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SYNTHESIS AND CHARACTERIZATION

OF TRIAZOLOTRIAZINES

by

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A thesis presented for the degree of

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SYNOPSIS

The Dimroth rearrangement in ring-fused 1,2,4-triazoles has been reviewed in detail in Part I and the synthesis of all known triazolotriazines is described in Part II.

Experimental investigations concerned the establishment of the skeletal arrangement of a variety of triazolotriazines formed by several synthetic routes.

Interaction of 3-amino-5-hydrazino-1,2,4-triazole and benzil afforded 2-amino-6,7-diphenyl-1,2,4-triazolo[5,1-c]-1,2,4-triazine whereas cyclization of 5,6-diphenyl-3-hydrazino-1,2,4-triazine with cyanogen bromide resulted in the isomeric 3-amino-6,7-diphenyl-1,2,4--triazolo[4,3-b]-1,2,4-triazine: both amines were deaminated with amyl nitrite in boiling tetrahydrofuran without rearrangement of the heterocyclic skeleton. 6,7-Diphenyl-1,2,4-triazolo[5,1-c]-1,2,4-triazine, synthesized from 3-hydrazino-1,2,4-triazole and benzil, formed a covalent hydrate which could be detected spectroscopically in solution, and a covalent methanolate and ethanolate which could be isolated.

A new route to 3-amino-5-hydrazino-pyrazole is described and cyclization to 7-amino-3,4-diphenyl-pyrazolo[5,1-c]-1,2,4-triazine was achieved with benzil.

The diazonium nitrate of 3-amino-1,2,4-triazole coupled with ethyl cyanoacetate to yield a mixture of two geometrical isomers of ethyl 2-(2H-1,2,4-triazol-3-ylhydrazono)cyanoacetate. Recrystallization of the crude coupling mixture from aqueous ethanol gave a single hydrazone which cyclized predominantly to ethyl 7-amino-1,2,4-triazolo[5,1-c]--1,2,4-triazine-6-carboxylate in acid conditions and 6-cyano-1,2,4--triazolo[5,1-c]-1,2,4-triazin-7(4H)-one under basic conditions. The nature of the cyclizing medium also controlled the cyclization of the

(pyrazol-ylhydrazono) cyanoacetate but the corresponding (tetrazol-ylhydrazono) cyanoacetate gave only ethyl 7-aminotetrazolo[5,1-c]-1,2,4--triazine-6-carboxylate. 2-(2H-1,2,4-Triazol-3-ylhydrazono)malononitrile cyclized unambiguously to 7-amino-6-cyano-1,2,4-triazolo-[5,1-c]-1,2,4-triazine.

Drastic hydrolysis of ethyl 2-(2H-1,2,4-triazol-3-ylhydrazono)-cyano-acetate, ethyl 7-amino-1,2,4-triazolo[5,1-c]-1,2,4-triazine-6-carboxylate, 6-cyano-1,2,4-triazolo[5,1-c]-1,2,4-triazin-7(4H)-one and 7-amino-6-cyano-1,2,4-triazolo[5,1-c]-1,2,4-triazine gave a hydrate of 1,2,4--triazolo[5,1-c]-1,2,4-triazin-7(4H)-one.

Mass spectral fragmentations of 7-aminoazolo-[5,1-c]-1,2,4-triazines confirm that the azole ring is more stable than the 1,2,4-triazine ring on electron impact.

ACKNOWLEDGEMENTS

The author wishes to express her gratitude to Dr. M.F.G. Stevens, Department of Pharmacy, Aston University for his counsel, encouragement and interest received during the course of this work.

The author extends thanks to all other members of the Pharmaceutical Chemistry Section, who helped in many ways.

The award of a post-graduate studentship by the 3M Company and the valuable discussions with Dr. G.F. Duffin are gratefully acknowledged.

'I retain the belief that one of the challenges of being a human being is that we are faced with the opportunity of deciding what we ought to think. If men had accepted what their generation found thinkable, we should have had no science and precious little humanness.'

David E. Jenkins

'The Glory of Man'
(New York, 1967), pp. 14-15.

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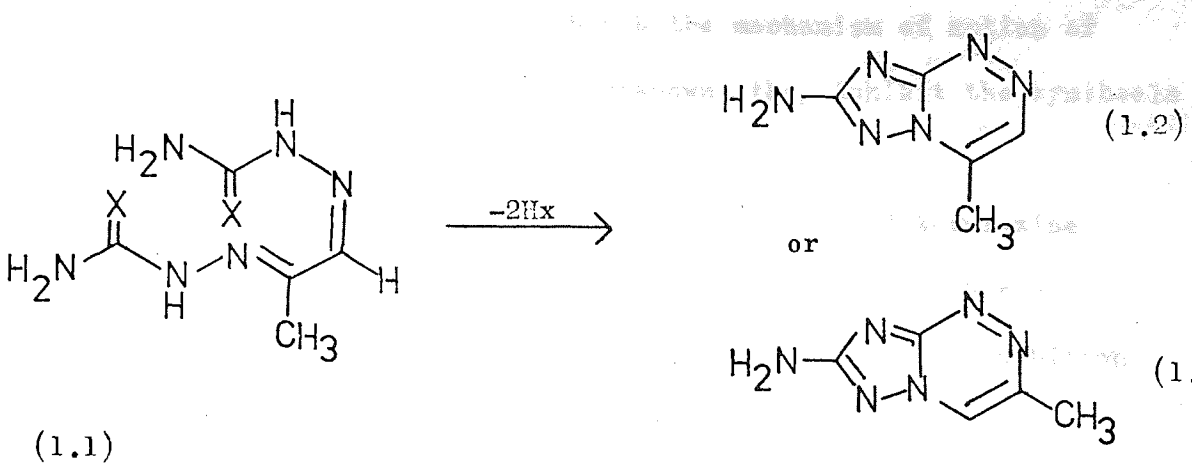
A. INTRODUCTION

Chemotherapy is the treatment of choice in certain types of malignant disease e.g. acute leukaemia in children, and those solid tumours unamenable to surgery and radiation therapy. However, chemotherapy is frequently of only secondary importance (but nevertheless beneficial) when used in conjunction with surgery or radiotherapy in the treatment of many other recalcitrant forms of cancer. The antimetabolites form one of the various classes of therapeutic agents used in the treatment of neoplastic diseases. An antimetabolite is defined as a compound that interferes with the formation or utilization of a normal cellular metabolite. Thus it is conceivable that 1,2,4-triazolo-1,2,4-triazines, as purine analogues, could act as antimetabolites and interfere with the normal synthesis or functions of the nucleic acids in tumour cells.

The antileukaemic action of methylglyoxal bis(guanylhydrazone) (1.1a) in man and animals is well known,[1] but its high toxicity prevents widespread use. Determination of the mechanism of action of methylglyoxal bis(guanylhydrazone) could aid the design of an active but less toxic compound. Both the bis(guanylhydrazone) (1.1a) and the corresponding bis(thiosemicarbazone) (1.1b), also cytotoxic against a range of tumours, evolve ammonia or hydrogen sulphide respectively when heated in water[2] and an attractive possibility is that they could be transformed in vivo to 1,2,4-triazolo[5,1-c]-1,2,4-triazines (1.2) or (1.3) (Scheme 1.1). Should cyclization to the active metabolite prove to be the case, it is likely that only one of the possible isomers is active (most drugs of this type have a high structural specificity).

Cytotoxic activity has also been demonstrated in other types of bis(thiosemicarbazones), notably the 1,5-dicarbonyl derivatives (1.4). These 1,5-bis(thiosemicarbazones) (1.4) have been shown[3] to cyclize in

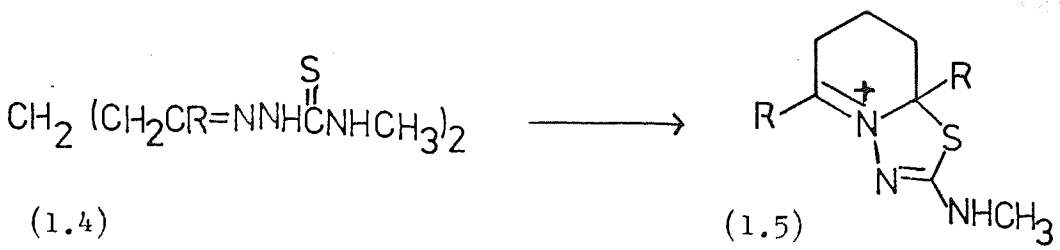


(1.1) (1.2) (1.3)

a x = NH

b x = S

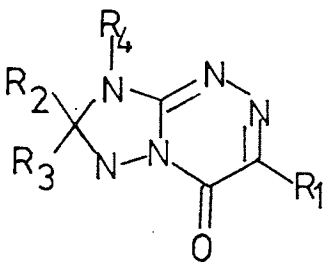
(Scheme 1.1)



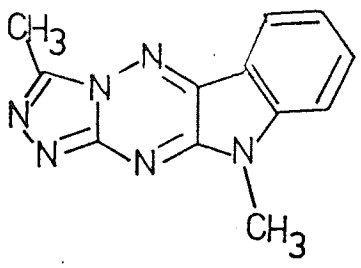
(1.4) (1.5)

a R = H

b R = CH_3



(1.6)



(1.7)

acid to novel water-soluble bicyclic quaternary salts (1.5) which also inhibit the growth of Ehrlich and Sarcoma 180 ascites tumours in mice but rapid hydrolysis of the heterocyclic compounds (1.5) may be a limiting factor in their potency. Although the mechanism of action of the 1,5-dicarbonyl derivatives (1.4) is unknown, they inhibit the synthesis of D.N.A.

The only biological results on the 1,2,4-triazolo-1,2,4-triazine systems reported to date are the herbicidal activity[4] of a number of triazolotriazinones of general structure (1.6) and rhinovirus inhibition exhibited[5] by the 1,2,4-triazolo-1,2,4-triazinoindole (1.7).

The aims of work invested in this thesis were to develop new synthetic routes to triazolotriazines and to establish their chemical properties. In particular, attention was focused on the elucidation of the skeletal disposition of the N atoms of the heterocyclic nuclei in question.

Part I

Review of the Dimroth rearrangement in ring-fused 1,2,4-triazoles

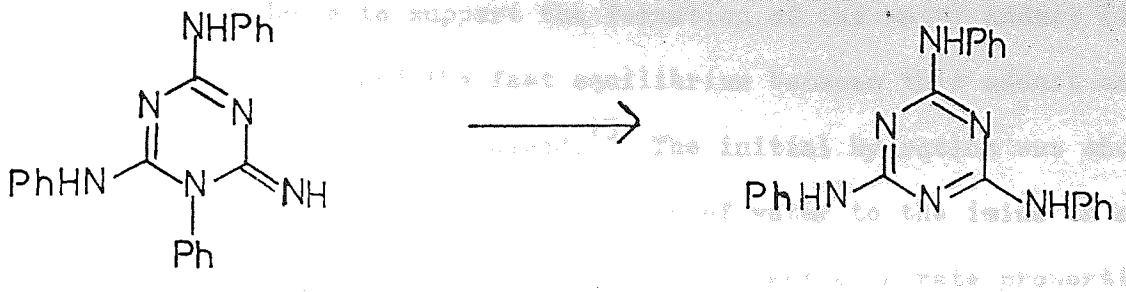
(1) Definition of the Dimroth rearrangement

The Dimroth rearrangement was the term[6] given in 1963 to describe an isomerization proceeding by ring-fission and subsequent recyclization, whereby a ring nitrogen and its attached substituent apparently exchanged places with an imino (or potential imino) group in the α-position.

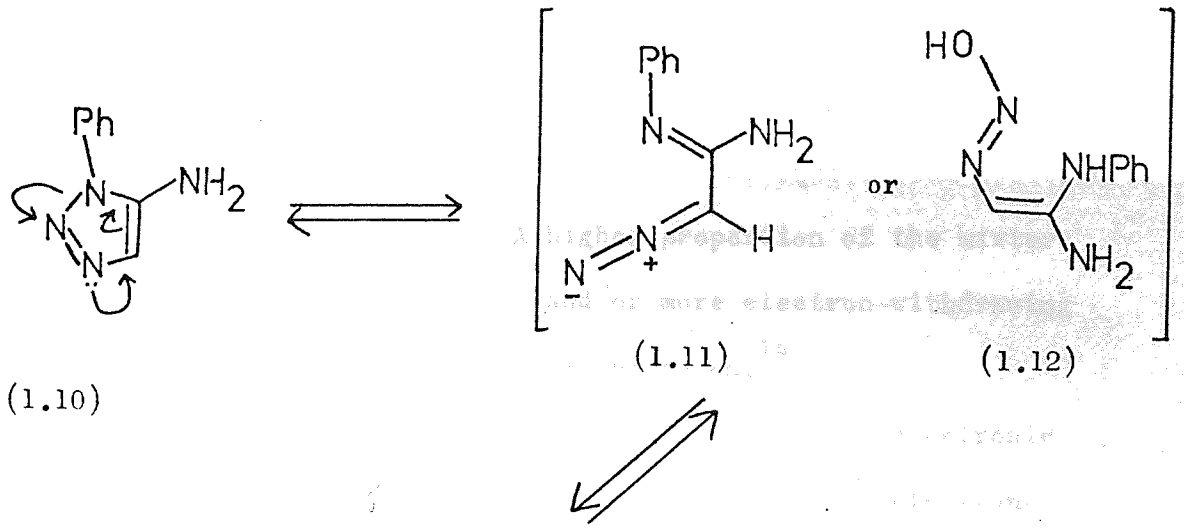
The first report[7] of such a rearrangement was in 1888 when it was shown that 4,6-dianilino-1,2-dihydro-2-imino-1-phenyl-1,3,5-triazine (1.8) was converted into 2,4,6-trianilino-1,3,5-triazine (1.9) on heating with alcoholic ammonia. The next report,[8] about 20 years later, was given by Otto Dimroth who was the first to postulate the correct general mechanism. He demonstrated[8] that a mixture of 5-amino-1-phenyl-1,2,3-triazole (1.10) and 5-anilino-1,2,3-triazole (1.13) resulted when either compound was melted, or boiled in water or pyridine. Dimroth proposed an acyclic diazoalkane (1.11) or diazohydroxide (1.12) as intermediate (Scheme 1.2).

Recognition of the Dimroth rearrangement as a more general phenomenon in heterocyclic chemistry was illustrated particularly in the pyrimidine series;[9] this work has been reviewed by Brown.[10]

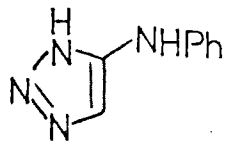
With the aid of ^{15}N-labelled ammonia the exchange of the endo-cyclic and exo-cyclic N-substituents has been confirmed.[11,12] For example 2-chloropyrimidine (1.14) was reacted with ^{15}N-ammonia to give 2-aminopyrimidine isotopically labelled on the exo-cyclic nitrogen (1.15). Methylation of the latter resulted in 1,2-dihydro-2-imino-1-methylpyrimidine (1.16) which was rearranged under alkaline conditions into 2-methylaminopyrimidine (1.20) (Scheme 1.3). This product (1.20) was hydrolysed to labelled pyrimidin-2-one and unlabelled methylamine.



(1.8) (1.9)



(1.10) (1.11) (1.12)



(1.13)

(Scheme 1.2)

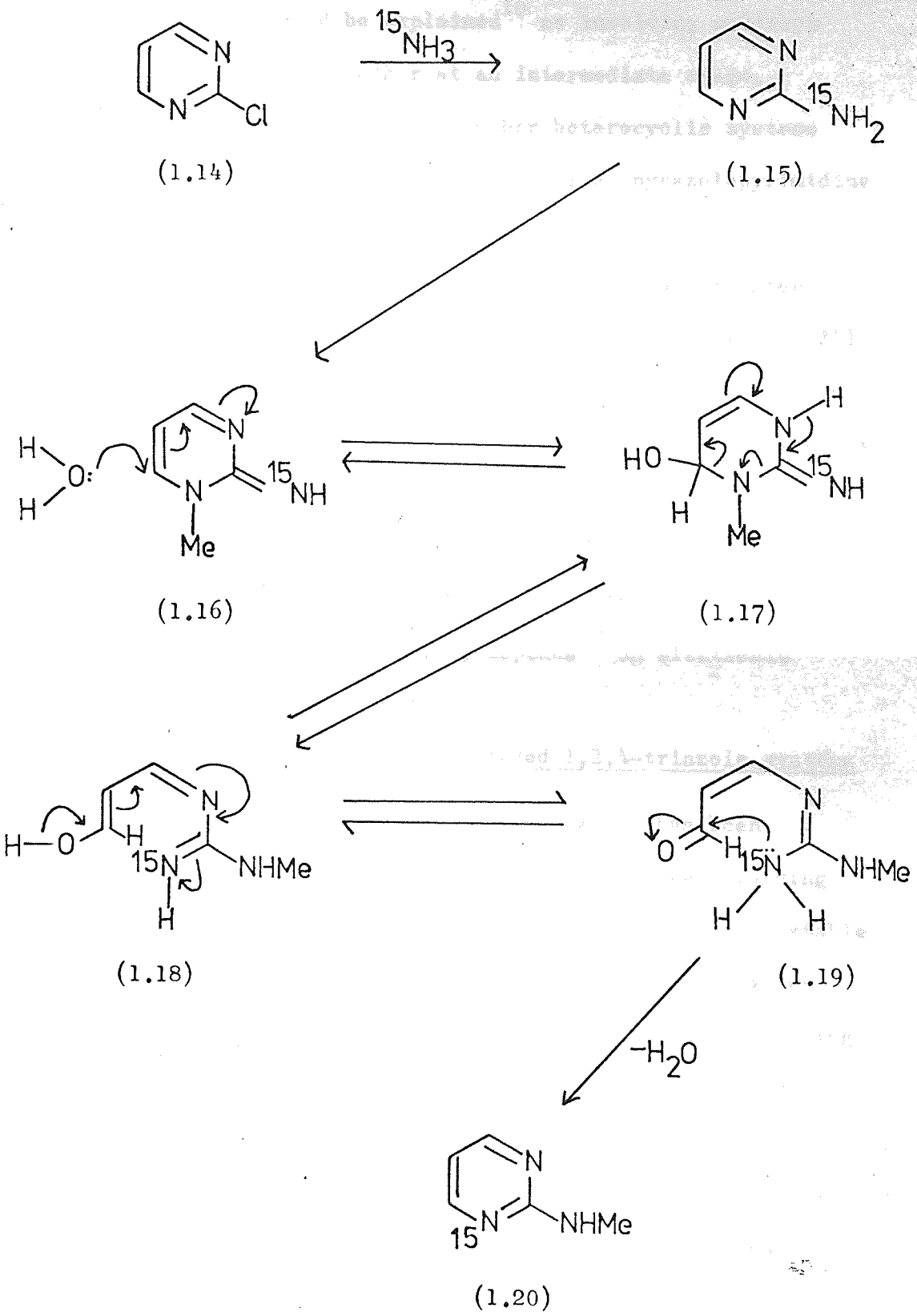
Strong evidence to support the formation of the water adduct (1.17) by initial hydration and the fast equilibrium between this adduct and the imine (1.16) has been obtained.[13] The initial hydration was shown to be a first-order reaction and addition of water to the imine in an aprotic solvent was found to induce rearrangement at a rate proportional to the concentration of water.

Ring-fission was corroborated[10] by the isolation and characterization of several intermediate aldehydes (e.g. 1.19) and their degradation products.

The two steps of ring-fission and recyclization in the mechanism of the Dimroth rearrangement are at least potentially reversible. However, the reclosure (1.19 to 1.20) is virtually irreversible when the imino group is unsubstituted, due to the formation of a stable aromatic product. Steric and electronic factors determine the equilibrium position when the imino group is substituted. A higher proportion of the mixture consists of the isomer with the bulkier and/or more electron-withdrawing group ultimately attached to the exo-cyclic nitrogen.[14]

The rate of Dimroth rearrangements is controlled by the electronic nature of attached substituents. In the pyrimidine series[10] electron-donating roups in the pyrimidine ring retard rearrangements, primarily by affecting the ring-fission step (1.16 to 1.18) while electron-withdrawing groups accelerate the reaction.

The water or alcohol, generally considered to be necessary in Dimroth rearrangements, can be replaced by another nucleophile. When the hydroiodide of 1,2-dihydro-2-imino-1-methylpyrimidine (1.16) was heated[10] in anhydrous diethylamine addition of the nucleophile occurred to give the diethylamino-analogue of the water adduct (1.17) which opened to an enamine and then eliminated diethylamine irreversibly to give 2-methylaminopyrimidine (1.20). As expected no reaction occurred with triethyl-



(Scheme 1.3)

amine. Thus the thermal rearrangement of 1-diphenylmethyl-1,2-dihydro-2-iminopyridine above 200° could be explained[10] as involving addition of one molecule of the imine to another at an intermediate stage.

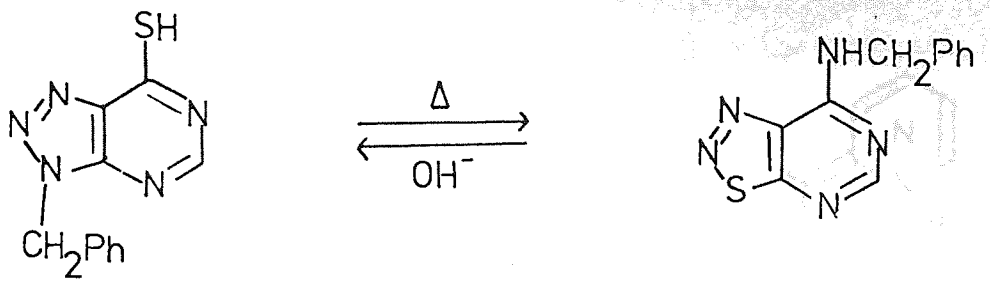
Examples of Dimroth rearrangements in other heterocyclic systems include the tetrazole, thiadiazole, pteridine, purine, pyrazolopyrimidine and quinazoline series.[10]

A "pseudo-Dimroth" transformation is exemplified[15] in the interconversion of 3-benzyl-7-mercapto-1,2,3-triazolo[4,5-d]pyrimidine (1.21) and 4-benzylamino-thiadiazolo[5,4-d]pyrimidine (1.22). Similarly, the isomerization[16] of 3-substituted-3,4-dihydro-4-imino-1,2,3-benzotriazines (1.23) to substituted 4-amino-1,2,3-benzotriazines (1.25) via the diazo intermediate (1.24) is related to the Dimroth rearrangement (Scheme 1.4). The comparison was further illustrated by the report that the rate of isomerization of iminobenzotriazines (1.23) depends[17] on electronic and steric effects of the 3-substituent.

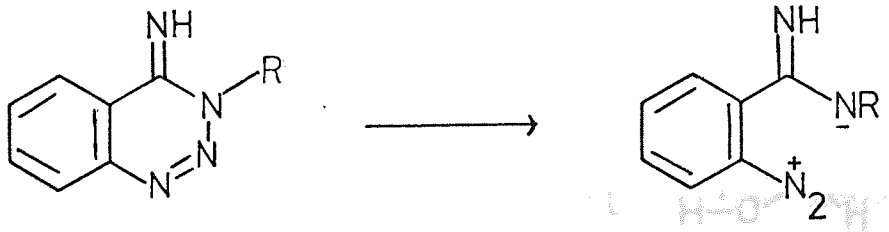
(2) The mechanism of rearrangement in ring-fused 1,2,4-triazole systems

Isomerization in several ring-fused 1,2,4-triazoles has been described in the literature. The transformation, in essence involving ring-fission followed by recyclization to a thermodynamically more stable isomer, parallels the Dimroth rearrangement described in the previous section. However, in the fused 1,2,4-triazole systems the corresponding endo- and exo-cyclic nitrogens are now part of the triazole ring which is represented by the dotted line in the rearrangement of (1.26) to (1.27). Without exception, it has been shown that the most stable fused 1,2,4-triazoles are those with N-1 of the triazole ring in the bridgehead position (i.e. 1.32) and not N-4 (as in 1.28) (Scheme 1.5).

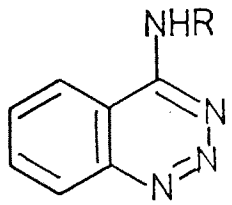
The application of dry heat often induces the isomerization but it is procured more readily in the presence of water and especially under



(1.21) (1.22)

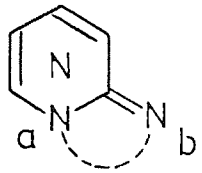


(1.23) (1.24)



(1.25)

(Scheme 1.4)



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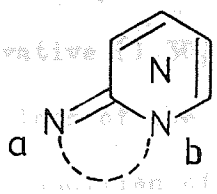

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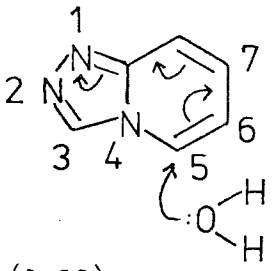

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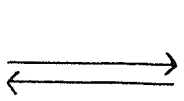
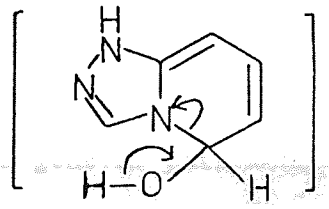
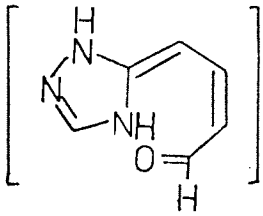




(1.29)

other tautomers

other tautomers



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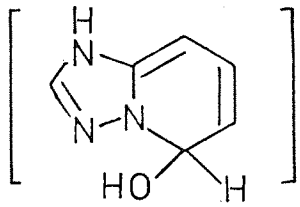

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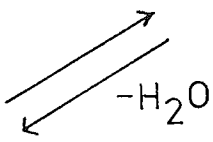
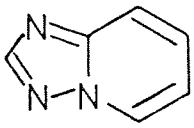




(1.32)

(Scheme 1.5)

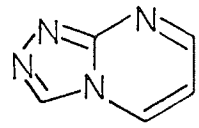
acidic or basic conditions. The initial step in an aqueous medium (Scheme 15) involves[18] nucleophilic attack by water at the azine ring carbon adjacent to the bridgehead hetero-atom to form the hydrate (1.29). Ring-opening of the 4,5- bond yields the carbonyl derivative (1.30) and subsequent ring-closure at the triazole N-atom - with loss of the elements of water - results in the isomer (1.32). Nucleophilic addition at the azine C-N bond and subsequent rearrangement is most effectively catalysed by bases. In anhydrous conditions the formation of the zwitterionic intermediate (1.34) formed by heterolysis of the 4,5-bond was proposed[19] (Scheme 1.6); preferential recyclization to N-1 of the triazole would give the isomer (1.35). An alternative possibility is that these thermal rearrangements are bi-molecular reactions with one mole of substrate acting as the electrophile and another as the nucleophile to facilitate ring-opening.[10] The Dimroth rearrangement, as a general phenomenon in ring-fused 1,2,4-triazoles, is illustrated in Table 1.

Due to the rapidity of isomerization in the fused 1,2,4-triazole system it has not yet been possible to measure equilibrium constants. This is in contrast to similar rearrangements in the imidazole series.[34,35]

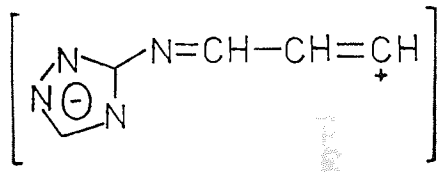
The triazolo[4,3-a]pyrazines (1.54a and b) were claimed[36] to rearrange in hot acid (with concomitant hydrolytic replacement of amino) to the oxotriazolo[2,3-a]pyrazines (1.56 a and b). A later report demonstrated[37] that the reaction took a different course to give the intriguing 1H-imidazo[2,1-c]-1,2,4-triazoles (1.55 a and b) (Scheme 1.7).

(3) Detection of acyclic intermediates

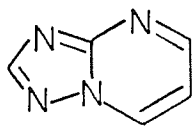
As yet, no acyclic intermediates have been detected in the rearrangements of fused 1,2,4-triazoles, but their formation can be inferred. The dimethoxytriazolo[4,3-a]pyrimidine (1.57) gave[38] the



(1.33)



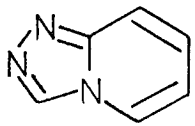
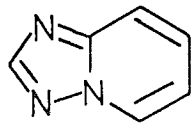
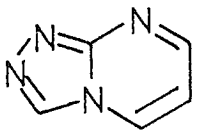
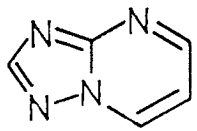
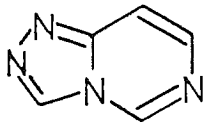
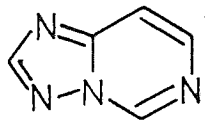
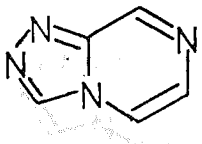
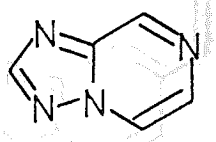
(1.34)



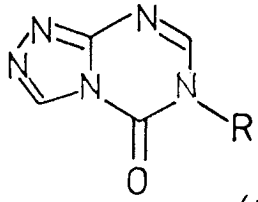
(1.35)

(Scheme 1.6)

Table 1: Dimroth-type rearrangements in the 1,2,4-triazoloazine series.

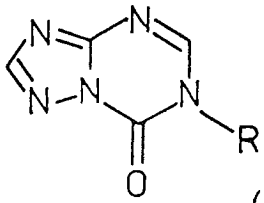
Initial ring-system	Rearranged ring-system	CONDITIONS	REFERENCES
(i) 1,2,4-triazolo[4,3-a]pyridine  (1.28)	1,2,4-triazolo[1,5-a]pyridine  (1.32)	Hot aqueous alkali	20,21
(ii) 1,2,4-triazolo[4,3-a]pyrimidine  (1.33)	1,2,4-triazolo[1,5-a]pyrimidine  (1.35)	Hot aqueous acid or alkali	18,22,23
(iii) 1,2,4-triazolo[4,3-c]pyrimidine  (1.36)	1,2,4-triazolo[1,5-c]pyrimidine  (1.37)	Aqueous acid or alkali at room temperature	24,25
(iv) 1,2,4-triazolo[4,3-a]pyrazine  (1.38)	1,2,4-triazolo[1,5-a]pyrazine  (1.39)	Hot aqueous alkali	26

(v) 1,2,4-triazolo[4,3-a]-1,3,5--triazine



(1.40)

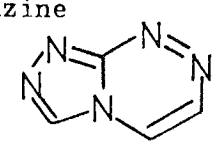
1,2,4-triazolo[1,5-a]-1,3,5-triazine



(1.41

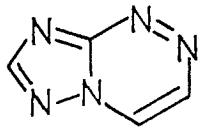
Hot neutral media 27

(vi) 1,2,4-triazolo[3,4-c]-1,2,4-triazine



(1.42)

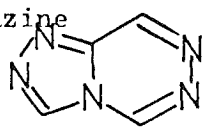
1,2,4-triazolo[5,1-c]-1,2,4-triazine



(1.43)

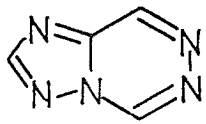
Acidic or neutral media at room temperature 28

(vii) 1,2,4-triazolo[4,3-d]-1,2,4--triazine



(1.44)

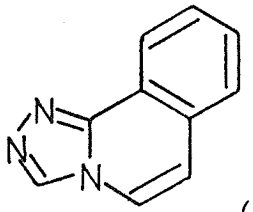
1,2,4-triazolo-[1,5-d]-1,2,4--triazine



(1.45)

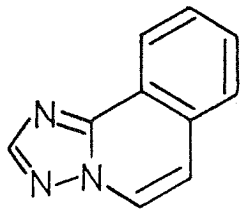
Acidic media at room temperature 29

(viii) 1,2,4-triazolo[3,4-a]isoquinoline



(1.46)

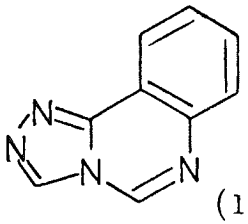
1,2,4-triazolo[5,1-a]isoquinoline



(1.47)

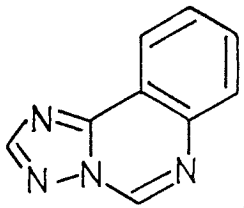
Hot aqueous alkali 30,31

(1x) 1,2,4-triazolo[4,3-c]quinazoline



(1.48)

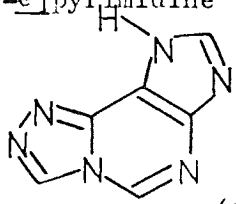
1,2,4-triazolo[1,5-c]quinazoline



(1.49)

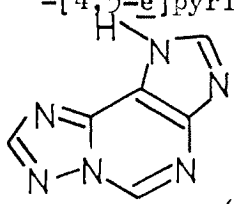
Warm neutral or acidic media. 32

(x) 1,2,4-triazolo[4,3-c]imidazo-[4,5-e]pyrimidine



(1.50)

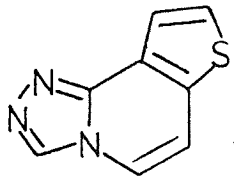
1,2,4-triazolo[1,5-c]imidazo-[4,5-e]pyrimidine



(1.51)

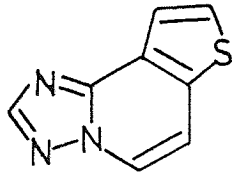
Hot formamide 33

(xl) 1,2,4-triazolo[4,3-a]thieno-[3,2-c]pyridine



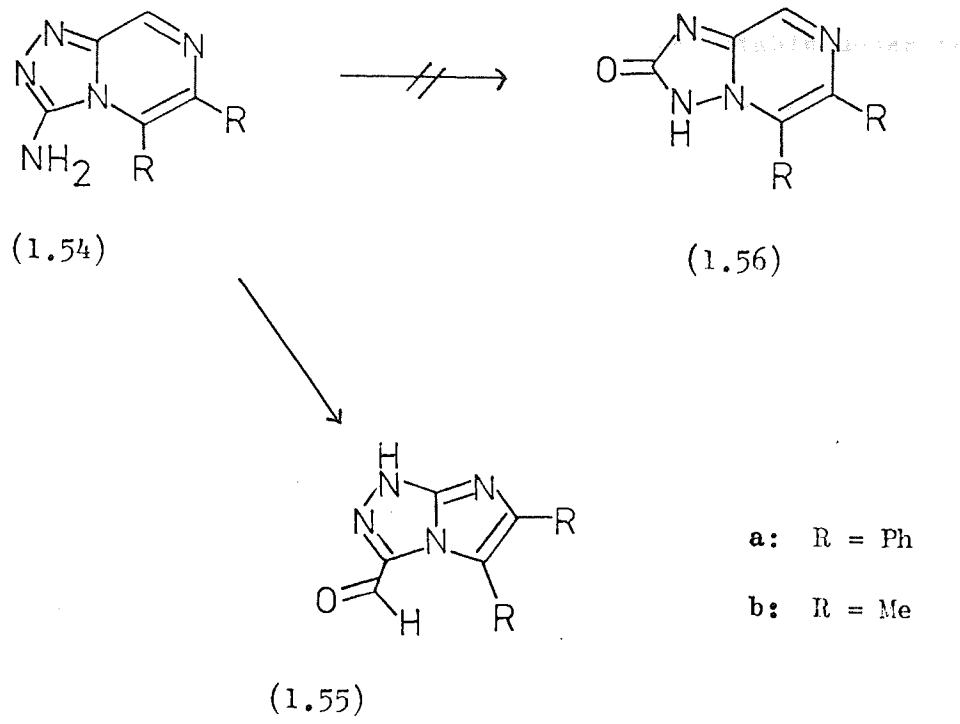
(1.52)

1,2,4-triazolo[1,5-a]thieno[3,2-c]pyridine

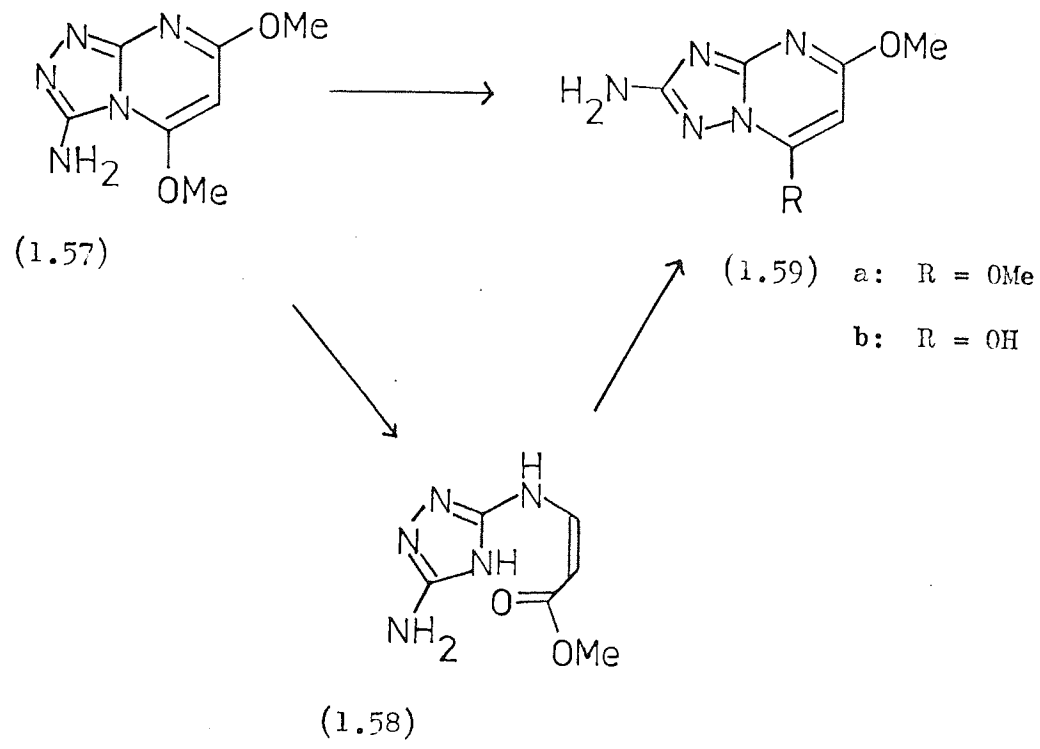


(1.53)

Hot aqueous alkali 31



(Scheme 1.7)

