STUDIES OF NOVEL NITRO-SUBSTITUTED NITROGEN HETEROCYCLIC COMPOUNDS

A thesis submitted for the degree of Doctor of Philosophy

by

Simon Patrick Philbin

Chemistry Unit, Institute of Physical and Environmental Sciences
Brunel University

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Contents

To Mum, Dad and Victoria

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Simon P. Philbin B.Sc. (Hons.) EurChem CChem MRSC
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List of Abbreviations

Ac	acetyl
AIBN	α,α'-azobis(isobutyronitrile)
ANFO	ammonium nitrate/fuel oil (explosive) mixture
ANPZ	2,6-dinitro-3,5-diaminopyrazine
ANPZ-i	2,5-diamino-3,6-dinitropyrazine
aq.	aqueous
Bz	benzoyl
c.	concentrated
°C	degree(s) celsius
ca.	*circa*
CAS	chemical abstracts
CRP	Corporate Research Programme
CSC	Cambridge Scientific Computing, Inc (molecular modelling software company)
δ	chemical shift (NMR)
D	detonation velocity
Δ	heat
DCM	dichloromethane
decomp.	decomposition
DERA	Defence Evaluation and Research Agency
DMA	*N,N*-dimethylaniline
DMD	dimethyldioxirane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
equiv.	equivalent
Et	ethyl
h	hours
HMPA	hexamethylphosphorus triamide
HMX	high melting explosive, also known as octogen, (cyclotetramethylenetetranitramine or octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine)
HPLC	high performance liquid chromatography, also known as, high pressure liquid chromatography
HRMS	high resolution mass spectrometry
IR	infra red (spectroscopy)
lit.	literature

m	*meta*
max.	maximum
M	mole.dm^{-3}
MCPBA	*meta*-chloroperbenzoic acid
Me	methyl
MoD	Ministry of Defence
MOLPAK	Crystal structure density code for CHNO explosives
MOPAC	Molecular orbital package (semi-empirical)
MS	mass spectrometry
MTO	methyltrioxorhenium
M.Pt.	melting point
m/z	mass-to-charge ratio, sometimes referred to as *m/e* (MS)
MW	molecular weight
N.A.	not applicable
NG	nitroglycerine
NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance (spectroscopy)
o	*ortho*
OB	oxygen balance
p	*para*
$P_{C\text{-}J}$	detonation pressure
PM3	Hamiltonian approximation - molecular orbital code
Pr	propyl
p-TSA	*para*-toluenesulfonic acid
PZO	2,6-diamino-3,5-dinitropyrazine-1-oxide
PZDO	2,5-diamino-3,6-dinitropyrazine-1,4-dioxide
RDX	research department explosive, also known as hexogen, (cyclotrimethylenetrinitramine or hexahydro-1,3,5-trinitro-1,3,5-triazine)
r.t.	room temperature
s	seconds
soln.	solution
T	temperature
TATB	1,3,5-triamino-2,4,6-trinitrobenzene
TBHP	*tert*-butylhydroperoxide
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMD	theoretical maximum density

TMHI	1,1,1-trimethylhydrazinium iodide
TNT	2,4,6-trinitrotoluene
TMS	tetramethylsilane
UV	ultra-violet (detection used in HPLC)
V_D	detonation velocity
VNS	vicarious nucleophilic substitution
wt./vol.	weight/volume

Glossary

Detonation Velocity (V_D or D)

The detonation velocity is the rate of propagation of a detonation (supersonic chemical reaction) in an explosive which can be either solid, liquid or gas. The unit used for V_D values is usually $km.s^{-1}$.

Detonation Pressure (P_{C-J})

The detonation pressure is the pressure immediately behind the detonation wave based on Chapman-Jouget theory. Chapman-Jouget theory is based on a one dimensional detonation where the transformation from explosive to gaseous products occurs very quickly and at a steady state. The unit used for P_{C-J} values is usually atm.

Figure of Insensitivity (F of I)

The 'Figure of Insensitivity' of an explosive or explosive composition is the distance a standard hammer or heavy weight can be raised above an explosive and then dropped before a detonation is observed. Therefore, the higher the hammer can be raised without the detonation occurring the more insensitive the explosive is. Conversely, if the hammer can only be raised a small distance above the explosive before a detonation is observed then the explosive is more sensitive or less insensitive. The test performed to measure F of I values is often referred to as the drop hammer test. The unit used for F of I values is usually cm.

Steric Energy

Steric energy can be calculated using the CSC Chem3D Plus molecular modelling package. The steric energy value is a summation of seven different types of energy terms. These energy terms relate to different attractive and repulsive energies which can be attributed to a molecule in the gaseous phase. The energies are as follows: stretch, bend, stretch-bend, torsion, non 1,4-Van der Waals, 1,4-Van der Waals and dipole/dipole energies (see Section 7.1 Molecular Modelling Studies: Introduction). The unit used for steric energy values is usually $kcal.mol^{-1}$.

1. Abstract

The novel candidate high energy insensitive explosive; 2,5-diamino-3,6-dinitropyrazine (ANPZ-i) (**10**) has been prepared in acceptable overall yield. ANPZ-i was synthesised by the nitration of 2,5-diethoxypyrazine (**149**, R=Et) using nitronium tetrafluoroborate ($NO_2^+BF_4^-$) in sulfolane and the subsequent amination of 2,5-diethoxy-3,6-dinitropyrazine (**150**, R=Et) under autoclave conditions. Oxidation studies towards the dioxide derivative of ANPZ-i, 2,5-diamino-3,6-dinitropyrazine-1,4-dioxide (PZDO) (**11**), were unsuccessful. The synthesis of existing high explosives; 2,6-diamino-3,5-dintropyrazine (ANPZ) (**95**) and 2,6-diamino-3,5-dinitropyrazine-1-oxide (PZO) (**9**) has been scaled up to produce approximately 25 g batches of material.

A number of novel nitrations using $NO_2^+BF_4^-$ have been carried out on a range of chloro-, methyl- and hydroxy-functionalised quinoxalines and quinazolines.

A range of novel functionalisations have been carried out on the platform molecule 2,4-diamino-6,8-dinitroquinazoline (**61**) giving rise to 2,4-diamino-6,8-dinitroquinazoline-1,3-dioxide (**141**) (di-*N*-oxidation product), 2,4,7-triamino-6,8-dinitroquinazoline (**142**) (monoamination product) and 2,4,6,8-tetra-aminoquinazoline (**143**) (dihydrogenation product).

Detonics molecular modelling was carried out on the following target molecules: 2,5-diamino-3,6-dinitropyrazine-1,4-dioxide (PZDO) (**11**), 2,5,8-triamino-3,6,7-trinitroquinoxaline-1-oxide (**151**) and 2,5,7-triamino-4,6,8-trinitroquinazoline-1-oxide (**138**). The detonation velocity of the new explosive molecule; 2,5-diamino-3,6-dinitropyrazine (ANPZ-i) (**10**) was calculated and it was found to be a similar value to that obtained experimentally for the existing high explosive RDX (**5**). Calculation by molecular modelling of the steric energies of ANPZ (**95**), PZO (**9**), ANPZ-i (**10**) and PZDO (**11**) gave a quantitative assessment of the difficulty in oxidising ANPZ-i to give PZDO.

Extensive analysis of carbon-13 NMR spectroscopy shift values was carried out for approximately twenty nitrogen heterocyclic compounds. Comparison of shift values indicated consistency in the interpretations.

On-line literature searches have shown that the following compounds prepared in this project are new: 2,3,6-trichloro-5-nitroquinoxaline (**120**), 2,3-dimethoxy-6,7-dinitroquinoxaline (**128**), 2,3,6-trichloroquinoxaline-1-oxide (**133**), 2,4-diamino-6,8-dinitroquinazoline-1,3-dioxide (**141**), 2,4,7-triamino-6,8-dinitroquinazoline (**142**) and 2,5-diamino-3,6-dinitropyrazine (ANPZ-i) (**10**). Furthermore, new synthetic routes have been used in the preparation of the following compounds: 2,3-dichloro-5-nitroquinoxaline (**118**), 2,3,6,7-tetrachloro-5-nitroquinoxaline (**123**), 2-hydroxy-6-nitroquinoxaline (**127**), 2-hydroxy-3-methyl-6-nitroquinoxaline (**126**) and 2,5-diethoxy-3,6-dinitropyrazine (**150**, R=Et).

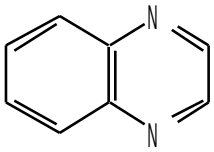
2. Introduction

2.1 Aims

There currently exists a continued requirement for high density explosives with both increased energy output and increased insensitiveness when compared to existing explosive compounds. This requirement is towards a global effort in preparing explosive compounds and their formulations with lower vulnerability to heat, mechanical shock and friction.

This project has been designed to address the synthesis of nitro-substituted nitrogen heterocyclic compounds as part of an integrated package of work funded by DERA (Defence Evaluation and Research Agency) within the overall UK MoD (Ministry of Defence) Corporate Research Programme (CRP).

The purpose of this Ph.D. project is to synthesise energetic nitro-substituted nitrogen heterocyclic compounds; principally quinoxalines (**1**), quinazolines (**2**) and pyrazines (**3**). Synthesis studies were primarily targeted towards the preparation of explosive compounds with nitro, amino and *N*-oxide functionalisation of the heterocyclic and carbocyclic ring systems. Such compounds were chosen because it is known that compounds which contain a high number of these functional groups have both a high detonation pressure and a high insensitivity to external stimuli (i.e. they have favourable energetic materials properties).



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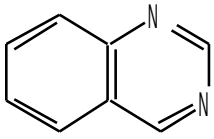

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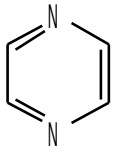

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The specific aims of the project include the following:

1. To carry out a comprehensive literature search on explosives and detonics chemistry as well as general nitration chemistry. Also, to review literature

on the synthesis, nitration, amination and oxidation reactions of quinoxaline, quinazoline and pyrazine compounds.

2. To perform calculations on a range of energetic materials including both target molecules and existing compounds using molecular modelling techniques and more established linear equations. Also, to use molecular modelling (computational studies) to back up and help interpret different experimental results.
3. To investigate in depth the nitration of quinoxaline, quinazoline and pyrazine compounds. These studies to focus on the fundamental nitration reactions of simple hydroxy-, methyl-, methoxy- and chloro- substituted nitrogen heterocycles. Such compounds were chosen because they are cheap and readily available and as such are ideal as precursor compounds for the synthesis of energetic materials.
4. To investigate the preparation of highly functionalised nitrogen heterocyclic compounds which contain nitro, amino and *N*-oxide groups. Consequently, to assess the suitability of a range of different reagents for the aforementioned reactions. In particular to focus on the use of many different types of nitration reagents and to identify and optimise the most efficient and high yielding systems. Furthermore, to investigate the use of different solvents as reaction media for nitration reactions.
5. To carry out a detailed analysis of the carbon-13 NMR spectroscopy shift values for a broad range of nitro-substituted nitrogen heterocyclic compounds and their precursor compounds.
6. To carry out the preparation of a known energetic material and to scale-up the synthesis to the production of 20 g batches of the final material. Consequently, to assess and modify the experimental procedures where appropriate.

2.2 Explosives Chemistry[1-3]

2.2.1 The Nature of Explosives

With the exception of gun powder, which is thought to have been discovered before the year 1000 AD, most explosives used today were discovered in the 16th to 19th centuries. One of the oldest explosives known is nitroglycerine (NG) (**4**).

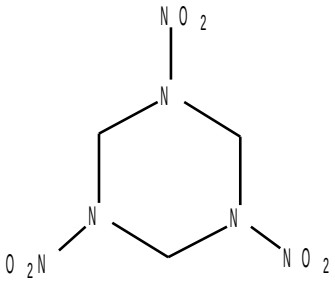
This compound has a high detonation velocity (7600 ms^{-1}) but unfortunately suffers from a high sensitivity.

The two high explosives most commonly used today are cyclotrimethylenetrinitramine (hexahydro-1,3,5-trinitro-1,3,5-triazine) (**5**) otherwise known as RDX and cyclotetramethylenetetranitramine (octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine) (**6**) known more commonly as HMX. Both RDX and HMX have very high detonation velocities (8750 ms^{-1} and 9100 ms^{-1} respectively) but are also relatively sensitive. Therefore, new explosives must have both high detonation velocities and high insensitivity.

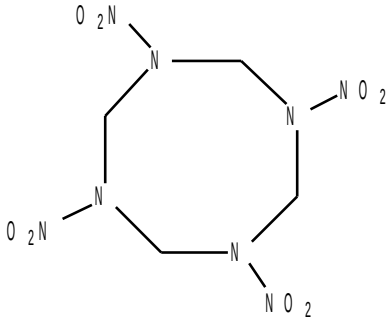
Compounds **4**, **5** and **6** all contain energetic functional groups which may facilitate the liberation of heat and/or gaseous compounds upon explosion. The C-NO_2 (nitro), N-NO_2 (nitramine), O-NO_2 (nitrate ester or nitrato) and C-N_3 (azido) groups are all energetic functionalities and in general, an explosive will contain one or more of these groups. Other explosive systems also exist such as those containing perchlorates or peroxides.

Commercially available blasting explosive usually consists of a slurry of ammonium nitrate (AN) and fuel oil (FO) and is commonly known as ANFO. Such a slurry is often mixed on the designated site of the explosion, so as to reduce the risk of handling this explosive mixture.

4, Nitroglycerine



5, RDX



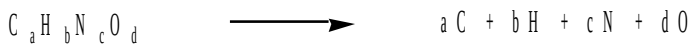
6, HMX

2.2.2 Oxygen Balance (OB)

Commonly, energetic compounds contain only the elements carbon, hydrogen, nitrogen and oxygen and consequently their composition can be expressed as

$C_aH_bN_cO_d$.

According to the model put forward by Rothstein and Peterson,[4] when an explosive compound detonates, its molecular structure breaks down to a momentarily disorganised mass of atoms, before recombining to form gases, i.e.



Such a description should be considered as an idealised model and it is recognised that in a real chemical reaction such as an explosion not all of the explosive molecule will be completely atomised. The proportionate amount of oxygen atoms (d) relative to the number of carbon and hydrogen atoms (a + b) will determine which gases are produced during the explosion. If d is large then CO_2, H_2O, CO and N_2 will be among the explosion products formed. But, if d is small then free carbon (visible as black smoke) will be produced in addition to CO, H_2 and N_2.

In an explosive compound the oxygen balance (OB) is the number of oxygen atoms minus the total number of carbon and hydrogen atoms. If the oxygen balance of a compound is a positive value then there is enough oxygen to oxidise fully all the carbon and hydrogen. However, if the explosive has a negative value for its oxygen balance then it is oxygen deficient, for example, 2,4,6-trinitrotoluene (TNT) (**7**) is oxygen deficient.

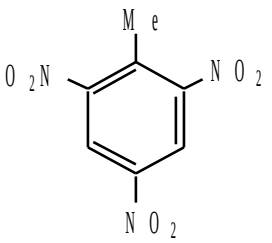
The optimum oxygen balance (OB) in explosives is usually achieved by the incorporation of the right amount of nitro, nitrato or nitramino groups in the molecule. In fact, nitroglycerine has a near zero oxygen balance which means that the production of heat per unit mass of explosive is a maximum, making nitroglycerine such an effective explosive.

It is recognised that achieving an oxygen balance close to that of nitroglycerine (NG) will be difficult. However, by the incorporation of enough nitro and *N*-oxide groups on the heterocyclic ring an optimum oxygen balance is envisaged, i.e. one as close to zero as possible.

2.2.3 Sensitivity of Explosives

The potential application and handling safety of an explosive are determined by its sensitivity to heat, mechanical stress or shock, impact, friction and detonation impact (detonability). Since all explosives are by nature sensitive compounds, a considerable challenge to synthetic chemists is to prepare insensitive explosives which have high detonation velocities.

One strategy employed to impart insensitivity to an explosive is the incorporation of amino (NH_2) groups in the explosive molecule. Having amino groups in the molecule means intermolecular hydrogen bonding takes place thus rendering the explosive less sensitive. An example of this strategy can be seen by comparison of the impact sensitivities of 2,4,6-trinitrotoluene (TNT) (**7**) and 1,3,5-triamino-2,4,6-trinitrobenzene (TATB) (**8**).



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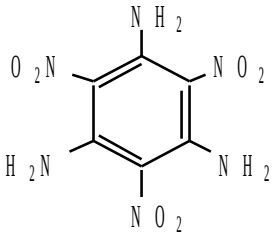

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Figure of Insensitivity: (F of I)	~ 120 cm	> 200 cm

The lower the 'Figure of Insensitivity' (F of I) the greater the sensitivity of the explosive and therefore **7** is markedly more sensitive than **8**, thus demonstrating the effect of having amino groups in the compound.

It is thought that the power output could be enhanced even further by oxidising the nitrogen heteroatom(s) in quinoxaline, quinazoline and pyrazine compounds giving *N*-oxide derivatives, thereby improving the oxygen balance of the compound. Due to the ionic nature of this functional group, the hydrogen

bonding should be even stronger, thereby imparting greater insensitivity to the compound.

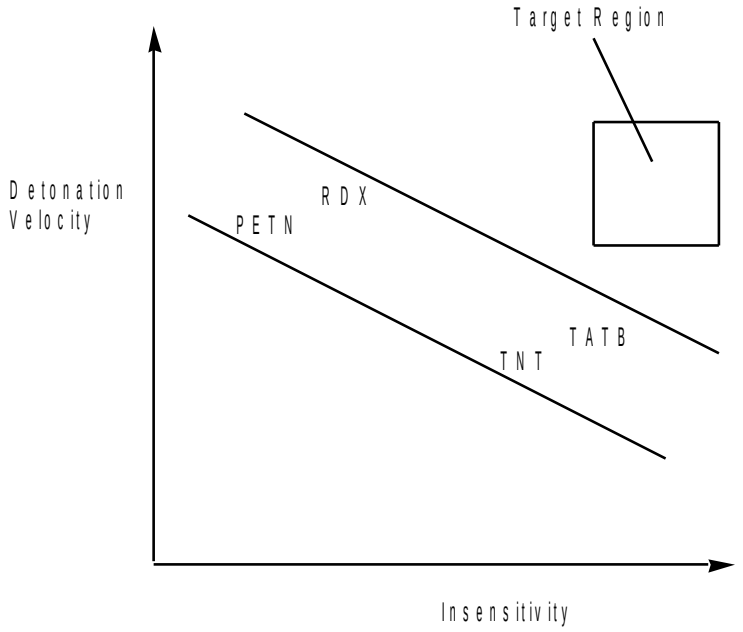


Figure 1: Graphical Schematic of Detonation Velocity (V_D) vs. Insensitivity

Figure 1 shows the relationship between detonation velocity (V_D) and insensitivity for some common explosive compounds. On this schematic graph, target molecules within this project lie in the target region shown. In this region the molecules have a high detonation velocity as well as high insensitivity and thus have optimum properties required for energetic materials.

2.2.4 Detonics Calculations[5,6]

Rothstein and Peterson[4] have developed an empirical, linear relationship between detonation velocity (D) at theoretical maximum density (TMD) and a factor F, which is determined solely by the explosive's composition and structure. This relationship has been reliably used to predict the detonation velocity of 63 common explosives, with 95% of the explosives having an error limit of 5% of the experimental value.

The factor F is calculated using a simple linear equation (**Figure 2**).

$$F = \left[100 \times \frac{n(O) + n(N) - \frac{n(H)}{2n(O)} + \frac{A}{3} - \frac{n(B)}{1.75} - \frac{n(D)}{4} - \frac{n(E)}{5}}{MW} \right] - G$$

Where G = 0.4 for liquid explosives, for solid explosives G = 0; A = 1 if the compound is aromatic, otherwise A = 0 and where for one mole of the composition:

n(O) = number of oxygen atoms
n(N) = number of nitrogen atoms
n(H) = number of hydrogen atoms
n(B) = number of oxygen atoms in excess of those already available to form CO_2 and H_2O
n(C) = number of oxygen atoms doubly bonded directly to carbon as in carbonyl >C=O
n(D) = number of oxygen atoms singly bonded directly to carbon as in a >C-O-R linkage where R can equal -H, -C, etc.
n(E) = number of nitrato groups existing as either in a nitrate ester configuration or as a nitric acid salt such as hydrazine mononitrate

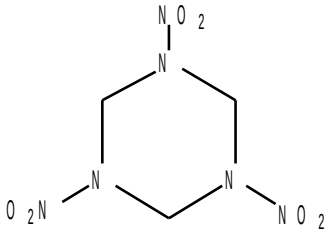
F = 0.55D + 0.26 where D is the detonation velocity

and hence $D = \frac{F - 0.26}{0.55}$

Figure 2: Rothstein and Peterson Linear Equation used for Calculating Detonation Velocities

Although not as accurate as modern computer detonation velocity calculations which are based on either semi-empirical or *ab-initio* codes, the above equation does, however, serve as a quick and approximate indicator of an explosive's capability.

Detonation velocities were calculated for the following explosives using the Rothstein and Peterson equation, the results of which are shown in **Table 1**.



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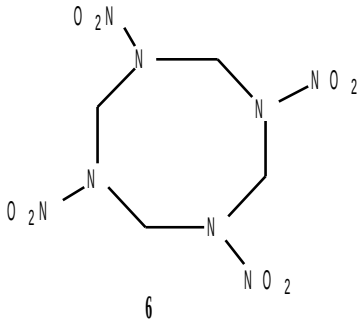

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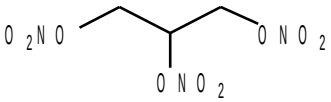

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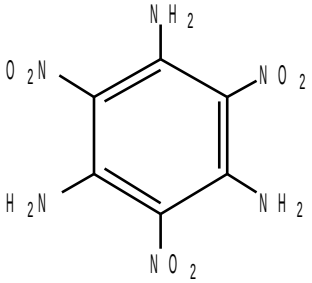

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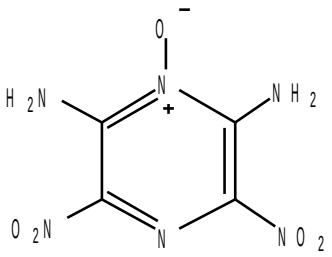

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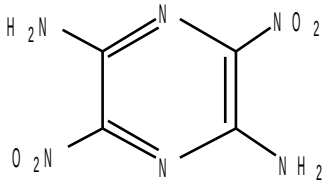

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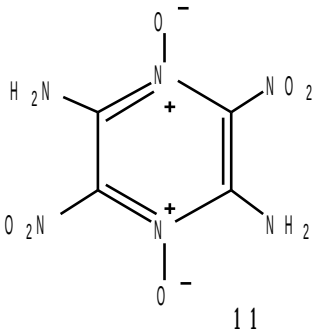

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Explosive	MW	Factor F	Exptl. D ($mm.\mu s^{-1}$)	Calc'd. D ($mm.\mu s^{-1}$)
RDX (**5**)	222	5.18	8.85	8.95
HMX (**6**)	296	5.24	9.14	9.05
NG (**4**)	227	4.35	7.60	7.44
TATB (**8**)	258	4.59	7.94	7.87
PZO (**9**)	216	5.06	N.A.	8.73
ANPZ-i (**10**)	200	4.92	N.A.	8.47
PZDO (**11**)	232	5.17	N.A.	8.93

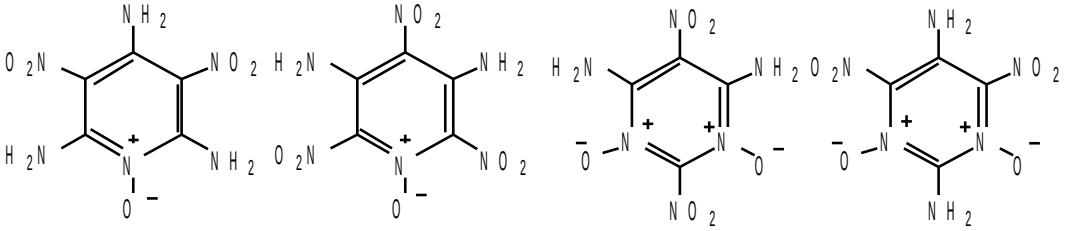
Table 1: Comparison of Experimental and Calculated Detonation Velocities (D) for a Number of Explosive Compounds

Both RDX (**5**) and HMX (**6**) have high calculated and experimental detonation velocities and these explosive compounds have been used for many years as ingredients in high energy propellant and explosive compositions. NG (**4**) was one of the first high explosives to be used but it suffers from a high sensitivity as well as poor performance (both its calculated and experimental detonation velocities are low). PZO (2,6-diamino-3,5-dinitropyrazine-1-oxide, **9**) is a candidate high explosive which was first prepared by researchers at the Lawrence Livermore National Laboratories (LLNL), California, USA and has a calculated detonation velocity greater than TATB but slightly lower than that of RDX.

ANPZ-i (2,5-diamino-3,6-dinitropyrazine, **10**) is a novel compound prepared in this project and has a very respectable calculated detonation velocity which is significantly greater than that of TATB. PZDO (2,5-diamino-3,6-dinitropyrazine-1,4-dioxide, **11**) is a target molecule which has yet to be prepared and has a very high calculated detonation velocity which is similar to that of RDX. It can be expected that the nitrogen heterocyclic compounds: PZO (**9**), ANPZ-i (**10**) and PZDO (**11**) would all have improved insensitivities compared to the nitramine explosives: RDX (**5**) and HMX (**6**).

Researchers from the Naval Air Warfare Centre Weapons (NAWCW) Division at China Lake, California, USA have employed a similar strategy to that employed

within this project except their work focused on the preparation of pyridine and pyrimidine compounds functionalised with nitro, amino and *N*-oxide groups.[7,8] Specific synthetic targets included; 3,5-dinitro-2,4,6-triaminopyridine-1-oxide (**12**), 3,5-diamino-2,4,6-trinitropyridine-1-oxide (**13**), 4,6-diamino-2,5-dinitropyrimidine-1,3-dioxide (**14**) and 2,5-diamino-4,6-dinitropyrimidine-1,3-dioxide (**15**).



12 **13** **14** **15**

The predicted detonation velocities of target compounds **12**, **13**, **14** and **15** are very good [they compare favourably to that of RDX (**5**)]. The syntheses of the above compounds have been reported[7,8] but in some cases the overall yields were rather low, *ca*. 10-20 %. Additionally, when these preparations were attempted by researchers at DERA Fort Halstead they could not always be repeated. Complementary work has also been carried out involving nitration and oxidation studies of functionalised pyrimidine compounds.[9]

2.3 Nitration Chemistry[10-12]

2.3.1 Nitration - An Overview

Nitration is the reaction of a nitrating agent with an organic compound. Nitration can be achieved at a carbon atom (*C*-nitration giving the C-NO_2 group), an oxygen atom (*O*-nitration giving the O-NO_2 group) and at a nitrogen atom (*N*-nitration giving the N-NO_2 group). The nitrations covered in this Ph.D. project will be those of resonance stabilised aromatic systems and thus aliphatic nitration will not be discussed.

The first aromatic nitration is thought to have been the reaction of nitric acid with benzene giving nitrobenzene, performed by Faraday in 1825. Since then nitration

has become one of the most established and well studied reactions in organic synthesis.

There exists a plethora of different nitrating agents; the oldest being just nitric acid. Dilute nitric acid is used to nitrate activated aromatic systems such as phenol; concentrated nitric acid can sometimes give unwanted oxidative reactions. *'Mixed Acid*' nitration (using a mixture of sulfuric and nitric acids) is the most commonly used form of nitration. Here the sulfuric acid acts as a dehydrating agent ensuring no aqueous dilution of the nitric acid. It should be noted that the rate of nitration of a substrate with nitric acid in a solution of sulfuric acid reaches a maximum at 10% (w./v.) water concentration. This phenomenon can be explained by protonation effects as well as the behaviour of the substrate to its chemical environment (activity coefficient effects) (see Section **2.3.3**).

Different ionisation pathways operate in the nitration reaction. These are dependent on the nature of the nitrating system; the common feature is the production of the nitronium ion (NO_2^+) which is usually believed to be the electrophile in aromatic nitration. In concentrated nitric acid, self dehydration is observed i.e.:

With concentrated sulfuric acid, the nitronium ion is formed concomitantly with the bisulfate ion, i.e.:

Whereas, nitric acid in oleum ionises in the following manner:

A mixture of nitric acid and oleum (sulfur trioxide dissolved in concentrated sulfuric acid, usually obtained commercially as a solution of 10% - 30% (w./v.) SO_3 in c. H_2SO_4) is an extremely powerful nitrating medium which is used to

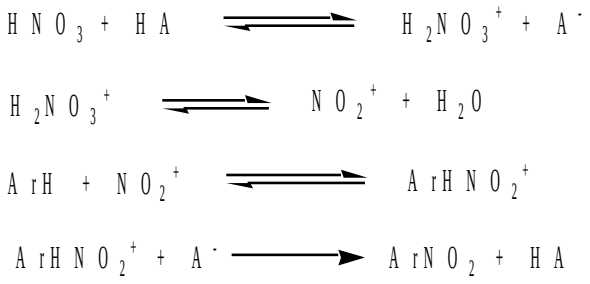
nitrate deactivated aromatic compounds. With more reactive aromatics, unwanted sulfonated and oxidised products can be formed.

A number of other acids can be used with nitric acid to form nitrating systems, these include aqueous perchloric acid, aqueous phosphoric acid, trifluoroacetic acid and aqueous methanesulfonic acid.

The range of systems which can be used for nitration is extensive. This range includes nitration by acyl/alkyl nitrates, nitryl halides, nitronium salts, transfer agents and metallation nitrating agents. All these nitrating systems are electrophilic by nature; a few examples of homolytic (radical) and nucleophilic nitrations have also been reported. Nitrogen oxides such as N_2O_4 (dinitrogen tetroxide) and N_2O_5 (dinitrogen pentoxide) have also been used as nitrating agents.

2.3.2 Aromatic Nitration - Some Mechanistic Aspects[11]

Though the concept of electrophilic nitration by the NO_2^+ ion was originally proposed by Euler in 1903, it was Ingold and Hughes in 1946 who first demonstrated the existence of the NO_2^+ ion and who subsequently proposed their mechanism for electrophilic aromatic nitration, which is as follows:



The NO_2^+ ion is the attacking species, reacting with the aromatic (ArH) to give the Wheland intermediate ($ArHNO_2^+$); the final step is the regeneration of the acid catalyst.

2.3.3 'Mixed Acid' Aromatic Nitration in Concentrated Sulfuric Acid[10]

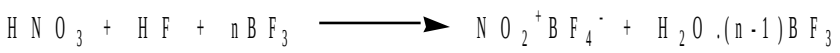
The majority of aromatic nitrations are performed using the mixed acid reagent and of these reactions the majority involve concentrated sulfuric acid acting as the dehydrating catalyst. It should therefore be noted that in aqueous solutions containing approximately >90% by weight of sulfuric acid stoichiometric amounts of nitric acid are present completely ionised as nitronium ions. Consequently, the mixed acid medium is an extremely powerful electrophilic system.

It has been observed that, generally, the rate constants for mixed acid nitration reach a maximum with increasing acidity at approximately 90% by weight of sulfuric acid concentration. Such a decrease in rate constant (i.e. above 90% sulfuric acid concentration) cannot be attributed to the extent of dissociation of nitric acid to nitronium ions since this process is almost complete.

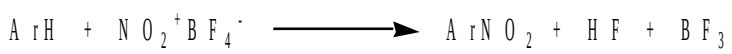
For sufficiently basic compounds, protonation is easily achieved in concentrated sulfuric acid. Therefore, if nitration is predominantly achieved via the free base, then increasing acidity will decrease the amount of free base, thereby lowering the rate constant of the reaction. However, the fall in rate constant between 90% and 100% sulfuric acid is still observed for less basic compounds, e.g. nitrobenzene, which are not easily protonated in concentrated sulfuric acid. This situation can be explained by the formation of intermolecular hydrogen bonds between the aromatic species and sulfuric acid. It is these hydrogen bonded species which have a lower rate of nitration than the free base and they are formed in higher proportions with increasing acidity of sulfuric acid (above 90% concentration). Several alternative suggestions have been put forward in the literature to explain this phenomenon, but will not be discussed here.

2.3.4 Nitration with Nitronium Salts

Nitronium salts have been used extensively as nitrating agents.[10] A number of different nitronium salts have been investigated, these include; $NO_2^+BF_4^-$, $NO_2^+PF_6^-$, $NO_2^+AsF_6^-$, $NO_2^+SbF_6^-$, $(NO_2^+)_2SiF_6^{2-}$ and $NO_2^+ClO_4^-$. There are a variety of methods available for the preparation of nitronium salts. An efficient method for the preparation of nitronium tetrafluoroborate was developed by Olah, *et al.*[13,14] involving the reaction of excess BF_3 with equimolar quantities of HNO_3 and anhydrous HF (see below).



In this reaction water is formed as a by-product and is bound to BF_3 as a stable hydrate. The BF_3 can be regenerated by distillation with either sulfuric acid or oleum. Nitronium tetrafluoroborate is the most commonly used nitronium salt in the nitration of aromatic compounds (see below).



Nitration of aromatic compounds with $NO_2^+BF_4^-$ is usually carried out in either sulfolane or nitromethane. Mononitration products are often formed in high yield with only a small amount (< 3%) of polynitration products usually obtained. Conversely, with mixed acid nitration because the mono-nitro aromatic compound can be highly soluble in the strongly acidic media this often gives rise to further nitration and hence production of dinitro products.

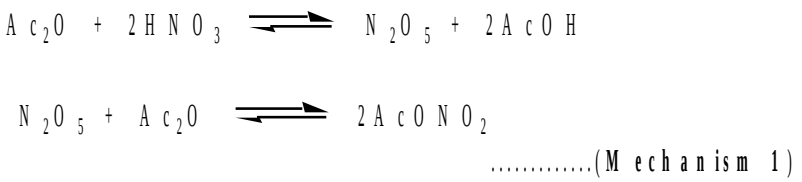
The reactivity of $NO_2^+BF_4^-$ can be enhanced by the use of strongly acidic solutions such as CF_3SO_3H, FSO_3H, HF or H_2SO_4 as the reaction medium. In fact, $NO_2^+BF_4^-$ in FSO_3H has been used to trinitrate benzene giving 1,3,5-trinitrobenzene, a reaction which was previously reported as only being achievable in low yield.[15-17]

The use of nitronium salts in the nitration of heterocyclic compounds has also been investigated. Early studies were based on the nitration of pyridine. The preparation of *N*-nitropyridinium from pyridine and nitronium tetrafluoroborate was reported by Olah et al.[18] The salt was found to be only of limited value as a *C*-nitration transfer agent.

2.3.5 Nitration with Acetyl Nitrate

Acyl nitrates are reactive nitrating agents, the most common of which is acetyl nitrate ($AcONO_2$). Acetyl nitrate is readily formed by the reaction of 100% nitric acid with acetic anhydride. It should be noted that some mixtures of acetic

anhydride and nitric acid which form acetyl nitrate may detonate[19] (see also ref. 20). 100% Nitric acid can be obtained by mixing concentrated sulfuric acid with potassium nitrate and then distilling the product which is then kept at -60°C as a solid and under nitrogen. A number of mechanisms[21] have been put forward for the production of acetyl nitrate, such as the following two:



$$Ac_2O + 2HNO_3 \rightleftharpoons N_2O_5 + 2AcOH$$

$$N_2O_5 + Ac_2O \rightleftharpoons 2AcONO_2$$

.....(Mechanism 1)

$$Ac_2O + HNO_3 \rightleftharpoons AcONO_2 + AcOH$$

.....(Mechanism 2)

The first mechanism involves the production of dinitrogen pentoxide which is consumed in the second reaction to give acetyl nitrate.[22] Whereas the second mechanism involves the simple reaction between nitric acid and acetic anhydride to give acetyl nitrate and acetic acid.[23] Whilst there has been some debate over the mechanism involved, extensive studies have shown that the nitrating agent is acetyl nitrate acting as a carrier for the NO_2^+ ion.[10]

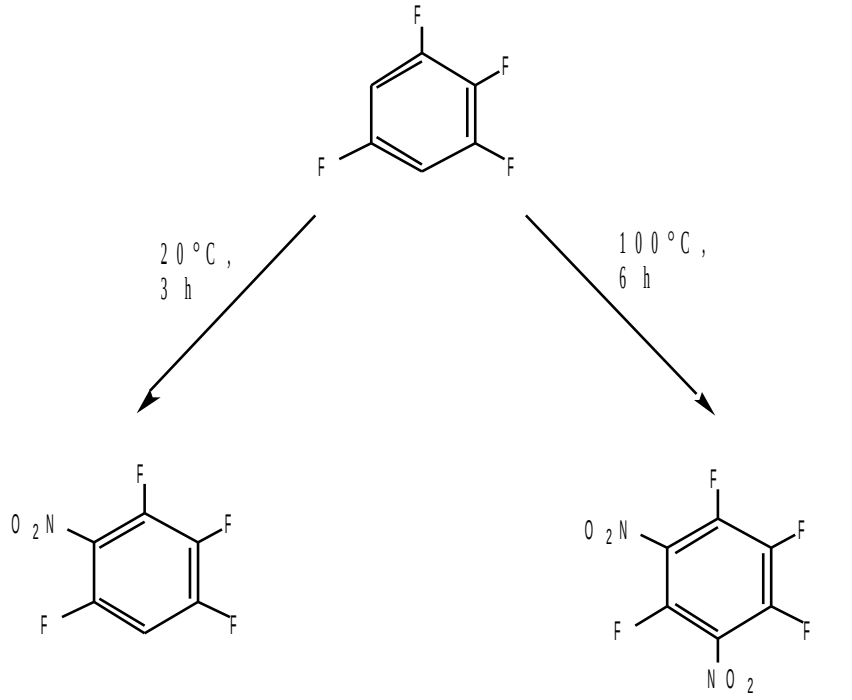
2.3.6 Miscellaneous Nitrations

The literature of a number of different nitration reagents has been studied and a selection of these systems is given below.

Nitration of Strongly Deactivated Systems

The electrophilic nature of nitrating systems is greatly enhanced by the addition of a Lewis or Brønsted acid catalyst. In fact, the activity of nitronium salts is enhanced by FSO_3H or CF_3SO_3H. Even stronger conjugate superacids have also been considered, such as HF-SbF_5, FSO_3H-SbF_5 or CF_3SO_3H-SbF_5. However, due to the strongly oxidising nature of SbF_5 and its resultant non-compatibility with many functional groups, these systems are limited.

Olah, *et al*.[24] used a superacidic mixed nitric-triflatoboric acid [$HNO_3/2CF_3SO_3H$-$B(O_3SCF_3)_3$] system to nitrate a series of deactivated aromatic compounds. Substrates nitrated in good yield included fluoro- and trifluoromethyl-functionalised aromatic compounds (**Scheme 1**).



Mononitro, 89% yield Dinitro, 83% yield

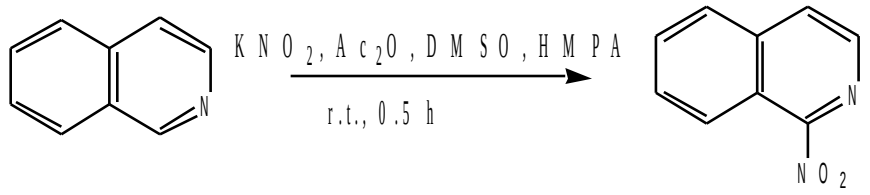
Scheme 1

The triflatoboric acid was prepared by the addition of CF_3SO_3H to BCl_3 at -25°C, the nitronium salt [$NO_2^+B(O_3SCF_3)_4^-$] was then formed by the addition of anhydrous nitric acid to the mixture.

Nucleophilic Nitration

Nucleophilic nitration of aromatic compounds is usually very difficult to achieve. In a few cases nitrolysis has been successful, e.g. the aqueous nitrolysis of 2,4-dinitroiodobenzene to give 1,2,4-trinitrobenzene using sodium nitrite. However, in this reaction the water competes with the nitrite ion and 2,4-dinitrophenol is produced as a major side product.[25]

Baik, *et al.*[26] successfully nitrated isoquinoline (**16**) with potassium nitrite/acetic anhydride in DMSO to give the 1-nitro derivative (**17**) in 88% yield (**Scheme 2**).



16 **17**

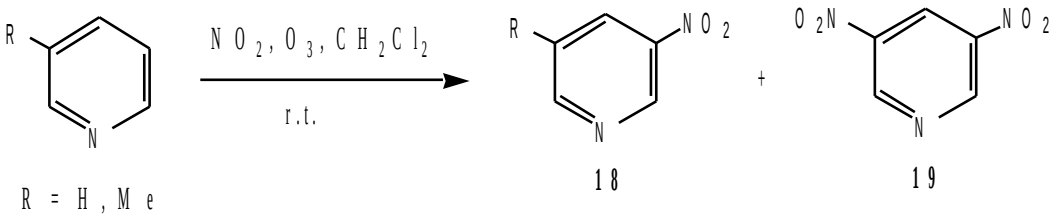
Scheme 2

The reaction is enhanced with HMPA (hexamethylphosphorus triamide) acting as the co-solvent. Initial electrophilic attack is by the DMSO/Ac_2O complex onto the nitrogen heteroatom. Then nucleophilic nitration is direct onto the 1-position.

Pyridine Nitrations

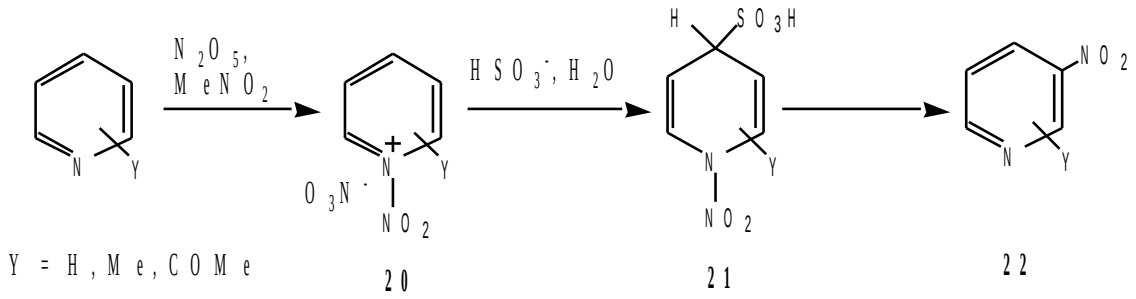
Direct *C*-nitration of pyridine is very difficult to achieve due to the strongly deactivating nature of the aza group. Consequently, 2- and 3-nitropyridines can only be prepared in low yield (*ca.* 5%) even when a mixture of alkali metal nitrate in fuming sulfuric acid at 300 - 450°C is used as the nitrating agent.

A mixture of 3-nitro- (**18**) and 3,5-dinitropyridine (**19**) can be prepared in a combined yield of 2-5% (**Scheme 3**).[27] In this system nitrogen dioxide (NO_2) is activated by ozone and the reaction is carried out in dichloromethane at room temperature.



Scheme 3

Recently, Bakke and co-workers have found that pyridine can be nitrated in 63% yield using dinitrogen pentoxide (N_2O_5) in liquid SO_2 to give the 3-nitro derivative.[28-30] Due to the difficulty in using liquid SO_2, an alternative procedure was devised which yielded a series of 3-nitropyridines in 20-70% yield (**Scheme 4**).



Scheme 4

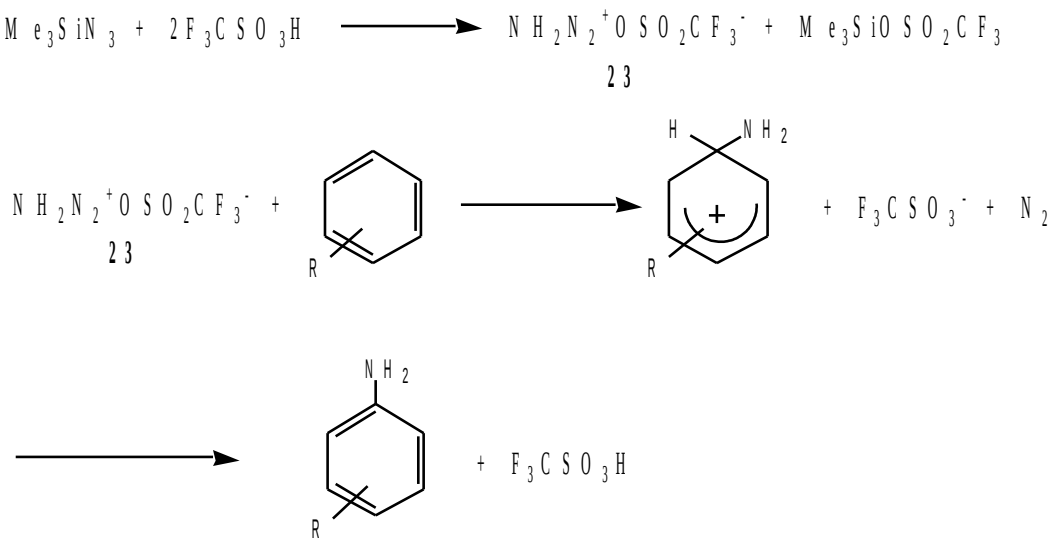
The pyridine compound is reacted with a nitrating agent, either N_2O_5 or $NO_2^+BF_4^-$, in an organic solvent to form a *N*-nitropyridinium ion (**20**). This species is then reacted with a suitable aqueous nucleophile (e.g. HSO_3^- aq.) to give a hydropyridine complex (**21**) which then goes on to the α-nitropyridine product (**22**).

2.4 Direct Aromatic Aminations

Aromatic amines are usually prepared by the nucleophilic displacement of a halogenoaromatic or by reduction of a nitroaromatic. There does, however, exist a number of direct aromatic aminations. The first direct aromatic amination was achieved using hydroxylamine, which often gives low to moderate yields of the aminated aromatic.

Trimethylsilyl azide/triflic acid System

Olah *et al.*[31] managed the amination of a number of simple aromatic compounds using trimethylsilyl azide (Me_3SiN_3)/triflic acid (F_3CSO_3H) (**Scheme 5**).

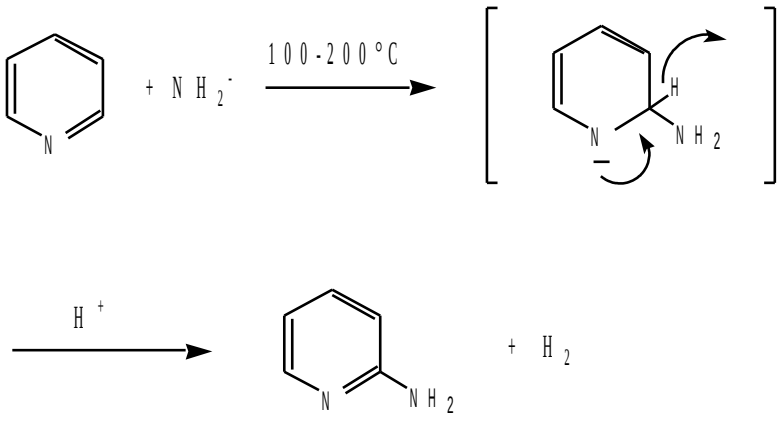


Scheme 5

The suggested reaction pathway indicates that the aminodiazonium triflate (**23**) is a synthon for NH_2^+. Using these reagents, benzene was aminated in 95% yield to give aniline.

Pyridine Aminations

Historically, pyridine has been aminated with alkali-metal amides in a process called the *Chichibabin Reaction* (**Scheme 6**). Nucleophilic attack is always at the 2-position unless both positions are occupied, in which case the 4-position is attacked.[32]

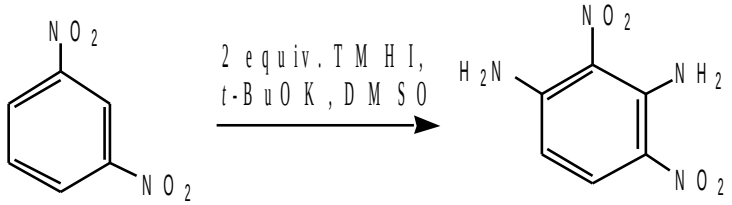


Scheme 6

3,5-Dinitropyridine has been aminated with liquid ammonia/potassium permanganate to give 2-amino-3,5-dinitropyridine in low yield (*ca.* 16%) with an unseparable mixture of 2,6-diamino-3,5-dinitropyridine and 2,4,6-triamino-3,5-dinitropyridine also produced.[33]

Trimethylhydrazinium Iodide (TMHI) System

Pagoria, *et al.*[34] used 1,1,1-trimethylhydrazinium iodide (TMHI) to aminate a series of 3-substituted nitrobenzenes by the vicarious nucleophilic substitution (VNS) of hydrogen. The reaction is carried out in DMSO with potassium *tert*-butoxide acting as the co-reagent. With 3-substituted nitrobenzenes an isomeric mixture of the 2-amino, 4-amino and 6-amino products is given. TMHI is easily prepared by the reaction of methyl iodide with 1,1-dimethylhydrazine in THF. TMHI was also used to diaminate 1,3-dinitrobenzene (**24**) to give 1,3-dinitro-2,6-diaminobenzene (**25**) in 76% yield (**Scheme 7**).

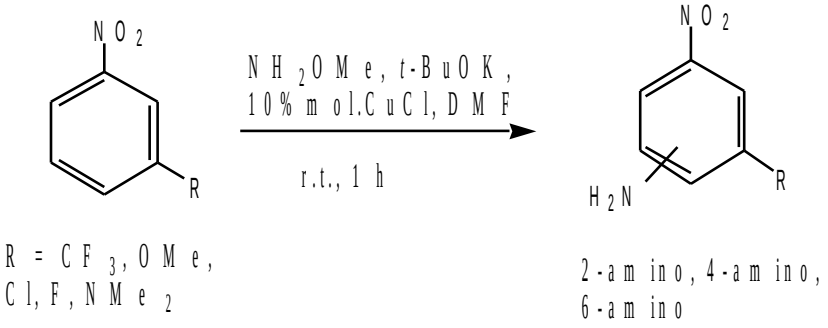


24 **25**

Scheme 7

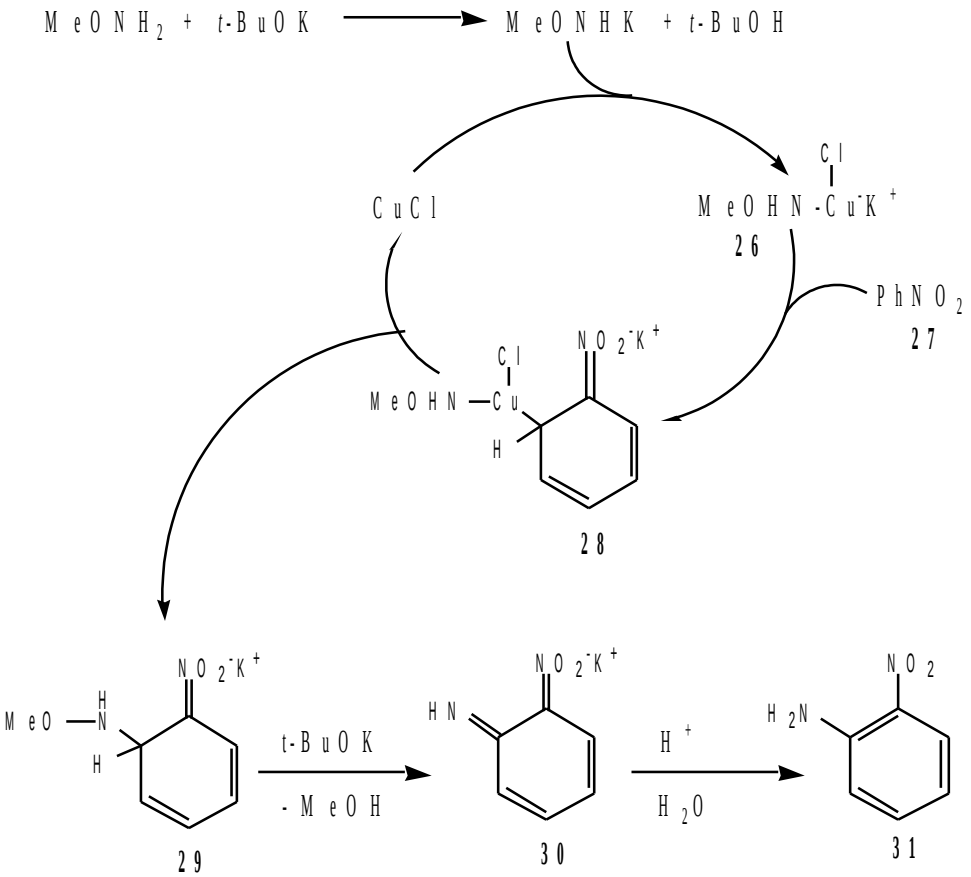
Copper Catalysed Amination

Direct aromatic amination has been achieved by Seko, *et al.*[35] using a copper catalysed *O*-alkylhydroxylamine system. A range of 3-substituted nitrobenzenes was aminated in good yield (80-99%) (**Scheme 8**).



Scheme 8

Seko, *et al.* proposed an ingenious reaction mechanism for the copper catalysed amination (**Scheme 9**).



Scheme 9

Oxidative addition of the copper amide complex (**26**) to the nitrobenzene (**27**) is thought to produce **28**, which readily undergoes reductive elimination of Cu_2Cl_2 to

give the Meisenheimer complex, **29**. Finally, base induced β-elimination gives the quinoid intermediate **30** which is easily protonated to give the amino product, **31**.

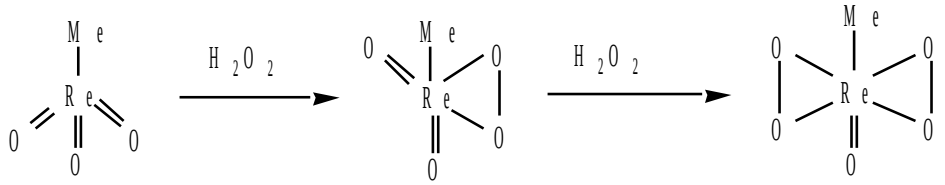
2.5 Oxidation of Aromatic Amines

Chromium-Silicalite Catalysed Oxidation System

A number of aniline and aliphatic primary amines have been oxidised to the corresponding nitro compounds by a chromium-silicalite catalysed oxidation system with *tert*-butylhydroperoxide (TBHP) acting as the oxidant.[36] This method uses a chromium-containing medium pore molecular sieve (Si:Cr = 140:1) as the catalyst and oxidises aniline to nitrobenzene in a claimed 92% yield. However, the method suffers from the unfortunate drawback that the zeolite catalyst has an elaborate method of preparation.

Methyltrioxorhenium-Hydrogen Peroxide Oxidation System

Murray, *et al.*[37] found that oxidation of organonitrogen compounds can be performed by a methyltrioxorhenium (MTO)-hydrogen peroxide system (**Scheme 10**).



32 **33**

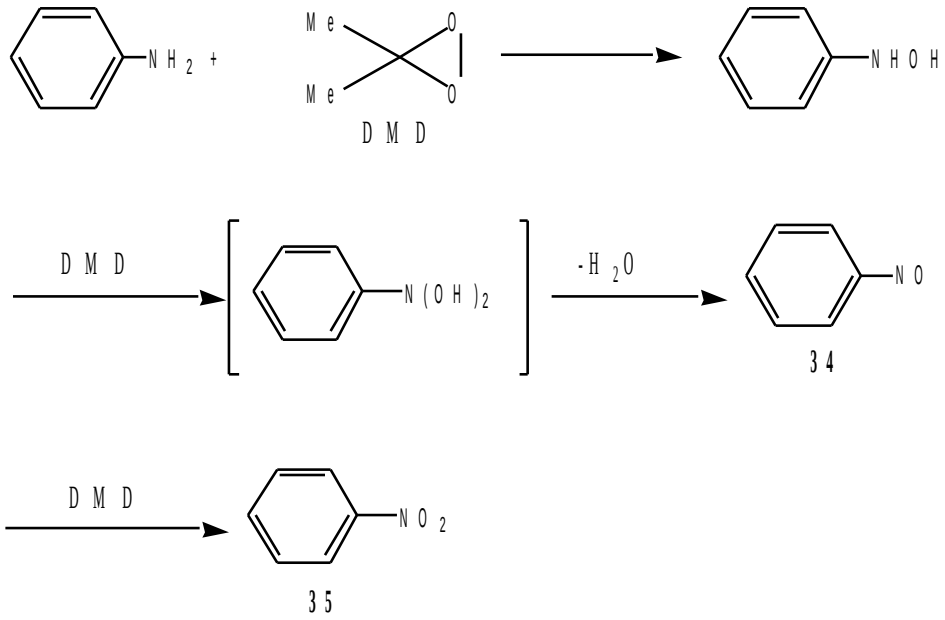
Scheme 10

Both the peroxyrhenium complexes **32** and **33** generated are capable of oxidising the nucleophilic nitrogen atoms. This system was found to be effective in a number of oxidations; aniline to nitrobenzene in 70% yield, nitrosobenzene to nitrobenzene in 100% yield and pyridine to pyridine-*N*-oxide in 100% yield.

Dimethyldioxirane (DMD) Oxidation System

Oxidation of aromatic amines[38] has also been achieved using dimethyldioxirane (DMD).[39,40] Nitrobenzene was prepared in 97% yield from aniline. This oxidation reagent was also used sucessfully on a range of other aromatic and aliphatic nitro compounds. DMD is prepared by the reaction of acetone with potassium monoperoxysulfate (oxone™) and aqueous sodium bicarbonate solution at pH 7.4 and a temperature of 5-10°C.[40] The DMD is obtained as a dilute acetone solution (*ca.* 5% yield).

The proposed mechanism for DMD oxidation involves consecutive hydroxylations of the amine nitrogen followed by elimination of water to give the nitroso compound (**34**). Final oxidation of the nitroso compound by DMD gives the nitro product (**35**) (**Scheme 11**).



Scheme 11

3. Benzodiazines

3.1 Introduction

Benzodiazines comprise a diazine aromatic heterocyclic ring fused to an aromatic carbocyclic ring; there are four structural isomers of this class of compound. These are quinoxaline (formerly known as benzopyrazine) (benzo-1,4-diazine), quinazoline (formerly known as benzopyrimidine) (benzo-1,3-diazine), cinnoline (benzo-1,2-diazine) and phthalazine (benzo-2,3-diazine).

Each of the benzodiazines shows markedly different chemical and physical properties, in fact both cinnoline and phthalazine exhibit undesirable properties such as lower thermal stabilities. This is due to the presence of a nitrogen-nitrogen bond in the ring which means there is a greater tendency to decompose with heating, thereby evolving gaseous nitrogen. Also, cinnoline and phthalazine compounds have chemical properties which are very hard to predict and therefore their synthesis will not be covered in this Ph.D. project.

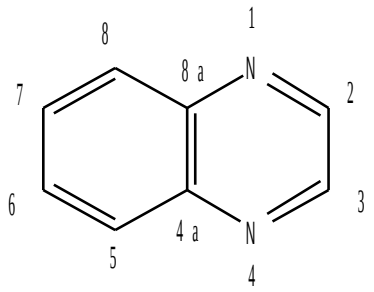
Quinoxaline and quinazoline compounds should be highly suited to the energetic materials application. It is proposed that the benzo ring can be nitrated to the highest extent with amino groups attached to either the heteroaromatic or carbocyclic rings, by either nucleophilic displacement of a chlorine atom or vicarious nucleophilic substitution of a hydrogen atom. Also, it is envisaged that *N*-oxide derivatives can be prepared thereby enhancing the oxygen balance (OB) as well as giving the explosive compound greater insensitivity.

The overall strategy with the benzodiazines initially involved nitration of a suitable chloro- precursor compound such as 2,3-dichloroquinoxaline or 2,4-dichloroquinazoline. Therefore, it was important to assess the literature for nitration reactions on simple compounds such as chloro-, methoxy- and hydroxy-functionalised quinoxalines and quinazolines. Furthermore, an assessment of the synthesis of the quinoxaline and quinazoline ring systems was required as well as discussion of amination and oxidation reactions.

3.2 Quinoxalines[41-46]

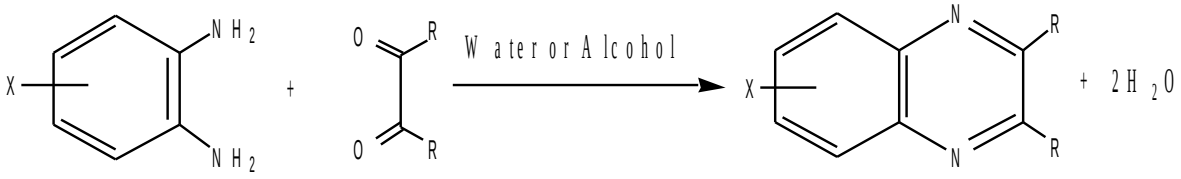
3.2.1 Synthesis

Quinoxaline (**1**) can be viewed as a member of the pyrazine system, since its structure is essentially a benzenoid ring fused to a pyrazine heterocyclic ring.



