Synthesis and Reinvestigation of Tetrazocines

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A thesis presented to
Dublin City University
for the degree of
Doctor of Philosophy

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January 2004

Declaration

I hereby certify that this material, which I now submit for assessment on the programme of study leading to the award of Ph.D. is entirely my own work and has not been taken from the work of others save and to the extent that such work has been cited and acknowledged within the text of my work.

Signed:.....

Date:.....29/06/04.

I.D No : 9797689

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Chapter 4 - Conclusion

Abstract

This thesis is concerned with the study of tetrazocines. These rare, eight-membered ring systems containing four nitrogen atoms are in the infancy of their development. Little is known of their potential application, properties and generation. It was endeavoured to learn more about this compound class by examining what has been presented in the literature (chapter 1), generating novel tetrazocines (chapter 3 and 4) and finally substantiating existing syntheses, which were viewed as unlikely or doubtful by this research group (chapter 2).

Previous work from this research group involving the photolytic ring expansion of hexahydropyrrolotriazoles led to a novel 1,2,3,5-tetrazocine system. Hexahydropyrrolotriazoles are cycloaddition products from the reaction of a 1,3-dipole with various activated dipolarophiles. This thesis was concerned with accelerating this reaction, manipulating functionality post cycloaddition and optimising the photochemical ring opening process leading ultimately to tetrazocines. In particular, the cycloaddition product of our standard 1,3-dipole with benzyne furnished a 1,3-diphenylindazole thermally and a tetrazocine photochemically. Other analogues of this tetrazocine have previously been postulated as being only intermediate.

In another area, four previously reported syntheses of tetrazocines were re-examined and found not to correlate with our observed results. This work was undertaken based on the relative instabilities of this compound class.

Finally, the proposed synthesis of the only second entry into the rare 1,2,4,7-tetrazocine ring system is described but has yet to be conclusively verified.

List of Abbreviations

DCM	Dichloromethane
DMF	Dimethyl fumarate
DMSO	Dimethyl sulfoxide
EDG	Electron donating group
EWG	Electron withdrawing group
FMO	Frontier molecular orbital
HMX	High melting explosive
HOMO	Highest occupied molecular orbital
IR	Infra-red
LAH	Lithium aluminium hydride
LUMO	Lowest unoccupied molecular orbital
NBS	*N*-Bromosuccinimide
NMR	Nuclear magnetic resonance
TLC	Thin layer chromatography
TPP	Triphenylphosphine
Ts	Tosyl (*p*-toluene sulfonate)
t-BuOK	Potassium *tert*- butoxide
UV	Ultraviolet

Acknowledgements

Who to thank? I hope nobody gets insulted here. I'll start with the people supporting the chemistry department on the ground. In my time there, I had a good laugh. I hope that never changes. Damien, Vinny, Maurice, Mick and Ambrose …thank you for the memories, the nitrile gloves, the TLC plates and for making us beg for such things. For the other unfortunates who had the luck of having to do a PhD when I was there, cheers for the company. There's a certain comfort to be had knowing that when a project isn't working, you're actually in the majority. Stress relief with others in the form of alcohol-tasting competitions and vigorous footballing sessions do wonders for problem solving. In short I would like to thank the following for allowing me to kick them on regular occasion in soccer and accepting my immediate apology, even if they got the apology before the kick. These people are Karl, Ray, Robbie, Ben, Colm, Ger, Adrian, Scott, Marco, Ciaran, Kev and Dec (goal scoring hatcher). To all others, thank you for the acquaintance and friendship. A special mention to Ger, Frank, Dec, Scott and Adrian. Thanks for answering my many probing questions and for the patience. And now for the biggies.

Paraic, thank you for the chemical knowledge, direction, advice, sarcasm (a rare art) and allowing me the opportunity to get where I am today. At the moment, I'm seeing the benefits of that opportunity.

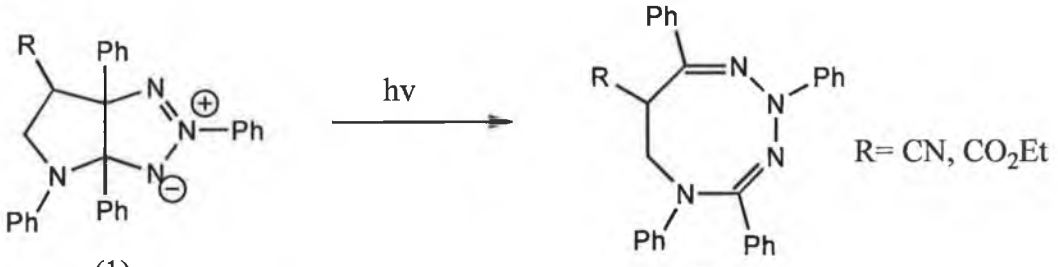
Susanne, thank you for supporting me and pushing me to finish. Even though it was borderline nagging at times, you meant well!

And finally my parents, this thesis is dedicated to you both. I know it's not much use to you as an everyday item but it'll make the shelf look classy. I can't thank you both enough in words for the support and opportunity throughout.

Much appreciated.

1. Introduction

Our current field of interest is the synthesis of tetrazocines. These heterocycles are eight-membered ring systems containing four nitrogen atoms. Our involvement in this area stems primarily from previous work undertaken by this research group in which the photochemical rearrangement of 6-ethoxycarbonyl-2,3a,4,6a-tetraphenyl-3,3a,4,5,6,6a,-hexahydropyrrolo[2,3-d]-1,2,3-triazole **(1)** led to the formation of a 1,2,3,5-tetrazocine **(2).**[1] However on examination of the literature regarding these ring systems, it became evident that little was known about these rare compounds of which none occur at all naturally. As the literature survey will show, tetrazocines have often been obtained as surprising side products of alternatively planned syntheses. Very little attention has been paid to developing general, more readily accessible routes to tetrazocines and as such, this warrants extensive research with respect to their physical properties and potential biological application.



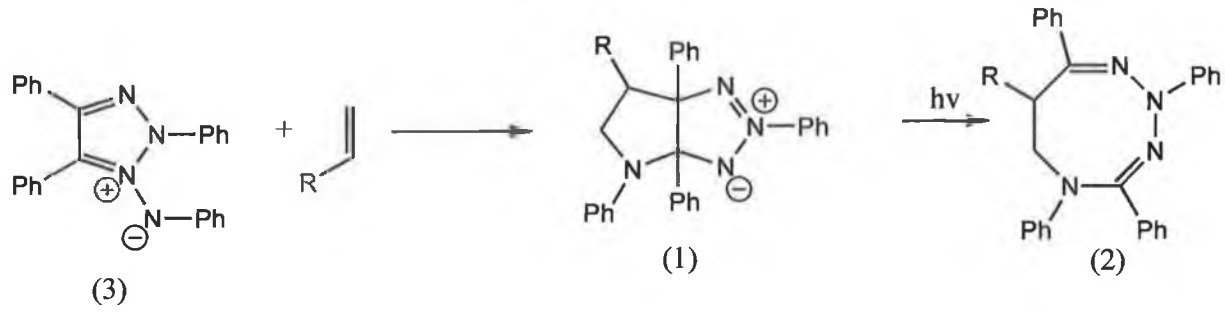
(1) (2)

Scheme 1.1 *Photochemical formation of a 1,2,3,5-tetrazocine.*

This report comprises of four chapters. Chapter 1 details and assesses the syntheses of tetrazocines as described in the literature. On examination of the literature, we became aware that many reported syntheses of tetrazocines were subsequently revised and we felt some needed to be verified due to non-conclusive analysis.

Each preparation is presented chronologically so to give an overview and a sense of development of these heterocycles. There is also a discussion on some of their properties and uses. In the second chapter some previous reports on the synthesis of tetrazocines are reported. Chapter 3 concerns novel development of tetrazocine

generation based on photochemical rearrangements of the 1,3-dipole's **(3)** cycloadduct. In the final chapter, a potential new route to tetrazocines is discussed.



(3) (1) (2)

Scheme 1.2 *Synthetic pathway to tetrazocines from the 1,3-dipole (3).*

Tetrazocines can be sub-divided into eight different classes in which the constitution of nitrogen atoms in the ring determines the class. Of the eight structural isomers presented in Fig.1.1, 1,2,3,6-tetrazocines remain unreported in the literature. However there exists some uncertainty as to the actual formation of a 1,2,4,6-tetrazocine based on our own observations (see Chapter 2). Similarly reports on the generation of the 1,2,3,4-tetrazocine must be viewed with some suspicion.

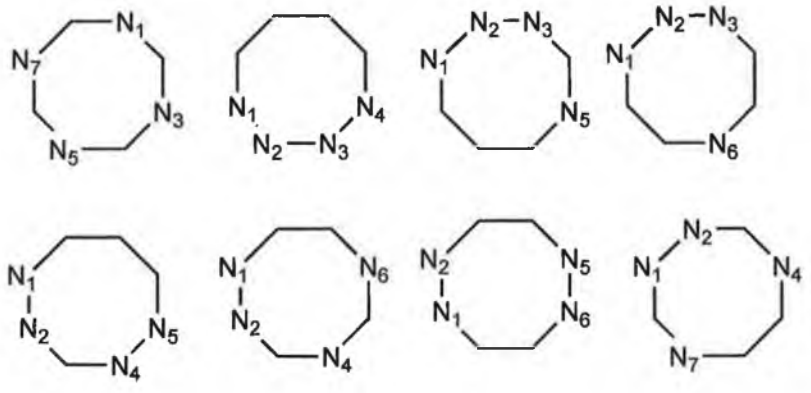
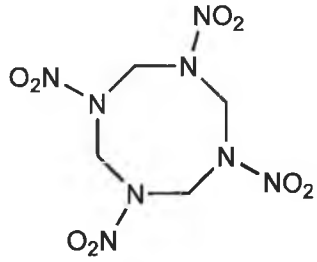


Figure 1.1 *Possible structural isomers of tetrazocines.*

1.1. Introduction to Tetrazocines

The majority of tetrazocines that have been discussed in the literature tend to be of the 1,3,5,7 type.[2] This keen interest is the result of extensive usage of perhydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine **(4)**, the most powerful military explosive and solid rocket fuel being twice as explosive than TNT. This tetrazocine is alternatively known as Octagen or HMX (High Melting Explosive). Other minor applications that HMX has lent itself to involve uses as a dispersant, suspending and blending agent.[3] Tetrazocines other than the 1,3,5,7 type have found no biological, physical or chemical appeal with the one exception of 4,7-dimethyl-3,5,7-hexahydro-1,2,4,7-tetrazocin-3,8-dione **(5)** which was recently used as a Mitsunobu reagent.[4]



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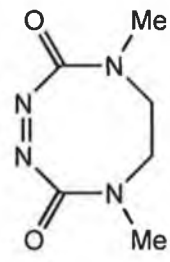
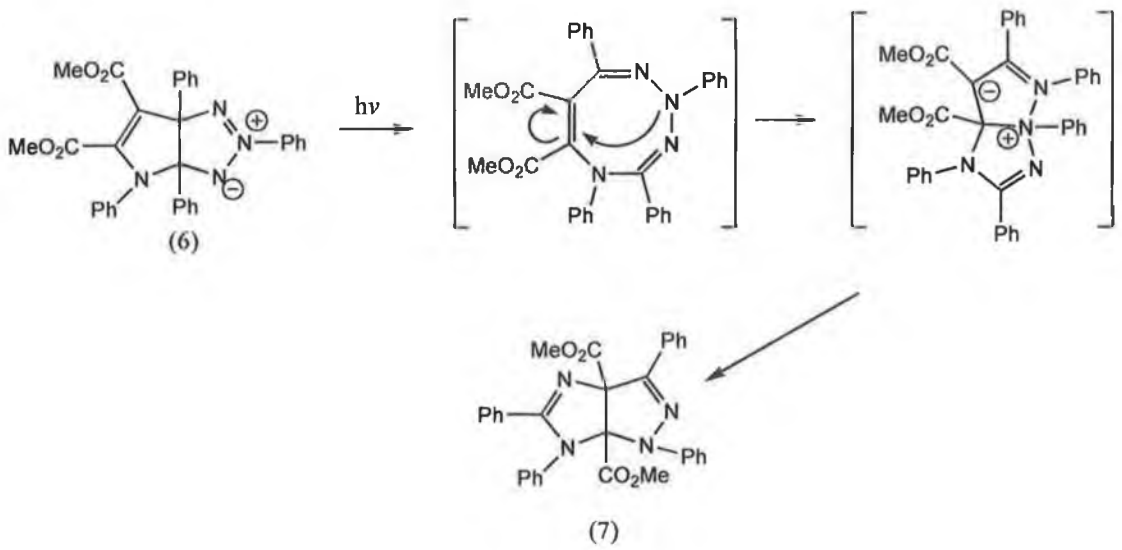


(5)

Figure 1.2 *Tetrazocines that have found use as explosives and Mitsunobi reagents commercially.*

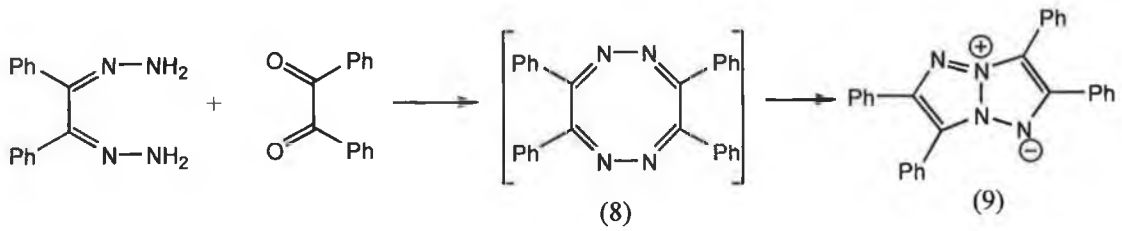
There exists many examples of secondary derivatives resulting from the instability of the eight-membered rings which contract to give more stable five or six-membered ring systems due to possible torsional strain or aromatisation effects. Similarly, other derivatives were obtained through mild hydrolysis of the relevant tetrazocine. The full syntheses of the tetrazocine compounds discussed in the following pages can be found in section 1.3.

A recent example of a suspected tetrazocine was reported by Butler. Upon irradiation of **(6)** with a UV light source, the intermediate 1,2,3,5- tetrazocine is believed initially to form but undergoes a rapid cyclisation to the more stable compound **(7)**.[5]



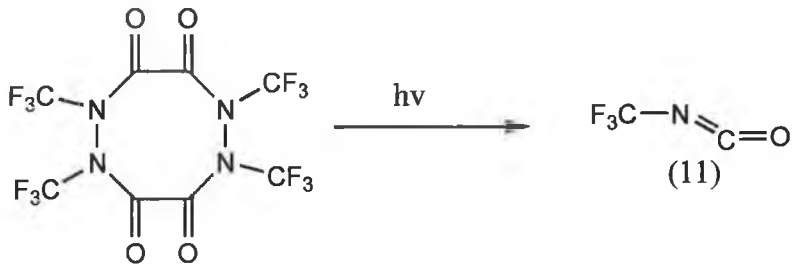
Scheme 1.3 *Photochemical intermediate formation of a 1,2,3,5-tetrazocine.*

Likewise the product produced from the dihydrazone of benzil and benzil was originally thought to be a tetrazocine. However the 1,2,5,6-tetrazocine **(8)** undergoes cyclisation to the more stable bicyclic mesoionic tetrazaapentalene **(9)** in high yield.[6]



Scheme 1.4 *Intermediate formation of a 1,2,5,6-tetrazocine with ring closure to give a tetrazaazapentalene.*

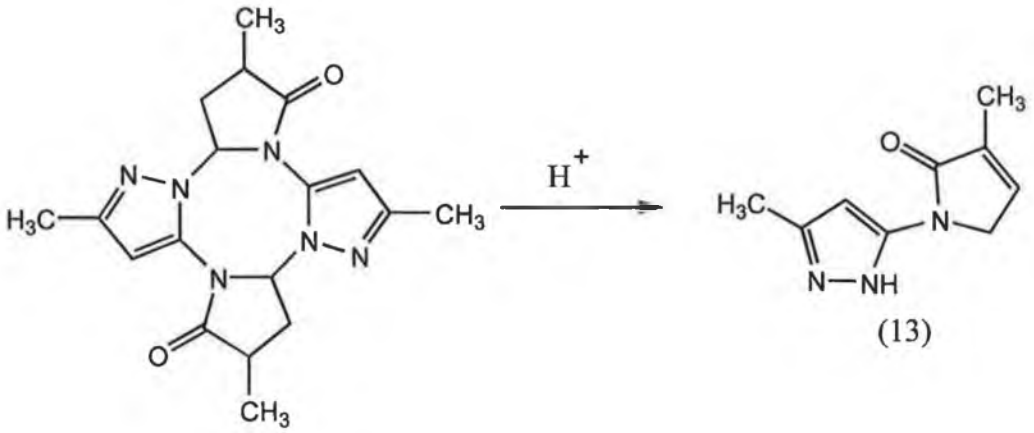
Ogden found that perfluoro-1,2,5,6-tetramethylperhydro-1,2,5,6-tetrazocine-3,4,7,8-tetraone **(10)** fragments producing trifluoromethylisocyanate **(11)** on light exposure.[7]



(10) (11)

Scheme 1.5 *Photochemical fragmentation of perfluoro-1,2,5,6-tetramethylperhydro-1,2,5,6-tetrazocine-3,4,7,8-tetraone.*

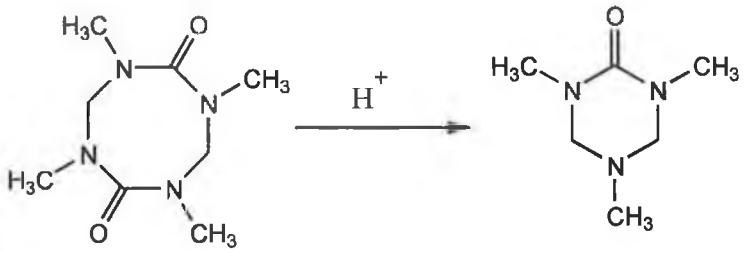
Brinkmeyer studied the stability of the 1,3,5,7-tetrazocine **(12)** by treating it with a catalytic amount of H_2SO_4 in refluxing xylene for 30 minutes and found it exclusively gave **(13)** in near quantitative yield.[8]



(12) (13)

Scheme 1.6 *Acid catalysed fragmentation of a 1,3,5,7-tetrazocine.*

Similarly when the 1,3,5,7-tetrazocine **(14)** was heated with a trace of acid, hydrolytic degradation occured with ring contraction to give 2-oxo-1,3,5-trimethylhexahydro-1,3,5-triazine **(15)**.[9]



(14) (15)

Scheme 1.7 *Acid catalysed degradation of a 1,3,5,7-tetrazocine.*

1.2. Conformations of Eight-Membered Rings

As X-ray diffraction data gives the atomic co-ordinates and thereby the conformations of molecules in the crystalline phase, the lowest energy conformation can be more or less characterised with some conformational energy barriers being determined and calculated. Cyclooctane is the arch-typical molecule in this class and the heterocyclic analogues should have closely related conformational features. [10,11,12] The syntheses of compounds covered in this section can be found in the subsequent section 1.3.

Cyclooctane exhibits no fewer than 10 symmetrical conformations which fall into four families. The most stable family of cyclooctane and it's derivatives is the boat-chair (BC) and the twist boat-chair (TBC) in which the boat chair represents the energy minimum. Inter-conversion of this family into the one of next higher energy gives the crown chair-chair (CC), the twist chair-chair (TCC) and the crown family. The crown family lies only slightly above the boat chair family in energy terms. The main problem in the crown form, in addition to high symmetry, and hence low entropy, is eclipsing strain. The third family comprises of the boat (B), twist-boat (TB) and boat-boat (BB). It is easily seen that these conformations suffer from severe eclipsing strain and they do not appear to be appreciably populated in cyclooctane even though the barrier to rotation between this family and the boat-chair family is very small. The remaining conformation, Chair (C) and twist-chair (TC) are calculated to be very high in energy and are not seen as viable conformations of cyclooctane.

A feature which contributes to the conformations of eight-membered rings is ring strain. It is at a maximum for small rings and a minimum for n=6 (n is the number of atoms in the ring). It increases strongly however from n=8 to 11 and becomes approximately zero for rings larger than n=14. Strain introduced to any molecule tends to be minimised by becoming distributed among several modes such as bond angle, torsional strain and van der Waals compression. Torsional constraints are generally the result of an endocyclic cis double bond or a related structural feature such as a cis epoxide group, a benzene ring or an amide group. A low energy

conformation in an eight-membered ring is a distorted boat-chair where the geometry is close to that of the transition state for the boat-chair to twist-boat-chair pseudorotation as is the case for cyclooctane.

Molecular mechanics and *ab initio* studies of azoalkanes by Kao and Huang showed that the chair conformation of *cis,cis*-1,2,5,6-tetraaza-1,5- cyclooctadiene was calculated to be the most stable of several possible conformations.[13] The boat and twist forms being 8.7 and 6.9 kcal mol^{-1} less stable respectively. This energy difference between boat and chair being mainly due to dipolar interactions.

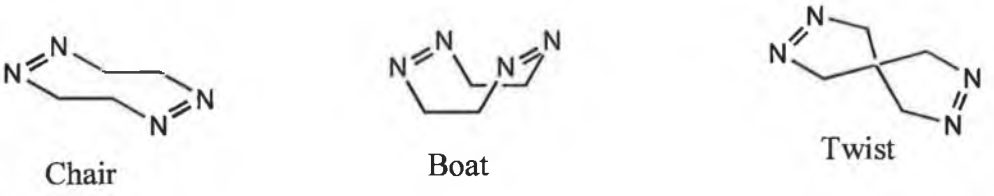


Figure 1.3 *The calculated more stable conformations of cis,cis-1,2,5,6-tetraaza-1,5- cyclooctadiene .*

For *trans,trans*-1,2,5,6-tetraaza-1,5-cyclooctadiene, the twist form is favoured over the chair. The major contribution to the chair-twist energy difference arises from the torsional interaction due to ethane-type H/H eclipsing and N/N eclipsing.

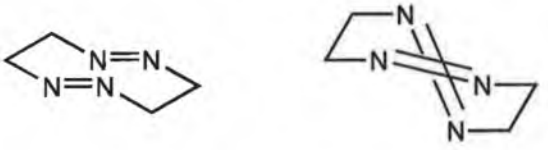


Figure 1.4 *The calculated more stable conformations of trans,trans-1,2,5,6-tetraaza-1,5-cyclooctadiene.*

The structure and conformation of the 1,2,5,6-tetraacinium dibromide **(16),** by Cabildo shows the 1,2,5,6-tetrazocine to adopt a chair conformation.[14] NMR study of an analogue showed **(17)** to be symmetrical due to rapid equilibrium between all possible conformations on going from the chair to boat.[15] However at lower

temperatures, the chair conformation is frozen. Calculations indicate also the chair to be the most stable; both Huang and Cabildo's observations appear to correlate with each other for the 1,2,5,6- tetrazocine system.

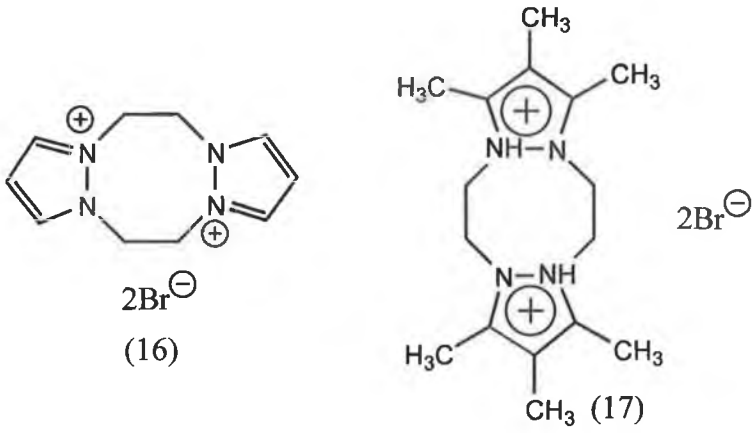


Figure 1.5 *Structure of 1,2,5,6-tetraacinium dibromide (16) and analogue (17).*

By far the most comprehensive conformational study relating to these heterocycles has to be that of HMX due to it's obvious usage. HMX exists in four crystalline forms designated *α, β, γ,* and *δ*. X-ray diffraction studies have revealed that both the *α* and *β* forms have a basket like shape or boat conformation with all four carbon atoms coplanar.[16] Neutron diffraction analysis indicated the ring in the *β*-polymorph assumes a chair conformation.[15] NMR and Raman spectroscopic data suggested a chair-chair shape for γ-HMX.[17] A correlation between the preferred conformations of *α-, β-, γ-* and *δ*-HMX and their stabilities is discussed in relation to specific temperatures ranging from room temperature to 190^0C displaying inter-conversion between conformations.

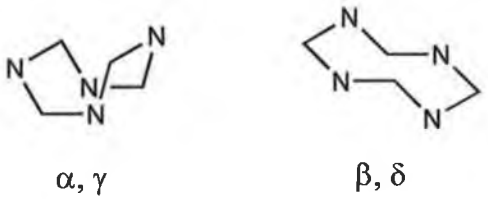


Figure 1.6 *Boat and chair conformations of different crystalline forms of HMX.*

Conformational analysis of non-HMX examples of the 1,3,5,7-tetrazocine type reported by Gompper show the fully unsaturated tetrazocine **(18)** to have a boat conformation.[18] The methylene-bridged analogue **(19)** which is slightly distorted however also possesses the same conformation.

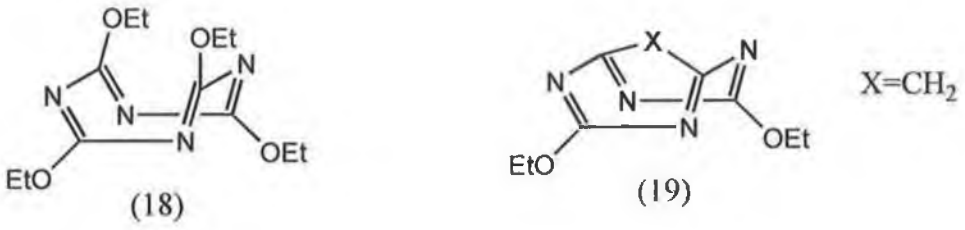


Figure 1.7 *Boat Conformations of two fully unsaturated 1,3,5,7-tetrazocines.*

Some years later, the same author developed the same ring system from a different route. [19]

A comparison of the boat shaped tetrazocine **(20)** with cyclooctatetraene showed it to be more planar which was accounted for due to substitution effects on the ring.

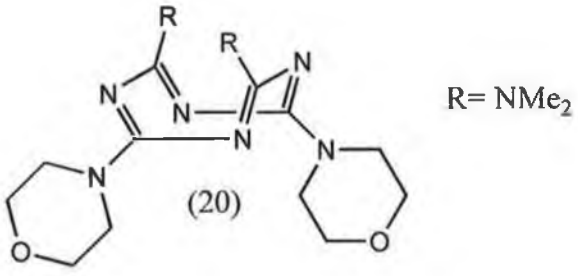
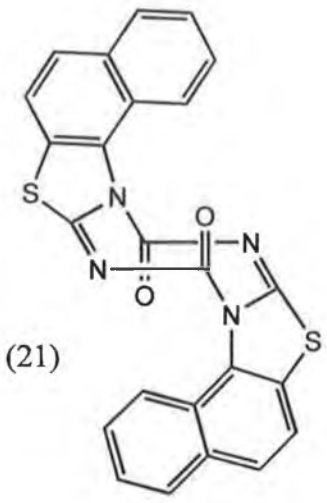


Figure 1.8 *Boat Conformation of a fully unsaturated 1,3,5,7- tetrazocine.*

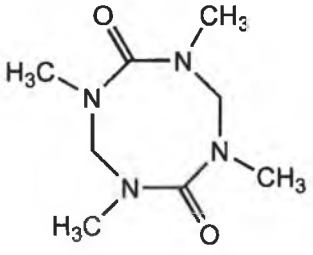
The bifused 1,3,5,7-tetrazocine **(21)** prepared by Liu was not suitable for X-ray analysis.[20] However the authors assume that the ring skeleton exists in a chair conformation. Eight-membered rings with two strong endocyclic torsional constraints should exist mainly in the chair conformation.



(21)

Figure 1.9 *Proposed chair conformation of (21).*

Finally a recent published crystal structure of the 1,3,5,7 type is 1,3,5,7-tetramethyltetrahydro-1,3,5,7-tetrazocine-2,6(1H,3H)-dione **(14)**. It was discussed by Ebisuno to have a practically planar shape.[21]



(14)

Figure 1.10 *Structure of (14) shown to have a planar shape by crystal structure.*

Of the remaining classes of tetrazocines, the only other crystal structure reported is that by Byrne and James who have shown the 1,2,3,5-tetrazocine **(2)** to have a boat conformation.[1]

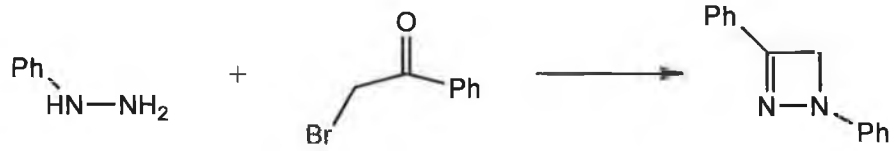
A quick summary of the conformations indicates that the most predominant are that of the boat followed by the chair. These represent mainly the 1,3,5,7- and 1,2,5,6–tetrazocines respectively. The fact that the low energy conformations of cyclooctane are not present in any of the examples given may be due to torsional constraints. It can be seen that in most cases that the rings have a spatial conformation such that nitrogen-nitrogen interactions are minimised and this appears to be the driving force for the preferred conformations observed in the absence of more forcing torsional constraints.

1.3. Synthesis of Tetrazocines

As already mentioned, the literature on HMX is voluminous and repetitive. However there are many other reported methods for synthesis of 1,3,5,7-tetrazocines of the non HMX type. In the following sections, the preparations of tetrazocines are subdivided into six sections, each discussing a particular tetrazocine , 1,2,5,6; 1,3,5,7; 1,2,4,5; 1,2,4,6; 1,2,3,5 and finally 1,2,4,7 type.

1.3.1. 1, 2, 5, 6-tetrazocines

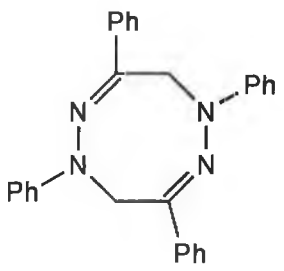
In 1919, Bodforss reviewed the reactions and observations of phenylhydrazine with bromoaccetophenone as reported by different authors.[22] Heβ proposed the formation of a 1,2-diazete ring **(22)** based on CHN analysis with these reagents.[23]



(22)

Scheme 1.8 *Formation of a 1,2-diazete ring from reaction of phenylhydrazine with bromoaccetophenone as reported by Heß.*

Earlier attempts at molecular weight determination by Culmann with Heβ's product showed that the actual assignment should in fact be a 1,2,5,6-tetraphenyltetracarbazone **(23)** which has a mass double that of the diazete ring **(22)**.[24] However some years later, Scholtz yet again obtained different results from the same reaction.[25] He observed a product which has an equal molecular weight as Culmann's eight-membered ring but with a different melting point. He believed that the correct assigment of his product should be the 1,2,3,4-tetrazocine **(24)**.



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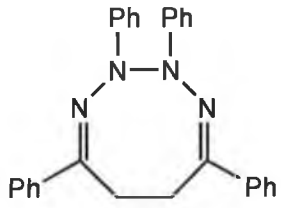
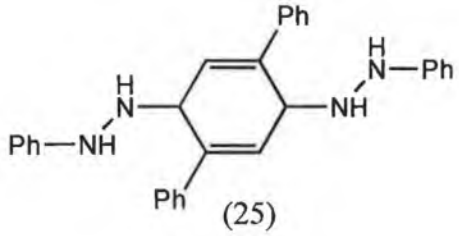


(24)

Figure 1.11 *Culmann's (23) and Scholz's (24) proposed tetrazocines from reaction of phenylhydrazine with bromoaccetophenone.*

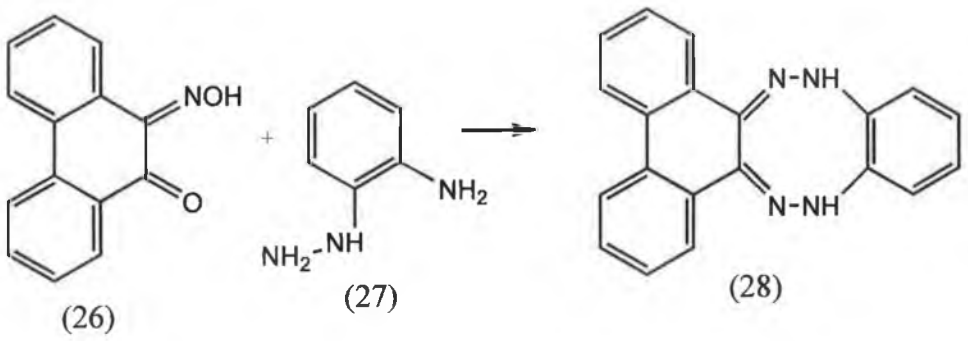
Finally Bodforss showed Culmann's molecular weight determination to be fundamentally flawed as it gives a molecular weight of 316 as opposed to 416 which would be double that of the diazete ring. Similarly he argues that the Scholtz structural assignment **(24)** is highly improbable and that it is most likely to be the susbstituted cyclohexadiene **(25)** as shown below.



(25)

Figure 1.12 *Bodforss's proposed product from reaction of phenylhydrazine with bromoaccetophenone.*

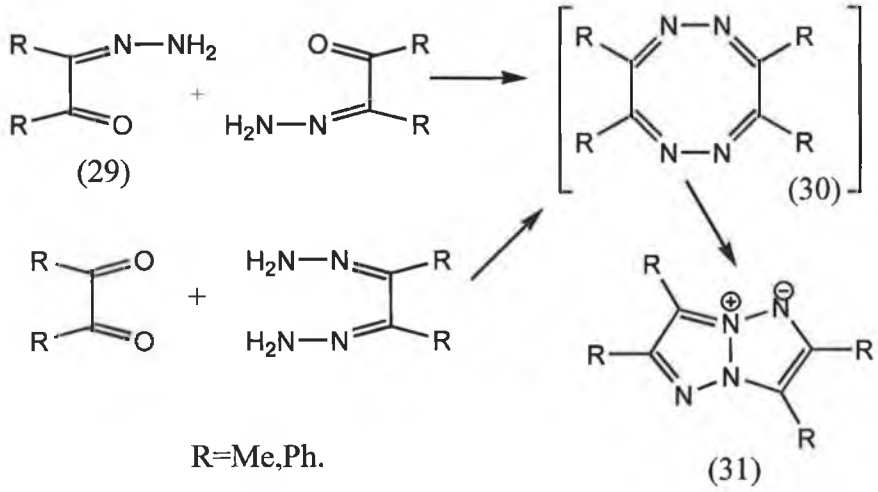
De and Guha successfully condensed the phenanthraquinone monooxime **(26)** with *o*-aminophenylhydrazine **(27)** to give the 1,2,5,6-tetrazocine **(28)**.[26] Reaction conditions involved a HCl acidified solution containing the reactants in a sealed container at 90^0C for 4 hours. Verification of the proposed cyclo-condensation product was through nitrogen analysis only.



(26) (27) (28)

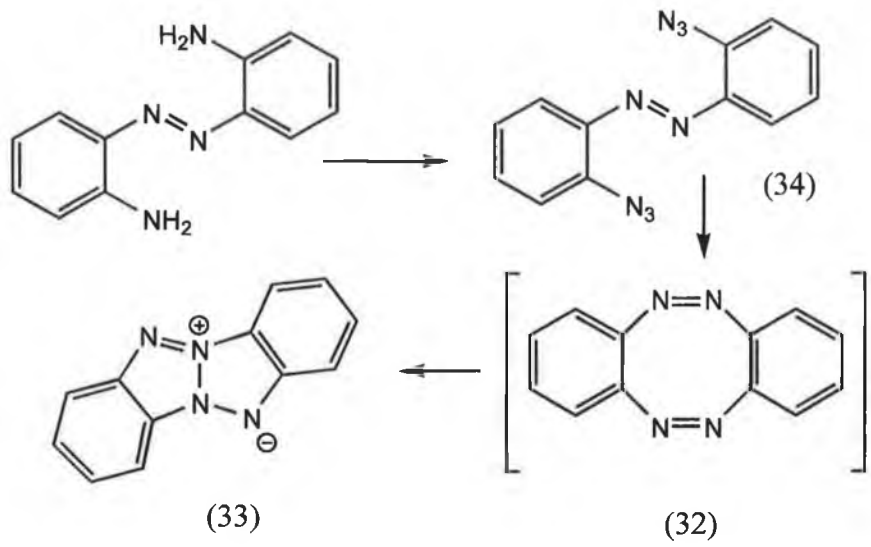
Scheme 1.9 *Condensation of phenanthraquinone monooxime with o-aminophenylhydrazine to give a 1,2,5,6-tetrazocine.*

Metze, carrying out self-condensation type reactions with benzil monohydrazones **(29)** reported the formation of the 1,2,5,6 tetrazocine **(30)** shown below.[27] Around this time Schlesinger also synthesised the proposed tetrazocine **(30)** by heating benzil with an equimolar amount of its dihydrazone.[28] At first they were formulated as the tetrazocine but Schlesinger recognised that the true structure was a bicyclic structure representative of the 1,2,3-triazolo[1,2,-b-]-1,2,3 triazole **(31),** commonly known as tetraazopentalenes. In the methods of preparation below it seems reasonable to suggest that the tetrazocine is initially formed but rapidly cyclises to the more thermodynamically stable bicyclic tetraazopentalene.



Scheme 1.10 *Intermediate formation of 1,2,5,6-tetrazocine by various condensation routes shown later to be a tetraazopentalene.*

Similarly the compound initially thought to be a 1,2,5,6-tetrazocine **(32)** was found to be the mesoionic heteroaromatic tetraazopentalene **(33)**. Carboni prepared the dibenzo-1,3a,4,6a-tetraazapentalene **(33)** in greater than 90% yield by thermal decomposition of *O,O'* diazidoazobenzene **(34)**.[29]

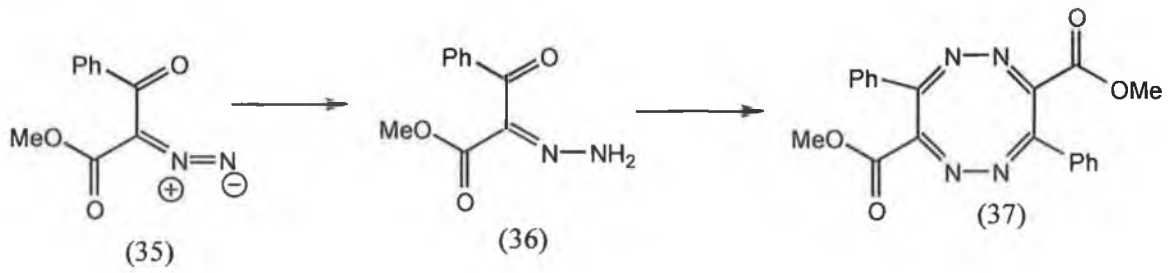


Scheme 1.11 *Intermediate formation of a 1,2,5,6-tetrazocine with subsequent ring contraction and formation of a tetraazopentalene.*

The planar tetraazopentalene structure **(33)** was conclusively established by X-ray diffraction analysis. This preference for a bicyclic over a monocyclic ring is supported by molecular orbital calculations. The relative stabilities of the 8π-electron tetrazocine structure and the 10π-electron pentalene structure can be deduced by considering the delocalisation energy of a presumed planar tetrazocine and known planar pentalene structure. Huckel theory predicts that the stabilisation energy per π electron is greater in the 10π- system.[30]

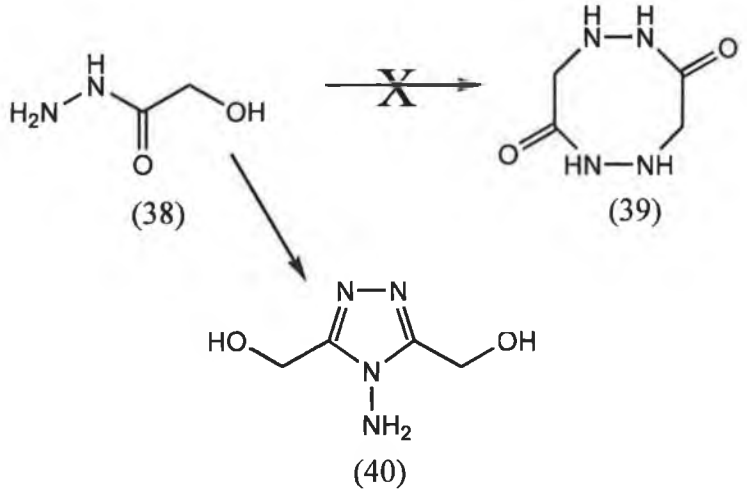
Pfleger and Rheinhardt obtained a fully saturated 1,2,5,6-tetrazocine ring system. Catalytic hydrogenation of benzoyldiazoacetate methyl ester **(35)** gave the α-hydrazone **(36)** in greater than 50% yield.[31] Refluxing the hydrazone in acetic acid

yields a compound which was stated as having the very probable structure, 3,7-diphenyl-1,2,5,6-tetrazocine-4,8-dimethyl ester **(37)**, based on elemental analysis.



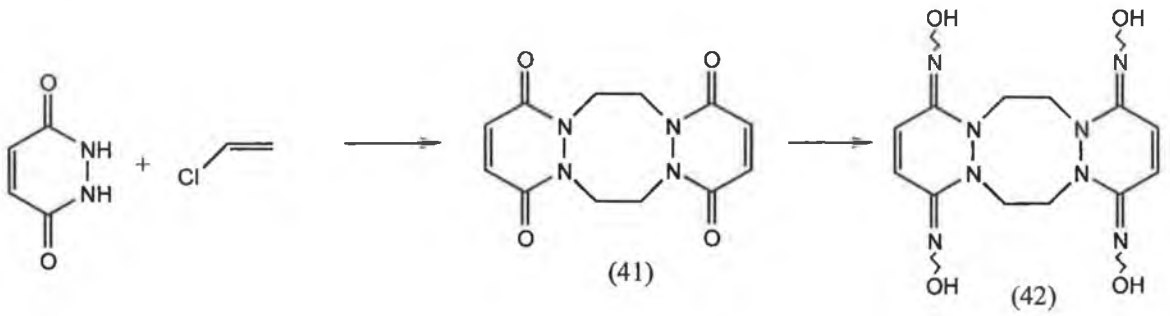
Scheme 1.12 *Formation of 3,7-diphenyl-1,2,5,6-tetrazocine-4,8-dimethyl ester.*

Ademek reproduced earlier work by Curtius and Schwann which described the condensation of two moles of glycol acid hydrazide **(38)** to give the 1,2,5,6-tetrazocine **(39)**.[32,33] The author obtained a compound identical with that reported by Curtius which he showed to be 4-amino-3,5-bis(ω-oxyalkly)-1,2,4-triazole **(40)** and not the proposed tetrazocine **(39)** by IR spectroscopy .



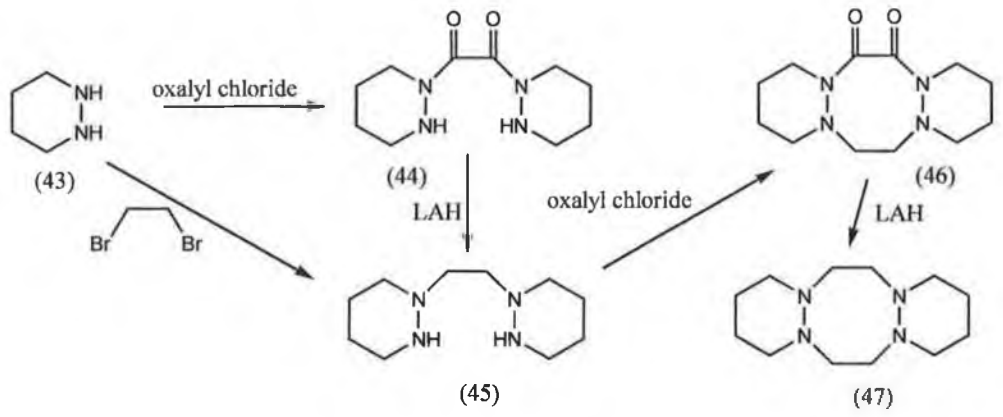
Scheme 1.13 *Reported condensation of two moles of glycol acid hydrazide to give the 1,2,5,6-tetrazocine, which was shown later to be (40).*

Three ring systems containing a tetrazocine ring were also prepared by Przezdiecki while investigating the syntheses and properties of cyclic maleic acid hydrazide.[34] Thus, compound **(41)** was prepared by the action of ethylene chloride on maleic acid hydrazide. Further reaction of the tetrazocine with hydroxylamine produced another derivative **(42)**.



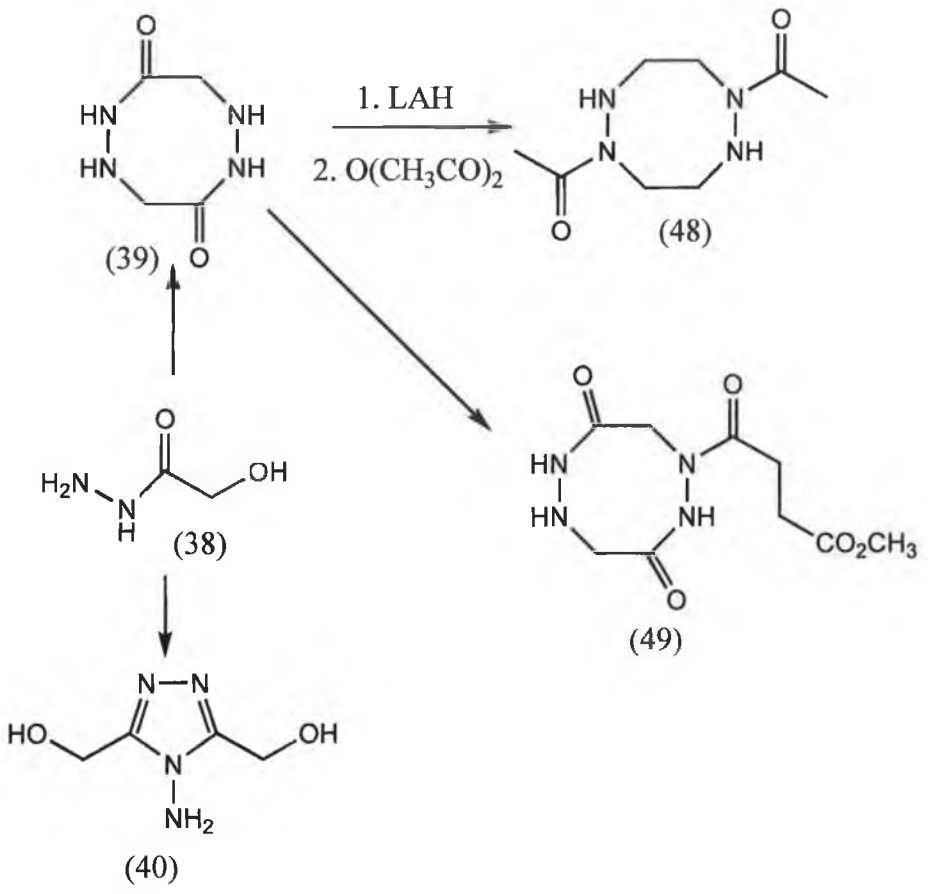
Scheme 1.14 *Formation of a 1,2,5,6-tetrazocine with oxime derivitisation.*

Rink published work on fully hydrated, linearly condensed three ring systems in which the middle ring contained a six, seven or eight-membered ring.[35] The piperazine **(43)** is condensed primarily with oxalyl chloride or 1,2-dibromoethane to give **(44)** and **(45)** respectively. The product **(45)** was obtained in high yield from **(44)** through reduction using lithium aluminium hydride. Reaction of **(45)** with oxalyl chloride in a dilute benzene solution affords the 1,2,5,6-tetrazocine **(46)** which itself can be further reduced to dipiperazino-(1',2'-a;1",2"-e)-perhydro-1,2,5,6-tetrazocine **(47)** using lithium aluminium hydride. This was the first perhydro-tetrazocine described in the literature.



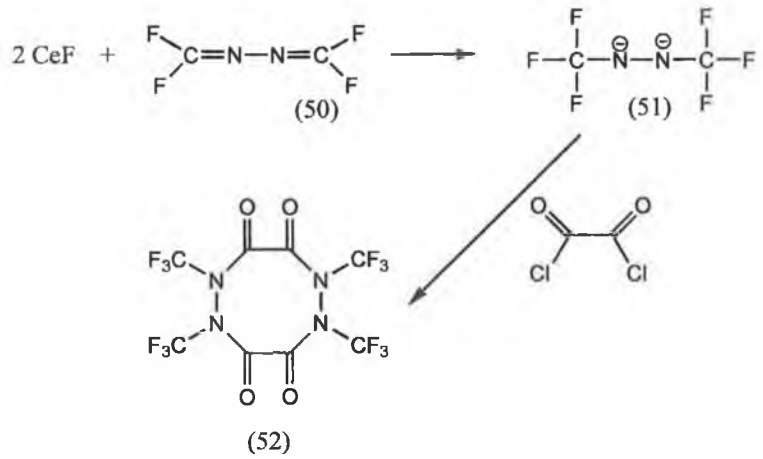
Scheme 1.15 *Linearly condensed three ringed tetrazocine systems.*

They also prepared a few derivatives **(48)** and **(49)** from Curtius's 1,2,5,6-tetrazocine **(39)**. This conflicts strongly with the evidence from Adamek who shows the tetrazocine assignment for **(39)** to be false indicating that the actual ring system was **(40).** The compounds **(48)** and **(49)** are more likely to be derivatives of the amino triazole **(40).**



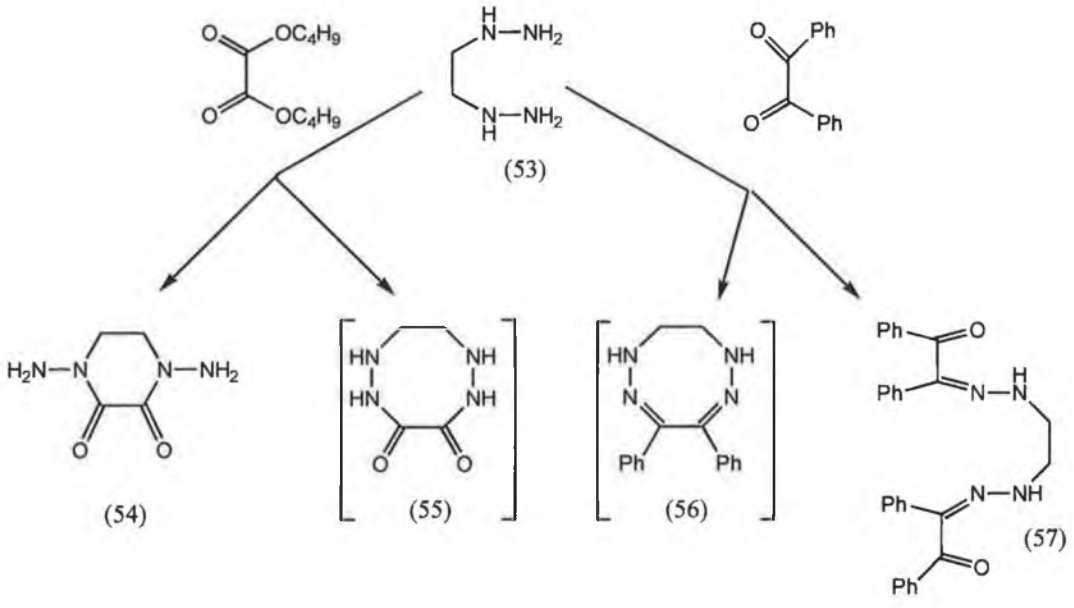
Scheme 1.16 *Proposed formation and derivatisation of the 1,2,5,6-tetrazocine (39), the existence of which is in doubt.*

Ogden condensed the tetrafluoroformaldazine **(50)** with oxalyl chloride in the presence of cesium fluoride to isolate tetrakis(trifluoromethyl)tetrazocine **(52)** in 55% yield.[7] Initially tetrafluoroformaldazine **(50)** reacts readily with cesium fluoride to generate a brown viscous liquid. It is proposed that fluoride ions attack at both unsaturated imine sites in the tetrafluoroformaldazine **(50)** involving the intermediacy of a perfluoro-nitranion **(51)** which reacts with oxalyl chloride to give the 1,2,5,6-tetrazocine **(52)**



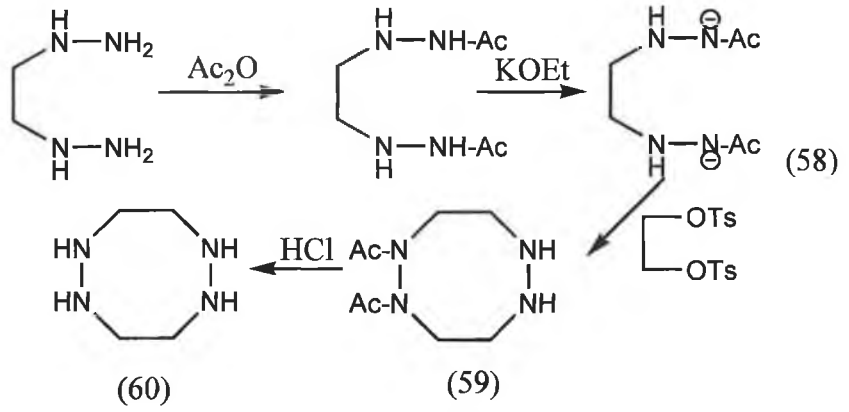
Scheme 1.17 *Reaction of tetrafluoroformaldazine with oxalyl chloride in the presence of cesium fluoride to isolate tetrakis(trifluoromethyl)tetrazocine.*

In 1976, Nielson submitted a report based on successful and failed attempts at 1,2,5,6-tetrazocine synthesis. His first attempt described the reaction of 1,2-bis(hydrazino)ethane **(53)** and diisobutyl oxalate in refluxing dimethylformamide which gave 1,4, diamino-2,3-diketonepiperazine **(54)** rather than 3,4-diketoperhydro-1,2,5,6–tetrazocine **(55)**.[36] Similarly **(53)** reacted with benzil to give 3,4,7,8-tetraaza-1,2,9,10-tetraphenyl-2,-8-decadien-1,10- dione **(57)** instead of the expected tetrazocine **(56)**.



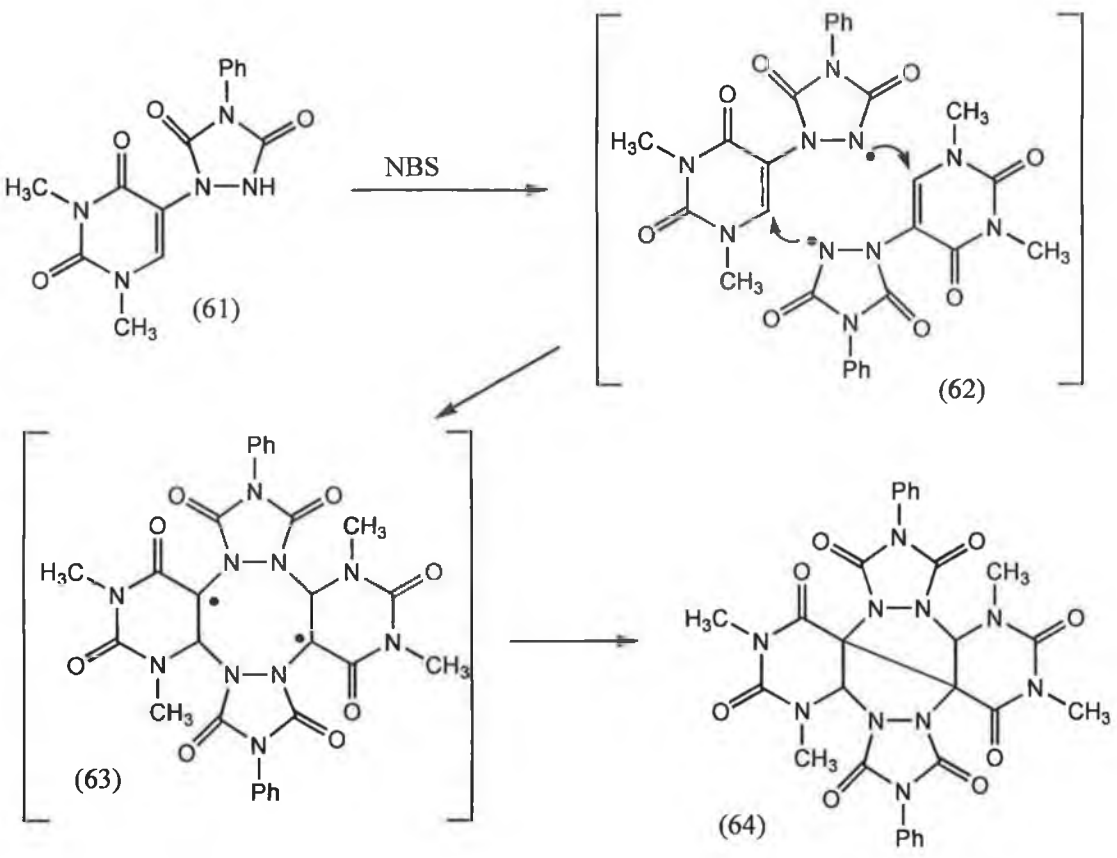
Scheme 1.18 *Unsuccessful attempts of 1,2,5,6-tetrazocine synthesis.*

However Nielson finally succeeded in making 1,2,5,6-tetraacetylperhydro-1,2,5,6-tetrazocine **(59)**. It was produced from ethylene glycol-bis-*p*-toluene sulfonate and the potassium salt of 1,2-bis(*N,N*-diacetylhydrazino)ethane **(58)** in refluxing mesitylene. Acid catalysed hydrolysis led to perhydro-1,2,5,6-tetrazocine **(60)**, an air sensitive crystalline solid, the first reported unsubstituted tetrazocine and the first example of an unsubstituted macrocycle incorporating two endocyclic hydrazine groups.