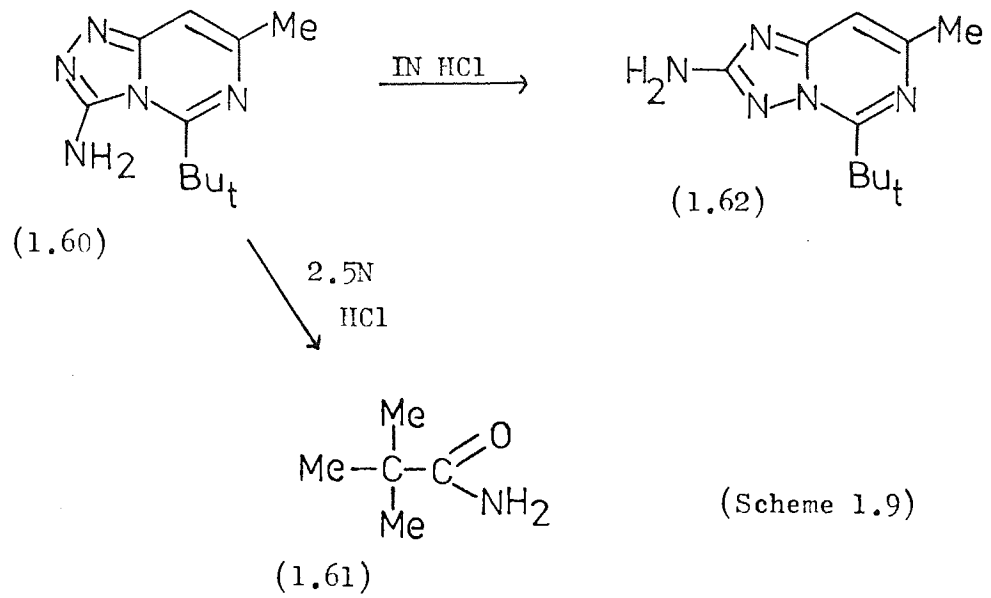


(Scheme 1.8)

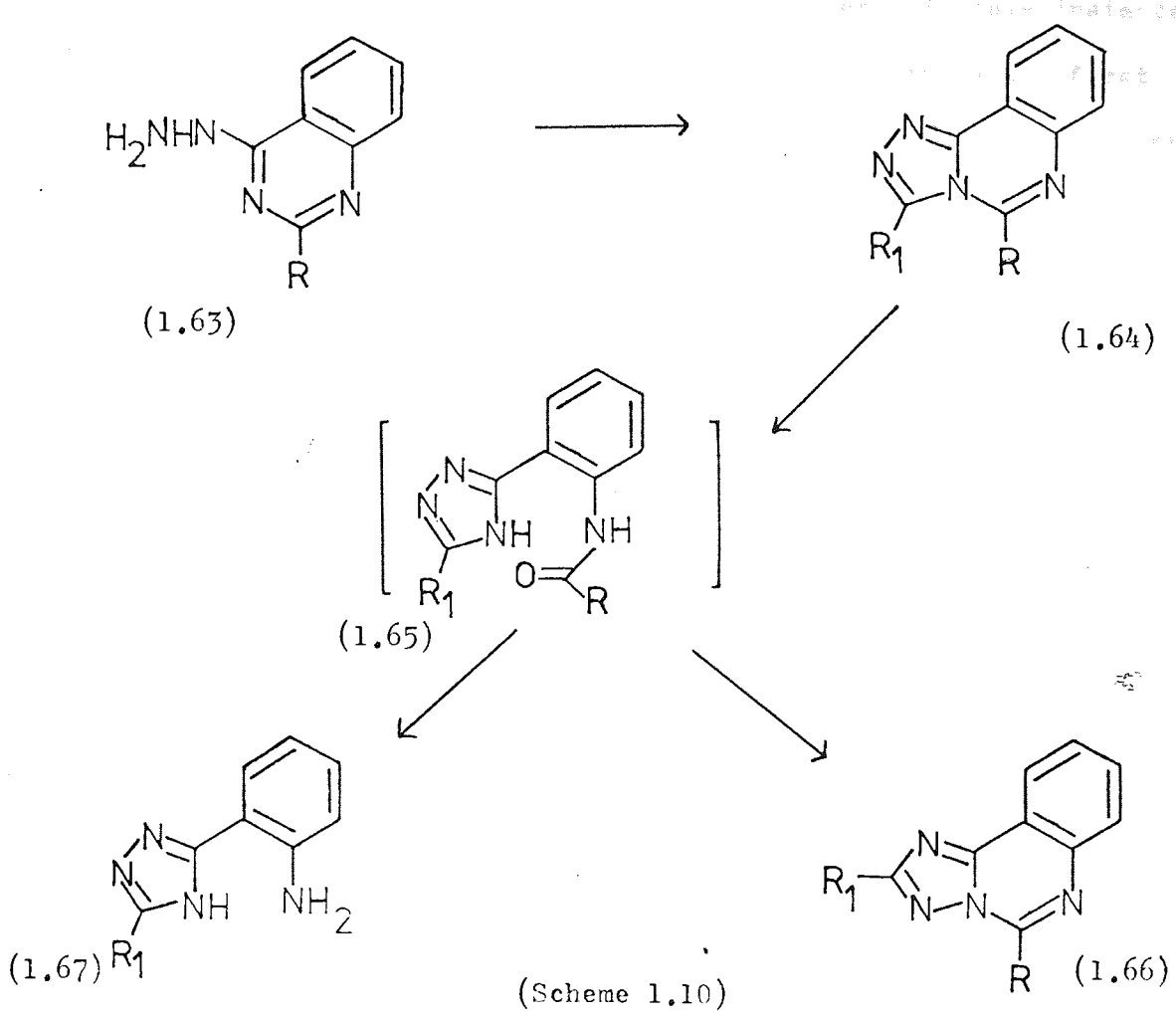
[1,5-a]isomer (1.59a) under dry thermal conditions whereas in hot dilute acid or alkali the 5-hydroxy-7-methoxy-[1,5-a]derivative (1.59b) was formed. Hydrolysis did not occur before or after isomerization since the dimethoxytriazolo[1,5-a]-pyrimidine (1.59a) was stable under rearrangement conditions, and the related 3-amino-5-hydroxy-7-methyl-1,2,4-triazolo[4,3-a]pyrimidine was not converted to its[1,5-a] isomer under the same conditions. Therefore, as predicted,[38] the alcohol proved a better leaving group than water from the proposed acyclic ester intermediate (1.58) (Scheme 1.8).

Further evidence for the existence of open-chain intermediates can be adduced[24] from the fragmentation reactions observed during the course of acid-induced isomerizations. One example was found in the isolation of a substantial amount of pivalamide (1.61) when compound (1.60) was kept for 65 hours in 2.5N-hydrochloric acid at room temperature; with IN-acid a certain amount of the [1,5-c]isomer (1.62) was isolated after a short period (Scheme 1.9). The steric influence of the t-butyl group was expected to have exaggerated the fragmentation in this manner.

In two instances, a compound predisposed to undergo a Dimroth rearrangement has yielded an anomalous product under conditions favourable to the formation of the isomer. In the first example,[32] 1,2,4-triazolo [1,5-c]quinazolines (1.66) were obtained in an extremely facile manner (acid or heat) from the corresponding[4,3-c]isomers (1.64), or when the hydrazinoquinazolines (1.63) were cyclized with orthoesters in the absence of buffer. 3-[2-aminophenyl]-1,2,4-triazoles (1.67) were isolated when (1.64) was subjected to alkaline conditions and it appeared hydrolysis of the intermediate amides (1.65) was more rapid than ring-closure to the isomeric[1,5-c]system (1.66) under these conditions (Scheme 1.10). In the second case,[33] treatment of 1,2,4-triazolo[4,3-c] imidazo[4,5-e]pyrimidine (1.50) under acidic or basic



(Scheme 1.9)

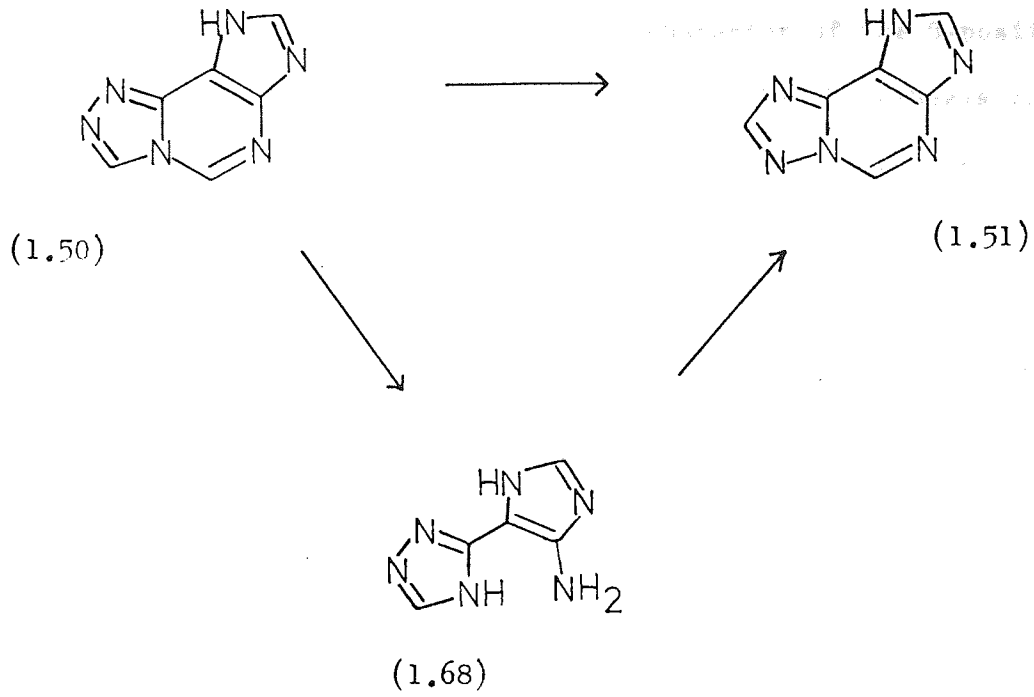


(Scheme 1.10)

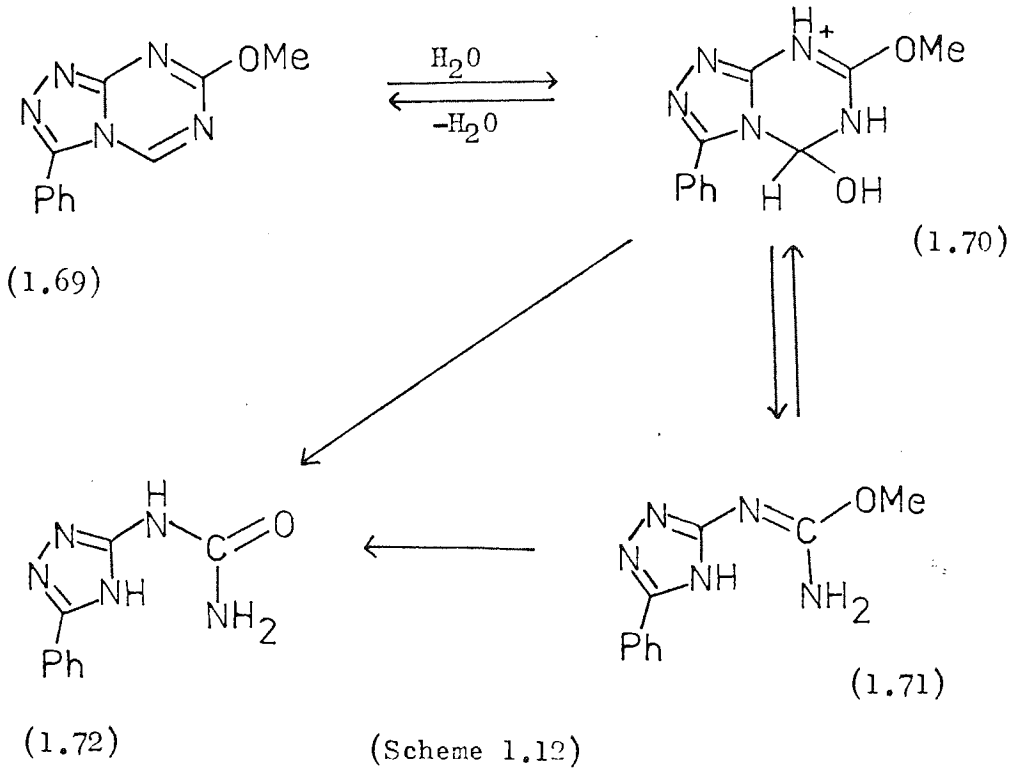
conditions resulted in 3-(5-aminoimidazol-4-yl)-1,2,4-triazole (1.68) which gave the [1,5-c] isomer (1.51) on reaction with diethoxymethylacetate. Direct conversion to the isomer (1.51) was the outcome when the triazoloimidazopyrimidine (1.50) was heated in formamide. (Scheme 1.11).

The protonated covalent hydrate (1.70) has been postulated[27] as an intermediate in reactions of the 1,2,4-triazolo-1,3,5-triazine (1.69). Unlike a related 1,2,4-triazolo-1,3,5-triazine system[27] the expected rearrangement to the [1,5-a] isomer did not occur when (1.69) was heated in conditions which normally favour Dimroth rearrangements. Instead the urea (1.72) was isolated from concentrated hydrochloric acid, whereas more selective hydrolysis in dilute sodium hydroxide or morpholine yielded the corresponding O-methylurea (1.71) (Scheme 1.12). The latter could be further hydrolysed to the urea (1.72) and surprisingly re-cyclized to the [4,3-a] isomer (1.69) with triethylorthoformate or diethoxymethylacetate but not to the [1,5-a] isomer. In this instance cyclization appears to be kinetically controlled. This is the first report of such a recyclization to the theoretically less stable isomer and should be re-examined (Scheme 1.12).

Intermediates have been detected in both the fused tetrazole and fused imidazole systems. The sodio-derivative (1.74) of the Dimroth intermediate formed by ring-opening of the tetrazolo[1,5-a] pyrimidine (1.73) can be isolated.[39] In the tetrazolo[1,5-c]-pyrimidine system, the covalent hydrate (1.75) can be isolated.[40] These phenomena were attributed to the electron-attracting effect of the tetrazole ring and adds support to the mechanism of initial hydration of a C=N bond in Dimroth-type rearrangements. Intermediates in the imidazo[1,2-a]-pyridine series have been studied[34,35] notably by ^{1}Hn.m.r. but in comparison to the 1,2,4-triazole systems this was facilitated by a



(Scheme 1.11)



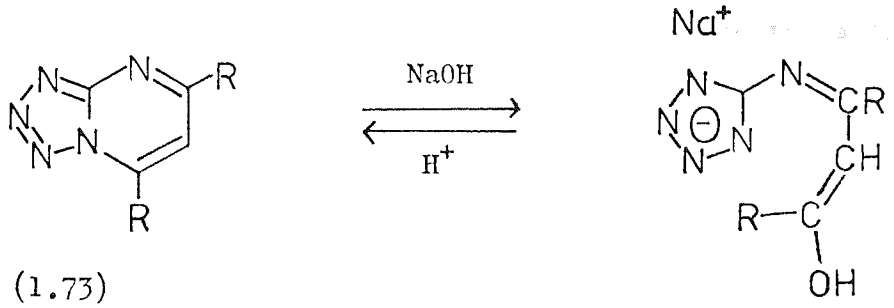
(Scheme 1.12)

decreased isomerization rate.

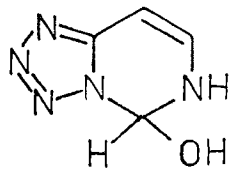
(4) Electronic effects on the rearrangement

Any factor increasing the electrophilic character of the 5-position in structure (1.28) should promote rearrangement. This hypothesis was given support by the enhanced ability of 1,2,4-triazolo[4,3-a]- (1.33) and 1,2,4-triazolo[4,3-c]pyrimidines (1.36) to undergo rearrangement to their respective [1,5-a] (1.35) and [1,5-c] (1.37) isomers in comparison to the pyridine system (1.28 to 1.32) (Table 1). On the other hand reactivity in the 1,2,4-triazolo-pyrazine system (1.38) appeared[26] unaffected. To justify the preceding experimental data Π-electron densities at the 5-position for a number of fused 1,2,4-triazole systems were calculated from Hückel Molecular Orbital calculations. The results confirmed that an additional nitrogen at position 6 or 8 rendered the 5-position more electrophilic but had little effect when it was situated at position 7.[26,35]

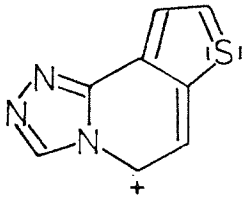
In view of these experimental results it could be predicted that appropriate substitution of electron-withdrawing groups would also increase the susceptibility of the 5-position to nucleophilic attack and promote rearrangement. The isomerization of 1,2,4-triazolo[4,3-a]-pyrimidines (1.28) into their [1,5-a] isomers (1.32) is greatly facilitated[21] by electron-withdrawing nitro substituents in positions 6 or 8 of the pyridine ring but retarded[21] with an electron-donating amino group in position 8. The enhanced rate of rearrangement was exacerbated by a 6-nitro group since it was then adjacent to the position under nucleophilic attack. Similarly a 6-ethoxycarbonyl group induced[41] a more rapid rearrangement of 1,2,4-triazolo[4,3-a]pyrimidin-7-ones and allowed for acid-catalysed rearrangement hitherto unreported in this system.



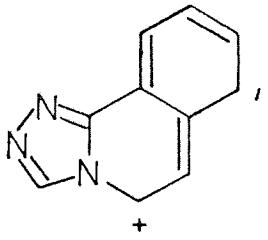
(1.73) (1.74)



(1.75)



(1.76)



(1.77)

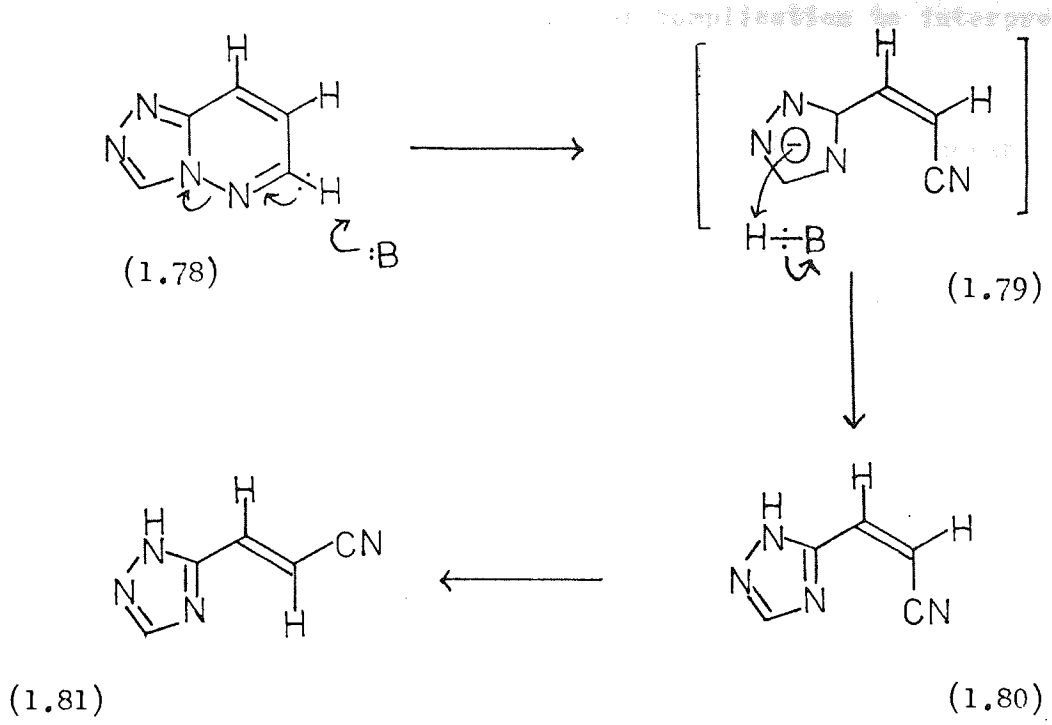
The inductive effect of a 7-bromo substituent in 1,2,4-triazolo [3,4-a]isoquinoline (1.46) induced[31] a more rapid isomerization and a similar increased rate in the 1,2,4-triazolo[4,3-a]thieno[3,2-c]pyridine system (1.52) in comparison to (1.46) was attributed to the sulphur atom.[31] The increased rate in the latter case was also explained[31] as a mesomeric effect. The resonance structure (1.76) rather than (1.77) is the more favoured mesomer because sulphur can extend its valence shell to a decet.

Analogous electronic effects have been described in a previous section for the Dimroth rearrangements in monocyclic systems.[10]

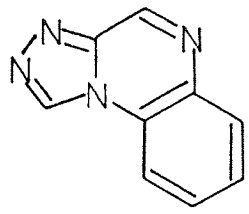
(5) Steric effects on the rearrangement

It is possible that a steric factor may have an effect on the reaction rate. For example, formation of the hydrated intermediate from (1.28) would relieve peri-interaction between two groups in the 3- and 5-positions due to a change in hybridization. Fission of the 4,5-bond would be more likely in (1.29) than (1.31) because of residual peri-interaction. This factor has been investigated[35] in the imidazopyridine system but not yet in the 1,2,4-triazoloazine system.

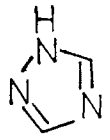
1,2,4-Triazolo[4,3-b]pyridazines (1.78) were predicted to be stable in conditions favourable to a Dimroth rearrangement due to unlikely cleavage of the N-N bond and the inability of the 5-position to suffer nucleophilic attack. The system was reported[42] to be stable but a subsequent publication[43] has shown that cleavage of the N-N bond occurs in alkali when the 6-position is unsubstituted. The resulting products were the geometrical isomers (1.80 and 1.81) (Scheme 1.13). This base-catalysed fission with removal, initially, of a β-proton (with respect to the bridgehead N-atom) is known to occur in various aldehyde hydrazones, aldoximes, isoxazoles and pyrazoles. A similar cleavage has



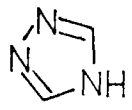
(Scheme 1.13)



(1.82)



(1.83)



(1.86)

been demonstrated[44] in the 1,2,4-triazolo[3,4-a]phthalazine system. This unexpected N-N fission adds a further complication to interpretations of Dimroth rearrangements.

In the 1,2,4-triazoloquinoxaline series (1.82), the vulnerable C-N bond is blocked by annelation and hence the compound cannot rearrange.[26]

(6) Thermodynamic considerations

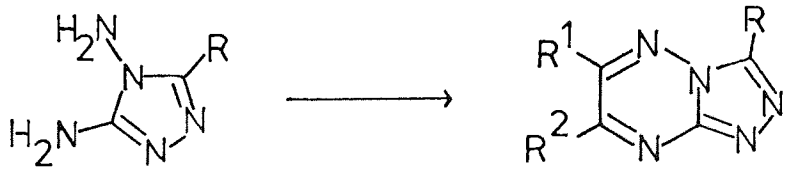
The experimental findings that 1,2,4-triazoloazines (1.28) undergo isomerization to (1.32) are in agreement with the theoretical calculations of the CNDO total electron densities.[35] The latter illustrated a larger interaction between N-1 and N-2 in (1.28) relative to N-1 and N-3 in (1.32). This was anticipated from energy calculations of components of the prototropic equilibrium in 1,2,4-triazole; they confirmed that 1H - 1,2,4 - triazole (1.83) is more stable[45] than the 4H- tautomer (1.84).

Part II

Review of the synthesis of 1,2,4-triazolo-1,2,4-triazines from:-

(1) 3,4-Diamino-1,2,4-triazoles

The first 1,2,4-triazolo-1,2,4-triazines described in the literature were the 6,7-disubstituted-1,2,4-triazolo[4,3-b]-1,2,4-triazines (2.2).[46-48] They were prepared in an attempt to identify the 1,2,4-triazoles formed from the reaction of hydrazine with benzoylthiosemicarbazide derivatives and NN'-dithiocarbamylhydrazine. 3,4-Diamino-1,2,4-triazoles (2.1) were differentiated from 3-hydrazino-1,2,4-triazoles on the questionable basis that the former gave triazolotriazines (2.2; R=H, Me, R^1=R^2=Me or Ph) with benzil or biacetyl, and dibenzylidene derivatives with benzaldehyde, whereas the latter gave only monobenzylidene derivatives. Attempts to react the 3-hydrazino-1,2,4-triazoles with benzil or biacetyl were not indicated although triazolotriazines are also formed in this case (see later).



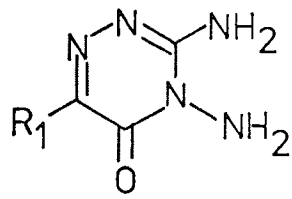
(2.1) R = H,Me,NH_2 (2.2) R = H,Me,NH_2
R^1 = R^2 = Me or Ph

A more successful approach to the 1,2,4-triazolo[4,3-b]-1,2,4-triazines (2.2) was found in the reaction of hydrazine with cyanogen bromide which afforded 3,4,5-triamino-1,2,4-triazole.[49] The latter (2.1; R=NH_2), when condensed with 1,2-dicarbonyl compounds gave 3-amino-6,7-disubstituted-1,2,4-triazolo[4,3-b]-1,2,4-triazines (2.2; R=NH_2, R^1=R^2 =Me or Ph). It was assumed that the [4,3-b] nucleus (2.2) would not undergo a Dimroth transformation since fission of the N-N bond

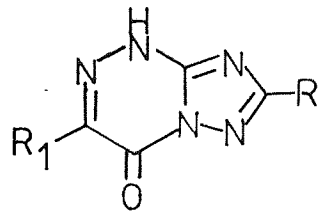
would be highly unlikely (see previous section).

(2) 3,4-Diamino-1,2,4-triazines

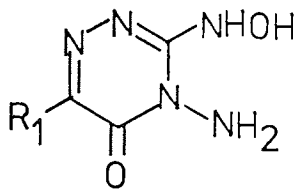
Diaminoguanidine and α-keto acids have been shown[50] to yield 3,4-diamino-5-oxo-1,2,4-triazines (2.3) and not the possible alternatives, 3-hydrazino-5-oxo-1,2,4-triazines. These diaminotriazines (2.3; R_1=H, Me, Ph)[51] and 4-amino-3-hydroxylamino-5-oxo-1,2,4-triazines (2.4; R_1= Me, Ph)[52] gave the corresponding bicyclic structures (2.5) when heated with carboxylic acids (e.g. formic or acetic acid). The [5,1c] configuration (2.5) was assumed since the derivatives were stable under conditions favourable to a Dimroth transformation.



(2.3) R_1 = H,Me,Ph



(2.5) R = H,Me
R_1 = H,Me,Ph

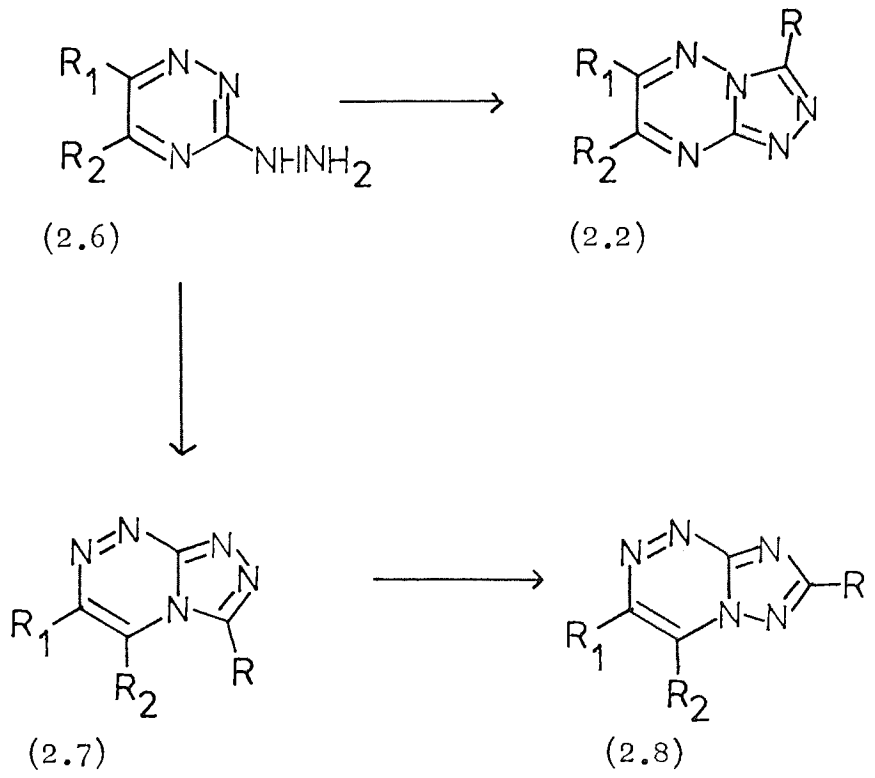


(2.4) R_1 = Me,Ph

(Scheme 2.1)

(3) 3-Hydrazino-1,2,4-triazines

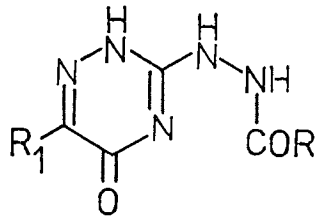
In order to assign the correct ring-structure to the triazolo-triazines resulting from the ring-closure of 3-hydrazino-1,2,4-triazines (2.6) it was necessary to overcome two problems: the first was to determine the direction of cyclization; the second, to detect the possible occurrence of a Dimroth rearrangement. Electrophilic attack at N-2 of the triazine (2.6) would result in the [4,3-b] isomers (2.2) which were predicted to be stable. Participation of N-4 in the cyclization would yield the [3,4-c] isomers (2.7) but these compounds should undergo a Dimroth rearrangement to the 1,2,4-triazolo[5,1-c]-1,2,4-triazines (2.8)



(Scheme 2.2)

In practise, it has been demonstrated that the mode of cyclization is dependent on pH, the cyclizing agent, and the nature of the triazine (2.6).

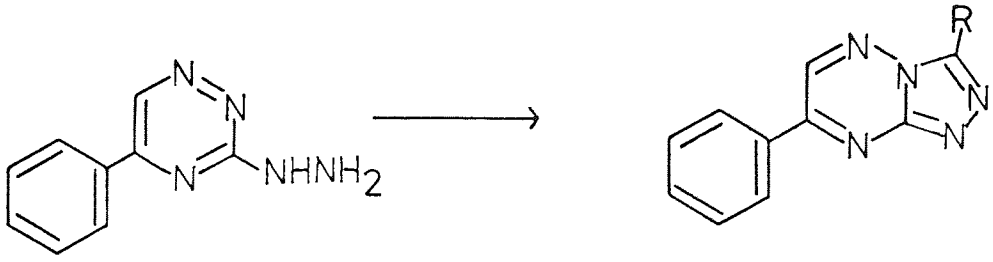
Several publications[53-57] have shown that acid conditions effect cyclization to N-2 except when the hydrazinotriazines (2.6) bear an electron-withdrawing group in the 6-position (e.g. CO_2H, CO_2Me, CO_2Et).[58] Thus when the hydrazinotriazines (2.6; R_1=H,Me or Ph, R_2=OH,Ph) were heated with a carbon-inserting carboxylic acid the corresponding triazolo[4,3-b]triazines (2.2) were formed. In certain cases mild conditions enabled the isolation of the appropriate open-chain carbonyl derivatives (2.9) to be achieved.



(2.9) R= H,Me

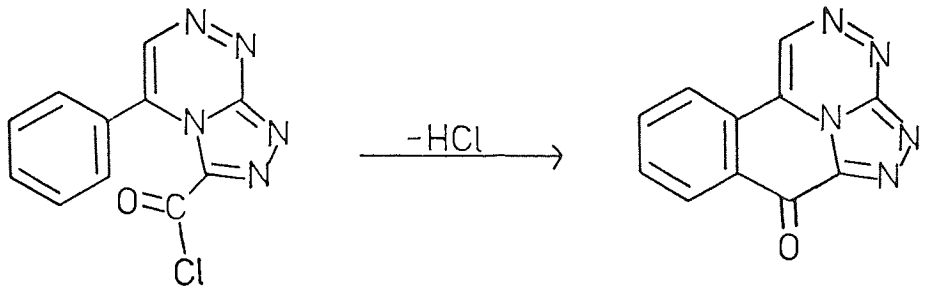
R_1= H,Me,Ph

Evidence supporting the[4,3-b] arrangement (2.2) was obtained by comparing[53,55-57] the products with those from reactions of substituted 3,4-diaminotriazoles (2.1) and the appropriate 1,2-dicarbonyl compounds. Further confirmation was obtained[53] when the hydrazinotriazine (2.10) was cyclized with ethoxyacetyl chloride to give (2.11; R=CH_2OEt) which, after treatment with hydrobromic acid followed by oxidation with potassium permanganate, gave compound (2.11; R=CO_2H).



(2.10) (2.11)

The acid chloride (2.11; R=COCl) was recovered unchanged from Friedel-Craft cyclization conditions and this eliminated the possibility of structure (2.12). The latter would probably have cyclized to (2.13) under Friedel-Craft conditions.

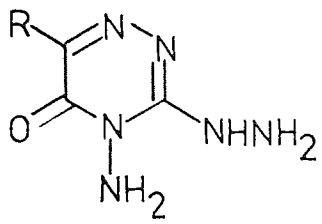


(2.12) (2.13)

However, if cyclization had occurred at N-4, the [3,4-c] isomer initially obtained could possibly have rearranged to the [5,1-c] isomer. The latter product, also, would not undergo a Friedel-Craft reaction.

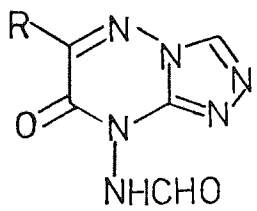
Electrophilic attack at N-4 was excluded with 4-amino-3-hydrazino-1,2,4-triazines (2.14)[59] and it was demonstrated that the triazolo[4,3-b]-triazines (2.16) and not the triazinotetrazines (2.15) resulted on heating (2.14) in excess formic acid. Hydrolysis and deamination of (2.16) yielded (2.17). The same triazolotriazine (2.17; R=Me) was obtained from the reaction of the hydrazinotriazinone (2.18) and formic acid (Scheme 2.3).

Further verification of the [4,3-b] form was found when 7-hydrazino-6-methyl-1,2,4-triazolo[4,3-b]-1,2,4-triazine (2.19) was cyclized unambiguously[60] in formic acid to the di-1,2,4-triazolo-1,2,4-triazine (2.20).



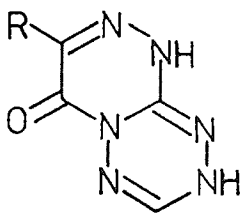
(2.14) a: R = Me
b: R = Ph

$\xrightarrow{2HCO_2H}$

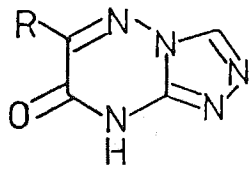


(2.16) a: R = Me
b: R = Ph

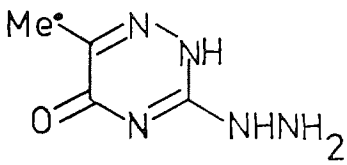
$\not\downarrow$ HCO_2H



(2.15) a: R = Me
b: R = Ph

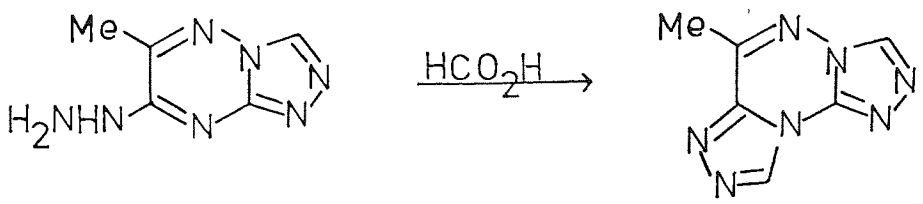


(2.17) a: R = Me
b: R = Ph



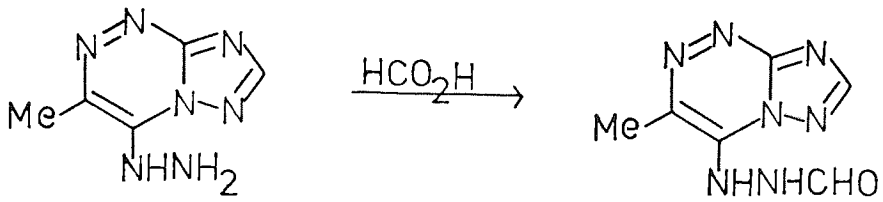
(2.18)

(Scheme 2.3)



(2.19) (2.20)

A logical extension to this work was the reaction of 7-hydrazino-6-methyl-1,2,4-triazolo[5,1-c]-1,2,4-triazine (2.21) under the same reaction conditions; a monoformyl derivative (2.22) proved to be the only product.[61]

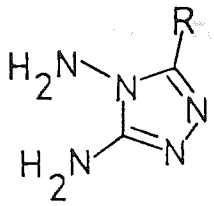


(2.21) (2.22)

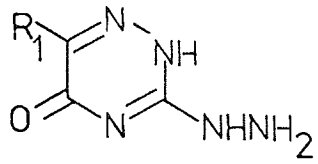
The triazolo[4,3-b]triazines were reported to be stable[56,57] in conditions which normally promote Dimroth rearrangements.

Utilization of esters and orthoesters to cyclize hydrazinotriazines enabled the reactivity of N-2 and N-4 of the triazine to be investigated under neutral conditions.

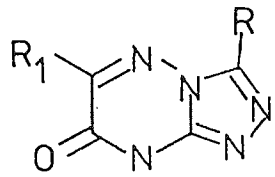
Contrary to the effect in acidic media, the hydrazinotriazines (2.23; R_1=H,Me) formed[57] a mixture of the [4,3-b] (2.24; R=H, R_1=H,Me) and [3,4-c] (2.25; R_1=H,Me) isomers when cyclized with ethyl formate. After separation by fractional recrystallization the [3,4-c] series (2.25) were found to rearrange to the [5,1-c] isomers (2.26; R_1=H,Me)



(2.1)

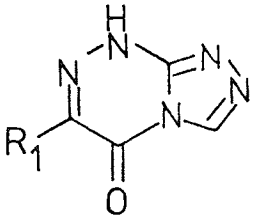


(2.23) R_1 = H,Me Ph

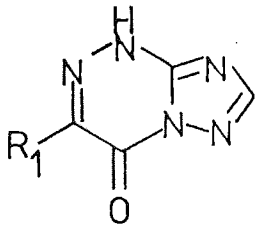


(2.24) R = H,Me

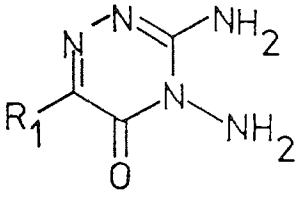
R_1 = H ,Me,Ph



(2.25) R_1 = H,Me



(2.26) R_1 = H,Me

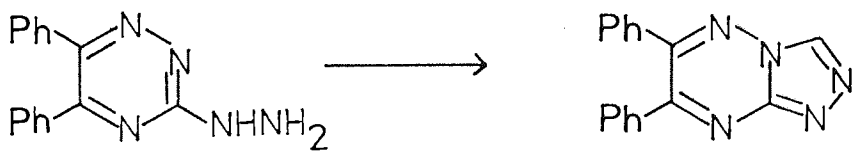


(2.3) R_1 = H,Me

(Scheme 2.4)

under acidic or thermal conditions. Confirmation of the [5,1-c] arrangement in structure (2.26) was given by their unequivocal synthesis from the 3,4-diamino-1,2,4-triazinones (2.3; R_1=H,Me) and formic acid. Similarly corroboration for the [4,3-b] orientation (2.24) was found by synthesizing the identical compounds from the 3,4-diamino-1,2,4-triazole (2.1; R=H) and the appropriate 1,2-dicarbonyl compounds. Cyclization of the triazines (2.23; R_1=H,Me), although not accomplished with ethyl acetate, gave only the [4,3-b] isomers (2.24; R=Me, R_1=H,Me) with triethylorthoacetate (Scheme 2.4).