1, Quinoxaline structure showing ring numbering

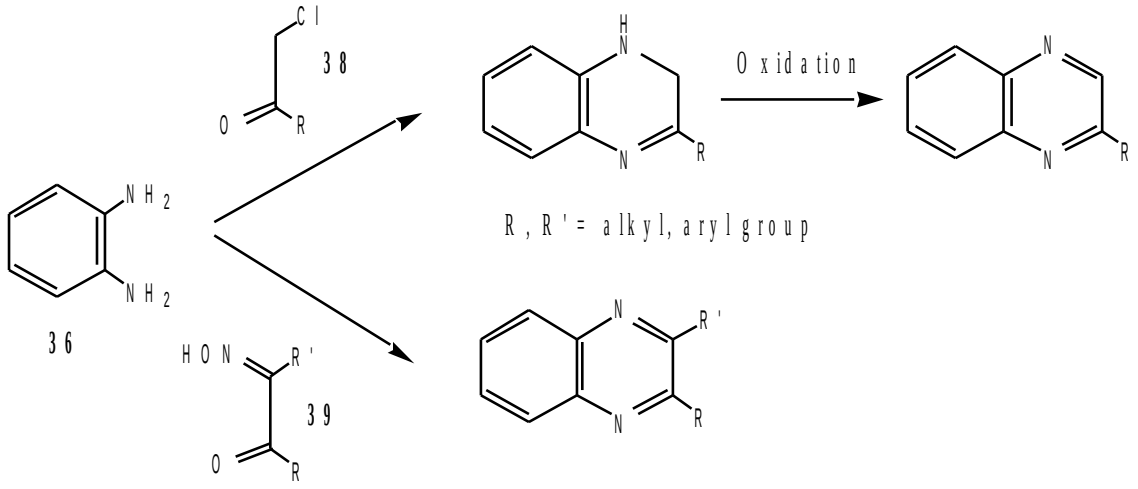
Quinoxalines (**1**) are obtained by the facile condensation of aromatic *o*-diamines (**36**) with 1,2-dicarbonyl compounds (**37**) (**Scheme 12**). This reaction was discovered independently towards the end of the last century by Korner[47] and Hinsberg.[48]



36 **37**

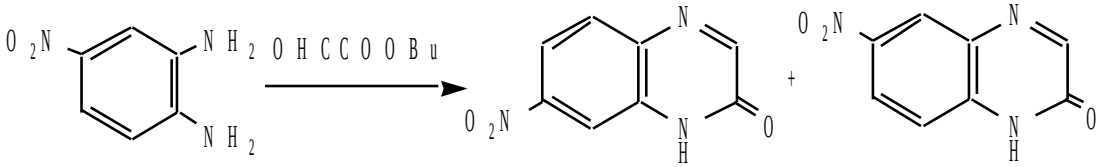
Scheme 12

The classical preparation of quinoxaline from the reaction of glyoxal (R=H) with *o*-phenylenediamine (X=H) followed by sodium carbonate addition yields quinoxaline in almost quantitative yield. There are several variants of this versatile approach to quinoxaline compounds; the two main ones are the condensations of a halogeno ketone (**38**) or an oxime ketone (**39**) with *o*-phenylenediamine (**Scheme 13**).[49,50]



Scheme 13

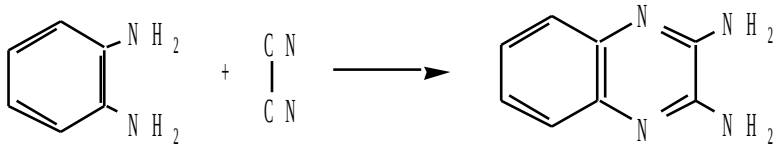
The majority of quinoxaline syntheses involve the preparation of aryl and alkyl substituted derivatives with complex structures containing a high proportion of carbon atoms; such compounds are of biological interest but are not applicable to energetic materials applications. Quinoxalin-2-one compounds can be prepared by the reaction of n-butyl glyoxylate with *o*-phenylenediamine: with 4-nitro-*o*-phenylenediamine (**40**) a mixture of 6- and 7-nitroquinoxalin-2-ones is produced (**Scheme 14**).



40

Scheme 14

2,3-Diaminoquinoxaline (**41**) can be prepared by the action of cyanogen (**42**) on an alcoholic solution of *o*-phenylenediamine (**36**) (**Scheme 15**).

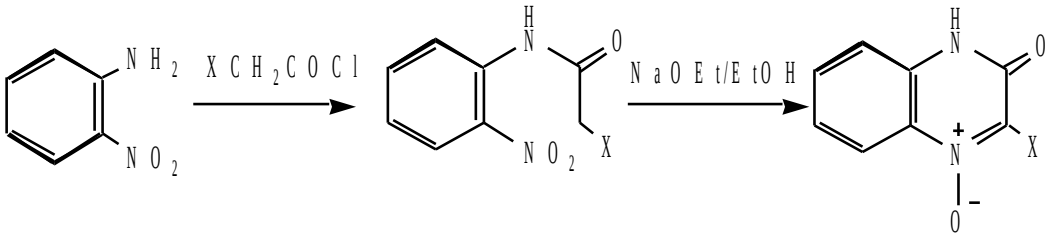


36 **42** **41**

Scheme 15

The above synthesis suffers from the unfortunate drawback that cyanogen is a lethal gas and as such experiments involving it should be avoided. Alternatively, 2,3-diaminoquinoxaline can be prepared by the nucleophilic amination of 2,3-dichloroquinoxaline with alcoholic ammonia under forcing conditions (autoclave, 12 h, 150°C).[44]

Quinoxaline mono-*N*-oxides are obtainable by a direct synthesis from *o*-nitroanilines. The condensation of *o*-nitroaniline (**42**) with acetyl chloride derivatives followed by reaction with sodium ethoxide in ethanol gives mono-*N*-oxides (**43**) in good yields (**Scheme 16**).



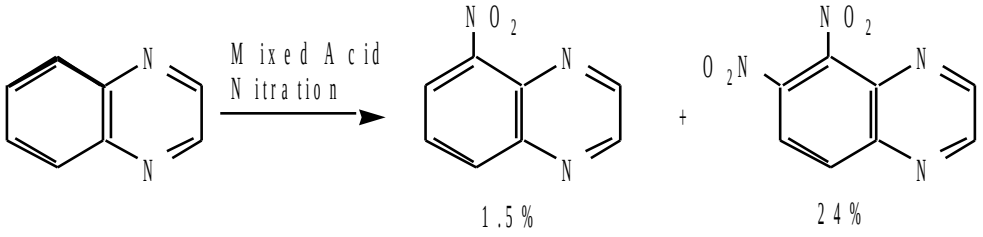
42 **43**

Scheme 16

Since chloro-functionalised quinoxalines (*viz*. 2,3-dichloro-, 2,3,6-trichloro- and 2,3,6,7-tetrachloroquinoxaline) are commercially available, initial synthetic efforts within this research project were centred on functional group interconversions of these molecules. However, the utility of the classical *o*-phenylenediamine/diketone condensation reaction will not be overlooked.

3.2.2 Quinoxaline Nitrations

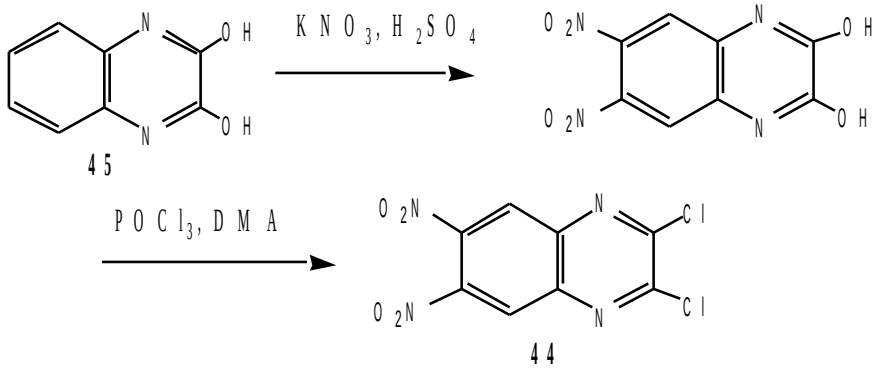
Due to the strongly deactivating effect of the two aza groups in the quinoxaline ring system, quinoxaline itself is feebly reactive towards electrophilic reagents. The nitration of quinoxaline has been achieved using 100% nitric acid and oleum (65% SO_3) with refluxing at 90°C for 24 hours (**Scheme 17**), but this route suffers from poor yields.



Scheme 17

Otamasu *et al.*[51] have described the resistance towards nitration of quinoxaline and some of its derivatives. They were unsuccessful in nitrating quinoxaline *N*-oxide, 2,3-dimethylquinoxaline and quinoxaline itself, but found that quinoxaline derivatives containing electron donating functionalities were much more susceptible to nitration. Successful mononitrations of 6-methoxyquinoxaline and 2-hydroxy-3-methylquinoxaline producing 5-nitro-6-methoxyquinoxaline and 2-hydroxy-3-methyl-6-nitroquinoxaline respectively were achieved. 5-Methoxyquinoxaline was dinitrated to give 5-methoxy-6,8-dinitroquinoxaline in 55% yield. They concluded that nitration of quinoxaline compounds containing two different functional groups of different polarisability at the 2- and 3-positions in the heteroaromatic ring proceeds smoothly with potassium nitrate in concentrated sulfuric acid at low temperatures (*ca.* 0-5°C).

Although no nitrations of chloroquinoxalines have been reported, 2,3-dichloro-6,7-dinitroquinoxaline (**44**) is accessible via the nitration of 2,3-dihydroxyquinoxaline (**45**)[52] and its subsequent chlorination with $POCl_3$ in *N*,*N*-dimethylaniline (DMA) (**Scheme 18**).

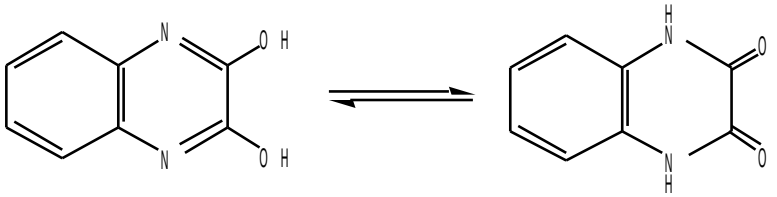


45 44

Scheme 18

The mononitro compound is produced by using the appropriate stoichiometric amount of potassium nitrate (KNO_3).

2,3-Dihydroxyquinoxaline (**45**) can also exist in the tautomeric di-keto form (**45a**) (**Scheme 19**). These two tautomeric structures are in equilibrium with each other. In solution the level of acidity will often play an important part in influencing where the position of equilibrium lies and hence which tautomer is present in the highest concentration. For consistency in the quinoxaline series, compounds with a hydroxy group on the heterocyclic rings will be referred to as hydroxy functionalised. In fact, IR spectroscopy has been used to show the presence of both structures (see Section 5.1.6: Preparation of 2,3-Dimethoxy-6,7-dinitroquinoxaline). However, it should be noted that the chemistry of these compounds can equally be explained in terms of the effect of the tautomeric keto structure.



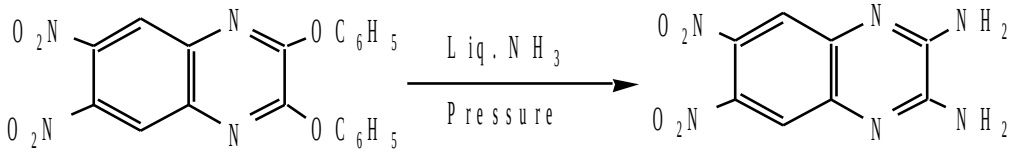
45 45a

Scheme 19

3.2.3 Quinoxaline Aminations

As mentioned earlier, 2,3-diaminoquinoxaline (**41**) is prepared from the amination of 2,3-dichloroquinoxaline with alcoholic ammonia under pressure and at high temperature (*ca.* 150°C).[53]

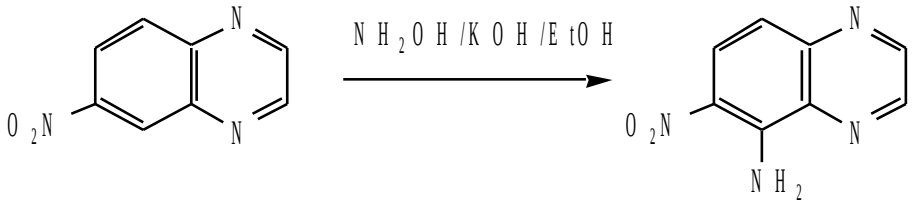
One might expect alkoxy/aryloxy- compounds to be more easily aminated than chloro-compounds. In fact, 2,3-diphenoxy-6,7-dinitroquinoxaline (**46**) is aminated at 60°C (i.e. at a lower pressure than for the amination of 2,3-dichloroquinoxaline) with stirring for 24 hours, producing 2,3-diamino-6,7-dinitroquinoxaline (**47**) (**Scheme 20**).[54]



46 **47**

Scheme 20

Nasielski-Hinkens, *et al.*[55] have reported the direct amination of 6-nitroquinoxaline (**48**) with hydroxylamine to produce the 5-amino derivative (**49**) (**Scheme 21**).



48 **49**

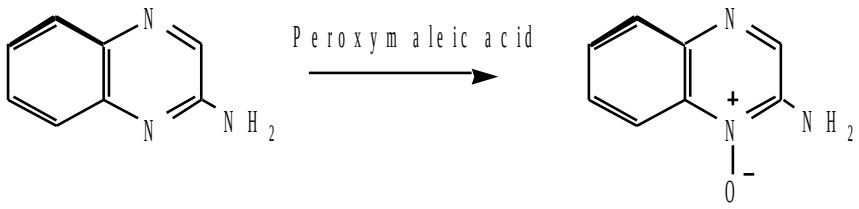
Scheme 21

3.2.4 Quinoxaline Oxidations

Oxidation of one of the nitrogen heteroatoms in many quinoxaline derivatives is easily achieved by a variety of oxidising agents including AcOH/H_2O_2, *meta*-chloroperoxybenzoic acid (MCPBA), monoperoxyphthalic acid, peroxymaleic acid and peroxytrifluoroacetic acid. The ease of oxidation is dependent on the quinoxaline substituents and their number. Although simple alkylated quinoxalines are easily oxidised with acetic acid/H_2O_2, quinoxaline itself is

oxidised to quinoxalin-2,3-dione. To prepare the di-*N*-oxides, long periods of heating are required and high yields for such a conversion are rare. It has been postulated that di-*N*-oxides often undergo thermal decomposition under the more forceful conditions required to prepare them.

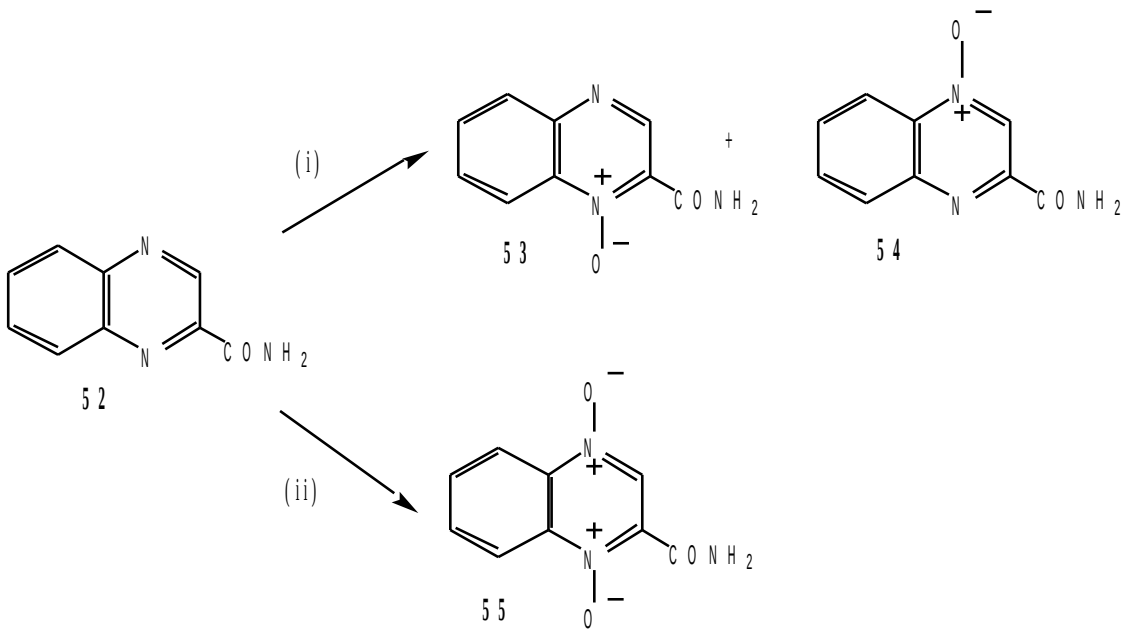
Substitution in quinoxaline compounds of deactivating groups such as halogens renders the nitrogen heteroatoms less susceptible to oxidation.[44] This effect is more pronounced if the substitution is in the heteroaromatic ring. Conversely, it is envisaged that amino groups located α to the ring nitrogens should activate the system towards *N*-oxidation. Indeed, 2-aminoquinoxaline (**50**) has been oxidised with peroxymaleic acid to give the 1-oxide (**51**) (**Scheme 22**), the position of substitution is thought to be affected by intramolecular hydrogen bonding between the oxide and amino groups.



50 **51**

Scheme 22

Oxidation of quinoxaline-2-carboxamide (**52**) in peracetic acid at 20-25°C gives a mixture of the 1- and 4-monoxides (**53** and **54** respectively), whereas reaction at 45-48°C gives the 1,4-dioxide (**55**) compound in 50% yield (**Scheme 23**).[43]



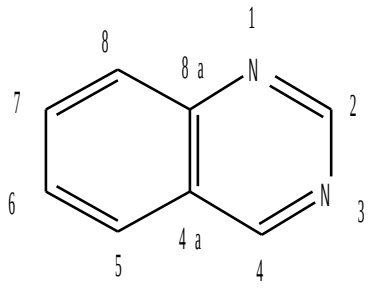
Reagents: $MeCO_3H$-NaOAc (i) 20-25°C/48h, (ii) 45-48°C/22h.

Scheme 23

3.3 Quinazolines[56-63]

3.3.1 Synthesis

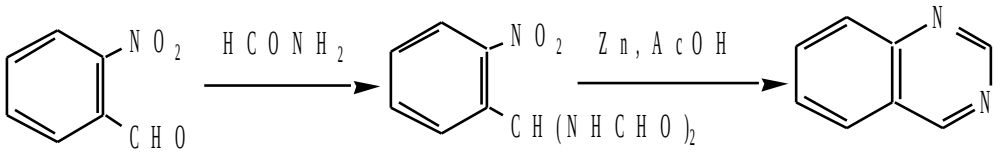
The first quinazoline derivative to be prepared was 2-cyano-3,4-dihydro-4-oxoquinazoline by Griess in 1869, by the action of cyanogen on anthranilic acid.[64]



2, Quinazoline structure showing ring numbering

A very early preparation of quinazoline itself (**2**) involved the reaction of *ortho*-nitrobenzaldehyde (**56**) with formamide to give the *ortho*-nitrobenzylidene

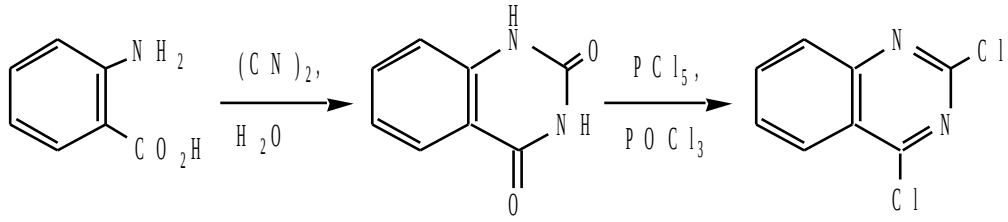
diformamide (**57**) and the subsequent reduction and ring closure was effected by zinc in dilute acetic acid. The overall yield was good (~65%) but the drawback of the synthesis is the difficulty in preparing the starting material, *ortho*-nitrobenzaldehyde (**Scheme 24**).[65]



56 **57** **2**

Scheme 24

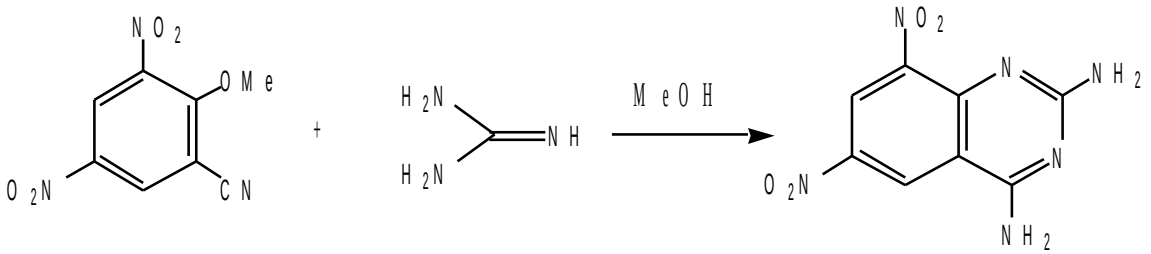
2,4-Dichloroquinazoline (**58**) can be prepared from anthranilic acid (**59**) via 2,4-dioxo-1,2,3,4-tetrahydroquinazoline (benzoylene urea) (**60**) (**Scheme 25**). There are many variations on this reaction, all of which yield quinazolinone compounds which can be easily converted into the corresponding chloroquinazolines.[66]



59 **60** **58**

Scheme 25

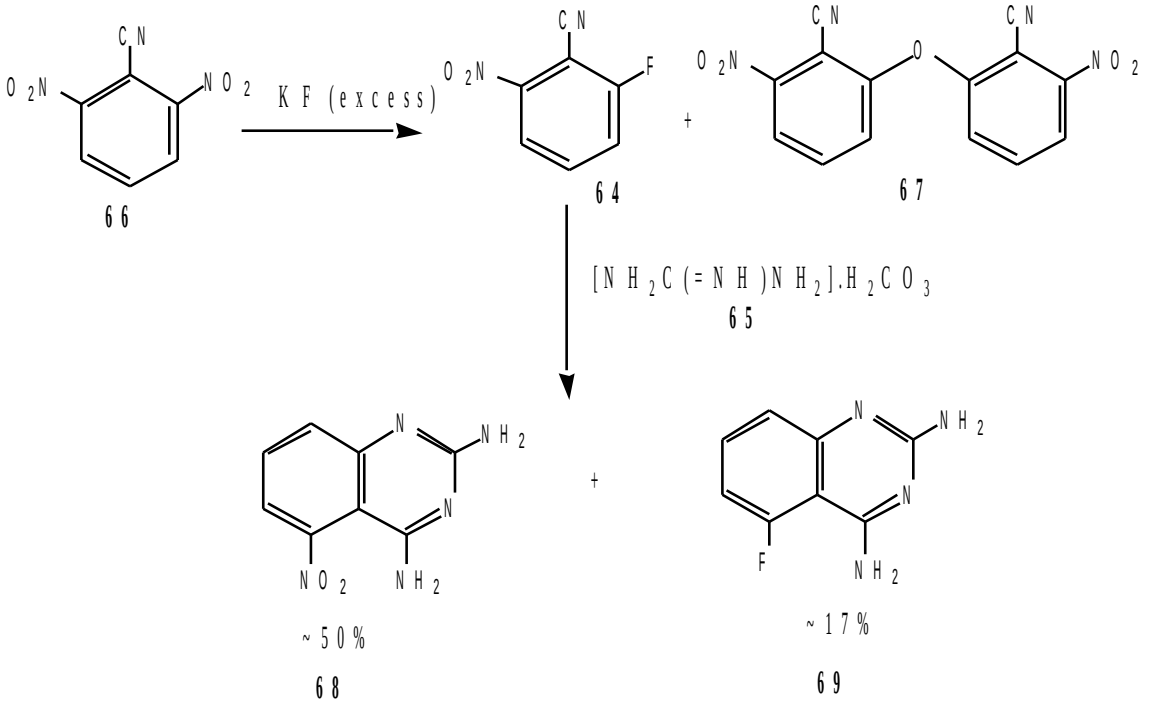
A number of quinazoline syntheses have been reported involving cyclisations of 2-substituted benzonitriles. In 1971 Roos and Wagner[67] reported the preparation of 2,4-diamino-6,8-dinitroquinazoline (**61**) from the cyclisation of 2,4-dinitro-6-cyanoanisole (**62**) with guanidine (**63**) giving a remarkable yield of 90% (**Scheme 26**).



62 **63** **61**

Scheme 26

More recently this methodology has been applied to the cyclisation of 2-nitro-6-fluorobenzonitrile (**64**) with guanidine hydrogen carbonate (**65**) (**Scheme 27**).[68]



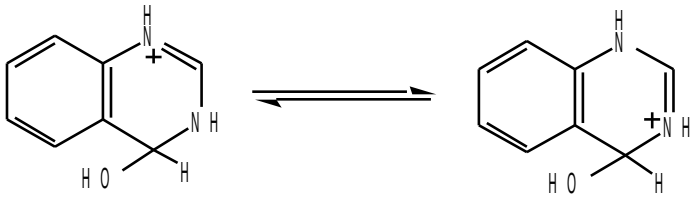
Scheme 27

2,6-Dinitrobenzonitrile (**66**) is fluorinated with anhydrous potassium fluoride, but despite the use of an 8-fold excess of potassium fluoride and the nitrite scavenger, phthalic anhydride, an appreciable amount of the by-product bis(2-cyano-3-nitrophenyl) ether (**67**) is still produced. The cyclisation of 2-nitro-6-fluorobenzonitrile with guanidine hydrogen carbonate gives a mixture of 2,4-

diamino-5-nitroquinazoline (**68**) and 2,4-diamino-5-fluoroquinazoline (**69**) in an approximate ratio of 3:1.

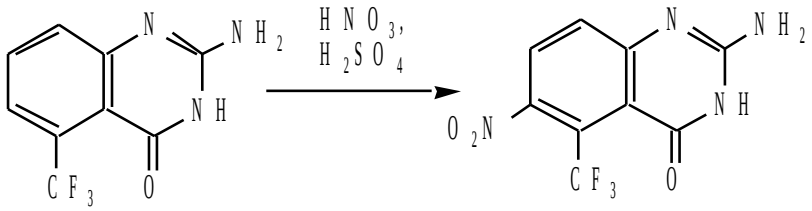
3.3.2 Quinazoline Nitrations

Nitration of quinazoline usually occurs at the 6-position on the carbocyclic ring, for example the sole nitration product of 2,4-diamino-7-fluoroquinazoline is 2,4-diamino-6-nitro-7-fluoroquinazoline.[68] However, the nitration of 2,4-diamino-5-fluoroquinazoline yields a mixture of the 6-nitro and 8-nitro isomers in an approximate ratio of 2:1. This result may partly be explained by analysis of the situation for quinazoline itself. It has been postulated that the conjugate acid of quinazoline readily adds a water molecule to form a cation (**Scheme 28**) which means electrophilic substitution might be expected to occur at the 8-position.[69]



Scheme 28

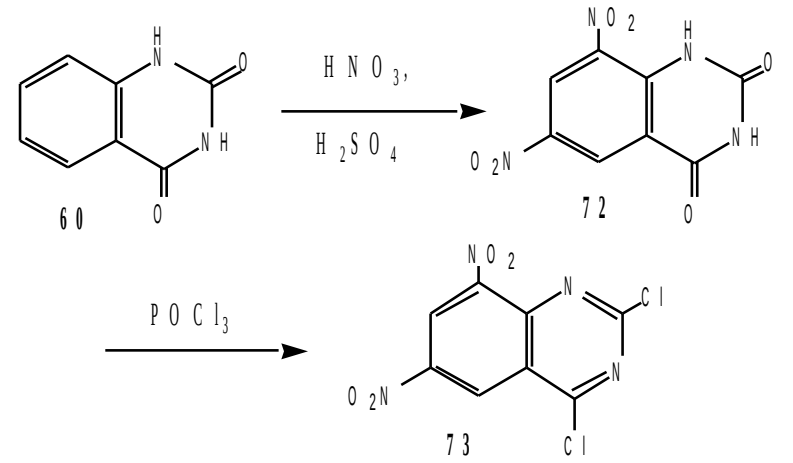
Mixed acid nitration of 2-amino-3,4-dihydro-4-oxo-5-(trifluoromethyl)quinazoline (**70**) gave the 6-nitro derivative (**71**), this conversion occurs in 61% yield with a mixture of 98% sulfuric acid and 90% nitric acid at 0° C (**Scheme 29**).[70]



70 **71**

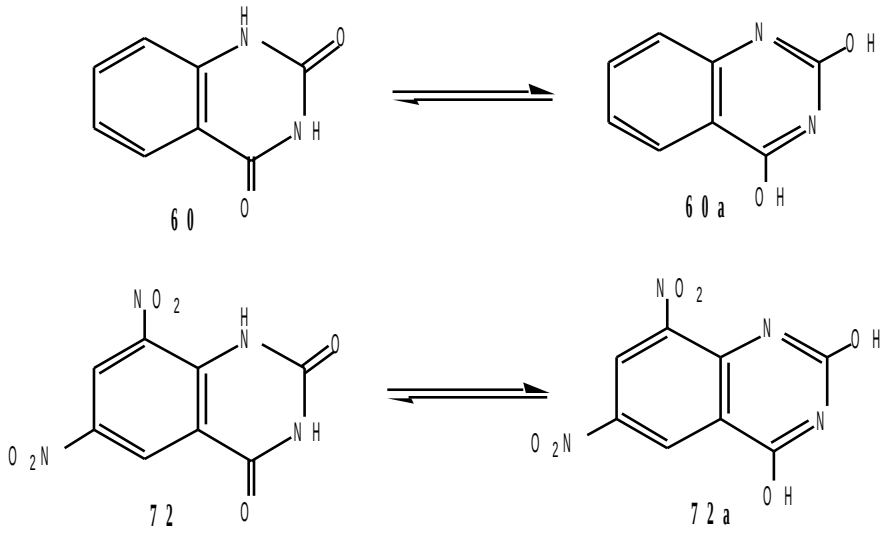
Scheme 29

As early as 1919 the mixed acid dinitration of benzoylene urea (**60**) was achieved giving the 6,8-dinitro-derivative (**72**) which in turn can be chlorinated to give 2,4-dichloro-6,8-dinitroquinazoline (**73**) (**Scheme 30**).[66]



Scheme 30

It should be recognised that both compounds **60** (benzoylene urea) and **72** (6,8-dinitrobenzoylene urea) can exist in the tautomeric dihydroxy forms; **60a** and **72a** respectively (**Scheme 31**).



Scheme 31

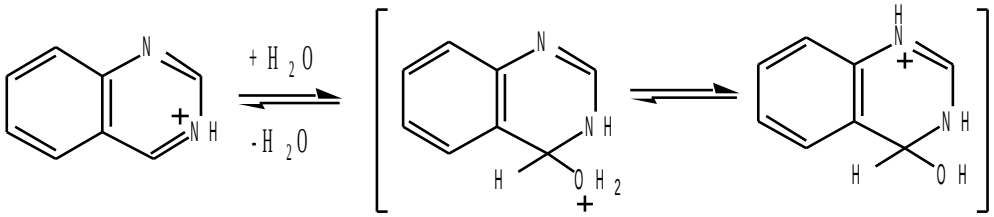
It can be difficult to determine the position of the equilibrium for the above tautomeric structures. However, in this case compounds **60** and **72** are envisaged to exist predominately in the di-keto form.

3.3.3 Quinazoline Aminations[58]

Chlorination of benzoylene urea (**60**) to give 2,4-dichloroquinazoline followed by nucleophilic substitution of the chloro groups by amino groups with alcoholic ammonia yields 2,4-diaminoquinazoline.

3.3.4 Quinazoline Oxidations[59]

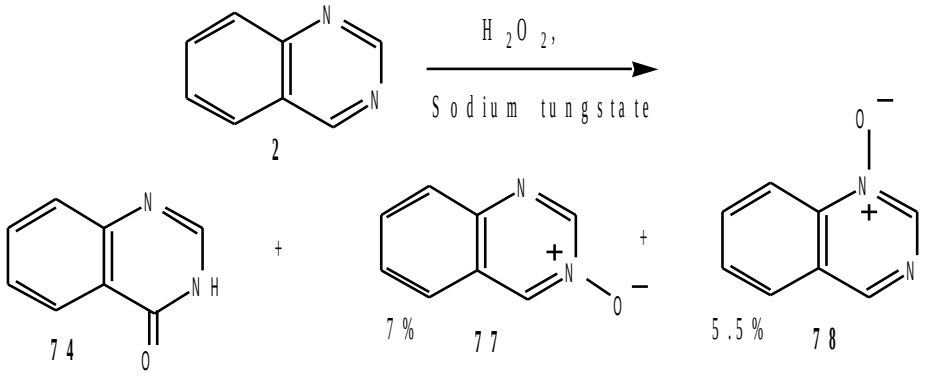
Oxidation of quinazoline itself with hydrogen peroxide (aq. H_2O_2 soln.) usually yields quinazolin-4(3*H*)-one (**74**) because the 3,4-hydrate (**75**) (**Scheme 32**) is oxidised faster than the anhydrous species (**76**).



76 **75**

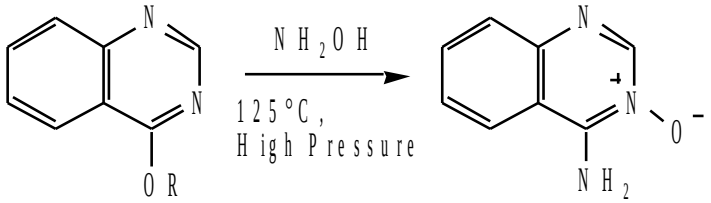
Scheme 32

However, oxidation of quinazoline with hydrogen peroxide and catalytic amounts of sodium tungstate gives a mixture of quinazolin-4(3*H*)-one (**74**), quinazoline-3-oxide (**77**) and quinazoline-1-oxide (**78**), the last two compounds being isolated in yields of 7% and 5.5% respectively (**Scheme 33**).



Scheme 33

It is interesting to note that 4-methoxy- and 4-phenoxyquinazoline (**79**, R=Me, Ph) can be converted into 4-aminoquinazoline-3-oxide (**80**) by the action of hydroxylamine (NH_2OH) at 125°C and under high pressure (**Scheme 34**). This reagent can also be used to prepare 2-aminoquinazoline-3-oxide from quinazoline.[58]



79 **80**

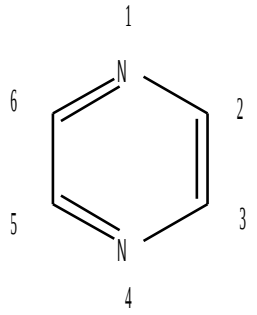
Scheme 34

4. Pyrazines

An initial literature assessment of the synthesis, nitration, amination and oxidation reactions associated with pyrazine compounds was carried out. It was decided that experimental activities would concentrate on functionalisation of pre-formed heterocyclic compounds such as 2,6-dichloropyrazine in the synthesis of 2,6-diamino-3,5-dinitropyrazine-1-oxide (PZO) (**9**) and piperazine-2,5-dione in the synthesis of 2,5-diamino-3,6-dinitropyrazine (ANPZ-i) (**10**).

4.1 Introduction

There exists a number of review articles on pyrazine compounds.[71-74] Pyrazine (**3**) is a symmetrical molecule which is very deactivated towards electrophilic attack because of the two aza groups in the ring. Pyrazines occur naturally and can be found in a variety of biological systems. In fact, hydroxyaspergillic acid, muta-aspergillic acid and neohydroxyaspergillic acid are all important pyrazine containing antibiotics which are isolated from different bacteria.



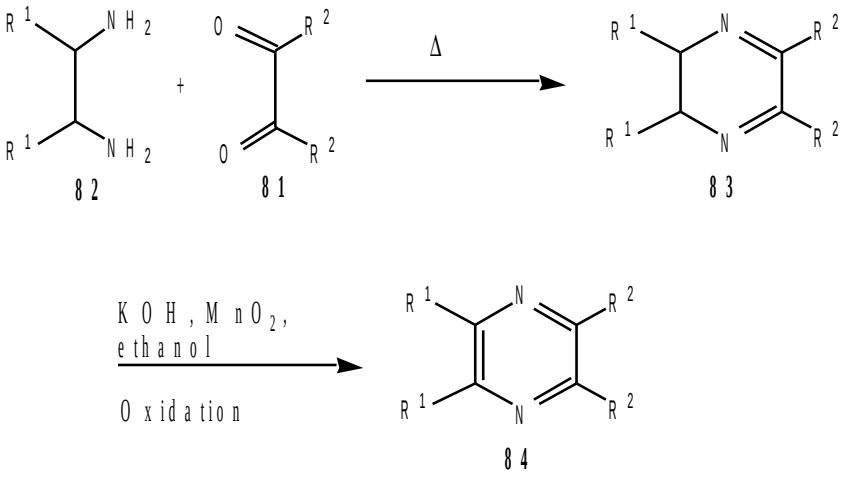
3, Pyrazine structure showing ring numbering

4.2 Synthesis

Many pyrazine compounds are prepared by functional group modification of existing pyrazines, although a number of useful pyrazines and piperazines (hexahydropyrazines) can be purchased from chemical suppliers.

In common with quinoxalines, pyrazines are often prepared by the condensation of an α -diketone (**81**) with a 1,2-diaminoalkane (**82**) (1,2-diaminoarene in the

case of quinoxalines) (**Scheme 35**). Compound **83** is oxidised by KOH/MnO_2 in ethanol to give the functionalised aromatic **84**.

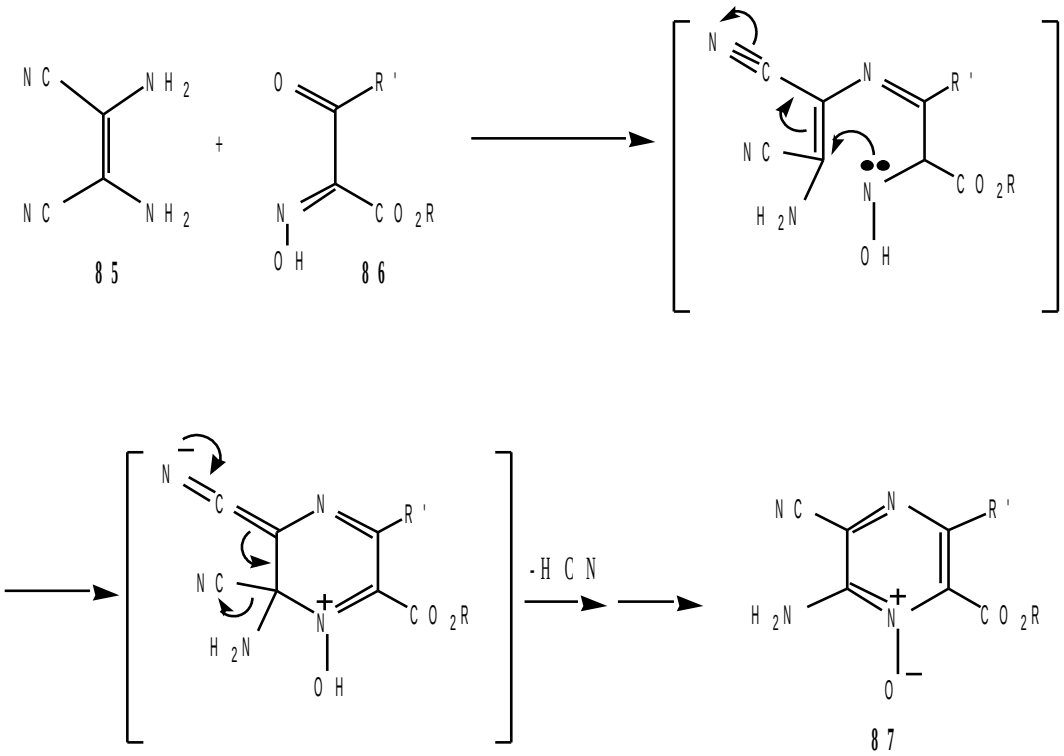


82 81 83 84

Scheme 35

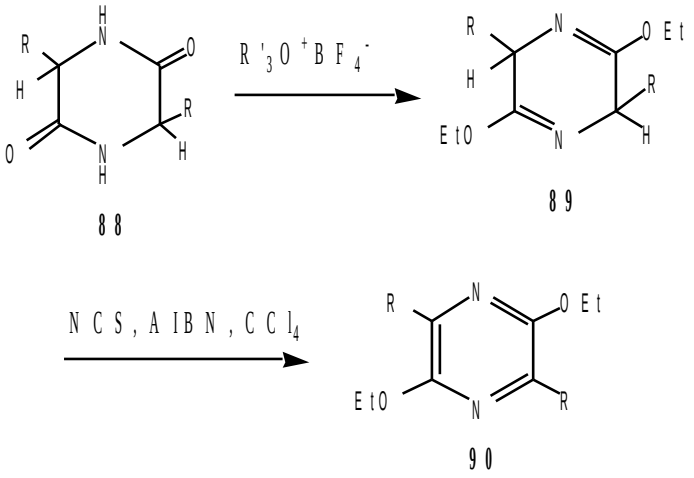
This double-condensation approach has many variants, most of which give rise to highly functionalised pyrazines which are not suitable for energetic materials applications, due to their high carbon content.

Diaminomaleonitrile (**85**) undergoes condensation with α-diketone monoximes (**86**) to yield pyrazine mono-*N*-oxides (**87**) (**Scheme 36**).[75]



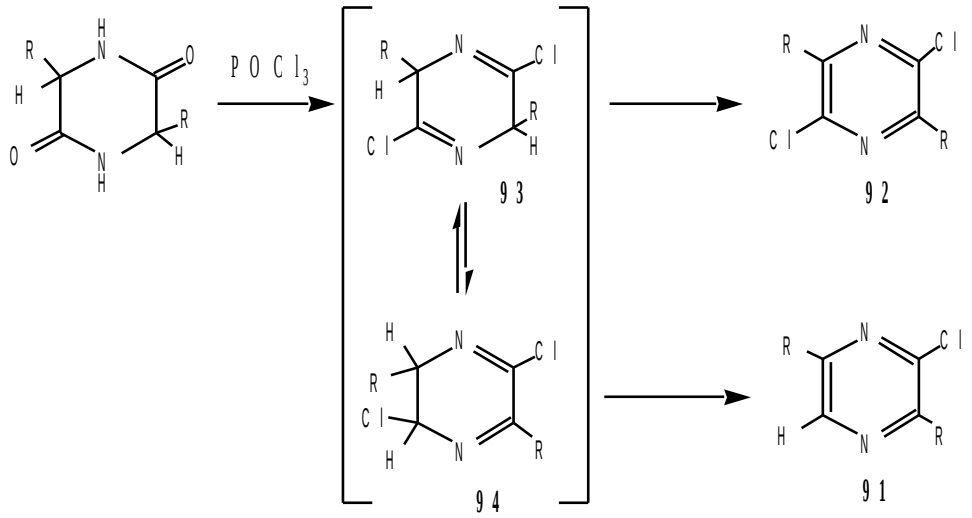
Scheme 36

2,5-Dioxopiperazines can be commonly found as components of natural products. A number of methods exist for their oxidation to the corresponding pyrazine. Sammes, *et al.*[76] reported the alkylation of piperazine-2,5-dione (**88**) with a trialkyloxonium tetrafluoroborate giving rise to the 3,6-dihydropyrazine compound **89**. Aromatisation of **89** was effected with NCS (*N*-chlorosuccinimide) and AIBN [α,α'-azobis(isobutyronitrile)] to yield compound **90** (**Scheme 37**).



Scheme 37

2,5-Dioxopiperazines can also be chlorinated[77] with either $POCl_3$ (phosphorus oxychloride) or PCl_5 (phosphorus pentachloride) to give either the monochloro- (**91**) or dichloro- species (**92**) (**Scheme 38**).



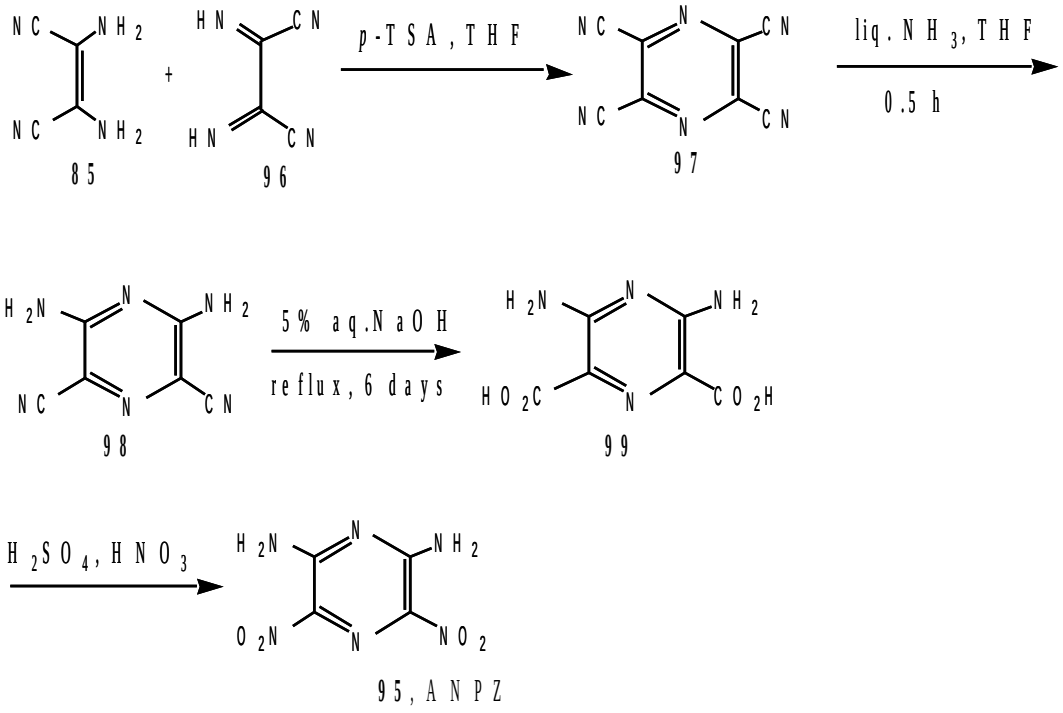
Scheme 38

The initial bisimidoyl chloride (**93**) is either oxidised to the dichloro- compound (**92**) or undergoes isomerisation to give **94**, followed by elimination to yield the monochloro- product (**91**). Dichlorination is dependent on the nature of the R substituent and hence the extent of isomerisation.

4.3 Pyrazine Nitrations

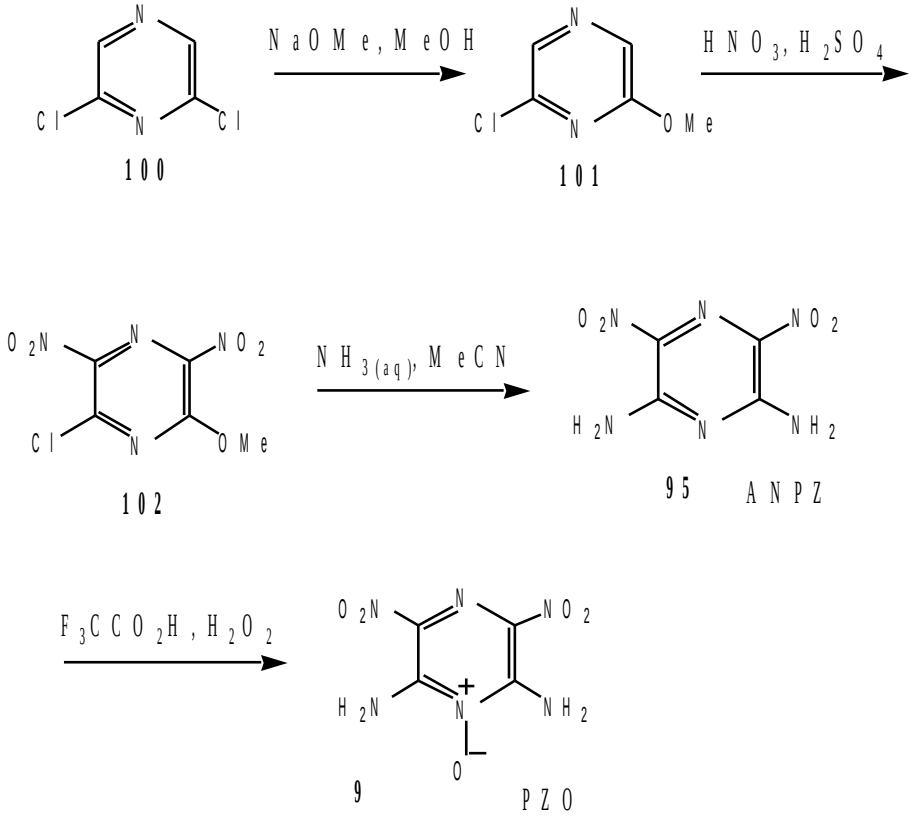
Given the reluctance of pyridine to be nitrated, it is not surprising that due to the presence of a second aza group in the ring, pyrazine is effectively inert to electrophilic reagents.

Literature on nitropyrazine systems is scarce. However, there has been a limited number of publications. 2,6-Dinitro-3,5-diaminopyrazine (ANPZ) (**95**) has been prepared by the nitration (nitrodecarboxylation) of 2,6-diamino-3,5-dicarboxypyrazine (**99**) in a yield of 84%.[78] This patented procedure begins with the preparation of tetracyanopyrazine (**97**) by the ring forming reaction between diaminomaleonitrile (**85**) and di-iminosuccinonitrile (**96**). Tetracyanopyrazine is then aminated to give 2,6-diamino-3,5-dicyanopyrazine (**98**) which is in turn hydrolysed to 2,6-diamino-3,5-dicarboxypyrazine (**99**) (**Scheme 39**).



Scheme 39

2,6-Diamino-3,5-dinitropyrazine (ANPZ) (**95**) can be prepared by an alternative more efficient synthesis.[79] This route also has an additional step involving oxidation of ANPZ into 2,6-diamino-3,5-dinitropyrazine-1-oxide (PZO) (**9**). 2,6-Dichloropyrazine (**100**) is a readily available precursor compound and the synthesis of PZO (**9**) involves nitration, amination and *N*-oxidation which are all common reactions in the preparation of energetic materials (**Scheme 40**).



Scheme 40

Initially, 2,6-dichloropyrazine (**100**) is mono-methoxylated to give 2-methoxy-6-chloropyrazine (**101**)[80] which in turn is dinitrated to give 2-methoxy-6-chloro-3,5-dinitropyrazine (**102**).[81] The presence of the methoxy- group in position 2 on the pyrazine ring activates the system towards electrophilic attack and therefore dinitration proceeds smoothly.

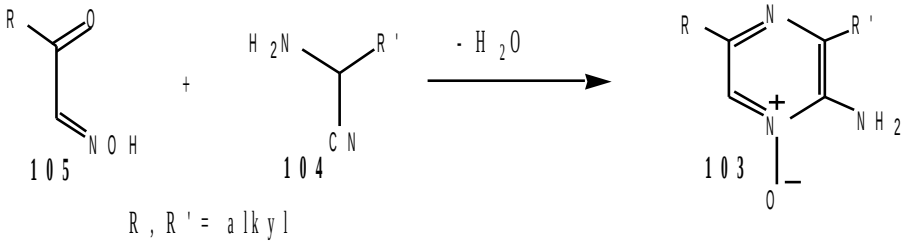
Nucleophilic amination of **102** with a saturated solution of ammonia in acetonitrile gives rise to 2,6-diamino-3,5-dinitropyrazine (ANPZ) (**95**). The two nitro groups in positions 3 and 5 on the pyrazine ring activate the respective adjacent carbons in positions 3 and 6 towards nucleophilic substitution and hence diamination proceeds easily. Finally, oxidation of **95** with peroxytrifluoroacetic acid (F_3CO_3H) yields 2,6-diamino-3,5-dinitropyrazine-1-oxide (PZO) (**9**).[81]

4.4 Pyrazine Aminations

As with the benzodiazine series, nucleophilic amination of halogeno-pyrazines requires forcing conditions (i.e. high temperature and high pressure), but the most reactive halogenopyrazines, fluoropyrazines, can be aminated at room temperature.

Aminopyrazines are not generally accessible by the reduction of nitropyrazines due to the lack of availability of the latter. 2,6-Diaminopyrazine can be prepared by the reduction of 2,6-diazidopyrazine but this method is usually avoided because of the high sensitivity to detonation attributed to the starting material.[82]

Aminopyrazine-*N*-oxides (**103**) can be directly synthesised by the condensation of an α-amino nitrile (**104**) with an α-oximino ketone (**105**) (**Scheme 41**).[83]

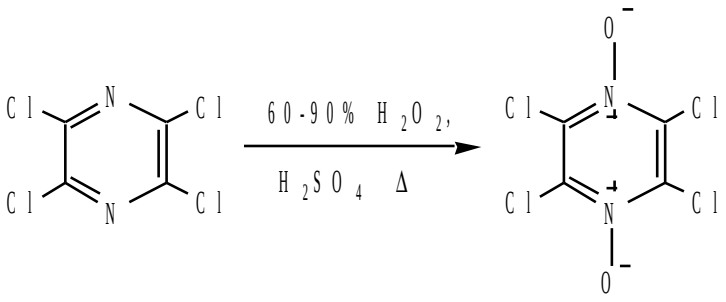


Scheme 41

There exist several other examples of aminopyrazine preparations but they all result in the formation of pyrazines with bulky side groups attached.

4.4 Pyrazine Oxidations

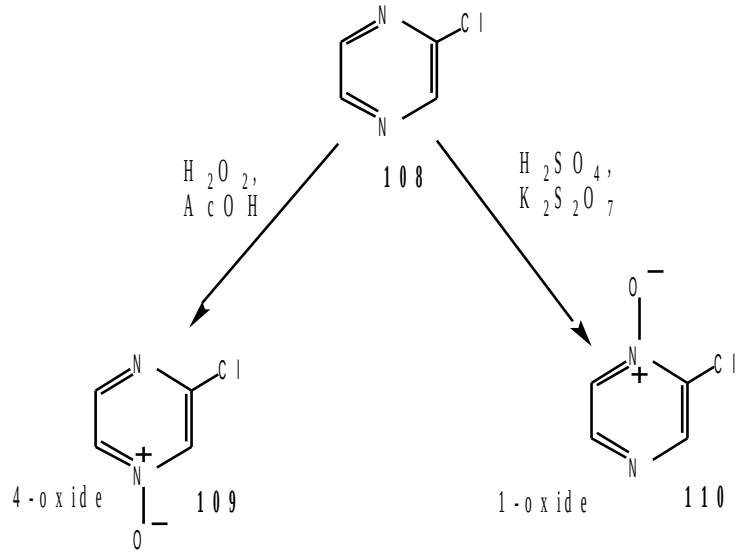
Pyrazine-*N*-oxides are typically prepared using conventional oxidation systems, *viz.* Ac_2O/H_2O_2, *meta*-chloroperbenzoic acid (MCPBA), monoperoxyphthalic acid, permaleic acid and peroxytrifluoroacetic acid. The ease of oxidation is dependent on the type and level of substitution on the pyrazine ring. Tetrachloropyrazine (**106**), an extremely deactivated compound, can be oxidised using strong solutions of aqueous hydrogen peroxide (*ca.* 60-90%) in sulfuric acid to give the di-*N*-oxide compound (**107**) (**Scheme 42**).[84]



106 **107**

Scheme 42

Due to the danger associated with using very strong solutions of hydrogen peroxide, it has been demonstrated that potassium peroxydisulfate (Caro's Acid) may be used instead. It has been reported that 2-chloropyrazine (**108**) exhibits anomalous behaviour to the aforementioned reagent (**Scheme 43**).[85]



Scheme 43

Since the N-4 atom is the more basic in 2-chloropyrazine, then oxidation with H_2O_2/AcOH gives the 4-oxide derivative (**109**). However, with strongly acidic systems such as $H_2SO_4/K_2S_2O_7$, the N-4 atom will be protonated first and therefore the N-1 atom will be preferentially oxidised to the 1-oxide (**110**). This occurs since although the nucleophilicity of the protonated pyrazine is reduced, the peroxysulfuric acid is so electrophilic that attack is still possible.

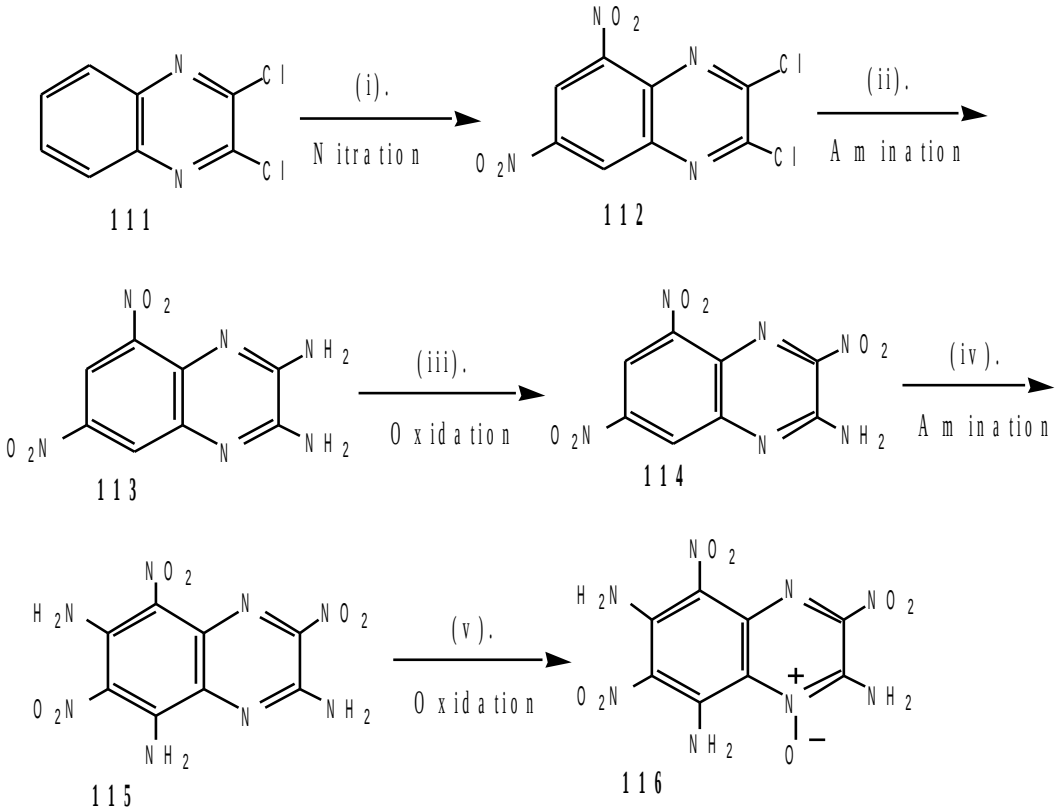
2-Chloropyrazine-4-oxide (**109**) is not oxidised to the di-*N*-oxide with Caro's acid. It has been postulated that the di-*N*-oxide may be formed but it is immediately deoxygenated back to the 4-oxide via electrophilic attack of the peracid on the oxygen of the *N*-oxide.[87]

5. Results and Discussion

5.1 Quinoxaline Reactions

5.1.1 General Strategy

The initial general strategy within this part of the project was to functionalise a pre-formed quinoxaline compound. The ready availability of the chloro-derivatives made them ideal candidates for such a strategy. **Scheme 44** shows an envisaged synthesis starting from 2,3-dichloroquinoxaline (**111**) which was the outline strategy in the first part of the project.



111 112 113 114 115 116

Reagents: (i). HNO_3, H_2SO_4; (ii). NH_3, MeCN; (iii). DMD; (iv). $[Me_3NNH_2]^+I^-$; (v). H_2O_2, F_3CCO_2H.

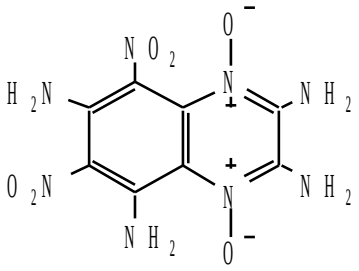
Scheme 44

Using the Rothstein and Peterson equation[4] the detonation velocity (D) for the target molecule, 2,6,8-trinitro-3,5,7-triaminoquinoxaline-4-oxide (**116**), was calculated to be 7.84 $mm.\mu s^{-1}$ (Factor F = 4.57). This value is slightly less than that of TATB (Calc'd. D = 7.87 $mm.\mu s^{-1}$) and is a reflection of the oxygen balance (OB) of this target compound. There are seven atoms of oxygen in the molecule (**116**) compared to a total of fourteen atoms of carbon and hydrogen. Consequently, upon detonation it could be expected that not all the carbon and hydrogen would be fully oxidised to carbon dioxide and water respectively.