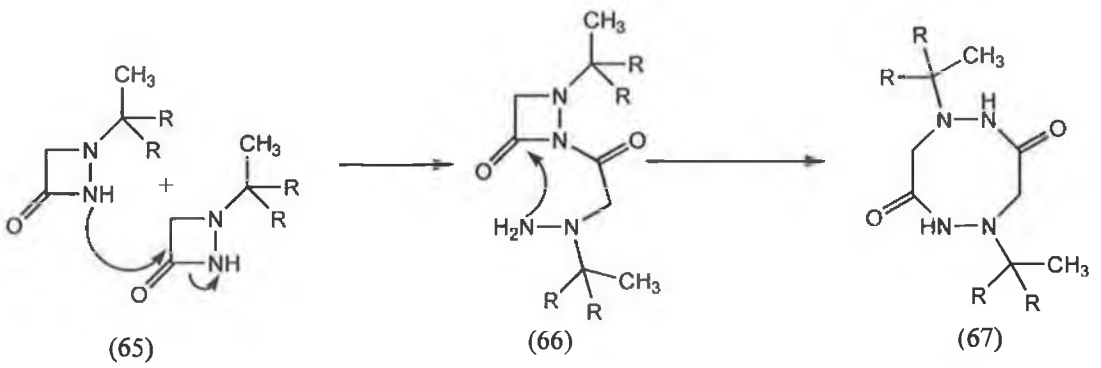
Scheme 1.19 *1,2,5,6-tetraacetylperhydro-1,2,5,6-tetrazocine formation from ethylene glycol-bis-p-toluene sulfonate and the potassium salt of 1,2-bis(N,N-diacetylhydrazino)ethane.*

Wamhoff reported the isolation of the novel bridged 1,2,5,6-tetrazocine **(64)** in 96% yield.[37] Reaction of *N*-bromosuccimide with 5-(1,2,4-triazolidin-1-yl)uracil **(61)** results in a radical head to tail dimerisation of the uracil to give the desired compound, the constitution of which was established by X-ray diffraction. The authors discuss the likelihood of a diradical tetrazocine **(63)** intermediate formation as shown below.



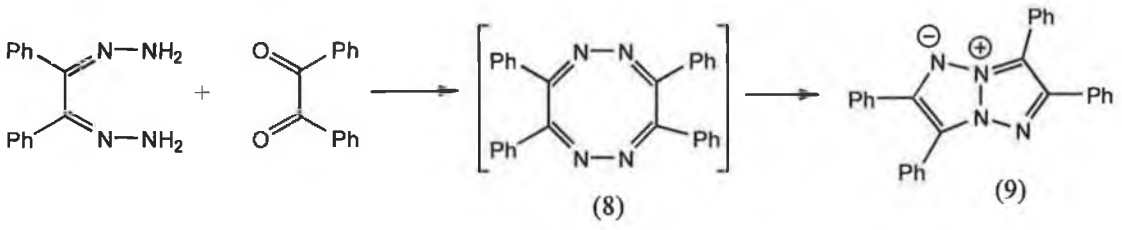
Scheme 1.20 *Formation of a bridged 1,2,5,6-tetrazocine from reaction of N-bromosuccimide with 5-(1,2,4-triazolidin-1-yl)uracil.*

The non-crystalline 1-substituted diazetidiones **(65)** slowly underwent a virtually quantitative transformation to eight-membered ring dimers **(67)** over 2 weeks.[38] Molecular weight determination suggested two dimers which no longer possessed an intact 1,2-diazetin-3-one ring. Formation of the 1,2,5,6-tetraazacyclooctane-3,7-diones **(67)** is considered to result through a six -membered intermediate **(66)** as shown below.



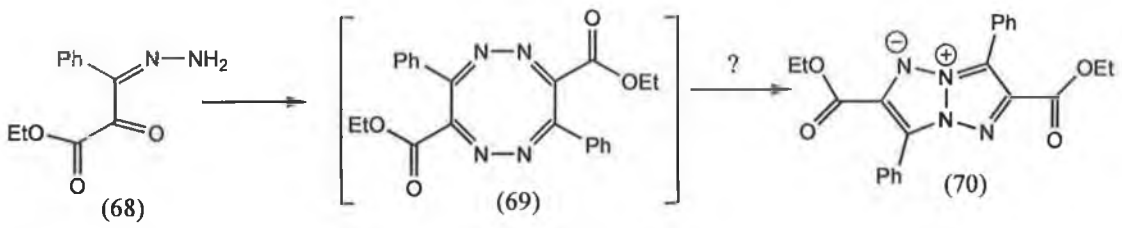
Scheme 1.21 *Formation of the 1,2,5,6-tetraazacyclooctane-3,7-diones from 1-substituted diazetidiones.*

Kopecky claims that the condensation product of benzil dihydrazone with benzil, as well as that of two moles of benzil monohydrazone was found by ^{1}H and ^{13}C NMR to be 2,3,6,7-tetraphenyl-triazo[1,2-b]-1,2,3-triazole **(9)** rather than 3,4,7,8-tetraphenyl-1,2,5,6-tetraazocyclo-2,4,6,8-tetraene **(8)** , as previously assumed by Schlesinger.[39] The structure represents a pseudoaromatic, mesoionic compound in agreement with Pfleger and Carboni's revised conclusions with these systems who Kopecky makes no reference to.[29,31]



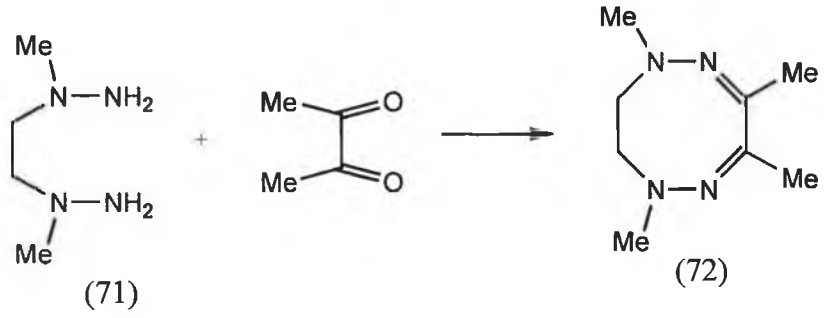
Scheme 1.22 *Condensation product of benzil dihydrazone with benzil to give 2,3,6,7-tetraphenyl-triazo[1,2-b]-1,2,3-triazole.*

Glidewell's acquisition of the fully unsaturated 1,2,5,6-tetrazocine **(69)** through the dimerisation of the hydrazone **(68)** when kept at room temperature is based on IR, NMR and elemental analysis.[40] No account in this report refers to the methylester analogue previously utilised by Pfleger and the recovery of the tetrazocine must be deemed doubtful.



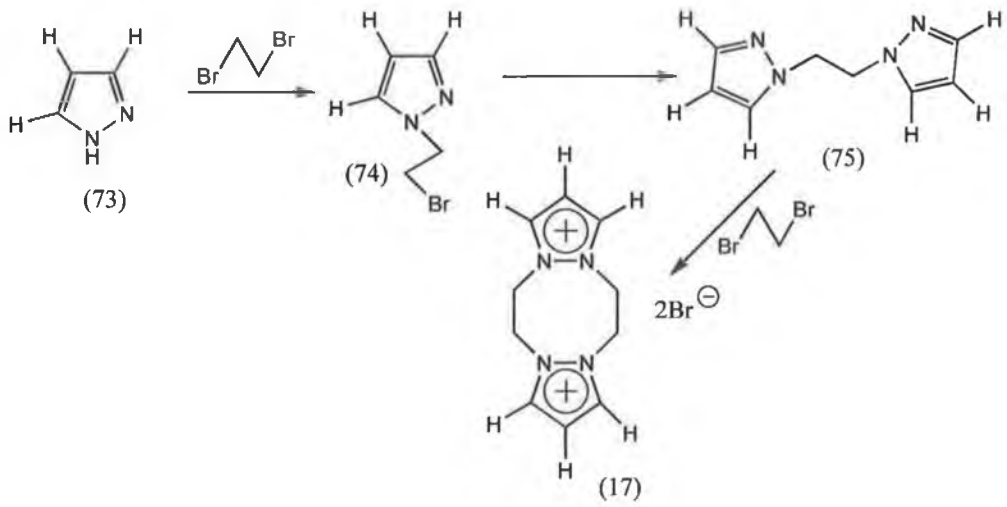
Scheme 1.23 *Proposed formation of the unsaturated 1,2,5,6-tetrazocine (69) through the dimerisation of the hydrazone (68)*

Gol'din and Tsiomo reacted the dihydrazine **(71)** with butane-2,4-dione to make polyhydrazones, but also obtained the low molecular weight tetrazocine **(72)** in low yield.[41]



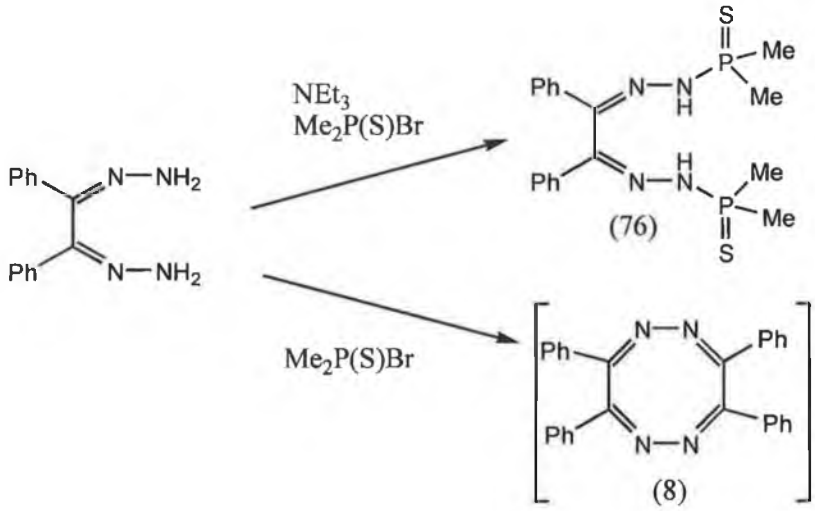
Scheme 1.24 *Formation of the 1,2,5,6-tetrazocine (72) through reaction of dihydrazine (71) with butane-2,4-dione.*

Cabildo has lately introduced the development of several 5,6,12,13-tetrahydrobispyrrolo[1,2-a:1,1',2'e][1,2,5,6]tetraazocinium dihalides **(17)**.[14] Synthesis of these systems is achieved by alkylation of the appropriate pyrazoles **(73)** with 1,2-dibromoethane. From pyrazole **(73)** and dibromoethane, the 1-bromoethylpyrazoles **(74)** are obtained. The subsequent treatment of **(74)** with an additional mole of pyrazole under phase transfer catalysis conditions gives **(75)**. Finally the quaternary salt was formed by treating the bis(pyrazol-1-yl)ethane derivatives **(17)** with excess 1,2-dibromoethane.



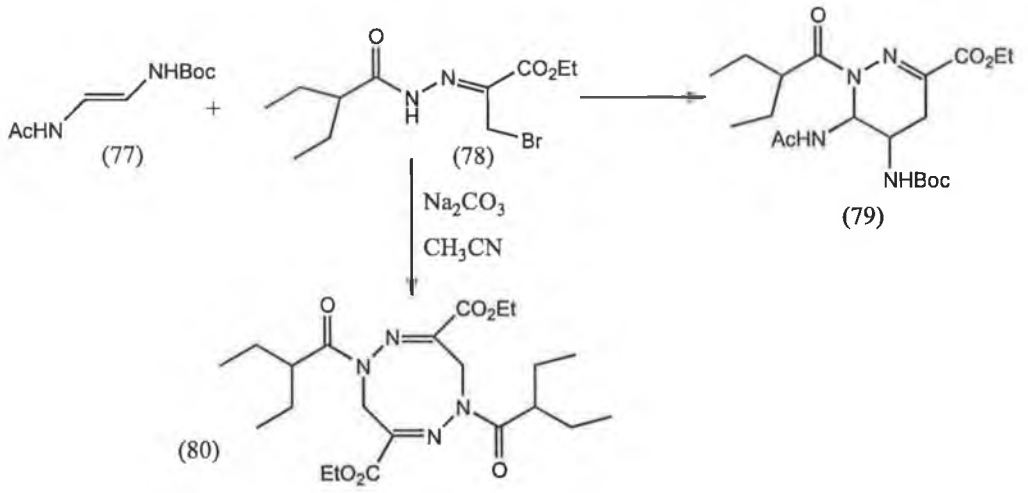
Scheme 1.25 *Formation of 5,6,12,13-tetrahydrobispyrrolo[1,2a:1,1',2'e][1,2,5,6]tetraazocinium dihalides.*

Batsanov, while carrying out work on hydrazone ligands, unexpectedly obtained the eight-membered heterocycle 3,4,7,8-tetraphenyl-1,2,5,6-tetrazocine **(8)**.[42] Reaction of $Me_2P(S)Br$ in CCl_4 with benzil dihydrazone in the presence of Et_3N gave the dihydrazone **(76)**. However in absence of base, a mixture of products results, including the tetrazocine **(8)**. Again this may be viewed as unlikely in light of Kopecky's re-examination of this compound and from work by Pfleger.[6,39]



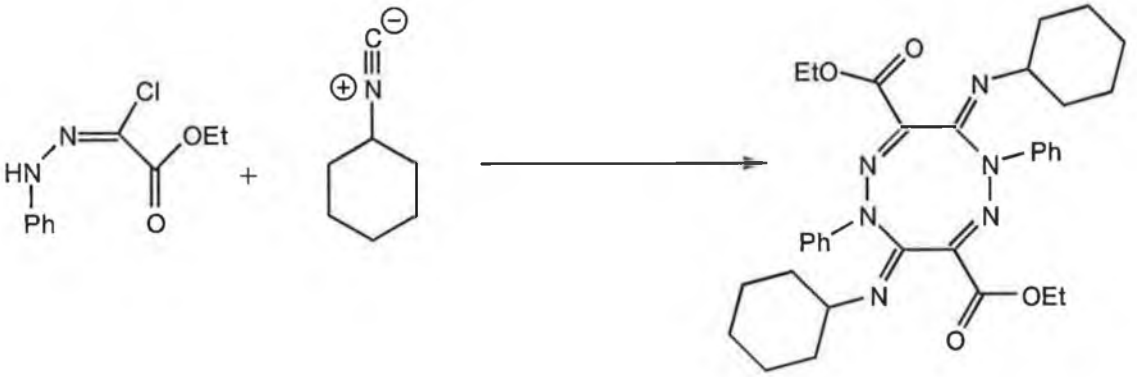
Scheme 1.26 *Bastanovs preposed formation of 3,4,7,8-tetraphenyl-1,2,5,6-tetrazocine.*

Formation of 1,2,5,6-tetrahydropyridazine derivatives assembled via a hetero Diels-Alder reaction between hydrazone **(78)** and alkene **(77)** afforded a 1:3 mixture of desired cycloadduct **(79)** and an unexpected tetrazocine **(80)** in 87% yield.[43] Thus two moles of the hydrazone dimerise to yield the 1,2,5,6-tetrazocine **(80)**. The authors offer no characterisation of the proposed compound



Scheme 1.27 *Dimerisation to yield a 1,2,5,6-tetrazocine.*

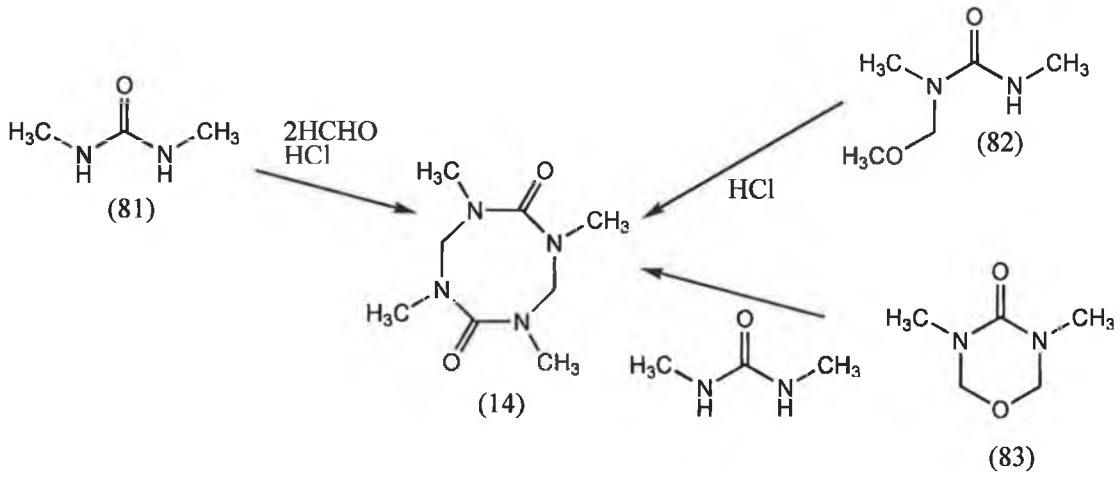
More recently, Moderhack prepared the 1,2,5,6-tetrazocine through reaction of chloro-*p*-tosylhydrazone acetic acid ethyl ester with isocyanocyclohexane.[44]



Scheme 1.28 *Formation of a 1,2,5,6-tetrazocine through reaction of chloro-p-tosylhydrazone acetic acid ethyl ester with isocyanocyclohexane*

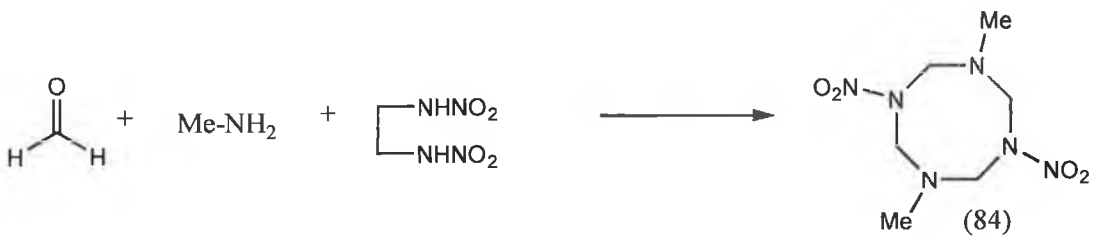
1.3.2. 1,3,5,7-tetrazocines

By condensation of *N,N'*-dimethylurea **(81)** with formaldehyde, Kadowaki obtained the tetramethyl-dimethyldiureide **(14)** in 13% yield.[9] This was the first reported synthesis of a 1,3,5,7-tetrazocine. No conclusive evidence was offered until forty years later when Peterson repeated Kadowaki's work . He also provided a fewalternative higher yielding routes to the eight-membered heterocycle. Thus **(14)** is obtained in 60% yield by reaction of *N,N'*-dimethyl-methoxymethylurea **(82)** in a saturated HCl dioxane solution. Kinetic studies conveyed that at low acid concentration and temperature, the yield was shown to be greater. Similarly **(83)** is a viable precursor to the 2,6-dioxo-1,3,5,7-tetramethyloctahydro-1,3,5,7-tetrazocine **(14)** as shown below.



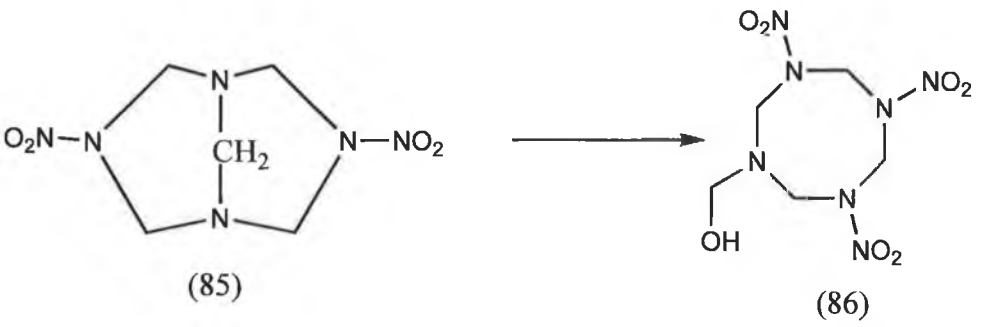
Scheme 1.29 *Various synthetic routes to the formation of the first reported 1,3,5,7-tetrazocine (14).*

In relation to studies of nitroamines, Chapman published work based on the reactions of nitroamines with primary or secondary amines and formaldeyde.[45] He successfully prepared a series of compounds from methylenedinitroamine, formaldehyde and methyl amine to give the 1,3,5,7-tetrazocine **(84)** shown below.



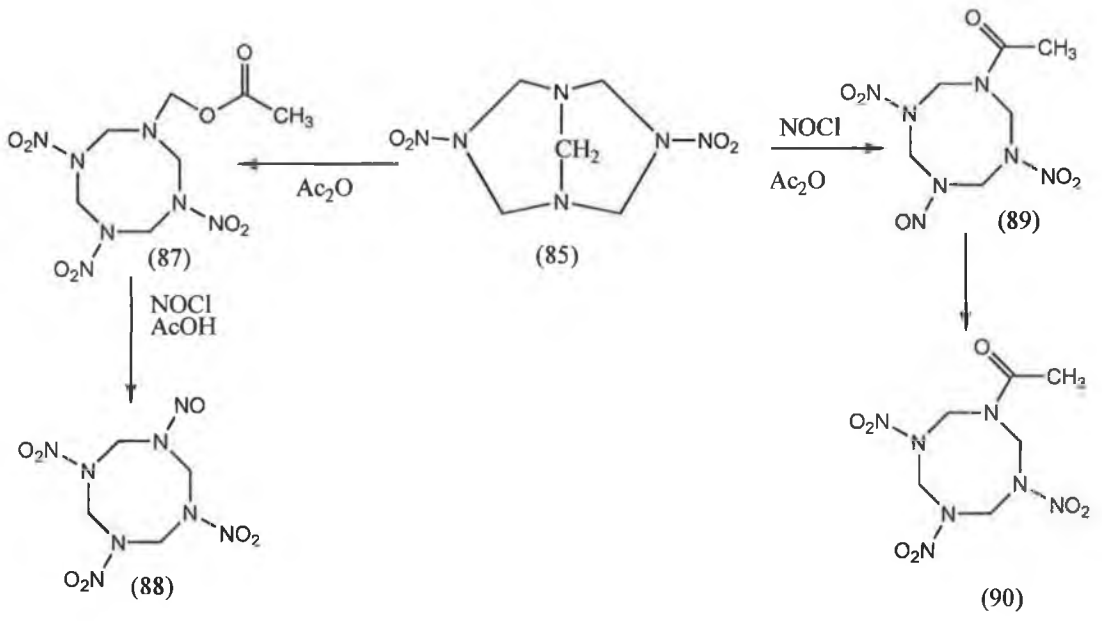
Scheme 1.30 *Formation of the 1,3,5,7-tetrazocine (84)*

Further publications on this chemistry by Lamberton refer to workers at Bristol (private communication) who prepared a compound similar to Chapman's which they believed to be **(86)** through nitrolysis of **(85)**.[46]



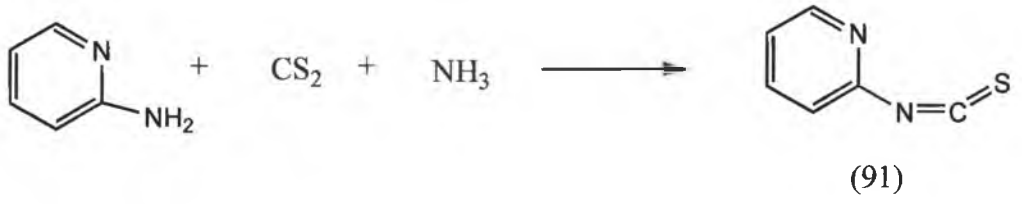
Scheme 1.31 *Formation of the 1,3,5,7-tetrazocine (86) through nitrolysis of (85).*

Around this time, Bachman reported formation and manipulation of similar heterocycles in the scheme shown below.[47] The 1,5-methylene-3,7-dinitro-1,3,5,7-tetrazocyclooctane **(85)** was simultaneously nitrosated and acylated with loss of the bridge methylene group to give 1-acetyl-3,7-dinito-5-nitroso-1,3,5,7-tetrazocyclooctane **(89)** in 60% yield. Structure **(89)** was converted by oxidation to the 1-acetyl-3,5,7-trinito-1,3,5,7-tetrazocyclooctane **(90)** using HNO_3 and H_2O_2. Nitrosyl chloride and acetic acid replaced the acetoxymethyl group of 1-acetyl-3,5,7-trinito-1,3,5,7-tetrazocyclooctane **(87)** by a nitroso group and produced 1-nitroso-3,5,7-trinito-1,3,5,7-tetrazocyclooctane **(88)**.



Scheme 1.32 *Formation and derivitisation of various 1,3,5,7-tetrazocines.*

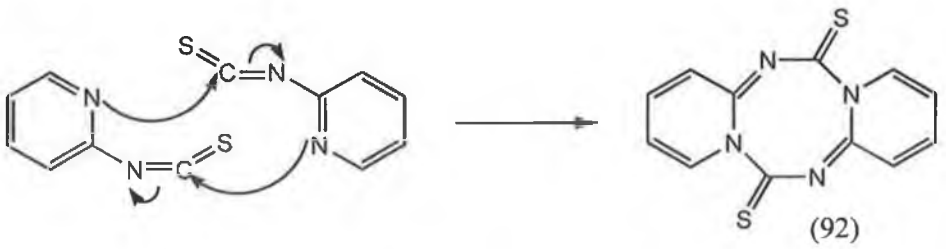
Fairfull and Peak reported that reaction of 2-aminopyridine, carbon disulphide and ammonia yielded the red solid 2-pyridyl-isothiocyanate **(91)**, based on elemental analysis.[48]



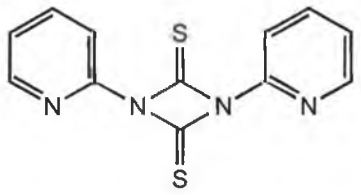
Scheme 1.33 *Formation of* 2-pyridyl-isothiocyanate.

However later investigation of this reaction by Howard and Michaels showed that the red solid was in fact a dimer **(92)**, which in solution underwent a dissociation to the monomer 2-pyridyl isothiocyanate **(91)**.[49] These claims were substantiated by IR spectroscopy. Two conceivable dimer structures were considered, **(93)** and **(92)**. Structural assignment **(93)** is ruled out as no typical absorptions of the pyridyl ring moiety are present. The authors propose that **(92)** is formed from a " Head to Tail" attack of one pyridyl nitrogen on the thiocarbonyl of the other, supported by

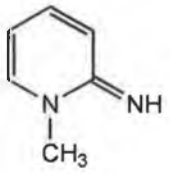
absorption observed at 6.07μ , a property shared with 1-methyl-2-pyridoneimine **(94)**.



(92)



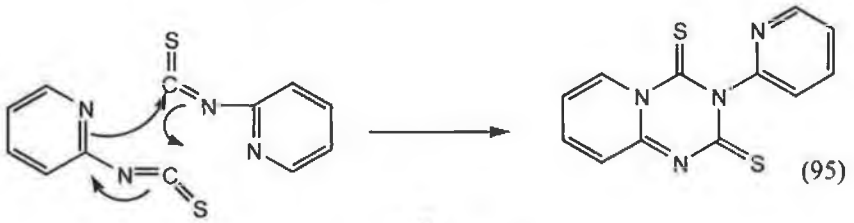
(93)



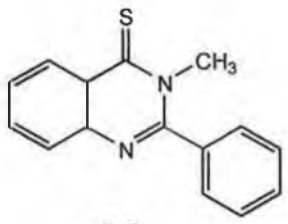
(94)

Scheme 1.34 *Proposed formation of a 1,3,5,7-tetrazocine formed from " Head to Tail" attack.*

But, yet again the dimer structure assignment was later revised by Blatter and Lukaszewski who claimed to have conclusively determined the real structure of the red solid.[50] They offer an alternative structure **(95)** which is formed from two isothiocyanate molecules and may be formally regarded as a Diels-Alder reaction in which the –N=C=S function serves as the dienophile and the –N=C–N=C=S system as the diene. The proposed structure was substantiated by NMR spectral data based on comparison with NMR shifts obtained from similar compounds such as **(96)**.



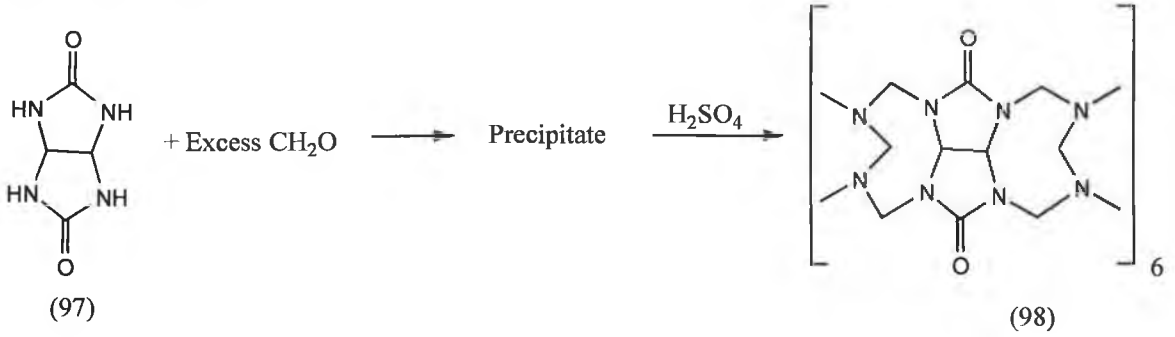
(95)



(96)

Scheme 1.35 Lukaszewskis proposed dimer product (95) from 2-pyridyl-isothiocyanate.

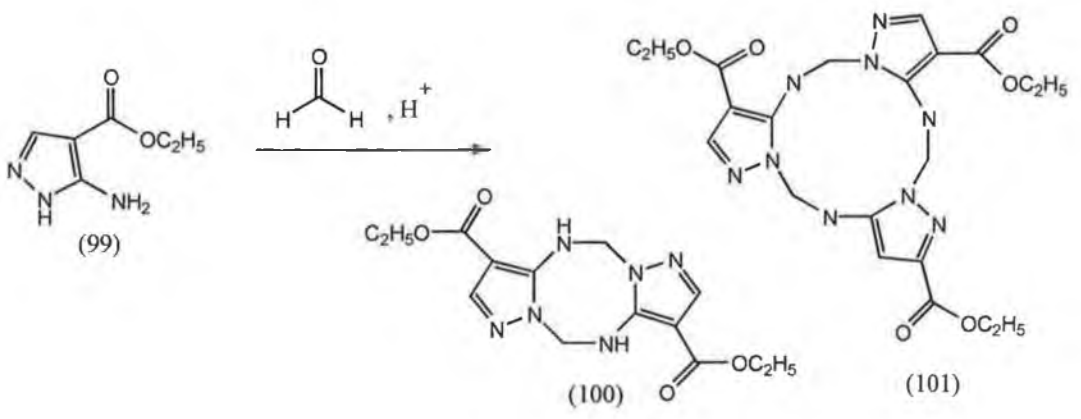
Repeating work by Behrend some 75 years ago, Freeman reported the acidic condensation of glycoluril **(97)** with excess formaldehyde to yield an unknown compound which should probably be regarded as an aminal type polymer.[51] However boiling this precipitate in hot H_2SO_4 yielded a more tractable crystalline product. Intrigued by Behrend's original report, X-ray diffraction analysis was undertaken unveiling the tetrazocine **(98)**, given the trivial name Cucurbituril. This compound **(98)** is a cyclic hexamer of dimethano-glycoluril containing six 1,3,5,7-tetrazocine rings.



(97) (98)

Scheme 1.36 *1,3,5,7-tetrazocine formed through the condensation of glycoluril with excess formaldehyde.*

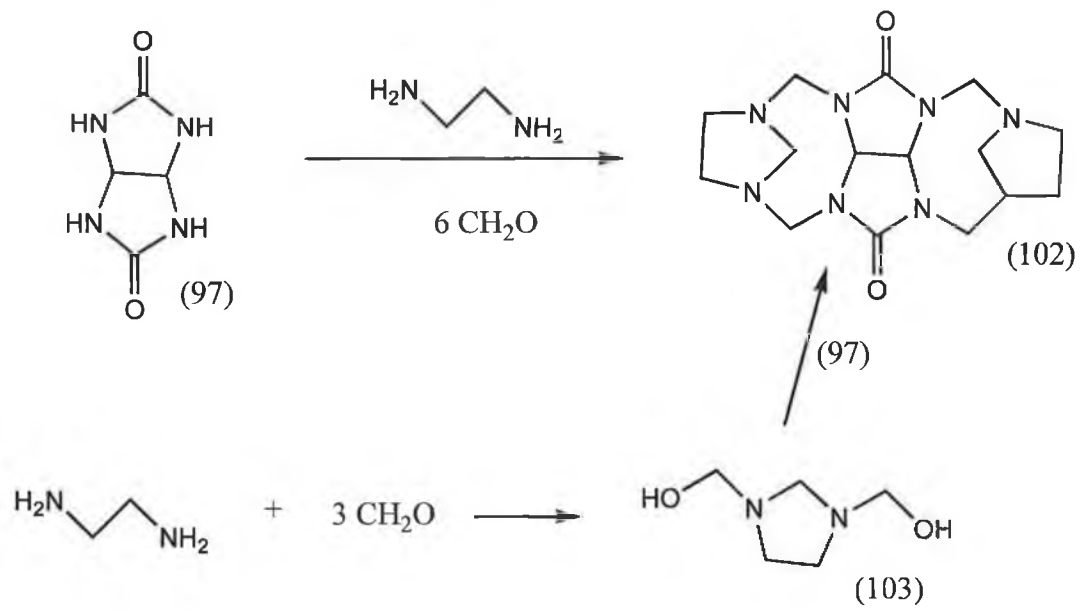
Wamhoff and coworkers successfully synthesised **(100)** in 31% yield through a "Head to Tail" acid catalysed condensation of the substituted pyrazole **(99)** resulting from reaction with formaldehyde.[52] The minor product **(101)** was also obtained.



(99) (100) (101)

Scheme 1.37 *"Head to tail" acid catalysed condensation of the substituted pyrazole (99) resulting from reaction with formaldehyde to yield 1,3,5,7-tetrazocine.*

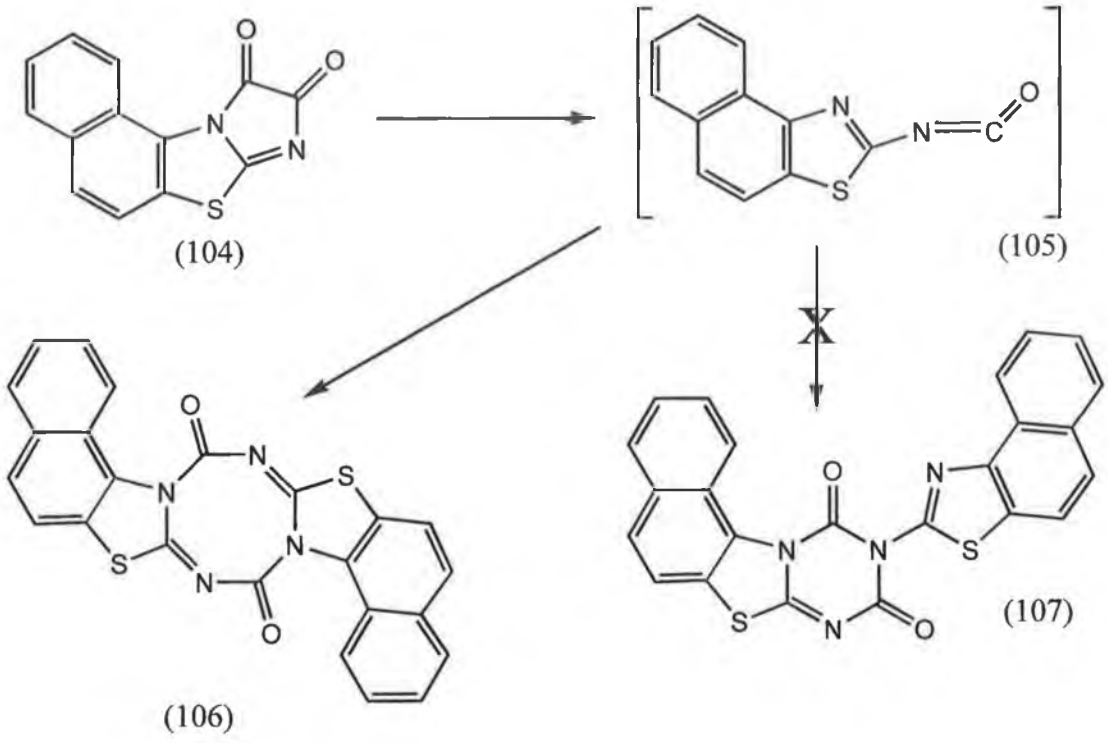
Further work by Mock on the versatility of polycyclic ring formation with gycoluril reports the condensation with paraformaldehyde but under less drastic conditions than that of Behrend and Freeman.[53] Slow addition of 1,2-ethanediamine to a refluxing mixture of **(97)** and formaldehyde in MeOH yields a high-melting crystalline solid shown by X-ray data to have the structure **(102)**. The authors speculate as to the mechanism to the ditetrazocine ring assembly which is believed to occur through intermediate **(103)** based on the relative nucleophilicity of aliphatic amino groups and urea nitrogens. The intermediate forms and subsequently condenses with glycoluril.



Scheme 1.38 *Formation of a 1,3,5,7-tetrazocine through reaction of gycoluril, 1,2-ethanediamine and formaldehyde.*

Liu and Shih while carrying out a pyrolysis of naphth[1,2,d]imidazo[2,1-b]thiazole-2,3-dione **(104)** in dimethylformamide recovered a yellow crystalline product with a melting point of 320^0C in 80% yield.[20] Elemental analysis of the product indicated the decarbonylated derivative, 2- isocyanatonaphth-[1,2-d]thiazole **(105)**. However re-examination of the mass spectra fragmentation pattern revealed a dimer of **(105)** was formed leading to both stuctures **(107)** and **(106)** as possible candidates. IR studies rule out structure **(107)** as only one distinct carbonyl absorption band was present. Furthermore NMR shows the symmetrical existence of the dimerised

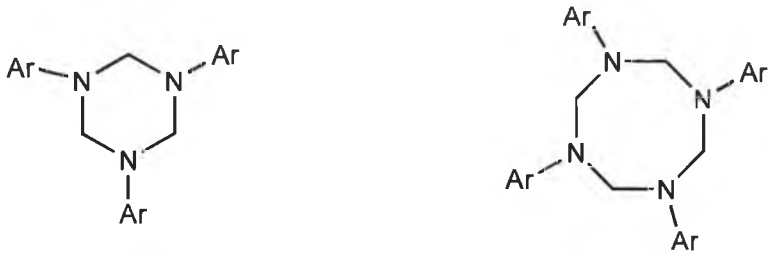
molecule which results from a [4+4] cycloaddition and was therefore assigned as the tetrazocine **(106)**.



Scheme 1.39 *Pyrolysis of naphth[1,2,d]imidazo[2,1-b]thiazole-2,3-dione in dimethylformamide yielding a 1,3,5,7-tetrazocine.*

This chemistry is analogous with that obtained from the dimerisation product of pyridyl isothiocyanate assigned by Blatter and Lukaszewski.[50]

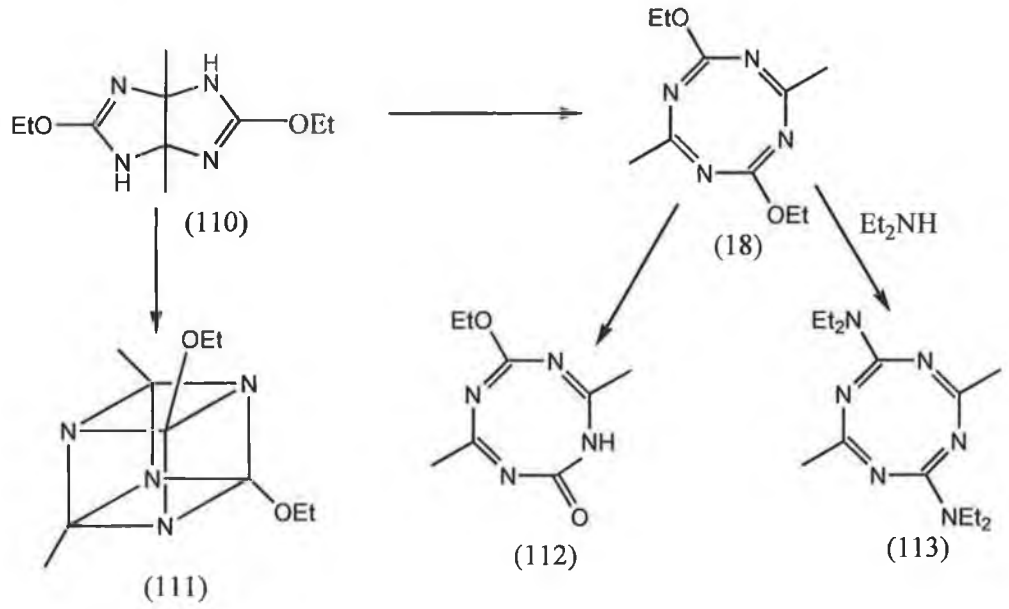
Re-visitation of aniline/formaldehyde chemistry by Giumanini gave a product outcome study of the reactions between a number of substituted aromatic amines with paraformaldehyde in inert solvents.[54] The main products obtained were ultimately 1,3,5-triaryl-1,3,5-hexahydrotriazocines **(108)** and 1,3,5,7-tetraaryl-1,3,5,7-tetrazocines **(109)**. The authors discuss the inability to correlate the product outcome with the actual structure of the amine substrate.



(108) (109)

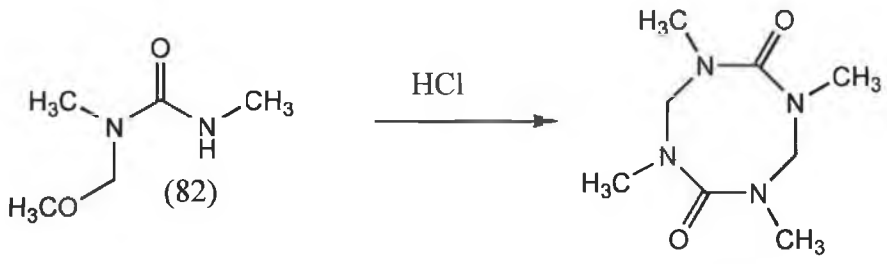
Figure 1.13 *Formation of a 1,3,5,7-tetraaryl-1,3,5,7-tetrazocine from aniline derivatives and paraformaldehyde.*

Gompper obtained the 2,6-diethoxy-4,8-dimethyl-1,3,5,7-tetraazobicyclo[3.3.0] octa-3,7-diene **(18)**, using *tert*-butylhypochorite and potassium *tert*-butoxide as the ring opening reagents for compound **(110)**.[55] No tetraazosemibullvalene structure such as **(111)** is involved as only sp^2-hybridised framework carbon atoms are present. When a solution of **(18)** is stirred for a few days in the presence of silica gel, 6-ethoxy-4,8-dimethyl- 1,3,5,7,-tetrazocin-2(1H)-one **(112)** results. Also heating **(18)** with diethylamine gives the tetrazocine **(113)**. According to X-ray analysis, the structure has a boat conformation.



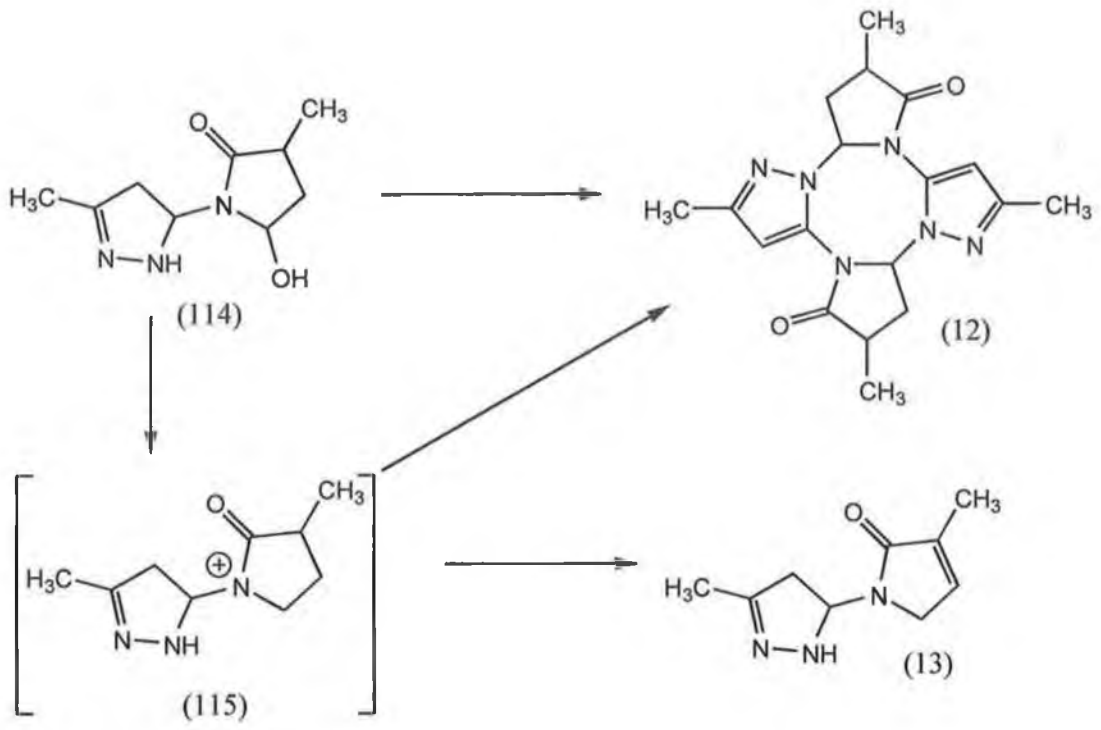
Scheme 1.40 *Formation and derivatisation of 2,6-diethoxy-4,8-dimethyl-1,3,5,7-tetraazobicyclo[3.3.0] octa-3,7-diene.*

In order to confirm the cyclic nature of the supposed 1,3,5,7-tetrazocine **(14)** as reported by Kadowaki, Ebisuno repeated the author's work.[21] As 1,3,5,7-tetramethyltetrahydro-1,3,5,7-tetrazocine-2-6(1H,3H)-dione **(14)** had only been generated in 13% yield, a modification of the original method was sought. The procedure involved optimisation of the yield to 71% through low acid concentration and temperature and through isolation of *N*-methoxymethyl-*N,N'*-dimethylurea **(82)**.



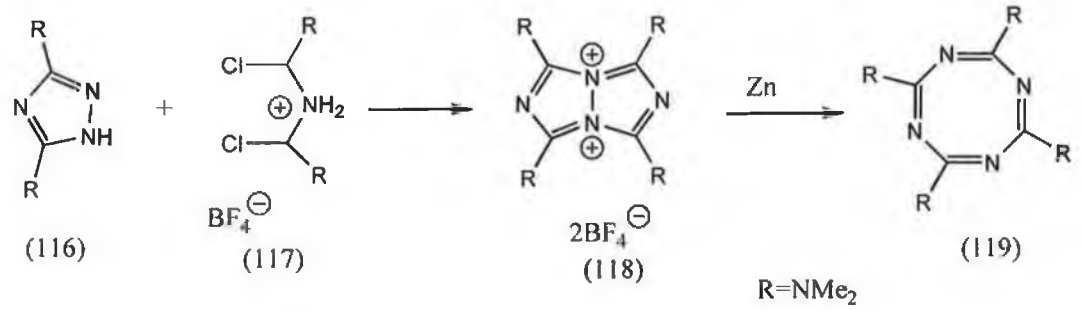
Scheme 1.41 *Formation of 1,3,5,7-tetramethyltetrahydro-1,3,5,7-tetrazocine-2-6(1H,3H)-dione from N-methoxymethyl-N,N'-dimethylurea under acidic conditions.*

Brinkmeyer and Teranso, working with *N*-pyrazolyl-5-hydroxypyrrolidiones **(114)**, discovered that treating these compounds with a catalytic amount of *p*-toluene sulphonic acid in toluene under reflux for 1 hour resulted in not only the desired saturated 3,4-pyrrolidionnes **(13)** through dehydration but also the tetrazocine **(12)** in 39% yield.[8] The mechanism offered involves the dimerisation of an iminium intermediate ion **(115)** yielding the eight-membered ring compound **(12)**.



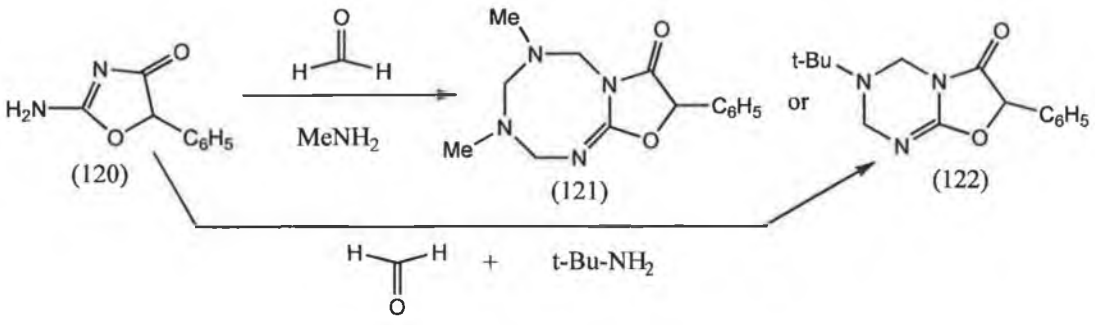
Scheme 1.42 *Formation of 1,3,5,7-tetrazocines from the acidic dimerisation of N-pyrazolyl-5-hydroxypyrrolidiones.*

Later work by Gompper reports the reaction of 3,5-diaminotriazoles **(116)** with **(117)** in the presence of triethylamine in chloroform yielding the triazolo[1,2-a]triazolediylium salts **(118)**.[19] These dication salts can be reduced with zinc in acetonitrile to give the tetraaminotetrazocine **(119)**.



Scheme 1.43 *Formation of the 1,3,5,7- tetrazocine (119).*

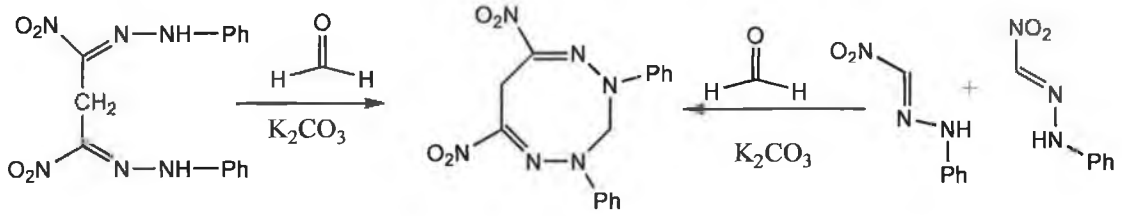
Finally a more recent 1,3,5,7-tetrazocine was synthesized and reported by Ramsch.[56] Reaction of 2-amino-5-phenyl-4-oxazolinone **(120)**, commonly known as pemoline, with primary amines and formaldehyde affords oxalo[3,2,-a]-1,3,5-triazines **(122)** or the oxalo[3,2,-a]-1,3,5,7-tetrazocine **(121)** depending on which amine was used. Butylamine and *tert*-butylamine yield the oxalo[3,2-a-]-1,3,5-triazines **(122)** whereas methylamine and cyclohexylamine give the required tetrazocine in 62% yield. Both compounds have been isolated and verified by NMR and mass spectral techniques. No explanations are offered as to the differing outcomes for the amines used.



Scheme 1.44 *Reaction of 2-amino-5-phenyl-4-oxazolinone with various amines and formaldehyde yielding the corresponding oxalo[3,2,-a]-1,3,5-triazines or oxalo[3,2,-a]-1,3,5,7-tetrazocine.*

1.3.3. 1, 2, 4, 5 – tetrazocines

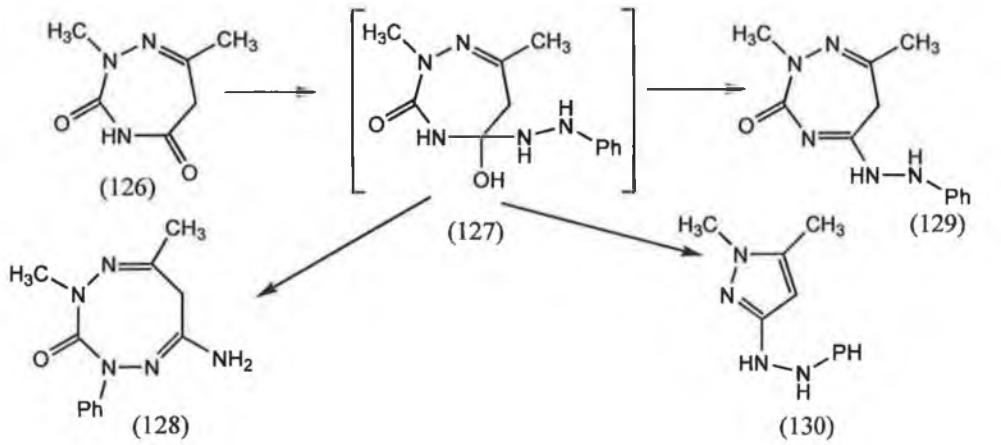
Hahn and Zawadzka condensed the bisphenyldihydrazone **(123)** with formaldeyde in the presence of potassium carbonate to give the tetrazocine **(124)** in unreported yield.[57] The same 1,2,3,5-tetrazocine could also be synthesized by an alternative route by reaction of nitroformaldehyde phenylhydrazone **(125)** and formaldehyde, again in the presence of potassium carbonate. Both compounds existence are supported by elemental analysis only.



(123) (124) (125)

Scheme 1.45 *Condensation of (123) with formaldeyde to yield a 1,2,4,5-tetrazocine.*

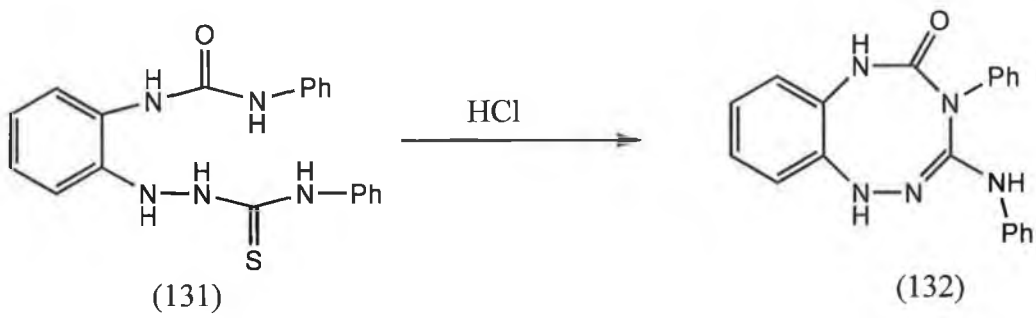
Hasnaoui and Laverge isolated three compounds by the reaction of the triazepine **(126)** with phenylhydrazine.[58] **(128)** and **(129)** is believed to be formed through the intermediate **(127)**. **(127)** undergoes a ring expansion to give the eight-membered ring **(128)** which is supported by NMR and mass spectral data.



