THE SYNTHESIS OF POTENTIAL ANTI-PARASITIC COMPOUNDS

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This thesis is dedicated to my late Grandfather, Shree Maganlal M. Bhatt

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ABSTRACT

Novel members of a homologous series of *N'*,*N'*-di-(2,6-dinitro-4-trifluoromethyl-phenyl)diamine dimers related to the anti-malarial compound trifluralin (2,6-dinitro-(*N*,*N*-dipropylamino-4-trifluoromethyl)benzene) have been synthesised in good yields for screening against several tropical diseases such as Leishmaniasis, Trypanosomiais, and Malarial in both humans and animals. This was achieved in a single step reaction where the starting material chloralin (1-chloro-2,6-dinitro-4-trifluoromethylbenzene) was reacted with various aliphatic and aromatic diamines via the key step involving nucleophilic aromatic *ipso*-substitution. The final compounds were obtained via the intermediate Jackson-Meisenheimer complexes. The formation of the corresponding tri- and tetra-substituted hydrazines were, however, not successful due to unfavourable steric interactions.

Previous investigations by other researchers have postulated tubulin (a dimeric protein) as a potential site of drug action. Based on this theory such compounds were synthesised that may play a role in mapping distances between tubulin binding sites.

As both the herbicides, trifluralin and oryzalin (3,5-dinitro-4-(*N*,*N*-dipropylamino)-benzenesulphonamide) have been shown to possess anti-leishmanial and anti-malarial activities against *Leishmania mexicana* (*in vivo*) and *Plasmodium falciparum* (*in vitro*) respectively, a new analogue of oryzalin, 4-(*N*,*N*-dipropylsulphamoyl)-2,6-dinitro-1-(*N*,*N*-dipropylamino)benzene has been synthesised for possible screening.

The study was extended to the synthesis of julolidine (2,3,6,7-tetrahydro-1*H*,5*H*-benzo[ij] quinolizine) and lilolidine (1,4,5,6-tetrahydro-2*H*-pyrrolo[3,2,1[ij]quinoline) analogues since the parent ring structures are known to exhibit anti-leishmanial activities. This was achieved by reacting several aromatic amines with a series of α, β-ketoesters to give the intermediate amides, which were then cyclised (*in situ*) via Friedel-Crafts acylation using polyphosphoric acid to the corresponding substituted julolidine and lilolidine analogues.

Spectroscopic data on trifluralins, julolidines and related compounds is presented in this thesis and were found to be consistent with the proposed structures.

Although in this study the emphasis lies on synthetic aspects and spectroscopic evaluations some preliminary biological data is summarised in the Appendix, while the remaining testing will form part of an ongoing programme of work by others.

CONTENTS

INTRODUCTION

1.1 Tropical Diseases: A Historical Perspective

The term "tropical diseases" refers to a group of disorders, usually localised to regions of our planet characterised by a hot climate; but it also carries the stigma that these affect particularly developing countries. The number and variety of diseases included in this term are vast, and comprise those with infectious, toxic and nutritional disorders.

The evolution of most diseases started when our planet developed its present geographic, climatic and environmental characteristics some 10,000 years ago [1] when human habitat changed from nomadic to stable and when agricultural practices were started. This produced a number of advantages, among others the fact that, not having to rely exclusively on hunting for survival, accidents decreased considerably. The drawbacks included accumulation of litter and sewage in close proximity of dwellings, hence the presence of high concentrations of bacteria and parasites. Furthermore, the change from a carnivorous to a vegetable diet altered the type of human parasites, whilst animal husbandry and the presence of domestic animals within the household introduced zoonoses. In addition, the need for a continuous water supply, essential for irrigation, led to construction of reservoirs with the consequent formation of marshes, an ideal background for insects and for the spread of malaria.

Although parasitic diseases are usually limited to some regions of the planet, the vast majority affect tropical and subtropical areas and are endemic among poverty-stricken populations. The increase of mass tourism in the last decades and the loosening of health controls have made it possible for some of these diseases to spread more easily to previously unaffected areas.

In the early times, the knowledge of diseases was based exclusively on the examination of human remains, the only ones available for the very early stages after man first appeared on the planet were bones, which understandably gave only a limited, and consequently a highly biased outline of the pattern of diseases at that time [1].

In the case of malaria, however, the examination of bones gave a reasonably good insight into its spread throughout the world [1]. Malaria remains a formidable global problem; more than 1 billion people live in malarious regions, including nearly 400 million in areas where eradication programs have not yet been started [2].

Today, cerebral malaria is found in substantial areas of the tropics and subtropics and is associated with widespread morbidity and mortality [3], especially in infants and children, as well as during pregnancy, producing a high morbidity among both mother and foetus [1, 4].

Sleeping sickness has been known for centuries and is present in East and Central Africa. It is caused by the protozoa of the family *Trypanosomatidae*, and was

discovered in 1902 [1]. Although African trypanosomiasis is predominantly a zoonosis, it is estimated that about 50 million people are at risk of infection [1]. Occurrence of this disease is caused by both, *T. brucei rhodescience* and *T. brucei gambience*. Chagas' disease, which was first recognised in 1909 is caused by *T. cruzi* and constitutes a major health problem in South and Central America, where it is estimated that 16 million people are infected and 90 million are at risk [1].

Cutaneous leishmaniasis traditionally has been a disease of special interest to dermatologists. This infection, transmitted by small blood-feeding phlebotomine sand flies, is one of the three clinical entities long recognised among the multifaceted manifestations caused by protozoans of the genus Leishmania; visceral leishmaniasis (VL), mucocutaneous leishmaniasis (MCL), and cutaneous leishmaniasis (CL) historically have been recognised [5]. During the past decade it has become increasingly apparent that all forms of leishmaniasis are much more prevalent than had been suspected, and the number of cases is increasing worldwide, and that the geographic distribution is becoming more widespread. Improved healthcare coverage has accounted for more frequent diagnosis, and better communication and reporting systems undoubtedly have contributed to an apparent increase in both prevalence and geographic distribution, primarily resulting from the opening of forest lands to new agricultural development.

Almost all forms of *leishmania* occur as zoonoses among wild animals, and humans are infected only accidentally when they become exposed to the natural transmission cycle. Leishmaniasis is endemic to 80 countries and is a major public health problem worldwide, with approximately 12 to 40 million cases estimated and 350 million people at risk [6].

In a sense, therefore, it is justifiable to say that tropical diseases could return to areas presently exempt from them should social and economic situations change dramatically for the worse and as a consequence the problem should be taken seriously by producing drugs that are more effective.

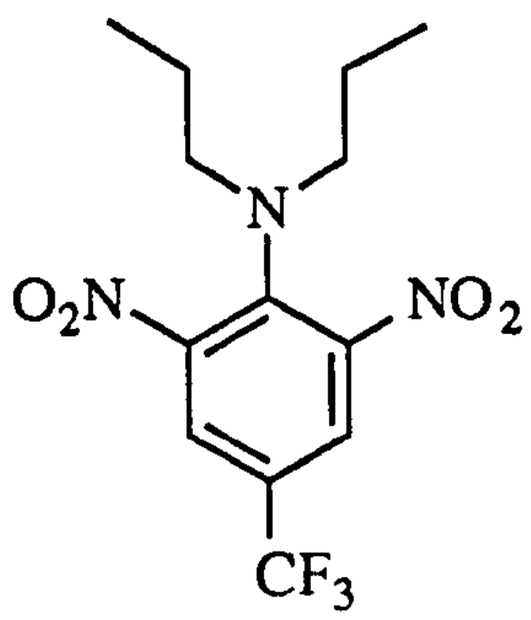
Although treatment for tropical diseases such as malaria (alkaloidal drugs), trypanosomiasis and leishmaniasis (trifluralins and antimonial drugs) are available, sadly, the occurrence of drug resistance has also been increasing in frequency worldwide.

Thus the purpose of this study is to synthesise a series of easily made compounds that may have potential medicinal interests. However, the biology of the diseases, their life cycles and the mode of action of the compounds is beyond the scope of this study. Hence, dinitroaniline dimers and monomers, julolidines and quinolinone analogues ('alkaloidal' compounds) were synthesised successfully because they are themselves interesting in terms of their chemical analyses. Most of the compounds are novel to the best of our knowledge, unless otherwise stated.

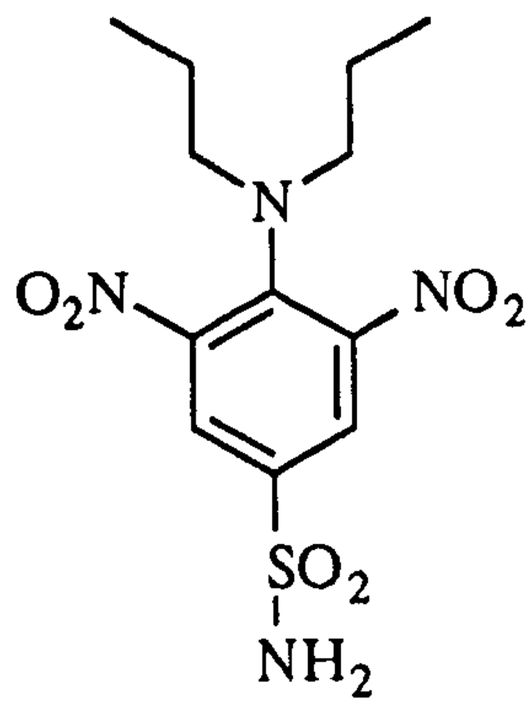
1.2 Dinitroanilines

An important series of selective dinitroaniline herbicides was introduced in agriculture in the 1960s [7]. As herbicides, the dinitroanilines cause multinucleation, accumulation of cells at the metaphase (in mitosis cell division), and the loss of microtubules from the root cells [8]. Studies suggest that they selectively bind to plant but not animal tubulins [7].

Traditionally, this group of closely related soil-applied herbicides is used in pre-plant or pre-emergence circumstances to control annual grasses [7]. Two important dinitroanilines are trifluralin, 2,6-dinitro-(*N*,*N*-dipropylamino-4-trifluoromethyl) benzene and oryzalin, 3,5-dinitro-4-(*N*,*N*-dipropylamino)benzenesulphonamide.



Trifluralin



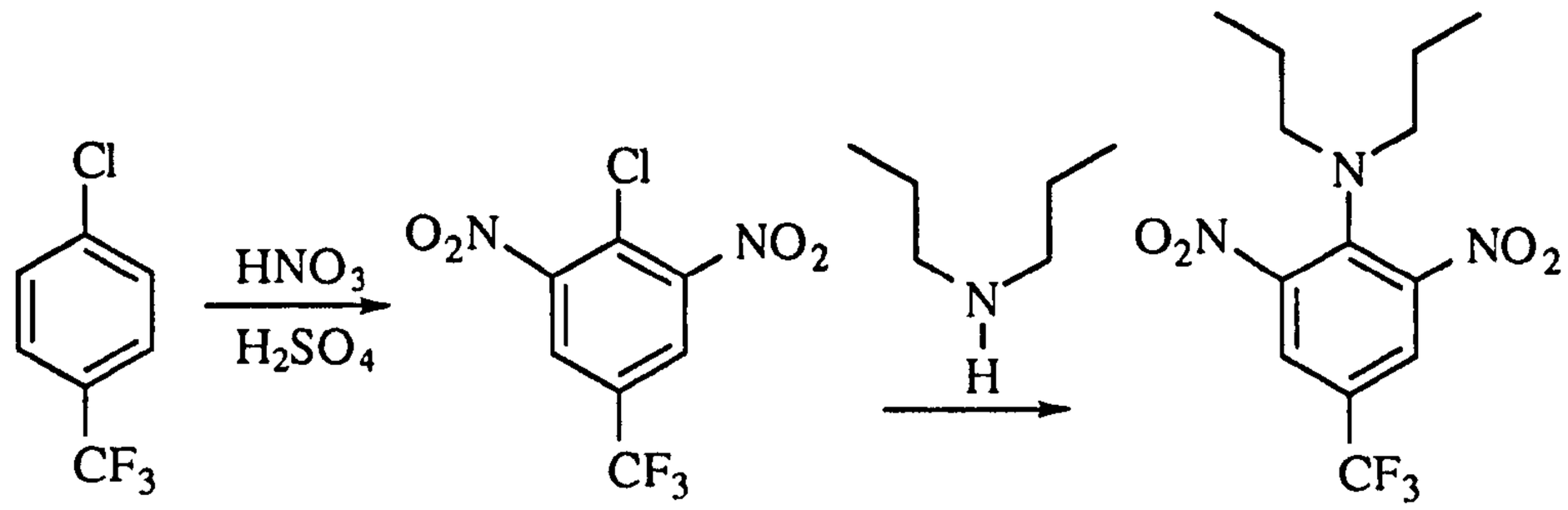
Oryzalin

In Great Britain, trifluralin is mainly used to remove weeds from land into which cabbage, cauliflower, kale and sprouts are to be planted [7]. It was, however, originally introduced for weed control in cotton and groundnut crops. Other uses include soil incorporation prior to planting or sowing carrots, swedes, turnips and beans (broad, field and runner), soyabeans, and sunflowers [7].

Oryzalin is used extensively as a pre-emergence treatment in soyabeans [7] and is also used as a directed spray pre-emergence of weeds in vines, ornamental bushes (eg. roses) and fruit trees.

From the class of herbicides listed in Table 1 (page 6), trifluralin and oryzalin were discovered to selectively inhibit leishmania proliferation and infectivity [6, 8-9]. Moreover, in addition to being effective against leishmania, trifluralin is effective against the *in vitro* proliferation of *Trypanosoma brucei* trypomastigotes [8] and the intraerythrocytic forms of the malaria parasite *Plasmodium falciparum* [8, 10]. Thus, trifluralin is effective against several species of protozoan parasites. Previously, the impurities in trifluralin were hypothesised to be the result of the photolability of trifluralin [11-12], however, recently researchers [6] have suggested that the activity of trifluralin is due to an impurity or contaminant, not to trifluralin itself. This contaminant, 1-chloro-2,6-dinitro-4-trifluoromethylbenzene (chloralin 2) was found to

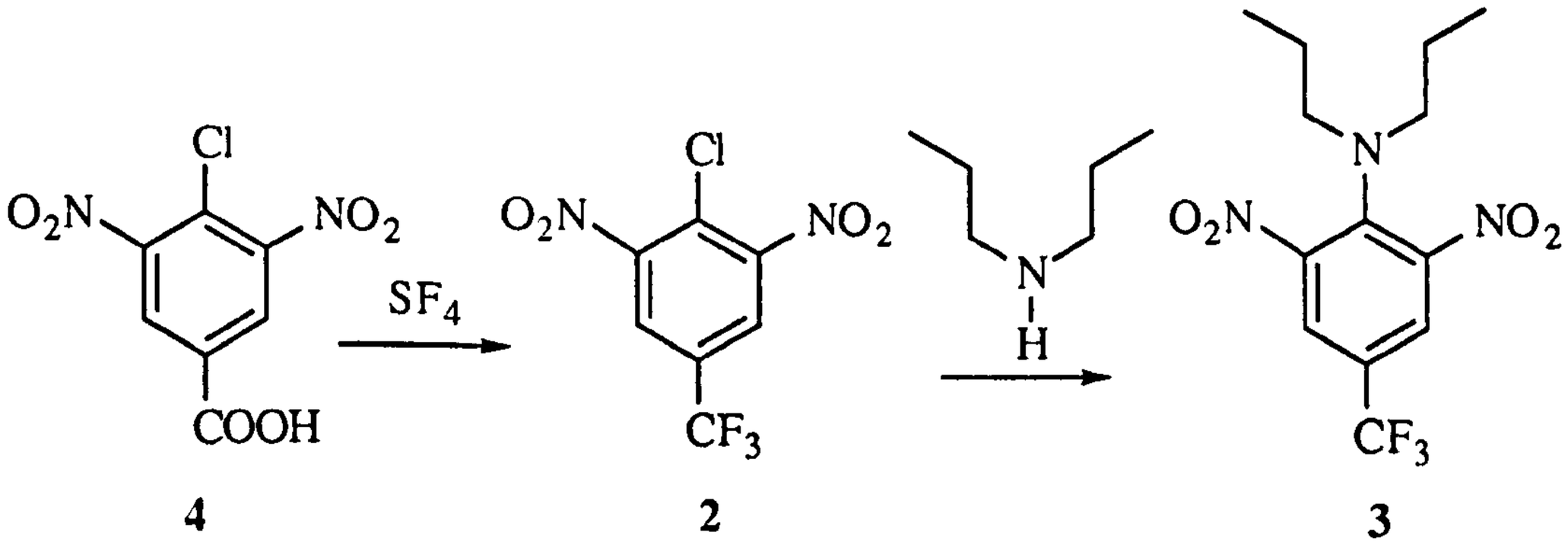
be 100 times more active than trifluralin [6] and is present in the commercial synthesis of trifluralin [6], as shown in **Scheme 1**. The nitration of *p*-chlorotrifluoromethylbenzene **1** (produced from the reaction of *p*-chlorobenzoic acid and sulphur tetrafluoride) gives 1-chloro-2,6-dinitro-4-trifluoromethylbenzene **2**, which is then reacted with dipropylamine to give 2,6-dinitro-(*N*,*N*-dipropylamino-4-trifluoromethyl) benzene **3**, or trifluralin. This scheme serves as a general method for the synthesis of the dinitroaniline herbicides by substituting an appropriate amine for dipropylamine (since **2** is readily available, we used it as the starting material in our syntheses).



1 **2** **3**

Scheme 1

The first synthesis of trifluralin was reported by Soper in 1966 [13] where he reacted 4-chloro-3,5-dinitrobenzoic acid **4** with sulphur tetrafluoride to give 1-chloro-2,6-dinitro-4-trifluoromethylbenzene **2** which was isolated and reacted with excess dipropylamine (which acted as both, solvent and acid scavenger) to give trifluralin **3**, as outlined in **Scheme 2**. The compound was identified by elemental analysis only and the yields were not reported.

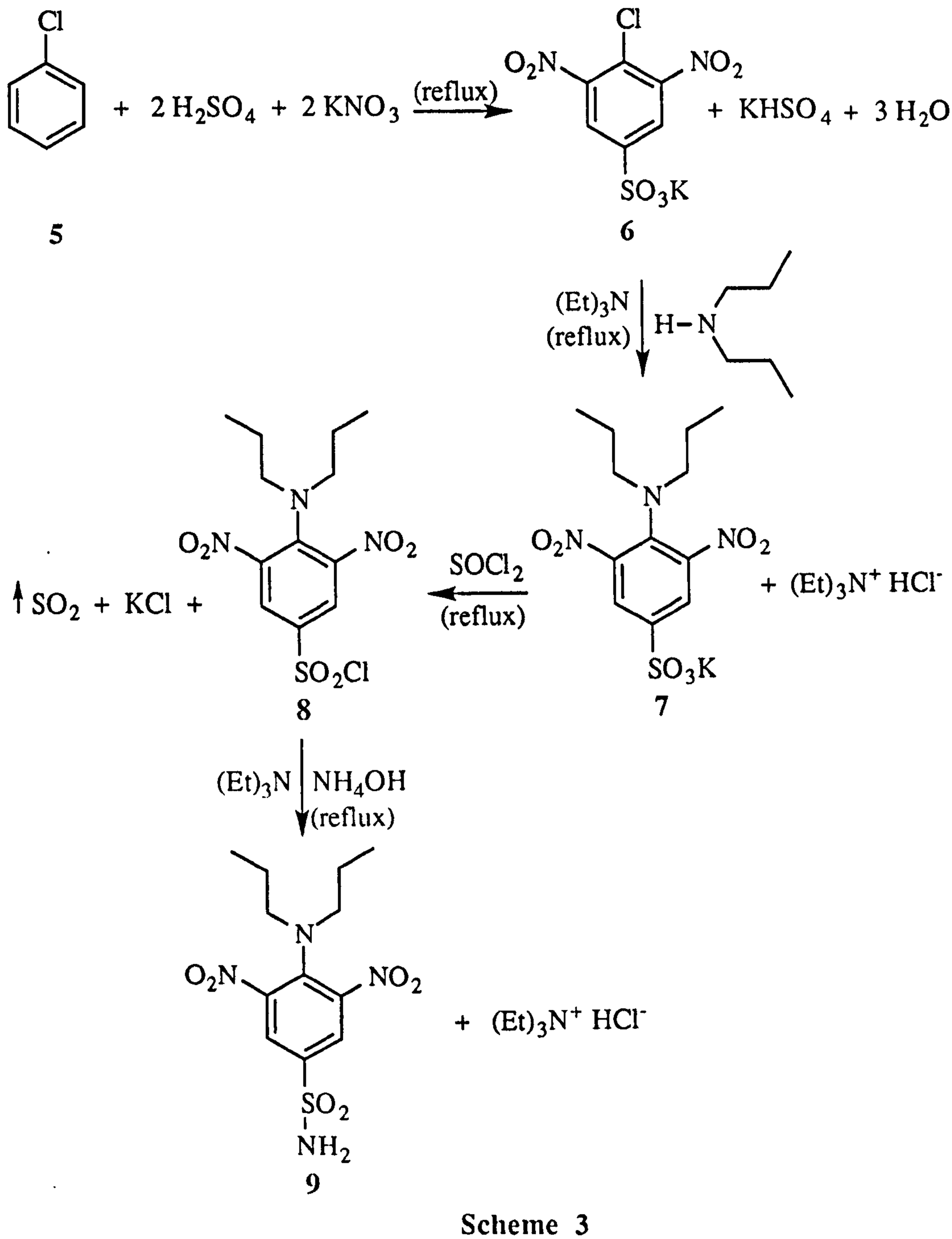


4 **2** **3**

Scheme 2

Commercial synthesis of oryzalin (**Scheme 3**) [7] involves sulphonation and nitration of chlorobenzene (**5**) to yield potassium 4-chloro-3,5-dinitrobenzene sulphonate (**6**). The potassium salt was reacted with dipropylamine to give potassium

3,5-dinitro-4-(*N*,*N*-dipropylamino)benzenesulphonate (**7**) followed by reaction with thionyl chloride to give 3,5-dinitro-4-(*N*,*N*-dipropylamino)benzenesulphonyl chloride (**8**) which was then reacted with ammonium hydroxide to yield 3,5-dinitro-4-(*N*,*N*-dipropylamino)benzenesulphonamide (**9**) (oryzalin).



Scheme 3

The dinitroaniline trifluralin has been shown to be non-carcinogenic, non-tetratogenic and non-mutagenic in standard *in vivo* genotoxicity and *in vitro* mutagenic assays [14-15]. Hence, this class of herbicides offers safe, promising lead compounds for development as antiprotozoan agents.

Recently, dinitroaniline compounds such as trifluralin, nitralin, pendimethalin, profluralin and fluchloralin (see Table **1**) have been found to have anticryptosporidial activity [14] (*Cryptosporidium parrum* is a protozoan organism that infects the epithelial cells of the small intestine causing diarrheal illness in animals and humans).

Figure **1** represents the general formula of the dinitroaniline. The substituents R_1, R_2, R_3 and R_4 are given in Table **1**, including their commercial names.

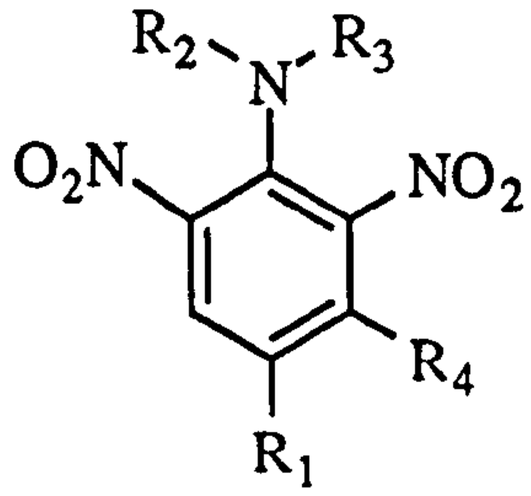


Figure 1

Name	R_1	R_2	R_3	R_4
Trifluralin	$-CF_3$	$-C_3H_7$	$-C_3H_7$	-H
Nitralin	$-SO_2CH_3$	$-C_3H_7$	$-C_3H_7$	-H
Oryzalin	$-SO_2NH_2$	$-C_3H_7$	$-C_3H_7$	-H
Pendimethalin	$-CH_3$	$-CH(C_2H_5)_2$	-H	$-CH_3$
Profluralin	$-CF_3$	$-CH_2(C_3H_5)$	$-C_3H_7$	-H
Benfluralin	$-CF_3$	$-C_2H_5$	$-C_4H_9$	-H
Ethalfluralin	$-CF_3$	$-C_2H_5$	$-CH_2C(CH_3)CH_2$	-H
Fluchloralin	$-CF_3$	$-C_3H_7$	$-CH_2CH_2Cl$	-H
Dinitramine	$-CF_3$	$-C_2H_5$	$-C_2H_5$	$-NH_2$
Prodiamine	$-CF_3$	$-C_3H_7$	$-C_3H_7$	$-NH_2$

Table 1

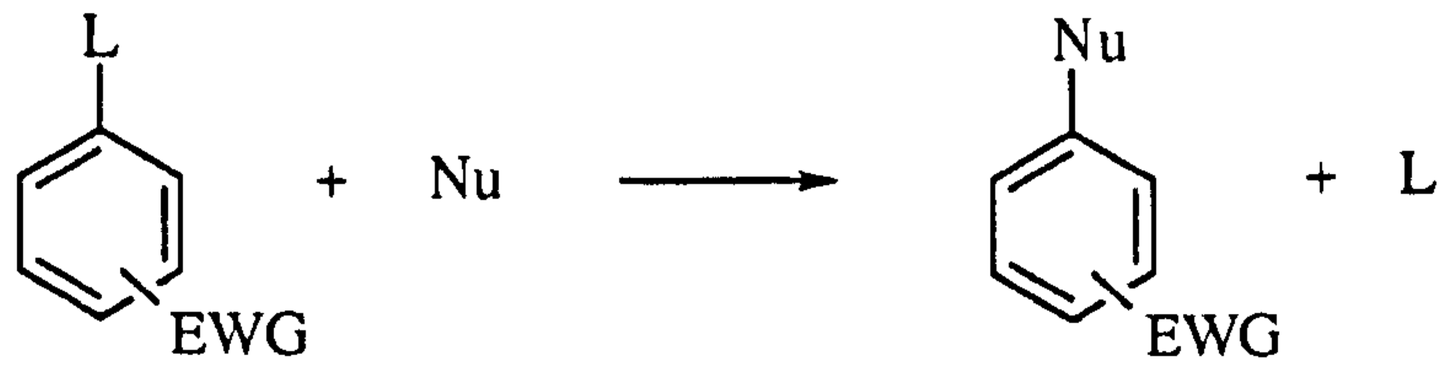
These compounds are also referred to as antimicrotubules [8-10]. Microtubules are made up of an array of tubulin (dimeric protein) molecules and most of the dinitroanilines are antimicrotubules, which means that since microtubules are involved critically in cell division, this provides a suitable target for tubulin disrupting drugs. Therefore, the dual role of trifluralins and oryzalins as herbicides and antileishmanials suggests a possible new source of chemotherapeutic compounds against such human protozoan diseases.

Antimicrotubule agents such as the vinca alkaloids [16] (e.g. vincristine, vindesine, vinorelbine or navelbine) are also used in cancer chemotherapeutics, thus indicating that microtubules are also possible drug targets in cancer [16].

1.3 The S_NAr Reaction: Mechanistic Aspects

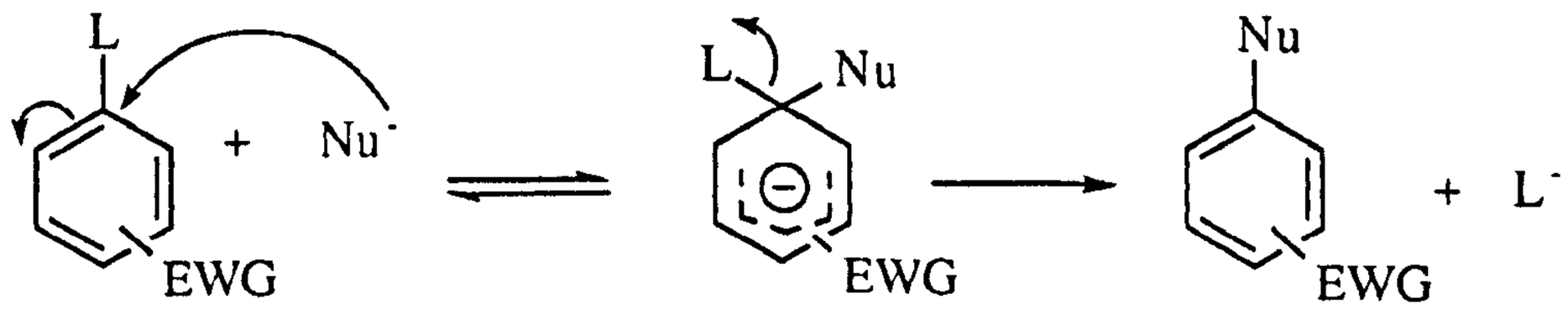
There is now much evidence that the S_NAr mechanisms fit very well with the great majority of intermolecular and intramolecular nucleophilic displacements involving nitro-activated aromatic and heteroaromatic substrates and the subject has been comprehensively reviewed [17-19].

A general nucleophilic aromatic S_NAr substitution reaction is common in haloarenes and is generalised in **Scheme 4**, where Nu represents an anionic or a neutral nucleophile and L a good leaving group. The leaving group (L) can be uncharged (e.g. F, Cl, Br, I), positively or negatively charged (e.g. NR_3^+, SO_3^-, respectively). EWG indicates the presence of one or more electron-withdrawing groups (e.g. NO_2 and CF_3 in the aromatic ring in trifluralin (**3**) and NO_2 in oryzalin (**9**)). The presence of an EWG is important for the S_NAr mechanism to activate the ring with respect to nucleophiles (deactivates with respect to electrophiles), and as a consequence the mechanism is referred to as an activated aromatic substitution process [17-18].



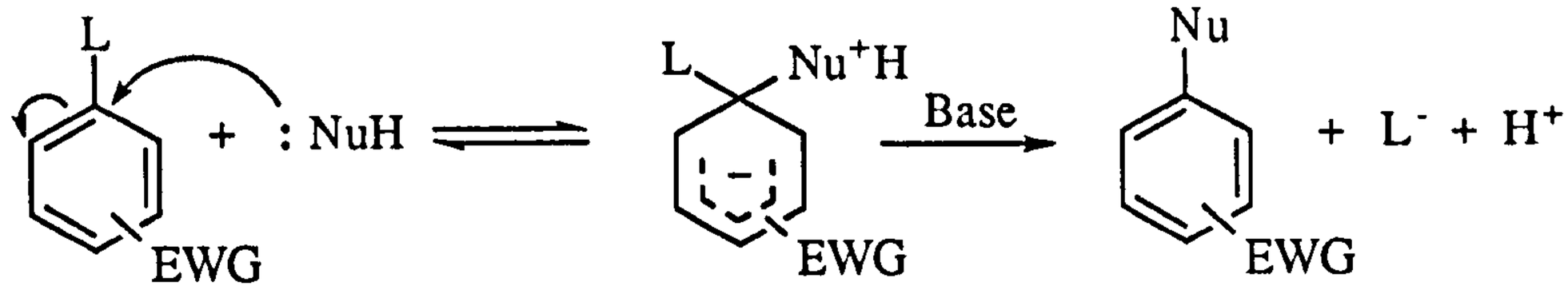
Scheme 4

As a first step, this involves addition of the nucleophile (Nu) to the aromatic electrophile **10** to form an intermediate cyclohexadienyl anion **11** in which the carbon undergoing the substitution becomes sp^3 hybridised, i.e. the benzenoid structure is broken. This intermediate, also known as σ-complex, or Jackson-Meisenheimer complex, [17-19] subsequently decomposes to give the substitution product **12**. For anionic products, this process is outlined in **Scheme 5**.



Scheme 5

For neutral nucleophiles (e.g. water, alcohols, amines) the postulated process is outlined in **Scheme 6**. In this case, the initially formed σ-complex **13** is zwitterionic and in most cases contains an acidic proton, which can be removed by a base such as the nucleophile itself.



13

Scheme 6

The S_NAr reactions are driven by the presence of the nitro group, which activates the aromatic system to nucleophilic attack [18]. Non-electron-deficient benzene derivatives are intrinsically reluctant to participate in nucleophilic substitution because of the evident repulsion between the π-electron system and the approaching nucleophile. Introduction of substituents such as nitro has the effect of reducing the electron density of the benzenoid system, especially at the *ortho* and *para* positions relative to the nitro group, thus favouring nucleophilic attack at these positions [18]. Hence the presence of the electron-withdrawing groups is an essential requirement for the S_NAr reactions shown in **Schemes 5** and **6**.

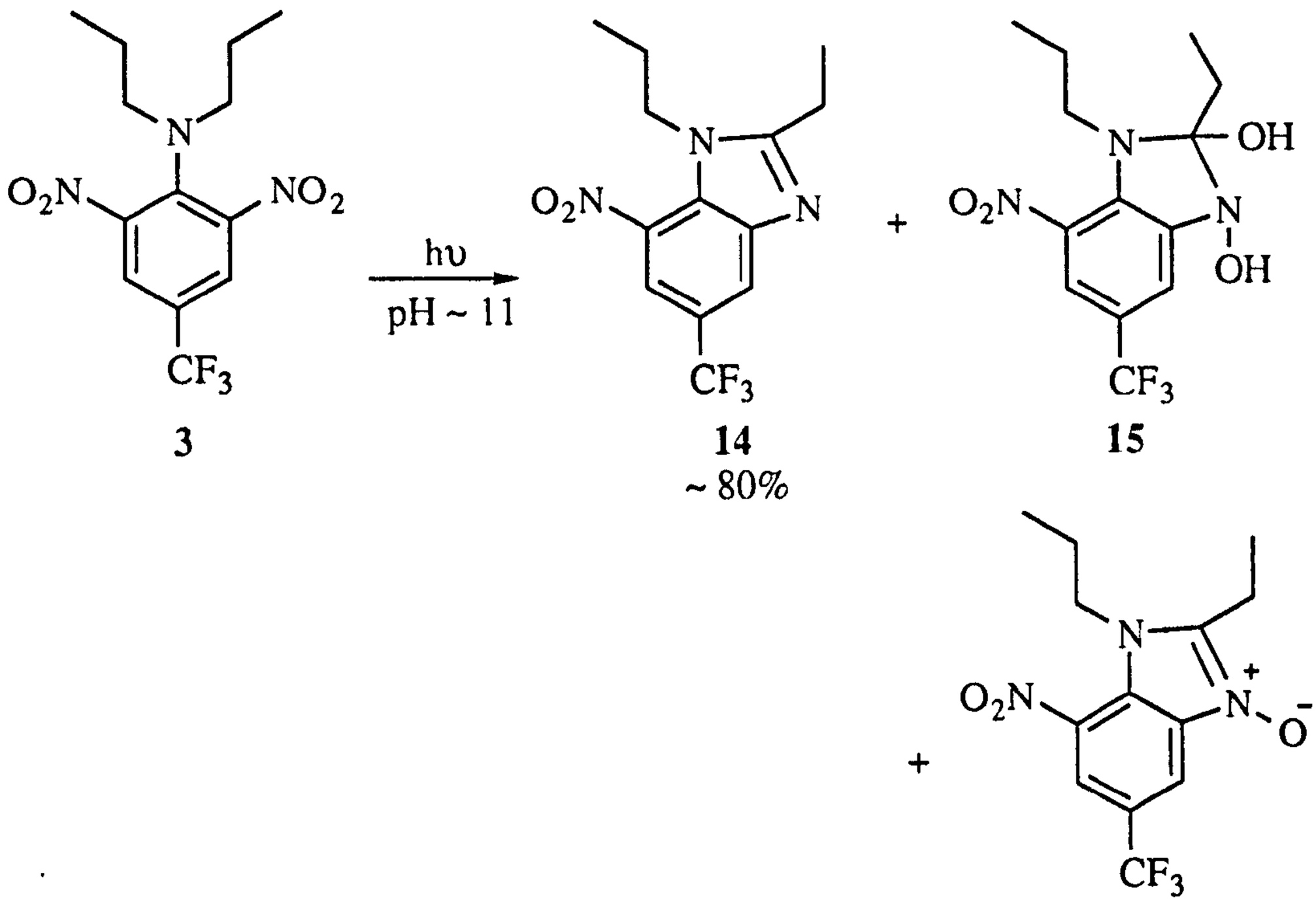
Halogens present in nitroarene compounds usually act as good leaving groups, the order of reactivity being F >> Cl ~ Br > I [19]. This order implies that the carbon-halogen bond cleavage is not involved in the rate-determining step [19]. This rules out a concerted mechanism but can be understood if the addition of the nucleophile is rate-determining in **Schemes 5** and **6**. These variations in the loss of halogens are one of the observations that led initially to the formation of the S_NAr substitutions [18].

Another factor to consider in the S_NAr reactions is the α-substituent, or *ipso* effect [18, 20]. It is known that groups with strong -I effects stabilise the intermediate σ-complex when attached to the sp^3-hybridised carbon [18]. Since a transition state lies between reactants and products, this *ipso* effect must contribute to some extent to stabilising the transition state for bond formation to the nucleophile, thus enhancing the reactivity of nitro aryl halides.

Generally in S_NAr processes a nitro group is more activating in the *ortho* than in the *para* position to the leaving group [18]. The prevailing view is that in the absence of other influences, a nitro group in the *ortho* position is inherently more activating than one in the *para* position, presumably as a result of the stronger inductive effect of the former [18]. For substitutions by anionic nucleophiles, however, this rate-enhancing

effect is counter-balanced by electrostatic repulsion between the highly polarizable *ortho*-nitro group and the incoming nucleophile.

