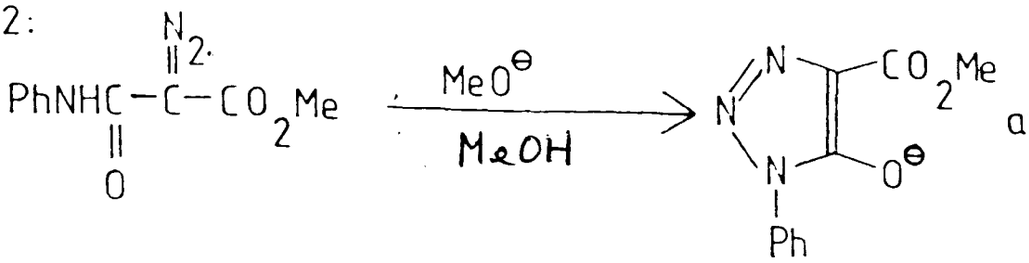


Fig 12:



at 30·5°C

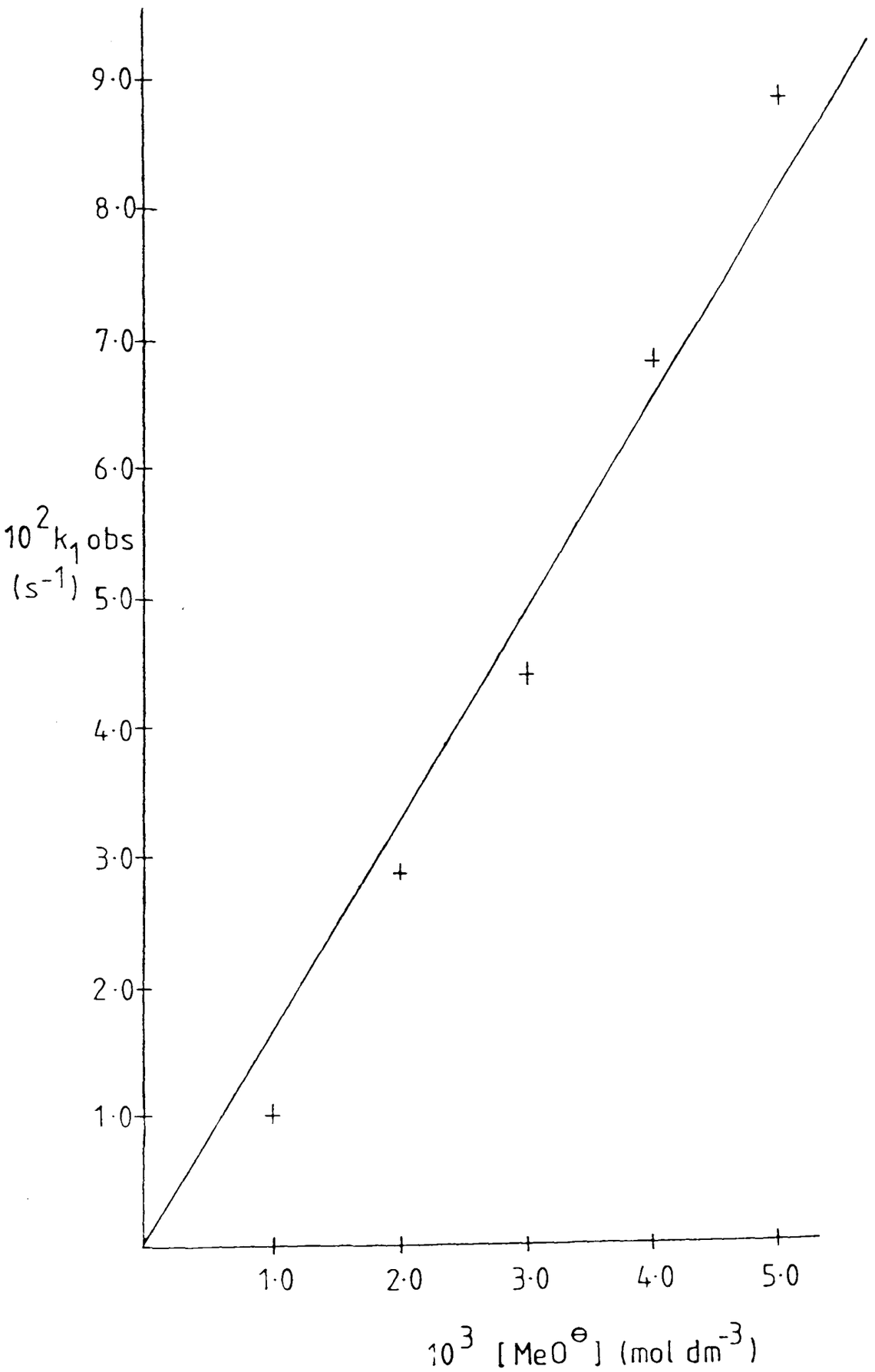
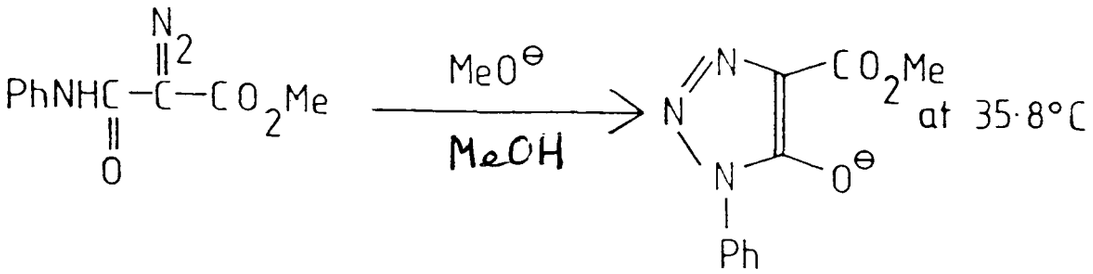


Fig13:


PhNHC(=O)–C(=N2)–CO2Me
MeO⊖
MeOH
CO2Me
O⊖
Ph
at 35·8°C

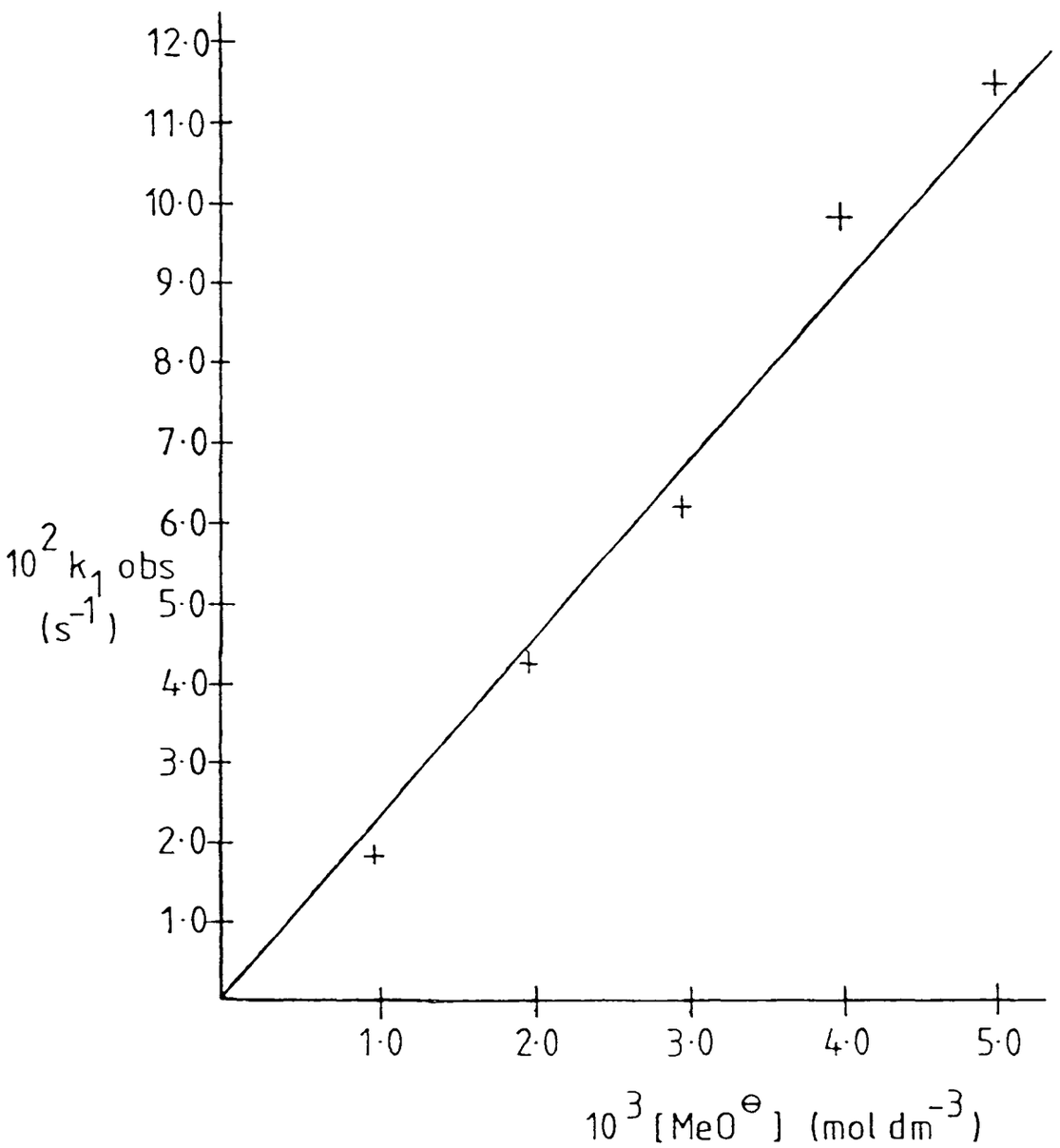
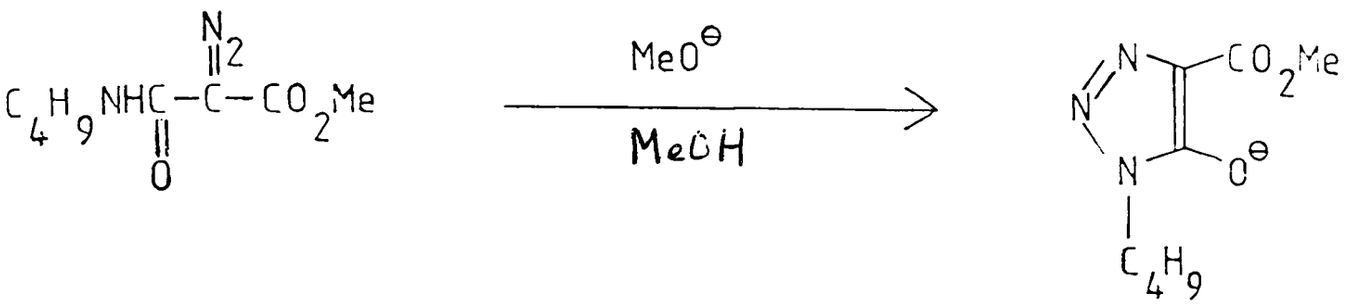

12·0
11·0
10·0
9·0
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
10^2 k1 obs (s^-1)
1·0
2·0
3·0
4·0
5·0
10^3 [MeO⊖] (mol dm^-3)

TABLE 4

N-Butyl triazole ring closure

First-order rate constants at various temperatures for

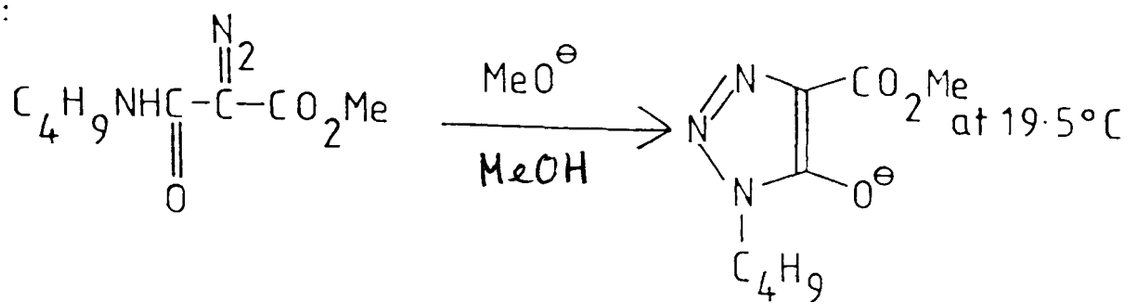


	$[MeO^{\ominus}]$ (mol dm^{-3})	k_1 (s^{-1})	Correlation Coefficient
19.5°C	0.08	9.77×10^{-4}	0.99943
	0.10	1.246×10^{-3}	0.99980
	0.20	3.404×10^{-3}	0.99987
	0.30	7.074×10^{-3}	0.99991
	0.40	1.098×10^{-2}	0.99994
25.2°C	0.08	1.675×10^{-3}	0.99990
	0.10	2.336×10^{-3}	0.99990
	0.20	6.849×10^{-3}	0.99985
	0.30	1.335×10^{-2}	0.99991
	0.40	2.169×10^{-2}	0.99992
31.3°C	0.08	3.581×10^{-3}	0.99988
	0.10	5.415×10^{-3}	0.99985
	0.20	1.420×10^{-2}	0.99995
	0.30	2.592×10^{-2}	0.99972
	0.40	3.888×10^{-2}	0.99667

Continued/

	$[MeO^{\ominus}]$ (mol dm^{-3})	k_1 (s^{-1})	Correlation Coefficient
36.0°C	0.08	3.996×10^{-3}	0.99985
	0.10	7.254×10^{-3}	0.99997
	0.20	2.285×10^{-2}	0.99981
	0.30	4.388×10^{-2}	0.99962
	0.40	6.920×10^{-2}	0.99976
42.0°C	0.08	9.213×10^{-3}	0.99995
	0.10	1.298×10^{-2}	0.99992
	0.20	3.002×10^{-2}	0.99978
	0.30	7.050×10^{-2}	0.99940
	0.40	1.363×10^{-1}	0.99824

Fig 14:


$C_4H_9NHC(=O)-C(=N_2)-CO_2Me$
$MeO^{\ominus}$
MeOH
CO_2Me
$O^{\ominus}$
C_4H_9
at 19·5°C