Reaction (i) in the synthesis of the target quinoxaline (**116**) is the mixed acid nitration of 2,3-dichloroquinoxaline (**111**) to give the nitrated product, **112**. This reaction was very problematic and will be discussed in more detail in Section 5.1.2. Reaction (ii) is the nucleophilic amination of **112** to give compound **113**; this apparently straightforward reaction requires harsh conditions (autoclave, 150° C, 12 h) to be successful. Reaction (iii) is the conversion of **113** into compound **114** by the oxidation of one of the amino groups to a nitro group. A related conversion has been reported in the literature by Murray *et al.*; aniline was converted in 97% yield to nitrobenzene.[37] It was hoped that such a clean reaction would be effective with benzodiazines, although, due to the markedly different chemical and electronic natures of aniline and aminated quinoxaline compounds, no such conversion was guaranteed.

Reaction (iv) is the amination of **114** to give compound **115**. This reaction might be achieved by the use of 1,1,1-trimethylhydrazinium iodide (TMHI) $[Me_3NNH_2]^+I^-$, which is easily prepared by the alkylation of dimethylhydrazine with methyl iodide in THF.[34] This recently reported aminating agent operates via a vicarious nucleophilic substitution (VNS) reaction, where hydrogen is substituted. For the case of amination the amine nucleophile is usually in the form XNH_2, where X is an auxiliary group capable of stabilising a negative charge and of being eliminated as HX. The elimination of HX drives the rearomatization of the σ-intermediate adduct, giving the aminated product. Substitution usually occurs *ortho* and *para* to the nitro group with the isomer distribution affected by other substituents on the carbocyclic ring.

Reaction (v) is the conversion of **115** into compound **116** by the oxidation of one of the nitrogen heteroatoms in the quinoxaline ring; this reaction might be achieved by the action of trifluoroperacetic acid (F_3CCO_3H) which is prepared *in situ* from trifluoroacetic acid (F_3CCO_2H) and hydrogen peroxide (aq. H_2O_2 soln.). Such an oxidation with trifluoroacetic acid may be difficult due to the strongly deactivated nature of the heterocyclic ring in compound **115**. Stronger oxidising systems may be needed, for example, sulfuric acid with potassium peroxydisulfate has been shown to give the di-*N*-oxide of strongly deactivated systems such as 2,3,5,6-tetrachloropyrazine.[52] Since the effect of substituents on *N*-oxidation is so crucial, a more realistic target molecule may be compound **117**.



117

The formation of compound **117** was envisaged to be easier due to the presence of amino groups in the 2- and 3- positions on the heterocyclic ring, which being electron donating should activate the system towards oxidation. Additionally, the formation of intramolecular hydrogen bonds between the *N*-oxide and amino functionalities should act as a driving force for this reaction. In this system the deactivating effect of the nitro groups on the benzenoid ring should not affect the oxidation of the heteroatoms on the heterocyclic ring.

5.1.2 Nitration of 2,3-Dichloroquinoxaline (111)

The nitration of 2,3-dichloroquinoxaline (**111**) was studied in depth because this molecule was the starting material in the proposed synthesis of 2,6,8-trinitro-3,5,7-triaminoquinoxaline-4-oxide (**116**). This substrate is cheap and is an ideal starting material for the strategy mentioned earlier. There were no reports in the literature of the nitration of 2,3-dichloroquinoxaline although it was mentioned

that chloroquinoxalines were in general difficult to nitrate. It was also mentioned that symmetrical systems with substitution on the 2- and 3- positions with the same polar group, e.g. a halogeno atom, were not susceptible to electrophilic attack.

Since the dinitration of quinoxaline itself requires very drastic conditions[36] it was decided that initial efforts towards the nitration of 2,3-dichloroquinoxaline (**111**) would involve mixed acid nitration using forceful conditions. It was surmised that the electron withdrawing effect of the chlorine atoms on the heterocyclic ring in **111** would only have a relatively small further deactivating effect on the quinoxaline structure towards electrophilic attack. **Table 2** summarises the initial mixed acid nitration conditions used and the results obtained.

Mixed acid nitration of 2,3-dichloroquinoxaline was carried out using the general reaction procedure given in the experimental section. By analysis of reactions 1-5 in **Table 2** we can see that reaction occurs after 1.0 hour [the melting point of 2,3-dichloroquinoxaline (**111**) is 152°C]. This nitration reaction gave a promising product which had IR and NMR spectral properties in accordance with the target compound, 2,3-dichloro-5,7-dinitroquinoxaline (**112**).

No.	Reagents	Reaction Temp. (°C)	Reaction Time (h)	M.Pt. of Product	HPLC* Elution Time (s)
1.	HNO_3, H_2SO_4	r.t.[a]	0.5	152	500
2.	"	"	1.0	152	500
3.	"	"	1.5	290	120
4.	"	"	2.0	286	120
5.	"	"	5.0	286	120
6.	"	60-70[a]	5.0	290	120
7.	HNO_3, 30% Oleum	80[a]	18.0	220-230 (decomp.)	300
8.	HNO_3, H_2SO_4	r.t.[a]	0.75	152	500
9.	"	"	4.0	290	120
10.	"	r.t.[b]	2.0	152	500
11.	"	"	5.0	210-220	200

Key: [a]: During addition of substrate to the HNO_3/H_2SO_4 mixture, the temperature was allowed to rise to 60-80°C.

[b]: During addition of substrate to the HNO_3/H_2SO_4 mixture, the temperature was kept below 10°C.

*: For HPLC experimental parameters see Section 10.1.4.

Table 2: Results from 2,3-Dichloroquinoxaline (111) Mixed Acid Nitration Studies

^1H NMR evidence pointed towards dinitration with two doublets at δ 8.0 and 8.3 ppm, a coupling constant of ~2.5 Hz indicated *meta* coupling of protons and hence *meta* orientation as would be expected in the 5,7-dinitro-derivative (**112**). EI mass spectral analysis of the product, however, showed it to be an unwanted product with a molecular weight of 260. The product contains a benzene ring (peaks between 76 and 79 m/z) and also contains at least one nitro group causing the peak at 30 m/z (due to NO cleavage). Since the mass spectral analysis could not confirm the presence of the desired product, 2,3-dichloro-5-nitroquinoxaline (**118**), it was concluded that the reaction had produced an unwanted product. For experimental results see Section 10.2.6: Attempted Mixed Acid Nitration (No. 1) of 2,3-Dichloroquinoxaline (**111**).

The melting point of this unwanted product was ~290°C and the compound eluted after 120 seconds during HPLC analysis; therefore when further nitrations were carried out (reactions 6 and 9, **Table 1**) if the product had these properties then it was assumed to be an unwanted product. HPLC analysis was carried out under standard conditions (see Section 10.1.4). Several different reaction conditions were used; all of which yielded the same unwanted product apart from reaction with an oleum based nitrating agent (reaction no. 7) which produced a totally different unwanted product. This was confirmed by MS analysis. This product eluted after 300 seconds in HPLC analysis and had a melting point of 220-230°C (decomposition temperature). For experimental results see Section 10.2.7: Attempted Mixed Acid Nitration (No. 2) of 2,3-Dichloroquinoxaline (**111**).

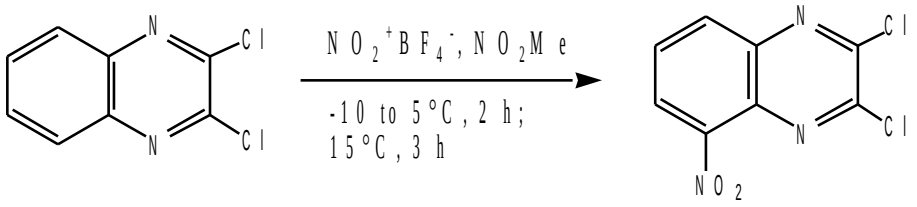
The reaction was now performed with temperature control during the addition of the substrate to the mixed acid mixture (reactions 10-11 in **Table 1**); the temperature was kept below 10°C. This experimental alteration coupled with only using a stoichiometric amount of nitric acid gave a new product (reaction no. 11) with both a melting point (210-220°C) and HPLC elution time (200 s) different from both starting material and the two previous unwanted products.

Due to inconclusive assignments of the IR spectrum of the reaction product (reaction no. 11) it was impossible to determine whether nitration had taken place. Initially, it was thought that the HPLC trace for this reaction product indicated the presence of three products. The ^{1}H NMR spectrum was also confusing since the spectrum showed peaks lying in three different regions which could potentially correspond to the three compounds detected in HPLC analysis. In order to determine the identity of these three compounds, the mass spectrum of the reaction products was taken. The EI mass spectrum of the reaction product mixture is almost exactly the same as that of the starting material; both having the same molecular ion peak and isotopic clustering associated with having two chlorine atoms in a molecule in addition to having identical fragmentation patterns. However, the HPLC trace of the reaction product mixture shows that there is clearly no starting material present. One possible explanation was that the strong acidic media could have been causing isomerisation of 2,3-dichloroquinoxaline (**111**) where the chlorine atoms were migrating round onto

the carbocyclic ring. For experimental results see Section 10.2.8: Attempted Mixed Acid Nitration (No. 3) of 2,3-Dichloroquinoxaline (**111**).

However, this supposition was not backed up by ^{1}H NMR spectroscopy evidence, since close examination of the peaks on the proton spectrum of the product showed that they did not correspond to isomerisation products. Thus it can be concluded that nitrating systems based on nitric acid were not effective in nitrating 2,3-dichloroquinoxaline (**111**) and consequently alternative reagents were investigated.

Nitration was attempted using dinitrogen pentoxide (N_2O_5) in dichloromethane at 0°C. HPLC analysis of the reaction product showed the presence of at least seven compounds. It was hoped that dinitrogen pentoxide would offer a mild nitration route since it has been used in previous studies to nitrate a number of different aromatic compounds. Nitrations with acetyl nitrate (generated *in situ* by acetic anhydride/nitric acid) and nitronium tetrafluoroborate ($NO_2^+BF_4^-$) in DCM were both attempted but only starting material was recovered in each case. With the former system it was concluded that the electrophilicity of the nitrating agent was not high enough to effect nitration. However, with the latter nitrating system, nitronium tetrafluoroborate, neither of the reactants was appreciably soluble in DCM. Therefore, nitration with $NO_2^+BF_4^-$ in nitromethane (NO_2Me) was attempted (**Scheme 45**).



111 **118**

Scheme 45

Using nitromethane as the solvent, which is inert from attack by nitronium ions and has a high solvating power, 2,3-dichloroquinoxaline was successfully

nitrated. Reaction was confirmed by CI mass spectral analysis (**Figure 3**) which shows the molecular ion $(M + 1)^+$ peak at 244 m/z as well as a peak at 261 m/z which corresponds to $[M + 1 + \text{ammonia (the carrier gas)}]^+$ for a mononitrated product (**118**). In the spectrum there is also a peak at 199 m/z which is the $(M + 1)^+$ peak for **111**. **Table 3** summarises the most significant peaks from the mass spectrum in **Figure 3**. The spectrum in **Figure 3** relates to compound **118** which contains two ^{35}Cl atoms.

No.	*m/z*	Species Identified
1.	261	$[M + 1 + 17\ (NH_3)]^+$
2.	244	$(M + 1)^+$ (**118**)
3.	214	$(M + 1)^+ - 30$ (NO)
4.	199	$(M + 1)^+$ (**111**)

Table 3: Summary of the Most Significant Peaks
From the Mass Spectrum 2,3-Dichloro-5-nitroquinoxaline (118)

Figure 3 also shows the appropriate splitting pattern associated with the isotopic abundance of chlorine containing compounds. The relative intensities of the peaks can be calculated using the binomial expansion of $(a + b)^n$ where a = relative abundance of ^{35}Cl; b = relative abundance of ^{37}Cl; n = number of chlorine atoms in the molecule.

Therefore, for **118**: $(a + b)^2 = a^2 + 2ab + b^2$,

since a = 3 and b = 1, then, $a^2 = 9$; $2ab = 6$; $b^2 = 1$,

hence the relative intensities of the three peaks are 9 : 6 : 1.

Figure 3 shows the above correlation where m/z values are separated by two mass units at m, (m + 2) and (m + 4). The presence of starting material in the sample is backed up by HPLC analysis of the reaction product mixture which indicated the presence of two compounds (**Figure 4**). The first compound was eluted at ~380 s

and the second at ~560 s. The latter compound has the same elution time as the starting material [as 2,3-dichloroquinoxaline (**111**)]. Therefore, the chromatogram indicates that there is only one reaction product.

Examination of the NMR spectrum (**Figure 5**) confirmed the presence of the mononitro product (nitration in the 5-position) (**118**) with starting material also present. The presence of the 5-nitro product is confirmed by close examination of the proton splitting patterns. The multiplets at δ 7.97 ppm and at 8.08 ppm are due to unreacted starting material. The triplet at δ 8.14 ppm ($J_{6,7} = J_{7,8} = 9.0$ Hz) is thought to be caused by the Ar-7H proton, whilst the doublet of doublets at δ 8.37 ppm ($J_{7,8} = 9.0$ Hz, $J_{6,8} = 1.2$ Hz) and δ 8.44 ppm ($J_{6,7} = 9.0$ Hz, $J_{6,8} = 1.2$ Hz) can be assigned to Ar-8H and Ar-6H protons respectively.

High resolution mass spectrometry (HRMS) was carried out on 2,3-dichloro-5-nitroquinoxaline (**118**). A good correlation between measured mass and actual mass of the molecular ion was found.

CHN Elemental analysis was carried out on 2,3-dichloro-5-nitroquinoxaline (**118**). There was a reasonable match on the C and H values but there was a difference of approximately 1% in the N values. This is probably because the product was not recrystallised due to its poor solubility in most organic solvents.

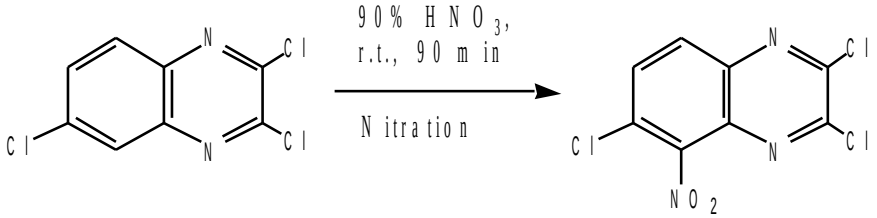
This nitration of 2,3-dichloroquinoxaline (**111**) is the first to be reported. The normal route towards 2,3-dichloronitroquinoxalines is via the nitration of the 2,3-dihydroxy compound and its subsequent chlorination.[88-90] The chlorination of hydroxyaromatics often gives disappointing yields and therefore this step can now be circumvented. The nitration of 2,3-dichloroquinoxaline (**111**) was also carried out using nitronium tetrafluoroborate ($NO_2^+BF_4^-$) in sulfolane (0.1M solution) but in a lower yield (*ca.* 60%).

5.1.3 Nitration of 2,3,6-Trichloroquinoxaline (119) and 2,3,6-

Trichloro-5-nitroquinoxaline (120)

Both 2,3,6-trichloroquinoxaline (**119**) and 2,3,6,7-tetrachloroquinoxaline (**120**) are readily available starting materials. Consequently, it was decided to extend the heterocyclic nitration studies to these substrates. In general chloronitroquinoxalines that appear in the literature are prepared by the nitration of hydroxy-precursor compounds followed by chlorination of the hydroxy-groups. It was therefore of synthetic interest to develop the nitration of chloroquinoxalines directly thus eliminating the unwanted chlorination step.

The nitration of 2,3,6-trichloroquinoxaline (**119**) (**Scheme 46**) was attempted under various conditions, and the mononitro derivative (**120**) was obtained in acceptable yield (64%) with nitric acid (90% aq. solution) as the nitrating agent. The ^{1}H NMR spectrum (**Figure 6**) has two doublets at δ 8.17 ppm and 8.32 ppm, these signals have coupling constants of 9.15 Hz indicating *ortho* coupling. Therefore, nitro substitution appears to have taken place in the 5-position on the quinoxaline ring giving 2,3,6-trichloro-5-nitroquinoxaline (**120**). Substitution was confirmed by mass spectral analysis which gave the molecular ion (M^{+}) peak of 278 m/z. On-line searching failed to identify a CAS registry entry and therefore 2,3,6-trichloro-5-nitroquinoxaline (**120**) can be regarded as a new compound.



119 **120**

Scheme 46

The appropriate splitting intensities were observed approximately in the mass spectrum of 2,3,6-trichloro-5-nitroquinoxaline (**120**). Using the rule described in Section 5.1.2:

For **120**: $(a + b)^3 = a^3 + 3a^2b + 3ab^2 + b^3$, since a = 3 and b = 1, then,

$a^3 = 27$; $3a^2b = 27$; $3ab^2 = 9$; $b^3 = 1$,

hence the relative intensities of the four peaks are 27 : 27 : 9 : 1.

Therefore, the mass spectrum for **120** should have splitting intensities of 27 : 27 : 9 : 1 for the M^+ peak, where m/z values are separated by two mass units at: [m (277 m/z)], [m + 2 (279 m/z)], [m + 4 (281 m/z)] and [m + 6 (283 m/z)].

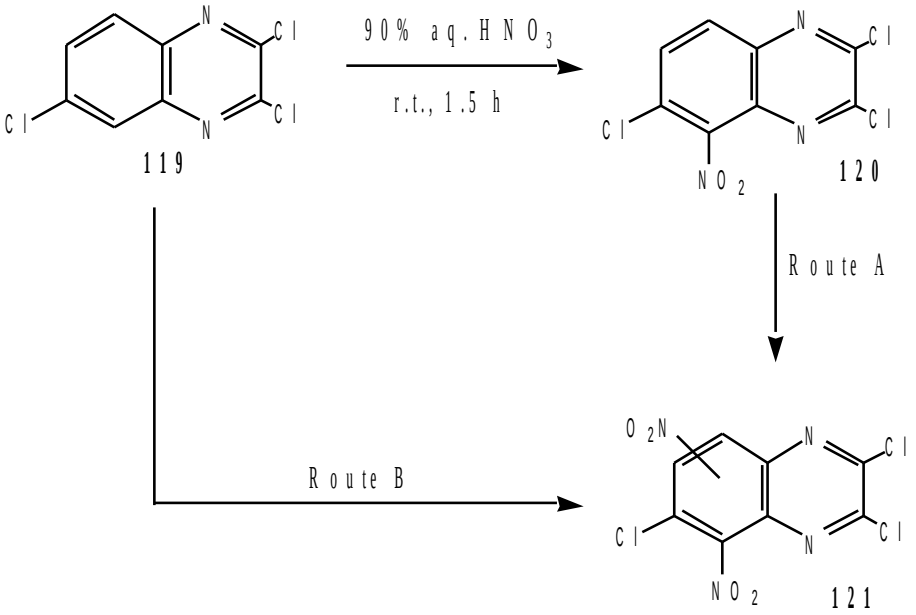
High resolution mass spectrometry (HRMS) was carried out on 2,3,6-trichloro-5-nitroquinoxaline (**120**). A good correlation between measured mass and actual mass of the molecular ion was found.

CHN Elemental analysis was carried out on 2,3,6-trichloro-5-nitroquinoxaline (**120**). There was found to be a good correlation between calculated and experimental values.

The nucleophilic nitration of 2,3,6-trichloroquinoxaline (**119**) was also attempted using sodium nitrite in toluene with tetrabutylammonium bromide acting as a phase transfer catalyst; with refluxing overnight the starting material was recovered unreacted. It was concluded that the trichloro- system was not sufficiently activated to nucleophilic attack.

The nitration of 2,3,6-trichloroquinoxaline (**119**) was attempted using nitronium tetrafluoroborate in sulfolane and the mono-nitro product was obtained in approximately 20% yield.

Several attempts were made to prepare the dinitro compound (**121**) but no such product was obtained (**Scheme 47**). Two routes are available in order to prepare **121**, the results from each are summarised in **Table 2**.



Scheme 47

Substrate	Reagent (s)	Reaction Conditions	Reaction Outcome/ Product
119	90% aq. HNO_3	r.t., 0.5 h	**119**
119	90% aq. HNO_3	r.t., 1.5 h	**120**
119	90% aq. HNO_3	r.t., 4 h	Decomposition
119	69% aq. HNO_3	r.t., overnight	Decomposition
119	c. HNO_3, c. H_2SO_4	60°C, 3 h	Decomposition
120	c. HNO_3, c. H_2SO_4	r.t., 0.5 h	**120**
120	c. HNO_3, c. H_2SO_4	r.t., 1.5 h	**120**
120	c. HNO_3, c. H_2SO_4	40°C, 2 h	Decomposition
120	c. HNO_3, c. H_2SO_4	50°C, 2 h	Decomposition

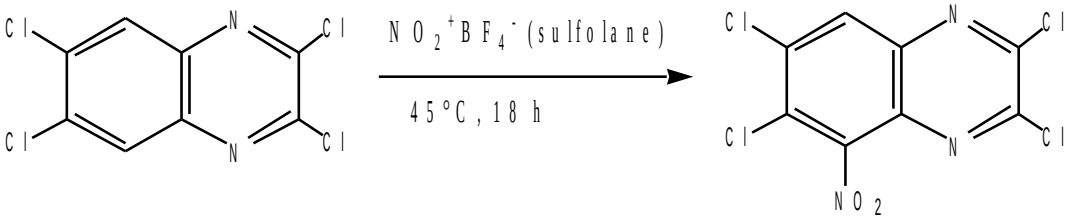
Table 4: Results from the Attempted Nitrations of 2,3,6-Trichloroquinoxaline (119) and 2,3,6-Trichloro-5-nitroquinoxaline (120)

By analysis of **Table 4** it can be seen that mixed acid nitration is not suitable for the preparation of 2,3,6-trichlorodinitroquinoxaline. It is thought that more effective nitrating systems such as $NO_2^+BF_4^-$ in nitromethane/sulfolane or possibly N_2O_5 may be more suited to this nitration.

5.1.4 Nitration of 2,3,6,7-Tetrachloroquinoxaline (122)

The nitration of 2,3,6,7-tetrachloroquinoxaline (**122**) was attempted using a mixed acid system. Initial nitration with 2.0 equivalents of nitric acid in sulfuric acid with the substrate addition carried out at a temperature of between 5 and 10°C with a reaction time of 3-4 h at r.t. resulted in recovery of starting material. The reaction was repeated with 2.0 equiv. of nitric acid in sulfuric acid at 55°C for 4 h. HPLC analysis of the reaction mixture indicated the presence of 2-3 compounds but the ^{1}H NMR spectrum had only one singlet. Mass spectral analysis of the reaction mixture indicated the presence of decomposition products.

The nitration of 2,3,6,7-tetrachloroquinoxaline (**122**) was successfully achieved using a stock solution of 0.1 M nitronium tetrafluoroborate ($NO_2^+BF_4^-$) in sulfolane; the 5-nitro derivative (**123**) was obtained in approximately 39% yield (**Scheme 48**).



122 **123**

Scheme 48

Figure 7 shows the IR spectrum for 2,3,6,7-tetrachloro-5-nitroquinoxaline (**123**). **Table 5** shows the most significant peaks from **Figure 7**. The peak at 897 cm^{-1} is of medium intensity and is characteristic of the C-Cl bond. The peaks at 1375 and 1560 cm^{-1} are also medium to strong intensity peaks and are characteristic of the NO_2 group.

No.	$\upsilon_{max}(cm^{-1})$	Bond Stretching
1	897	C-Cl (m)
2	1375	NO_2 symm. (m)
3	1560	NO_2 asymm. (m)
4	3056	C-H (w)

Table 5: Summary of the Most Significant Peaks of the IR Spectrum of 2,3,6,7-Tetrachloro-5-nitroquinoxaline (123)

Mass spectral analysis of 2,3,6,7-tetrachloro-5-nitroquinoxaline (**123**) was carried out. A very good match of isotopic clustering was found since this compound contains four chlorine atoms. Using the binomial expansion analysis described in Section 5.1.2, for compond **123**, the following peak intensities can be calculated:

For **123**: $(a + b)^4 = a^4 + 4a^3b + 6a^2b^2 + 4ab^3 + b^4$, since a = 3 and b = 1,

then, $a^4 = 81$; $4a^3b = 108$; $6a^2b^2 = 54$; $4ab^3 = 36$; $b^4 = 1$,

hence the relative intensities of the five peaks are 81 : 108 : 54 : 36 : 1.

Therefore, the mass spectrum for **123** should have splitting intensities of 81 : 108 : 54 : 36 : 1 for the M^+ peak, where m/z values are separated by two mass units at: [m (311 m/z)], [m + 2 (313 m/z)], [m + 4 (315 m/z)], [m + 6 (317 m/z)], [m + 8 (319 m/z)].

High resolution mass spectrometry (HRMS) was carried out on 2,3,6,7-tetrachloro-5-nitroquinoxaline (**123**). A good correlation between measured mass and actual mass of the molecular ion was found.

CHN Elemental analysis was carried out on 2,3,6,7-tetrachloro-5-nitroquinoxaline (**123**). There was found to be a good correlation between calculated and experimental values.

2,3,6,7-Tetrachloroquinoxaline (**122**) was found to be significantly more difficult to nitrate than both 2,3,6-trichloroquinoxaline (**119**) and 2,3-dichloroquinoxaline (**111**). 2,3,6,7-Tetrachloro-5-nitroquinoxaline (**123**) has previously been prepared by the nitration of 6,7-dichloroquinoxalin-2,4(1*H*, 3*H*)-dione and its subsequent dichlorination.[91] An experimental melting point of >280°C was obtained whereas the literature value is 118-120°C.[91] It is possible that the literature value may have been wrongly reported.

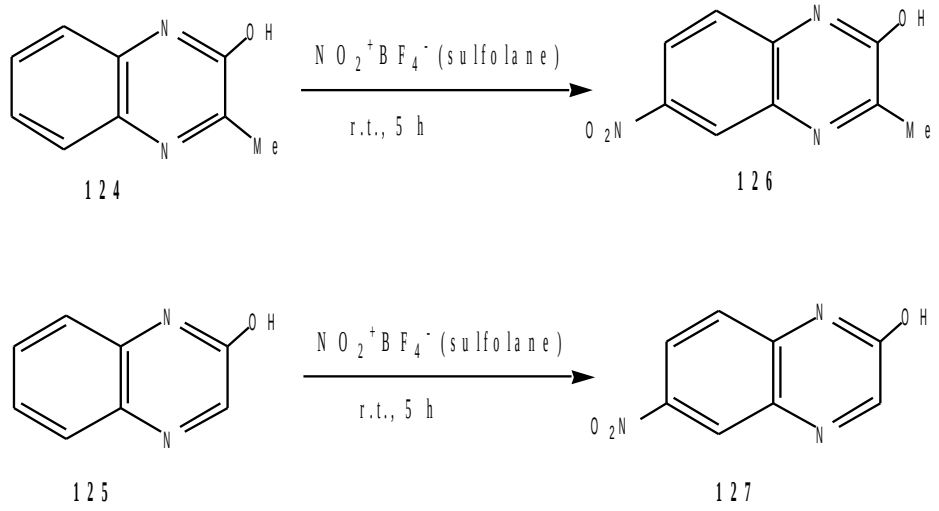
It is known that chloro- groups attached to an aromatic ring are electron withdrawing and therefore have a deactivating effect towards electrophilic attack such as nitration involving a nitronium ion (NO_2^+). Thus it is not surprising that highly chlorinated aromatics are strongly deactivated towards nitration. Overcoming this level of deactivation can sometimes be achieved by the use of extremely electrophilic systems such as dinitrogen pentoxide (N_2O_5) dissolved in pure nitric acid or mixtures of pure nitric acid and oleum (SO_3 dissolved in pure sulfuric acid). However, the use of these extremely aggressive agents with heterocyclic substrates such as chloroquinoxalines has been shown to result in cleavage of the heterocyclic ring and the production of low molecular weight (MW) decomposition products. Furthermore, nitronium tetrafluoroborate ($NO_2^+BF_4^-$) which is a very strong nitrating agent has been shown to be highly effective for functionalised quinoxalines when used in dilute solutions of either nitromethane or sulfolane and as such seems to be the reagent of choice when carrying out such nitrations.

5.1.5 Nitration of 2-Hydroxy-3-methylquinoxaline (124) and 2-Hydroxyquinoxaline (125)

Initial nitration studies concentrated on the reaction of chloroquinoxaline substrates. It was decided, however, to extend these nitration experiments to include 2-hydroxy-3-methylquinoxaline (**124**) and 2-hydroxyquinoxaline (**125**). Such studies would form a useful comparison of the reactivity of

chloroquinoxalines and hydroxyquinoxalines. This comparison would involve the use of both mixed acid and $NO_2^+BF_4^-$ (sulfolane) nitration systems. The nitration of both substrates has been studied previously with mixed acid systems (H_2SO_4 and KNO_3). In these studies both substrates were mono-nitrated in approximately 80% yield.[92,93]

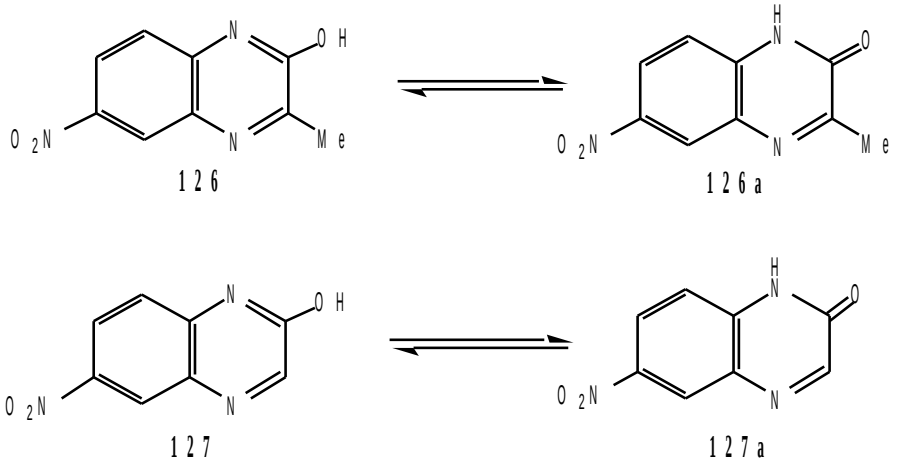
The nitrations of both 2-hydroxy-3-methylquinoxaline (**124**) and 2-hydroxyquinoxaline (**125**) were attempted a number of times using a variety of nitrating agents, including mixed acid, nitric acid and nitronium tetrafluoroborate ($NO_2^+BF_4^-$) in sulfolane under a range of reaction conditions. The latter system was found to be effective in producing the mono-nitro products; 2-hydroxy-3-methyl-6-nitroquinoxaline (**126**) (69% yield) and 2-hydroxy-6-nitroquinoxaline (**127**) (60% yield) (**Scheme 49**). With these substrates the nitric acid and mixed acid nitration systems tended to give decomposition products.



Scheme 49

It is recognised that compounds **124**, **125**, **126** and **127** will all exist in equilibrium with the corresponding tautomeric keto structures. For example, for compounds **126** (2-hydroxy-3-methyl-6-nitroquinoxaline) and **127** (2-hydroxy-6-

nitroquinoxaline) the tautomeric structures would be **126a** and **127a** respectively (**Scheme 50**).



Scheme 50

The IR spectra for 2-hydroxy-3-methyl-6-nitroquinoxaline (**126**) and 2-hydroxy-6-nitroquinoxaline (**127**) show the presence of signals at 1666 and 1672 cm^{-1} respectively which can be attributed to the absorbance frequency of the keto group. In the IR spectra for **126** and **127** there are also broad signals at 2979 and 3463 cm^{-1} respectively which can be assigned to the stretching frequency for the O-H group. The OH group is also detected by ^{1}H NMR spectroscopy since both compounds have broad signals at δ 3.51 ppm (caused by the resonance of the hydroxy proton). Consequently, it is recognised that the chemistry of these compounds can be influenced by both the hydroxy and keto tautomeric structures. For consistency these compounds will be referred to as hydroxy functionalised.

Figures 8 and **9** show the ^{13}C NMR spectra for 2-hydroxy-3-methyl-6-nitroquinoxaline (**126**) and 2-hydroxy-6-nitroquinoxaline (**127**) respectively. The individual assignments are detailed in Section 6.2: Quinoxaline ^{13}C NMR Spectroscopy Shift Values. Interpretation of the spectra for compounds **126** and **127** shows that the carbons in positions 2 and 3 on the heterocyclic rings both appear around δ 155 - 160. This is often the case with quinoxaline compounds

since these carbons are α to the nitrogen heteroatoms which have the effect of shifting the signal significantly downfield. This is also observed to a lesser extent for carbons in positions 8a and 4a on the heterocyclic ring, which are in the range δ 137 - 142 for compounds **126** and **127**. Carbons attached to nitro groups will usually be shifted downfield as well (*ipso* effect of the NO_2 group), as is the case for the C-NO_2 (both in position 6) carbons in both compounds **126** and **127** which have resonances in the range δ 130 - 137.

Figure 10 shows the mass spectrum for 2-hydroxy-3-methyl-6-nitroquinoxaline (**126**) which has a strong M^+ peak at 177 *m/z*. There is also a large peak at 147 m/z which is 30 mass units less than that of the molecular ion. Such a peak can be attributed to a structure produced by the loss of NO from the molecular ion. The loss of NO is often observed in the mass spectra of aromatic nitro compounds. Within this spectrum there is also a large peak at 205 m/z, which can probably be attributed to a reaction impurity. Although this peak is large it is magnified by a factor of (x 50) and therefore only represents a small proportion of the sample.

Although there is NMR evidence for the production of the 6-nitro derivative in both the nitrations of 2-hydroxy-3-methylquinoxaline (**126**) and 2-hydroxyquinoxaline (**127**) the product structures are only tentative.

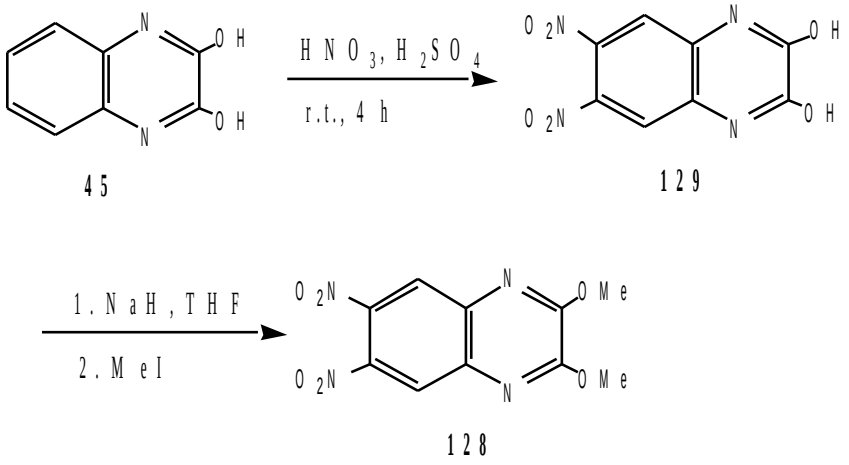
CHN Elemental analyses were carried out on both 2-hydroxy-3-methyl-6-nitroquinoxaline (**126**) and 2-hydroxy-6-nitroquinoxaline (**127**). Both samples were found to have reasonable correlations between calculated and experimental values.

Comparison of the experimental melting points of compounds **126** and **127** with the literature values for these compounds, in references 92 and 93 respectively, shows a discrepancy of approximately 30°C in both cases. The experimental values are probably lower than the literature values because the samples were not recrystallised due to their lack of solubility in most organic solvents.

A comparison of the reactivity of chloroquinoxalines and hydroxyquinoxalines shows that both classes of compounds are nitrated by nitronium tetrafluoroborate in either nitromethane or sulfolane and are also often subject to decomposition when treated with mixed acid or nitric acid based nitrating agents.

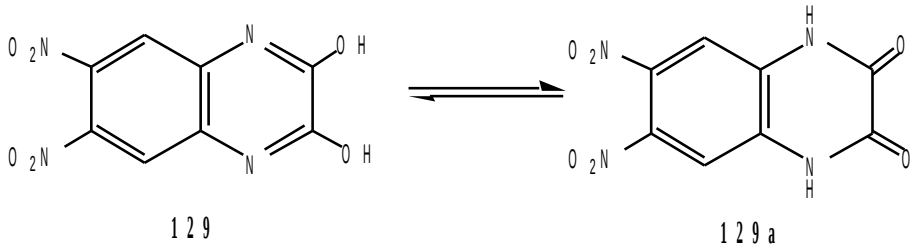
5.1.6 Preparation of 2,3-Dimethoxy-6,7-Dinitroquinoxaline (128)

2,3-Dimethoxy-6,7-dinitroquinoxaline (**128**) was prepared by the mixed acid nitration of 2,3-dihydroxyquinoxaline (**45**) to give 2,3-dihydroxy-6,7-dinitroquinoxaline (**129**), which was then methylated with methyl iodide (MeI) (**Scheme 51**).



Scheme 51

Nitration of 2,3-dihydroxyquinoxaline (**45**) occurred in good yield (79%) to give 2,3-dihydroxy-6,7-dinitroquinoxaline (**129**).[54] It has been postulated that this isomer is produced because the two aza groups in the heterocyclic ring are *meta* directing and hence positions 6- and 7- will be nitrated. Additionally, since structure **129** is likely to exist in equilibrium with the di-keto tautomer (**129a**) then the 6,7-disubstitution may be produced by the effect of the two keto groups in **129a** (**Scheme 52**).



129 129a

Scheme 52

IR spectral analysis of **129** confirms the presence of the di-keto form (**129a**) since there is an absorbance signal at 1719 cm^{-1} which corresponds to the stretching frequency of the ketone group. The IR spectrum has a substantial OH peak at 3151 cm^{-1} which is a characteristic broad signal. The ^{1}H NMR spectrum of **129** also provides evidence of the OH group in the form of a broad signal at δ 4.45 ppm which corresponds to the resonance of a hydroxy proton. Consequently, for consistency **129** is regarded as the 2,3-dihydroxy functionalised tautomer although it is recognised that the chemistry of this compound can be influenced as much by the presence of the two hydroxy-groups in **129** as it can by the the presence of the two keto-groups in **129a**.

The nitration of **45** was attempted with nitronium tetrafluoroborate ($NO_2^+BF_4^-$) in sulfolane but only a small amount of the mononitro- derivative could be obtained. Thus, it can be concluded that the 2,3-dihydroxy- compound is more susceptible to mixed acid nitration than the chloro-quinoxalines but is not easily nitrated by nitronium salts.

Methylation of 2,3-dihydroxy-6,7-dinitroquinoxaline (**129**) occurs smoothly in ~76% yield, producing 2,3-dimethoxy-6,7-dinitroquinoxaline (**128**). Sodium hydride (NaH) in THF is used to prepare the sodium alkoxide salt *in situ* and then methyl iodide is added to the reaction mixture to effect the methylation of the oxygen atoms. Amination of **128** was attempted with both methanolic ammonia

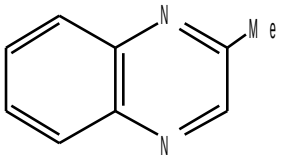
and acetonitrile/ammonia with stirring overnight at room temperature, but both systems were ineffective in aminating the substrate.

Figure 11 shows the proton NMR spectrum for 2,3-dimethoxy-6,7-dinitroquinoxaline (**128**). This ^{1}H NMR spectrum clearly shows the presence of the methyl protons at δ 3.44 ppm, which are shifted downfield due to the alkoxy oxygen atom. There is a singlet at δ 8.12 ppm which corresponds to the two aromatic protons, Ar-5H and Ar-8H. These signals both have resonances downfield compared to normal benzene protons due to the *ortho* effect of the nitro groups.

On-line searching failed to identify a CAS registry entry and therefore 2,3-dimethoxy-6,7-dinitroquinoxaline (**128**) may be regarded as a new compound. Autoclave amination of 2,3-dimethoxy-6,7-dinitroquinoxaline (**128**) was attempted only once to give unreacted starting material. It is believed that further investigation of this reaction could give access to the aminated derivative, 2,3-diamino-6,7-dinitroquinoxaline.

5.1.7 Other Quinoxaline Nitrations

In order to extend the fundamental nitration studies further, the nitrations of 2-methylquinoxaline (**130**) and quinoxaline 2-carboxylic acid (**131**) were attempted using both mixed acid systems as well as nitronium tetrafluoroborate in sulfolane. The nitration of 2-methylquinoxaline was in all cases a very vigorous reaction which resulted in the production of decomposition products. Whereas, the nitration of quinoxaline 2-carboxylic acid resulted in recovery of unreacted starting material in all cases.



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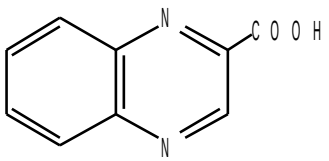

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5.1.8 Quinoxaline Nitrations Summary

A number of quinoxaline compounds, which included 2,3-dichloroquinoxaline (**111**), 2,3,6-trichloroquinoxaline (**119**), 2,3,6,7-tetrachloroquinoxaline (**122**), 2-hydroxyquinoxaline (**125**) and 2-methyl-3-hydroxyquinoxaline (**124**), were in general found to be very difficult to nitrate. However, by the use of nitronium tetrafluoroborate in an organic solvent (either nitromethane or sulfolane) the successful nitration of these quinoxalines was achieved. The nitration of 2,3-dihydroxyquinoxaline (**45**) was achieved easily by the use of mixed acid nitration whereas 2-methylquinoxaline (**130**) and quinoxaline 2-carboxylic acid (**131**) could not be nitrated. These nitration studies have helped survey a range of quinoxaline compounds for use as starting materials in the synthesis of high energy insensitive compounds.

5.1.9 *N*-Oxidation of a Number of Quinoxaline Compounds

It was decided to investigate the effect the presence of an *N*-oxide group has on the quinoxaline ring towards nitration. Therefore, the *N*-oxidation of a range of quinoxaline compounds was attempted. It was surmised that electron release by the *N*-oxide group into the heterocyclic ring would activate the system towards electrophilic attack and hence nitration.

N-Oxidation was attempted using 30% (w./v.) aqueous hydrogen peroxide solution in trifluoroacetic acid (TFA). The reacting species is thought to be trifluoroperacetic acid and thus the TFA behaves as both the solvent and precursor to the reactant.

All the reactions were carried out at an addition temperature of $0°C < T < 5°C$ and were then allowed to warm to room temperature. **Table 6** shows the results from the attempted *N*-oxidations of the range of quinoxaline substrates.

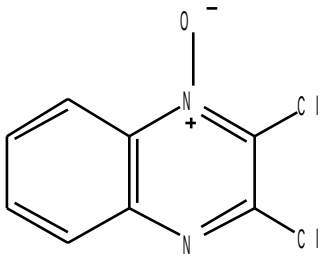
No.	Substrate	Result
1.	2-Methylquinoxaline (**130**)	Decomposition of starting material
2.	2-Methyl-3-hydroxyquinoxaline (**124**)	Decomposition of starting material

3.	2-Hydroxyquinoxaline (**125**)	No reaction after 3 days stirring
4.	2,3-Dihydroxyquinoxaline (**45**)	No reaction after 3 days stirring
5.	2,3-Dichloroquinoxaline (**111**)	Formation of mono-oxide species
6.	2,3,6-Trichloroquinoxaline (**119**)	Formation of mono-oxide species
7.	2,3,6,7-Tetrachloroquinoxaline (**122**)	No reaction after 3 days stirring

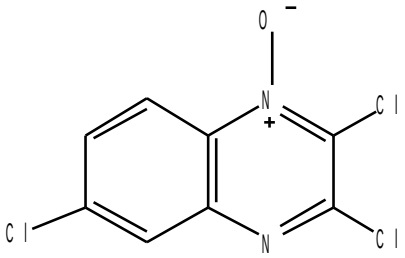
Table 6: Results from the Attempted *N*-oxidation of a Range of Quinoxaline Compounds

Reactions 1 and 2 both resulted in decomposition of the starting material since the reaction mixtures were converted into brown intractable gums which are characteristic of breakdown products. With both reactions 3 and 4 only unreacted starting material was recovered and therefore it may be concluded that the hydroxy functionalised quinoxalines are relatively unreactive to peracids. It could be postulated that the presence of a hydroxy group adjacent to an *N*-oxide group would have a destabilising effect and therefore *N*-oxidation does not proceed easily.

Both reactions 5 and 6 were successful with the mono-oxide species formed in good yield. On-line searching failed to identify a CAS registry entry and therefore 2,3,6-trichloroquinoxaline-1-oxide (**133**) may be regarded as a new compound. 2,3-Dichloroquinoxaline (**111**) has been oxidised previously to give the mono-*N*-oxide in 80% yield using Caro's acid (peroxysulfuric acid in c. H_2SO_4).[85]



132



133

Figures 12 and **13** show the mass spectra for 2,3-dichloroquinoxaline-1-oxide (**132**) and 2,3,6-trichloroquinoxaline-1-oxide (**133**) respectively. The mass spectrum for **132** (**Figure 12**) clearly has a peak at 214 m/z, which corresponds to the molecular ion of the mono-*N*-oxide derivative of 2,3-dichloroquinoxaline (**111**). This peak is part of the isotopic cluster associated with the mass spectra of chlorine containing compounds and hence it is part of a group of peaks at 214, 216 and 218 m/z (peak intensity ratio of 9 : 6 : 1). There is also a peak at 230 m/z, which is part of a cluster of peaks containing 230, 232 and 234 m/z (peak intensity ratio 9 : 6 : 1). This peak corresponds to the di-*N*-oxide derivative of 2,3-dichloroquinoxaline (**111**).

The mass spectrum of **133** (**Figure 13**) has a peak cluster at 248 m/z, which corresponds to the mono-*N*-oxide derivative of 2,3,6-trichloroquinoxaline (**119**). This cluster has an approximate peak intensity ratio of 27 : 27 : 9 : 1.

High resolution mass spectrometry (HRMS) was carried out on 2,3,6-trichloroquinoxaline-1-oxide (**133**). A good correlation between measured mass and actual mass of the molecular ion was found.

CHN Elemental analysis of 2,3-dichloroquinoxaline-1-oxide (**132**) revealed a reasonable correlation between calculated and experimental values. CHN Elemental analysis of 2,3,6-trichloroquinoxaline-1-oxide (**133**) showed a good match for N and H values but a poor match for the calculated and experimental C values. This is probably due to impurities since this sample could not be recrystallised due to its poor solubility in organic solvents.

5.1.10 Attempted Nitration of 2,3-Dichloroquinoxaline-1-oxide (132) and 2,3,6-Trichloroquinoxaline-1-oxide (133)

The nitrations of both 2,3-dichloroquinoxaline-1-oxide (**132**) and 2,3,6-trichloroquinoxaline-1-oxide (**133**) were attempted without success. **Table 7** shows the results from these attempted nitrations.

Substrate	Result from nitration	Result from nitration by

	by mixed acid system	$NO_2^+BF_4^-$/sulfolane
2,3-Dichloro-quinoxaline-1-oxide (**132**)	No reaction	Decomposition of starting material
2,3,6-Trichloro-quinoxaline-1-oxide (**133**)	No reaction	No reaction

Table 7: Results from the Attempted Nitration of 2,3-Dichloroquinoxaline-1-oxide (132) and 2,3,6-Trichloroquinoxaline-1-oxide (133)

It was initially thought that the *N*-oxidation of nitrogen heterocyclic compounds would activate them towards electrophilic attack. However, as can be seen from the above results no such activation was observed. In fact, no reaction was detected in the attempted mixed acid nitration of either substrate.

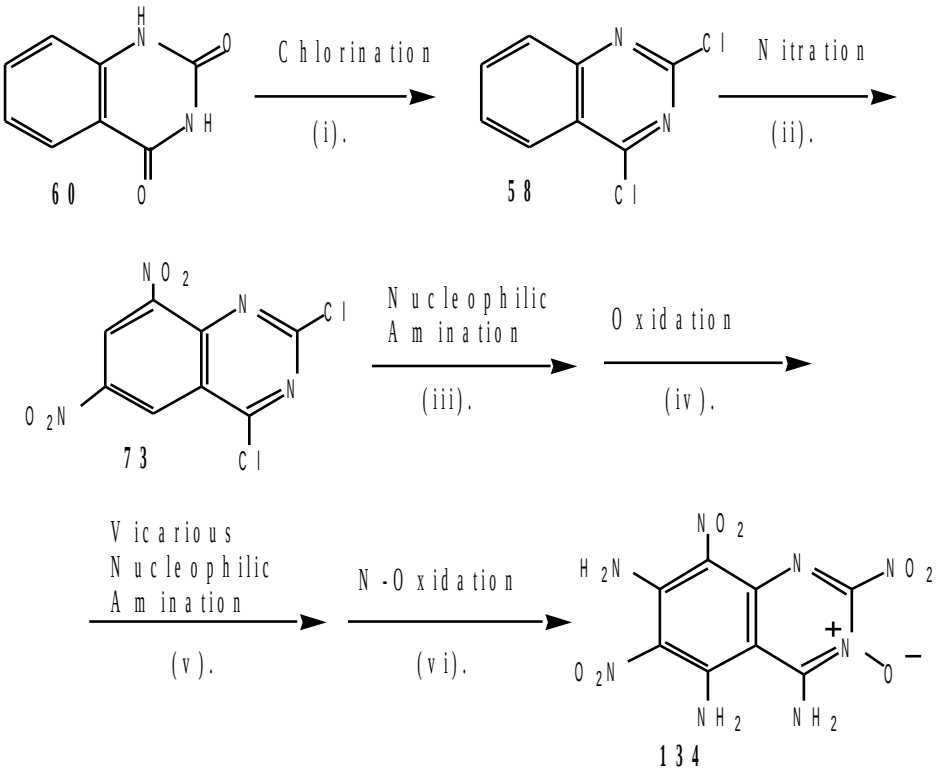
With the attempted nitration using nitronium tetrafluoroborate ($NO_2^+BF_4^-$) in sulfolane of 2,3,6-trichloroquinoxaline-1-oxide (**132**), again no reaction was observed but with 2,3-dichloroquinoxaline-1-oxide (**133**), decomposition of the starting material occurred. It can be concluded therefore that *N*-oxidation of chloroquinoxalines has little effect upon their subsequent nitration.

5.2 Quinazoline Reactions

5.2.1 General Strategy

Quinazoline syntheses within this project were initially based on a similar approach to that of quinoxalines (**Scheme 44**). It was decided that 2,4-dichloroquinazoline (**58**) was a suitable precursor to nitration studies.

In **Scheme 53** the starting material is benzoylene urea (**60**) which was easily converted in good yield into 2,4-dichloroquinazoline (**58**) with phosphorus oxychloride ($POCl_3$) in DMA (*N*,*N*-dimethylaniline). With this reaction, and in such aromatic chlorinations in general, it was found to be crucial that the $POCl_3$ is dried and distilled immediately prior to use.



Reagents: (i). $POCl_3$, DMA; (ii). HNO_3, H_2SO_4; (iii). NH_3, MeCN; (iv). DMD; (v). $[Me_3NNH_2]^+I^-$; (vi). H_2O_2, F_3CCO_2H.

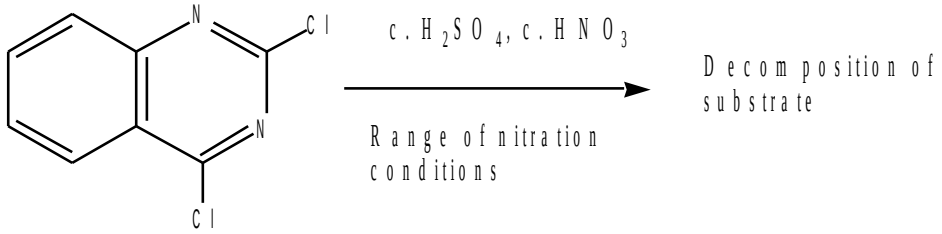
Scheme 53

Since the above scheme is analogous to that in the quinoxaline series it was expected that the reagents would act in a similar manner.

Target compound **134**, 2,6,8-trinitro-4,5,7-triaminoquinazoline-4-oxide, has the same empirical formula as the target quinoxaline compound: 2,6,8-trinitro-3,5,7-triaminoquinoxaline-4-oxide (**116**) which is $C_8H_6N_8O_7$. Therefore, using the Rothstein and Peterson equation[4] its detonation velocity (D) was calculated to be 7.84 mm.μs^{-1} (Factor F = 4.57). This means compound **134** has a predicted performance slightly less than that of TATB (1,3,5-triamino-2,4,6-trinitrobenzene, **8**) which can probably be related to the oxygen balance (OB) of this molecule (**134**).

5.2.2 Quinazoline Nitrations

Initially the nitration of 2,4-dichloroquinazoline (**58**) was attempted with forcing conditions such as excess quantities of mixed acids with heating (**Scheme 54**). Just as with the mixed acid nitration of 2,3-dichloroquinoxaline (**111**), mass spectral analysis of the product indicated that decomposition had taken place. A series of mixed acid nitrations under different conditions, ranging from nitric acid and sulfuric acid at r.t. to nitric acid and 30% oleum at 60°C for 18 h, were attempted but all gave a decomposition product, which melted at 256°C. Mass spectral analysis of the products confirmed that a decomposition product had been formed. Experimental conditions used were based on the standard nitration procedure described in Section 10.2.2.



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Scheme 54: Attempted Nitration of 2,4-Dichloroquinazoline (58)

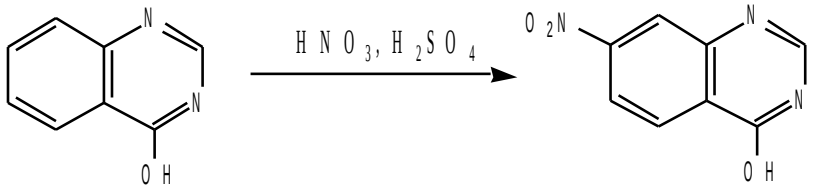
When nitration of 2,4-dichloroquinazoline (**58**) was finally attempted with stoichiometric amounts of mixed acid with the temperature of the reaction kept below 10°C during the addition of the substrate, the melting point of the product was 210-220°C. Both the ^{1}H NMR and MS analysis of the product indicated the presence of several breakdown products.

It was concluded that the nitration of 2,4-dichloroquinazoline (**58**) was a very difficult reaction and therefore experimental efforts were focused in alternative directions.

5.2.3 Nitration of 4-Hydroxyquinazoline (135)

It was decided to investigate the nitration of 4-hydroxyquinazoline (**135**) as a comparison to the nitration of 2,4-dichloroquinazoline (**58**). This was to assess the effect that changing the functional group on the quinazoline ring has on nitration.

The nitration of 4-hydroxyquinazoline (**135**) (**Scheme 55**) was attempted under a variety of conditions (**Table 8**).



135 **136**

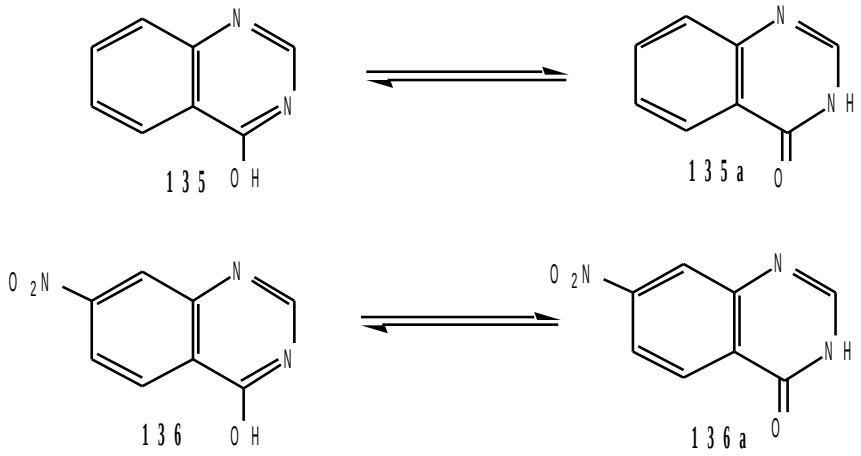
Scheme 55

Reagents	Conditions	Reaction Product
1.1 equiv. HNO_3, H_2SO_4	r.t., 2 h	**136**
2.0 equiv. HNO_3, H_2SO_4	r.t., 2 h	**136**
2.0 equiv. HNO_3, H_2SO_4	45°C, 3 h	**136**
N_2O_5, DCM	5 - 15°C, 4 h	Decomposition product

Table 8: Results from the Nitration of 4-Hydroxyquinazoline (135)

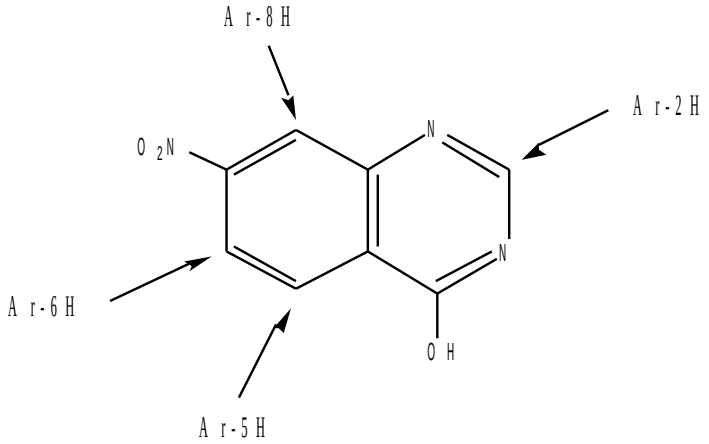
All mixed acid systems gave compound **136** in respectable yields (~70-75%). It is postulated that nitration takes place at the 7-position in **135** and therefore **136** is a tentative structure for the mono-nitro product. The purity of the compounds was measured by HPLC analysis. **Figure 14** shows a typical HPLC trace for a mixed acid nitration product. The chromatogram has a single peak at 130 seconds corresponding to a single column eluant and hence a single product. Such an HPLC trace can be easily used to show the purity of a sample and hence help identify the number of reaction products.

It is recognised that compounds **135** (4-hydroxyquinazoline) and **136** (4-hydroxy-7-nitroquinazoline) can exist as tautomeric keto structures; compounds **135a** and **136a** respectively (**Scheme 56**). In fact, analysis of the IR spectrum of **136** shows the presence of a signal at 1672 cm^{-1} which is at the characteristic stretching frequency for absorbance of the C=O bond. In this IR spectrum there is also a broad signal at 3748 cm^{-1} which can be attributed to the hydroxy group (O-H bond).



Scheme 56

Figure 15 shows the proton NMR spectrum for 4-hydroxy-7-nitroquinazoline (**136**), clarifying the purity of the compound. **Table 9** shows a summary of ^{1}H NMR spectroscopy shift values for **136**.



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Proton	δ (ppm)	Peak	Coupling constant (s), *J*
Ar-2H	8.32	s	N.A.
Ar-5H	7.63	d	$J_{5,6}$ = 9.0 Hz
Ar-6H	8.52	d-d	$J_{6,8}$ = 2.7 Hz, $J_{5,6}$ = 9.0 Hz
Ar-8H	8.76	d	$J_{6,8}$ = 2.7 Hz

Table 9: Summary of ^{1}H NMR Spectroscopy Shift Values for 4-Hydroxy-7-nitroquinazoline (136)

The proton in position 2 (Ar-2H) on the heterocyclic ring of 4-hydroxy-7-nitroquinazoline (**136**) has a resonance which is shifted downfield to δ 8.32 ppm, since the carbon it is attached to is flanked by two nitrogen heteroatoms. The peak for this proton is a singlet since it is not near any other protons. Ar-5H has a resonance at δ 7.63 ppm which is a doublet with a coupling constant ($J_{5,6}$) of 9.0 Hz. This coupling constant can be attributed to *ortho* coupling with Ar-6H. Both Ar-6H and Ar-8H have resonances which are shifted downfield since these protons are attached to carbons which are *ortho* to a C-NO_2 group. Ar-6H has a peak at δ 8.52 ppm which is a doublet of doublets. This is because of coupling with both Ar-5H ($J_{5,6}$ = 9.0 Hz, *ortho* coupling) and Ar-8H ($J_{6,8}$ = 2.7 Hz, *meta* coupling). Ar-8H has a peak at δ 8.76 ppm which is doublet. This doublet arises due to meta coupling with Ar-6H ($J_{6,8}$ = 2.7 Hz).

CHN Elemental analysis was carried out on 4-hydroxy-7-nitroquinazoline (**136**) and a good correlation between calculated and experimental values was obtained.

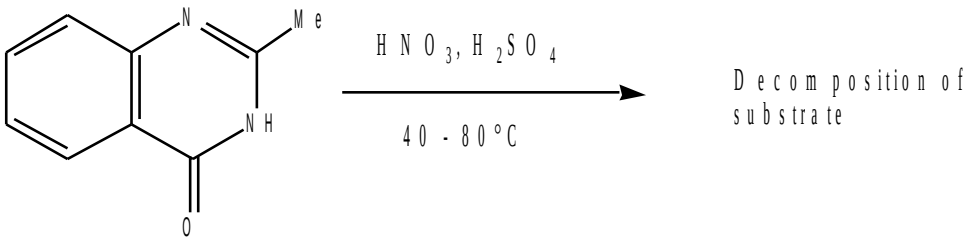
The nitration of 4-hydroxyquinazoline (**135**) was also attempted using nitronium tetrafluoroborate ($NO_2^+BF_4^-$) in sulfolane. The mono-nitro product, 4-hydroxy-7-nitroquinazoline (**136**), was again produced but in a slightly lower yield of 60%.