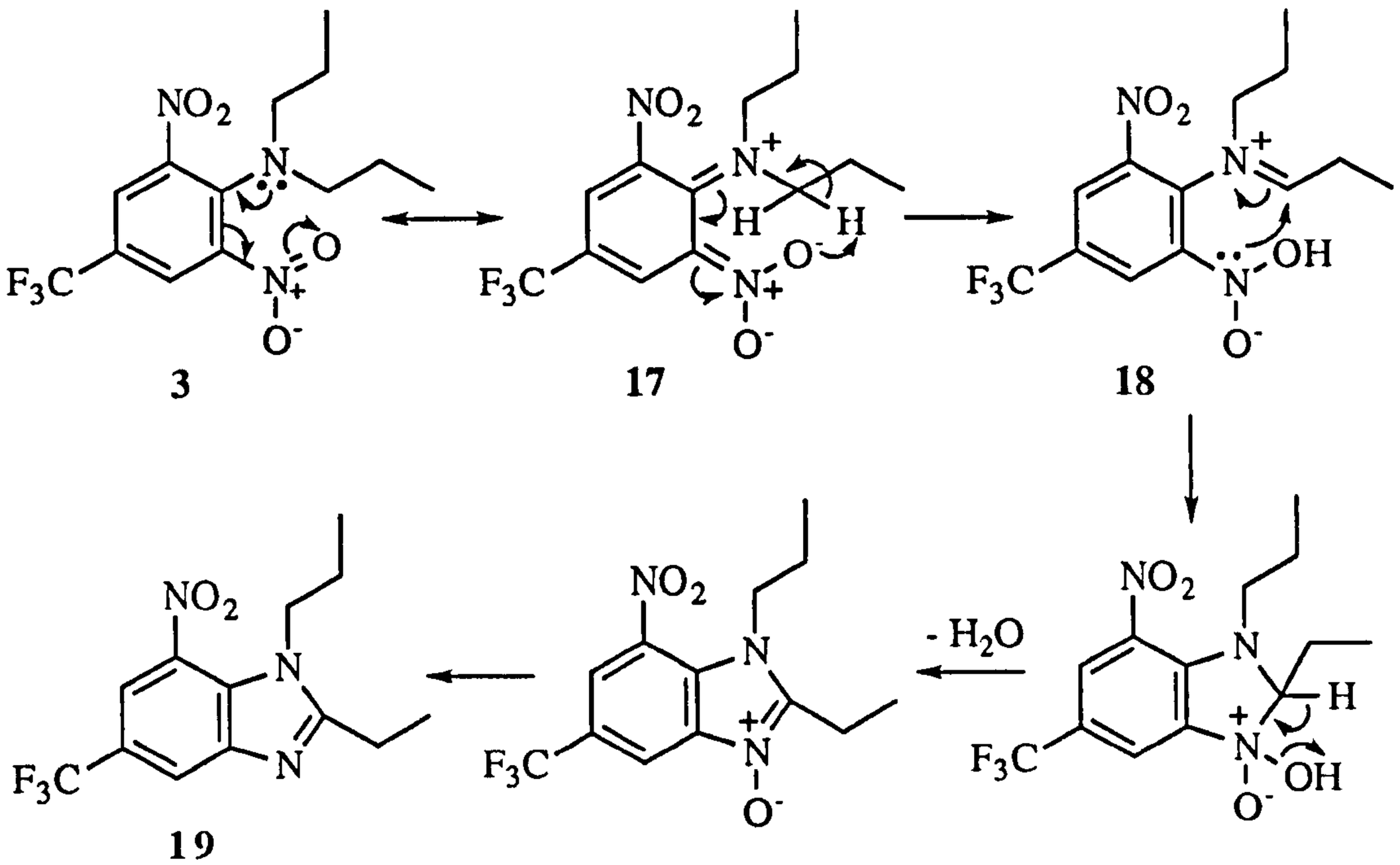
A major group of pre-emergent herbicides undergo photodecomposition and one such example is trifluralin (**3**). Since this compound contains a tertiary aniline bearing an *ortho* substituent, it undergoes the *t*-amino-effect as reported by Otto Meth-Cohn [21] leading to cyclisation. This is classified as a type 1 reaction: formation of five-membered rings from *t*-amino-effect reactions. The major product from the action of sunlight in aqueous alkaline media was the benzimidazole (**14**), and the by-products included the dihydroxybenzimidazoline (**15**) and benzimidazole N-oxide (**16**), all being derived from the *t*-amino-effect [21] (**Scheme 7**).



3 **14** ~ 80% **15** **16**

Scheme 7

The mechanism of the *t*-amino-effect was suggested by Meth-Cohn *et al* [22] and is outlined in **Scheme 8** for an unsaturated *ortho* substituent (NO_2 in this case). The *ortho* substituent in **3** is capable of mesomerism to **17**. The polarised mesomer is then set up for further reaction since the hydrogens of the α-methylene group are rendered labile by the charged nitrogen and are consequently abstracted by the nucleophilic centre (O^-). The resulting immonium ion **18** may cyclise to **19** yielding a five-membered benzimidazole system.



Scheme 8

1.4 Strategies to increase desired pharmacological effects

Structural modifications are often necessary to increase the activity of a lead substance or drug with poor activity. There are various, standard molecular modification approaches that have been developed [23] to make a drug more active and less toxic to the host organism. A number of these structural modification methodologies are discussed in the following sections.

1.4.1 Lipophilicity

Lipophilicity is one of the most important concepts in drug design. For the drug to reach the site of action in humans, it must be able to interact with two different environments, i.e. lipophilic (e.g. membranes) and aqueous (e.g. cytoplasm). The drug has to travel from its point of entry into the body to the site of action (pharmacokinetics) and also interact with the specific site (pharmacodynamics). Therefore, it is important to maintain the balance between partitioning in the cytoplasm and lipid membranes. The more lipophilic a drug, the more chance it has of penetrating the blood brain barrier. This is one of the most important membranes which surrounds the capillaries of the circulatory system in the brain and protects it from passive diffusion of undesirable chemicals from the blood stream [23].

The most used halogens in medicinal chemistry are chlorine and fluorine attached to a non-activated carbon atom [24]. Fluorine presents the advantage of its small bulkiness (Van der waals radius of fluorine = 0.64 versus hydrogen = 0.29) [24]. The trifluoromethyl group (CF_3) is comparable in atomic size to chlorine [25] and can

advantageously replace it when it is placed in an activated position. A chlorine substituent produces simultaneously an increase in lipophilicity, an electron-attracting effect and a metabolic obstruction [24].

Bromine has fewer applications than either fluorine or chlorine, and is more often incorporated as a bromoaryl group. Iodine as a substituent group is the least used of the halogens because the weakness of the carbon-iodine bond means that the iodide ions may be readily released and this can trigger acute hypersensitivity reactions (e.g. larynx oedema, cutaneous haemorrhages, fever) [24]. However, iodine has useful applications for the treatment of certain thyroidal deficiencies.

The importance of the halogens in the exploration of structure-activity relationships extends to steric, electronic and hydrophobic effects [24]. Sterically, the halogens can sometimes prevent free rotation in certain molecules because of their bulky size, causing an increase in binding affinity [24]. The electronic effects of the halogens are ascribed to their inductive electron-withdrawing properties. Introduction of a more electronegative group often increases the potency of the molecule [24]. The accumulation of halogen atoms increases the hydrophobic effects and favours the passage of the biomembranes and access to the central nervous system (CNS) [24].

Callahan *et al* [6] studied the electron-withdrawing effects of the groups against the *in vitro* activity of *Leishmania* promastigotes, using the compound chloralin (**2**) as the standard. They studied the antileishmanial activities of analogues of chloralin with electron-withdrawing groups of different strengths (but keeping the same leaving group, chlorine) and found that the most active compound was still chloralin, which has two nitro groups (nitro groups were the strongest electron-withdrawing groups of the analogues tested). Replacement of a single nitro group with a sulphonyl group (4-chloro-3-nitro-5-sulphonylbenzotrifluoride) resulted in an almost sevenfold loss of antileishmanial activity, which correlates with the loss of electron-withdrawing ability since the sulphonyl substituent is not as strongly electron-withdrawing as a nitro (NO_2) group [6]. Similarly, the absence of one of the nitro groups (i.e. 4-chloro-3-nitro-benzotrifluoride) resulted in an even greater loss of antileishmanial activity. When the nitro group in 4-chloro-3-nitrobenzotrifluoride was substituted with an amino group (3-amino-4-chlorobenzotrifluoride), there was an additional loss of activity compared to the chloralin compound (amino groups are much weaker electron-withdrawing moieties than nitro substituents). The addition of a trifluoromethyl (CF_3) substituent (e.g. 2-bromo-3,5-*bis*(trifluoromethyl)aniline), resulted in an increase in antileishmanial activity, despite the presence of a bromine leaving group rather than a chlorine leaving group (chlorine is a better leaving group than bromine), because trifluoromethyl group is considered as a good electron-withdrawing substituent.

1.4.2 Homologation

A homologous series is a group of compounds that differ by a constant unit, usually a methylene group. Biological properties of homologous compounds sometimes show regular patterns of increasing or decreasing activity. It is understood that in certain cases lengthening of a saturated carbon side chain from one carbon to several carbons results in an increase in pharmacological effects [23]. However, sometimes further lengthening of the carbon chain may result in a sudden decrease in effect (see Figure 2). This phenomenon corresponds to increased lipophilicity of the molecule which then permits penetration into cell membranes. Therefore there has to be a balance between the aqueous and the lipophilic phase for the drug to travel into the membranes. One of the earliest examples of this phenomenon was the hypnotic activity of alcohols. The maximum effect occurred for 1-hexanol to 1-octanol; then the potency declined upon chain lengthening until no activity was observed for hexadecanol [23].

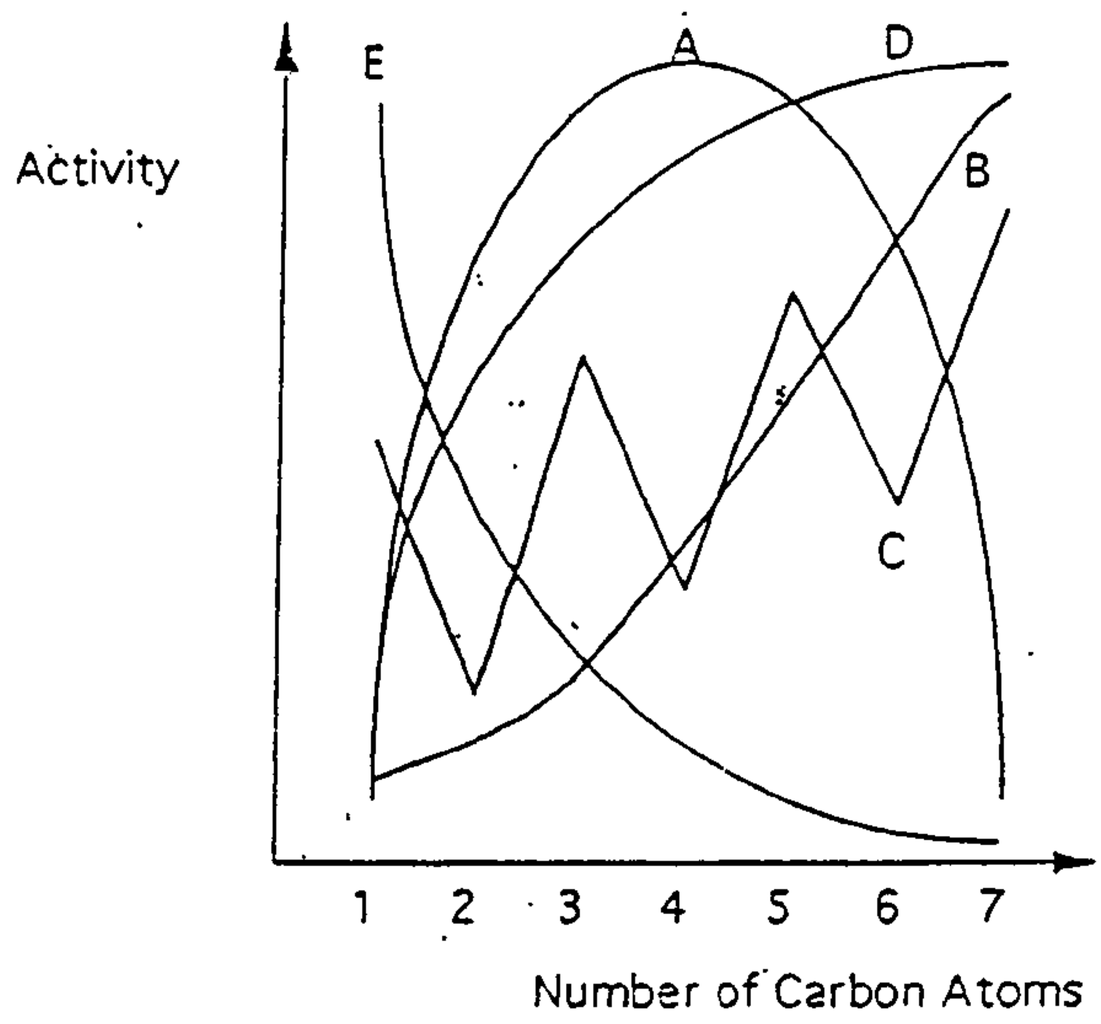


Figure 2

The most common curves are bell-shaped (curve A), the peak activity corresponding to a given value of the number *n* of carbon atoms. However, many other relationships have been found among homologous series. The activity can increase, without any particular pattern, with the number of carbon atoms (curve B). The biological activity can alternate with the number of carbon atoms, resulting in a zigzag pattern (curve C). In other series the activity first increases with the number of carbon atoms and then reaches a plateau (curve D). The activity can also decrease regularly, starting with the first member of the series (curve E) [26].

In order for the receptor to recognise an approaching drug molecule for binding, the molecule has to be very specific and uniquely three-dimensional in structure and this characteristic set of structural elements is called the pharmacophore [24]. Experimental knowledge about the particular three-dimensional structure of receptors for most of the

drugs in therapeutic use is still unavailable [24], as a consequence, corresponding hypothetical pharmacophore models are an important source for understanding drug-receptor interactions on the molecular level. The availability of a set of compounds from a distinct class of candidates showing a large variety in chemical structure and which interact via the same binding mechanism with the same receptor is an ideal starting point for the identification of a pharmacophore. Hence the search for a suitable lead substance, based on previous potential compounds, forms the basis for our research.

1.4.3 Topliss tree and Craig plots

The Topliss substitution scheme can be used to optimise aromatic and aliphatic substituents using a fixed set of substituents [27]. For example, a Topliss tree starts with the assumption that the lead compound has an unsubstituted phenyl ring. In the first step, a *para* chloro derivative is made and its activity measured. Depending on whether the activity is less than, equal to, or greater than the parent compound, the next step is made. This consists of replacing the *para* chloro substituent by either a methoxy or methyl group, or adding an additional chlorine substituent. This scheme applies manually the basic features of a good design plan, without statistical considerations, making it easier to apply for most chemists.

A Craig plot [23-24] is a two-dimensional plot of selected substituents, e.g. Hammett σ and Hansch π values (see Figure 3). From this plot substituents can be selected from each quadrant such that they vary widely in their properties, e.g. lipophilic and hydrophilic, electron donor and electron acceptor. This is a plot of electronic properties (Hammett σ constants for *meta* and *para* substituents) against lipophilic substituent properties (Hansch-Fujita π values).

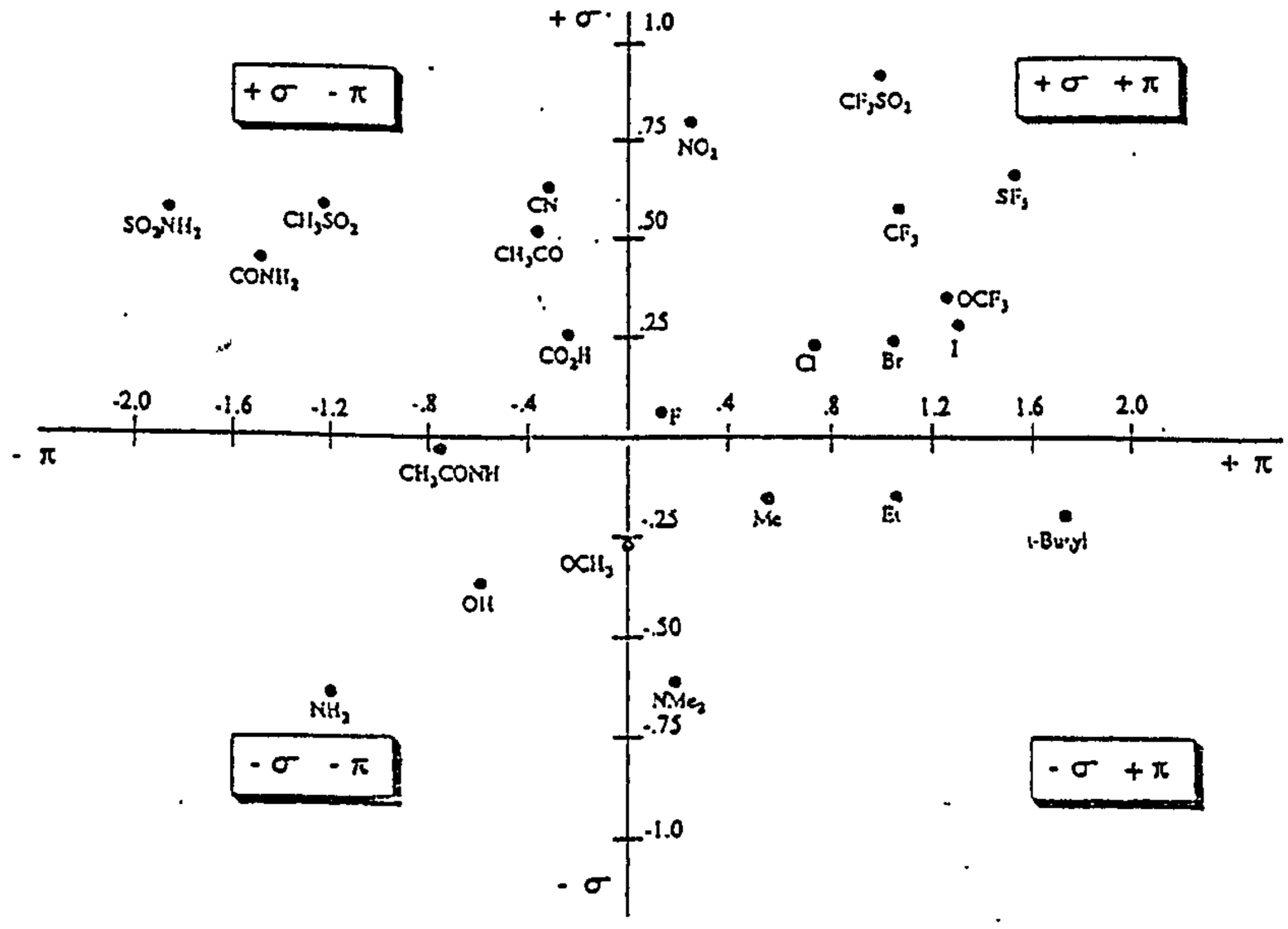


Figure 3

The Hammett parameter characterising electronic effects of the substituent on the reaction centre is defined by equation **1**, where log K is the intrinsic activity of the drug, k_1 and k_2 are proportionality constants and σ being the Hammett parameter, for example it is a measure of the electron-withdrawing or electron-donating ability of a substituent and has been determined by measuring the dissociation of a series of substituted benzoic acids compared to the dissociation of benzoic acid itself [28-29]. Equation **1** is called the linear free-energy equation (LFE) [28].

$$\log K = k_1 \sigma + k_2 \quad (1)$$

The biological activity of most drugs is related to a combination of physicochemical properties. In such cases, simple equations involving only one parameter are relevant only if the other parameters are kept constants. In reality this is not easy to achieve and equations which relate biological activity to more than one parameter are more common. These equations are known as Hansch equations [28-29] and they usually relate biological activity to the most commonly used physicochemical properties (e.g. partition coefficient (P) and/or electronic (σ), lipophilic (π) and a steric factor). Thus, by analogy with Hammett, Hansch proposed equation **2** which relates linear free-energy parameter to lipophilicity (hydrophobicity) [29].

$$\log \frac{P_x}{P_{II}} = \rho \pi \quad (2)$$

where ρ is a constant for the reaction or equilibrium being studied. $\rho = 1$ for the model system of partitioning between octanol and water, in which P_x and P_{II} are partition coefficients of the derivative and parent, respectively. Thus, equation **2** can be rewritten as equation **3** [28].

$$\pi = \log P_x - \log P_{II} \quad (3)$$

From equation **3**, either π, a substituent parameter from tables, or log P, which may be measured or estimated by adding π values to log P_{II}, can be used as a hydrophobicity parameter. Thus, values of σ and π parameters are plotted graphically (Craig plot) and the plot offers a number of advantages, some of which are outlined below.

The plot (figure **3**) shows clearly that there is no overall relationship between π and σ parameters. The various substituents are scattered around all four quadrants of the plot and thus it is possible to tell at a glance which substituents have positive π and σ parameters, which substituents have negative π and σ parameters, and which substituents have one positive and one negative parameter [29]. It is also easy to see

which substituents have similar π values. For example, the ethyl, bromo, trifluoromethyl and trifluoromethylsulphonyl groups are all approximately on the same vertical line on the plot (see Figure 3). In theory, these groups could be interchangeable on drugs where the principal factor affecting biological activity is the π factor. Similarly, groups which form a horizontal line can be identified as being isoelectronic or having similar σ values (e.g. carboxylic acid, chlorine, bromine and iodine).

The Craig plot is useful in planning which substituents should be used in a quantitative structure-activity relationship (QSAR) study. In order to derive the most accurate equation involving π and σ, analogues should be synthesised with substituents from each quadrant. For example, halide substituents are useful representatives of substituents with increased hydrophobicity and electron-withdrawing properties (positive π and σ values), whereas an OH substituent has more hydrophobic and electron-donating properties (negative π and σ values). Alkyl groups have positive π and negative σ values, whereas acyl groups have negative π and positive σ values. Once the Hansch equation has been derived, it will show whether π or σ should be negative or positive in order to get good biological activity. Further developments would then concentrate on substituents from the relevant quadrant. For example, if the equation shows that positive π and σ values are necessary, then further substituents should only be taken from the top right quadrant (see Figure 3).

1.4.4 Bioisosterism

Bioisosteres are substituents or groups often having very different structures, but which have chemical or physical similarities, and hence they produce broadly similar biological properties [23].

The concept of classical isosterism was defined by Langmuir [30] in 1919 when he proposed that the co-molecules are isosteric if they contain the same number and arrangement of electrons. The co-molecules of isosteres must, therefore contain the same number of atoms. The essential differences between isosteres are confined to the charges on the nuclei of the constituent atoms. Some examples of isosteres are, O^{2-}, F^{-}, Ne, Na^{+}, Mg^{2+}, Al^{3+}, ClO_4^{-}, SO_4^{2-} and PO_4^{3-}. This example clearly demonstrates that isosterism does not inevitably imply isoelectronic structures (having the same total electric charge), but it becomes evident that isoelectronic isosteres show the closest analogues, such as, C=O and N=N, CO_2 and NO_2, and $N{=}N^{+}{=}N^{-}$ and $-N{=}C{=}O^{-}$.

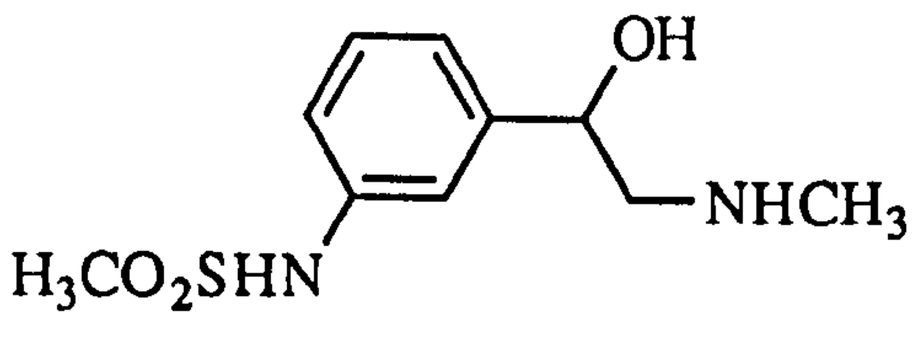
The main criterion for isosterism is that two isoelectronic molecules must present similar, if not identical, volumes and shapes [30]. Among the other physical properties that isosteric compounds usually share are boiling point, density, viscosity and thermal conductivity. However, certain properties must be different, such as, dipolar moments, polarity and polarisation.

Subsequently, Burger [31] classified and subdivided bioisosterism along its evolutionary path, classical and nonclassical bioisosteres and are illustrated in Table **2**.

Classical bioisosteres	Nonclassical bioisosteres
1. Monovalent atoms and groups e.g. $-CH_3$, $-NH_2$, -OH, -F, -Cl -Cl, -SH -Br, -i-Pr	1. Exchangeable groups e.g. see text below
2. Divalent atoms and groups e.g. $-CH_2-$, -NH-, -O-, -S- $-COCH_2R$, -CONHR $-CO_2R$, -COSR	2. Rings versus noncyclic structures e.g. see text below
3. Trivalent atoms and groups e.g. -CH=, -N=	
4. Tetrasubstituted atoms e.g. =C=, =N=, =P=	
5. Ring equivalents e.g. interchange of -CH=CH-, -S-, -O-, -NH, $-CH_2-$	

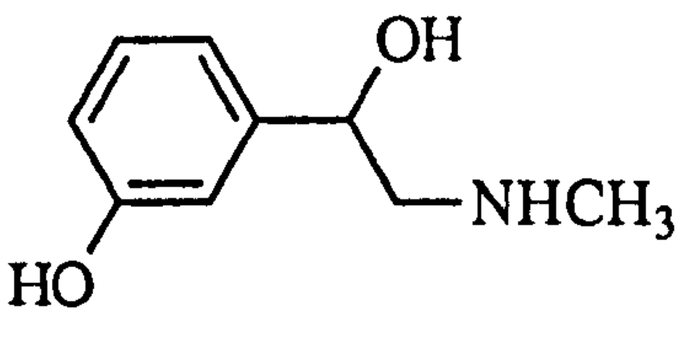
Table 2

The nonclassic bioisosteres do not rigidly fit the steric and electronic rules of the classic bioisosteres. An example of exchangeable groups is the sulphonamido isosteres of the catecholamines [32]. An alkyl sulphonamido group may be substituted for the phenolic hydroxy group of certain catecholamines (adrenergic receptor site), for example, alkyl sulphonamidophenethanolamine **20** and phenylephrine **21**. Both these compounds have similar pK_a values (**20** = 9.1 and **21** = 9.6).



Pk_a 9.1

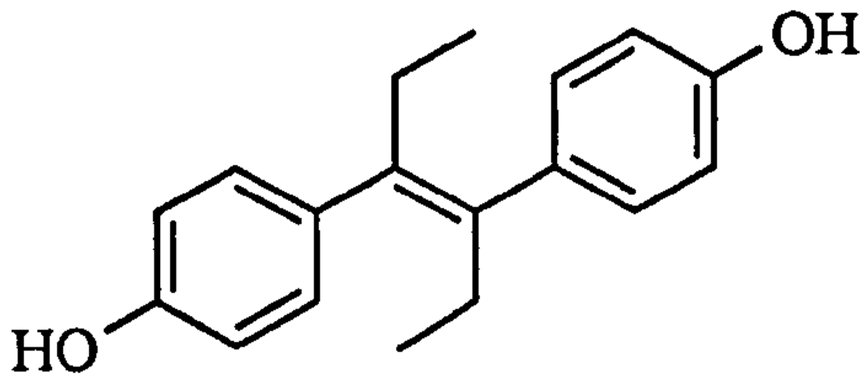
20



Pk_a 9.6

21

An example of cyclic versus noncyclic bioisosterism is diethyl stilbestrol **22** and estradiol **23** [32]. Diethyl stilbestrol has about the same potency as the naturally occurring estradiol [32].



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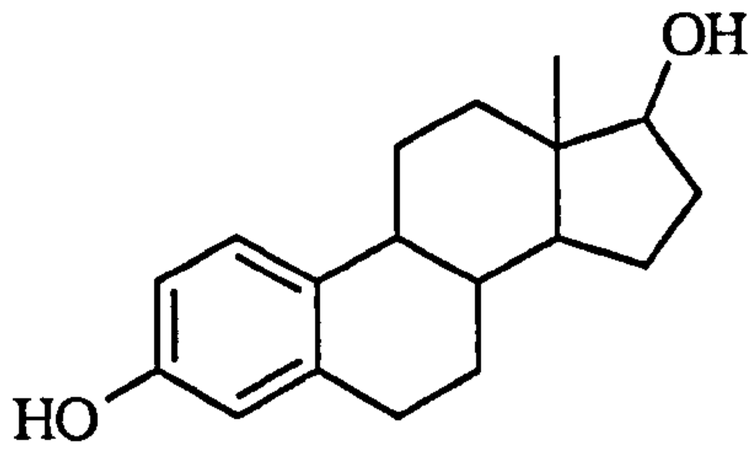


23

A table of substituent constants (Table **3**) is available for various physicochemical properties. A knowledge of these constants allows identification of substituents which may be potential bioisosteres [33].

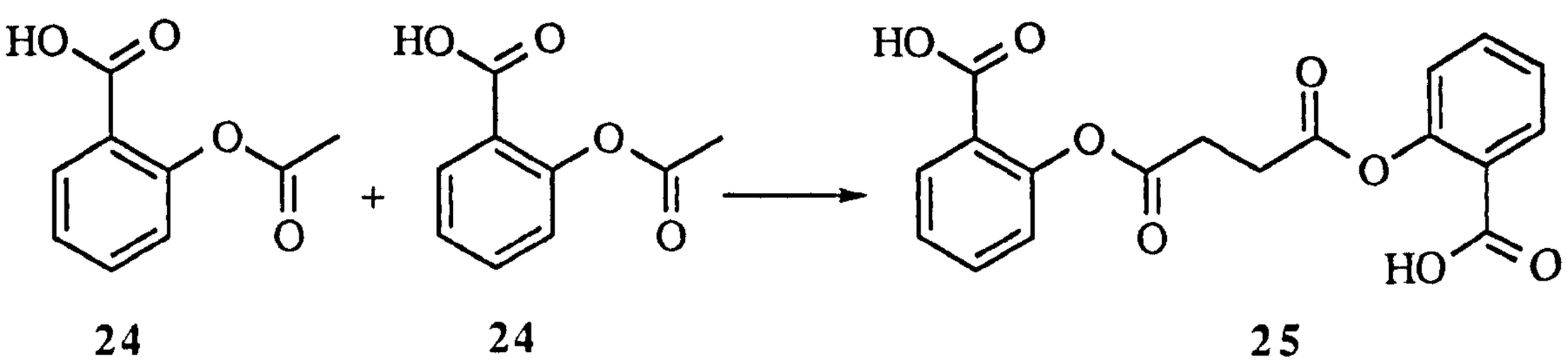
Substituent	$COCH_3$	$SOCH_3$	SO_2CH_3	SO_2NHCH_3	$CON(CH_3)_2$
π	-0.55	-1.58	-1.63	-1.82	-1.51
σ_p	0.50	0.49	0.72	0.57	0.36
σ_m	0.38	0.52	0.60	0.46	0.35

Table 3

This table shows some physicochemical parameters for five different substituents. For example, if the most important physicochemical parameter for biological activity is σ_p, then the $COCH_3$ group (0.50) would be a reasonable bioisostere for the $SOCH_3$ group (0.49). If, on the other hand, the dominant parameter is π, then a more suitable bioisostere for $SOCH_3$ (-1.58) would be SO_2CH_3 (-1.63).

1.4.5 Twin drugs

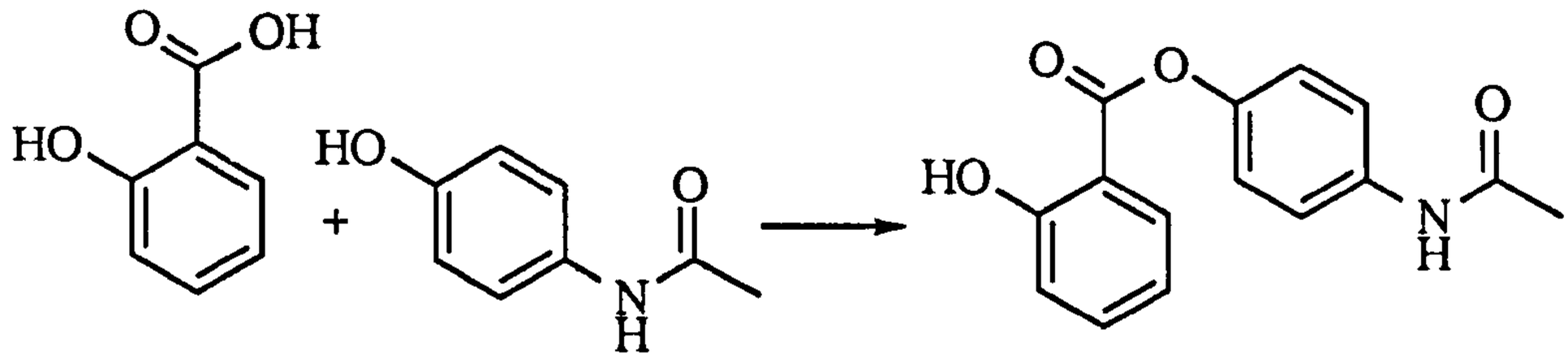
The term twin drugs means drugs containing two pharmacophoric groups combined covalently in a single molecule [34]. Twin drugs may result from the combination of two identical moieties (identical twin drugs), as shown in **Scheme 9**, where two molecules of aspirin **24** are dimerised to form diaspirin **25**.



24 **24** **25**

Scheme 9

Twin drugs may also result from combination of two different drug entities (nonidentical twin drugs), as shown in **Scheme 10**, where salicylic acid **26** and paracetamol **27** are combined to give acetaminosalol **28** [34].



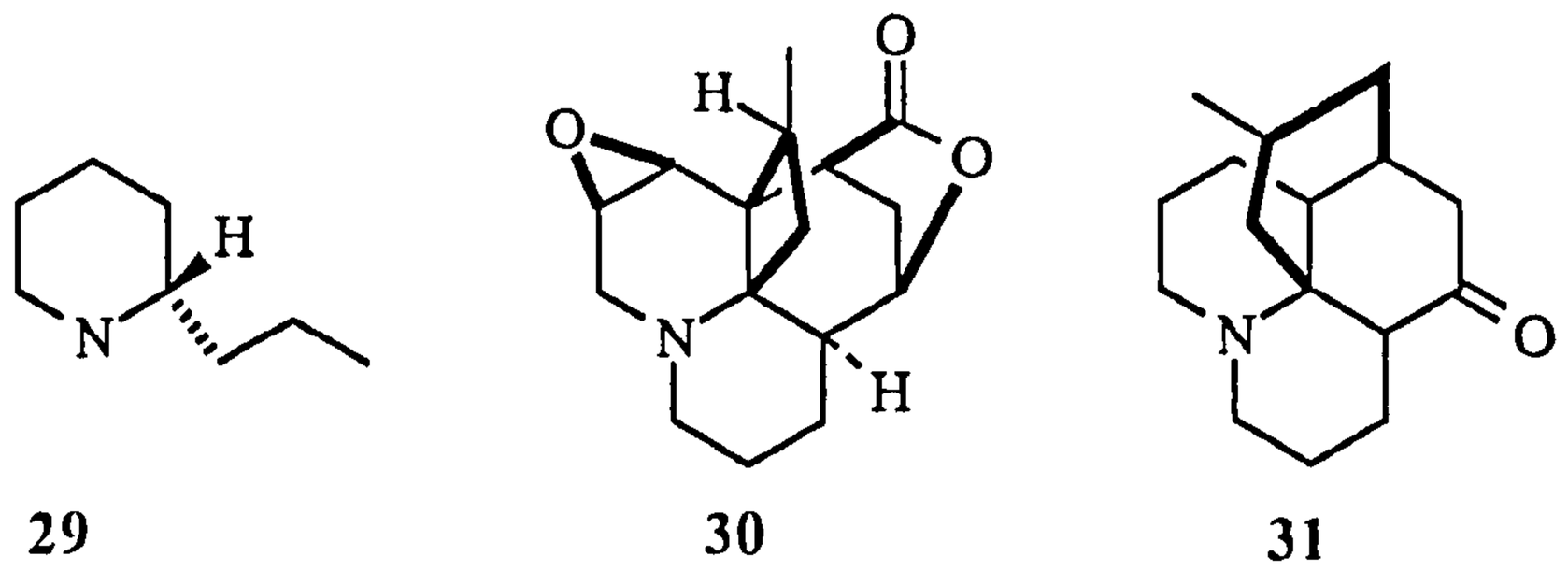
26 **27** **28**

Scheme 10

The first strategy consists of molecular variations based on duplication, while the second one consists of associative synthesis. The two drug entities have to be located at the most appropriate distance for interaction with the specific binding sites. They can be linked by a spacer group, placed closed together (no linker), or even overlap [34]. Sometimes the spacer group can establish additional interactions, thus increasing the affinity for a specific target.