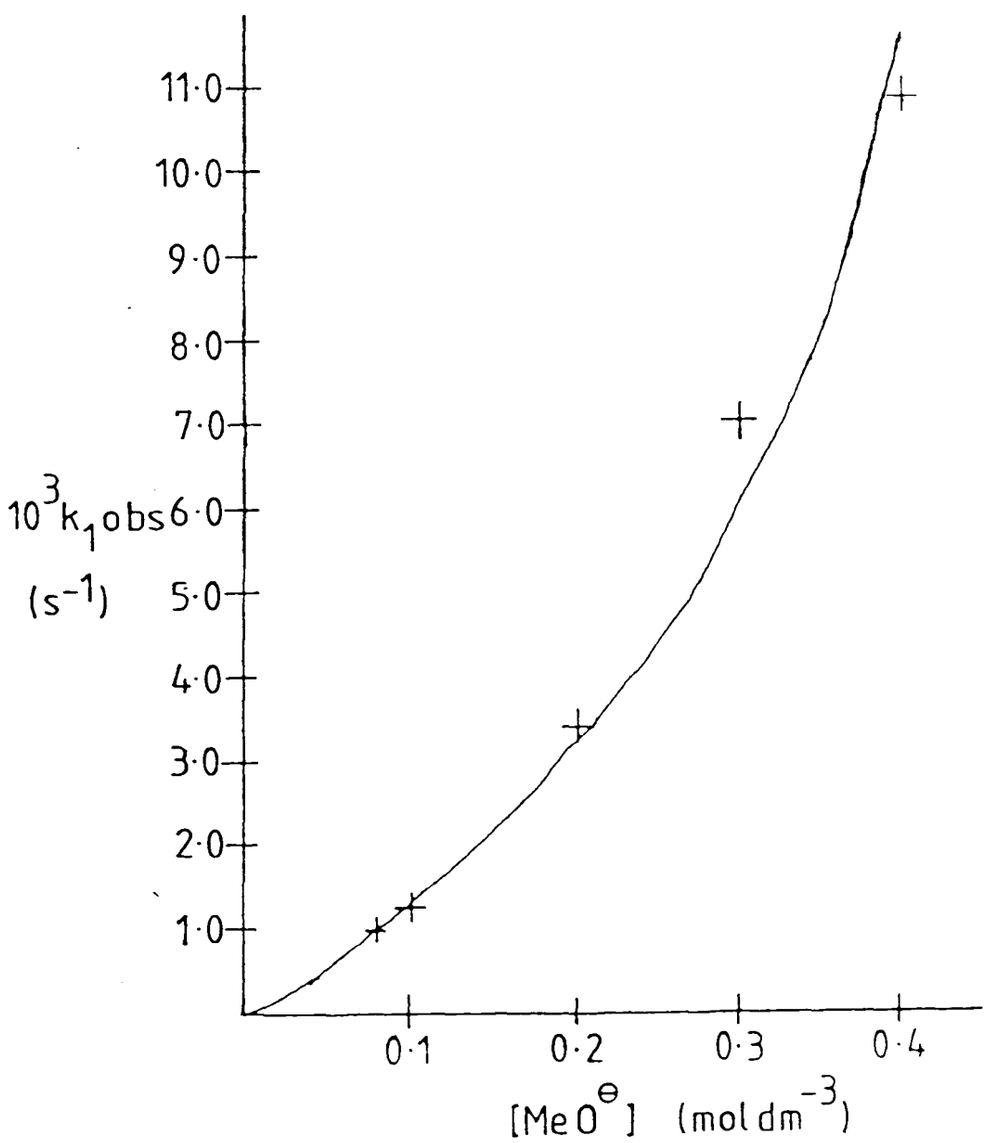
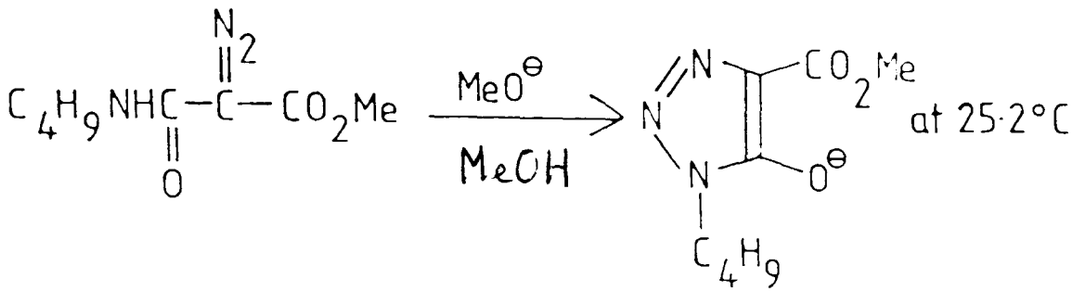

11·0
10·0
9·0
8·0
7·0
$10^3 k_1 obs$ 6·0
(s^{-1})
5·0
4·0
3·0
2·0
1·0
0·1
0·2
0·3
0·4
$[MeO^{\ominus}]$ $(mol\,dm^{-3})$

Fig 15 :


$C_4H_9NHC(=O)-C(=N_2)-CO_2Me$
$MeO^{\ominus}$
MeOH
CO_2Me
$O^{\ominus}$
C_4H_9
at 25·2°C