Scheme 1.46 *Formation of a 1,2,4,5-tetrazocine by reaction of a triazepine with phenylhydrazine.*

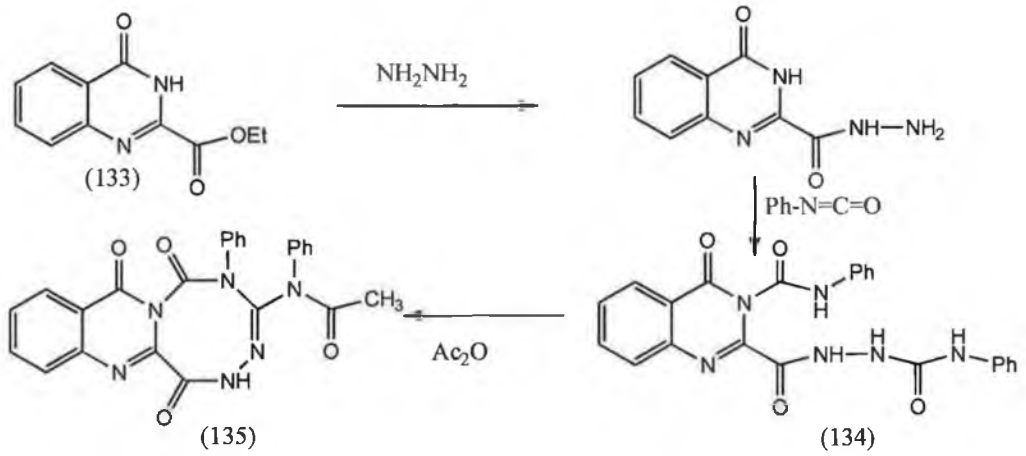
1.3.4. 1,2,4,6-tetrazocines

Guha was responsible for the synthesis of the tetrazocine **(132)** by ring closure of the thiosemicarbazide **(131)** induced with either acid catalysis to obtain the benzotetrazocine **(132)** in moderate yields. The structure however is based only on nitrogen analysis.[59]



Scheme 1.47 *Formation of a 1,2,4,6-benzotetrazocine through acid catalysed ring closure.*

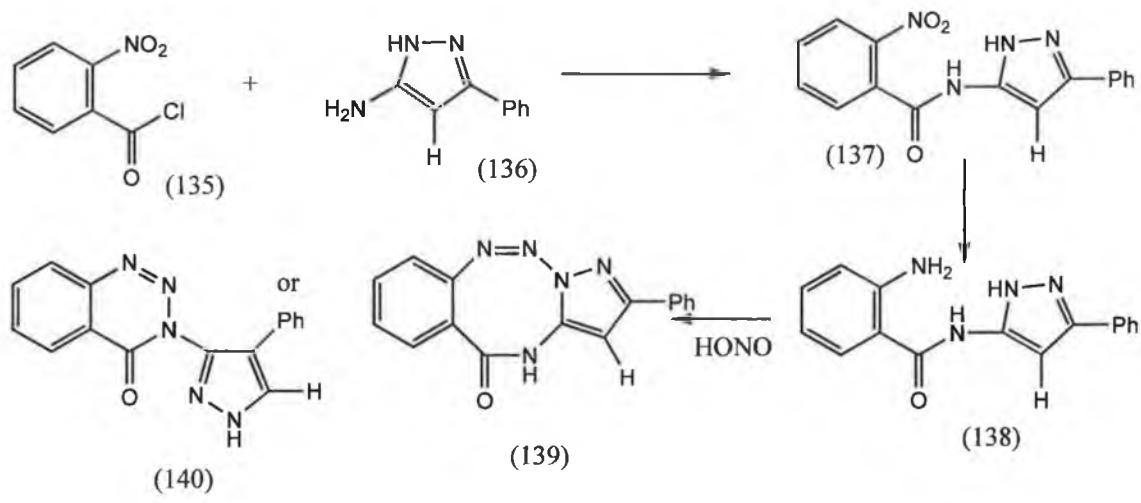
Amine and El-Hashash reported the isolation of the tetrazocine **(135)** in 70% yield from the precursor **(134)** through cyclisation using acetic anhydride.[60] The quinazolinone derivative **(134)** can be made from the starting product **(133)** in the reaction scheme shown below. The tetrazocine is supported by NMR and elemental analysis.



Scheme 1.48 *Formation of a 1,2,4,6-tetrazocine from ring closure of quinazolinone precursor (134) with acetic anhydride.*

1.3.5. 1,2,3,5-tetrazocines

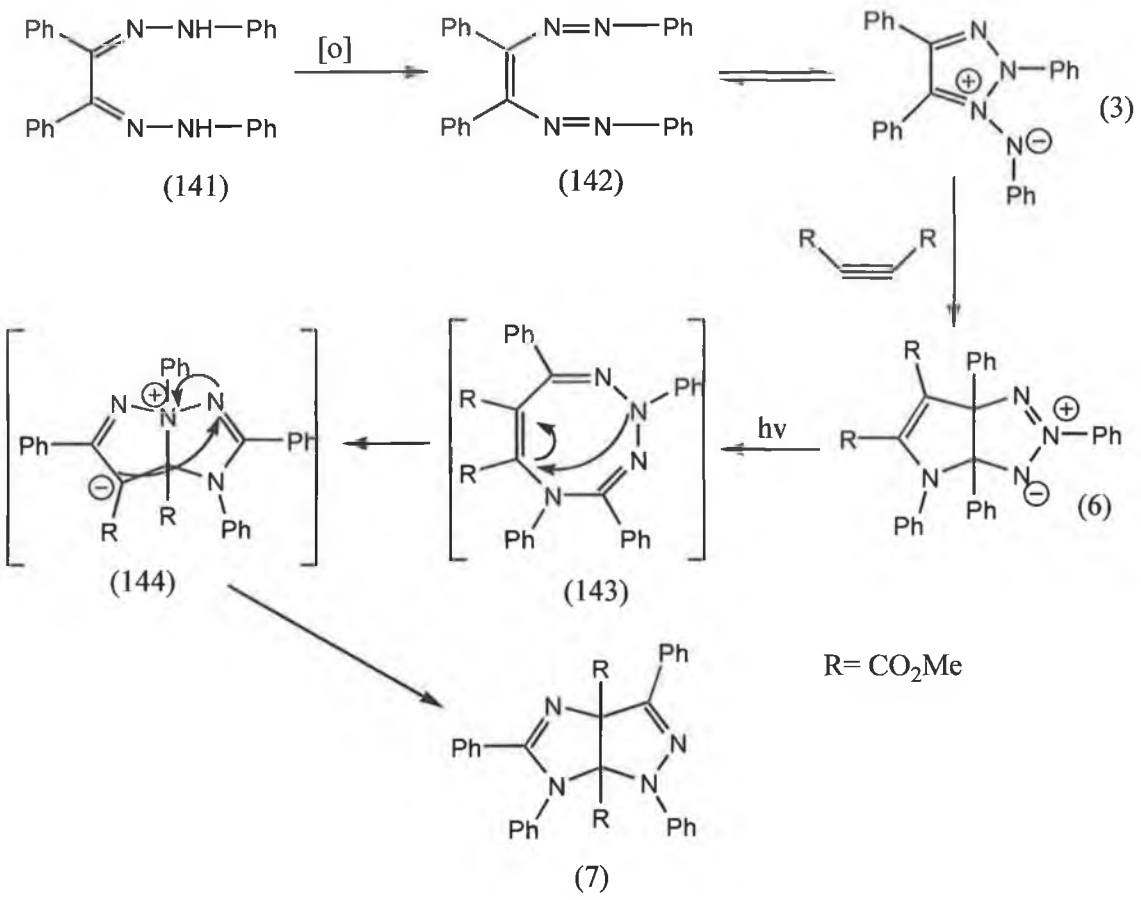
Plescia and Ajello, while developing new types of polycondensed heterocycles for potential biological activity, reacted *o*-nitrobenzoylchloride **(135)** and the aminopyrazole **(136)** to form compounds of type **(137)** which underwent facile catalytic reduction in the presence of palladium on charcoal to yield *N*-(3,4-R, R'-pyrazol-5-yl)-*o*-aminobenzamides **(138)**.[61]



Scheme 1.49 *Proposed formation of a 1,2,3,5- tetrazocine through diazotization of ortho-substituted aniline precursor.*

The tetrazocine **(139)** is formed via a smooth diazotization step using nitrous acid in 70% yield. Although NMR, IR and mass spectral data all confirmed the tetrazocines **(139)** existence, the authors did not rule out structure **(140)** as a distinct possibility.

Butler reported an entirely new high yield route to the pyrrolo-[2,3-d-]-1,2,3 triazoles **(7)** from a cycloaddition between the oxidation products of substituted benzil dihydrazones **(141)** and dialkylacetylenedicarboxylates.[5] Oxidation of the dihydrazone **(141)** with lead(IV)acetate yields **(142)**, which rearranges to form a 1,3-dipole **(3)** .



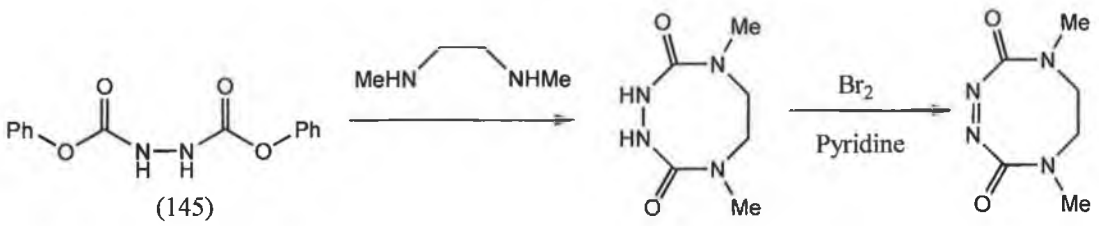
(141) (142) (3) (144) (143) (6) (7)

Scheme 1.50 *Photochemically induced intermediate 1,2,3,5-tetrazocine formation and subsequent rearrangement.*

Upon irradiation of the cycloadduct **(6)** with wavelengths of 350nm in dry dichloromethane, it undergoes a photochemical rearrangement to the imadazo[4,5,c] pyrazoles **(7)**. Structure validity is based on X-ray diffraction. The proposed mechanism involves a disrotatory opening of the bridgehead C-C bond of **(6)** to give the 1,2,3,5–tetrazocine intermediate **(143)** which then undergoes a rapid cyclisation to an intermediate **(144)** that finally rearranges to give the reported imidazo[4,5-c]pyrazole **(7)**. Unfortunately subsequent attempts to trap the tetrazocine by varying the R-substituents of the dipolarophile were not successful.

1.3.6. 1,2,4,7-tetrazocine

Tsunoda was the first to synthesise the only 1,2,4,7-tetrazocine in this class recently.[4] His efficiency with azodicarboxylic acid derivatives in Mitsunobu type C–C bond formation was rewarded by using this reagent, 4,7-dimethyl-3,5,7-hexahydro-1,2,4,7-tetrazocin-3,8-dione **(147)**, to prevent cyclisation of acyclic azocarboxamides to oxadiazides. Thus, the 1,2,4,7 heterocycle **(146)** was prepared from diphenylhydrazo-1,2-dicarboxylate **(145)** by successive treatment with *N,N'*-dimethyl-ethylenediamine to give **(146)** and then bromine to give **(147)**.



(145) (146) (147)

Scheme 1.51 *Formation and derivatisation of a 1,2,4,7-tetrazocine.*

Chapter 2

Reinvestigation of Previously Reported Tetrazocines

2.1. Reinvestigation of a 1,2,4,6-tetrazocine derived from Quinazolinones

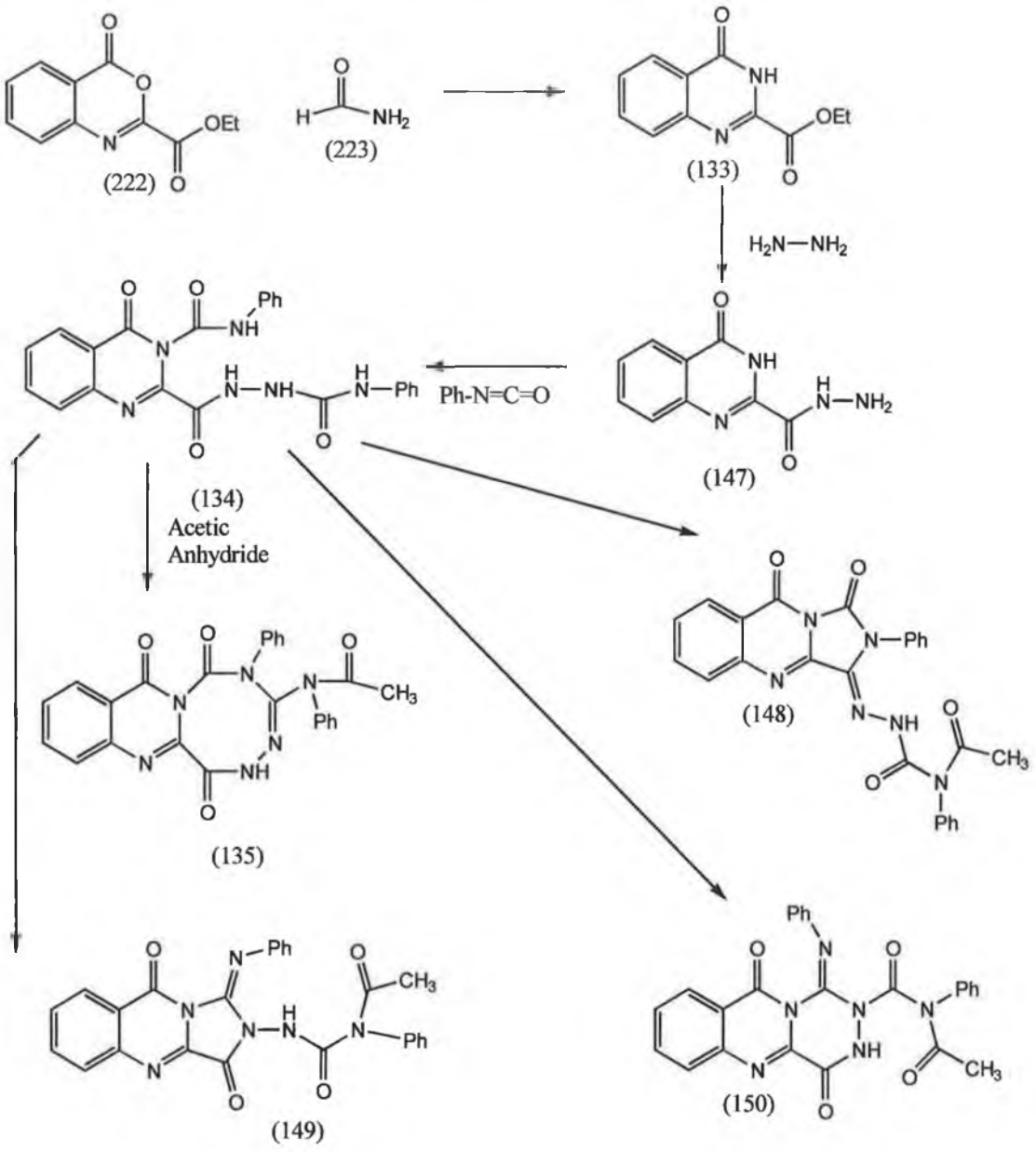
2.1.1. Introduction

A brief overview of the previous chapter leads to the following conclusions. Tetrazocines are generally rare. They are in many cases easily transformed to more stable five and six-membered rings under mild conditions either through intramolecular cyclisation or rearrangement. Their syntheses, in general, have been documented as sideline rather than designed. Very few examples of crystal structures exist. Their secondary derivatives often have the same elemental analysis as the tetrazocine itself. With this weight of argument against the existence of some tetrazocines, we felt it necessary to revisit some proposed, previously reported syntheses to substantiate some authors work which we viewed as inconclusive.

A recent publication describing the syntheses and reaction of 2-ethoxycarbonyl-4(3H)-quinazolinone **(133)** with nitrogen nucleophiles attracted our attention.[60] Described within is a five step synthesis leading to a 1,2,4,6-tetrazocine of which only one other example exists in the literature. More unusual however was the penultimate step in which the tetrazocine precursor **(134)** is cyclised to the eight-membered ring via cyclocondensation of **(134)** using acetic anhydride. We regard the limited spectral evidence (^{1}H-NMR and IR) offered by the authors as insufficient and the actual product obtained could equally be assigned to other plausible structures **(148)**, **(149)** or **(150)**. These alternative compounds would also satisfy the CHN analysis offered.

Five- and six-membered heterocycles are by far more commonly encountered in cyclisations in organic chemistry. If one considers the ease of cyclisation as a function of ring size, then attention must be drawn to the entropy of cyclisation. In general, eight-membered rings despite their low strain present synthetic difficulties. The possibility of rotation about a large number of bonds leads to high conformational entropy in the open-chain precursor which is largely lost in the cyclic product. Six-membered rings usually cyclise less rapidly than five-membered rings.

Although strain in the six-membered rings is less, this is out-weighed by the greater loss in entropy. In short, five- and six-membered rings represent the best balance between entropy and enthalpy terms and their rates of ring closure should be considerably higher than an eight-membered ring which undergoes more severe dimerisation or polymerisation competing reactions. Such reasoning provided a basis to repeat the author's work and verify the actual isolation of **(135)**.



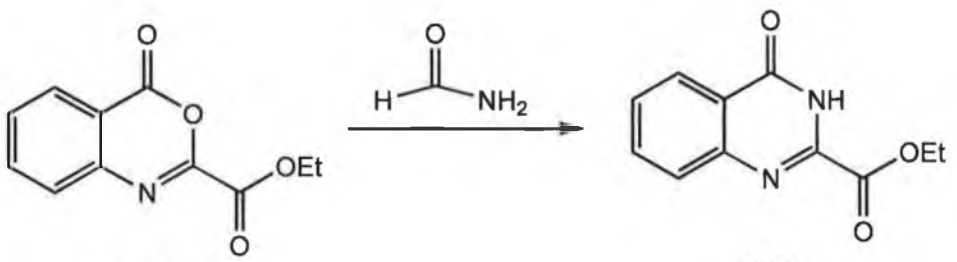
Scheme 2.1 *Synthetic route to formation of authors 1,2,4,6-tetrazocine. Alternative structural isomers which would also satisfy the CHN analysis offered.*

Quinazolin-4(3H)-ones are plentiful and common throughout the literature due to the biological activity associated with them. The pharmacological properties are conveniently summarised by their use as hypnotics, narcotics, irreversible enzyme inhibitors and more commonly as anti-malarial and sleeping drugs found on the market as Melsedin® and Revonal® respectively. They have also been shown to exhibit antimicrobial and cardionic activity.[62] More unusually, they have been employed as thermostable polymers.[63]

2.1.2. Results and Discussion

2.1.2.1. Verification of the reported procedure

The synthetic route to the tetrazocine **(134)** was repeated following the procedure described in the literature. Reaction of benzooxazinone with formamide yields 2-ethoxycarbonylquinazolinone **(133)** in 65% yield as described by the authors.

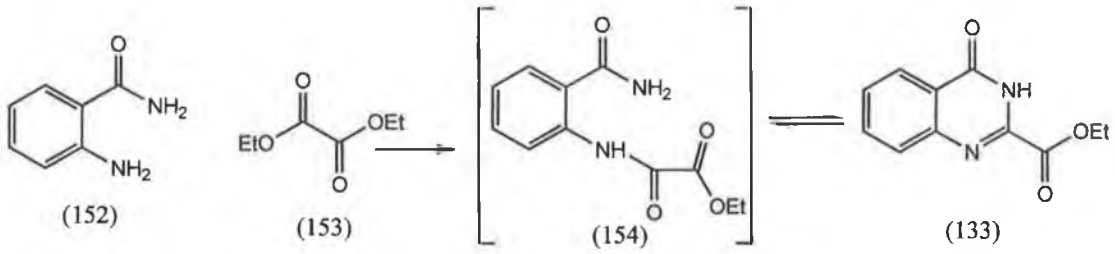


(151) (133)

Scheme 2.2 *Formation of 2-ethoxycarbonylquinazolinone through reaction of benzooxazinone with formamide.*

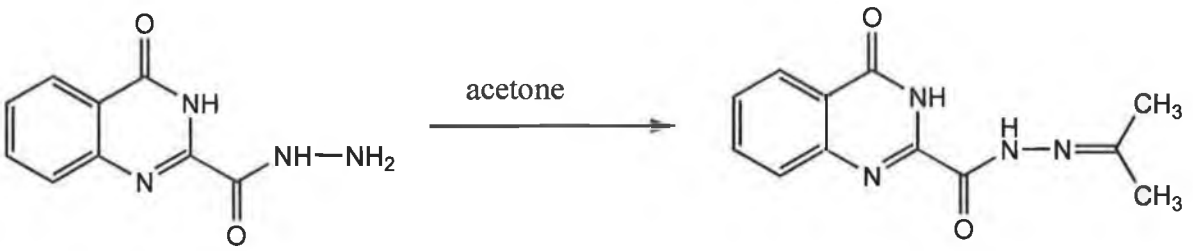
However we found this reaction not very satisfactory due to low yield and side products. Instead we sought a more direct route to the quinazolin-4(3H)-one **(133)**. Baker and Almaula describe fusion of anthranilamide **(152)** with diethyloxalate **(153)** at 170-180^{0}C resulting in concurrent ring closure of the initial adduct **(154)** leading ultimately to 2-ethoxycarbonylquinazolin-4(3H)-one in 50-60% yields.[64] When reaction temperatures below 180^{0}C were used, **(154)** was obtained as the major

product. However the yield of the desired quinazolinone can be increased by employing a Dean-Stark apparatus at temperatures above 180^0C. This effectively removes any ethanol and water condensed from the reaction thereby pushing equilibrium to the right.



Scheme 2.3 *Formation of 2-ethoxycarbonylquinazolinone through reaction of anthranilamide with diethyloxalate*

Characterisation of the compound agreed with that of the authors. Synthesis of the hydrazide proceeded smoothly by reaction of hydrazine with **(133)** in refluxing butanol. However some concern here is offered to the melting point of the hydrazide obtained by the authors. George and Mehta have also prepared this derivative and state a literature value of 250^0C in agreement with our value.[65] However the authors obtained a compound giving a melting point of 202^0C. No NMR or IR spectra are presented and it's proposed recovery was only accounted for by CHN analysis. The hydrazide was remarkably insoluble, only dissolving in boiling DMSO and was purified by refluxing the crude solid in methanol and hot filtering the pure hydrazide. However, with each subsequent purification, the growth of another product was observed by TLC which we believe to be consistent with structure **(155)**. This assumption is verified by the conversion of the hydrazide to the imine by refluxing it in excess acetone giving a mirrored result. Technical grade methanol contains sufficiently small amounts of acetone with which the hydrazide reacts.



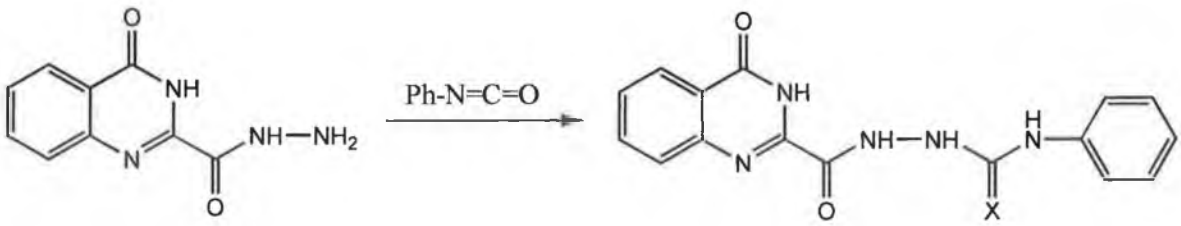
(147) (155)

Scheme 2.4 *Reaction of the hydrazide (147) with acetone to form an imine.*

This poses another uncertainty to which the authors themselves refer to in the penultimate step. The hydrazide is allowed react with a 4 molar equivalent of phenylisocyanate in refluxing acetone for 20 hours, the reactions being catalysed by K_2CO_3. The authors question why formation of **(155)** is not observed even though acetone is present in huge excess. They propose that imine formation is a reversible process. Also the phenylisocyanate derivative is a more thermodynamically stable process due to hydrogen bonding. Imine formation is in general an acid catalysed process. Rate of reaction is pH dependent with a pH of 4-5 being optimal. Under our basic conditions, it can be assumed that imine formation would be severely hindered.

Reaction of the hydrazide **(147)** with phenylisocyanate never led to the disubstituted phenyl isocyanate derivative **(134)** as proposed by the authors. After 20 hours of reflux, the excess acetone is removed. The base is then simply removed by washing the remaining crude solid with water. Finally the solid is recrystallised from toluene to give **(134)** in 65% yield according to the orders.

The crude solid was extremely insoluble, even in hot DMSO, indicating the formation of an organic salt. Neutralisation of excess K_2CO_3 and the white solid in aqueous acid solution gave a far more soluble product in DMSO which we have shown to be **(156a)**. This was confirmed by running a similar reaction in which **(147)** and a molar equivalent of phenylisocyanate gave **(156a)** in 90% yield.

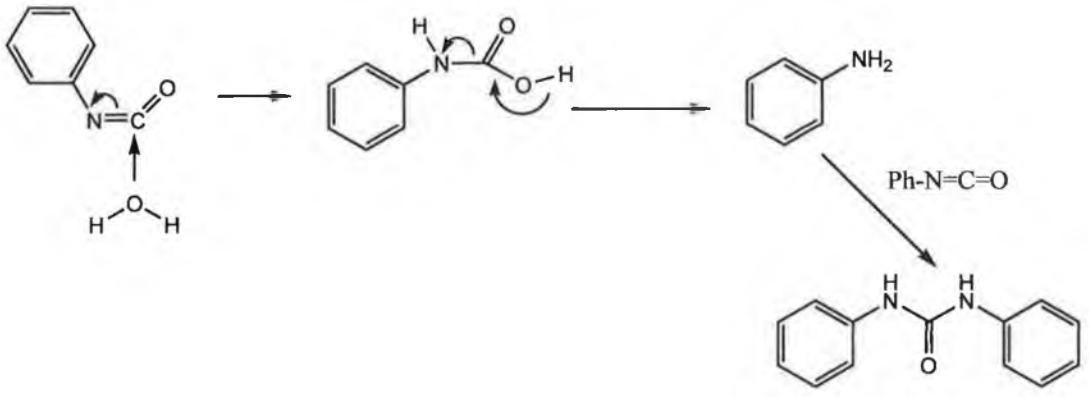


(147)

156a, X=O
156b, X=S

Scheme 2.5 *Reaction of the hydrazide (147) with phenylisocyante to form the semi carbazide (156).*

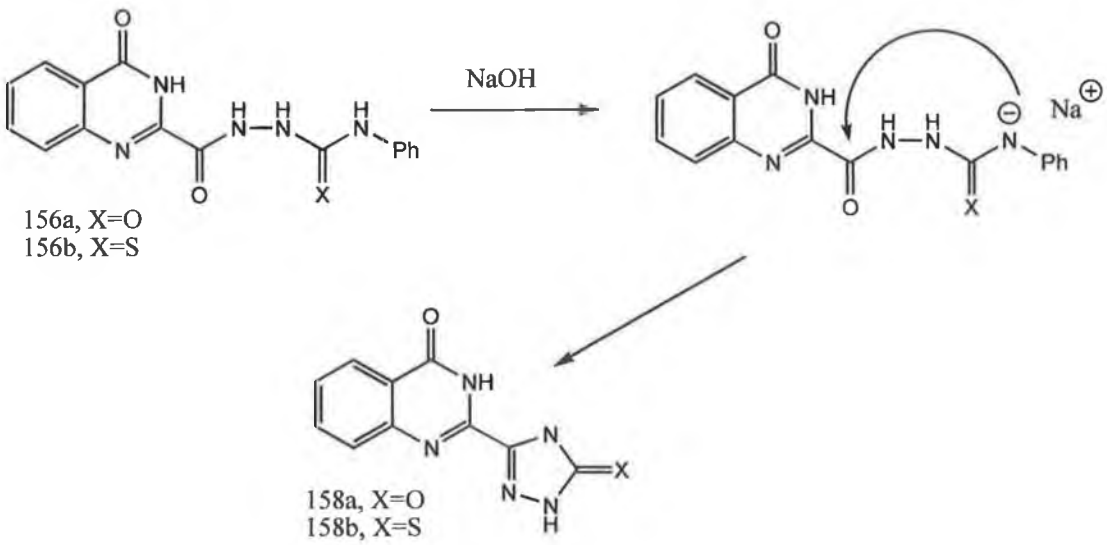
The only other product obtained was carbanilide **(157)** formed by trace amounts of water in solution reacting with the phenylisocyanate followed by decarboxylation to give aniline, which subsequently adds to another molecule of isocyanate.



(157)

Scheme 2.6 *Decomposition of phenylisocyanate with water to form carbanilide.*

With regard to the use of the base to catalyse the reaction, our attention was drawn to a report in which the thio analogue **(156b)** was heated under reflux in excess NaOH solution. Reddy has shown the base catalysed cyclocondensation of **(156b)** affording **(158b)** in moderate yields.[66] The amide carbonyl of the side chain is attacked by the more acidic imido nitrogen of the phenylthioimide with ensuing dehydration.



Scheme 2.7 *Base catalysed cyclocondensation to form triazole ring.*

Reaction of **(156a)** with NaOH or K_2CO_3 gave two differing results. The stronger base effects formation of the triazole ring **(158a)** readily. However utilisation of K_2CO_3 results in the formation of an insoluble salt which on neutralisation yields the starting material **(156a)**. Based on the above discussion, we feel that the phenyl imido-nitrogen is the more acidic in this molecule. This would then put into question the primary role of the base expected by the authors. It is self evident that they intend to make the pyrimidone amide ring nitrogen more nucleophilic. However, this does not appear to be the preferred site of attack by the base.

Due to the possibility of a higher E_{act} and solvent effects, numerous other solvents and bases were tried. However in each case either the **(156a)** or **(158a)** were recovered.

Reaction of the hydrazide **(147)** in the absence of base with phenylisocyanate was attempted. On reaction completion, the insoluble solid is simply filtered off and washed with dry acetone and allowed to dry. ^{1}H-NMR of this solid showed the presence of two unique phenyl groups arising from phenylisocyanate substitution with both groups each integrating for five protons. This would indicate substitution of phenyisocyanate at the pyrimidone amide nitrogen but for retention of the amide

proton signal at 12.5 ppm. Quinazolin-4(3H)-ones characteristically have the ring amide proton signal in this region and its up-field chemical shift may be attributed to ring current effects and lactam-lactim type tautomerism. Similarly a broad singlet was observed at 5ppm integrating for two protons. This signal would be too low for a proton from a phenylisocyanate amide nitrogen. This observation was finally solved by the small spiked addition of aniline to **(156a)**. The mixture was stirred for some time and filtered. ^{1}H-NMR gave a spectrum with identical chemical shifts as before. However integration of the second phenyl ring and broad singlet at 5 ppm did not agree with the rest of the spectrum. It appears our original recovered product is a 1:1 mixture of **(165a)** and aniline. However more unusual is the reproducibility of the result. If the filtered solid is boiled in MeOH and hot filtered, **(156a)** is recovered in it's pure form with complete absence of aniline.

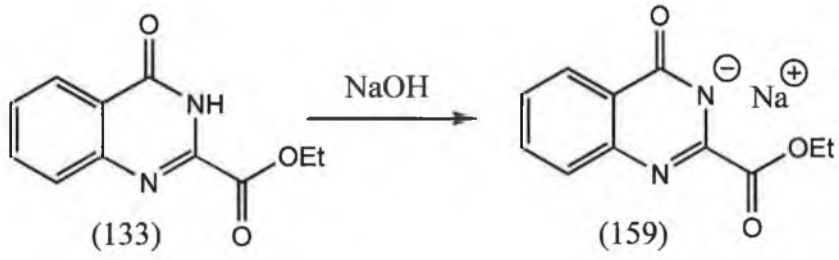
A suitable explanation for the above observations is difficult to rationalise. One could support the idea that under the reaction conditions some H-bonding interaction between **(156a)** and aniline occurs in a 1:1 ratio and is sufficiently strong in acetone. Methanol on the other hand prevents this bonding through it's own H-bonding interactions. Nevertheless, it is conceivable that the authors in question may have mistakenly interpreted such an observation by ^{1}H-NMR.

The observations of all these reactions can be conveniently summarised. It is clear that **(156a)** is initially formed from the hydrazide and is completely unreactive towards phenylisocyanate at the pyrimidone amide site. This may be accounted for by the following reasons. **(156a)** is extremely insoluble in acetone. Stereochemically, it may also be difficult for the pyrimidone amide site to attack phenylisocyanate due to the large side chain hindering any nucleophilic attack through internal H-bonding. Finally, the amide is insufficiently nucleophilic to attack phenylisocyanate. Base catalysis does not enhance the attacking power of the amide because the phenylimido nitrogen is shown to be far more acidic. With such evidence, we view the actual isolation of the tetrazocine by the method described as doubtful.

2.1.2.2. Alternative Synthetic Exploration- Part (a)

The reported procedure for obtaining **(135)** presented us with a challenge. It was decided to undertake a different method of approach. To eliminate problems such as insolubility, a more soluble quinazolinone derivative was sought. 2-Ethoxycarbonylquinazolinone **(133)** is soluble in most moderately polar solvents.

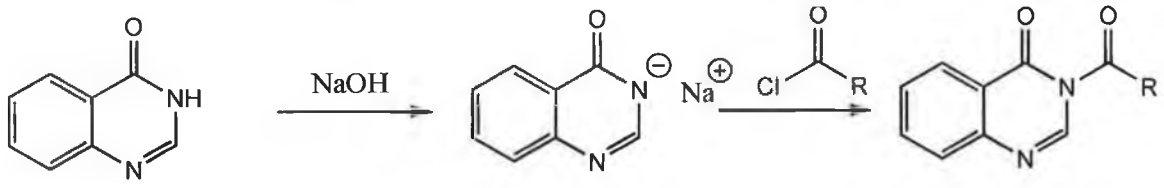
Amides are in general weak bases and in most cases are converted to their conjugate, more nucleophilic bases. Imides have been successfully prepared by the attack of amide salts on acyl halides, anhydrides, acids and esters in a Gabriel synthesis type reaction. Reaction is slow and the reaction rate is increased by the use of polar solvents to solvate the salt more readily. Reaction of **(133)** with a molar equivalent of NaOH afforded the amide salt **(159)** in excellent yields.



(133) (159)

Scheme 2.8 *Formation of sodium salt of 2-ethoxycarbonylquinazolinone.*

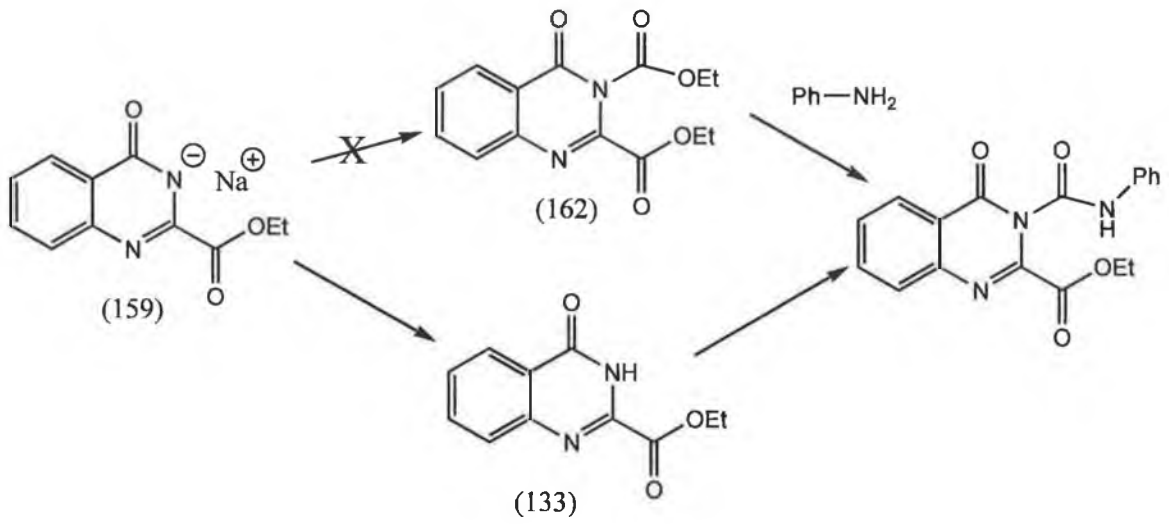
Baker *et al* have shown C2 non-substituted quinazolin-4(3H)-ones **(160)** to be reactive toward acyl chlorides through initial generation of the amide salt **(161)**. However, yields are low.[67]



(160) (161)

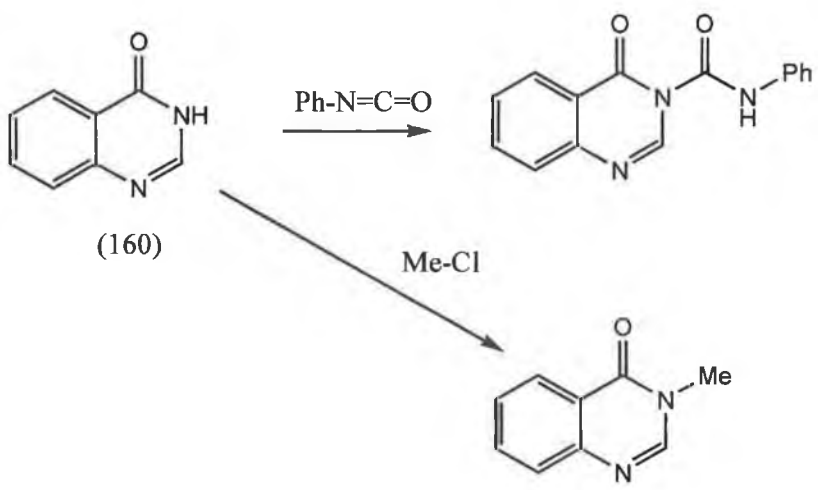
Scheme 2.9 *Ring amide substitution of quinazolin-4(3H)-ones with acyl chlorides.*

Reaction of ethylchloroformate, a powerful electrophile, with the amide salt **(159)** in dry DMF resulted only in formation of **(133)**. To explain one aspect of the lack of attacking power by the amide, one must consider the conjugative effect of the ester group on the quinazolinone ring system. Electron density at the ring amide nitrogen is decreased as the lone pair of electrons do not now reside entirely on the nitrogen atom. The net effect is a reduction in nucleophilicity due to electron withdrawing capacity of the ester group.



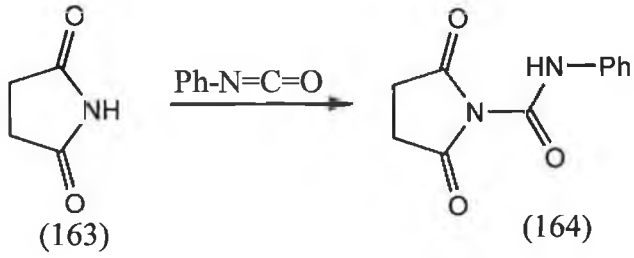
Scheme 2.10 *Unsuccessful substitution at ring amide site of (159) with ethylchloroformate.*

This argument is further substantiated where the C2 non-substituted quinazolinone **(160)** has been found to react with phenyiso- and thiocyanate in 75% yields.[68] No procedure has been found by us in the literature where the amide group has been acylated or alkylated when the quinazolinone is substituted in the 2-position.



Scheme 2.11 *Ring amide substitution of quinazolin-4(3H)-ones with methyl chloride and phenylisocyanate.*

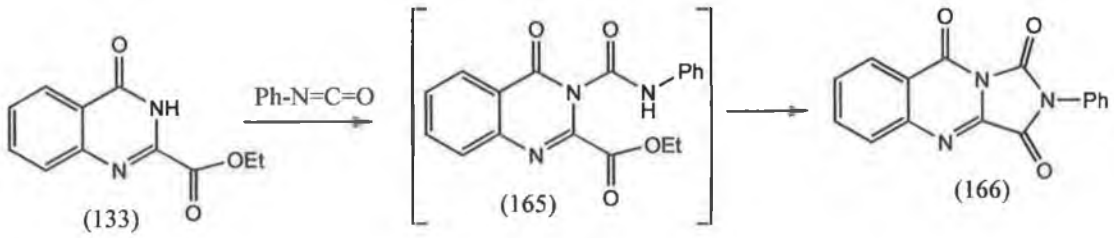
The more direct approach of reacting **(133)** and phenylisocyanate in various solvents and bases was unsuccessful. However a method was found in which unreactive amides where shown to couple with phenylisocyanate by heating the amide at the reflux temperature of phenylisocyanate. Yields are usually low and the reaction mixture complex. Wiley obtained 2,5-dioxo-pyrrolidine-1-carboxylic acid anilide **(164)** by refluxing succinimide **(163)** in phenylisocyanate at 165-180^{0}C.[69]



Scheme 2.12 *Successful imide substitution of succinimide with phenylisocyanate at high temperature.*

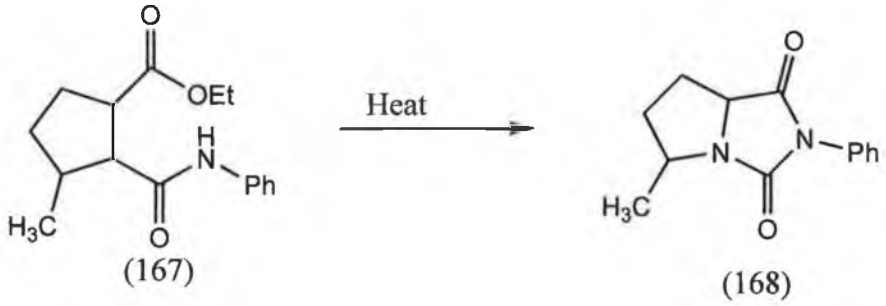
Reaction of **(133)** in a stirred solution of phenylisocyanate at 160^{0}C for 24 hours gave a product which falls out of solution during the course of the reaction. Hot filtration and subsequent washing with acetone to remove carbanilide yields a single product in 30% yield. NMR, IR and C:H:N analysis lead us to conclude that **(166)** was obtained. Phenylisocyanate initially undergoes nucleophilic attack and forms the

phenylamide which intramolecularly attacks the ester moiety resulting in a cyclo-condensation product.



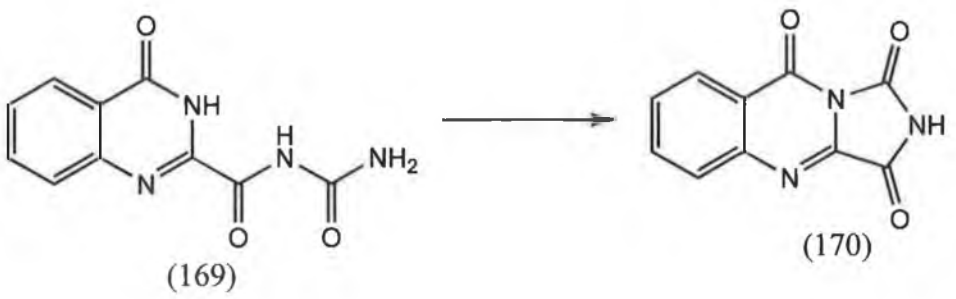
Scheme 2.13 *Reaction of 2-ethoxycarbonylquinazolinone with phenylisocyanate at high temperature to form a three ringed quinazolinone system.*

Fontanella has shown similar condensation reactions obtaining **(168)** from heating **(167)**.[70]



Scheme 2.14 *Cyclocondensation with imide formation.*

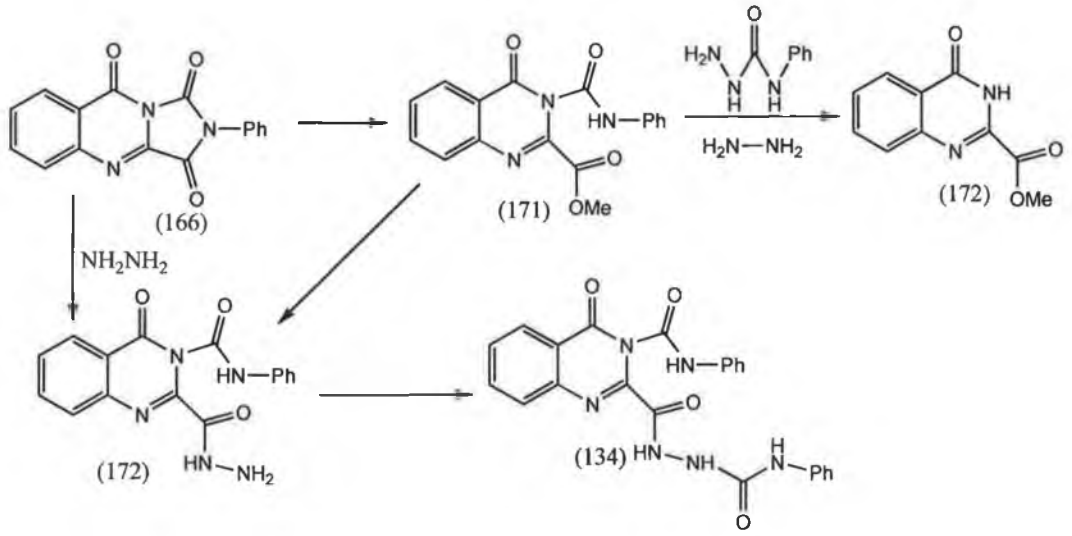
This constitutes novel formation for this three ring quinazolinone system. Tsuboto has prepared the only analogue **(170)** from thermolysis of the benzooxazinone **(169)** in low yield.[71]



Scheme 2.15 *Alternative formation of an analogue of (166).*

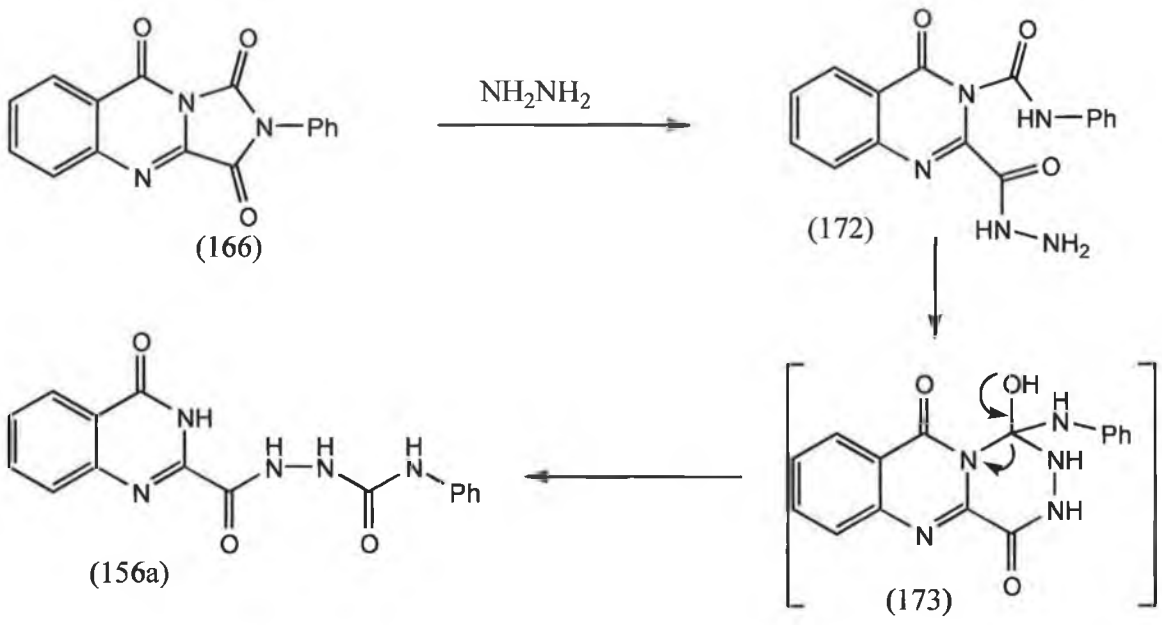
Attempts to isolate the intermediate **(165)** at lower temperatures were unsuccessful, with **(166)** being formed in lower yields. Formation of **(166)** is maximised at 180^0C over 10 hours giving 70% yield. It appears the relative nucleophilicity of the amide is enhanced at this temperature which is also the melting point of **(133)** and the temperature at which it is formed from diethyloxalate and anthranilamide.

Generation of **(166)** gives a potentially useful synthetic product which through the route shown below, could give us ultimately the desired tetrazocine precursor **(134)**. Compound **(166)** undergoes rapid ring opening with NaOMe in methanol in excellent yields to give **(171)**. Subsequent reaction of **(171)** with hydrazine involves removal of the imide group and not substitution of the ester moiety giving 2-methoxycarbonylquinazolin-4(3H)-one **(172)**. This was also shown to be the case for 4-phenylsemicarbazide.



Scheme 2.16 *Alternative synthetic routes to tetrazocine precursor (134).*

Direct reaction of the hydrazine with **(166)** would then hopefully lead to **(172)**. Our initial concern was the loss of aniline with an ensuing cyclocondensation which is very often the case with imides in the Gabriel synthesis. Addition of hydrazine to a stirred methanolic solution of **(166)** gives an immediate white to yellow colour change which dissipates over the course of the reaction (30 minutes) to give a white solid. Characterisation of the unknown product indicated the formation of **(156a)**. This was formally verified by direct comparison of m.p, NMR and CHN. We believe formation of **(156a)** to occur through the intermediate **(173)** shown below.

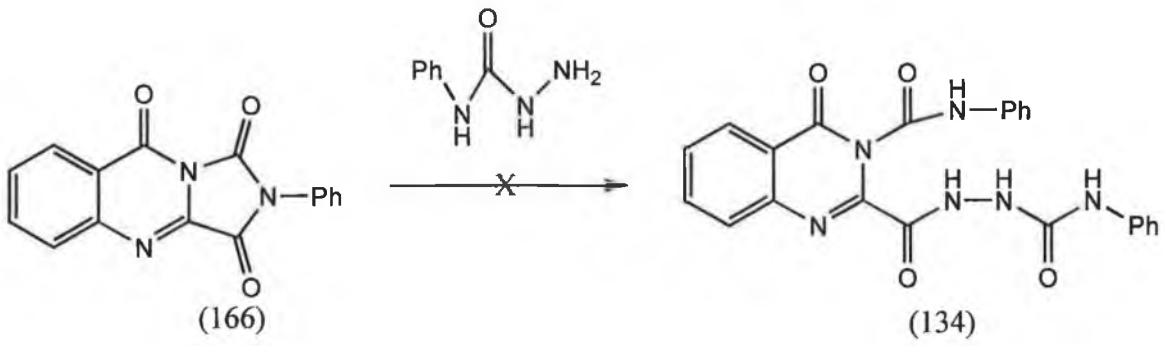


Scheme 2.17 *Reaction of hydrazine with (166) to form (156a) through a proposed 6-membered ring intermediate with subsequent ring opening.*

In order to substantiate the intermediacy of both **(172)** and **(173)**, the reaction mixture was filtered off after 5 minutes and 15 minutes and the resulting solids submitted for ^{1}H-NMR. Due to the complexity of the reaction mixture, especially in the aromatic region, a more reliable comparison was to follow the growth and disappearance of amide and hydrazide protons. After 5 minutes, the occurrence of a broad singlet at 6 ppm indicated the formation of the hydrazide amino group. After 15 minutes, the signal intensity decreases substantially with the growth of an –NH

signal at 9 ppm. Finally the signals at 6 and 9 ppm disappear completely yielding **(156a)** after 30 minutes. The above observations would suggest that **(172)** is formed. Attempts to isolate **(172)** by carrying the reaction out at lower temperatures failed. Similarly, addition of phenylisocyanate to the reaction after 5 minutes gave largely **(156a)**.

A final attempt of **(134)** isolation through **(166)** involved reaction with 4-phenylsemicarbazide. In this instance, no reaction was observed and this may be interpreted due to the large stereochemical factors associated or relative lack of reactivity in nucleophilic terms.



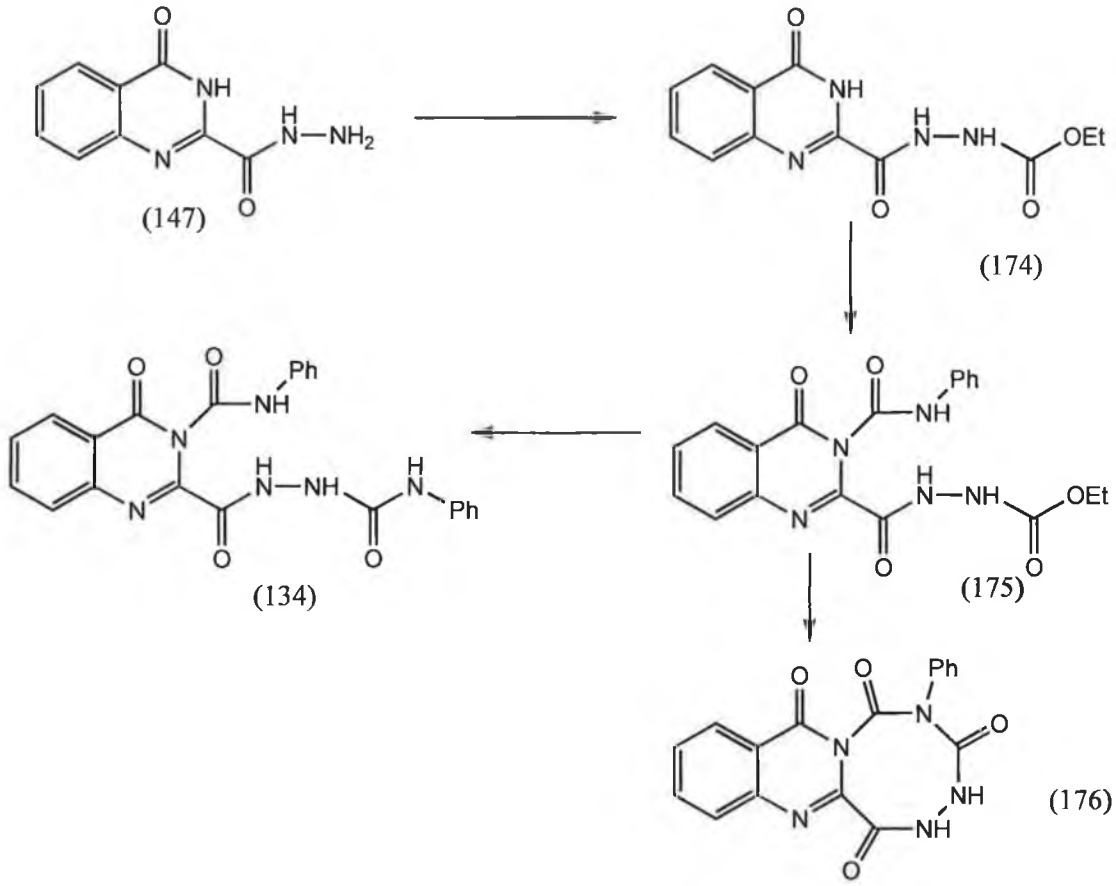
(166) (134)

Scheme 2.18 *Unsuccessful ring opening of (166).*

It has proved somewhat unrewarding, the attempt to obtain **(134)** through 2-ethoxycarbonylquinazolin-4(3H)-one and it's phenylisocyanate derivative **(171)**. The main feature is the ease in which the imide site of **(171)** is attacked by nucleophiles giving back **(172)**. Refluxing **(172)** in aqueous methanol also results in substitution of the imide with ease and this relative instability would lend weight to the argument against the actual isolation of **(134)** by the authors method.

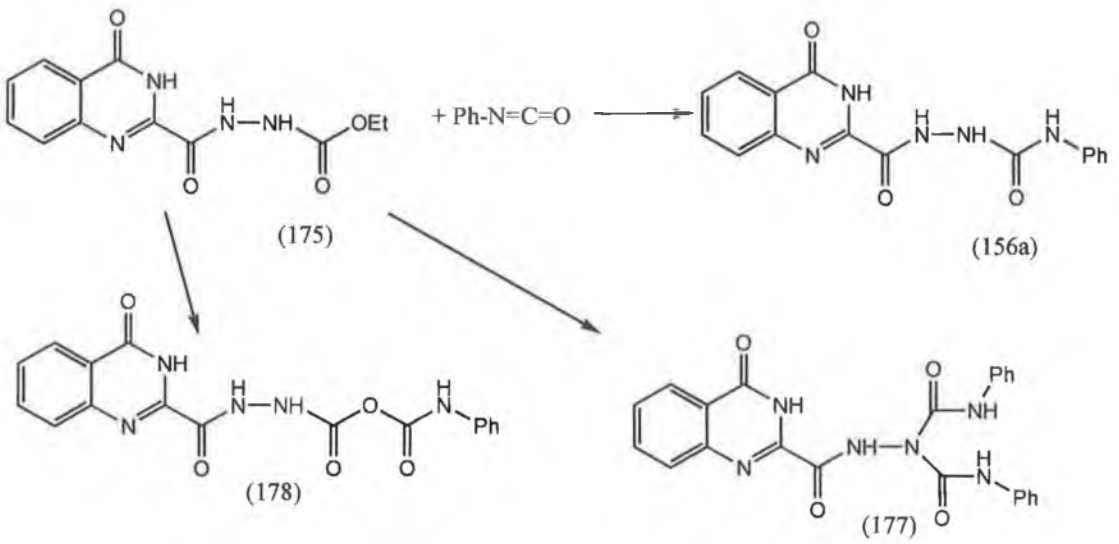
2.1.2.3. Alternative Synthetic Exploration-Part (b)

A further attempt at the synthesis of **(134)** was attempted using **(174)**. This compound is conveniently made by reaction of the hydrazide **(147)** with ethylchloroformate. The synthetic approach in this case had two advantages. Compound **(174)** was soluble in most solvents. Substitution at the pyrimidone ring amide site with phenylioscyanate would lead to **(175)**. If the phenylamide nitrogen attacks and substitutes the ester group, this would generate a 1,2,4,6-tetrazocine **(176)**. However if there was no cyclisation, we would be only one step away from the reported tetrazocine precursor **(134)**.



Scheme 2.19 *Proposed alternative synthetic route to tetrazocine precursor (134) formation from (174).*

A stirred solution of **(174)** was heated to 180^0C in excess phenylisocyanate for 24 hours. Work-up of the reaction gave three provisional products, **(156a)**, **(177)** and **(178)** that have yet to conclusively verified.



Scheme 2.20 *Formation of (177) which would give the same CHN analysis as the authors tetrazocine precursor (134).*

The most relevant of these three is compound **(177)**. ^{1}H- and ^{13}C-NMR show a pattern consistent with two symmetrical phenyl groups and a phenyl amide proton signal integrating to two. The pyrimidone ring amide is still intact by the presence of a broad singlet integrating for one proton at 12.5 ppm.