2.0 Alkaloids: Historical background

Alkaloids, in a broad sense, are nitrogenous bases which occur naturally in plants. The majority of the alkaloids contain nitrogen as part of a heterocyclic system, and are structually a most diverse class of compounds. Their structures can be as simple as that of coniine **29** (from hemlock) [35], or as complicated as that of annotinine **30** and lycopodine **31** (from the lycopodium alkaloids) [36].

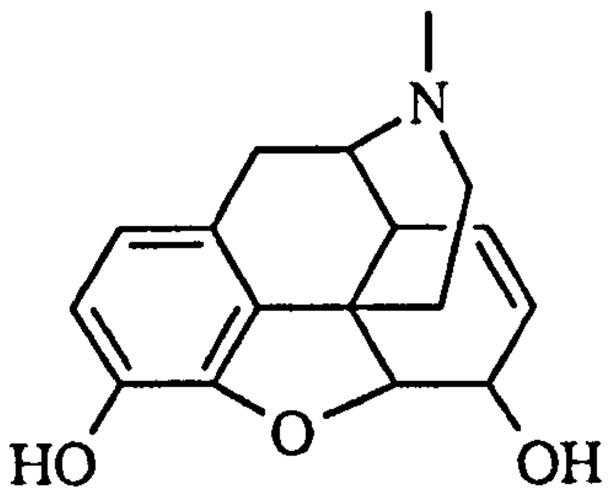


29 **30** **31**

The original definition of an alkaloid was first proposed in 1879 by the pharmacist, W. Meissner [35], who described the alkaloids as nitrogenous compounds of complex molecular structure and significant pharmacological activity confined to the plant kingdom. More recently in 1982, Pelletier [35] re-defined alkaloids as cyclic nitrogen-

containing molecules which are true secondary metabolites (i.e. of limited occurance) produced by living organisms.

Interest in the medicinal value of alkaloids goes back for thousands of years, mainly concentrating on the plant kingdom. Many of the compounds extracted from plants contained alkaloids and have been used as poisons for hunting purposes (coniine **29**), as analgesics (morphine **32**, from opium) [37], or as medicines (quinine **33**, or 6'-methoxycinchonan-9-ol, from the bark of the mountain tree called quinquina, later called cinchona after Francisca Henriquez de Ribera (1576-1639), Countess of Chinchona, and wife of the Peruvian Viceroy) [38].



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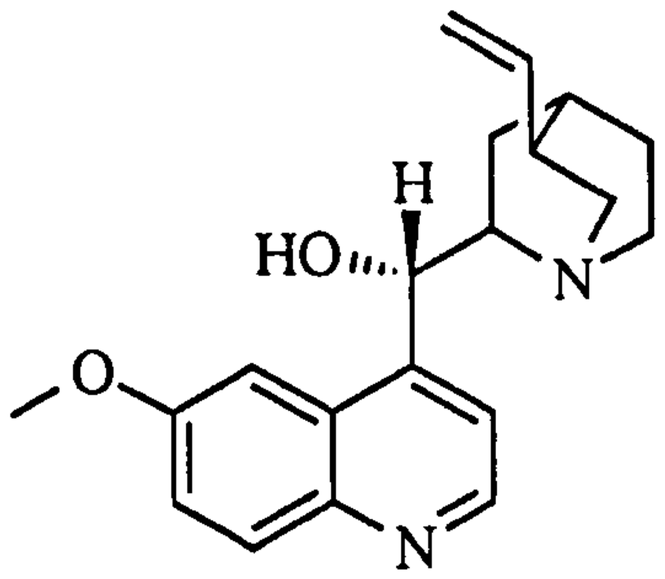
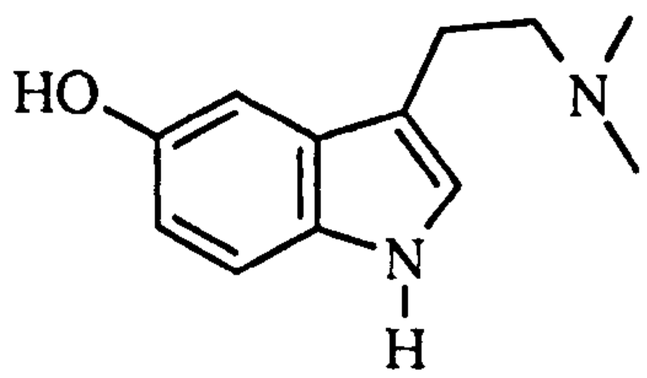


33

The number of alkaloids isolated from animals (e.g. bufotenin **34**, from the common European toad) [39], insects (e.g. quinazolinones **35**, from the European millipede) [39] and microorganisms (e.g. saxitoxin, from marine red-coloured dinoflagellate) [40] continue to increase. These alkaloids have ecological significance since they act as potent deterrents to would-be predators.



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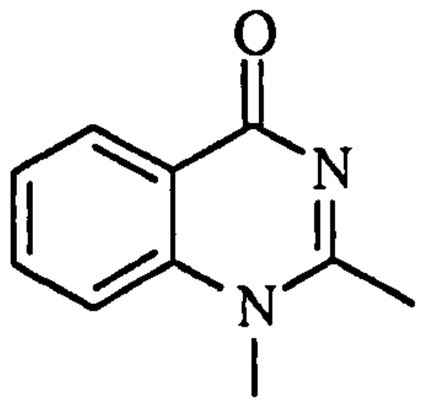
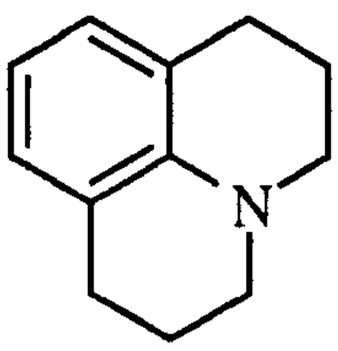


35

The diverse pharmacological activities of the alkaloids and the consequent interest from the medicinal point of view has caused many modern drugs to contain structural similarities to the alkaloids (or their synthetic analogues) and the pharmacological and toxicological properties of these compounds are thus of immense interest and importance.

Although many alkaloids and their structures are known in the literature, there is still plenty of scope for finding new and useful drugs using two strategies; one of which is to search for alkaloids in plant species not yet investigated, and the other is to study and synthesise analogues of known alkaloids in the hope that they possess some

pharmacological activity. Hence the aim of this project was to follow the latter strategy, i.e. the synthesis of analogues of carefully chosen compounds such as julolidine **36** (2, 3,6,7-tetrahydro-1*H*,5*H*-benzo[ij]quinolizine) and lilolidine **37** (1,4,5,6-tetrahydro-2*H*-pyrrolo[3,2,1[ij]quinoline) and screening them in models of parasitic diseases like malaria, leishmania and possibly African trypanosomiasis. One of the reasons for the selection of these compounds is that their pharmacology remains to be exploited, and not many drugs contain the julolidine/lilolidine type of ring skeleton. Thus compounds incorporating the julolidine/lilolidine ring skeleton attracts much attention as targets for organic syntheses.



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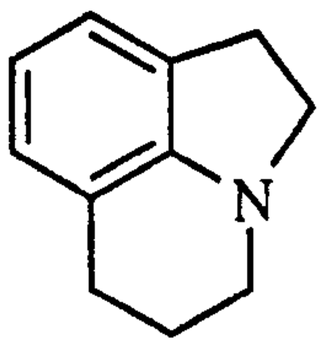

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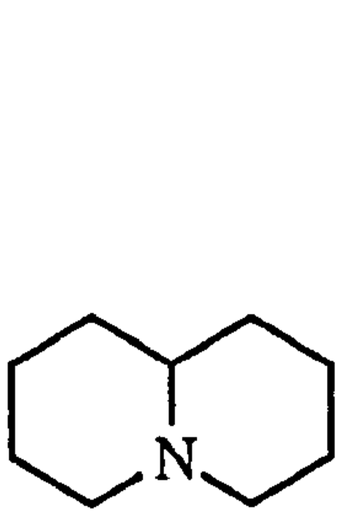
2.1 Julolidine

The quinolizine ring system has been the object of considerable synthetic effort because this ring is present in some types of alkaloid skeletons, as previously mentioned. This fact, along with interests in its compounds from a pharmacological point of view, has influenced the synthetic work in this area.

The quinolizidine ring **38** is the basis of annotinine **30** [36, 41], matrine **39** (in the Chinese drug *kuh seng*) [42], sparteine **40** (in yellow and black lupin beans, possibly a cardiovascular drug) [43], and occurs in a large group of indoles [44], isoquinolines [45] and julolidines **36** [46].



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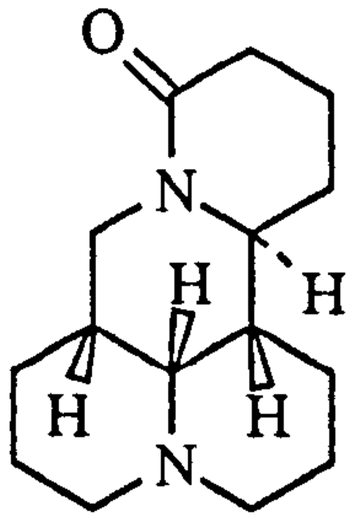

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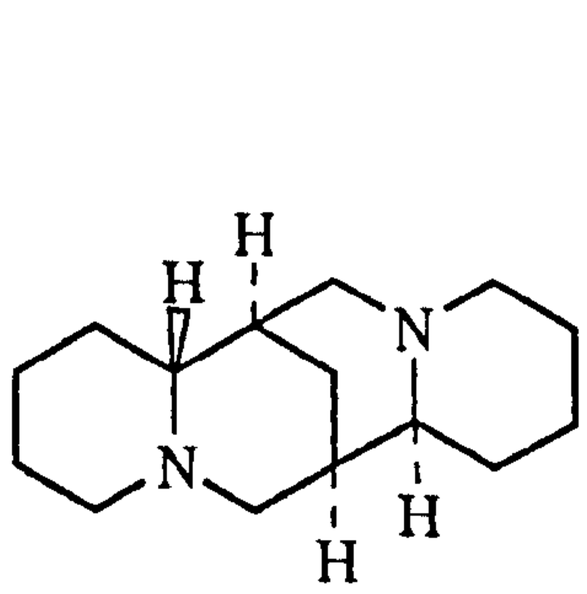

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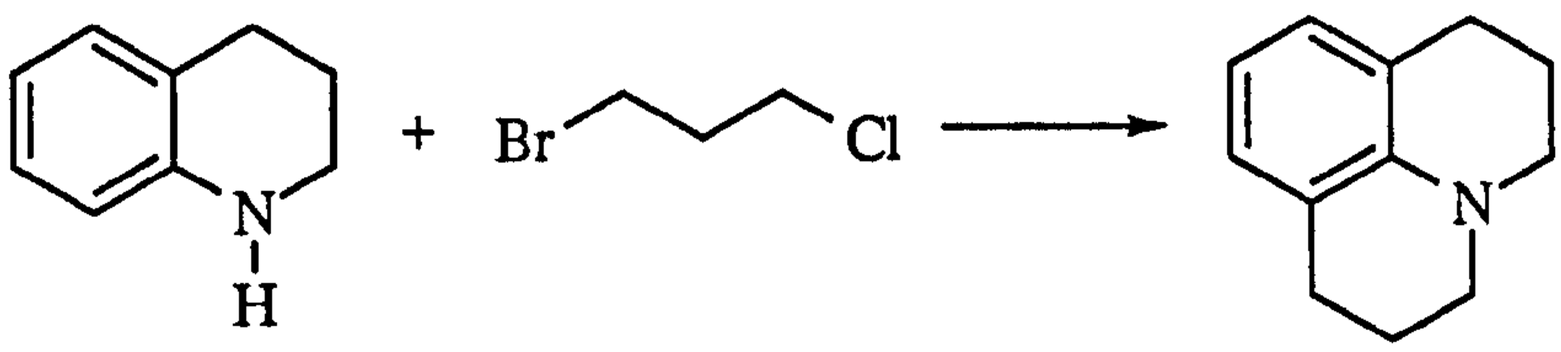
The name "julolidine", surprisingly, does not originate from a plant species, as is normally the case with alkaloids, but was so named by Reissert [47] in the last century. It was first synthesised in 1892 by Pinkus [48] when he reacted trimethylene chlorobromide with various starting materials such as formanilide [48], aniline [48],

methylaniline [48] and tetrahydroquinoline [48-49], and by the reduction of 8,10-diketojulolidine [48]. Other workers have synthesised julolidine by dehydration of *N*-(γ-hydroxypropyl)tetrahydroquinoline [50], or di-(γ-hydroxypropyl)aniline with phosphorus pentoxide [50], or by the intra-molecular condensation of *N*-(γ-bromopropyl)tetrahydroquinoline [51].

Glass and Weissberger [46] reported an improved synthesis of julolidine **36** when they reacted tetrahydroquinoline **41** and trimethylene chlorobromide **42** under reflux for 20 hours, as outlined in **Scheme 11**.



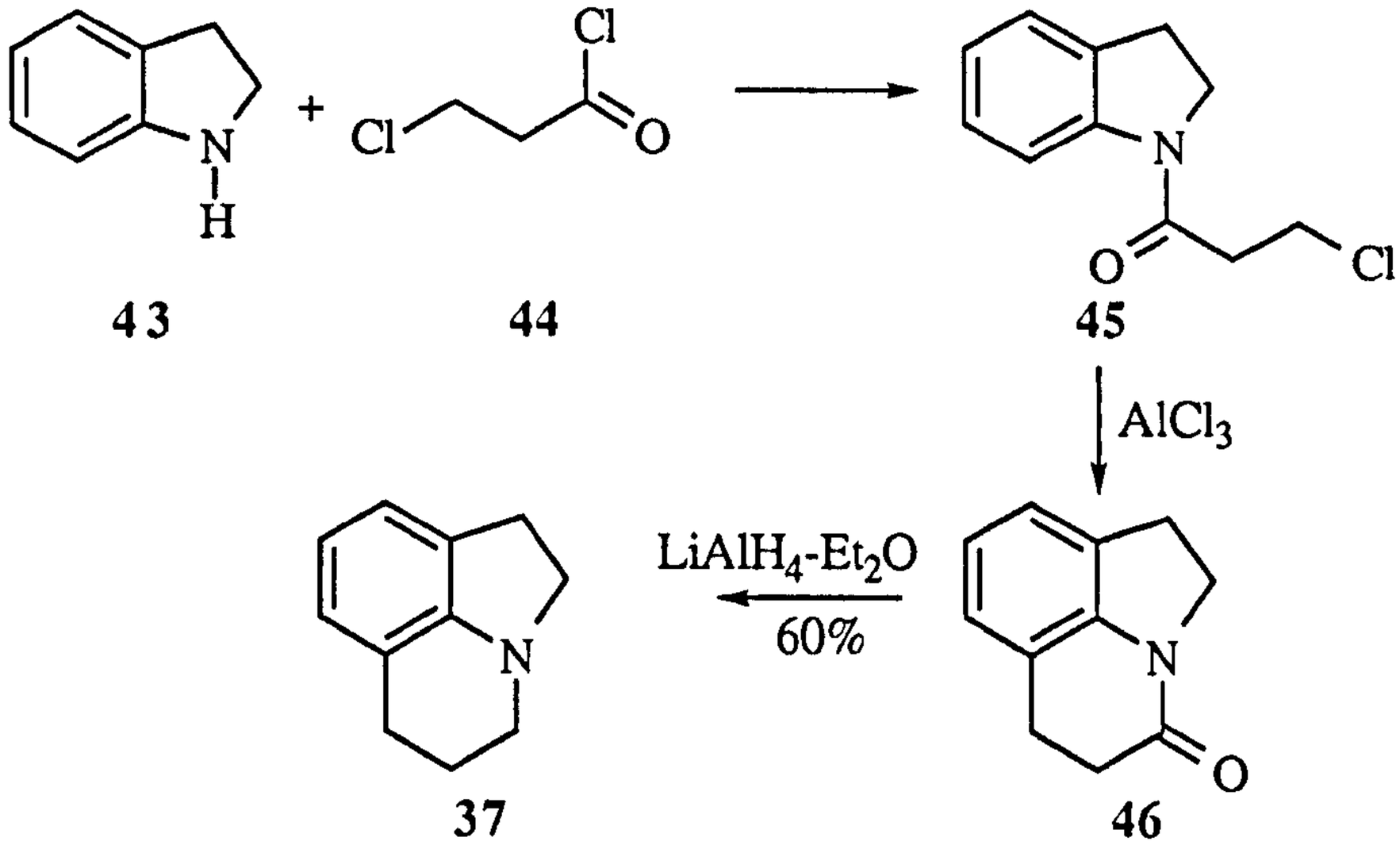
41 **42** **36**

Scheme 11

Although dimers of julolidine have been prepared for use as dyes over the years by Hallas *et al* [52-54], functionalised julolidine compounds are also of interest from the medicinal point of view.

2.2 Lilolidine

This name was also given by Reissert, as stated in Bamberger and Sternitzki's [47] paper. This analogue of julolidine was first prepared in 1918 by von Braun *et al* [49] in reasonable yield by reacting indoline with 1-bromo-3-chloropropane. Other routes have been used to synthesise the lilolidine ring system. Barger and Dyer [55] obtained lilolidine in poor yield from 1-amino-1,2,3,4-tetrahydroquinoline and pyruvic acid by using the Fischer indolisation, followed by decarboxylation and hydrogenation of the product. Hallas and Taylor [56] reported an improved synthesis of lilolidine based on a synthesis of julolidine [57], which involved the initial formation of 1-β-chloropropionylindoline (**45**) by reacting indoline (**43**) with β-chloropropionyl chloride (**44**). Compound **45** was then cyclised to form 4-oxolilolidine (**46**) using aluminium trichloride as the cyclising agent. Reduction of **46** using lithium aluminium hydride in ether gave lilolidine (**37**) as the free base in 60% yield, as shown in **Scheme 12**.



43 44 45 37 46

Scheme 12

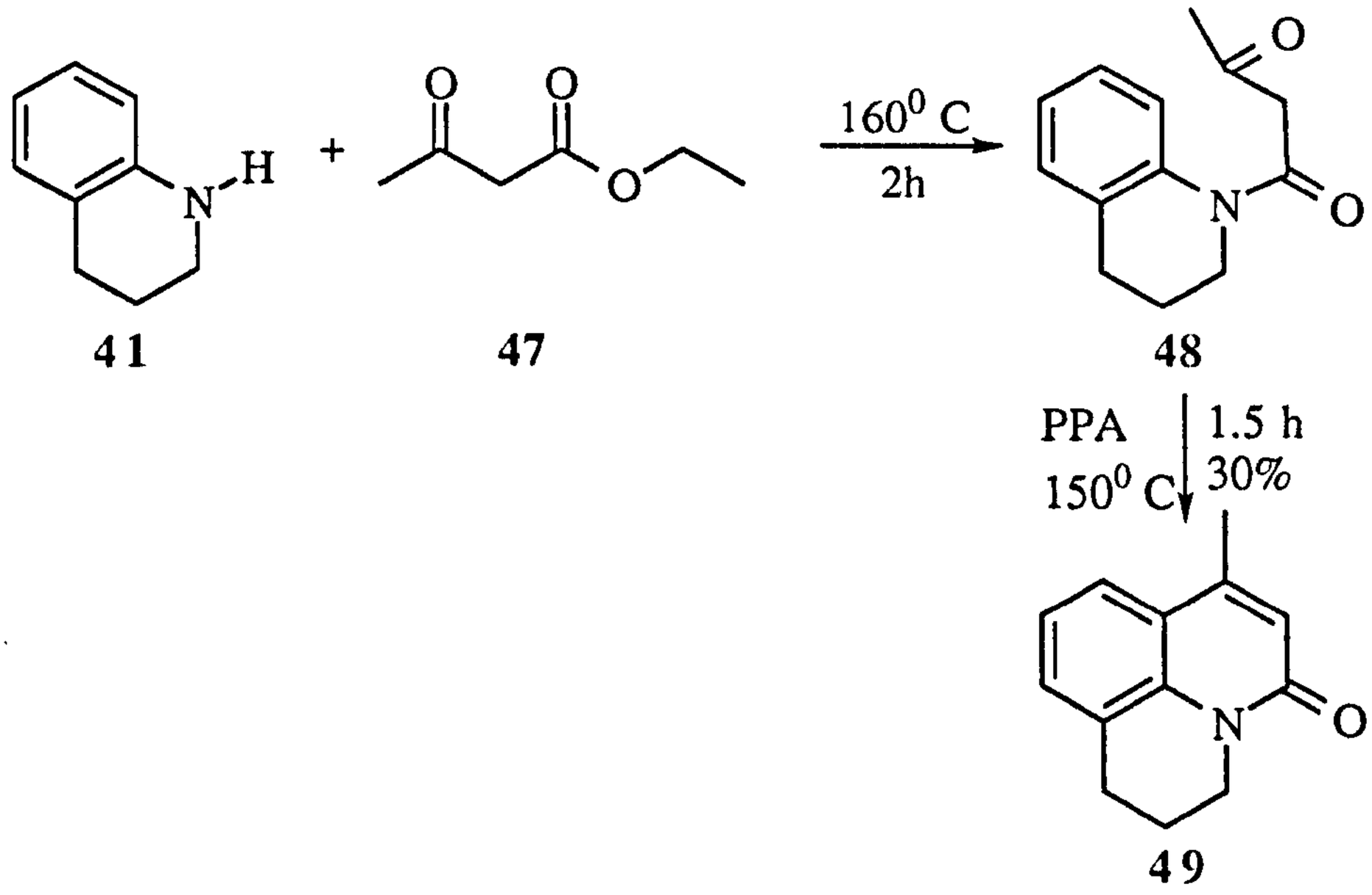
Again, keto lilolidines [58-60] and dimers of lilolidines [53, 61] are known to exist in the literature, it was of interest to prepare functionalised keto lilolidines for reasons mentioned earlier.

2.3 Syntheses of the julolidine ring skeleton

The first synthesis of julolidine was reported by Pinkus [48] in 1892. Following this synthesis, Glass and Weissberger [46] reported an improved yield of julolidine (77-81%) in 1967, when they reacted tetrahydroquinoline with trimethylene chlorobromide (see **Scheme 11**).

Julolidine ring preparation using electro-organic chemistry is known [62] but the method is long and complicated, as it involves anodic oxidation of amines or their derivatives in methanol to generate iminium ions, which in turn are reacted with nucleophiles such as electron-rich alkenes, styrene, enol ethers, and ring closed by reaction with ethyl vinyl ether to yield julolidine skeleton [62].

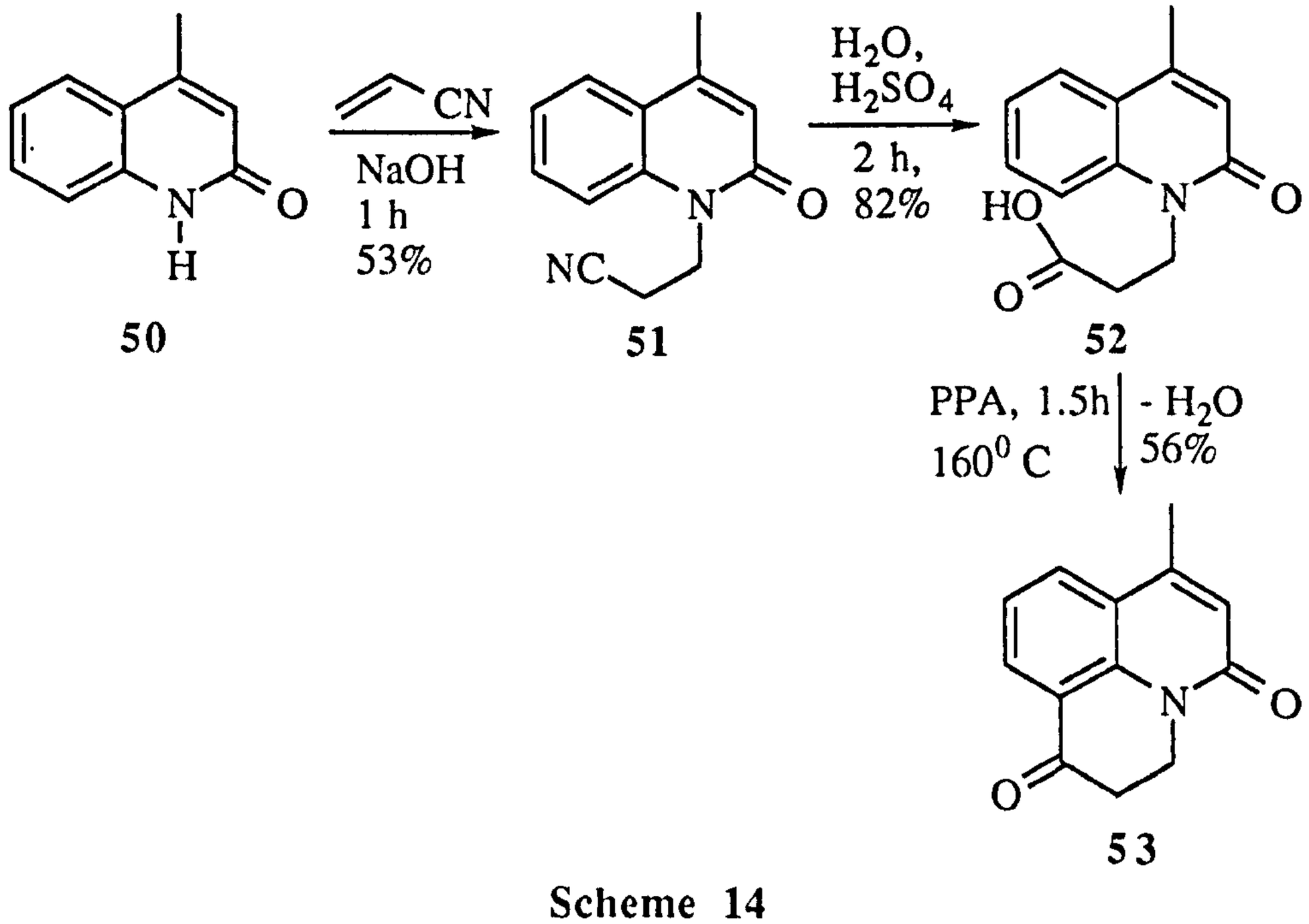
A more convenient approach to the preparation of the julolidine ring system was used by Afsah *et al* [63] in 1993 when they investigated the possibility of using ethyl acetoacetate (EAA) as one of the starting materials. The synthesis of functionalised julolidines was achieved by two different routes. The first involved treating tetrahydroquinoline **41** with ethyl acetoacetate **47** to give *N*-acetoacetyltetrahydroquinoline **48**, which was subjected to acid-catalysed cyclisation using polyphosphoric acid (PPA) to give 6,7-dihydro-1-methyl-3*H*,5*H*-benzo[ij]quinolizin-3-one (**49**), as shown in **Scheme 13**.



41 47 48 49

Scheme 13

In the second route, Afsah *et al* [63] used 4-methylquinolone (**50**), which was prepared from ethyl acetoacetate and aniline. Cyanoethylation using acrylonitrile and sodium hydroxide gave β-(*N*-4-methyl-2-quinolone)-propionitrile (**51**) which was readily hydrolysed to the corresponding propionic acid **52**. Cyclisation of **52** with polyphosphoric acid afforded 6,7-dihydro-1-methyl-3*H*,5*H*-benzo[ij]quinolizin-3,7-dione (**53**), as shown in **Scheme 14**.



50 51 52 53

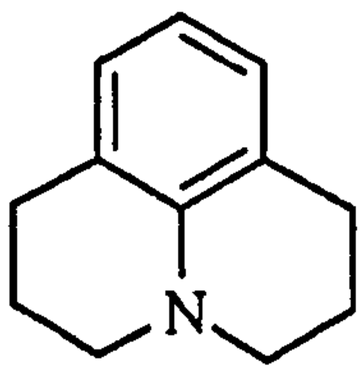
Scheme 14

More recently (1996), syntheses of julolidines based on benzotriazole methodology were reported by Katritzky *et al* (64). This is especially useful for the preparation of symmetrically and unsymmetrically 1,7-disubstituted julolidines as well as for the introduction of one, two or three substituents, in any combination at C-1, C-2 and C-3 in the julolidine system.

2.4 Nomenclature of quinolizine derivatives

2.4.1 Use of numbers and letters to designate positions and edges of the parent system julolidine

The correct way of numbering and lettering similar fused systems is explained by Stowell (65) and is applied consistently in this thesis. Hence to name julolidine (**36**), the linear fused-ring system (here, quinolizine) is numbered and edges are lettered in the standard way for quinolizine (66), as shown in Figure **4**.



36

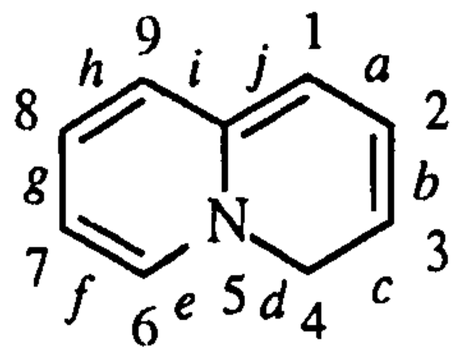


Figure 4

The order of lettering is such that where carbons were numbered 1 and 2, they constitute side *a* and 2 and 3 constitute side *b*, continuing in order for all sides. When the benzene ring is introduced on the quinolizine ring, it is clearly fused along the *i*, *j* edges, and thus the parent name becomes benzo[ij]quinolizine. Then the final combination is re-numbered to locate substituents, or sites of reduced unsaturation (65). To re-number, the parent system is firstly orientated so that a maximum number of fused rings are in a horizontal row. The system is then re-numbered clockwise starting with the carbon not involved in the fusion in the most counterclockwise position in the uppermost, or uppermost-farthest right ring. The lettering of the parent system remains the same.

Due to the re-numbering rule of the total fused system, it is important to realise that the numbering system in the 'parent' molecule will inevitably be different from that in the total fused system. Hence, Figure **4** is re-drawn to show the totally fused ring system at the *i*, *j* edges, and to indicate the new numbering of the carbons (see Figure **5**).

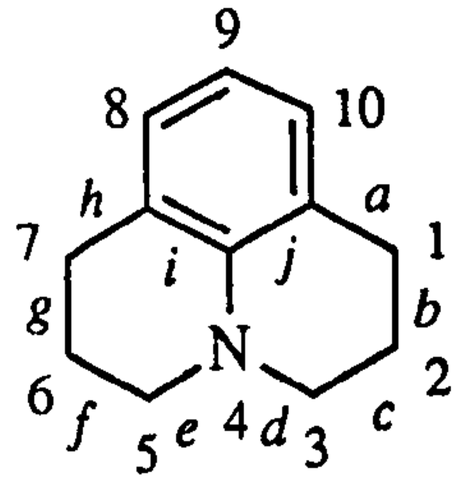
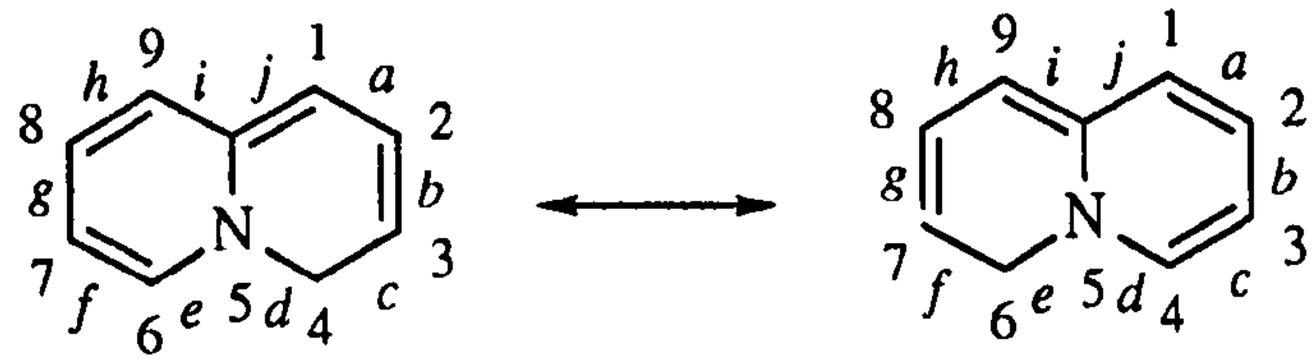


Figure 5: Parent name: benzo[ij]quinolizine

After assigning the numbers and letters correctly the next step is to designate the 'sites of reduced unsaturation' in the fused system.

2.4.2 Use of hydro/*H* to indicate sites of reduced unsaturation

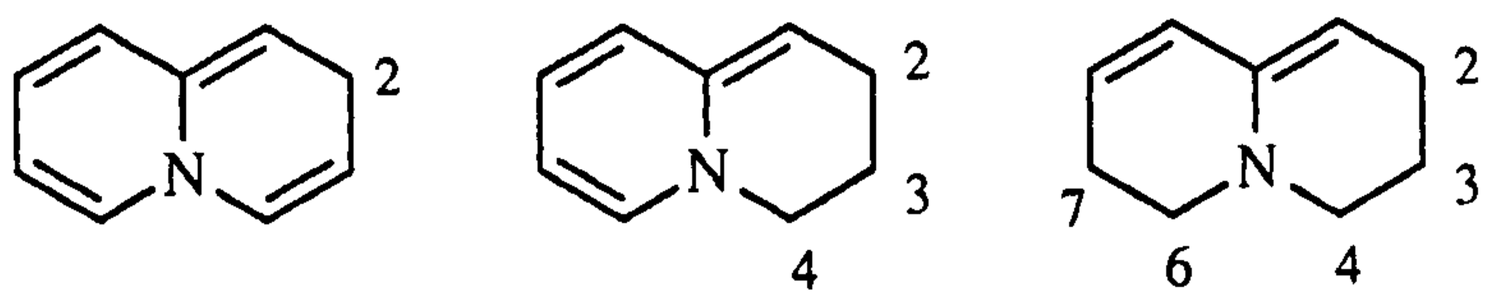
The italicised capital *H*s are used to designate the possible tautomers of the parent system. For instance, using the same example of the quinolizine parent system, possible tautomers are 4*H*-quinolizine (**54**), 6*H*-quinolizine (**55**), etc, as shown in Figure **6**.



54 **55**

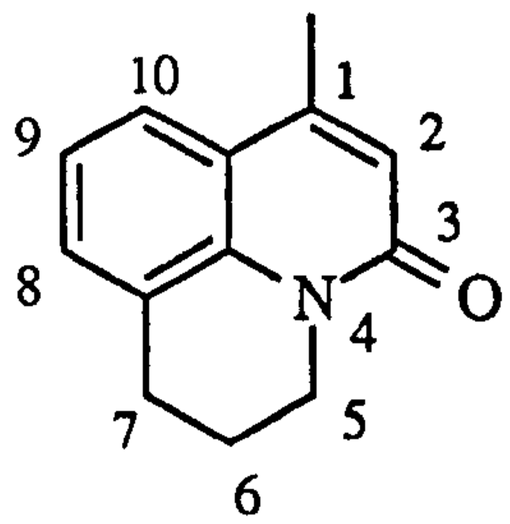
Figure 6

The terms dihydro, tetrahydro etc are used to indicate any further double bond reductions, once the 'parent' tautomer is fixed. For example, 4*H*-quinolizine (**54**), 2*H*-quinolizine (**56**), 2,3-dihydro-4*H*-quinolizine (**57**) and 2,3,6,7-tetrahydro-4*H*-quinolizine (**58**).



56 **57** **58**

Hence using the combination of all the rules mentioned, the full chemical name of julolidine (Figure **5**) becomes 2,3,6,7-tetrahydro-1*H*,5*H*-benzo[ij]quinolizine, realising that the italicised capital *H*s are given the lowest possible numbers in the system. When the fused ring system is substituted (e.g. compound **49**, see **Scheme 13**) the full chemical name becomes 1-methyl-6,7-dihydro-3*H*,5*H*-benzo[ij]quinolizin-3-one.

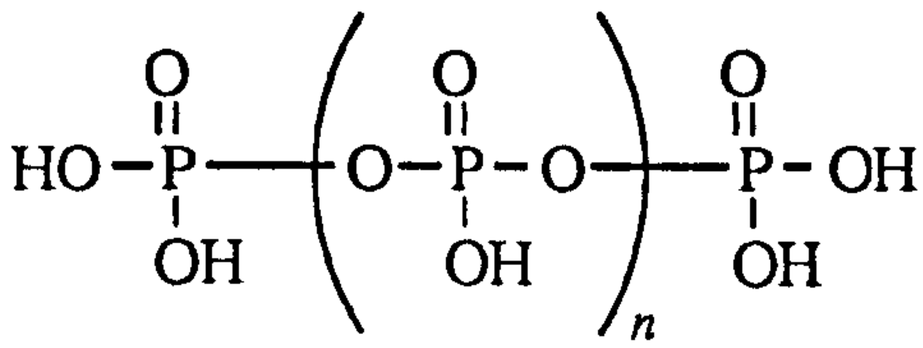


49

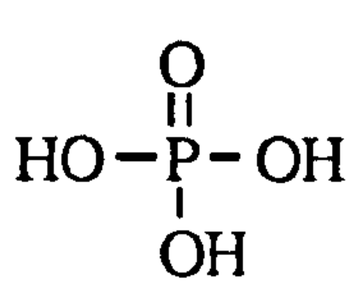
This method of numbering and lettering of fused systems is consistent with that used by Afsah *et al* [63] and Katritzky *et al* [64], although Afsah named compound **49** as, 6, 7-dihydro-1-methyl-3*H*,5*H*-benzo[ij]quinolizin-3-one.