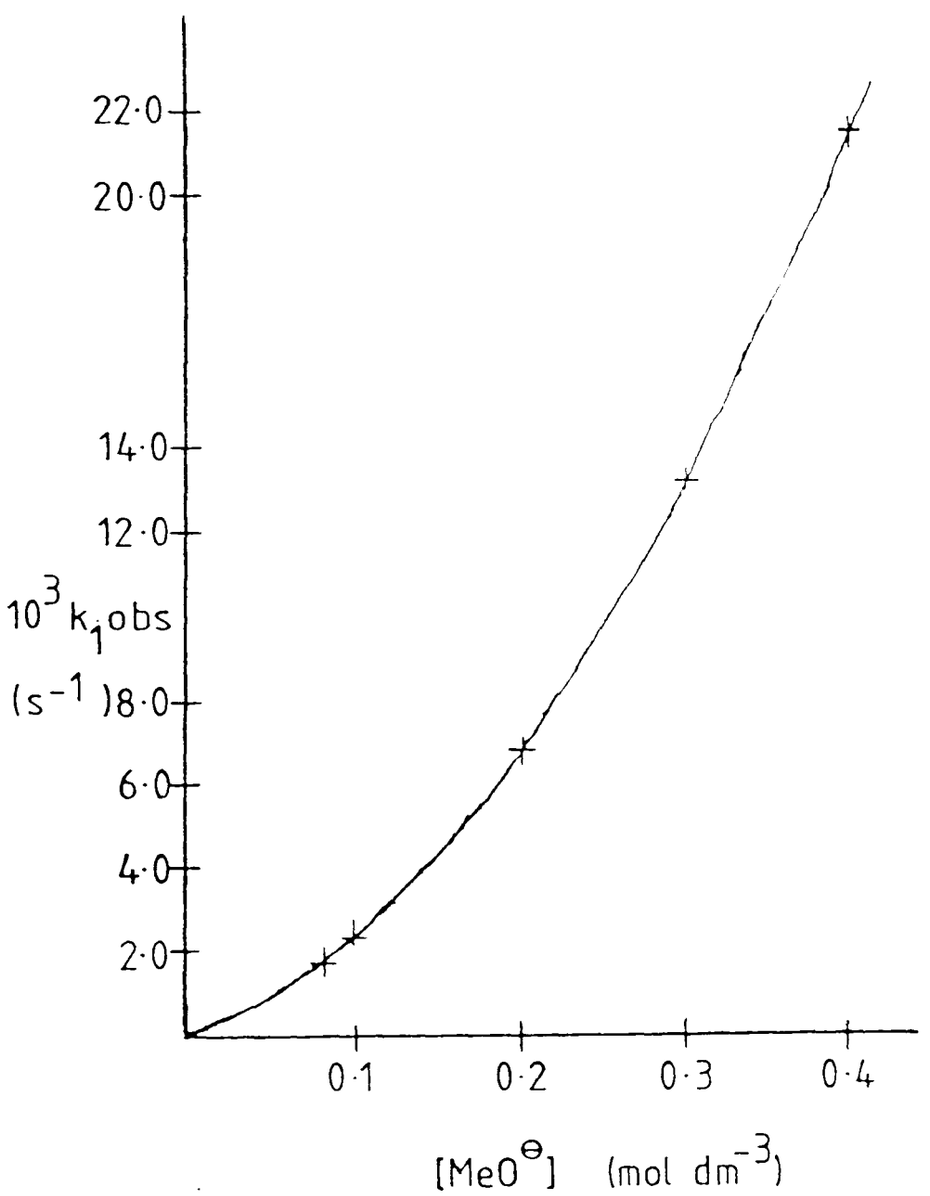
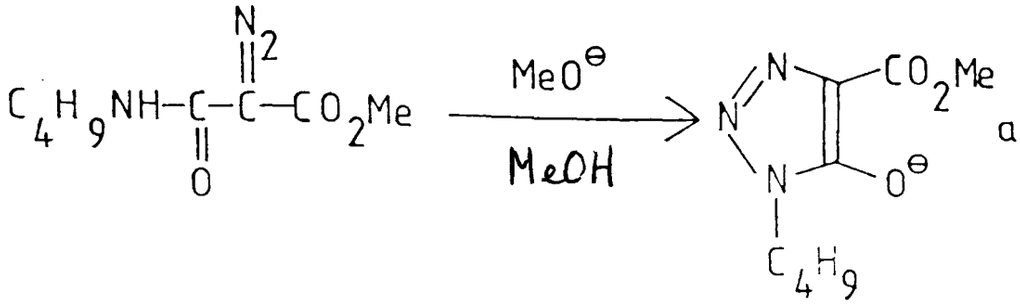

22·0
20·0
14·0
12·0
$10^3 k_1 obs$
(s^{-1})
8·0
6·0
4·0
2·0
0·1
0·2
0·3
0·4
$[MeO^{\ominus}]$ (mol dm^{-3})

Fig 16 :



at 31·3°C

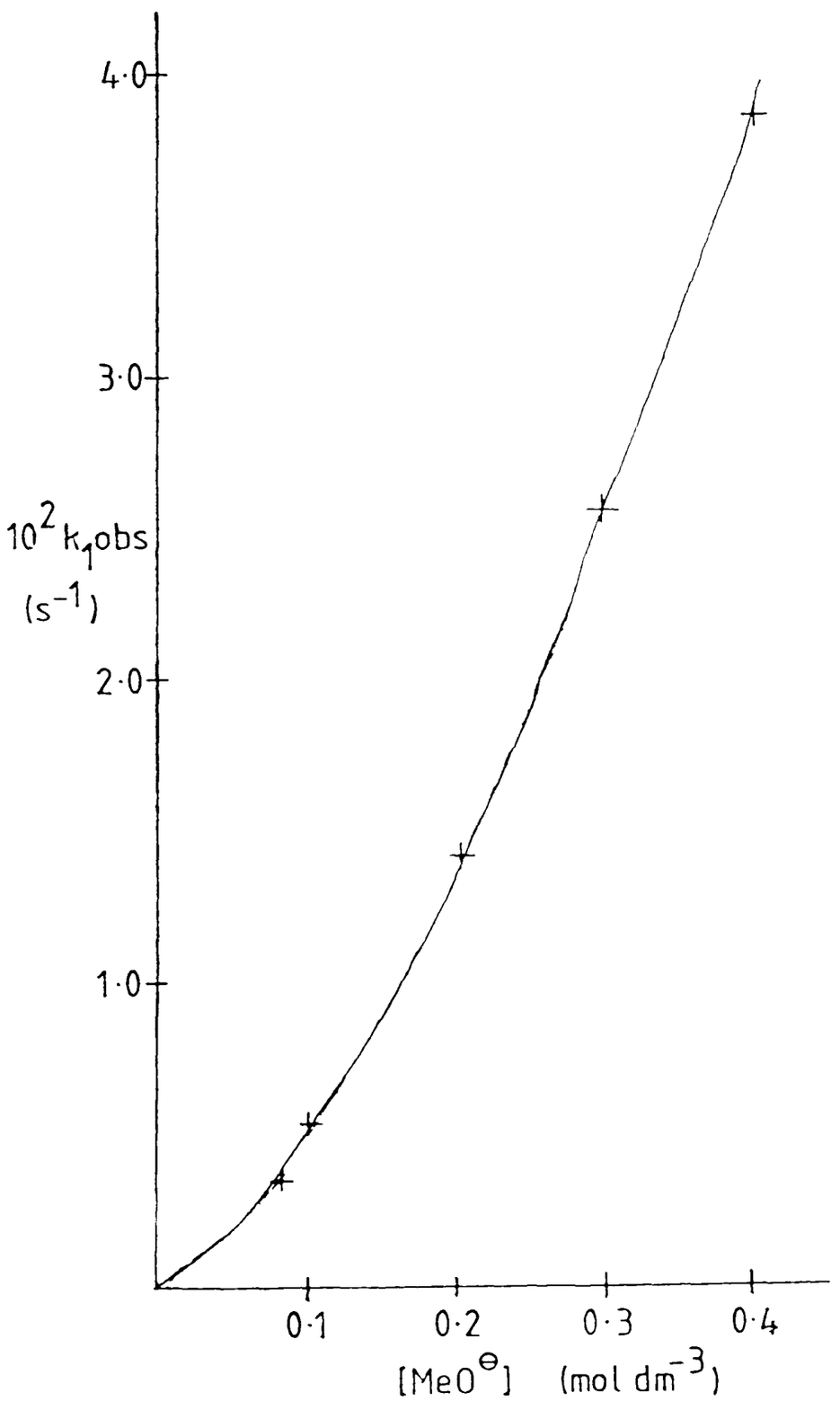
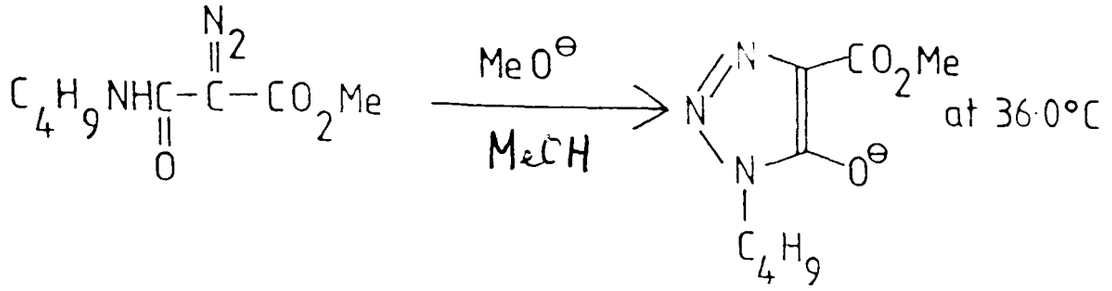