The hydrazinotriazines (2.23; R_1=Ph) and (2.27) yielded only the [4,3-b] isomers (2.24; R=H, R_1=Ph) and (2.28) respectively when cyclized under acidic or neutral conditions.[56,57]



(2.27) (2.28)

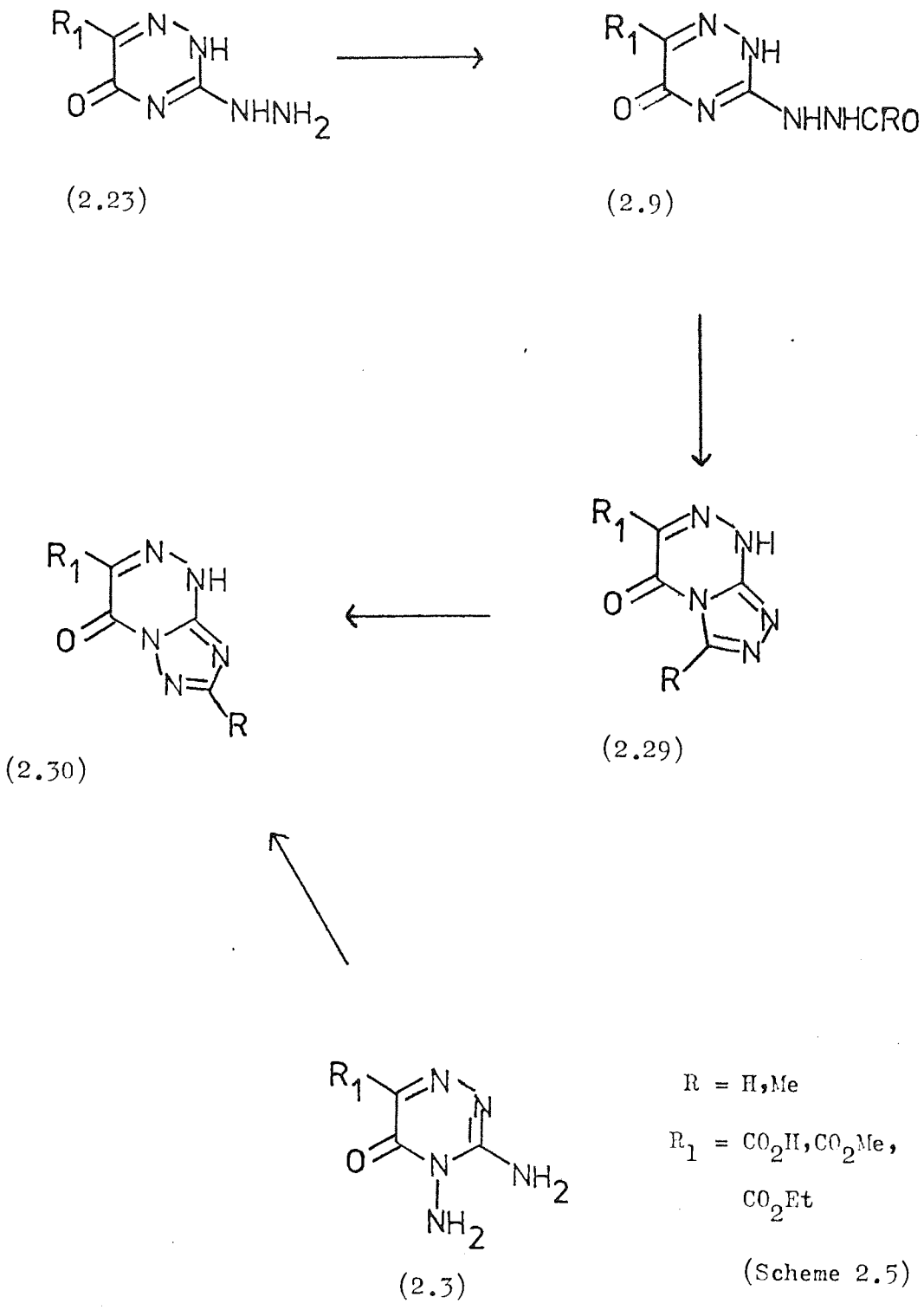
Again the [4,3-b] arrangement was confirmed[56,57] by synthesis from the alternative route (i.e. diaminotriazole with the appropriate 1,2-dicarbonyl compounds).

Electron-withdrawing groups in the 6-position of the triazine (2.23; R_1=CO_2H,CO_2Me,CO_2Et) caused a difference in the reactivity of the ring nitrogens.[58] The acylated intermediates (2.9; R=H,Me, R^1=CO_2H, CO_2Me,CO_2Et) resulted when the hydrazino-triazines (2.23; R_1=CO_2H,CO_2Me, CO_2Et) were stirred at room temperature with formic or acetic acids,

triethylorthoformate or ethylorthoacetate. Each of the intermediates (2.9) afforded a mixture[58] of the [3,4-c] (2.29; R=H,Me, R_1=CO_2H,CO_2Me, CO_2Et) and [5,1-c] (2.30; R=H,Me, R_1=CO_2H,CO_2Me,CO_2Et) isomers when heated in neutral or acidic conditions (Scheme 2.5). Prolonged reaction time yielded an increase in the proportion of the rearranged [5,1-c] series (2.30) at the expense of the corresponding [3,4-c] isomers (2.29). It was verified after separation of the two isomers that the [3,4-c] compounds (2.29) were converted quantitatively to the [5,1-c] isomers (2.30) under the cyclizing conditions. The [5,1-c] isomers (2.30) were prepared unequivocally from the appropriate 3,4-diaminotriazines (2.3; R_1=CO_2H,CO_2Me,CO_2Et) and the corresponding ester (Scheme 2.5).

It was concluded[58] that the electron-withdrawing groups on the triazines (2.23; R_1=CO_2H, CO_2Me, CO_2Et) had diminished the electron density on N-2 to a greater extent than N-4 because the triazolo[4,3-b]-triazines were not isolated. In comparison[21,41] with other fused 1,2,4-triazole systems the electron-withdrawing groups apparently facilitated rearrangement of the [3,4-c] isomers (2.29) to the [5,1-c] isomers (2.30).

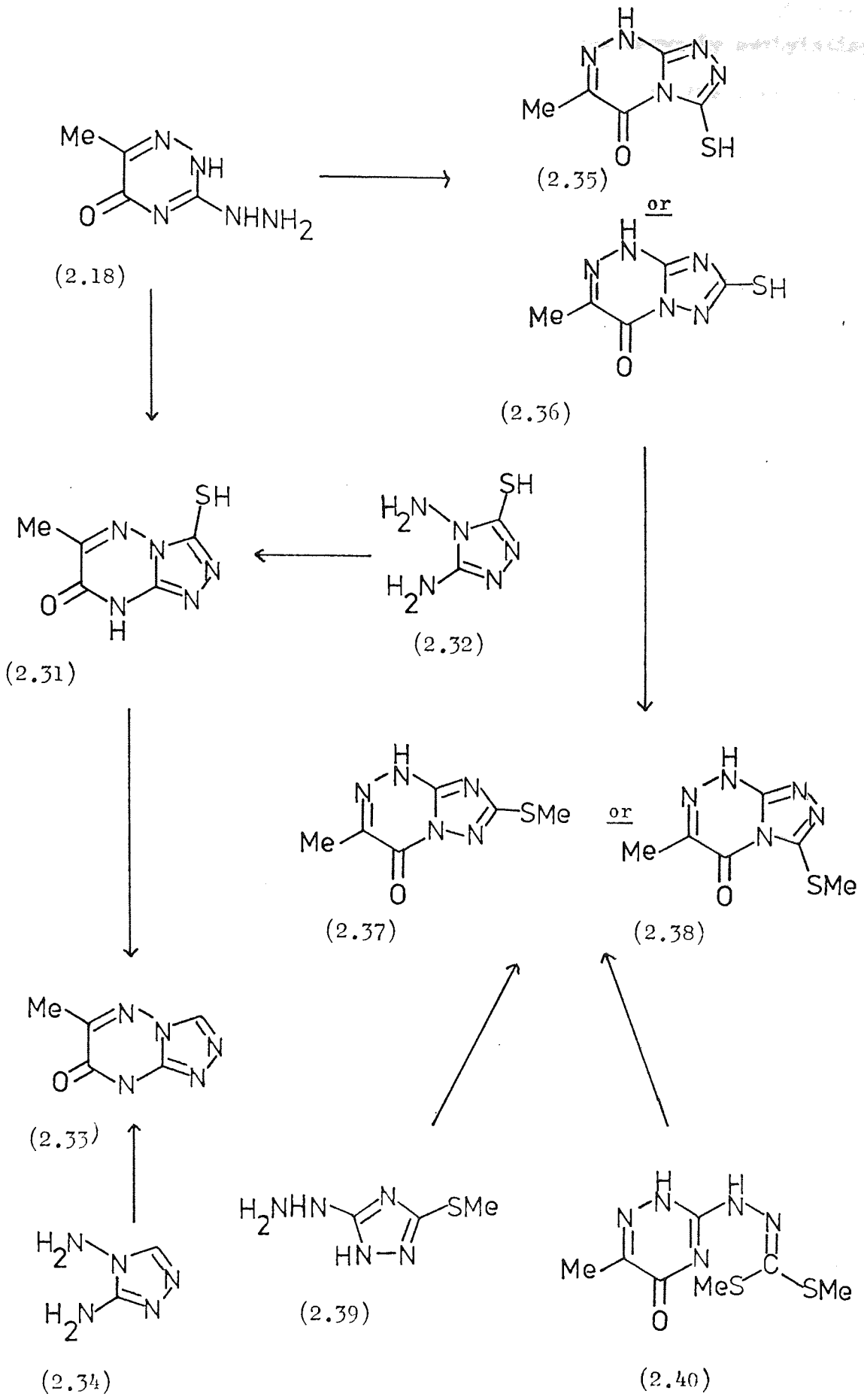
Evidence for the participation of both N-2 and N-4 of the triazine ring was discerned when carbon disulphide was used to cyclize the hydrazinotriazine (2.18) [62] (Scheme 2.6). The triazolo[4,3-b] triazine (2.31) precipitated from the reaction and was shown to be identical[55,63] to the compound formed from 3,4-diamino-5-mercapto-1,2,4-triazole and pyruvic acid. Furthermore, Raney nickel desulphuration of the 3-mercapto-triazolo[4,3-b]-triazine (2.31) gave (2.33) which was shown to be identical to the product formed from the condensation of 3,4-diamino-triazole (2.34) and pyruvic acid.[55] Either the triazolo[3,4-c]-1,2,4-triazinone (2.35) or the [5,1-c] isomer (2.36) was isolated[62] from the filtrate. No attempt was made to differentiate between the two isomers



R = H,Me

R_1 = CO_2H, CO_2Me, CO_2Et

(Scheme 2.5)


Me
NH
NHNH2
(2.18)
(2.35)
or
(2.36)
SH
(2.31)
(2.32)
SMe
(2.37)
(2.38)
(2.33)
(2.34)
H2NHN
(2.39)
MeS
(2.40)

(Scheme 2.6)

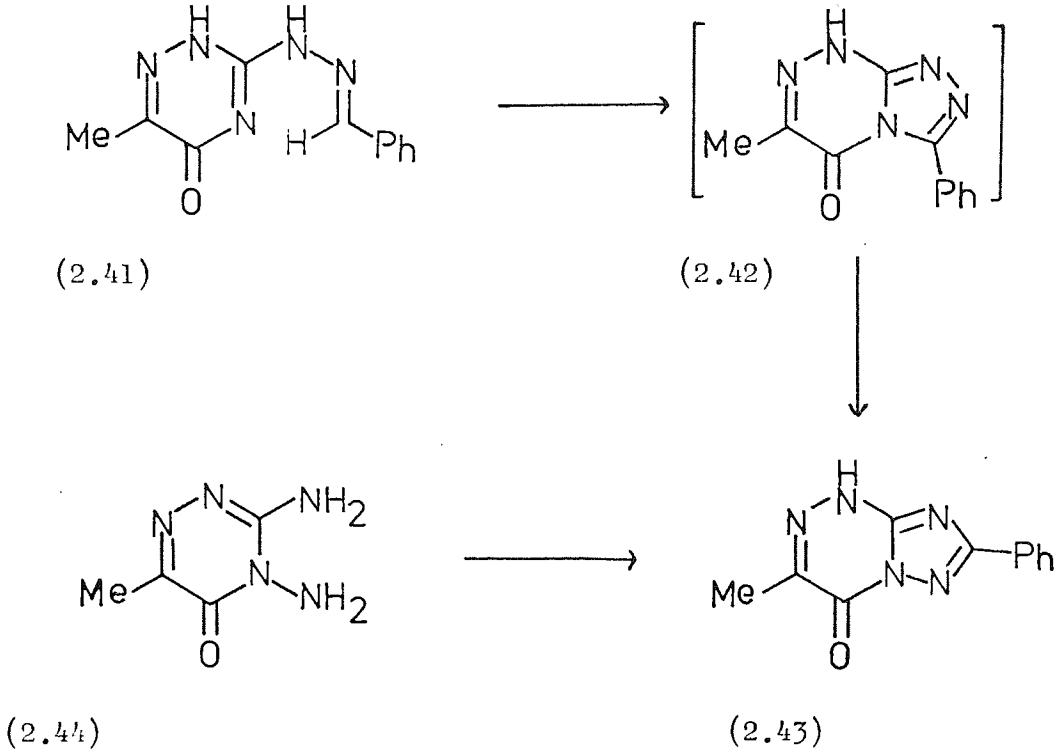
but involvement of N-4 in the cyclization was shown by methylating the product obtained and demonstrating its identity to the condensation product (2.37) or (2.38) of 3-hydrazino-5-methylthio-1,2,4-triazole and ethyl pyruvate.[62] Heating the hydrazone (2.40) above its melting point provided another route[62] to this triazolo-triazine (2.37) or (2.38) (Scheme 26). It is of interest that the [4,3-b] isomer was not detected in this fusion reaction.

Another example of attack at N-4 of the triazine was found in the oxidative cyclization[57] of the hydrazone (2.41) in bromine or lead tetracetate; a 20% yield of the triazolo[5,1-c]triazine (2.43) was recorded. The product was identified by unequivocal synthesis from 3,4-diaminotriazinone (2.44) and benzoyl chloride. Therefore it is reasonable to assume the hydrazone (2.41) cyclized first to the [3,4-c] isomer (2.42) which then rearranged to the more stable [5,1-c] arrangement (2.43) under the acid conditions of the reaction (Scheme 27).

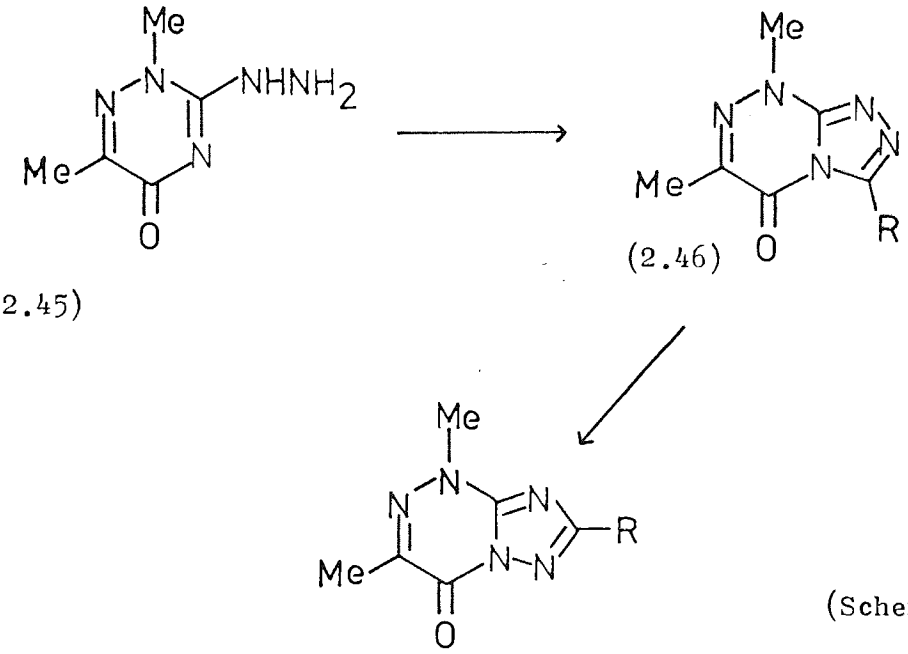
Cyclization to N-4 was obligatory[57,64] when the 2-methyl-3-hydrazino-1,2,4-triazinone (2.45) was heated with a carboxylic acid. The [3,4-c] isomers (2.46; R=H,Me) were isolated in neutral conditions (ethylformate or ethylorthoacetate)[57] while only the rearranged triazolo[5,1-c]triazines (2.47; R=H,Me) were isolated in acidic conditions (Scheme 2.8).[57] These two isomers could be compared with the third isomer of the [4,3-b] configuration which was synthesized *via* 4,6-dimethyl-5-hydroxy-3-methylmercapto-1,2,4-triazine.[57]

(4) 3-Hydrazino-1,2,4-triazoles

The synthesis of 1,2,4-triazolo-1,2,4-triazines from 3-hydrazino-1,2,4-triazoles (2.48) has been comparatively little studied. Direction of cyclization may involve either N-1 or N-4 of the triazole and there



(Scheme 2.7)

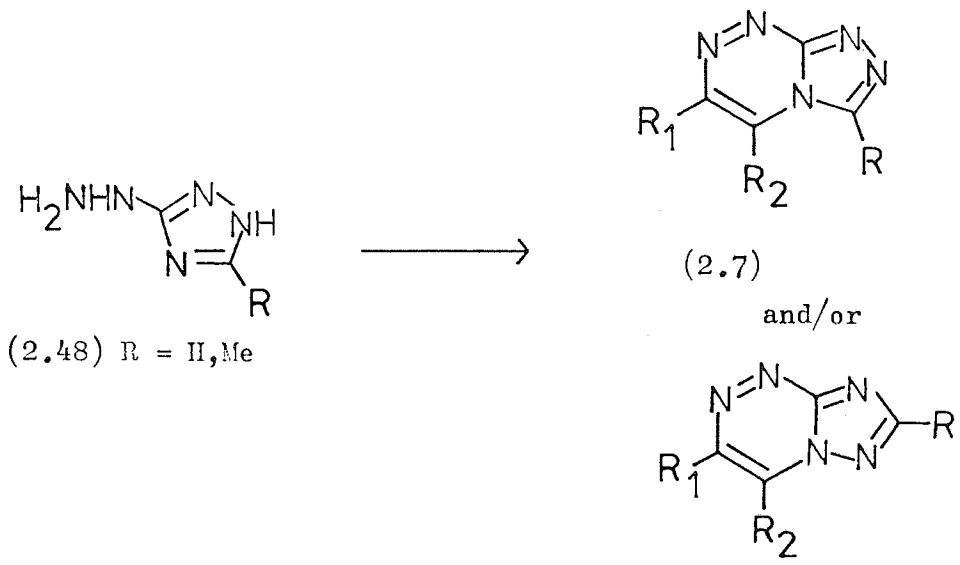


R = H,Me

(Scheme 2.8)

is a possibility of a Dimroth rearrangement.

A publication[62] illustrated the use of 3-hydrazinotriazoles (2.48) and 1,2-dicarbonyl compounds in the synthesis of triazolotriazines but made no attempt to differentiate between the [3,4-c] series (2.7) or the [5,1-c] isomers (2.8) (Scheme 2.9).

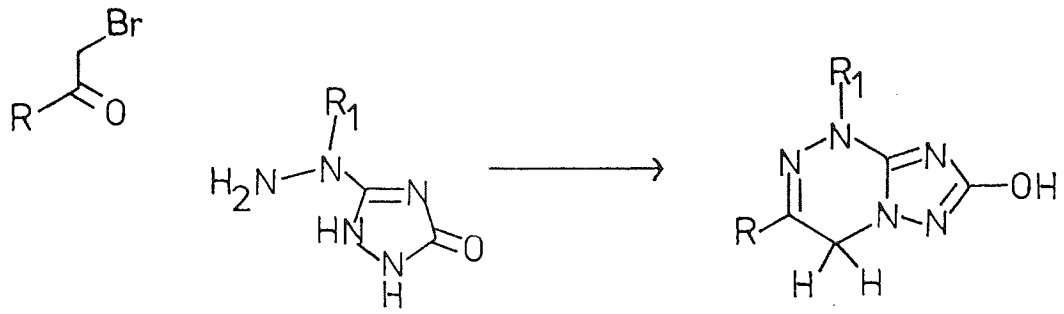


(Scheme 2.9)

A later report demonstrated[65] that triazolo[5,1-c] triazines (2.8; R=H,Me) were the products formed from the condensation of hydrazinotriazoles with ethylpyruvate. The [5,1-c] configuration was confirmed by unequivocal synthesis from 3,4-diamino-6-methyl-1,2,4-triazin-5(4H)-one and ethylorthoformate. It was acknowledged that the [3,4-c] isomers (2.7) could have been intermediates in the synthesis from the hydrazinotriazoles (2.48).

α-Haloketones were reported[66] to react with 3-hydrazino-1,2,4-triazolones (2.49) to yield 2-hydroxy-6-(R-substituted)-4-(R'-substituted)-7H-1,2,4-triazolo[5,1-c]-1,2,4-triazines (2.50) but no evidence was

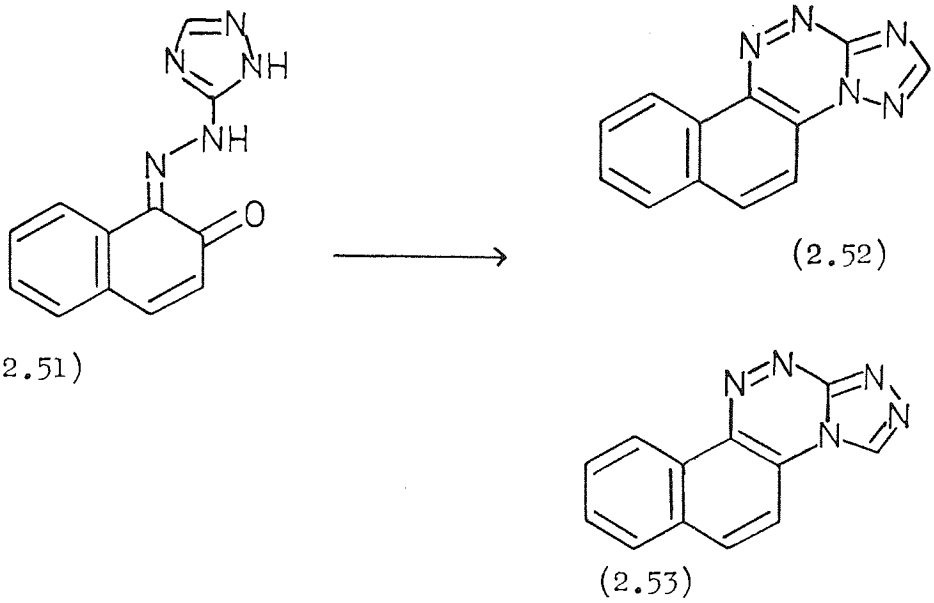
given to support this structure.



(2.49) (2.50)

Naphtho[2,1-e]-1,2,4-triazolo[5,1-c]-1,2,4-triazin-2-carboxylic acid was claimed to be the product from coupling 3-diazo-1,2,4-triazol-5-carboxylic acid and β-naphthylamine but no evidence was given to exclude the [3,4-c] isomer.[67]

A similar coupling reaction was investigated more fully when 3-diazo-1,2,4-triazole was coupled[68] with β-naphthol. The coupling product (2.51) was cyclized either in glacial acetic acid or by prolonged boiling in methanol to naphtho[2,1-e]-1,2,4-triazolo[5,1-c]-1,2,4-triazine (2.52). When heated under reflux in methanol with some concentrated sulphuric acid the hydrazone (2.51) yielded a mixture of the [3,4-c] (2.53) and [5,1-c] (2.52) isomers. They were separated by column chromatography and differentiated by their ^{1}H n.m.r. spectra. The [3,4-c] isomer (2.53) was stable under conditions favourable to a Dimroth rearrangement (e.g. boiling glacial acetic acid or ethylene glycol) but similar tests on the [5,1-c] isomer (2.52) were not reported.



(2.51) (2.52) (2.53)

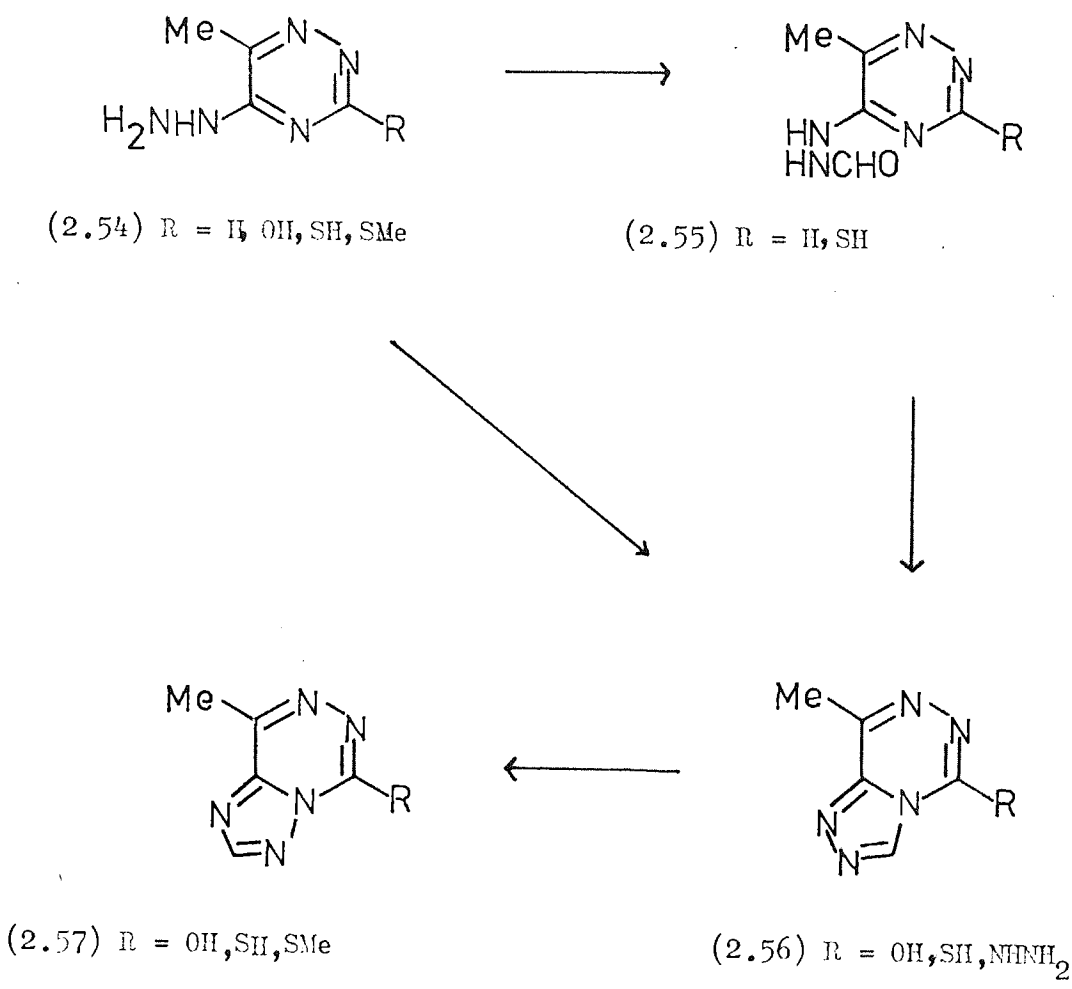
(Scheme 2.10)

(5) 5-Hydrazino-1,2,4-triazines

There have been several publications[60,61,69-73] concerning the synthesis of 1,2,4-triazolo [4,3-d]- 1,2,4-triazines (2.56) from 5-hydrazino-1,2,4-triazines (2.54).

The lability towards nucleophilic substitution of the 5-alkylthio group in comparison to the 3-[70,73] and 6-[73] alkylthio groups of 1,2,4-triazines proved useful in the synthesis of the required 5-hydrazino-triazines. Cyclizing (2.54) with the aid of a carbon-inserting agent (e.g. a carboxylic acid, ester or carbon disulphide) can effect cyclization at only N-4 in contrast to the 3-hydrazino-1,2,4-triazines. However, after the formation of the triazolo[4,3-d] triazine (2.56) there is a possibility that the 4,5-bond could break and that recyclization could occur at N-1 of the triazole resulting in the[1,5-d] isomer (2.57) (Scheme 2.11).

In practise, it was found[61] that the triazolo[4,3-d] triazines (2.56; R=OH,SH) were isolated when the 5-hydrazinotriazines (2.54; R=OH, SH) were reacted under mild conditions in formic acid, but that they



(2.54) R = H, OH, SH, SMe

(2.55) R = H, SH

(2.56) R = OH, SH, $NHNH_2$

(2.57) R = OH, SH, SMe

(Scheme 2.11)

rearranged on heating to the corresponding [1,5-d] isomers (2.57)[61]. The 5-hydrazino-3-mercapto-triazine (2.54; R=SH) cyclized[61] at a slower rate than the corresponding 3-hydroxy compound (2.54; R=OH) due to a diminished reactivity of N-4 caused by the adjacent sulphur atom. In addition, the rate of rearrangement to the [1,5-d] isomer (2.57 ;R=SH) was also decreased when the mercapto group was present. Cyclization did not occur when 5-hydrazino-6-methyl-1,2,4-triazine (2.54; R=H) was reacted[61] in formic acid; the formyl derivative (2.55; R=H) was the only product isolated.

An interesting difference in the rate of cyclization was noted when 3-hydroxy-5-hydrazino-6-methyl-1,2,4-triazine (2.54; R=OH) gave the cyclized product (2.56; R=OH) in formic acid at room temperature[61] whereas 3-hydrazino-5-hydroxy-6-methyl-1,2,4-triazine (2.23; R=Me) afforded the formyl derivative (2.9; R=H, R_1=Me) under the same conditions.

Degradation products were obtained when the synthesis of 8-methyl-5-methylthio-1,2,4-triazolo[1,5-d]-1,2,4-triazine (2.57; R=SMe) was attempted from each of the following routes:- (1) Cyclization of 5-hydrazino-6-methyl-3-methylthio-1,2,4-triazine (2.54; R=SMe) in formic acid ; (2) Methylation of 5-mercapto-8-methyl-1,2,4-triazolo[4,3-d] - 1,2,4-triazine (2.56; R=SH), followed by attempted rearrangement in various acids ; (3) Methylation of 5-mercapto-8-methyl-1,2,4-triazolo - [1,5-d] -1,2,4-triazine (2.57; R=SH).

In addition to synthesizing the tricyclic triazine (2.20) from 7-hydrazinotriazolo[4,3-b]-triazine (2.19) as previously described, the compound (2.20) was also obtained by cyclizing 3,5-dihydrazino-6-methyl-1,2,4-triazine and 5-hydrazino-8-methyl-1,2,4-triazolo[4,3-d] -1,2,4-triazine (2.56; R=$NHNH_2$) in formic acid.[61] The strong evidence shown for the configuration of (2.20) demonstrated that ring closure of (2.56; R=$NHNH_2$) in formic acid was more rapid than rearrangement to the

[1,5-d] isomer. However, the apparent instability of 8-methyl-5-methylthio-1,2,4-triazolo[1,5-d]-1,2,4-triazine (2.57; R=SMe) raises doubts concerning the stability of the [1,5-d] isomers of compounds (2.20) and (2.56; R=$NHNH_2$).

The reaction of 5-hydroxy-3-mercapto-6,6-dimethyl-1,6-dihydro-1,2,4-triazine with hydrazine and the subsequent ring closure with formic acid gave 5-mercapto-8,8-dimethyl-7,8-dihydro-1,2,4-triazolo[4,3-d]-1,2,4-triazine which was thermo-stable.[72]

(6) 4-Amino-1,2,4-triazoles

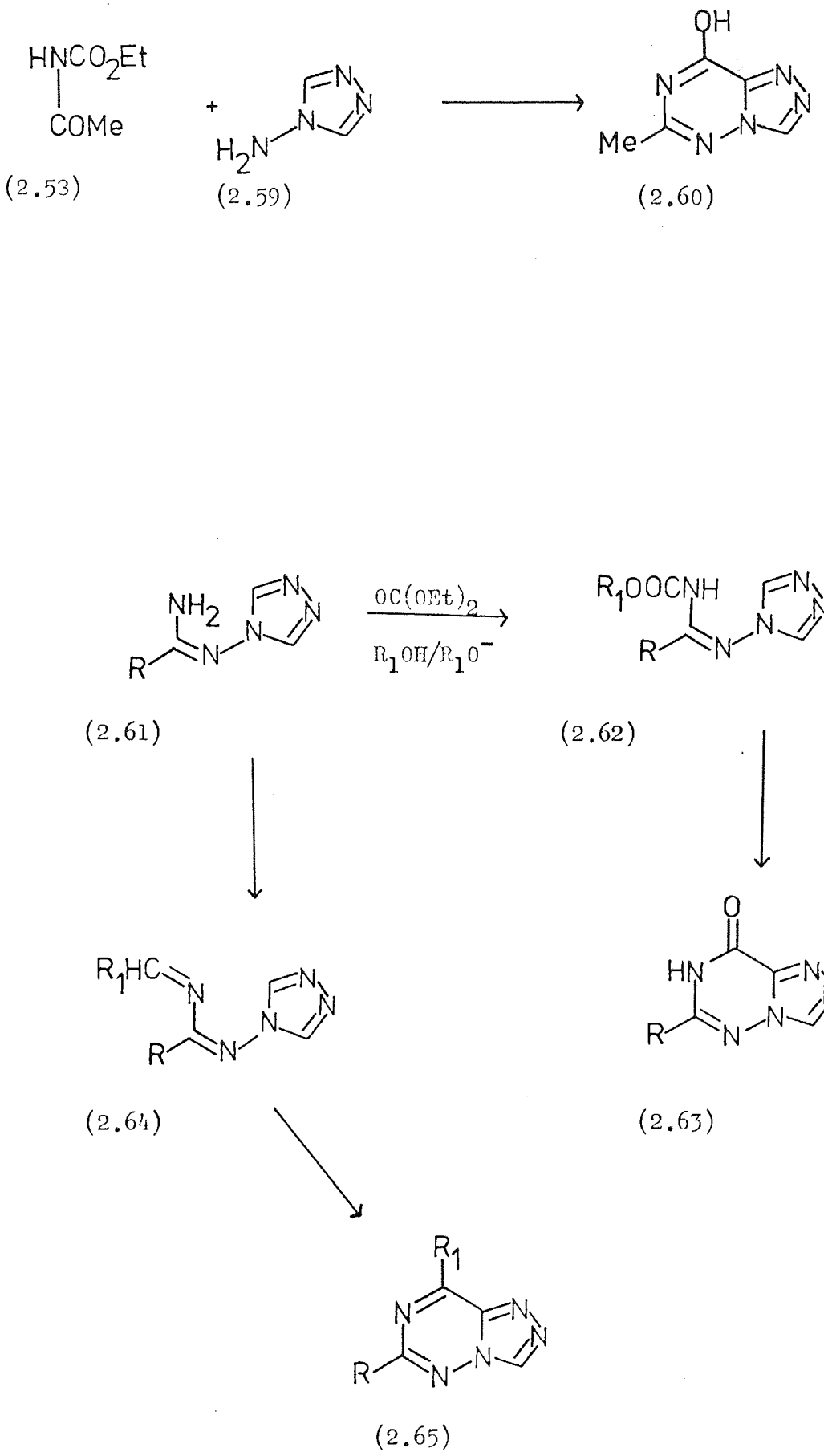
The preparation of the 1,2,4-triazolo[3,4-f]-1,2,4-triazine (2.60) from (2.58) and the 4-amino-1,2,4-triazole (2.59) has been suggested[74] but no further information was available.

Triazolylamidines (2.61) were cyclized[75] with diethylcarbonate and sodium alkoxide in butanol to yield 1,2,4-triazolo[3,4-f]-1,2,4-triazines (2.63) via the carbalkoxyamidine intermediates (2.62). The [3,4-f] derivatives (2.65) were also synthesized directly by cyclizing the triazolylamidines (2.61) with triethylorthoformate or indirectly via the intermediate (2.64).