The nitration of 4-hydroxyquinazoline (**135**) was achieved relatively easily whereas the nitration of 2,4-dichloroquinazoline (**58**) could not be achieved.

Therefore, in this case it was concluded that as expected hydroxyquinazolines are more susceptible to nitration than chloroquinazolines. 2,4-Dichloroquinazoline was found to decompose under highly reactive nitration conditions whereas 4-hydroxyquinazoline was stable to mixed acid systems and could be nitrated.

5.2.4 Nitration of 2-Methyl-4(3*H*)-quinazolinone (137)

A further quinazoline nitration was investigated so that a greater insight could be gained into the nitration of this class of benzodiazines. The nitration of 2-methyl-4(3*H*)-quinazolinone (**137**) was attempted under a range of mixed acid nitration conditions (**Scheme 57**). In each case, upon addition of the mixed acid reaction medium to crushed ice in the work-up phase of the reaction no precipitate developed. Furthermore, washing the aqueous layer with ethyl acetate did not yield any material in the organic extract. This confirms that decomposition of the starting material had occurred. It is expected that 2-methyl-4(3*H*)-quinazolinone (**137**) will exist in equilibrium with the tautomeric 2-methyl-4-hydroxyquinazoline structure.



137

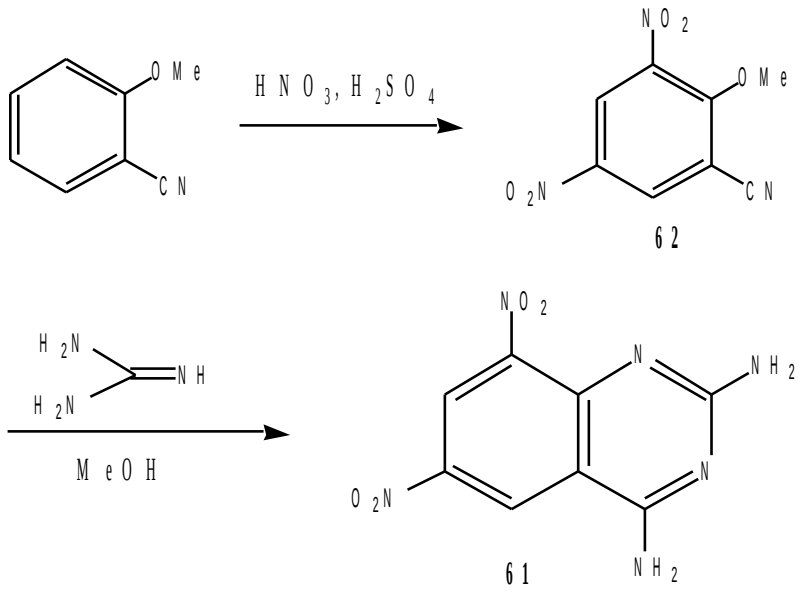
Scheme 57: Attempted Nitration of 2-Methyl-4(3*H*)-quinazolinone

The nitration of quinazoline compounds was not studied further since it was concluded that these substrates are very difficult to nitrate and as such alternative routes to energetic quinazoline compounds were required.

5.2.5 Preparation of 2,4-Diaminoquinazoline Derivatives

Since quinazoline nitrations proved to be difficult, as was the case with the isomeric quinoxaline series, an alternative approach was pursued. This approach was based on the cyclisation of an aromatic nitro compound into a quinazoline ring system. Crucially, such an approach did not require the nitration of the benzenoid ring within the quinazoline structure but relied on the nitro- groups to be already present when the heterocyclic ring was formed.

The preparation of 2,4-diaminoquinazoline was attempted from 2-methoxybenzonitrile with guanidine acting as the cyclisation agent; no reaction was observed. The original patent[67] for this procedure claims that this cyclisation reaction only works with 2-methoxybenzonitrile compounds functionalized in the 3- and 5- positions with electronegative groups such as nitro-, cyano- or sulfonyl-groups. Therefore, 2-methoxy-3,5-dinitrobenzonitrile (**62**) was prepared in quantitative yield via the mixed acid nitration of 2-methoxybenzonitrile (**Scheme 58**).



Scheme 58

The subsequent cyclisation was effected with guanidine to yield 2,4-diamino-6,8-dinitroquinazoline (**61**) in ~85% yield (**Scheme 58**). The proton NMR spectrum (**Figure 16**) of the product has two doublets at δ 8.52 ppm and 8.95 ppm both

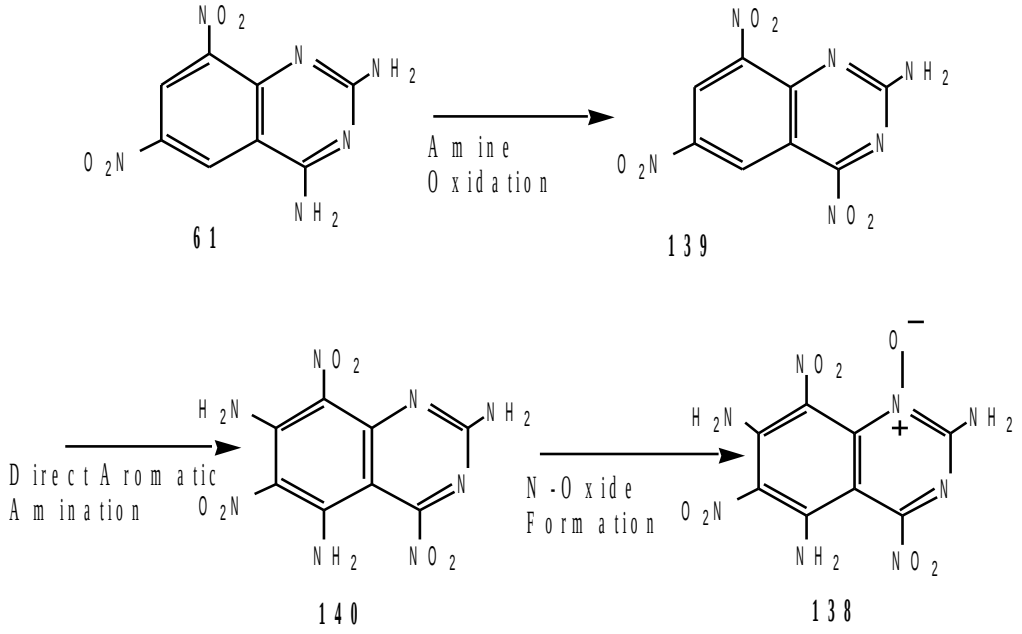
having coupling constants of 2.60 Hz which is indicative of *meta* coupling and hence *meta* nitro substitution on the quinazoline ring. HPLC analysis of the product (**Figure 17**) shows a single peak at 150 seconds (the solvent front is at 90-100 s.) showing the product to be pure. The preparation of the compound was confirmed by mass spectral analysis which shows the molecular ion peak at 250 m/z.

CHN Elemental analysis of 2,4-diamino-6,8-dinitroquinazoline (**61**) was carried out. There was found to be a poor match between calculated and experimental values. This is probably because the reaction product was not recrystallised due to its very poor solubility in most organic solvents.

5.2.6 Strategy for Functionalisation of 2,4-Diamino-6,8-dinitroquinazoline (61)

It was thought that 2,4-diamino-6,8-dinitroquinazoline (**61**) would act as an ideal synthetic platform for subsequent functionalisation to a range of high energy insensitive energetic materials. Consequently, various reactions of 2,4-diamino-6,8-dinitroquinazoline were investigated.

Initially, compound **138** was the target molecule and it was hoped that this species could be prepared by the use of the strategy shown in **Scheme 59**. Oxidation of one of the amino groups, preferably the 4-amino substituent, on compound **55** would yield **139**. Then direct aromatic amination of **139** would give **140** and finally oxidation of one of the heteroatoms on the quinazoline ring, preferably the 1-aza group, may give rise to **138**.



Scheme 59

The formation of the 1-oxide (**138**) in the final reaction was envisaged since it may be stabilised by intramolecular hydrogen bonding effects. This structure is a tentative target molecule and it is recognised that there may also be a degree of *N*-oxidation at the N3 atom. Since compound **61** is very insoluble it was expected that the preparation and purification steps in the synthesis of compounds **139**, **140** and **138** would be particularly challenging.

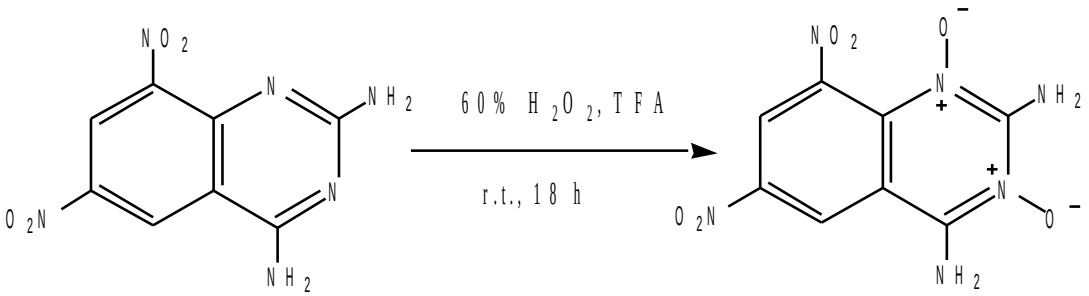
A number of functionalisations of 2,4-diamino-6,8-dinitroquinazoline (**61**) were attempted with varying degrees of success

5.2.7 *N*-Oxidation of 2,4-Diamino-6,8-dinitroquinazoline (61)

It was thought that *N*-oxidation of 2,4-diamino-6,8-dinitroquinazoline (**61**) would serve as a useful functionalisation to investigate and furthermore such a reaction has not been reported previously. Also, oxidation of **61** should improve the

oxygen balance of the molecule as well as provide valuable information on the ease of which highly functionalised quinazolines can be oxidised.

The *N*-oxidation of 2,4-diamino-6,8-dinitroquinazoline (**61**) was attempted a number of times using aqueous hydrogen peroxide solution and trifluoroacetic acid (TFA). Initially, a 30% aqueous solution of H_2O_2 was used. However, no reaction was detected. Conversely, when a 60% aqueous solution of H_2O_2 was used the di-*N*-oxide derivative (**141**) was prepared in approximately 35% yield (**Scheme 60**). On-line searching failed to identify a CAS registry entry and therefore 2,4-diamino-6,8-dinitroquinazoline-1,3-dioxide (**141**) can be regarded as a new compound.



61 **141**

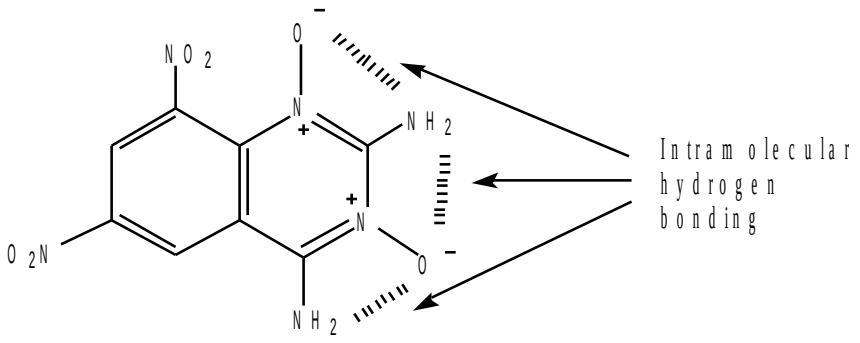
Scheme 60

The presence of 2,4-diamino-6,8-dinitroquinazoline-1,3-dioxide (**141**) was confirmed by mass spectral analysis which gave a $(M - 1)^+$ peak at 281 m/z (**Figure 18**). This structure may correspond to the loss of hydrogen from the molecular ion (M^+) and was detected by MS as the first component of the sample. There are a number of smaller peaks with higher m/z values which may correspond to unwanted products.

The second component of the sample had a mass spectrum identical to that of the starting material, 2,4-diamino-6,8-dinitroquinazoline (**61**), which had peaks at 220, 250 and 267 m/z corresponding to [M^+ - 30 (NO)], M^+ and [M^+ + 17 (NH_3)]

molecular ions respectively. This second component of the sample could either be due to unreacted starting material or to a structure resulting from the removal of the two oxide groups from the molecular ion of **141**.

It is postulated that the *N*-oxide groups could be stabilised via intramolecular bonding with the flanking amino groups (see below).



141

Comparison of the IR spectrum for the starting material and that of the di-*N*-oxide reaction product shows a splitting of the broad amino signals (**Figure 19**) which could be a consequence of the previously described hydrogen bonding. The IR spectrum of 2,4-diamino-6,8-dinitroquinazoline-1,3-dioxide (**141**) has a number of significant peaks which are summarised in **Table 10**.

No.	υ_{max} (cm^{-1})	Bond Stretching
1	1208	N-O (m)
2	1348	NO_2 symm. (m)
3	1533	NO_2 asymm. (m)
4	3308 - 3350	NH_2 (bs)
5	3409 - 3456	NH_2 (bs)

Table 10: Summary of the Most Significant Peaks from the IR Spectrum of 2,4-Diamino-6,8-dinitroquinazoline-1,3-dioxide (141)

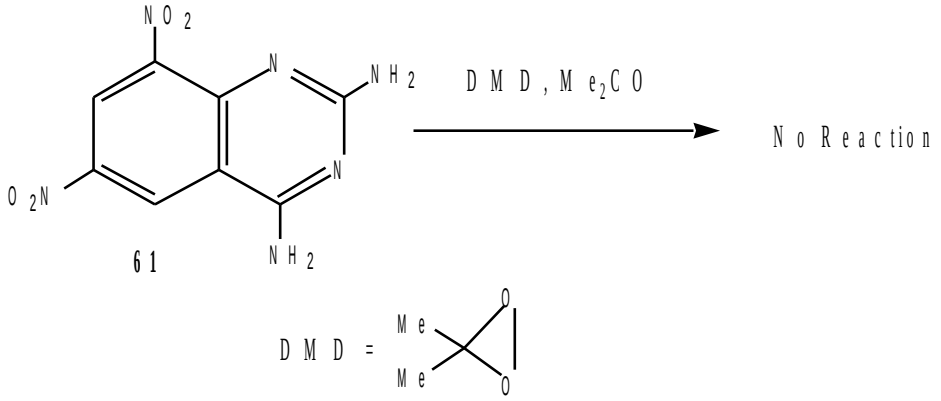
In the IR spectrum of 2,4-diamino-6,8-dinitroquinazoline-1,3-dioxide (**141**) the peaks for the N-O bond stretching (1208 cm^{-1}) as well as the symmetrical and asymmetrical NO_2 stretching frequencies (1348 and 1533 cm^{-1} respectively) are all of medium intensity. The amino (NH_2) bond stretching has two broad peaks in the 3300 - 3500 cm^{-1} range.

The *N*-oxidation of 2,4-diamino-6,8-dinitroquinazoline (**61**) was only achieved when a strong oxidising agent was used (60% aq. H_2O_2 soln., TFA) and only in the modest yield of 35%. Therefore, it can be concluded that the *N*-oxidation of highly functionalised quinazoline compounds is difficult to achieve in high yield and as such highly reactive reagents are required.

5.2.8 Attempted Amine Oxidation of 2,4-Diamino-6,8-dinitroquinazoline (61)

Oxidation of the amino groups in 2,4-diamino-6,8-dinitroquinazoline (**61**) should significantly improve the oxygen balance (OB) of this molecule as well as provide a useful insight into the application of oxidation reactions to this type of heterocyclic compounds.

The oxidation of the amine groups of 2,4-diamino-6,8-dinitroquinazoline (**61**) was attempted using dimethyldioxirane (DMD) which has been shown to convert amino groups into nitro groups.[39,40] **Scheme 61** shows the proposed reaction but despite repeating the reaction a number of times with varying experimental conditions only starting material could be recovered.

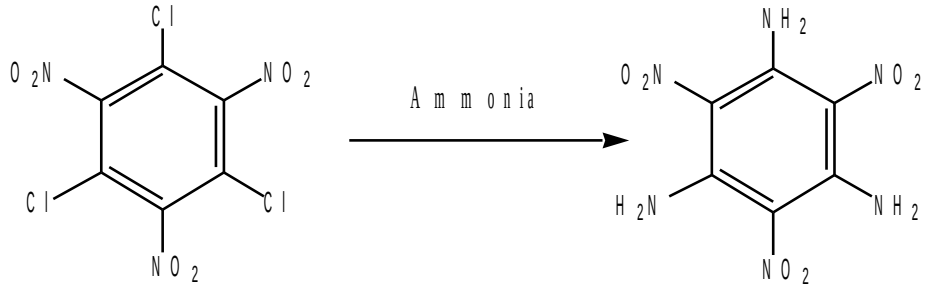


Scheme 61

The oxidation of the amino groups in compound **61** was not achieved, which was further evidence of the difficulty in functionalising this compound.

5.2.9 Amination of 2,4-Diamino-6,8-dinitroquinazoline (61)

In the preparation of energetic materials, amination is often a key reaction, for example, in the preparation of 1,3,5-triamino-2,4,6-trinitrobenzene (TATB) (**8**) from 1,3,5-trichloro-2,4,6-trinitrobenzene (**Scheme 62**).



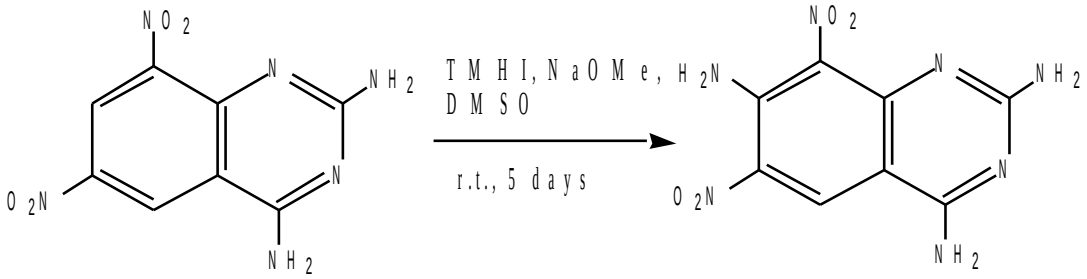
8

Scheme 62

Consequently, it was decided to investigate the amination of 2,4-diamino-6,8-dinitroquinazoline (**61**). The amination of **61** was attempted a number of times. Initially, hydroxylamine was used both as the free base (NH_2OH) and as the

hydrochloride salt ($NH_2OH.HCl$). In both cases, however, only starting material could be recovered.

An alternative reagent was therefore employed which operated by a vicarious nucleophilic substitution (VNS) pathway; 1,1,1-trimethylhydrazinium iodide (TMHI) $[Me_3NNH_2]^+I^-$.[34] At first when the TMHI was used no amination was observed, However, when a large excess of the reagents was used, a mono-aminated product, 2,4,7-triamino-6,8-dinitroquinazoline (**142**), was obtained in approximately 24% yield (**Scheme 63**). On-line searching failed to identify a CAS registry entry and therefore 2,4,7-triamino-6,8-dinitroquinazoline (**142**) may be regarded as a new compound.

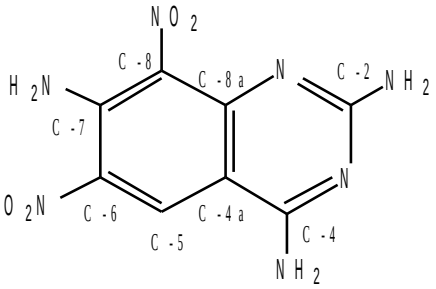


61 **142**

Scheme 63

Figures 20 and **21** show the ^1H and ^{13}C NMR spectra respectively for 2,4,7-diamino-6,8-dinitroquinazoline (**142**). The proton NMR spectrum for **142** has a single peak at δ 9.22 ppm which is due to the resonance of the Ar-5H proton.

The carbon-13 NMR spectroscopy shift values are shown in **Table 11** (see below). The carbon-13 NMR spectrum has an additional peak at δ 130.47 which may be due to an impurity. Therefore, the following assignments are tentative.



142

Carbon	C-2	C-4	C-5	C-6	C-7	C-8	C-8a	C-4a
δ (ppm)	161.70	155.07	131.73	144.10	150.65	148.62	153.13	129.50

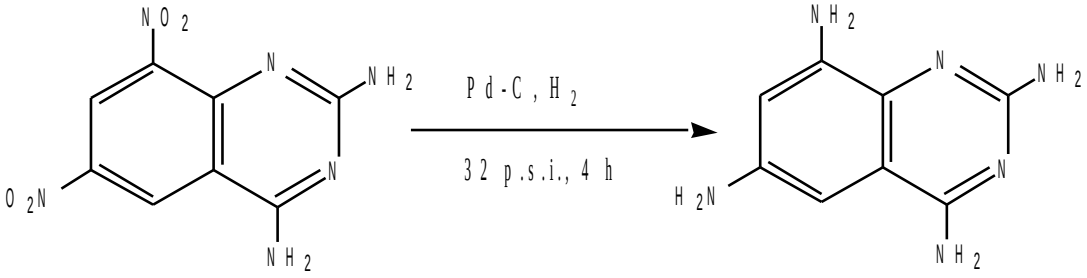
Table 11: ^{13}C NMR Spectroscopy Shift Values for 2,4,7-Triamino-6,8-dinitroquinazoline (142)

The resonances for carbons 2, 4 and 8a are all shifted significantly downfield due to being adjacent to nitrogen heteroatoms. The resonances for carbons 6 and 8 are shifted downfield due to being *ipso* to a nitro group, whereas the resonance for carbon 7 is shifted downfield because it is *ipso* to an amino group. Further analysis of quinazoline carbon-13 NMR spectral assignments is presented in Section 6.3: Quinazoline ^{13}C NMR Spectroscopy Shift Values.

High resolution mass spectrometry (HRMS) was carried out on 2,4,7-triamino-6,8-dinitroquinazoline (**142**). A good correlation between measured mass and actual mass of the molecular ion was found.

5.2.10 Hydrogenation of 2,4-Diamino-6,8-dinitroquinazoline (61)

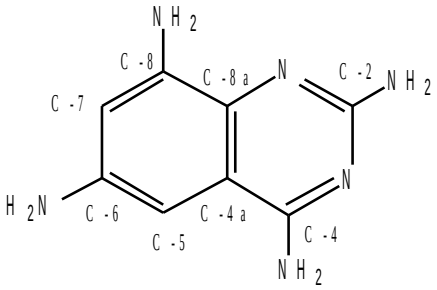
In order to extend the investigation into the functionalisation of 2,4-diamino-6,8-dinitroquinazoline (**61**) it was decided to include its hydrogenation in this study. The hydrogenation of **61** was carried out using a shaker-type hydrogenator. The reaction produced 2,4,6,8-tetra-aminoquinazoline (**143**) in good yield (approximately 80%) (**Scheme 64**).



61 **143**

Scheme 64

Figures 22 and **23** show the mass spectrum and ^{13}C NMR spectrum respectively for 2,4,6,8-tetra-aminoquinazoline (**143**). The mass spectrum for **143** has a very strong peak at 190 m/z which corresponds to the molecular ion (M^+). The carbon-13 NMR spectroscopy shift values are shown in **Table 12** (see below). The carbon-13 NMR spectrum has a number of additional peaks which may be due to the presence of an impurity. Therefore, the following assignments are tentative.



143

Carbon	C-2	C-4	C-5	C-6	C-7	C-8	C-8a	C-4a
δ (ppm)	163.46	163.27	103.71	142.53	102.31	144.52	148.84	121.00

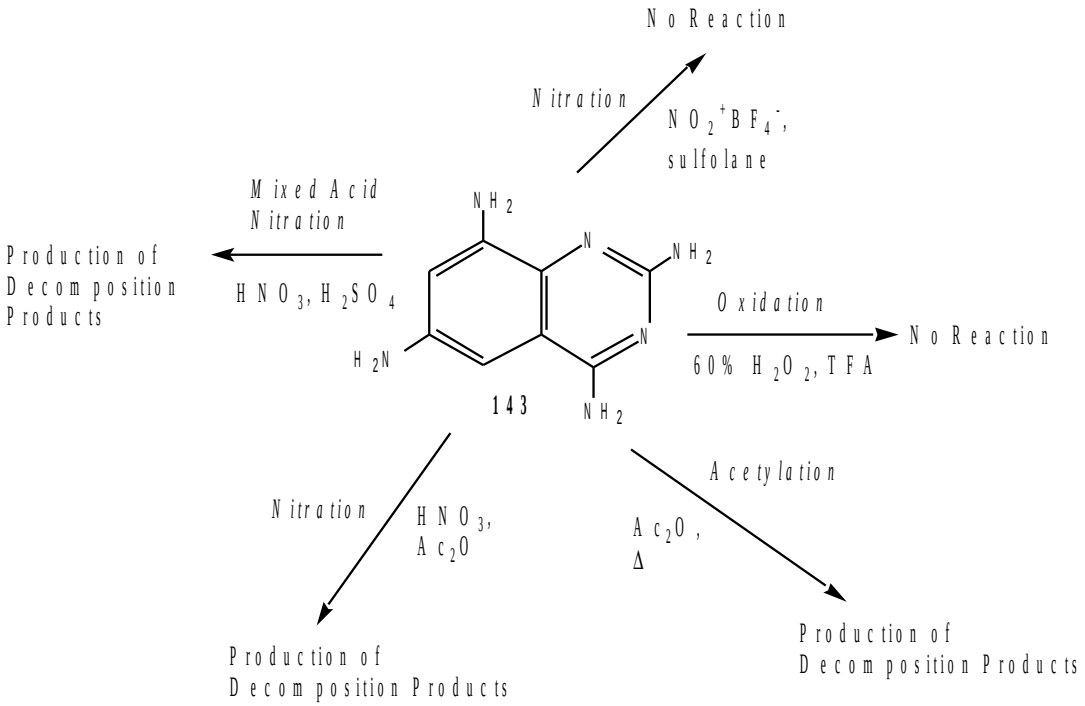
Table 12: ^{13}C NMR Spectroscopy Shift Values for 2,4,6,8-Tetra-aminoquinazoline (143)

The resonances for carbons 2 and 4 are predictably shifted significantly downfield due to being α to nitrogen heteroatoms. The carbon at position 8a is shifted downfield due to being next to the heterocyclic 1-aza group as well as being shifted upfield by being *ortho* to a C-NH_2 group. Further analysis of quinazoline carbon-13 NMR spectral assignments is presented in Section 6.3: Quinazoline ^{13}C NMR Spectroscopy Shift Values.

High resolution mass spectrometry (HRMS) was carried out on 2,4,6,8-tetra-aminoquinazoline (**143**). A good correlation between measured mass and actual mass of the molecular ion was found.

5.2.11 Attempted Functionalisations of 2,4,6,8-Tetra-aminoquinazoline (143)

A number of functionalisations were attempted on 2,4,6,8-tetra-aminoquinazoline (**143**) including nitration, acetylation and oxidation (**Scheme 65**).



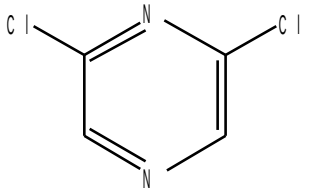
Scheme 65

A number of different functionalisation reactions were attempted on 2,4,6,8-tetra-aminoquinazoline (**143**) without success. Mixed acid nitration, nitration using acetyl nitrate and acetylation all resulted in the production of decomposition products. Conversely, *N*-oxidation and nitration (using $NO_2^+BF_4^-$ in sulfolane) both resulted in the recovery of unreacted starting material.

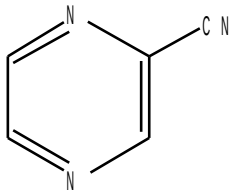
5.3 Pyrazine Reactions

5.3.1 Nitration of 2,6-Dichloropyrazine (100), 2-Pyrazinecarbonitrile (144), 2,3-Pyrazinedicarbonitrile (145) and 2-Pyrazinecarboxylic acid (146)

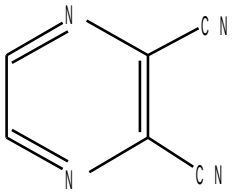
In order to gain information on the fundamental behaviour of pyrazine compounds towards nitration it was decided to carry out a number of nitrations on a range of pyrazine substrates. Consequently, the nitrations of 2,6-dichloropyrazine (**100**), 2-pyrazinecarbonitrile (**144**), 2,3-pyrazine-dicarbonitrile (**145**) and 2-pyrazinecarboxylic acid (**146**) were all attempted using mixed acid systems.



100



144



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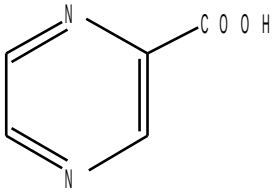


146

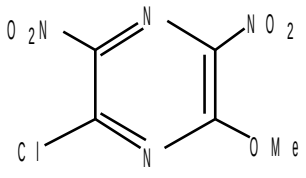
The nitration of 2,6-dichloropyrazine (**100**) was carried out at a number of different temperatures: 10°C, 20°C and 40°C, all of which yielded a decomposition product. The nitration of **100** was also attempted using the $NO_2^+BF_4^-$/sulfolane system, but only decomposition products could be isolated. Conversely, the nitration of **144**, **145** and **146** resulted in recovery of starting material in each case [mixed acid (H_2SO_4 and HNO_3) nitrations were carried out at 40°C and 80°C]. It is thought that this is due to the -CN and -COOH groups deactivating the pyrazine ring towards electrophilic attack.

These limited nitration studies have highlighted the difficulty in nitrating simple pyrazine compounds. Pyrazine itself is very difficult to nitrate, which is largely a consequence of the deactivating effect of the two nitrogen atoms. The nitrogen heteroatoms pull electrons from the ring thus rendering the pyrazine carbon atoms less susceptible to electrophilic attack.

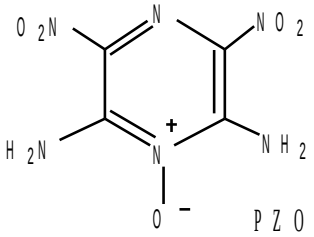
Since nitrating pyrazine compounds can be difficult and can often require very forceful conditions, such as the use of boiling mixtures of concentrated nitric acid and oleum [30% sulfur trioxide (SO_3) dissolved in concentrated sulfuric acid (H_2SO_4)], it is logical to adopt an alternative approach. One such approach is to functionalise the pyrazine substrate with activating groups, such as alkoxy groups, which have the effect of countering the deactivating effect of the two nitrogen heteroatoms.

5.3.2 Preparation of 2,6-Diamino-3,5-Dinitropyrazine-1-oxide (PZO) (9)

Early studies within this project were directed towards repeating the literature synthesis of 2,6-diamino-3,5-dinitropyrazine-1-oxide (PZO) (**9**) (See Section 4.3, **Scheme 40**).[80,81] **Figures 24** and **25** show the IR spectra of 2-methoxy-6-chloro-3,5-dinitropyrazine (**102**) and 2,6-diamino-3,5-dinitropyrazine-1-oxide (PZO) (**9**) respectively. **Tables 13** and **14** show a summary of some of the significant peaks from the IR spectra of (**102**) and (PZO) (**9**).



102



9

2-Methoxy-6-chloro-3,5-dinitropyrazine (**102**)

No.	υ (cm^{-1})	Bond Stretching
1	831	C-Cl, w
2	1282	NO_2 symm., s
3	1345	O-Me, s
4	1593	NO_2 asymm., s

2,6-Diamino-3,5-dinitropyrazine-1-oxide (**9**)

No.	υ (cm^{-1})	Bond Stretching
1	1235	NO_2 symm., s
2	1334	N-O, s
3	1560	NO_2 asymm, s
4	1646	N-H, s
5	3250	NH_2, bs
6	3420	NH_2, bs

Tables 13 and 14: Summary of Significant Peaks from the IR Spectra of 2-Methoxy-6-chloro-3,5-dinitropyrazine (102) and 2,6-Diamino-3,5-dinitropyrazine-1-oxide (PZO) (9)

Both the IR spectra of **102** and **9** have strong peaks associated with the symmetrical and asymmetrical stretching of the nitro group, which for aromatic compounds usually appear in the following ranges respectively: 1230 - 1350 cm^{-1} and 1550 - 1630 cm^{-1}. Compound **102** is also characterised by the presence of the stretching frequencies associated with the C-Cl and O-Me groups. Whilst compound **9** can be characterised by the presence of stretching frequencies associated with the N-O and NH_2 groups.

All the reactions towards the preparation of PZO (**9**) were high yielding and the synthesis has been scaled up to provide 20 - 25 g batches of PZO. In order to produce approximately 20 - 25 g of PZO it was found that approximately 40 g of the starting material, 2,6-dichloropyrazine (**100**), was required per batch.

CHN Elemental analysis was carried out on 2,6-diamino-3,5-dinitropyrazine-1-oxide (PZO) (**9**). There was an approximate correlation for C and H values. However, the calculated and experimental values for N did not match well. This is probably because the reaction product was not recrystallised due to its poor solubility in most organic solvents.

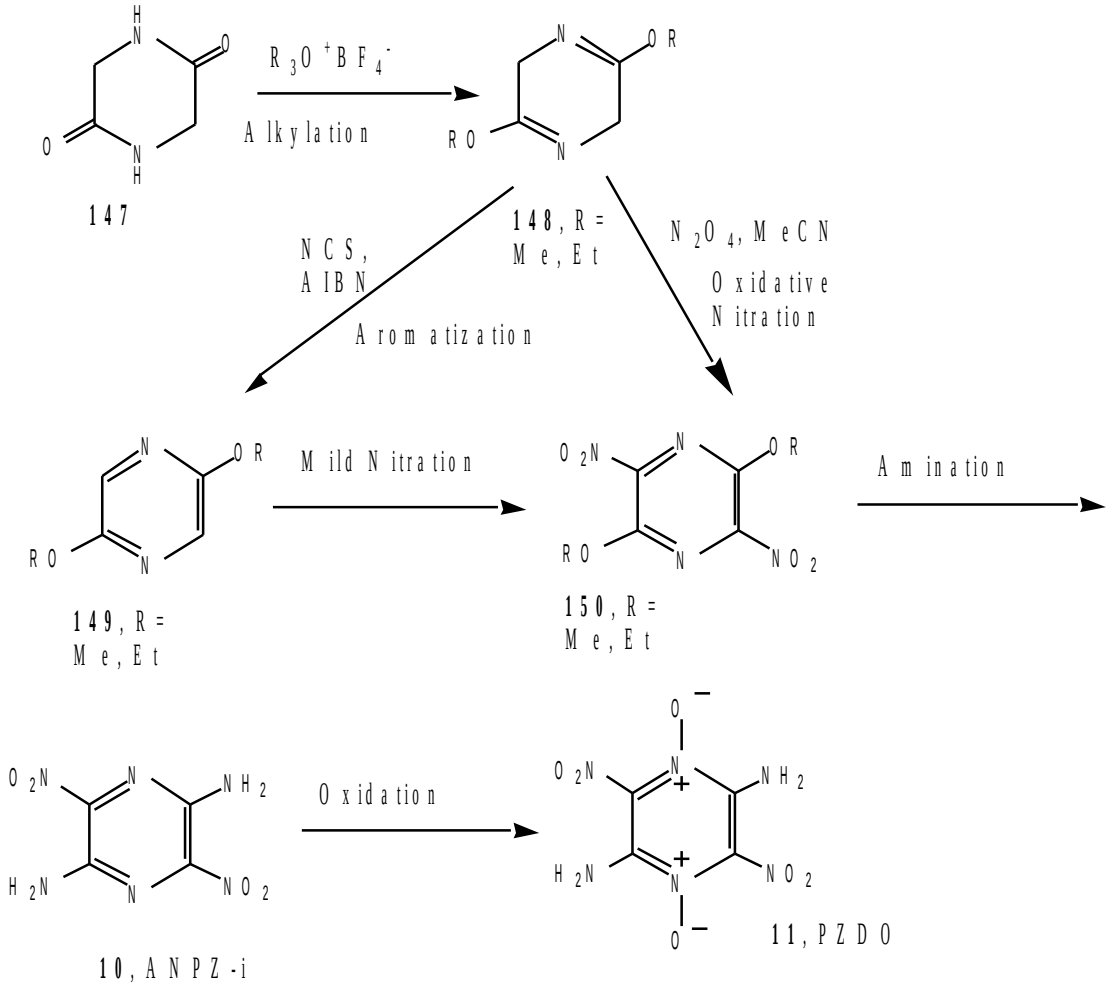
Despite the presence of two deactivating aza groups in the pyrazine ring of 2-methoxy-6-chloropyrazine (**101**), this substrate is very reactive towards electrophilic reagents. This is because of the strongly activating effect of the methoxy group. As part of the scale-up of the synthesis of PZO, a key intermediate reaction was the dinitration of 2-methoxy-6-chloropyrazine (**101**) which was scaled up to *ca.* 20-30 g scale. When carrying out this reaction on larger quantities of substrate it was found to be very important to have stringent temperature control of the reaction mixture during addition of the substrate, otherwise the exothermicity of the reaction causes the temperature to rise very quickly and can lead to the reaction going out of control.

Both ANPZ (**95**) and PZO (**9**) are expected to have very attractive energetic material properties such as a high detonation velocity as well as insensitivity towards external stimuli such as heat, mechanical shock and friction. These expected properties can be attributed to their molecular structures, since both compounds contain high levels of oxygen and nitrogen which can be expected to contribute to the expected good detonation properties of these compounds. The presence of amino groups adjacent to nitro groups in both molecules is likely to contribute to a good level of insensitivity in both systems.

5.3.3 Preparation of 2,5-Diamino-3,6-dinitropyrazine-1,4-dioxide (PZDO) (11)

It was decided that the dioxide derivative of the alternative isomer to PZO would be an attractive target molecule; 2,5-diamino-3,6-dinitropyrazine-1,4-dioxide (PZDO) (**11**). Such a compound should have very desirable properties for insensitive, high energy material applications. This is because of the two *N*-oxide groups on the compound which should facilitate very strong hydrogen bonding thereby imparting insensitivity (both thermal and impact) to the compound. Also, the symmetrical nature (giving rise to dense packing) of the compound and its favourable oxygen balance should render the compound highly energetic, see Section 2.2.4: Detonics Calculations.

The proposed preparation of 2,5-diamino-3,6-dinitropyrazine-1,4-dioxide (PZDO) (**11**) starts from piperazine-2,5-dione (**147**) which can be alkylated to compound **148** (**Scheme 66**). Piperazine-2,5-dione (**147**) is a cheap and readily available starting material and is therefore an ideal precursor compound for this synthesis.



Scheme 66

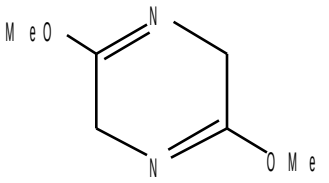
Alkylations of piperazine-2,5-dione (**147**)[76,94,95] were attempted with triethyloxonium tetrafluoroborate, triethyloxonium hexafluorophosphate, trimethyloxonium tetrafluoroborate and methyl trifluoromesylate (various reaction times and temperatures). Most were ineffective in producing sufficient quantities of the desired 2,5-dihydro-3,6-dialkoxypyrazine. Fresh solutions of

triethyloxonium tetrafluoroborate ($Et_3O^+BF_4^-$) and trimethyloxonium tetrafluoroborate ($Me_3O^+BF_4^-$) were, however, effective.

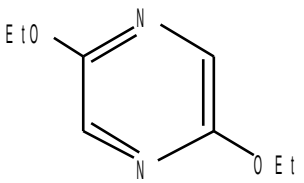
It is thought that the commercially available triethyloxonium tetrafluoroborate or Meerwein's salt is contaminated with fluoroboric acid.[96] The fluoroboric acid protonates piperazine-2,5-dione (**147**) forming an unreactive salt. Consequently, triethyloxonium tetrafluoroborate was generated *in situ*, by the reaction between epichlorohydrin and boron trifluoride diethyl etherate, and then used in the alkylation of piperazine-2,5-dione. In this reaction it is essential that the Meerwein's salt is prepared in dry conditions and therefore all the reagents were freshly distilled and the reaction was kept under nitrogen at all times. The Meerwein's salt was formed in quantitative yield and was kept in the reaction vessel where it was used to alkylate **147** in dichloromethane solvent again in very high yield.

Aromatization of both the dialkyl species[76,94] (**148**) was achieved with NCS (*N*-chlorosuccinimide) and AIBN [α,α'-azobis(isobutyronitrile)] in carbon tetrachloride in almost quantitative yield to give the 3,6-dialkoxypyrazine (**149**).

Figures 26 and **27** show the proton NMR spectra for 2,5-dimethoxy-3,6-dihydropyrazine (**148**, R=Me) and 2,5-diethoxypyrazine (**149**, R=Et) respectively.



148, R=Me



149, R=Et

The ^{1}H NMR spectrum of 2,5-dimethoxy-3,6-dihydropyrazine (**148**, R=Me) has a singlet at δ 3.80 ppm, which is a resonance of the six methoxy protons (2 x OMe). These protons are shifted downfield since they are attached to an alkoxy carbon atom. The other protons, which have a resonance of δ 4.15 ppm are also shifted downfield since these protons are adjacent to both a nitrogen heteroatom and a C=N double bond.

The ^{1}H NMR spectrum of 2,5-diethoxypyrazine (**149**, R=Et) has a triplet at δ 1.35 ppm which is a resonance of the six methyl protons. These methyl protons are split by the adjacent methylene protons. The peak at δ 4.30 ppm is due to the resonance of the methylene protons. This peak is shifted downfield since the methylene group is attached to an alkoxy oxygen atom. The final peak at δ 7.75 ppm is caused by the resonance of the two aromatic protons and is a singlet since there are no adjacent protons.

5.3.4 Nitration of 2,5-Diethoxypyrazine (149, R=Et)

The electrophilic nitration of 2,5-diethoxypyrazine (**149**, R=Et) was attempted under a wide range of conditions (**Table 15**). Mixed acid nitration of **149**, R=Et resulted in an extremely violent reaction where decomposition of the starting material was very fast above a certain temperature (*ca.* -10°C). Therefore, it was thought that a milder nitrating agent would be more effective for the nitration of this highly activated aromatic species.

No.	Nitrating System	Result
1.	c. HNO_3, 30% oleum, r.t.	Violent decomposition
2.	c. HNO_3, c. H_2SO_4, 0°C	Decomposition
3.	69% aq. HNO_3, 0°C	Decomposition
4.	c. HNO_3, -10°C	Decomposition
5.	N_2O_5, CH_2Cl_2, -20°C < T < +10°C	Several breakdown products
6.	100% HNO_3, Ac_2O	No reaction
7.	100% HNO_3, AcOH	Decomposition
8.	*i*-Pr-ONO_2	No reaction
9.	$NO_2^+BF_4^-$, NO_2Me	No reaction
10.	$NaNO_2$, aq. HCl, 2 h, 0°C	Decomposition
11.	BzCl, $AgNO_3$, MeCN	Decomposition
12.	$NO_2^+BF_4^-$, sulfolane (high concentration)	Decomposition
13.	$NO_2^+BF_4^-$, sulfolane (0.5M commercial grade)	Successful dinitration
14.	$NO_2^+SbF_6^-$, sulfolane	Successful dinitration

Table 15: Nitrating Systems Employed in the Attempted Nitration of 2,5-Diethoxypyrazine (149, R=Et)

The use of nitronium tetrafluoroborate ($NO_2^+BF_4^-$) in sulfolane was found to be effective in dinitrating 2,5-diethoxypyrazine (**149**, R=Et), typically with a reaction yield of 30-40% of 2,5-diethoxy-3,6-dinitropyrazine (**150**, R=Et). A range of conditions were used in order to optimise this reaction (**Table 16**), however, the optimum yield appears to be *ca.* 35-40%. It is thought that the relatively low reaction yield with the tetrafluoroborate salt may be due to some decomposition of the salt.

No.	Reaction length	Reaction Temperature (°C)	Stoichiometry (substrate: salt)	Reaction yield (%)
1	15 h	r.t.	1:2	30 - 35
2	5 d	r.t.	1:2	35
3	2 - 5 d	40	1:2	35 - 40

4	3 d	r.t.	1:4	< 5
5	2 - 3 h	100	1:2	20
6	15 h	75	1:2	20

Table 16: Reaction Conditions Used in the $NO_2^+BF_4^-$/Sulfolane Nitration of 2,5-Diethoxypyrazine (149, R=Et)

In the nitration of 2,5-diethoxypyrazine (**149**, R=Et) it was found that the reaction yield is dramatically decreased when the stoichiometry (substrate: salt) is increased, e.g. reaction number 4. Similarly when the reaction temperature is increased dramatically to *ca.* 75°C or 100°C (e.g. reaction numbers 5 and 6) again the reaction yield decreases.

CHN Elemental analysis was carried out on 2,5-diethoxy-3,6-dinitropyrazine (**150**, R=Et). A good correlation between calculated and experimental values was obtained.

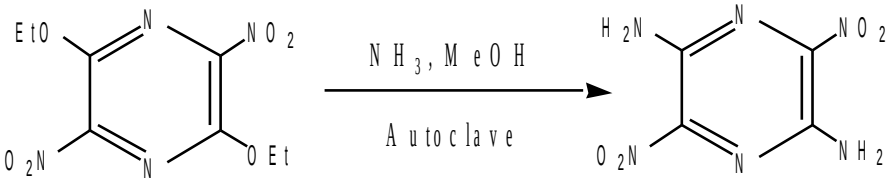
2,5-Diethoxypyrazine (**149**, R=Et) was also successfully nitrated using nitronium hexafluoroantimonate (V) ($NO_2^+SbF_6^-$) in dry sulfolane with a reaction yield of ~35%. However, a large excess of the nitrating agent was required in order to achieve this reaction yield. The experimental procedure used with the $NO_2^+SbF_6^-$ reaction was the same as that used for the nitration involving $NO_2^+BF_4^-$.

5.3.5 Oxidative Nitration of 2,5-Diethoxy-3,6-dihydropyrazine (148, R=Et)[97]

The oxidative nitration of 2,5-diethoxy-3,6-dihydropyrazine (**148**, R=Et) was attempted a number of times using dinitrogen tetroxide (N_2O_4). For each reaction a decomposition product was obtained and it is the author's opinion that this reaction is not repeatable.

5.3.6 Amination of 2,5-Diethoxy-3,6-dinitropyrazine (150, R=Et)

The amination of 2,5-diethoxy-3,6-dinitropyrazine (**150**, R=Et) was attempted using aqueous ammonia solution in acetonitrile at atmospheric pressure. However, unreacted starting material was recovered. Therefore, amination of the substrate was attempted with an ammonia saturated solution of methanol under autoclave conditions (**Scheme 67**). 2,5-Diamino-3,6-dinitropyrazine (ANPZ-i) (**10**) was obtained in almost quantitative yield. On-line searching failed to identify a CAS registry entry and therefore 2,5-diamino-3,6-dinitropyrazine (ANPZ-i) (**10**) may be regarded as a new compound.

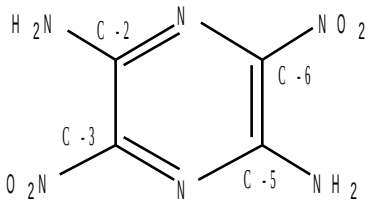


150, R=Et **10**, ANPZ-i

Scheme 67

Both HPLC and IR analysis indicated the presence of a pure compound but the ^{1}H NMR spectrum (**Figure 28**) of ANPZ-i (**10**) did show small levels of ethyl (Et) protons, with resonances at δ 1.38 and 4.35 ppm. The major peak in the spectrum was caused by the amino protons, which had a resonance at δ 2.84 ppm. This broad signal collapsed and formed a doublet on D_2O addition.

^{13}C NMR spectral analysis has also been carried out (**Figure 29**). **Table 17** shows the carbon-13 NMR spectroscopy shift values of 2,5-diamino-3,6-dinitropyrazine (ANPZ-i) (**10**). The carbon-13 NMR spectrum has additional peaks which may be caused by an impurity. Therefore, the following assignments are tentative.



10

Carbon	C-2	C-3	C-5	C-6
δ (ppm)	150.30	149.49	150.30	149.49

Table 17: Summary of ^{13}C NMR Spectroscopy Shift Values for 2,5-diamino-3,6-dinitropyrazine (ANPZ-i) (10)

Further details on pyrazine carbon-13 NMR spectra can be found in Section 6.4: Pyrazine ^{13}C NMR Spectroscopy Shift Values. The shift values for all the carbon atoms in 2,5-diamino-3,6-dinitropyrazine (ANPZ-i) (**10**) are shifted downfield significantly due the presence of nitro and amino groups on the heterocyclic ring as well as the effect of the two nitrogen heteroatoms.

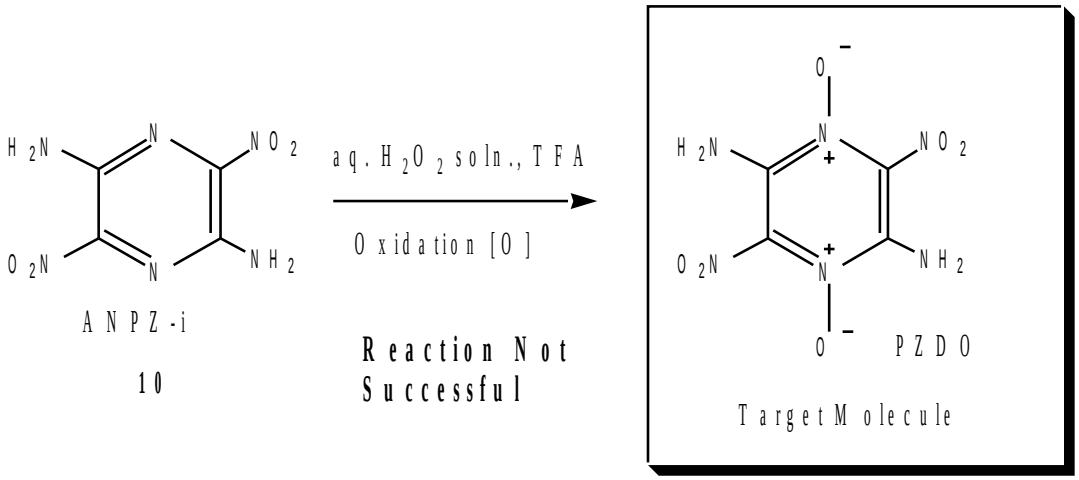
Figure 30 shows the mass spectrum for 2,5-diamino-3,6-dinitropyrazine (**10**) (ANPZ-i). The mass spectrum of ANPZ-i (**10**) has a very strong peak at 200 m/z, which can be attributed to the molecular ion (M^+). There is also a peak at 170 m/z which is due to the presence of a breakdown product caused by the loss of NO from the molecular ion.

CHN Elemental analysis was carried out on 2,5-diamino-3,6-dinitropyrazine (ANPZ-i) (**10**). There was a variable correlation between calculated and experimental values with the values for H being the furthest apart. This may be because the experimental sample was not recrystallised due to its poor solubility in organic solvents.

5.3.7 Attempted *N*-Oxidation of 2,5-Diamino-3,6-dinitropyrazine (ANPZ-i) (10)

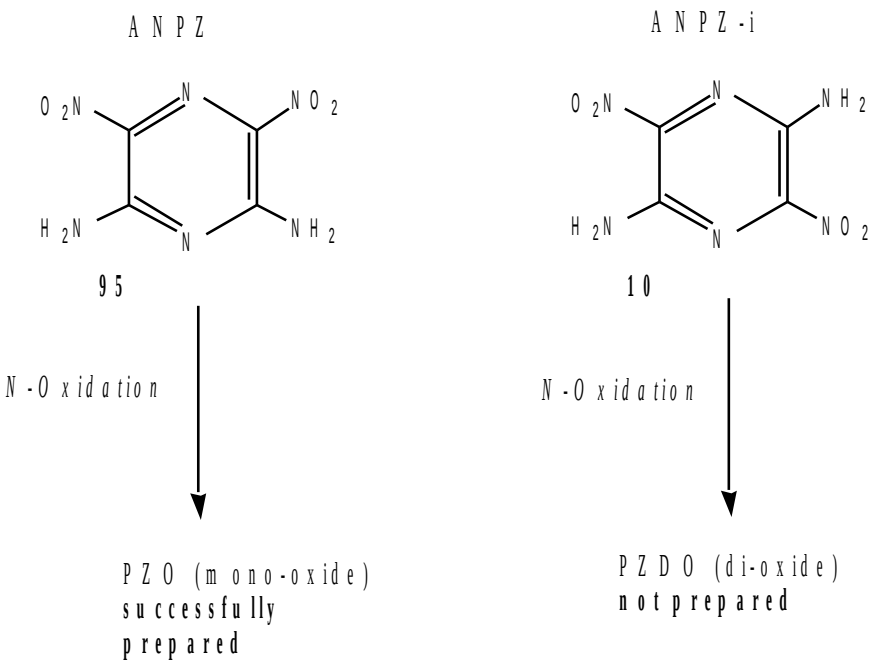
A number of attempted oxidations of 2,5-diamino-3,6-dinitropyrazine (ANPZ-i) (**10**) (**Scheme 68**) have been carried out using both 30% and 60% aqueous solutions of hydrogen peroxide (H_2O_2) and trifluoroacetic acid (TFA) (*in situ* generation of trifluoroperacetic acid) Typically, upon work-up of the reaction

mixture, no product could be obtained since the starting material/product could not be extracted from the aqueous acidic layer. In most cases the reaction gave a negative ferric chloride test result except in one case where a positive outcome was observed, thereby indicating the presence of an *N*-oxide species. However, mass spectral analysis of this compound indicated that it was a breakdown product.



Scheme 68

A much more powerful oxidation system was also used in the attempted *N*-oxidation of 2,5-diamino-3,6-dinitropyrazine (ANPZ-i) (**10**). This system was based on MCPBA with 48% aq. HF solution in DMF. Even this extremely powerful oxidising system was not capable of oxidising ANPZ-i. The oxidation of 2,6-diamino-3,5-dinitropyrazine (ANPZ) (**95**) was achieved using the MCPBA/HF system, thereby demonstrating that the *N*-oxidation of ANPZ-i, with its isomeric structure to ANPZ, is more difficult (**Scheme 69**).


ANPZ
ANPZ-i
95
10
N-Oxidation
N-Oxidation
PZO (mono-oxide)
successfully
prepared
PZDO (di-oxide)
not prepared

Scheme 69

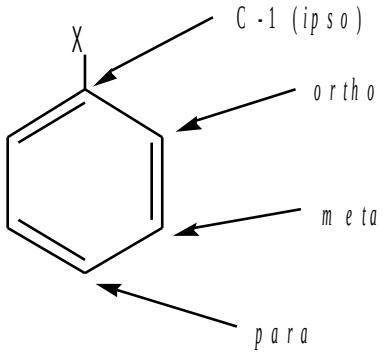
6. ^{13}C NMR Spectroscopy Results

6.1 Introduction

It can be very difficult to use carbon-13 NMR spectroscopy by itself to assign chemical structures. However, when used in conjunction with proton NMR spectroscopy and, for example, IR spectroscopy a reasonably accurate structural determination can be made. In order to assign the carbon atoms for the compounds given in this section, the following simple correlations and rules have been used.[98]

- Resonances due to aliphatic carbons usually lie in the range
  δ 0.0 - 80.0.
- Resonances due to aromatic carbons usually lie in the range
  δ 110.0 - 160.0.
- Resonances due to alcohols and ether carbons usually lie in the
  range δ 50.0 - 80.0.

The following table (**Table 18**) can be used to show the influence of functional group X on the chemical shift (δ) of nearby carbons on an aromatic ring. Chemical shifts are relative to TMS (tetramethylsilane).



Benzene (δ 128)

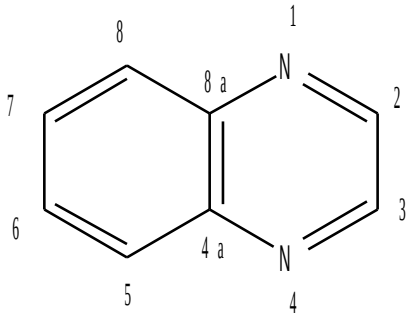
X	*ipso*	*ortho*	*meta*	*para*
$-NO_2$	+20	-5	+1	+6
$-NR_2$	+22	-16	+1	-10
-OH	+27	-13	+1	-7
-OR	+30	-15	+1	-8
$-CH_3$	+9	0	0	-2
-Cl	+6	0	+1	-2

Table 18: Influence of Functional Group X on the Chemical Shift (δ) of Nearby Carbons on an Aromatic Ring

It should be noted that the ^{13}C NMR spectral assignments in this chapter are estimations based on the above table. Many of the spectral assignments should be regarded as tentative, representing reasonable interpretations of the observed spectra using the available information.

6.2 Quinoxaline ^{13}C NMR Spectroscopy Shift Values

The following structure shows the numbering system used for quinoxaline nitrogen and carbons atoms.



1

(i). Quinoxaline (**1**)[73]

(ii). 2,3-Dichloro-5-nitroquinoxaline (**118**)

(iii). 2,3,6-Trichloro-5-nitroquinoxaline (**120**)

(iv). 2,3,6,7-Tetrachloro-5-nitroquinoxaline (**123**)

(v). 2-Hydroxy-3-methyl-6-nitroquinoxaline (**126**)

(vi). 2-Hydroxy-6-nitroquinoxaline (**127**)

(vii). 2,3-Dichloroquinoxaline-1-oxide (**132**)

(viii). 2,3,6-Trichloroquinoxaline-1-oxide (**133**)

Table 19 shows the ^{13}C NMR spectroscopy assigned shift values for the compounds listed above.

		C-2	**C-3**	**C-5**	**C-6**	**C-7**	**C-8**	**C-8a**	**C-4a**	**Me**
(i).	**1**	144.80	144.80	129.60	129.40	129.40	129.60	142.80	142.80	____
(ii).	**118**	146.92	147.31	139.91	125.90	127.82	130.82	132.43	131.73	____
(iii).	**120**	148.94	148.02	144.27	138.94	126.59	131.83	132.50	132.50	____
(iv).	**123**	149.16	149.05	145.13	131.27	131.10	126.15	138.94	134.74	____
(v).	**126**	162.58	155.21	123.66	130.82	124.40	116.55	142.70	137.61	20.94
(vi).	**127**	155.12	154.52	124.66	131.13	125.68	117.10	142.81	137.50	____
(vii).	**132**	146.28	140.51	129.37	128.88	130.67	131.54	137.10	132.95	____
(viii).	**133**	138.67	135.73	129.58	135.73	132.12	130.94	132.95	131.30	____

Table 19

(i). Quinoxaline (1)[73]

Quinoxaline is a symmetrical molecule and therefore the following carbons have the same resonance values: 2 = 3, 5 = 8, 6 = 7 and 8a = 4a. Positions 2 and 3 in quinoxaline itself (**1**) (both at δ 144.80) are markedly downfield compared to the resonances of the other carbons. This is because being adjacent to the nitrogen atoms on the heterocyclic ring, which are highly electronegative, will cause α-carbons to be shifted significantly downfield. Analysis of quinoxaline (**1**) shows that positions 2 and 3 are further downfield than positions 8a and 4a. This is due to positions 8a and 4a being tertiary carbons whereas positions 2 and 3 are secondary carbons, the effect of being adjacent to aza groups being more pronounced for secondary carbons. Positions 5 - 8 in quinoxaline are all close to the resonance value for benzene (δ 128), since these carbocyclic carbons are in a similar electronic environment to those in the standard benzene structure.

(ii). 2,3-Dichloro-5-nitroquinoxaline (118)

Positions 2 and 3 on the heterocyclic ring on **118** are furthest downfield at δ 146.92 and 147.31, this may be due to a combination of effects; the effect of having a chloro group *ipso* to each carbon as well as being adjacent to the heterocyclic aza groups. Since these shift values are so close it is very difficult to distinguish which one corresponds to either the C2 or the C3 carbon atom and hence these assignments are tentative. Position 5 in **118** has a resonance at δ 139.91 due to the effect of having a nitro group attached to this carbon. Positions 8a and 4a in **118** have resonances at δ 132.43 and 131.73 respectively since these positions are both adjacent to the heterocyclic aza groups. Position 8 in **118** has a resonance at δ 130.82 due to the *para* effect of the nitro group at position number 5. Position 6 in **118** has a resonance at δ 125.90 due to the *ortho* effect of the nitro group at position number 5. The only remaining carbon, at position 7, probably has a resonance at δ 127.82.

(iii). 2,3,6-Trichloro-5-nitroquinoxaline (120)

Positions 2 and 3 in **120** may have resonances at δ 148.94 and 148.02, which are the furthest downfield resonances. Since these shift values are very close it is difficult to distinguish which one corresponds to either the C2 or the C3 carbon atom and hence these assignments are tentative. Position 5 in **120** has a resonance at δ 144.27 because of the *ipso* effect of the nitro group attached to this carbon, which has an effect of shifting the carbon resonance downfield. Position 6 has a resonance at δ 138.94, due to the downfield effect of the attached chloro group (this effect is partly cancelled by the *ortho* effect of the nitro group). Positions 8a and 4a have resonances both at δ 132.50, since they are both shifted downfield due to being α-carbons to the heterocyclic aza groups. Position 8 has a resonance at δ 131.83 due to the *para* effect of the nitro group attached to carbon number 5.