Fig 17:


$C_4H_9NHC(=O)-C(=N_2)-CO_2Me$
$MeO^{\ominus}$
MeCH
CO_2Me
$O^{\ominus}$
C_4H_9
at 36·0°C

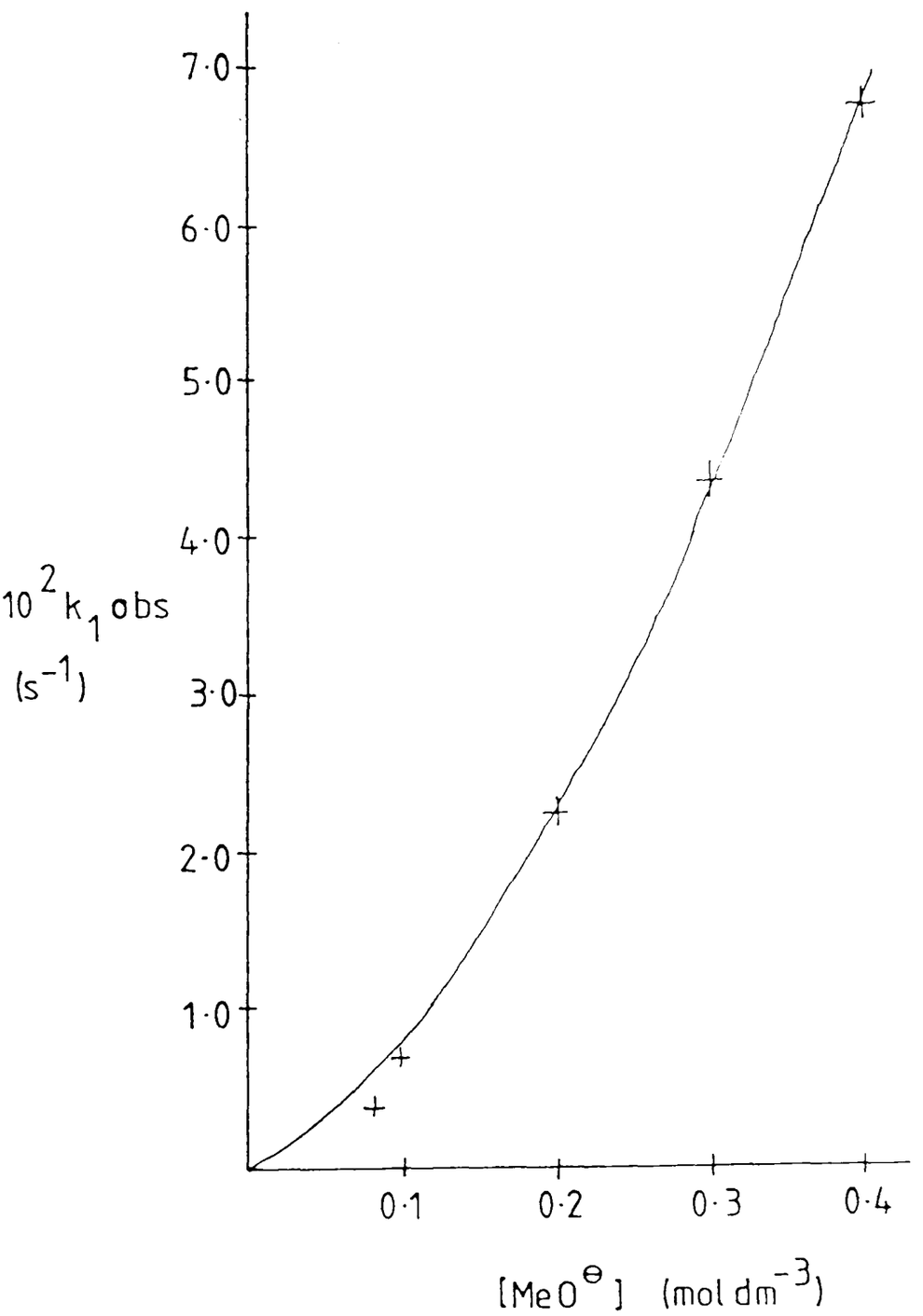
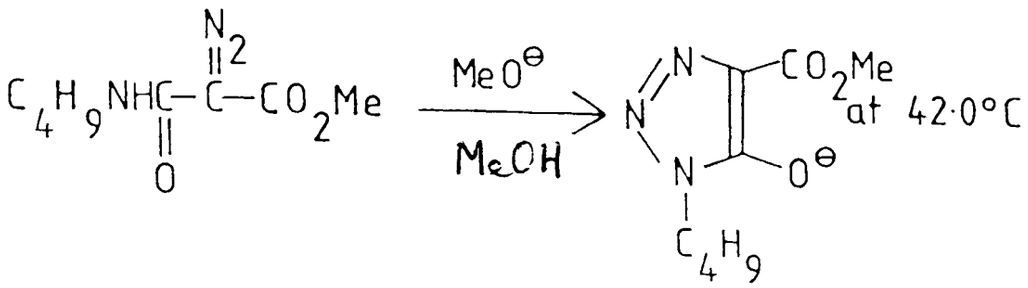

7·0
6·0
5·0
4·0
3·0
2·0
1·0
$10^2 k_1$ obs
(s^{-1})
0·1
0·2
0·3
0·4
$[MeO^{\ominus}]$ (mol dm^{-3})

Fig 18 :