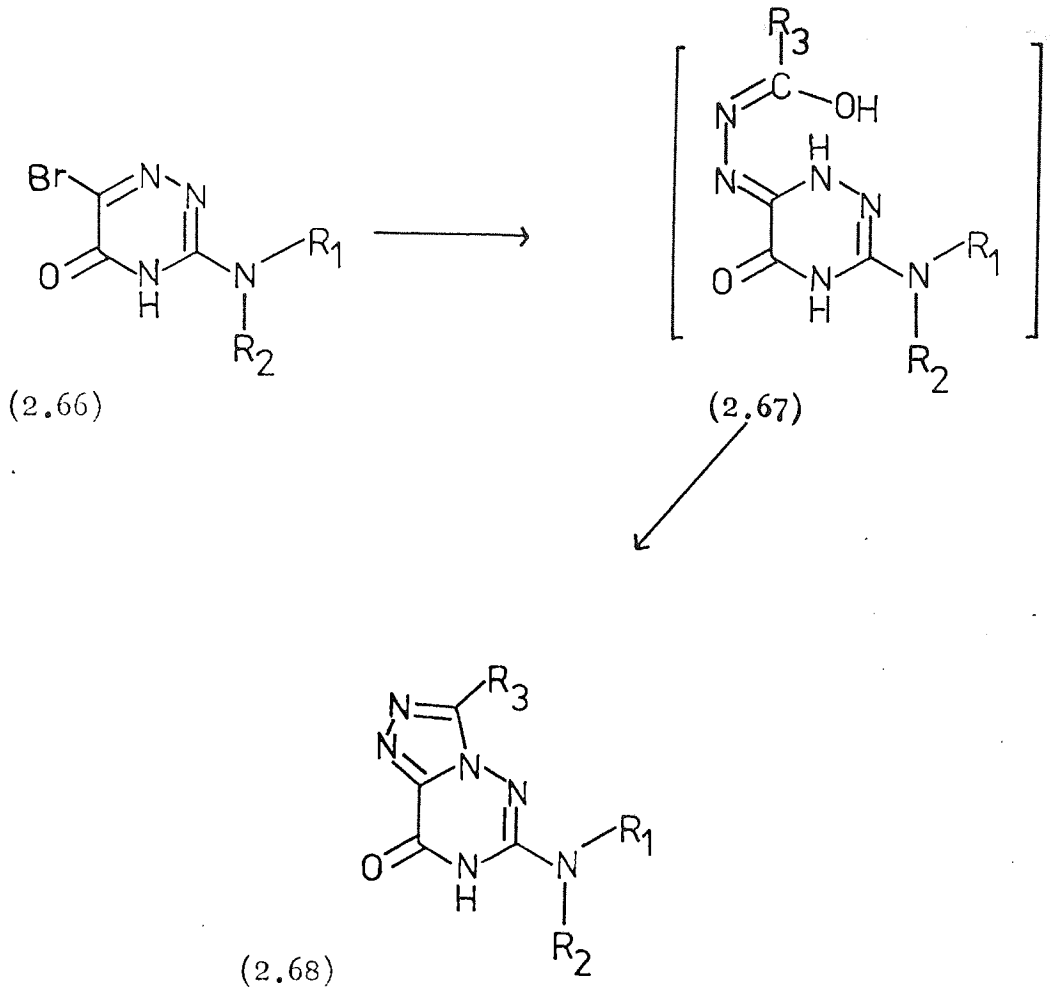
It is pre-supposed that these triazolo[3,4-f]-triazines (2.63) and (2.65) will be stable under conditions favourable towards Dimroth rearrangements because such a reaction would involve highly unlikely fission of an N-N bond. In agreement with the theory, isomerizations of these compounds have not been reported.

(7) 6-Bromo-1,2,4-triazines

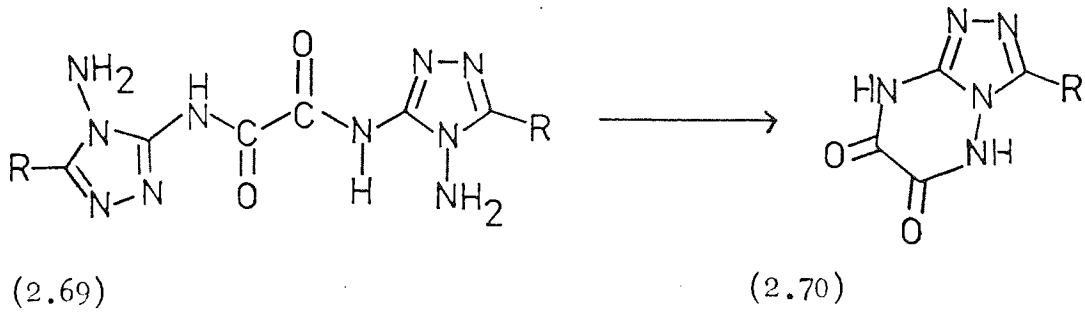
An alternative route to substituted 1,2,4-triazolo[3,4-f]-1,2,4-triazines (2.68) was illustrated[76] by the nucleophilic attack of hydrazides (R^3-$CONHNH_2$) on 6-bromo-1,2,4-triazines (2.66). The bicyclic compound (2.68) was obtained directly via the non-isolable substituted triazine hydrazone intermediate (2.67).


HNCO2Et
COMe
(2.53)
+
H2N
(2.59)
OH
Me
(2.60)
NH2
R
(2.61)
OC(OEt)2
R1OH/R1O−
R1OOCNH
R
(2.62)
R1HC
R
(2.64)
O
HN
R
(2.63)
R1
R
(2.65)

(Scheme 2.12)


Br
N
N
O
N
H
N
R1
R2
(2.66)
R3
C
OH
N
N
H
N
N
O
N
H
N
R1
R2
(2.67)
R3
N
N
N
N
O
N
H
N
R1
R2
(2.68)

(Scheme 2.13)


NH2
N
R
N
N
H
N
C
O
C
O
N
H
N
N
N
R
NH2
(2.69)
HN
N
N
R
O
NH
O
(2.70)

(8) Other routes

Derivatives of the 1,2,4-triazolo[4,3-b]-1,2,4-triazin-6,7-diones (2.70) were prepared[77] from the triazole dimer (2.69) and they were found to have the same melting points as the triazolotriazines prepared from 3,4-diamino-1,2,4-triazoles and diethyloxalate.[78]

B. DISCUSSION OF EXPERIMENTAL RESULTS

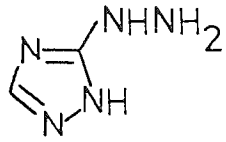
Part III

Synthesis and characterization of 1,2,4-triazolo[5,1-c]- and pyrazolo[5,1-c]-1,2,4-triazines from hydrazines.

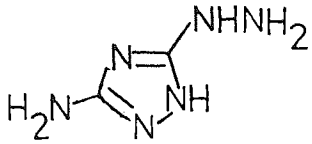
(1) Synthesis of 3-hydrazino-1,2,4-triazole and 3-amino-5-hydrazino--1,2,4-triazole

The hydrazino- (3.1) and aminohydrazino-triazole (3.2) were indispensable in schemes designed for the formation and characterization of diphenyltriazolotriazines. Unexpected difficulties were encountered in the synthesis of these triazoles: a standard hydrazine preparation involving reduction of the appropriate diazonium salts was attempted from the readily available amino- and diamino-triazoles.

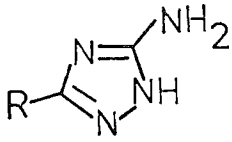
A number of diazonium salts (3.4) (e.g. chlorides, tetrafluoroborates, perchlorates and nitrates) have been prepared[79] from the diazotization of amino-1,2,4-triazoles (3.3); the ring N-H is reported to be highly acidic.[79] Diazotization of the 4-N-substituted aminotriazoles (3.5a) with sodium nitrite and dilute hydrochloric acid gave the triazenes (3.6a) but over a prolonged period in more concentrated acid (20%), 3-chlorotriazoles (3.7a) were formed, while stable primary nitrosoamines (3.8a) were isolated after 30 minutes in 18% hydrochloric acid.[80] Characterization of the nitrosoamines (3.8a) has included[80] analysis, positive Liebermann tests, reduction to hydrazines under mild conditions with zinc in acetic acid, and azo-coupling reactions with NN-dimethylaniline in acidic alcoholic solutions. Thus direct evidence is provided for the proposition that primary nitrosoamines are intermediates in the diazotization of carbocyclic aromatic amines.



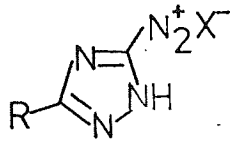
(3.1)



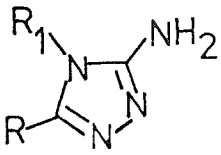
(3.2)



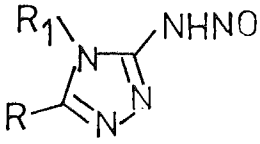
(3.3) R = Alk,Ar



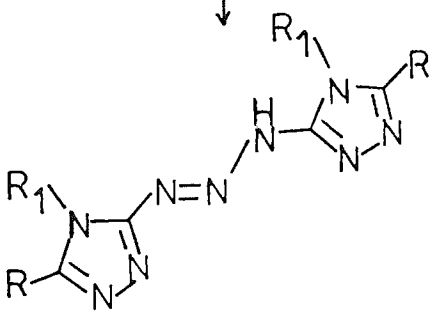
(3.4)



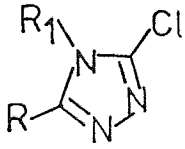
(3.5)



(3.8)



(3.6)



(3.7)

a: R = Alk; R_1 = Ar

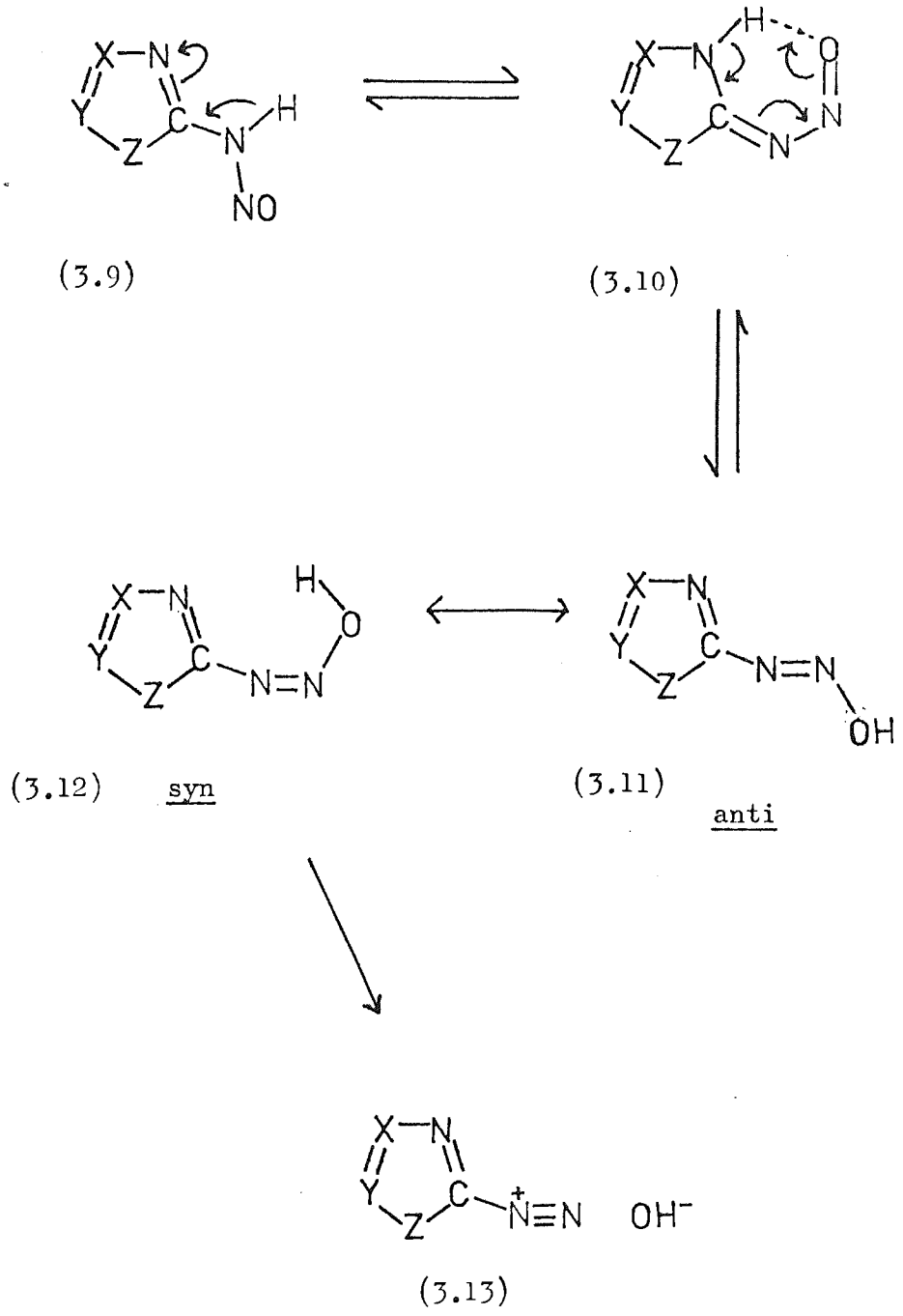
b: R = H; R_1 = H

c: R = NHNO; R_1 = H

(Scheme 3.1)

Possible tautomers of azole nitrosoamines are depicted in (Scheme 3.2). Spectroscopic evidence confirms[79,81] contributions from (3.9) and the diazohydroxide (3.11) and/ or (3.12) but excluded the imino-form (3.10). The possibility of syn-anti isomerization of the diazohydroxide has not been investigated. Formation of nitrosoamines, previously considered unstable, can be envisaged if sequence (3.9) to (3.13) (Scheme 3.2) is impeded prior to diazonium formation. The syn-diazohydroxide (3.12), stabilized by intramolecular H-bonding, would be a favoured blocking-point; labile protons undergoing annular tautomerism would disrupt this stabilization thereby facilitating diazonium formation. Strong acid may similarly prevent stabilization of the syn-diazohydroxide (3.12) by protonating not only the nitrosoamino moiety but also the cyclic imine linkage although protonation of these 5-membered systems in relatively dilute acid has not been investigated. Electron-withdrawing substituents or rings favour the isolation of primary nitrosoamines and this is reflected in these compounds being more ubiquitous in the higher azoles. Isolation of nitrosoamines from benzenediazoates with an electron-withdrawing p-substituent was suggested on spectroscopic grounds but definite assignments could not be made due to the instability and impurity of the products.[79]

An apparent exception to the theory of nitrosoamine formation is recorded in the isolation of the mono- and di-nitrosoamino-1,2,4-triazoles (3.8b and c).[82,83] However transformations employed in their characterization would also be possible by invoking a triazene intermediate; the mononitrosoamine (3.8b) formed the diazonium ion in concentrated hydrochloric acid and the dinitrosoaminotriazole (3.8c) was reduced in concentrated acid with stannous chloride to the hydrazine (3.2). Although this afforded an efficient route to one of the required hydrazines (3.2) the anomaly should be further examined.

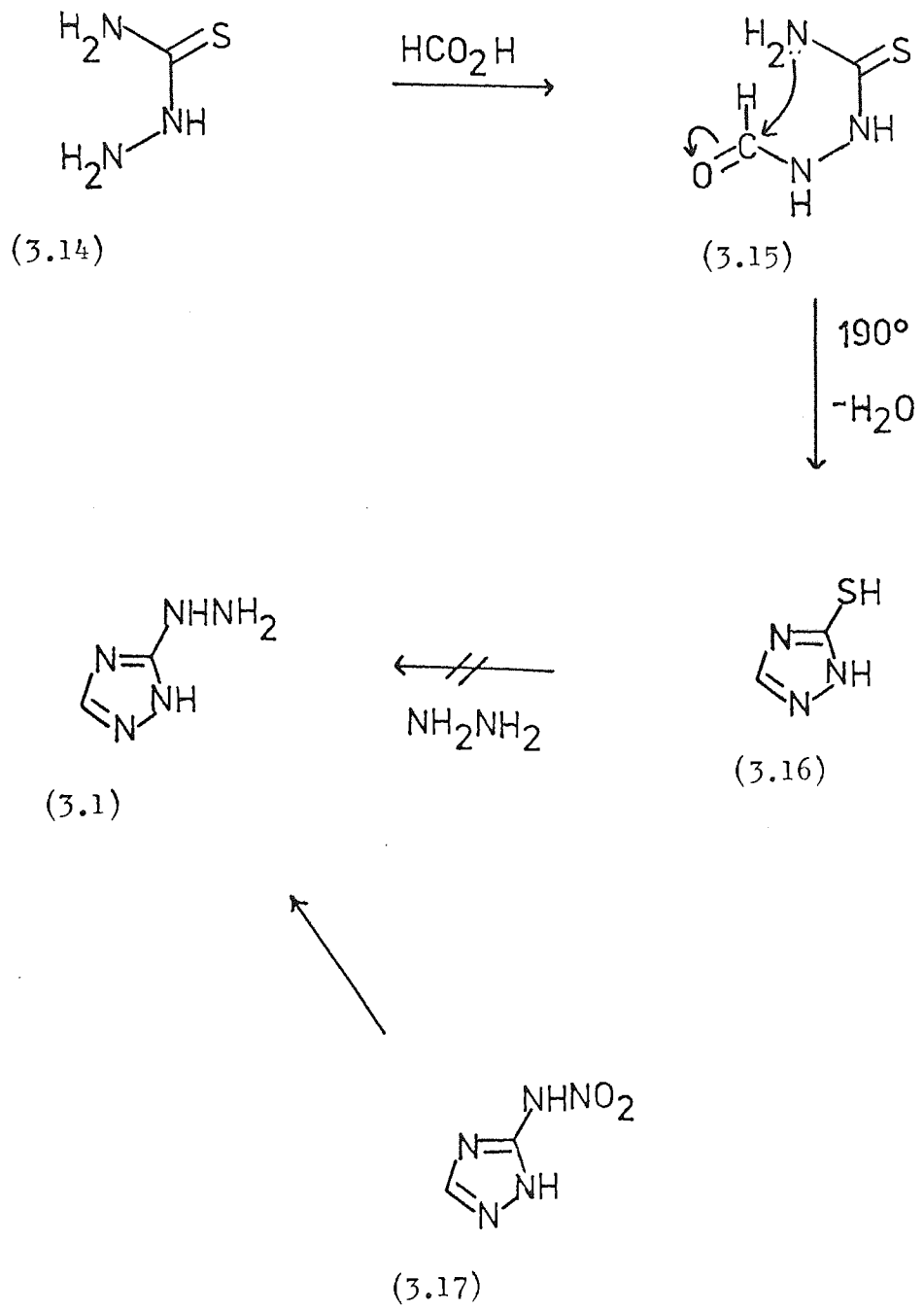


(Scheme 3.2)

A similar preparation of 3-hydrazino-1,2,4-triazole hydrochloride (3.1) proved successful on only one occasion. The yellow precipitate from diazotizing 3-aminotriazole was not a diazonium salt (no i.r. absorption at 2200-2300cm^{-1}) and because it has a labile triazole proton it is unlikely to be a nitrosoamine. Instability and insolubility in most solvents impeded attempts to purify the yellow precipitate, and its unreliable reduction indicated a mixture of varying proportions may be formed containing e.g. the diazoamino compound, 3-chlorotriazole or 3-hydroxytriazole. The instability of triazole diazonium salts,[84] particularly the chloride,[85,86] is well-known and this was further illustrated when attempted diazotization of 3-aminotriazole in alcoholic hydrochloric acid (7N) with amyl nitrite resulted in a substantial yield of 3-chlorotriazole (3.7b).

Further unsuccessful attempts to prepare 3-hydrazinotriazole (3.1) included the use of zinc and acetic acid to reduce the yellow precipitate described above; reduction of 2H-1,2,4-triazol-3-yldiazonium nitrate with sodium sulphite; and nucleophilic displacement of the 3-thiol (3.16) with hydrazine (Scheme 3.3). It was appreciated that the latter could be difficult due to the electron-rich azole ring. This difficulty experienced in attempted nucleophilic substitution of the triazole even under forcing conditions is in accord with the reported[87] synthesis of 3-hydrazinotriazole from the 3-chloro derivative and excess hydrazine under pressure.

Eventually, a successful synthesis of 3-hydrazinotriazole (3.1) was achieved by reduction of the readily available 3-nitroaminotriazole[88] (3.17) with zinc in acetic acid.


H2N
S
NH
H2N
(3.14)
HCO2H
H2N
S
H
C
O
N
H
NH
(3.15)
190°
-H2O
SH
N
NH
N
(3.16)
NH2NH2
NHNH2
N
NH
N
(3.1)
NHNO2
N
NH
N
(3.17)

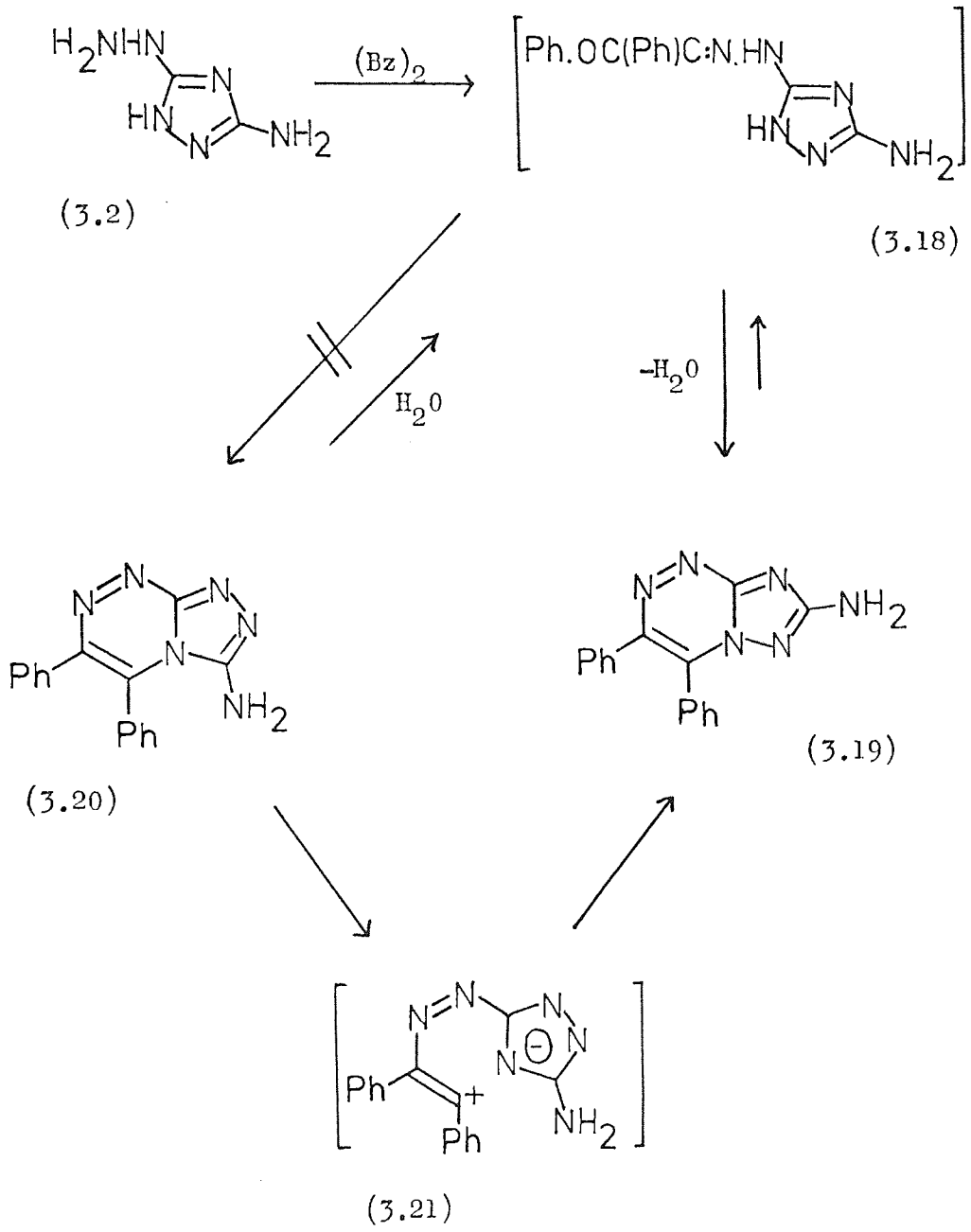
(Scheme 3.3)

(2) 2-Amino-6,7-diphenyl-1,2,4-triazolo [5,1-c]-1,2,4-triazine.

3-Amino-5-hydrazino-1,2,4-triazole dihydrochloride (3.2)and benzil yielded a single pale yellow product when heated under reflux in ethanol or methanol with or without sodium acetate. The i.r. (KBr) spectrum portrayed ν N-H at 3470 and 3350cm^{-1}, and ν C=N at 1620cm^{-1} consistent with an aminotriazolotriazine structure. Further characterization was afforded by the preparation of mono- and diacetyl- derivatives; both showed spectroscopic (i.r., u.v. and n.m.r.) and analytical data consistent with acetylation on the exocyclic nitrogen.

Two isomeric triazolotriazines could be formed in this reaction. The triazolo[5,1-c] triazine (3.19) would result from cyclization of the presumed intermediate hydrazone (3.18) to N-1 of the triazole while involvement of N-4 would yield the [3,4-c] isomer (3.20) (Scheme 3.4). Strong evidence (see Part I) suggests that such a [3,4-c]isomer (3.20) would rearrange to the [5,1-c]isomer (3.19). A quantitative recovery of the initial triazolotriazine from conditions favourable to a Dimroth rearrangement (e.g. heat, boiling acetic acid, pyridine and piperidine) proved substantial evidence for the [5,1-c] skeletal arrangement (3.19).

Although the [3,4-c] isomer (3.20) was not detected (t.l.c.) at any stage, the triazolo[5,1-c] triazine (3.19) could have resulted by a rapid Dimroth rearrangement via the zwitterionic intermediate (3.21) or (3.18) in aqueous conditions. The phenyl substituents would enhance rearrangement by causing electron depletion[21,41] in the azine ring and stabilizing the cationic site in (3.21). On the other hand, direct cyclization at the triazole N-1 is more likely due to the absence of steric repulsion between the amino and phenyl groups which would hinder the development of the transition state leading to the isomer (3.20).


H2NHN
HN
N
NH2
(3.2)
(Bz)2
Ph.OC(Ph)C:N.HN
HN
N
NH2
(3.18)
-H2O
H2O
Ph
Ph
NH2
(3.20)
Ph
Ph
NH2
(3.19)
Ph
Ph
NH2
(3.21)

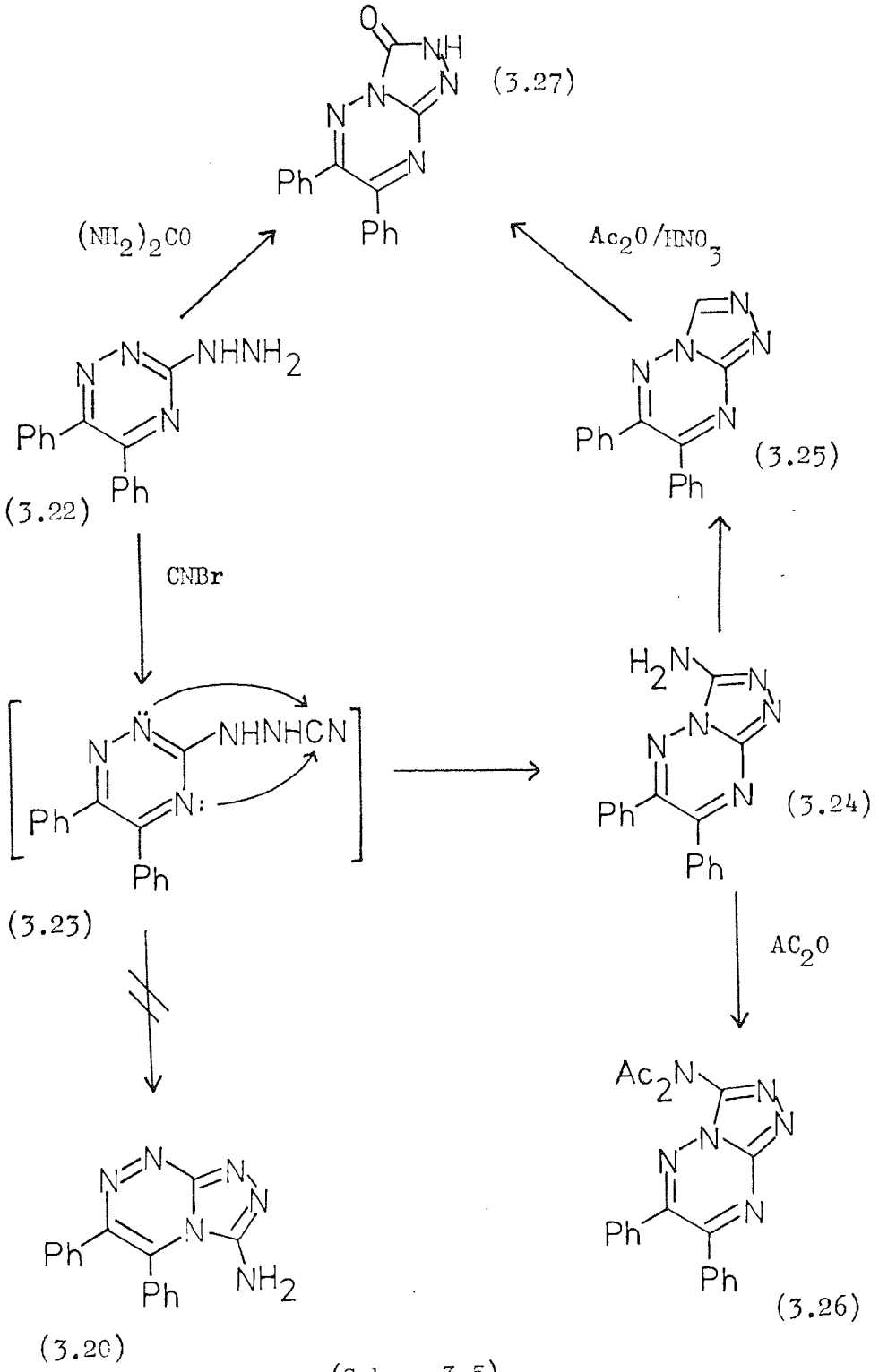
(Scheme 3.4)

(3) 3-Amino-6,7-diphenyl-1,2,4-triazolo [4,3-b]-1,2,4-triazine.

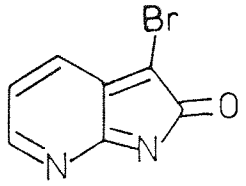
Cyanogen bromide reacted with 5,6-diphenyl-3-hydrazino-1,2,4-triazine (3.22) in boiling methanol to afford the hydrobromide of a weakly basic aminotriazolotriazine; this salt readily dissociated in water to give the free base. Two modes of cyclization are open to the (presumed) intermediate hydrazine (3.23). Nucleophilic attack at cyano by the triazine N-2 would give the aminotriazolo-[4,3-b] triazine (3.24) while cyclization to N-4 of the triazine would give the isomeric[3,4-c] compound (3.20) (Scheme 3.5).

Compound (3.20) would be expected to rearrange via the zwitterionic intermediate (3.21) or (3.18) in aqueous conditions to the aforementioned triazolo[5,1-c] triazine (3.19) (Scheme 3.4). However, the single product isolated was isomeric with this[5,1-c] compound (3.19) and stable to Dimroth conditions (heat, boiling acetic acid, pyridine and piperidine) which provided conclusive evidence for structure (3.24). There is no plausible mechanism whereby this isomer could rearrange unless an unlikely fission of the triazine N-N bond is envisaged. Fission of the N-N bond has been observed with 1,2,4-triazolo[4,3-b] pyridazine[43] but in the present case it is mechanistically impossible.

As expected the diacetyl derivative of the aminotriazolo[4,3-b]-triazine (3.24) differed from the diacetyl derivative of the[5,1-c] isomer (3.19). The ^{1}H n.m.r. spectrum of the diacetylamino derivative (3.26) showed a sharp singlet at 7.77 ($CDCl_3$) integrating for two methyl groups.



(Scheme 3.5)



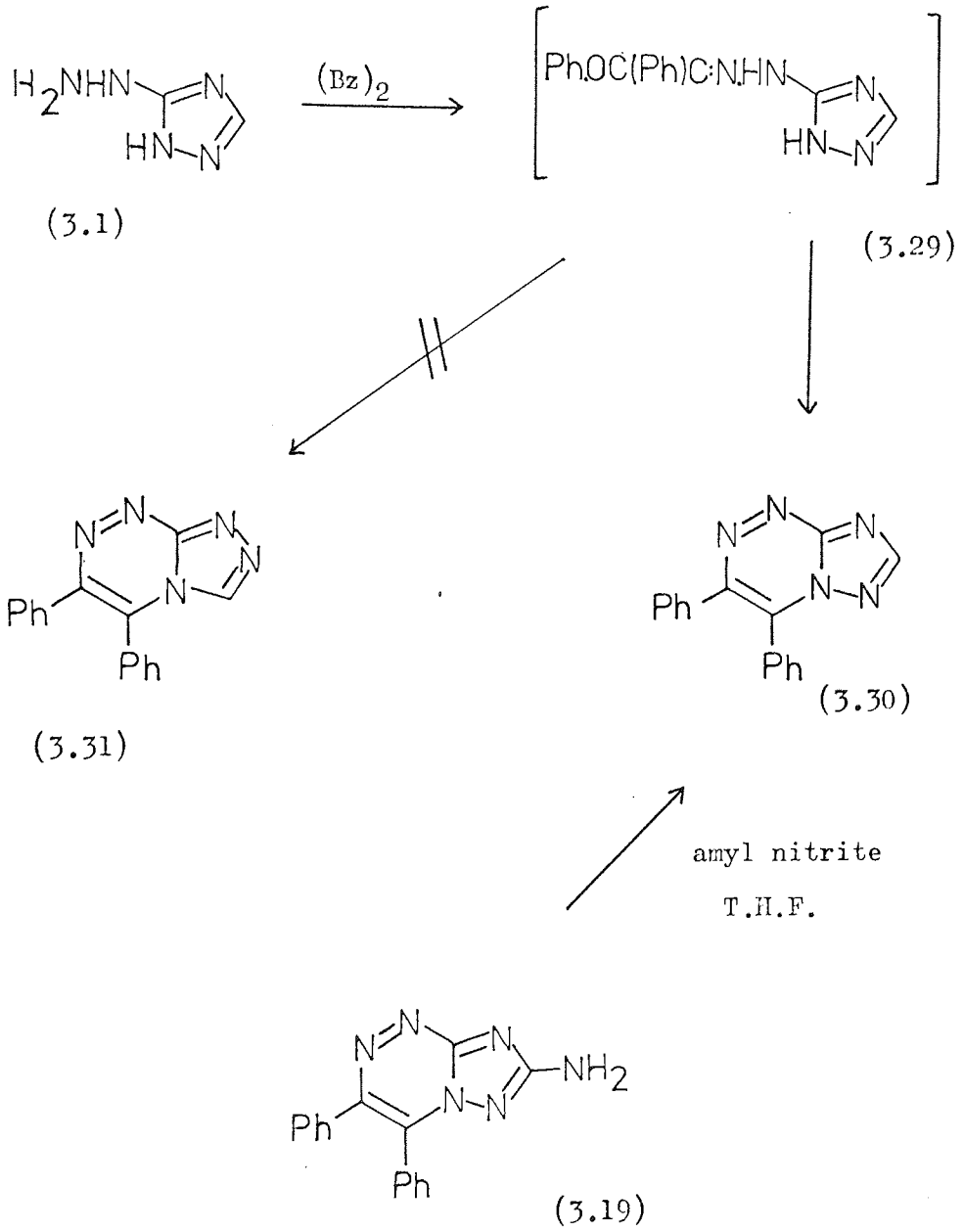
(3.28)

Further support for the [4,3-b] configuration (3.24) was furnished by deamination[89] in tetrahydrofuran with amyl nitrite. The product was 6,7-diphenyl-1,2,4-triazolo[4,3-b]-1,2,4-triazine (3.25) which has been previously synthesized (ambiguously) from the hydrazinotriazine (3.22)[56] and carbon-inserting reagents, or (unambiguously) from 3,4-diamino-1,2,4--triazole and benzil.[48,56]

Nitration of the more readily available triazolotriazine (3.25), followed by reduction, was anticipated to provide an alternative synthesis of the aminotriazolotriazine (3.24). Nitric acid in acetic anhydride was chosen to avoid nitration of the phenyl rings but, unexpectedly, this yielded the oxidised product (3.27), previously isolated from fusion[63] of the hydrazine (3.22) with urea (Scheme 3.5). This result is analogous to the attempted nitration of 3-bromo-1H-pyrrolo[2,3-b] pyridine which yields 3-bromopyrrolo[2,3-b] pyridin-2-one (3.28).[90]

(4) 6,7-Diphenyl-1,2,4-triazolo[5,1-c]-1,2,4-triazine.

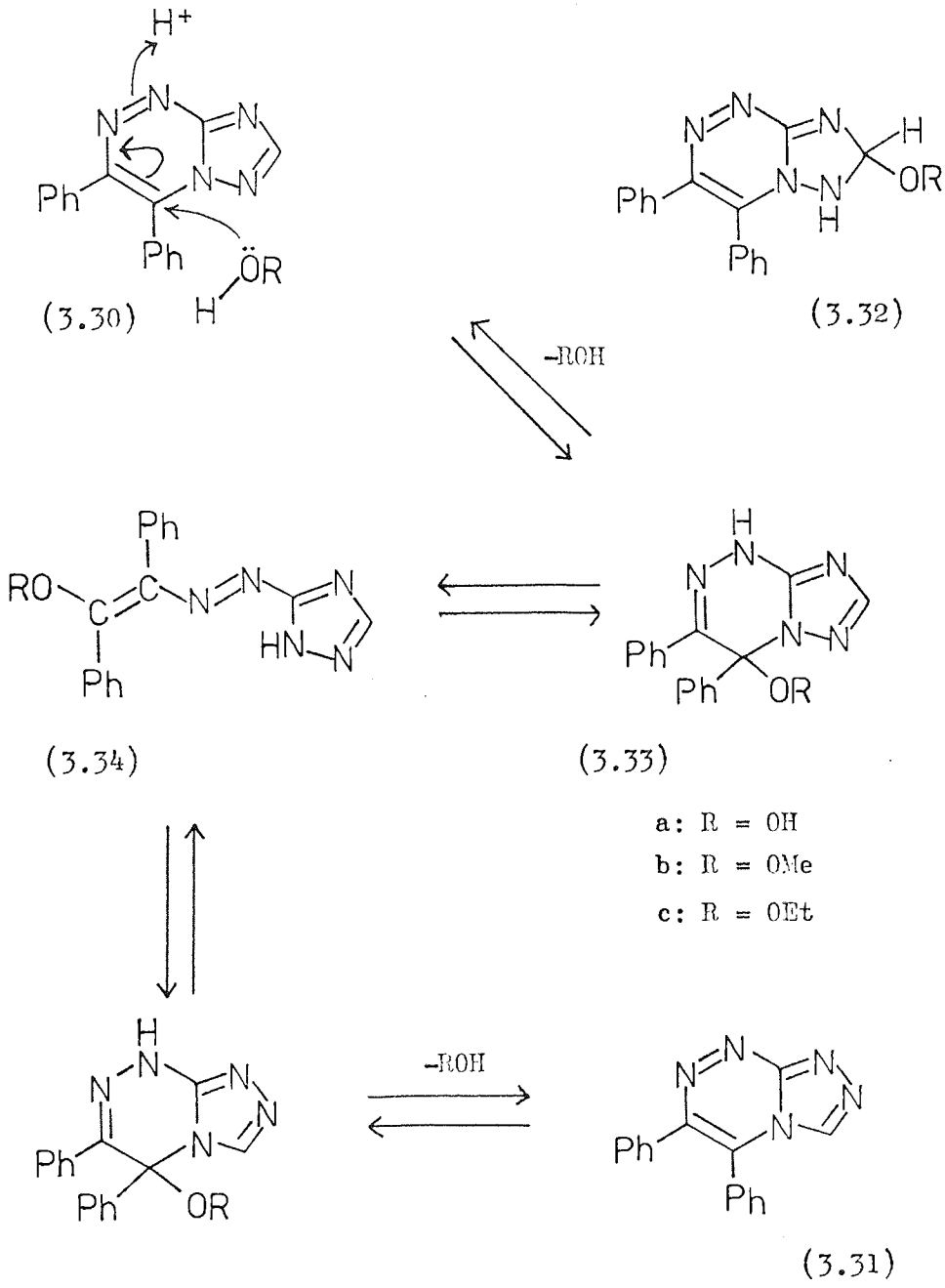
Interaction of 3-hydrazino-1,2,4-triazole hydrochloride and benzil in methanol containing excess sodium acetate gave a single product with a u.v. spectrum typical of a bicyclic system (λmax 349 and 249) and a mass spectrum showing the appropriate molecular ion at m/e 273. The presumed intermediate hydrazone (3.29) once more could have cyclized in two ways to yield the triazolo[3,4-c]triazine (3.31) or the [5,1-c] isomer (3.30) but since the product was stable to heat and a range of boiling organic acids and bases, the [5,1-c]configuration (3.30) is implied (Scheme 3.6). The product was identical to the triazolotriazine (3.30) prepared by deamination of the corresponding aminotriazolotriazine (3.19) which has been previously deduced to have the same skeletal arrangement of N atoms (Scheme 3.6).