The only remaining carbon atom in **120** is at position number 7 which may have a resonance at δ 126.59. The carbon in position 7 does not have a functional group attached and therefore is not shifted significantly downfield.

(iv). 2,3,6,7-Tetrachloro-5-nitroquinoxaline (123)

Positions 2 and 3 in **123** have resonances furthest downfield, at δ 149.16 and 149.05 respectively, since they are α-carbons to the two heterocyclic nitrogen atoms. Since these shift values are very close it is difficult to distinguish which one corresponds to either the C2 or the C3 carbon atom and hence these assignments are tentative. Position 5 has a resonance at δ 145.13, due to the *ortho* effect of the attached nitro group. Positions 8a and 4a have resonances at δ 138.94 and 134.74 respectively, since they are both shifted downfield due to being adjacent to the aza groups at positions 1 and 4 on the heterocyclic ring. Positions 6 and 7 have resonances at δ 131.27 and 131.10 respectively, due to the slightly downfield effect of the attached chloro groups. Again because these two shift values are so close it is difficult to distinguish them apart and hence these assignments are tentative. The only remaining carbon in **123** is at position number 8 which has a resonance at δ 126.15. This carbon is not attached to a functional group and therefore may not be shifted significantly downfield.

(v). 2-Hydroxy-3-methyl-6-nitroquinoxaline (126)

Position number 2 in **126** is the furthest downfield at δ 162.58 since this carbon has the double effect of being attached to both a hydroxy group and a nitrogen heteroatom, both of which cause a substantial shift downfield. Position number 3 in **126** is also downfield considerably at δ 155.21, since this carbon is attached to both a methyl group and a nitrogen heteroatom where again both groups have a downfield effect on the carbon resonance. The *ipso* effect of a hydroxy group is stronger than that of a methyl group and therefore position 2 is downfield to position 3. Positions 8a and 4a have resonances at δ 142.70 and 137.61

respectively since they are both attached to the heteroatoms in **126**. The resonance for position 8a is downfield compared to that of position 4a because of the *para* effect of the nitro group on C8a. Position 6 has a resonance at δ 130.82, which is due to the downfield effect of being attached to a nitro group. The remaining aromatic carbons in **115** are at positions 5, 7 and 8 and have resonances at δ 123.66, 124.40 and 116.55 respectively. It is difficult to assign carbon atoms C5, C7 and C8 and therefore these assignments are only tentative. The methyl carbon has a resonance at δ 20.94 which is a consequence of being an aliphatic carbon.

(vi). 2-Hydroxy-6-nitroquinoxaline (127)

Positions 2 and 3 in **127** have resonances at δ 155.12 and 154.52 respectively. Position 2 is further downfield since it is attached to a hydroxy group. Positions 8a and 4a have resonances at δ 142.81 and 137.50 respectively, since they are both attached to nitrogen heteroatoms. The resonance for position 8a is downfield compared to that of position 4a because of the *para* effect of the nitro group on C8a. Position 6 has a resonance at δ 131.13, which is shifted downfield due to the effect of being *ipso* to a nitro group. The remaining carbons in **127** are at positions 5, 7 and 8 and may have resonances at δ 124.66, 125.68 and 117.10 respectively. It is difficult to assign carbon atoms C5, C7 and C8 and therefore these assignments are only tentative.

(vii). 2,3-Dichloroquinoxaline-1-oxide (132)

Positions 2 and 3 in **132** have resonances at δ 146.28 and 140.51 respectively, since they are both attached to nitrogen heteroatoms. Position 2 is furthest downfield due to the effect of being α to an *N*-oxide group. Positions 8a and 4a may have resonances at δ 137.10 and 132.95 respectively since they are also attached to the nitrogen heteroatoms. Due to the difficulty in allocating resonance values to carbon atoms in **132** the remaining assignments are only tentative. The

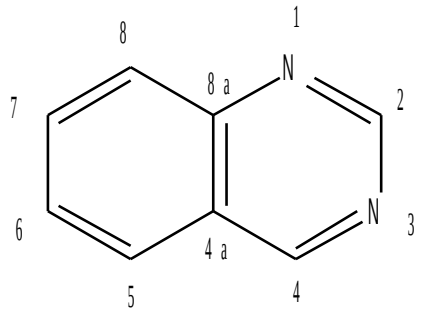
following carbons have been assigned the corresponding resonances: C-5 (δ 129.37), C-6 (δ 128.88), C-7 (δ 130.67) and C-8 (δ 131.54).

(viii). 2,3,6-Trichloroquinoxaline-1-oxide (133)

Positions 2 and 3 in **133** have resonances at δ 138.67 and 135.92 respectively, since they are both attached to nitrogen heteroatoms. Position 2 is furthest downfield due to the effect of being α to an *N*-oxide group. Positions 8a and 4a may have resonances at δ 132.95 and 131.30 respectively since they are also attached to the nitrogen heteroatoms. Position 6 has a resonance of δ 135.73 due to the *ipso* effect of the attached chloro group. Due to the difficulty in allocating resonance values to carbon atoms in **133** the remaining assignments are only tentative. The following carbons have been assigned the corresponding resonances: C-5 (δ 129.58), C-7 (δ 132.12) and C-8 (δ 130.94).

6.3 Quinazoline ^{13}C NMR Spectroscopy Shift Values

The following structure shows the numbering system used for quinazoline nitrogens and carbon atoms.



2

(i). Quinazoline (**2**)[59]

(ii). 2,4-Dichloroquinazoline (**58**)

(iii). 4-Hydroxy-7-nitroquinazoline (**136**)

(iv). 2,4-Diamino-6,8-dinitroquinazoline (**61**)

(v). 2,4,7-Triamino-6,8-dinitroquinazoline (**142**)

(vi). 2,4-Diamino-6,8-dinitroquinazoline-di-*N*-oxide (**141**)

(vii). 2,4,6,8-Tetra-aminoquinazoline (**143**)

Table 20 shows the ^{13}C NMR spectroscopy assigned shift values for the compounds listed above.

		C-2	**C-4**	**C-5**	**C-6**	**C-7**	**C-8**	**C-8a**	**C-4a**
(i).	**2**	160.70	155.90	127.60	128.10	134.30	128.60	150.30	125.40
(ii).	**58**	155.47	153.41	128.73	126.88	123.27	130.69	137.52	135.64
(iii).	**136**	160.31	153.16	129.30	122.13	145.17	122.92	149.14	128.47
(iv).	**61**	163.31	162.71	132.86	140.02	123.34	153.10	158.73	120.44
(v).	**142**	161.70	155.07	131.73	144.10	150.65	148.62	153.13	129.50
(vi).	**141**	123.05	123.36	126.52	144.80	125.88	136.91	123.90	124.38
(vii).	**143**	163.46	163.27	103.71	142.53	102.31	144.52	148.84	121.00

Table 20

(i). Quinazoline (2)[59]

Position 2 in quinazoline (**2**) has a resonance of δ 160.70. This value is the furthest value downfield since the carbon at this position is flanked by two nitrogen heteroatoms and therefore the effect of shifting the resonance downfield is doubled. Positions 4 and 8a are also shifted downfield to resonances of δ 155.90 and 150.30 respectively. Both carbon atoms 4 and 8a are attached to nitrogen heteroatoms in the heterocyclic ring. However, the resonance for position 4 is shifted further downfield because it is a secondary carbon whereas position 8a is a tertiary carbon. Positions 4a, 5, 6, 7 and 8 all have resonance values which approximate to that of standard benzene carbons (δ 128).

(ii). 2,4-Dichloroquinazoline (58)

Position 2 in **58** has a resonance of δ 155.47 because this carbon is flanked by two nitrogen heteroatoms. Position 4 in **58** has a resonance of δ 153.41 since this carbon is next to a nitrogen heteroatom. Due to the difficulty in allocating carbon atoms to resonance values in **58** the remaining assignments are all only tentative. The following carbons have been assigned the corresponding resonances: C-5 (δ 128.73), C-6 (δ 126.88), C-7 (δ 123.27), C-8 (δ 130.69), C-8a (δ 137.52) and C-4a (δ 135.64).

(iii). 4-Hydroxy-7-nitroquinazoline (136)

Position 2 in **136** has a resonance of δ 160.31, which can be expected since this carbon is attached to two aza groups and is therefore shifted significantly downfield. Position 4 in **136** has a resonance of δ 153.16, which can also be expected since this carbon is attached to a nitrogen heteroatom and is therefore shifted downfield, as well as being shifted further through being *ipso* to a hydroxy-group. The C4 carbon in **136** is upfield compared to that in **2**, when it could have been expected to have been further downfield. This observation demonstrates the complex nature of the carbon-13 NMR spectra of nitrogen heterocyclic compounds. Position 8a has a resonance of δ 149.14 since this carbon is attached directly to a nitrogen heteroatom and is therefore shifted downfield. Position 7, which has a resonance of δ 145.17, is also shifted significantly downfield though this time through being attached to a nitro group. Positions 6 and 8 have resonances of δ 122.13 and 122.92 respectively since they are both *ortho* to a carbon attached to a nitro group. Position 4a has a resonance of δ 128.47. The resonance of this carbon is effected by being *para* to a nitro terminated carbon as well as being *ortho* to a hydroxy terminated carbon. The remaining carbon in **136** is position 5, could potentially have a resonance of δ 129.30.

(iv). 2,4-Diamino-6,8-dinitroquinazoline (61)

Position 2 in **61** has a resonance of δ 163.31 and is shifted significantly downfield due to being flanked by two nitrogen heterotaoms and being attached to an amino group. Position 4 in **61** has a resonance of δ 162.71 which is also shifted downfield significantly through being attached to one heteroatom as well as an amino group. Position 8a has a resonance of δ 158.73 which is shifted downfield since this carbon is δ to a nitrogen heteroatom. The resonances for carbons at positions 6 and 8, which are δ 140.02 and 153.10 respectively, are also shifted downfield since these carbons are both attached to nitro groups. Position 6 is shifted less downfield than position 8, since it is also effected by being *para* to the 4-amino group. Position 4a has a resonance of δ 120.44 since this carbon is *ortho* to an amino terminated carbon. The two remaining carbons in **61** are at positions 5 and 7, could potentially have resonances at δ 132.86 and 123.34 respectively.

(v). 2,4,7-Triamino-6,8-dinitroquinazoline (142)

Position 2 in **130** has a resonance of δ 161.70. This carbon is shifted significantly downfield since it is flanked by two nitrogen heteroatoms and is attached to an amino group. Position 4 in **142** has a resonance of δ 155.07, which is also shifted downfield but this time through being attached to an amino group and just one nitrogen heteroatom. Position 8a has a resonance of δ 153.13 due to being α to the 1-aza group, which has a downfield effect. The carbon in position 7 has a resonance of δ 150.65 and is shifted downfield because it is attached to an amino group. The shift values for carbon atoms C4, C7 and C8a are close together and hence these assignments are tentative. The two C-NO_2 carbons, at positions 6 and 8, have resonances of δ 144.10 and 148.62 respectively. This is because a carbon attached to a nitro group is shifted downfield. Position 4a has a resonance of δ 129.50, this is because this carbon is *ortho* to a C-NH_2 group. The remaining carbon in **142** at position 5 has a resonance of δ 131.73. This carbon atom does

not have a functional group attached and may therefore potentially not be shifted significantly downfield.

(vi). 2,4-Diamino-6,8-dinitroquinazoline-di-*N*-oxide (141)

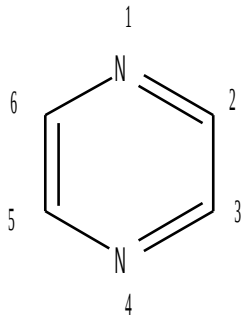
Position 2 in **141** has a resonance of δ 123.05. The carbon in this position is shifted upfield considerably since it is flanked by two *N*-oxide groups. Positions 4 and 8a in **141**, which have resonances of δ 123.36 and 123.90 respectively, are also shifted significantly upfield since they are each attached to an *N*-oxide group. Positions 6 and 8, which have resonances of δ 144.80 and 136.91 respectively, are shifted significantly downfield since they are both *ipso* to a nitro group. The remaining carbons in **141**, which are at positions 5, 7 and 10 potentially have resonances of δ 126.52, 125.88 and 124.38 respectively. The shift values for carbon atoms C5, C7 and C4a are close together and hence these assignments are tentative.

(vii). 2,4,6,8-Tetra-aminoquinazoline (143)

Position 2 in **143** has a resonance of δ 163.46. The carbon in this position is shifted significantly downfield since it is attached to amino group and is flanked by the two heterocyclic aza groups. Position 4 in **143**, which has a resonance of δ 163.27, is also shifted significantly downfield since it is attached to both an amino group and a nitrogen heteroatom. The carbon in position 8a has a resonance of δ 148.84. This is because of the conflicting effects of being attached to a nitrogen heteroatom (downfield effect) and *ortho* to a C-NH_2 group (upfield effect). The carbons in positions 6 and 8, which have resonances of δ 142.53 and 144.52 respectively, are both shifted downfield since they are *ipso* to NH_2 groups. The carbons in positions 5 and 7, which have resonances at δ 103.71 and 102.31 respectively, are both shifted upfield significantly since they are both *ortho* to C-NH_2 groups. The remaining carbon in **143**, which is at position number 4a has a resonance of δ 121.00.

6.4 Pyrazine ^{13}C NMR Spectroscopy Shift Values

The following structure shows the numbering system used for pyrazine nitrogen and carbon atoms.



3

(i). Pyrazine (**3**)[73]

(ii). 2,6-Diamino-3,5-dinitropyrazine (**95**) (ANPZ)

(iii). 2,6-Diamino-3,5-dinitropyrazine-1-oxide (**9**) (PZO)

(iv). 2,5-Diethoxy-3,6-dihydropyrazine (**148**, R=Et)

(v). 2,5-Diethoxypyrazine (**149**, R=Et)

(vi). 2,5-Diethoxy-3,6-dinitropyrazine (**150**, R=Et)

(vii). 2,5-Diamino-3,6-dinitropyrazine (**10**) (ANPZ-i)

Table 21 shows the ^{13}C NMR spectroscopy assigned shift values for the compounds listed above.

		C-2	**C-3**	**C-5**	**C-6**	**CH_3**	**CH_2**
(i).	**3**	145.00	145.00	145.00	145.00	-------	-------
(ii).	**95**	151.12	125.56	125.56	151.12	-------	-------
(iii).	**9**	144.59	124.88	124.88	144.59	-------	-------
(iv).	**148**	162.70	46.65	162.70	46.65	14.30	61.00
(v).	**149**	156.28	128.75	156.28	128.75	15.00	62.80
(vi).	**150**	144.41	139.61	144.41	139.61	14.65	66.10

(vii).	**10**	150.30	149.49	150.30	149.49	-------	-------

Table 21

(i). Pyrazine (3)[73]

The proton decoupled ^{13}C NMR spectrum of pyrazine (**3**) shows a single resonance at δ 145.00. The four carbons all have the same resonance value because the molecule is symmetrical. Each carbon is shifted downfield from the standard benzene resonance (δ 128) since it is attached to a nitrogen heteroatom.

(ii). 2,6-Diamino-3,5-dinitropyrazine (95) (ANPZ)

2,6-Diamino-3,5-dinitropyrazine (**95**) (ANPZ) is a symmetrical molecule and therefore the following carbons have the same resonances: 2 = 6 and 3 = 5. The carbons in positions 2 and 6 on the heterocyclic ring both have resonances of δ 151.12, which is due to the effect of being attached to amino groups as well as the being both simultaneously *ortho* and *para* to different nitro groups. The carbons in positions 3 and 5, which are both attached to nitro groups, have resonances of δ 125.56. This is because whilst these carbons are attached to nitro groups they are also simultaneously *ortho* and *para* to different amino groups.

(iii). 2,6-Diamino-3,5-dinitropyrazine-1-oxide (9) (PZO)

2,6-Diamino-3,5-dinitropyrazine-1-oxide (**9**) (PZO) is also a symmetrical molecule and therefore the following carbons have the same resonances: 2 = 6 and 3 = 5. The presence of the *N*-oxide functionality has the effect of shifting the resonance values slightly upfield when compared to those of ANPZ (**95**). Therefore, positions 2 and 6 both have resonances of δ 144.59 while positions 3 and 5 both have resonances of δ 124.88.

(iv). 2,5-Diethoxy-3,6-dihydropyrazine (148, R=Et)

2,5-Diethoxy-3,6-dihydropyrazine (**148**, R=Et) is a symmetrical molecule. Positions 2 and 5 both have resonances of δ 162.70. These carbons are shifted significantly downfield due to a combination of effects; attachment to ethoxy groups, being adjacent to nitrogen heteroatoms and also attachment to alkenic protons and hence can be considered as alkene carbons. Positions 3 and 6 both have resonances of δ 46.65. This is because these carbons are aliphatic in nature and are also adjacent to the nitrogen heteroatoms, which has a downfield effect. The methyl carbon has a resonance of δ 14.30 because it is an aliphatic terminal alkyl group. Finally, the CH_2O carbon has a resonance of δ 61.00 since this carbon is attached to an ether group which has the effect of shifting it downfield.

(v). 2,5-Diethoxypyrazine (149, R=Et)[96]

2,5-Diethoxypyrazine (**143**, R=Et) is a symmetrical molecule. Positions 2 and 5 both have resonances of δ 156.28 because they are aromatic carbons which are attached to nitrogen heteroatoms and ethoxy groups which both have a downfield effect. The carbons in positions 3 and 6 are aromatic carbons attached to nitrogen heteroatoms and have resonances of δ 128.75. The methyl carbon has a resonance of δ 15.00 because it is an aliphatic terminal alkyl group. Finally, the CH_2O carbon has a resonance of δ 62.80 since this carbon is attached to an ether group which has the effect of shifting it downfield.

(vi). 2,5-Diethoxy-3,6-dinitropyrazine (150, R=Et)[96]

2,5-Diethoxy-3,6-dinitropyrazine (**150**, R=Et) is a symmetrical molecule. Positions 2 and 5 both have resonances of δ 144.41 since these aromatic carbons are attached to both ethoxy groups and nitrogen heteroatoms. Positions 3 and 6 both have resonances of δ 139.61 since these aromatic carbons are attached to both nitro groups and nitrogen heteroatoms. Comparing (**150**, R=Et) to (**149**,

R=Et), replacing the protons in positions 3 and 6 with nitro groups, has the effect of moving the resonances for carbons 3 and 6 downfield (*ipso* nitro group effect) and the effect of moving the resonances for carbons 2 and 5 upfield (*ortho* nitro group effect). The methyl carbon has a resonance of δ 14.65 because it is an aliphatic terminal alkyl group. Finally, the CH_2O carbon has a resonance of δ 66.10 since this carbon is attached to an ether group which has the effect of shifting it downfield.

(vii). 2,5-Diamino-3,6-dinitropyrazine (10) (ANPZ-i)

2,5-Diamino-3,6-dinitropyrazine (**10**) (ANPZ-i) is a symmetrical molecule. Positions 3 and 6 have resonances of δ 149.49 because these aromatic carbons are attached to nitrogen heteroatoms and nitro groups and are therefore shifted significantly downfield. Positions 2 and 5 have resonances of δ 150.30 because these aromatic carbons are attached to nitrogen heteroatoms and amino groups and are therefore also shifted significantly downfield. There is so little difference between the δ values for carbons in positions (3=6) and (2=5) that the above assignments could be reversed.

7. Molecular Modelling Studies

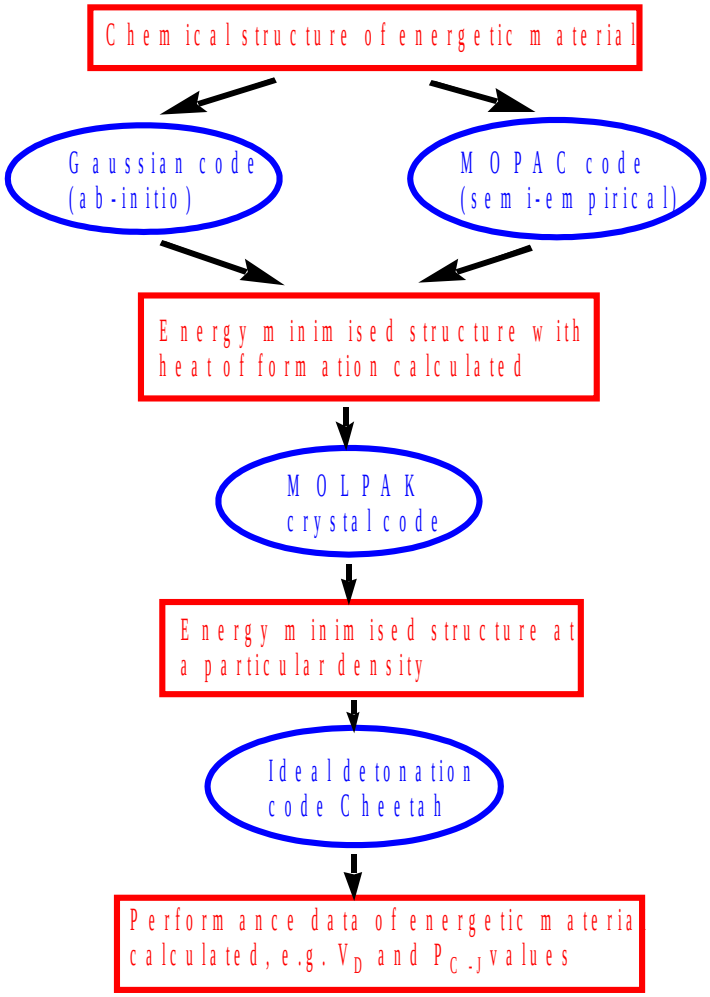
7.1 Introduction

The branch of chemistry which deals with the molecular modelling of chemicals and their properties is called computational chemistry.[99] Computational chemistry can be used in theoretical, physical, organic and inorganic applications but in this study it was used to predict a number of physical properties of nitrogen heterocyclic compounds. Molecular modelling was carried out on a number of target nitrogen heterocyclic compounds in order to predict their expected energetic performance. **Scheme 70** shows the sequence of calculations required to predict the performance characteristics of an energetic material.

Firstly the heat of formation of an energy minimised structure must be calculated from the chemical structure, this can be done by either one of two ways which are as follows: MOPAC which is a semi-empirical code or by Gaussian which is an *ab-initio* code. Then the energy minimised structure is fed into MOLPAK which is a crystal parameters code which will calculate a density for a particular crystal structure (other physical parameters such as lattice energies can also be calculated at this stage). Finally the energy minimised structure with a given density is fed into the Cheetah code which is a quantum chemistry code.

The Cheetah programme compares the heats of formation of the reactants to the products and thereby gives information on the energy produced during detonation. The Cheetah code is used to calculate detonation velocities (V_D) and detonation pressures ($P_{C\text{-}J}$). The above calculations were carried out on a Silicon Graphics 02 Workstation (IRIX, R10000).

Note: All detonation property molecular modelling calculations (including MOLPAK and Cheetah calculations) were carried out by Mr. Justin Fellows (see Acknowledgements Section).



Scheme 70: Sequence of Calculations Required to Predict the Performance Characteristics of an Energetic Material

A further study was carried out on a number of key compounds in order to obtain information such as heats of formation, steric energies and atomic charges. These calculations were carried out using CSC (Cambridge Scientific Computing) Chem3D/Plus 1998 version on a PowerPC Apple Macintosh 6500/300. Note: Steric energy calculations were carried out by the author.

With this user friendly molecular modelling programme the structure is drawn then a number of calculations are carried out. Firstly, the structure has its energy minimised using the MOPAC PM3 code, at this point information such as heat of

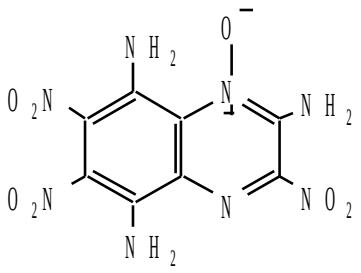
formation of the compound or the charge densities can be calculated. After the use of the MOPAC programme the molecular mechanics (MM) code can be used to obtain further information such as the steric energy of the compound.

The steric energy is calculated as a summation of seven particular types of steric energy which are as follows:

1. The stretch term. The energy associated with stretching and compressing bonds from their optimal length.
2. The bend term. The energy associated with deforming bond angles from their optimal values.
3. The stretch-bend term. The energy required to stretch the two bonds involved in a bond angle when that bond is severely compressed.
4. The torsion term. The energy associated with deforming torsional angles in the molecule.
5. The non 1,4-Van der Waals energy term. The energy relating to the interaction of atoms bonded to non-adjacent atoms.
6. The 1,4-Van der Waals energy term. The energy relating to the interaction of atoms bonded to adjacent atoms.
7. The dipole/dipole energy term. The energy associated with the interaction of bond dipoles. This term has the following contributions; charge/charge energy, charge/dipole energy and dipole/dipole energy.

7.2 Molecular Modelling of Quinoxalines

Molecular modelling calculations were carried out on the target molecule; 2,5,8-triamino-3,6,7-trinitroquinoxaline-1-oxide (**151**) using MOLPAK and Cheetah. **Figure 31** shows molecular modelling information, structure and data for **151**.



151

The detonation velocity of **151** was calculated to be 7.86 km.s^{-1} which is slightly lower than that of TATB (**8**) which is 7.94 km.s^{-1}. This detonation velocity is slightly lower than expected and can be attributed to its density which was calculated to be 1.788 g.cm^{-3}. This is the case since detonation velocity is largely dependent on density and a density as close to 2 g.cm^{-3} or above is usually required in order for the compound to have a very high detonation velocity.

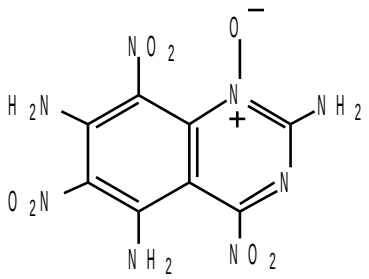
Table 22 shows the calculated atomic charge values from MOPAC (PM3) given in **Figure 31** [Molecular modelling diagram and information for 2,5,8-triamino-3,6,7-trinitroquinoxaline-1-oxide (**151**)].

Ring Position	Atom	Charge (au)
N1	Nitrogen Atom	+0.973
	Oxide Atom	-0.623
C2	Carbon Atom	-0.373
	Nitrogen Atom	+0.169
	Hydrogen Atoms	-0.053, -0.066
C3	Carbon Atom	-0.305
	Nitrogen Atom	+1.302
	Oxygen Atoms	-0.551, -0.571
N4	Nitrogen Atom	+0.021
C5	Carbon Atom	-0.045
	Nitrogen Atom	+0.129
	Hydrogen Atoms	-0.066, -0.111
C6	Carbon Atom	-0.419
	Nitrogen Atom	+1.320
	Oxygen Atoms	-1.578, -0.615
C7	Carbon Atom	-0.345
	Nitrogen Atom	+1.331
	Oxygen Atoms	-0.569, -0.579
C8	Carbon Atom	-0.022
	Nitrogen Atom	+0.051
	Hydrogen Atoms	-0.069, -0.114
C8a	Carbon Atom	-0.285
C4a	Carbon Atom	-0.029

Table 22: Calculated Atomic Charge Values for 2,5,8-Triamino-3,6,7-trinitroquinoxaline-1-oxide (151)

7.3 Molecular Modelling of Quinazolines

Molecular modelling calculations were also carried out on the target molecule; 2,5,7-triamino-4,6,8-trinitroquinazoline-1-oxide (**138**) using MOLPAK and Cheetah. **Figure 32** shows molecular modelling information, structure and data for **138**.



138

Both the detonation velocity (8.0 $km.s^{-1}$) and density (1.812 $g.cm^{-3}$) of **138** were calculated to be higher than those of both compound **151** and TATB. Since compounds **151** and **138** have the same empirical formulae ($C_8H_6N_8O_7$) then the molecular packing in compound **138** must be tighter than that of **151**, giving rise to a higher density and hence a higher detonation velocity.

Table 23 shows the calculated atomic charge values from MOPAC (PM3) given in **Figure 32** [Molecular modelling diagram and information for 2,5,7-triamino-4,6,8-trinitroquinazoline-1-oxide (**138**)].

Ring Position	Atom	Charge (au)
N1	Nitrogen Atom	+0.930
	Oxide Atom	-0.581
C2	Carbon Atom	-0.389
	Nitrogen Atom	+0.163
	Hydrogen Atoms	-0.047, -0.058
N3	Nitrogen Atom	+0.062
C4	Carbon Atom	-0.342
	Nitrogen Atom	+1.297
	Oxygen Atoms	-0.564, -0.570
C5	Carbon Atom	-0.151
	Nitrogen Atom	+0.188
	Hydrogen Atoms	-0.055, -0.089
C6	Carbon Atom	-0.619
	Nitrogen Atom	+1.347
	Oxygen Atoms	-0.592, -0.626
C7	Carbon Atom	-0.167
	Nitrogen Atom	+0.117
	Hydrogen Atoms	-0.087, -0.116
C8	Carbon Atom	-0.534
	Nitrogen Atom	+1.335
	Oxygen Atoms	-0.532, -0.623
C8a	Carbon Atom	-0.092
C4a	Carbon Atom	-0.145

Table 23: Calculated Atomic Charge Values for 2,5,7-Triamino-4,6,8-trinitroquinazoline-1-oxide (138)

7.4 Molecular Modelling of Pyrazines

Detonics studies were carried out on ANPZ-i (**10**) and PZDO (**11**) using the following molecular modelling calculations; MOPAC PM3, MOLPAK and Cheetah codes. **Table 24** shows a comparison of calculated performance data for ANPZ-i and PZDO against empirical data for TATB (**8**) and RDX (**5**).

Compound	*Calculated Performance Data (From Molecular Modelling)*
ANPZ-i	V_D = 8.63 km.s^{-1}, P_{C-J} = 34.9 GPa (at density = 1.88 g.cm^{-3})
PZDO	V_D = 9.04 km.s^{-1}, P_{C-J} = 40.4 GPa (at density = 1.92 g.cm^{-3})

	Empirical Performance Data
TATB	V_D = 7.62 km.s^{-1}, P_{C-J} = 25.9 GPa (at density = 1.85 g.cm^{-3})
RDX	V_D = 8.64 km.s^{-1}, P_{C-J} = 33.8 GPa (at density = 1.77 g.cm^{-3})

Table 24: Comparision of Detonation Properties for ANPZ-i, PZDO, TATB and RDX

The calculated detonation velocity of ANPZ-i (8.63 km.s^{-1}) is approximately equal to the empirical value of RDX (8.64 km.s^{-1}). The calculated value for PZDO (9.04 km. s^{-1}) is in excess of the empirical value of RDX. It should be noted that the empirical detonation velocities for both TATB and RDX are within 1-2 % of their respective calculated values.

The calculated densities of both ANPZ-i and PZDO are both quite high; 1.88 and 1.92 g.cm^{-3} respectively and it is this property combined with the high nitrogen and oxygen content of the molecules which contribute to the high performance. Both molecules contain significant amounts of nitrogen; ANPZ-i and PZDO have the following empirical formulae $C_4H_4N_6O_4$ and $C_4H_4N_6O_6$ respectively. However, PZDO has even more oxygen than ANPZ-i and therefore its calculated detonation velocity is even higher. **Figure 33** shows the energy minimised structure for PZDO.

Table 25 shows the calculated atomic charge values from MOPAC (PM3) given in **Figure 33** [Molecular modelling diagram and information for2,5-diamino-3,6-dinitropyrazine-1,4-dioxide (PZDO) (**11**)].

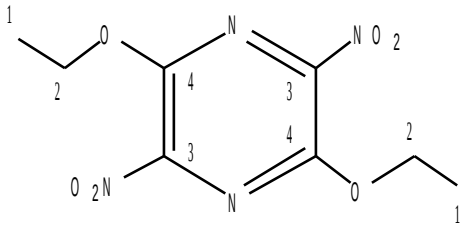
Ring Position	Atom	Charge (au)
N1	Nitrogen Atom	+1.117
	Oxide Atom	-0.561
C2	Carbon Atom	-0.483
	Nitrogen Atom	+0.082
	Hydrogen Atoms	-0.050, -0.051
C3	Carbon Atom	-0.517

	Nitrogen Atom	+1.377
	Oxygen Atoms	-0.561, -0.561
N4	Nitrogen Atom	+0.927
	Oxide Atom	-0.637
C5	Carbon Atom	-0.143
	Nitrogen Atom	+0.249
	Hydrogen Atoms	-0.099, -0.137
C6	Carbon Atom	-0.822
	Nitrogen Atom	+1.365
	Oxygen Atoms	-0.515, -0.653

Table 25: Calculated Atomic Charge Values for 2,5-Diamino-3,6-dinitropyrazine-1,4-dioxide (PZDO) (11)

By analysis of the molecular structure of both ANPZ-i (**10**) and PZDO (**11**) they can both be expected to have good insensitivity values (a drop hammer test value of 150-200 cm could be expected), whereas both RDX (**5**) and HMX (**6**) have very low insensitivities (i.e. they are relatively sensitive). The drop hammer test value for RDX is approximately 80 cm, whereas it can be in the range from 40 to 60 cm for HMX depending on the polymorphic structure of the crystal. Therefore, both ANPZ-i and PZDO are expected to be high energy, high density explosives with high insensitivities and hence low vulnerability to external stimuli.

Molecular modelling calculations were also carried out on compound 2,5-diethoxy-3,6-dinitropyrazine (**150**, R=Et). **Figure 34** shows the Gaussian optimised structure and predicted ^{13}C NMR shifts for compound (**150**, R=Et).



150, R=Et

Table 26 shows a comparison of the calculated ^{13}C NMR shifts for (**150**, R=Et) against the observed values.

Carbon Atom	Calculated ^{13}C NMR Shift	Observed ^{13}C NMR Shift
1	13.46	14.65
2	56.69	66.10
3	139.11	139.61
4	137.30	144.41

Table 26: Comparison of ^{13}C NMR Shift Values

The calculated NMR shift values are significantly different from the observed values and clearly in order for this technique to be useful in predicting nitrogen heterocyclic compound shift values then the difference must be smaller.

Assignment of ^{13}C NMR shift values can be complicated in molecules such as (**150**, R=Et) where there are a number of different electronic effects present, e.g. the influence of the nitro group, ethoxy group and the nitrogen heteroatoms. All these functionalities are in close proximity to each other in the symmetrical molecule and therefore such difficulties are compounded.

Molecular modelling was carried out on ANPZ-i (**10**), PZDO (**11**), ANPZ (**95**), PZO (**9**) and the hypothetical dioxide of PZO. Subsequent to modelling of these compounds using MOPAC PM3 and MM codes a comparison of their respective steric energies was performed. **Figure 35** shows a comparison of steric energies for ANPZ-i, PZDO, ANPZ, PZO and the hypothetical dioxide of ANPZ (**152**).

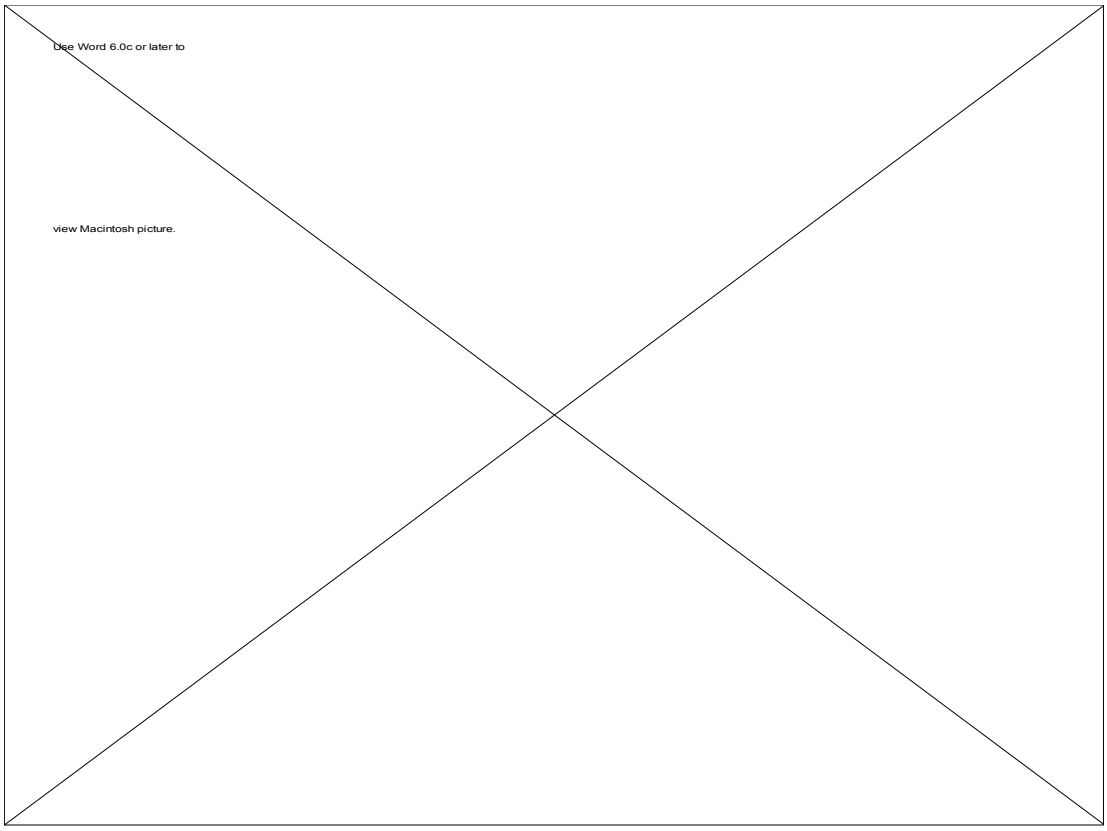


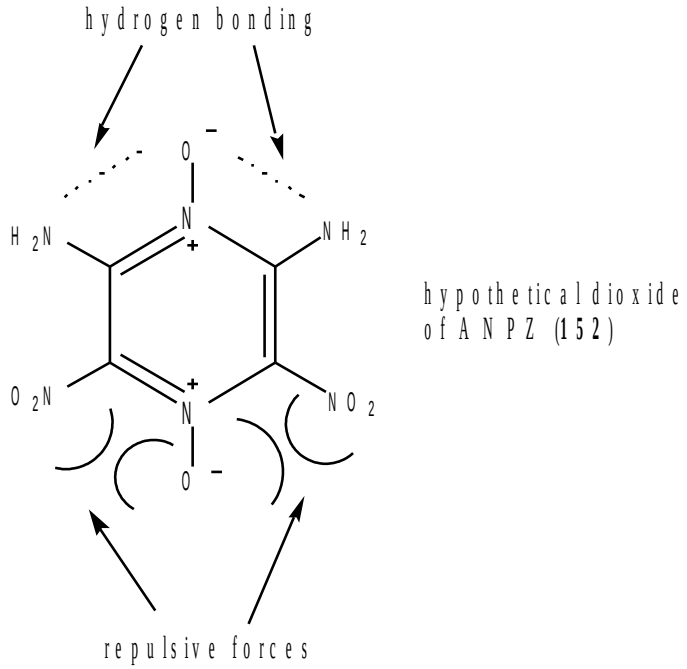
Figure 35

By comparison of the steric energies of ANPZ-i (**10**) and its dioxide derivative PZDO (**11**) a dramatic increase can clearly be seen upon the addition of the two *N*-oxides to the heterocyclic ring. Upon analysis of the steric energy terms for PZDO the charge/charge contributor is by far the largest. This can be expected since it was envisaged that there would be strong repulsion between the negatively charged oxide atoms in PZDO with the adjacent nitro oxygen atoms which are also electronegative.

In chemical terms the dramatic increase in steric energy of ANPZ-i to PZDO could be one of the major factors why ANPZ-i could not be oxidised and hence this steric energy was acting as an energy barrier which could not be overcome. **Figure 36** shows the energy minimised structures (from MOPAC) for ANPZ-i (top) and PZDO (bottom).

By comparison of the steric energies of ANPZ (**95**) and PZO (**9**) it can be seen that upon mono-*N*-oxidation of ANPZ to PZO the increase in steric energy is not too dramatic. This observation is consistent with experimental data since ANPZ is easily oxidised to the mono-*N*-oxide.

The steric energy of the hypothetical dioxide derivative of ANPZ (**152**) was also determined and not surprisingly the value was very high. This is expected since there would be very strong repulsive forces between the *N*-oxide on position number 4 of the heterocyclic ring and the two flanking nitro groups (**Scheme 71**).



Scheme 71: Proposed Hydrogen Bonding and Repulsive Forces in the Hypothetical Dioxide of ANPZ (152)

8. Conclusions

The novel candidate high energy insensitive explosive, 2,5-diamino-3,6-dinitropyrazine (ANPZ-i) (**10**), has been prepared. This new explosive was synthesised via the dinitration of 2,5-diethoxypyrazine (**149**, R=Et) using nitronium tetrafluoroborate ($NO_2^+BF_4^-$) in sulfolane, with an optimised yield of *ca.* 35-40%. In order to achieve this reaction a large number of nitrations, using different nitrating agents, were carried out. Subsequent to this nitration reaction the product, 2,5-diethoxy-3,6-dinitropyrazine (**150**, R=Et), was aminated using methanolic ammonia under high pressure autoclave conditions.

In the preparation of ANPZ-i, it was found to be crucial that the precursor compound, 2,5-diethoxy-3,6-dihydropyrazine (**148**, R=Et), is prepared *in situ* with freshly made triethyloxonium tetrafluoroborate (Meerwein's salt) ($Et_3O^+BF_4^-$). The preparation of the dioxide derivative of ANPZ-i, 2,5-diamino-3,6-dinitropyrazine-1,4-dioxide (PZDO) (**11**), was attempted a number of times without success.

The existing explosives 2,6-diamino-3,5-dinitropyrazine (ANPZ) (**95**) and 2,6-diamino-3,5-dinitropyrazine (PZO) (**9**) have been prepared in good overall yield. Initially, the synthesis of these compounds on the small scale (*ca.* 1 g scale) was repeated from the literature.

The reactions were then scaled up and as a result parts of the experimental procedures were modified. The synthesis of both ANPZ (**95**) and PZO (**9**) has been scaled up to *ca.* 20 g scale. As part of this scale-up the dinitration of 2-chloro-6-methoxypyrazine (**101**) giving 2-chloro-3,5-dinitro-6-methoxypyrazine (**102**) was found to be a crucial reaction. Careful control of the reaction temperature was required so as to avoid a large exotherm which could result in the reaction becoming out of control.

A significant number of nitrations have been carried out on a range of both quinoxalines and quinazolines. Nitronium tetrafluoroborate ($NO_2^+BF_4^-$) in either nitromethane or

sulfolane as solvent has been widely used as the nitrating agent of choice for a number of benzodiazines, in particular for the nitration of chloroquinoxalines, a reaction which had not previously been achieved.

The mononitrations of 2,3-dichloroquinoxaline (**111**) and 2,3,6,7-tetrachloroquinoxaline (**122**) were achieved using nitronium tetrafluoroborate in an organic solvent. The mononitration of 2,3,6-trichloroquinoxaline (**119**) was achieved with 90% aqueous nitric acid. Previous routes to chloronitroquinoxalines often involved the nitration of hydroxy functionalised compounds followed by chlorination which could often be a difficult reaction that required aggressive reagents.

It was found that hydroxybenzodiazines could usually be nitrated by mixed acid or nitric acid alone whereas these reagents often gave rise to decomposition products when reacted with chlorobenzodiazines. Consequently, the mononitrations of 2-hydroxy-3-methylquinoxaline (**124**), 2-hydroxyquinoxaline (**125**), 2,3-dihydroxyquinoxaline (**45**) and 4-hydroxyquinazoline (**135**) were all carried out.

The *N*-oxidation of 2,3-dichloroquinoxaline (**111**) and 2,3,6-trichloroquinoxaline (**119**) was carried out giving rise to the respective mono-*N*-oxide compounds. The nitration of these *N*-oxide species was then attempted with both nitronium tetrafluoroborate and mixed acid systems without success. These experiments demonstrated that the presence of the *N*-oxide group on the heterocyclic ring did not activate the system sufficiently towards electrophilic attack.

Initial quinazoline studies focused on the nitration of 2,4-dichloroquinazoline (**58**). This reaction was attempted a number of times without success. Therefore, a different strategy was used for obtaining nitroquinazoline compounds. 2,4-Diamino-6,8-dinitroquinazoline (**61**) was prepared via an existing patent method in good yield.

A number of functionalisations of 2,4-diamino-6,8-dinitroquinazoline (**61**) were achieved, in particular; *N*-oxidation [producing 2,4-diamino-6,8-dinitroquinazoline-1,4-

dioxide (**141**)], amination [producing 2,4,7-triamino-6,8-dinitroquinazoline (**142**)] and hydrogenation [producing 2,4,6,8-tetra-aminoquinazoline (**143**)]. The functionalisation of 2,4,6,8-tetra-aminoquinazoline was attempted a number of times without success.

The chemistry of 2,4-diamino-6,8-dinitroquinazoline (**61**) was studied extensively. However, in general this compound and its derivatives were found to be difficult compounds to work with. They usually had very low solubilities in most common organic solvents (except DMSO) and were also generally found to be either susceptible to decomposition or resistant to a range of different chemical reactions.

Molecular modelling studies have been carried out on a range of relevant compounds. The steric energies of a number of pyrazines have been calculated and consequently, an analysis was carried out on the relative ease of oxidising the nitrogen heteroatoms of both ANPZ (**95**) and ANPZ-i (**10**).

The detonation properties were calculated for a range of molecules including 2,5-diamino-3,6-dinitropyrazine-1,4-dioxide (PZDO) (**11**), 2,5,8-triamino-3,6,7-trinitroquinoxaline-1-oxide (**151**) and 2,5,7-triamino-4,6,8-trinitroquinazoline-1-oxide (**138**). These three target molecules were all found to have good predicted detonation properties, comparing very well to the known explosives RDX (**5**) and TATB (**8**). The detonation velocity of the new energetic compound; 2,5-diamino-3,6-dinitropyrazine (ANPZ-i) (**10**) has been calculated by molecular modelling and it was found to be a similar value to that of the experimental value for RDX.

The detonation velocities of RDX (**5**), HMX (**6**), NG (**4**), TATB (**8**), PZO (**9**), ANPZ-i (**10**) and PZDO (**11**) were calculated using the Rothstein and Peterson linear equation which allows for a quick and relatively accurate prediction of the performance of energetic materials.

Furthermore the use of molecular modelling to predict ^{13}C NMR spectroscopy shift values for a pyrazine compound has been evaluated. It was found that this method may

require further modification in order to be used as a robust structural characterisation tool for this class of nitrogen heterocyclic compounds.

Extensive analysis of the ^{13}C NMR spectroscopy shift values for approximately twenty nitrogen heterocyclic compounds was carried out. Comparison of the shift values allowed for consistency in the interpretations obtained.

Literature studies were carried out on explosives and detonics chemistry as well as general nitration chemistry. The properties and chemistry of high energy insensitive molecules have been evaluated in great detail. Furthermore, literature studies were carried out on the synthesis, nitration, amination and oxidation reactions of quinoxaline, quinazoline and pyrazine compounds.

On-line literature searches have shown that the following compounds prepared in this project are new: 2,3,6-trichloro-5-nitroquinoxaline (**120**), 2,3-dimethoxy-6,7-dinitroquinoxaline (**128**), 2,3,6-trichloroquinoxaline-1-oxide (**133**), 2,4-diamino-6,8-dinitroquinazoline-1,3-dioxide (**141**), 2,4,7-triamino-6,8-dinitroquinazoline (**142**) and 2,5-diamino-3,6-dinitropyrazine (ANPZ-i) (**10**). Furthermore, new synthetic routes have been used in the preparation of the following compounds: 2,3-dichloro-5-nitroquinoxaline (**118**), 2,3,6,7-tetrachloro-5-nitroquinoxaline (**123**), 2-hydroxy-6-nitroquinoxaline (**127**), 2-hydroxy-3-methyl-6-nitroquinoxaline (**126**) and 2,5-diethoxy-3,6-dinitropyrazine (**150**, R=Et).

In summary, a much greater understanding has been gained into the chemistry of nitro functionalised nitrogen heterocyclic compounds, in particular pyrazines, quinoxalines and quinazolines. A significant amount of synthetic work has been carried out giving rise to new routes to a number of nitrobenzodiazines as well as producing a novel candidate high energy explosive. Additionally, a significant amount of molecular modelling has been carried out on these heterocyclic systems as well as interpretation of a number of ^{13}C NMR spectroscopy shift values.

9. Future Work

There remains a number of extremely reactive oxidising agents based on molecular fluorine (F_2) and HOF and it is envisaged that the use of these systems may be successful in achieving the di-*N*-oxidation of 2,5-diamino-3,6-dinitropyrazine (ANPZ-i) (**10**) producing 2,5-diamino-3,6-dinitropyrazine-1,4-dioxide (PZDO) (**11**). Also, it is suggested that it may be worthwhile investigating alternative routes to the ANPZ-i precursor molecule, 2,5-diethoxy-3,6-dinitropyrazine, since the nitration of 2,5-diethoxypyrazine (**149**, R=Et) could not be increased above approximately 35-40% yield.

Nitronium tetrafluoroborate ($NO_2^+BF_4^-$) in either sulfolane or nitromethane has been shown to be a very versatile nitrating agent for functionalised nitrobenzodiazines, especially for the production of hitherto inaccessible nitro compounds. It is recommended that this reagent is used on a wider selection of nitrogen heterocyclic componds, in particular, other chloro-functionalised molecules which have been shown to be difficult to nitrate.

No further work is suggested on the 2,4-diamino-6,8-dinitroquinazoline (**61**) series since the chemistry associated with these molecules was found to be difficult. Furthermore, achieving a very high level of functionalisation (a level required in order to produce a molecule with sufficient energy) of 2,4-diamino-6,8-dinitroquinazoline (**61**) was found to be extremely difficult.

10. Experimental

10.1 Materials and Characterisation

The following chemicals were used during the course of this project:

Acetone, Romil Chemical Co. Ltd, used as supplied.
Acetonitrile, Romil Chemical Co. Ltd, ued as supplied.
Ammonia (gaseous), Aldrich Chemical Co. Ltd, used as supplied.
30% Aqueous ammonia solution, Aldrich Chemical Co. Ltd, used as supplied.
30% Aqueous hydrogen peroxide solution, Aldrich Chemical Co. Ltd, used as supplied.
60% Aqueous hydrogen peroxide solution, BDH Chemical Co. Ltd, used as supplied.
α,α'-azobis(isobutyronitrile) (AIBN), Aldrich Chemical Co. Ltd, used as supplied.
Benzoylene urea, Aldrich Chemical Co. Ltd, used as supplied.
Boron trifluoride diethyl etherate, Aldrich Chemical Co. Ltd, distilled over calcium hydride and kept under nitrogen.
Carbon tetrachloride, Aldrich Chemical Co. Ltd, used as supplied.
Deutero acetone (d_6-acetone), Aldrich Chemical Co. Ltd, used as supplied.
Deutero chloroform ($CDCl_3$), Aldrich Chemical Co. Ltd, used as supplied.
Deutero dimethylsulfoxide (d_6-DMSO), Aldrich Chemical Co. Ltd, used as supplied.
Dichloromethane (DCM), Romil Chemical Co. Ltd, used as supplied.
2,6-Dichloropyrazine, Aldrich Chemical Co. Ltd and Lancaster Chemical Co. Ltd, used as supplied.
2,3-Dichloroquinoxaline, Aldrich Chemical Co. Ltd, used as supplied.
Diethyl ether, Aldrich Chemical Co. Ltd and Rommil Chemical Co. Ltd, used as supplied or distilled over sodium and kept under argon).
2,3-Dihydroxyquinoxaline, Aldrich Chemical Co. Ltd, used as supplied.
Dimethylformamide (DMF), Aldrich Chemical Co. Ltd, used as supplied.
1,1-Dimethylhydrazine, Aldrich Chemical Co. Ltd, used as supplied.
Dimethylsulfoxide (DMSO), Aldrich Chemical Co. Ltd, used as supplied or distilled over anhydrous magnesium sulfate and kept under argon.
Epichlorohydrin, Aldrich Chemical Co. Ltd, distilled over magnesium sulfate and kept under nitrogen.
Ethanol, Aldrich Chemical Co. Ltd, used as supplied.
Ethyl acetate, Romil Chemical Co. Ltd, used as supplied.
Guanidine hydrochloride, Aldrich Chemical Co. Ltd, used as supplied.
Hydrogen (gaseous), Aldrich Chemical Co. Ltd, used as supplied.

4-Hydroxyquinazoline, Aldrich Chemical Co. Ltd, used as supplied.
2-Hydroxyquinoxaline, Aldrich Chemical Co. Ltd, used as supplied.
Magnesium sulfate (anhydrous), Aldrich Chemical Co. Ltd, used as supplied.
Meta-chloroperbenzoic acid (MCPBA), Aldrich Chemical Co. Ltd, used as supplied.
Methanol, Romil Chemical Co. Ltd, used as supplied or distilled over calcium hydride and kept under nitrogen.
2-Methoxybenzonitrile, Aldrich Chemical Co. Ltd, used as supplied.
2-Methyl-3-hydroxyquinoxaline, Aldrich Chemical Co. Ltd, used as supplied.
Methyl iodide, Aldrich Chemical Co. Ltd, used as supplied.
N-Chlorosuccinimide (NCS), Aldrich Chemical Co. Ltd, used as supplied.
Nitric acid (99%), Aldrich Chemical Co. Ltd, used as supplied.
Nitric acid (100%), produced by the reaction between sulfuric acid and potassium nitrate followed by distillation and then storage at -60°C under nitrogen.
Nitronium tetrafluoroborate, Aldrich Chemical Co. Ltd, used as supplied.
Nitronium tetrafluoroborate in sulfolane (0.1M solution), Aldrich Chemical Co. Ltd, used as supplied.
N,*N*-Dimethylaniline (DMA), Aldrich Chemical Co. Ltd, used as supplied.
20% Oleum (20% (w./v.) sulfur trioxide dissolved in sulfuric acid), Aldrich Chemical Co. Ltd, used as supplied.
Oxone™ (mixture containing $KHSO_5$), Aldrich Chemical Co. Ltd, used as supplied.
3% Palladium on carbon catalyst, Aldrich Chemical Co. Ltd, used as supplied.
Phosphorus oxychloride, Aldrich Chemical Co. Ltd, freshly distilled and kept under nitrogen.
Potassium bromide, Aldrich Chemical Co. Ltd, used as supplied.
Potassium nitrate, Aldrich Chemical Co. Ltd, used as supplied.
Sodium (chunks), Aldrich Chemical Co. Ltd, kept under oil, used as supplied.
Sodium amide (sodamide), Aldrich Chemical Co. Ltd, used as supplied.
Sodium hydride, Aldrich Chemical Co. Ltd, used as supplied.
Sodium hydrogen carbonate, Aldrich Chemical Co. Ltd, used as supplied.
Sodium hydroxide (solid), Aldrich Chemical Co. Ltd, used as supplied.
Sulfuric acid (99%), Aldrich Chemical Co. Ltd, used as supplied.
Sulfolane, Aldrich Chemical Co. Ltd, used as supplied.
2,3,6,7-Tetrachloroquinoxaline, Aldrich Chemical Co. Ltd, used as supplied.
Tetrahydrofuran (THF), Romil Chemical Co. Ltd, distilled over sodium and kept under argon.
Trimethyloxonium tetrafluoroborate, Aldrich Chemical Co. Ltd, used as supplied.

2,3,6-Trichloroquinoxaline, Maybridge Chemical Co. Ltd, used as supplied.
Trifluoroacetic acid (TFA), Aldrich Chemical Co. Ltd, used as supplied.

10.1.1 NMR Spectroscopy

NMR (nuclear magnetic resonance) spectra were recorded on either a Bruker MSL-300 FT spectrometer (300 MHz) or a Varian EM 360A spectrometer (60 MHz) at ambient temperature. All samples were recorded as solutions in deuterated solvents (concentrations of 1-2% and approximately 10% for the 300 and 60 MHz machines respectively) with TMS as the internal reference for ^{1}H and ^{13}C NMR spectroscopy.

10.1.2 Mass Spectrometry (MS)

The analysis was carried out using a VG 7070EQ mass spectrometer. Spectra were acquired in either CI (chemical ionization) or +EI (electron impact) mode between masses 10 and 400 at 1 decade $sec.^{-1}$ while the probe was heated at 5°C s^{-1} from ambient temperature to 650°C. High resolution mass spectrometry (HRMS) was carried out in FAB (fast atom bombardment) mode on a VG Analytical ZAB-SE mass spectrometer. Accurate mass measurements were measured by comparison with those of either caesium iodide or glycerol standards.

10.1.3 Infra-Red (IR) Spectroscopy

Infra-Red (IR) spectral measurements were carried out using a Nicolet 710 FT-IR spectrometer equipped with MCT(A) detector. Liquids were characterised as films between KBr plates and solids as KBr discs.

10.1.4 HPLC Analysis

HPLC (high pressure liquid chromatography) analyses were performed on an ATI Unicam Diamond 600 system using 22 cm x 5 mm i.d. columns with Lichrosorb RP18 (7) packings (Merck), fitted with a UV detector system; the eluent was acetonitrile-water 50:50 (v./v.) at flow rate 1.0 $ml.min^{-1}$ and monitoring wavelength 254 nm.

10.1.5 Melting Point Determination

Melting points were usually determined using a Köfler Hotbench, model Leica VM HB. Before melting points were determined the instrument was calibrated using a test substance with a melting point not more than 50°C different from that of the sample. In the case of high melting point solids (M.Pt. > 280°C) the melting point was sometimes

measured on a Electrothermal Digital Melting Point Apparatus (model no. 1A 8102, F250 mA), 450°C max. temp. (20 W power output).

10.1.6 CHN Analysis

The CHN elemental analyser used was a Perkin-Elmer CHN-2400 instrument. For each sample, a total of four analyses were carried out and the average values were calculated. During analysis the combustion time, mix time (*ca.* 120 s) and temperature (*ca.* 975°C) were optimised in order to ensure complete combustion and reproducible results. For instrument calibrations the reference material was acetanilide.

10.1.7 Autoclave Apparatus

Autoclave reactions (aminations) were carried out in a Scientific & Medical (Parr) autoclave fitted with a 500 ml bomb (reaction vessel). The system was pressurised with ammonia and then isolated whereupon it was heated to the desired temperature and corresponding pressure.

10.1.8 Hydrogenator Apparatus

Hydrogenations were carried out in a Parr shaker-type hydrogenator fitted with a 500 ml bottle and pressurised under hydrogen (H_2).

10.2 Experimental Details

10.2.1 Procedure for Distillation of Nitric Acid

The distillation apparatus was oven-dried overnight and assembled in a stream of nitrogen. The distillation flask was charged with sulfuric acid (200.0 g, 2.02 mol) and potassium nitrate (103.1 g, 1.02 mol) and this mixture was then stirred for 0.5 hour. A mild vacuum was then applied to the system with a slow stream of nitrogen constantly purging the apparatus. The temperature of the system was gradually increased until colourless nitric acid started to distil over. Initially 20-30 g of nitric acid was obtained with a distillation head temperature of 85-90°C and a pot temperature of approximately 110°C. A further 20-30 g of pure nitric acid was obtained by dramatically increasing the rate of nitrogen purge which drove the second portion over very quickly. The nitric acid distillate was collected in a nitrogen purged round bottomed flask which was cooled to -78°C. The nitric acid solidified upon collection and could then be kept as a colourless solid at a temperature of -60°C or below indefinitely.

10.2.2 General Procedure for Mixed Acid Nitrations

All nitrations were first carried out on small scale (*ca.* 0.5-1.0g of substrate). Reactions were usually monitored by the removal of aliquots which were worked-up and analysed using HPLC.

With cooling in an ice bath the nitric acid was added slowly to the sulfuric acid in a round bottom flask, the temperature being kept below ~20°C. To the stirred mixed acid solution the crystalline substrate was added gradually (the temperature was sometimes controlled during the addition, otherwise it was allowed to rise). After the addition was complete the reaction mixture was stirred with or without heating for the required amount of time. The reaction mixture was then poured into a beaker of crushed ice with vigorous stirring. The resultant precipitate was filtered under suction to give the nitrated product as the filtration residue.

10.2.3 General Procedure for Nitronium Tetrafluoroborate ($NO_2^+BF_4^-$) Nitrations

A round bottomed flask was set up which was fitted with a nitrogen bleed, magnetic stirring bar and cooled by a dry ice/acetone bath. To this vessel was first added nitronium tetrafluoroborate ($NO_2^+BF_4^-$) in either dry sulfolane or nitromethane followed

by the substrate. The resulting mixture was stirred for the desired length of time at a given temperature whereupon it was added to crushed ice.

The resulting precipitate was filtered and dried to yield the nitrated nitrogen heterocyclic compound. If no such precipitate developed then the reaction would most likely have given rise to water soluble decomposition products. Occasionally, depending on solubilities, organic material could be extracted from the aqueous layer using a suitable solvent such as ethyl acetate.