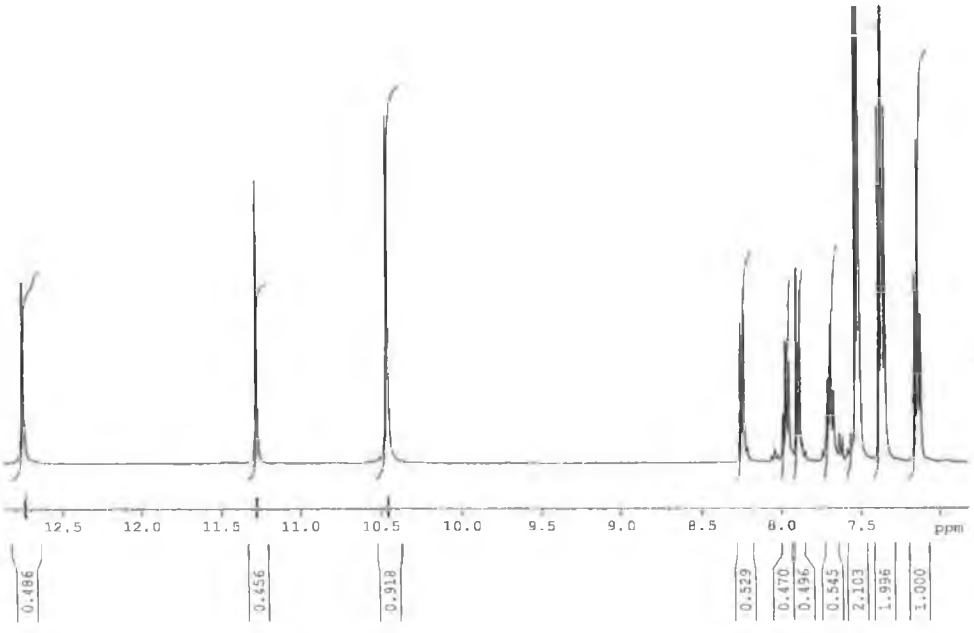
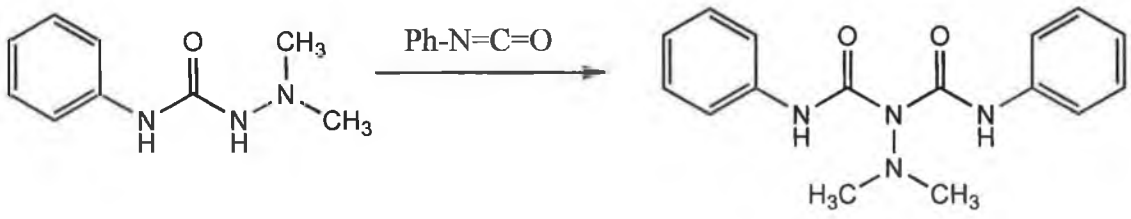


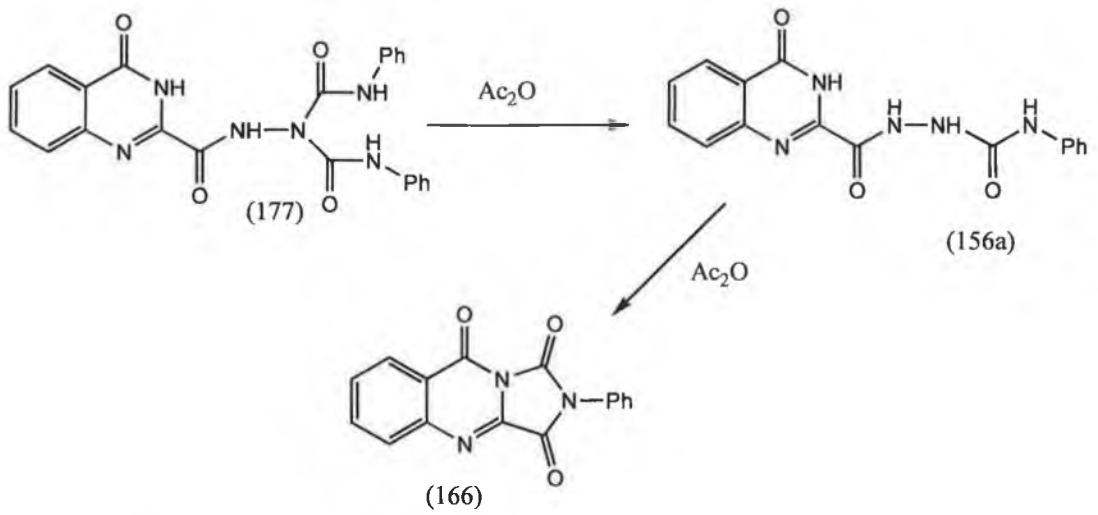
Figure 2.1 *^{1}H-NMR of (177).*

Iorio and others have obtained similar results to our own.[72]



Scheme 2.21 *Disubstitution of an amide site with phenylisocyanate.*

This compound would then satisfy the elemental analysis offered by the authors. Perhaps this compound is what the authors have mistakenly assumed to be **(134)**. In the concluding step, the tetrazocine **(135)** is obtained by cyclisation of **(134)** with acetic anhydride. ^{1}H-NMR is offered for the compound. In order to verify our position, we submitted **(177)** to the same reaction conditions to compare product outcome and ^{1}H-NMR results. Compound **(177)** was refluxed in excess acetic anhydride for 1 hour. The major product formed was **(156a)** due to loss of one phenylamide group. If the reaction is left for 10 hours a secondary product was obtained which was shown to be **(166)**. To ensure that **(166)** was formed from **(156a)**, a reaction of **(156a)** in acetic anhydride was set up which afforded the same result. Although the generation of **(166)** from **(156a)** is not understood, the isolation of **(166)** is verified by it's previous characterization (scheme 2.14).

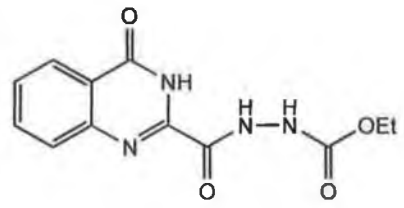


Scheme 2.22 *Reaction of acetic anhydride with (177) to from both (156a) and (166).*

Under no circumstances have we been able to repeat the authors work. Based on our findings covering this area, we feel it highly unlikely that the 1,2,5,6-tetrazocine was ever recovered and that the authors may have misinterpreted their results. This is further evidence to the degree of difficulty in formation of this compound class and prompted us to look more critically at other similarly described systems.

2.1.4. Experimental

N'(4-Oxo-3,4-dihydro-quinzoline-2-carbonyl)-hydrazinecarboxylic acid ethyl ester (174)



To a solution of the acid hydrazide **(147)** (5g, 0.022 mol) in 50ml of acetonitrile was added an excess of ethylchloroformate (24g, 0.227mol). The solution was allowed to stir at reflux for 30 minutes and then cooled to room temperature. The white solid was filtered off and washed with water. The solid **(179)** was then heated in ethanol and quickly hot filtered to give the pure solid. Yield (4.26g, 68%).m.p. 232-235^{0}C

IR : 3328, 3243, 3066, 1714, 1679, 1604, 1524, 1277, 1060, 896, 779

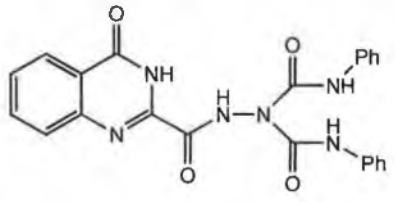
δH-(DMSO-d_6)(ppm): 1.19 (3H, t), 4.05 (2H, q), 7.61 (1H, m), 7.77 (1H, m), 7.87 (1H, m), 8.15 (1H,m), 9.81 (1H, s), 11.24 (1H, s), 12.96 (1H,s)

δC-(DMSO-d_6)(ppm): 14.42, 61.23, 123.31, 126.48, 127.98, 128.73, 135.24, 145.28, 146.97, 156.18, 159.18, 161.34.

	%Theory	**%Found**
C:	52.15	51.84
H:	4.37	4.24
N:	20.28	19.71

Action of Phenyl Isocyanate on (174)

The ester **(174)** (2g, 7.24mmol) was added to phenylisocyanate (10g, 0.84 mol) and the mixture heated under stirring at 180^{0}C for 24 hours. At 130^{0}C, the white solid dissolves into the phenylisocyanate to give a brown liquid. On completion of the reaction, the mixture was allowed to cool whereby a solid precipitated out. This solid **(177)** was quickly filtered. Leaving the mother liquor to further cool, another solid **(178)** fell out. Finally the mother liquor was left overnight and crystals of **(156a)** were obtained. Each compound was purified by heating it in methanol and quickly hot filtering the solid by vacuum filtration. Yields of **(177)** ,**(178)** and **(156a)** were (0.48g, 15%), (.58g, 22%) and (0.22g, 9%)respectively.



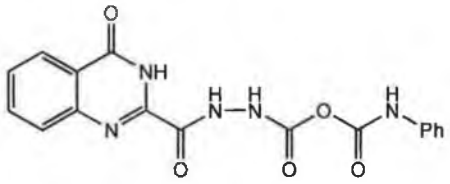
(177)

m.p. 243-245^{0}C

IR : 3322, 3288, 3065, 1714, 1732, 1684, 1565, 1333, 1219, 1178, 743, 685.

δH-(DMSO-d_6)(ppm): 7.14 (2H, m), 7.37 (4H, m), 7.52 (4H, m), 7.69 (1H, m), 7.89 (1H, m), 7.97 (1H,m), 8.25 (1H, m), 10.45 (2H, s), 11.29 (1H,s), 12.72 (1H,s).

δC-(DMSO-d_6)(ppm): 121.32, 123.37, 124.71, 126.82, 128.23, 128.91, 129.34, 129.72, 135.36, 137.98, 145.09, 147.29, 152.61, 161.09, 161.24.



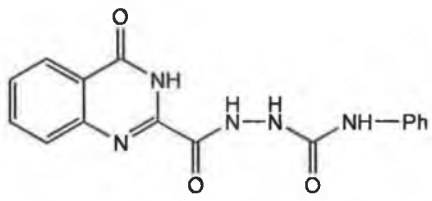
(178)

m.p. 226-228^{0}C

IR: 3301, 3099, 2926, 1755, 1596, 1447, 1130, 899, 878, 766, 731.

δH-(DMSO-d_6)(ppm): 6.96 (1H, m), 7.25(2H, m), 7.45(2H, m), 7.63(1H, m), 7.82(1H, m), 7.91 (1H,m), 8.18(1H, m), 8.38(1H, s), 8.87(1H,s), 10.78(1H, bs), 12.51(1H,bs).

δC-(DMSO- d_6)(ppm): 119.19, 122.57, 123.10, 126.51, 128.25, 128.77, 129.01, 129.1, 135.29, 139.69, 145.28, 147.26, 155.44, 160.17.



(156a)

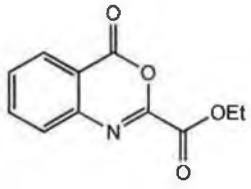
m.p. 252-254^{0}C.

IR(KBr)(cm^{-1}): 1690cm^{-1} (C=O,amide).

δH(DMSO-d_6)(ppm): 6.95(1H, m), 7.25(2H, m), 7.46(2H, m), 7.63(1H,m), 7.80(1H,m), 7.85(1H,m), 8.19(1H, m), 8.38(1H, bs), 8.81(1H, bs), 10.70(1H, bs),12.50(1H,bs).

δC(DMSO-d_6)(ppm): 119.14, 122.44, 123.17, 126.51, 128.15, 128.61, 129.97, 137.17, 139.83, 145.39, 147.27, 155.44, 160.19, 161.27.

4-Oxo-4H-benzo[d][1,3]oxazine-2-carboxylic acid ethyl ester (151)



Compound **(153)** (10g, 0.44 mol) was refluxed in 100ml of acetic anhydride for 1 hour. On cooling 200ml of water was added, whereby a white solid mass fell out which was then filtered. Recrystallisation of the solid from water gave **(151)** . Yield (4.78g, 52%).

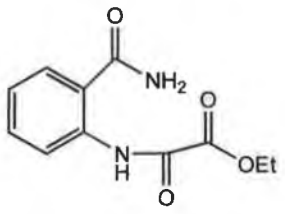
IR(KBr)(cm^{-1}): 1615cm^{-1} (C=N), 1681cm^{-1} (C=O).

δH(DMSO-d_6)(ppm): 1.34(3H, t), 4.30(2H, q), 7.24 (1H, m), 7.62 (1H, m), 8.02 (1H, m), 8.55 (1H, m).

δC(DMSO-d_6)(ppm): 14.24, 63.19, 117.36, 118.67, 124.32, 131.74, 134.65, 139.65, 154.58, 160.13, 169.61.

	%Theory	%Found
C:	60.25	59.82
H:	4.14	3.84
N:	6.39	6.51

N-(2-Carbamoyl-phenyl)-oxalamic acid ethyl ester (154)



A mixture of anthranilamide (6.80g ,0.05 mol) and ethyl oxalate (14.6g, 0.1 mol) was heated on an oil bath at 170°C- 180°C for 6 hours. On cooling the mixture, a solid was obtained. The solid was recrystallised from 300ml of ethanol, filtering the hot solution to remove any insoluble, unwanted side product. On cooling of the filtrate, white crystals were obtained. Yield (7.16g, 64%). m.p. 175-177°C.

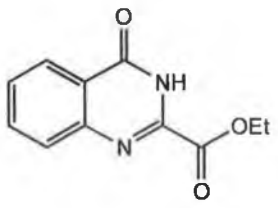
IR(KBr)(cm^{-1}): 1675cm^{-1} (C=O), 1712cm^{-1} (C=O, ester).

δH(DMSO-d_6)(ppm): 1.29(3H,t), 4.29(2H,q), 7.20(1H,m), 7.55(1H,m), 7.82-7.88(2H,m), 8.35(1H,bs), 8.53(1H,m), 13.10(1H, bs).

δC(DMSO-d_6)(ppm):13.82, 62.74, 120.01, 120.24, 123.84, 128.81, 132.52, 138.15, 154.28, 159.97, 170.39.

	%Theory	%Found
C:	55.90	56.12
H:	5.12	4.94
N:	11.86	12.29

4-Oxo-3,4-dihydro-quinazoline-2-carboxylic acid ethyl ester (133)



Method 1:

A mixture of of anthranilamide (5g, 0.022 mol) and ethyl oxalate (14.6g, 0.1 mol) was heated on an oil bath at 180°C for 4 hours under reflux equipped with a Dean-Stark apparatus. Any ethanol or water trapped during the course of the reaction was removed every 30 minutes. On cooling the mixture, a solid was obtained. The solid was recrystallised from 300ml of ethanol, filtering the hot solution to remove any insoluble, unwanted side product. On cooling of the filtrate, white crystals were obtained. Yield (8.06g, 70.2%). m.p. 179-180°C.

Method 2:

A mixture of 2-ethoxycarbonylbenzooxazin-4-one **(151)** (20.7g, 0.1mol) and formamide (13.5g, 0.3mol) were heated under reflux for 6 hours. The reaction mixture was diluted with 100ml of iced water whereby a white solid falls out which was filtered and dried. Flash chormatography of the solid (pet ether 40-60^0:ethyl acetate:50:50) gave a yield (5.15g, 26%) of the title compound. m.p. = 178-180^{0}C.

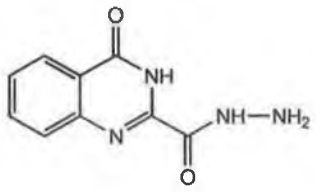
IR(KBr)(cm^{-1}): 1730(C=O, ester), 1670(C=O, amide).

δH(DMSO-d_6)(ppm): 1.35(3H,t), 4.38(2H, q), 7.62(1H,m), 7.81(1H,m), 7.88(1H, m), 8.15(1H,m), 12.55(1H,bs).

δC(DMSO-d_6)(ppm): 14.23, 63.01, 123.28, 126.38, 128.01, 129.01, 135.15, 143.72, 147.56, 160.49, 161.35.

	%Theory	**%Found**
C:	60.52	60.41
H:	4.61	4.87
N:	12.84	12.66

4-Oxo-3,4-dihydro-quinazolin-2-carboxylic acid hydrazide (147)



A solution of **(133)** (5g, 0.022 mol) and hydrazine hydrate (0.71g, .022 mol) in 30ml of n-butanol was heated under reflux for 4 hours. The white solid which falls out over the course of the reaction was hot filtered. This solid was further refluxed in methanol and again hot filtered to remove any unreacted starting material to give **(147)**. Yield (4.56g, 83%).m.p.250-251°C

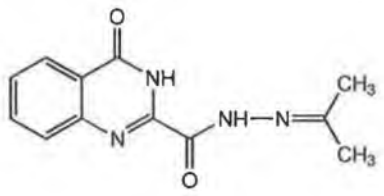
IR(KBr)(cm^{-1}): 1695 (C=O,amide), 1605 (C=N), 2840-3200 (NH_2).

δH(DMSO-d_6)(ppm): 4.71(2H,bs), 7.59(1H,m), 7.71(1H,m), 7.85(1H,m), 8.15(1H,m), 10.28(1H,bs), 12.22(1H,bs).

δC(DMSO-d_6)(ppm): 122.65, 126.15, 127.71, 127.93, 134.75, 145.64, 147.20, 157.95, 160.90

	%Theory	**%Found**
C:	52.92	53.03
H:	3.95	4.12
N:	27.45	27.17

4-Oxo-3,4-dihydoxy-quinazoline-2-carboxylic acid isopropylidene-hydrazide (155)



The hydrazide **(147)** (5g, 0.024 mol) was put in 100ml of acetone and allowed to reflux for 5 minutes. Removal of the solvent under reduced pressure yielded **(155)**. Yield (5.98g, 100%). No further purification was necessary. m.p. 239-240°C.

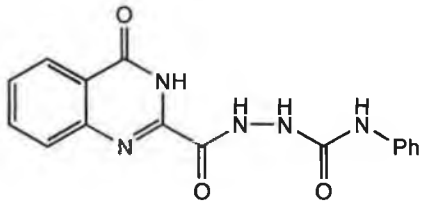
IR(KBr)(cm^{-1}): 1625 (C=N), 1682 (C=O).

δH(DMSO-d_6)(ppm): 1.99(3H, s), 2.04(3H, s), 7.60(1H, m), 7.80(1H, m), 7.85(1H,m),

8.15(1H, m), 12.37(1H,bs).

δC(DMSO-d_6)(ppm): 17.73, 25.16, 122.80, 126.23, 127.94, 128.26, 134.87, 145.93, 146.94, 155.47, 161.00, 161.99.

Formation of (156a):



Method 1

Compound **(147)** (0.51g, 2.5mmol) was added to a solution of 30ml of dry acetonitrile containing phenylisocyanate (0.29g, 2.5mmol) and the mixture was refluxed under nitrogen for 4 hours. The reaction mixture was quickly hot filtered and the white solid obtained further refluxed in methanol and again hot filtered give a white solid **(156a)** . Yield (0.64g, 81%). m.p. 252-254°C.

Method 2

An equimolar solution of **(166)** (1g, 3.43 mmol) and hydrazine hydrate (0.11g, 3.43mmol) in DMF was heated under reflux for 30 minutes. The reaction mixture was allowed to cool. Addition of water resulted in **(156a)** falling out as a white powder. It was filtered and washed with water. Further purification involved heating crude **(156a)** in hot methanol and hot filtering to give **(156a)** as a pure product. Yield (0.81g, 73%) m.p. 252-254°C.

Method 3

Compound **(177)** (1g, 2.26mmol) was heated in 15ml of acetic anhydride for 1 hour. The insoluble solid was hot filtered and washed with hot MeOH and water to give crude **(156a)**. The sample was then refluxed in hot MeOH and hot filtered to give **(156a)**. Yield (0.52g, 72%). m.p. 252-254°C.

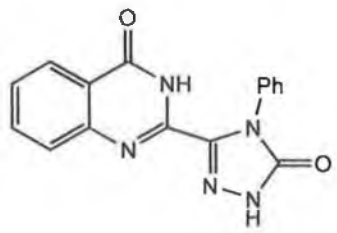
IR(KBr)(cm^{-1}): 1690cm^{-1} (C=O,amide).

δH(DMSO-d_6)(ppm): 6.95(1H, m), 7.25(2H, m), 7.46(2H, m), 7.63(1H,m), 7.80(1H,m), 7.85(1H,m), 8.19(1H, m), 8.38(1H, bs), 8.81(1H, bs), 10.70(1H, bs),12.50(1H,bs).

δC(DMSO-d_6)(ppm): 119.14, 122.44, 123.17, 126.51, 128.15, 128.61, 129.97, 137.17, 139.83, 145.39, 147.27, 155.44, 160.19, 161.27.

	%Theory	**%Found**
C:	59.42	60.12
H:	4.05	4.22
N:	21.67	21.29

2-(5-Oxo-4-phenyl-4,5-dihydro-1H-[1,2,3]triazol-3-yl)-3H-quinazolin-4-one (158a)



Compound **(156a)** (1g, 3.09mmol) was added to 15 ml of a 2N NaOH solution. The mixture was refluxed for 2 hours. After cooling, the solution was filtered and the filtrate neutralised with conc. HCl. The precipitate that results from the aqueous solution was filtered and washed repeatedly with water and left to dry overnight. The solid was refluxed in 25ml of methanol and hot filtered to give **(158a)**. Yield (0.59g, 63%). m.p. 235-237°C.

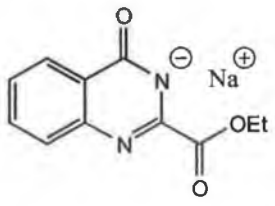
IR(KBr)(cm^{-1}): 1670 (C=O,amide), 1600-1625 (C=N).

δH(DMSO-d_6)(ppm): 6.91(1H, m), 7.27(2H, m), 7.48(2H, m), 7.64(1H, m), 7.80(1H, m), 7.92(1H, m), 8.20(1H, m), 8.72(1H, bs), 12.20(1H, bs).

δC(DMSO-d_6)(ppm): 119.12, 122.39, 126.54, 126.93, 128.13, 128.59, 128.96, 135.16, 139.88, 145.51, 147.30, 155.40, 160.10, 161.26.

	%Theory	**%Found**
C:	62.92	62.68
H:	3.63	3.84
N:	22.95	22.84

Sodium salt of 4-oxo-3,4-dihydro-quinazoline-2-carboxylic acid ethyl ester (159)



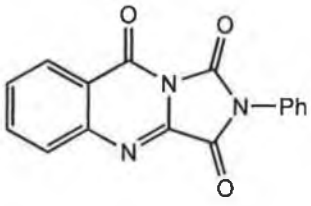
Compound **(133)** (1g, 4.58mmol) was added to a 100ml solution of methanol containing 4.5mmol of NaOH. The solution was heated under reflux for 25 minutes. Removal of excess solvent resulted in a white powder falling out on cooling of the mixture, which was filtered, washed with water and allowed to dry. No further purification was necessary. Yield (0.815g, 78%). m.p.= 262-264^{o}C.

IR(KBr)(cm^{-1}): 1689cm^{-1} (C=O,ester).

δH(DMSO-d_6)(ppm): 3.19 (3H,s), 3.80 (2H,s), 7.31 (1H,m), 7.58 (2H,m), 8.01 (1H,m)

δC(DMSO-d_6)(ppm): 48.94, 52.21, 123.31, 124.52, 126.07, 126.84, 131.48, 151.24, 156.31, 167.29, 172.11.

2-Phenyl-imadazo[5,1-b]quinazoline-1,3,9-trione (166)



Method 1

Compound **(156a)** (1g, 3.09 mol) was heated in 15ml of acetic anhydride for 10 hours. The insoluble solid was hot filtered and washed with hot MeOH and water to give crude **(166)**. The sample was then heated under reflux in hot MeOH and hot filtered to give pure **(166)**. Yield (0.50g, 56%). m.p. = 322-325^{0}C.

Method 2

Compound **(133)** (5g, 0.022 mol) was added to excess phenylisocyanate (20g, 0.168 mol) and heated under reflux at 180°C for 4 hours under nitrogen. On cooling, a crystalline mass separates which was filtered off. The solid is then heated under reflux in 200ml of acetone and quickly filtered off so as to remove unwanted carbanilide formed during the reaction. The remaining white crystalline solid was dried and **(166)** was obtained. Yield (4.93g, 74%) m.p. 322-325°C.

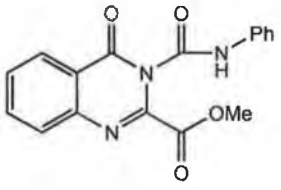
IR(KBr)(cm^{-1}): 1618 cm^{-1} (C=N), 1682 cm^{-1} (C=O,amide).

δH(DMSO-d_6)(ppm): 7.40-7.72(6H, m), 7.80(1H, m), 8.05(1H, s), 8.35(1H, m).

δC(DMSO-d_6)(ppm): 122.97, 127.41, 127.91, 129.61, 129.72, 130.02, 130.04, 130.61, 136.66, 142.28, 146.13, 148.34, 155.96, 157.86.

	%Theory	**%Found**
C:	65.96	66.02
H:	3.11	3.54
N:	14.43	14.26

4-Oxo-3-phenylcarbamoyl-3,4-dihydro-quinazoline-2-carboxylic acid methyl ester: (171)



Compound **(166)** (2g, 6.87mmol) in 100ml of dry methanol containing NaOMe (0.37g, 6.87mmol) was heated under reflux for 10 minutes. Removal of excess solvent under reduced pressure results in a crude white solid falling out which is washed with 50ml of water to remove any remaining base. The solid was allowed to dry. Yield (1.45g, 66%). m.p. 294-296°C.

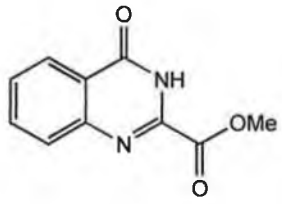
IR(KBr)(cm^{-1}): 1612 (C=N), 1684 (C=O).

δH(DMSO-d_6)(ppm): 3.90 (3H,s), 7.02 (1H,m), 7.32 (2H,m), 7.54 (1H,m), 7.62 (1H,m), 7.80-7.94 (3H,m), 8.02 (1H,m), 9.88 (1H, bs).

δC(DMSO-d_6)(ppm): 55.47, 122.46, 126.48, 127.18, 127.89, 128.14, 128.82, 128.99, 129.56, 129.93, 134.43, 145.68, 148.95, 162.43, 164.56.

	%Theory	**%Found**
C:	63.14	63.56
H:	4.05	3.94
N:	13.00	12.78

4-Oxo-3,4-dihydro-quinazoline-2-carboxylic acid methyl ester (172)



Refluxing **(171)** in a solution consisting of 100ml of methanol with an equimolar amount of hydrazine hydrate or 4-phenylsemicarbazide results in both cases with the recovery of the title compound in yields of 44% and 35% respectively. After 30 minutes, both reaction mixtures were concentrated by solvent removal under reduced pressure, with **(172)** falling out as a white solid which was filtered and then recrystallised from ethanol. m.p. 194-196°C.

IR(KBr)(cm^{-1}): 1684 (C=O), 1622 (C=N).

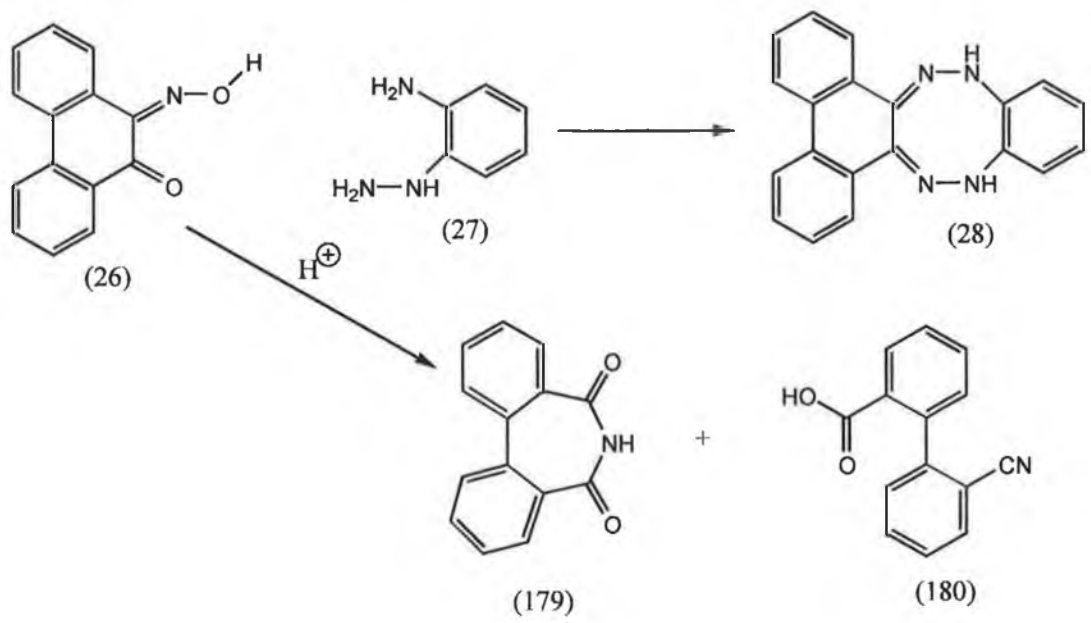
δH(DMSO-d_6)(ppm): 3.91(3H, s), 7.62 (1H, m), 7.82 (1H, m), 7.91(1H, m), 8.15 (1H, m), 12.01(1H, bs)

δC(DMSO-d_6)(ppm): 53.71, 123.29, 126.38, 128.69, 129.02, 135.14, 143.58, 147.51, 161.01, 161.35.

2.2. Reinvestigation of a 1,2,5,6-tetrazocine derived from the Phenanthraquinone Monooxime System

2.2.1. Introduction

In 1926, De & Guha published work referring to the formation of a 1,2,5,6-tetrazocine **(28)**.[26] This report describes the bicyclocondensation between *o*-aminophenyl hydrazine **(27)** and phenanthraquinone monooxime **(26)**. The reaction is catalysed by acetic acid and under high temperature and pressure i.e. a bomb calorimeter heated to 90^0C. Since other reports of 1,2,5,6-tetrazocines were shown to be incorrect reports of synthesis, we felt it necessary to repeat the authors work. The nitrogen elemental analysis offered was insufficient to proof for the actual isolation of these systems which are more often given to ring contraction. Also, it has been shown previously that phenanthraquinone monooximes under sufficiently acidic conditions, undergo a Beckmann rearrangement to yield **(180)** and **(179)**.[73]



Scheme 2.24 *Bicyclocondensation between o-aminophenyl hydrazine and phenanthraquinone monooxime. Beckmann rearrangement products of phenanthraquinone monooxime.*

This coupled with the instability of *o*-aminophenylhydrazine **(27)** warranted a reexamination of the procedure described.

2.2.2. Results and discussion

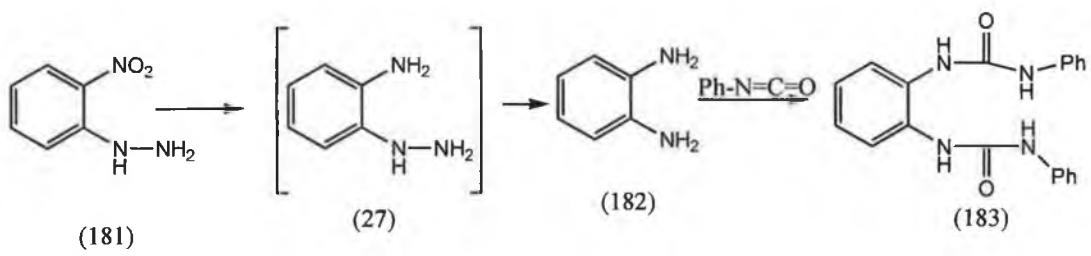
Formation of the phenanthraquinone monooxime was achieved by reaction between phenanthraquinone and excess hydroxylamine hydrochloride in MeOH. Pyridine was employed to mop up any excess HCl given off in the reaction so as to prevent an ensuing Beckmann rearrangement. No formation of the dioxime was shown to be present. A catalytic amount of acetic acid was added to speed up the reaction. Acid reaction involves protonation of the intermediate carbonolamine, thereby converting the hydroxyl into a better leaving group. If too much acid is present however, the attacking amine nucleophile is completely protonated and the initial nucleophilic addition step cannot occur.

By and large, the synthesis of the phenanthraquinone system has been achieved classically through reaction of phenanthrene with CrO_3 or similar aggressive oxidants. Many synthetic schemes have been investigated for the preparation of phenanthrene and its derivatives. Stimulation for these studies has been provided by the fact that many naturally occurring compounds of biological and therapeutic interest contain a phenanthrene or a reduced phenanthrene nucleus e.g. steroids and morphine. The reaction sequences used in the synthesis of phenanthrenes can be broadly classified into three types: Carbocyclic ring expansion, intramolecular cyclisation and intermolecular cycloaddition.

The next step in our synthesis was the generation of *o*-aminophenylhydrazine **(27)**. Few recordings of its utilisation were found in the literature. Guha offered the first high yield synthesis of this nucleophile through reduction of *o*-nitrophenylhydrazine **(181)** in $SnCl_2.H_2O$/acid solution.[74] Many reducing agents have been used to reduce aromatic nitro compounds, the most common being Zn, Sn or Fe with acid. With some reducing agents, especially aromatic nitro compounds, the reduction can be stopped at an intermediate stage e.g. hydroxylamines, azobenzenes etc. However, reduction by metals in mineral acids cannot be stopped and almost always proceed to

the amine. The mechanisms of metal/acid reduction has been studied very little, though it is usually presumed that, at least with some reducing agents, nitroso compounds and hydroxylamines are intermediates.

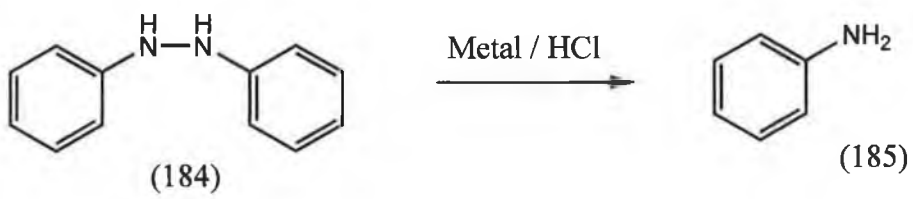
Following the author's procedure, a single white crystalline product was obtained in 35% yield. However subsequent NMR spectroscopy showed two distinct doublets integrating for one proton in the aromatic region along with a broad peak at 4 ppm integrating for two protons. Derivitisation of the unknown with excess phenylisocyanate in acetonitrile yielded an insoluble solid almost immediately, which was conclusively verified as being **(183)**.



(181) (27) (182) (183)

Scheme 2.25 *Reduction of o-nitrophenylhydrazine resulting in loss of ammonia yielding aminoaniline and subsequent reaction with phenylisocyanate.*

The question arises here as to which functionality is reduced first. Hydrazo compounds **(184)** can likewise be reduced to amines **(185)** under metal/acid conditions similar to our own.[75] It is also conceivable that the acid is playing a large role here. Protonation of the non-terminal amino group of the hydrazine **(27)** may result in loss of ammonia yielding aminoaniline **(182)**.

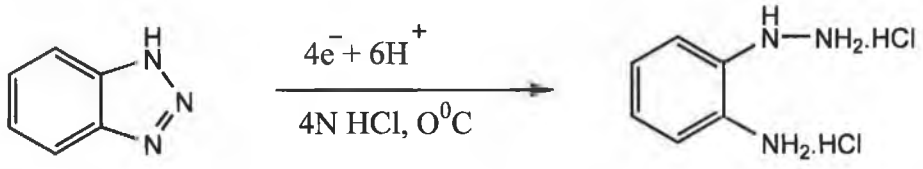


(184) (185)

Scheme 2.26 *N-N bond cleavage under acidic conditions.*

The reaction was carried out under less harsh conditions i.e. at lower temperatures and by reducing the concentration of the acid. In this instance a new product was recovered. However, attempts to isolate this compound purely proved futile. In acid solution the compound slowly decomposes and any attempts to extract it from the acid through various work-ups resulted in a complex mixture. This product appears to be air-sensitive, being easily oxidised. A new method of obtaining **(27)** was sought.

A procedure for the preparation of 2-aminophenylhydrazine **(27)** in high yield was described by Lund and Kwee.[76] They were carrying out reductive studies of benzotriazole **(186)** and related compounds. Benzotriazole was reduced in 4N hydrochloric acid at –1 V (SCE). The reaction consumes four electrons per molecule. On evaporation of the catholyte *in vacuo* under reduced pressure, a compound was isolated which is considered to be *o*-aminophenylhydrazine hydrochloride **(187)** from analysis. The overall reaction may be considered as follows.



(186) (187)

Scheme 2.27 *Electrolytic reduction of benzotriazole to give 2-aminophenylhydrazine.*

Some years later Falsig and Iversen scaled up the electrolytic reduction from 1g to 50-100g scale to make *o*-aminophenyhydrazine **(187)** an available starting material for synthetic purposes.[77] In both preparative instances, the authors refer to the synthesis of the desired compound using tin and hydrochloric acid as described by Guha. However they equally express the difficulty in obtaining the compound pure and in reasonable yield. The yield of **(187)** from cathodic reduction of **(186)** is probably nearly quantitative, but certain losses were inevitable during the time-consuming electrolysis and work-up due to the very easy oxidation of **(187)** even in

acidic media. The experimental setup of this reduction can be shown diagrammatically.

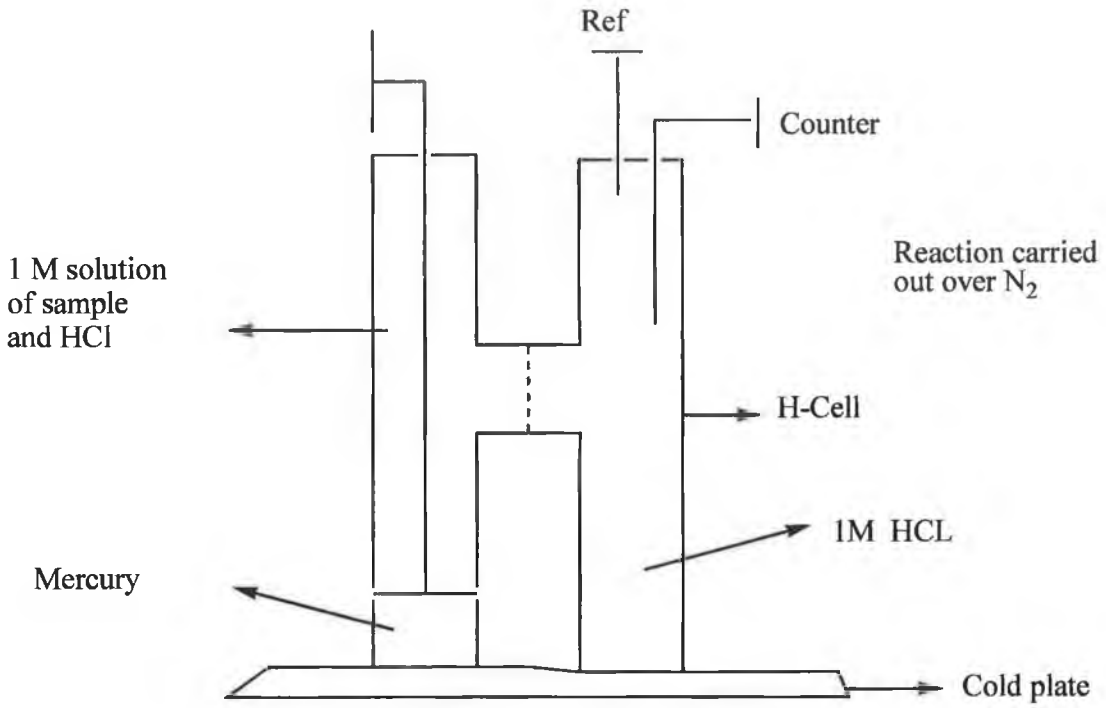
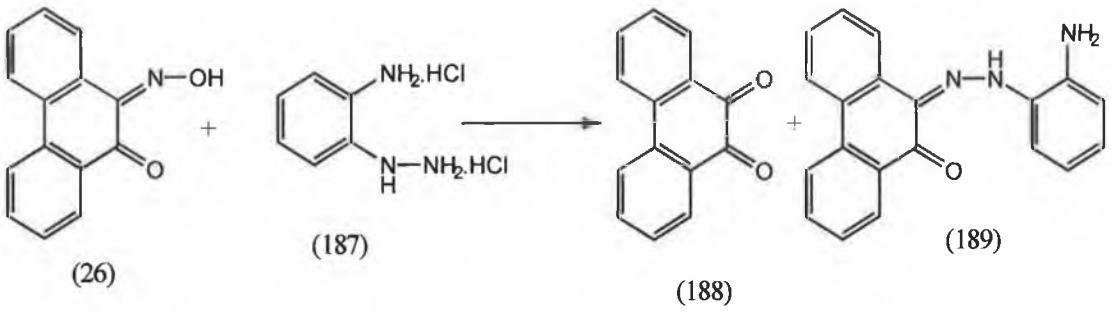


Figure 2.2 *H-cell setup for the electrolytic reduction of benzotriazole to give 2-aminophenylhydrazine.*

A comparison of the infrared spectrum of **(187)** with that of Lund and Kwee gave identical characteristic absorptions. Proton NMR showed two aromatic multiplets integrating for two protons along with a broad bump at six ppm integrating for five protons. Any attempts at ^{13}C spectra were unsuccessful, due the instability of the product in organic solvent over the ^{13}C experiment lifetime.

And so equal parts of phenanthraquinone monooxime **(26)** and *o*-aminophenylhydrazine hydrochloride **(187)** in ethanol saturated with HCl were

reacted in a sealed tube at 100^0C for 4-5 hours. The solvent was removed under reduced pressure and the residue neutralised in aqueous NaOH at which point the solid residue was filtered. Separation of this mixture gave products, which we have shown to be mainly phenanthraquinone **(188)** and small amounts of the *o*-aminophenylmonohydrazone of phenanthraquinone **(189)**.

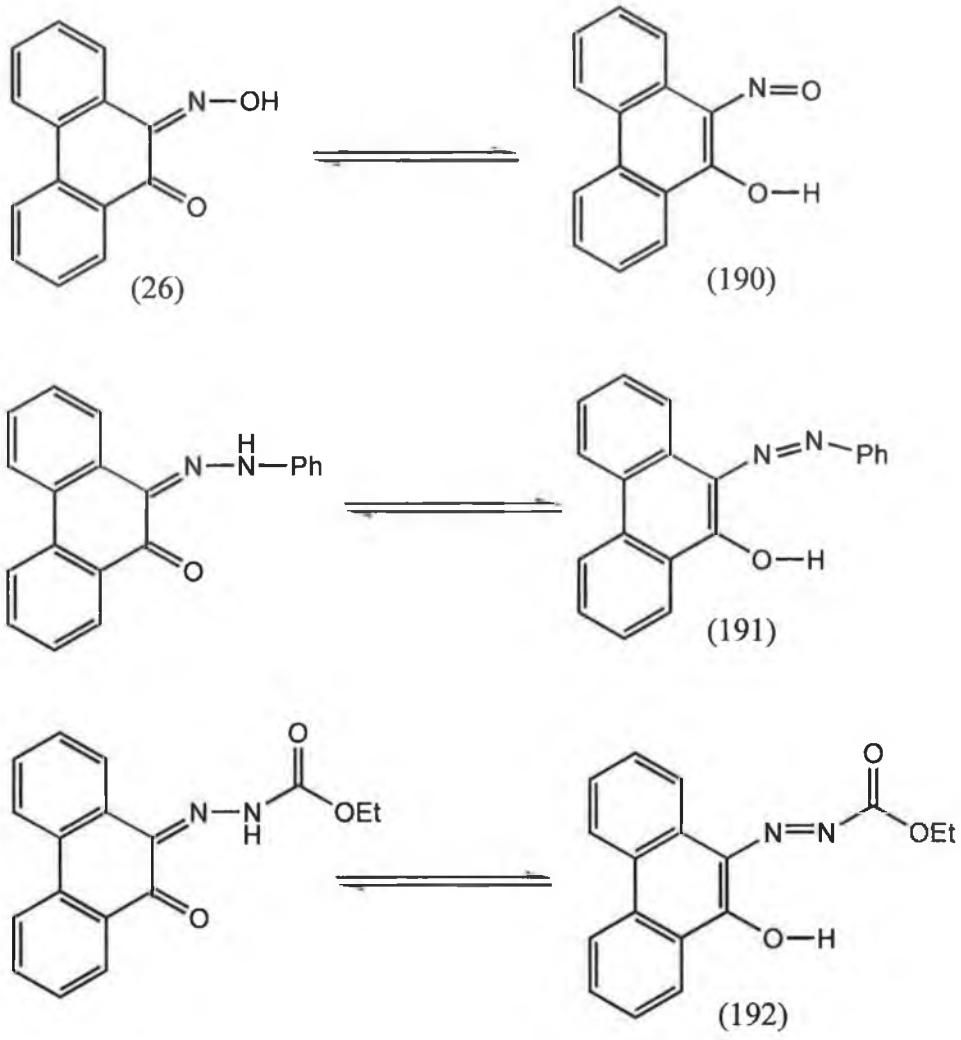


(26) (187) (188) (189)

Scheme 2.28 *Observed condensation products between o-aminophenyl hydrazine and phenanthraquinone monooxime.*

It is perhaps apparent here that there is inadequate time for the nucleophile **(187)** to attack before it decomposes as no trace of the *o*-aminophenylhydrazine **(27)** was observed in the work-up. Excess **(187)** was reacted with **(26)**. However, only a marginal increase in the yield of **(189)** was noted.

More noteworthy perhaps then was the preferential attack of the oxime group of the phenanthraquinone monoxime **(26)** rather than the keto group by the attacking nucleophile. It has been shown for the phenanthraquinone monooxime and other similar systems that their structure can be best formulated to being 9-hydroxy-10-azophenanthrenes **(190)**, **(191)** and **(192)**. [78,79,80]

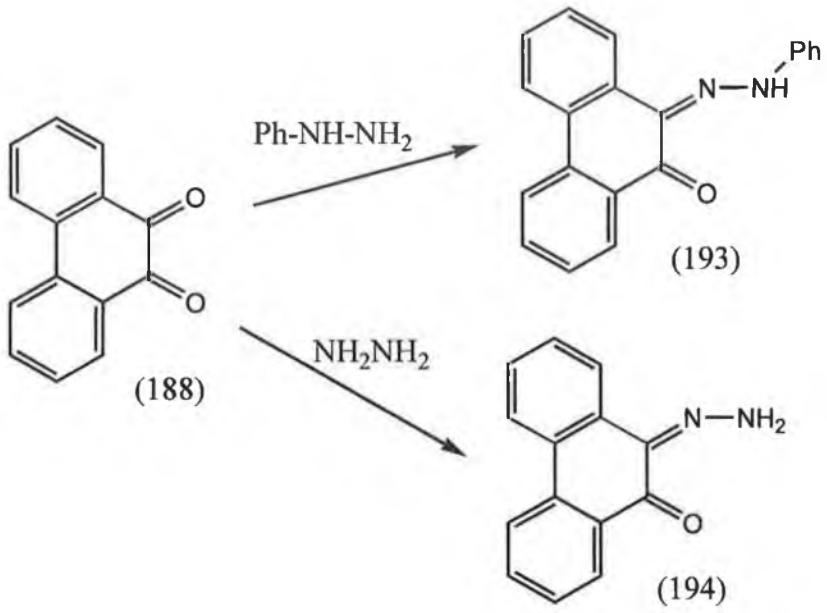


Scheme 2.29 *Keto-enol tautomerism of phenanthraquinone monooxime and similar molecules.*

In $CDCl_3$, a broad signal integrating to one is observed for the monooxime **(190)** at 17.1ppm. The enolic proton in general is downfield relative to alcohol protons and in the case of the enolic form of some diketones may be found as far downfield as 16.6 ppm. In DMSO there was a shift upfield to 13.8ppm along with a broad signal at 8.7 ppm, the polarity of the solvent playing a role in the keto-enol equilibrium.

If we consider the monooxime **(190)** to exist in it's enol form, then nucleophilic attack would become very difficult by *o*-aminophenylhydrazine. Such observations have been shown experimentally to be the case. Attempts by Butler to form the diphenylhydrazone of phenanthraquinone **(188)** resulted only in the monohydrazone

(193).[81] Likewise endeavours by Wittig to obtain the dihydrazone similarly gave the monohydraone **(194)**.[82] In both cases, the monohydrazone derivatives tautomerise to the unreactive conjugated 9-hydroxy-10-azo form regardless of the excess of nucleophile used.

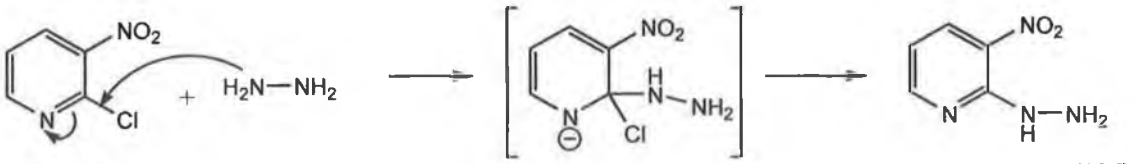


Scheme 2.30 *Monocondensations of phenanthraquinone with various hydrazines.*

With such considerations it seems highly unlikely that the authors condensed the *o*-aminophenylhydrazine at the keto position and that they did in fact displace the oxime group. This was further shown to be the case when the stable analogue, 2-amino-pyridinehydrazine **(197)**, was employed by us.[83] 2-Chloro-nitro-pyridine **(195)** is commercially available. Reaction with hydrazine results in substitution of the chloro position. Aromatic systems undergo nucleophilic substitution with great difficulty. However this is not the case for the pyridine analogue.

Pyridine rings undergo substitution with relative ease. Both 2 and 4 halo-substituted pyridines react particularly well. Pyridines are sufficiently activated by the electron-withdrawing capacity of the ring nitrogen. Reaction occurs by addition of the nucleophile to the C=N bond, followed by loss of halide ion from the anion

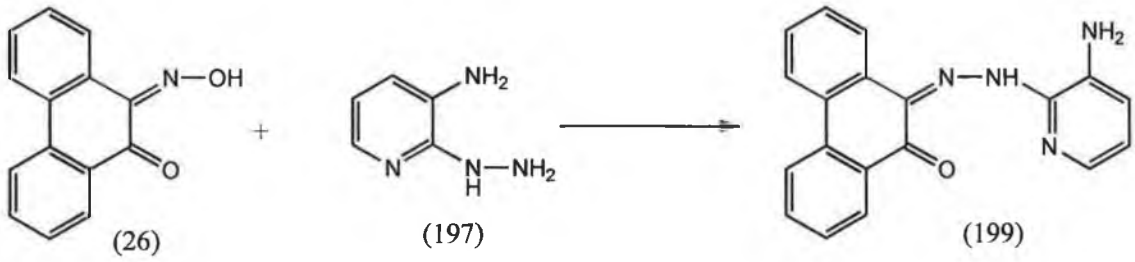
intermediate. The initial addition step is favoured by the ability of the electronegative nitrogen to stabilise the anion intermediate.



(195) (196)

Scheme 2.31 *Preparation of 2-hydrazino-3-nitro-pyridine.*

Our system is further activated by the presence of a nitro group on the 3-position. Reduction of the nitro group with hydrogen and palladium/charcoal gave 2-hydrazino-3-amino-pyridine **(197)** in excellent yield. This compound was observed to be relatively stable to air. However prolonged periods of storage resulted in decomposition. Reaction of **(26)** with 2-hydrazino-3-amino-pyridine **(197)** in varying ratios led principally to **(199)**. Again the oxime group was favorably removed.



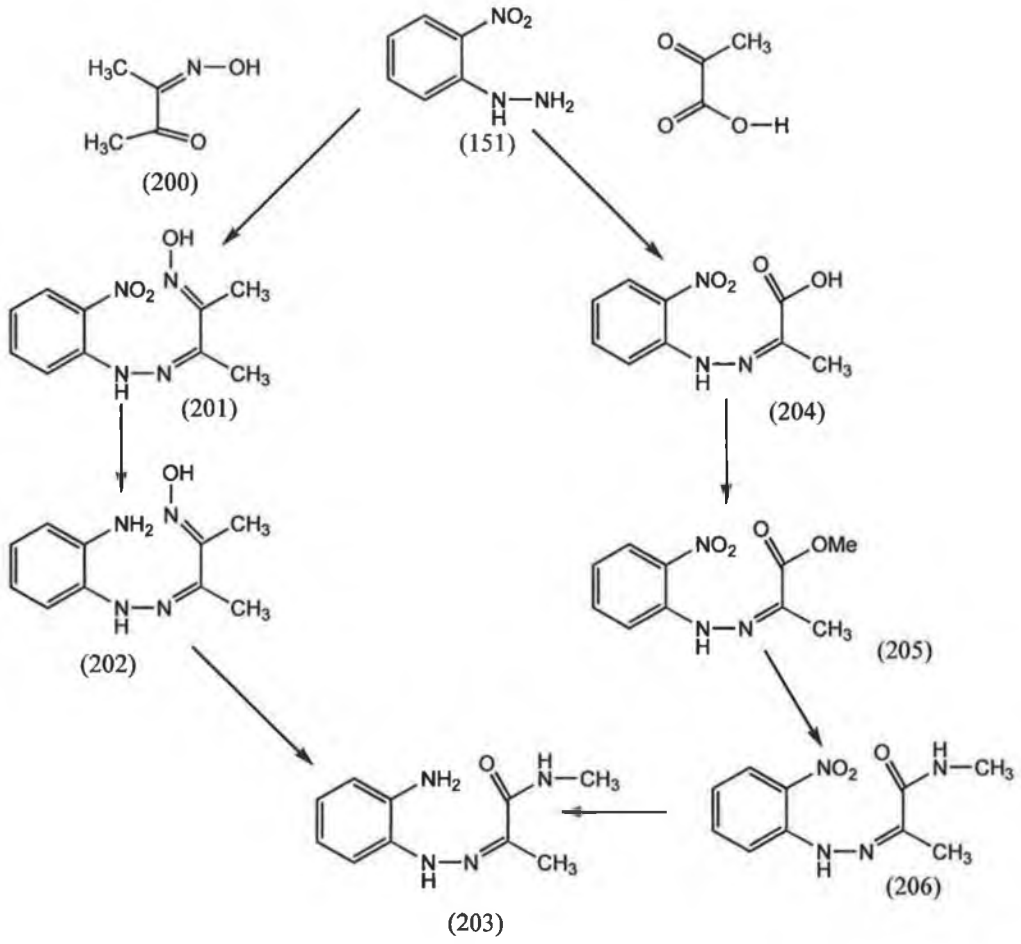
(26) (197) (199)

Scheme 2.32 *Reaction of 2-hydrazino-3-amino-pyridine with phenanthraquinone monooxime to give monocondensed product (199).*

At this point, it was decided to approach this reaction in a more stepwise manner. Due to the inability of this diketo system to undergo disubstitution with nitrogen nucleophiles, a more synthetically useful analogue was sought. Butane-2,3-dione monooxime **(200)** is commercially available and was reacted with *o*-nitrophenylhydrazine to give **(201)**. Reduction of the nitro group was effected by passing H_2 through a hot methanol solution and 10% palladium on charcoal to give

(202). The amine was recovered in near quantitative yield. The final step here involves a cyclodehydration of the amine/oxime functionalities.

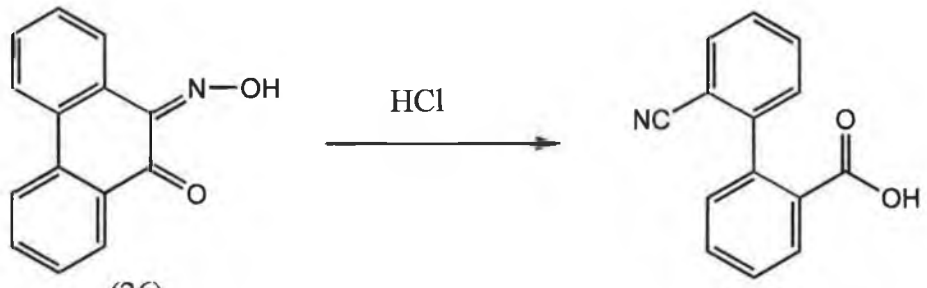
The cyclisation was carried out by the methods described by the authors. Isolation of a solid gave NMR data, which we believe to be consistent with the structure **(203)**. The oxime group undergoes a simple Beckmann rearrangement with resultant amide formation. In order to rule out any other product perhaps through a tetrazocine intermediate, the Beckmann rearrangement product **(203)** was made by the alternative reaction sequence outlined below. Likewise using a less acidic solution, carrying the reaction out in acetic acid or without the use of a sealed container, these conditions all gave **(203)** in varying yields.