H2NHN
HN
N
N
(3.1)
(Bz)2
PhOC(Ph)C:N.HN
HN
N
N
(3.29)
N
N
N
N
Ph
N
Ph
(3.31)
N
N
N
N
Ph
N
N
Ph
(3.30)
amyl nitrite
T.H.F.
N
N
N
NH2
Ph
N
N
Ph
(3.19)

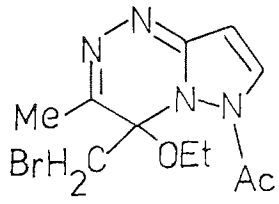
(Scheme 3.6)

When the triazolotriazine (3.30) was stirred at room temperature in dilute hydrochloric acid, the u.v. spectrum underwent a progressive change, and the two peaks were replaced by a single broad band at 294nm. within 20 minutes. On basifying the solution to pH 10 the two peaks reappeared at 349 and 249nm; similar spectral changes were noted when methanol and ethanol solutions of the triazolotriazine (3.30) were treated with dilute hydrochloric acid. When 3-hydrazinotriazole hydrochloride and benzil were boiled in alcohols in the absence of sodium acetate, products were obtained in high yields which analysed correctly for the triazolotriazine (3.30) plus the incorporation of methanol or ethanol: these derivatives reverted to the aromatic bicyclic system in hot acetic acid or pyridine. It was evident that the alcohols were covalently bound from the mass spectra of the adducts (molecular ions at m/e 305 and 319 for the methanolate and ethanolate respectively).

Structures (3.33 a-c) are proposed for the covalent solvates rather than the isomers (3.32 a-c) since acid-catalysed nucleophilic attack at the π-deficient triazine ring is more likely than at the π-excessive triazole ring.[91] Nucleophilic addition to the most electrophilic centre (C-7) of the triazolotriazine (Scheme 3.7) is analogous to the process known to initiate the Dimroth rearrangement in other mono- and bicyclic-systems. Covalent adducts have only rarely been isolated[40] and addition is normally followed by ring-opening and rearrangement. Although the bicyclic adducts (3.33 a-c) may well exist in equilibrium with their acyclic isomers (3.34), recyclization to the less-favoured triazolo[3,4-c] triazine (3.31) does not occur. Thus proof is obtained for the [5,1-c] configuration (3.33) of the solvates.



(Scheme 3.7)



(3.35)

Conclusive proof for the structure of the covalent solvate (3.33) was obtained from the ^{1}H n.m.r. spectrum of the ethanolate (Figure 1) which showed that the triazole proton had moved upfield to τ 2.22 and that the methylene group of the ethoxy substituent appeared as a complex multiplet centred at τ 6.65 characteristic of an AB part of an ABX_3 system; the methyl group appeared as a conventional triplet at τ 8.78. The methylene protons are magnetically unequivalent because of the adjacent asymmetric centre. A similar complex multiplet was recorded for the $-OCH_2CH_3$ group of the ethoxy compound (3.35).[92]

(5) 2-Amino-6,7-disubstituted pyrazolo[5,1-c]-1,2,4-triazines.

Hydrazine hydrate in the presence of excess malononitrile has been reported[93] to yield the aminopyrazole (3.36) as the main product, whereas with excess hydrazine the main product was claimed to be the dihydrotriazine (3.37). It was conceeded, however, that structure (3.38) also fitted the analytical figures: the latter structure was discarded because the product apparently did not react with carbonyl compounds. In actual fact, the second product is the potentially useful 3-amino-5--hydrazinopyrazole (3.38) (isolated as its dihydrochloride), and it reacts readily with benzil and diacetyl to afford high yields of the aminopyrazolo[5,1-c]-1,2,4-triazines (3.39a) and (3.39b) respectively (Scheme 3.9). The aminodiphenylpyrazolotriazine (3.39a) was further characterized by the preparation of a monoacetyl derivative, and deamination[89] to the known diphenylpyrazolotriazine (3.40)[94] with amyl nitrite in tetrahydrofuran.

100 MHz ^{1}H n.m.r. spectrum of 4,7-dihydro-6,7-diphenyl-7-ethoxy--1,2,4-triazolo[5,1-c]-1,2,4-triazine (3.33) in deuterochloroform

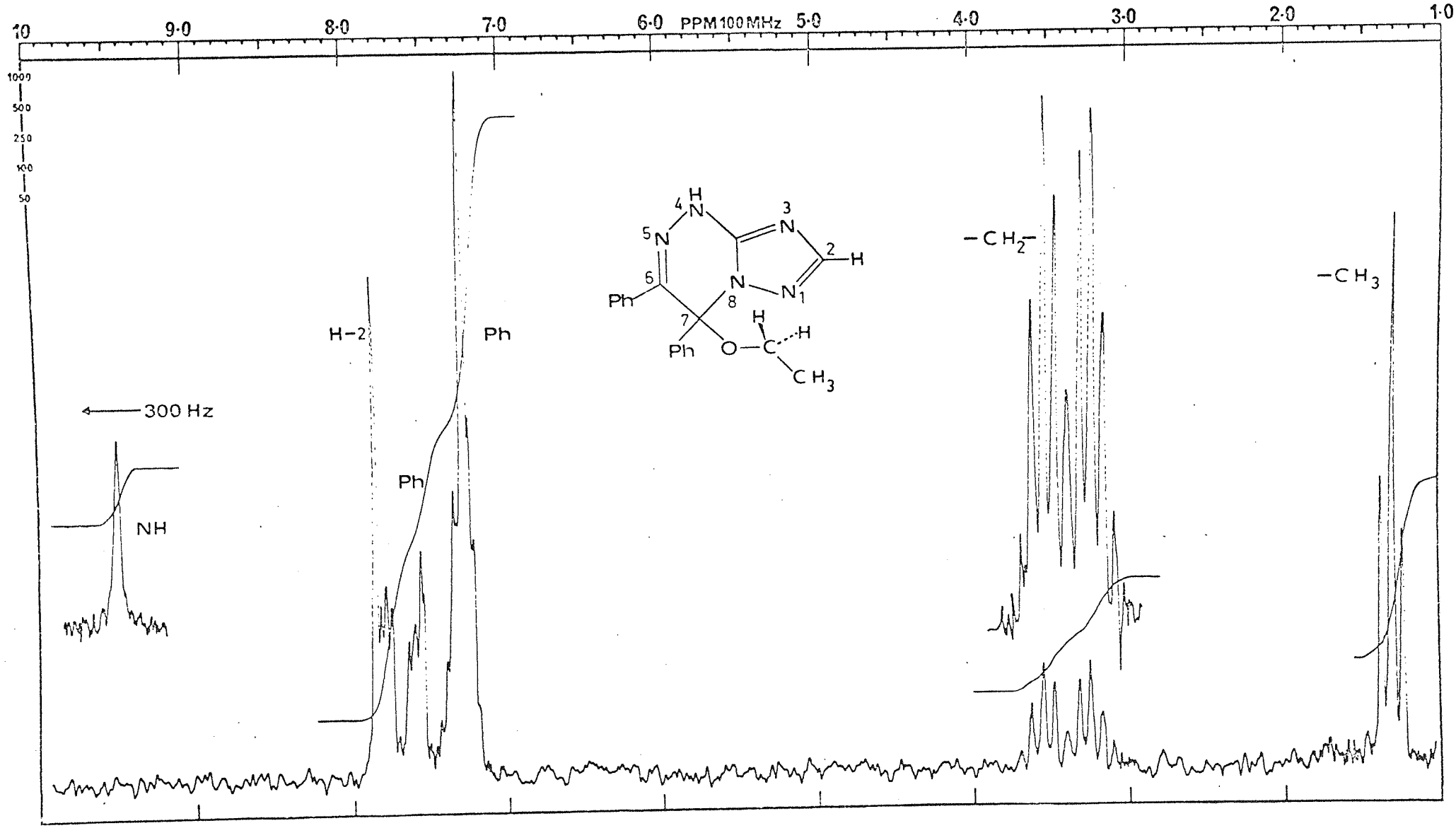
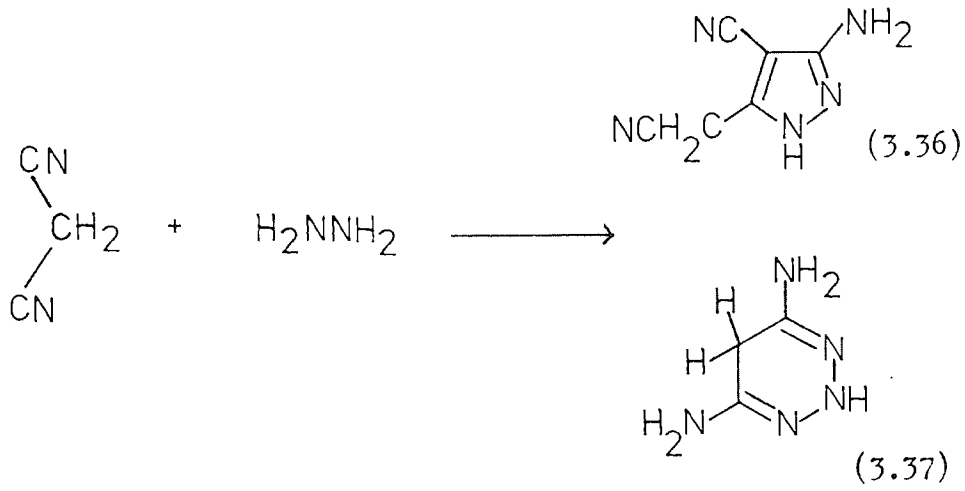
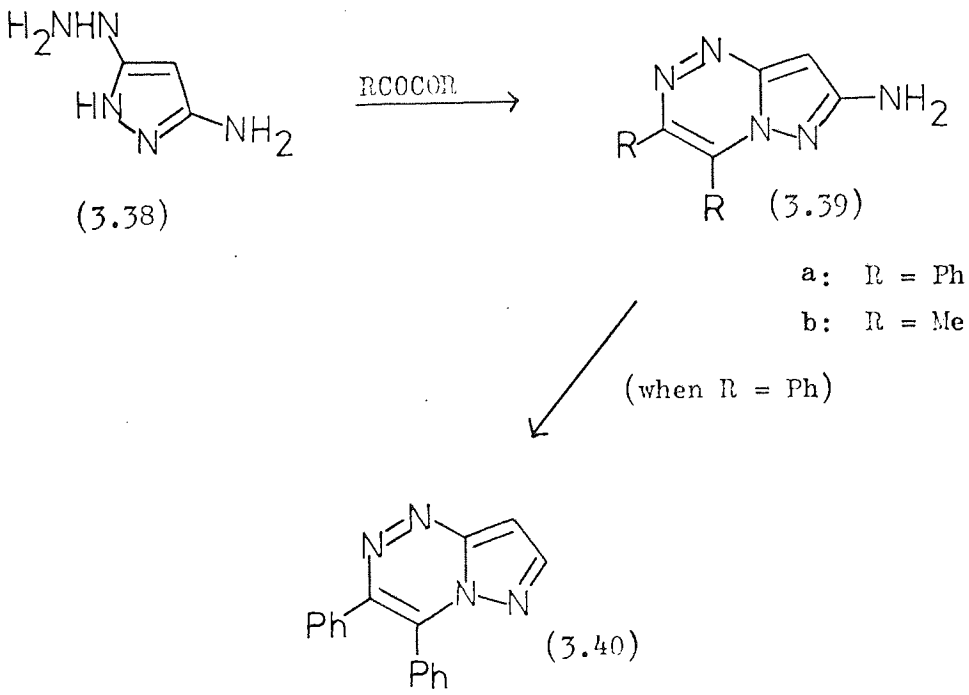


Figure 1



(Scheme 3.8)



(Scheme 3.9)

(6) Mass spectra of diphenyltriazolotriazines.

Dominant fragmentations of diphenyltriazolotriazines which led to the formation of the highly delocalized diphenylacetylene radical ion at m/e 178 and the phenyl cation at m/e 77 are summarized in Tables (2) and (3). No molecular ion was recorded with the diacetyl derivative (3.26) but peaks corresponding to the loss of one and two ketene fragments were observed; the molecular ion of the diacetyl derivative of the aminotriazolo[5,1-c]triazine (3.19) had a relative intensity of 2.5% (Table 3). This is in accord with the intensity of the molecular ion (5%) of the diacetyl derivative of aniline.[95] The methanolate (3.33b) and ethanolate (3.33c) compounds showed large peaks corresponding to the loss of methanol or ethanol moieties respectively.

Peaks at m/e 68, 84 and 96 in the spectra of all the triazolotriazines were absent or insignificant indicating that breakdown to the triazole ion (m/e 68), the 3-aminotriazole radical ion (m/e 84) or the 3-diazotriazole ion (m/e 96) was not an important pathway.

(7) U.v. spectra of diphenylazolotriazines.

It was anticipated that considerable differences between the electronic absorption spectra of the different skeletal arrangements of the diphenyltriazolotriazines would be apparent. For example, the rearrangement of 6-methyl-1,2,4-triazolo[3,4-c]-1,2,4-triazin-7(4H)-one into the [5,1-c] isomer was accompanied by a hypsochromic shift and a strong hyperchromic effect of the absorption at longer wavelength.[28] Similar differences were reported for the two isomers in the [4,3-c][24] and [4,3-a][38] series of the triazolopyrimidines.

Figures (2) and (3) illustrate the close similarity of the pyrazolo [5,1-c]- and triazolo[5,1-c]-1,2,4-triazines in contrast to the triazolo [4,3-b]-1,2,4-triazine skeletal arrangement. A hypsochromic shift

Table 2

Relative intensities (% of base peak) of significant ions in the mass spectra of 6,7-diphenyltriazolo[4,3-b]triazines

Compound Number	M^+	$PhC \equiv CPh^{+\cdot}$	Ph^+
(3.25)	100(273)	18	18
(3.24)	5(288)	100	17
(3.26)	absent	30	56
(3.27)	100(289)	11	18

Table 3

Relative intensities (% of base peak) of significant ions in the mass spectra of 6,7-diphenyltriazolo[5,1-c]triazines

Compound Number	M^+	$PhC \equiv CPh^{+\cdot}$	Ph^+
(3.30)	100 (273)	31	13
(3.19)	18 (288)	6	36
(3.19) monoacetyl derivative	73 (330)	38	21
(3.19) diacetyl derivative	2.5 (372)	11	4
(3.33b)	47 (305)	20	30
(3.33c)	17 (319)	50	100

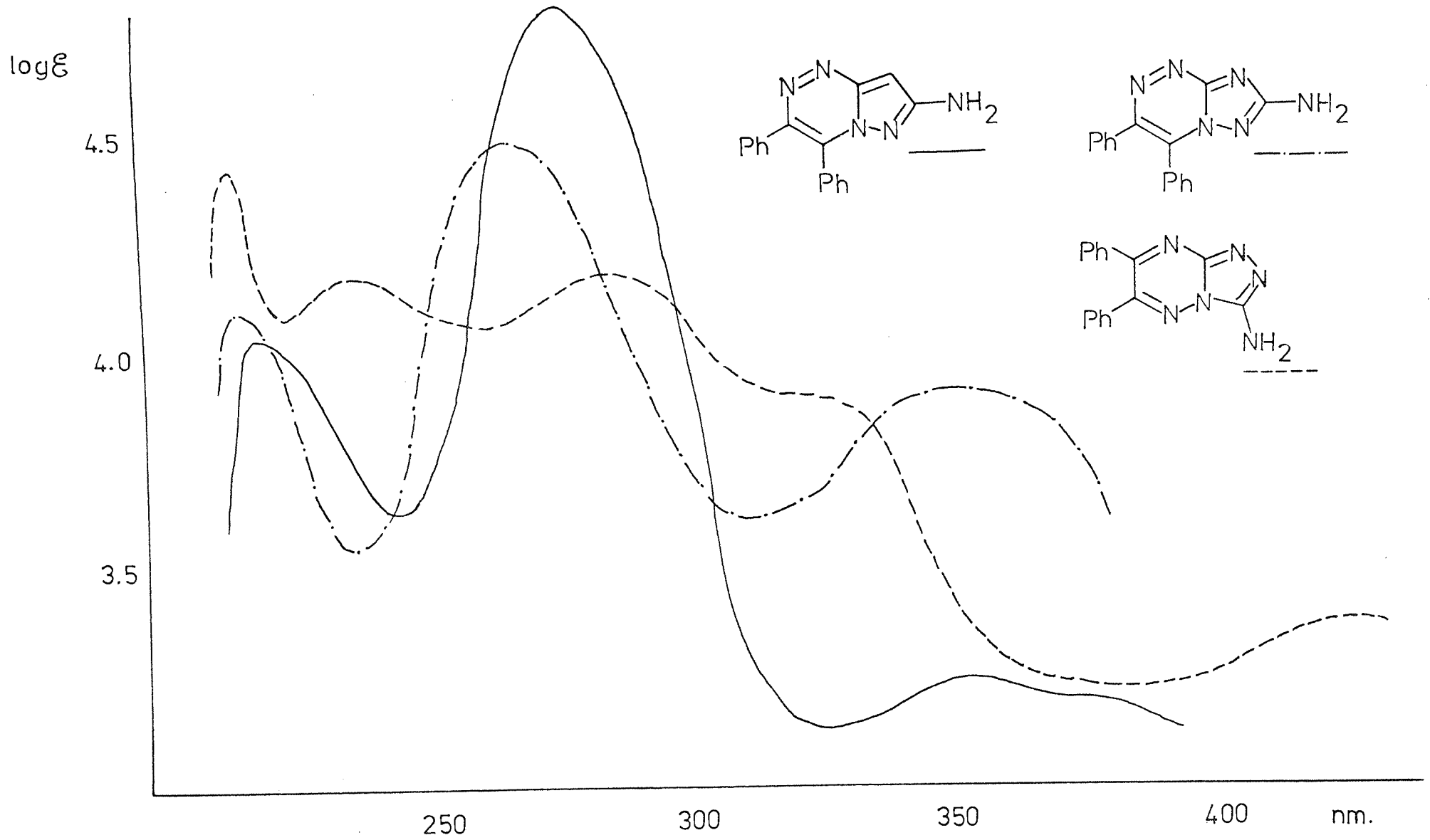


Figure 2

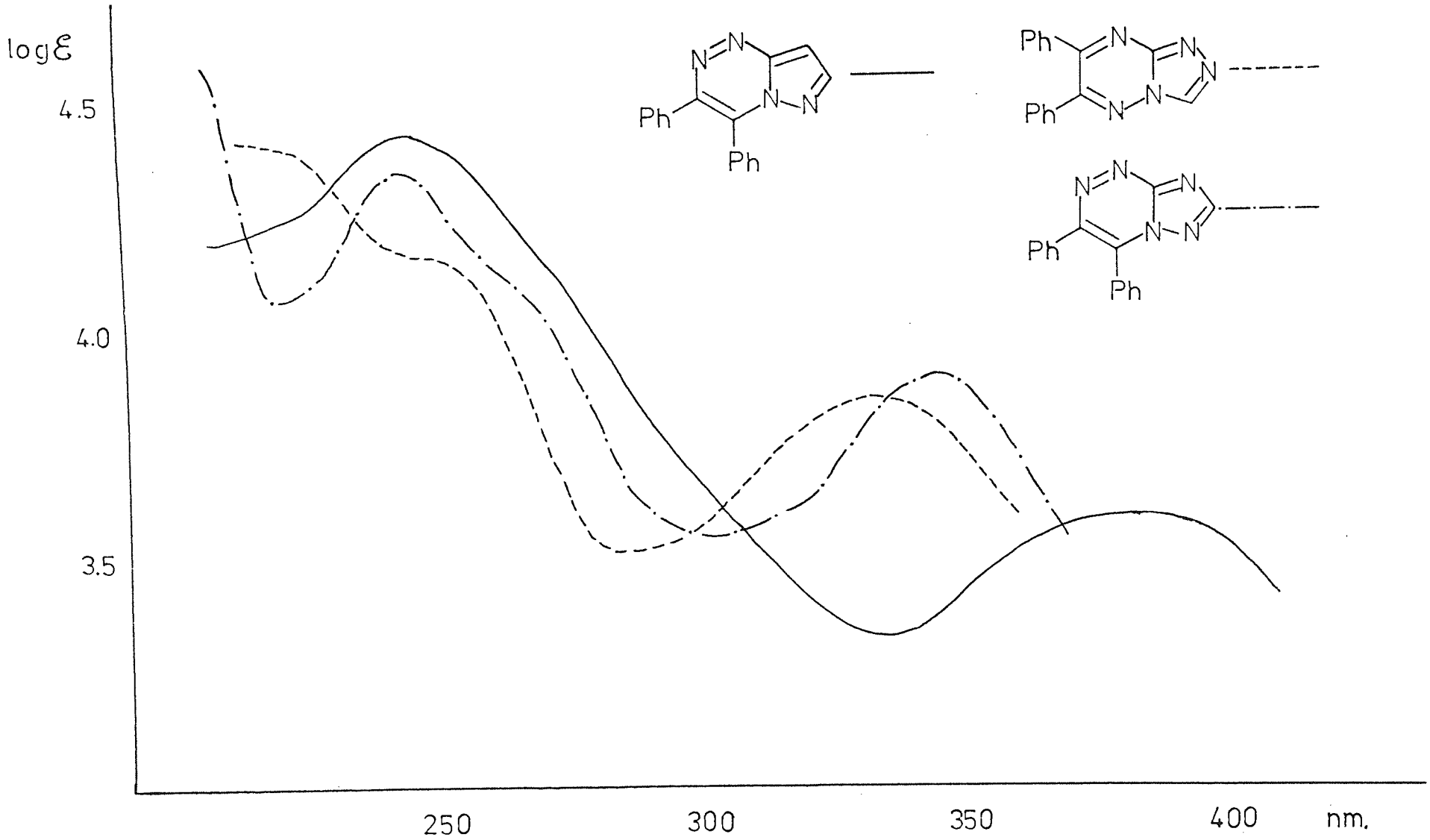

log ε
4.5
4.0
3.5
250
300
350
400
nm.
Ph
Ph
Ph
Ph
Ph
Ph
Ph
Ph
N
N
N
N
N
N
N
N
N
N
N
N

Figure 3

of the long wavelength absorption was observed when diphenyltriazolo[5,1-c]-triazine (3.19) was acetylated but the rest of the spectrum remained remarkably similar.

As expected, triazolotriazines with phenyl substituents show a bathochromic shift with respect to those with hydrogen, hydroxy or methyl groups in the triazine ring.[28]

(8) N.m.r: the chemical shift of the triazole proton in triazoloazines.

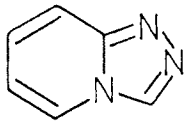
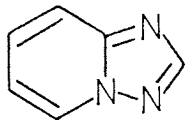
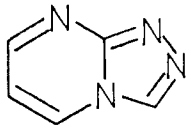
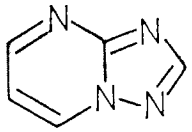
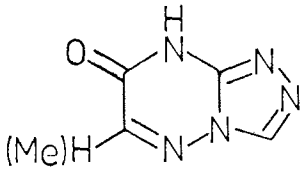
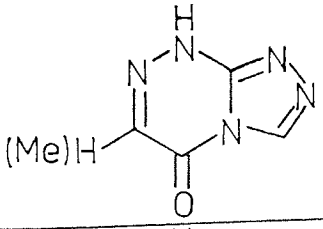
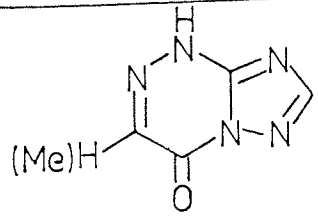
N.m.r. spectroscopy is a technique that has proved useful in demonstrating the existence of two isomers that differ in their skeletal arrangement. It has been shown[96,97] that the triazole protons in a series of triazoloazines with N-4 of the triazole ring at a ring junction [as in (1.28)] are deshielded in comparison with the triazole protons in the isomeric series with the triazole N-1 at the ring junction [as in (1.32)] . (Table 4).

The triazole protons of hydroxy and/or methyl substituted triazolo[5,1-c]--triazines absorbed at higher τ values than the corresponding [4,3-b] isomers which, in turn, resonated at higher frequencies than their [3,4-c] counterparts.[28] The chemical shift of the diphenyl-triazolo[5,1-c]triazine (3.30;τ1.3)is within the expected range for this type of fused triazole and contrasts with the more deshielded proton (τ 0.83) of the [4,3-b] isomer (3.25).

Substituents in the azine ring may influence the triazole proton in addition to the effect of the type of ring fusion [c.f. (3.41) τ= 0.8 and (1.46) τ = 1.25].[98]

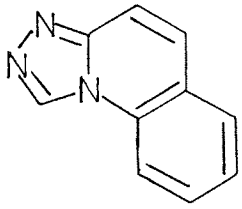
Table 4.

N.M.R. Spectra (τ values of triazole protons) of triazoloazines.

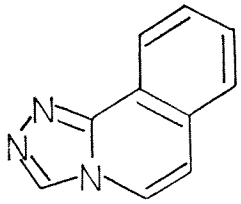
	1.14*
	1.65*
	0.73
	1.24
	0.93 (1.02)
	0.79 (0.87)
	1.60 (1.60)

Solvent:- DMSO except *

* $CDCl_3$



(3.41)



(1.46)

PART IV

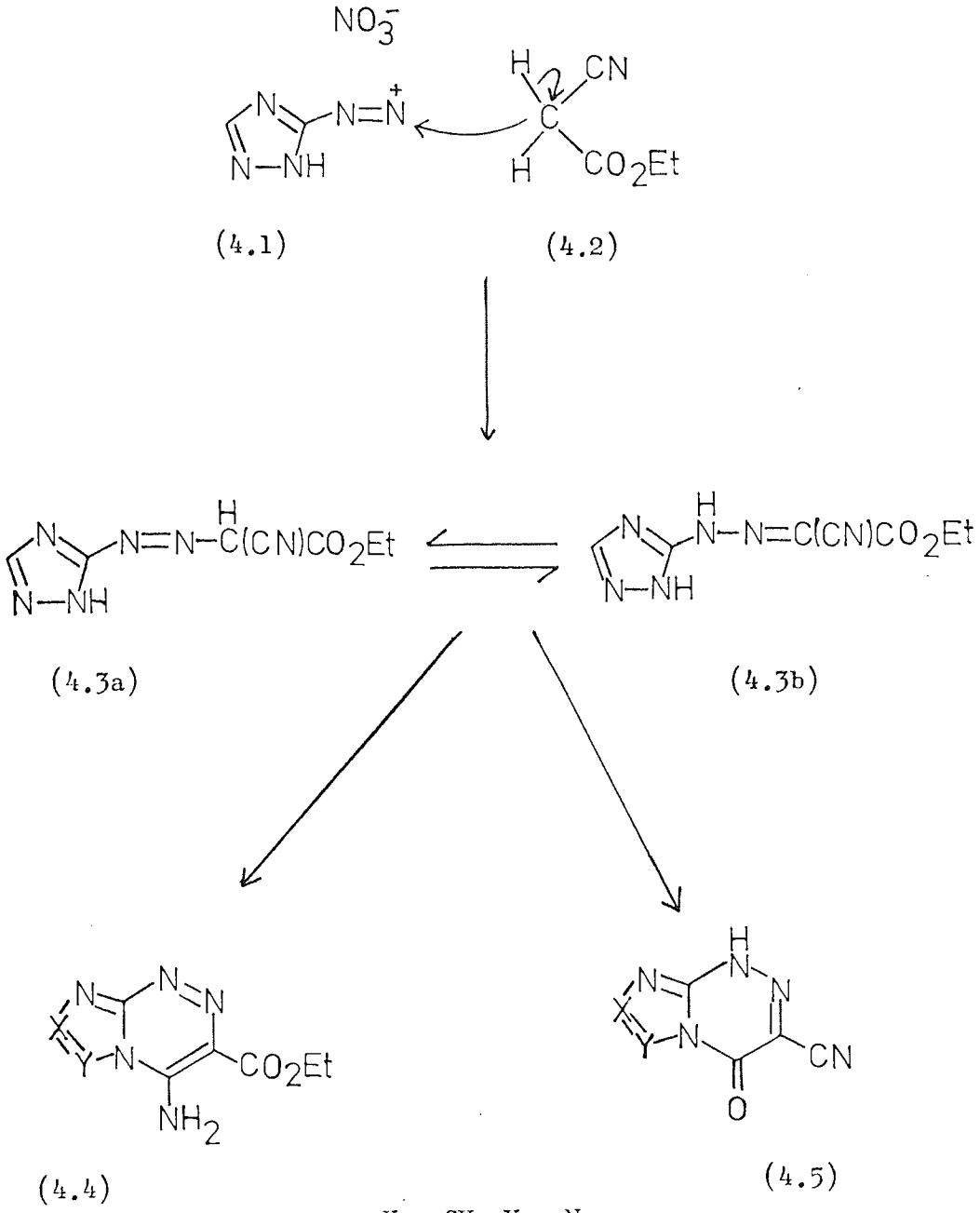
Synthesis and characterization of pyrazolo[5,1-c]-, 1,2,4-triazolo[5,1-c]- and tetrazolo[5,1-c]-1,2,4-triazines from the coupling of diazotized aminoazoles with active methylene compounds.

(1) 2H-1,2,4-triazol-3-yldiazonium nitrate and ethyl cyonacetate

A yellow precipitate forms when 2H-1,2,4-triazol-3-yldiazonium nitrate[99] (4.1) is coupled with ethyl cyanoacetate in a sodium acetate buffer. After careful recrystallization from 70% aqueous ethanol, the product analysed for $C_7H_8N_6O_2H_2O$ consistent with structures (4.3) or (4.4) but the C≡N absorption (2225cm^{-1}) in the i.r. spectrum (Figure 4) eliminated the possibility of a hydrated cyclized product (4.4). After boiling the initial product, (Form A), in acetone for five hours the i.r. (KBr) spectrum showed large C≡N and C=O absorptions at 2204cm^{-1} and 1740cm^{-1} respectively in addition to the original absorptions - now of reduced intensity - at 2225cm^{-1} (C≡N) and 1720cm^{-1} (C=O). A similar effect was noted in ethyl acetate but prolonged boiling (25 hours) in either solvent gave no further change. On recrystallization from aqueous ethanol, Form A was regained and the presence of only one isomer was confirmed by the ^{1}H n.m.r. spectrum which showed a sharp singlet at τ 1.62 for the triazole C-H proton, a methylene quartet at 5.74 (J~7 Hz) and a methyl triplet at 8.72 . Apparently two forms of the 3- substituted triazole (4.3, Form A and Form B, Figure 5) were present in acetone in a 50:50 mixture (estimated from the i.r. spectra).

There are several possibilities which could account for these i.r. spectra.

(i) Solvation:- Form A is known to exist as the hydrate and it is conceivable that desolvation occurs by heating in acetone; recrystallization from aqueous ethanol could regenerate the original hydrate.

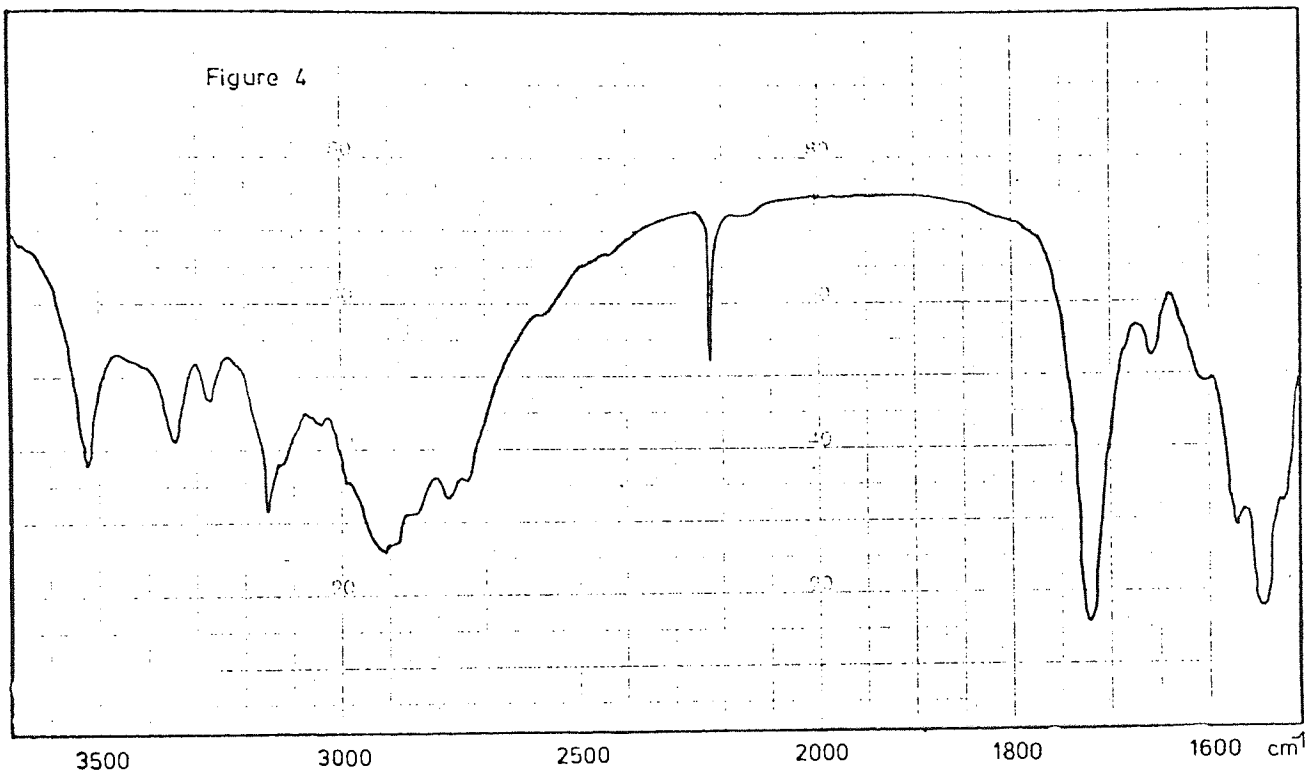


a: X = CH, Y = N

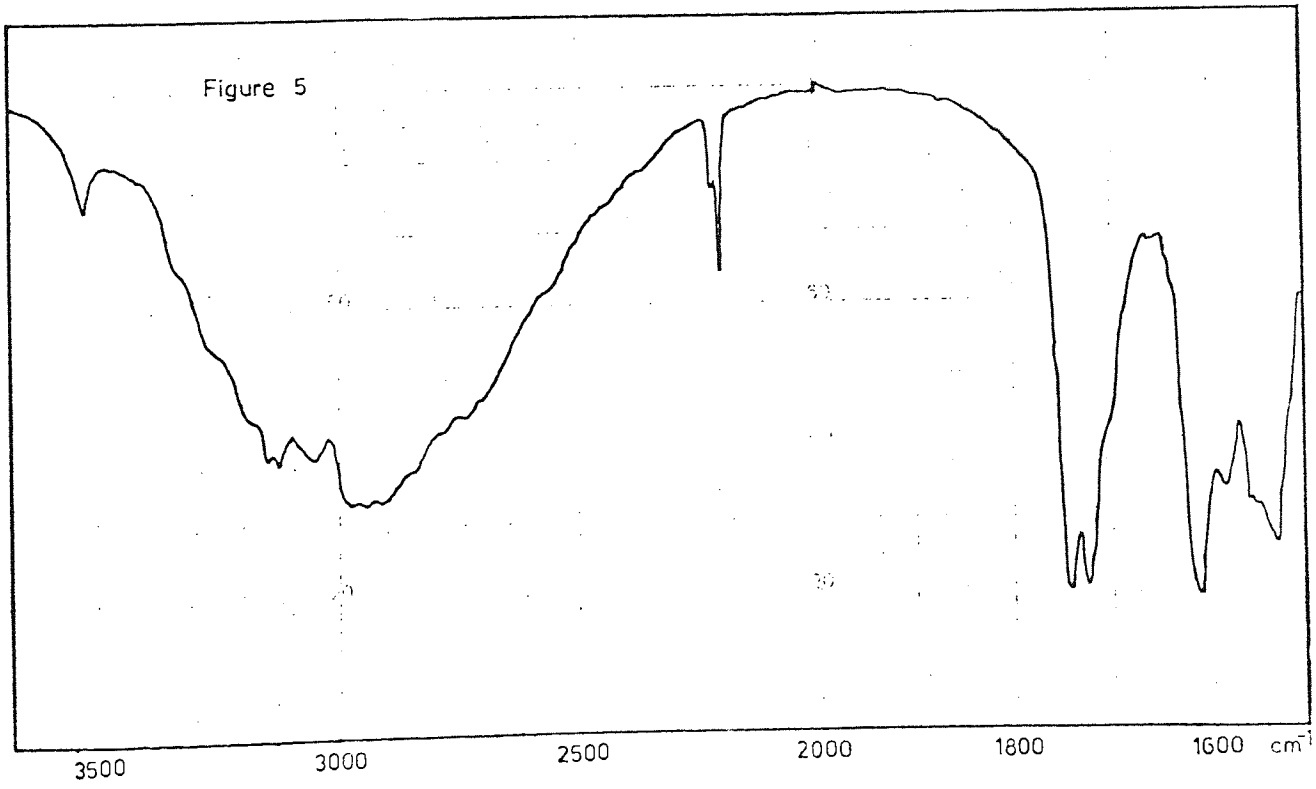
b: X = N, Y = CH

(Scheme 4.1)

I.r. spectrum (KBr) of (4.3), Form A.