10.2.4 General Procedure for Dinitrogen Pentoxide (N_2O_5) Nitrations

A solution of the substrate in dry dichloromethane (DCM) was added dropwise, so that the temperature was kept within the $0 < T < +5°C$ range, to a stirring solution of dinitrogen pentoxide (N_2O_5) in dry dichloromethane under an atmosphere of nitrogen. The reaction was kept cool by an acetone/dry ice cooling bath.

The reaction mixture was stirred for the desired length of time at a given temperature whereupon it was quenched with saturated aqueous sodium hydrogen carbonate ($NaHCO_3$) solution. The organic phase was separated and washed with brine and then the combined organic layers dried over anhydrous magnesium sulfate ($MgSO_4$), filtered and concentrated *in vacuo* to yield the nitrated nitrogen heterocyclic compound. If no organic compound was obtained from the dichloromethane layer and, when the aqueous phase was further washed with ethyl acetate, still no organic compound was obtained it was concluded that the reaction had produced water soluble decomposition products.

10.2.5 General Procedure for Attempted Nucleophilic Aminations using Ammonia at Atmospheric Pressure

Gaseous ammonia (NH_3) was bubbled through a stirred solution of the substrate (chlorobenzodiazine) in either acetonitrile or methanol for 5-10 minutes or until the solution was saturated. The resultant solution was then stirred for the desired length of time (usually overnight). The solvent and ammonia were removed *in vacuo* to yield in all cases unreacted starting material.

10.2.6 Attempted Mixed Acid Nitration (No. 1) of 2,3-Dichloroquinoxaline (111)

With cooling in an ice bath nitric acid (0.95 g, 15 mmol) was added slowly to sulfuric acid (10 ml) in a round bottom flask, the temperature being kept below ~20°C. To the stirred mixed acid solution 2,3-dichloroquinoxaline (1.0 g, 5.0 mmol) was added gradually, during the addition the temperature was allowed to rise to 60-80°C. After the addition was complete the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was then poured into a beaker of crushed ice with vigorous stirring. The resultant precipitate was filtered under suction to give the unwanted product as the filtration residue.

M.Pt. = 286°C.

δ^1H (300 MHz, d_6-DMSO): 8.00 (d, Ar-H, J = 2.50 Hz), 8.30 (d, Ar-H, J = 2.50 Hz).

m/z: 260.

10.2.7 Attempted Mixed Acid Nitration (No. 2) of 2,3-Dichloroquinoxaline (111)

With cooling in an ice bath nitric acid (0.95 g, 15 mmol) was added slowly to a 30% oleum solution (5 ml) in a round bottom flask, the temperature being kept below ~5°C. To the stirred mixed acid solution 2,3-dichloroquinoxaline (1.0 g, 5.0 mmol) was added gradually, during the addition the temperature was allowed to rise to *ca*. 40°C. After the addition was complete the reaction mixture was stirred at 80°C for 18 hours. The reaction mixture was then poured into a beaker of crushed ice with vigorous stirring. The resultant precipitate was filtered under suction to give the unwanted product as the filtration residue.

M.Pt. = 220-230°C (decomposition).

m/z: 143, 120.

10.2.8 Attempted Mixed Acid Nitration (No. 3) of 2,3-Dichloroquinoxaline (111)

With cooling in an ice bath nitric acid (0.32 g, 5 mmol) was added slowly to sulfuric acid (10 ml) in a round bottom flask, the temperature being kept below ~20°C. To the stirred mixed acid solution 2,3-dichloroquinoxaline (1.0 g, 5.0 mmol) was added gradually, during the addition the temperature was kept below 10°C. After the addition was complete the reaction mixture was stirred at room temperature for 5 hours. The reaction mixture was then poured into a beaker of crushed ice with vigorous stirring. The resultant precipitate was filtered under suction to give the unwanted product as the filtration residue.

M.Pt. = 210-220°C.

δ^1H (300 MHz, d_6-DMSO): 7.63 (s, Ar-H), 7.66 (s, Ar-H), 7.97 (m, Ar-H), 8.05 (m, Ar-H), 8.46 (d, Ar-H, J = 2.44 Hz), 8.81 (d, Ar-H, J = 2.44 Hz).
m/z: 198 (M^+: **111**).

10.2.9 2,3-Dichloro-5-nitroquinoxaline (118)

An oven-dried round bottom flask was charged with nitromethane (50 ml) and kept dry under a stream of nitrogen. To this was added 2,3-dichloroquinoxaline (2.00 g, 10 mmol) followed by a nitronium tetrafluoroborate (3.00 g, 22 mmol) solution in nitromethane (15 ml). The resulting mixture was stirred at -10°C to 5°C for 2 hours and then at 15°C for a further 2 hours. The mixture was then poured onto crushed ice (65 ml) and the resulting precipitate filtered to give an off-white solid, 2,3-dichloro-5-nitroquinoxaline (2.12 g, 8.7 mmol, 87% yield).
M.Pt. = 127°C.
δ^1H (300 MHz, d_6-acetone): 8.14 (t, 1H, Ar-7H, $J_{6,7} = J_{7,8}$ = 9.0 Hz), 8.37 (d-d, 1H, Ar-8H, $J_{7,8}$ = 9.0 Hz, $J_{6,8}$ = 1.2 Hz), 8.44 (d-d, 1H, Ar-6H, $J_{6,7}$ = 9.0 Hz, $J_{6,8}$ = 1.2 Hz).
δ^{13}C (75 MHz, d_6-DMSO): 125.90 (C-6), 127.82 (C-7), 130.82 (C-8), 131.73 (C-4a), 132.43 (C-8a), 139.91 (C-5), 146.92 (C-2), 147.31 (C-3).
m/z: 261 $(M + 1 + NH_3)^+$ (Note: This value corresponds to compound **118** containing two ^{35}Cl atoms); 244, 246, 248 $(M + 1)^+$.
HRMS: Calculated Mass = 243.9681 for $C_8H_3N_3O_2{}^{35}Cl_2$, Measured Mass = 243.9672 $(M + 1)^+$.
CHN Elemental Analysis - Calculated for $C_8H_3N_3O_2Cl_2$: C, 39.34; H, 1.23; N, 17.21. Found: C, 39.53; H, 0.80; N, 16.13.
Note: 2,3-Dichloro-5-nitroquinoxaline (**118**) was also prepared by nitration with nitronium tetrafluoroborate in sulfolane but in lower yield (*ca.* 60%).

10.2.10 2,3,6-Trichloro-5-nitroquinoxaline (120)

2,3,6-Trichloroquinoxaline (2.00 g, 9 mmol) was added gradually to 90% aqueous nitric acid solution (10 ml, 23 mmol) which was stirred throughout; during the addition the temperature rose to ~65°C but the mixture cooled quickly afterwards. The reaction mixture was then stirred at room temperature for 90 min., and then added to crushed ice (30 ml) with vigorous stirring. The resultant precipitate was allowed to stand overnight, then filtered under suction and dried in a vacuum oven overnight (r.t.) to give 1.8 g (6 mmol) of 2,3,6-trichloro-5-nitroquinoxaline (64 % yield).
M.Pt.: 170°C.

δ^1H (300 MHz, d_6-acetone): 8.20 (d, 1H, Ar-H, $J_{7,8}$= 9.15), 8.35 (d, 1H, Ar-H, $J_{7,8}$= 9.15).

δ^{13}C (75 MHz, d_6-acetone): 126.59 (C-7), 131.83 (C-8), 132.50 (C-8a), 132.50 (C-4a), 138.94 (C-6), 144.27 (C-5), 148.02 (C-3), 148.94 (C-2).

υ_{max}(cm^{-1}): 831 (C-Cl, m), 1366 (NO_2 symm., m), 1562 (NO_2 asymm., s), 1612 (C=N, w), 3073 (ArH, w).

m/z: 277 (M^+ for $C_8H_2N_3O_2{}^{35}Cl_3$), 279, 281, 283 (M^+).

HRMS: Calculated Mass = 277.9291 for $C_8H_2N_3O_2{}^{35}Cl_3$, Measured Mass = 277.9280 $(M + 1)^+$.

CHN Elemental Analysis - Calculated for $C_8H_2N_3O_2Cl_3$: C, 34.47; H, 0.72; N, 15.08. Found: C, 34.31; H, 0.70; N, 14.93.

Note: 2,3,6-Trichloro-5-nitroquinoxaline (**120**) was also prepared by nitration with nitronium tetrafluoroborate ($NO_2^+BF_4^-$) in sulfolane but in lower yield (*ca.* 20%).

10.2.11 Attempted Mixed Acid Nitration of 2,3,6-Trichloro-5-nitroquinoxaline (120)

With cooling in an ice bath nitric acid (0.65 g, 10 mmol) was added slowly to sulfuric acid (15 ml) in a round bottom flask, the temperature being kept below ~20°C. To the stirred mixed acid solution 2,3,6-trichloro-5-nitroquinoxaline (2.20 g, 8.0 mmol) was added gradually, during the addition the temperature was kept below 10°C. After the addition was complete the reaction mixture was stirred at 40°C for 2 hours. The reaction mixture was then poured into a beaker of crushed ice with vigorous stirring. No precipitate developed and it was concluded that the reaction had resulted in the production of a decomposition product which was soluble in the aqueous phase.

10.2.12 2,3,6,7-Tetrachloro-5-nitroquinoxaline (123)

2,3,6,7-Tetrachloroquinoxaline (1.0 g, 3.7 mmol) was added at room temperature to a stirring solution of nitronium tetrafluoroborate in sulfolane (0.1M solution, 50 ml). The resulting mixture was stirred at 45°C overnight whereupon it was poured on to crushed ice (100 ml). A precipitate then formed which was filtered and dried to yield a yellow crystalline solid, 2,3,6,7-tetrachloro-5-nitroquinoxaline (0.45 g, 1.4 mmol, 39% yield).

M.Pt.: > 280°C (decomposition), lit. 118-120°C.[91]

δ^1H (300 MHz, d_6-DMSO): 8.75 (s, 1H, Ar-8H).

δ^{13}C (75 MHz, d_6-DMSO): 126.15 (C-8), 131.10 (C-7), 131.27 (C-6), 134.74 (C-4a), 138.94 (C-8a), 145.13 (C-5), 149.05 (C-3), 149.16 (C-2).

υ_{max}(cm^{-1}): 897 (C-Cl, m), 1375 (NO_2 symm., m), 1560 (NO_2, asymm., m), 3056 (C-H, w).

m/z: 311, 313, 315, 317, 319 (M^+).

HRMS: Calculated Mass = 311.8901 for $C_8HN_3O_2{}^{35}Cl_4$, Measured Mass = 311.8915 $(M + 1)^+$.

CHN Elemental Analysis - Calculated for $C_8HN_3O_2Cl_4$: C, 30.67; H, 0.32; N, 13.42. Found: C, 30.52; H, 0.25; N, 13.33.

10.2.13 2-Hydroxy-3-methyl-6-nitroquinoxaline (126)

2-Methyl-3-hydroxyquinoxaline (0.8 g, 5.0 mmol) was added to a stirring solution of nitronium tetrafluoroborate in sulfolane (0.1M solution, 20 ml). The resulting mixture was stirred at room temperature for 5 hours whereupon it was poured on to crushed ice (100 ml). A precipitate then formed which was filtered and dried to yield a cream coloured solid, 2-hydroxy-3-methyl-6-nitroquinoxaline (0.71 g, 3.5 mmol, 69% yield).

M.Pt.: > 300°C (decomposition), lit. 270°C.[92]

δ^1H (300 MHz, d_6-DMSO): 2.42 (s, 3H, Me), 3.51 (s, 1H, OH), 7.38 (d, 1H, Ar-8H, $J_{7,8}$ = 8.9 Hz), 8.27 (d-d, 1H, Ar-7H, $J_{7,8}$ = 8.9 Hz, $J_{5,7}$ = 2.8 Hz), 8.43 (d, 1H, Ar-5H, $J_{5,7}$ = 2.8 Hz).

δ^{13}C (75 MHz, d_6-DMSO): 20.94 (Me), 116.55 (C-8), 123.66 (C-5), 124.40 (C-7), 130.82 (C-6), 137.61 (C-4a), 142.70 (C-8a), 155.21 (C-3), 162.58 (C-2).

υ_{max}(cm^{-1}): 1341 (NO_2 symm., m), 1534 (NO_2 asymm., m), 1666 (C=O, m), 2979 (OH, bs).

m/z: 205 (M^+).

CHN Elemental Analysis - Calculated for $C_9H_7N_3O_3$: C, 52.69; H, 3.42; N, 20.49. Found: C, 52.27; H, 3.10; N, 20.12.

10.2.14 2-Hydroxy-6-nitroquinoxaline (127)

2-Hydroxyquinoxaline (0.75 g, 5.0 mmol) was added to a stirring solution of nitronium tetrafluoroborate in sulfolane (0.1M solution, 20 ml). The resulting mixture was stirred at room temperature for 5 hours whereupon it was poured on to crushed ice (100 ml). A precipitate then formed which was filtered and dried to yield a cream coloured solid, 2-hydroxy-6-nitroquinoxaline (0.59 g, 3.0 mmol, 61% yield).

M.Pt. = 265-270°C (decomposition), lit. 298-302°C.[93]

δ^1H (300 MHz, d_6-DMSO): 3.51 (bs, 1H, OH), 7.42 (d, 1H, Ar-8H, $J_{7,8}$ = 9.0 Hz), 8.28 (s, 1H, Ar-5H, $J_{5,7}$ = 3.0 Hz), 8.36 (d, 1H, Ar-7H, $J_{7,8}$ = 9.0 Hz, $J_{5,7}$ = 3.0 Hz), 8.50 (s, 1H, Ar-3H).

δ^{13}C (75 MHz, d_6-DMSO): 117.10 (C-8), 124.66 (C-5), 125.68 (C-7), 131.13 (C-6), 137.50 (C-4a), 142.81 (C-8a), 154.52 (C-3), 155.12 (C-2).

υ_{max}(cm^{-1}): 1341 (NO_2 symm., m), 1520 (NO_2 asymm., m), 1619 (C=N, m), 1672 (C=O, m), 3463 (OH, bs).

m/z: 191 (M^+).

CHN Elemental Analysis - Calculated for $C_8H_5N_3O_3$: C, 50.26; H, 2.62; N, 21.99. Found: C, 48.99; H, 2.49; N, 21.33.

10.2.15 2,3-Dihydroxy-6,7-dinitroquinoxaline (129)

2,3-Dihydroxyquinoxaline (4.86 g, 30 mmol) was added rapidly to a stirring mixture of concentrated sulfuric acid (32 ml) at 0°C and potassium nitrate (6.00 g, 60 mmol). The resultant mixture was stirred at 0°C for 15 minutes and then at room temperature for 4 hours. After 4 hours, the reaction mixture was poured into ice-water (200 ml) and the resultant precipitate filtered (Buchner apparatus) and dried (suction) overnight to yield a yellow solid, 2,3-dihydroxy-6,7-dinitroquinoxaline (6.01 g, 24 mmol, 80% yield).

M.Pt.: > 280°C, lit. > 280°C.[54]

δ^1H (300 MHz, d_6-DMSO): 4.45 (bs, 2H, OH), 7.72 (s, 2H, Ar-H).

υ_{max}(cm^{-1}): 1335 (NO_2, s, symm.), 1560 (NO_2, s, asymm.), 1719 (C=O, m), 3151 (OH, bs).

10.2.16 2,3-Dimethoxy-6,7-dinitroquinoxaline (128)

Sodium hydride (2.2 equiv., 0.42 g, 18 mmol) was added slowly over 5 minutes to a stirring solution of 2,3-dihydroxy-6,7-dinitroquinoxaline (2.00 g, 8 mmol) in freshly distilled THF (50 ml) and the resulting mixture was then refluxed for 2 hours. After 2 hours, methyl iodide (2.2 equiv., 2.50 g, 18 mmol) was added to the mixture, which was then refluxed for a further 2 hours. Following this the reaction mixture was poured onto crushed ice (30 ml) and the resulting two layers separated. The mixture was extracted with DCM (3 x 35 ml) and the combined organic layers were dried (anhydrous $MgSO_4$), filtered and the solvent was removed *in vacuo* to yield a red crystalline solid, 2,3-dimethoxy-6,7-dinitroquinoxaline (1.49 g, 5.3 mmol, 67% yield).

M.Pt.: > 280°C (decomposition).

δ^1H (300 MHz, DMSO-d_6): 3.44 (s, 6H, OMe), 8.12 (s, 2H, Ar-H).

υ_{max}(cm^{-1}): 1360 NO_2, m, symm.), 1527 (NO_2, m, asymm.).

10.2.17 Attempted Mixed Acid Nitration of 2-Methylquinoxaline (130)

With cooling in an ice bath nitric acid (0.65 g, 10 mmol) was added slowly to sulfuric acid (20 ml) in a round bottom flask, the temperature being kept below ~20°C. To the stirred mixed acid solution 2-methylquinoxaline (1.5 g, 10 mmol) was added gradually, during the addition the temperature was kept below 20°C. During addition of the substrate to the reaction mixture there was a significant exotherm observed (the temperature rose quickly from *ca*. 20°C to *ca*. 40-50°C) and the reaction mixture turned black and had a consistency similar to that of tar. After the addition was complete the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was then poured into a beaker of crushed ice with vigorous stirring. No precipitate developed and it was concluded that the reaction had resulted in the production of a decomposition product which was soluble in the aqueous phase.

10.2.18 Attempted Mixed Acid Nitration of Quinoxaline 2-Carboxylic Acid (131)

With cooling in an ice bath nitric acid (1.2 g, 20 mmol) was added slowly to sulfuric acid (25 ml) in a round bottom flask, the temperature being kept below ~20°C. To the stirred mixed acid solution quinoxaline 2-carboxylic acid (2.0 g, 11.5 mmol) was added gradually, during the addition the temperature was kept below 20°C. After the addition was complete the reaction mixture was stirred at 40°C for 4 hours. The reaction mixture

was then poured into a beaker of crushed ice with vigorous stirring. A precipitate then formed which was filtered and dried to yield a cream coloured solid, unreacted quinoxaline 2-carboxylic acid.

M.Pt.: 208°C (decomposition).

10.2.19 2,3-Dichloroquinoxaline-1-oxide (132)

Aqueous hydrogen peroxide solution 30% (wt./vol.) (4 ml) was added gradually to a stirring volume of trifluoroacetic acid (20 ml) at a temperature of 0°C < T < 5°C. 2,3-Dichloroquinoxaline (0.80 g, 4.0 mmol) was then added to the reaction quickly whereupon the stirring mixture was allowed to warm to room temperature. The resultant reaction mixture was stirred at room temperature for 2 days at which point a white precipitate formed. The precipitate was filtered and dried to give a white powder, 2,3-dichloroquinoxaline-1-oxide, which gave a positive ferric chloride test (0.34 g, 1.6 mmol, 40% yield).

M.Pt. = 136-142°C (decomposition), lit. 138-139°C.[85]

δ^{1}H (300 MHz, d_6-DMSO): 7.89 - 8.40 (m, 4H, Ar-5H, Ar-6H, Ar-7H & Ar-8H).

δ^{13}C (75 MHz, d_6-DMSO): 128.88 (C-6), 129.37 (C-5), 130.67 (C-7), 131.54 (C-8), 132.95 (C-4a), 137.10 (C-8a), 140.51 (C-3), 146.28 (C-2).

m/z: 214, 216, 218 (M^+), note a small amount of the di-*N*-oxide was also detected.

CHN Elemental Analysis - Calculated for $C_8H_4N_2O_1Cl_2$: C, 44.68; H, 1.88; N, 13.03. Found: C, 44.33; H, 1.50; N, 13.01.

10.2.20 2,3,6-Trichloroquinoxaline-1-oxide (133)

Aqueous hydrogen peroxide solution 30% (wt./vol.) (4 ml) was added gradually to a stirring volume of trifluoroacetic acid (20 ml) at a temperature of 0°C < T < 5°C. 2,3,6-Trichloroquinoxaline (0.80 g, 3.4 mmol) was then added to the reaction quickly whereupon the stirred mixture was allowed to warm to room temperature. The resultant reaction mixture was stirred at room temperature for 2 days at which point a white precipitate formed. The precipitate was filtered and dried to give a white powder, 2,3,6-trichloroquinoxaline-1-oxide, which gave a positive ferric chloride test (0.28 g, 1.0 mmol, 29% yield).

M.Pt.: 212-215°C (decomposition).

δ^{1}H (300 MHz, d_6-DMSO): 8.09 - 8.36 (m, 3H, Ar-5H, Ar-6H and Ar-8H).

$\delta^{13}C$ (75 MHz, d_6-DMSO): 129.58 (C-5), 130.94 (C-8), 131.30 (C-4a), 132.12 (C-7), 132.95 (C-8a), 135.92 (C-3), 138.67 (C-2).
m/z: 248, 250, 252, 254 (M^+).
HRMS: Calculated Mass = 248.9389 for $C_8H_3N_2O^{35}Cl_3$, Measured Mass = 248.9399 (M^+).
CHN Elemental Analysis - Calculated for $C_8H_3N_2OCl_3$: C, 38.52; H, 1.21; N, 11.23. Found: C, 40.07; H, 0.90; N, 10.71.

10.2.21 Attempted Nitration of 2,3-Dichloroquinoxaline-1-oxide (132)

2,3-Dichloroquinoxaline-1-oxide (1.0 g, 4.7 mmol) was added at room temperature to a stirring solution of nitronium tetrafluoroborate ($NO_2^+BF_4^-$) in sulfolane (0.1M solution, 50 ml). The resulting mixture was stirred at 40°C overnight whereupon it was poured on to crushed ice (100 ml) but no precipitate developed. The aqueous layer was washed with ethyl acetate, however, no organic material could be isolated. It was concluded that the reaction had resulted in the production of a decomposition product which was soluble in the aqueous phase.

10.2.22 Attempted Nitration of 2,3,6-Trichloroquinoxaline-1-oxide (133)

2,3,6-Trichloroquinoxaline-1-oxide (1.0 g, 4.0 mmol) was added at room temperature to a stirring solution of nitronium tetrafluoroborate ($NO_2^+BF_4^-$) in sulfolane (0.1M solution, 50 ml). The resulting mixture was stirred at 40°C overnight whereupon it was poured on to crushed ice (100 ml). A precipitate then formed which was filtered and dried to yield a white crystalline solid, unreacted 2,3,6-trichloroquinoxaline-1-oxide.
M.Pt.: 212-215°C (decomposition).
m/z: 248, 250, 252, 254 (M^+).

10.2.23 2,4-Dichloroquinazoline (58)

N,*N*-Dimethylaniline (DMA) (10 ml, 79 mmol) and benzoylene urea (5.00 g, 31 mmol) were added to a round bottom flask fitted with nitrogen line, thermometer and reflux condenser with an attached silica gel guard tube. To this mixture, phosphorus oxychloride ($POCl_3$) (20 ml, 216 mmol) was added slowly, the reaction was then refluxed for 4 h (pot temp. of 116°C). During the course of the reaction the mixture changed colour from yellow to green then to black. After refluxing, the hot reaction mixture was poured onto crushed ice (150 ml) with vigorous stirring. A colourless precipitate was

filtered off under suction and dried in a vacuum oven overnight (r.t.) to give 5.50 g (28 mmol) of 2,4-dichloroquinazoline (89% yield).

M.Pt.: 150°C, lit. 115°C.[66]

δ^1H (300 MHz, d_6-DMSO): 7.90 (m, 1H, Ar-H), 8.10 (m, 1H, Ar-H), 8.20 (m, 1H, Ar-H), 8.35 (m, 1H, Ar-H).

δ^{13}C (75 MHz, d_6-DMSO): 123.27 (C-7), 126.88 (C-6), 128.73 (C-5), 130.69 (C-8), 135.64 (C-4a), 137.52 (C-8a), 153.41 (C-4), 155.47 (C-2).

υ_{max}(cm^{-1}): 779 (C-Cl, s), 1613 (C=N, m), 3030 and 3070 (Ar-H, w).

10.2.24 Attempted Mixed Acid Nitration of 2,4-Dichloroquinazoline (58)

With cooling in an ice bath nitric acid (0.95 g, 15 mmol) was added slowly to sulfuric acid (5 ml) in a round bottom flask, the temperature being kept below ~20°C. To the stirred mixed acid solution 2,4-dichloroquinazoline (1.0 g, 5.0 mmol) was added gradually, during the addition the temperature was allowed to rise to 40-50°C. After the addition was complete the reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was then poured into a beaker of crushed ice with vigorous stirring. The resultant precipitate was filtered under suction to give the unwanted product as the filtration residue.

M.Pt. = 256°C (decomposition).

m/z: 120, 152.

10.2.25 4-Hydroxy-7-nitroquinazoline (136)

Nitric acid (0.95 g, 15 mmol) was added slowly to sulfuric acid (5 ml) at a temperature of 0 to 5°C and to this mixture was added 4-hydroxyquinazoline (2.00 g, 14 mmol) slowly over 5 minutes. Cooling of the reaction mixture was by a dry ice/acetone cooling bath and upon each addition of substrate there was a sharp exotherm of 2 to 3°C. After all the substate had been added the reaction was allowed to warm to room temperature and left stirring for 4 hours. The reaction mixture was then poured onto crushed ice (35 ml) and the resulting precipitate was filtered and dried (suction) to give a pale yellow powder; 4-hydroxy-7-nitroquinazoline (1.97 g, 10 mmol, 75% yield).

M.Pt.: 275-280°C (decomposition point).

δ^1H (300 MHz, DMSO-d_6): 7.63 (d, 1H, Ar-5H, $J_{5,6}$ = 9.0 Hz), 8.32 (s, 1H, Ar-2H), 8.52 (d-d, 1H, Ar-6H, $J_{6,8}$ = 2.7 Hz, $J_{5,6}$ = 9.0 Hz), 8.76 (d, 1H, Ar-8H, $J_{5,6}$ = 2.7 Hz).

$\delta^{13}C$ (75 MHz, d_6-DMSO): 122.13 (C-6), 122.92 (C-8), 128.47 (C-4a), 129.30 (C-5), 145.17 (C-7), 149.14 (C-8a), 153.16 (C-4), 160.31 (C-2).

$\upsilon_{max}(cm^{-1})$: 1341 (NO_2 symm., m), 1520 (NO_2 asymm., m), 1616 (C=N, m), 1672 (C=O, m), 3045 (C-H, bs), 3748 (OH, bs).

m/z: 191 (M^+).

CHN Elemental Analysis - Calculated for $C_8H_5N_3O_3$: C, 50.26; H, 2.62; N, 21.99. Found: C, 49.82; H, 2.35; N, 22.04.

Note: 4-Hydroxy-7-nitroquinazoline (**136**) was also prepared in similar yield (*ca.* 70%) by the nitration of 4-hydroxyquinazoline with nitronium tetrafluoroborate ($NO_2^+BF_4^-$) in sulfolane.

10.2.26 Attempted Mixed Acid Nitration of 2-Methyl-4(3*H*)-quinazolinone (137)

With cooling in an ice bath nitric acid (0.95 g, 15 mmol) was added slowly to sulfuric acid (5 ml) in a round bottom flask, the temperature being kept below ~20°C. To the stirred mixed acid solution 2-methyl-4(3*H*)-quinazolinone (1.0 g, 6.3 mmol) was added gradually, during the addition the temperature was allowed to rise to 50°C. After the addition was complete the reaction mixture was stirred at 60°C for 4 hours. The reaction mixture was then poured into a beaker of crushed ice with vigorous stirring however no precipitae formed. The aqueous layer was washed with ethyl acetate a number of times (3 x 50 ml) but no organic product could be isolated. It was therefore concluded that the reaction had resulted in the production of a water soluble decomposition product.

10.2.27 2-Methoxy-3,5-dinitrobenzonitrile (62)

90% Nitric acid (1.5 ml, 35 mmol) was added slowly to concentrated sulfuric acid (3 ml, 59 mmol) in a 50 ml round bottom flask with the temperature kept below 20°C by a dry ice/acetone cooling bath. To the stirring mixed acid mixture, 2-methoxybenzonitrile (2.00 g, 15 mmol) was added very slowly; due to the high exothermicity of the reaction the addition was carried out over 10 minutes and during the addition the reaction temperature was kept below 20°C. Once the addition was complete the reaction mixture was stirred at r.t. for 1 hour, whereupon it was poured onto crushed ice (25 ml) with vigorous stirring. The subsequent precipitate was suction filtered and dried under vacuum overnight to give 2-methoxy-3,5-dinitrobenzonitrile (3.29 g, 15 mmol, 98% yield).

M.Pt.: 72°C, lit. 73°C.[100]

δ^1H (300 MHz, d_6-acetone): 4.37 (s, 3H, OCH_3), 8.97 (d, 1H, Ar-6H, $J_{4,6}$ = 2.70 Hz), 9.00 (d, 1H, Ar-4H, $J_{4,6}$ = 2.70 Hz).
δ^{13}C (75 MHz, d_6-acetone): 109.28 (CN), 114.34 (C-6), 126.06 (C-5), 134.24 (C-3), 143.06 (C-1), 143.92 (OMe), 160.27 (C-2), 160.27 (C-4).
υ_{max}(cm^{-1}): 1100 (OMe, m), 1341 (NO_2 symm, s), 1533 (NO_2 asymm., s), 2236 (CN, s), 3078 (ArH, w).

10.2.28 2,4-Diamino-6,8-dinitroquinazoline (61)

A 500 ml round bottom flask fitted with a nitrogen line and magnetic stirring bar was charged with freshly distilled methanol (125 ml). Over a period of 30 minutes sodium (lumps) (6.00 g, 261 mmol) was added to the stirring methanol. After the addition of sodium was complete, guanidine hydrochloride (1.50 g, 15 mmol) was added and the resulting mixture, from which sodium chloride had precipitated, was stirred for 45 minutes. The reaction mixture was then filtered under nitrogen to remove all the sodium chloride leaving the free guanidine base/methanol solution.

A solution of 2-methoxy-3,5-dinitrobenzonitrile (3.00 g, 13.4 mmol) in dry methanol (50 ml) was added to an oven dried round bottom flask fitted with thermometer, nitrogen line, magnetic stirring bar and reflux condenser. This stirring solution was heated to 50°C and then the guanidine free base/methanol solution (125 ml) was added slowly over 10 min.

Upon addition of the guanidine solution the reaction mixture turned an orange/red colour and as more guanidine solution was added more orange precipitate was formed. The resulting mixture was stirred at 65°C for 3 h 15 min. whereupon the reaction vessel was cooled in ice followed by filtration of the reaction mixture (Buchner filter, vacuum line) to give an orange/brown residue. The residue was washed with cold methanol and then dried overnight under vacuum to yield a brown product, 2,4-diamino-6,8-dinitroquinazoline (2.80 g, 11 mmol, 85% yield).
M.Pt.: 345°C (decomposition), (lit. 340°C).[67]
δ^1H (300 MHz, d_6-DMSO): 3.47 (bs, 4H, 2 x NH_2), 8.52 (d, Ar-H, $J_{5,7}$ = 2.6 Hz), 8.96 (d, 1H, Ar-H, $J_{5,7}$ = 2.6 Hz).
δ^{13}C (75 MHz, d_6-DMSO): 120.44 (C-4a), 123.34 (C-7), 132.86 (C-5), 140.02 (C-6), 153.10 (C-8), 158.73 (C-8a), 162.71 (C-4), 163.31 (C-2).

υ_{max}(cm^{-1}): 1368 (NO_2 symm., m), 1553 (NO_2 asymm., m), 1627 (C=N, m), 3172 (NH_2, bs), 3334 (NH_2, bs).

m/z: 250 (M^+).

CHN Elemental Analysis - Calculated for $C_8H_6N_6O_4$: C, 38.40; H, 2.40; N, 33.60. Found: C, 35.33; H, 2.12; N, 31.80.

10.2.29 Dimethyldioxirane (DMD)[40]

A reaction flask was cooled to 5-10°C and fitted with a nitrogen bleed, to the flask was added water (25 ml), acetone (20 ml) and $NaHCO_3$ (6 g). With vigorous stirring and cooling, a portion of oxone™ (mixture containing $KHSO_5$) was added over 10 minutes to the reaction vessel. Five minutes after the last addition of oxone™ a distillation head was placed on the round bottom flask with the collection vessel kept at -78°C by means of a dry ice/acetone cooling bath. A mild vacuum was then applied to the system and approximately 15 ml of liquid was collected (~0.10 M, *ca*. 5% yield).

10.2.30 Attempted Amine Oxidation of 2,4-Diamino-6,8-dinitroquinazoline (61)

2,4-Diamino-6,8-dinitroquinazoline (1.0 g, 4 mmol) was added to a stirring solution (*ca*. 0.1 M) of dimethyldioxirane (DMD) in acetone (50 ml). The resulting mixture was stirred at room temperature for 24 hours whereupon the brown mixture was filtered to leave unreacted starting material as the filtration residue.

M.Pt.: 345°C (decomposition), (lit. 340°C).[67]

m/z: 250 (M^+).

10.2.31 2,4-Diamino-6,8-dinitroquinazoline-*N, N'*-dioxide (141)

A solution of 60% (wt./vol.) aq. H_2O_2 soln. (0.70 g, 12 mmol) in TFA (20 ml) was added dropwise to a stirring solution of 2,4-diamino-6,8-dinitroquinazoline (1.0 g, 4 mmol) in trifluoroacetic acid (TFA) (35 ml). During the addition the reaction temperature increased from 0°C to 5°C. The reaction mixture was then left stirring at room temperature overnight whereupon it was added to crushed ice. The TFA was neutralised by sodium hydrogen carbonate and the resulting aqueous layer washed and evaporated to dryness. The remaining solid was washed with acetone and the organic layer filtered off and concentrated at

atmospheric pressure to give an orange/brown solid, 2,4-diamino-6,8-dinitroquinazoline-*N,N'*-dioxide (yield = 0.40 g, 1.4 mmol, 36%).

M.Pt. > 280°C.

δ^{1}H (300 MHz, d_6-DMSO): 3.43 (bs, 2 x NH_2), 6.92 - 7.58 (Ar-5H and Ar-7H).

δ^{13}C (75 MHz, d_6-DMSO): 123.05 (C-2), 123.36 (C-4), 123.90 (C-8a), 124.38 (C-4a), 125.88 (C-7), 126.52 (C-5), 136.91 (C-8), 144.80 (C-6).

u_{max}(cm^{-1}): 1208 (N-O, m), 1348 (NO_2 symm., m), 1533 (NO_2 asymm., m), 3308 - 3350 (NH_2, bs), 3409 - 3456 (NH_2, bs).

m/z: 281 $(M - 1)^+$.

10.2.32 1,1,1-Trimethylhydrazinium Iodide (TMHI)[34]

Methyl iodide (26.05 g, 1.1 equiv., 0.183 mol) was added to a stirred solution of 1,1-dimethylhydrazine (10.00 g, 0.166 mol) in dry THF (75 ml). This mixture was stirred under an atmosphere of nitrogen at room temperature for 0.5 hour. The resulting precipitate was filtered to give an off-white solid which was recrystallised (95% ethanol) to give white plates (~80% yield). The compound was stored at -20°C.

M.Pt.: 233-235°C, lit. 235°C.[101]

10.2.33 2,4,7-Triamino-6,8-dinitroquinazoline (142)

2,4-Diamino-6,8-dinitroquinazoline (1.0 g, 4 mmol) was added to a stirring solution of 1,1-dimethylhydrazine (3.6 g, 60 mmol, 15 equiv.) and methyl iodide (8.52 g, 60 mmol, 15 equiv.) in freshly distilled DMSO (50 ml). To this brown solution was added a freshly prepared solution of methanolic sodium methoxide [sodium (2.6 g) in dry methanol (30ml)]. The mixture turned brilliant red and was stirred at ambient temperature under an atmosphere of nitrogen for 5 days. The resulting mixture was quenched with aqueous 35% hydrochloric acid (~50 ml), i.e. until white fumes were no longer produced. The mixture was then added to crushed ice (125 ml). No precipitate was formed so the aqueous layer was extracted with ethyl acetate (3 x 300 ml). The combined organic layers were then dried (anhydrous $MgSO_4$), filtered and concentrated *in vacuo* to leave a small

amount of brown liquid. Column chromatography was carried out on the liquid with silica gel 40 as the stationary phase and a mobile phase starting with a 2:1 mixture of ethyl acetate/hexane and then changing to pure ethyl acetate. Upon evaporation of the mobile phase a brown solid residue remained, 2,4,7-triamino-6,8-dinitroquinazoline (yield = 0.25 g, 0.9 mmol, 24%).

M.Pt. > 280°C.

δ^{1}H (300 MHz, d_6-DMSO): 3.27 (bs, 3 x NH_2), 9.22 (s, Ar-5H).

δ^{13}C (75 MHz, d_6-DMSO): 129.50 (C-4a), 131.73 (C-5), 144.10 (C-6), 148.62 (C-8), 150.65 (C-7), 153.13 (C-8a), 155.07 (C-4), 161.70 (C-2).

υ_{max} (cm^{-1}): 1275 (NO_2 symm., m), 1626 (NO_2 asymm., m), 3462 (NH_2, bs).

m/z: 265 (M^+).

HRMS: Calculated Mass = 266.0638, Measured Mass = 266.0646 $(M + 1)^+$.

10.2.34 2,4,6,8-Tetra-aminoquinazoline (143)

A mixture of 2,4-diamino-6,8-dinitroquinazoline (1.0 g, 4 mmol) and 3% palladium on carbon catalyst (0.25 g) in ethanol (250 ml) was hydrogenated (using a Parr shaker-type hydrogenator) with H_2 (g) at a pressure of 32 psi over 4 hours. The resulting mixture was filtered and the brown filtrate concentrated *in vacuo* to yield a light brown solid, 2,4,6,8-tetra-aminoquinazoline (0.60 g, 3 mmol, 79% yield).

M.Pt. > 280°C.

δ^{1}H (300 MHz, d_6-DMSO): 3.41 (bs, 2 x NH_2), 6.24 (d, Ar-7H, $J_{5,7}$ = 3.0 Hz), 7.08 (d, Ar-5H, $J_{5,7}$ = 3.0 Hz).

δ^{13}C (75 MHz, d_6-DMSO): 102.31 (C-7), 103.71 (C-5), 121.00 (C-4a), 142.53 (C-6), 144. 52 (C-8), 148.84 (C-8a), 163.27 (C-4), 163.46 (C-2).

υ_{max}(cm^{-1}): 3185 (NH_2, bs), 3323 (NH_2, bs).

m/z: 190 (M^+).

HRMS: Calculated Mass = 190.0967, Measured Mass = 190.0958 $(M)^+$.

CHN Elemental Analysis - Calculated for $C_8H_{10}N_6$: C, 50.53; H, 5.26; N, 44.21. Found: C, 42.63; H, 5.07; N, 35.75.

Caution: Care should be taken when filtering off the Pd-C. The catalyst should be kept moist with ethanol since it is pyrophoric.

10.2.35 Attempted Acetylation of 2,4,6,8-Tetra-aminoquinazoline (143)

A mixture of the substrate (0.25 g, 1.3 mmol) and acetic anhydride (50 ml) was heated to reflux (100°C) and stirred at this temperature overnight. The reaction mixture was then added to crushed ice (50 ml) and the resulting aqueous solution extracted with ethyl acetate (3 x 50 ml). The organic layer was worked up to yield a brown solid which when characterised by mass spectral analysis confirmed the presence of reaction breakdown products.

10.2.36 Attempted Nitration of 2,4,6,8-Tetra-aminoquinazoline (143)

100% Nitric acid (2 ml) was added dropwise to stirring acetic anhydride (35 ml) at a temperature of approximately 0°C < T < 5°C. The substrate (0.25 g, 1.3 mmol) was then added to this mixture whereupon the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was added to crushed ice (50 ml) and extracted with ethyl acetate. No reaction product could be isolated and therefore it is believed that the reaction produced a decomposition product.

10.2.37 2-Chloro-6-methoxypyrazine (101)

2,6-Dichloropyrazine (40.00 g, 268 mmol) was added to methanolic sodium methoxide [from sodium (5.6g) and methanol (200 ml)]. The mixture was heated under reflux conditions for 6 hours, then cooled and diluted with water (600 ml). The product was isolated by extraction with ether (6 x 100 ml); the extracts were dried overnight (anhydrous $MgSO_4$) and the solvent removed *in vacuo*. Distillation (49°C, 18 mm Hg) of the residue afforded 2-chloro-6-methoxypyrazine as a colourless liquid (30.85 g, 80% yield).

δ^1H (60 MHz, $CDCl_3$): 3.99 (s, 3H, OMe), 8.14 (d, 1H, Ar-H, $J_{3,5}$ = 2.50 Hz), 8.18 (d, 1H, Ar-H, $J_{3,5}$ = 2.50 Hz).

10.2.38 2-Chloro-3,5-dinitro-6-methoxypyrazine (102)

2-Chloro-6-methoxypyrazine (25.0 g, 173 mmol) was added dropwise over 1 hour to a stirring mixture of 98% HNO_3 (50 ml) and 20% oleum (150 ml). Throughout the addition the mixed acid mixture was kept at 75-80°C by the use of a jacketed vessel attached to a Haake heated water circulator. The substrate was added at such a rate so

that the reaction temperature did not exceed 80°C. Subsequent to the addition of all the pyrazine the mixture was then stirred for 4 hours at 75°C and finally allowed to cool to room temperature and poured onto crushed ice (500 g). The resultant precipitate was suction filtered and dried under vacuum to yield 2-chloro-3,5-dinitro-6-methoxypyrazine (29.48 g, 77% yield).

M.Pt.: 175°C.

δ^1H (60 MHz, d_6-DMSO): 3.98 (s, 3H, OMe).

υ_{max} (cm^{-1}): 831 (C-Cl, w), 1282 (NO_2 symm., s), 1345 (C-O, s), 1593 (NO_2 asymm., s).

Caution: Care should be taken when adding the pyrazine substrate to the mixed acid mixture as the reaction is strongly exothermic and can get out of control.

10.2.39 2,6-Diamino-3,5-dinitropyrazine (ANPZ) (95)

Aqueous ammonia solution 30% (wt./vol.) (160 ml) was added rapidly to a stirring solution of 2-chloro-3,5-dinitro-6-methoxypyrazine (26.0 g, 118 mmol) in acetonitrile (350 ml). After stirring for 40 minutes at 60°C the mixture was allowed to cool and filtered to yield 2,6-diamino-3,5-dinitropyrazine (ANPZ) (23.09 g, 98% yield).

M.Pt.: 355°C (decomposition), lit. 350°C.[79]

δ^1H (300 MHz, d_6-DMSO): 3.34 (bs, 4H, NH_2).

δ^{13}C (75 MHz, d_6-DMSO): 125.56 (C-NO_2), 151.12 (C-NH_2).

υ_{max}(cm^{-1}): 1235 (NO_2, symm., s), 1620 (NO_2, asymm., s), 3303 (NH_2, bs), 3350 (NH_2, bs).

Caution: Since ANPZ is an explosive compound the above reaction was carried out in an armoured fume cabinet.

10.2.40 2,6-Diamino-3,5-dinitropyrazine-1-oxide (PZO) (9)

Aqueous H_2O_2 solution 30% (wt./vol.) (50 ml) was added dropwise at -5°C to a stirring solution of ANPZ (23.0 g, 115 mmol) in trifluoroacetic acid (400 ml), the temperature was kept below 0°C by the use of a dry ice/acetone cooling bath. The reaction mixture was allowed to warm to room temperature and stirred for 48 hours. After 24 hours, 36 hours and 48 hours 50 ml aliquots of 30% H_2O_2 aq. soln. were added and finally after 48 hours the reaction mixture was heated to 45°C for a further 1 hour. The reaction mixture was then allowed to cool and the resulting precipitate was filtered and washed with water

(2 x 100 ml), 50% $NaHCO_3$ solution (2 x 50 ml) and again with water (100 ml) to yield 2,6-diamino-3,5-dinitropyrazine-1-oxide (PZO) (20.55g, 83% yield).

M.Pt.: 345°C, lit.: 347°C.[80]

δ^1H (300 MHz, d_6-DMSO): 3.35 (bs, 4H, NH_2).

$\delta^{13}C$ (75 MHz, d_6-DMSO): 124.88 (C-NO_2), 144.59 (C-NH_2).

$\upsilon_{max}(cm^{-1})$: 1235 (N-O, s), 1334 (NO_2, symm., s), 1560 (NO_2, asymm., s), 1646 (N-H, s), 3250 (NH_2, bs), 3420 (NH_2, bs).

m/z: 216 (M^+).

CHN Elemental Analysis - Calculated for $C_4H_4N_6O_5$: C, 22.22; H, 1.85; N, 38.89. Found: C, 22.56; H, 1.16; N, 40.12.

Caution: Since PZO is an explosive compound the above reaction was carried out in an armoured fume cabinet.

10.2.41 2,5-Dimethoxy-3,6-dihydropyrazine (148, R = Me)

A suspension of piperazine-2,5-dione (1.14 g, 10 mmol) and trimethyloxonium tetrafluoroborate ($Me_3O^+BF_4^-$) (4.44 g, 30 mmol) in dichloromethane (90 ml) was stirred at r.t. for 1 day and then refluxed for 2 days. Subsequently more $Me_3O^+BF_4^-$ (0.74 g, 5 mmol) was added and stirring was continued under reflux for 2 additional days. The resulting sticky suspension was cooled to 0°C and 2.5 M NaOH(aq) solution (20 ml) was added at 0°C. The layers were separated, the aqueous layer was extracted with dichloromethane (2 x 25 ml) and the combined organic layers were washed with H_2O (3 x 20 ml) and then dried over anhydrous $MgSO_4$. After filtration the solvent was removed *in vacuo* to afford a light brown solid, 2,5-dimethoxy-3,6-dihydropyrazine (0.39 g, 27% yield).

M.Pt.: 55-57°C, (lit. 57°C).[76]

δ^1H (60 MHz, $CDCl_3$): 3.80 (6H, s, 2 x OCH_3), 4.15 (4H, s, 3-CH_2 and 6-CH_2).

10.2.42 2,5-Dimethoxypyrazine (149, R = Me)

A stirred suspension of 2,5-dimethoxy-3,6-dihydropyrazine (0.50 g, 4 mmol), *N*-chlorosuccinimide (NCS) (0.60 g, 4 mmol) and α,α'-azobis(isobutyronitrile) (AIBN) (0.02 g, catalytic amount) in carbon tetrachloride (CCl_4) (40 ml) was slowly heated under an atmosphere of nitrogen to 80°C. At around 70°C the suspension changed to a homogeneous mixture, indicating that the reaction had commenced. The stirring mixture was heated at reflux overnight (15 h), whereupon it was allowed to cool to 0°C. The succinimide by-product was filtered off and washed with carbon tetrachloride (25 ml). The organic layers were then combined and the solvent removed *in vacuo* to yield a pink liquid, 2,5-dimethoxypyrazine (0.39 g, 79% yield).
δ^1H (60 MHz, $CDCl_3$): 3.90 (s, 6H, OMe), 7.80 (s, 2H, Ar-H).

10.2.43 Triethyloxonium Tetrafluoroborate (Meerwein's salt)

Epichlorohydrin (freshly distilled over anhydrous $MgSO_4$) (66 ml, 78.08 g, 1.03 mol) was added dropwise to a stirring solution of boron trifluoride diethyl etherate (freshly distilled over CaH_2) (140 ml, 156.80 g, 1.39 mol) in dry diethyl ether (freshly distilled over sodium) (300 ml). The addition was carried out at such a rate so that the reaction mixture refluxed gently and this would typically last for 15 minutes. Throughout the addition of reagents the reaction must be kept under a constant stream of nitrogen in order to ensure very dry conditions. The reaction mixture was then refluxed for 1.5 hours whereupon it was left to stand at room temperature overnight. The condenser was replaced with a filtration stick (sealed with a rubber septum) and whilst still under a positive pressure of nitrogen the liquid was removed from the reaction vessel by vacuum suction. The white solid that remained in the reaction vessel was washed with cold, dry diethyl ether (3 x 250 ml) with the solvent each time removed via the filtration stick. Approximately 145 g of pure white solid, triethyloxonium tetrafluoroborate ($Et_3O^+BF_4^-$) (Meerwein's salt), was left in the reaction vessel.

M.Pt. = 92°C (lit. 91-92°C, decomposition).[102]

10.2.44 2,5-Diethoxy-3,6-dihydropyrazine (148, R = Et)

Freshly distilled dichloromethane (350 ml) and piperazine-2,5-dione (dried overnight under vacuum) (32.9 g, 0.29 mol) were added sequentially to the

Meerwein's salt ($Et_3O^+BF_4^-$) (~145 g) from the previous experiment. The resulting mixture was then stirred at room temperature and under nitrogen for 5 days. After the first day a large amount of sticky white solid was generated in the reaction vessel and the liquid changes from colourless to light brown. After the 5 days the reaction mixture was quenched with aqueous sodium hydroxide solution (2.5 M) and the organic layer separated. The aqueous layer was washed with dichloromethane (2 x 125 ml) and then the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to yield a light brown fluffy solid, 2,5-diethoxy-3,6-dihydropyrazine (28.0 g, 0.16 mol, 71% yield).

M.Pt.: 83-85°C (lit. 84°C).[96]

δ^1H (60 MHz, $CDCl_3$): 1.30 (6H, t, 2 x Me, J = 6.0 Hz), 4.10 (4H, s, 2 x NCH_2), 4.15 (4H, q, 2 x CH_2O, J = 6.0 Hz).

δ^{13}C (75 MHz, $CDCl_3$): 14.30 (CH_3), 46.65 (C-3 and C-6), 61.00 (OCH_2), 162.70 (C-2 and C-5).

10.2.45 2,5-Diethoxypyrazine (149, R = Et)

A stirred suspension of 2,5-diethoxy-3,6-dihydropyrazine (2.00 g, 12 mmol), *N*-chlorosuccinimide (NCS) (1.80 g, 13 mmol) and α,α'azobis-(isobutyronitrile) (AIBN) (0.03 g, catalytic amount) in carbon tetrachloride (40 ml) was slowly heated under an atmosphere of nitrogen to 80°C. At around 70°C the suspension changed to a homogeneous mixture, indicating that the reaction had commenced. The stirring mixture was heated at reflux overnight (15 h), whereupon it was cooled to 0°C. The succinimide by-product was filtered off and washed with carbon tetrachloride (25 ml). The filtrate and wahings were then combined and the solvent removed *in vacuo* to yield a pink liquid, 2,5-diethoxypyrazine (1.83 g, 91% yield).

δ^1H (60 MHz, $CDCl_3$): 1.35 (6H, t, 2 x CH_3, J = 6.0 Hz), 4.30 (4H, q, 2 x OCH_2, J = 6.0 Hz), 7.75 (2H, s, Ar-H).

δ^{13}C (75 MHz, $CDCl_3$): 15.00 (CH_3), 62.80 (OCH_2), 128.75 (C-3 and C-6), 156.28 (C-2 and C-5).

υ_{max}(cm^{-1}): 1685 (C=N), 2900 (C-H).

10.2.46 2,5-Diethoxy-3,6-dinitropyrazine (150, R = Et)

2,5-Diethoxypyrazine (0.5 g, 2.9 mmol) was added quickly at room temperature to a stirring 0.5 M solution of nitronium tetrafluoroborate ($NO_2^+BF_4^-$) in sulfolane (7 ml). Stirring was continued overnight at room temperature whereupon the orange/red solution was poured onto crushed ice (30 ml). A precipitate developed which was filtered to give a bright yellow solid, 2,5-diethoxy-3,6-dinitropyrazine (0.23 g, 0.9 mmol, 30% yield).

M.Pt. = 112°C (lit. 118°C).[96]

δ^1H (60 MHz, $CDCl_3$): 1.50 (6H, t, 2 x CH_3, J = 7.00 Hz), 4.55 (4H, q, 2 x CH_2, J = 7.00 Hz).

δ^{13}C (75 MHz, $CDCl_3$): 14.65 (CH_3), 66.10 (OCH_2), 139.61 (C-3 and C-6), 144.41 (C-2 and C-5).

υ_{max}(cm^{-1}): 1335 (NO_2 symm.), 1554 (NO_2 asymm.), 2986 (C-H).

m/z: 258 (M^+), 259 ($M^+ + 1$).

CHN Elemental Analysis - Calculated for $C_8H_{10}N_4O_6$: C, 37.21; H, 3.88; N, 21.71. Found: C, 37.35; H, 3.81; N, 21.81.

10.2.47 Attempted Oxidative Nitration of 2,5-Diethoxy-3,6-dihydropyrazine (148, R=Et)

2,5-Diethoxy-3,6-dihydropyrazine (0.75 g, 4.4 mmol) was added to a stirring solution of dinitrogen tetroxide (N_2O_4) (1.5 g) in acetonitrile (35 ml). The resulting mixture was stirred under nitrogen at room temperature for 8 hours. The mixture was then poured on to crushed ice (50 ml). The organic layer was separated from the aqueous layer, but despite washing the aqueous layer a number of times with ethyl acetate, no organic material could be isolated from the organic phase. It was concluded that the reaction had resulted in the production of a decomposition product which was soluble in the aqueous phase.

10.2.48 2,5-Diamino-3,6-dinitropyrazine (ANPZ-i) (10)

Ammonia gas was bubbled through dry MeOH (35 ml) in an autoclave vessel for 5 minutes whereupon 2,5-diethoxy-3,6-dinitropyrazine (350 mg, 1.4 mmol) was added. The reaction mixture was heated in the sealed autoclave system for 4 hours (150°C, 250 psi). The autoclave was then allowed to cool down to room temperature whereupon the reaction mixture was added to acetonitrile. It was expected that a precipitate would form but it did not. Therefore, the ammonia saturated acetonitrile/methanol solvent was allowed to evaporate at room temperature to leave a dark yellow solid, 2,5-diamino-3,6-dinitropyrazine (270 mg, 1.4 mmol, ~100% yield).

M.Pt. = 288°C (decomposition point).

$\delta^{1}H$ (60 MHz, $CDCl_3$): 2.00 (bs, 4H, 2 x NH_2).

$\delta^{13}C$ (75 MHz, $CDCl_3$): 149.49 (C-NO_2), 150.30 (C-NH_2).

$\upsilon_{max}(cm^{-1})$: 1248 (NO_2 symm., m), 1632 (NO_2 asymm., m), 3316 (NH_2, bs), 3387 (NH_2, bs).

m/z: 200 (M^+).

CHN Elemental Analysis - Calculated for $C_4H_4N_6O_4$: C, 24.08; H, 2.02; N, 42.00. Found: C, 23.79; H, 1.99; N, 42.00.

Caution: Since ANPZ-i is an explosive compound the above reaction was carried out in an armoured fume cabinet.

10.2.49 Attempted Oxidation of 2,5-Diamino-3,6-dinitropyrazine (ANPZ-i) (10)

Aqueous hydrogen peroxide solution 30% (wt.vol.) (3 ml) was added gradually, at a temperature of between 0°C and 5°C with cooling by an acetone/dry ice bath, to a stirring suspension of 2,5-diamino-3,6-dinitropyrazine (100 mg, 0.5 mmol) in trifluoroacetic acid (TFA) (15 ml). The reaction mixture was then allowed to warm to room temperature and stirred for 3 days. After this period a further 2 ml of 30% (wt./vol.) aq. H_2O_2 solution was added and stirring continued for 24 hours. The reaction mixture was then added to water and the acid neutralised with solid

$NaHCO_3$; any excess $NaHCO_3$ was filtered off. The aqueous layer was then heated to evaporation at atmospheric pressure and the solid that remained was washed with acetone. The mixture was then filtered of any insoluble inorganic material and the acetone layer concentrated *in vacuo* to yield a brown solid. Mass spectral analysis of this solid showed it to be a decomposition product. Additionally, a negative ferric chloride test was observed.

Caution: Since ANPZ-i is an explosive compound the above reaction was carried out in an armoured fume cabinet.

10.2.50 2,6-Diamino-3,5-dinitropyrazine-*N*-oxide (PZO) (9)

Aqueous HF solution 48% (wt./vol.) (0.1 ml) was added gradually to a stirring mixture of 2,6-diamino-3,5-dinitropyrazine (ANPZ) (0.24 g, 1.2 mmol), MCPBA (1.0 g), DMF (30 ml) and MeOH (10 ml). The resulting mixture was stirred at room temperature for 4 hours whereupon it was added to crushed ice (50 ml), at this point no precipitate developed but addition of the crude reaction mixture to aqueous ferric chloride solution did give a positive result. Repeated washings of the aqueous reaction mixture with ethyl acetate (8 x 75 ml) yielded a yellow coloured organic layer. The organic layer was dried over magnesium sulfate, filtered and reduced by evaporation on a rotavapor to yield a bright yellow crystalline solid, 2,6-diamino-3,5-dinitropyrazine-*N*-oxide (PZO) (0.10 g, 0.5 mmol, 39% yield).

M.Pt.: 345°C, lit.: 347°C.[79]

Caution: Since PZO is an explosive compound the above reaction was carried out in an armoured fume cabinet.

Caution: Care should be taken when working with HF solutions since they are highly corrosive and extremely toxic. When HF solutions are used the appropriate antidote should always be placed in an easily accessible location.[103]

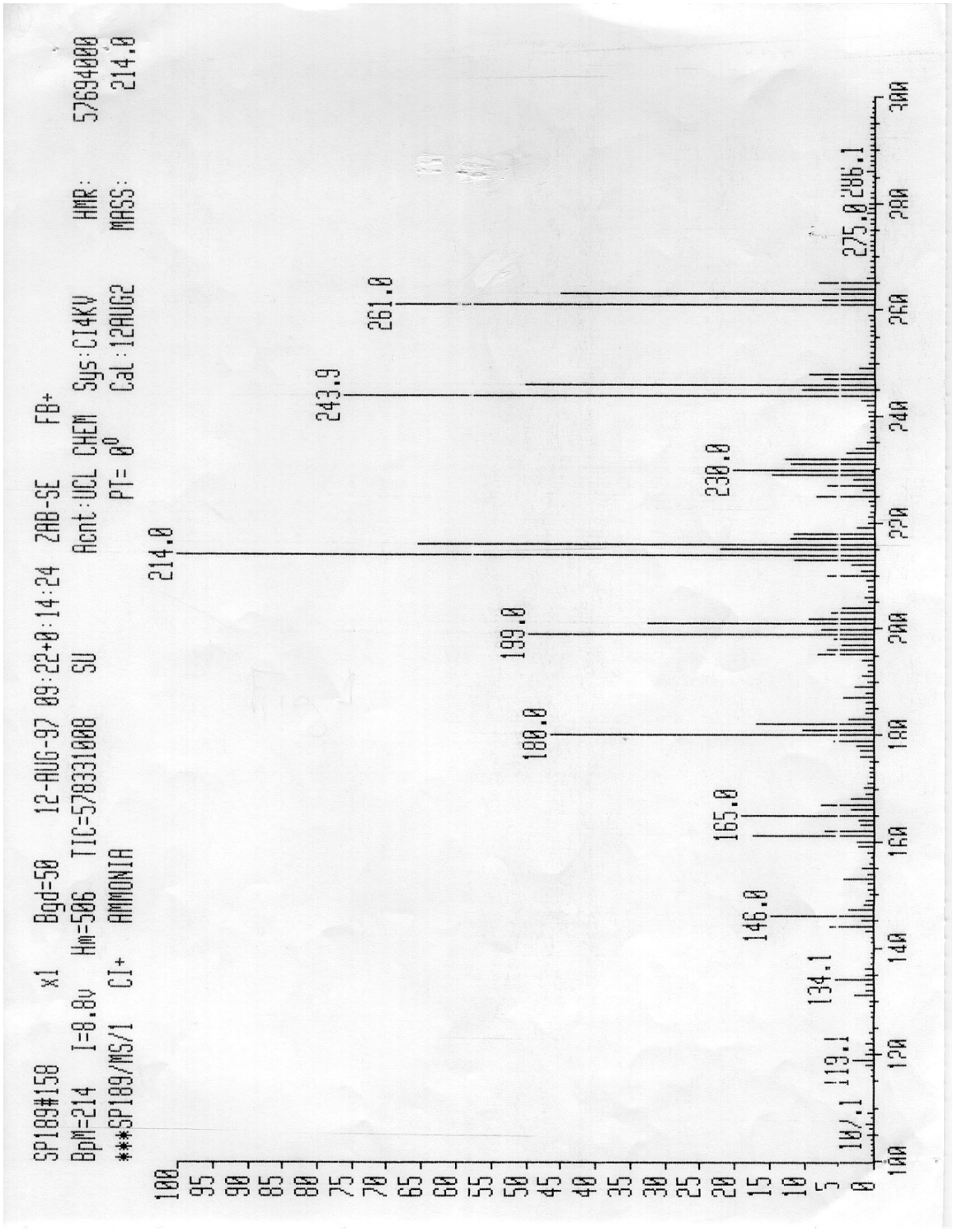
Characterisation by NMR analysis and mass spectrometry (see below) showed the reaction product to be the same as that prepared previously with trifluoroacetic acid (TFA) and hydrogen peroxide (H_2O_2).