2.5 Uses of Polyphosphoric acid

Polyphosphoric acid (PPA) is a good solvent for many organic compounds and has been used extensively in organic synthesis. Polyphosphoric acid **59** is a mixture of orthophosphoric acid **60** and linear phosphoric acids. Its preparation includes mixing *x* mL of phosphoric acid (85%, *d* 1.7 g mL^{-1}) with 2.2 equivalents of *x* g of phosphorus (V) oxide (P_2O_5), followed by heating to 200° C for 30 minutes.



59



60

In numerous instances the use of polyphosphoric acid offers advantages in yields, ease of manipulation, and the prevention of side reactions. In many synthetic processes the use of polyphosphoric acid allows the combination of two or more steps, so that the isolation of an intermediate is avoided. For instance, many cyclic ketones can be made directly from aryl-substituted acids or esters as an alternative to conversion to the acid chlorides and ring closure with aluminium chloride [67].

Polyphosphoric acid is one of the most effective reagents for carrying out acid-catalysed reactions [67], alkylation [68], acylation [68-69], hydrolysis of nitriles [68-69], cyclisation [67-68, 70-72], and dehydration [68, 73]. It is often the reagent of choice for a variety of transformations such as rearrangements [68], and syntheses of nitrogen containing heterocycles [67-68, 74].

2.5.1 Properties of polyphosphoric acid

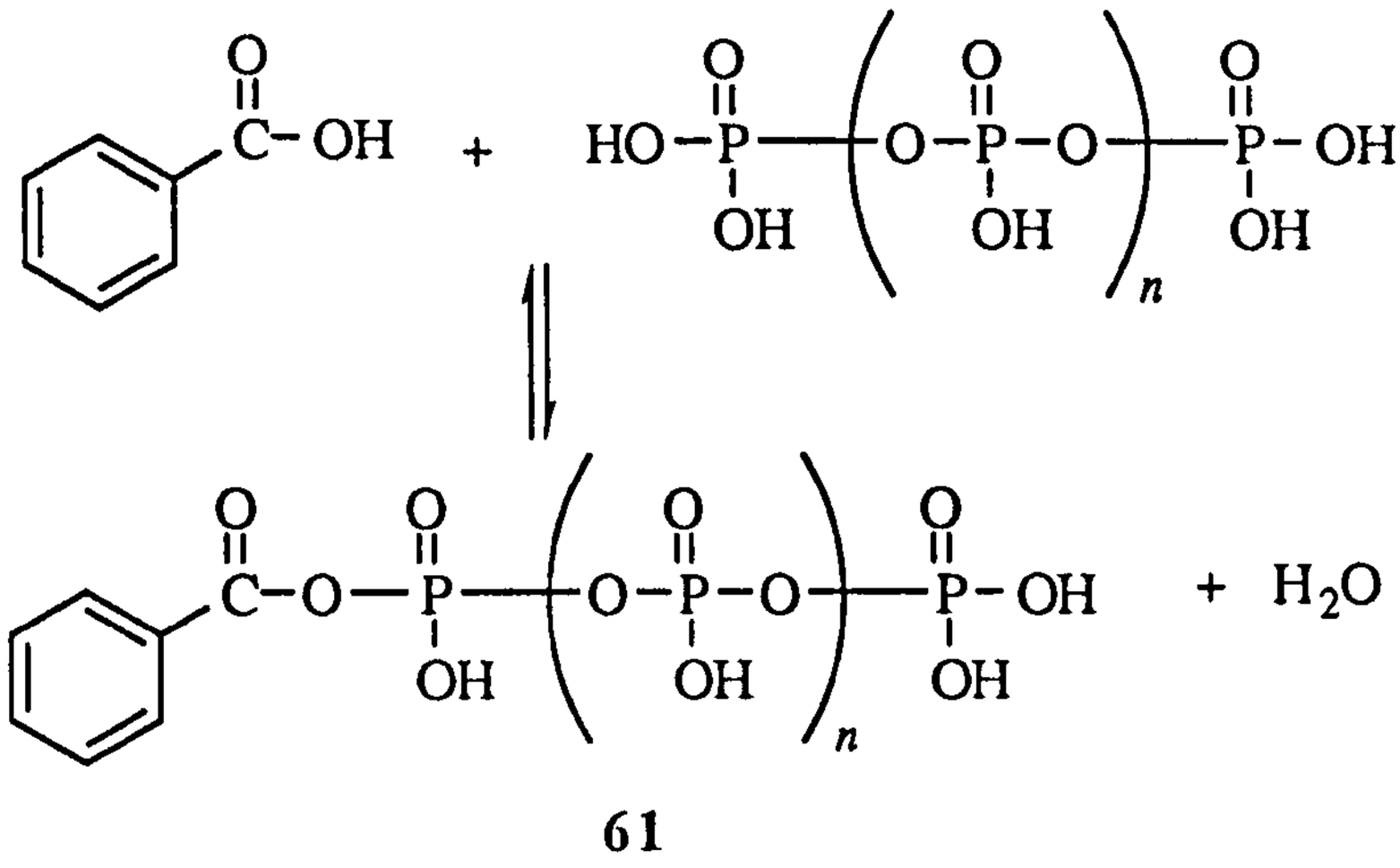
Polyphosphoric acid is a mild mineral acid; it is hygroscopic, highly viscous, clear and colourless [67]. It is often used instead of a stronger acidic reagent such as aluminium chloride or concentrated sulphuric acid. As a result, molecules containing functional groups such as esters, which are sensitive to more vigorous reagents may be dealt with satisfactorily in polyphosphoric acid. The fact that polyphosphoric acid is not a strong oxidising agent and has little or no tendency to cause substitution on aromatic nuclei give it further advantages over concentrated sulphuric acid [68]. As compared to hydrogen fluoride, particularly for cyclising aryl-substituted carboxylic acids, polyphosphoric acid has advantages in that its handling requires no special precautions, so that simple apparatus can be used [75].

Due to polyphosphoric acid's high viscocity, it is a poor medium for crystallisations, and thus reaction intermediates cannot easily be isolated from it. The most obvious function of polyphosphoric acid is that it acts as a protonic acid (Lewis acid), and as a phosphorylating agent [68]. Hence, the powerful dehydrating properties of polyphosphoric acid, low nucleophilicity of the phosphoric acid media and the moderate acidity lead to the use of this reagent in the current reactions.

2.5.2 Mechanism involving polyphosphoric acid

The most obvious possibilities are that it functions as a protonic acid, as a Lewis acid, and as a phosphorylating agent. Inspite of the large number of publications on the synthetic applications of PPA , little is established on how PPA works as a synthetic reagent. The high viscosity and complex composition of PPA make it extremely difficult to investigate the mechanism of reactions occuring in it. Most of the proposed mechanistic pathways mentioned in the literature involving PPA are not supported with experimental data.

The reaction of *o*-aminophenol and benzoic acid in PPA with phosphorus (V) oxide (P_2O_5) was recently studied by Ying-Hung So *et al* [76]. They showed that the reaction was faster with higher initial P_2O_5 content. Higher reaction rates and higher anhydride to benzoic acid ratios, when the P_2O_5 was increased, suggested that the mixed anhydride was the reacting intermediate. In their investigation, the carboxylic group in benzoic acid was transformed into benzoic-phosphoric anhydride and benzoic-polyphosphoric anhydride **61**, as outlined in **Scheme 15**.



61

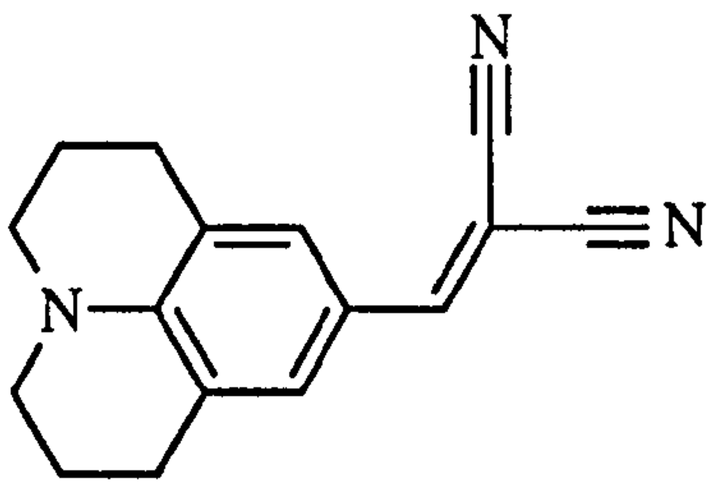
Scheme 15

The effectiveness of polyphosphoric acid reagent in the hydrolysis of nitriles to amides is known [69] and thus indicates the rather exceptional stability of amides in this reagent.

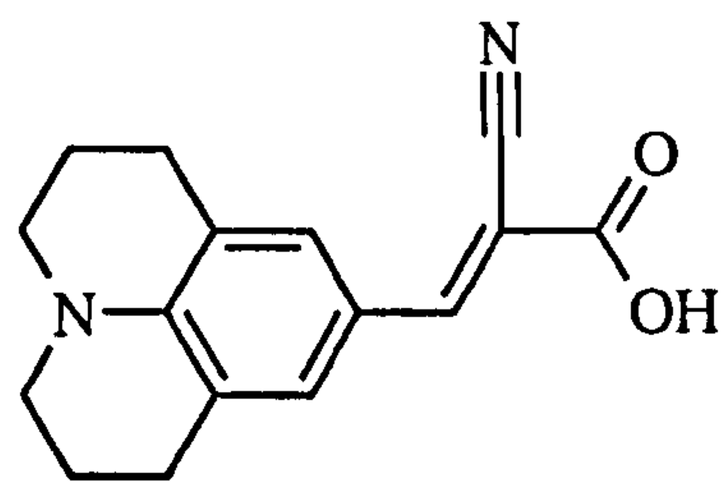
2.6 Aims of the project

2.6.1 Quinolizines

The presence of julolidine ring system in some molecules makes them useful as dyes, whilst the dimers of julolidine analogues are currently used as commercial fluorescent dyes [54, 77-78] in dye industries. The formation of these dyes is mainly associated with the nitrogen being sp^2 hybridised [54] which allows more efficient conjugation with the aromatic nucleus. Lilolidine analogues of some dyes have been prepared by Castelino *et al* [61] but they found that the conjugation of the terminal nitrogen atoms with the aromatic rings is less efficient than in julolidines because the terminal nitrogen atoms are twisted from the position of optimum conjugation found in the julolidine derivatives. More recently, fluorescent dyes, especially 9-(dicyanovinyl)julolidine (DCVJ) [79] **62** and 9-(2-carboxy-2-cyanovinyl)julolidine (CCVJ) [80] **63**, have been referred to as molecular rotors which act as probes for tubulin structure and protein assembly *in vitro* and *in vivo*. These fluorescent molecular rotors are used to monitor the Zn^{2+}-induced polymerisation of tubulin dimers into tubulin sheets. Studies have shown that **62** binds to tubulin with a high affinity [79]. This discovery is interesting since drugs used in the treatment of parasitic disease such as leishmania act by disrupting the tubulin (protein) assembly.



62



63

Amides have been known to have anti-inflammatory (81) and agrochemical (82) activities, hence the intention to incorporate the amide function into some of the compounds synthesised in this study.

While some individual quinolizines have been reported with full proton NMR data, there has been no systematic study in the literature. Since few previous studies have been reported on these types of compounds in medicinal chemistry this prompted detailed investigation of the spectra of these compounds in order to understand the steric and electronic behaviour of these compounds as well as their substituents. Similarly, there is little mass spectrometric data available in the literature and as a consequence proposed fragmentation pathways are discussed in some detail.

Analogues were to be synthesised for homologation studies to give insight into the structure-activity relationships of these compounds. Finally, the syntheses are extended to quinolinone derivatives.

2.6.2 Quinolinones

A number of cyclisation reactions closely related to the Skraup and Doebner-von Miller syntheses lead to 2-quinolones and 4-quinolones (83). The original Conrad and Limpach synthesis involves reacting an aromatic aniline with an α, β-ketoester and has been used more widely than any other route to 4-quinolones. The use of paraffin oil as the cyclisation medium, and subsequently boiling diphenyl ether or a mixture of diphenyl ether and diphenyl (Dowtherm) have been reported (83) as superior in high temperatures (260-280° C) and minimum time, maintaining high dilutions, causing cyclisations to be completed in few minutes. Older procedures using acid catalysts (or heating without solvents) gave much poorer yields, but more recently, a number of 4-quinolones have been prepared by cyclisation (83) using polyphosphoric acid.

The Knorr synthesis (83) produces 2-quinolones from β-ketoesters, via β-ketoanilides. Hence, a wide range of 2-quinolones is available by the acid-catalysed cyclisation of β-ketoanilides as are the 4-quinolones by the Conrad-Limpach method.

DISCUSSION

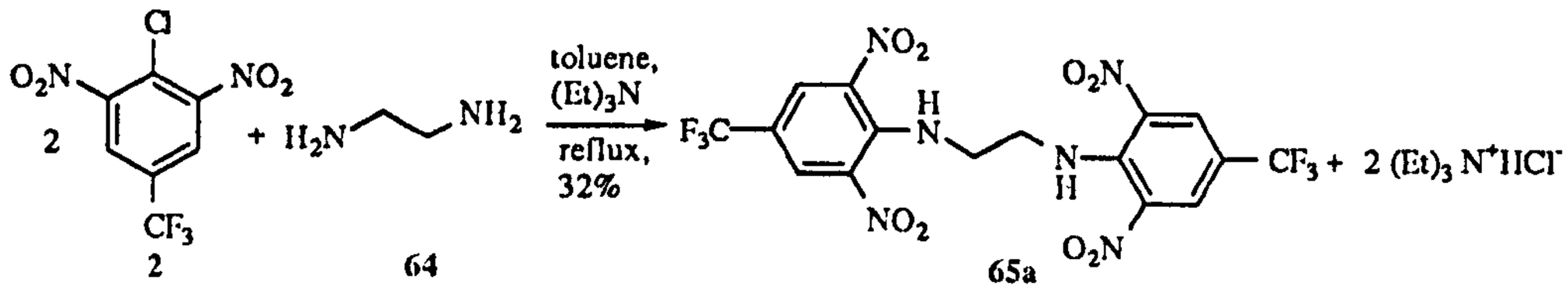
3.0 Trifluralin dimers

It was of interest to explore the structure-activity relationships of trifluralin dimers, especially the stereo-electronic and solubility properties, since currently experimental drugs have not been optimised to produce clinically adequate antiparasitic compounds. Such groups of compounds could form the basis of biological studies aimed at targeting the site and mechanism of action of trifluralin dimers, especially against *Leishmania* and possibly malaria in mammals. Trifluralin has potent activity when applied topically [9] and, *in vitro*, actively reduces *leishmaniasis*. These dimers were fully characterised using NMR, MS and IR techniques and were consistent with the proposed structures.

3.1 Syntheses of trifluralin dimers

The syntheses of several novel dimers (**65a - n**) as analogues of trifluralin were successfully carried out. As mentioned in the introduction, the commercial synthesis of trifluralin is from *p*-chlorotrifluoromethylbenzene (see **Scheme 1**), but in the current study, a slight modification to the original synthesis was adopted. Chloralin, or 1-chloro-2,6-dinitro-4-trifluoromethylbenzene (**2**) was used as the starting material (instead of *p*-chlorobenzoic acid); triethylamine (organic base) was introduced into the reaction as the acid scavenger (instead of utilising the respective diamines); and anhydrous toluene was used as the solvent. This made the reaction work-up easier and the reactions were carried out as one-pot syntheses. The route for the synthesis of N^1,N^2-di-(2,6-dinitro-4-trifluoromethylphenyl)-1,2-diaminoethane (**65a**) is outlined in **Scheme 16**, and is typical of the routes to all the other dimers (**65a-n**) synthesised in this series.

Two equivalents of 1-chloro-2,6-dinitro-4-trifluoromethylbenzene (**2**) were reacted with one equivalent of the ethylenediamine (**64**) in the presence of excess triethylamine to give 32% of the bright yellow compound (**65a**). Synthesis of compounds **65a**, **65b** and **65h** is similar to that of Jing-Shun *et al* [84], except their synthetic efforts involved ethanol as the reaction solvent instead of toluene.



Scheme 16

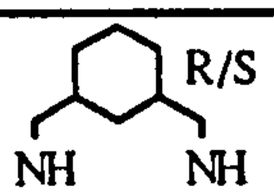
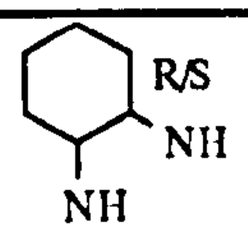
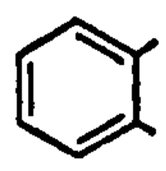
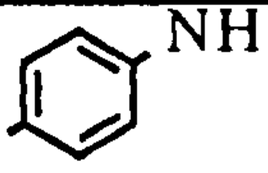
65	Name	R	Yield (%)	mp (°C)
a	N^1,N^2-di-(2,6-dinitro-4-trifluoro-methylphenyl)-1,2-ethylenediamine	NH-$(CH_2)_2$-NH	32	204-206 (84)
b	N^1,N^2-di-(2,6-dinitro-4-trifluoro-methylphenyl)-1,3-propylenediamine	NH-$(CH_2)_3$-NH	71	171-174 (84)
c	N^1,N^2-di-(2,6-dinitro-4-trifluoro-methylphenyl)-1,4-diaminobutane	NH-$(CH_2)_4$-NH	53	193-195
d	N^1,N^2-di-(2,6-dinitro-4-trifluoro-methylphenyl)-1,5-diaminopentane	NH-$(CH_2)_5$-NH	68	130-134
e	N^1,N^2-di-(2,6-dinitro-4-trifluoro-methylphenyl)-1,6-diaminohexane	NH-$(CH_2)_6$-NH	25	157-160
f	N^1,N^2-di-(2,6-dinitro-4-trifluoro-methylphenyl)-1,10-diaminodecane	NH-$(CH_2)_{10}$-NH	55	109-110
g	N^1,N^2-di-(2,6-dinitro-4-trifluoro-methylphenyl)-1,12-diaminododecane	NH-$(CH_2)_{12}$-NH	88	98-100
h	N^1,N^2-di-(2,6-dinitro-4-trifluoro-methylphenyl)piperazine		81	226-228 (84)
i	N^1,N^2-di-(2,6-dinitro-4-trifluoro-methylphenyl)-1,3-cyclohexanebis-(methylamine)		52	190-192
j	N^1,N^2-di-(2,6-dinitro-4-trifluoro-methylphenyl)-1,2-diaminocyclo-hexane		67	264-265
k	N^1,N^2-di-(2,6-dinitro-4-trifluoro-methylphenyl)-diethylenetriamine	NH-$(CH_2)_2$-NH-$(CH_2)_2$-NH	73	132-136
l	N^1,N^2-di-(2,6-dinitro-4-trifluoro-methylphenyl)-1,2-phenylenediamine		58	252-254
m	N^1,N^2-di-(2,6-dinitro-4-trifluoro-methylphenyl)-1,3-phenylenediamine		70	264-266
n	N^1,N^2-di-(2,6-dinitro-4-trifluoro-methylphenyl)-1,4-phenylenediamine		45	316-318

Table 4

The generalised structure for all the products (**65a-n**) is shown in Figure **7** and the range of values for R are given in Table **4**. The R groups were selectively chosen

to synthesise a homologous series of compounds to explore the hypothesis that it is possible to estimate the distance between two binding sites in the tubulin polymers.

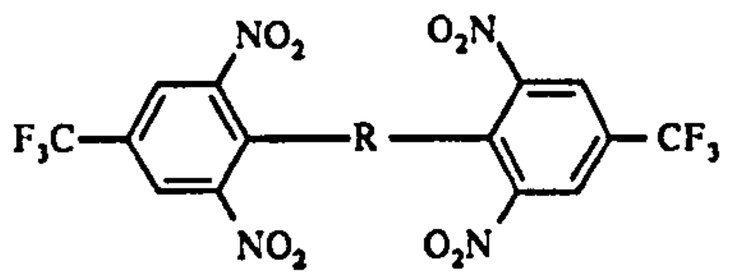
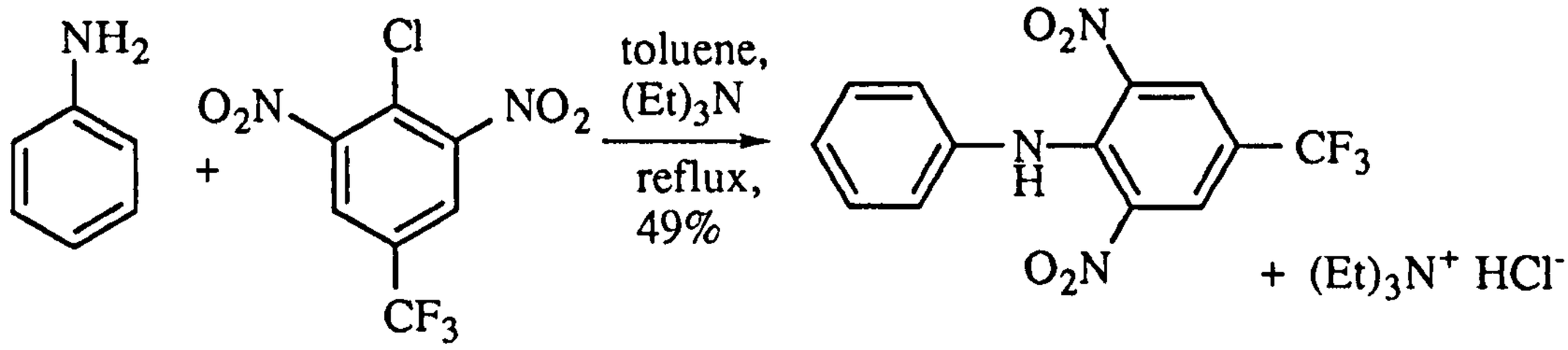


Figure 7 (65a - n)

We have synthesised derivatives of the dinitroaniline herbicide trifluralin (**3**) in which amine substituents have been altered to increase the hydrophobicity of the molecule. The incorporation of more hydrophilic groups into the molecules would cause the water solubility properties of these compounds to change, which is important since this allows effective transport of a drug candidate to the target site. However, a compound's motility in lipophilic membranes is finely balanced between hydrophilic and hydrophobic groups. Thus, the substituents (R groups) were selected using the Hansch parameter [log (*P*) or π value] [23] which is a useful tool for predicting this motility. A log (*P*) value of between 2.00 and 2.40 [23, 85] is considered optimum for a substance that must traverse cellular membranes. With these considerations, we chose a series of R groups based on Topliss chart.

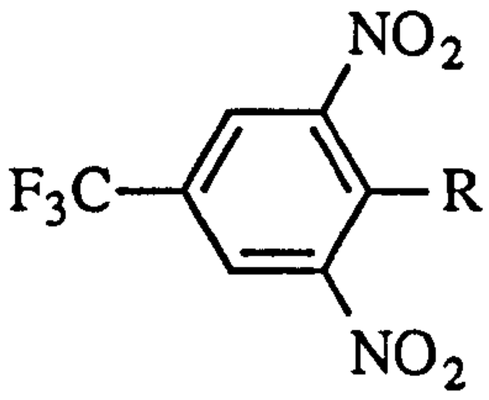
Thus, a series of monomers of trifluralin (compounds **67a-j**) were synthesised successfully by reacting a variety of substituted aromatic amines with 1-chloro-2,6-dinitro-4-trifluoromethylbenzene (**2**), as outlined in **Scheme 17** for aniline (**66**) under reflux in triethylamine and toluene to give 1-[*N*-(2,6-dinitro-4-trifluoromethylphenyl)-amino]benzene (**67a**).



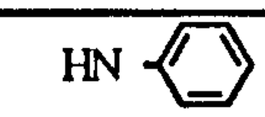
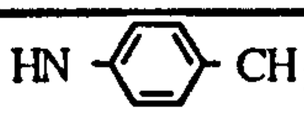
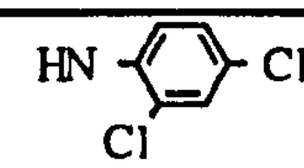
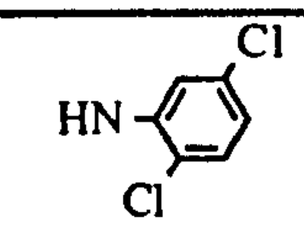
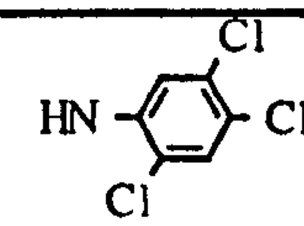
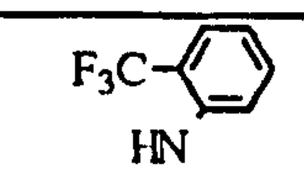
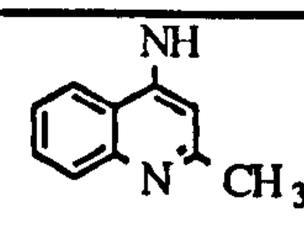
66 **2** **67a**

Scheme 17

The route outlined in **Scheme 17** is representative of the routes to all the other monomers synthesised (**67a-j**) in this series and the results are summarised in Table **5**.



(67a-j)

67	Name	R	Yield (%)	mp (°C)
a	*N*-(2,6-dinitro-4-trifluoro-methylphenyl)aminobenzene		49	118-120 (86)
b	4-methyl-1-[*N*-(2,6-dinitro-4-trifluoromethylphenyl)-amino]benzene		68	138-140
c	4-methoxy-1-[*N*-(2,6-dinitro-4-trifluoromethylphenyl)-amino]benzene		74	133-135 (86)
d	4-chloro-1-*N*-(2,6-dinitro-4-trifluoromethylphenyl)-amino]benzene		93	98-104
e	2,4-dichloro-1-[*N*-(2,6-dinitro-4-trifluoromethyl-phenyl)amino]benzene		22	150-151
f	2,5-dichloro-1-[*N*-(2,6-dinitro-4-trifluoromethyl-phenyl)amino]benzene		-	oil
g	2,4,5-trichloro-1-[*N*-(2,6-dinitro-4-trifluoromethyl-phenyl)amino]benzene		35*	oil
h	*N*-morpholino-(2,6-dinitro-4-trifluoromethylphenylamine)		95	142-144 (85,87)
i	2-[*N*-(2,6-dinitro-4-trifluoro-methylphenyl)amino]benzotri-fluoride		75	oil
j	2-methyl-4-[*N*-(2,6-dinitro-4-trifluoromethylphenyl)-amino]quinoline		51	> 270

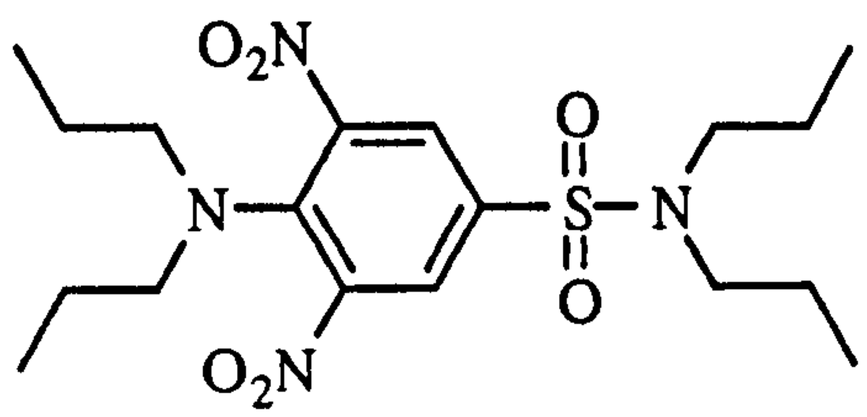
* crude yield

Table 5

3.2 The synthesis of 4-(*N*,*N*-dipropylsulphamoyl)-2,6-dinitro -1-(*N*,*N*-dipropylamino)benzene (68)

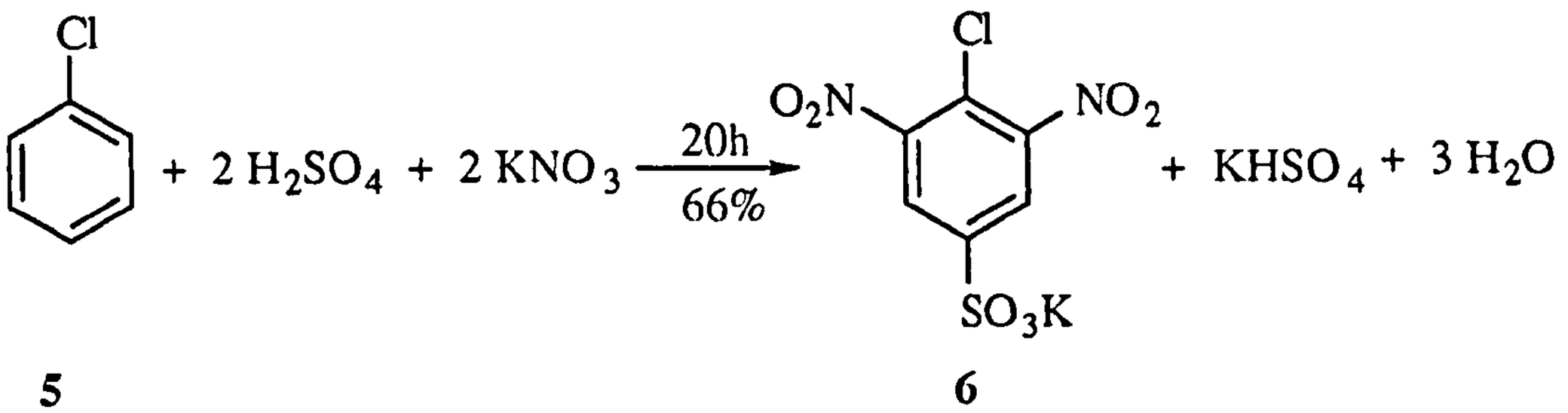
Oryzalin, (3,5-dinitro-4-(*N*,*N*-dipropylamino)benzenesulphonamide) (**9**) (see **Scheme 3**), is a member of the dinitroaniline herbicide group of molecules. Its herbicidal activity is attributed to the disruption of microtubules and, therefore, cell division. In a recent study, Chan and co-workers [88] found that oryzalin inhibited the growth and cell differentiation of a parasitic protozoan, *Leishmania mexicana*, whereas it had no effect on the proliferation of mammalian cells *in vitro*. They found that oryzalin, which is a selective, pre-emergence herbicide for the control of annual grasses and certain broad leaf weeds in soyabeans, inhibited cell differentiation by 60%. The sulphonamide group in oryzalin reduces the lipophilicity and increases the aqueous solubility [89].

To exploit the weak base accumulation effect for targetting the acidic vacuole of *plasmodia* and to replace the relatively expensive trifluoromethyl group, 4-(*N*,*N*-dipropylsulphamoyl)-2,6-dinitro-1-(*N*,*N*-dipropylamino)benzene (**68**) was synthesised successfully in good yield (87%).



68

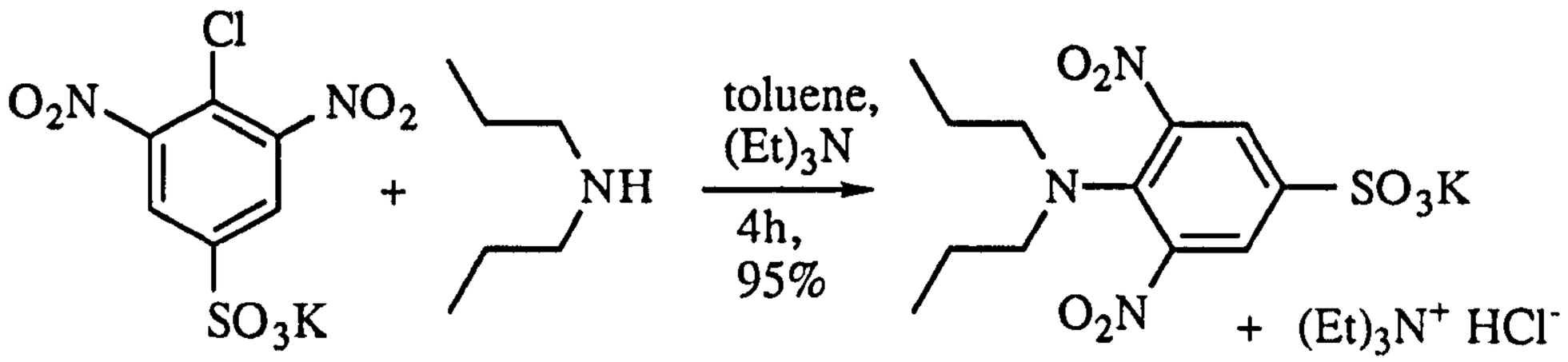
There are four steps involved in the synthesis of this compound. The first step involves the formation of potassium 4-chloro-3,5-dinitrobenzene sulphonate (**6**), when chlorobenzene (**5**) is reacted with two equivalents of concentrated sulphuric acid and potassium nitrate, as outlined in **Scheme 18**.



5 **6**

Scheme 18

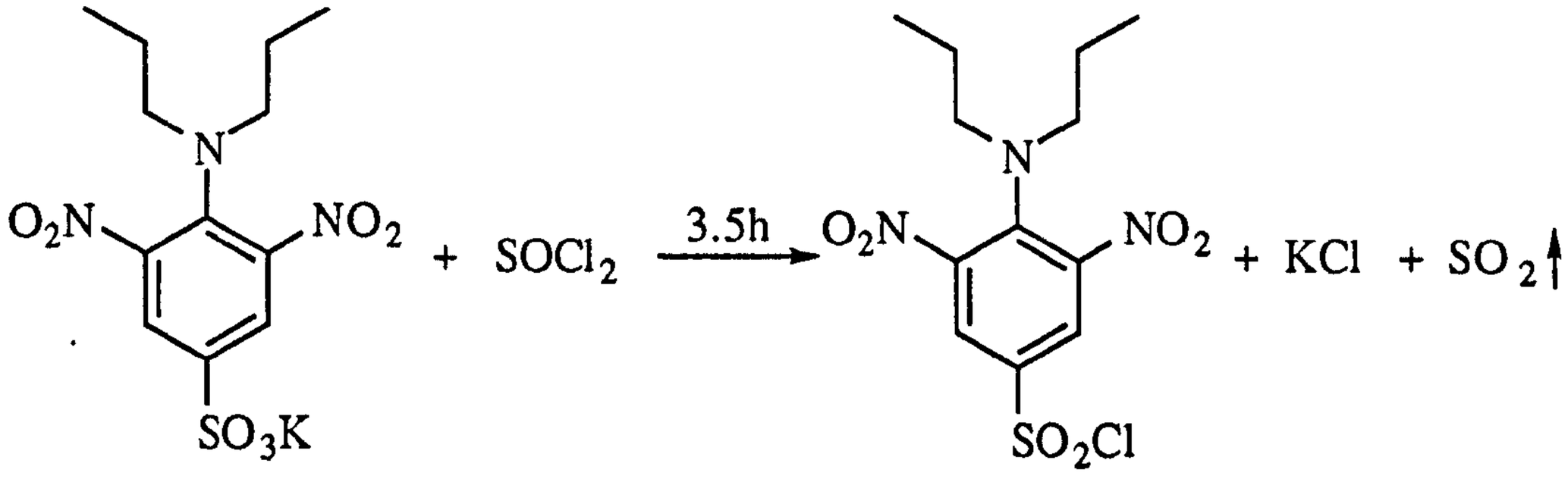
The second step involves the conversion of **6** (without further purification) into potassium 4-(*N*, *N*-dipropylamino)-3,5-dinitrobenzene sulphonate (**7**), by reaction with one equivalent of dipropylamine (**6a**) under reflux, in the presence of triethylamine and toluene, as outlined in **Scheme 19**.



6 **6a** **7**

Scheme 19

The crude product of **7** was used in the next step to form 2,6-dinitro-4-(*N*,*N*-dipropylamino)benzenesulphonyl chloride (**8**) when heated under reflux with one equivalent of thionyl chloride (**Scheme 20**).