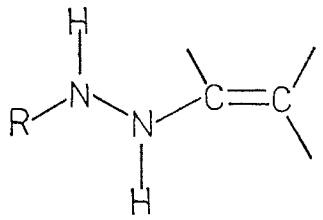
I.r. spectrum (KBr) of (4.3), Form A and Form B



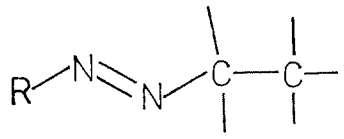
(ii) Tautomerism:- Of the possible triazole tautomers, the 2H form (as in 4.3) is preferred rather than the 4H or 1H tautomers since 3-amino-1,2,4-triazoles are known to exist predominantly in the 2H form.[100]

Theoretically, unsaturated compounds of the basic R-N-N-C-C- structure can exist as the ene-hydrazine (4.6), azo (4.7) or hydrazono (4.8) forms.[101] In general, the ene-hydrazine (4.6) is not the preferred form although it is thought to be an intermediate in β-elimination reactions of arylhydrazones, and cyclohexane-1,3-dione (phenylhydrazone) is thought to exist partially as the ene-hydrazine (4.9). However, the ene-hydrazine form is structurally impossible for the 3-substituted triazole (4.3). The preference for the azo (4.6) or hydrazono (4.7) forms remains controversial.[101] In many cases it has been found that the hydrazone is more stable than the azo compound[102] and reactions accompanied by hydrazone to azo conversion (e.g. ketophenylhydrazones with lead tetracetate form the azoacetates), may be an equilibrium displacement due to consumption of the azo form.[101,102] On treatment with acid or base the azo form reverts to the hydrazone.[101]

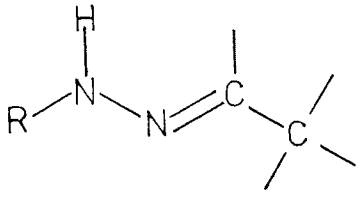
Mass spectroscopy was utilized[103] to confirm that structures of type (4.10) existed partially in the azo form (4.11): the diazonium ions (4.12) were detected in the spectra. The diazotriazole expected in the mass spectrum of an azo-1,2,4-triazole (e.g. 4.3a) would have m/e 96 but the coupling product (4.3) exhibited a similar mass spectrum to the subsequently procured amino-ester (4.4) which also gave m/e 96 as a major breakdown peak. This resemblance was not surprising since cyclization of the 3-substituted triazole (4.3) in the mass spectrometer can be readily envisaged. In addition, the coupling product (4.3) gave a peak at m/e 161 corresponding to the cyano-triazolotriazinone (4.5) formed from the alternative mode of cyclization.



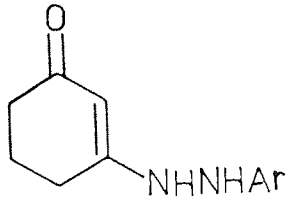
(4.6)



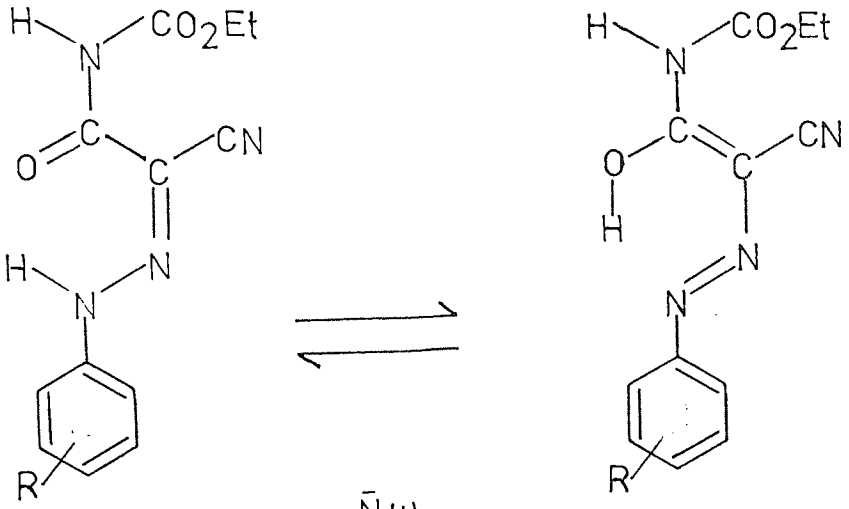
(4.7)



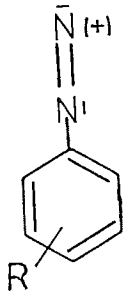
(4.8)



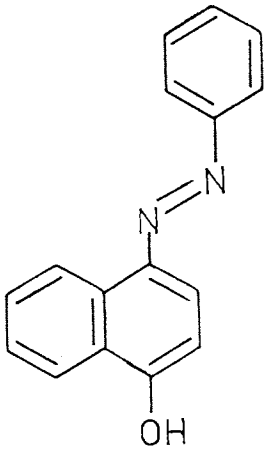
(4.9)



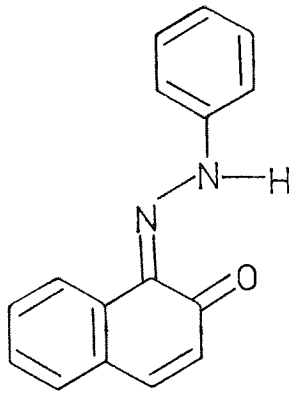
(4.10) (4.11)



(4.12)



(4.13)

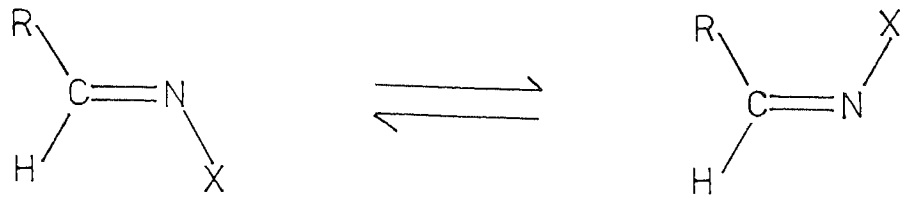


(4.14)

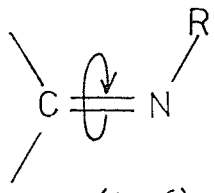
Azo compounds and their hydrazone tautomers give significantly different u.v. spectra.[102,104] Azo compounds of type (4.7) generally absorb in the region of 270 to 280 nm while their hydrazone counterparts (4.8) give peaks at 285 to 295 and 312 to 335 nm.[102] In agreement, compound (4.13) which exists largely as the azo form (λ max 400nm.) contrasts with structure (4.14) predominantly found as the hydrazone (λ max 470 and 500nm.).[104] Absorptions of the triazole coupling products (4.3) - Form A (371nm) and Form B (373nm) - are practically the same and therefore hydrazone (4.3b) to azo (4.3a) isomerization is unlikely. The high λ max. found for this type of compound is typical of other arylhydrazones.[105]

(iii) Geometrical isomerism:- Both azo and hydrazono compounds are capable of existing as geometrical isomers.[101,106] When X = NHY (4.15) both syn (E) and anti (Z) isomers (4.15 a and b) can assume conformations that allow considerable overlap of the unshared pair of electrons on the nitrogen of the substituent with the π electrons of the double bond. When X = $N(Me)_2$ (4.15) this phenomenon is only possible with the E isomer and this is the only form encountered. Initially, both hydrazone geometrical isomers may form, followed by equilibration;[107] the latter is often found to be solvent dependent.[106,107] Z to E isomerizations may be slow[106] at room temperature but can be accelerated by acid.[107] When the presence of two isomers has been detected spectroscopically, yet both have identical melting points, isomerization during the heating process is inferred.[107] Separation of the isomers has proved possible in certain cases due to differential solubility.[107]

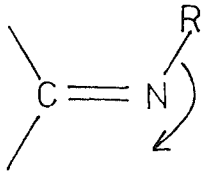
The mechanism of isomerization may be by rotation, inversion or tautomerism. Rotation (4.16) would involve heterolytic fission or extreme polarization of the C=N linkage with loss of π-bond energy, followed by rotation around the C=N axis. Inversion (4.17) or lateral shift requires



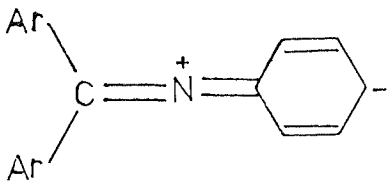
(4.15) a E b Z



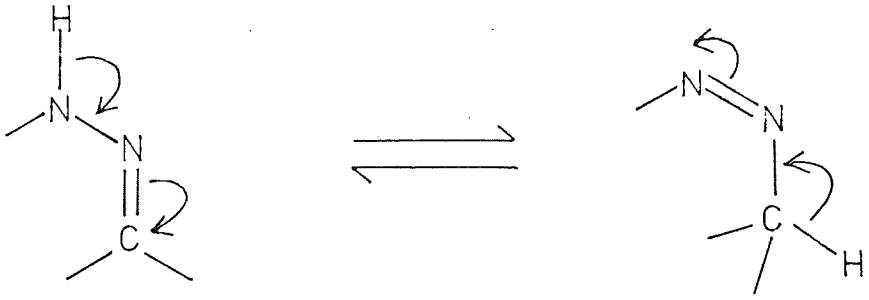
(4.16)



(4.17)



(4.18)



(4.19) (4.20)

the substituent attached to the nitrogen (R) to move to the opposite side through a transition state where the nitrogen adopts sp bonds and the π-bond remains intact. The electronegativity of substituents has proved useful in elucidating the mechanism in certain cases [e.g. the accelerating effect produced by electron-withdrawing groups in the p-position of (4.18) implies inversion]. Tautomerism of the hydrazone (4.19) to the azo form (4.20) allows rotation around the C-N single bond; further shift of the hydrogen results in the geometrical isomer. This mechanism has been proved for certain hydrazones[108] but the lateral shift mechanism shows that it is not necessary. In one case the tautomeric pathway was excluded when proton exchange was found to be much slower than isomerization.[109]

(iv) Polymorphism:- Identical compounds with different crystalline forms can have different i.r. spectra and melting points.

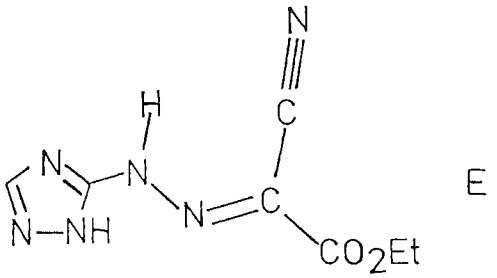
Elucidation of the structures of the coupling products (4.3b, Form A and Form B) was aided by their cyclization patterns. The effects of various solvents on Form A and mixtures of Form A and B were followed by t.l.c.

After heating Form A for two hours in acetic acid, the amino-ester (4.4) precipitated in a 60% yield while, under similar conditions, the mixture of Form A and Form B gave only a 20% yield. The cyanotriazolotriazinone (4.5) was present in the mother liquors in both cases. In the boiling bases, pyridine and collidine, the cyanotriazolotriazinone (4.5) was exclusively formed (as its pyridine and collidine salts respectively). Acidification of the salts in IN-hydrochloric acid furnished the pure cyanotriazolotriazinone (4.5) which crystallized as the unsolvated acid from ethanol. After three hours in boiling water, Form A yielded the amino-ester (4.4; 70%) and cyanotriazolotriazinone (4.5; 30%) which contrasted with the much higher proportion of (4.5) produced by the mixture of Form A and B.

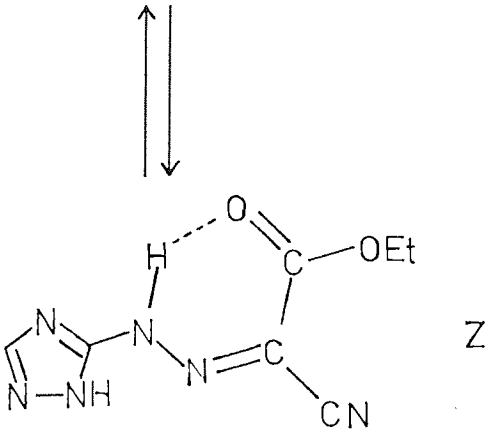
This pattern eliminated polymorphism and solvation as the source of the dissimilar i.r. spectra of the two forms (4.3b) and favoured the geometrical isomerism explanation. Structures (4.21) and (4.22) clearly illustrate that after rotation of the triazole substituent about the C-N single bond in (4.21), it is orientated for attack by the triazole nitrogen at the cyano group to yield the amino-ester (4.4); conversely, (4.22) is sterically more suited to form the cyanotriazolotriazinone (4.5).

Significant support for this argument is given with the model hydrazone (4.23).[105] It crystallizes in an unsolvated form but shows split cyano absorptions (2236 and 2210cm^{-1}) in the i.r. spectrum. These values for the nitrile groups in two distinct geometrical environments correspond closely to the nitrile peaks encountered in the mixed hydrazone (4.3b, Table 4). Two distinct forms were also isolated[105] for the hydrazone (4.24). A deep yellow compound (m.p. 185°) from aqueous ethanol or pyridine, analysed without solvent while it crystallized from acetic acid as a pale yellow modification (m.p. 202-204°)which analysed as a hemi-acetate. The high-melting form reverted to the low-melting form in pyridine. The mass spectra were nearly identical but significant differences in the i.r. and ^{1}H n.m.r. spectra were apparent.[105] In addition, two distinct forms of each of the hydrazones formed by coupling diazotized 4-chloro-[110] and 2-nitro-anilines[111] with ethyl cyanoacetate are recorded in the literature and similar significant differences in the C≡N and C=O absorptions in their i.r. spectra were found (Table 4).

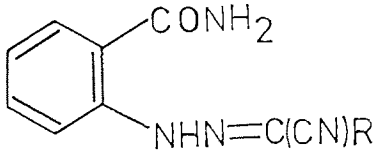
It is conceivable that Form A of the triazole hydrazone (4.21) crystallizes favourably as the hydrate but on boiling in an organic solvent (e.g. acetone or ethylacetate), water is lost and the preferred, intra-molecularly bonded Form B (4.22) results. An analogous solvent effect has been observed[112] in the increased proportion of the Z-isomer (4.25) in t-butyl alcohol compared



(4.21)



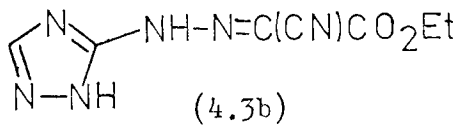
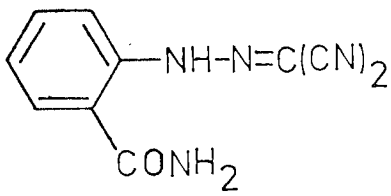
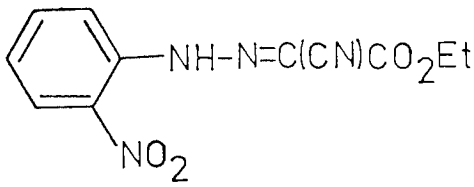
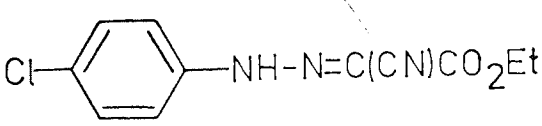
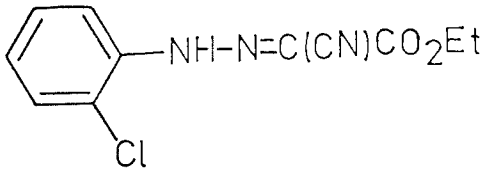
(4.22)



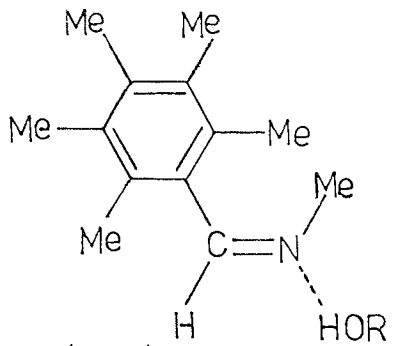
(4.23) R = CN

(4.24) R = CO_2Et

Table 4. I.r. absorptions (cm^{-1}) of geometrical isomers of hydrazones

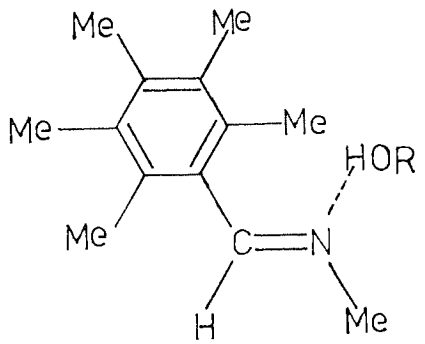
		C≡N	C=O
 (4.3b)	(A)	2225	1720
	(B)	2204	1740
		2236 and 2210	
	(A)	2228 (2235)	1704 (1702)
	(B)	2218 (2218)	1720 (1720)
	(A)	2215 (2225)	1685 (1685)
	(B)	2215 (2210)	1685 (1710)
	(A)	2225 (2225) (from ethanol)	1685 (1685)
	(B)	2205 (2205) (from benzene)	1730 (1730)

Spectra recorded as KBr discs (chloroform solution results in brackets).



Z

(4.25)



E

(4.26)

to the lower alcohols. An increased propensity for the bulky t-butyl alcohol to hydrogen-bond more readily to the less sterically hindered N-lone pair in the Z-isomer (4.25) was proposed to explain this phenomenon. The lack of a similar effect in methanol may be due to the ability of the smaller methanol to hydrogen-bond effectively with both isomers (4.25) and (4.26).

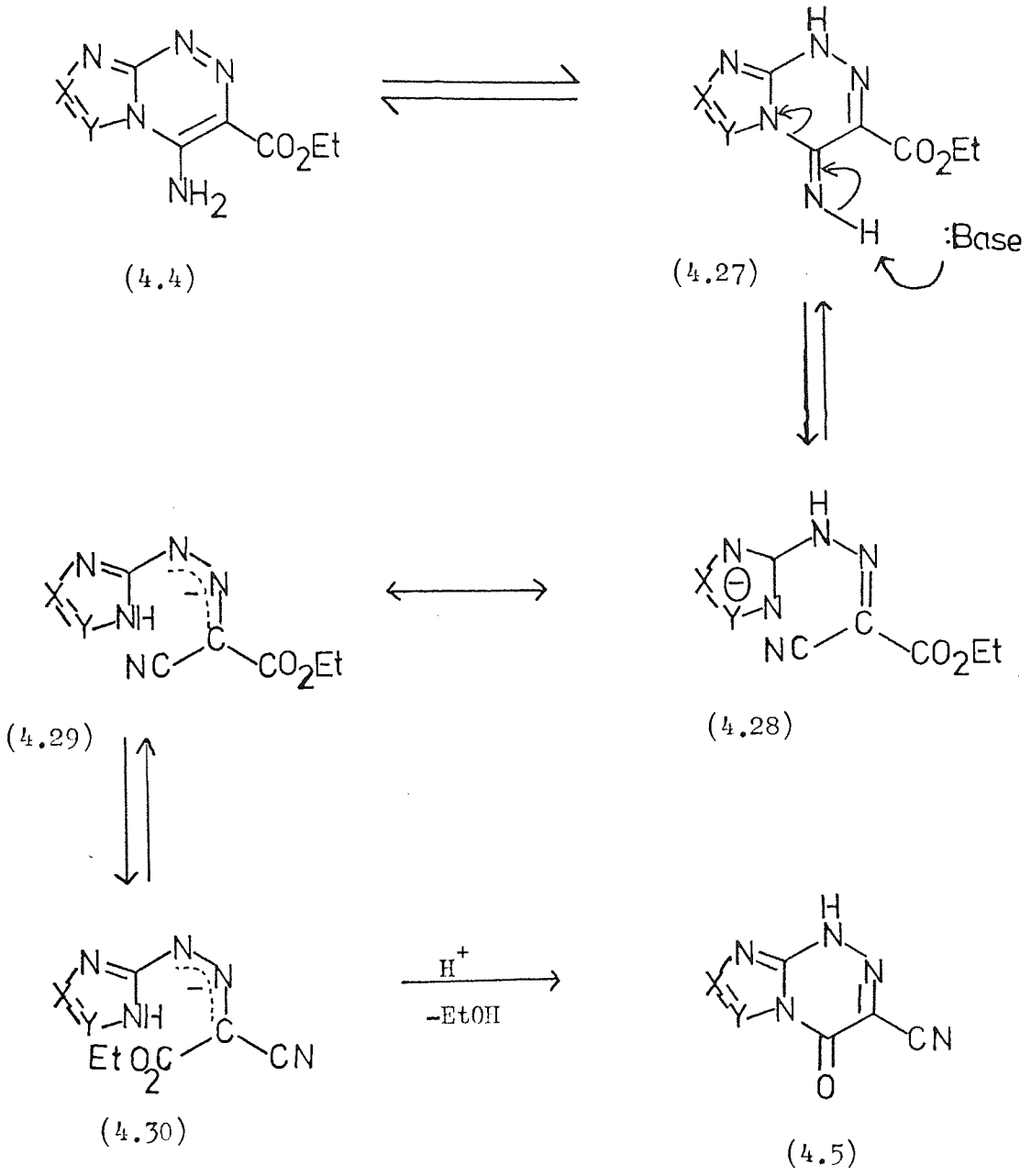
Form A (4.21) and Form B (4.22) are insoluble in chloroform, carbon tetrachloride and insufficiently soluble in water to allow the use of i.r. spectroscopy to examine the possibility that the two geometrical isomers may exist as an equilibrium mixture in solution. However, the solid state spectra (KBr) (Table 4) were in accord with the theory of geometrical isomerism of the hydrazone (4.3b). Intramolecular hydrogen bonds are not necessarily stronger than intermolecular hydrogen bonds[113] so it was not surprising to note the rise in ν C=O in Form B (4.22). In fact the position of ν C=O and ν C=N reflects the expected better conjugation of the trans-form (4.21) and the marked rise in ν C=N of Form B is a characteristic feature of E to Z isomerization, mostly due to coupling with the N-H deformation mode.[113]

The cyclization pattern of (4.3b) infers that the isomerization of Form A to Form B is more rapid in base than water and in addition, the cyano-triazolotriazinone (4.5) must be the thermodynamic and/or kinetically favoured product. The very low dielectric constant of glacial acetic acid may be responsible for the retention of geometrical integrity by Form A and thus allows for a reasonable yield of the amino-ester (4.4) to be obtained in that solvent. Conversely, it is possible that preferred formation of the more basic amino-ester (4.4) results in the acidic medium but of the acidic cyanotriazolotriazinone (4.5) in base.

It was considered feasible that the cyanotriazolotriazinone (4.5) might originate from the amino-ester (4.4) by a base-catalysed ring-opening of the iminotriazine tautomer (4.27) similar to that involved in the base-initiated ring-opening of 4(3H)-imino-1,2,3-benzotriazines.[16] The intermediacy of extensively delocalised hydrazone anions (4.28 - 4.30) would provide a logical mechanism for the isomerization of the hydrazone which could then cyclize irreversibly to the cyanotriazolotriazinone (4.5) (Scheme 4.2). No evidence for this alternative route was found and the amino-ester (4.4) was recovered unchanged from boiling pyridine, collidine and triethylamine.

It is interesting to note that the cyclization of 3-aminotriazole with ethyl 2-cyano-3-ethoxylmethylenepropionate (4.32) in glacial acetic acid yields the corresponding triazolopyrimidine amino-ester (4.33) whereas in alkali the reaction furnished the cyanotriazolopyrimidinone (4.34, Scheme 4.3).[114] On the other hand, the same reaction was reported independently[115] to yield both (4.33) and (4.34) from a basic medium.

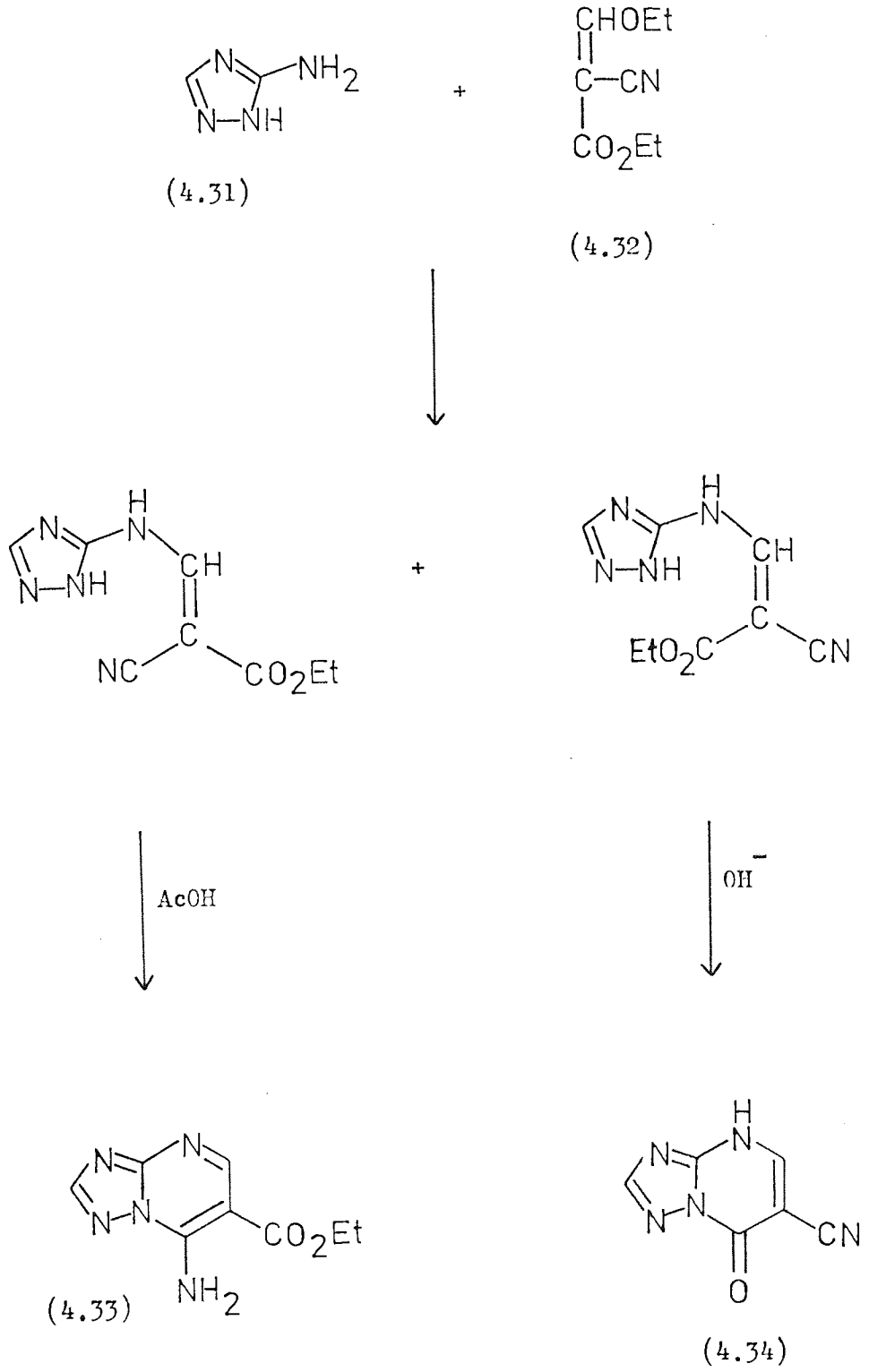
Structure (4.4a) for the amino-ester is supported by its stability in a number of boiling bases described above, in addition to its stability when heated in glacial acetic acid or in the dry state. This structure assignment is also corroborated by the chemical shift of the H-2 proton (τ 1.23) which is well within the range expected for an N-1 fused triazole in contrast to that anticipated for an N-4 fused skeletal isomer.[96] In boiling piperidine, the amino-ester (4.4a) was converted to the piperidino-amide (4.35) with a similar chemical shift for the triazole proton (τ 1.45). As anticipated, the C=O absorption in the i.r. spectrum decreased from 1707cm^{-1} in the amino-ester (4.4a) to 1655cm^{-1} for the corresponding amide (4.35).



a: X = CH, or N

b: Y = N or CH

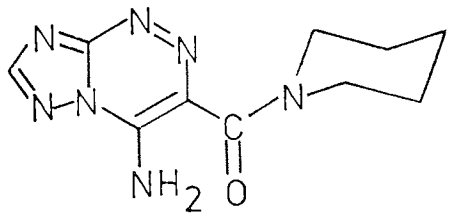
(Scheme 4.2)


NH2
N
N–NH
(4.31)
+
CHOEt
C–CN
CO2Et
(4.32)
H
N
CH
C
NC
CO2Et
+
EtO2C
CN
AcOH
OH⁻
CO2Et
NH2
(4.33)
CN
O
(4.34)

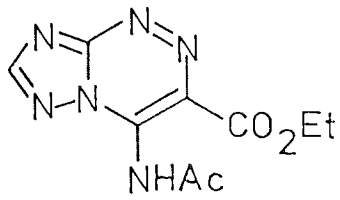
(Scheme 4.3)

The amino-ester (4.4a) formed a mono-acetyl derivative (4.36) in boiling acetic anhydride which differed from the mono-acetyl derivative formed from the hydrazone hydrate (4.3b, Form A). The absence of a C≡N absorption in the i.r. spectrum of this latter product confirms a cyclic structure. Support for the 4-acetyl formulation (4.37) was given by the u.v. spectrum (λ max 278nm) - cf. λ max 303, 223nm. for (4.36) - indicative of the loss of the N=N chromophore.[94] As the preparation of (4.36) required 2.5h in boiling acetic anhydride in contrast to 0.5h for the hydrazone mono-acetyl derivative, the hydrazone must acetylate before cyclization and a 1-acetyltriazolotriazine (4.38) is excluded. Both acetyl derivatives decomposed over prolonged periods.

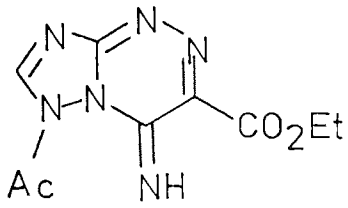
As the pyridine salt of the cyanotriazolotriazinone (4.5) was stable in glacial acetic acid, the pKa of this triazolotriazine must be below that of acetic acid (pKa 4.76)[116]. The C=O absorption in the free cyanotriazolo-triazinone (4.5) is decreased from 1710cm^{-1} to 1670 and 1680cm^{-1} in the pyridine and collidine derivatives respectively; this is consistent with salt formation rather than complex formation. The chemical shift of the triazole proton (τ 1.45) in the free cyanotriazolotriazinone (4.5) coupled with its stability under conditions similar to those imposed on the amino-ester confirm the [5,1-c] fusion (4.5a) of the two rings. The absorptions of the pyridine protons in the ^{1}H n.m.r. spectrum of the pyridinium salt closely correspond to those of pyridine picrate.



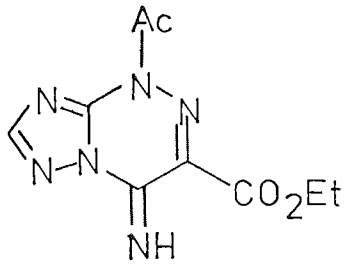
(4.35)



(4.36)



(4.38)



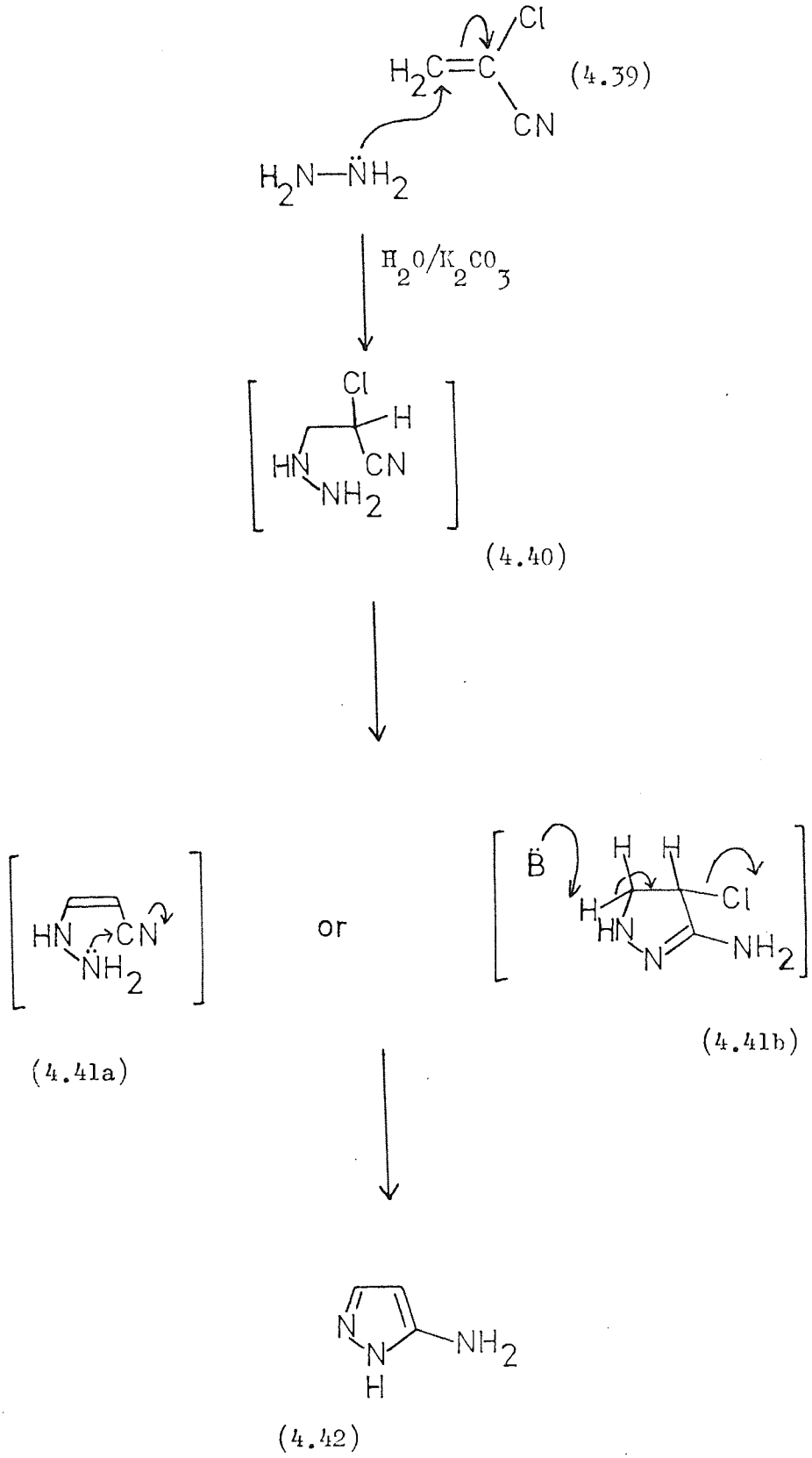
(4.37)

(2) 2H-pyrazol-3-yldiazonium chloride and ethyl cyanoacetate.

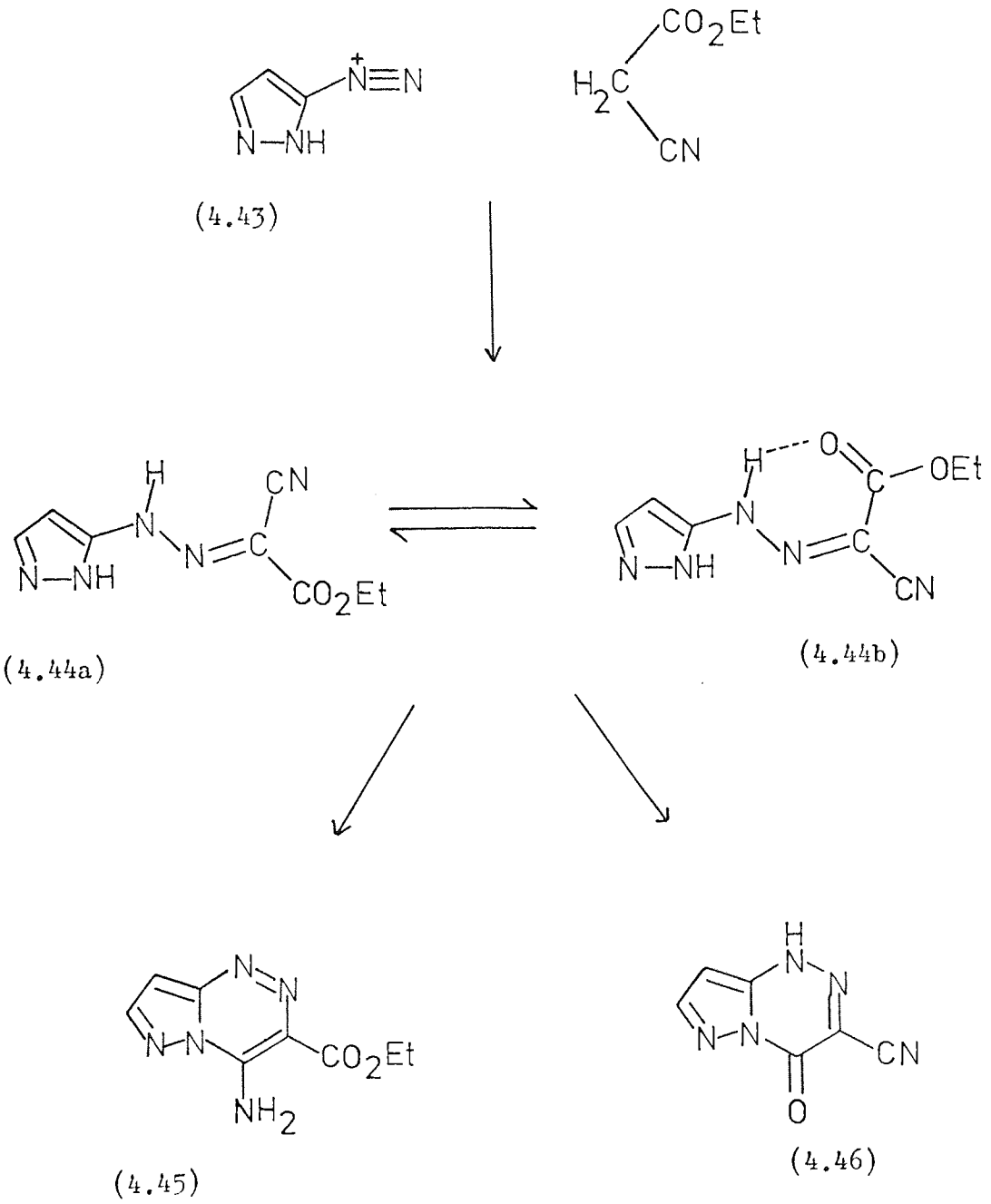
The coupling of the pyrazolodiazonium salt with ethyl cyanoacetate[94] was re-examined in the light of the results obtained in the triazole series.