$\delta^{1}H$ (300 MHz, d_6-DMSO): 3.35 (bs, 4H, 2 x NH_2).

$\delta^{13}C$ (75 MHz, d_6-DMSO): 124.88 (C-NH_2), 144.59 (C-NO_2).

m/z: 216 (M^+).

11. Figures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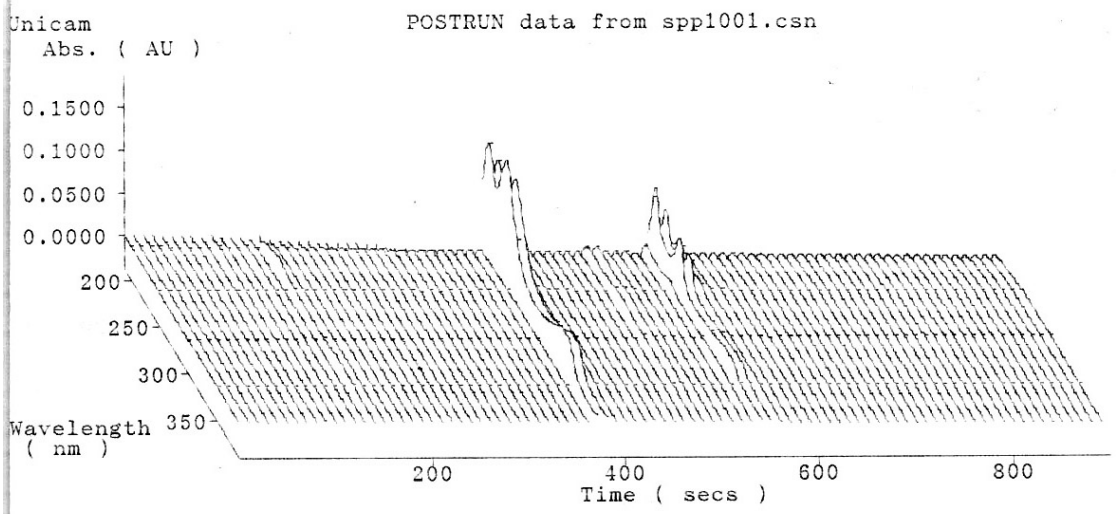
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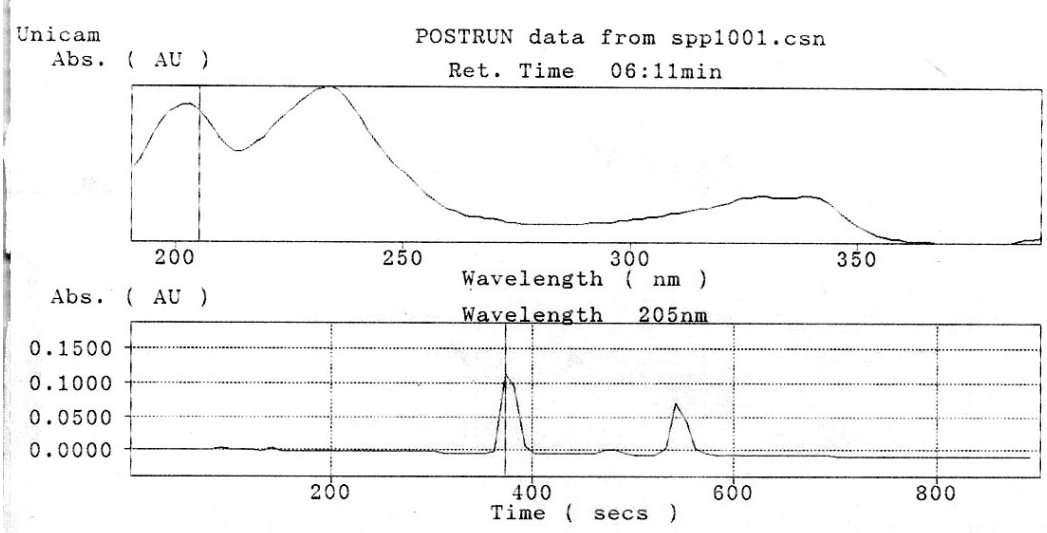
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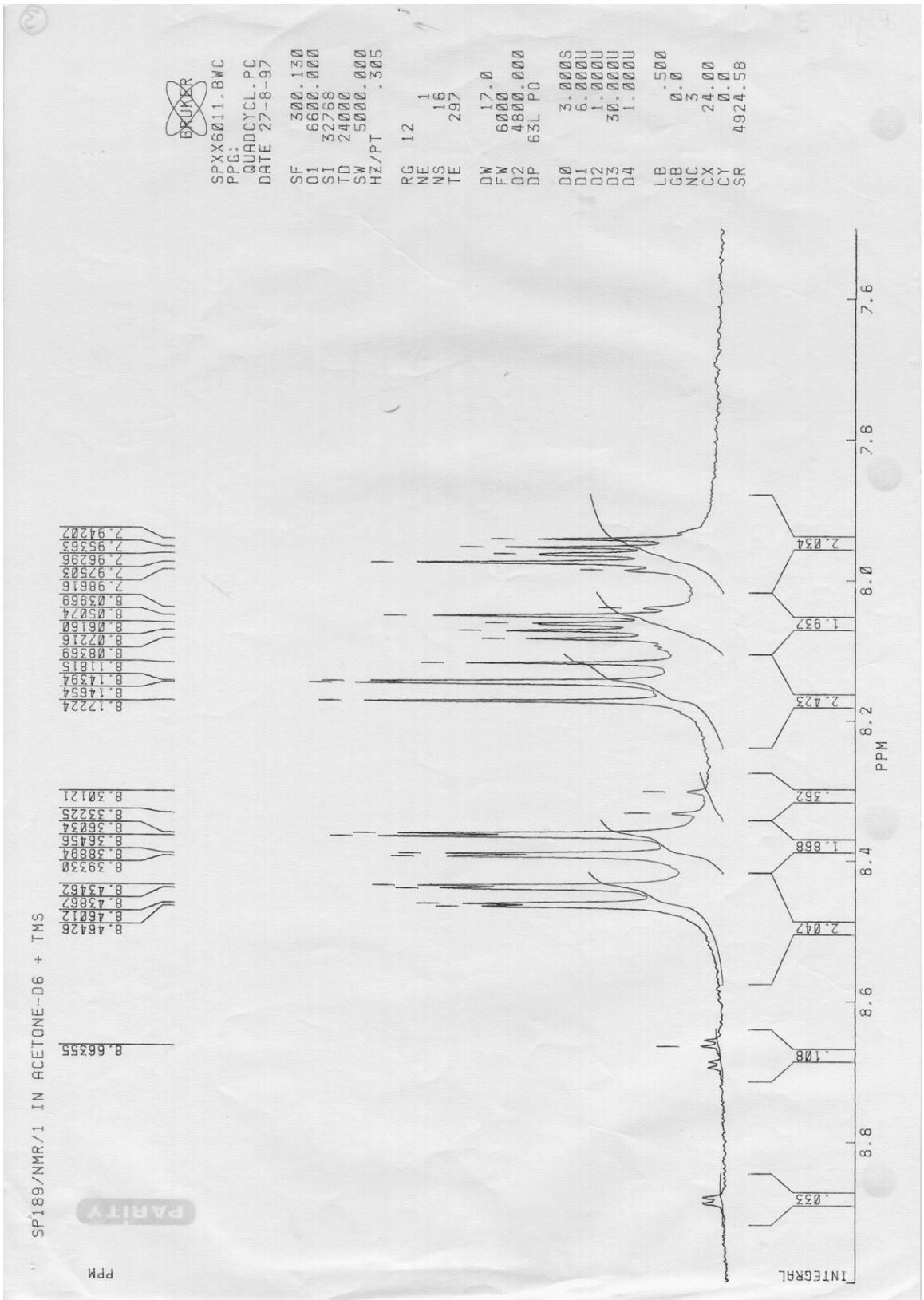
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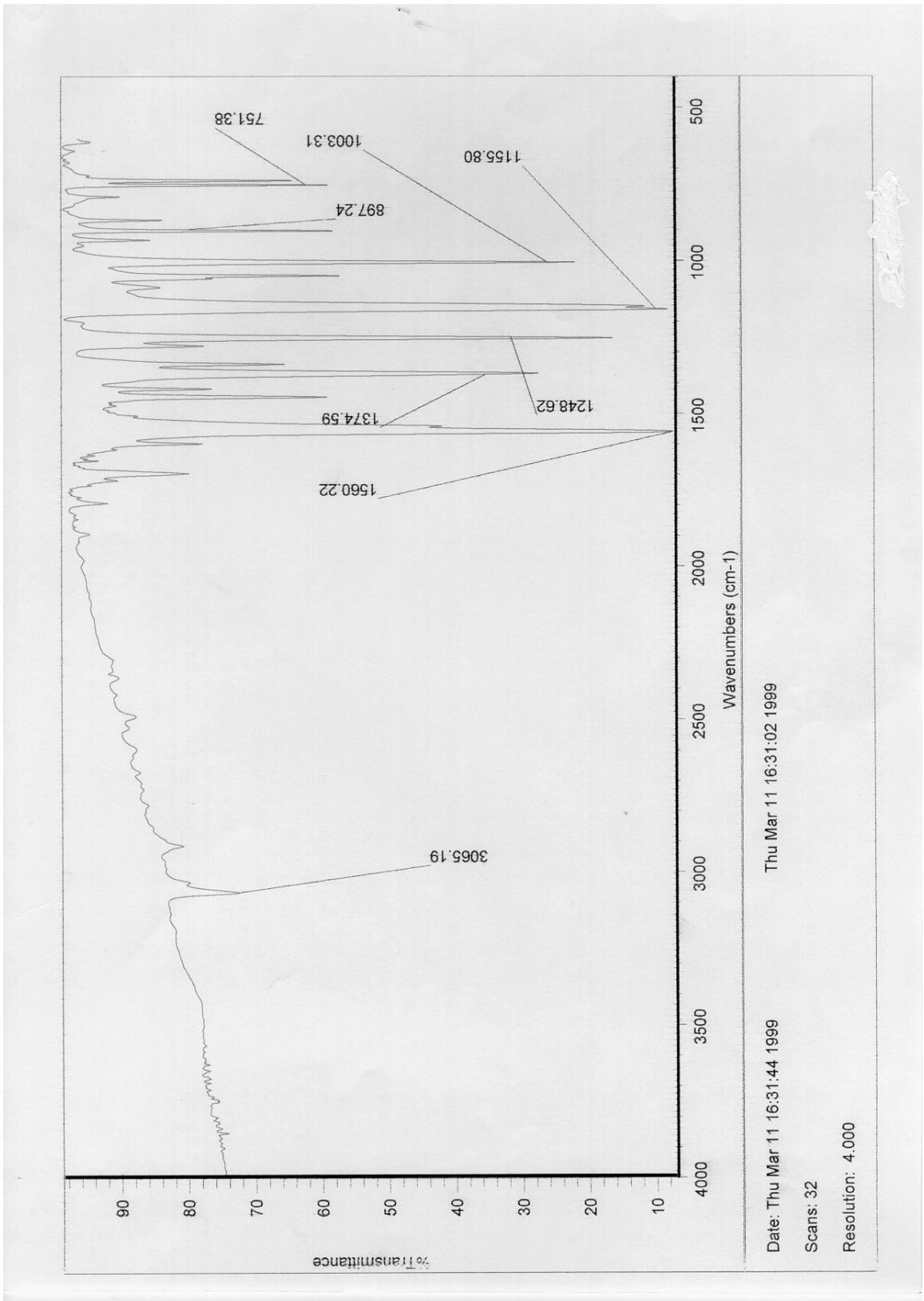
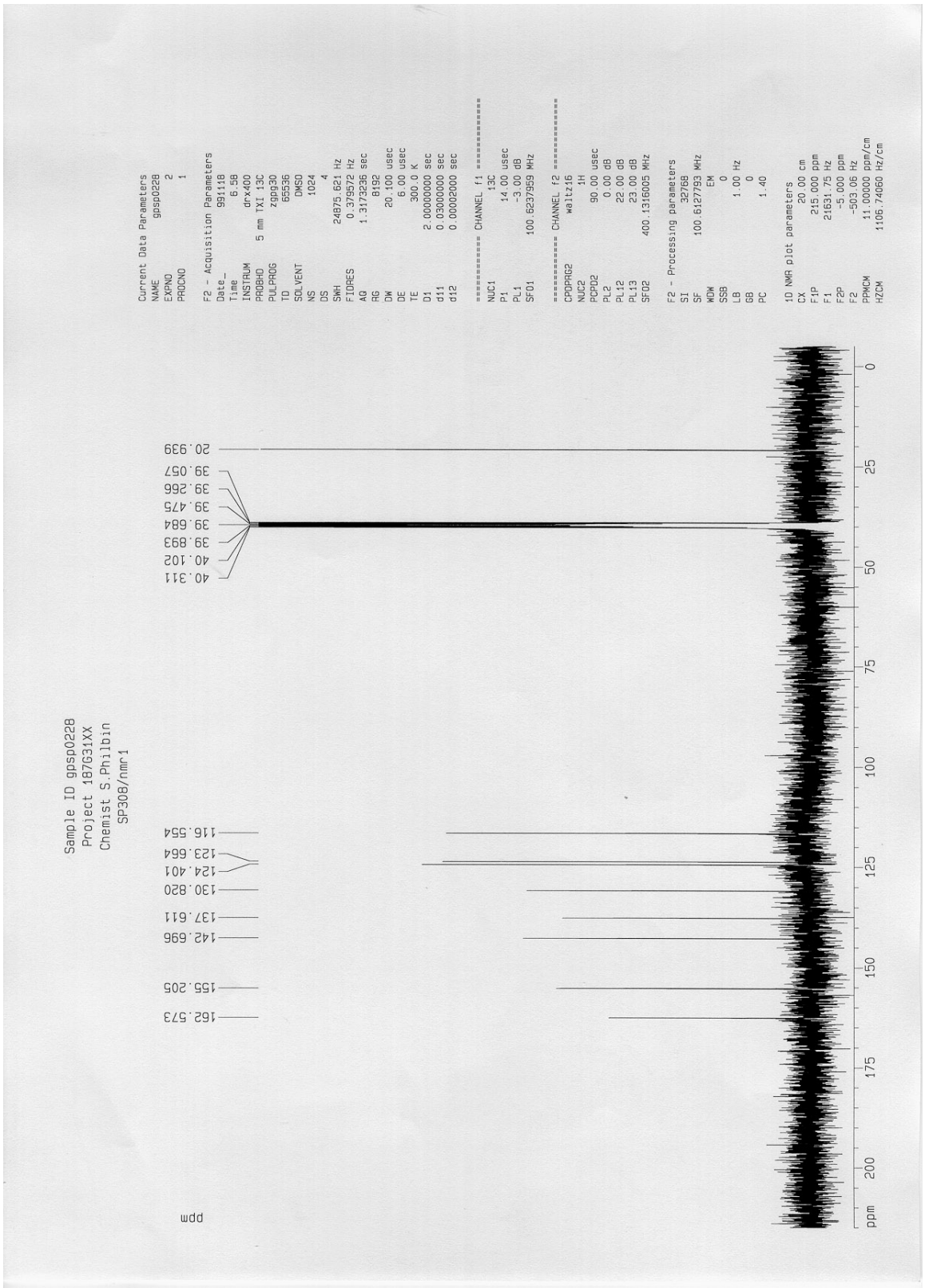
7.6
PPM


751.38
1003.31
1155.80
897.24
1248.62
1374.59
1560.22
3065.19
% Transmittance
Wavenumbers (cm-1)
Date: Thu Mar 11 16:31:44 1999
Thu Mar 11 16:31:02 1999
Scans: 32
Resolution: 4.000


Sample ID gpsp0228
Project 187631XX
Chemist S.Philbin
SP308/nmr1
Current Data Parameters
NAME gpsp0228
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 991118
Time 6.58
INSTRUM drx400
PROBHD 5 mm TXI 13C
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 1024
DS 4
SWH 24875.621 Hz
FIDRES 0.379572 Hz
AQ 1.3173236 sec
RG 8192
DW 20.100 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 14.00 usec
PL1 -3.00 dB
SF01 100.6237959 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 usec
PL2 0.00 dB
PL12 22.00 dB
PL13 23.00 dB
SF02 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127793 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 20.00 cm
F1P 215.000 ppm
F1 21631.75 Hz
F2P -5.000 ppm
F2 -503.06 Hz
PPMCM 11.00000 ppm/cm
HZCM 1106.74060 Hz/cm
20.939
39.057
39.266
39.475
39.684
39.893
40.102
40.311
116.554
123.664
124.401
130.820
137.611
142.696
155.205
162.573
ppm
200
175
150
125
100
75
50
25
0

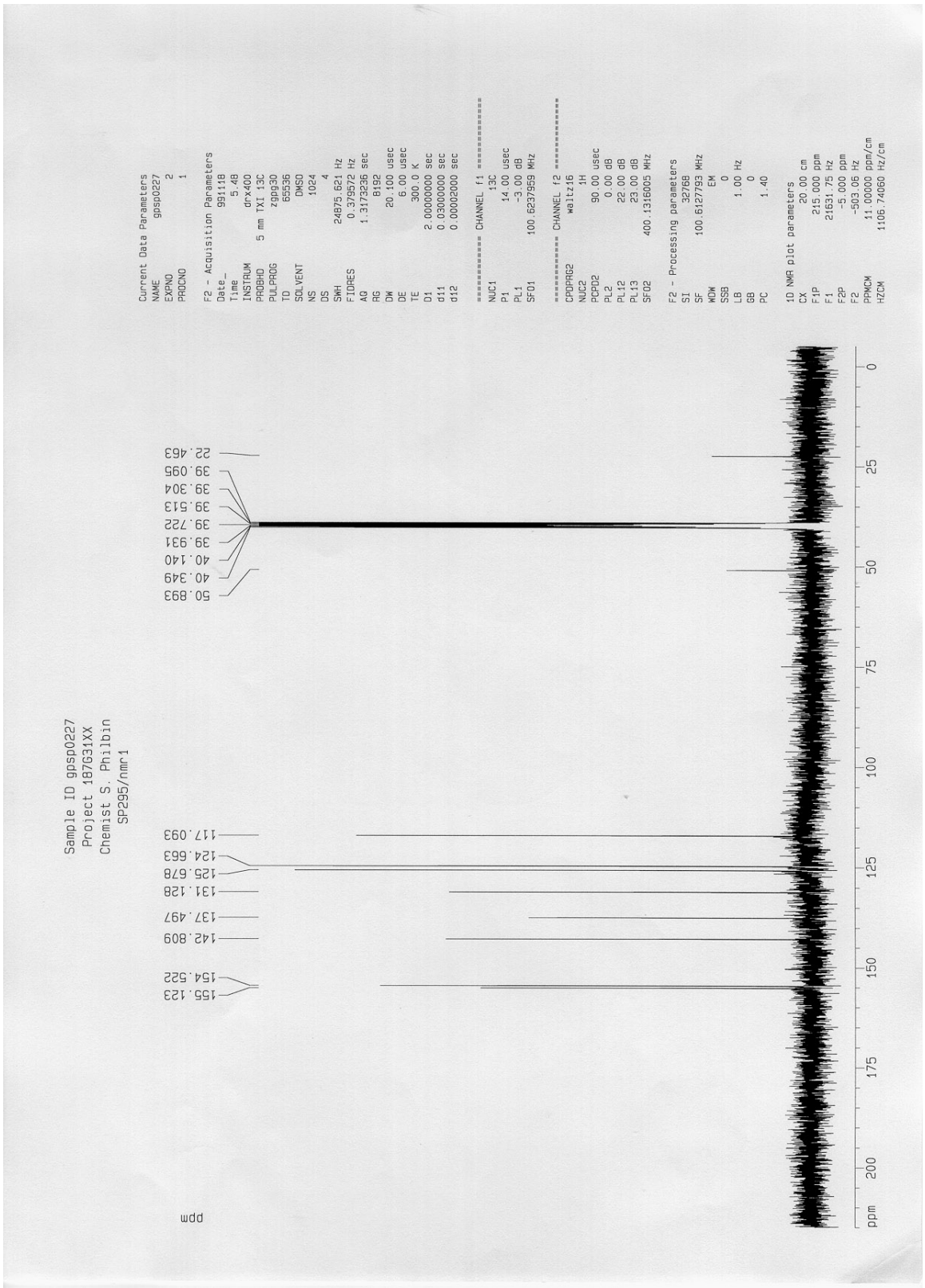
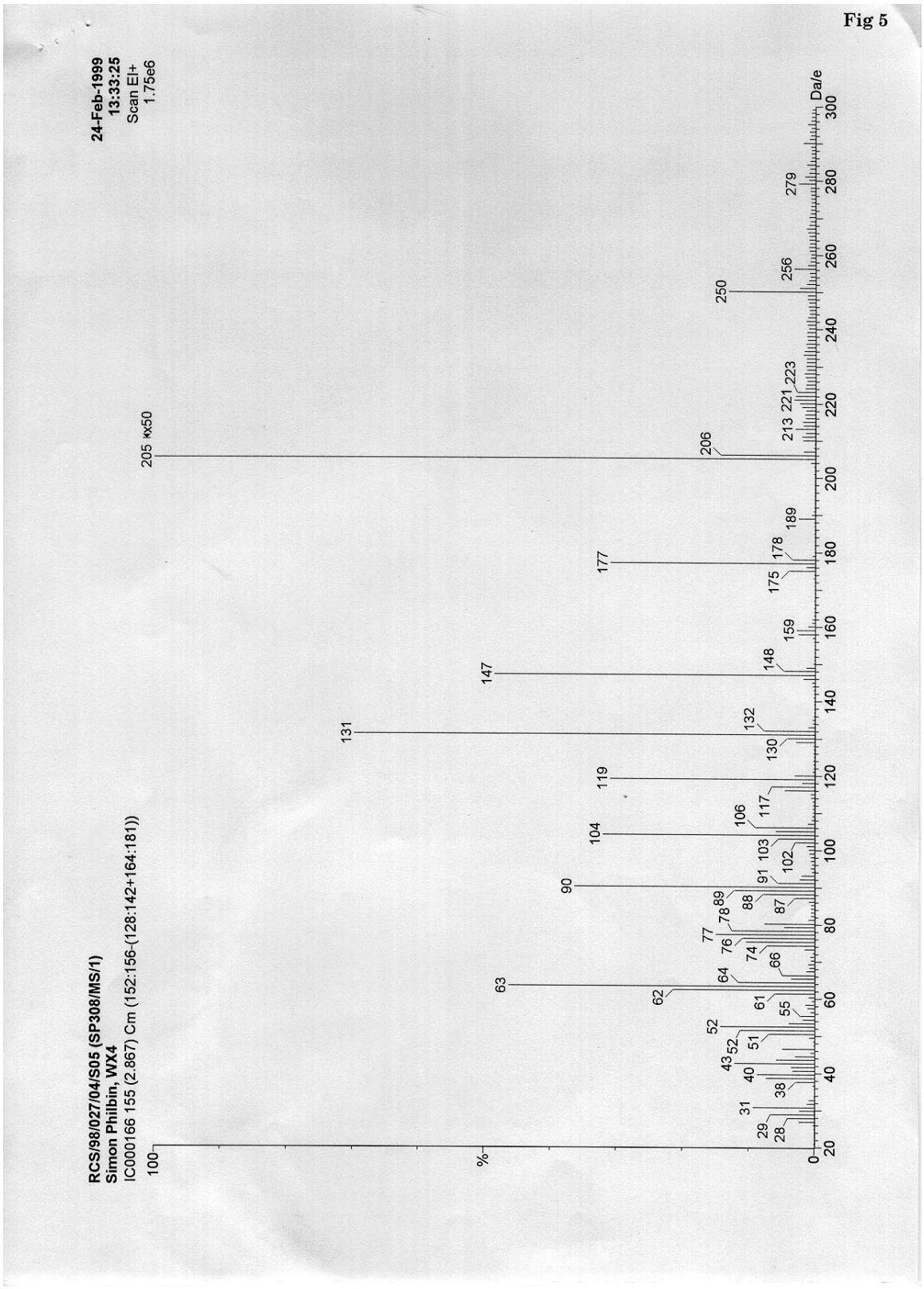

Sample ID gpsp0227
Project 187631XX
Chemist S. Philbin
SP295/nmr1
Current Data Parameters
NAME gpsp0227
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 991118
Time 5.48
INSTRUM drx400
PROBHD 5 mm TXI 13C
PULPROG zgpg30
TD 65536
SOLVENT DMSO
NS 1024
DS 4
SWH 24875.621 Hz
FIDRES 0.379572 Hz
AQ 1.3173236 sec
RG 8192
DW 20.100 usec
DE 6.00 usec
TE 300.0 K
D1 2.00000000 sec
d11 0.03000000 sec
d12 0.00002000 sec
======== CHANNEL f1 ========
NUC1 13C
P1 14.00 usec
PL1 -3.00 dB
SFO1 100.6237959 MHz
======== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 90.00 usec
PL2 0.00 dB
PL12 22.00 dB
PL13 23.00 dB
SFO2 400.1316005 MHz
F2 - Processing parameters
SI 32768
SF 100.6127793 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 20.00 cm
F1P 215.000 ppm
F1 21631.75 Hz
F2P -5.000 ppm
F2 -503.06 Hz
PPMCM 11.00000 ppm/cm
HZCM 1106.74060 Hz/cm
50.893
40.349
40.140
39.931
39.722
39.513
39.304
39.095
22.463
155.123
154.522
142.809
137.497
131.128
125.678
124.663
117.093
ppm
200
175
150
125
100
75
50
25
0

Fig 5


RCS/98/027/04/S05 (SP308/MS/1)
Simon Philbin, WX4
IC000166 155 (2.867) Cm (152:156-(128:142+164:181))
24-Feb-1999
13:33:25
Scan EI+
1.75e6
205 *x50
100
%
0
Da/e

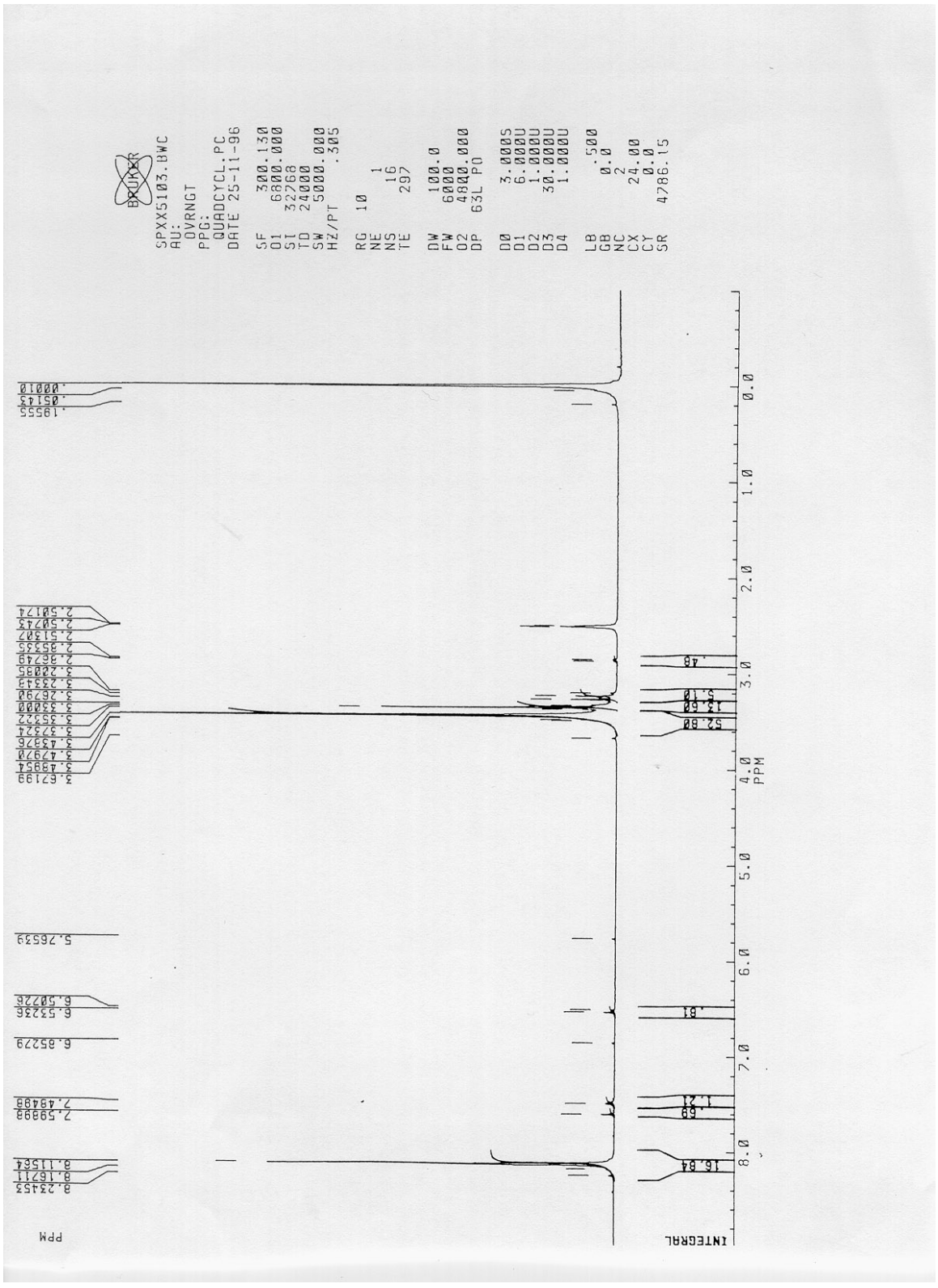
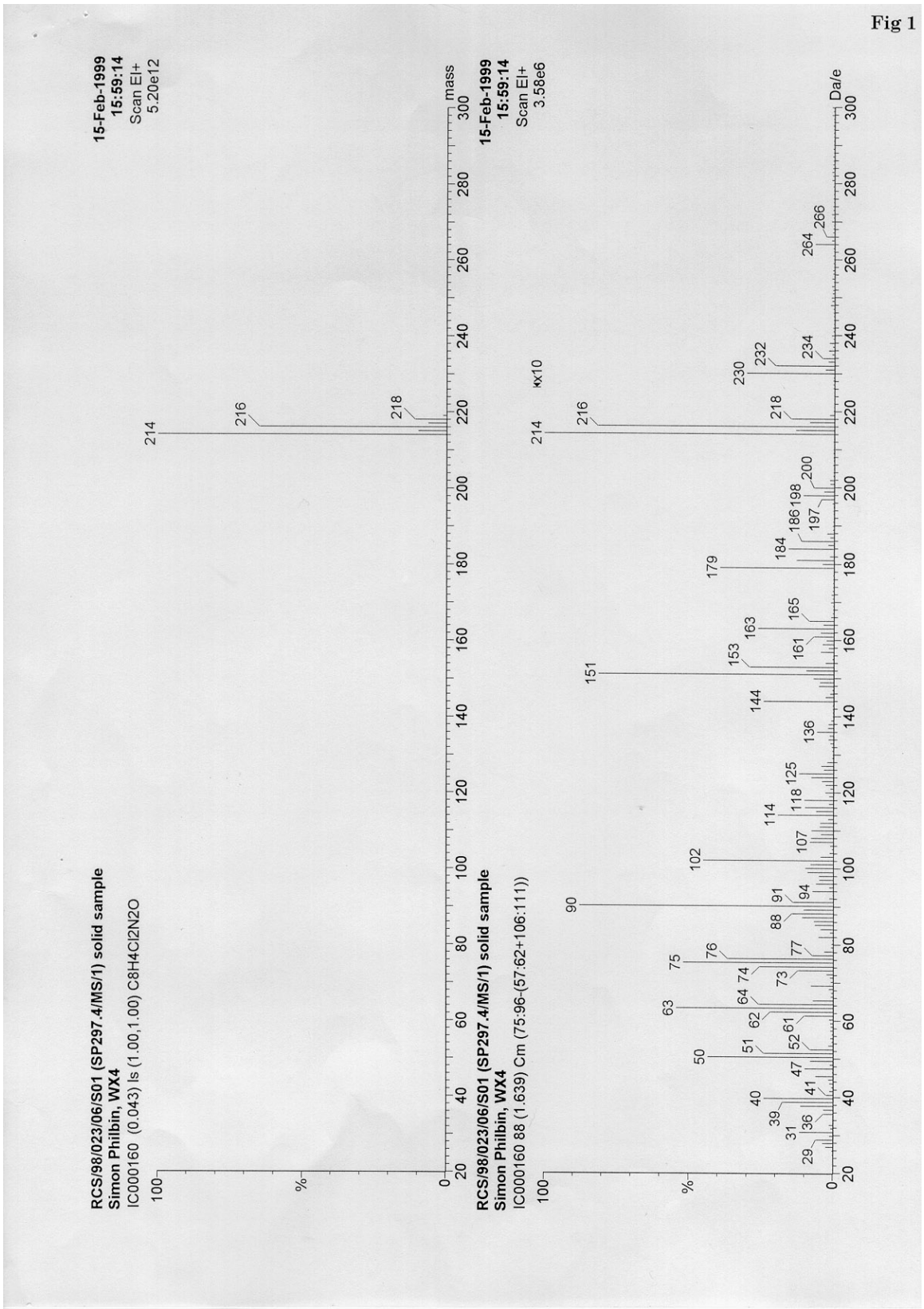

BRUKER
SPXX5103.BWC
AU:
OVRNGT
PPG:
QUADCYCL.PC
DATE 25-11-96
SF 300.130
O1 6800.000
SI 32768
TD 24000
SW 5000.000
HZ/PT .305
RG 10
NE 1
NS 16
TE 297
DW 100.0
FW 6000
O2 4800.000
DP 63L PO
D0 3.0005
D1 6.000U
D2 1.000U
D3 30.000U
D4 1.000U
LB .500
GB 0.0
NC 2
CX 24.00
CY 0.0
SR 4786.15
PPM
INTEGRAL

Fig 1


RCS/98/023/06/S01 (SP297.4/MS/1) solid sample
Simon Philbin, WX4
IC000160 (0.043) Is (1.00,1.00) C8H4Cl2N2O
15-Feb-1999
15:59:14
Scan EI+
5.20e12
RCS/98/023/06/S01 (SP297.4/MS/1) solid sample
Simon Philbin, WX4
IC000160 88 (1.639) Cm (75:96-(57:62+106:111))
15-Feb-1999
15:59:14
Scan EI+
3.58e6
mass
Da/e
%
214
216
218
151
90
102
179
230
232
234
264
266
x10

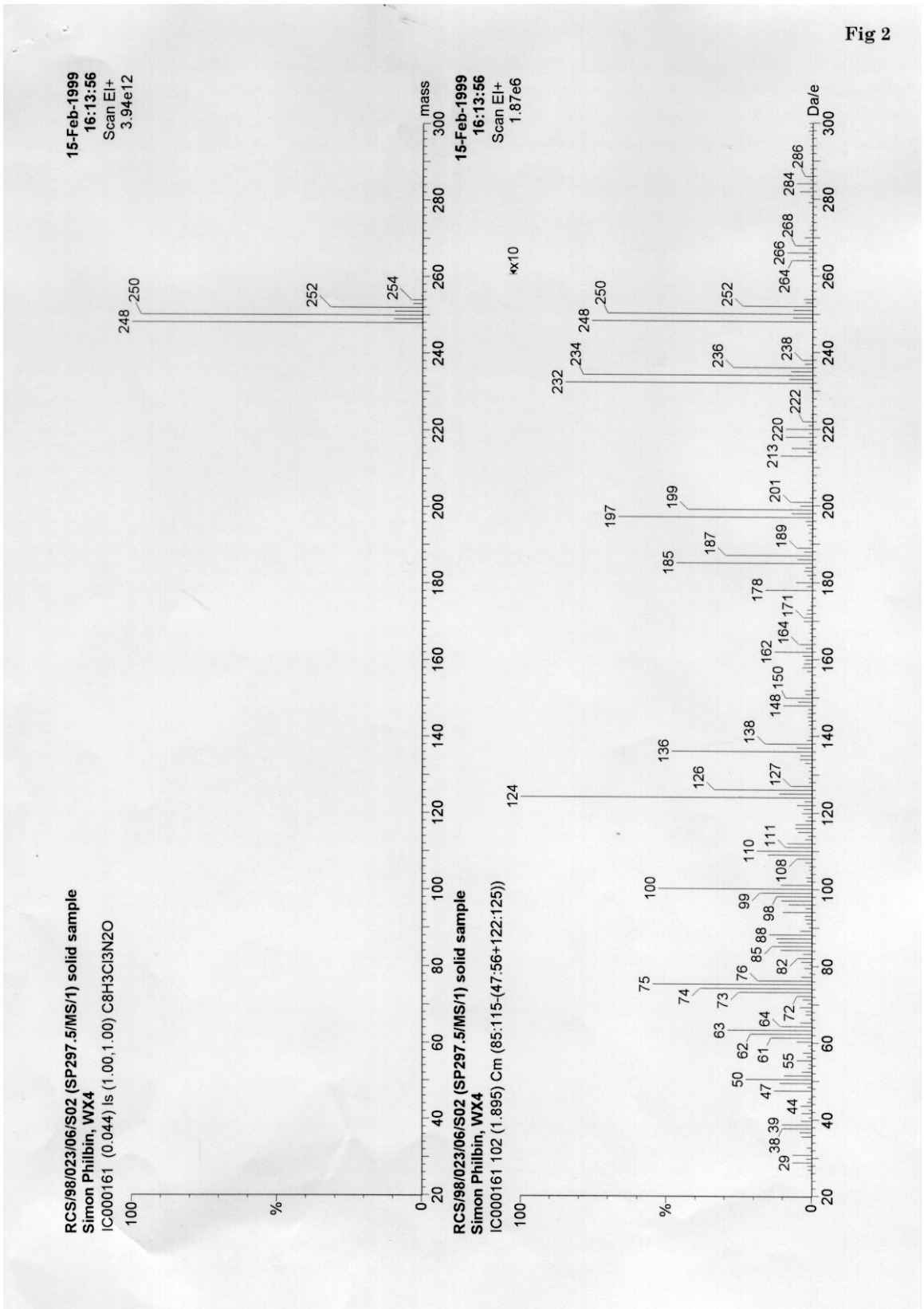
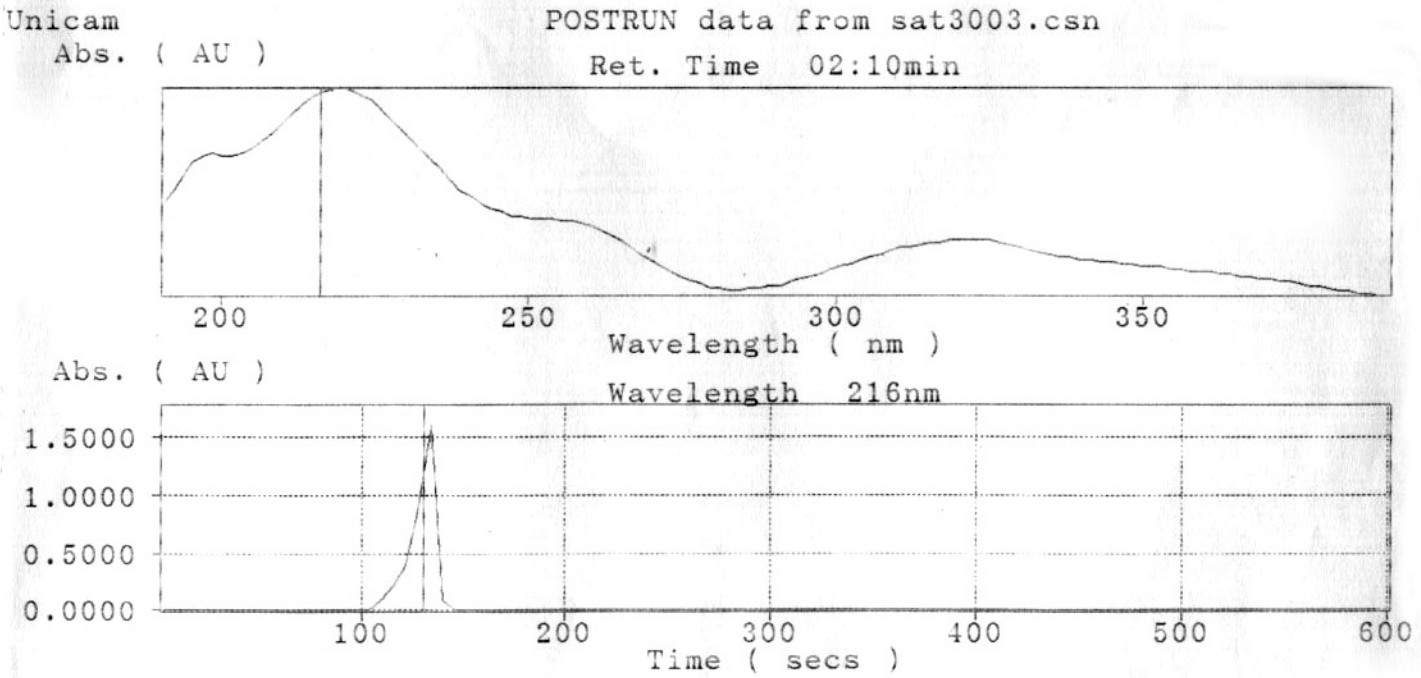
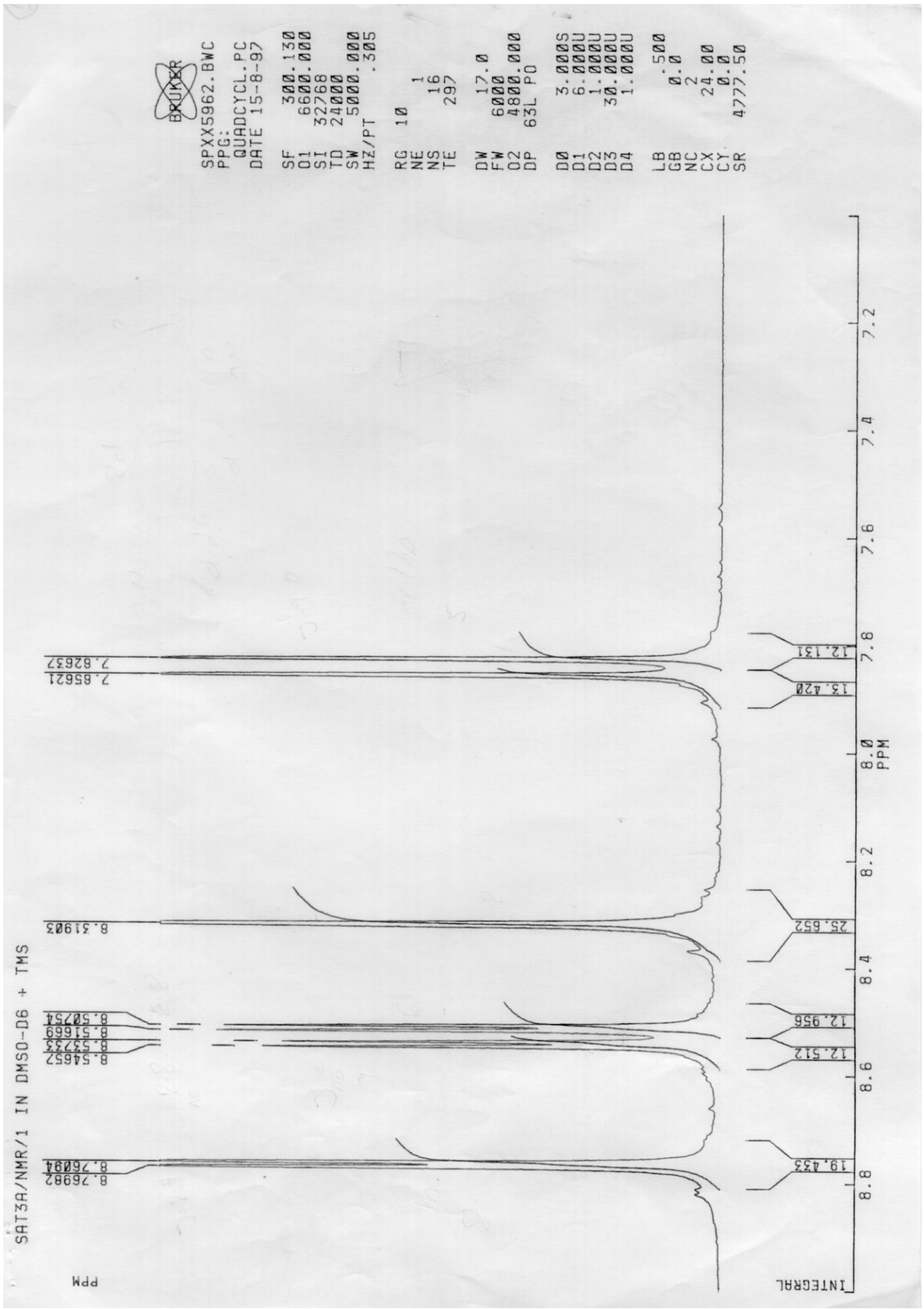

RCS/98/023/06/S02 (SP297.5/MS/1) solid sample
Simon Philbin, WX4
IC00161 (0.044) Is (1.00,1.00) C8H3Cl3N2O
15-Feb-1999
16:13:56
Scan EI+
3.94e12
mass
RCS/98/023/06/S02 (SP297.5/MS/1) solid sample
Simon Philbin, WX4
IC00161 102 (1.895) Cm (85:115-(47:56+122:125))
15-Feb-1999
16:13:56
Scan EI+
1.87e6
x10
Da/e
%

Fig 2


Unicam
POSTRUN data from sat3003.csn
Abs. (AU)
Ret. Time 02:10min
200
250
300
350
Wavelength (nm)
Abs. (AU)
Wavelength 216nm
1.5000
1.0000
0.5000
0.0000
100
200
300
400
500
600
Time (secs)


SAT3A/NMR/1 IN DMSO-D6 + TMS
SPXX5962.BWC
PPG:
QUADCYCL.PC
DATE 15-8-97
SF 300.130
O1 6600.000
SI 32768
TD 24000
SW 5000.000
HZ/PT .305
RG 10
NE 1
NS 16
TE 297
DW 17.0
FW 6000
O2 4800.000
DP 63L PO
D0 3.000S
D1 6.000U
D2 1.000U
D3 30.000U
D4 1.000U
LB .500
GB 0.0
NC 2
CX 24.00
CY 0.0
SR 4777.50
8.76982
8.76084
8.54657
8.53733
8.51669
8.50754
8.31903
7.85621
7.82637
19.433
12.512
12.956
25.652
13.420
12.131
8.8
8.6
8.4
8.2
8.0
PPM
7.8
7.6
7.4
7.2
PPM
INTEGRAL

SP134/NMR/1 IN DMSO-D6 + TMS
SPXX4982.BWC
AU:
OVRNGT
PPG:
QUADCYCL.PC
DATE 18-9-96
SF 300.130
O1 6800.000
SI 32768
TD 24000
SW 5000.000
HZ/PT .305
RG 8
NE 1
NS 16
TE 297
DW 100.0
FW 6000
O2 4800.000
DP 63L PO
D0 3.000S
D1 6.000U
D2 1.000U
D3 30.000U
D4 1.000U
LB .500
GB 0.0
NC 1
CX 24.00
CY 0.0
SR 4788.29
8.96552
8.95653
8.53245
8.52858
3.95448
3.47160
3.16840
2.94566
2.84736
2.51035
2.50439
2.49852
.04935
.00001
.01060
.04996
1.8
1.4
156.6
11.3
5.5
PPM
INTEGRAL

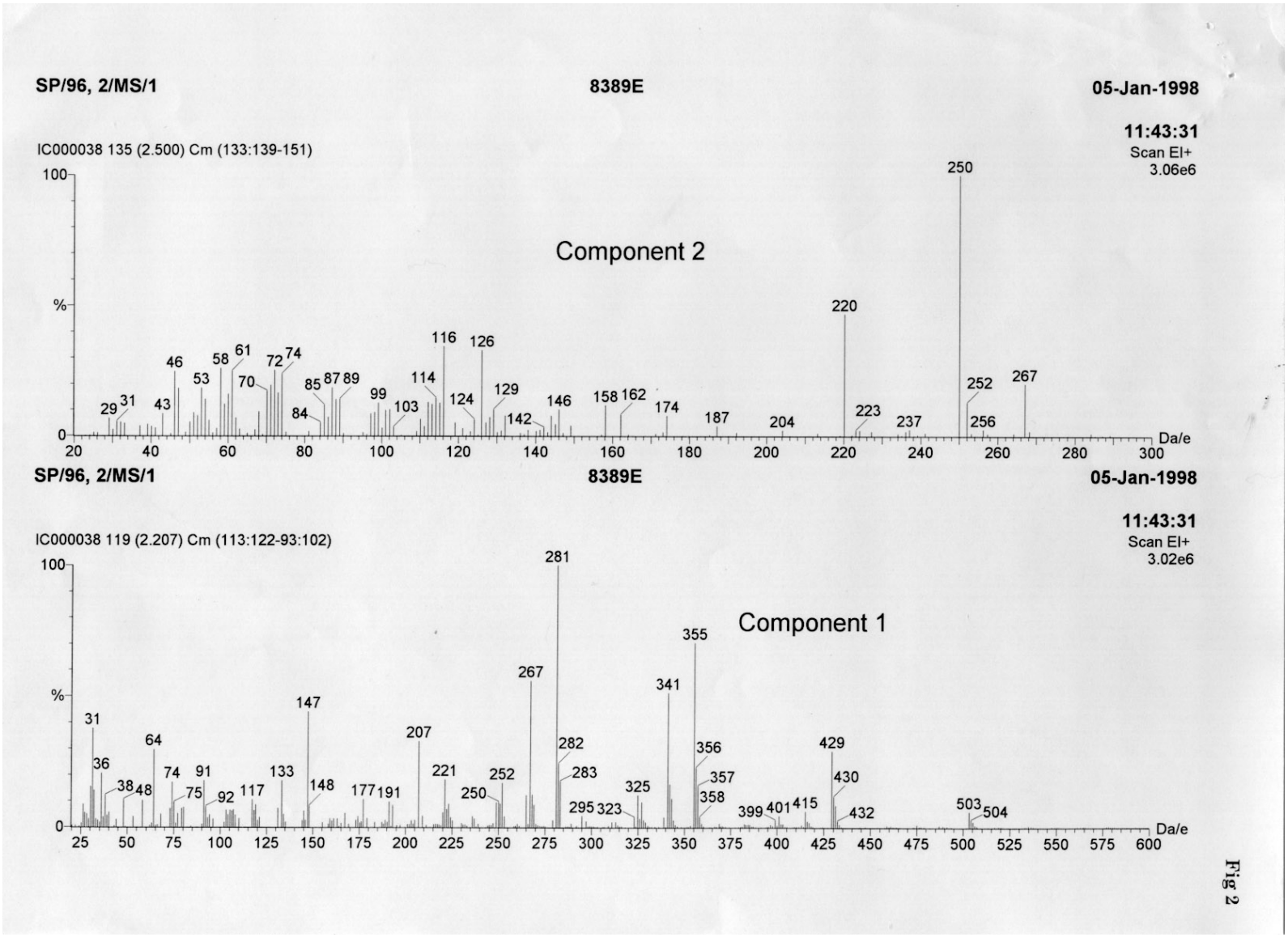
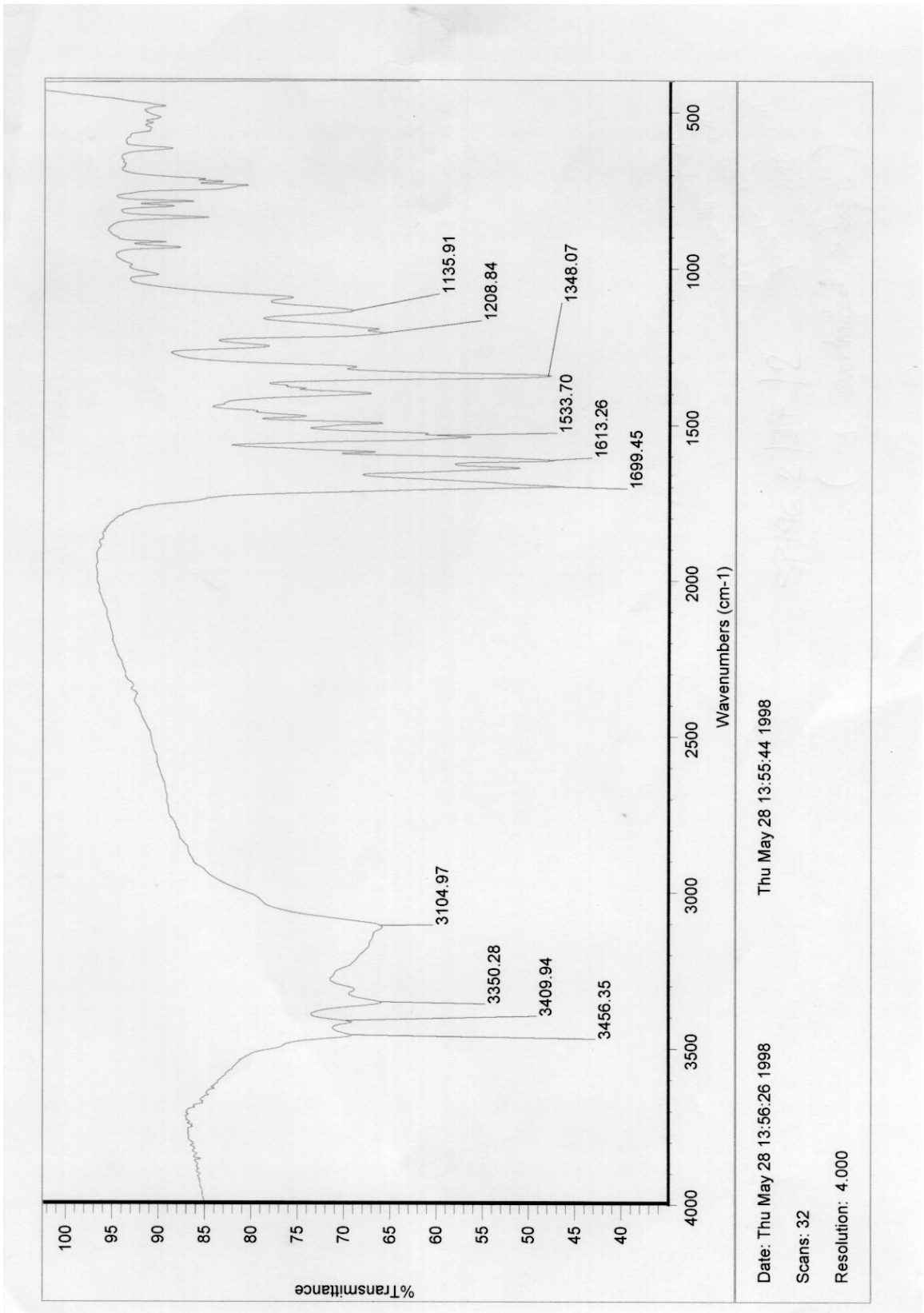
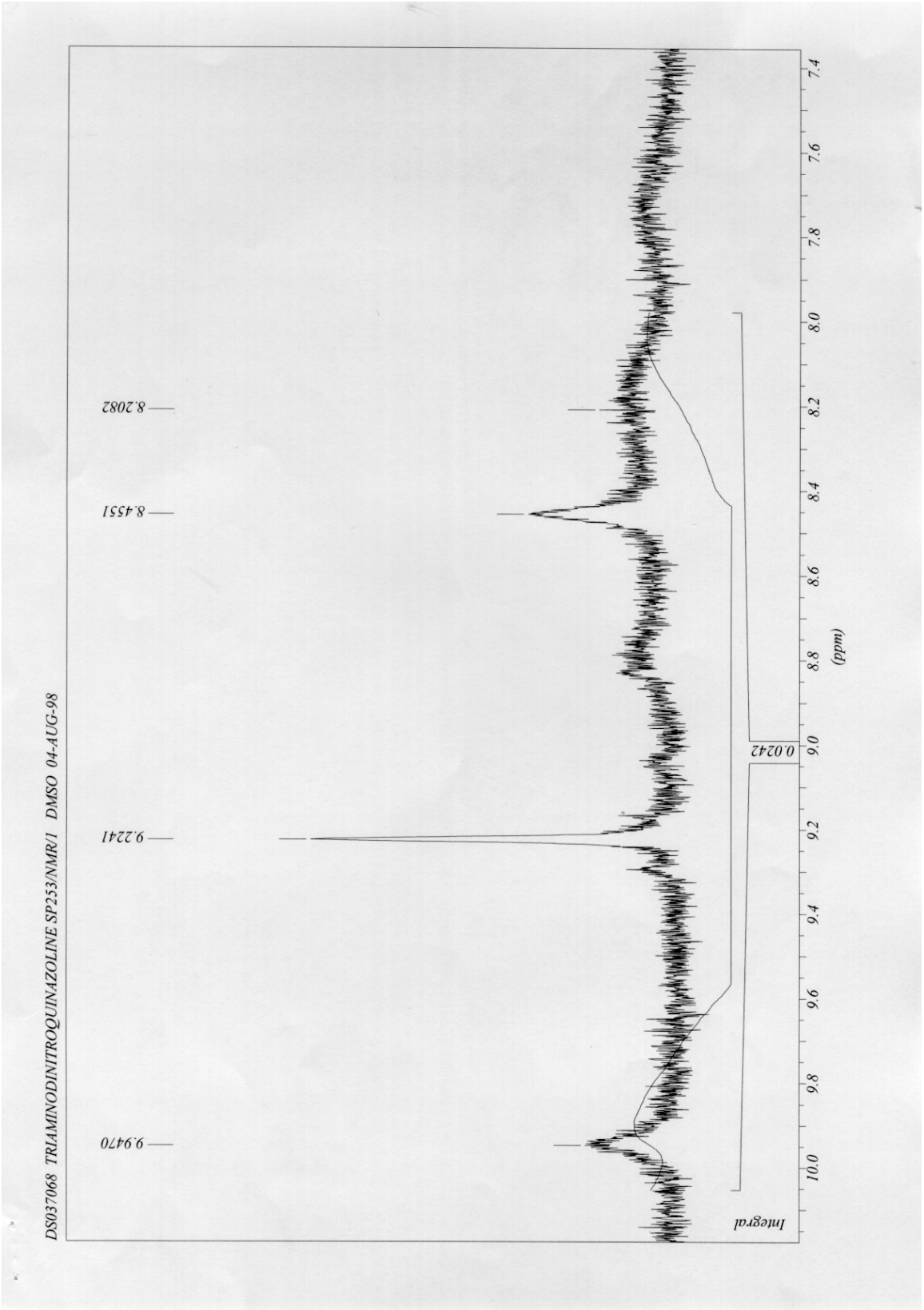

SP/96, 2/MS/1
8389E
05-Jan-1998
11:43:31
Scan EI+
3.06e6
IC000038 135 (2.500) Cm (133:139-151)
Component 2
100
%
0
Da/e
20 40 60 80 100 120 140 160 180 200 220 240 260 280 300
29 31 43 46 53 58 61 70 72 74 84 85 87 89 99 103 114 116 124 126 129 142 146 158 162 174 187 204 220 223 237 250 252 256 267
SP/96, 2/MS/1
8389E
05-Jan-1998
11:43:31
Scan EI+
3.02e6
IC000038 119 (2.207) Cm (113:122-93:102)
Component 1
100
%
0
Da/e
25 50 75 100 125 150 175 200 225 250 275 300 325 350 375 400 425 450 475 500 525 550 575 600
31 36 38 48 64 74 75 91 92 117 133 147 148 177 191 207 221 250 252 267 281 282 283 295 323 325 341 355 356 357 358 399 401 415 429 430 432 503 504

Fig 2


%Transmittance
100
95
90
85
80
75
70
65
60
55
50
45
40
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)
3104.97
3350.28
3409.94
3456.35
1135.91
1208.84
1348.07
1533.70
1613.26
1699.45
Date: Thu May 28 13:56:26 1998
Thu May 28 13:55:44 1998
Scans: 32
Resolution: 4.000


DS037068 TRIAMINODINITROQUINAZOLINE SP253/NMR/1 DMSO 04-AUG-98
9.9470
9.2241
8.4551
8.2082
Integral
0.0242
(ppm)
10.0
9.8
9.6
9.4
9.2
9.0
8.8
8.6
8.4
8.2
8.0
7.8
7.6
7.4