N2
C4H9NHC
C
CO2Me
O
MeO⊖
MeOH
N
N
N
CO2Me
O⊖
C4H9
at 42·0°C

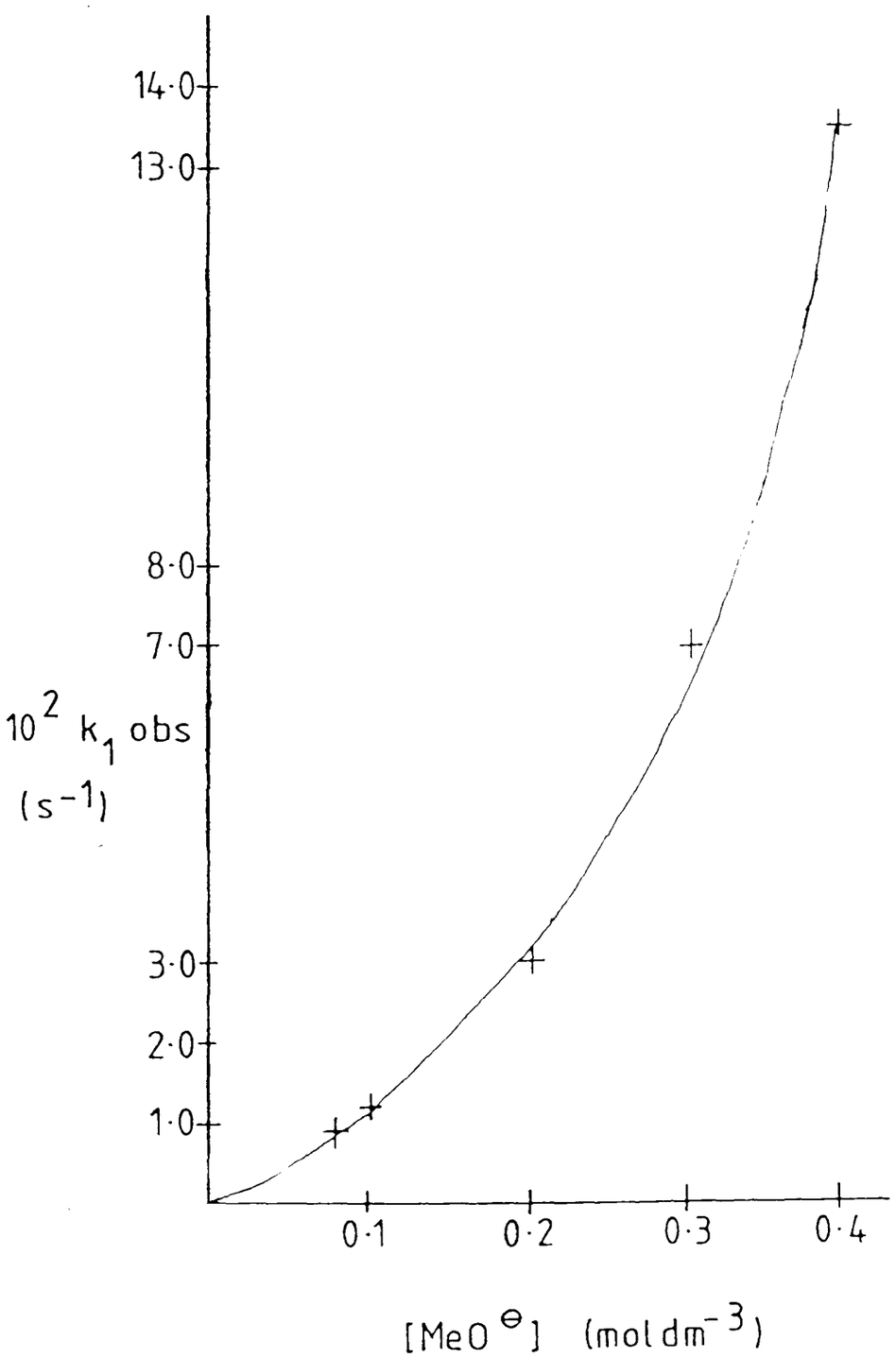
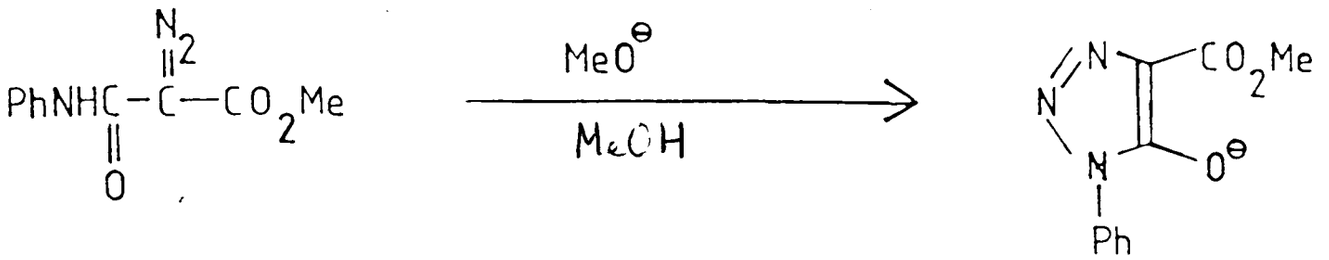

14·0
13·0
8·0
7·0
3·0
2·0
1·0
10² k₁ obs
(s⁻¹)
0·1
0·2
0·3
0·4
[MeO⊖] (mol dm⁻³)

TABLE 5

Kinetic data for the reaction

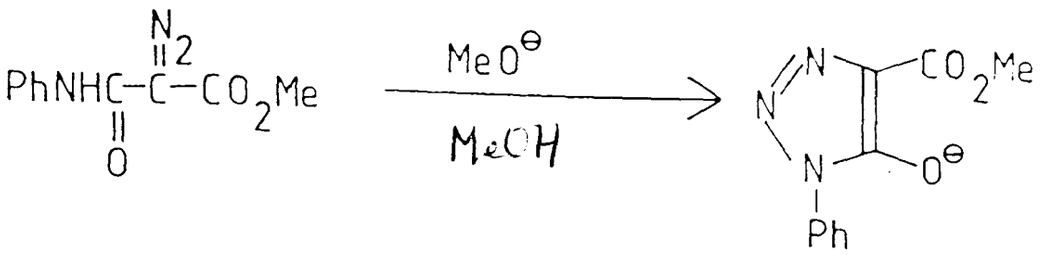


$$\text{Rate} = K_{eq}\, k_2\, [MeO^{\ominus}]\, [\text{diazoanilide}]$$

T (°C)	$K_{eq}\, k_2$ ($mol^{-1}\, dm^3\, s^{-1}$)	T (K)	1/T (K^{-1})	$\ln k_2 K_{eq}$
16.25	4.325	289.25	3.457×10^{-3}	1.464
20.6	6.413	293.6	3.406×10^{-3}	1.858
25.2	10.256	298.2	3.335×10^{-3}	2.328
30.5	18.221	303.5	3.295×10^{-3}	2.903
35.8	24.083	308.8	3.238×10^{-3}	3.182

Fig 19:

Plot of ln Keq k_2 vs 1/T for



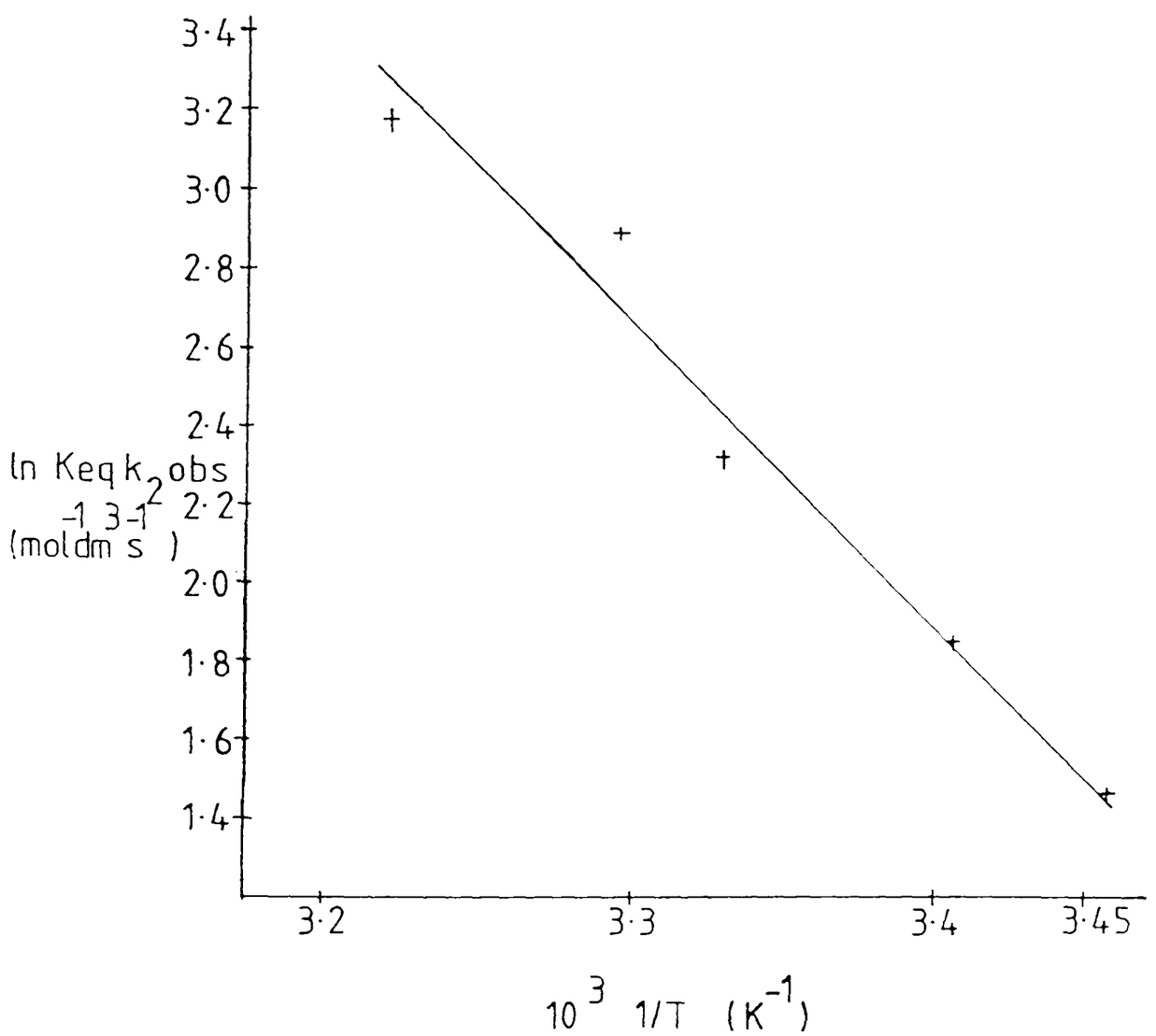
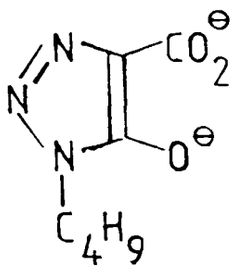


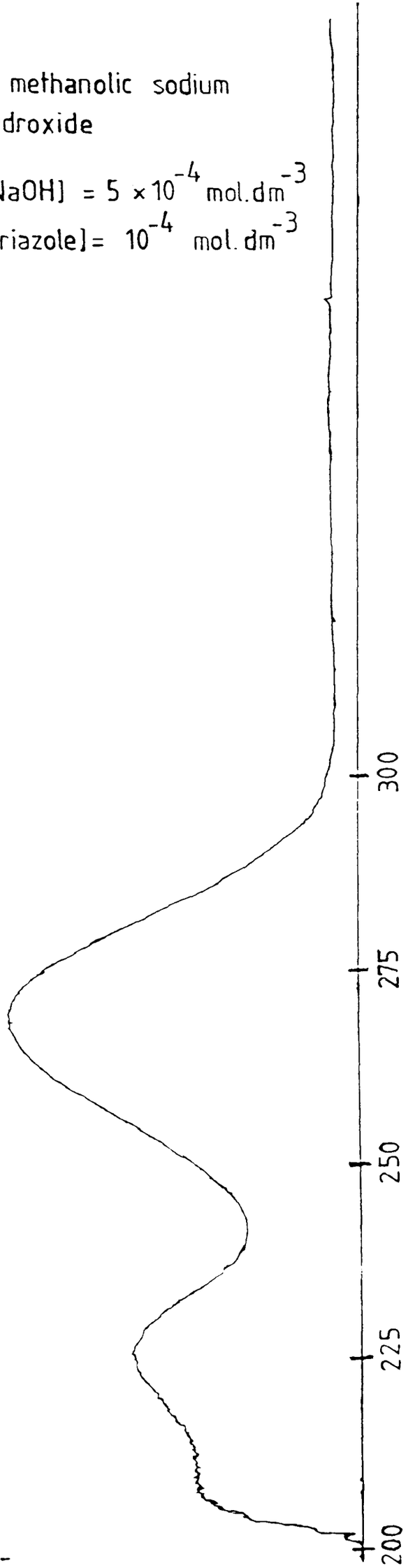
Fig 20 :



in methanolic sodium hydroxide

$[NaOH] = 5 \times 10^{-4}$ mol.dm^{-3}

$[triazole] = 10^{-4}$ mol.dm^{-3}

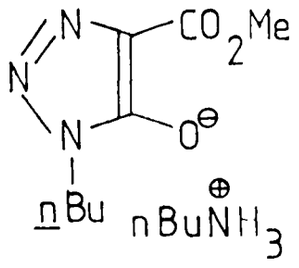
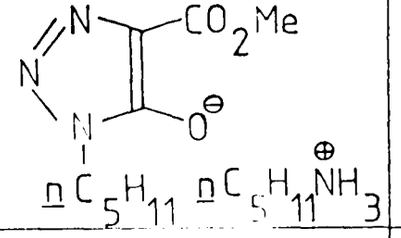
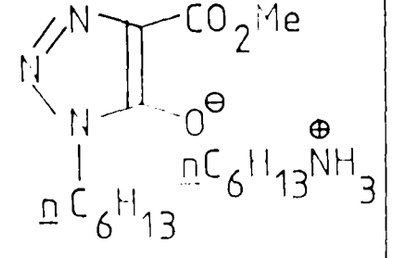


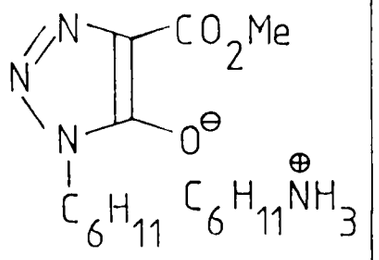
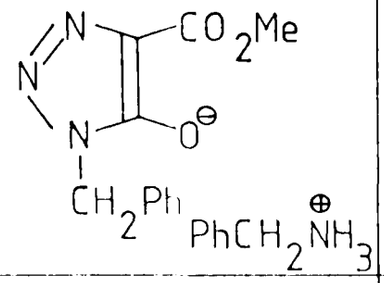
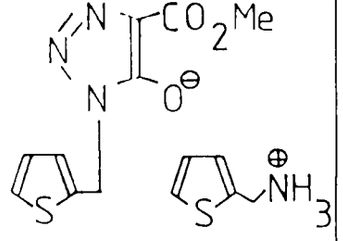
APPENDIX 2