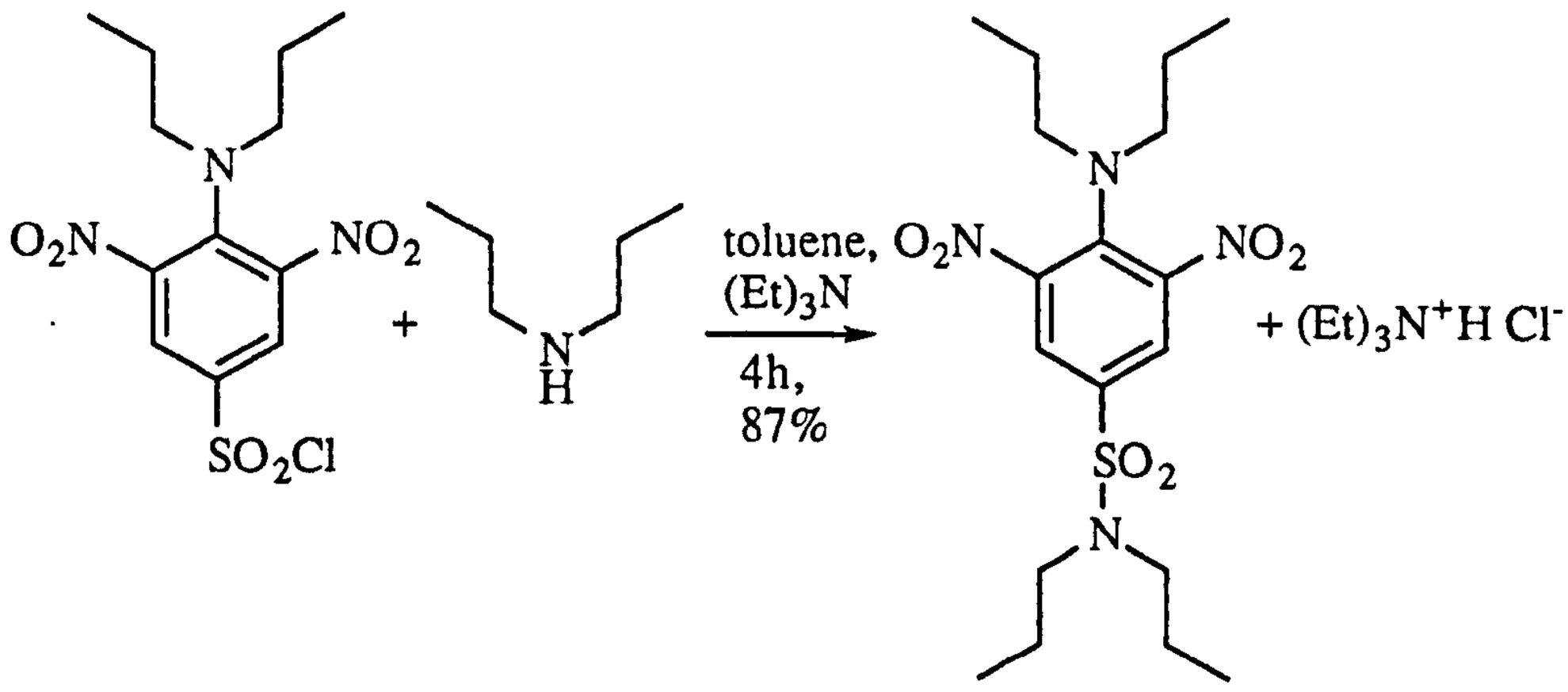


7 **8**

Scheme 20

The reactions outlined in **Schemes 18-20** are similar to the reaction outlined in **Scheme 3** in the Introduction, for the synthesis of oryzalin **9**.

The product **8** was not isolated from the reaction mixture but was heated under reflux with dipropylamine (**6a**) and gave 4-(*N*,*N*-dipropylsulphamoyl)-2,6-dinitro-1-(*N*,*N*-dipropylamino)benzene (**68**) as shown in **Scheme 21**.



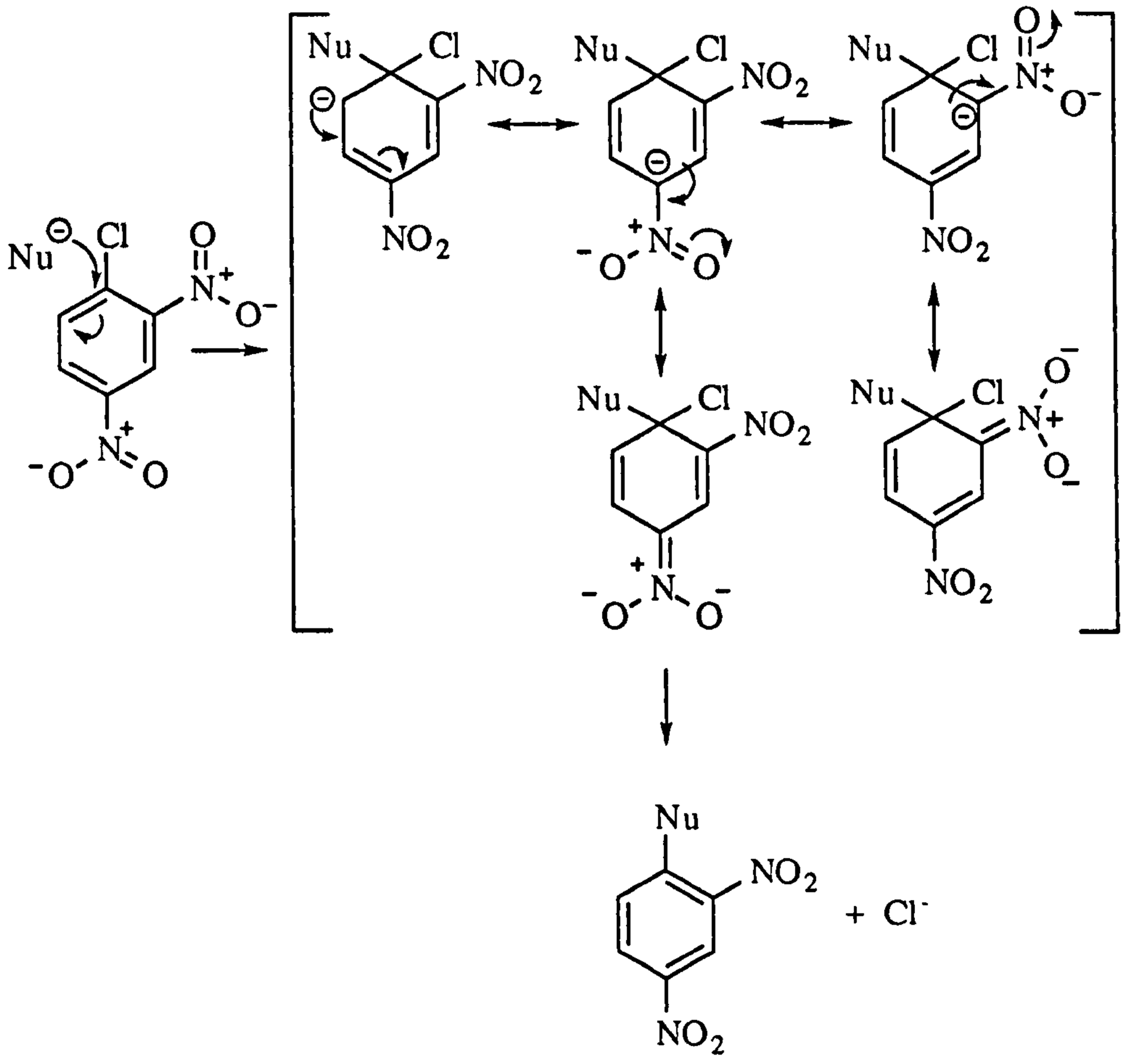
8 **6a** **68**

Scheme 21

3.3 Proposed mechanism of formation of the trifluralin dimers

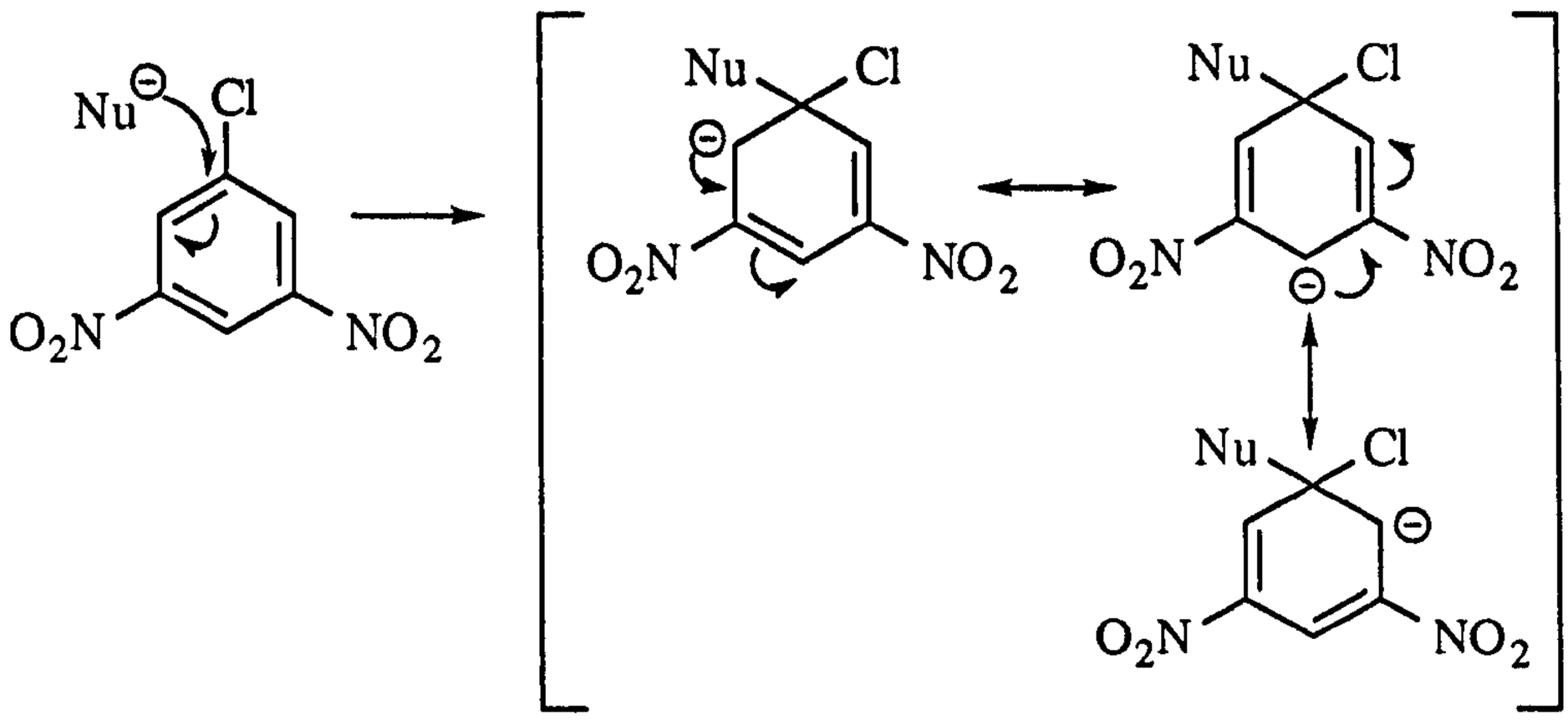
Nucleophilic aromatic substitution (S_NAr) mechanisms of haloarenes involve a two step mechanism, an addition-elimination process. These reactions are facilitated by increasing nucleophilic power of the reagents used, and the number of electron-withdrawing groups present in the ring, particularly if they are in the *ortho* and *para* positions relative to the group being displaced.

The reaction in **Scheme 16**, (see page 30) is favoured by the presence of the two electron-withdrawing (-I, -M) nitro groups on the benzene ring *ortho* to the chlorine and the trifluoromethyl group *para* to the chlorine. These nitro groups decrease the electron density in the benzene ring generally (and in particular at the carbon carrying the chlorine group), thus increasing the positive character of the carbon atom and making it more susceptible to nucleophilic attack. They also stabilise the intermediate anions by resonance delocalisation. This delocalisation is most effective when the nitro groups are *ortho* and *para* to the chlorine, as shown in **Scheme 22**.



Scheme 22

In the *meta*-position the nitro groups are out of conjugation with the carbanion initially formed in the *ipso* substitution and so do not stabilise it, as outlined in **Scheme 23**.

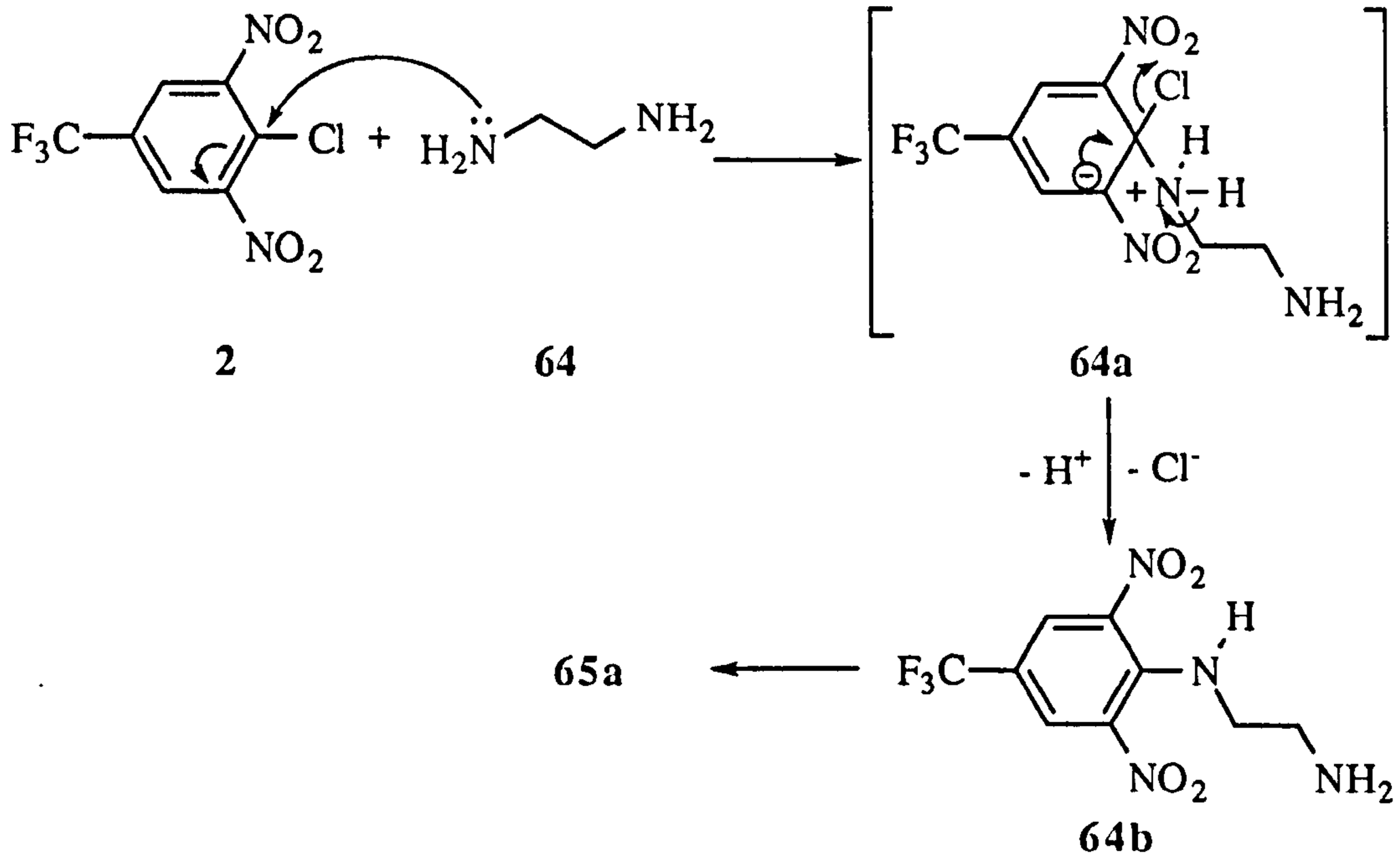


Scheme 23

The nucleophilic attack must occur from the same side of the carbon atom as the leaving group (cf. in aliphatic S_N2 reactions where the attack is from the opposite side) to form the transition state [84, 90-91], the Jackson-Meisenheimer complex (see **Scheme 24**).

It is not known whether addition (step 1) or elimination (step 2) is the rate-limiting step because the relative rates for the reactions involving displacement of iodine, chlorine and bromine in aromatic systems do not correlate with their relative carbon-halogen bond strengths which they would be expected to do in the second, (elimination) step [90].

Thus the mechanism proposed for the reaction shown in **Scheme 16** (page 30) is nucleophilic aromatic *ipso* substitution (or pseudo S_N2) where the first (addition) step involves the nucleophilic attack on carbon carrying the chlorine in 1-chloro-2,6-dinitro-4-trifluoromethylbenzene (**2**) by ethylene diamine (**64**) to generate the Jackson-Meisenheimer complex (**64a**), as shown in **Scheme 24**. This complex is stabilised by resonance as mentioned before. The second step involves the elimination of chloride ion from **64a** to give the monomer, *N*-(2,6-dinitro-4-trifluoromethylphenyl)-1,2-ethylenediamine (**64b**). The primary amino group in **64b** then reacts with a second molecule of **2** by the same mechanistic process to yield the dimer, N^1,N^2-di-(2,6-dinitro-4-trifluoromethylphenyl)-1,2-ethylenediamine (**65a**).



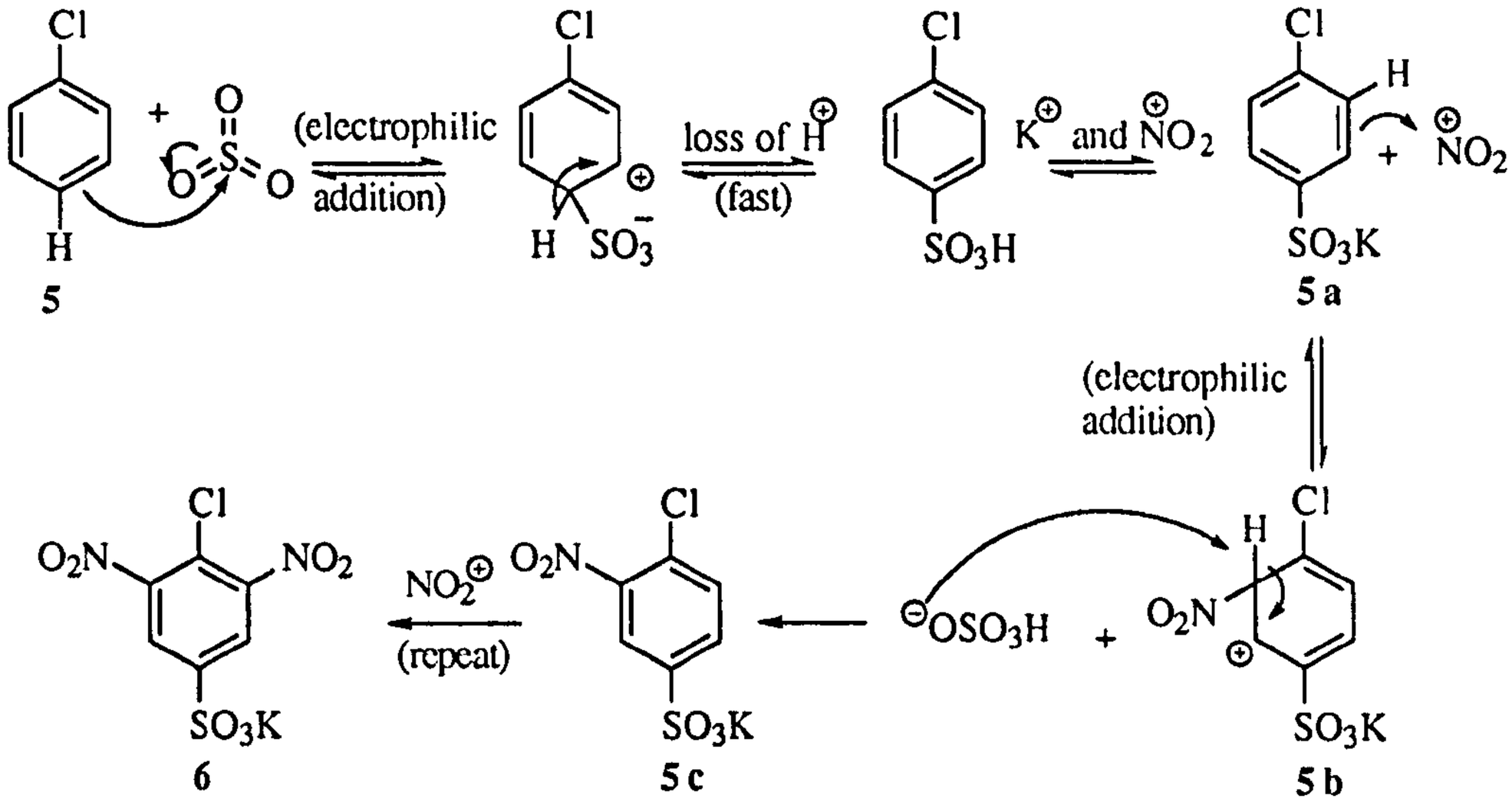
Scheme 24

The other possible mechanism (of elimination-addition involving a benzyne-type intermediate) does not apply here, as there are no hydrogen atoms available *ortho* to the chlorine in compound **2**.

There have been a number of claims that radical anions are precursors in the substitution reactions of certain nitro compounds, but interestingly nitro compounds are among the substrates which do not undergo substitution by the SRN_1 radical chain mechanism (91).

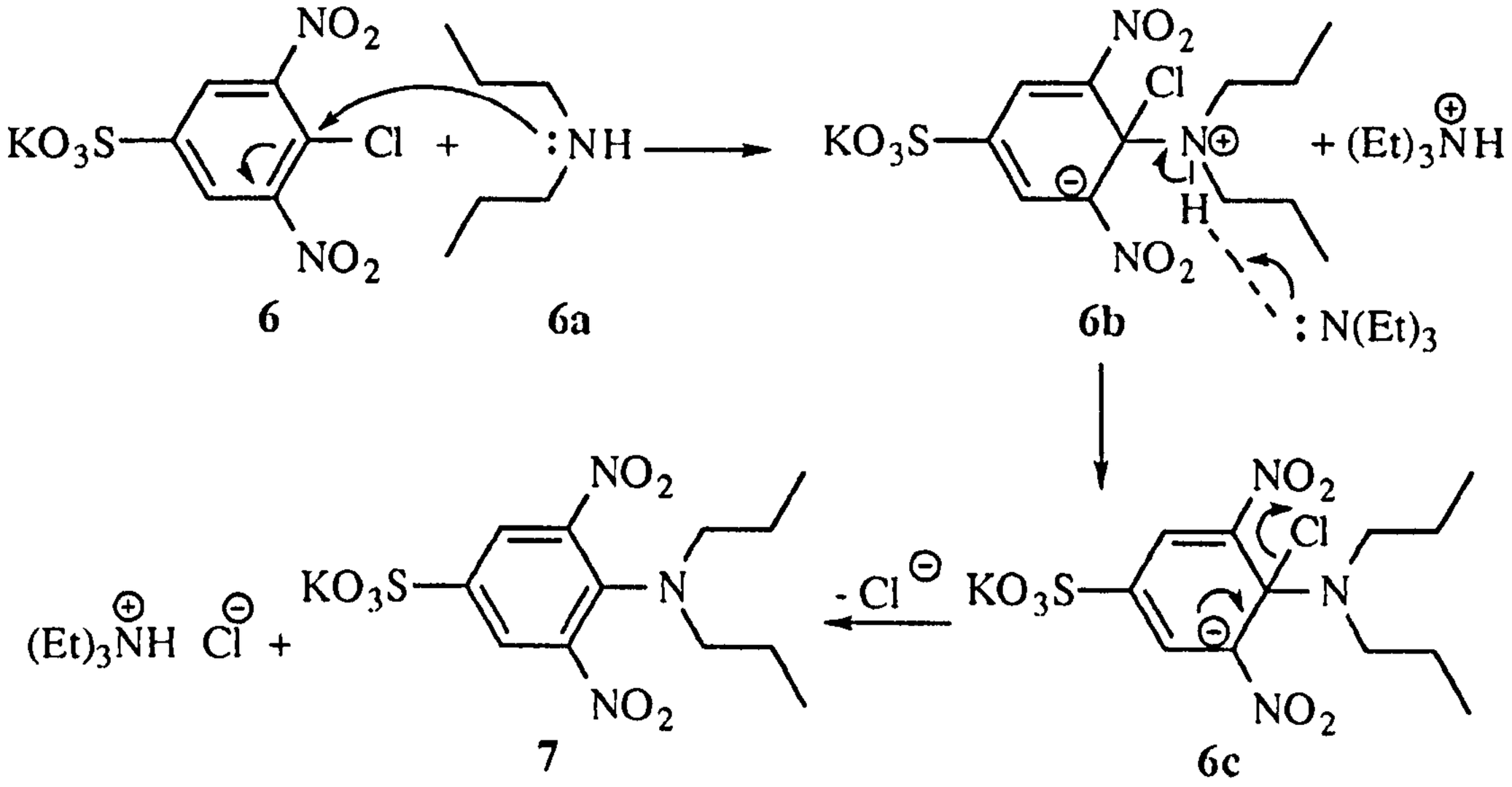
3.4 Proposed mechanism of formation of 4-(*N*,*N*-dipropyl-sulphamoyl)-2,6-dinitro-1-(*N*,*N*-dipropylamino)benzene (68)

The proposed mechanism of formation of **68** (see **Schemes 18-21**) involves initial sulphonation at the 4-position in chlorobenzene (**5**) to give **5a**. The potassium sulphonate group occupies this position and forces the nitration to occur at the 2- and 6-positions in **5b**, as shown in **Scheme 25**. Due to the electron-withdrawing effect of the three oxygen atoms, the sulphur in SO_3 is electron-deficient and sufficiently electrophilic to attack the benzene ring *para* to the chlorine (the +M effect of the chlorine making it *ortho/para*-directing towards electrophiles). Protonation of the potassium nitrate by the sulphuric acid yields the nitronium ion, which as a strong electrophile attacks the 2-position to yield **5c**, with the process being repeated at the 6-position to give the dinitro compound **6**.



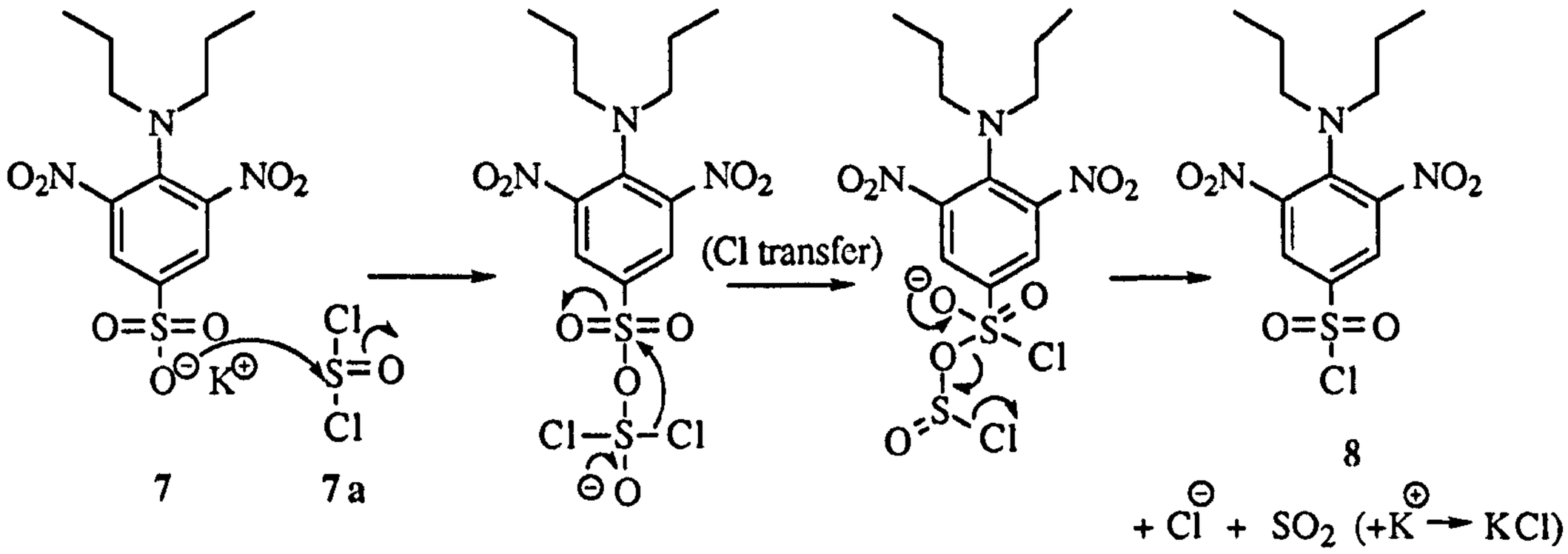
Scheme 25

Potassium 4-chloro-3,5-dinitrobenzene sulphonate (**6**) is then subjected to nucleophilic attack (nucleophilic aromatic *ipso* substitution, or pseudo S_N2) by dipropylamine **6a** on the carbon bearing the chlorine group to generate the Jackson-Meisenheimer complex **6b**, as outlined in **Scheme 26**. The second step involves the elimination of the chloride ion from **6c** to give potassium 4-(*N*,*N*-dipropylamino)-3,5-dinitrobenzene sulphonate (**7**).



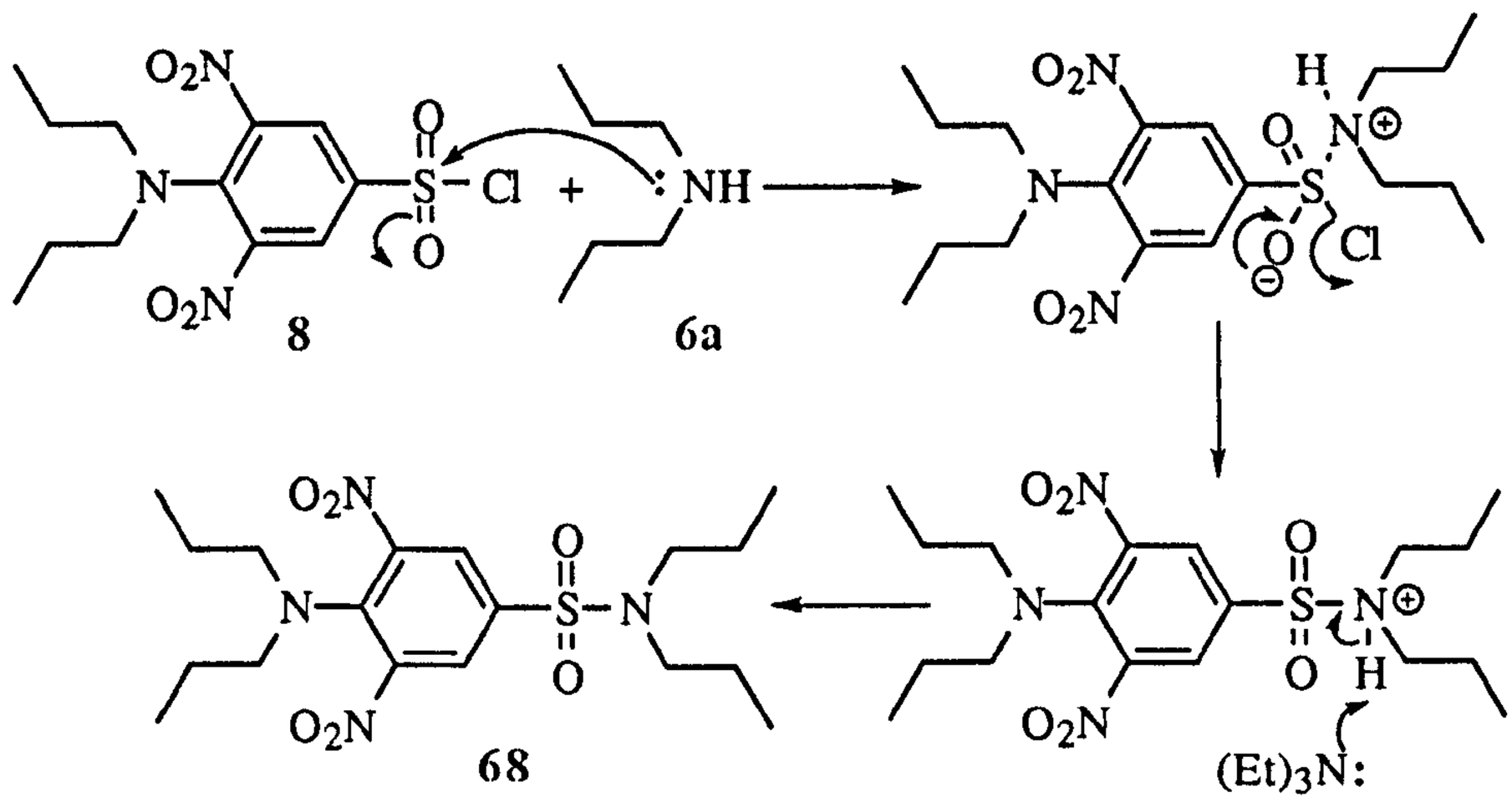
Scheme 26

Nucleophilic substitution at the sulphur atom of thionyl chloride (**7a**) by the sulphonate anion **7** gives 2,6-dinitro-4-(*N*,*N*-dipropylamino)benzenesulphonyl chloride (**8**), (**Scheme 27**).



Scheme 27

The final step in the mechanism involves nucleophilic attack on the sulphur atom of the chlorosulphonyl group in **8** by dipropylamine **6a**, with the displacement of the chloride ion, to give the desired compound **68**, as outlined in **Scheme 28**.

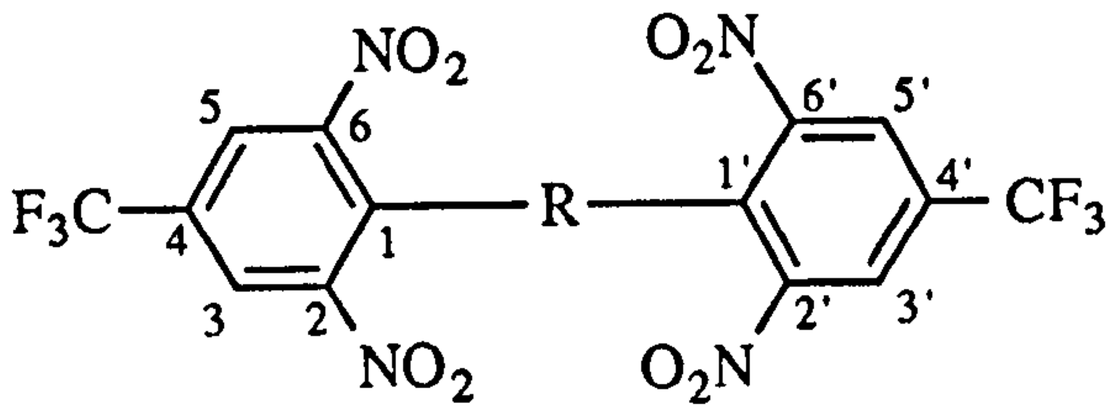


Scheme 28

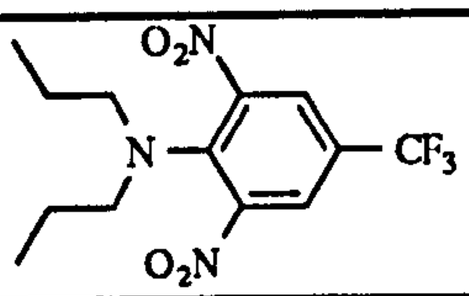
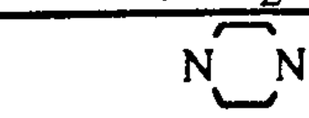
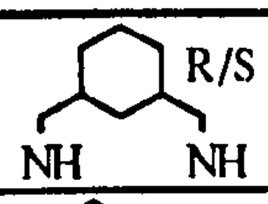
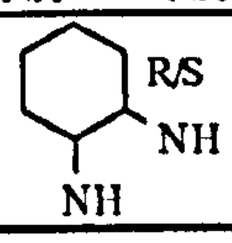
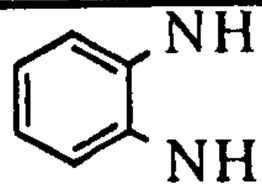
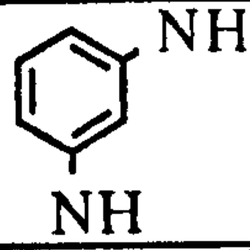
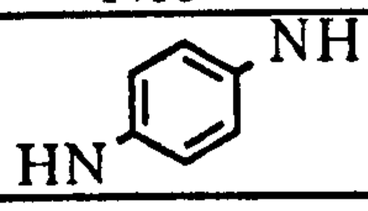
3.5 NMR spectroscopic analysis of the trifluralin dimers and monomers

The proton, carbon-13 and DEPT spectra were consistent with the proposed structures (**65a-n**, Table **4**; **67a-j**, Table **5**). All the compounds showed exchangable protons when subjected to deuterium exchange assigned to the NH groups.

The main findings from the proton and fluorine-19 NMR spectral analyses of the compounds **65a-n** are listed in Table **6**. The proton chemical shift in these compounds was found to be fairly deshielded probably due to the influence of the highly electron-withdrawing groups (NO_2 and CF_3) adjacent to the hydrogen. The proton peaks were observed as singlets since the hydrogens are equivalent. In the fluorine-19 NMR, 2,6-dinitro-(*N*,*N*-dipropylamino)-4-trifluoromethyl)benzene (**3**) showed a single peak at -62.69 ppm with fluorotrichloromethane ($CFCl_3$) as the internal standard [12].



(65a-n)

No.	R	H-3/H-3'/ H-5/H-5' (ppm)	CF_3 (92-93) (ppm)	N-H (ppm)
3		8.07 (H-3/H-5)	-62.69 (lit. -63.67, TFMA) (12)	-
65a	NH-$(CH_2)_2$-NH	8.53	-59.90	8.56
b	NH-$(CH_2)_3$-NH	*	*	*
c	NH-$(CH_2)_4$-NH	8.53	-59.79	8.65
d	NH-$(CH_2)_5$-NH	8.41	-59.84	8.64
e	NH-$(CH_2)_6$-NH	8.40	-59.77	8.66
f	NH-$(CH_2)_{10}$-NH	8.40	-59.79	8.66
g	NH-$(CH_2)_{12}$-NH	8.40	-59.76	8.66
h		8.62	-59.80	-
i		8.42	-59.80	8.69
j		**	**	**
k	NH-$(CH_2)_2$-NH-$(CH_2)_2$-NH	8.53	-59.78	8.65
l		8.61	-60.12	9.68
m		8.16	-60.15	9.67
n		8.57	-60.04	9.79

* insoluble ** mixture of products

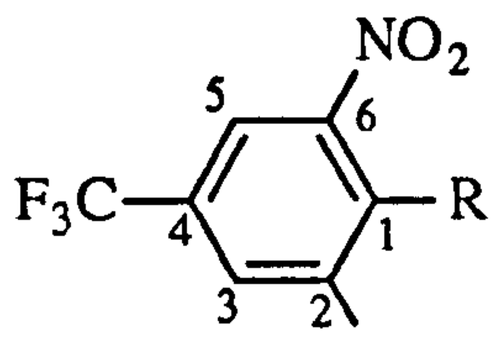
TFMA = 4-(trifluoromethoxy)acetanilide

Table 6

The aliphatic and aromatic bridged compounds show two distinct sets of trifluoromethyl (CF_3) values since we expect the presence of mesomeric effects in the latter. This causes the CF_3 groups to be more deshielded than the aliphatic system where no such through bond effects exist. In the aromatic system (compounds **65l-n**) there is also a possibility of additional mesomeric effects presumably through coupling of torsional barriers between the carbon and nitrogen bonds of the bridging aromatic diamines (change in double bond character). This may contribute to the downfield shift of the CF_3 groups. Surprisingly, however, it is observed that trifluralin (**3**) itself is more downfield than the aromatic diamines in particular. As yet we cannot offer a feasible explanation for this observation.