Scheme 2.33 *Synthetic pathway to (202) which was observed to undergo a Beckmann rearragement in the final step under reaction conditions described by the authors to give (203).*

2.2.3. Conclusion

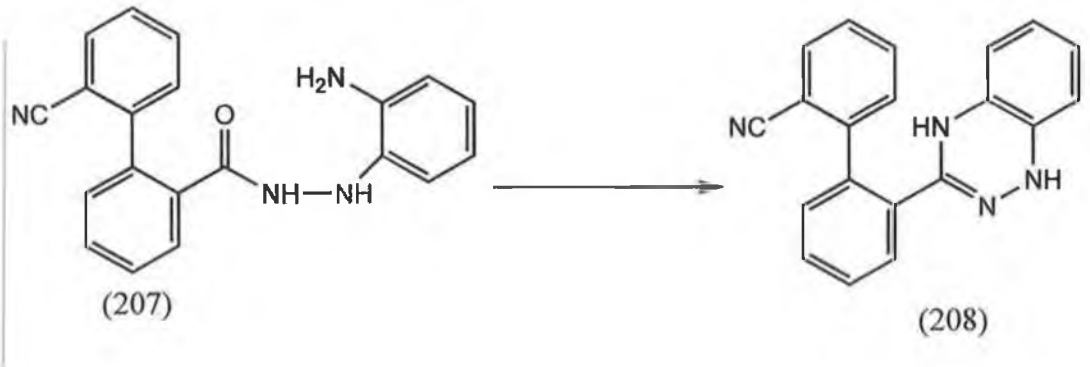
Under no circumstances have we been able to repeat the author's work. We find that the most opposing piece of evidence contrary to the actual existence of the 1,2,5,6-tetrazocine lies in the fact that the oxime group and not the keto group of the phenanthraquinone monooxime undergoes nucleophilic attack initially in all cases. This observation was also substantiated by others in subsequent publications whereby only monosubstituted hydrazones were isolated and found to be considerably unreactive to further nucleophilic attack. In relation to the compound the authors did recover giving the correct nitrogen analysis, one tentative possibility involves the conversion of this ketooxime to a nitrile **(179)** by the action of acid. This reaction has already been shown to result when using phenanthraquinone monooxime.[73]



(26) (179)

Scheme 2.34 *Acid induced rearrangement product of phenanthrene monooxime.*

Under such aggressive conditions a hydrazide **(207)** may result from attack of **(179)** by *o*-aminophenylhydrazine followed by a cyclocondensation to give a six-membered heterocycle **(208)**.



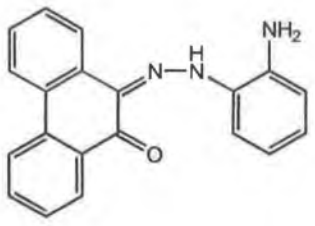
(207) (208)

Scheme 2.35 *Alternative product, which would satisfy the CHN analysis offered by the authors.*

This compound would fit the limited analysis offered, however it was never generated in our hands. Similarly one must question whether it is energetically favorable for condensation between an oxime and amine resulting in ring closure to give an eight-membered ring based on results obtained on going from **(202)** to **(203)**. This again highlights the difficulty of ring closure of these systems.

2.2.4. Experimental

10-[(2-Amino-phenyl)-hydrazono]-10H-phenanthren-9-one (189)



Phenanthraquinone monooxime **(26)** (1.8g, 8.07mmol) was dissolved in 10ml of an ethanolic solution containing 2 ml of 36% HCl. This solution was placed in a bomb calorimeter. *O*-aminophenylhydrazine **(187)** (1.55g, 0.021mol) was quickly added to the solution. The vessel was sealed and placed in a thermally controlled oven at 90^0C for 4-5 hours. The solvent was removed under reduced pressure and the residue dissolved in water whereby the solution was neutralised with aqueous NaOH. The aqueous solution was extracted into DCM. The solvent was removed from the organic phase and the main products separated by column chromatography (pet.ether(40-60^0) 50% : Ethyl acetate 50%). Yield (0.45g, 18%). m.p.168^0C

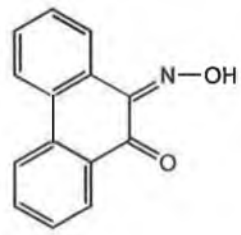
IR(KBr) (cm^{-1}): 3332, 1699, 1634, 1499, 1373, 758, 738, 724.

δH(DMSO-d_6)(ppm): 5.50(2H,bs), 6.73(1H,m), 6.93(1H,m), 7.31(2H,m), 7.77(5H,m), 8.44(1H, m), 8.78(2H, m), 9.05(1H,bs).

δC(DMSO-d_6)(ppm): Too insoluble to give a reasonable signal above noise level of spectrum.

	%Theory	**%Found**
C:	76.64	76.52
H:	4.82	5.11
N:	13.41	13.26

Phenanthrene-9,10-dione monooxime (26)



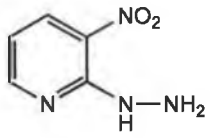
A solution containing phenanthraquinone **(188)** (5g, 0.024mol), $NH_2OH.HCl$ (2g, 0.028mol), 2.5ml of pyridine and 2ml of acetic acid, was heated under reflux in 50 ml of methanol for 2 hours. During the course of the reaction, a brown precipitate falls out which at the end is quickly hot filtered to give pure monooxime **(26)**. The solvent of the filtrate is removed under reduced pressure. The solid residue is dissolved in 100ml of dichloromethane and the solution extracted with 100ml of water three times. The organic layer was washed with aqueous NaOH solution and finally washed once more with water. The organic layer is dried with $MgSO_4$ and the solvent removed. The residue is recrystallised from methanol/acetonitrile. Yield (4.61g, 86%). m.p. 157-158^{0}C, Lit.Val.: 157-158^{0}C.

IR(KBr) (cm^{-1}): 1674, 1599, 1448, 1341, 1280, 984, 756, 722.

δH($CDCl_3$)(ppm):7.31-7.43(3H,m), 7.66(1H,m),7.91(1H,m), 7.98(1H,m), 8.17(1H,m), 8.22(1H,m), 17.01(1H,s).

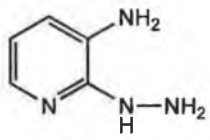
δC($CDCl_3$)(ppm): 118.39, 118.51, 118.91, 123.21, 123.40, 123.89, 124.04, 124.17, 124.44, 125.08, 131.30, 132.49, 139.02, 177.27.

2-Hydrazino, 3-nitro-pyridine (196)



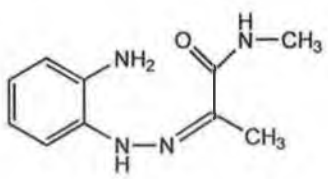
Hydrazine hydrate (20g, 0.625 mol) was added drop-wise to a stirred solution of 2-chloro-3-nitropyridine **(195)** (31.7g, 0.2 mol) in 200ml of ethanol. After addition was complete, the reaction mixture was stirred for 3 hours, then concentrated under reduced pressure. 250ml of water was added to the residue and the mixture extracted with dichloromethane (5 X 100ml). The combined organic layers were dried with $MgSO_4$, filtered and the solvent removed under reduced pressure to give the hydrazine **(196)** which was recrystallised from ethanol. Yield (25.02g, 81%). m.p. 171-173^{0}C, Lit.Val.: 171-172^{0}C.

3-Amino, 2-hydrazino-pyridine (197)



10% Palladium/charcoal (0.1g) was added to a hot solution of 2-hydrazino-3-nitropyridine **(196)** (1g, 6.49 mmol) in 100ml of methanol over N_2. H_2 was bubbled through the solution until the reaction was complete (30 minutes). The reaction was followed by T.L.C. The Pd/C was filtered and the methanol removed under reduced pressure to give 2-hydrazino-3-aminopyridine **(197)** as a solid. Yield (0.7g, 87 %) m.p. 111-112^{0}C, Lit.Val.: 111-112^{0}C

2-[(2-Amino-phenyl)-hydrazono]-*N*-methyl-propionamide (203)



Method 1

(202) (1g, 4.85 mmol) was dissolved in $10cm^3$ of ethanol solution containing 2ml of conc.HCl. The solution was placed in a bomb calorimeter. The vessel was sealed and placed in an oven at 90^0C for 4-5 hours. The solvent was removed under reduced pressure and the remaining liquid added to 20ml of water whereby it was neutralised with aqueous NaOH solution. This solution was extracted with dichloromethane (2 X 50ml), the organic phase dried with $MgSO_4$ and then filtered. The solvent was removed from the filtrate and the remaining residue flash columned (pet.ether(40-60) 25%: Ethylacetate 75%) to the desired compound. Yield (0.38g, 38%). m.p. 147-149^0C

Method 2

10% Palladium/charcoal (0.1g) was added to a hot solution of **(205)** (1g, 4.23 mmol) in 100ml of MeOH over N_2. H_2 was bubbled through the solution for 35 minutes. The Pd/C was filtered off and the methanol reduced under reduced pressure from the filtrate yielding an oil. This oil was separated by flash chromatography to give **(203)**,(pet.ether(40-60^0) 25%: ethylacetate 75%). Yield (0.76g, 88%). m.p= 147-149^0C

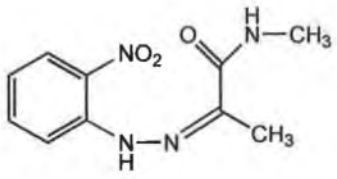
IR(KBr) (cm^{-1}): 3458, 3374, 1699, 1595, 1584, 1462, 1404, 1375, 1264, 1159, 1042, 765.

δH($CDCl_3$)(ppm):2.01(3H,s),2.81(3H,d),3.72(2H,bs),5.80(1H,bs),6.59-6.65(1H,m), 6.66(2H, m), 7.12-7.16(1H, m), 12.74(1H, s).

δC($CDCl_3$)(ppm): 9.12, 26.34, 116.20, 118.93, 121.10, 123.21, 133.42, 134.56, 138.13, 165.53.

	%Theory	%Found
C:	58.20	58.42
H:	6.84	6.74
N:	27.17	27.17

_N_-Methyl-2-[(2-nitro-phenyl)-hydrazono]-propionamide (206)



Excess methyl hydrazine was added to a stirred solution of **(205)** (5g, 0.021 mol) in 100ml of MeOH. The reaction was left to reflux for 5 hours. Excess methyl hydrazine and the solvent were removed under reduced pressure. The desired product **(206)** was separated by flash chromatography (pet.ether(40-60^0) 50%: ethylacetate 50%). Yield (3.6g, 72.4%), m.p.152-153^{0}C

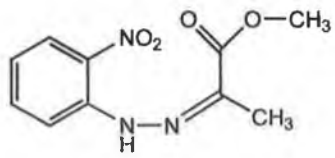
IR(KBr) (cm^{-1}): 3406, 1656, 1564, 1317, 1193, 1077, 720.

δH($CDCl_3$)(ppm): 2.18(3H,s), 2.91(3H,d), 6.90(1H,m), 6.95(1H,bs), 7.53(1H,m), 7.78(1H, m), 8.14(1H,m), 10.78(1H, bs).

δC($CDCl_3$)(ppm): 10.72, 26.85, 116.14, 120.08, 126.43, 132.65, 136.55, 140.09, 143.45, 164.98.

	%Theory	%Found
C:	50.84	50.63
H:	5.11	5.02
N:	23.71	23.58

2-[(2-Nitrophenyl)-hydrazono]-propionic acid methyl ester (205)



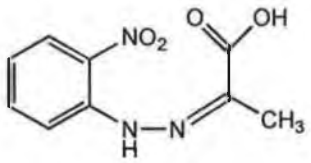
(204) (5g, 0.02 mol) was dissolved in 100ml of MeOH and placed in an ice bath. 10ml of thionyl chloride was added in 1ml portions over a period of 3 minutes. When evolution of HCl had ceased, the reaction mixture was heated under reflux for 20 minutes. Removal of the solvent under reduced pressure gave an oil to which 50ml of water was carefully added. The solution was extracted into DCM (2 X 100ml). The organic phase was separated, dried with $MgSO_4$ and filtered. The solvent was removed giving an oil which on cooling overnight yielded a pure semi-crystalline product which was filtered and washed with hexane. Yield (4.83g, 91%). m.p. 132-134^{0}C

IR(KBr) (cm^{-1}): 3234, 1701, 1613, 1566, 1525, 1273, 748.

δH($CDCl_3$)(ppm): 2.25(3H,s), 3.91(3H,s), 6.94 (1H,m), 7.55(1H,m), 8.01(1H,m), 8.19(1H, m), 13.93(1H, bs).

δC($CDCl_3$)(ppm): 12.07, 52.73, 116.27, 120.24, 126.29, 133.07, 136.12, 139.32, 141.12, 163.31.

2-[(2-Nitrophenyl)-hydrazono]-propionic acid (204)



O-Nitrophenylhydrazine **(181)** (5g, 0.03 mol) and pyruvic acid (2.87g, 0.03 mol) was heated under reflux in 50ml of acetonitrile for 5 hours. Yellow needles were obtained on cooling of the solution overnight which were filtered and washed with

pet.ether(40-60^0). Removal of excess acetonitrile gave a second crop of needles from the remaining solution. Yield (6.9g, 94%). m.p. 143-145^{0}C

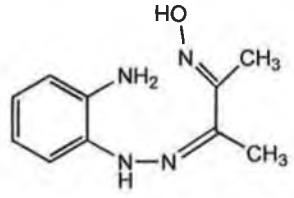
IR(KBr) (cm^{-1}): 3260, 1699, 1652, 1431, 1268, 780

δH($CDCl_3$)(ppm): 2.22(3H,s), 7.01(1H,m) 7.62(1H,m), 7.73(1H,m), 8.19(1H,m), 11.01(1H,s).

δC($CDCl_3$)(ppm): 11.39, 116.55, 120.70, 125.91, 132.61, 136.90, 140.32, 140.44, 165.75.

	%Theory	**%Found**
C:	48.43	48.33
H:	4.06	4.02
N:	18.82	18.75

2-[(2-Amino-phenyl)-hydrazono]-propionaldehyde oxime (202)



10% Palladium/charcoal (0.1g) was added to a solution of **(201)** (1g, 4.23 mmol) in 100ml of MeOH over N_2. H_2 was bubbled through the solution until reaction was complete (15-20 minutes). The reaction was followed by T.L.C. The Pd/C was filtered and the methanol removed under reduced pressure to give **(202)**. Yield (0.79g, 91%). m.p. 161-163^{0}C.

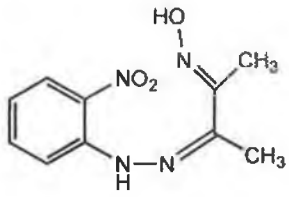
IR(KBr) (cm^{-1}): 3384, 3305, 1593, 1579, 1264, 926, 790.

δH(DMSO-d_6)(ppm): 2.06(3H,s), 2.11(3H,s), 3.91(2H,bs), 6.58-6.63(3H,m), 7.24(1H,m), 8.11(1H, s).

δC(DMSO-d_6)(ppm): 9.63, 10.66, 114.56, 116.56, 118.15, 121.10, 132.53, 135.23, 141.26, 155.36.

	%Theory	%Found
C:	58.21	58.16
H:	6.84	7.11
N:	27.17	27.45

2-[(2-Nitro-phenyl)-hydrazono]-propionaldehyde oxime (201)



2-Nitrophenylhydrazine **(181)** (5g, 0.03 mol) and 2,3-butadione monooxime **(200)** (3.23g, 0.03 mol) in 50ml of ethanol was allowed to reflux for 4 hours. On cooling overnight, orange brown needles fell out which were filtered and washed with cold ethanol. Removal of excess ethanol yields a second crop of needles on cooling. Yield (5.7g, 74 %). m.p. 151-153^{0}C.

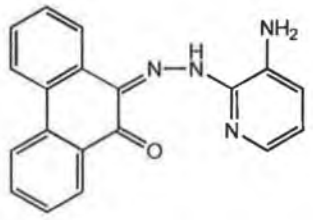
IR(KBr) (cm^{-1}): 3321, 3236, 1614, 1578, 1441, 1323, 1271, 1141, 929, 739.

δH($CDCl_3$)(ppm): 2.06(3H,s), 2.14(3H,s), 6.94(1H,m), 7.66(1H,m), 7.83(1H,m), 8.10(1H, m), 10.68(1H, s), 11.69(1H, s).

δC($CDCl_3$)(ppm): 9.56, 10.68, 115.88, 119.30, 126.02, 131.51, 137.09, 141.36, 147.98, 154.65.

	%Theory	%Found
C:	50.84	50.54
H:	5.1	5.05
N:	23.71	23.77

10-[(2-Amino-pyridin-2-yl)-hydrazone]-10H-phenanthren-9-one (199)



Phenanthraquinone monooxime **(26)** (1.8g, 8.07 mmol) was dissolved in 10ml of ethanolic solution containing 2 ml of 36% HCl. This solution was placed in a bomb calorimeter. 2-hydrazino-3-amino-pyridine **(197)** (1g, 8.07 mmol) was quickly added to the solution. The vessel was sealed and placed in a thermally controlled oven at 90^0C for 4-5 hours. The solvent was removed under reduced pressure and the residue dissolved in water whereby the solution was neutralised with aqueous NaOH. The aqueous solution was extracted with DCM. The solvent was removed from the organic layer and the main product separated by column chromatography (pet.ether(40- 60^0) 50%: Ethyl acetate 50%). Yield (0.99g, 39.4%). m.p. 175-177^{0}C

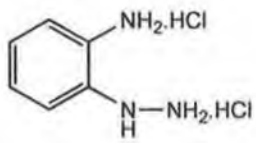
IR(KBr) (cm^{-1}): 1600, 1541, 1447, 1359, 757, 723.

δH($CDCl_3$)(ppm): 7.63(1H,m), 7.66-7.79(4H,m), 8.44(2H,m), 8.58(1H,m), 9.18(1H,m), 9.27(1H,m), 9.43(1H,m).

δC($CDCl_3$)(ppm): 123.23, 123.35, 125.27, 126.80, 127.69, 128.48, 128.61, 129.82, 130.08, 131.21, 131.53, 132.59, 132.81, 137.64, 138.79, 143.90, 145.35, 150.26, 154.96.

	%Theory	**%Found**
C:	72.60	72.87
H:	4.49	4.31
N:	17.82	17.75

2-Aminophenylhydrazine (187)



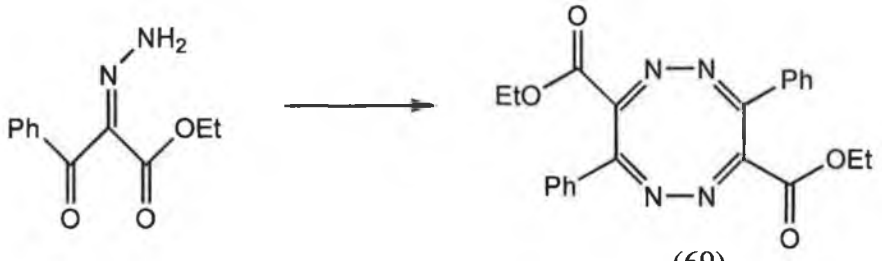
1g of benzotriazole **(186)** was dissolved in 10ml of 4N HCl. The acid was added to the H-cell of previously shown diagrammatically in Figure 2.2. The HCl solution was de-aerated by bubbling a stream of N_2 continually through the solution. Benzotriazole was reduced at –1.0V (SCE) at 0-5^{0}C over 2-3 hours. The acid solution was placed in a dry round-bottomed flask over N_2 and the catolyte evaporated under vacuum at room temperature. After 24 hours, long white needles were obtained. Further attempts at purification served only to oxidise the air sensitive compound.

δH($CDCl_3$)(ppm): 7.43(2H,m), 7.88(2H,m), 8.91(5H,bs).

2.3. Investigation of a 1,2,5,6-tetrazocine derived from the Monohydrazone of Ethylbenzoylglyoxalate

2.3.1. Introduction

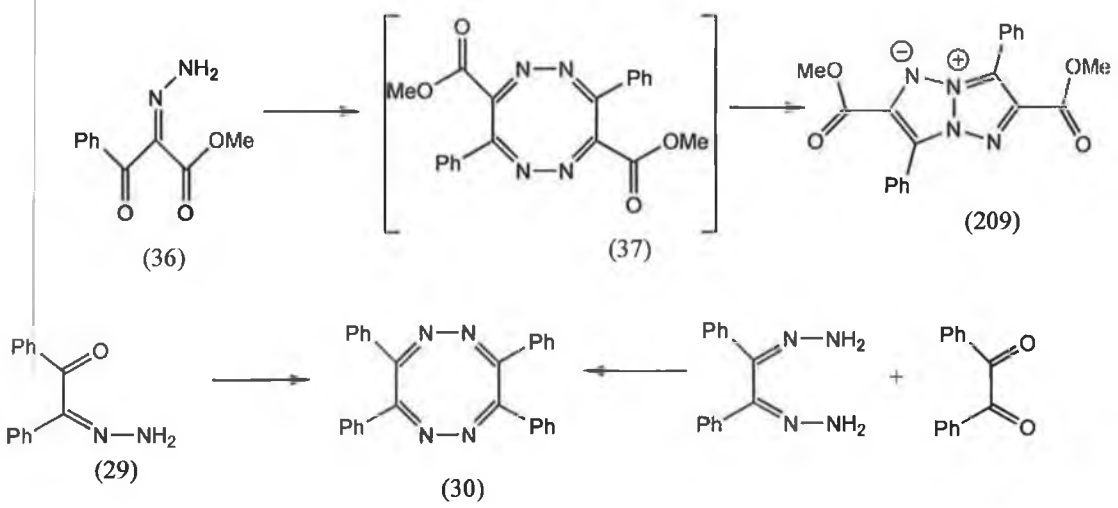
A recent journal concerning the formation of germanium-nitrogen double bonds using a range of diazo compounds reported by Glidewell *et al* shows the spontaneous dimerisation of the hydrazone, ethylbenzoylglyoxylate **(68)** to yield the 1,2,5,6-tetrazocine **(69)**, the existance of which is verified by IR, NMR and elemental analysis.[40]



(68) (69)

Scheme 2.36 *Dimerisation of ethylbenzoylglyoxylate to yield a 1,2,5,6-tetrazocine.*

The fact that this ring system was completely free of saturation and the nitrogen atom configuration was of great interest to us. The authors argue the ample precedence of this 1,2,5,6-tetrazocine by comparing its structure to similar analogues prepared by Metze, Schlesinger and Pfleger respectively.[27,28,31] The methods of preparation of these compounds are based on the cyclic condensation of hydrazones with carbonyl functionalities. Metze showed that benzil monohydrazone **(29)** when heated above it's melting point, gave a compound believed to be tetraazacyclooctatetraene **(30)**. Similarly Schlesinger heated benzil with an equimolar quantity of it's dihydrazone to give the same compound. Finally Pfleger using the methyl ester analogue **(36)** of Glidewell's hydrazone also describes a similar condensation to the 1,2,5,6-tetrazocine **(37)**. In all methods of preparation, it seems reasonable to suppose that the tetrazocine is initially formed.



Scheme 2.37 *Precedent synthesis of previously prepared fully saturated 1,2,5,6-tetrazocines as referenced by the authors.*

However some years later, Brufani working in collaboration with Pfleger corrected their proposed eight-membered ring **(37)** structure through conclusive X-ray and derivitisation studies.[84] It was shown that the tetrazocine rapidly cyclises to a bicyclic structure representative of the 1,2,3-triazolo[1,2-b]-1,2,3-triazoles **(209)**, more commonly known as tetraazopentalenes. The formation of this single isomer can be attributed to the greater thermodynamic stability of the observed product.

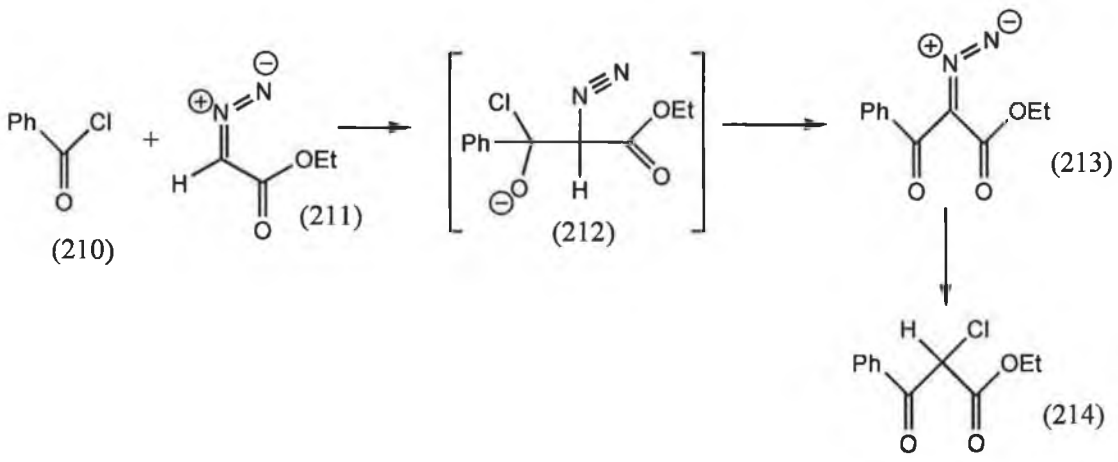
Calculation by Chia and Simmons on analogous systems showed the relationship between the structure of the tetraazapentalenes and the valence tetrazocine isomer.[85] The 8π electron tetrazocine destroys aromaticity. Huckel's rule states that cyclic molecules having 4n+2 π-electrons possess closed shells of electrons and large delocalisation energies. The relative stabilties of the 8π electron tetrazocine and the 10π electron tetrazopentalene structure can be deduced by considering the delocalisation energy of both species. Stabilisation energy per π electron is greater in the pentalene 10π system.

With this volume of conflicting evidence, we felt it necessary to verify the authors claims. To date, no 1,2,5,6- fully unsaturated tetrazocine has been prepared successfully or trapped long enough for detection.

2.3.2. Results and discussion

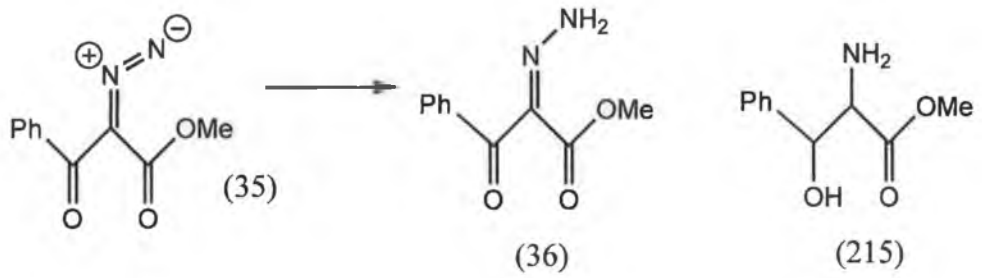
Our initial concern was the validity of the hydrazone of ethylbenzoylglyoxalate **(68)** as described by Glidewell. It was decided to prepare the α-keto hydrazone by an alternative method and compare our findings.

Bestmann and Kolm first described a high yield route to ethylbenzoylglyoxlate hydrazone **(68)** whilst developing a new synthetic pathway to β-ketoesters.[86] The first step involves reaction of benzoyl chloride **(210)** and ethyldiazoacetate **(211)**. Excess ethyldiazoacetate is required as any HCl produced would further react with the diazoketone to produce an α-halo ketone **(214)**.



Scheme 2.38 *Formation of ethyl benzoyl diazoacetate (213) as described by Bestmann and Kolm.*

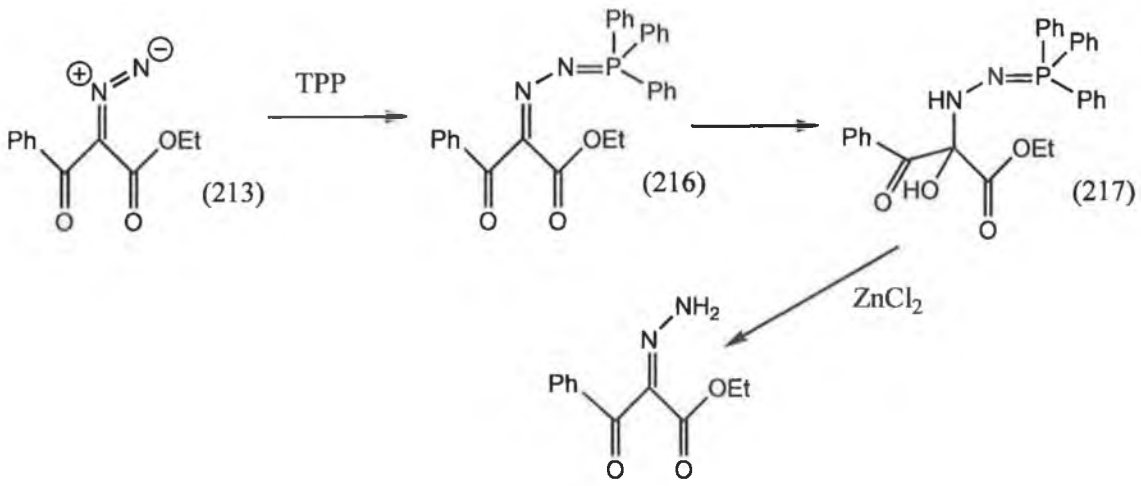
The reaction proceeded smoothly to give a yellow oil **(213)** in 75% yield with no further purification necessary. In many instances other authors have reduced the diazo group directly. Pfleger successfully hydrogenated **(35)** in acetic acid to form **(36)** at room temperature catalysed by $PdCl_2$ in 55% yield.[31] However the reaction is relatively unclean with β-phenyl-serine-methyl ester **(215)** as a major impurity.



Scheme 2.39 *Reduction of (35) to yield ethylbenzoylglyoxlate hydrazone.*

The coupling of a diazo functionality and triphenylphosphine yields a phosphinazine. Triphenylphosphine is a very good reducing agent due to it's thermodynamically favourable conversion to triphenylphosphine oxide, a stable solid in air in comparison to the phosphine. Phosphinazines can be hydrolysed directly to the corresponding hydrazone by mildly refluxing them in aqueous solvent such as THF or ethanol. The reaction is catalysed by trace acid. Yields are generally high. In some instances a secondary product is observed and may lower overall yields. This is the result of the phosphinazine absorbing one mole of water across the C=N bond to form a "phosphinazine hydrate".

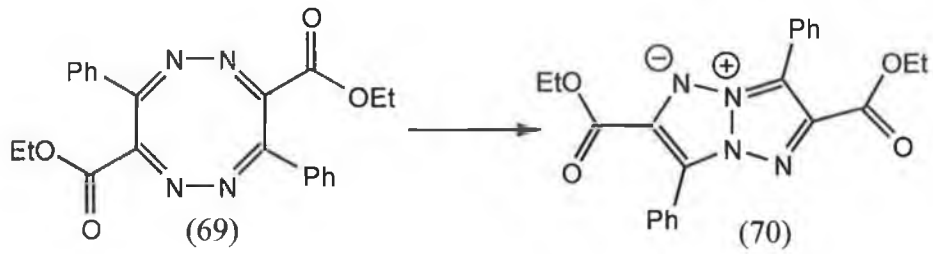
Ethylbenzoyldiazoacetate triphenylphosphine **(216)** was generated in quantitative yield from ethylbenzoyldiazoacetate **(213)**. Attempts to directly obtain the hydrazone **(68)** through acid catalysed hydration gave the desired compound in 62% yield. However the phosphinazine hydrate **(217)** was present no matter how long the reaction was allowed to reflux, which complicated the work-up overall. Bestmann suggests forming the hydrate **(217)** by simple reflux of the phosphinazine in aqueous methanol. Zinc chloride is then employed to dehydrate the hydrate giving the hydrazone **(68)** in high yield and a zinc phosphineoxide complex, $ZnCl_2[(C_6H_5)_3PO]_2$.



Scheme 2.40 *Alternative preparation for the hydrazone of ethylbenzoyl glyoxalate as described by Bestmann and Kolm.*

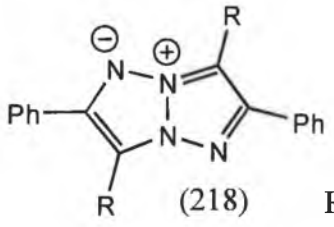
The resulting hydrazone **(68)** is a yellow oil which when left under high vacuum for a week gives a tanned waxy solid. The oil gave identical NMR spectroscopy to that of Glidewell's hydrazone. Two separate samples of the hydrazone were left stirring simultaneously in light and in its absence to see which, if any, effected the dimerisation more readily. In both instances, a reaction time of up to a month was sufficient to obtain the proposed tetrazocine **(69)**, however in low comparable yields. Spectroscopic comparisons of both compounds produced by Glidewell and ourselves showed them to be exactly the same.

NMR does not conclusively elucidate the correct structure. The proposed tetrazocine **(69)** is highly symmetrical. The question arises here as to whether the tetrazopentalene **(70)** is in fact symmetrical so as to make the two sets of ester and phenyl moieties equivalent in chemical shift terms.



Scheme 2.40 *Ring contraction of the intermediate 1,2,5,6-tetrazocine to give a tetraazapentalene.*

Tetraazapentalenes are termed as mesionic spicies with formal charge separation. However **(70)** may be represented by a series of equal contributing resonance structures. The chemical and physical properties of the dipolar tetraazopentalene might be expected to reflect a structure which lies between these set of charge separated structures. Hall has shown the NMR splitting patterns of similar tetraazopentalenes **(218)** indicating that both benzenoid rings are equivalent.[87] In summary, our proposed tetraazapentalene should be viewed as a symmetrical aromatic compound due to a closed decet of π electrons in a cyclic molecule, which obeys Huckels 4n+2 rule.



(218) R=Ph, CO_2Me

Figure 2.3 *NMR splitting patterns of the tetraazopentalenes (218) indicates that both benzenoid rings are equivalent.*

During the course of our work, we became aware of two publications in relation to these systems. Following on from previous work, Pfleger patented the tetraazapentalene **(70)** from ethyl acetyl glyoxalate hydrazone **(68)** as a potential starting material for pharmaceuticals.[88] By refluxing the hydrazone in aqueous glacial acetic acid for 1 hour, he recovered the tetraazapentalene in 64% yield. We

repeated this procedure with Glidewell's hydrazone and recovered a compound which is identical to Glidewell's spontaneous dimerisation product i.e. the 1,2,5,6-tetrazocine.

However, our most conclusive piece of evidence, contrary to the isolation of the eight-membered heterocycle was reported by Brufani.[89] The X-ray crystallographic analysis of the condensation product obtained, in acidic solution, from the α-monohydrazone of methylbenzoylglyoxalate **(36)** shows that the tetraazopentalene **(37)** ring system is formed. That this hydrazone differs from our own only by a methyl ester group as opposed to an ethyl ester group, we feel that this work alone is sufficient to satisfactorily rule out the isolation of the tetrazocine by Glidewell.

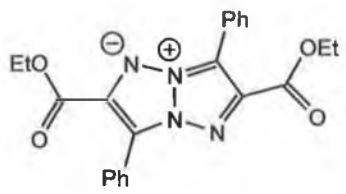
Brufani has done work on other analogues of the tetrazaapentalene system which collectively rule out any possible stabilizing effect the ester group may have in maintaining the tetrazocine ring from inevitable contraction to more stable tetraazapentalene.[30]

2.3.3. Conclusion

In conclusion it seems reasonable to assume that the authors in question may have simply overlooked the literature available to them. Also, this work highlights the relative instability and fleeting existence of these ring systems showing their preference to contract to more stable five-membered rings.

2.3.4. Experimental

Formation of tetraazapentalene (70)



Method 1

α-monohydrazone of ethylbenzoylglyoxalate **(68)** (1g, 4.54mmol) was stirred in an opened 10ml round bottomed flask for 1 month. Following the reaction by TLC, the small growth of the tetraazapentalene **(70)** was observed to form. The tetraazapentalene was isolated by column chromatography . Yield (0.18g, 20%). (Pet.ether (40-60^0) 70: ethyl acetate 30).

Method 2

α-monohydrazone of ethylbenzoylglyoxalate **(68)** (1g, 4.54mmol) was added to 10ml of glacial acetic acid and heated for 1 hour. The reaction mixture was cooled to room temperature to give crystals of the tetraazapentalene **(70)**. The solution was left overnight and the crystal mass filtered off and washed with water and left to dry to give **(70)**. Yield = 0.49g, 54%). m.p. 195-197^{0}C, Lit.Val.: 195-196^{0}C.

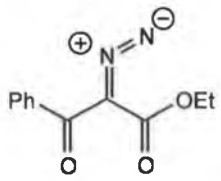
IR (KBr)(cm^{-1}): 1710

δH ($CDCl_3$)(ppm): 1.27(3H,t), 4.36(2H,q), 7.43(3H,m), 7.73(2H,m).

δC ($CDCl_3$)(ppm): 14.98, 61.25, 108.45, 128.47, 129.64, 130.57, 130.63, 153.12, 158.18.

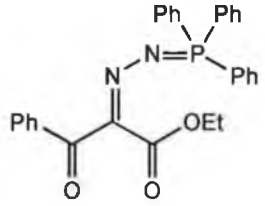
	%Theory	**%Found**
C:	65.31	65.14
H:	4.98	5.07
N:	13.86	13.78

Ethyl Benzoyl Diazoacetate (213)



Ethyldiazoacetate **(211)** (25g, 0.219 mol) was added to benzoylchloride **(210)** (21.25g, 0.151 mol) . The reagents were stirred for 4 days in light absence in a 100ml round-bottomed flask equipped with a drying tube. The mixture was heated to 50^0C and put under vacuum for 24 hours to remove any ethyl chloroacetate formed during the reaction. The reaction vessel was further left under vacuum for 3 days to yield a yellow oil. The oil was used directly in the next step, i.e. formation of **(216).**

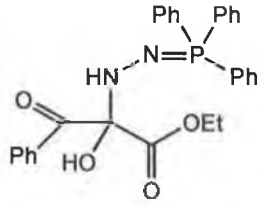
Ethyl Benzoyl Diazoacetate Triphenylphosphinazine (216)



Unpurified ethylbenzoylacetate oil **(213)** (25g) in 20ml of absolute isopropylether was added to triphenylphosphine (20.35g, 0.07 mol) in 75ml of absolute isopropylether. The mixture was stirred vigorously until an oil separated out. The reaction vessel was left overnight in the fridge whereby the crystalline solid (305) fell out. The solid **(216)** was filtered and washed lightly with cold isopropylether. Yield (84g, 80%). m.p 125^0C, Lit.val.: 125^0C.

δH(DMSO-d_6)(ppm): 1.34(3H,t), 4.46(2H,q), 7.15- 7.80 (20H,m).

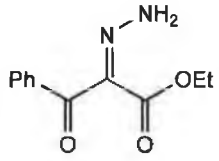
Phosphinazine Hydrate (217)



Ethylbenzoyldiazoacetate triphenylphosphinazine **(216)** (20g, 0.04 mol) in 60ml of 80% aqueous methanol was under reflux for 4 hours. The excess solvent was removed and the solution allowed to cool at which point an oil separates out. The oil was left overnight in the fridge and the resultant crystals gathered by vacuum filtration to the hydrate **(217)**. Yield = 17.22g, 84 %. m.p. 94-96^{0}C, Lit.Value.: 94-96^{0}C.

δH(DMSO-d_6)(ppm): 1.19(3H,t), 4.22(2H,q), 7.42- 7.74 (20H,m), 10.14(2H, bs).

α- Monohydrazone of Ethylbenzoylglyoxalate (68)



The hydrate **(217)** (15g, 0.03 moles) was dissolved in 500ml of absolute diethyl ether over nitrogen. Anhydrous zincchloride (13g, 0.09 mol) in 200ml of absolute ether was added slowly over 5 minutes. The stirred solution was left for 1 hour at which point 100ml of water was added dropwise and the solution left to stir for 45 minutes. The two layers were separated. Excess ether was removed and the remaining solution then washed twice with water. The organic phase was dried with $MgSO_4$ and all the remaining solvent removed under reduced pressure to give an oil. Yield = 5.10g, 77%.

IR (KBr) (cm^{-1}): 3387, 3211,1682, 1650.

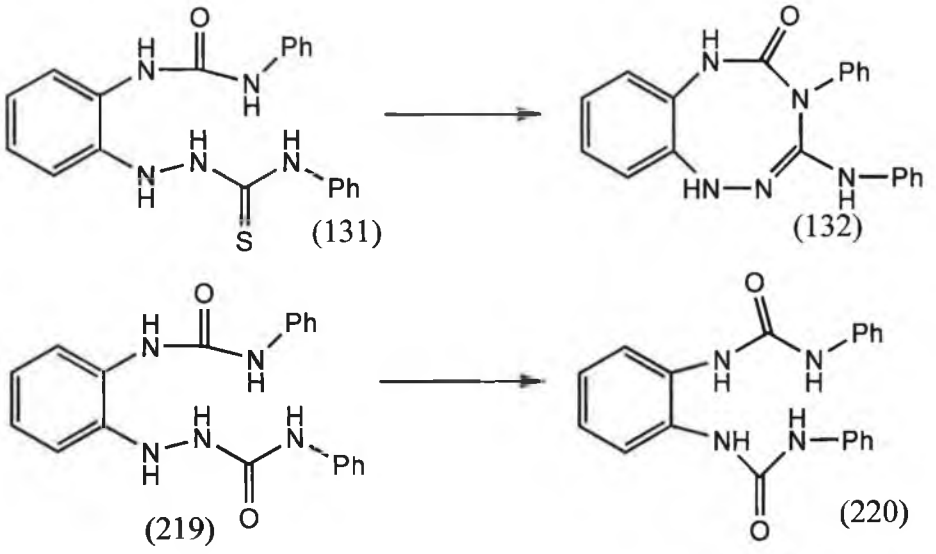
δH(DMSO-d_6)(ppm): 1.24(3H,t), 4.16(2H,q), 7.46-7.78 (5H,m), 8.4-9.42(2H, bs).

δC(DMSO-d_6)(ppm): 14.0, 60.8, 128.0, 128.6, 130.0, 132.2, 138.0, 163.0, 190.5

2.4. Reinvestigation of a 1,2,4,6-tetrazocine derived from 1-phenylcarbamido-2-phenylsemicarbazidebenzene

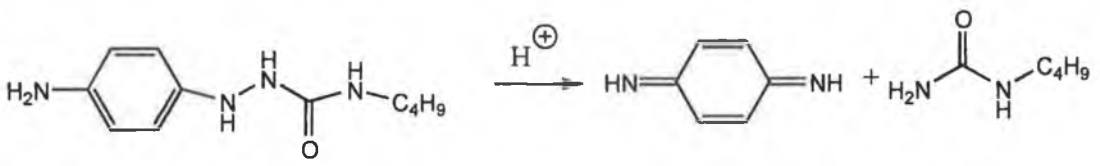
2.4.1. Introduction

Another area examined was the proposed ring closure of **(131)** to give **(132)** under acidic and high temperature/pressure conditions by Guha & Ghosh.[59] This must be deemed suspicious in light of preliminary work carried out by this research group.



Scheme 2.41 *Proposed ring closure as described by the authors with resultant 1,2,4,6-tetrazocine formation. Observed hydrazide N-N cleavage of keto analogue (219).*

We found that heating **(219)** resulted in cleavage of the hydrazide N–N bond with subsequent loss of NH_3 as opposed to water as reported by the author. We have conclusive analysis to confirm the existence of **(220)**. Eckard has shown the adequate precedence of this fragmentation with similar systems.[90]

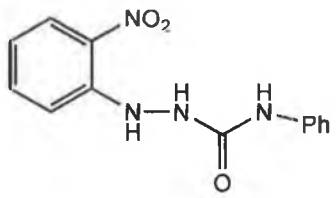


Scheme 2.42 *Hydrazide N-N cleavage in similar systems under acidic conditions.*

Based on the above observations, it is highly conceivable that **(131)** will give the thio analogue of **(220)** and not **(132)** and put into question the authors work. This is an area that needs to be investigated further. The existence of **(132)** is highly unlikely for many reasons. Apart from the entropic constraints the molecule must overcome in order to form the eight-membered ring, hindrance must also play a negative part with respect to the two bulky phenyl rings. Likewise if the tetrazocine were to form, it could contract in any number of ways. The precursor to ring closure bears a striking resemblance to the quinazolinone **(134)** discussed earlier in section 2.1.

2.4.2. Experimental

_O_-Nitrophenyl-4-phenylsemicarbazide



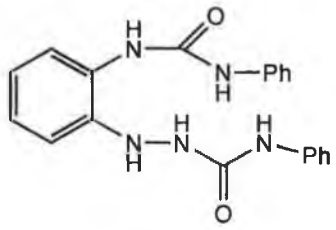
2-Nitrophenyl hydrazine (1g, 6.53mmol) was added to a stirred solution of phenylisocyanate (1g, 8.40mmol) in 50ml of acetonitrile. The reaction mixture was allowed to reflux for 1 hour whereby the solvent was removed under reduced pressure. The solid was washed with 10ml X 2 of cold methanol (0^0C) give a pure solid . Yield (1.63g, 92%). m.p. 202^0C.

IR(KBr) (cm^{-1}): 3341, 3289, 1699, 1652, 1418

δH(DMSO-d_6)(ppm): 6.82(1H, m), 6.97(1H, m), 7.25(3H, m), 7.51(2H, m), 7.62(1H, m), 8.13(1H, m), 8.56(1H, bs), 8.98(1H, bs), 9.28(1H, bs).

δC(DMSO-d_6)(ppm): 115.02, 117.93, 119.34, 122.46, 126.10, 128.89, 132.31, 136.65, 139.84, 146.44, 156.07.

1-Phenylcarbamido-2-phenylsemicarbazidebenzene (319)



1-_O_-Nitrophenyl-4-phenylsemicarbazide (1g, 3.67mmol) was added to a solution of 50ml of MeOH and Pd/C (0.1g). H_2 was bubbled through the solution at room temperature. The reaction was followed by T.L.C. When complete disappearance of 1-_O_-Nitrophenyl-4-phenylsemicarbazide was noted, the source of H_2 was removed. The catalyst was filtered off and phenylisocyanate (1g, 8.40 mmol) quickly added to

the filtrate whereby a white mass fell out. This solid was filtered off and washed with with 2 X 50 ml of MeOH to give pure **(219)**. Yield (1.07g, 78%). m.p. Above 300^0C

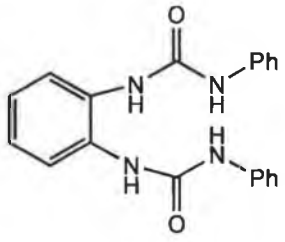
IR(KBr)(cm^{-1}): 3299, 1701, 1654, 900, 747.

δH(DMSO-d_6)(ppm): 6.82(1H, m), 6.94(3H, m), 7.09(1H, m), 7.33(5H, m), 7.51(2H, m), 7.64(2H, m), 8.09(1H, bs), 8.09(1H, bs), 8.39(1H, bs), 9.02 (2H, m).

δC(DMSO-d_6)(ppm): 112.59, 118.52, 118.78, 119.47, 122.03, 122.12, 124.90, 125.27, 125.63, 128.90, 129.09, 140.16, 140.38, 142.56, 153.75, 156.91

	%Theory	**%Found**
C:	66.46	66.76
H:	5.29	5.24
N:	19.37	19.05

1-Phenyl-3[2-(3-phenyl-ureido)-phenyl]-urea (220)



(219) (5g, 0.01 mol) was added to 100ml of 36% HCl and heated at 80^0C for 1 hour. The reaction solution was carefully poured onto 50g of ice whereby a white mass falls out. The solid was filtered off. The white material was then washed 3 X 100 ml of water and then allowed to dry. Finally, the solid was recrystallised from aqueous methanol. Yield (2.14g, 48%). m.p. 212-214^{0}C.

IR(KBr)(cm^{-1}): 3279, 3053, 1699, 1176, 888, 749.

δH(DMSO-d_6)(ppm): 6.95(1H, m), 7.08(1H, m), 7.27(2H, m), 7.47(2H, m), 7.59(1H, m), 8.06(1H, bs), 9.07(1H, bs).

δC(DMSO-d_6)(ppm): 118.48, 122.12, 124.32, 124.36, 129.14, 131.61, 140.20, 153.55.

	%Theory	**%Found**
C:	69.35	69.18
H:	5.23	5.23
N:	16.17	16.19

Chapter 3

Synthesis and transformations of the 1,3-dipolar cycloadducts derived from 1,2,3-triazolium-*N*-imides

3. Preamble

This chapter is concerned with cycloaddition reactions of the 1,3-dipole, triazolium-*N*-imide **(3)**, with various dipolarophiles. It also provides the secondary derivatives formed from these cycloadducts through manipulation of functionality and by thermal and photochemical means. A brief introduction to this area of chemistry is initially presented followed by discussion of results. Our overlying priority was however to produce novel tetrazocines.

As mentioned previously in the literature survey, we entered the area of tetrazocine synthesis through the photochemical rearrangements of **(1)** and it's analogues. This method of tetrazocine ring construction served us well as it circumvented the necessity for ring closure and all it's short comings. The key step involves the cleavage of a C-C bond to yield the eight-membered ring. However keeping the eight-membered ring and preventing contraction or rearrangement was another task in itself.

3.1. Introduction

3.1.1. The 1,3-dipole

1,3-dipole cycloadditions provide a versatile route to a wide variety of five membered heterocycles. As early as 1883 Theodore Curtius discovered diazoacetic ester and upon suggestion to an unaware Edward Buchner, he carried out the first 1,3-dipolar cycloaddition with the diazoacetic acid and fumaric acid in 1888. However it wasn't until 1938 that Lee Urwin Smith even proposed the general idea of a 1,3-dipole.[91] Later again in the 1960s Huisigen submitted the now accepted concept of a 1,3-dipole.[92] A 1,3-dipole is a three atom system, a-b-c, which contains 4π-electrons in three parallel *p*-orbitals. This system can be portrayed by a dipolar resonance structure. The two octet structures illustrate the allyl anion type where the middle center b^+, is an onium ion (oxonium, iminium, sulfonium) which delocalises the negative charge at either a or b. In dipoles of the propargyl-allenyl type, the allyl anion systems contains an extra double bond between a and c. The π-orbitals of this bond are in a plane orthoganal to that of the 4π-molecular orbital.

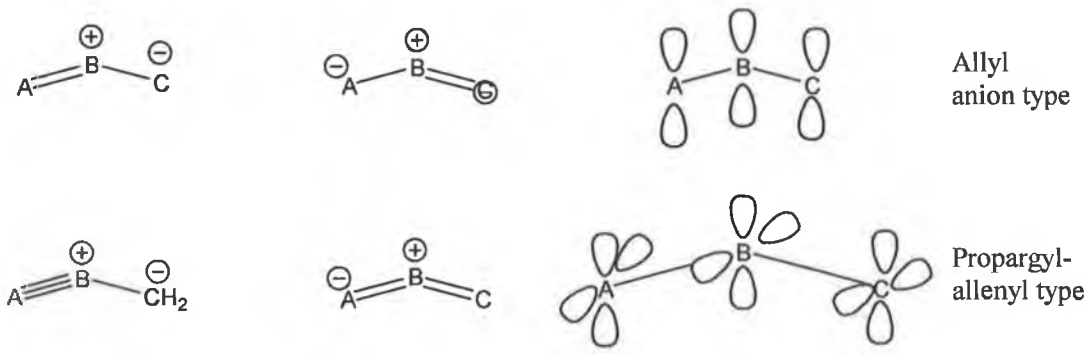


Figure 3.1 *Octet and sextet structures of 1,3-dipoles.*

The name 1,3-dipole is perhaps unfortunate and should not be taken that the system has a dipole moment or even shows high polarity. And although the resonance structures show zwitterions, this is not the case as there is no localisation of charge. In fact 1,3-dipoles have low dipole moments. In 1,3-dipolar cycloaddition reactions, the 1,3-dipole reacts with a dipolarophile, generally a compound containing a double or triple bond. These are 6π pericylic reactions, 4π electrons coming from the 1,3-dipole component and 2π-electrons from the dipolarophile. The product of the reaction is a five membered heterocyclic compound.

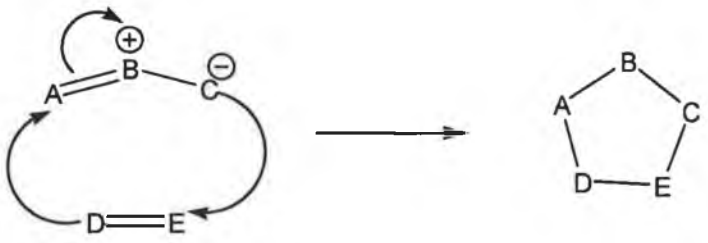
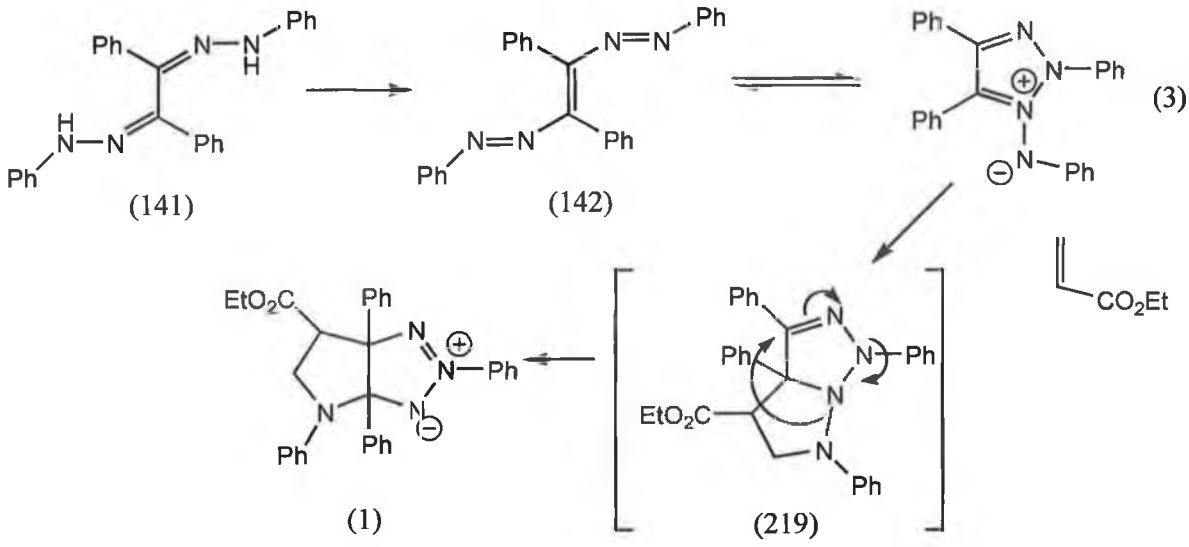


Figure 3.2 *1,3-dipolar cycloaddition.*

3.1.2. Previous 1,2,3-triazolium-*N*-imides and their derivatives

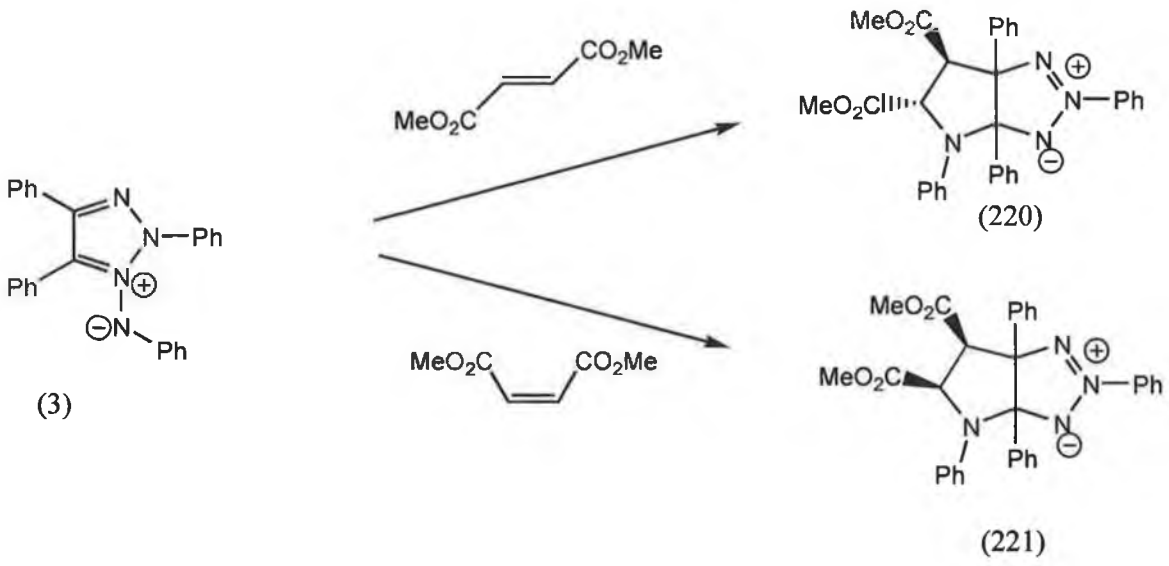
This section describes the synthetic route of the 1,2,3-triazolium-*N*-imides **(2)** to tetrazocines. This also covers a brief introduction on their properties and derivatives.

In 1953, Spasov and coworkers reported that benzil diphenyl hydrazone **(141)** existed in different tautomeric forms and that the product formed on oxidation with sodium ethoxide and iodine was phenylazostilbene **(142)**.[93] However it was not until 1971 that Sukumaran realised that reaction of the stilbene with various dipolarophiles to give cycloadducts of the form **(219)** could only be rationalised through the mesionic intermediate **(3)** which represents a 1,3-dipolar system.[94] Indeed, in solution the stilbene was found to undergo *E,Z*-isomerisation followed by electrocyclisation to give the cyclic 1, 2, 3 – triazolium imide form **(3)**. This dynamic equilibrium of the open chain form has been detected by NMR.[95] The identified 1,3-dipole was of the azomethine imine type. In 1983 and following years, Butler realised that on re-examination of these cycloadducts through NMR and X-ray analysis, that the proposed structure of the cycloadducts offered by Sukumaran was incorrect and that the proper assignment should in fact be **(1)**. In their proposed mechanism, Sukumaran's cycloadduct is an intermediate, which undergoes a tandem 1,4-sigmatropic rearrangement to yield **(1)** driven by the formation of a C–N bond over a N–N bond.