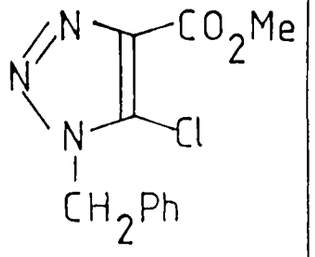
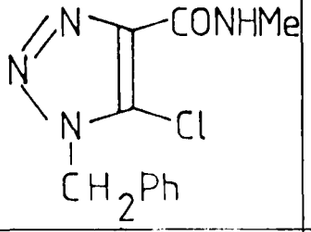
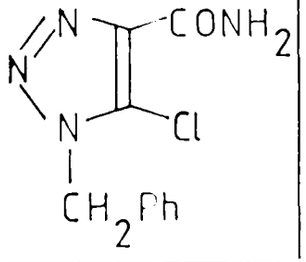
Biological Screening

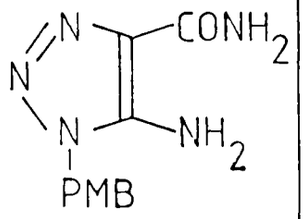
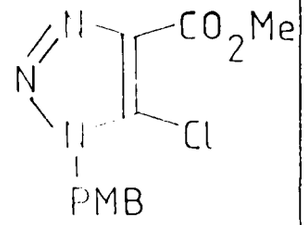
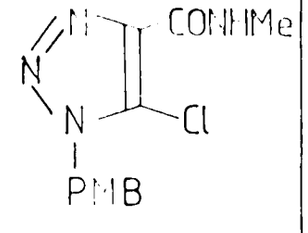
The following pages contain the results, where available, of tests on newly synthesised compounds. These data are the results of screening performed under the auspices of the Developmental Therapeutics Programme, Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland.

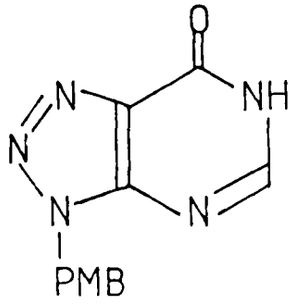
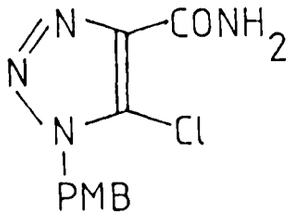
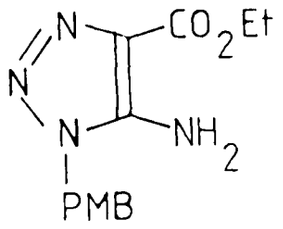
The newly synthesised compounds were only screened against L-5178Y lymphatic leukemia (mouse), but results are typical for deep tumours.

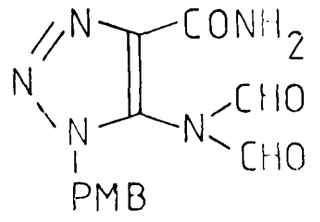
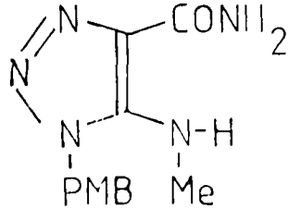
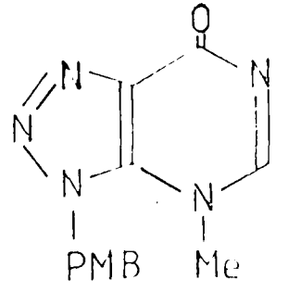
Compound	Identification	M.Pt. (°C)	N.S.C. No.	Comments
	AP/SL/1	111 - 113	360324	Inactive
	AP/SL/2	110 - 113	360325	Inactive
	AP/SL/3	119·5 -122	360325	Inactive

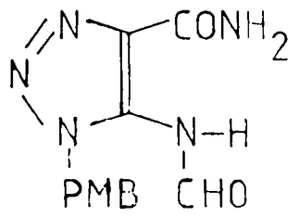
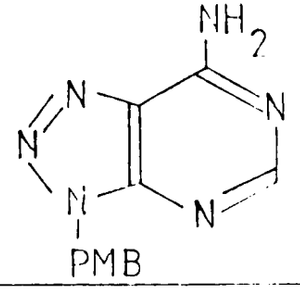
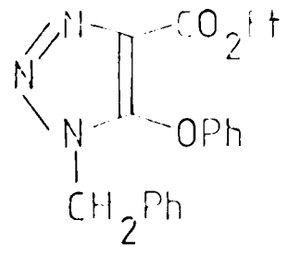
Compound	Identification	M.Pt.(°C)	N.S.C. No.	Comments
	AP/SL/4	154-157	360327	Inactive
	AP/SL/5	153 -156	360328	Inactive
	AP/SL/6	160 - 161	360329	Inactive

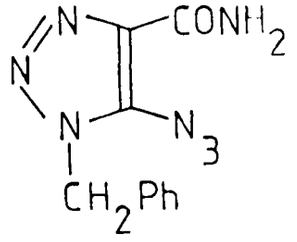
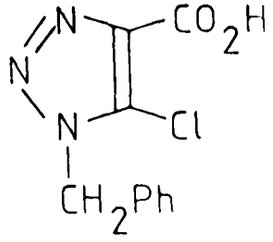
Compound	Identification	M.Pt. (°C)	N.S.C. No.	Comments
	AP/SL/7	77 - 79	360330	Toxic at test doses Inactive at lower doses
	AP/SL/8	149-150·5	810168 (T I D No)	Results not available
	AP/SL/9	164 - 166	810169 (TID No)	Inactive

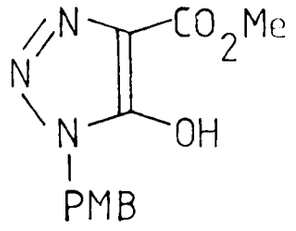
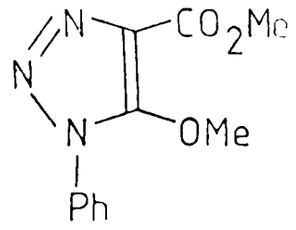
Compound	Identification	M.Pt. (°C)	N.S.C. No.	Comments
	AP/SL/10	207 - 209·5	365418	Inactive
	AP/SL/11	93 - 95	810171 (TID No.)	Results not available
	AP/SL/12	109 - 110·5	365492	Results not available

Compound	Identification	M.Pt. (°C)	N.S.C. No.	Comments
	AP/SL/13	215 (softens) 223 - 225	365419	Inactive
	AP/SL/14	167 - 171	365420	Inactive
	AP/SL/15	160 - 161·5	810175 (TID No)	Results not available

Compound	Identification	M.Pt (°C)	N.S.C. No.	Comments
	SPL27	148 - 150	No Number Assigned	Results not Available
	SPL28	157-158·5	" "	" "
	SPL29	222-224	" "	" "

Compound	Identification	M.Pt. (°C)	N.S.C. No.	Comments
	SPL32	196	No Number Assigned	Results not available
	SPL35	253 - 255	" "	" "
	SPL40	82 - 83	" "	" "

Compound	Identification	M.Pt. (°C)	N.S.C. No.	Comments
	SPL52	159 -161 (d)	No Number Assigned	Results not available
	SPL 37	133 -135	" "	" "

Compound	Identification	M.Pt. (°C)	N.S.C. No.	Comments
	SPL 42	109 -111·5	No Number Assigned	Results not Available
	SPL 60	81 - 83	" "	" "