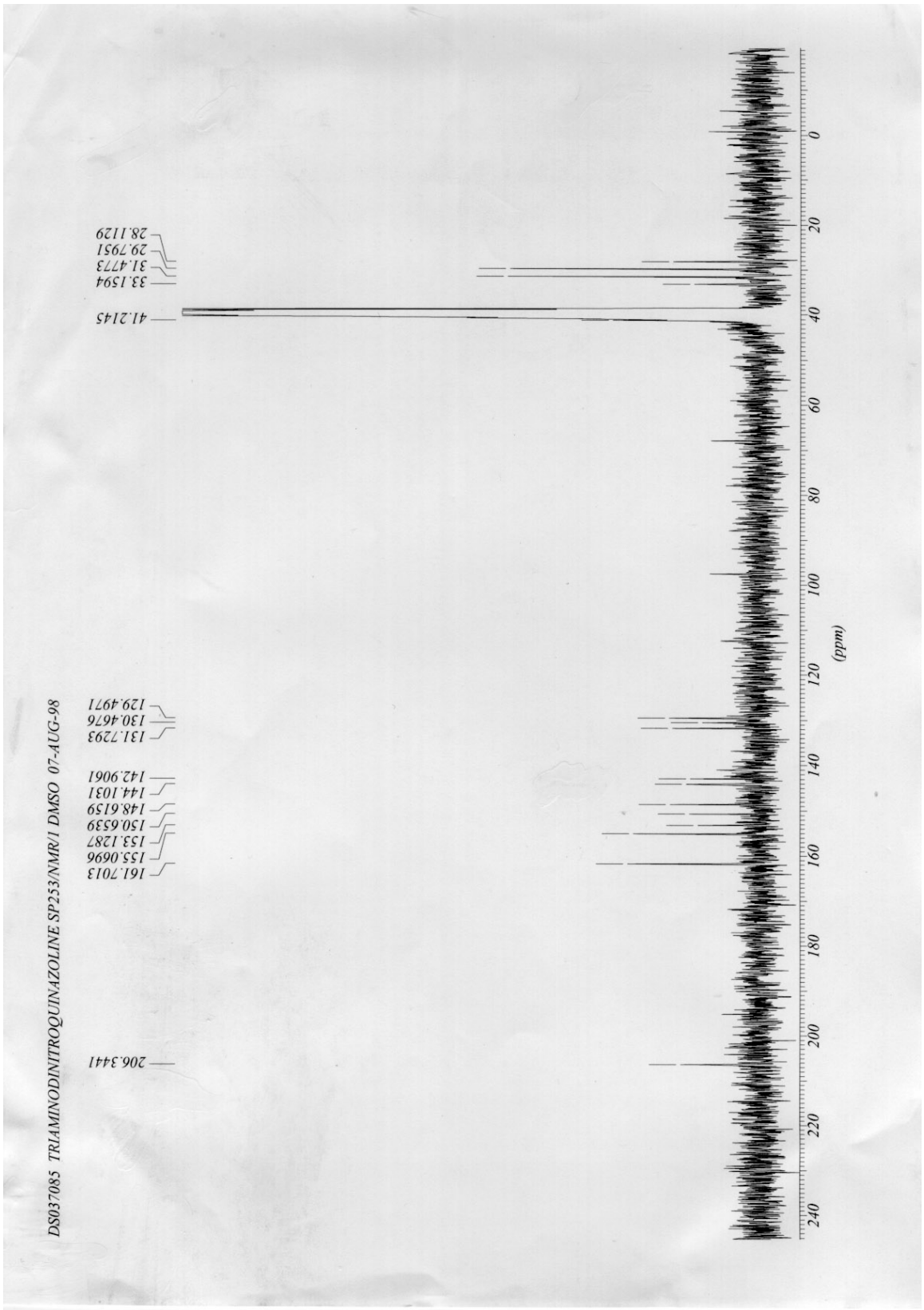
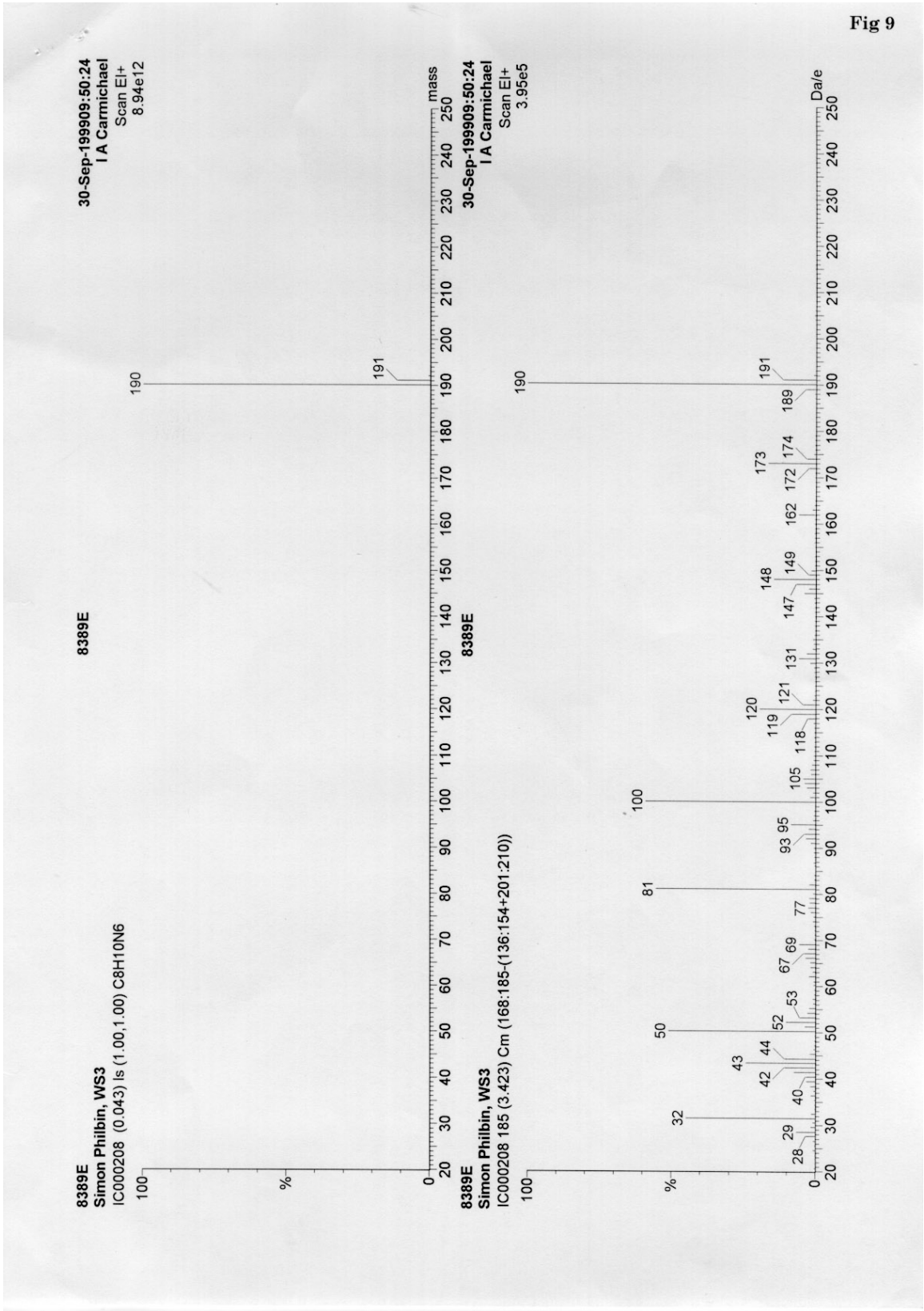
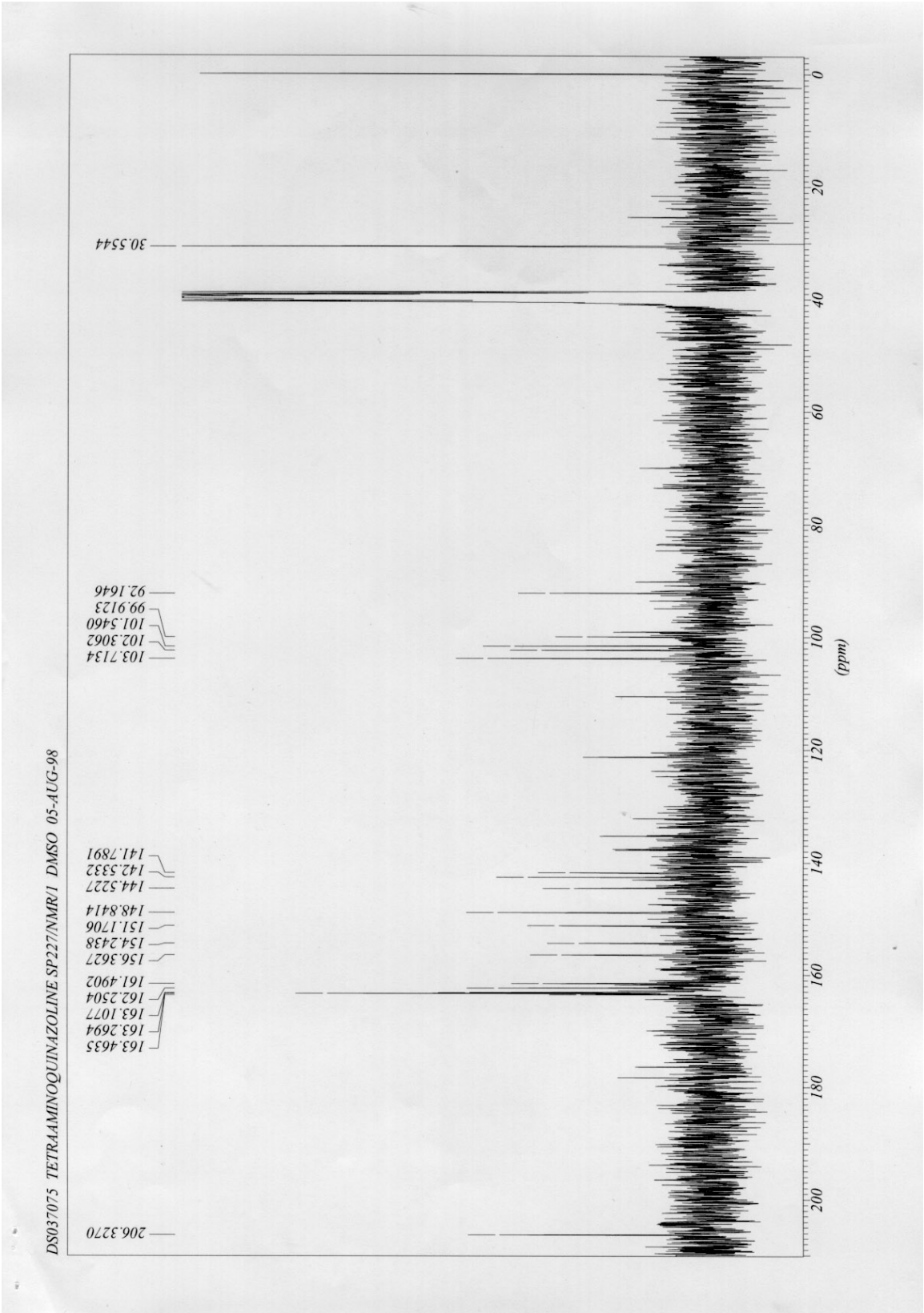
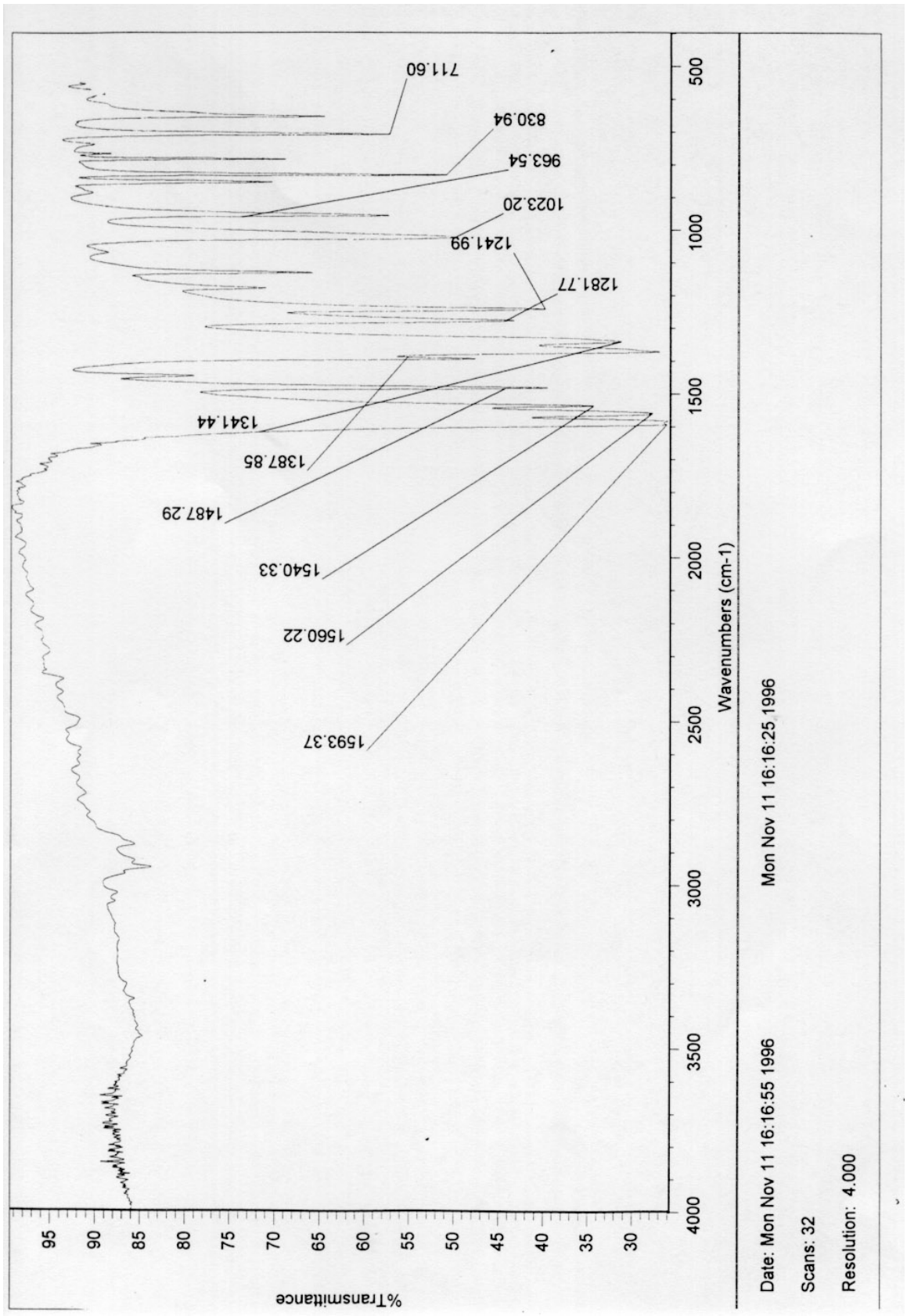
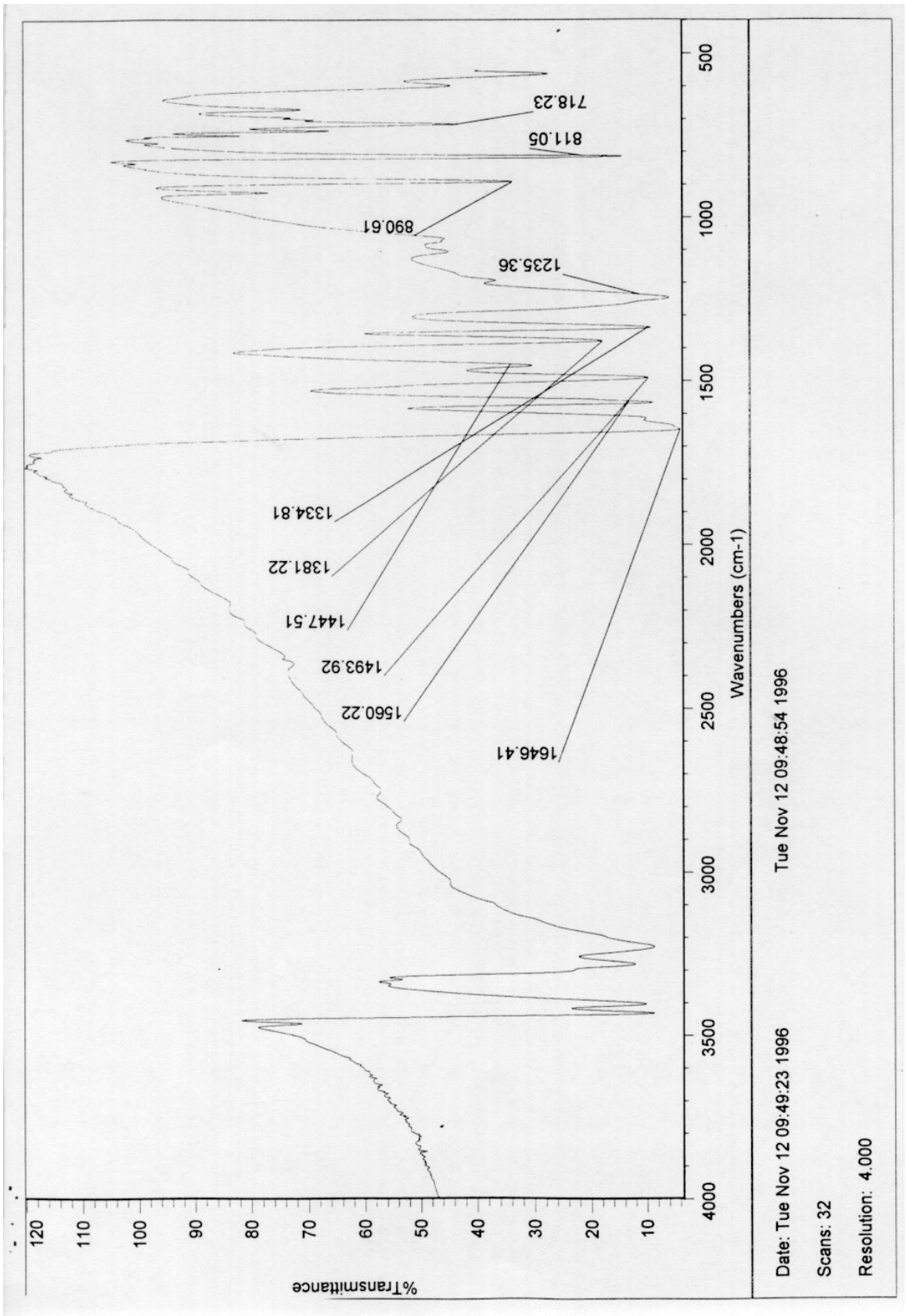

DS037085 TRIAMINODINITROQUINAZOLINE SP253/NMR/1 DMSO 07-AUG-98
206.3441
161.7013
155.0696
153.1287
150.6539
148.6159
144.1031
142.9061
131.7293
130.4676
129.4971
41.2145
33.1594
31.4773
29.7951
28.1129
0
20
40
60
80
100
120
140
160
180
200
220
240
(ppm)

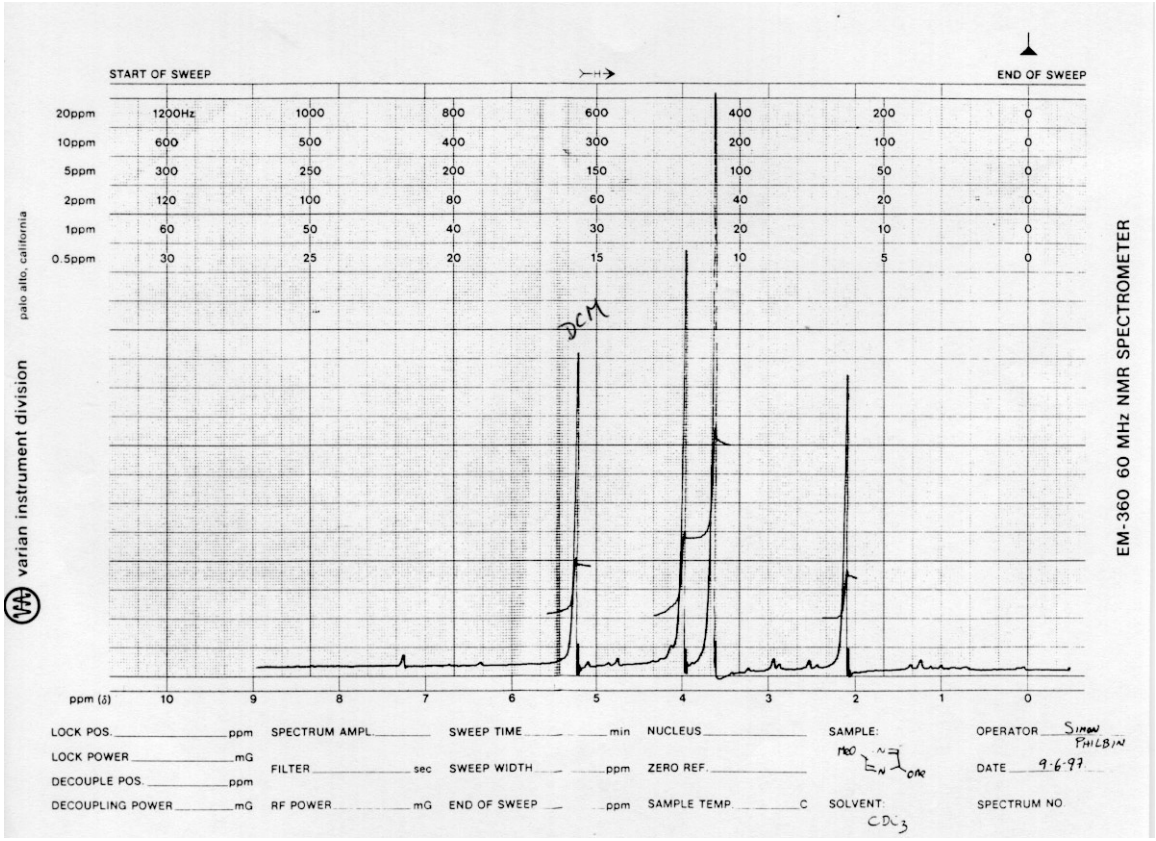
Fig 9

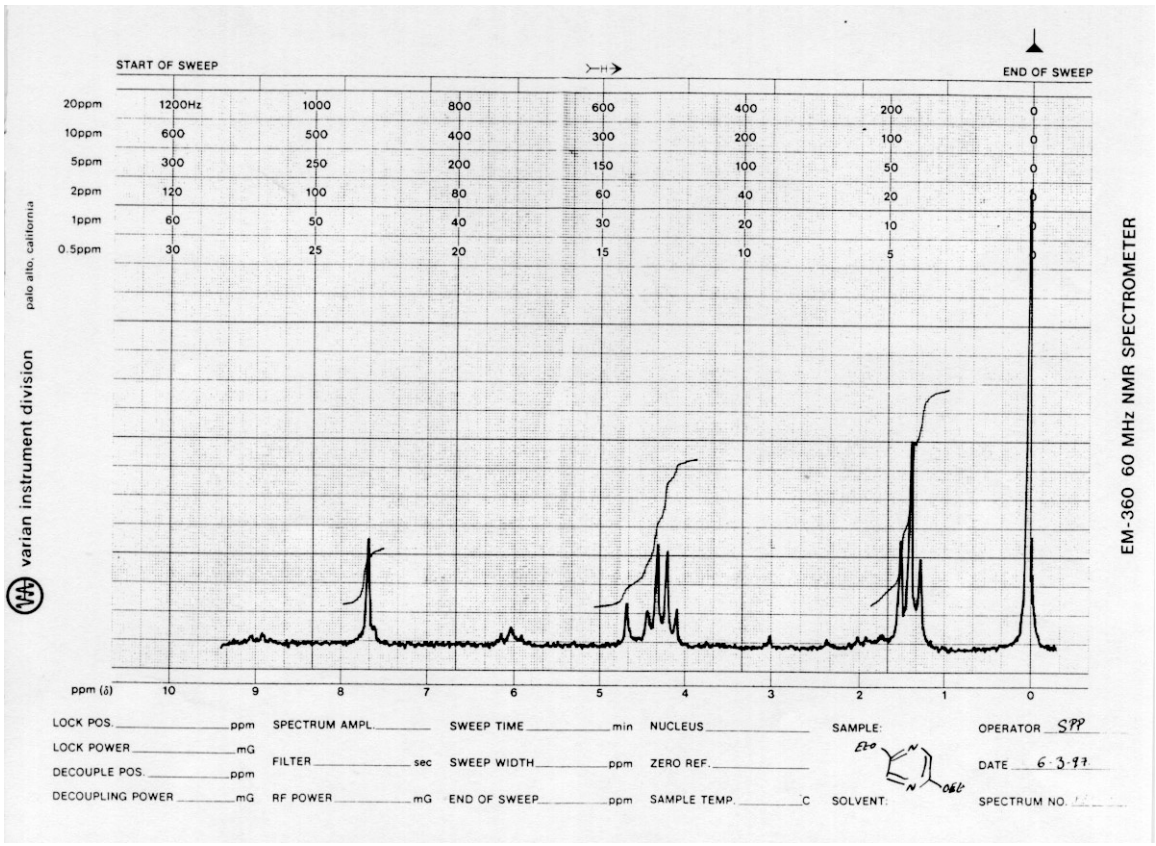

8389E
Simon Philbin, WS3
IC000208 (0.043) Is (1.00,1.00) C8H10N6
30-Sep-199909:50:24
I A Carmichael
Scan EI+
8.94e12
8389E
30-Sep-199909:50:24
I A Carmichael
Scan EI+
3.95e5
8389E
Simon Philbin, WS3
IC000208 185 (3.423) Cm (168:185-(136:154+201:210))
%
mass
Da/e

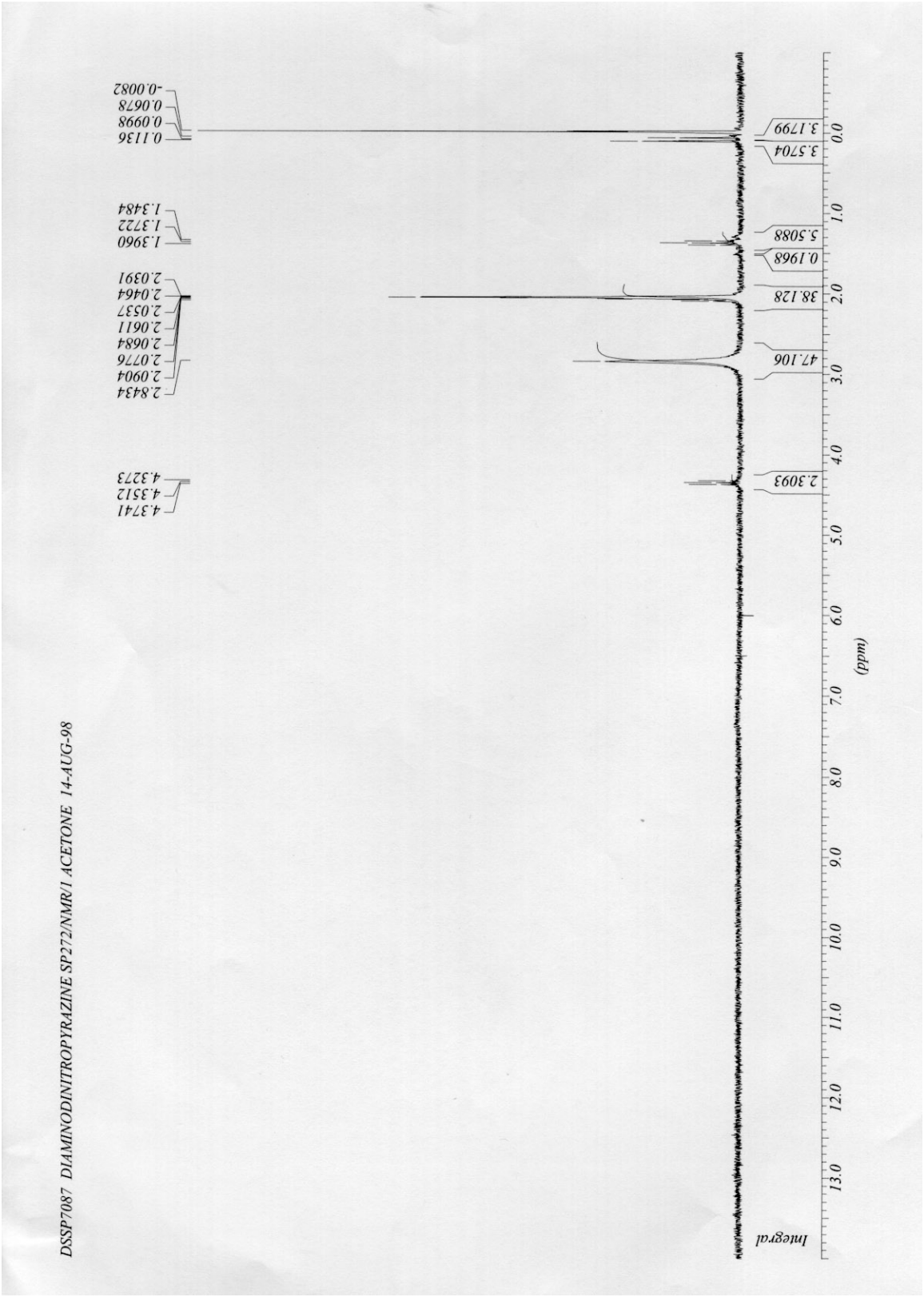

DS037075 TETRAAMINOQUINAZOLINE SP227/NMR/1 DMSO 05-AUG-98
206.3270
163.4635
163.2694
163.1077
162.2504
161.4902
156.3627
154.2438
151.1706
148.8414
144.5227
142.5332
141.7891
103.7134
102.3062
101.5460
99.9123
92.1646
30.5544
0
20
40
60
80
100
120
140
160
180
200
(ppm)


711.60
830.94
963.54
1023.20
1241.99
1281.77
1341.44
1387.85
1487.29
1540.33
1560.22
1593.37
%Transmittance
Wavenumbers (cm-1)
Date: Mon Nov 11 16:16:55 1996
Mon Nov 11 16:16:25 1996
Scans: 32
Resolution: 4.000


%Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
500
120
110
100
90
80
70
60
50
40
30
20
10
1646.41
1560.22
1493.92
1447.51
1381.22
1334.81
1235.36
890.61
811.05
718.23
Date: Tue Nov 12 09:49:23 1996
Tue Nov 12 09:48:54 1996
Scans: 32
Resolution: 4.000


START OF SWEEP
END OF SWEEP
20ppm 1200Hz 1000 800 600 400 200 0
10ppm 600 500 400 300 200 100 0
5ppm 300 250 200 150 100 50 0
2ppm 120 100 80 60 40 20 0
1ppm 60 50 40 30 20 10 0
0.5ppm 30 25 20 15 10 5 0
DCM
ppm (δ) 10 9 8 7 6 5 4 3 2 1 0
varian instrument division
palo alto, california
EM-360 60 MHz NMR SPECTROMETER
LOCK POS. ppm
LOCK POWER mG
DECOUPLE POS. ppm
DECOUPLING POWER mG
SPECTRUM AMPL.
FILTER sec
RF POWER mG
SWEEP TIME min
SWEEP WIDTH ppm
END OF SWEEP ppm
NUCLEUS
ZERO REF.
SAMPLE TEMP. C
SAMPLE:
SOLVENT
CDCl3
OPERATOR Simon Philbin
DATE 9-6-97
SPECTRUM NO.


START OF SWEEP
END OF SWEEP
20ppm 1200Hz 1000 800 600 400 200 0
10ppm 600 500 400 300 200 100 0
5ppm 300 250 200 150 100 50 0
2ppm 120 100 80 60 40 20 0
1ppm 60 50 40 30 20 10 0
0.5ppm 30 25 20 15 10 5 0
ppm (δ) 10 9 8 7 6 5 4 3 2 1 0
varian instrument division
palo alto, california
EM-360 60 MHz NMR SPECTROMETER
LOCK POS. ppm
LOCK POWER mG
DECOUPLE POS. ppm
DECOUPLING POWER mG
SPECTRUM AMPL.
FILTER sec
RF POWER mG
SWEEP TIME min
SWEEP WIDTH ppm
END OF SWEEP ppm
NUCLEUS
ZERO REF.
SAMPLE TEMP. C
SAMPLE:
SOLVENT:
OPERATOR SPP
DATE 6-3-97
SPECTRUM NO.


DSSP7087 DIAMINODINITROPYRAZINE SP272/NMR/1 ACETONE 14-AUG-98
Integral
3.1799
3.5704
5.5088
0.1968
38.128
47.106
2.3093
0.1136
0.0998
0.0678
-0.0082
1.3960
1.3722
1.3484
2.8434
2.0904
2.0776
2.0684
2.0611
2.0537
2.0464
2.0391
4.3741
4.3512
4.3273
(ppm)

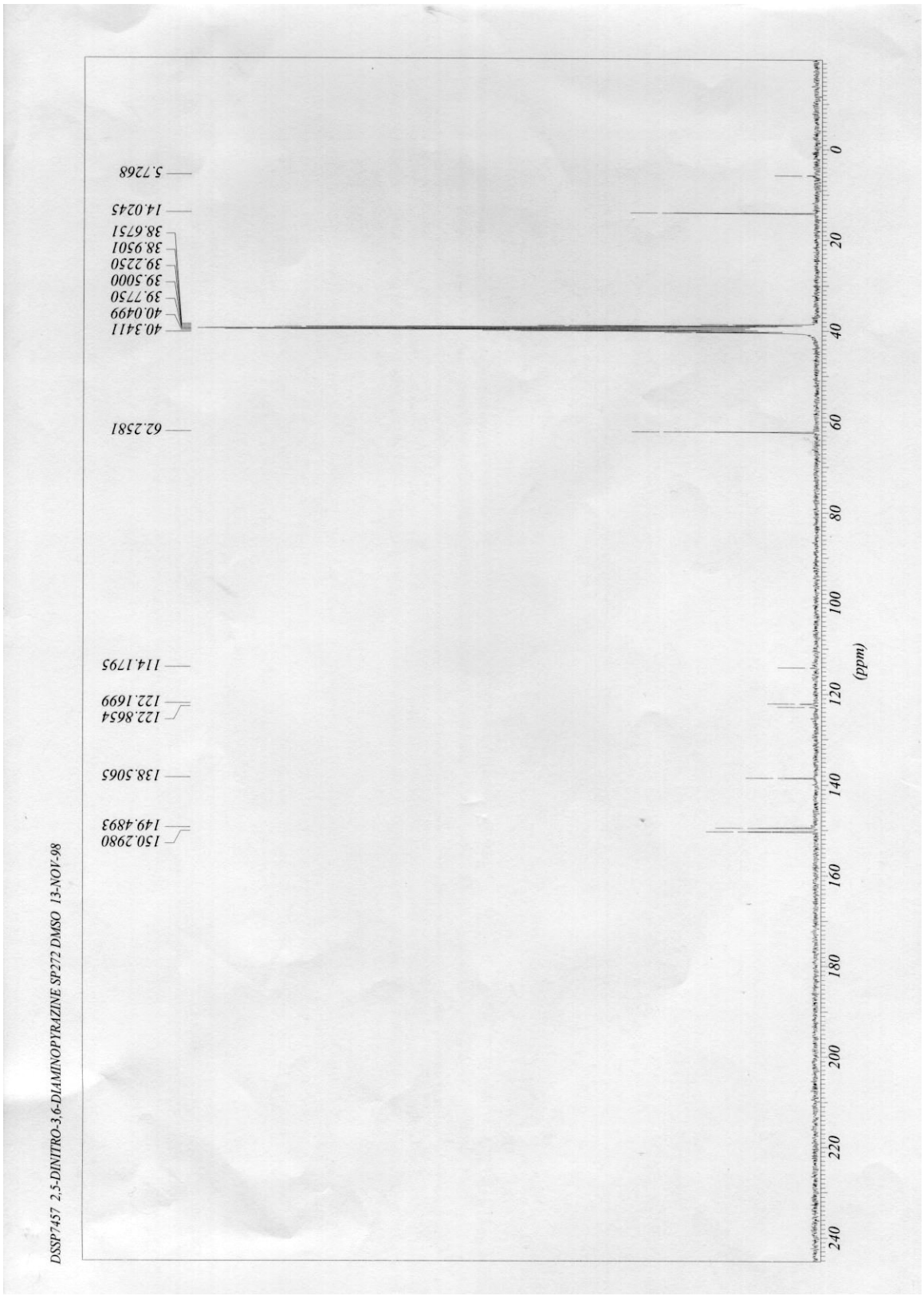
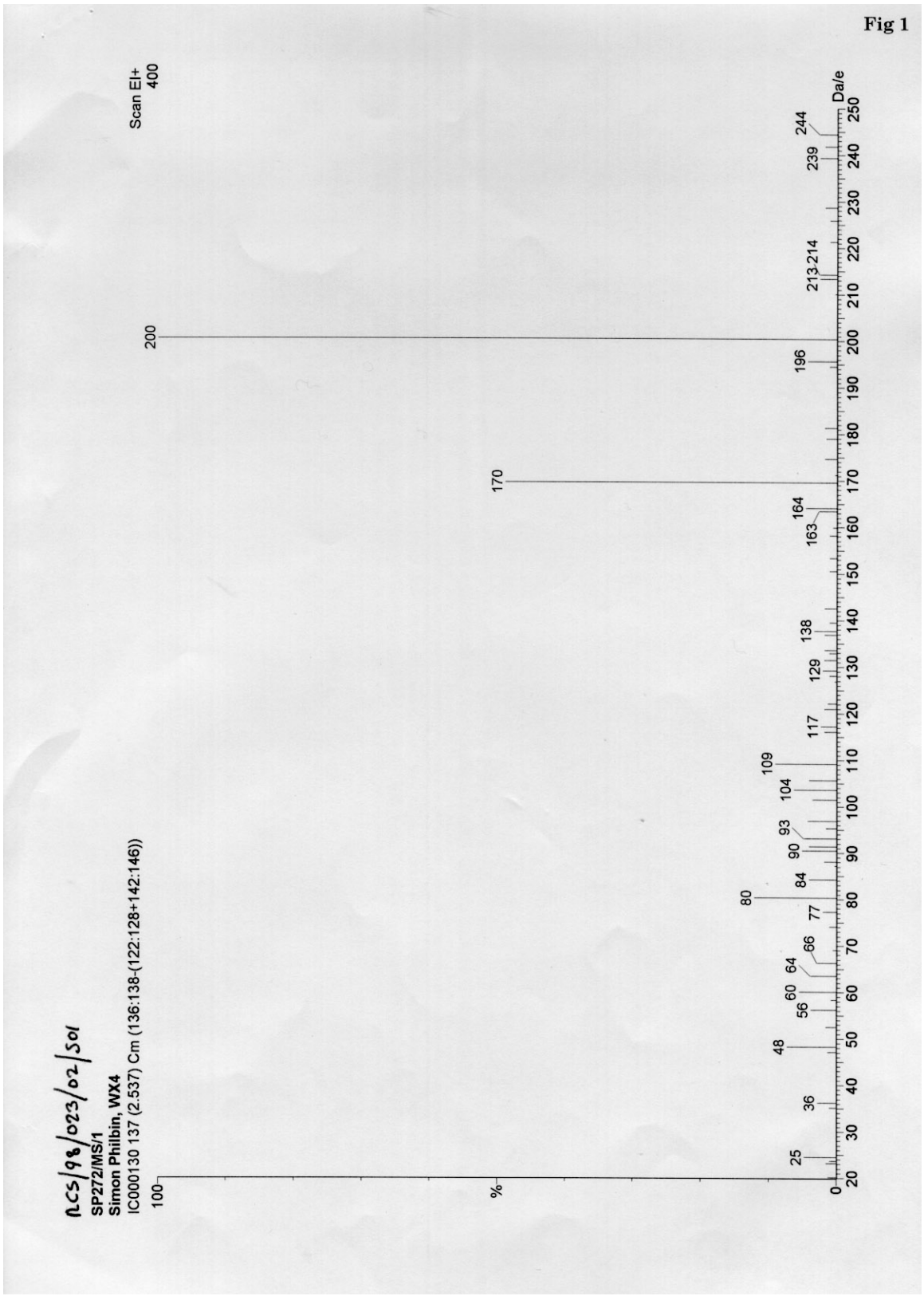

DSSP7457 2,5-DINITRO-3,6-DIAMINOPYRAZINE SP272 DMSO 13-NOV-98
150.2980
149.4893
138.5065
122.8654
122.1699
114.1795
62.2581
40.3411
40.0499
39.7750
39.5000
39.2250
38.9501
38.6751
14.0245
5.7268
(ppm)

Fig 1


NCS/98/023/02/S01
SP272/MS/1
Simon Philbin, WX4
IC000130 137 (2.537) Cm (136:138-(122:128+142:146))
Scan EI+
100
%
0
400
200
170
80
48
25
36
56
60
64
66
77
84
90
93
104
109
117
129
138
163
164
196
213
214
239
244
Da/e

SPPMM/06 Summary of Calculations

Data:

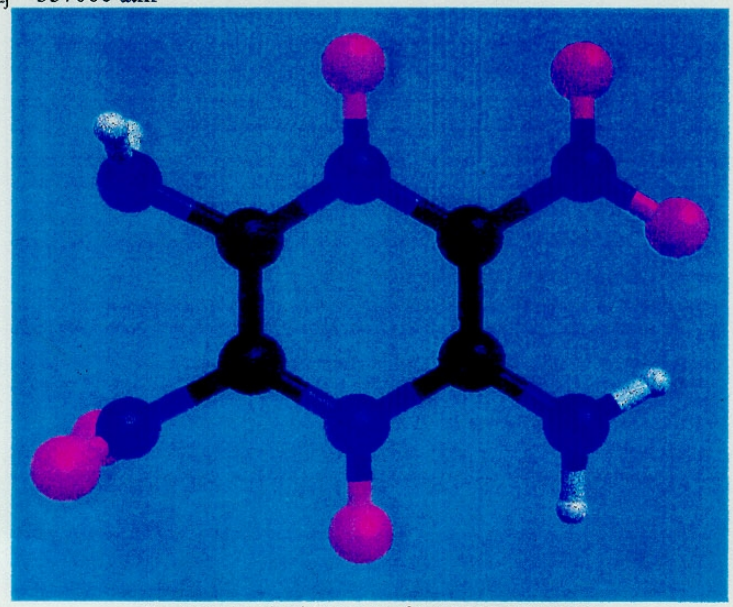
MM = 232.112 amu

H_{f298} = 38 kcal/mol

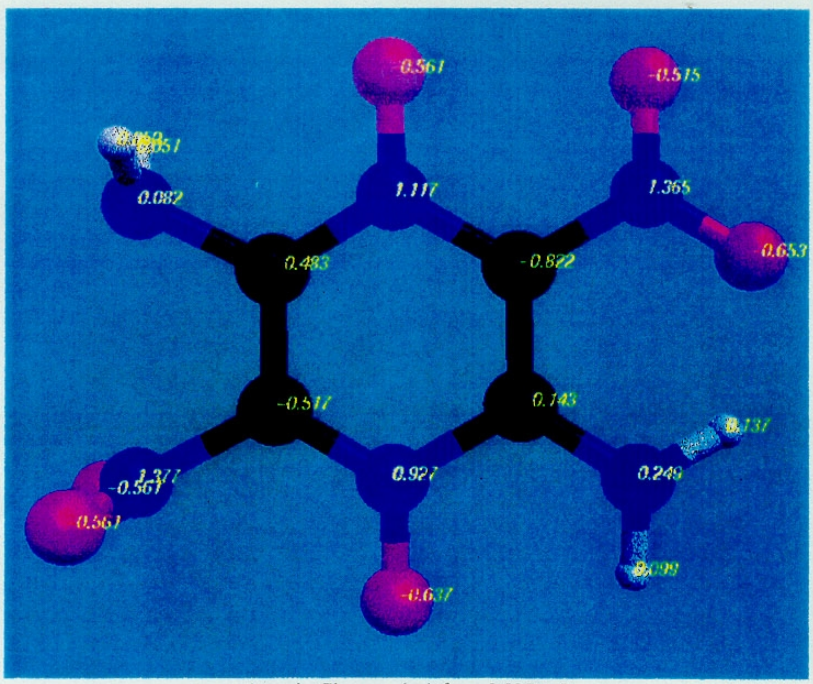
Density = 1.842 g/cm^3 (max from MOLPAK)

V_D = 8.54 km/s

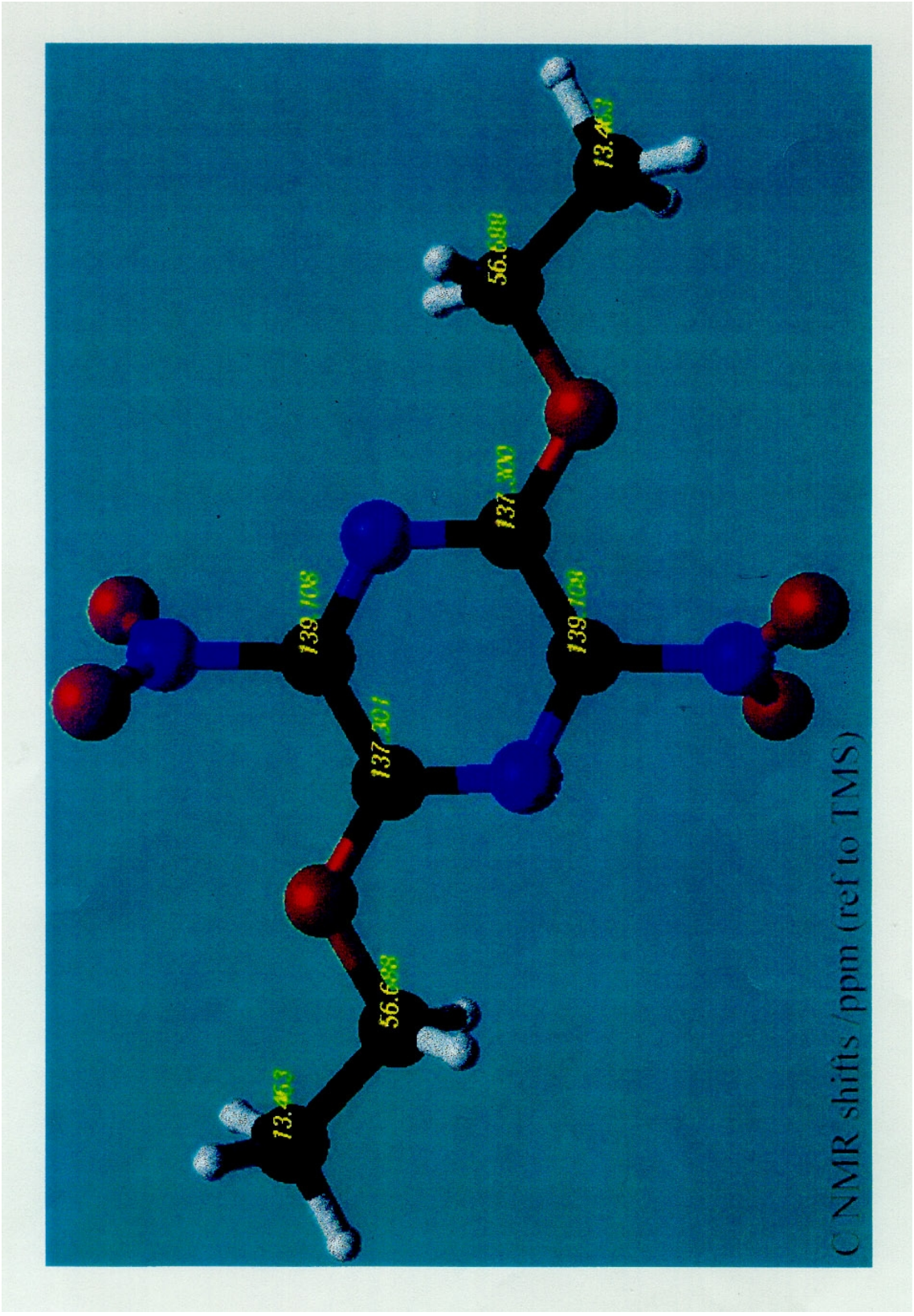
P_{c-j} = 337000 atm

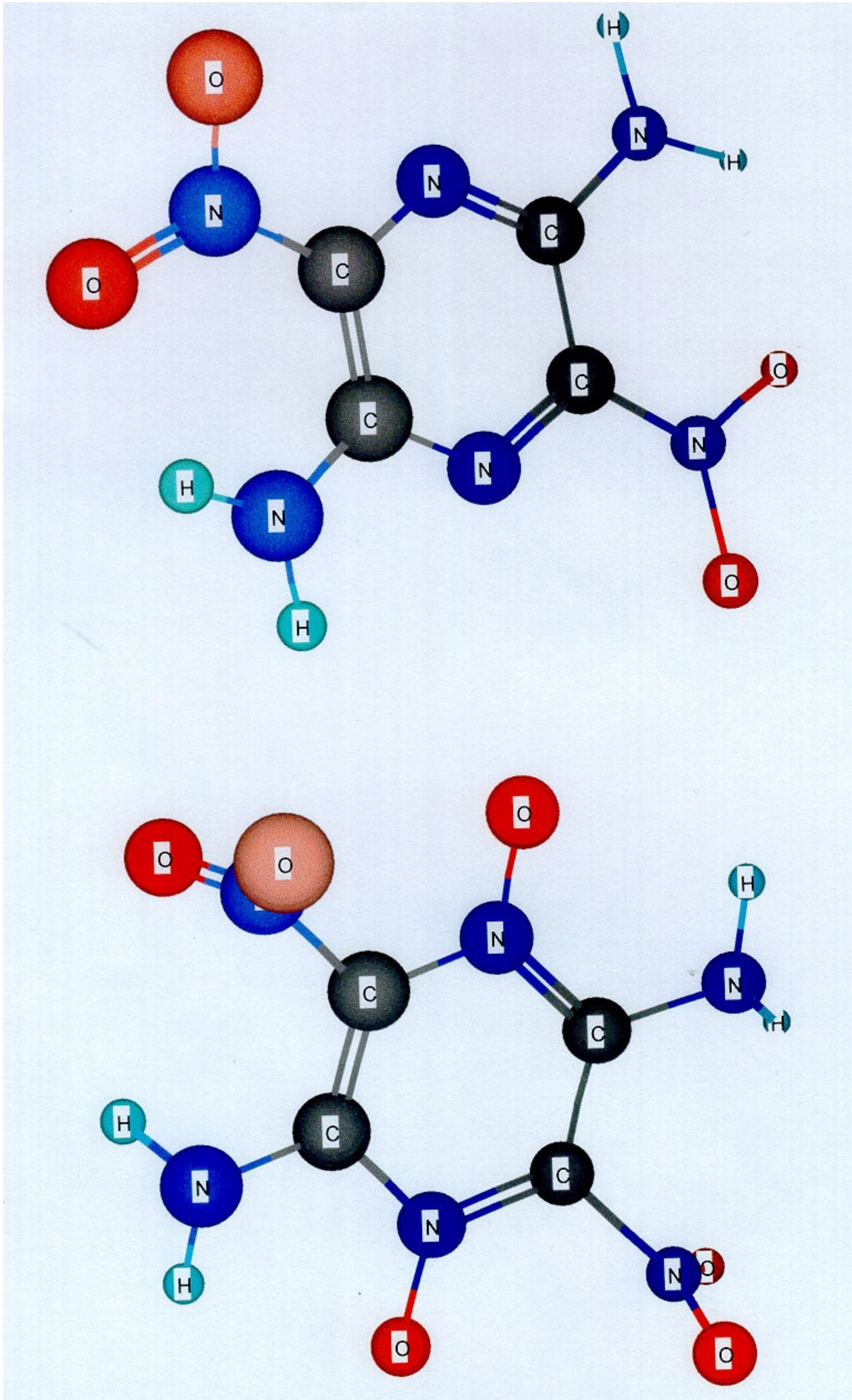


Energy minimised geometry from MOPAC (PM3)



Atomic Charges (au) from MOPAC


C NMR shifts /ppm (ref to TMS)


H
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H
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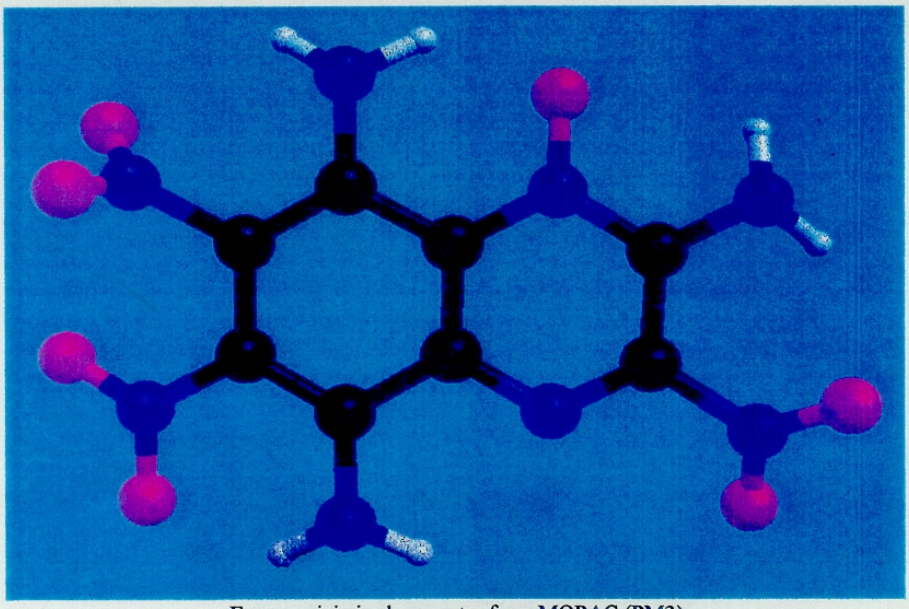
O

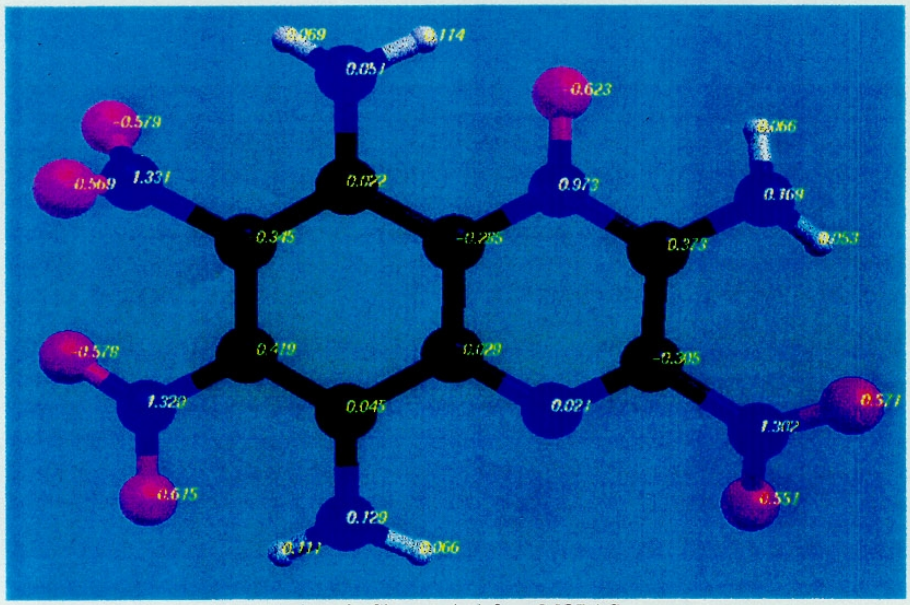
SPPMM/04 Summary of Calculations

Data:

MM = 326.185 amu
$H_{f,298}$ = 59.5 kcal/mol
Density = 1.788 g/cm^3 (max from MOLPAK)
V_D = 7.86 km/s
$P_{c\text{-}j}$ = 271100 atm



Energy minimised geometry from MOPAC (PM3)

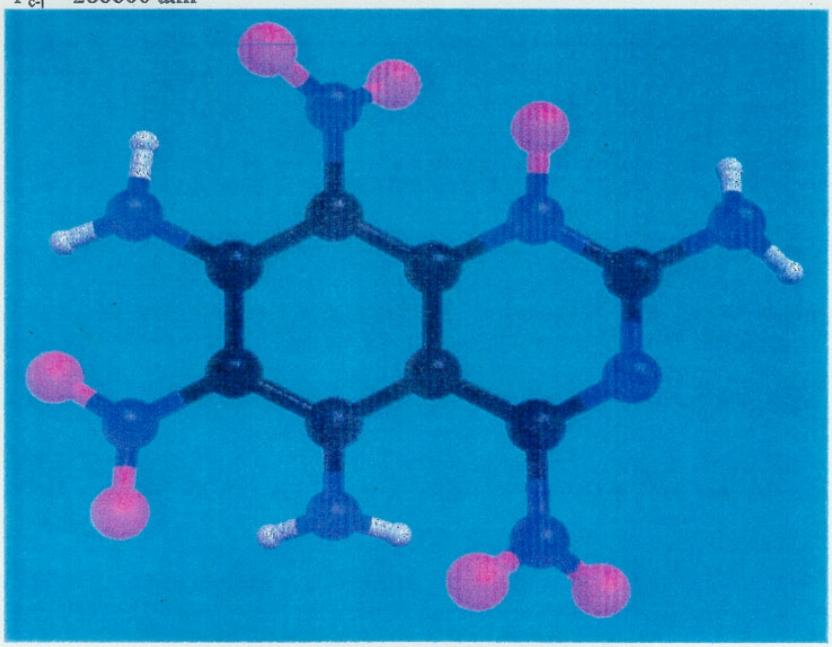


Atomic Charges (au) from MOPAC

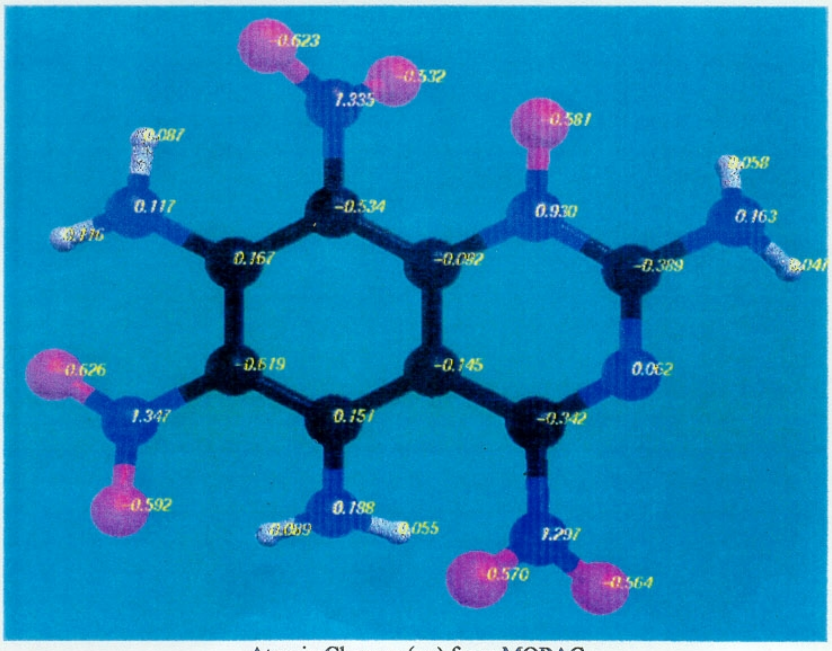
SPPMM/05 Summary of Calculations

Data:

MM = 326.185 amu
$H_{f,298}$ = 78.5 kcal/mol
Density = 1.812 g/cm^3 (max from MOLPAK)
V_D = 8.0 km/s
P_{c-j} = 286600 atm



Energy minimised geometry from MOPAC (PM3)



Atomic Charges (au) from MOPAC

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13. Appendix 1: Publications and Presentations Arising From this Work (to Date)

13.1 External Publications

1. S. P. Philbin,* R. W. Millar, R. G. Coombes, Preparation of 2,5-Diamino-3,6-dinitropyrazine (ANPZ-i): A Novel Candidate High Energy Insensitive Explosive, *Propellants, Explosives, Pyrotechnics*, **25**, 302-306 (2000).

13.2 Oral Presentations

1. S. P. Philbin,* High Energy Insensitive Explosives, TEEMAC [Terminal Effects and Energetic Materials Advisory Committee (MoD)] Meeting, DERA Fort Halstead, Kent, UK, 1998.
2. S. P. Philbin,* R. W. Millar, R. G. Coombes, Studies of Novel Nitro-Substituted Benzodiazines, Royal Society of Chemistry (RSC) National Congress, Younger Researchers Meeting (Perkin Division), Durham University, UK, 1998.[a]
3. S. P. Philbin,* R. W. Millar, R. G. Coombes, Studies of Novel Nitro-Substituted Nitrogen Heterocyclic Compounds, NDIA (National Defence Industrial Association) Insensitive Munitions and Energetic Materials (IM/EM) Technology Symposium, Tampa (FL), USA, 1999.[b]

13.3 Poster Presentations

1. S. P. Philbin,* R. W. Millar, R. G. Coombes, Studies of Novel Nitro-Substituted Nitrogen Heterocyclic Compounds, 13th Lakeland International Heterocyclic Symposium, Grasmere, UK, 1997.
2. S. P. Philbin,* R. W. Millar, R. G. Coombes, Studies of Novel Nitroquinoxaline and Nitroquinazoline Compounds, Winter School on Organic Reactivity (WISOR VII), Bressanone, Italy, 1998.

Key: * Principal author/presenter.
a Abstract published in abstract proceedings.
b Full paper published in conference proceedings.