Scheme 3.1 *Cycloaddition mechanism of a 1,3-dipole with ethylacrylate.*

The 1,3 dipolar cycloadditions of 1,2,3–triazolium-1-(*N*-aryl)-imides to various dipolarophiles are shown to be remarkably stereo- and regioselective. Treatment of the dipole **(3)** with dimethyl fumarate gave the stereospecific *trans*-addition product **(220)** whereas addition of dimethyl maleate gave the *cis*-addition product **(221)**.[96]



Scheme 3.2 *Stereospecificity of the 1,3-dipolar cycloaddition.*

Kinetic studies by Butler showed that the cycloaddition process of the 1,2,3–triazolium-*N*-imides to be a concerted dipole HOMO-controlled cycloaddition with orbital controlled regioselectivity giving a transition state where the dipolarophile approaches over the plane of the triazolium imide dipole to give an initial unstable adduct.[97] A rapid 1,4 sigmatropic rearrangement ensues. The regioselectivity observed agreed with calculated orbital coefficients of HOMO and LUMO energies of the dipole and dipolarophile respectively. It has been shown for a variety of dipolarophiles that acetylenic compounds react quicker than vinylic compounds. The greater the electron withdrawing capacity of the substituent on the dipolarophile, the greater the rate of reaction. Electron withdrawing groups reduce the LUMO energy of the dipolarophile making the ΔE gap between HOMO/LUMO smaller, hence speeding up of the HOMO dipole controlled reaction.

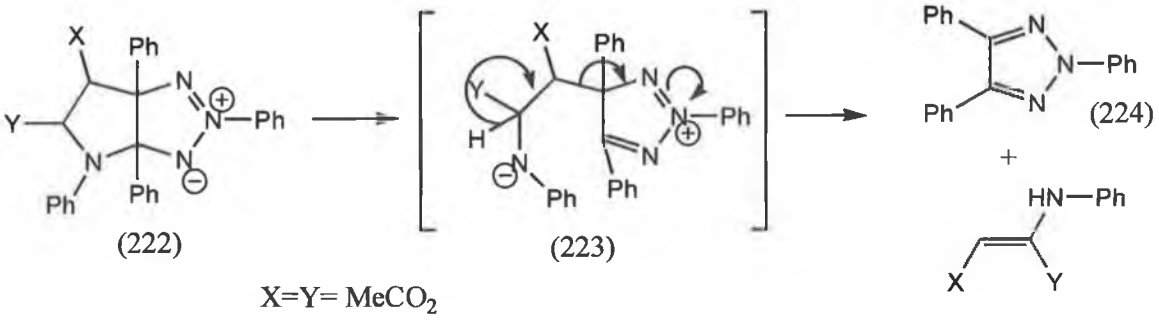
This research group has shown that depending on the bridgehead substituents and also whether saturation/unsaturation occurs between the C5–C6 bond, this can greatly alter the outcome of products when these cycloadducts are thermally or photochemically reacted. The table below conveniently summarises the thermal rearrangements observed.

Brigdehead substituent	**C5-C6 Bond**	**Product**
Ph	Saturated	1,2,3-triazole **(224)**.
Me	Saturated	No reaction.
Ph	Unsaturated	1,2,3-triazine **(225)**.
Me	Unsaturated	1,2,3-triazine **(225)**.

Table 3.1 *Thermal rearrangement products of 1,3-dipolar cycloadducts.*

Thermolysis of **(222)** in refluxing toluene results in a high yield route to the 2,4,5-triphenyl-1,2,3- triazole **(224)** which is effected by an initial cleavage of the C3a–N4

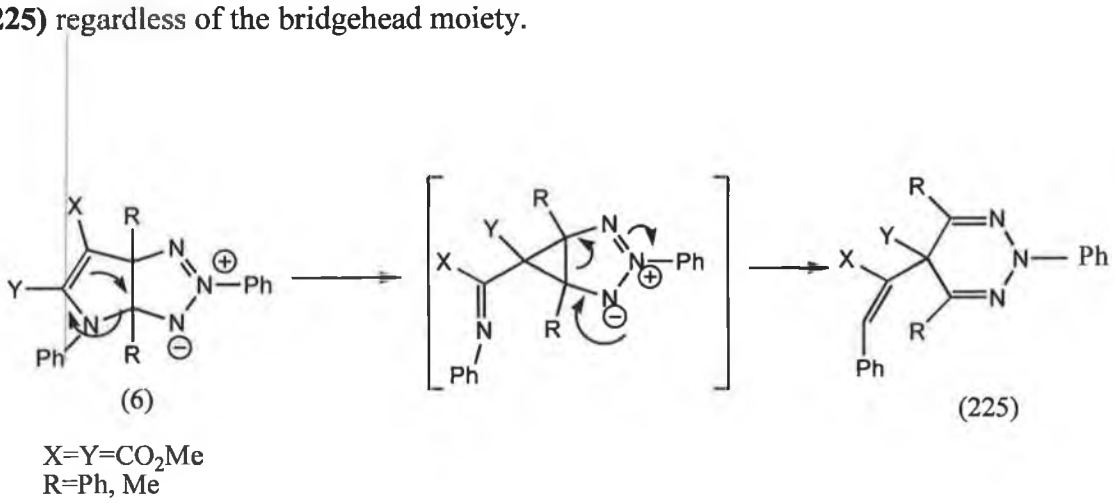
bond to afford the intermediate **(223)** which then further fragments to the triazole **(224)**.



Scheme 3.3 *Thermal transformations of substituted hexahydropyrrolo[2,3-d]-1,2,3-triazoles.*

When 3a,6a-dimethyl analogues where put under similar conditions no reaction resulted. The substitution to the phenyl group may result in weakening of the C3a–N4 bond making it more prone to heterolysis.

Unsaturation of the C5–C6 bond always led to the 5,5-disubstituted 1,2,3- triazine **(225)** regardless of the bridgehead moiety.



Scheme 3.4 *Thermal transformations of substituted tetrahydropyrrolo[2,3-d]-1,2,3-triazoles.*

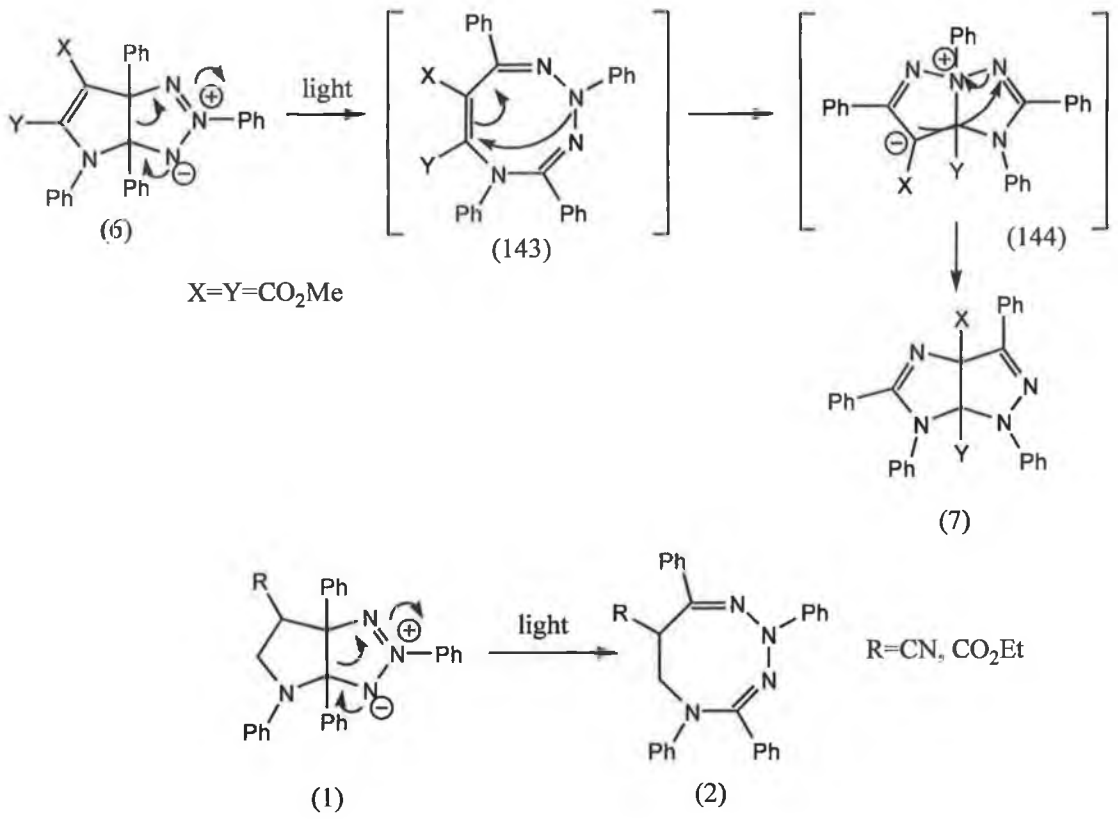
The mechanism proposed involves an initial 1,3-sigmatropic rearrangement to yield a highly strained cyclopropane intermediate which undergoes a disrotatory outward ring expansion to give the triazine **(225)**.[98]

Photochemical rearrangements of the pyrrolo[2,3-d] triazole systems also vary greatly with unsaturation/saturation between the C5–C6 bond and varying bridgehead substituents. The products recovered are shown in the table below.

Bridgehead Substituent	**C5-C6 Bond**	**Product**
Ph	Saturated	1,2,3,5-tetrazocine **(2)**.
Ph	Unsaturated	Imidazo[4,5c]pyrazole **(7)**.
Me	Saturated	Pyrrolo[3,2-b]indole **(234)**.
Me	Unsaturated	Pyrrole **(236)** .

Table 3.2 *Photochemical rearrangement products of 1,3-dipolar cycloadducts.*

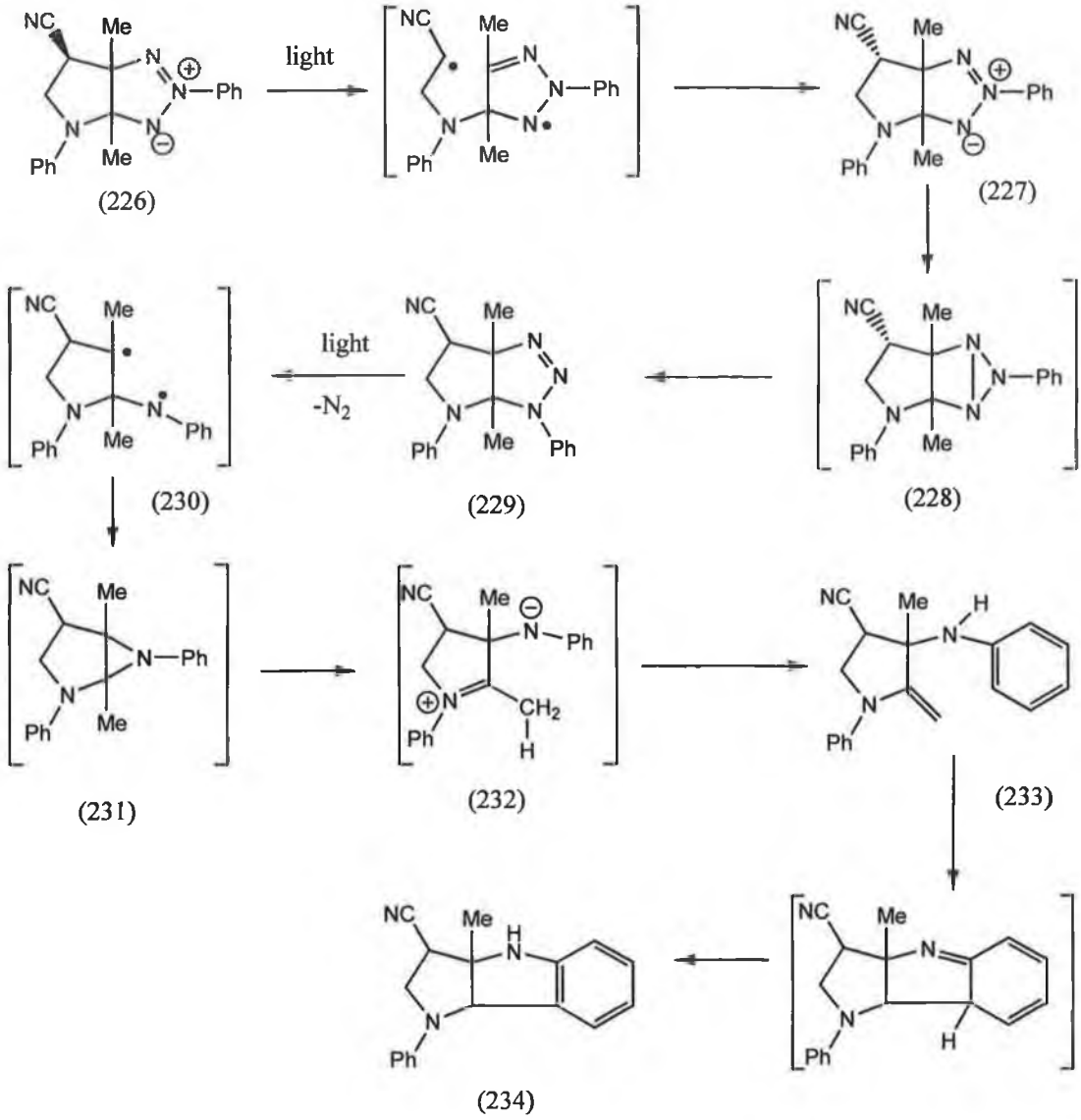
Both unsaturated/saturated compounds containing an aryl substituted bridgehead carbon group undergo cleavage of the C3a–C6a bond which lead to the formation of the 1,2,3,5-tetrazocines **(2)** and **(143)**. However where unsaturation is involved, the tetrazocine **(143)** formed is only intermediate. A transannular ring contraction to the imadazo-[4,5-c]-pyrazole **(144)** follows with a 1,4-sigmatropic rearrangement involving N–N cleavage and C–N formation. Initial ring contraction can be explained by FMO calculations in terms of the substantial resonance stabilisation gained.[5] Similar tetrazocines have been shown to contract to the more stable 10π systems such as the tetrazopentalenes previously discussed.



Scheme 3.5 *Photorearrangement of substituted tetrahydropyrrolo[2,3-d]-1,2,3-triazoles and hexahydropyrrolo[2,3-d]-1,2,3-triazoles.*

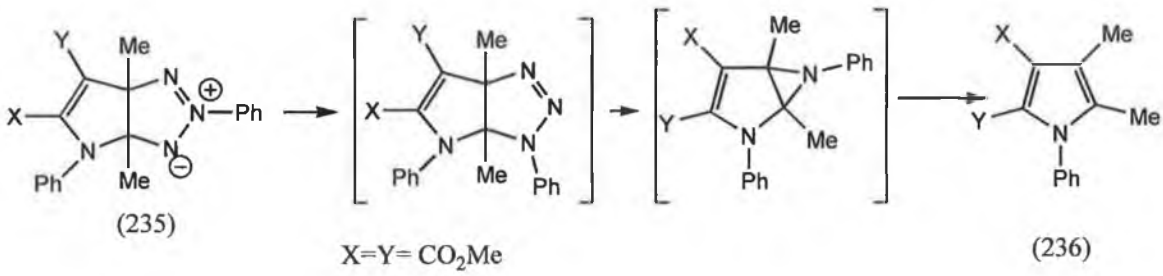
Irradiation of saturated methyl bridgehead substituents results in the formation of a pyrrolo-[3,2-6]-indole **(234)** whose mechanism is outlined below.[98] Initially a photoepimerisation of the exoproduct **(226)** results in an initial cleavage of the C5–C6 bond forming the endo product **(227)**. Isolation of **(229)** was confirmed by X-ray diffraction analysis and can be explained through the triaziridine intermediate **(228)** which undergoes a tandem ring opening and 1,3-sigmatropic rearrangement of the phenyl group. The intermediacy of compounds **(230)** and **(231)** are believed to involve the photochemical extrusion of nitrogen followed by cyclisation of the diradical. The aziridine **(231)** in turn relieves strain by opening, which finally rearranges through the intermediate **(232)** to yield the isolated structure **(233)**, again

verified by X-ray analysis. Finally **(234)** results from a 5-exo-trig ring closure and constitutes a new pathway to the benzodiazapentalene system



Scheme 3.6 *Photorearrangement of substituted hexahydropyrrolo[2,3-d]-1,2,3-triazoles with methyl bridgehead substituents.*

Photochemical transformations of unsaturated C5–C6 bonds with methyl bridgehead substituents yields the substituted pyrrole **(236)** and is thought to occur through a somewhat similar mechanism as above with the resulting loss of nitrogen, followed by subsequent loss of the aryl nitrene as the driving force in the formation of the aromatic five membered ring **(236)**.



Scheme 3.7 *Photorearrangement of substituted tetrahydropyrrolo[2,3-d]-1,2,3-triazoles with methyl bridgehead substituents.*

3.2. Results and discussion

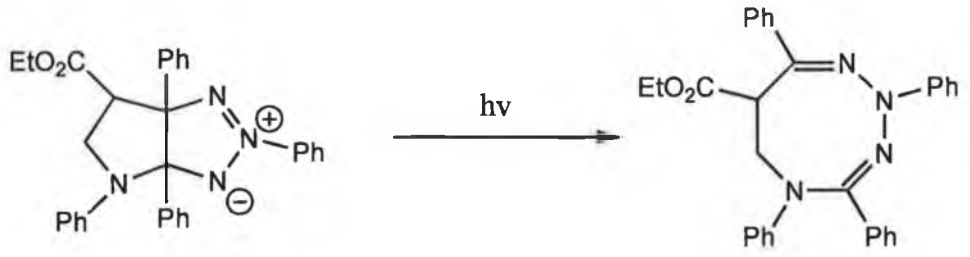
Our work to date stems from previous success already achieved by this research group in the novel synthesis of the 1,2,3,5-tetrazocine **(2)**. Photolysis of 3a,6a-diphenylhexahydro-pyrrol[2,3-d] triazoles led to the eight-membered heterocycles through an electrocyclic outward disrotatory rotation of the p-orbitals of the bridgehead carbons.

The synthetic step was carried out by two methods. Photolysis of the cycloadduct in dry dichlormethane using a 450 W mercury arc lamp for 30 minutes or allowing a stirred solution to stand in direct sunlight. Both methods were inefficient, the lamp being low yielding through generation of a complex mixture of products and the latter method having impractical reaction times (up to 1 month), however affording high yields. And so our aim here was to develop a more efficient method for effecting the ring opening process. This would allow for facile examination and isolation of secondary products formed. This method would then be hopefully applied to a host of differing substituted pyrrolo[2,3-d] projects with the aim of generating a range of tetrazocines.

3.2.1. Development of a general photochemical method

Chemical bonds have certain energies associated with them as does light of a particular intensity. If light of correct wavelength with an energy is incident on the molecule, then the high energy state orbitals resulting may rehybridise so as to have a lower overall energy state which may result in some molecular rearrangement i.e. the making and breaking of bonds.[99,100] In our systems, it is thought that the C6a–C3a bond undergoes photolytic cleavage by rehybridisation of the initial sp^3 carbons to sp^2 carbons by a disrotatory rotation of the p-orbitals upon irradiation.

Photochemical reactions are very often capricious and many parameters can influence the outcome of a reaction such as solvent choice, purity of starting material and the light source to name but a few. It was of interest to find optimum conditions for the ring opening process of **(1b)** to afford the tetrazocine **(2b)**.



(1b) (2b)

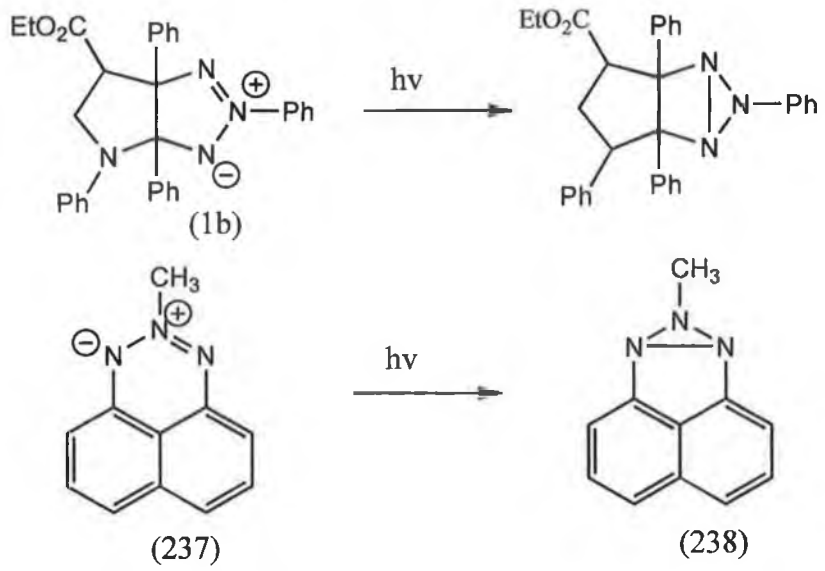
Scheme 3.8 *Photorearrangement of a substituted hexahydropyrrolo[2,3-d]-1,2,3-triazole.*

UV spectra of the substrate indicates the region of the UV absorption spectra the molecule is absorbing. In our case a broad absorption band was observed between 320-450 nm with a more pronounced peak at 256 nm. This was to be expected as the compound was coloured and therefore absorbs in the visible region. Also important was the photoadduct **(2b)**, which was shown also to be photoactive within this region (340-430nm).

The solvents, acetone and DCM, were chosen to mediate the photolysis mainly due to the good solubility of **(1)** in these solvents at room temperature. Also acetone and dichloromethane do not absorb above 330 nm and 270 nm respectively. In early runs using a 450W mercury low, pressure lamp, it was observed that a more complex reaction mixture was observed when acetone was employed. This could be rationalised in terms of intermediates such as biradicals or zwitterions being more readily stabilised by the more polar acetone solvent sphere.

One of the previous methods described how a stirred solution of **(1)** was left in direct sunlight in a normal round bottom flask in dry dichloromethane solution yielding the tetrazocine over a month. Glass of this type does not allow light of wavelength lower than 340 nm to pass through it. The UV region of the sun's emission spectra at the earths surface consists of 3% UV-A (315-380nm) and 5% UV-B (280-315nm) where the visible region ranges from 385-800nm. This effectively rules out UV-B absorptions. Our UV spectra of **(1)**, shows the molecule to absorb between 320-450nm. Therefore the compound
can only be absorbing between 340-450nm.

Our deduced range would then explain ideally the observed results when the 450 W mercury lamp was used. The lamp has a very large UV-visible range, typically between 180-600 nm in which many other transformations could occur other then the C–C cleavage. The lamp was also surrounded by a completely UV transparent quartz cover and the reaction filtered by a pyrex reaction vessel which itself only allows light of wavelength higher than 300 nm through which may have been enough to yield the complex reaction mixture when using this method. One possible photorearrangement is outlined below of which there is precedence.[101]



Scheme 3.9 *Photorearrangement with triaziridine formation.*

In an attempt to reduce the number of photoproducts, out attention was drawn to solid-state photochemistry.[102] Here the substrate is simply irradiated with light in the solid state. The advantage of this procedure is to limit the number of transformations resulting as there is no solvent cage to mediate such rearrangements. However low yields are inherent. This method proved somewhat successful giving a reaction mixture containing only 2,4,5 tripheny-1,2,3-triazole **(224)**, unreacted starting product **(1)** and the tetrazocine **(2)** in 40% yield in 50 min using the 450 W mercury lamp. However this reaction was still relatively unclean and it was difficult to separate the products and so an alternative light source was sought.

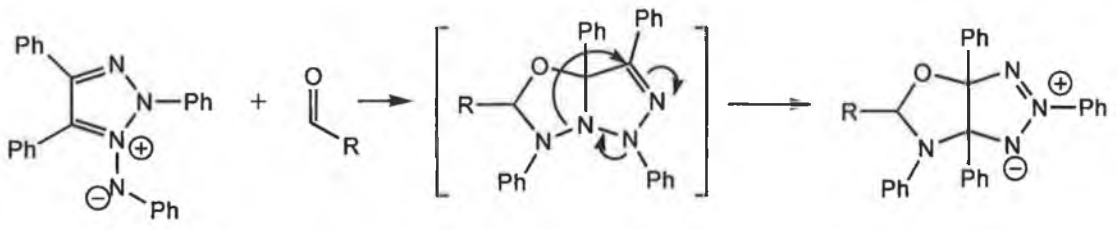
Normal household light-bulbs emit visible radiation. A 250 W Tungsten bulb was incident on a stirred solution of **(1)** in degassed, dry dichloromethane for 3 hours. Removal of the solvent by evaporation yielded a single product in quantitative yield which was confirmed by NMR as being the tetrazocine **(2)**.

In conclusion a very mild photolytic method has been developed which affords the tetrazocine in excellent yields. More importantly, the absorption range of our systems to light irradiation has been optimised significantly. In effect, we have found a very

useful tool, which affords tetrazocines in a very quick and simple manner. We need now only manipulate the dipolarophile and functionality to gain a wide selection of tetrazocines with varying properties.

3.2.2. Photolysis of the substituted bicyclic oxazolo-[4,5-d]-1,2,3-triazole System.

Our aim here was to obtain a novel oxalo-tetrazocine through photolysis of the bicyclic oxazolo-[4,5-d]-1,2,3-triazole system. The synthetic route to the oxazolo[4,5-d]-1,2,3 triazole **(239)** system involves cycloaddition of the 1,3-dipole with various aldehydes and ketones. Butler has extensively described such procedures. Our dipolarophiles of choice were benzaldehyde and acetaldehyde owing to their high yielding cycloadditions and also the relative inertness of such substituents to photolysis.[103] More polar functionalities may undergo heterolysis or homolysis more easily. The aim here was to simplify the reaction mixture upon photolysis.



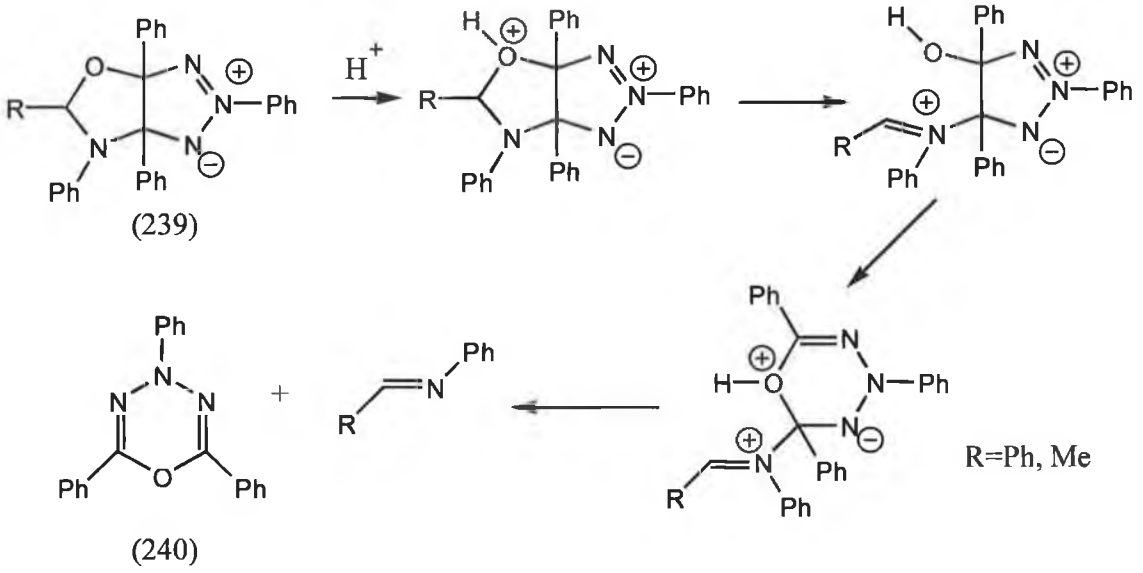
(3) R=Me,Ph (239a), R=Me (239b), R=Ph

Scheme 3.10 *Cycloaddition of the 1,3-dipole with ketones to give oxazolo[4,5-d]-1,2,3 triazoles.*

A solution of the 1,2,3-triazolium-*N*-imide **(3)** was heated in xylene with either acetaldehyde or benzaldehyde for 2 hours at 70^{0}C to yield whitish coloured powders. The cycloadduct was then dried, added to dichloromethane, flushed with dry nitrogen and the photolysis flask stoppered. After 2 hours of photolysis with the 250 W tungsten lamp, the solution was observed to undergo a yellow to red colour change. Following the reaction by TLC, the generation of three new products was observed. However, subsequent attempts to separate the products formed by flash chromatography only ever led to one red coloured product being isolated and 2,4,5-triphenyl-1,2,3-triazole **(224)**. The disappearance of the third product from the

column prompted the consideration that it was acid sensitive to the silica used and underwent some protonation rearrangement to yield the red product or the triazole.

NMR and IR studies of the red crystalline product gave spectra which were consistent with Butler's 1,3,4,5-oxatriazine systems **(240)** which were made in high yield from protonation of the oxalo[4,5-d]-1,2,3-triazoles **(239)** with glacial acetic acid in refluxing ethanol.[104]

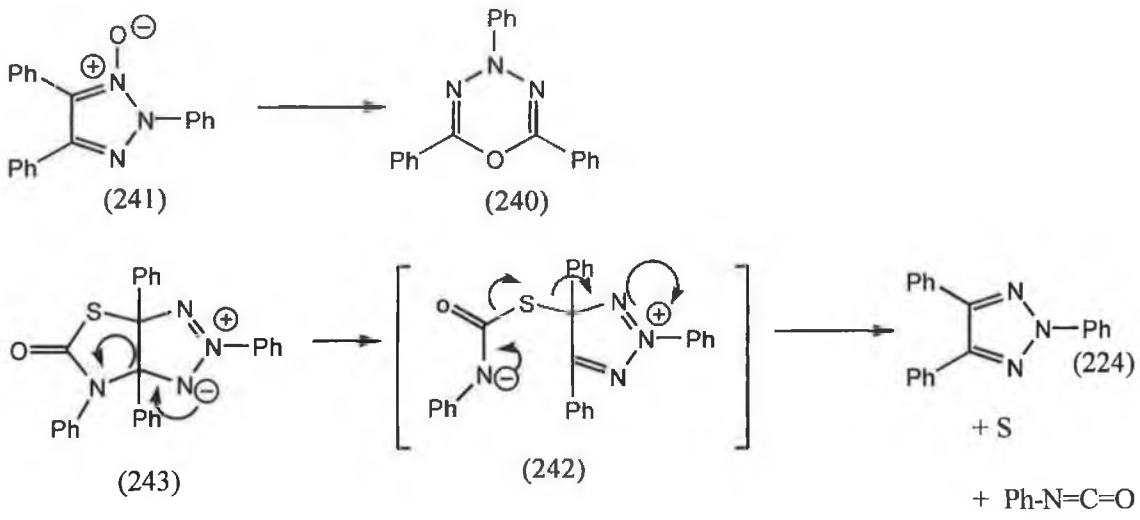


Scheme 3.11 *Reaction of oxazolo[4,5-d]-1,2,3 triazoles with acid to give 1,3,4,5-oxatriazine systems.*

A switch to alumina with dry solvent again gave the same results. Two-dimensional chromatography under dry nitrogen also conclusively showed that the oxatriazine came from a reactive intermediate. In order to rule out any possible protonation effects of the solvent, an experiment was set up in which the oxazolo-[4,5-d]-1,2,3-triazole **(239)** was photolysed with the 450 W mercury low pressure lamp as a solid under dry nitrogen. Again

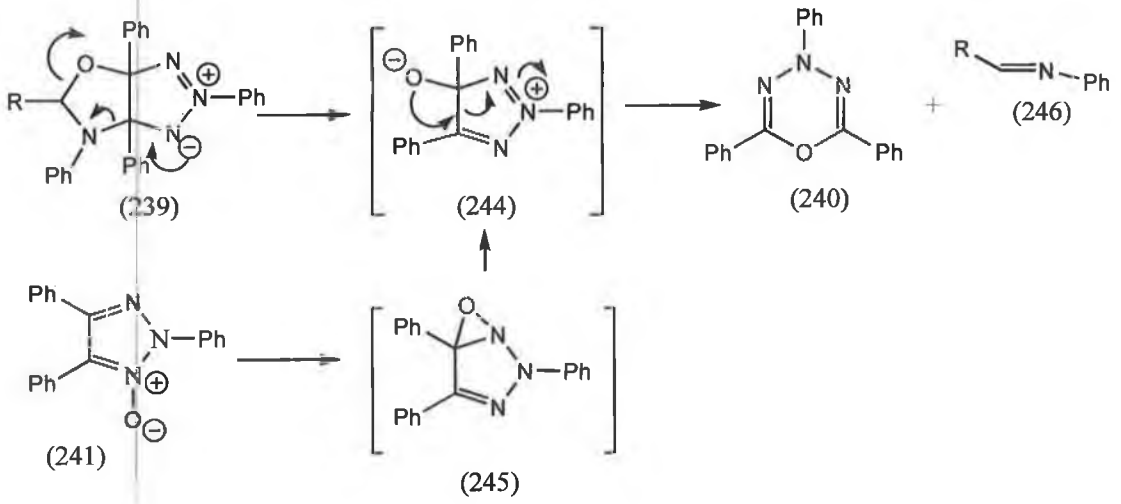
the oxatriazine **(240)** was formed but in somewhat lower yields which is to be expected as there is no solvent cage to mediate the rearrangement.

From the preceding evidence, it is perhaps conceivable that formation of the oxatriazine occurs through an alternative mechanism to that offered by Butler. In order to rationalise a potential mechanism, our attention was drawn to two previous publications. Gainsford describes the high yield route to the oxatriazine **(240)** through photolysis of 2,4,5-triphenyl-[2H,1,3,3]triazole-*N*-oxide **(241)**.[105] Additionally relevant is the photolysis by Sukumaran of a thio analogue **(243)** of our compound in question. The formation of 2,4,5-triphenyl-1,2,3-triazole **(224)** is believed to result from initial cleavage of the C3a–C4 bond.[106]



Scheme 3.12 *High yield route to the oxatriazine (240) through photolysis of 2,4,5-triphenyl-[2H,1,3,3]triazole-N-oxide. Photolytic formation of (224) from (243) with initial C3a-C4 bond cleavage.*

Based on the above observations, it seems reasonable to assume that cleavage of the C3a–N4 bond in our oxalotriazole **(239)** could occur with resulting loss of the imine giving the active intermediate **(244)** which undergoes cyclisation to form the **(240)**. The intermediate **(244)** complements Gainsford's proposed mechanism for the formation of **(240)** from **(241)**.



Scheme 3.13 *Proposed mechanism for oxatriazine formation through photolysis of oxalo[4,5-d]-1,2,3 triazoles.*

From the proposed mechanism, the imine or the highly reactive 2,4,5-triphenyl-[2H-1,2,3]triazole-*N*-oxide **(176)** were never observed and so as of yet, this mechanism must be considered provisional. However a new photolytic method to the oxatrizine ring system in moderate yields has been developed.

3.3. Lewis Acid Catalysis of 1,3-dipole Cycloaddition

The use of Lewis acid catalysis for Diels-Alder reactions is advantageous not only for it's ability to increase the reaction rate but also the stereo- and regioselectivity associated with it in the cycloaddition process. There are many excellent reviews in which the solvent effects, the strength of Lewis acid and donor atoms are all discussed. Satchell & Satchell have given a qualitative model of Lewis acid strength in the following order.[107]

$$\mathbf{BX_3 > AlX_3 > FeX_3 > GaX_3 > SbX_5 > InX_3 > SnX_4 > AsX_5 > ZnX_2 > HgX_2.}$$

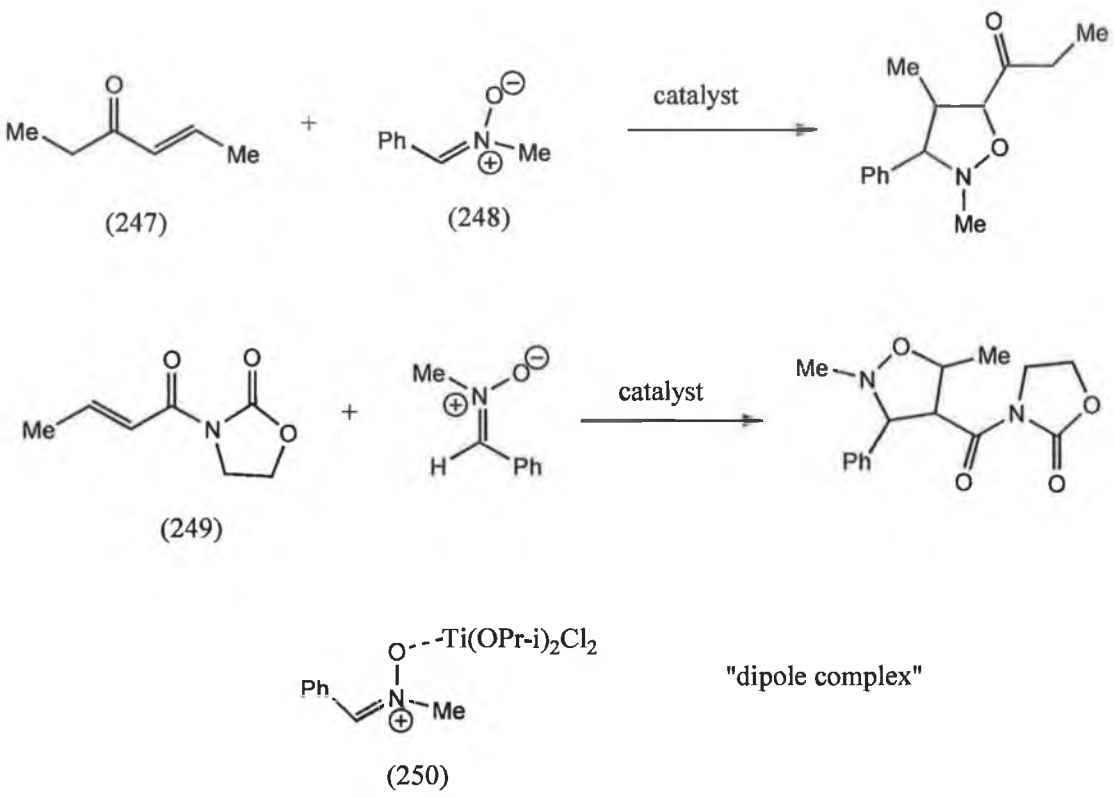
Figure 3.3 *Lewis acid strength.*

These are the strongest Lewis acids available. In general the Lewis acid will accept electron pairs from elements of the oxygen, nitrogen and halogen groups (F<Cl<Br<I), which have non bonding electron pairs available for donation. Unsaturated compounds can also act as bases owing to their π-electron systems. Bases can therefore be classed as n- or π donors, *n*-donors being more common and oxygen being the most common n-donor.

Butler has shown that reactions of 1,2,3-triazolium imides with various dipolarophiles to be a dipole-HOMO controlled process. Also the second order rate constants were insensitive to solvent polarity. Therefore electron-withdrawing groups on the dipolarophile should result in a decrease in LUMO energy in the absence of steric effects and thereby speed up the reaction rate due to a decrease in the HOMO/LUMO energy separation. Complexation of a Lewis acid to the dipolarophile serves only to further decrease the LUMO energy by creating a super electron withdrawing group.

Kanemasa designed the first new electron-deficient olefinic dipolarophiles that have a chelate ligand structure.[108] Dichlorodiisopropoxytitanium was found to accelerate the cycloadditions of nitrones **(248)** to the mono dentate enone **(247)** in some cases. However in many runs, it was clear that the "dipole complex" **(250)** was staggering

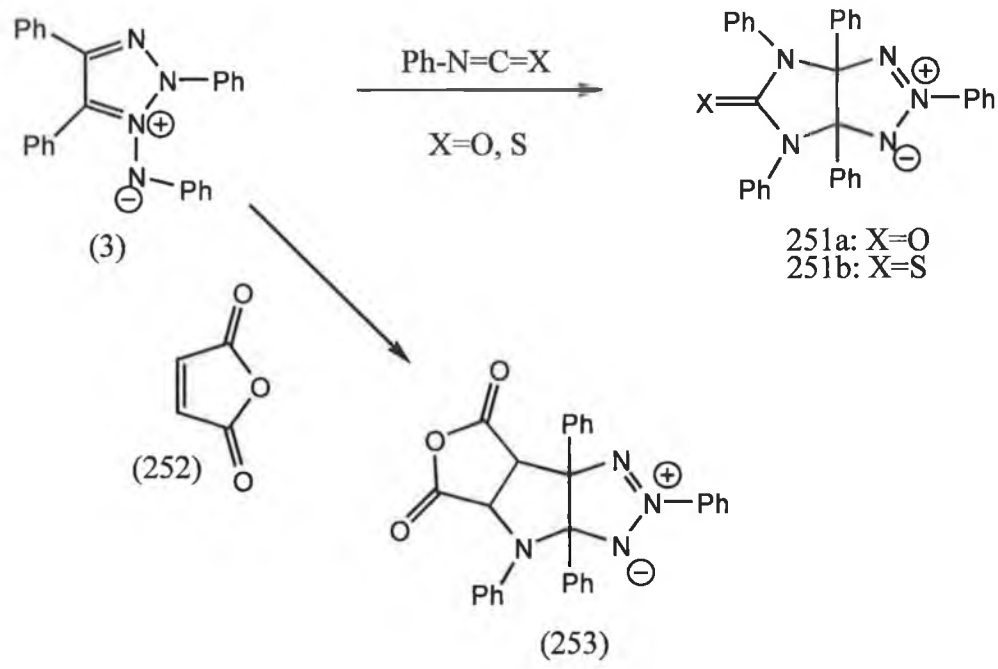
cycloaddition. The same catalyst was also employed some years later in the cycloaddition of **(249)** to benzylidenephenylamine-*N*-oxide.[109]



Scheme 3.14 *Dichlorodiisopropoxytitanium accelerating rates of cycloaddition of nitrones.*

FMO calculations on these reactions showed that complexation of the Lewis acid to the dipole, in this case a nitrone, served to lower the HOMO and LUMO energies of the nitrone-metal complex compared to that of the free nitrone. The "dipolarophile-complex" also reduces in LUMO energy and this should in theory speed up the reaction rate as the HOMO-LUMO energy gap has decreased. However energy calculations on a model 1,3-dipolar addition between benzylidene methylamine and styrene also revealed an increase in the transition state energy of the 1,3-dipolar cycloaddition compared to when the reaction was carried out in the absence of the Lewis acid. In short the authors propose that an effective catalysed cycloaddtion can only be achieved when there is no "dipole-complex".

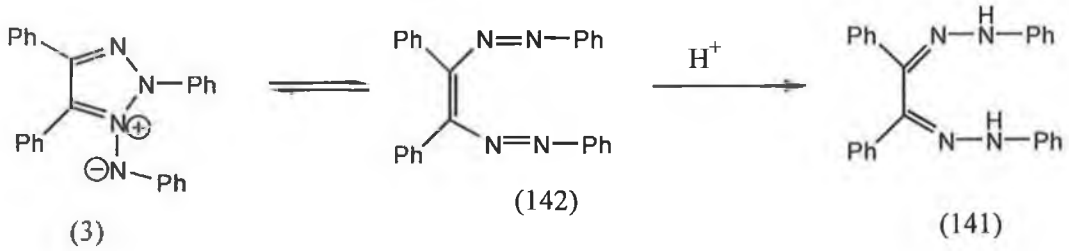
Our aim here was to find a suitable catalyst that would not complex with the dipole but with a dipolarophile containing an imino group which might ultimately lead to a pentazocine by UV irradiation of the cycloadduct. Cycloaddition to our 1,3-dipole has already been achieved by Sukumaran using phenyliso- and thiocyanate and the photochemistry of these cycloadducts was investigated.[110]



Scheme 3.15 *Cycloaddition of 1,3-dipoles with phenylisocyanates and maleic anhydride.*

It was first decided to take a known reaction, measure the reaction kinetics and then apply the Lewis acid for comparison. Maleic anhydride and the 1,3-dipole were shown to undergo 80% conversion to the cycloadduct **(253)** in 30 minutes. Lewis acid experiments were carried out by trying the strongest Lewis acid and descending the acid strength table. The general procedure involved complexing the Lewis acid to the dipolarophile and then adding the dipole solution dropwise under anhydrous conditions.

Reaction of solid aluminium(III)chloride resulted in isolation of a yellow compound in a matter of seconds which was shown to be the hydrazone **(141)**. Clearly trace amounts of water on reaction produced HCl which protonated the 1,3-dipole. This proved to be very problematic with most Lewis acids used, the 1,3-dipole being super acid sensitive requiring very little HCl.



Scheme 3.16 *Protonation of the 1,3-dipole to reform the hydrazone.*

Eventually a method was found in which anhydrous aluminium(III)chloride in nitrobenzene solution could be used. However the Lewis acid was found to complex immediately with the 1,3-dipole even when pre-complexed with maleic anhydride on addition. This was observed by TLC by complete disappearance of the 1,3-dipole on addition to the dipolarophile-Lewis acid solution. On addition of water, the 1,3-dipole partially reappeared along with **(141)**. The dipole is obviously a more effective base than the dipolarophile which has three potential complexation sites. Other diplarophiles were also tried but all yielded similar results. A list of dipolarophiles and Lewis acids tried are listed below.

Lewis Acids	**Dipolarophiles**
Aluminium(III)chloride Gallium(III)chloride Titanium isopropoxide Boron(III)chloride Tin(IV)chloride Zinc(II)chloride Silver iodide Silver nitrate Iron(III)chloride.	Ethyl acrylate Acrylonitrile. Maleic anhydride

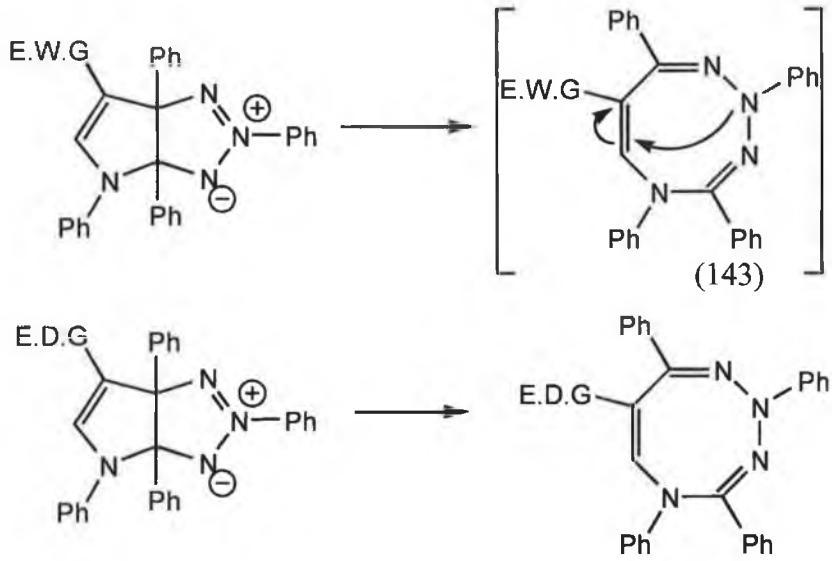
Table 3.3 *List of Lewis acids tried to catalyse the 1,3-dipole cycloaddition and dipolarophiles used.*

Initial work in this area shows the regioselectivity problem associated with the Lewis acids utilised. Unfortunately due to the lack of literature available, it was felt that further investigation was not prudent in terms of time and effort that would be necessary to develop or find a suitable catalyst.

3.4. Exploration of C5-C6 electron-donating substituents of 2,3a,4,6a-tetraphenyl-3,3a,4,6a-tetrahydropyrrolo[2,3-d]-1,2,3-triazoles

Butler has postulated the intermediacy of the 1,2,3,5-tetrazocine **(143)** through photolysis of various substituted 2,3a,4,6a-tetraphenyl-3,3a,4,6a-tetrahydropyrrolo[2,3-d]-1,2,3-triazoles **(6)** giving ultimately imidazo[4,5-c] pyrazoles.[5] The transitory tetrazocine is believed to undergo an initial transannular ring contraction. Attack at the unsaturated C-6 atom by N-2 is most likely due to the presence of electron-withdrawing groups on C5 making it prone to nucleophilic attack.

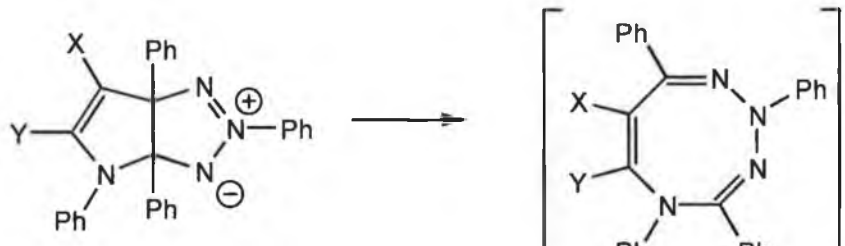
It was of interest to examine whether electron-donating groups, or simply the absence of substitution at C5 or C6 would result in the isolation of a dihydro-1,2,3,5-tetrazocine by making the double bond more electron rich and thus less attractive to nucleophilic attack.



Scheme 3.17 *Proposed photorearrangement of a substituted tetrahydropyrrolo[2,3-d]-1,2,3-triazole with a C6 E.D.G with tetrazocine formation in contrast to ring contraction of (143).*

3.4.1. Electron-rich Substituents

It is apparent that the cycloaddition reaction is particularly efficient when the dipolarophile has electron-withdrawing groups. There exists no reference in the literature on these systems where cycloaddition is effected by the use of electron-donating groups regardless of whether it contains a vinylic or acetylinic moiety. To attempt such an experiment in our view would prove time-consuming and non-viable based on kinetic studies, which show the dipole to be HOMO-controlled. A more practical approach would be the manipulation of the alkyne substituent after cycloaddition. Of the acetylenic dipolarophiles that permit cycloaddition with the 1,3-dipole, all contain an ester group. The most obvious procedure for conversion of an ester group to an electron-donating group would involve reduction of the ester. However employment of $LiBH_4$, $NaBH_4$ or $LiAlH_4$ previously by this research group did not facilitate the desired reaction. Instead, a more competitive reduction of the C5–C6 double bond was observed furnishing the hexahydro analogue (1a). A reagent was therefore sought that would selectively differentiate between the two competing functional groups.



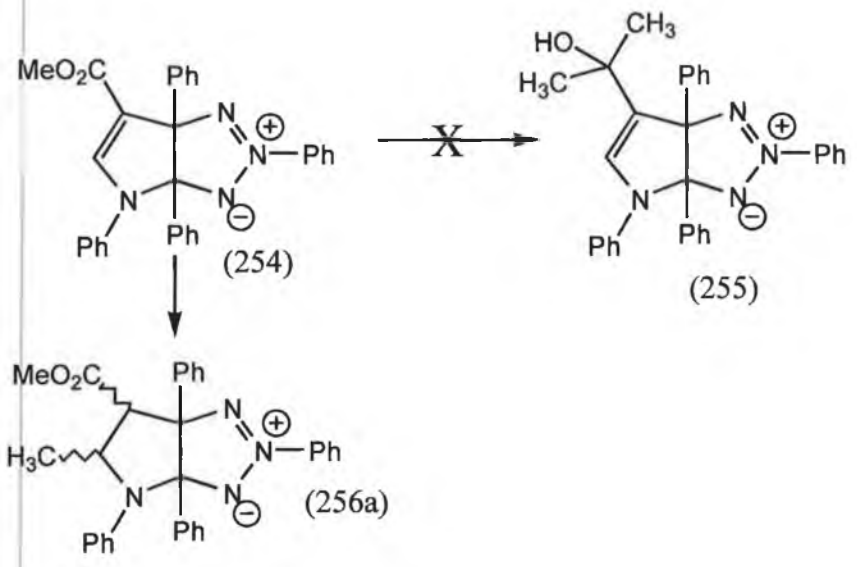
6a X=CO_2Me, Y=H
6b X=CO_2Me, Y= CO_2Me

Scheme 3.18 *Photorearrangement of a substituted tetrahydropyrrolo[2,3-d]-1,2,3-triazoles.*

Grignard reagents are the result of reaction between magnesium with organic halides in ether or THF. The magesium-carbon is highly polar covalent making the carbon atom nucleophilic and it is sometimes considered a carbanion. Esters react with two

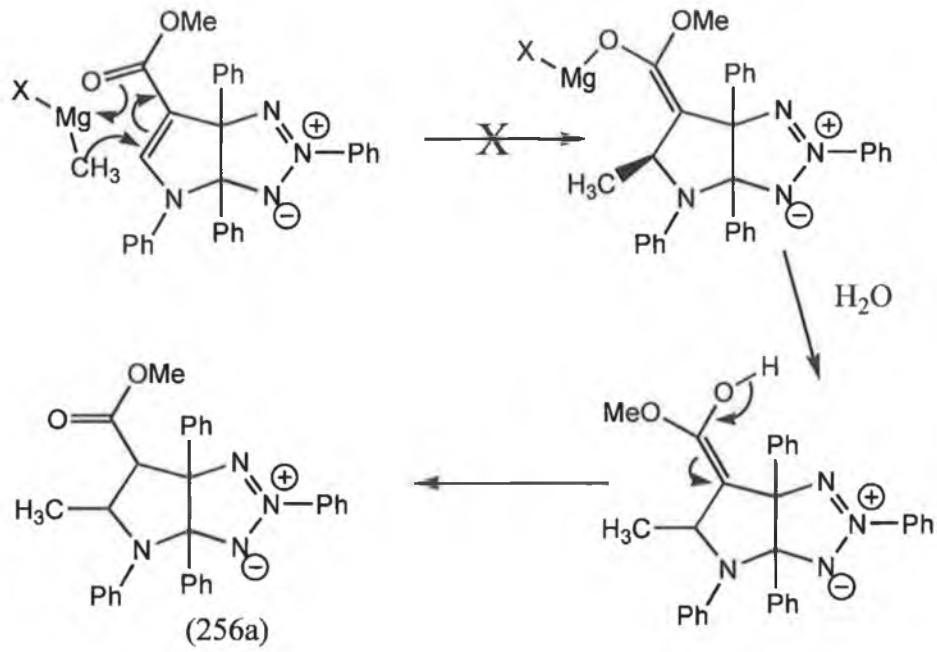
equivalents of Grignard reagent to yield tertiary alcohols readily in excellent yield. However Grignard reagents exhibit no marked reaction with alkenes in general.

Reaction of the 1,3-dipole with methyl propiolate gave **(254)** in high yield. The cycloadduct was added to a stirred solution of anhydrous methyl magnesium bromide in dry diethyl ether/THF. Work-up of the reaction gave a yellow oil in high yield. A doublet integrating for one proton at 4.47 ppm and a quintet at 5.12 ppm integrating for one was proton observed for the unknown oil. However the methyl ester singlet remained intact in the product. Both signals at 4.47 ppm and 1.34 ppm were shown to have common coupling constants with the quintet at 5.12 ppm. All phenyl signals were accounted for. Consequently the isolated oil must have structure in accordance with **(256a)** based on the splitting pattern.



Scheme 3.19 *Reaction a substituted tetrahydropyrrolo[2,3-d]-1,2,3-triazole with a Grignard reagent to give addition across the double bond.*

It appears that **(256a)** has been formed through addition of the Grignard reagent across the double bond. This selectivity maybe attributed to the electron-withdrawing capacity of the ester group with resultant double bond polarisation. The mechanism of such a reaction is not well understood. However it has been suggested that addition may occur through the cyclic mechanism shown below.[111]

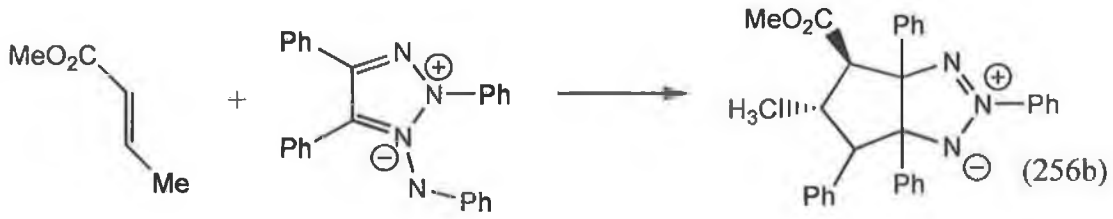


Scheme 3.20 *Grignard addition reaction with an ester through a proposed cyclic mechanism.*

The *cis*-configuration of the C5-methyl and C6-ester groups are rationalised when one compares the C5-H/C6-H vicinal coupling constants of **(256a)** with **(256b)**. **(256b)** is formed through reaction of the 1,3-dipole with methyl crotonate which is a *trans* α,β-unsaturated ester. Since the 1,3-dipole has been shown to be remarkably regio- and stereoselective, one would expect the *trans*-geometry to be retained in the cycloadduct.

Sukumaran has calculated the coupling constants of **(256b)** and other *trans*-analogues to range between 5 and 6.5 Hz with dihedral angles lying between 95^0 and 105^0.[112] In the Karplus relationship, protons that are located *cis*- to each other (torsional angle 0^0) have a greater coupling constant than those situated *trans*-(torsional angle 120^0) in a corresponding chemical environment. The coupling constant of C6 as obtained by us for **256(a)** had a value of 8 Hz showing the torsional angle between neighbouring protons to be minimal when viewed along a Newman projection. The proposed *cis*-conformation is further supported by the C6-H chemical shift at 4.44 ppm which is compared to the trans analogue **(256b)** at 3.36 ppm. The C6-H would now be *cis*- relative to the C6a bridgehead phenyl group. Due to the

proximity of both groups, the C6-H would be shifted downfield due to shielding effects offered by phenyl ring currents.