In general, there is a downfield shift of H3/H5 protons in compounds **65a-n** compared to trifluralin (**3**) which suggests that these dimeric systems indicate the presence of π-π stacking which is not apparent in the trifluralin monomer (**3**). Clearly, further experiments (e.g. Ultra Violet and molecular modelling) are needed to ascertain these speculations.

Similarly, results from the proton and fluorine-19 NMR spectral analyses of the compounds **67a-j** (monomers) are listed in Table **7**.

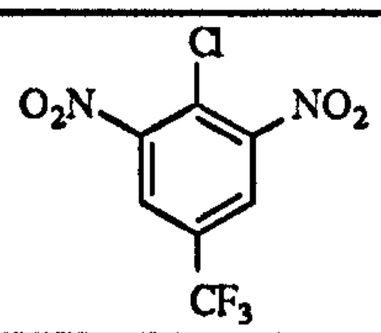
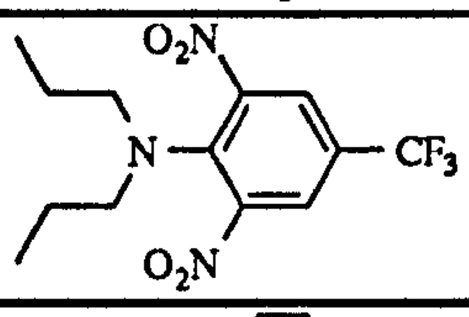
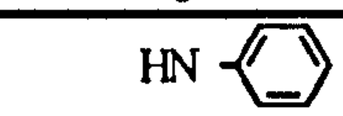
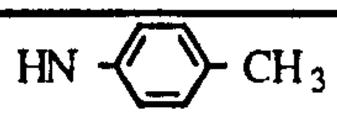
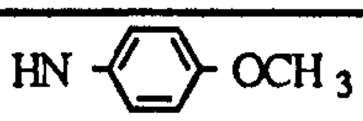
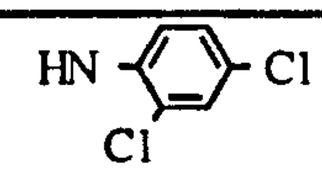
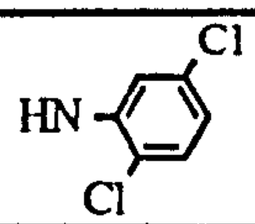
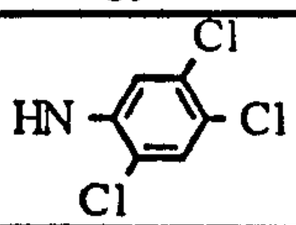
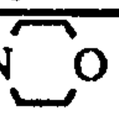
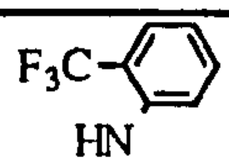
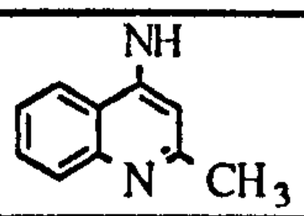


NO_2

(67a-j)

It is seen from the results that the H3/H5 shifts are further downfield when chlorine is present as a substituent. This could account for the electron-withdrawing effects of chlorine.

The proposed structure of 4-(*N*,*N*-dipropylsulphamoyl)-2,6-dinitro-1-(*N*,*N*-dipropylamino)benzene **68** was consistent with its proton NMR specrum and the chemical shift values, including the multiplicity, are shown in Figure **8**.

No.	R	H-3/H-5 (ppm)	CF_3 (ppm)	N-H (ppm)
2		8.92	-61.38	–
3		8.07	-62.69 (12)	–
67a		8.58	-60.06	9.79
b		8.56	-60.01	9.77
c		8.53	-60.09	9.81
d		8.59	-60.33	9.81
e		8.64	-60.16	9.53
f		**	**	**
g		8.67	-60.15	7.35
h		8.08	-60.37	–
i		8.27	-61.16 (C-1) -61.08 (C-4)	4.16
j		8.56	-59.86	12.01

** mixture of products

Table 7

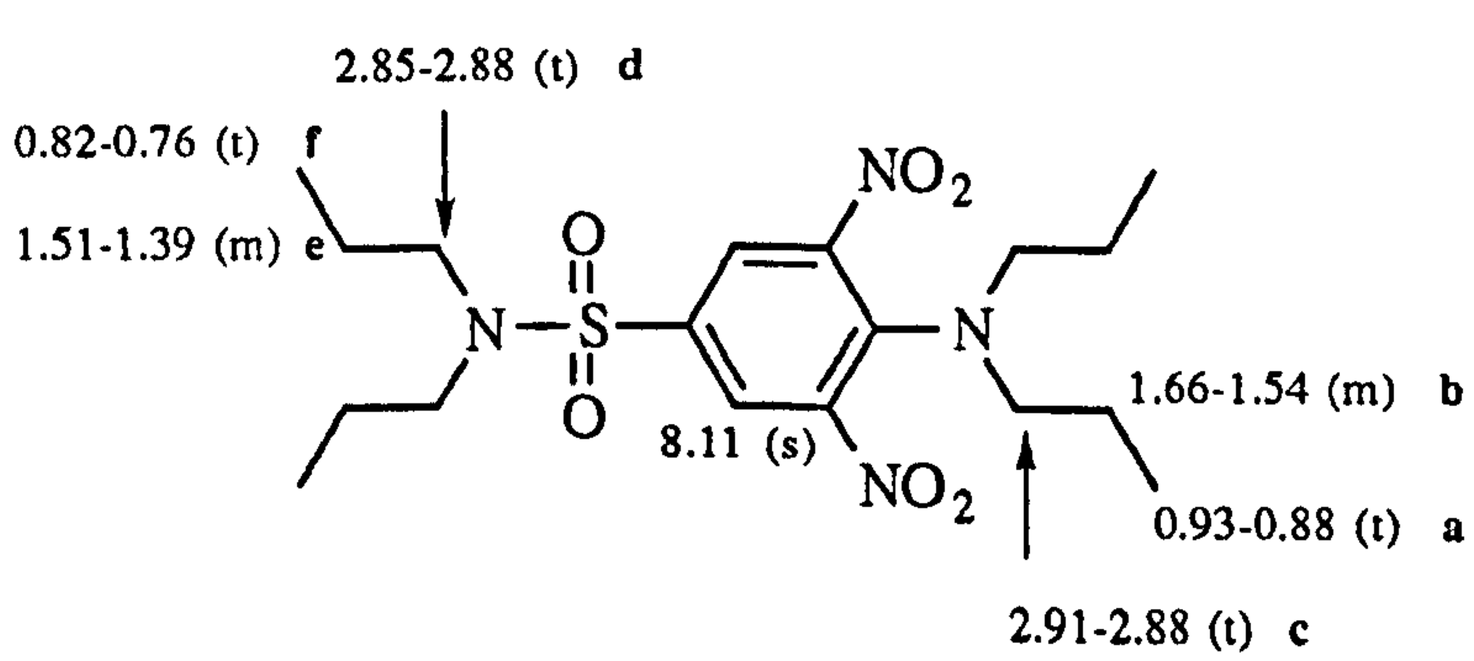


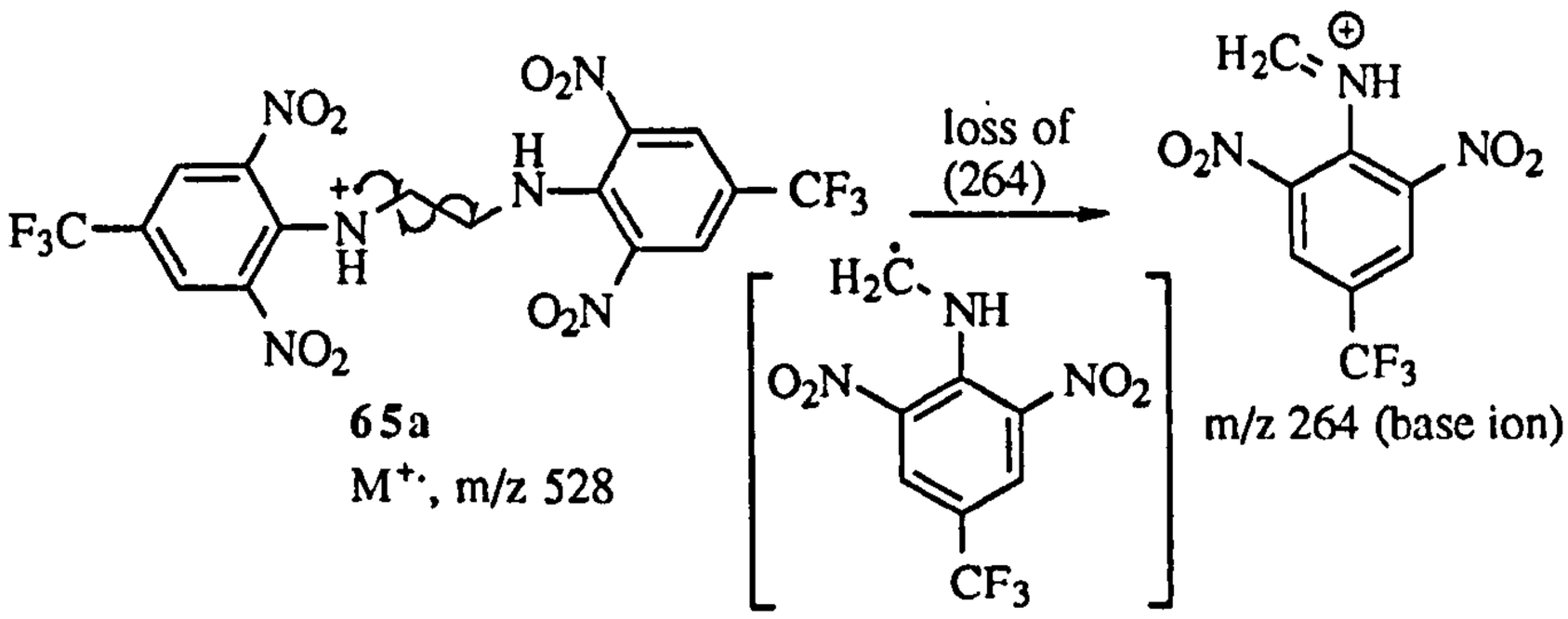
Figure 8

The interesting features of its spectrum are the signals at positions (**c**) and (**d**). These two signals have similar chemical shifts so that overlapping of their peaks makes assignment difficult. Instead of the expected two triplets for (**c**) and (**d**), they converge into a "quartet" even though they are in different chemical environments. The signal for (**c**) is slightly more deshielded than (**d**) probably due to the greater -M effect of the 2,4-dinitrophenyl group relative to the phenylsulphonate group (see spectrum no. 50, appendix).

3.6 Mass spectrometric analysis of the trifluralin dimers and monomers

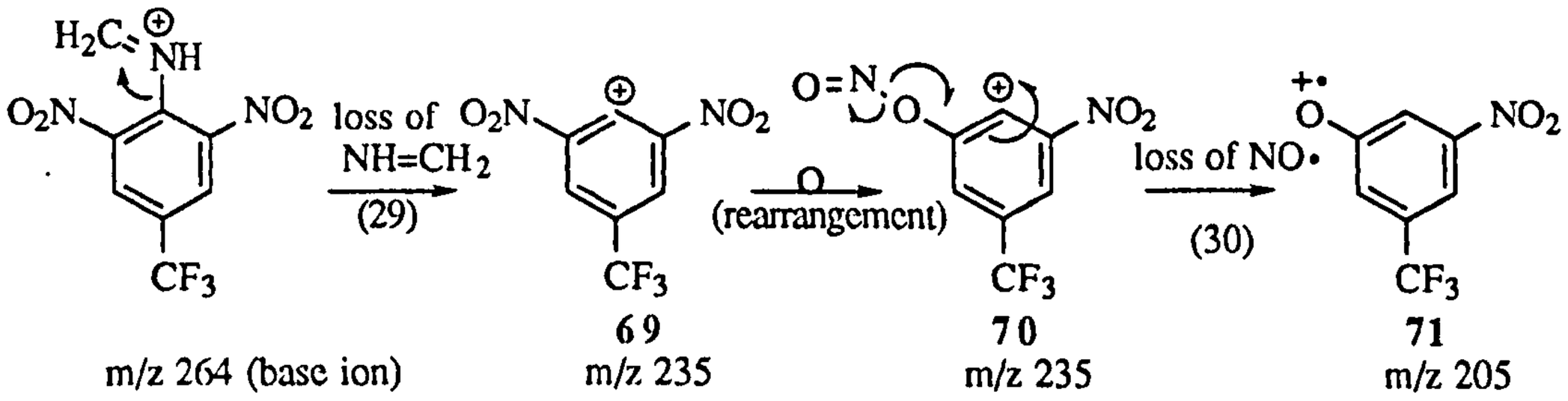
The most general features seen in the electron impact (EI) mass spectra of these diamine compounds are losses of 30 (NO), 46 (NO_2) and 19 (F) mass units in various sequences as expected.

These typical fragmentation were observed consistently in the spectra of all the dimers (**65a-n**) via α, β homolytic fission, as shown for **65a** in **Scheme 29**.



Scheme 29

Another feature of these aromatic nitro compounds is the standard rearrangement of the nitro group [94] in **69** into a nitrite group (**70**) which readily loses nitric oxide (NO) to give the aryloxycation **71**, as shown in **Scheme 30**.

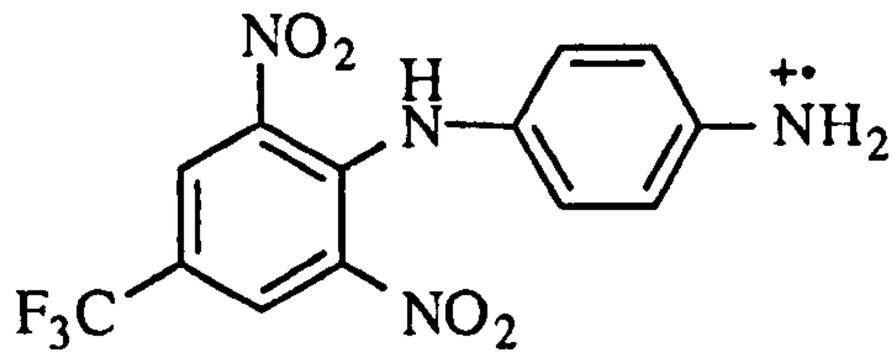


Scheme 30

The *ortho*-phenylenediamine derivative (**65l**) alone showed intense ions resulting from two successive losses of 47 mass units, thought to be due to loss of HON=O, followed by minor conventional NO, NO_2 and F losses (see **Schemes 31** and **33**), even though the possibility of similar HON=O elimination exits in all three isomers (**65l-n**).

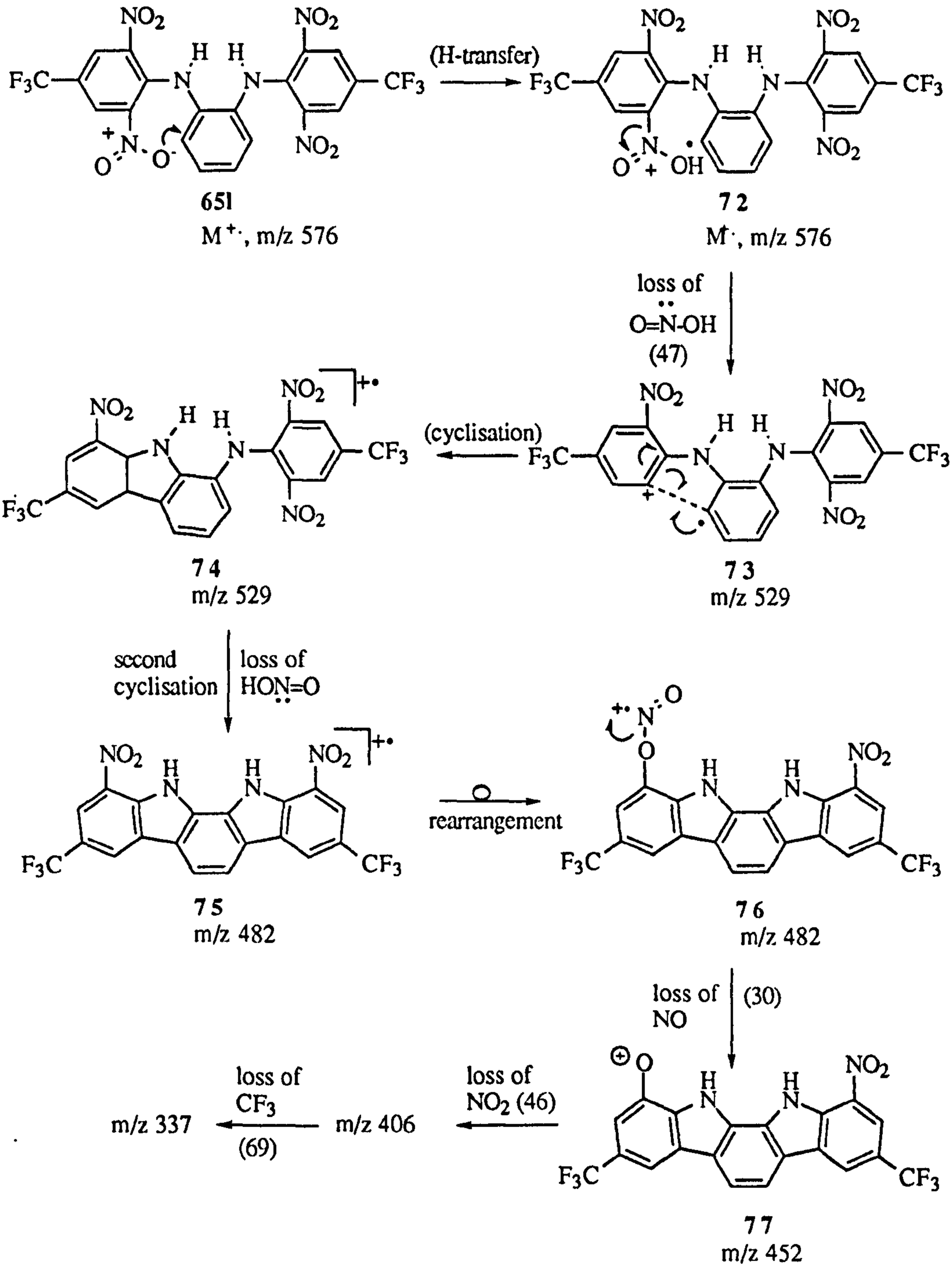
An unusual cyclisation was observed in the mass spectrum of dimer **65l** derived from *ortho*-phenylenediamine as the bridging group. This was not observed in the related compounds **65m** and **65n** (see Table **9**). The proposed fragmentation of **65l** is outlined in **Scheme 31**. Hydrogen transfer and subsequent loss of HNO_2 from **65l** gave **73** which probably cyclises to **74** (m/z 529) in the gas phase. This process is repeated and a second loss of HNO_2 is observed to give **75** (m/z 482), followed by rearrangement of the nitro group to give the nitrite group (**76**) [94]. Subsequent loss of NO from species 76 gives aryloxycation **77** (**Scheme 31**).

The EI mass spectra of the *ortho*-, *meta*- and *para*-phenylenediamine adducts of 2, 6-dinitro-4-trifluoromethylbenzenes (**65l-n**) are shown in Figures **9**, **10** and **11**, respectively. It is immediately apparent that the meta and para derivatives give intense stable molecular ions with restricted losses of OH, F, NO and NO_2 fragments, as expected for aromatic nitro compounds and trifluoromethyl groups [95]. There is some evidence for α-cleavage at the imino groups with either hydrogen transfer or self-protonation to yield the $M^{+\cdot}$ ions of the mono-trifluorodinitrobenzene adduct of m/z 342 (**78**) in all three spectra. This ion could also be due to the presence of the mono-adduct, even though these compounds have been recrystallised twice.



78, m/z 342

The spectrum of the *ortho*-bis-trifluorodiphenylenediamine adduct **65l**, by contrast is very distinctive (Figure **9**). About 25% relative intensity of $M^{+\cdot}$ ion is seen, but the base peak is at m/z 529 $[M - HNO_2]^{+\cdot}$, while the ion at m/z 482 (**75**), resulting from second, consecutive loss of the element of HNO_2 from m/z 529 is of 80% relative abundance.



651
$M^{+\cdot}$, m/z 576

72
$M^{+\cdot}$, m/z 576

73
m/z 529

74
m/z 529

75
m/z 482

76
m/z 482

77
m/z 452

m/z 406

m/z 337

Scheme 31

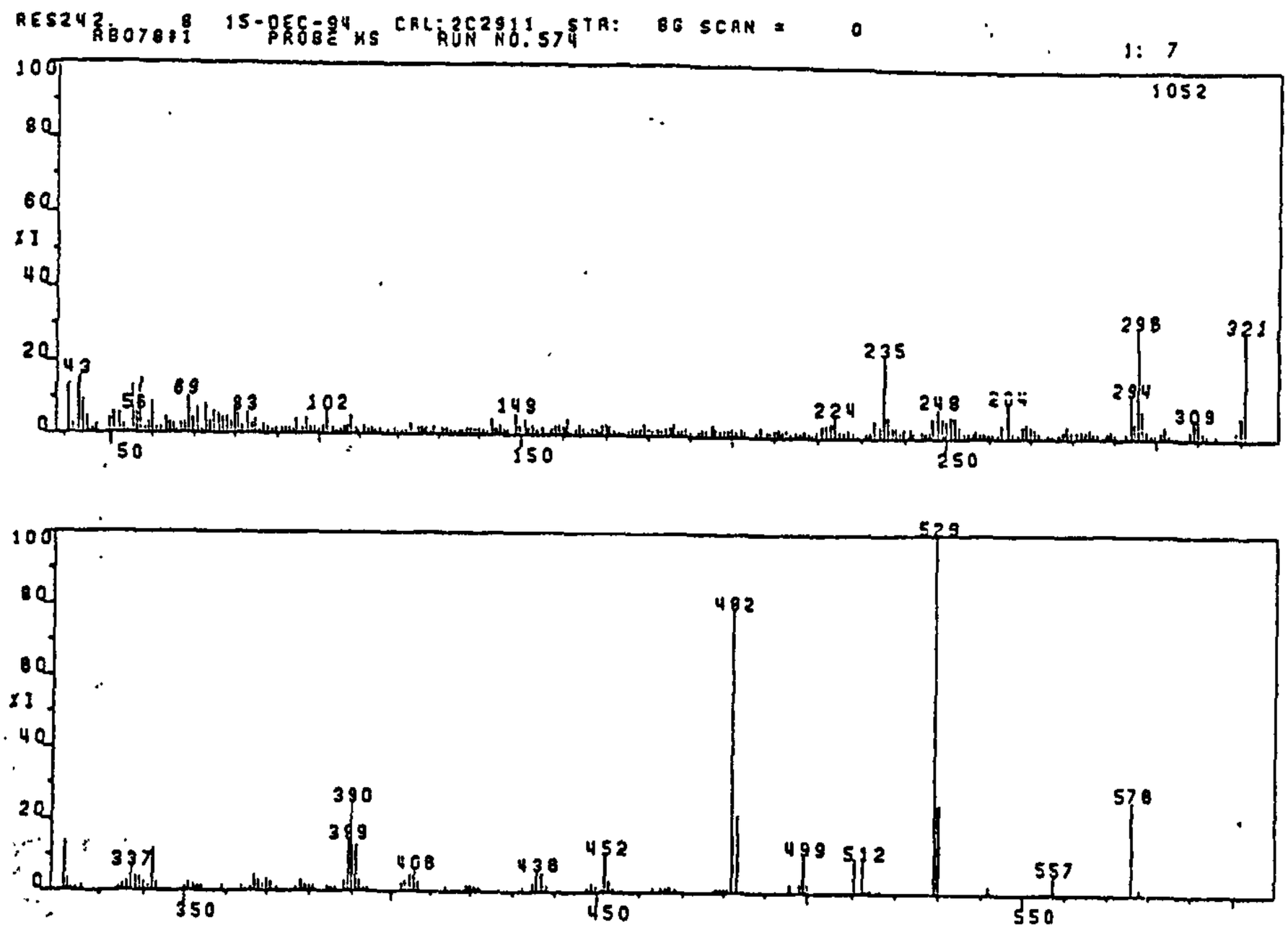


FIGURE 9

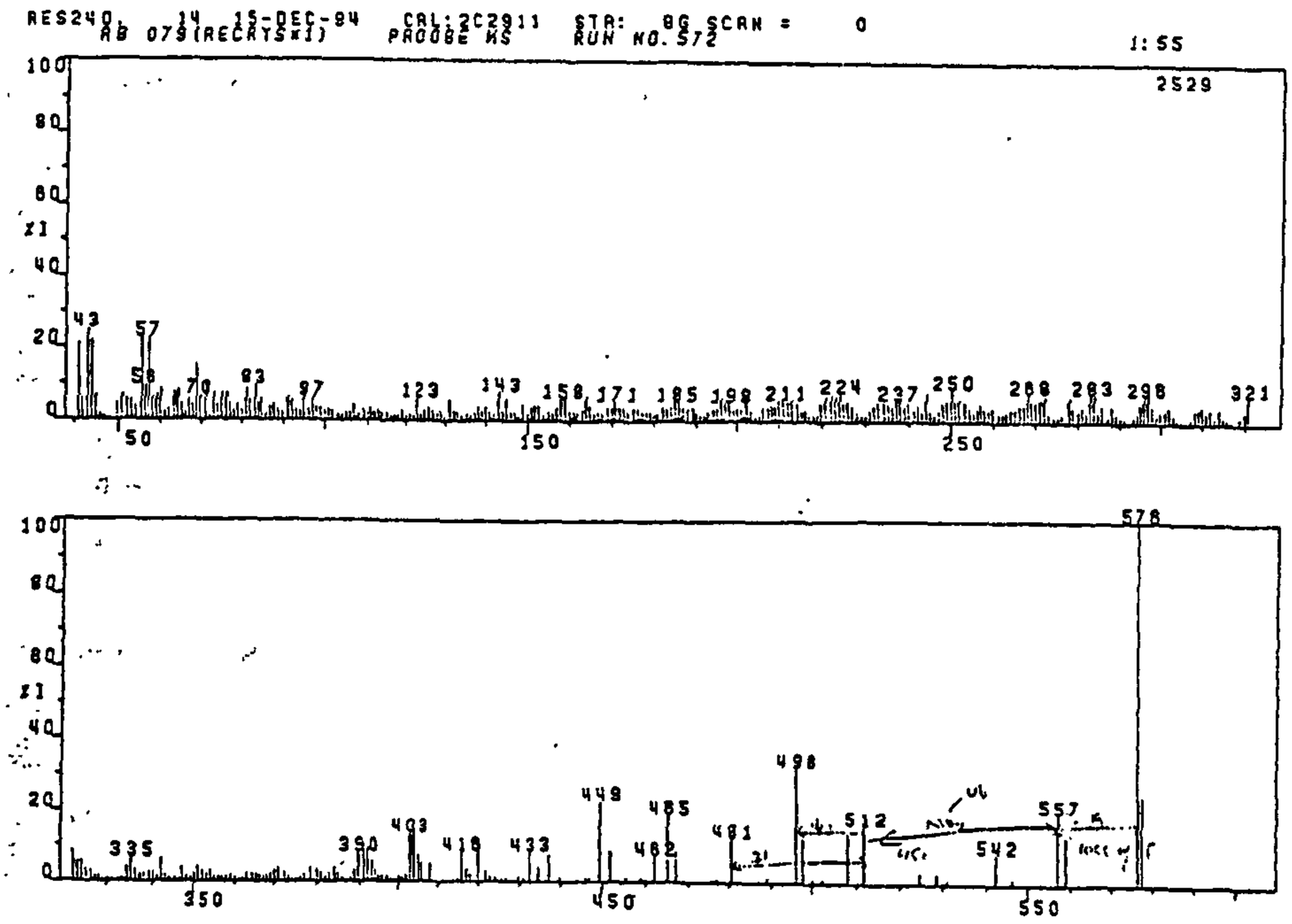


FIGURE 10

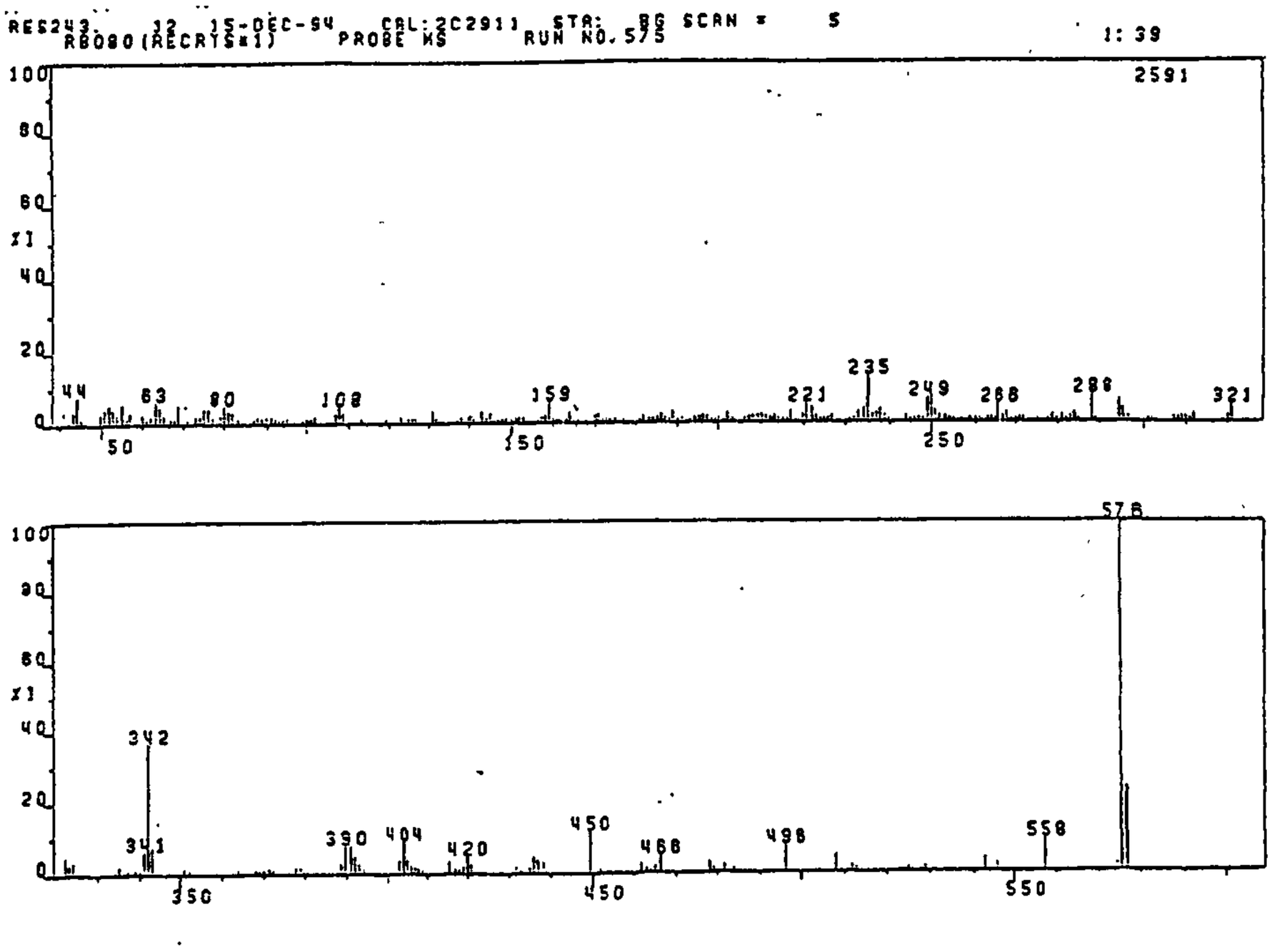


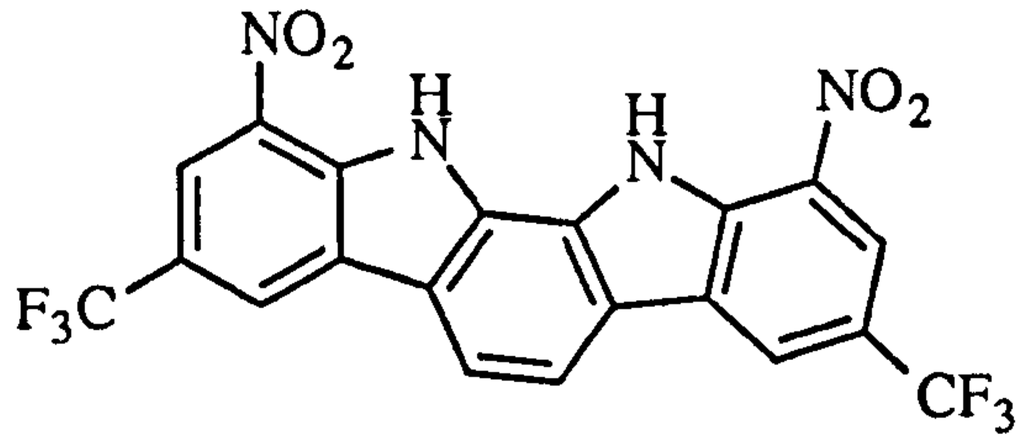
FIGURE 11

Since there are no literature reports of HNO_2 losses from aromatic nitro compounds (loss of HO· is common [95]), we have confirmed these processes by high resolution mass measurements on the fragment ions at m/z 576, 529 and 482 (see table 8).

Formula	Measured mass	Theoretical mass
$C_{20}H_{10}N_6O_8F_6$	576.0445	576.04643
$C_{20}H_9N_5O_6F_6$	529.0471	529.04570
$C_{20}H_8N_4O_4F_6$	482.0455	482.04497

Table 8

Since the *ortho* compound shows the HNO_2 losses and the *meta* and *para* isomers do not, it is tempting to ascribe them to an *ortho* effect and leave it at that. However, it is perfectly possible to devise novel pentacyclic structures for the (M - 2 HNO_2) ions by elimination of both *ortho* hydrogens of the diamino rings and a nitro group from each trifluralin ring in all three isomers. An example of such a structure **75** has been proposed [96] and outlined in **Scheme 31**.

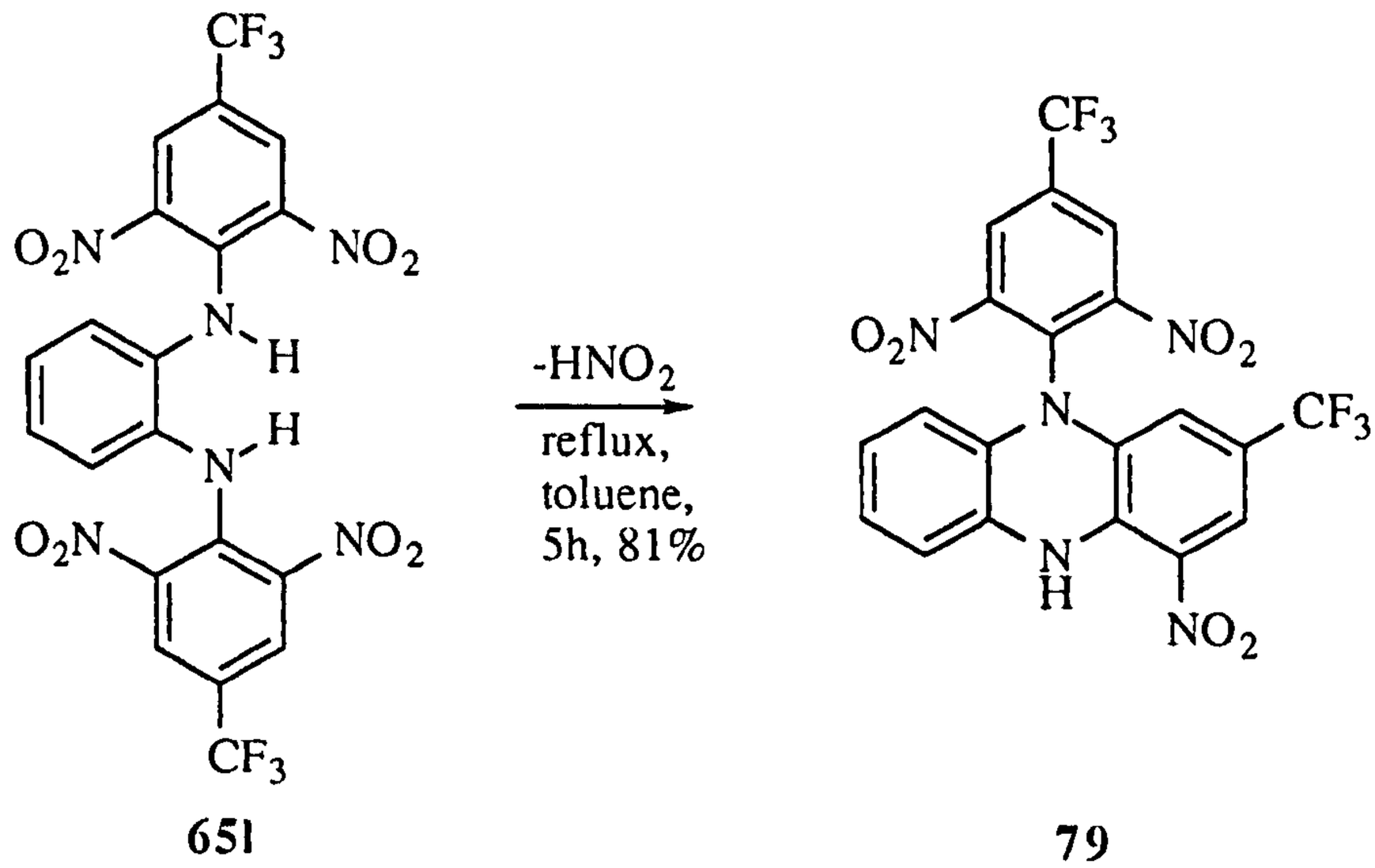


75, m/z 482

In the case of the *meta* isomer this leads to two structures depending on whether the 2, 4- or 2, 6-hydrogens are involved. There is no obvious reason why the *ortho*-phenylenediamine derived ion should be so intrinsically more stable than those of the *meta* and *para* isomers as to cause its domination of the mass spectrum to the extent observed.