3-Aminopyrazole (4.42) was prepared from a new one-step route[117] (Scheme 4.4) by reacting hydrazine and 2-chloroacrylonitrile(4.39) in aqueous potassium carbonate. The stage at which dehydrochlorination occurs is not yet established [i.e. before (4.41a) or after (4.41b) cyclization]. Diazotization of 3-aminopyrazole in hydrochloric acid and coupling with ethyl cyanoacetate in a sodium acetate buffer yielded a pure hydrazone (4.44) (from aqueous ethanol) as originally claimed (m.p. 172-3°).[94] When recrystallized from benzene, or boiled in acetone or ethyl acetate for 1.5h, this hydrazone changed to a different form (m.p. 165°), although variations in the i.r. characteristics of the two forms were not as pronounced as in the triazole series; the second form reverted to the original form in aqueous ethanol. Both forms analysed correctly without solvent, had identical u.v. spectra which eliminated the possibility of azo-hydrazone tautomerism, and gave the same two spots on a t.l.c. plate. An ^{1}H n.m.r. spectrum of the original form from aqueous ethanol in [$^{2}H_{6}$]dimethylsulphoxide showed it to be a mixture of two closely similar isomers in that solvent.

With an appreciation of the triazole series, it is proposed the two forms of the hydrazone (4.44) are the geometrical isomers (4.44a) and (4.44b) but in the pyrazole system the hydrazone (from aqueous ethanol) is not stabilized by hydration and therefore allows more facile conversion to the other isomer. The isolation of the isomer with the more exposed polar groups (4.44a) from aqueous ethanol and the intramolecularly hydrogen-bonded (4.44b) from benzene can be envisaged.


Cl
$H_2C=C$
CN
(4.39)
$H_2N-\ddot{N}H_2$
H_2O/K_2CO_3
Cl
H
HN
CN
NH_2
(4.40)
HN
CN
$\ddot{N}H_2$
(4.41a)
or
$\ddot{B}$
H
H
H
HN
N
Cl
NH_2
(4.41b)
N
N
H
NH_2
(4.42)

(Scheme 4.4)



(Scheme 4.5)

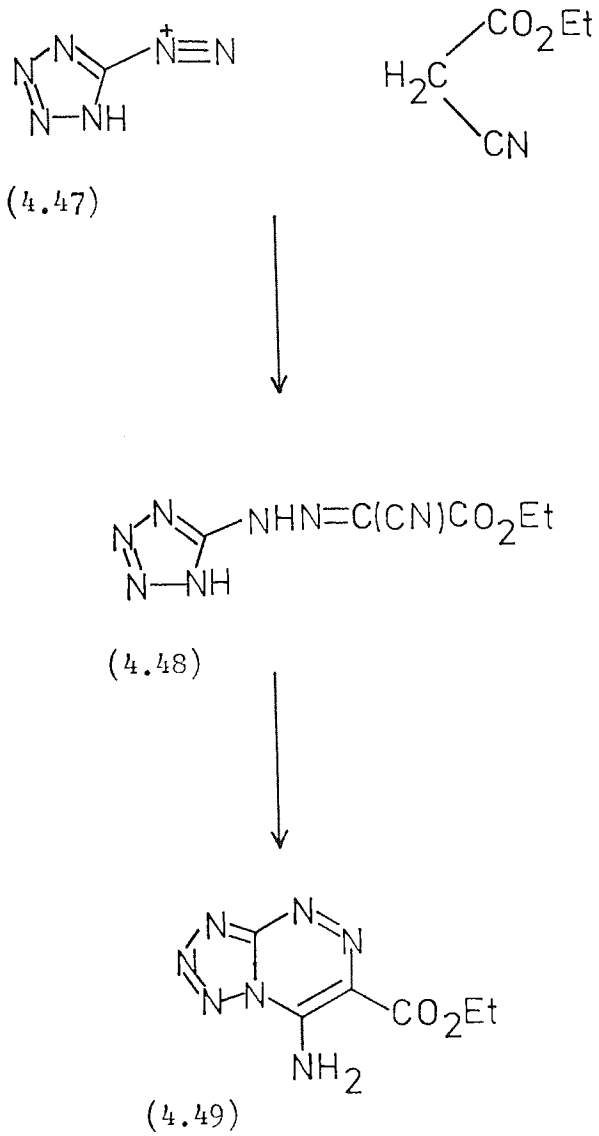
The pyrazol-3-ylhydrazone (4.44) (from aqueous ethanol) cyclized in boiling acetic acid to give the amino-ester (95%) (4.45) as originally reported[94] but traces of the cyanopyrazolotriazinone (4.46) were detected in the reaction mixture (t.l.c.). This derivative (4.46) was the major product when the hydrazone (4.44) was boiled in aqueous ammonia and the sole product (as the pyridine salt) when cyclization was performed in pyridine. The salt partially dissociated in boiling aqueous ethanol which indicates a decreased acidity relative to the corresponding triazole analogue (4.5). The free acidic cyanopyrazolo-triazinone (4.46) was liberated from the salt with 1N- hydrochloric acid and the spectral characteristics of this compound (4.46) and its salts accorded well with those of the corresponding triazole series.

(3) 1H-tetrazol-5-yldiazonium chloride and ethyl cyanoacetate.

Investigations in this series were complicated by the explosive nature of the tetrazole diazonium salt (4.47);[118] a concentration of $< 0.2M$ was imperative. Therefore a 0.1M solution of 5-aminotetrazole was diazotized in hydrochloric acid at $0^{o}C$ for ten minutes, the pH was adjusted to 3 with sodium hydroxide, and ethyl cyanoacetate was added. The precipitate analysed as a monohydrate of the hydrazone (4.48) (m.p. 175°) but on further purification it crystallized as the non-solvated form (m.p. 160-$2^{o}C$) (from ethanol). In a sodium acetate buffer (pH 6) the sodium salt of the strongly acidic hydrazone was obtained.

Both the salt and the free acid hydrazones (4.48) cyclized in glacial acetic acid to give the amino-ester (4.49) in a high yield. This derivative (4.49) was also obtained when the free acid hydrazone (4.48) was boiled in pyridine, but the hydrazone salt was recovered unchanged in this medium. Cyclization of the hydrazone (4.48) and its salt was examined under a variety of conditions (aqueous ammonia, water, ethanol, dry heat) but no indication was found of a corresponding cyanotetrazolotriazinone.

A comparison of the u.v. spectra of the amino-esters in the triazolo- (4.4a), pyrazolo- (4.45), and tetrazolo- (4.49) series is illustrated in Figure 6.



(Scheme 4.6)

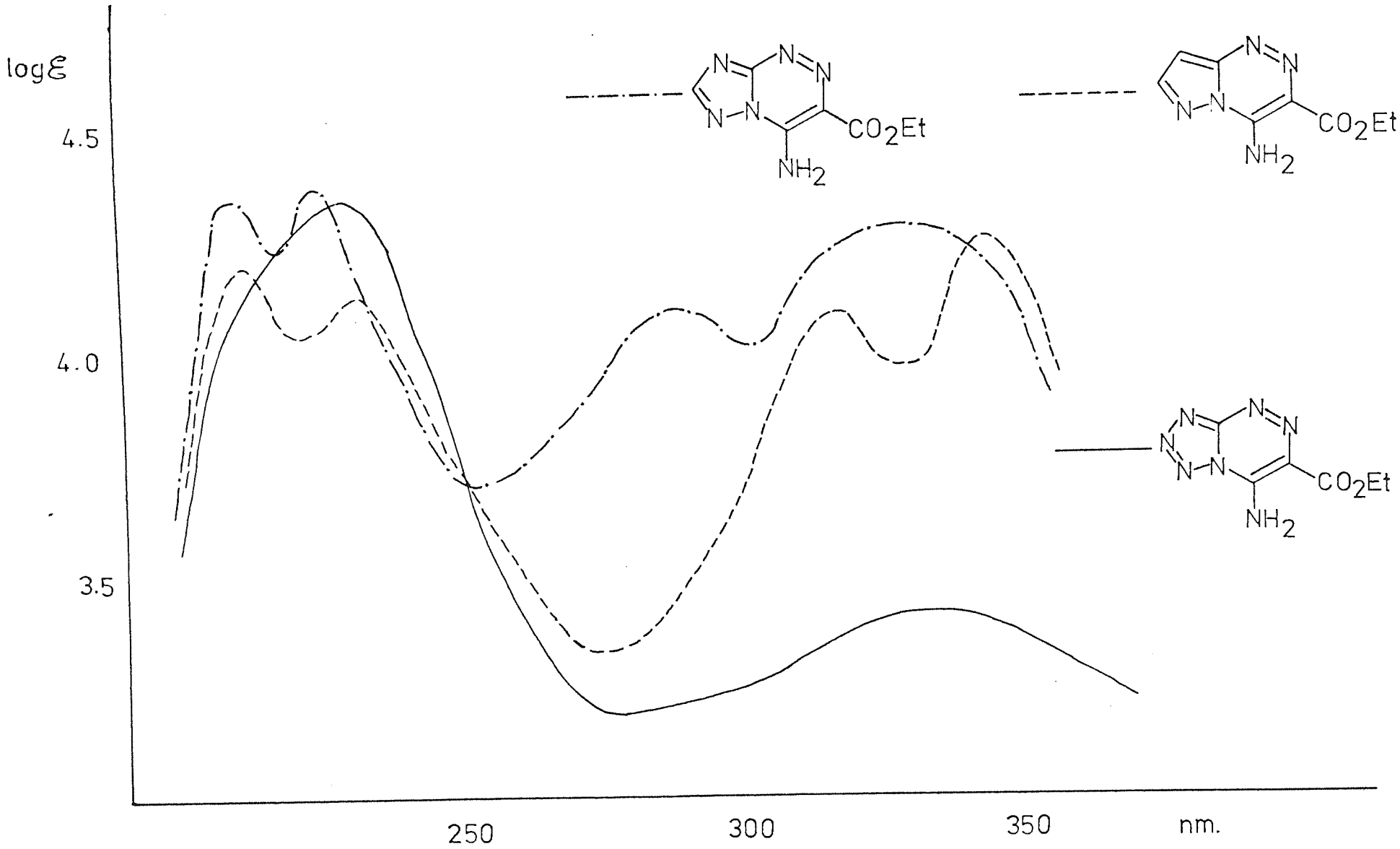
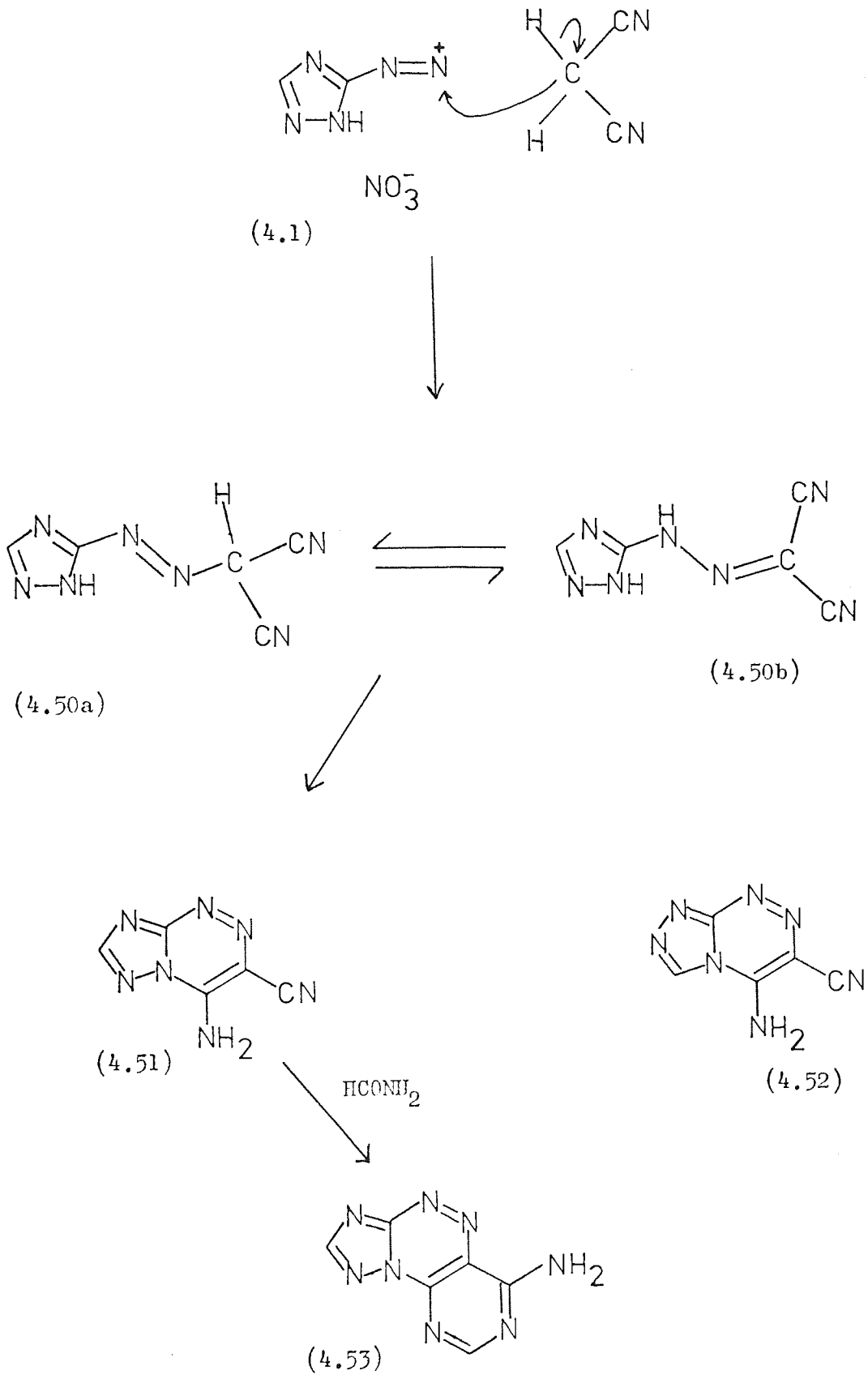


Figure 6

(4) 2H-1,2,4-triazol-3-yldiazonium nitrate with malononitrile.

The triazole diazonium salt (4.1) coupled smoothly with malononitrile in a sodium acetate buffer to give a yellow precipitate which was filtered in portions while maintaining a low temperature. The single broad absorption in the u.v. spectrum (λ max 370nm.) for the crude material indicated the hydrazone (4.50b) [cf. hydrazones (4.3b) (4.44) and (4.48)] but on attempted purification new absorptions arose in the u.v. spectrum at 350, 288 and 277 nm. After prolonged coupling, the precipitate isolated (Compound A), gave the same u.v. absorptions (λ max 350, 288 and 277nm) and further spectroscopic data (i.r. and mass spectra) were consistent with an aminocyanotriazolotriazine (4.51) or (4.52) (Scheme 4.7). Although Compound A could be carefully recrystallized several times from methanol it proved to be unstable and was converted by prolonged boiling in methanol or on heating in glacial acetic acid to a stable form B, also isolated by slow precipitation from the filtrate of the coupling medium. The two forms (A and B) gave similar mass spectra and a single C≡N absorption in their i.r spectra (2250cm^{-1}). Compound A also absorbed at 1635cm^{-1} (C=N) in its i.r. spectrum in contrast to Compound B which gave absorptions at 1695 (N-H deformation) and 1620cm^{-1} (C=N) in addition to a different u.v. spectrum λ max 331, 285 (in fl.) and 274 nm . Compound B was accordingly assigned structure (4.51) as a hydrate on the basis of a C, H and N analysis. As expected for this configuration (4.51) it was stable in boiling pyridine and acetic acid.

N.m.r. evidence [Part III (8)] militates against the otherwise attractive suggestion that Compound A could be the unstable Dimroth isomer (4.52): the triazole proton of Compound A resonates at τ = 1.94 in contrast to that of Compound B at τ = 1.4. It is possible that the unstable intermediate (Compound A) is an unusual solvate or even a salt but its structure



(Scheme 4.7)

must remain open at the present time.

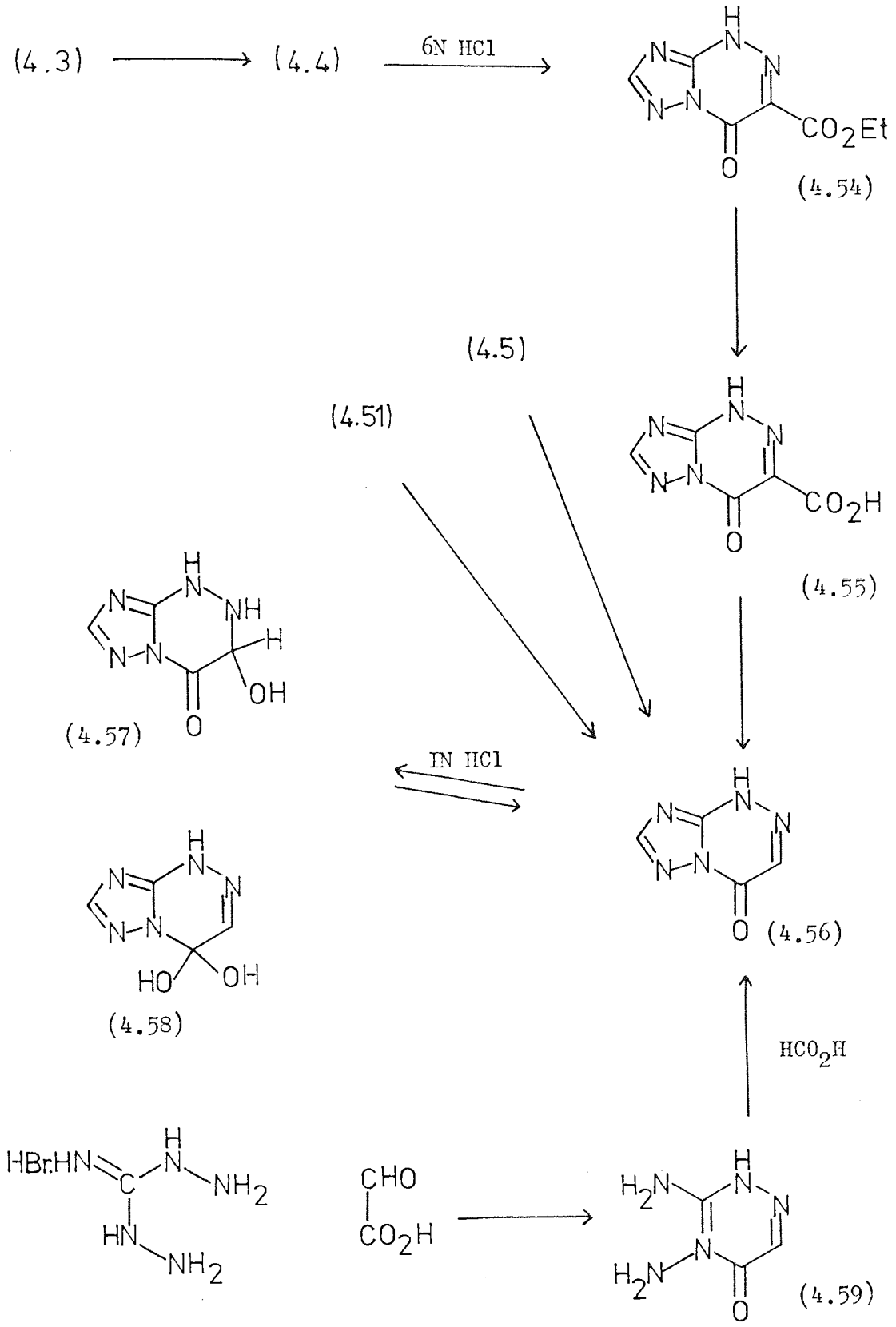
Like many o-aminonitriles[119] (4.51) and Compound A cyclized to the fused aminopyrimidine (4.53) in boiling formamide.

(5) Hydrolytic transformations of 1,2,4-triazolo[5,1-c]-1,2,4-triazines.

Hydrolysis of the hydrazones (4.3b), (4.50b), the triazolotriazines (4.4a), (4.5a) and (4.51) in 6N-hydrochloric acid gave a product (55-65%) in each case which was a hydrate of the triazinone (4.56). In boiling acetic acid this hydrate gave the pure triazinone (4.56), also independently formed by an alternative route (Scheme 4.8);[28] it reverted to the hydrate in 1N-hydrochloric acid. It is feasible that hydrolysis of the hydrazone proceeds as depicted in Scheme 4.8 and it is worth noting that the corresponding pyrazol-3-ylhydrazone (4.44) and pyrazolotriazine amino-ester (4.45) both hydrolyse in 6N-hydrochloric acid to form pyrazolo[5,1-c]--1,2,4-triazin-7(4H)-one in a related process.[94]

The exact structure of the hydrate of the triazolotriazinone (4.56) is not clear. Although the mass spectrum of the hydrate showed a molecular ion (m/e 137) corresponding to the unsolvated triazinone (4.56), the hydrate appears not to be a simple water solvate because of substantial differences in the u.v. spectrum - notably the strong absorption at 240nm. in the triazinone (4.56) is absent in the hydrate. Moreover, the proton in the unsolvated triazolotriazinone (4.56) at H-6 (τ 2.20)[28,120] is moved upfield (to τ 2.54) in the hydrate; the H-2 proton on the other hand is little modified.

On the reasonable assumption that covalent hydration would involve the π-deficient triazine ring of (4.56)[91] two adducts (4.57) and (4.58) are possible involving nucleophilic addition at C-6 or C-7 respectively. Structure (4.57) is supported by the i.r. spectrum of the hydrate which shows a weak carbonyl band (1710cm^{-1}) but is contraindicated by the afore-mentioned ^{1}H n.m.r. spectrum. The H-6 proton in the hydrate (4.57) would be expected to absorb considerably upfield of the observed signal at τ 2.54.[121] This value is reasonable for H-6 in the gem-diol (4.58),


(4.3)
(4.4)
6N HCl
CO2Et
(4.54)
(4.5)
(4.51)
CO2H
(4.55)
(4.57)
IN HCl
(4.56)
(4.58)
HCO2H
HBr.HN
NH2
CHO
CO2H
(4.59)

(Scheme 4.8)

yet the i.r. spectrum militates against this structural assignment.

Although 6,7-diphenyl-1,2,4-triazolo[5,1-c]-1,2,4-triazine (3.30) is known to undergo acid-promoted nucleophilic addition at C-7 to yield the adducts (3.31 a-c) which give remarkably similar u.v. spectra (λ max $\simeq$ 295nm) to that of the hydrate (λ max 290nm), nevertheless, because of conflicting spectroscopic evidence the structure of the hydrate of the triazolotriazinone (4.56) must remain open. Indeed the whole problem of adduct formation in mono-cyclic 1,2,4-triazines[121] and bicyclic 1,2,4-triazines is worthy of further study.

Table 5 U.V. spectra λ max. (n.m.), log ε in parentheses of 6,7-disubstituted-1,2,4-triazolo[5,1-c]-1,2,4-triazines

4.4a	325(4.29)	282(4.17)	229(4.35)	215(4.32)
4.35	332(4.01)	280(3.87)	223(4.16)	
4.36	303	223		
4.37	275			
4.5a.	319(4.41) 217sh(4.35)	275(3.95) 213(4.35)	257sh(4.05)	253(4.06)
4.5a (pyridine salt).	332(4.11) 250(3.74)	273sh(3.76) 244sh(3.58)	263(3.89) 223(4.05)	257(3.86)
4.5l	332(3.90) 210(4.11)	284sh(3.77)	279(3.78)	228(4.03)
4.56[28]	296(3.80)	240(3.58)		

(6) 2H-pyrazol-3-yldiazonium chloride and 2H-1,2,4-triazol-3-yldiazonium nitrate with 2-naphthol.

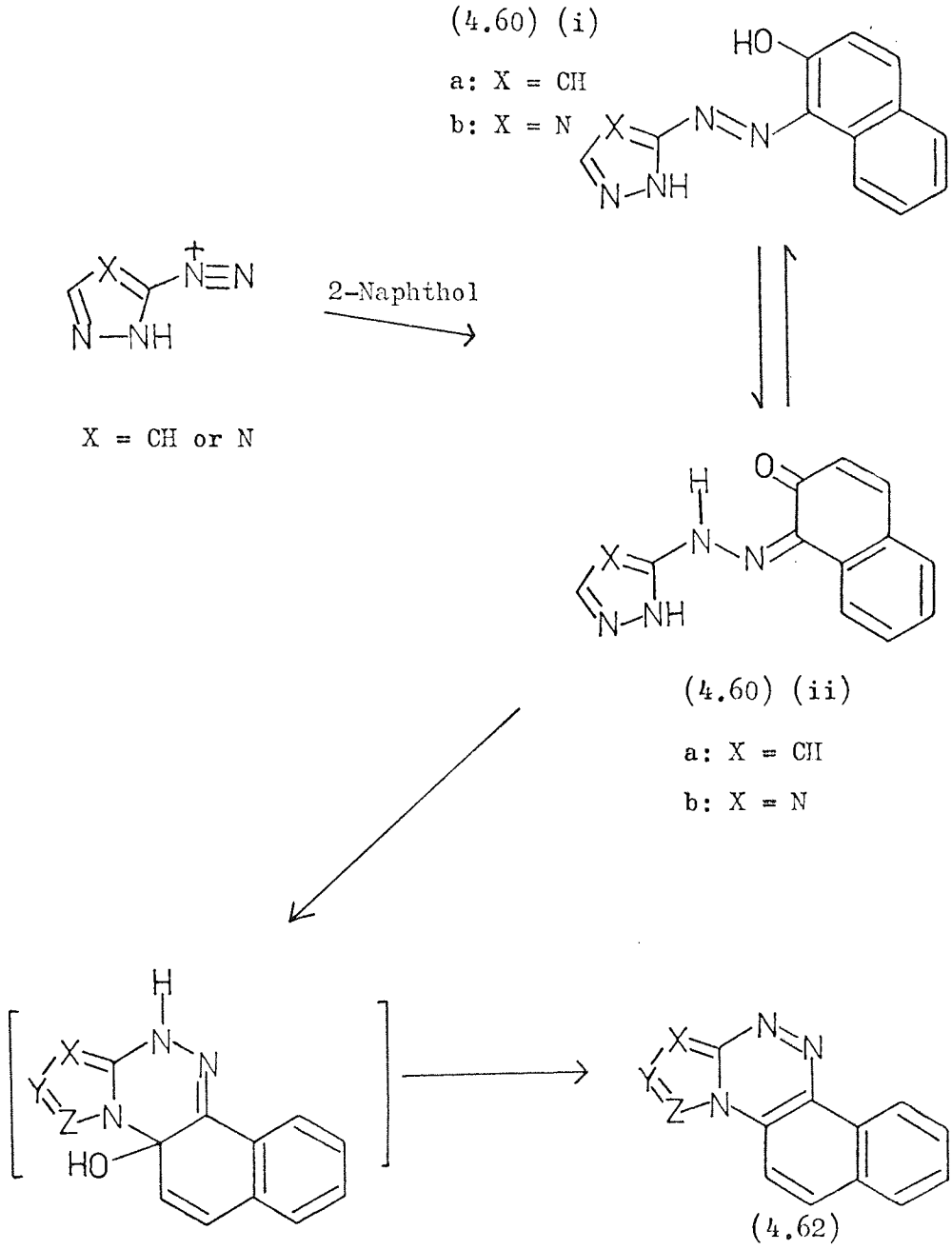
Reaction of the pyrazolodiazonium chloride and the triazolodiazonium nitrate in a sodium acetate buffer with 2-naphthol resulted in the respective open-chain coupling products (4.60a) and (4.60b) by electrophilic attack at position 1 in the 2-naphthol molecule. The presence of the hydrazone tautomer (4.60 ii) is suggested by the i.r. absorption at 1626cm^{-1} in the pyrazole (4.60a) and at 1650cm^{-1} in the triazole (4.60b). Further support for this tautomer (4.60ii) was indicated in the mass spectra: the diazo ions[103] at m/e 95 or 171 in the pyrazole system (4.60a) and at m/e 96 or 171 in the triazole system (4.60b) were absent.

The pyrazole analogue (4.60a) cyclized in boiling ethanol (6 hours), glacial acetic acid (2 hours) or dilute hydrochloric acid (4 hours) to naphtho[2,1-e]pyrazolo[5,1-c]-1,2,4-triazine (4.62a) with appropriate disappearance of the C=O absorption (at 1626cm^{-1}). On gentle heating in methanol or ethanol the triazole compound (4.60b) gave an isolable unstable intermediate. This intermediate, or the initial open-chain derivative (4.60b), on prolonged boiling in alcohols or in glacial acetic acid gave the stable naphthotriazolotriazine (4.62b). This structure (4.62b) was assigned because of the stability of the naphthotriazolotriazine in the familiar solvents (pyridine, piperidine, acetic acid) and to dry heat.

The exact structure of the unstable intermediate remains controversial. However, the following properties suggest cyclization has occurred:

(1) A peak at m/e 221 corresponding to (4.62 b or c) is the highest peak in the mass spectrum.

(2) The compound analysed for $C_{12}H_7N_5 \cdot 0.5\ CH_3OH$ from reaction in methanol but for $C_{12}H_7N_5\ 0.5\ CH_3CH_2OH$ from reaction in ethanol.



a: X = Y = CH, Z = N

b: X = Z = N, Y = CH

c: X = Y = N, Z = CH

(Scheme 4.9)

(3) Significant differences in the u.v. spectra (Figure 7) distinguish the intermediate from (4.60b) and (4.62b).

(4) The peak at $1650 cm^{-1}$ in the i.r. spectrum of (4.60b) is replaced by a new absorption at $1620 cm^{-1}$ in the intermediate.

It is possible that the intermediate is an unusual solvate.

A group concurrently working in this field[68] similarly found that cyclization of (4.60b) gave (4.62b) but when methanol with some drops of concentrated sulphuric acid was employed, a mixture of (4.62 b and c) was obtained; evidence for the two isomers was given by n.m.r. spectroscopy. It is interesting to note structure (4.62c) was reported[68] to be stable.

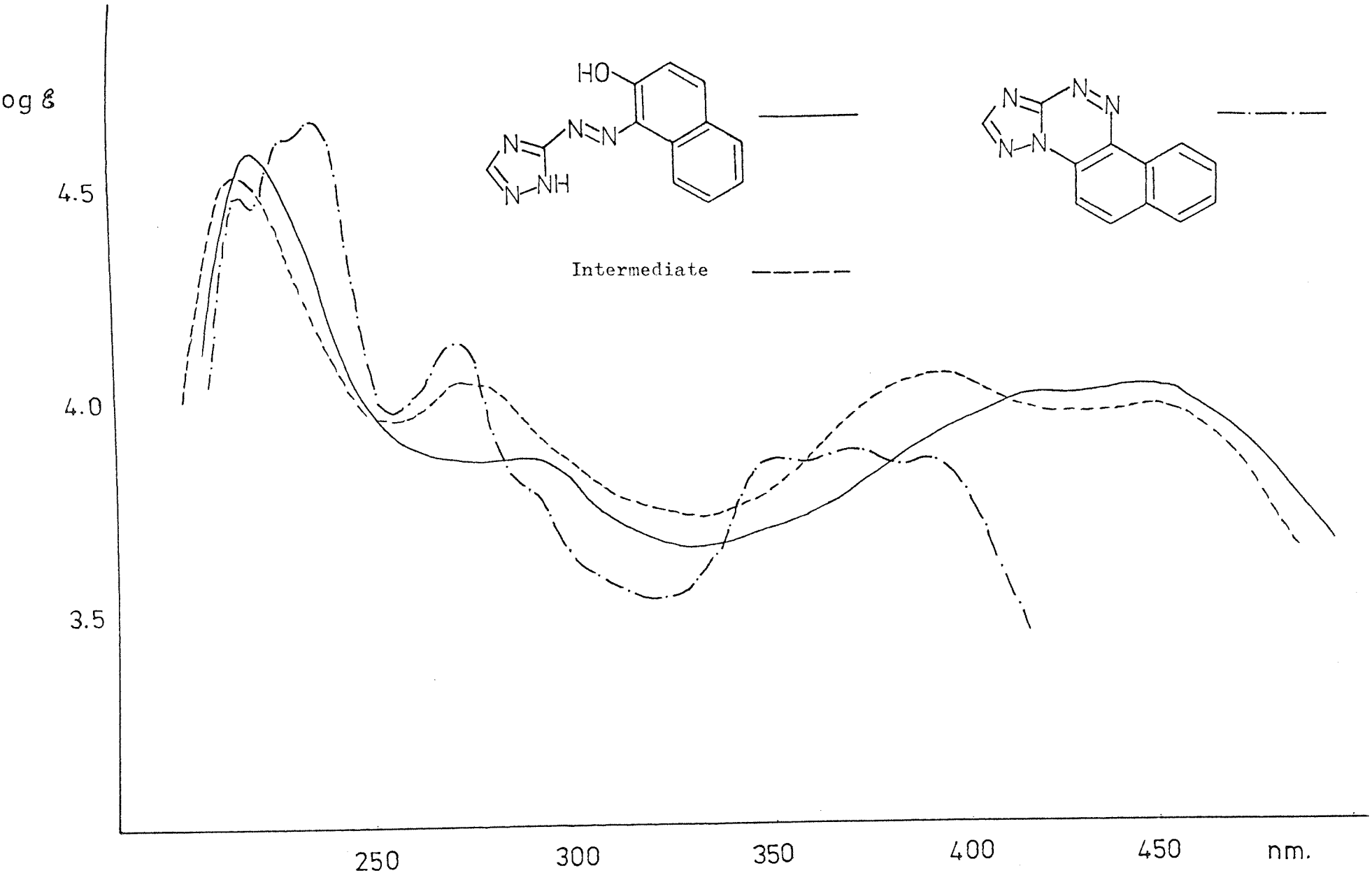

og ε
4.5
4.0
3.5
250
300
350
400
450
nm.
HO
N
N
N
NH
N
N
N
N
N
N
Intermediate

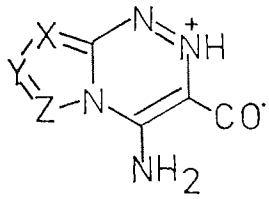
Figure 7

(7) Mass spectra of azolo[5,1-c]-1,2,4-triazines

The mass spectra (measured at 70eV on an A.E.I. MS9 spectrometer) of the 1,2,4-triazolotriazine amino-ester (4.4a) and the corresponding tetrazolotriazine derivative (4.49) closely parallel the spectrum of the pyrazolotriazine amino-ester (4.45).[122] The major fragmentation pathways of these compounds together with possible structures for the important ions are recorded in Scheme 4.10 (metastable supported transition are denoted by an asterisk). Although a minor N_2 loss from the tetrazole ring in the tetrazolotriazine amino-ester (4.49) was observed, the available data (Table 6) confirm that of the two rings in the bicyclic systems the azole ring is the more stable. The triazolotriazine piperidino-amide (4.35) shows a similar fragmentation, but the related amino-nitrile (4.51) deviates substantially from this pathway; the latter (4.51) shows only two ions of significance - the molecular ion (m/e 161) and the triazol-3-yldiazonium ion (m/e 96). The spectra of the two acetyl-derivatives (4.36) and (4.37) were substantially similar to that of the parent amino-ester (4.4a) after an initial ketene loss.

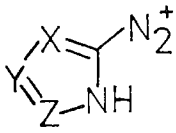
(4.4a) (4.45) (4.49)

$\downarrow$ $-e$, $-C_2H_4O$



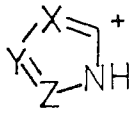
4.4a: m/e 164
4.45: m/e 163
4.49: m/e 165

$\swarrow$ $-C_3H_2NO^{\bullet}$



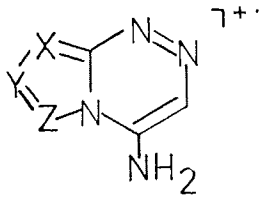
4.4a: m/e 96
4.45: m/e 95
4.49: m/e 97

$\downarrow$ $-N_2^*$



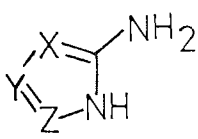
4.4a: m/e 68
4.45: m/e 67
4.49: m/e 69

$\downarrow$ $-CO^*$



4.4a: m/e 136
4.45: m/e 135
4.46: m/e 137

$\downarrow$ $-C_2N_2$



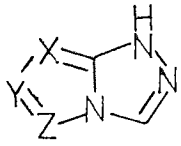
4.4a: m/e 84
4.45: m/e 83
4.49: m/e 85

$\searrow$ $-CHN_3XYZ^{\bullet}$

$H_2N.C{:}C.CO^+$

m/e 68

$\searrow$ $-HCN^*$



4.4a: m/e 109
4.45: m/e 108
4.49: m/e 110

4.4a: X=Z=N, Y=CH
4.45: X=Y=CH, Z=N
4.49: X=Y=Z=N

(Scheme 4.10)

TABLE 6

Mass spectra of azolylhydrazones and azolo[5,1-c]-1,2,4-triazines measured at 70eV on an A.E.I.-G.E.C. MS 902 spectrometer, with a source temperature in the range 100-150° (relative intensities in parentheses).

Compound	
(4.3)	208M(9) 164(27) 162(27) 136(100) 135(46) 109(18) 96(18) 84(36) 68(27) 54(27) 53(36) 52(27) 45(73)
(4.48)	209(15) 181(9) 165(36) 137(13) 69(8) 68(19) 54(10) 53(7)
(4.4a)	208M(18) 164(33) 136(100) 109(15) 96(23) 84(23) 68(30) 54(23) 53(39)
(4.45)	207M(100) 163(100) 135(100) 108(48) 95(70) 83(100) 68(38) 67(31) 54(28) 53(86) 52(86)
(4.49)	209M(22) 181(22) 165(86) 137(30) 110(3) 97(4) 81(13) 69(38) 68(85) 54(50) 53(36).
(4.35)	247M(7) 164(3) 136(6) 109(6) 96(15) 84(100) 68(15)
(4.36)	250M(12) 235(40) 208(38) 164(77) 136(100) 135(18) 109(17) 96(24) 84(34) 68(24) 54(15) 53(22) 43(20)
(4.37)	250M(9) 208(70) 164(54) 136(100) 135(23) 109(12) 96(23) 84(26) 68(18) 54(9) 53(12) 43(62)
(4.51)	161M(100) 134(18) 109(3) 96(76) 68(20) 53(33)

C. Experimental.

(1) I.r. spectra were recorded as KBr discs on a Perkin-Elmer 157G spectrometer unless specified as a nujol suspension. The latter were recorded on a Unicam SP 200 spectrometer.

(2) U.v. spectra were recorded on a Unicam SP 8000 spectrometer (in 95% ethanol).

(3) ^{1}H N.m.r. spectra were recorded on a Varian HA - 100D spectrometer (Me_4Si as internal standard).

(4) Mass spectra were measured at 70eV on an A.E.I. - G.E.C. MS 902 spectrometer with a source temperature in the range 100-150° (relative intensities in parentheses).

(5) T.l.c. separations were accomplished on silica gel (0.25mm) with benzene-acetone (6:4) as developing solvent.

Part V

(1) Synthesis of 1,2,4-triazolo[5,1-c]-1,2,4-triazines from hydrazines.