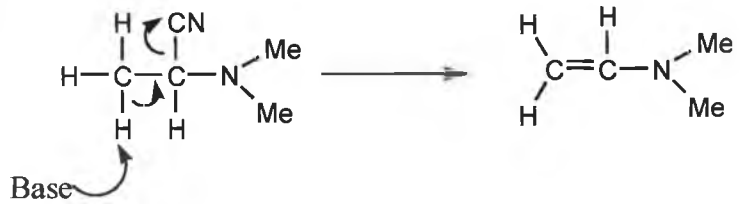
(256b)

Scheme 3.21 *Reaction of the 1,3-dipole with methyl crotonate to give trans-geometry.*

3.5. Exploration of non C5–C6 substituted 2,3a,4,6a-tetraphenyl-3,3a,4,6a-tetrahydropyrrolo[2,3-d]-1,2,3-triazoles

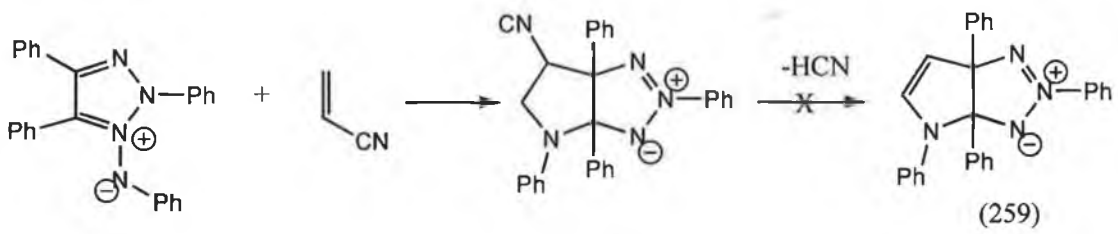
It is perhaps evident that the most direct route to the title compounds involves cycloaddition of the 1,3-dipole with acetylene. As anticipated, acetylene is a poor dipolarophile and is particularly unreactive in most [4+2]-cycloadditions at normal conditions, which makes its application a serious drawback. Additionally the safety hazards in handling gaseous acetylene at high temperatures and pressures that are normally required must be weighed up against other options.

The method of insertion of an ethylenic bridge by cycloaddition reactions has been circumvented by the use of acetylene equivalents. In general, the acetylene synthon is ethylenic. Unsaturation is conveniently introduced by the loss of substituents from the parent alkene after cycloaddition. An overview of the available methods shows decarboxylation to be the most commonly employed.[113] However the more recent role of sulphur functionalities in activating and directing olefins in cycloaddition has also found widespread usage.[114] In order to synthesise the desired non-substituted C5 imadazo[4,5-d]pyrrazole, it was decided to approach this through readily available precursors that were well documented. The starting product of choice was the cycloadduct of the reaction of the 1,3-dipole **(3)** with acrylonitrile. Ahlbrecht has described an effective method of preparing enamines **(258)** from α-cyano tertiary amines **(257)** by treatment with KOH or *t*-BuOK in boiling benzene or toluene.[115] The mechanism here involves removal of a β-hydrogen with base with simultaneous departure of the leaving group. This β-elimination is an E2 mechanism.



(257) (258)

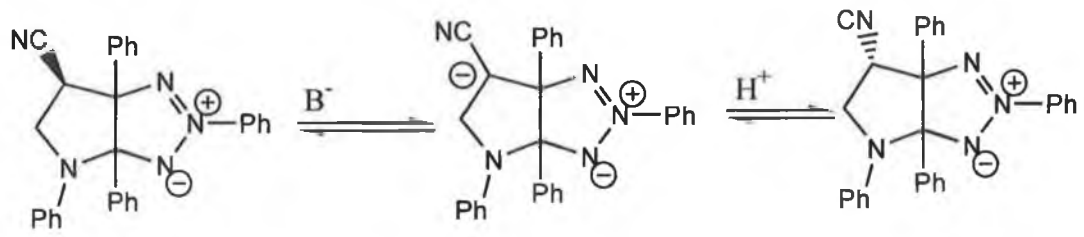
Scheme 3.22 *Base induced removal of a β-hydrogen from α-cyano tertiary amine.*



(3) (1a) (259)

Scheme 3.23 *Reaction of the 1,3-dipole with acrylonitrile and subsequent base catalysed dehydrocyanation.*

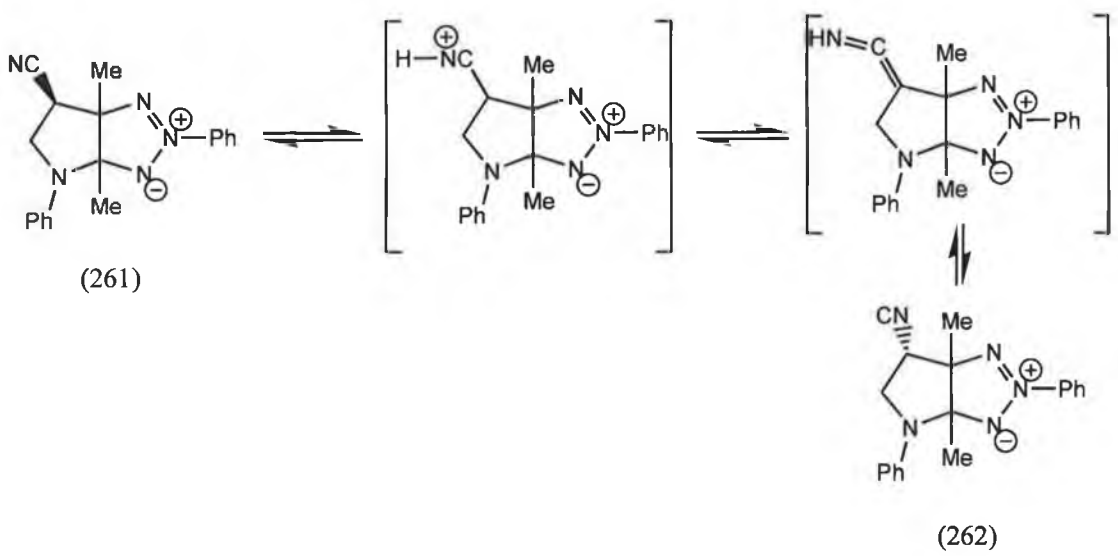
Reaction of the pyrolotriazole **(1a)** with KOH in refluxing toluene yielded no new product, no matter how long the mixture was left to react. Perhaps the base utilised was insufficiently strong to effect proton elimination. However employment of a molar equivalent of *t*-BuOK, a stronger base, under similar conditions yielded a single new major product. ^{13}C-NMR showed the compound to have an almost identical spectra with the starting product in terms of the number of carbons present. However a slight shift of the order of 1-2 ppm was observed for every carbon signal. Attempts to purely isolate this compound however were unsuccessful. Any attempt in isolating the unknown, resulted in it reverting slowly back to the starting product. It is believed that the pyrolotriazole **(1a)** has undergone a base catalysed epimerisation in which the cyano group has been converted to an *endo*-orientation **(260)**. A proposed mechanism for the transformation is shown below.



(1a) (260)

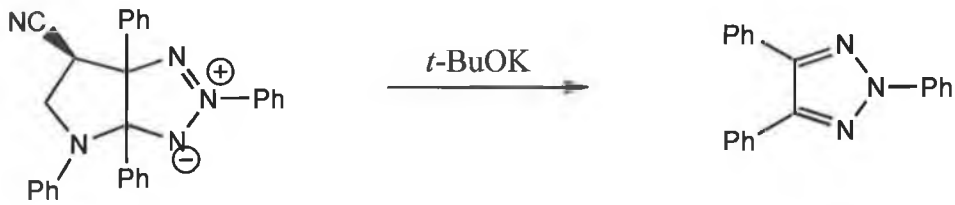
Scheme 3.24 *Base catalysed epimerisation of (1a).*

In light of similar epimerisations of these systems carried out earlier by this research group where the bridgehead substituents were methyl groups, it seems reasonable to suggest that such an *endo* to *exo* epimerisation is in fact occurring here. This research group has showed that compound **(261)** underwent an acid catalysed epimerisation to the *exo* isomer **(262)**.[98] However attempts at the base catalysed epimerisation was not observed when sodium hydrogen carbonate was refluxed for up to 10 days. Two reasons for this are proposed. Firstly, the base used was simply not strong enough in proton abstraction and also the bridgehead substituent effect which could stabilise more efficiently the ion intermediate formed in the mechanism offered.



(261) (262)

Scheme 3.25 *Proposed mechanism for observed epimerisation of (261).*

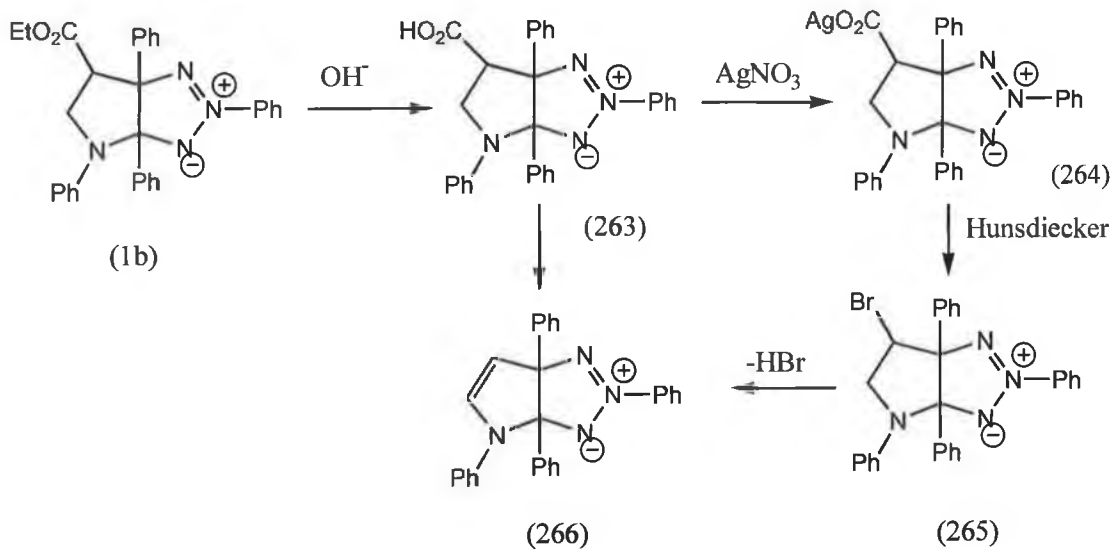


(1a) (224)

Scheme 3.26 *Base induced triazole formation from (1a)*

As an E2-mechanism is kinetically second order, first order in the substrate and first order in the base, it was thought that an excess of base would initially effect the endo-exo orientation but more importantly afford the dehydrocyanation process through a quicker rate of reaction. A two fold excess of t-BuOK was refluxed as in previous conditions and after some hours a new product was observed which on isolation in moderate yields was characterised as being 2,4,5-triphenyl-1,2,3-triazole **(224)**. This was verified by NMR comparison of 2,4,5-triphenyl-1,2,3-triazole which has already been produced through thermolysis of the 1,3-dipole **(3)**.

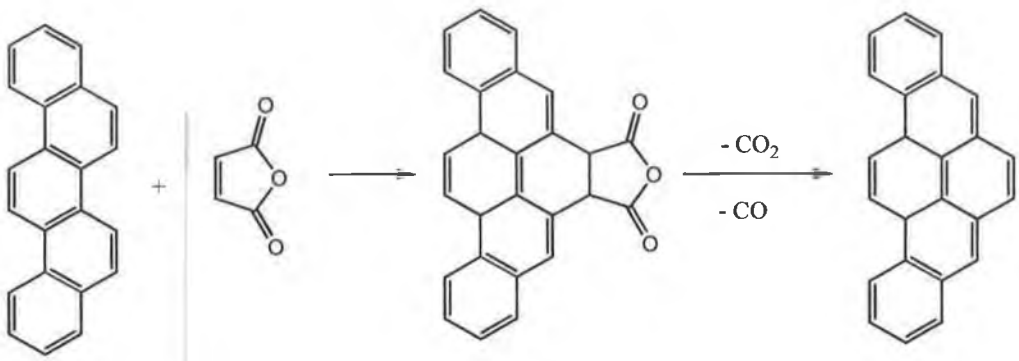
Unfortunately, it did not seem worthwhile to pursue this route any further as it appears that proton removal seems to be occurring at C6 more readily rather than at C5. Our attention turned to the pyrolotriazole **(1b)** which is made conveniently by the cycloaddition of the 1,3-dipole and ethyl acrylate. This compound could potentially provide two accessible routes to the desired product **(266)**, which is shown below.



Scheme 3.27 *Proposed synthetic route to non C5–C6 substituted 2,3a,4,6a-tetraphenyl-3,3a,4,6a-tetrahydropyrrolo[2,3-d]-1,2,3-triazoles using the Hunsdiecker reaction.*

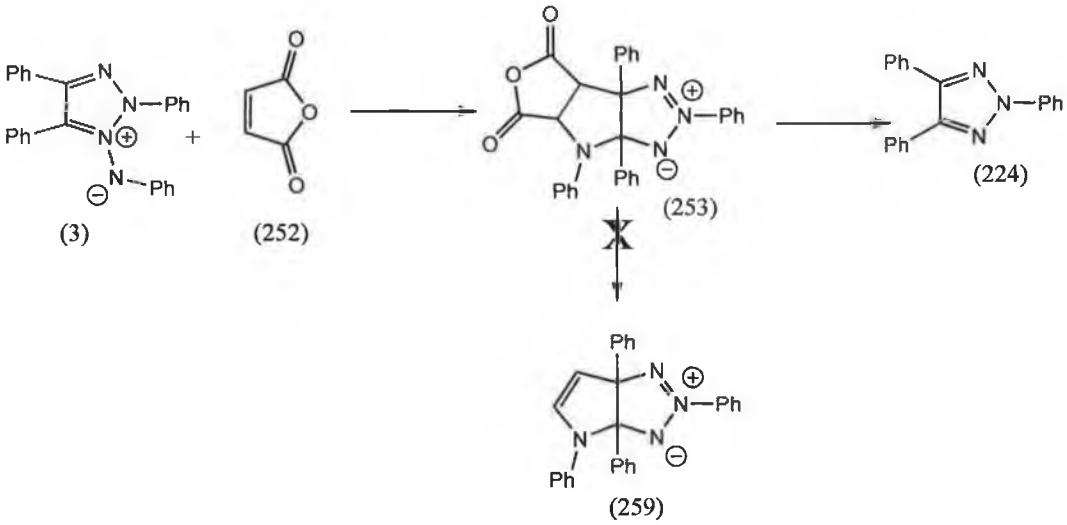
The hydrolysis of the ester group to the carboxylic acid **(263)** proceeded smoothly by base catalysis. Decarboxylation, however proved more difficult. The decarboxylating reagent used here was lead(IV)acetate as Bachi and Kochi have shown the oxidative decarboxylation of the strained cyclic structures in high yield.[116] The mechanism involves abstraction of the carboxylic proton giving a lead acetate-carboxylate ion salt. A second β-proton is then removed resulting in a β-elimination type alkene formation. Reaction of lead(IV)acetate in dry refluxing toluene led unfortunately to a inseparable complex reaction mixture. The assumed production of small amounts of 2,4,5-triphenyl-1,2,3-triazole **(224)** could only be attributed by running a comparative sample with the reaction mixture by TLC. Lead (IV)acetate appears here to be too harsh. However a repeat experiment using the lesser oxidative agent mercury(II)acetate obtained a similar result. This avenue of synthesis seemed unyielding.

Maleic anhydride is one of the most widely used dienophiles owing to it's high C=C reactivity given by it's *cis*-locked conformation. Reaction of the 1,3-dipole with maleic anhydride proceeds in high yield. This cycloadduct would then provide potentially three synthetic routes to the desired compound. Thermal decarboxylation of maleic anhydride cycloadducts has been shown to proceed with ease in many cases with one example shown below.[117]



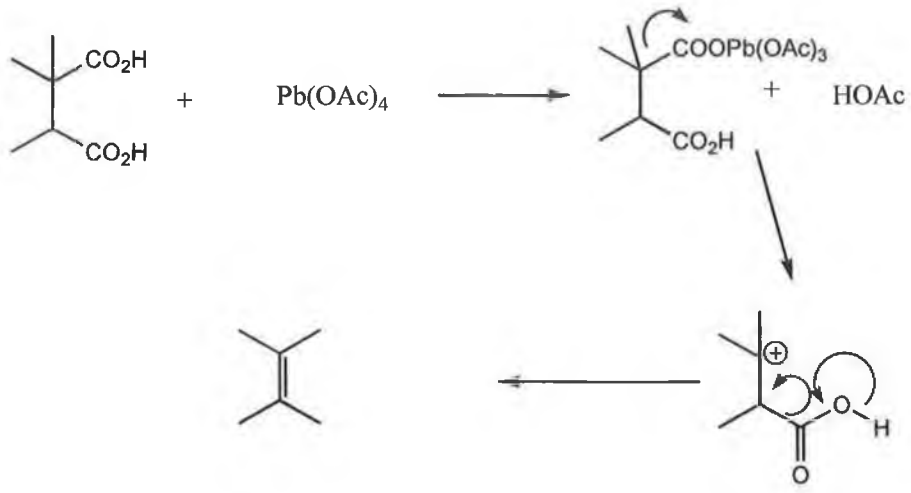
Scheme 3.28 *Cycloaddition of maleic anhydride with subsequent bis-decarboxylation.*

However a prerequisite for this reaction is the isolation of particularly stable products. A speculative application of this method to our cycloadduct **(253)** gave primarily 2,4,5-triphenyl-1,2,3-triazole **(224)** revealing the possible formation of **(259)** to be heat sensitive.



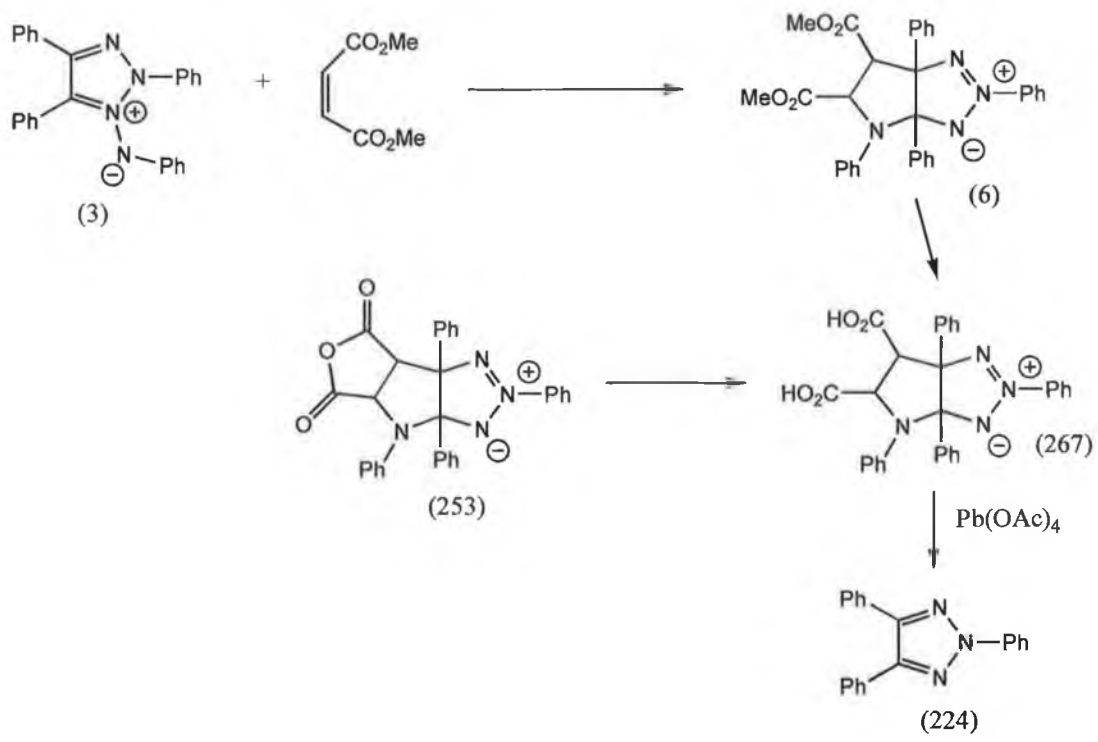
Scheme 3.29 *Cycloaddition of maleic anhydride with 1,3-dipole (3) to give triazole (224) and not bis-decarboxylation.*

The maleic anhydride cycloadduct can be hydrolysed to the corresponding dicarboxylic acid under standard hydrolysis conditions. Subsequent bisdecarboxylation with lead(IV)acetate gives the alkene. The reaction is of wide scope. The mechanism is believed to be consistent with the following steps.



Scheme 3.30 *Mechanism for bisdecarboxylation using lead(IV)acetate.*

Hydrolysis of **(253)** with a NaOH solution gives a low yield of **(267)**. It was much more efficient to hydrolyse the diester cycloadduct **(6)** to the diacid **(267)**. The diester **(6)** can be obtained by reaction of the dipole with dimethyl maleate, which has been previously achieved. Unfortunately bisdecarboxylation by this method was unsuccessful again giving 2,4,5-triphenyl-1,2,3-triazole **(224)** as the only observed product.

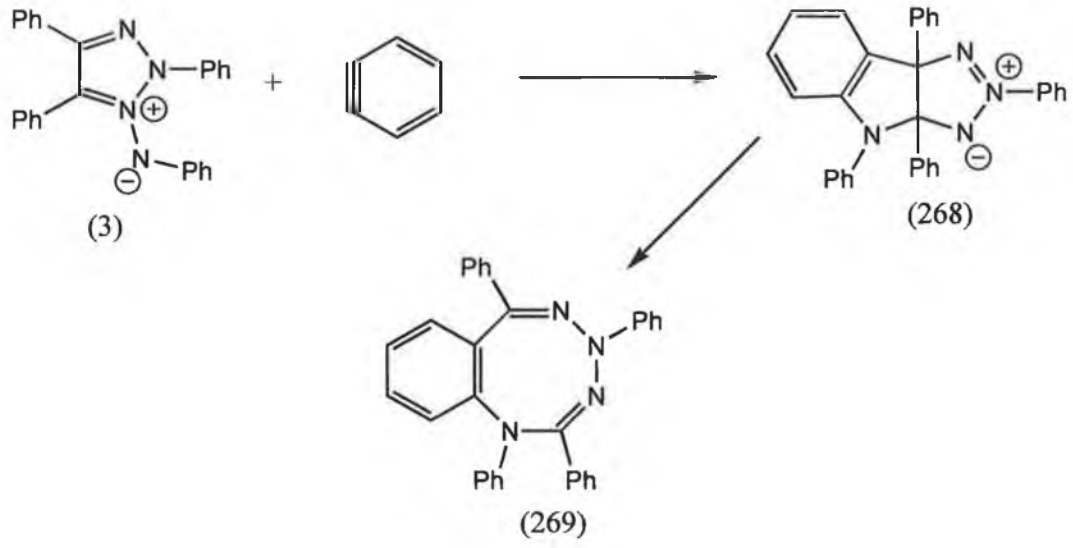


Scheme 3.31 *Unsuccessful bisdecarboxylation of (267) with lead(IV)acetate. Formation of triazole (224).*

Finally it has been shown with somewhat limited success the direct decarboxylation of maleic anhydride cycloadducts with lead(IV)acetate.[118] Yields are inherently low. In our case, there was no positive reaction. Speculation at this point would suggest that the oxidative reagent is too harsh for these systems or likewise that the non-substistuted C5–C6 compound is initially formed but under reaction conditions decomposes to the triazole **(224)**. The last major area in effecting acetylene equivalents is the sulphur containing olefin. In general a sulfone presents a higher electron withdrawing capacity than a sulphoxide due to its oxidation state. A disubstituted alkene containing two sulfonyl groups serves only to doubly activate the π-system. Indeed disulphonyl ethylenes have dieneophilic reactivity as high as that of maleic anhydide. (*E*)-diphenylsulfonylethylene is frequently observed to add to rather inert dienes. Reaction of the 1,3-dipole with the aforementioned dipolarophile gave no cycloaddition regardless of solvent effects or reaction time. This was also shown to be the case for vinyl sulfoxide.[119]

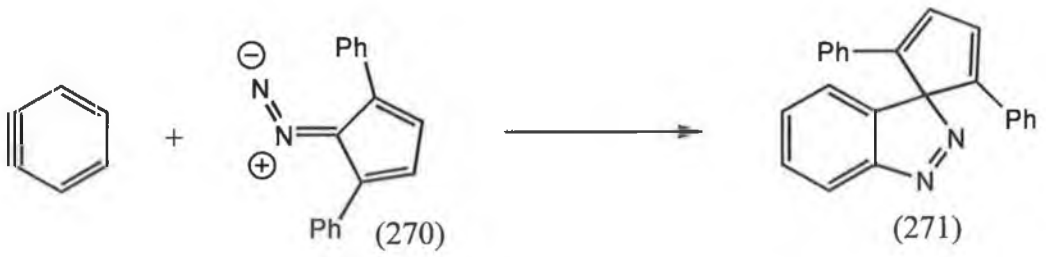
3.5.1. Benzyne reaction

A benzyne cycloadduct would in theory provide us with unsaturation between the C5–C6 bond. Absence of electron-withdrawing group on the benzyne dipolarophile would similarly result in no net activation of the C5–C6 aromatic bridge. More important however is the photochemical ring opening process. The intermediate tetrazocine would not intuitively undergo contraction as before as this would involve attack by N–2 on a closed aromatic sextet of electrons, a highly unfavourable process.



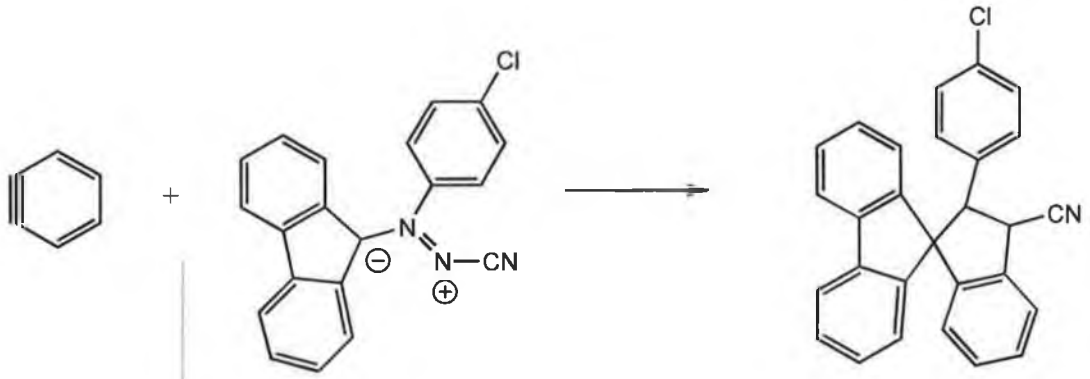
Scheme 3.32 *Cycloadditon of benzyne with the 1,3-dipole and 1,2,3,5-tetrazocine formation.*

Benzyne should therefore satisfy all the present criteria and compound the postulation that electron-withdrawing groups on C5–C6 bond are the driving force for ring contraction. Benzyne has shown itself to be a suitable 2π component for cycloaddition to 1,3-dipoles. Addition of benzyne to azides and to diazo compounds is perhaps the earliest and most commonly observed reaction, an example being reaction of diazocyclopentadienes **(270)** with benzyne to furnish **(271)**.[120]



Scheme 3.33 *Cycloadditon of benzyne with a diazocyclopentadiene.*

The established reactions with more formal 1,3-dipoles however have been less frequent. Nevertheless benzyne has undergone cycloaddition with nitrones, heterocyclic *N*-oxides, syndones, azomethine imides and more recently pyridinium-3-oxides, one example being shown below.



Scheme 3.34 *Cycloadditon of benzyne with a 1,3-dipole.*

Diels-Alder type reactions are of utmost importance in benzyne chemistry, not only as a synthetic tool but also as a method of detecting them. The highly electrophilic benzyne is known to react with a whole range of dienophiles that would not normally be regarded as viable partners such as thiophenes and styrene. The reactivity of benzyne can be explained in terms of its high enthalpy of formation, of which strain energy comes out to be nearly 63 Kcal mol^{-4} due to bending distortion on the triple bond. The electronic structure of benzyne can be compared to that of a highly distorted alkyne. The benzyne triple bond composes of a σ-bond formed by sp^2-sp^2

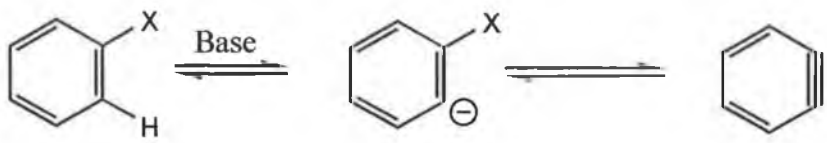
overlap, one π-bond formed from *p-p* overlap and another formed from sp^2-sp^2 overlap. The latter π-bond is in the plane of the ring and is extremely weak due to inefficient orbital overlap.

Figure 3.4 *Poor π overlap of sp^2 orbitals of benzyne.*

The HOMO energy of benzyne is –9.58 eV which is of little difference in energy terms to that of acetylene. However the LUMO energy is calculated as being 1.33 eV which is substantially lower than the acetylene LUMO energy and this feature is attributed to bending of the triple bond which results in an efficient mixing of the π^* orbital and σ^* orbital lying only slightly higher in energy. The lowering on the benzyne LUMO decreases it's energy gap with the HOMO of a dipole and makes for easy reaction between the two.

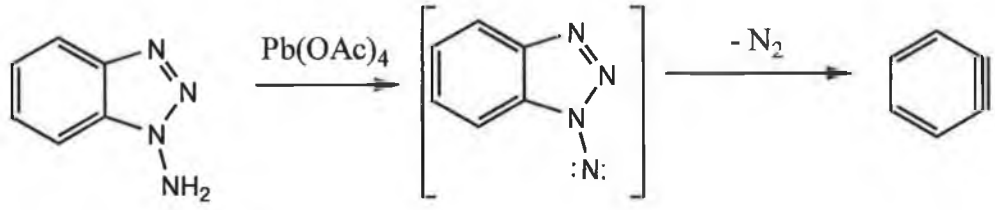
The literature gives numerous methods of benzyne generation. However the most common, reliable procedures can be categorised into three general classes; (a) from 2-halogeno phenyl anions, (b) from fragmentation of benzo-fused cyclic systems and (c) from benzenediazonium salts.

The first method involves elimination of HX from a halobenzene with a strong base such as sodiumamide or lithium dialkylamide, at or below room temperature to yield the benzene intermediate. The reaction involves two steps of which both are reversible, hence the use of a strong base.



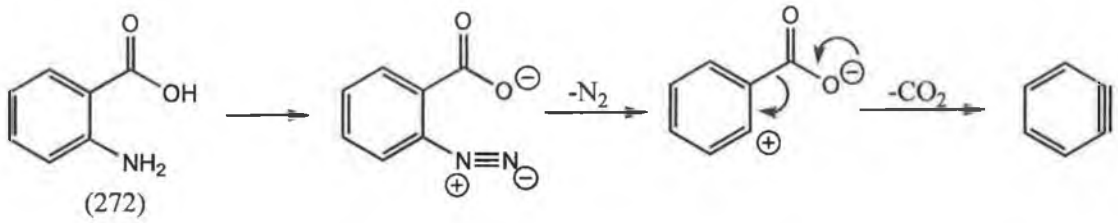
Scheme 3.35 *Benzyne formation through dehydrohalogenation of a phenylhalide.*

Oxidation of 1-aminobenzotriazole with lead(IV)acetate exemplifies the second general procedure. Benzyne is formed in high yield in a very clean and rapid reaction at low temperatures. The reaction is postulated to proceed through a nitrene intermediate.



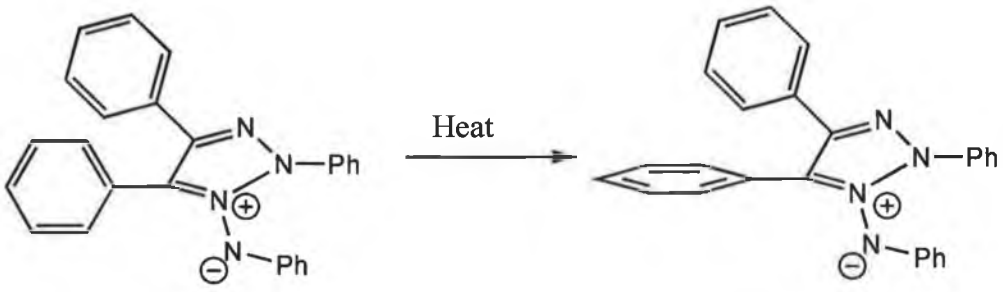
Scheme 3.36 *Benzyne formation through oxidation of 1-aminobenzotriazole with lead(IV)acetate.*

The final way of generating benzyne, which is probably the most widely used because of its convenience, is the aprotic diazotisation of anthranilic acid, using organic nitrites such as isoamylnitrite leading to formation of benzenediazonium-2-carboxylate. This internal salt decomposes at temperatures between 40^0C and 80^0C to give benzyne. The mechanism is believed to be stepwise with initial loss of nitrogen followed by concurrent loss of CO_2. The salt can be isolated but is best used *in situ* due to it's explosive nature when dry. Yields of benzyne are said to be moderate relative to the other procedures.



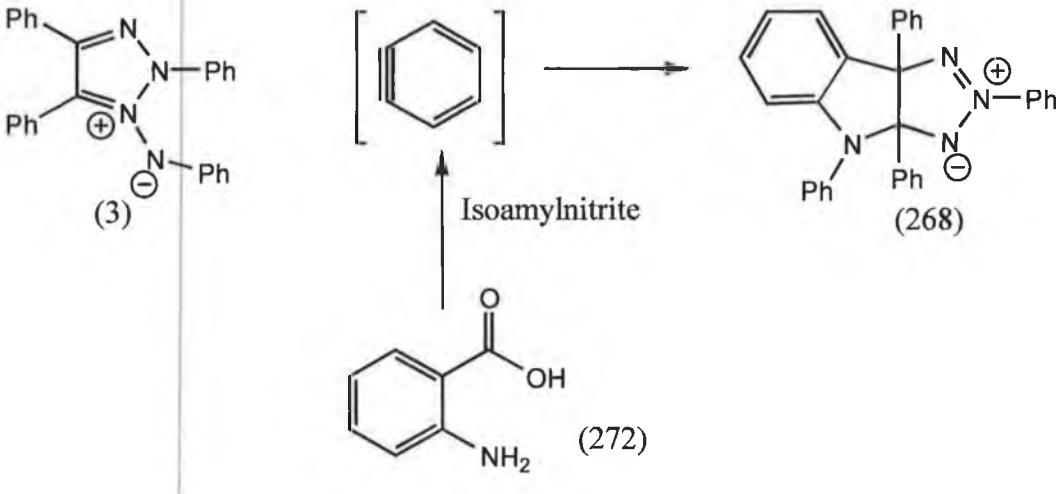
Scheme 3.37 *Benzyne formation through aprotic diazotisation of anthranilic acid.*

Of the methods of benzyne generation surveyed here, the first two in theory would not be experimentally practical for our 1,3-dipole. The rate of reaction of the dipole has been shown to be quicker at elevated temperatures. Kinetics dictate that at higher temperatures, molecules have more energy to effectively collide and hence react. However there is a stereochemical reason as to the necessity of higher temperature for the dipole cycloaddition. X-ray crystallography data coupled with NMR studies has alluded that the geometry of the dipoles C-terminal phenyl group is temperature dependent. At low temperatures, the geometry of the phenyl ring is such that it stereochemically hinders the concerted cycloaddition process by preventing the necessary line of approach of the dipolarophile to the 1,3-dipole. Rotation of the phenyl group about it's C1-phenyl/C4-triazole axis at higher temperatures gives the dipolarophile a clear route of accessibility.



Scheme 3.38 *Rotation of the phenyl group of the 1,3-dipole about it's C1-phenyl/C4-triazole axis at higher temperatures.*

In situ formation of benzyne through diazotisataion of anthranilic acid and isoamylnitrite in 1,2-dimethoxyethane with the 1,3-dipole yielded the cycloadduct **(268)**. Details of this work has been since published.[121] Reaction conditions were optimised by heating a stirred solution of the 1,3-dipole at the reflux temperature of the solvent, thereby increasing the reactivity of the dipole within the short, transitory lifetime of benzyne. Similarly, it was observed that yields were maximised by simultaneous addition of solvent solutions of anthranilic acid and isoamylnitrite every 5 min in 2 ml aliquots. With respect to the dipole, the total amount of anthranilic acid and isoamylnitrite was present in a 10 molar excess which gave a yield of 40%. Subsequent attempts to increase the yield by an increased molar ratio were unsatisfactory as separation of the cycloadduct by column chromatography became more problematic.



Scheme 3.39 *Cycloaddition of the 1,3-dipole with benzyne generated in situ.*

A concerted reaction between benzyne and a 1,3-dipole necessitates a transition state in which there is simultaneous overlap between the orbitals of the formal triple bond in the plane of the phenyl ring and the terminal lobes of the dipoles π-orbital system. The more important interaction lies between the low-lying lowest unoccupied molecular orbitals of benzyne and the highest occupied π-orbital of the diene having the correct phases shown below.

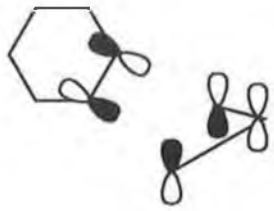
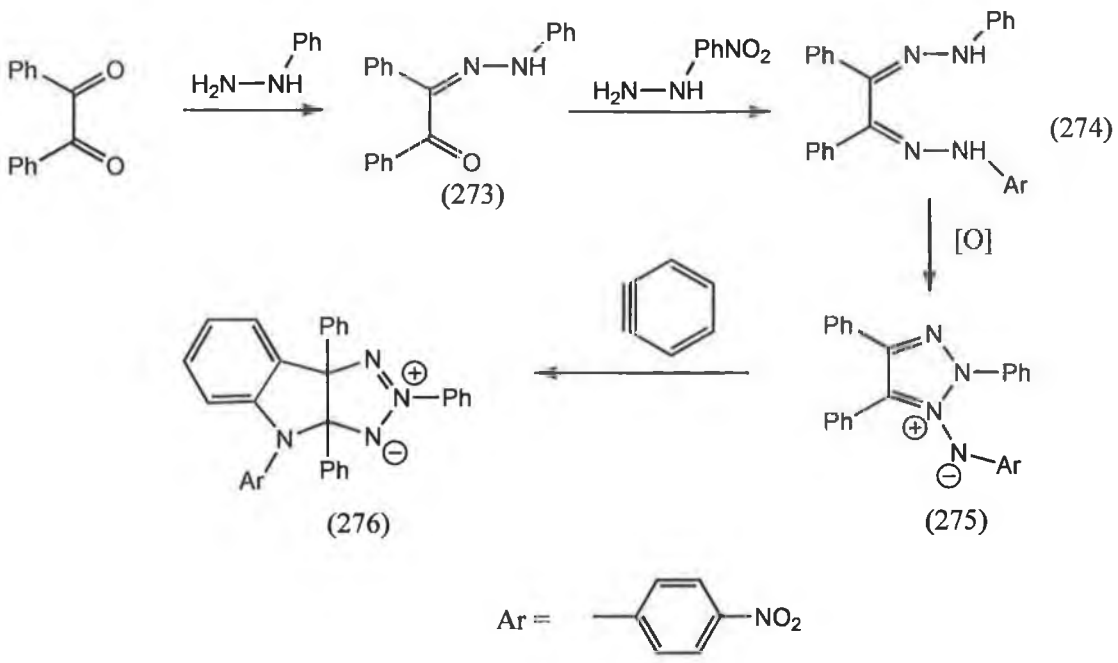


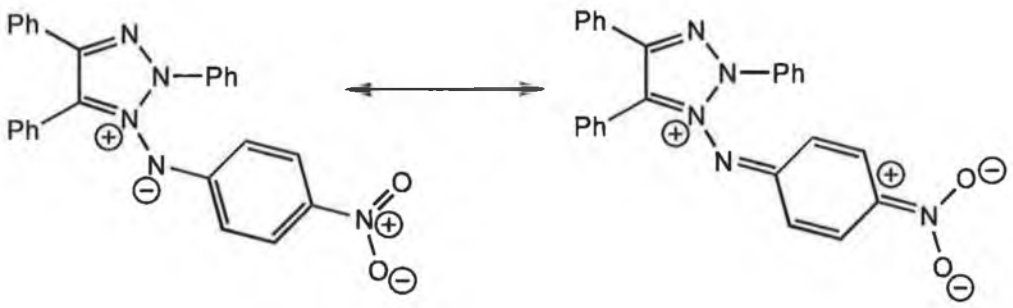
Figure 3.5 *Overlap between the orbitals of the formal triple bond of benzyne in the plane of the phenyl ring and the terminal lobes of the dipoles π-orbital system.*

The π system of a 1,3-dipole is almost planar and the termini are the correct distance apart for effective overlap with the arynic orbital, a factor, which enhances the reactivity of benzyne with 1,3-dipoles. Stereoselectivity is a consequence of concerted addition, which holds for the 1,3-dipole and based on previous cycloadditions, one would expect the benzene group to lie *cis*- to the bridgehead phenyls in the cycloadduct **(268)**. By placing a nitro group para on the phenyl of the nitrogen terminus of the dipole, the yield of the reaction was considerably increased to 57%. This dipole **(275)** can be obtained from the reaction pathway shown below. Post the oxidation of **(274)**, it may cyclise in two ways to form two dipoles. **(275)** has been shown conclusively to be the dominant form i.e. the nitro substituted phenyl on the nitrogen terminus of the 1,3-dipole. [110]



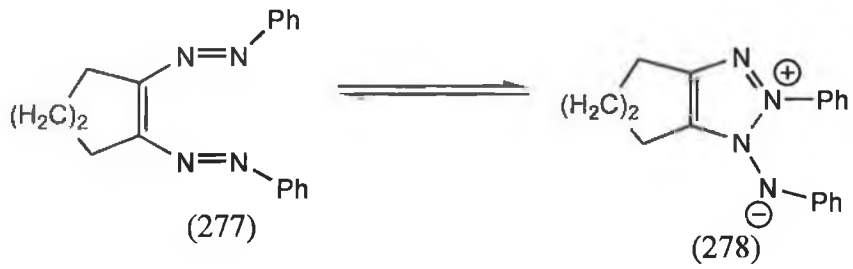
Scheme 3.40 *Synthetic route to the cycloaddition of 1,3-dipole nitro analogue (275) with benzyne.*

Kinetic studies of the 1,2,3-triazolium-*N*-imides with various dipolarophiles showed that the rate of reaction was inhibited regardless of whether the nitrogen terminus phenyl group contained electron withdrawing or donating groups with respect to hydrogen.[122] This phenomenon is explained through resonance destruction of the 1,3-dipole character. In both forms, the orthogonal π-electrons on the nitrogen terminus of the dipole are replaced by the π-bond to the aryl substituent. This feature has been detected by NMR work at low temperatures.



Scheme 3.41 *Resonance destruction of the 1,3-dipole character due to para-substituted nitro group .*

It has also been shown by variable temperature NMR studies on 1,2-bis(arylazo)cycloalkenes that when the Ar group contains a strongly electron-withdrawing *para*-NO_2 substituent, the dominant form is cyclic giving the correct geometry for concerted addition as shown below for **(277)** and **(278).**[123]



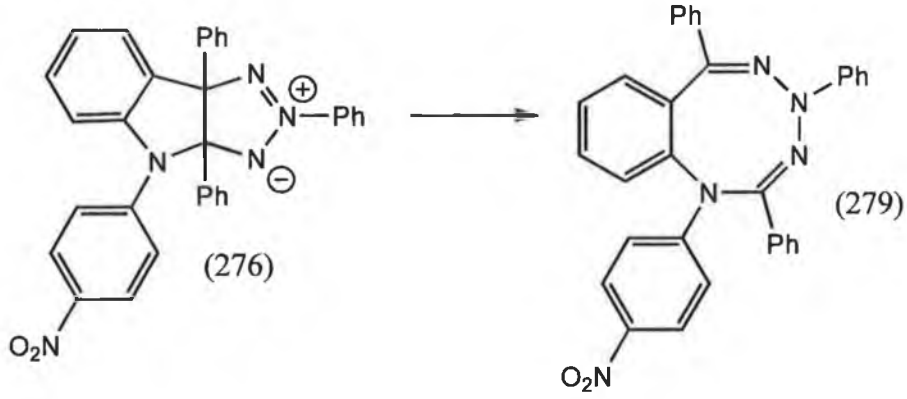
(277) (278)

Scheme 3.42 *Cyclic and open chained forms of bis(arylazo)cycloalkenes*

Reaction of nucleophilic dipoles with benzyne in general is more favourable as the HOMO-LUMO energy gap is smaller. Introduction of electron-donating groups on the dipole should show a quicker rate of reaction. However studies have shown the relative rates of electron donating groups or electron withdrawing groups to be quite small. Although benzyne is regarded as the electrophilic partner in cycloaddition, it can quite easily add to electron-deficient systems, provided they have necessary geometry for concerted reaction. This broad reactivity is explained in terms of the huge release of strain energy of the benzyne ring once cycloaddition has resulted. A quick review of the literature around the time of isolation of the benzyne cycloadduct yielded no previous report of reaction of a 1,3-dipole type, azomethine imine, with benzyne. However more important is the potential tetrazocine, that if shown to exist, lends weight to the argument that electon withdrawing groups on the C5-C6 bond are the driving force for ring contraction post tetrazocine formation.

3.6. Photolysis of Benzo[1,2-b]-2,3a,4,6a-tetraphenyl-3,3a,4,6a-tetrahydropyrrolo[2,3-d]-1,2,3-triazole (268) and Benzo[1,2-b]-4-*p*-nitrophenyl,2,3a,6a-triphenyl-3,3a,4,6a-tetrahydropyrrolo[2,3-d]-1,2,3-triazole (276)

UV analysis of **(268)** and it's nitro analogue **(276)** would indicate the region of the ultraviolet spectrum with which both were absorbing light. This would allow for optimisation of the desired photochemical conversion from **(268)** to **(269)**. Both compounds contained very broad peaks in the visible region as they were coloured. λ-max peaks at 279 nm for **(268)** and two at 244 nm and 400 nm for **(276)** were observed respectively. Both peaks at 279 nm and 244 nm are most likely due to π-π^* transitions from the benzene chromophore. The signal at 400 nm was initially assumed to be the result of a n-π^* transition from the nitro group. However it is more conceivable to be resulting from a π-π^* transition of the disubstituted benzene ring at N4. In general aromatic π-π^* transitions occur between 150-300 nm. Nevertheless when auxochromic groups appear on the same ring as the chromophore, both groups influence the absorption. This is most pronounced when an electron-donating group and an electron-withdrawing group are *para* to one another. *P*-nitroaniline has a π-π^* transitions measured at 380 nm which is a similar absorption to our own C5-bisubstituted phenyl ring of **(276)**.



Scheme 3.43 *Synthesis of novel 1,2,3,5-tetrazocine by the irradiation of (276).*

The photolysis of **(269)** and **(276)** were carried out using different light sources, namely a 450 W low pressure mercury lamp and a 250 W tungsten lamp. Both gave a single product. The efficiency of the photoconversion was best effected with the 450W lamp due to it's higher intensity as a light source and broader range with reaction times of 3 hours as opposed to 24 with the 250 W lamp. It was observed that the yield of isolated product was greater for the nitro-analogue **(279)** than for **(269)**. This may be explained in terms of some contribution given by the phenyl nitro π-π^* transition to the bridgehead C–C σ-σ^* which would lead to ring opening of the fused bicyclic system. The phenyl nitro π-π^* transition has a wavelength and hence energy level similar to that required to cleave the bridgehead bond. Perhaps an efficient energy transfer between the energy levels of both the π-π^* and σ-σ^* is at work here.

The isolated, single unknown gave NMR, IR and elemental analysis data, which we believe to be in agreement with structure **(269)**. The most convincing aspect of its isolation, is the disappearance of both bridgehead ^{13}C signals at 91.40 ppm and 105.42 ppm along with the corresponding presence of two sp^2 hybridised signals at 142.54 ppm and 178.12 ppm for **(269)**. A comparison of the bridgehead ^{13}C signals of previously known hexehydro-1,2,3,5-tetrazocines and their precursors with our new ring system shows the formation of the signals with the above chemical shifts to be characteristic of the ring-opening process.[98]

Perhaps the most important aspect of this result is the tetrazocine remaining intact and not undergoing contraction by attack of the C=C component of the ring by N2 as was previously the case in all examples. This will be invaluable information in light of future tetrazocine design through this photolytic method. Electron withdrawing groups will either be avoided or converted to electron donating groups prior to ring opening. We should again highlight the remarkable sensitivity of tetrazocine existence, the slightest change affecting the ring structure. Similarly previous tetrazocines with this degree of unsaturation have undergone ring contraction with the exception of the 1,3,5,7-tetrazocines as is conveyed in the literature survey. There is a stabilising characteristic to this ring system, which may be explained by the anchoring of conformation by the benzene ring or perhaps there is some resonance

stabilisation effect. In summary, a novel entry to the 1,2,3,7-tetrazocine has been achieved which may act as the base component of many more tetrazocines to come.

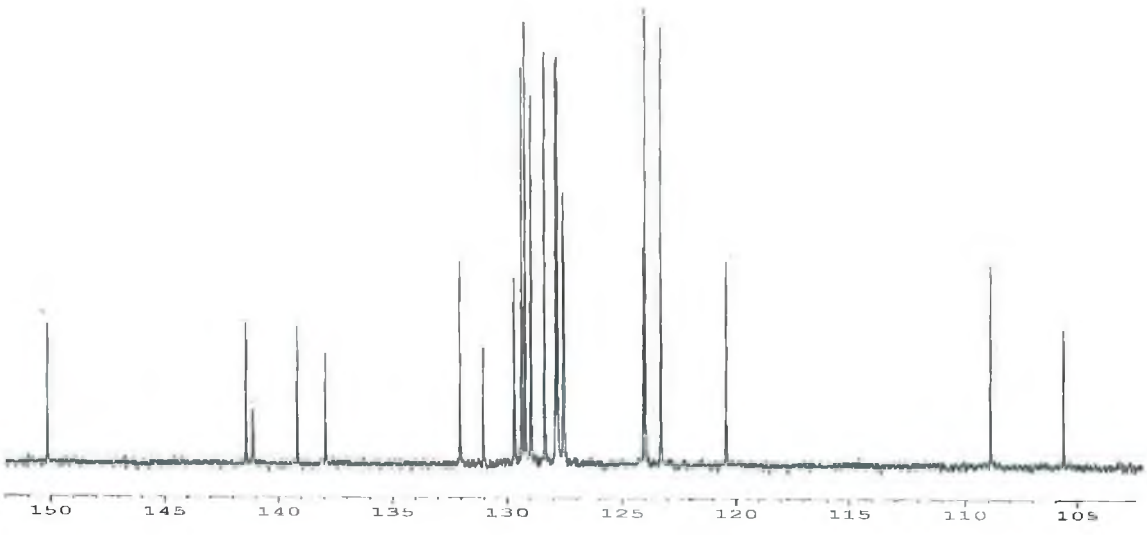


Figure 3.6 *^{13}C-NMR of (268).*

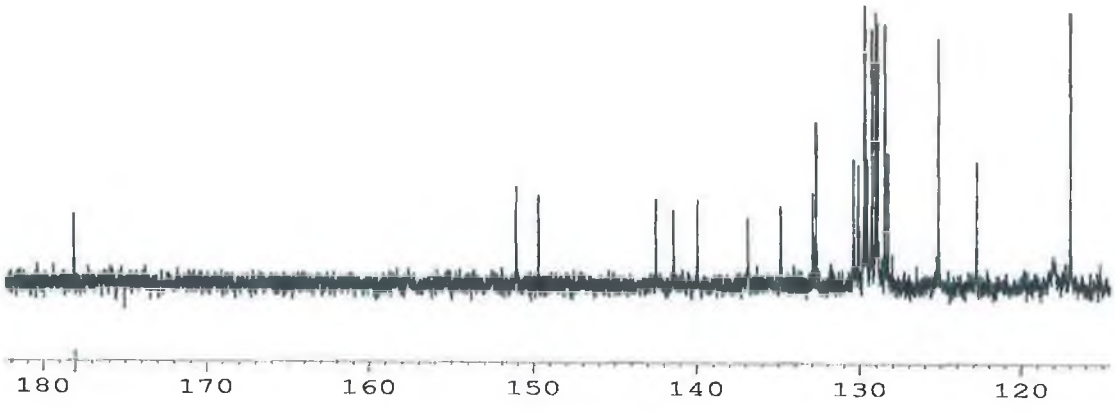
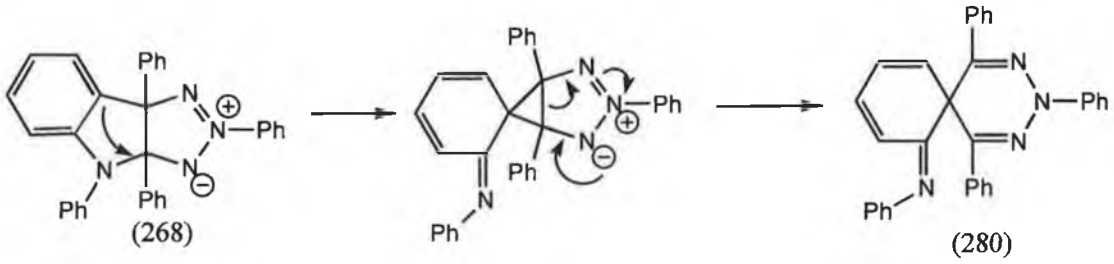


Figure 3.7 *^{13}C-NMR of (269).*

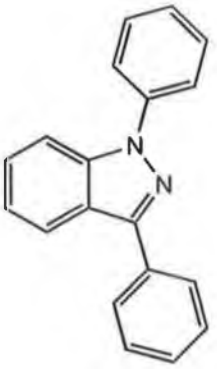
3.7. Thermolysis of Benzo[1,2-b]-2,3a,4,6a-tetraphenyl-3,3a,4,6a-tetrahydropyrrolo[2,3-d]-1,2,3-triazole (268) and Benzo[1,2-b]-4-*p*-nitrophenyl,2,3a,6a-triphenyl-3,3a,4,6a-tetrahydropyrrolo[2,3-d]-1,2,3-triazole(276)

Thermolysis of tetrahydropyrrolo[2,3-d]-1,2,3-triazoles **(6)** has always led to 5,5-disubstituted-1,2,3-triazines as previously discussed. If our benzo derivative **(268)** were to undergo the same mechanism, then we would expect to generate the spiro-triazole **(280)**. This is a highly improbable transformation as it would involve loss of aromaticity in generating an intermediate. Therefore, the potential of a possibly new secondary derivative from the tetrahydropyrrolo[2,3-d]-1,2,3-triazoles intrigued us greatly.



Scheme 3.44 *Highly improbable thermolytic transformation of Benzo[1,2-b]-2,3a,4,6a-tetraphenyl-3,3a,4,6a-tetrahydropyrrolo[2,3-d]-1,2,3-triazole.*

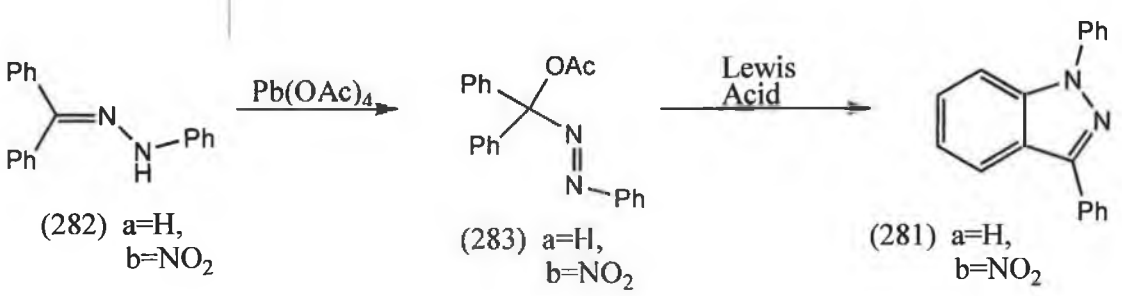
A solution of **(268)** in toluene was heated to reflux temperature and followed by thin layer chromatography. After one week the slight formation of the tetrazocine **(269)** was observed and initially attributed to a photochemical conversion by the surrounding light. However more forcing conditions involving heating the solid **(268)** in a Schlenk tube under vacuum at the melting point of **(268)** gave a major new product in 32% yield. Isolation of this compound gave NMR, IR and elemental analysis, which suggested the generation of 1,3-diphenylindazole **(281)**.



(281)

Figure 3.7 *1,3-diphenylindazole.*

This was later confirmed by comparison of data with 1-arylindazoles as prepared by Gladstone who reported the convenient 2-step method for preparing 1-aryl-indazoles from arylhydrazones of aromatic ketones.[124] The hydrazone **(282)** is first treated with lead(IV)acetate in methylene chloride to give the azo-compound **(283)** which is then cyclised to the indazole induced by the Lewis acid e.g. BF_3 etherate.