Simple ball and stick models and molecular modelling of the un-ionised isomers showed that three possible factors might be involved. In the *ortho* isomer the preferred conformation has a hairpin shape brought about by π-π stacking interactions, bringing the nitrated rings together in a favourable orientation for single-electron transfer (SET) processes to occur [96]. In the *meta* isomer steric crowding arising from the nitro groups of the two trifluralin rings could inhibit the transfer of the 2-hydrogen, though not the 4- and 6-hydrogens, while the *para* isomer's shape would not allow close approach of the nitro oxygens to the 2-hydrogen positions.

However, on further investigations, it was found that the *ortho*-phenylenediamine adduct **651**, when subjected to thermal reactions lost one molecule of HNO_2 and did not yield the predicted structure **74**. Instead, on the basis of its proton, carbon-13, 2-D COSY and HECTOR NMR spectra, a revised structure **79**, as shown in **Scheme 32** is proposed.

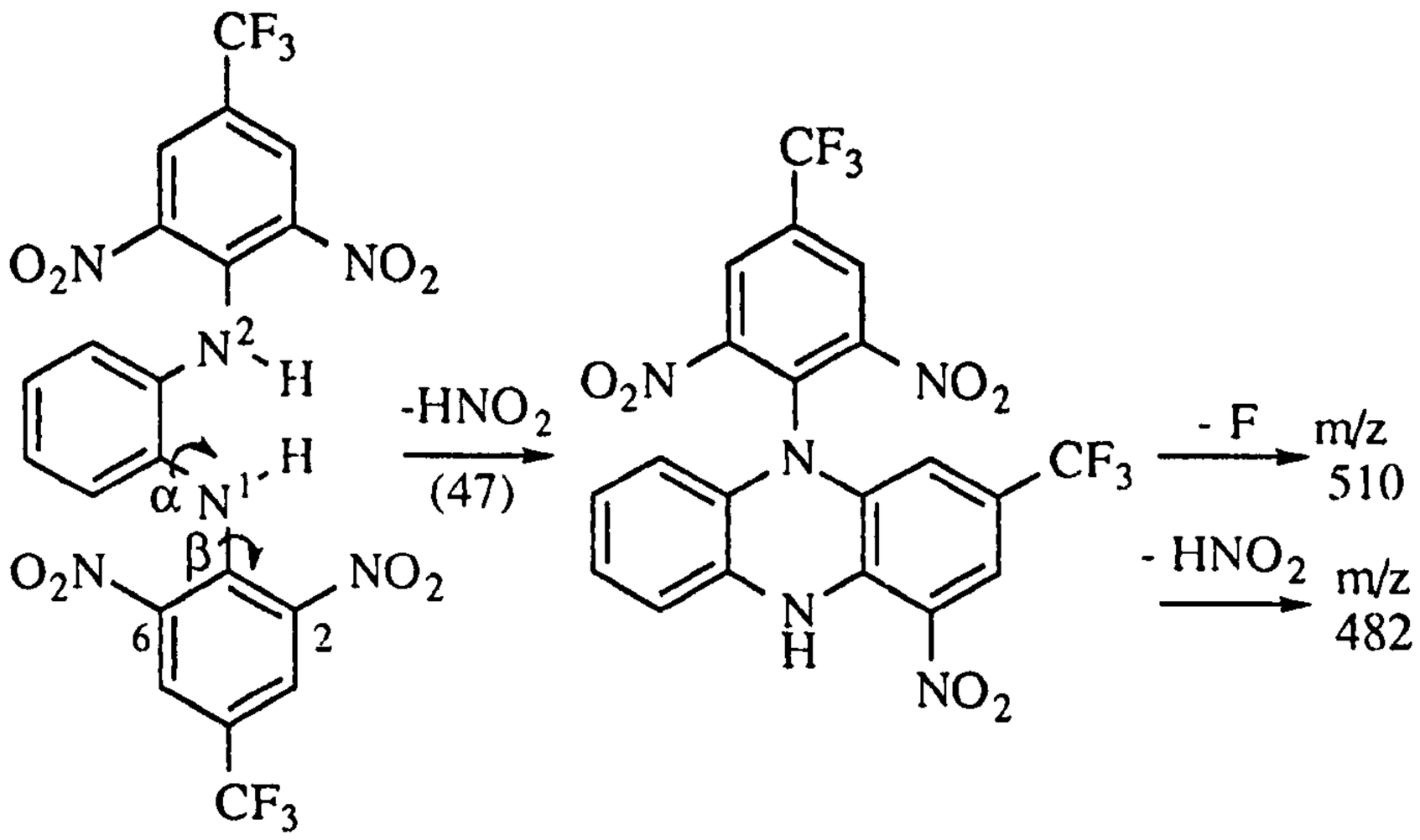


651 **79**

Scheme 32

Conversion of N^1,N^2-di-(2,6-dinitro-4-trifluoromethylphenyl)-1,2-phenylene diamine **651** into the phenazine compound **79** can be adduced from its proton and carbon-13 spectra. The proton spectrum of **79** shows four distinct aromatic signals consistent with the aromatic phenazine ring. The carbon-13 spectrum shows eighteen ^{13}C resonances of which two have distinct ^{19}F peaks split into a pair of quartets, suggesting an asymmetrical structure that is consistent with the acquired structure. Spectrum number 58 (see Appendix) shows two types of ^{19}F nuclei within the molecule that resonate strongly at -61.71 ppm and -61.53 ppm. The HETCOR spectrum (spectrum no 59, Appendix) of **79** indicates that of the seven methyne carbons identified by the DEPT-90 experiment (spectrum number 57, Appendix), three protons show long range coupling to proximal fluorine nuclei, producing a broad singlet, doublet and multiplet resonating at 110.1, 116.3 and 129.2 ppm respectively. Further evidence from the ^1H-^1H COSY 2-D spectrum (spectrum number 60, Appendix) indicates the presence of two distinct spin systems, one of which shows four protons strongly $^3J_{H\text{-}H}$ coupled, immediately discounting the earlier predicted structure **74** in the gas phase as a candidate structure. The remaining spin system has a weaker cross peaks consistent with a $^5J_{H\text{-}H}$ W coupling. Importantly, the N-H singlet integrating to one proton suggests the presence of only one N-H group in the molecule thereby unequivocally establishing **79** as the compound formed during the reaction.

Thus, a new fragmentation pathway is proposed for the elimination of HNO_2 from the *ortho*-phenylenediamine adduct, as shown in **Scheme 33**. Rotation about α or β bonds brings either one of the nitro groups at position 2 or 6 into close proximity with the hydrogen on N^2. Thus, the elimination of HNO_2 produces the phenazine skeleton **79** (N^{10}-(2,6-dinitro-4-trifluoromethylphenyl)-2-trifluoromethyl-4-nitro-5,10-dihydrophenazine) (see spectra 55-62, appendix).



651, m/z 576 **79**, m/z 529

Scheme 33

Some of the common fragments of the dimers lost in the vapour phase are summarised in Table 9, and the structures of some common fragments observed are shown in Figure 12.

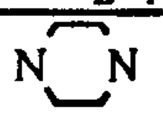
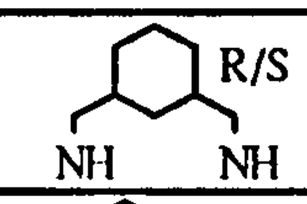
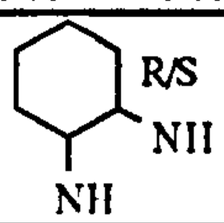
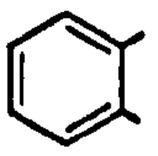
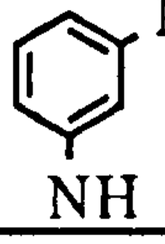
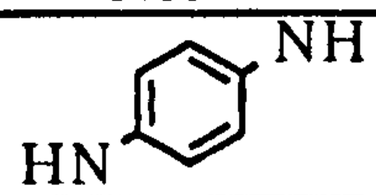
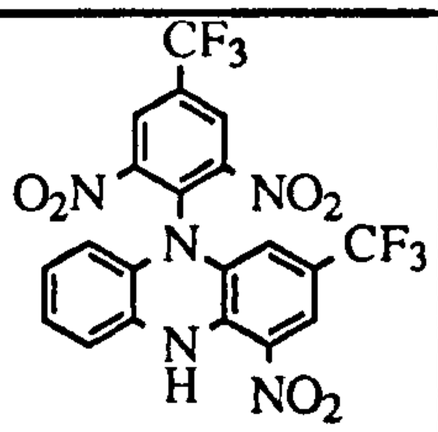
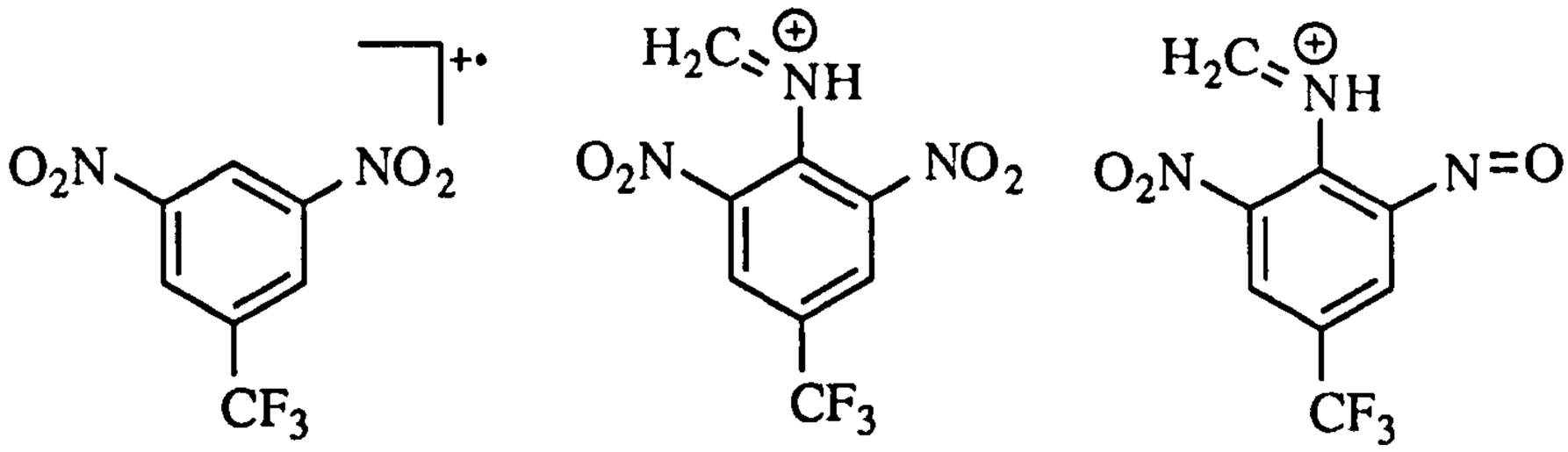
65	R	$M^{+\cdot}$ ($M^{+\cdot}$ - F)	base peak	M^+ due to loss of HNO_2	M^+ due to loss of NO_2	M^+ due to loss of NO
a	NH-$(CH_2)_2$-NH	509	264 ($M^{+\cdot}$ - $C_8H_5N_3O_4F_2$)	-	-	-
b	NH-$(CH_2)_3$-NH	523	278 ($M^{+\cdot}$ - $ArCH_2NH$)	-	-	-
c	NH-$(CH_2)_4$-NH	537	71	-	-	-
d	NH-$(CH_2)_5$-NH	551	235	-	-	-
e	NH-$(CH_2)_6$-NH	565	264	-	-	-
f	NH-$(CH_2)_{10}$-NH	621	248	-	-	-
g	NH-$(CH_2)_{12}$-NH	649	248	-	-	-
h		554 (535)	554	507	-	524
i		591	264	-	-	-
j		563	235	-	-	-
k	NH-$(CH_2)_2$-NH -$(CH_2)_2$-NH	552	307 ($M^{+\cdot}$ - $ArCH_2NH$)	-	-	-
l		576 (557)	529	482 (529 - HNO_2)	406 (452 - NO_2)	452 (482 - NO)
m		576 (557)	576	-	463 (557 - $2HNO_2$)	-
n		576 (557)	576	-	-	-
79.		529 (510)	529	482	390 (482 - $2HNO_2$)	-

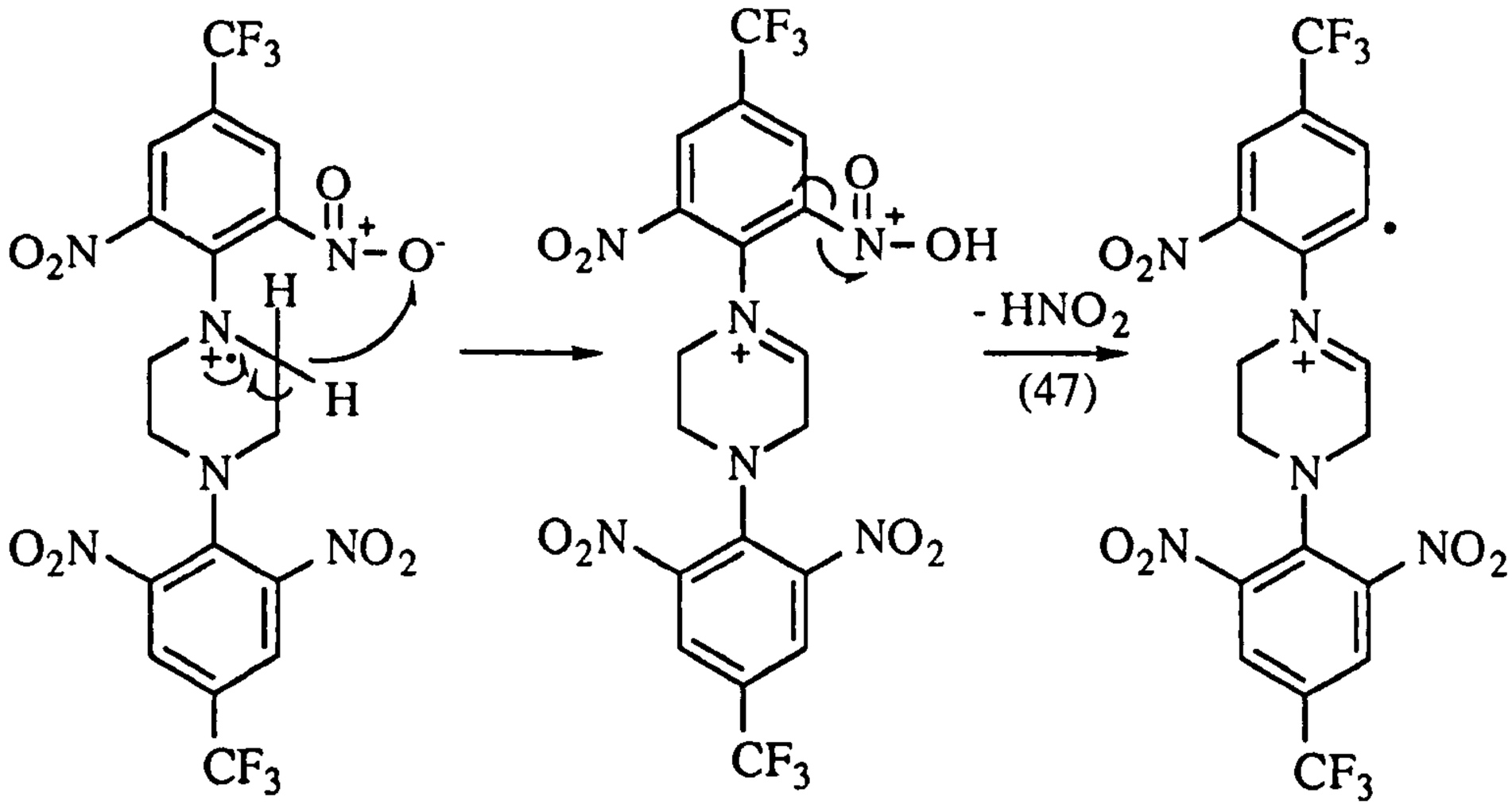
Table 9



m/z 235 m/z 264 m/z 248

Figure 12

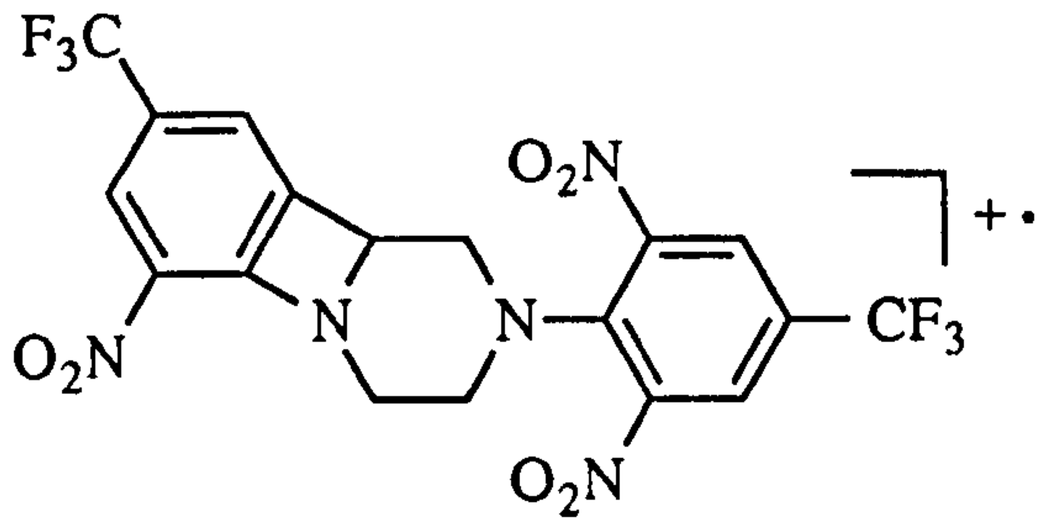
From the table there is no apparent relationship between the fragments lost and the electronic, or steric effects of the substituents, the exception being compound **65l**, where cyclisation via loss of HNO_2 is proposed (see **Scheme 31**). However, compound **65h** showed loss of HNO_2 (40% intensity) from the molecular ion to give ion at m/z 507 (as proposed in **Scheme 34**). Interestingly, because there is no N-H group to eliminate (for cyclisation) in this structure, the hydrogen from one of the methylene groups in **65h** is transferred via a six-membered transition state (**81**) to give species **82**.



65h, m/z 554 **81**, m/z 554 **82**, m/z 507

Scheme 34

There is a second possibility, that of forming a 4-membered ring compound in the gas phase to give the fragment ion **83** via loss of hydrogen directly from one of the methylene groups and a nitro group from the aromatic ring of compound **65h**, but there is no particular reason for this to happen. Hence, the elimination of HNO_2 proposed in **Scheme 34** might therefore be a favoured process in this (special) structure.



83

Similarly, for the monomer adducts of trifluralin (**67a-j**), some of the major fragmentations are summarised in Table **10**.

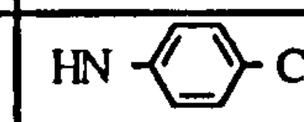
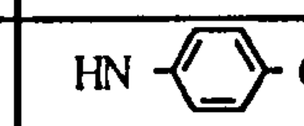
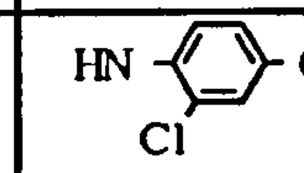
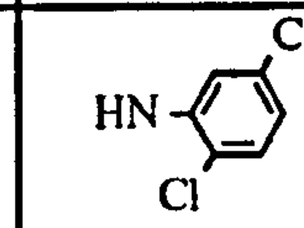
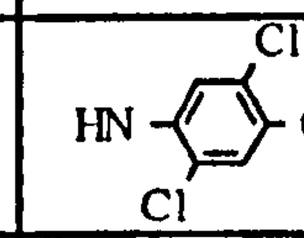
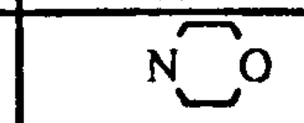
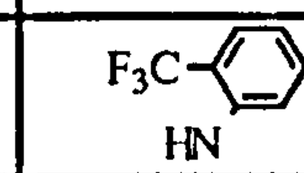
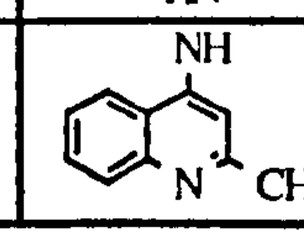
67	R	$M^{+\cdot}$	base peak	$M^{+\cdot}$ - F	loss of NO_2	M^+ due to loss of HNO_2	other fragmentations
a		327	327	308	216 (308 - 2 NO_2)	-	-
b		341	341	322	248 (294 - NO_2)	294	-
c		357	357	338	264 (310 - NO_2)	310	342 ($M^{+\cdot}$ - CH_3)
d		361	361	342	268 (314 - NO_2)	314	-
e		395/397 /399	395/397/ 399	376/378 /380	303 ($M^{+\cdot}$ - 2 NO_2)	-	360/362 ($M^{+\cdot}$ - Cl)
f		395/397 /399	270/272 (starting material)	-	-	-	-
g		429/431 /433	195/197/ 199	-	-	-	-
h		321	73	302	-	-	304 ($M^{+\cdot}$ - OH) 291($M^{+\cdot}$ - NO)
i		395	395	376	-	348	-
j		392	328 (358 -NO)	371	346	-	362 ($M^{+\cdot}$ - NO)

Table 10

These compounds fragmented in a similar way to the dimers **65a-n** (see **Schemes 29** and **30**). In these compounds, the loss of HNO_2 was not as predominant as in the case of the dimers and was observed in low relative abundancies (5-10%).

3.7 FT-IR analysis of the trifluralin dimers and monomers

The results are summarised in Tables **11** and **12** and include the absorption ranges (in cm^{-1}) of various functional groups commonly associated with the trifluralin dimers (**65a-n**) and monomers (**67a-j**), respectively.

65	N-H (str.)	Ar. C-H (str.)	Al. C-H (str.)	NO_2 (asymm str.)	NO_2 (H-bonded)	C-F (str.)	N-H (2° bend)
a	3347	3069	2877	1536	1291	1125	1640
b	3289	3104	~2900	1538	1291	1137	1639
c	3353	3063	2965	1542	1294	1130	1639
d	3342	~3100	2924	1544	1274	1131	1640
e	3330	3103	2919	1545	1291	1126	1643
f	3318	3310	2927	1549	1292	1148	1639
g	3352	3063	2925	1542	1278	1136	1638
h	-	3066	~2900	1547	~1290	1155	1631
i	3346	3099	2935	1533	1297	1123	1640
j	3321	3097	2934	1544	~1290	1134	1642
k	3323	3211	~2900	1544	~1290	1121	1639
l	3304	3105	-	1542	~1300	1129	1638
m	3355	3091	-	1537	1297	1136	1641
n	3289	~3100	-	~1550	1272	1125	1633

Table 11

The results indicate that there is almost no variation in frequencies amongst these dimers worthy of note. This suggests that increasing the alkyl chain, or introducing a phenyl group in these dimers has very little effect in terms of functional group vibrations.

Aromatic nitro groups absorb near the same frequencies as observed for conjugated aliphatic nitro compounds (around 1600 cm^{-1}) [97]. Interaction between the NO_2 out-of-plane bending and ring C-H out-of-plane bending frequencies destroys the reliability of the substitution pattern observed for nitroaromatics in the long wavelength

region of the spectrum. Due to strong resonance in these nitro compounds, the symmetrical nitro vibration is observed at lower frequencies (~ 1550 cm^{-1}) and higher intensities than non-conjugated nitro compounds (97). A broad peak in the region of 1290 cm^{-1} was observed in the spectra of all the dimers, and is the symmetrical Nitro N-O stretch associated with intra-molecular hydrogen bonding as shown in Figure **13**.

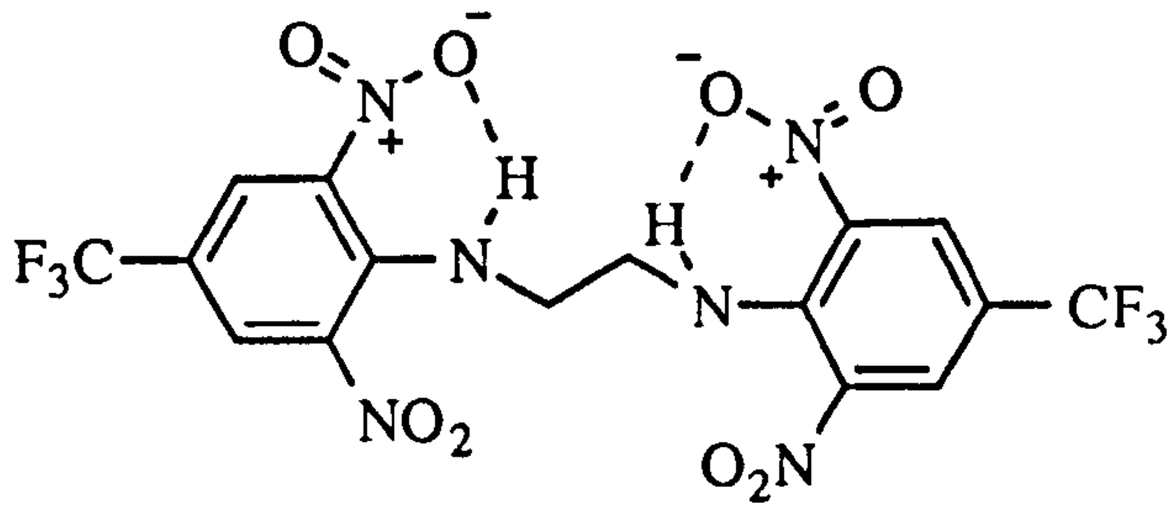


Figure 13

Similarly, data in Table **12** is consistent with the proposed structures for the trifluralin monomers (**67a-j**).

No	N-H (str.)	Ar. C-H (str.)	Al. C-H (str.)	NO_2 (asymm str.)	N-H (bend)	C-F (str.)	N-H (2° bend)
2	-	3063	-	1549	~ 1490	1119	-
3	-	3069	2975	1537	-	1132	1629
67a	3331	3069	-	1531	~ 1500	1124	1637
b	3335	3101	2923	1544	1490	1132	1643
c	3298	3096	2924	1511	1461	1140	1638
d	3295	3090	-	1532	1490	1131	1637
e	3321	3092	-	1538	~ 1490	1117	1639
f	3459	3083	-	1542	1490	1124	1637
g	3465	3083	-	1545	1490	1139	1635
h	-	3080	2885	1542	-	1139	1632
i	3432	3083	-	1551	~ 1450	1119	1625
j	3401	3100	-	1550	~ 1490	1131	~ 1620

Table 12

Similarly, the FT-IR results for monomers indicate very little variation in frequencies of the functional groups to mention any significant trends.

In summary, all the spectral results were consistent with the proposed structures for the trifluralin dimers and monomers. The fluorine-19 NMR spectra of these

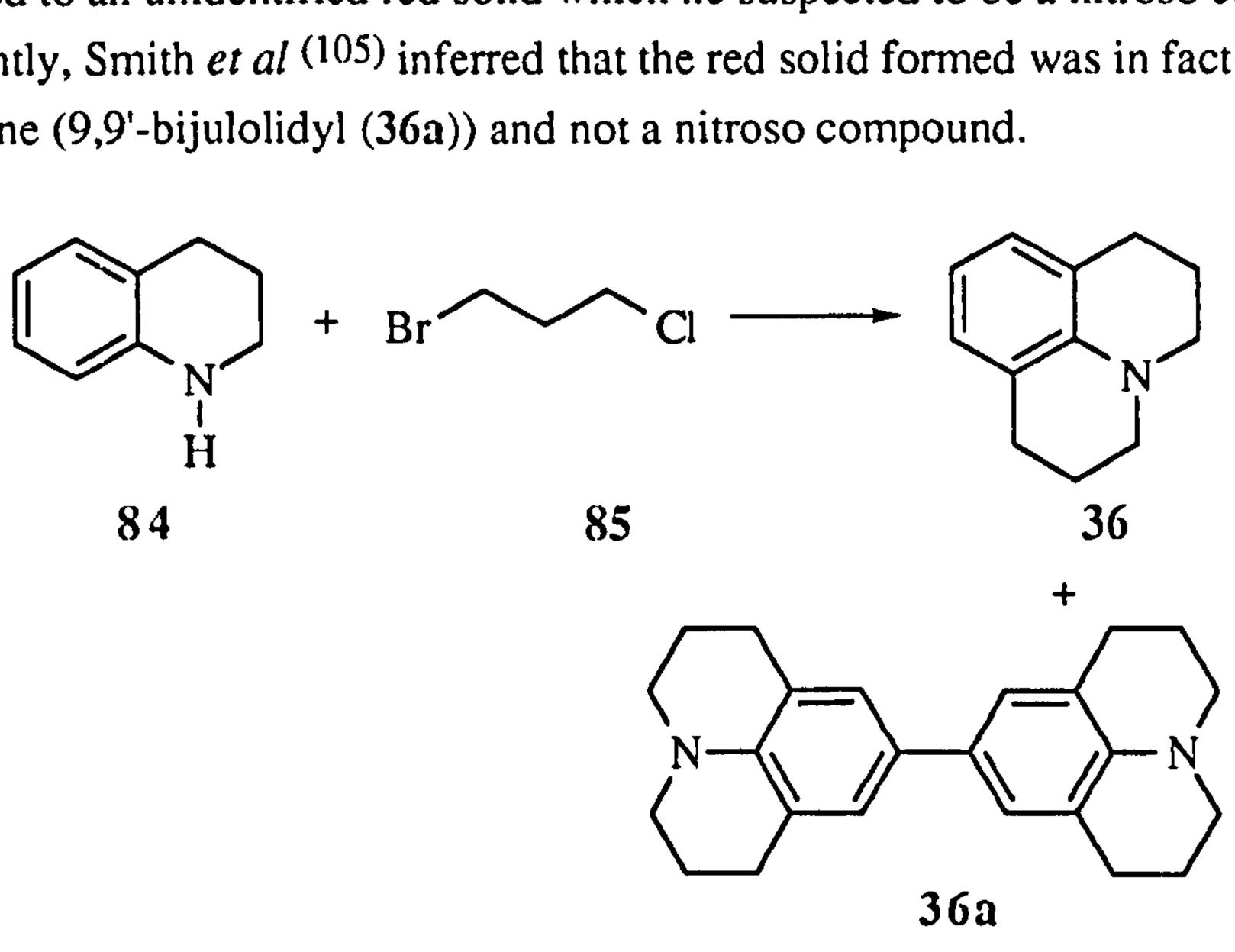
compounds showed typical trifluoromethyl group signals and the carbon-13 NMR spectra supported this by showing a quartet signal associated to the carbon of the CF_3 group. The FT-IR results supported the proposed structures by showing the presence of the N-H, CF_3 and NO_2 functional groups. The mass spectra indicated conventional losses of NO, NO_2, F and the novel loss of the nitrous acid groups. The *ortho*-phenylaminediamine adduct **65l** cyclised with elimination of nitrous acid whilst the *meta*- and *para*-analogues (**65m** and **n**, respectively) did not cyclise in the gas phase.

Cyclisation of **65l** on prolonged heating under reflux produced compound **79**, which could be a novel route to the formation of the phenazine ring skeleton from relatively simple starting materials such as the halonitrobenzenes and *ortho*-substituted aryl diamines.

4.0 Quinolizine and its derivatives

Julolidine (2,3,6,7-tetra-hydro-1*H*,5*H*-benzo[ij]quinolizine) (**36, Scheme 35**) is one of the simpler nitrogen containing tricyclic heterocycles. Compounds containing the quinolizine parent ring structure are of wide-spread occurrence in naturally-occuring compounds [98-99], including biologically active alkaloids [100]. This compound and its derivatives have been incorporated into synthetic heterocyclic dyes and pigments [53], potential anti-depressants and tranquillisers [64], while the amide derivatives of julolidines possess potential anti-inflammatory, anti-bacterial and fungicidal, anti-coagulant and herbicidal activities [81]. More importantly, compounds containing the julolidine parent ring skeleton have recently been introduced as a new class of fluorescent probes, called motor rotors [79, 101-104] to study the assembly of proteins (tubulins) *in vitro* and *in vivo*.

Attempts to repeat the synthesis of julolidine using the method of Glass and Weissberger [46] gave julolidine (**36**) in 25% yield and 9, 9'-bijulolidyl **36a**, a pink-coloured dimer of julolidine in 2% yield, when 1,2,3,4-tetrahydroquinoline **84** and 1-bromo-3-chloropropane **85** were heated under reflux (**Scheme 35**). This dimer was formed in the aqueous layer during the work-up, probably due to oxidative coupling at the 9-position [105]. When Pinkus [48] first attempted nitrosation of julolidine, the reaction led to an unidentified red solid which he suspected to be a nitroso compound. Subsequently, Smith *et al* [105] inferred that the red solid formed was in fact the dimer of julolidine (9,9'-bijulolidyl (**36a**)) and not a nitroso compound.



84 **85** **36**

+

36a

Scheme 35

The julolidine (**36**) and its dimer **36a** obtained in this study were consistent in structure with the results obtained by Smith *et al* [105]. However, they analysed the structures of their products using CHN analysis only without the advantage of modern spectroscopic techniques.

In this study, syntheses of various novel substituted julolidines were achieved

successfully using Afsah's method [63] (see **Scheme 13**) where three different aromatic amines, tetrahydroquinoline **84** (**Scheme 36**), indoline **91** (**Scheme 38**) and aniline **94** (**Scheme 39**), were reacted with various α, β-ketoesters to give substituted julolidine and lilolidine analogues in order to study their spectroscopic behaviour. Based on results obtained from spectral analysis, mainly NMR studies, properties such as strain, and the unusual behaviour of the lone pair on the nitrogen atom were investigated. Mass spectrometric studies revealed interesting fragmentations, such as the loss of a methyl radical via rearrangement from the molecular ion. Fragmentation pathways have been proposed and are described later.