3-Amino-5-hydrazino-1,2,4-triazole dihydrochloride

3,5-Diamino-1,2,4-triazole (10g) in IN-hydrochloric acid (200ml) was diazotized at 0° with a solution of sodium nitrite (7.5g) in water (25ml). The red precipitate was collected and stirred at $0^{o}C$ for 1h. with stannous chloride dihydrate (56g) in 10N-hydrochloric acid (100ml). Then the mixture was heated to 80°, filtered, cooled and the filtrate saturated with hydrogen chloride gas. The aminohydrazinotriazole dihydrochloride (8.3g) separated as a white crystalline solid, m.p. $214-216^{o}$ (efferv.) (Lit.[83] m.p. 217°).

3-Hydrazino-1,2,4-triazole hydrochloride

(1) 3-Amino-1,2,4-triazole (8.4g) in IN-hydrochloric acid (80ml) was diazotized at 0° with a solution of sodium nitrite (8.3g) in water (25ml). The yellow precipitate was collected and slowly added to a mixture of stannous chloride dihydrate (20g) and 10N-hydrochloric acid (25ml) at 0°. The mixture was maintained at 0° overnight, filtered and the filtrate was saturated with hydrogen chloride gas. The hydrazinotriazole hydrochloride (3.7g) separated as a white crystalline solid, m.p. $224-5^{o}$ (Lit.,[85] 224°).

(2) 3-Nitroamino-1,2,4-triazole (20g)[88] and activated zinc dust (40g) were moistened with water and ground to a paste. The paste was suspended in water (100ml) at 10° and treated with 50% aqueous acetic acid (200ml) over 2h, the temperature being maintained at 10-20°. The mixture was stirred at 20° for a further 4h, heated to 60° (1h) and allowed to cool. Excess zinc was filtered off and the filtrate saturated with hydrogen sulphide (2h). After removal of zinc sulphide, the filtrate and washings were treated with 10N-hydrochloric acid. The evaporated solution afforded a gum which was boiled with chloroform (10ml) for 30min. 3-Hydrazino-1,2,4-triazole hydrochloride (10g) separated on the addition of absolute ethanol (50ml); m.p. 225° (Lit.,[85] 224°)

3-Chloro-1,2,4-triazole.

3-Amino-1,2,4-triazole (5g) was diazotised at 0° in 7N-methanolic hydrogen chloride (30ml) with amyl nitrite (5.85g). After stirring at 0° for 3h, the mixture was stirred for a further 2h at 25°. The chloro-triazole (2.7g) separated as a yellow solid.

Attempted synthesis of 3-hydrazino-1,2,4-triazole

(1) Reduction of diazotized 3-aminotriazole with zinc and acetic acid.

The yellow precipitate (4g), isolated from diazotization of amino-triazole in hydrochloric acid with sodium nitrite (see above), was added to a suspension of activated zinc dust (3g) in water (50ml). 10% Aqueous acetic acid (100ml) was slowly added, the suspension was stirred at 10° for 7h and filtered. Benzil (2g) in ethanol (50ml) was added to the filtrate and the solution was heated under reflux for 3h. Benzil crystals (2g) precipitated on cooling.

(2) Reduction with sodium sulphite.

3-Amino-1,2,4-triazole (10g) in 50% aqueous nitric acid (100ml) was diazotized at 0° with a solution of sodium nitrite (9.6g) in water (30ml). The mixture was added to a solution at 0° of sodium sulphite (41g) in water (100ml) with sodium hydroxide (4g) over 10 min. After 0.5h, the solution was acidfied with 10N-hydrochloric acid (70ml) and slowly warmed to 50-80° for 0.5-1h. No product was isolated.

(3) Nucleophilic displacement of 3-mercapto-1,2,4-triazole with hydrazine.

Thiosemicarbazide (18.2g) and 100% formic acid (10ml) were heated on a water bath for 20mins. Formylthiosemicarbazide (18g), as white crystals, resulted on cooling (m.p. 185-7°).

Formylthiosemicarbazide (5g) was heated for 1h at 190-200° in an oil bath to give the mercaptotriazole (2.4g) m.p. 227-8° (water).

The mercaptotriazole (1g) and hydrazine hydrate (0.625g) were heated under reflux in butanol (17ml). 3-Hydrazino-1,2,4-triazole was not detected.

2-Amino-6,7-diphenyl-1,2,4-triazolo[5,1-c]-1,2,4-triazine (3.19)

3-Amino-5-hydrazino-1,2,4-triazole dihydrochloride (1.88g) was boiled in methanol (50ml) containing benzil (2.10g) for 2h. The triazolo-triazine (94%) deposited from the cooled solution and crystallized from aqueous ethanol as yellow needles, m.p. 272-274° (Found: C,66.4; H,4.2; N,29.6. $C_{16}H_{12}N_6$ requires C,66.7; H,4.2; N,29.2%); λ max.350 and 260nm (logε 3.89 and 4.43 respectively); ν max.3470 and 3325 (NH), 1620cm^{-1} (C=N); m/e 288 (M^{+}, 8), 287(11), 210(42), 178(6), 165(4), 152(4), 142(9), 106(7), 105(100), 77(37). The monoacetyl derivative (85%) which formed

in 1h from the triazolotriazine and boiling acetic acid-acetic anhydride (1:1), crystallized from ethanol with m.p. 294-5° (Found: C,65.1; H,4.5; N,25.7. $C_{18}H_{14}N_6O$ requires C,65.5; H,4.2; N,25.5%); λ max. 325 and 257nm (log ε 3.94 and 4.45); ν max. 3220 (NH) and 1700cm^{-1} (C=O); m/e 331(16), 330(M^+,73), 288(18), 287(100), 286(56), 259(19), 218(17), 190(21), 178(38), 165(20), 106(16), 103(17), 89(26), 77(21). The diacetyl derivative (78%) from the triazolotriazine in boiling acetic anhydride (2h) had m.p. 195-196° (from aqueous ethanol) (Found: C,64.6; H,4.4, $C_{20}H_{16}N_6O_2$ requires C,64.5; H,4.3%); τ ($CDCl_3$) 2.4-2.6(m, 10H, 2xPh) and 7.74 (s, 6H, 2xMe); m/e 372(M^+, 3), 331(19), 317(8), 316(33), 288(19), 287(11), 259(3), 218(5), 190(4), 178(11), 165(6), 116(3), 103(10), 89(8), 77(4).

2-Amino-6,7-diphenyl-1,2,4-triazolo[5,1-c]-1,2,4-triazine was recovered unchanged after being subjected to the following conditions: dry heat at 300°(1h); boiling acetic acid, pyridine or piperidine (10h).

3-Amino-6,7-diphenyl-1,2,4-triazolo[4,3-b]-1,2,4-triazine (3.24).

5,6-Diphenyl-3-hydrazino-1,2,4-triazine (2.63g)[124] and cyanogen bromide (1.16g, 1.1mol) were boiled in methanol (125ml) for 2h. Addition of cold ether (150ml) precipitated a hydrobromide salt which was collected and stirred in an aqueous sodium acetate solution. The red triazolotriazine (73%) crystallized from ethanol with m.p. 263-264° (Lit.,[49] m.p. 263-264°) (Found: C,66.7; H,4.1; N,29.1. Calc. for $C_{16}H_{12}N_6$: C,66.7; H,4.2; N,29.2%); λ max. 420, 335(in fl.), 284 and 243nm (log ε 3.38, 3.80, 4.17 and 4.17); ν max. 3395(NH), 3060(broad, bonded NH), 1623cm^{-1} (C=N); m/e 288(M^+,5), 261(13), 190(6), 179(17), 178(100), 177(8),

176(13), 165(10), 115(25), 114(10), 104(52), 103(13), 89(6), 77(17), 76(8). The diacetyl derivative (92%), from the base and boiling acetic anhydride (1h) had m.p. 190-191° (from methanol) (Found: C,64.2; H,4.2; N,22.7. $C_{20}H_{16}N_6O_2$ requires C,64.5; H,4.3; N,22.9%); λ max. 340 and 229nm (log ε 3.84 and 4.41); ν max. 1740 and 1723cm^{-1} (C=O); τ ($CDCl_3$) 2.55-2.90 (m, 10H, 2xPh) and 7.79 (s, 6H, 2xMe); m/e 331(15), 330(75), 315(75), 288(27), 212(54), 178(27), 165(9), 157(27), 104(36), 103(100), 95(24), 91(84), 89(12), 81(24), 77(51), 76(27).

The amino-diphenyltriazolotriazine was stable to dry heat (270 for 1h) and in boiling acetic acid, pyridine or piperidine (14h).

The triazolotriazine (0.12g) in anhydrous tetrahydrofuran (25ml) was added dropwise (2h) to a boiling solution of amyl nitrite (0.44g) in tetrahydrofuran (5ml). The solution was boiled for a further 3h and the solvent vacuum evaporated. The product, purified by column chromatography on neutral alumina with elution by a benzene-chloroform mixture, afforded 6,7-diphenyl-1,2,4-triazolo[4,3-b]-1,2,4-triazine (3.25) (0.07g) identical (i.r. and mass spectrum) to an authentic sample prepared by reacting 5,6-diphenyl-3-hydrazino-1,2,4-triazine with 100% formic acid or triethyl orthoformate.[56]

6,7-Diphenyl-1,2,4-triazolo[4,3-b]-1,2,4-triazin-3(2H)-one (3.27).

6,7-Diphenyl-1,2,4-triazolo[4,3-b]-1,2,4-triazine (5.43g) in acetic anhydride (12ml) at -5° was treated dropwise (30min) with a solution of nitric acid (s.g. 1.5, 1.26g) in acetic anhydride (5ml). The temperature was allowed to warm to 0° and the mixture was quenched with ice-water. The precipitated triazolotriazine (2.7g) crystallized from methanol with m.p. 285-286° and was identical (i.r. and mass spectrum) to an authentic

sample prepared from 5,6-diphenyl-3-hydrazino-1,2,4-triazine and urea.[63]

6,7-Diphenyl-1,2,4-triazolo[5,1-c]-1,2,4-triazine (3.30).

(1) 2-Amino-6,7-diphenyl-1,2,4-triazolo[5,1-c]-1,2,4-triazine (3.19) (0.24g) in tetrahydrofuran (60ml) was added dropwise over 2h to a boiling solution of amyl nitrite (0.88g) in tetrahydrofuran (10ml). The solution was boiled (3h) and solvent vacuum evaporated. The residue was dissolved in benzene and chromatographically fractionated on a neutral alumina column. Evaporation of the benzene eluate afforded the diphenyltriazolotriazine (0.09g), m.p. 193-5° (from methanol) (Found: C,70.2; H,4.3; N,25.7. $C_{16}H_{11}N_5$ requires C,70.3; H,4.0; N,25.6%); τ ($CDCl_3$) 1.34 (s, H-2), 2.3-2.7 (m, 10H, 2xPh); λ max 349 and 248nm (logε 3.84 and 4.32); m/e 274(13), 273(M^+,100), 272(56), 219(13), 218(13), 205(6), 190(31), 189(25), 178(31), 165(19), 105(13), 77(13), 76(13).

(2) 3-Hydrazino-1,2,4-triazole hydrochloride (0.5g), benzil (0.6g) and sodium acetate trihydrate (2g) were boiled in methanol (50ml) for 2h. The same triazolotriazine (40%) was deposited when the solution was diluted with water.

The triazolotriazine was stable at 200° (1h) and in boiling acetic acid, pyridine and piperidine (10h).

4,7-Dihydro-6,7-diphenyl-7-methoxy-1,2,4-triazolo-[5,1-c]-1,2,4-triazine (3.33b).

3-Hydrazino-1,2,4-triazole hydrochloride (0.5g) and benzil (0.6g) were boiled in methanol (6h) and the solvent vacuum-evaporated. Crystallization of the residue from methanol afforded the methoxytriazolo-

triazine (60%), m.p. 211-212° (Found: C,66.6; H,5.0; N,23.4. $C_{17}H_{15}N_5O$ requires C,66.9; H,5.0; N,23.4%); λ max. 297nm (log ε 4.16); τ ($CDCl_3$) 2.15 (s, H-2), 2.18-2.75 (m, 10H, 2xPh) and 6.76 (s, OMe); M.W. (mass spectrum) 305.127264. $C_{17}H_{15}N_5O$ requires 305.127653; m/e 306(9), 305 (M^+, 47), 275(12), 274(67), 273(100), 272(57), 218(13), 201(33), 190(26), 189(20), 178(20), 165(17). 115(9), 105(22), 104(12), 103(12), 77(30), 76(12).

The methoxytriazolotriazine (0.2g) was converted in boiling acetic acid (3ml) to 6,7-diphenyl-1,2,4-triazolo[5,1-c]-1,2,4-triazine (i.r. and u.v.) after 2h, in 90% yield.

4,7-Dihydro-6,7-diphenyl-7-ethoxy-1,2,4-triazolo[5,1-c]-1,2,4-triazine (3.33c).

Reaction of 3-hydrazino-1,2,4-triazole hydrochloride and benzil in ethanol as above afforded the ethoxytriazolotriazine (65%), m.p. 205-206° (from methanol) (Found: C,67.6; H,5.4; N,21.9. $C_{18}H_{17}N_5O$ requires C,67.7; H,5.3; N,21.9%), λ max. 298nm (log ε 4.16); M.W. (mass spectrum) 319.142546. $C_{18}H_{17}N_5O$ requires 319.143302; m/e 319(17), 275(10), 274(53), 273(86); 272(46), 218(17), 205(10), 190(43), 189(33), 188(27), 178(50), 165(33), 115(27), 105(86), 104(33), 103(30), 89(20), 88(10), 78(10), 77(100), 76(33).

The ethoxytriazolotriazine (0.5g) was boiled in acetic acid (5ml) for 2h and solvent removed under vacuum. The product (93%) was identical (ir) to 6,7-diphenyl-1,2,4-triazolo[5,1-c]-1,2,4-triazine (3.30). The ethoxytriazolotriazine was similarly converted to (3.30) by heat (1h at 220°) and boiling pyridine (2h) in 90 and 95% yields respectively.

3-Amino-5-hydrazinopyrazole dihydrochloride (3.38).

Malononitrile (6.6g) in ethanol (30ml) was treated with a solution of 80% aqueous hydrazine hydrate (10ml) over 10min. The mixture was stirred for 4h at 20-25° and solvent removed to yield a red oil. Addition of 10N-hydrochloric acid (30ml) gave a brown solid which was collected after being kept at 0° for 24h. The solid crystallized from 18% aqueous hydrochloric acid to afford the pyrazole dihydrochloride (7.8g), m.p. 205° [Lit.,[93] 205° for the triazine dihydrochloride (3.37)].

7-Amino-3,4-diphenylpyrazolo[5,1-c]-1,2,4-triazine (3.39a).

3-amino-5-hydrazinopyrazole dihydrochloride (0.93g) and benzil (1.1g) in boiling ethanol (30ml) yielded a yellow precipitate. After 1h the diphenylpyrazolotriazine was collected (95%), m.p. 338° (from n-butanol) (Found: C,70.8; H,4.6; N,24.6. $C_{17}H_{13}N_5$ requires C,71.1; H,4.5; N,24.4%); λ max. 353 and 281nm (log ε , 3.48 and 4.45); m/e 288 (18), 287(M^+, 100), 286(45), 230(11), 205(8), 202(11), 178(28), 176(9), 165(14), 152(8), 104(9), 103(8), 89(11), 83(10), 77(22).

The monoacetyl derivative (83%), from the pyrazolotriazine and boiling acetic anhydride (1h) had m.p. 324° (Found: C,68.9; H,4.6; N,20.9. $C_{19}H_{15}N_5O$ requires C,69.3; H,4.6; N,21.3%); λ max. 348 and 271nm (log ε 3.46 and 4.57); m/e 329 (M^+, 78), 287(31), 286(31), 178(78), 176(12), 165(12), 139(24), 119(42), 111(65), 103(100), 77(60), 76(56).

The pyrazolotriazine (3.39a) (0.2g) in anhydrous tetrahydrofuran (125ml) was added dropwise (2h) to a boiling solution of amyl nitrite (1.22g) in tetrahydrofuran (10ml). The solution was boiled for a further 3h and solvent vacuum-evaporated. The product, purified by

column chromatography on neutral alumina with elution by light petroleum (60-80°), afforded 3,4-diphenylpyrazolo[5,1-c]-1,2,4-triazine (0.07g) identical (ir and mass spectrum) to an authentic sample prepared from reduced pyrazole-3-diazonium chloride and benzil.[94]

7-Amino-3,4-dimethylpyrazolo[5,1-c]-1,2,4-triazine (3.39b).

3-Amino-1,2,4-hydrazinopyrazole dihydrochloride (0.5g) and diacetyl (0.23g) in boiling aqueous ethanol (50ml) with excess sodium acetate trihydrate, afforded a precipitate of the dimethylpyrazolotriazine (94%), m.p. 202-3° (Found: C,51.7; H,5.7; N,42.5. $C_7H_9N_5$ requires C,51.3; H,5.5; N,42.9%); λ max. 337 and 254nm (log ε 3.46 and 4.52); m/e 164(20), 163(M^+, 100), 162(6), 134(4), 120(4), 106(8), 92(14), 82(14), 81(36), 79(14), 78(70), 77(22), 68(10), 67(16), 66(16).

(2) Synthesis of 1,2,4-triazolo[5,1-c]-, pyrazolo[5,1-c]- and tetrazolo[5,1-c]-1,2,4-triazines from coupling the diazonium azole with active methylene compounds.

Ethyl 2-(2H-1,2,4-triazol-3-ylhydrazono)cyanoacetate (4.3b).

3-Amino-2H-1,2,4-triazole (2.0g) in 50% aqueous nitric acid (50ml) was diazotized at 0° by the slow addition of sodium nitrite (1.9g) in water (4ml). The pale yellow diazonium solution was stirred for a further 1h at $0-5^{o}$, neutralised with sodium acetate trihydrate (6g), and reacted with ethyl cyanoacetate (2.6g) run in dropwise (10min). After stirring for a further 2h at $0-5^{o}$, the yellow solid was collected, washed with a minimum of ice-water, dried and crystallized from 70% aqueous ethanol to afford the (hydrazono) cyanoacetate hydrate as cream needles (98%) m.p. $177-178^{o}$ (Found: C,36.9; H,4.8; N,37.1. $C_7H_8N_6O_2.H_2O$ requires C,37.2; H,4.4; N,37.2%); λ max. 371nm (log ε 4.19); τ (DMSO-d_6) 1.79 (s, triazole C-H), 5.88(q,CH_2), 8.88(t,CH_3); m/e 208(M^+, 9), 164(27), 163(14), 162(27), 137(5), 136(100, 135(46), 109(18), 96(18), 84(36), 68(27), 54(27), 53(36), 52(27).

Solutions of the (hydrazono)cyanoacetate hydrate (4.3b) (2g) were boiled in water (100ml) for 10 and 45 min. and kept at 0°. After 7 days unreacted hydrazone (0.8g and 0.35g respectively) was recovered. Examination of the mother liquors (t.l.c.) showed the presence of ethyl 7-amino-1,2,4-triazolo[5,1-c]-1,2,4-triazine-6-carboxylate (4.4a) and 6-cyano-1,2,4-triazolo[5,1-c]-1,2,4-triazin-7-(4H)-one (4.5a).

Ethyl 7-amino-1,2,4-triazolo[5,1-c]-1,2,4-triazine-6-carboxylate (4.4a).

The hydrazone hydrate (4.3b) (1g) was boiled in acetic acid (6ml) for 2h and the solvent vacuum evaporated. The residue, triturated with ethanol, afforded the triazolotriazine (88%), m.p. 210-211°, (Found: C,40.0; H,4.0; N,40.2. $C_7H_8N_6O_2$ requires C,40.4; H,3.9; N,40.4%); ν max. 3355, 3280, 3210 and 3140 (NH), 1707(C=O) and 1640cm^{-1} (C=N); λ max. 325, 281 and 227 nm (log ε 4.01, 3.89 and 4.10); τ (DMSO-d_6) 1.2(s, triazole CH), 5.54(q,CH_2), 8.6(t,CH_3); m/e 208(M^+, 8), 164(33), 137(8), 136(100), 109(15), 96(23), 84(23), 68(30), 54(23), 53(39).

The amino-ester (4.4a) was recovered unchanged after being heated at 220° for 1h, or from boiling acetic acid, pyridine, collidine or triethylamine (10h).

Mother liquors of the reaction contained the cyanotriazolotriazinone (4.5a) (t.l.c).

7-Amino-1,2,4-triazolo[5,1-c]-1,2,4-triazine-6-piperidinoamide (4.35).

The amino-ester (4.4a) (1g) was heated under reflux in piperidine (8ml) for 30min and the solvent vacuum evaporated. The piperidino-amide (84%) crystallized from acetone with m.p. 234-5° (Found: C,48.3; H,5.8; N,39.4. $C_{10}H_{13}N_7O$ requires C,48.6; H,5.7; N,39.7%); ν max. 3300 and 3130 (NH), 2940, 2920 and 2860 (CH), 1655(C=O) and 1620cm^{-1} (C=N); λ max. 332, 280 and 223nm (log ε 4.01, 3.87 and 4.16); τ (DMSO-d_6) 1.29(s,NH), 1.45(s,CH), 6.53(s,2xCH_2-N), 8.53(s,3xCH_2); m/e 247(M^+, 7), 163(3), 136(6), 96(15), 85(12), 84(100), 68(15).

Ethyl 7-acetylamino-1,2,4-triazolo[5,1-c]-1,2,4-triazine-6-carboxylate (4.36).

The amino-ester (4.4a) (1g) was boiled in acetic anhydride (5ml) for 2.5h. Trituration of the cooled solution with ethyl acetate furnished the acetylaminotriazolotriazine (1g), m.p. 188-189° (Found: C,42.8; H,4.3; N,33.6. $C_9H_{10}N_6O_3$ requires C,43.2; H,4.0; N,33.6%); ν max. 3290 (NH), 1725 and 1700cm^{-1} (C=O); λ max. 303 and 223nm; τ (DMSO-d6) 1.23 (s, triazole CH), 5.75(q,CH_2), 7.8(s, $COCH_3$), 8.79(t,CH_3); m/e 250(M^+, 12) 236(4), 235(40), 222(12), 208(38), 205(8), 177(7), 165(7), 164(77), 163(13), 137(13), 136(100), 135(18), 109(17), 96(24), 84(34).

The amino-ester (4.4a) was recovered unchanged after being heated under reflux in acetic anhydride for 0.5h.

Ethyl 4-acetyl-7(4H)-imino-1,2,4-triazolo[5,1-c]-1,2,4-triazine-6-carboxylate (4.37).

The hydrazone hydrate (4.3b) (1g) was boiled in acetic anhydride for 0.5h and the solvent vacuum-evaporated. Trituration with ethyl acetate afforded the acetyliminotriazolotriazine (86%), m.p. 178-179° (Found: C,42.9; H,4.4; N,33.5. $C_9H_{10}N_6O_3$ requires C,43.2; H,4.0; N,33.6%); ν max. 1730cm^{-1} (C=O); λ max. 275nm; τ (DMSO-d_6) 1.3(s, triazole CH), 5.79(q,CH_2), 7.6(s, $COCH_3$), 8.83(t,CH_3); m/e 250 (M^+, 9), 209(7), 208(70), 164(54), 137(10), 136(100), 135(23), 109(12), 96(23), 84(26), 68(18).

6-Cyano-1,2,4-triazolo[5,1-c]-1,2,4-triazine-7(4H)-one (4.5a).

The hydrazone hydrate (4.3b) (1g) was boiled in 10% aqueous ammonia for 2h to afford the cyanotriazolotriazinone (t.l.c).[127]

The hydrazone hydrate (4.3b) (1g) was boiled in pyridine (5ml) for 30min. The cooled solution deposited the cyanotriazolotriazinone pyridinium salt (0.9g) which crystallized from acetone as white needles, m.p. 208-210° (sinters 185) (Found: C,49.4; H,3.0; N,40.9. $C_5H_2N_6O$. C_5H_5N requires C,49.8; H,2.9; N,40.7%); ν max. 3450(NH), 3120-3020(CH), 2800-2400(bonded OH or NH), 2230(C≡N), 1675(CO)and 1630cm^{-1}(C=N); λ max. 332, 273, 263, 257, 250(infl), and 225nm (log ε 4.11, 3.76, 3.89, 3.86, 3.74 and 4.05); τ (DMSO-d6) 0.4(s,NH), 1.75(s, triazole CH), 1-3.3 (m, pyridine CH); m/e 162(M^+, 70).

The same pyridinium salt (80%) was obtained when the cyanotriazolotriazinone (4.5a) was boiled in pyridine (5ml). The pyridinium salt was recovered unchanged from boiling acetic acid (14h).

When the pyridinium salt was acidified with 2N-hydrochloric acid a precipitate of the cyanotriazolotriazinone hydrate was obtained, identical (i.r.) to that concurrently prepared.[123]

The hydrazone hydrate (4.3b) (1g) in boiling collidine similarly afforded the cyanotriazolotriazinone collidinium salt (85%), m.p. 203-205° (from acetone) (Found: C,55.0; H,4.6. $C_5H_2N_6O$. $C_8H_{11}N$ requires C,54.6; H,4.7%); ν max. 3450(NH), 3110, 3060(CH), 2800-2400 (bonded OH or NH), 2223(C≡N) and 1685cm^{-1} (C=O); λ max. 332, 266 and 222nm (log ε 4.06, 4.01 and 4.06); τ (DMSO-d6) 1.69(s, triazole CH), 2.36 (s, collidine CH), 7.50(s, 3xCH_3); m/e 162 (M^+, 100).

Acidification of the salt with 2N-hydrochloric acid yielded the cyanotriazolotriazinone hydrate, identical (ir) to the previous samples.

The cyanotriazolotriazinone was stable in boiling glacial acetic acid (2h).

Further attempted cyclization conditions for ethyl 7-amino-1,2,4-triazolo [5,1-c]-1,2,4-triazine-6-carboxylate (4.4a).

The hydrazone hydrate (4.3b) when heated above its melting point or in boiling piperidine (2h) afforded a mixture of products (t.l.c.) including the amino-ester (4.4a) and the cyanotriazolotriazinone (4.5a).

Ethyl 7-aminopyrazolo[5,1-c]-1,2,4-triazine-6-carboxylate (4.45).

Ethyl 2-(2H-pyrazol-3-ylhydrazono)cyanoacetate (4.44)[94] (1g) was boiled in ethanol (50ml) for 48h. T.l.c. examination showed the presence of the amino-ester[94] (4.45), the cyanopyrazolotriazinone (4.46), and the starting hydrazone (4.44).

6-Cyanopyrazolo[5,1-c]-1,2,4-triazin-7(4H)-one (4.46).

Ethyl 2-(2H-pyrazol-3-ylhydrazono)cyanoacetate (4.44, from aqueous ethanol)[94] (1.0g) was boiled in pyridine (5ml) for 15 min. The pyridinium salt (1g, m.p. > 300° decomp.) which crystallized from the cooled solution did not give reliable micro-analyses. It partially dissociated in boiling ethanol (reduction in intensity of the pyridine protons in the ^{1}H n.m.r. spectrum). Acidification of the crude pyridinium salt with IN-hydrochloric acid afforded the cyanopyrazolotriazinone, m.p. 250° (decomp.) (from ethanol) (Found: C,44.5; H,2.0. $C_6H_3N_5O$ requires C,44.7; H,1.9%); ν max. 3100-2700 (broad,NH), 2250(C≡N) and 1698cm^{-1} (C=O); λ max 345, 295, 287 (shoulder), 275 and 269 (shoulder) (log ε 3.97, 3.69, 3.70, 3.86 and 3.84); τ(DMSO-d_6) 1.0(1xNH), 1.70(d,H-2), 3.30(d,H-3); m/e 161(M^+, 100), 135(32), 122(65), 94(72), 83(14), 79(20).

Ethyl 2-(1H-tetrazol-5-ylhydrazono)cyanoacetate (4.48).

5-Amino-1H-tetrazole (2g) in 0.5N-hydrochloric acid (200ml) at 0° was diazotized with sodium nitrite (1.4g) in water (10ml). (WARNING: a violent detonation of the diazotetrazole occurred when this reaction was carried out with a concentration of the tetrazole greater than 0.2M). The diazonium solution was gently stirred at 0° for 10min, adjusted to pH3 with powdered sodium hydroxide (4g), and treated dropwise (10 min) with ethylcyanoacetate (2.6g). The precipitate was stirred at 0° (1h), collected, and crystallized from aqueous ethanol to yield the (hydrazono)-cyanoacetate hydrate (85%) m.p. 175-176° (decomp.) (Found: C,31.4; H,4.2; N,43.5; M^{+}, 209 $C_6H_7N_7O_2 \cdot H_2O$ requires C,31.7; H,4.0; N,43.2%; M, 209). Further crystallization from ethanol furnished the unsolvated (hydrazono)cyanoacetate, m.p. 160-162° (decomp.) (Found: C,34.3; H,3.2; N,46.7. $C_6H_7N_7O_2$ requires C,34.4; H,3.3; N,46.9%); ν max 3280(NH), 3000-2800(bonded NH), 2235(C≡N) and 1710cm^{-1}(C=O); λ max. 368 (log ε 3.99); m/e 209 (M^{+}, 45), 181(24), 165(100), 139(9), 137(38), 111(9), 69(24), 68(56), 54(29).

When the coupling medium was adjusted to pH with excess sodium acetate trihydrate, the product was the yellow sodium salt (76%) of the hydrazono(cyanoacetate) hydrate, m.p. 134° (decomp.) from aqueous ethanol (Found: C,29.2; H,3.3; N,39.4. $C_6H_6NaN_7O_2 \cdot H_2O$ requires C,28.9; H,3.2; N,39.4%).

Ethyl 7-aminotetrazolo[5,1-c]-1,2,4-triazine-6-carboxylate (4.49).

Ethyl 2-(1H-tetrazol-5-ylhydrazono)cyanoacetate (4.48) (1g) was boiled in acetic acid (20ml) for 3h and the solvent vacuum evaporated. The residue, crystallized from ethanol, afforded the tetrazolotriazine

(0.9g), m.p. 128-130° (Found: C,34.2; H,3.4; N,47.2. $C_6H_7N_7O_2$ requires C,34.4; H,3.3; N,46.9%); ν max. 3590, 3380, 3290 and 3200(NH), 1720(C=O) and 1640cm^{-1}(NHdef.); λ max. 329 and 236nm (log ε 3.48 and 4.28); m/e 209(M^+, 24), 181(25), 165(100), 137(36), 107(4), 97(4), 81(16), 80(16), 79(15), 69(42), 68(100), 54(59), 53(42).

7-Amino-6-cyano-1,2,4-triazolo[5,1-c]-1,2,4-triazine (4.51).

3-Amino-2H-1,2,4-triazole (1.3g) was diazotized in aqueous nitric acid in the manner previously described, neutralized with excess sodium acetate trihydrate and coupled slowly with malononitrile (1g) in ethanol (10ml) at 0°. The mixture was stirred at 0° (2h) and the crude 2-(2H--1,2,4-triazol-3-ylhydrazono)-malononitrile (4.50) (1.9g) collected, m.p. > 190° (decomp.); λ max. 374nm. Attempted purification of the hydrazone (4.50) resulted in (Compound A) which gave a different U.V. spectrum λ max. 349, 281 (in fl.) and 276nm (log ε 3.97, 3.87 and 3.94 respectively); ν max. 2225(C ≡ N) and 1630cm^{-1}(C=N); τ (DMSO-d_6) 1.94. The crude hydrazone (4.50) (1g) was heated under reflux in acetic acid (10ml.) for 2h and the solvent vacuum evaporated. The residue afforded the aminocyanotriazolotriazine hydrate (0.9g), m.p. > 300° (decomp.) (from ethanol) (Found: C,33.5; H,3.0; N,55.0. $C_5H_3N_7.H_2O$ requires C,33.5; H,2.8; N,54.8%), ν max. 2235(C ≡ N), 1690 and 1615cm^{-1}(C=N); λ max. 334, 284(shoulder), 277 and 227nm (log ε 3.96, 3.83, 3.86 and 4.07); τ (DMSO-d_6) 0.6(s,NH), 1.41(s,CH); m/e 161(M^+, 100), 134(18), 109(3), 96(76), 68(20), 53(33).

The same triazolotriazine hydrate (4.51) was obtained from the filtrate of the coupling mixture by slow precipitation at room temperature and from (Compound A) by prolonged boiling in methanol or heating

in acetic acid.

The triazolotriazine hydrate (4.51) was recovered unchanged from boiling acetic acid or pyridine (14h).

6-Amino-1,2,4-triazolo[5,1-c]pyrimido[4,5-e]-1,2,4-triazine (4.53).

The aminocyanotriazolotriazine hydrate (4.51) (1g) was boiled in formamide (10ml) for 1h and the dark mixture diluted with water. The dried solid was purified by sublimation (300° at 5mm Hg) to yield the aminotriazolopyrimidotriazine (55%), m.p. > 350° (Found: C,38.1; H,2.4; N,59.4; $C_6H_4N_8$ requires C,38.3; H,2.1; N,59.6%); ν max. 3380, 3300, 3230, 3195 and 3110 (NH) and 1628cm^{-1} (C=N); λ max 350, 270, 260 and 257nm (log ε 4.62, 4.71, 4.75 and 4.78); m/e 188(M^+, 100), 135(8), 133(13), 106(13), 91(10), 81(8), 80(8), 79(11), 78(22), 77(19), 69(11), 68(13), 67(16), 66(22), 65(22), 64(38).

The same aminotriazolopyrimidotriazine (ir and mass spectrum) was obtained when (Compound A) was treated in a similar fashion.

1,2,4-Triazolo[5,1-c]-1,2,4-triazin-7(4H)-one (4.56)

Ethyl 2-(2H-1,2,4-triazol-3-ylhydrazono)cyanoacetate (4.3b) (1g) was boiled in 6N-hydrochloric acid (2h) and the solvent vacuum-evaporated. The residue, crystallized from aqueous ethanol, yielded the triazinone hydrate (55%), m.p. 199-200° (Found: C,31.0; H,3.2. $C_4H_3N_5O.H_2O$ requires C,30.9; H,3.5%); ν max. (nujol suspension) 1710$_w$(C=O) and 1655cm^{-1} (C=N); λ max. 290(log ε 3.93); τ (DMSO-d_6) 1.71(s, H-2), 2.54(s,H-6); m/e 137(M^+, 70). When the triazinone hydrate (0.5g) was boiled in acetic acid (5ml) it afforded the unsolvated triazolotriazinone (0.4g), identical

(m.p., mixed m.p., and ir spectrum) to a sample prepared by heating 4-amino-3(2H)-imino-1,2,4-triazin-5(4H)-one (4.49) in formic acid.[28]

When the unsolvated triazolotriazinone (4.56)[28] (0.3g) was boiled in 1N-hydrochloric acid (20ml) for 4h the triazolotriazinone hydrate (60%) was formed, identical (UV and ir) to the aforementioned sample.

The same triazolotriazinone hydrate (55, 58 and 60% yields respectively) was obtained when the triazolotriazines (4.4a), (4.5a) and (4.51) were boiled in 6N-hydrochloric acid (2h).

Naphtho[2,1-e]pyrazolo[5,1-c]-1,2,4-triazine (4.62a)

3-Aminopyrazole (1.5g) in 1N-hydrochloric acid (55ml) was diazotized at -5° with sodium nitrite (1.37g) in water (5ml) and neutralised with excess sodium acetate trihydrate. 2-Naphthol (2.7g) in ethanol (10ml) was added dropwise at 0° to afford an orange precipitate of the azo compound (4.60a) (85%) (from chloroform) m.p. 210-212° (Lit.,[68] 193-194°) (Found: C,65.85; H,4.04; N,23.76. $C_{13}H_{10}N_4O$ requires C,65.54; H,4.20; 23.52%); ν max. (nujol suspension) 1626cm^{-1} (C=O); m/e 238(M^+, 14), 221(29), 220(100), 165(34), 164(27), 144(86), 138(16), 127(13), 126(71), 115(33), 114(29), 85(26), 83(71), 75(11).

The azo compound (4.60a) (1g) was boiled in acetic acid (50ml) (2h) and the solvent vacuum-evaporated to afford the naphthopyrazolotriazine (4.62a) (95%), m.p. 194-196° (Lit.,[68] 193-4°); (Found: C,70.4; H,3.7; N,25.8. $C_{13}H_8N_4$ requires C,70.9; H,3.6; N,25.5%); ν max. (nujol suspension) 3120(CH) and 1595cm^{-1} (C=N); λ max. 400, 350, 296, 275 (shoulder), 267, 249 and 218 (log ε 3.78, 3.74, 3.86, 4.29, 4.31, 4.65 and 4.45); m/e 220(M^+, 100), 165(16), 164(12), 138(10), 126(30), 114(10).

Naphtho[2,1-e]-1,2,4-triazolo[5,1-c]-1,2,4-triazine (4.62b)

3-Amino-2H-1,2,4-triazole (5g) was diazotized in aqueous nitric acid in the manner previously described and neutralised with excess sodium acetate trihydrate. 2-Naphthol (9g) in ethanol (30ml) was added dropwise to afford a red precipitate of the azo compound (4.60b) (88%) (from methanol) m.p. 249-250° (Lit.,[68] 269-272°); ν max. (nujol suspension) 1626cm^{-1} (C=O); λ max. 450, 416, 295, 275 and 222 (log ε 4.04, 4.01, 3.85, 3.83 and 4.55); m/e 239(M^+, 52), 221(69), 210(27), 166(15), 143(25), 142(42), 140(19), 129(19), 128(29), 125(44), 124(100), 102(17), 101(21), 77(13), 76(10), 75(15).

The azo compound (4.60b) (1g) was boiled in methanol for 2h to afford an unidentified unstable intermediate (60%, from ethanol) m.p. 274-275° (Found: C,61.9; H,3.6. $C_{12}H_7N_5 \cdot \frac{1}{2}MeOH$ requires C,61.5; H,3.8%); ν max. (nujol suspension) 1620cm^{-1}; λ max. 450(shoulder), 395, 275, 265 and 220nm; m/e 222(16), 221(100), 166(22), 165(12), 140(34), 139(23), 114(10), 113(8), 88(7), 63(11).

The azo compound (4.60b) (2g) was boiled in acetic acid (15ml) (3h) to furnish a precipitate on cooling of the naphthotriazolotriazine (4.62b) (90%) m.p. 274-5°C (Lit.,[68] 272-4°) (Found: C,64.7; H,3.2; N,31.7. $C_{12}H_7N_5$ requires C,65.1; 3.2; N,31.7%); ν max. (nujol suspension) 1590cm^{-1}; λ max 390 (shoulder), 372, 350, 290 (shoulder), 267, 241, 236 and 221nm (log ε 3.85, 3.89, 3.87, 3.75, 4.12, 4.59, 4.57 and 4.50); m/e 221(M^+, 100), 166(16), 165(11), 140(27), 139(18), 138(6), 114(6), 113(6).

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