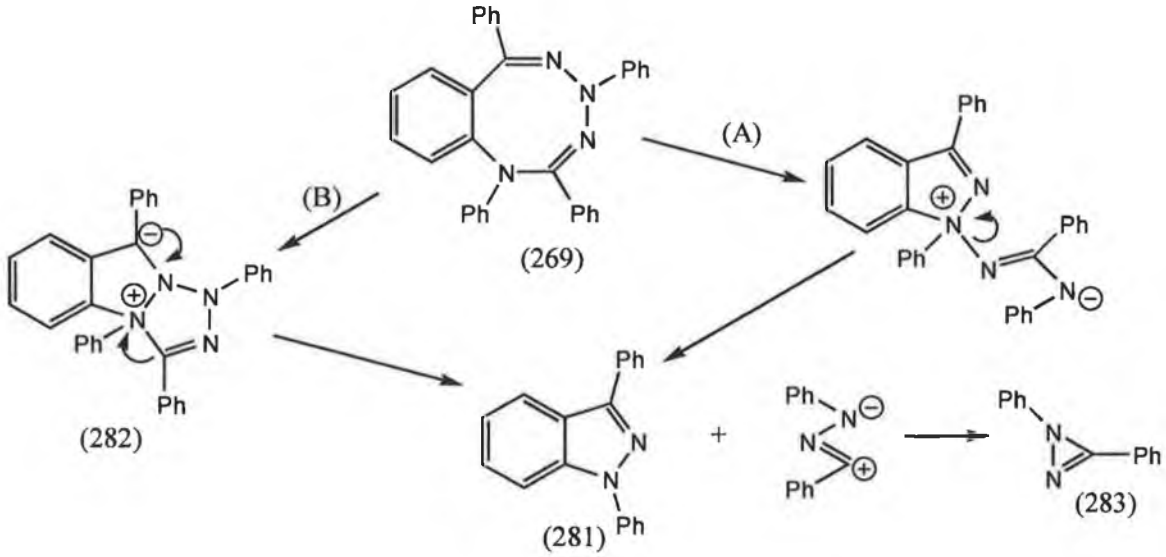


(282) a=H, b=NO_2 (283) a=H, b=NO_2 (281) a=H, b=NO_2

Scheme 3.45 *Alternative synthetic route to 1,3-diphenylindazole as described by Gladstone.*

The driving force in the formation of the indazole **(281a)** by thermolysis of **(268)** may be due to the stability of the indazole in respect of its modified aromatic character as it is a benzo-fused ring system. Hückel's rule strictly applies only to monocyclic systems. Nevertheless many benzo-fused derivatives retain their aromatic properties and indazoles are best regarded as delocalised aromatic systems.

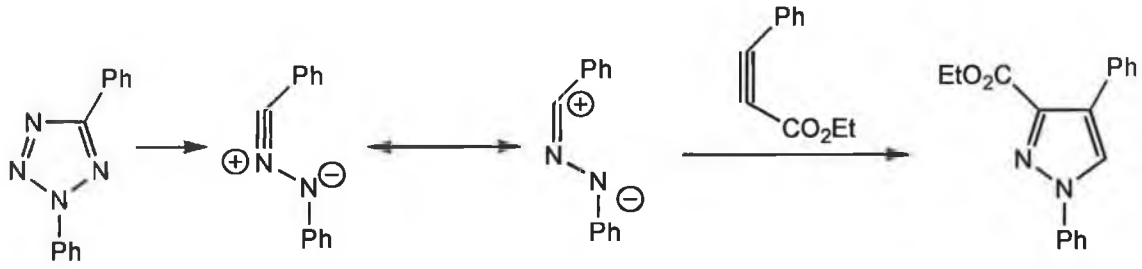
The mode of generation of the indazole **(281a)** from the precursor was a point of debate and it became apparent through weight of argument that the most facile way for this to occur was through initial ring opening giving the 1,2,3,5-tetrazocine. Thermolysis of the tetrazocine **(269)** using similar conditions as that of **(268)** gave the indazole **(281a)**. Subsequent attempts to isolate the tetrazocine by thermolysis of **(268)** at lower, less forcing conditions failed. The temperature required to open-up the bicyclic fused system is probably too harsh for the survival of the tetrazocine and it quickly rearranges. Ring opening of **(268)** by electrocyclic disrotatory rotation of the bridgehead carbon *p*-orbitals is a photochemically allowed process involving 4π electrons. If the *p*-orbitals were to rotate in a conrotatory fashion, then ring opening by this thermally allowed process would be facilitated according to Woodward-Hoffman rules for pericyclic reactions. However this is not favourable as stereochemical hindrance of the phenyls with ring atoms would play a large role inhibiting such a movement. Instead it is more plausible that the thermal ring opening process is not a concerted one and is the result of a stepwise rearrangement. With respect to the eight-membered ring, there are two more obvious methods of furnishing the indazole and their mechanisms are shown diagramaticly below.



Scheme 3.46 *Proposed mechanisms of 1,3-diphenylindazole formation from thermolysis of Benzo[1,2-b]-2,3a,4,6a-tetraphenyl-3,3a,4,6a-tetrahydropyrrolo[2,3-d]-1,2,3-triazole.*

Route (A) involves attack of the aromatic π-system at C-6 by the ring nitrogen at N2 with resultant nucleophilic substitution. Intuitively this would be deemed improbable as this form of substitution is not characteristic of aromatic rings. However under such pressing conditions, formation of the indazole by this route may be inevitable.

The alternative pathway, route (B), supposes an initial transannular ring contraction affording the dipolar structure **(282)** through N1 and N5 bond formation. The three ringed system contains a tetrazole ring. Tetrazoles have a proclivity to cleave readily on heating with extrusion of nitrogen. Huisgen has shown that the tetrazole when heated generates the 1,3-dipole, which is trapped by cycloaddition with ethylphenylpropiolate.[125]



Scheme 3.47 *Huisgens mechanism showing that a tetrazole when heated generates a 1,3-dipole, which is trapped by cycloaddition with ethylphenylpropiolate.*

The mechanism proposed by Huisgen bears similarity to that by route (B) and substantiates it's validity. In order to differentiate and hence propose the most likely mechanism by route (A) or (B), the nitro analogue **(276)** was heated and the thermoadduct shown conclusively to be 1-*p*-nitrophenyl-3-phenylindazole. Retention of the nitrophenyl group appreciably verifies the mechanism as described by route (B) and effectively rules out route (A).

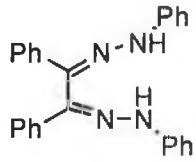
In conclusion, a new entry concerning secondary derivatives of cycloadducts formed from the 1,2,3-triazolium-1(*N*-aryl)imide has been acquired. Diphenylindazoles are

most probably formed through the heretofore unobserved thermal ring intermediate **(282)**, obtained from the benzotetrahydro-pyrroloimadazole precursor **(219)**, by a transannular ring contraction with subsequent extrusion of N_2. These molecules are truly remarkable in that a whole variety of secondary thermo derivatives can be obtained through subtle changes in functionality/saturation from the base bifused ring structure.

3.8. Experimental

The solvent system used in each experiment for flash chromatography and TLC was 90% pet. ether 40-60: 10% ethylacetate. All NMR spectra were recorded on a Bruker AC 400 spectrometer and IR spectra were recorded on a Perkin Elmer 2000 FT-IR spectrophotometer.

1,2-bis(phenylhydrazone)stilbene (141)

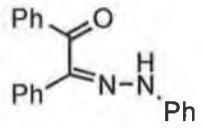


A three molar excess of phenyl hydrazine (15.56g, 0.142 mol) was added to a 200ml solution of 100% glacial acetic acid containing 10g of benzil (.047 moles). The solution was gently refluxed for one hour. On cooling, yellow crystals of benzil dihydrazone fell out. The crystals were collected by vacuum filtration and washed with 300ml of pet. ether ($40\text{-}60^0$) to remove the excess phenyl hydrazine. Yield (15.19g, 84%). m.p .222- 224 ^{0}C,

2,4,5-triphenyl-1,2,3-triazolium-1-(*N*-phenyl)imide (3)

Lead(IV)acetate (26g, 0.060mol), previously washed with 100ml of pet. ether ($40\text{-}60^0$) was added to a stirred solution of benzil phenyl dihyrazone (20g, 0.05 moles) **(141)** in 250ml of conc.glacial acetic acid. The reaction was set up over N_2 and after 25 min at room temperature, the brown solution was filtered and the solid washed with 200ml of pet. ether ($40\text{-}60^0$). The 1,3 dipole was recrystallised from ethyl acetate. Yield (6.19g, 65%), m.p. 174-176^{0}C, Lit.Val. 178-179^{0}C.

Benzil monophenylhydrazone (273)



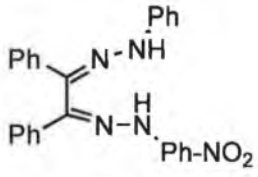
Benzil (10g, 0.047 mol) was added to 150ml solution of methanol and 20ml of acetic acid. On addition of phenyl hydrazine (5.18g, 0.047 mol), the reaction was heated under reflux for 2 hours. Cooling the solution gives a yellow crystalline mass, which was filtered and washed with cold pet.ether (40-60^0) (100ml). Yield (11.13g, 78%). m.p. 134^{0}C, Lit.Val. 135^{0}C.

IR(KBr) (cm^{-1}): 1714 (C=0)

δH($CDCl_3$)(ppm): 7.07(2H,m), 7.29-7.67(11H,m), 8.16(2H,m), 8.46(1H,bs)

δC($CDCl_3$)(ppm): 114.69, 123.37, 128.24, 129.72, 129.93, 130.03, 130.12, 130.20, 131.11, 132.07, 138.64, 142.58, 143.09, 191.68.

Benzil-phenyl-*p*-nitrophenylosazone (274)



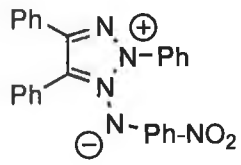
Benzil monohydrazone (3g, 0.01mol) (200) and *p*-nitrophenylhydrazine (1.53g, 0.01mol) were heated without solvent at 150^{0}C for 2 hours. By cooling and adding acetic acid, the osazone was obtained by hot filtration to give (201). Yield (2.78g, 64%). m.p. 222-224 ^{o}C, Lit.val.: 223-225^{0}C.

IR(KBr) (cm^{-1}): 3320, 1605, 1550, 1525, 1532, 842, 690 cm^{-1}.

δH($CDCl_3$)(ppm): 6.92(1H,m), 7.16(4H,m), 7.22-7.46(8H,m), 7.62-7.83(5H,m), 8.08(1H,s), 8.16(2H,m).

δC($CDCl_3$)(ppm): 113.21, 113.97, 121.97, 125.91, 126.48, 126.64, 129.62, 129.75, 129.81, 130.55, 133.82, 134.54, 135.56, 141.32, 141.63, 144.01, 149.23.

2,4,5-triphenyl-1,2,3-triazolium-1-(*N*-*p*-nitrophenyl)imide (275)



(274) (10g, 0.022mol) was added to 85ml of glacial acetic acid. Previously washed Pb(IV)acetate (10g, 0.023mol) with pet.ether ($40\text{-}60^0$) was added quickly to the solution and the reaction vessel covered with a N_2 atmosphere. An immediate orange to brown colour change was observed. The mixture was stirred for 30 minutes at which point the solid was filtered and washed with cold pet.ether ($40\text{-}60^0$). Yield (6.19g, 65.2%). m.p. 92^0C

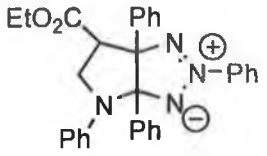
IR(KBr) (cm^{-1}): 1703, 1589,1539, 1320, 752, 726, 684.

δH($CDCl_3$)(ppm): 6.10(2H,m), 7.27-7.43(11H,m), 7.51(2H,m), 7.65(2H,m), 7.75(2H,m).

δC($CDCl_3$)(ppm): 123.91, 125.72, 127.02, 128.02, 128.36, 129.44, 129.57, 129.83, 129.85, 130.75, 131.78, 131.84, 134.79, 136.81, 138.26, 146.17, 161.53, 175.84.

Cycloadditions of the 1,3 dipole with various dipolarophiles.

6-ethoxycarbonyl-2,3a,4,6a-tetraphenyl-3,3a,4,5,6,6a-hexahydropyrrolo[2,3-d]-1,2,3-triazole (2b)



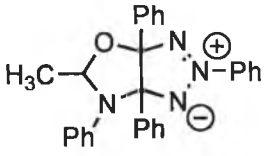
Ethyl acrylate (1g, 0.01mol) was added to a stirred solution containing (3) (1g, 2.5mmol) in 30ml of dry acetone. The solution was heated under reflux for 3 hours in the absence of light. The solvent was removed under reduced pressure and the resulting solid recrystallised from ethanol. TLC showed the crude product to contain some triazole **(224)**. Yield (0.88g, 70%) , m.p. 200-201°C, Lit.Val.: 200-202°C.

IR(KBr) (cm^{-1}): 1724 (ester, C=O)

δH($CDCl_3$)(ppm): 0.77(3H,t), 3.70(1H,t), 3.89(2H,m), 4.43(2H,q), 6.75(3H,m), 6.94(8H,m), 7.14(4H,m), 7.57(3H,m), 8.42(2H,m).

δC($CDCl_3$)(ppm): 13.46, 18.43, 57.44, 60.84, 89.46, 101.21, 116.11, 117.87, 122.99, 126.90, 127.0, 127.09, 127.15, 127.54, 127.98, 128.93, 129.05, 131.62, 137.41, 137.41, 140.92, 145.14, 170.45.

5-exo-methyl-2,3a,4,6a-tetraphenyl-3a,6,6a-tetrahydro-3H-oxazolo[4,5-d]-1,2,3-triazol-2-ium-3-ide (239a)



To a solution of **(3)** (0.5g, 1.28mmol) in 20ml of dry xylene was added acetaldehyde (0.27g, 6.36mmol). The mixture was stirred for 2 hours at 70°C under nitrogen in the dark. Evaporation of the solvent under reduced pressure yielded a crude solid, which

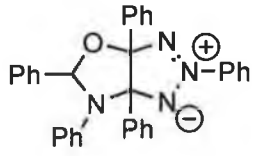
was recrystallised from ethanol. Yield (0.432g, 80%), m.p.192-193°C, Lit.Val.: 192-193°C

IR(KBr) (cm^{-1}): 1600 [$N=N^{+}(Ph)-N^{-}$]

δH($CDCl_3$)(ppm): 1.7(3H,d), 5.49(1H,q), 6.7-7.4(18H,m), 8.13-8.33(2H,m)

δC($CDCl_3$)(ppm): 19.86, 87.32, 98.48, 112.38, 117.39, 120.46, 122.89, 126.78, 127.56, 127.68, 128.10, 128.56, 129.09, 132.12, 136.88, 138.27, 140.6, 143.1, .

5-exo-phenyl-2,3a,4,6a-tetraphenyl-3a,6,6a-tetrahydro-3H-oxazolo[4,5-d]-1,2,3-triazol-2-ium-3-ide (239b)



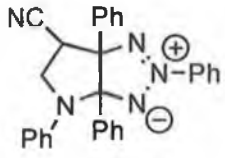
(3) (3g, 7.7mmol) was dissolved in 100ml of dry acetone to which benzaldehyde (4.98g, 0.047mol) was added. The stirred solution was allowed to reflux under nitrogen in light absence for 3 hours. The solvent was removed under reduced pressure yielding an oil. A few drops of hot, dry ethanol was added to the oil at which point yellow precipitate fell out on cooling. Yield (2.42g, 65%), m.p. 175-176°C, Lit.Val.: 174-175°C

IR(KBr) (cm^{-1}): 1600 [$N=N^{+}(Ph)-N^{-}$]

δH($CDCl_3$)(ppm): 5.06(1H,d), 6.74-6.81(2H,m), 7.00-7.22(12H,m), 7.45-7.59(4H,m), 8.34-8.39(2H,m).

δC($CDCl_3$)(ppm): 80.83, 95.95, 114.87, 115.95, 119.20, 123.03, 126.83, 127.14, 127.46, 127.78, 128.03, 128.16, 129.92, 129.04, 136.75, 137.2, 140.62.

6-cyano-2,3a,4,6a-tetraphenyl-3,3a,4,5,6,6a-hexahydropyrrolo[2,3-d]-1,2,3-triazole (1a)



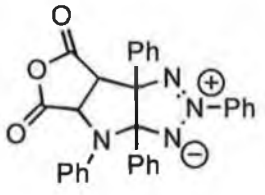
(3) (2g, 5.15mmol) and acrylonitrile (1.32g, 0.25 mol) were refluxed in 50ml of dry acetone for 45 minutes under nitrogen in the absence of light. Removal of the solvent under reduced pressure gave a solid, which upon recrystallisation from dry methanol gave (1a). Yield (1.81g, 82%). m.p. 249-250°C, Lit.Val.: 249^{0}C

IR(KBr) (cm^{-1}): 2242 cm^{-1}(CN)

δH($CDCl_3$)(ppm):3.86(1H,dd), 4.00(1H,dd), 4.32(1H,dd), 6.78(1H,m), 6.93(2H,m), 7.05(8H,m), 7.14(2H,m), 7.22(2H,m), 7.50(2H,m), 7.59(1H,m), 8.30(2H,m).

δC($CDCl_3$)(ppm): 41.42, 51.42, 88.16, 99.71, 115.49, 116.69, 119.69, 122.80, 127.48,127.53,127.92,127.97,128.63,129.08,132.05,135.31,136.59,140.28,144.07.

5,6-carboxylicanhydride-2,3a,4,6a-tetraphenyl-3,3a,4,5,6,6a-hexahydropyrrolo[2,3-d]-1,2,3-triazole (253)



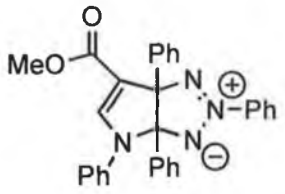
To a solution of **(3)** (0.7g, 1.85mmol) in acetone (2ml), maleic anydride (0.25g, 2.55mmol) was added and stirred under reflux for 30 minutes. The solvent was removed under reduced pressure and the residue recrystallised from ethanol to give **(253)**.Yield (0.7g, 80%). m.p. 226-228°C, Lit.Val.: 228^{0}C.

IR(KBr) (cm^{-1}):1790 and 1860 cm^{-1} (C=O)

δH($CDCl_3$)(ppm): 4.60(1H,d), 5.7(1H,d), 7.00 (14H,m), 7.56(4H,m), 8.31(2H,m).

δC($CDCl_3$)(ppm): 60.01, 63.65, 88.92, 103.85, 118.24, 120.61, 122.13, 127.14, 127.46, 127.83, 128.14, 128.57, 129.16, 132.25, 133.74, 135.67, 144.46, 166.43, 171.37.

6-methoxycarbonyl-2,3a,4,6a-tetraphenyl-3,3a,4,6a-tetrahydropyrrolo [2,3-d]-1,2,3-triazole (254)



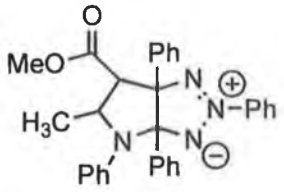
(3) (1g, 2.64mmol) and methyl propiolate (0.45g, 5.29mmol) were heated under reflux in 50ml of absolute acetone until the solution turned yellow. The solvent was removed under reduced pressure and an oil resulted. The oil was stirred vigorously with the addition of hot ethanol dropwise. A yellow solid fell out which was filtered and washed with cold ethanol. Yield (0.857g, 70%). m.p.195-197^{0}C, Lit.Val.: 196-198^{0}C

IR(KBr) (cm^{-1}): 1708 (ester C=O), 772, 760, 750, 726, 698, 688.

δH($CDCl_3$)(ppm): 2.02(3H,s), 3.63(1H,d), 3.85(1H,t), 4.49(1H,t) 6.91(3H,m), 6.94(8H,m), 7.13(4H,m), 7.61(3H,m), 8.49(2H,m).

δC($CDCl_3$)(ppm): 30.92, 47.79, 66.04, 88.51, 101.89, 116.04, 117.7, 122.74, 127.07, 127.09, 127.50, 127.57, 127.59, 128.47, 131.78, 136.56 137.09, 140.82, 145.15, 205.95.

6-methoxycarbonyl-5-methyl-2,3a,4,6a-tetraphenyl-3,3a,4,5,6-hexahydropyrrolo [2,3-d]-1,2,3-triazole (256a)



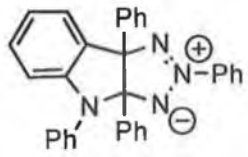
(254) (1g, 2.64 mmol) was dissolved in 50ml of absolute T.H.F. and stirred over a nitrogen atmosphere. 45 ml of methylmagnesiumiodide-ether solution was added to the reaction drop-wise by syringe. When all the Grignard had been added, the reaction was heated to reflux and left for 1 hour. The solvent was completely removed and the remainder added to 20ml of water. The aqueous solution was extracted twice with 20ml of dichloromethane, the organic phase dried with $MgSO_4$ and the solution filtered. All the solvent was removed under reduced pressure and an oil obtained by flash chromatography (pet.ether (40-60^0) 70%:30% ethyl acetate) to give a pure yellow oil. Yield (0.79g, 63%). m.p. 201-203^{0}C, Lit.Val.: 203^{0}C

IR(KBr) (cm^{-1}): 1720, 1570, 1475, 1440, 1360, 1205, 1025, 730.

δH($CDCl_3$)(ppm): 1.34(3H, d), 3.67(3H, s), 4.47(1H, d), 5.03(1H, q), 6.64(1H, m), 6.72-7.59(17H, m), 8.37(2H,m).

δC($CDCl_3$)(ppm): 14.21 ,50.79, 51.90, 53.01, 86.22, 99.00, 115.55, 116.27, 118.59, 122.08, 124.31, 125.88, 126.42, 127.01, 127.40, 128.25, 128.45, 130.49, 135.95, 136.42, 139.95, 141.43, 168.12.

Benzo[1,2-b]-2,3a,4,6a-tetraphenyl-3,3a,4,6a-tetrahydropyrrolo[2,3-d]-1,2,3-triazole (268)



The dipole **(3)** (1g, 2.64mmol) was added to 30ml of dimethoxyethane and the solution heated to reflux temperature. 5ml of isoamylnitrite was added to a conical flask containing 15ml of dimethoxyethane. Similarly a 20ml solution of 3.5g of anthranilic acid in dimethoxyethane was made up. 2ml of each solution was added simultaneously to the reaction through the condenser every 5 minutes. When this was complete the reaction was further heated to reflux with vigorous stirring for 25 minutes. Excess solvent and isoamylnitrite were removed under reduced pressure and the remaining oil absorbed onto 10g of silica. The isolation of **(268)** was achieved by flash chromatography. (Pet.ether (80:20) 80%:ether 20%) to give **(268)**. Yield (0.60g, 51%). m.p. 142^0C

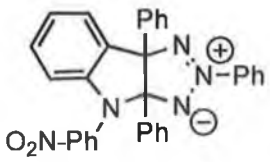
IR(KBr) (cm^{-1}): 1600, 1588, 1499, 761, 774, 754.

δH($CDCl_3$)(ppm): 6.81-6.93(4H,m), 6.94-7.07(8H,m), 7.11(1H,m), 7.15-7.28(4H,m), 7.44-7.59(5H,m), 8.34(2H,m).

δC($CDCl_3$)(ppm): 91.40 (C-6a), 105.42 (C-3a), 108.92, 125.42, 123.31, 123.97, 124.05, 127.51, 127.58, 127.80, 127.87, 128.34, 129.94, 129.20, 129.35, 129.64, 131.01, 132.05, 137.99 (6a-C-Ph, C-1'), 139.24 (3a-C-Ph, C-1'), 141.12(4-N-Ph, C-1'), 141.56 (2-N-Ph, C-1'), 150.03 (C5).

	%Theory	**%Found**
C:	82.73	82.56
H:	5.20	4.98
N:	12.05	12.12

Benzo[1,2-b]-4-*p*-nitrophenyl,2,3a,6a-triphenyl-3,3a,4,6a-tetrahydropyrrolo[2,3-d]-1,2,3-triazole (276)



The dipole **(275)** (1g, 2.64mmol) was added to 30ml of dimethoxyethane and the solution heated to reflux temperature. 5ml of isoamylnitrite was added to a conical flask containing 15ml of dimethoxyethane. Similarly a 20ml solution of 3.5g of anthranilic acid in dimethoxyethane was made up. 2ml of each solution was added simultaneously to the reaction through the condenser every 5 minutes. When this was complete the reaction was further heated under vigorous stirring for 25 minutes. Excess solvent and isoamylnitrile were removed under reduced pressure and the remaining oil absorbed onto 10g of silica. The isolation of **(276)** was achieved by flash chromatograpy. (Pet.ether (80:20) 80%: Diethyl ether 20%). Yield (0.92g, 57%). m.p. 158^0C

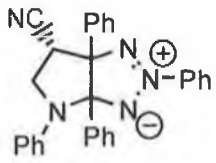
IR(KBr) (cm^{-1}): 1585, 1480, 1468, 1324, 762, 747, .685.

δH($CDCl_3$)(ppm):6.84-7.21(10H,m),7.27-7.36(2H,m),7.42-7.68(7H,m),8.08(2H,m), 8.32(2H,m).

δC($CDCl_3$)(ppm): 91.26 (C-6a), 105.41 (C-3a), 110.09, 120.71, 122.80 ,123.31, 125.25, 127.81, 127.93, 128.07, 128.25, 128.31, 128.38, 128.83, 129.62, 129.83, 132.21, 132.52, 136.94 (6a-C-Ph, C-1'), 138.09 (3a-C-Ph, C-1'), 140.78 (4-N-Ph, C-1'), 142.01 (2-N-Ph, C-1'), 147.20 (4-N-Ph, C-4'), 147.41 (C5).

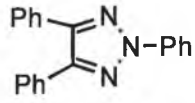
	%Theory	**%Found**
C:	75.42	75.61
H:	4.54	4.33
N:	13.74	13.51

Base catalysed epimerisation of (1a) to (260)



To **(1a)** (1g, 2.26mmol) in 70ml of toluene was added a molar equivalent of *t*-BuOK. The solution was refluxed for 1 hour whereby the solvent was removed to give (180) and unreacted **(1a)**. On leaving to stand, the growth of (1a) was observed by T.L.C.

Formation of 2,4,5-triphenyl-1,2,3-triazole (224)



Method 1

A two molar excess of *t*-BuOK was added to **(1a)** (1g, 2.26mmol) in 70ml of toluene and the refluxing mixture left for 24 hours to react. The triazole was recovered by flash chromatography. Yield (0.31g, 47%)

Method 2

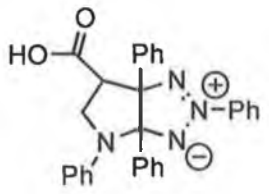
(3) (1g, 2.5mmol) was heated to melting point in a Schlenk tube under vacuum for 10 minutes using a heating gun. The triazole was separated by flash chromatography. Yield (0.22g, 31%). m.p. 119-121°C.

IR(KBr) (cm^{-1}): 617, 655, 689, 736, 775, 782 cm^{-1}.

δH($CDCl_3$)(ppm): 7.36(7H,m), 7.47(2H,m), 7.63(4H,m), 8.16(2H,m).

δC($CDCl_3$)(ppm): 118.70, 127.34, 127.41, 128.58, 128.61, 129.23, 130.71, 139.66, 149.91.

6-carboxylicacid-2,3a,4,6a-tetraphenyl-3,3a,4,5,6,6a-hexahydropyrrolo[2,3-d]-1,2,3-triazole (263)



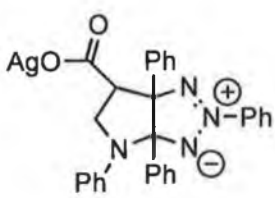
(1b) (1g, 2.1mmol) was dissolved in 30 ml of dichloromethane to which NaOH (0.1g, 0.4 mol) was added and the reaction mixture was allowed to stir under reflux for 20 minutes. The salt of the acid was extracted into water whereby conc. HCl was added drop-wise. The solution was left to stir for 30 minutes at which point the carboxylic acid was re-extracted into dichloromethane and the organic phase dried with magnesium sulphate and filtered. Removal of the solvent under reduced pressure gave a crude solid, which was recrystallised from ethanol. Yield (0.77g, 82%). m.p 191-194°C.

IR(KBr) (cm^{-1}): 1742, 2831-3080.

δH($CDCl_3$)(ppm): 3.80(1H,t), 3.94(2H,m), 6.82(3H,m), 6.90-7.16(12H,m), 7.71(3H,m), 8.52(2H,m), 11.61(1H,bs).

δC($CDCl_3$)(ppm): 18.5, 60.9, 90.1, 102.4, 117.12, 121.94, 126.91, 127.0, 127.11, 127.17, 127.34, 127.92, 128.94, 129.13, 131.54, 137.40, 137.81, 140.93, 146.83, 173.82.

Silver metal salt of the carboxylic acid derivative (264)



(263) (1g, 2.2mmol) was dissolved in 50 ml of dichloromethane to which silver nitrate (0.36g, 2.17mmol) was added. The heavy metal salt immediately falls out of

solution. The solution was filtered and the solid washed with water. The pure solid was left to dry overnight under vacuum. Yield (0.91g, 76%). m.p. 221^{0}C

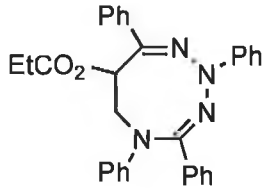
IR(KBr) (cm^{-1}): 1761cm^{-1} (C=O).

δH($CDCl_3$)(ppm): 3.99(1H,t), 4.23(2H,m), 7.04(3H,m), 7.24-7.50 (12H,m), 7.91(3H,m), 8.74(2H,m).

δC($CDCl_3$)(ppm): 19.21, 62.46, 91.82, 103.46, 118.19, 121.99, 125.99, 127.5, 127.72, 127.81, 127.93, 128.46, 130.10, 131.45, 132.99, 138.56, 139.42, 142.96, 147.41, 178.42.

Photochemistry

Photochemical rearrangement of 6-ethoxycarbonyl-2,3a,4,6a-tetraphenyl-3,3a,4,5,6,6a-hexahydropyrrolo[2,3-d]-1,2,3-triazole (1c) to yield 7-ethoxycarbonyl-2,4,5,8-tetraphenyl-2,3,6,7-tetrahydro-1,2,3,5-tetrazocine (2)



m.p. 101-105°C.

IR(KBr) (cm^{-1}): 1730(C=O, ester), 1621(C=N).

δH($CDCl_3$)(ppm):0.56(3H,t),3.36(1H,m),3.52(1H,m),3.96(2H,m),4.21(1H,dd),6.30(3H,m), 6.52(1H,m), 6.57(1H,m), 6.81(12H,m), 7.25(2H,m).

δC($CDCl_3$)(ppm):13.72, 48.08, 49.55, 61.60, 116.95, 122.15, 122.52, 127.46, 127.98, 127.60, 127.98, 128.20, 129.04, 129.26, 129.79, 130.43, 134.88, 136.34, 143.18, 150.15, 154.40, 168.81, 176.05.

Method 1 (sunlight)

(1a) (0.4g, 0.81mmol) was dissolved in 100ml of dry dichloromethane. The solution was flushed with dry nitrogen for 5 minutes and the flask stoppered. The stirring mixture was followed by T.L.C over a month, upon which time all the cycloadduct

had been converted to the tetrazocine **(2)**. The solvent was removed and the terazocine was recrystallised from 1:1 diethyl ether: hexane. Yield (0.4g, 100%)

Method 2 (450 W mercury lamp)

(1a) (0.4g, 0.81mmol) was dissolved in 350ml of dry dichloromethane. The solution was flushed with nitrogen for 5 minutes. The stirred solution was photolysed with the lamp under nitrogen for 50 minutes. TLC showed a complex mixture of products. Separation by flash chromatography gave the tetrazocine. Yield (0.1, 26%) Other products recovered where shown to be the triazole **(153)** and some starting material.

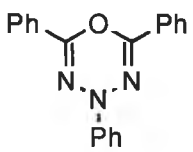
Method 3 (solid state photolysis)

(1a) (1g, 2mmol) was dissolved in the minimum amount of dichloromethane required. The solution was spread out even over a large glass surface (e.g an oil bath) and the solvent allowed to evaporate off leaving a thin film of (1a) coating the glass surface. The solid was irradiated with the 450W mercury lamp for 50 minutes under nitrogen. (0.52g, 50%) of the tetrazocine was recovered by flash chromatography.

Method 4 (250W tungsten lamp)

(1a) (0.2g, 0.4mmol)) was placed in a 50ml Duran round bottomed flask to which 20 ml of dry dicholormethane was added. The solution was degassed with nitrogen for 5 minutes and the flask then stoppered. The stirred solution was irradiated with the lamp for 3 hours giving a 100 % conversion of **(1a)** to the tetrazocine **(2)**. Yield (0.2g, 100%)

Formation of the 1,3,4,5-Oxatriazine (240)



1g of **(239a)** or **(239b)** were converted to the oxatriazine in yields between 25-40% when using identical procedures as described above in methods one, two and three

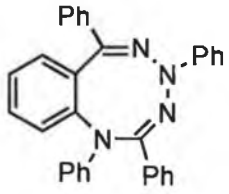
for **(1a)**. Solid-state photolysis was found to be the more high yielding. Each experiment required **(240)** being recovered from flash chromatography. m.p. 170-171°C, Lit.Val.: 170-171^{0}C

IR(KBr) (cm^{-1}): 1591cm^{-1}(C=N).

δH($CDCl_3$)(ppm): 7.04(1H,m), 7.40(1H,m), 7.54(8H,m), 7.67(1H,m), 7.80 (4H,m).

δC($CDCl_3$)(ppm): 115.38, 122.45, 126.22, 128.38, 128.57, 128.74, 131.12, 144.76, 147.03.

Photolysis of (268) to Benzo[1,2-f]-2,4,5,8-tetraphenyl-2,5-dihydro-1,2,3,5-tetrazocine (269)



(268) (0.5g, 1.10mmol) was dissolved in absolute dichloromethane (3ml) and placed in a UV-VIS millicuvette. The solution was de-aerated with N_2 and the container stoppered. The solution was irradiated with a 250 W tungsten lamp for 24 hours with stirring at which point the formation of the tetrazocine appears to stop. The solvent was removed and **(269)** was separated by flash chromatography (pet.ether (40:60^0)80%: ether 20%) to give the tetrazocine. Yield (0.2g, 40%). m.p.128^{0}C

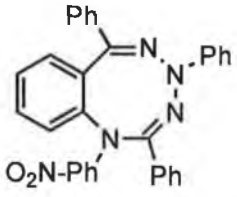
IR(KBr) (cm^{-1}): 1592, 1559, 1486, 1243, 751.5, 689.71.

δH($CDCl_3$)(ppm): 6.45(2H,m), 6.51(1H,m), 6.76(2H,m), 6.90 (1H, m), 7.12(2H,m), 7.21-7.29(9H,m), 7.41(3H,m), 7.58(2H,m), 7.91(2H,m).

δC($CDCl_3$)(ppm): 115.4, 119.1, 120.5, 120.6, 126.6, 127.01, 127.15, 127.26, 127.37, 127.67, 128.34, 128.43, 129.15, 130.40, 130.48, 132.35, 134.60, 138.54 (8-C-Ph, C-1'), 138.67 (4-C-Ph, C-1'), 142.09 (C-8), 144.30 (4-N-Ph, C-1'), 145.74 (C-6), 148.93 (2-N-Ph, C-1'), 172.51 (C-4).

	%Theory	%Found
C:	82.73	82.43
H:	5.20	5.26
N:	12.05	11.95

Photolysis of (276) to Benzo[1,2-f]-5-*p*-nitrophenyl-2,4,8-tetraphenyl-2,5-dihydro-1,2,3,5-tetrazocine (279)



(276) (0.5g, 0.98mmol) was dissolved in 250ml of absolute dichloromethane. The solution was placed in a photolysis set-up which consisted of a 450 W mercury low pressure lamp immersed in a quartz water cooled flask which itself was immersed in a pyrex container containing the DCM solution. The solution was continually stirred and de-aerated with N_2. After 90 minutes, the solvent was removed under reduced pressure and the remaining solid separated by column chromatography (pet.ether ($40\text{-}60^0$) 80%: ether 20%). Yield (0.285g, 57%) .m.p. 136-138^{0}C

IR(KBr) (cm^{-1}): 1589,, 1559, 1507, 1486, 761, 751, 690

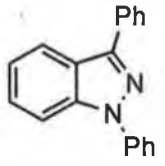
δH($CDCl_3$)(ppm): 6.51(2H,m), 7.01(1H,m), 7.15-7.83(18H,m), 7.93(2H,m).

δC($CDCl_3$)(ppm): 116.91, 122.75, 125.12, 128.23, 128.41, 128.87, 128.99, 129.24, 129.55, 129.68, 130.07, 130.37, 132.82, 132.98, 134.87, 136.85 (8-C-Ph, C-1'), 139.95 (4-C-Ph, C-1'), 141.45 (C-8), 142.54 (N-5-Ph, C-4'), 149.73 (N-5-Ph, C-1'), 151.11 (N-2-Ph, C-1'), 178.12 (C-4).

	%Theory	%Found
C:	75.42	74.79
H:	4.54	4.56
N:	13.74	13.81

Thermolysis of (268) and Related Reactions

1,3-diphenylindazole (281a)



Method 1

(268) (1g, 2.2mmol) was heated to melting point in a Schlenk tube with stirring for about 2 minutes using a heating gun. The dark solid obtained on cooling was purified by flash chromatography (pet.ether (40-60) 70%:30% ethylacetate). Yield (0.19g, 32%).

Method 2

A solution of benzophenone-phenylhydrazone (217a) (13.5g, 0.05mol) in dichloromethane (100ml) was added to $Pb(OAc)_4$ (22g, 0.05 mol) in 250ml of dry DCM at 0-5^{0}C. After 10-15 minutes, the solution volume was halved by distillation and 100ml of BF_3.ether complex was added. The mixture was heated for 20 minutes at which point the hot solution was poured into ice/water solution (200ml). The aqueous solution was extracted with 2 X 100ml of dichloromethane, dried with $MgSO_4$ and the solvent removed to give an oil like substance. Purification of the oil by column chromatography (ethyl acetate 70%:30% pet.ether (40-60^0) gave the desired compound. Yield (6.34g, 47%). m.p.146-148°C, Lit.Val.: 145-147^{0}C

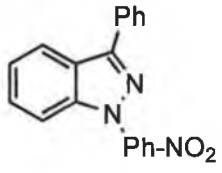
IR(KBr) (cm^{-1}): 1699, 1634, 760, 745, 694.

δH($CDCl_3$)(ppm): 7.28(1H,m), 7.35(2H, m), 7.36(1H, m), 7.53(4H, m), 7.78(3H, m), 8.51(3H, m)

δC($CDCl_3$)(ppm): 108.97, 119.84, 120.17, 121.23, 121.47, 124.91, 125.47 ,126.01, 126.52, 127.08, 127.71, 131.42, 138.47, 138.64, 144.37.

	%Theory	**%Found**
C:	84.41	84.53
H:	5.21	5.02
N:	10.36	10.17

1-*p*-nitrophenyl-3-phenylindazole (281b)



Method 1

(276) (1g, 1.96 mmol) was heated to melting point in Schlenk tube with stirring for about 2 minutes using a heating gun. The dark solid obtained on cooling was purified by flash chromatography (pet.ether (40-60) 50:50% ethylacetate). Yield of (0.281g, 48%).

Method 2

A solution of benzophenone-p-nitro-phenylhydrazone **(282)** (13.5g,0.04 mol) in dichloromethane (100ml) was added to $Pb(OAc)_4$ (22g, 0.05 mol) in 250ml of dry dichloromethane at 0-5^{0}C. After 10-15 minutes, the solution was halved by distillation and 100ml of BF_3.ether complex was added. The mixture was heated for 20 minutes at which point the hot solution was poured into ice/water solution (200ml). The aqueous solution was extracted with 2 X 100ml of dichloromethane, dried with $MgSO_4$ and the solvent removed to give an oil like substance. Purification

of the oil by column chromatography (ethyl acetate 50%:50% pet.ether (40-60^0) gave the desired compound. Yield (7.5g, 56%). m.p. 161-162^{0}C, Lit.Val. 161-162^{0}C

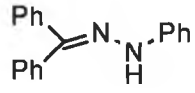
IR(KBr) (cm^{-1}): 1593, 1487, 1335, 770, 746, 689, 664.

δH($CDCl_3$)(ppm): 7.35(2H, m), 7.42-7.61(4H, m), 7.84(1H, d), 7.97-8.04(4H, m), 8.08(1H, m), 8.36(2H, m).

δC($CDCl_3$)(ppm): 111.12, 121.74, 122.69, 123.51, 124.71, 125.68, 128.31, 128.63, 129.38, 129.41, 132.74, 140.06, 145.03, 145.08, 148.07.

	%Theory	**%Found**
C:	72.37	72.51
H:	4.15	3.98
N:	13.32	13.41

Benzophenone phenylhydrazone (282a)



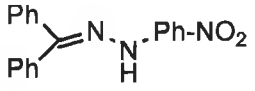
Benzophenone (5.1g, 0.047 moles) was added to a stirred solution of phenyl hydrazine (5g, 0.047 moles) and 5ml of acetic acid in 70ml of methanol. The solution was heated for 2 hours. The excess solvent was removed and the remaining solution allowed to cool which gave a precipitate. The solid was filtered and washed with 20ml of H_2O and then 100ml of pet.ether (40-60) and allowed to dry. Yield (5.92g, 64%).

IR(KBr) (cm^{-1}): 1612, 1504, 1310, 1248, 1128, 1086, 883, 776, 684.

δH($CDCl_3$)(ppm): 6.98(1H, m), 7.24(2H, m), 7.36-7.54(7H, m), 7.58-7.88(6H, m).

δC($CDCl_3$)(ppm): 113.48, 120.64, 127.05, 128.60, 128.78, 129.71, 129.81, 129.83, 130.27, 133.29, 138.94, 144.66, 145.14.

Benzophenone-*p*-nitro-phenylhydrazone(282b)



Benzophenone (10g, 0. 094 mol) was added to a stirred solution of p-nitrophenyl hydrazine (10g, 0.094 mol) and 5ml of acetic acid in 70ml of methanol. The solution was heated for 2 hours. The excess solvent was removed and the remaining solution allowed to cool which gave a precipitate. The solid was filtered and washed with 20ml of H_2O and then 100ml of pet.ether (40^0-60^0) and allowed to dry. Yield (13.59g, 60%).

IR(KBr) (cm^{-1}): 1509, 1258, 1162, 1105, 855, 776.

δH($CDCl_3$)(ppm): 7.13(2H, m), 7.30-7.43(5H, m), 7.52-7.69(5H, m), 8.07(1H, bs), 8.14(2H, m).

δC($CDCl_3$)(ppm): 112.49, 126.52, 127.52, 128.83, 129.29, 129.62, 130.32, 132.21, 137.85, 140.50, 149.19, 149.96.

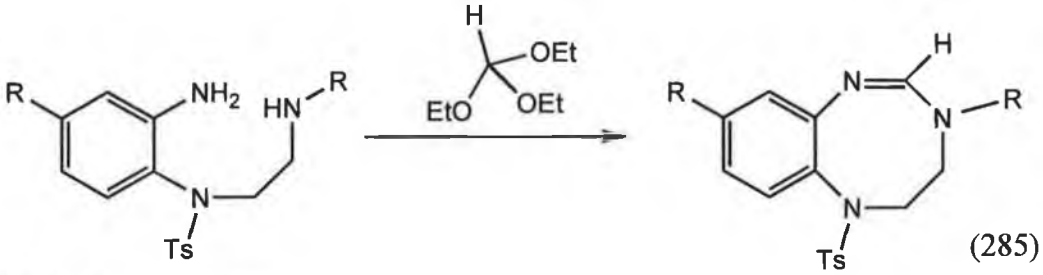
Chapter 4

Conclusion

4. Introduction

The previous three chapters give insight into the formation and properties of this ring class. In summary, the knowledge gained over the course of this work reinforced our initial suspicions that tetrazocines are rare and required more focused attention. Many other synthetic avenues were explored that are not described in the body of this thesis. These were based on obtaining 1,2,5,6-tetrazoines. Unfortunately polymerisation rather than ring closure was generally observed even at high dilution. However towards the end of this project, a promising route was developed which requires more conclusive structure verification. This area may be the subject of future work by this research group.

We began to look at ring closing methods, more specifically of eight-membered rings. A survey of triazocine literature yielded a procedure, which involved the facile cyclisation of **(284)** to **(285)**. What's more, this reaction has been derivatised, yields are high and the cyclisation step proceeded with the expected outcome each time.[126] Ring cyclisation of two terminal amino chains is a useful tool. More importantly, substitution of one of the chain carbons with nitrogen may yield a desired tetrazocine.

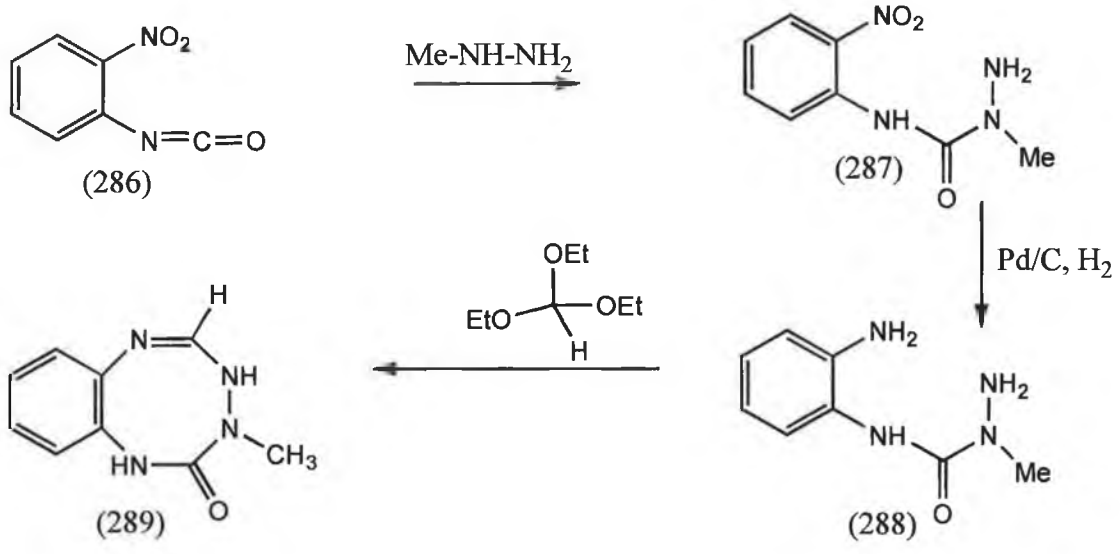


R=H, Me (284) (285)

Scheme 4.1 *Successful ring closure of two terminal amino groups with triethyl formate to form a triazocine.*

4.1. Results and Discussion

Before considering the synthesis below, a few prerequisites were kept in mind based on previous experience and Bertha's triazocine precursor **(285)**. Firstly the ring-closing step should be intramolecular. This would limit the possible number of potential product outcomes to a minimum. Similarly in order to control the number of orientations in space of these two chains to be coupled, they should be bound to an anchoring unit such as a benzene ring. Finally once ring closure has occurred, the tetrazocine ring should have functional groups such that ring closure or rearrangement would be unlikely. This would also be the case for the nitrogen order within the ring. The proposed synthesis of tetrazocine **(289)** below would hopefully satisfy all of these criteria.



Scheme 4.2 *Proposed novel formation of 1,2,4,7-tetrazocine (289).*

It can be seen that intramolecular ring contraction by attack at C5–C6 is unlikely by any of the ring nitrogens because of the aromatic ring. Of the other potential ring closing positions, attack at C3 and C8 is the most likely. However this is also unfavourable due to the non nucleophilic nature of amide nitrogens at N7 and N1. One would expect this ring to remain as an eight-membered ring.

Each step of the outlined synthesis gave reasonable yields. The product **(288)** was formed at room temperature to avoid any substitution of the hydrazide functionality by the ring amine with resultant ring closure. Triethyl formate was utilised as the ring closing reagent due to it's previous success in ring closure of triazocines with terminal amine groups on both chains to be linked.

As previously mentioned, the 1,2,4,7-tetrazocine structure has yet to be conclusively verified. Attempts at crystal growth over several months with various solvent systems always resulted in a fine powder. Also NMR spectra of the proposed tetrazocine remains a point of conjecture. The ^{1}H-NMR obtained for **(289)** in DMSO initially indicated that the substance had an impurity or decomposition product. However on closer analysis, there appears to be a second minor isomer existing in a 1:3 ratio based on the splitting patterns and integrations. In order to see whether the ratio of these isomers was solvent dependent, the sample was run in $CDCl_3$ but a similar spectra was obtained. However it was finally shown that by recording the spectra at 100^{0}C in DMSO, one major isomer was observed with correct integration and chemical shift that would indicate the existence of **(289)**. Due to the slight solubility of **(289)** in DMSO, a ^{13}C spectrum was unobtainable

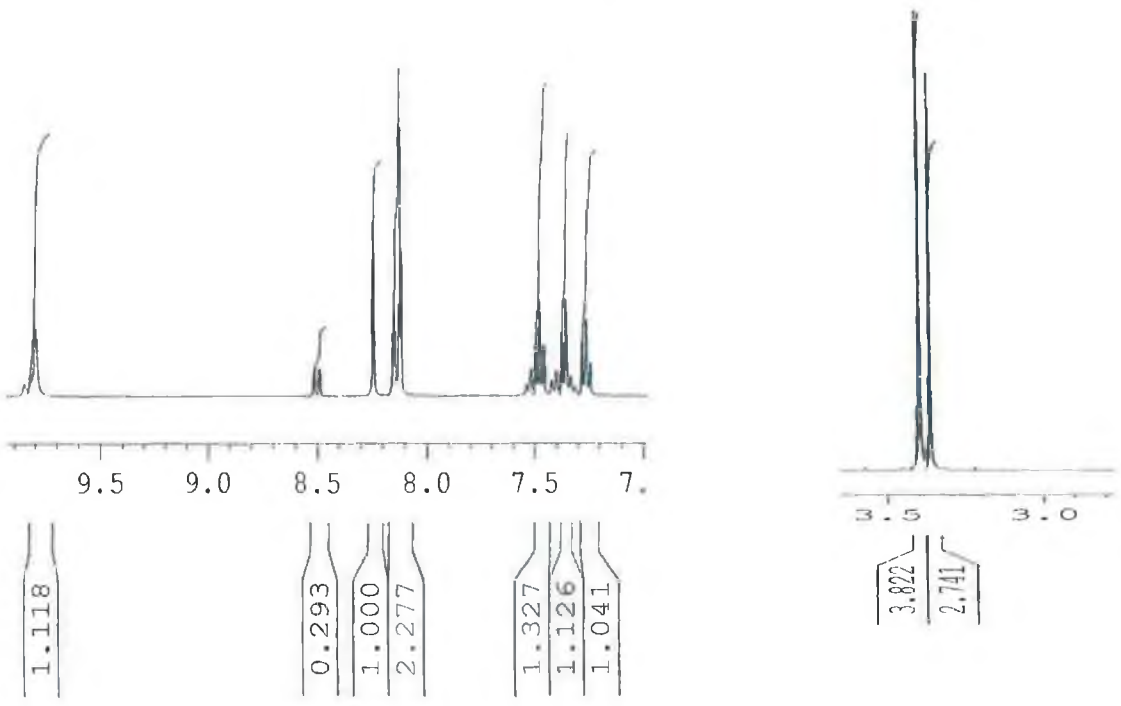


Figure 4.1 *^{1}H-NMR of (289) at room temperature in DMSO.*

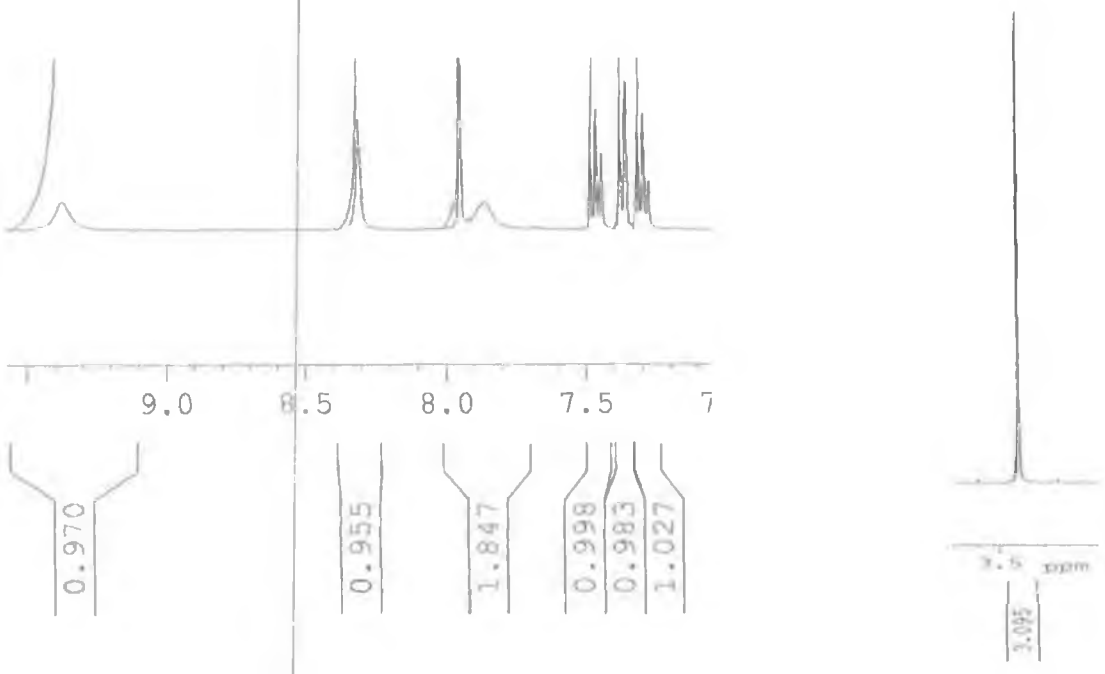
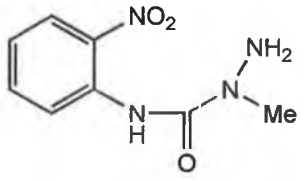


Figure 4.1 *^{1}H-NMR of (289) at 100^{0}C in DMSO.*

This work needs to be verified by generating analogues, which may give crystals suitable for X-ray analysis. Alternatively the molecule in question could be derivitised to give a more easily identifiable substrate.

4.2. Experimental

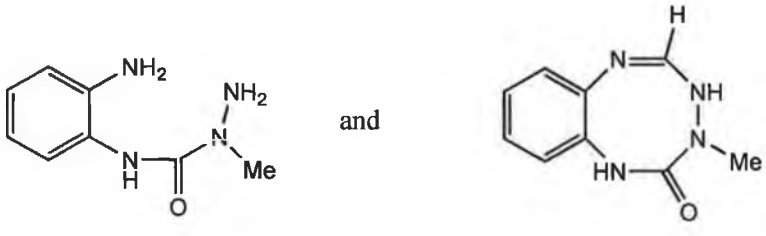
Formation of (287)



The isocyanate **(286)** (5g, 0.03 mol) was added to a solution of methylhydrazine (1.4g, 0.03 mol) in 25mls of acetonitrile. The solution was stirred at room temperature for 2 hours. Over the course of the reaction, a solid precipitates out of solution which was filtered on reaction completion. The excess solvent from the filtrate was removed under reduced pressure at room temperature to give more solid which again was filtered off. Finally the solid was heated in 50ml of pet.ether(40-60^0) and hot filtered to give **(287)** . Yield (5.31g, 83%). m.p.135-136^{0}C

IR(KBr)(cm^{-1}): 3320, 3334, 3260, 2936, 1690, 1668, 1410, 1316, 1145, 744, 735.
δH(DMSO-d_6)(ppm): 3.09(3H, s), 4.96(2H, bs) 7.04(1H, m), 7.60(1H, m), 8.06(1H, m), 8.59(1H, m), 11.41(1H, bs).
δC(DMSO-d_6)(ppm): 37.45, 120.15, 121.22, 125.85, 135.53, 135.92, 136.66, 155.76

Formation of (288) and (289)



The nitro derivative **(287)** (1g, 4.76mmol) in 30ml of anhydrous dioxane and 0.1g of Palladium/carbon was stirred at room temperature while bubbling H_2 at atmospheric pressure through the solution. The reaction was followed by T.L.C. After 20 minutes, the H_2 source was stopped and the reaction flask and solution flushed with N_2 for 2 minutes. The catalyst was removed by filtration over N_2. The filtrate was

transferred to a 100ml round bottomed flask to which triethylformate (0.53g, 4.76mmol) and acetic acid was added. The reaction mixture was heated to reflux for 3 hours whereby the solvent was removed under reduced pressure to dryness. The remaining oil was triturated with a small amount of methanol to obtain **(289)**. Yield (0.57g, 63%). m.p. 181-183^{0}C

IR(KBr)(cm^{-1}): 3237, 3192, 2876, 1693, 1464, 1305, 970, 751.
δH(DMSO-6)(ppm) (100^{0}C): 3.42(3H, s) (N-2-CH_3), 7.31(1H, m), 7.38(1H, m), 7.44(1H, m), 7.84-7.92(2H, m), 8.41(1H, bs) (N-1-H), 9.39(1H, bs) (N-4-H).

On one occasion **(288)** was isolated, purified and gave the following spectrum.

δH(DMSO-d_6)(ppm): 3.07(3H,s), 3.78(2H, bs), 3.96(2H, bs), 6.76(2H, m), 6.97(1H, m), 7.21(1H, m), 8.21(1H, bs).

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