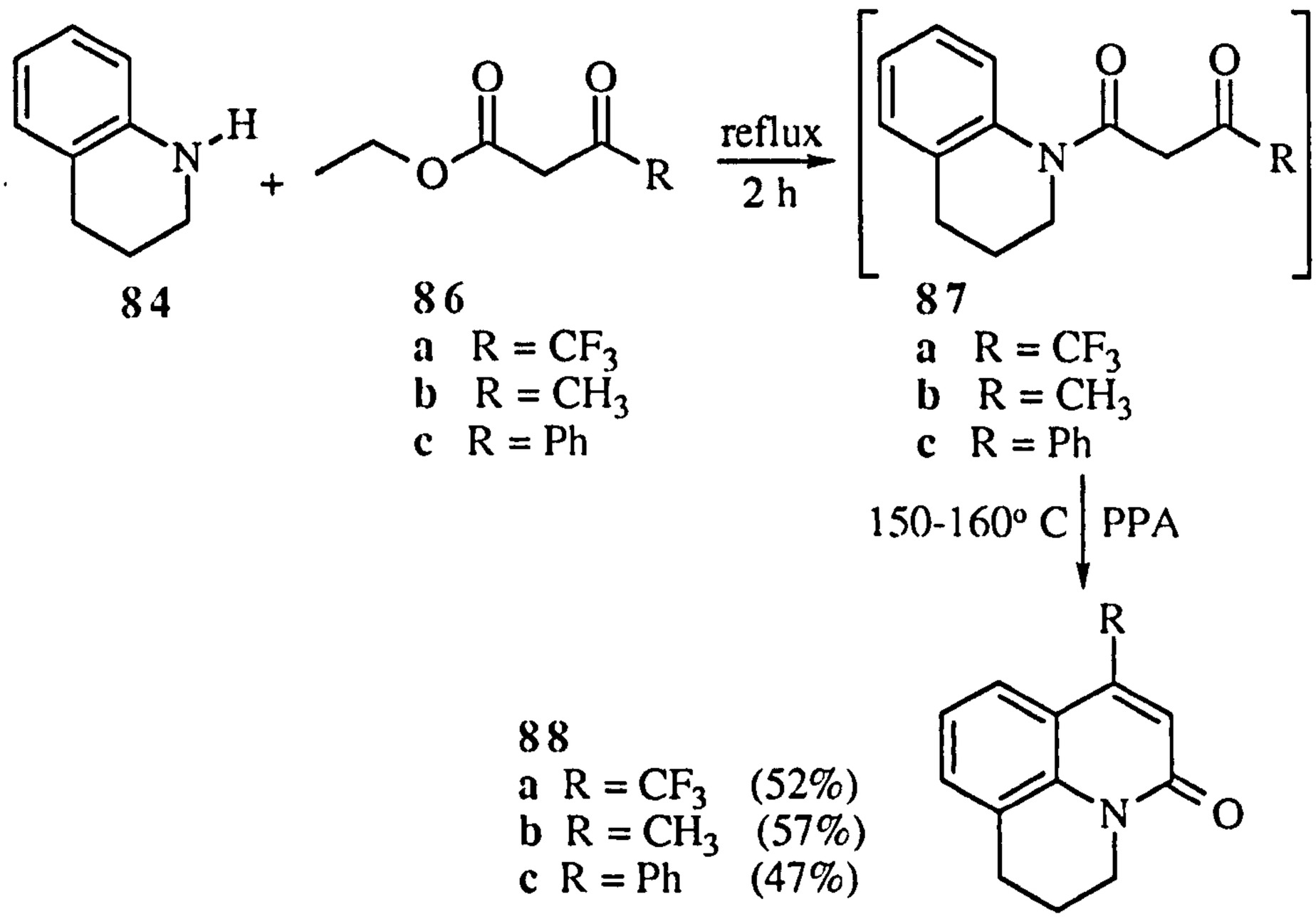
The advantage of following Afsah's method [63] is that it uses cheap and readily available amines as starting materials and polyphosphoric acid (PPA) as the cyclising agent. The yields are generally reasonable (4-57%) considering the process involves a single-step reaction sequence. In contrast to other commonly used acidic reagents such as aluminium chloride [106], phosphorus pentoxide [106], hydrogen fluoride [106], and concentrated sulphuric acid [106], polyphosphoric acid often leads to fewer side reactions (such as oxidations, charring, aromatic substitutions, or unwanted rearrangements) and to higher yields of the desired products [107].

Reaction work-up involving polyphosphoric acid was both convenient and easy, and was carried out by simply pouring the warm reaction mixture into water or cautiously into an ice/water slurry , followed, if necessary by extraction with a suitable organic solvent, and sometimes basification of the aqueous layer. However, experimental difficulties sometimes occurred in the isolation of product prepared in polyphosphoric acid. As a result it was necessary to hydrolyse the excess polyphosphoric acid and diluting it with water to the point where the solubility of the product was negligible. Since all the products were basic in nature, it was also necessary to neutralise the diluted phosphoric acid before isolation was carried out. Since the reactions were carried out in excess polyphosphoric acid sufficient to serve as solvent as well as the reagent, the quantities of the aqueous solutions became inconveniently large. Whilst polyphosphoric acid needs to be handled with care to avoid skin and eye contact, it is much easier to handle than other comparable acidic reagents (e.g. aluminium chloride). The main disadvantage of polyphosphoric acid was its high viscosity since it is mobile only when heated above 60° C. With polyphosphoric acid catalysed reactions, the temperature and duration of the reaction times were critical factors for obtaining optimum yields. The reaction times were optimised from reaction to reaction for best yields by isolating and working-up products from samples removed. It proved difficult to monitor these reactions using thin layer chromatography since the withdrawal of samples from the reaction mixture was somewhat difficult due to the viscosity of the polyphosphoric acid reagent.

Reissert first reported the preparation of 1-methyl-6,7-dihydro-3*H*,5*H*-benzo-

[ij]quinolizine-3-one (compound **88b**) by the action of ethyl acetoacetate on tetra hydroquinoline [108]. Subsequently, Cook *et al* improved this preparation by using diketene with tetrahydroquinoline [109].

For reasons mentioned earlier, Afsah's [63] method was adopted to synthesise a series of novel, substituted julolidines where tetrahydroquinoline **84** was reacted with various β-ketoesters **86a-c** to initially form the proposed intermediate amides **87a-c** through a nucleophilic addition-elimination process. These intermediates were not isolated but were subjected to a polyphosphoric acid-catalysed intramolecular Friedel-Crafts acylation to give the corresponding julolidine derivatives **88-c** in the yields shown as outlined in **Scheme 36.**



84

86
a R = CF_3
b R = CH_3
c R = Ph

87
a R = CF_3
b R = CH_3
c R = Ph

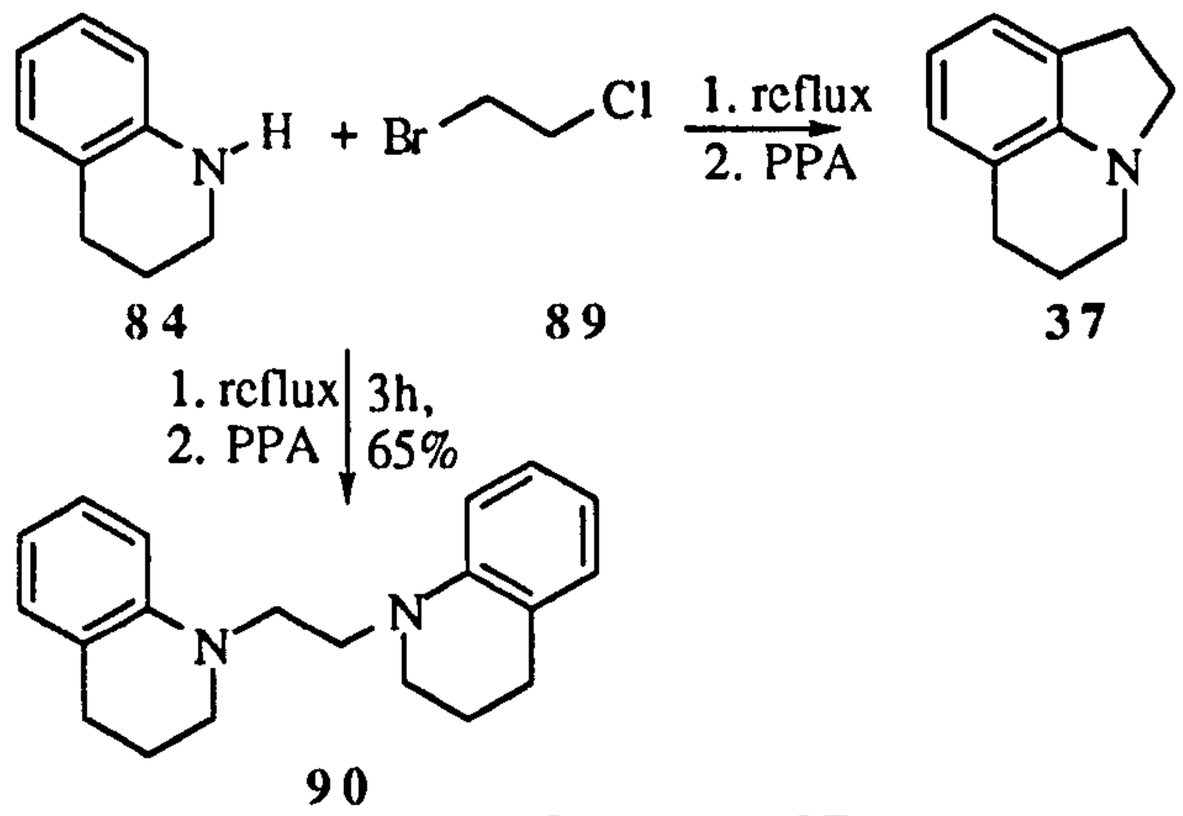
88
a R = CF_3 (52%)
b R = CH_3 (57%)
c R = Ph (47%)

Scheme 36

An improved synthesis of the cyclic 5-membered ring analogue of julolidine, called lilolidine (**37**), has been reported by Hallas *et al* [56]. He described a new route to the formation of lilolidine (see **Scheme 12**) in 60% yield.

A synthesis of lilolidine **37** was attempted using Afsah's method [63] in which tetrahydroquinoline **84** was heated with 1-bromo-2-chloroethane **89** under reflux, followed by addition of polyphosphoric acid reagent. This gave the unexpected dimer, 1,2-di(1,2,3,4-tetrahydroquinolin-1-yl)ethane **90** in 65% yield instead of the expected lilolidine **37**, as shown in **Scheme 37**. This may be due to the reaction mixture having been insufficiently dilute. Therefore, the dilution of 1-bromo-2-chloroethane was increased and the reaction repeated, but with the same results. The proton NMR and mass spectrometry results were entirely consistent with the proposed structure of the dimer **90** and with those obtained by Abu-Surrah *et al* [110]. Dimer **90** was also

prepared earlier by Wilhemus *et al* (111) by reacting tetrahydroquinoline with dibromo-ethane under reflux conditions for 10 hours. Both earlier preparations (110-111) produced yields of between 54 - 58%. Our method gave an increased yield of 65% and thus **Scheme 37** may represent an alternate route to synthesising such bridged systems efficiently in approximately 3 hours.

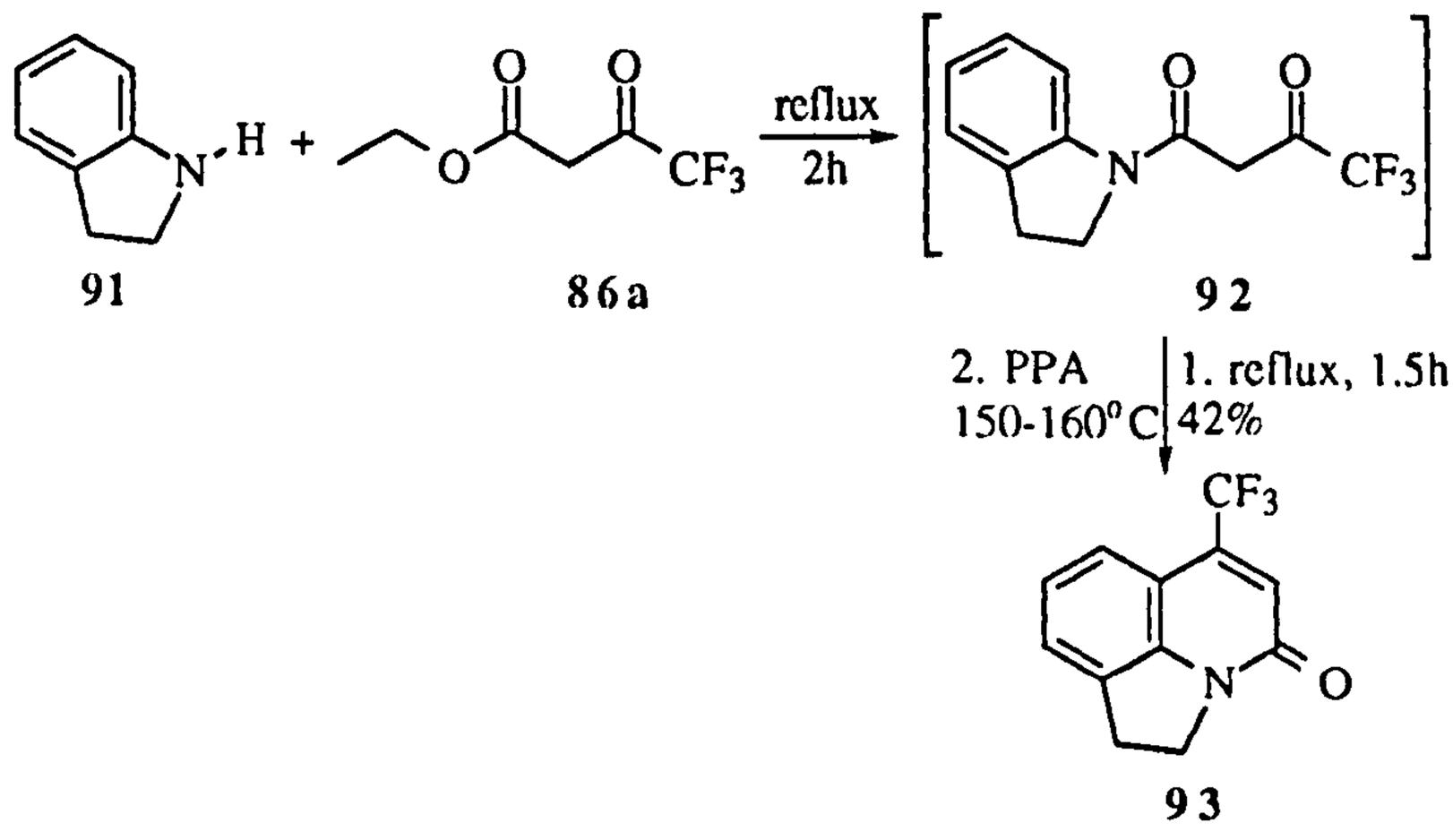


84 89 37

90

Scheme 37

Ketolilolidines have been synthesised previously by Boekelheide *et al* (59) in syntheses directed towards apo-β-erythroidines and by Rapoport *et al* (60) as a possible path towards the synthesis of 7-substituted indoles and indolines. In our case, synthesis of a substituted lilolidine **93** was achieved successfully in a one-pot synthesis using Afsah's method (63) where indoline (**91**) and ethyl trifluoroacetate (**86a**) were heated under reflux to produce the desired product, 4-triflurомethyl-1,8-dimethylene-1,2-dihydroquinolin-2-one (**93**) in 42% yield, presumably via cyclisation of the intermediate amide **92** by the polyphosphoric acid, as outlined in **Scheme 38**. Our method is comparable to other workers (59-60) in terms of yields obtained but has the advantage of a one-pot synthesis, convenient work-up and the use of relatively cheaper starting materials.

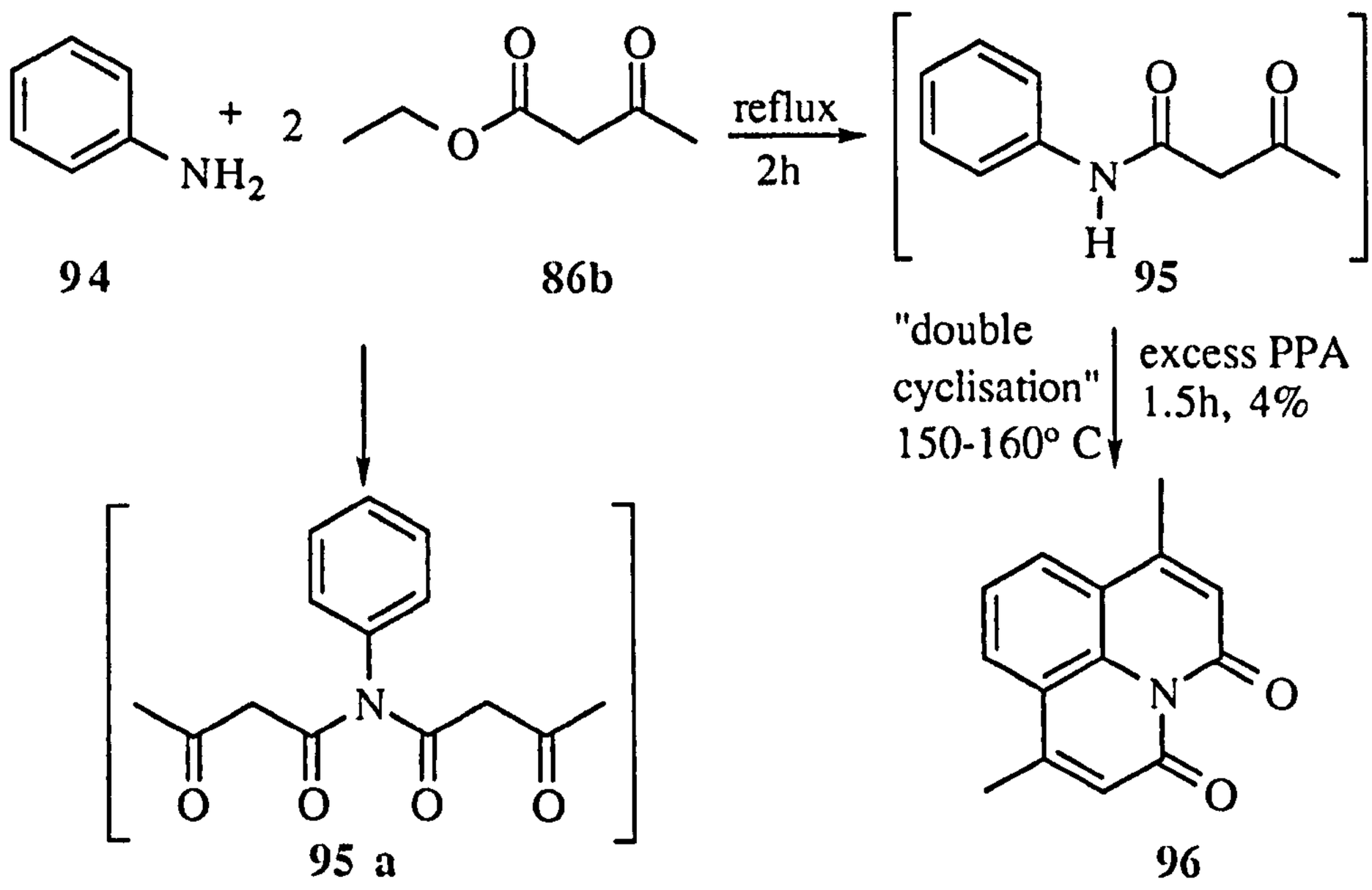


91 86a 92

93

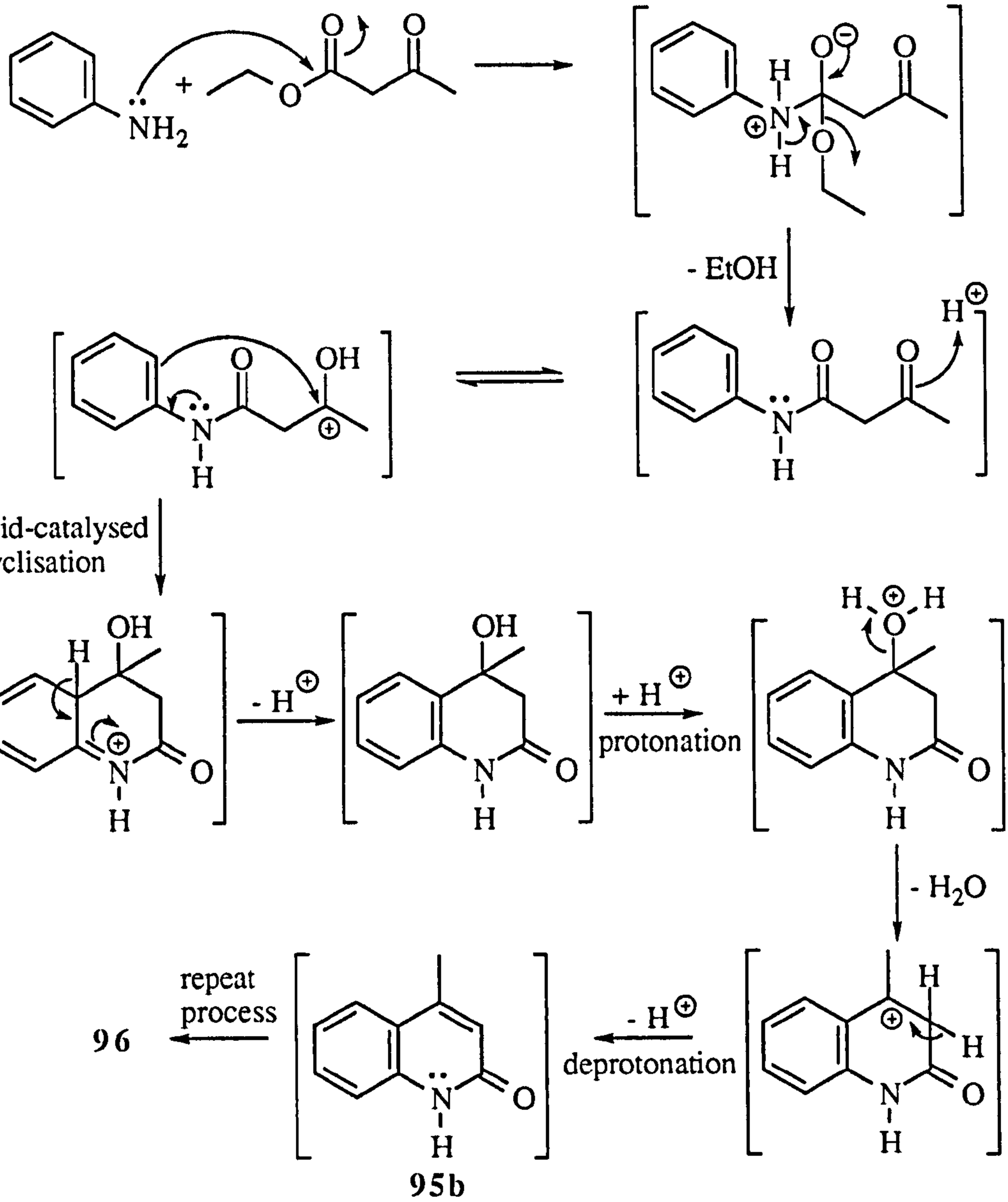
Scheme 38

The synthesis of 1,7-dimethyl-3*H*,5*H*-benzo[ij]quinolizin-3,5-dione (**96**) was obtained in low yield (4%) when aniline (**94**) was reacted with two equivalents of ethyl acetoacetate (**86b**), as shown in **Scheme 39**. The proposed intermediate mono amide, *N*-(phenyl)-3-oxopropanamide (**95**), undergoes acid-catalysed cyclisation in the excess polyphosphoric acid. It is thought that the amide nitrogen in the intermediate **95** is a very poor nucleophile due to the - M effects of the adjacent phenyl and carbonyl groups and therefore it probably exists as the mono and not the diamide **95a**, before cyclising to give **96**.



Scheme 39

There is no literature evidence to support the formation of the diamide **95a**, and the mechanism of formation of **96** from **95** is outlined in **Scheme 40**. We propose that the mechanism, in this case, proceeds via acid-catalysed nucleophilic addition-elimination process followed by acid-promoted cyclisation and subsequent dehydration to give (**95b**). This process is repeated where the lone pair on the heterocyclic nitrogen in **95b** attacks the carbonyl carbon of a second molecule of β-ketoester through the same mechanistic process to give **96** (see also **Scheme 42**).

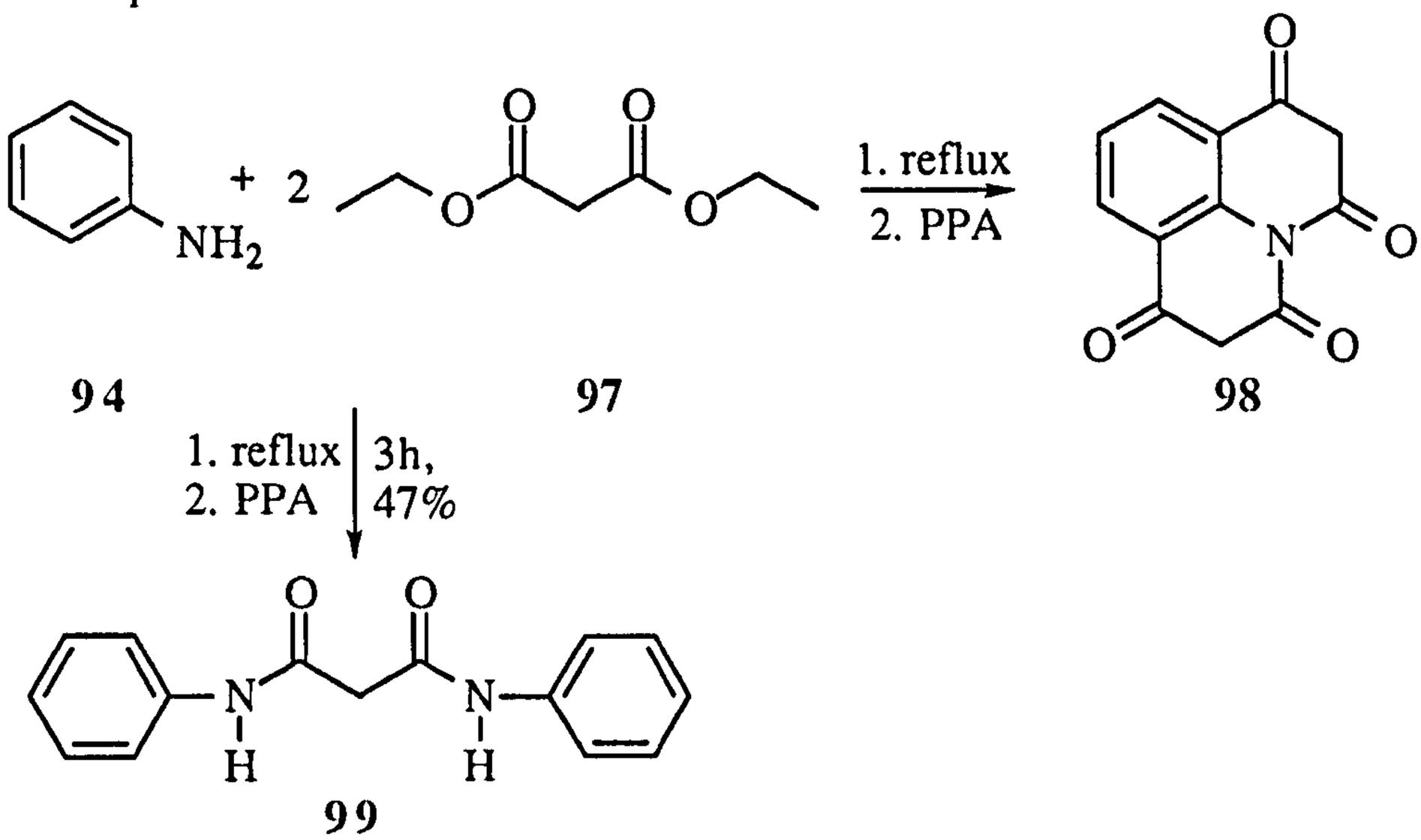


Scheme 40

The NMR spectrum of **96** could not be obtained because it was insoluble in standard NMR solvents, such as deuterated dimethyl sulphoxide (DMSO-d_6), chloroform ($CDCl_3$-d), acetone ($(CH_3)_2CO$-d_6), methanol (MeOH-d_4) and water (H_2O-d_2). However, its mass spectrum showed an ion at m/z 225 (60%), corresponding to the molecular ion. The infra-red spectrum of the product had a strong signal at 1633 cm^{-1} attributed to the carbonyl group of 6-membered ring amide carbonyls [112].

A synthesis of 1,7-dicarbonyl-3*H*,5*H*-benzo[ij]quinolizin-3,5-dione (**98**) (see **Scheme 41**) was attempted by reacting aniline (**94**) with diethyl malonate (**97**). This was unsuccessful and only N^1,N^2-diphenyl malonamide (**99**) was isolated, in 47%

yield [113]. Its structure was supported by NMR and mass spectrometric analysis. Even when excess polyphosphoric acid was used to promote cyclisation in this reaction, the expected product (98) was not obtained. A possible explanation for this could be that the nucleophilic attack by aniline (94) may be favoured over the cyclisation process.



94 97 98

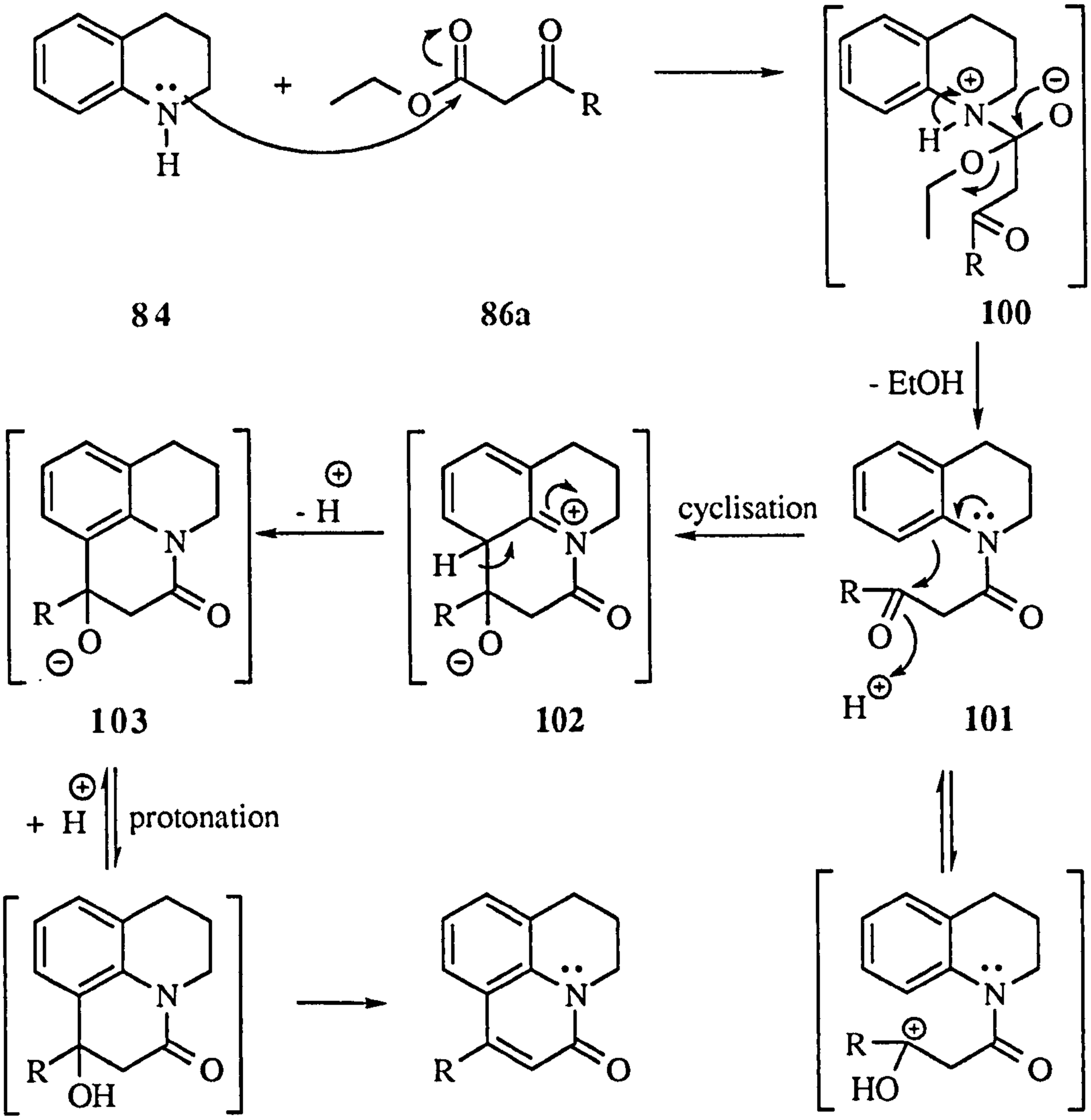
99

Scheme 41

4.10 Proposed mechanism of quinolizine cyclisation

Polyphosphoric acid is used in classic Friedel-Crafts acylation reactions [114] and is often used in preference to more strongly acidic reagents, such as concentrated sulphuric acid and hydrogen fluoride, or Lewis acids, such as aluminium chloride or zinc chloride[106]. It is a useful reagent because of its dehydrating ability which allows slow intramolecular cyclisations to take place over a wide range of temperatures (90-175° C) [115].

The mechanism proposed for the reaction is outlined in **Scheme 42** and is an acid-catalysed nucleophilic addition-elimination process where the lone pair of electron on the heterocyclic nitrogen in (**84**) attacks the carbonyl carbon atom in the β-keto ester **86a** to give the intermediate **100**, followed by loss of an ethanol molecule to give the amide **101**. Acid promoted intramolecular cyclisation produces a quaternary nitrogen in intermediate **102** from which loss of a proton probably results in the oxy-anion **103**, followed by protonation to give the tertiary alcohol (**104**). Acid catalysed elimination of water from **104** yields **88a**, as shown in **Scheme 42**.



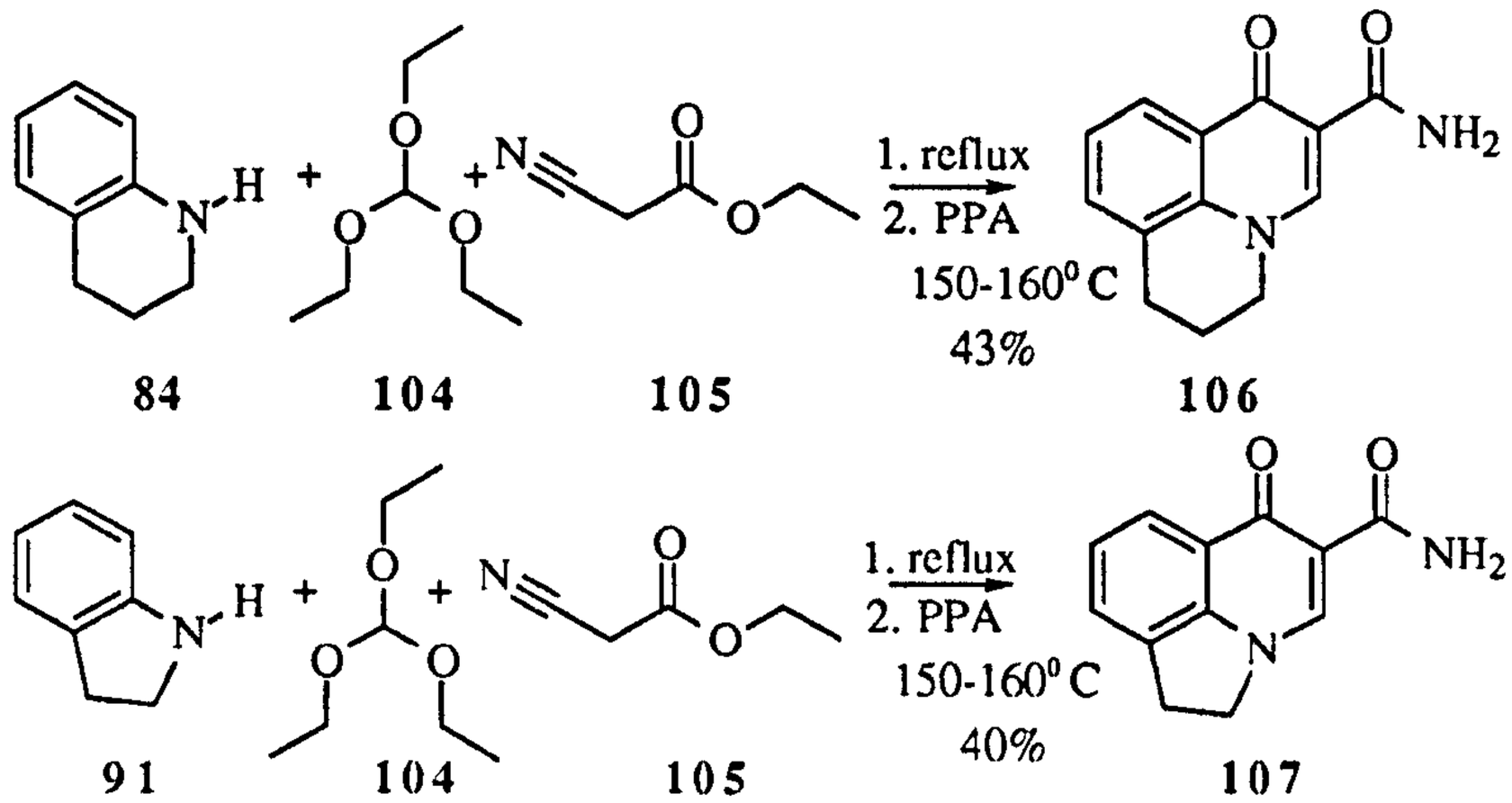
Scheme 42

The mechanism outlined in **Scheme 42** is also applicable to the reaction sequences shown in **Schemes 38** and **39**.

This opens up a new method for synthesising fused ring systems which could be adopted for synthesising a variety of heterocyclic compounds and is outlined in **Scheme 43**. In this one-pot synthesis an amide function is introduced onto the ring system, since an amide function is known to play an important role in medicine mainly due to its physical properties [81, 116]. For instance, hydrogen bonding is considered to be a useful property of amides because it makes the compounds water-soluble, i.e. it increases hydrophilicity in otherwise hydrophobic molecules [116].

The syntheses of 2-carbamoyl-6,7-dihydro-1*H*,5*H*-benzo[ij]quinolizin-1-one (**106**) and 3-carbamoyl-1,8-dimethylene-1,4-dihydroquinolin-4-one (**107**) is outlined

in **Scheme 43.** Tetrahydroquinoline (**84**) was heated with a mixture of triethyl orthoformate (**104**) [117] and ethyl cyanoacetate (**105**) [118] under reflux for 2 hours, followed by cyclisation using polyphosphoric acid for 1.5 hours and gave **106** in 43% yield. Similarly, Indoline (**91**) gave **107** in 40% yield. The NMR, mass spectrometric and infra-red results were consistent with their proposed structures.

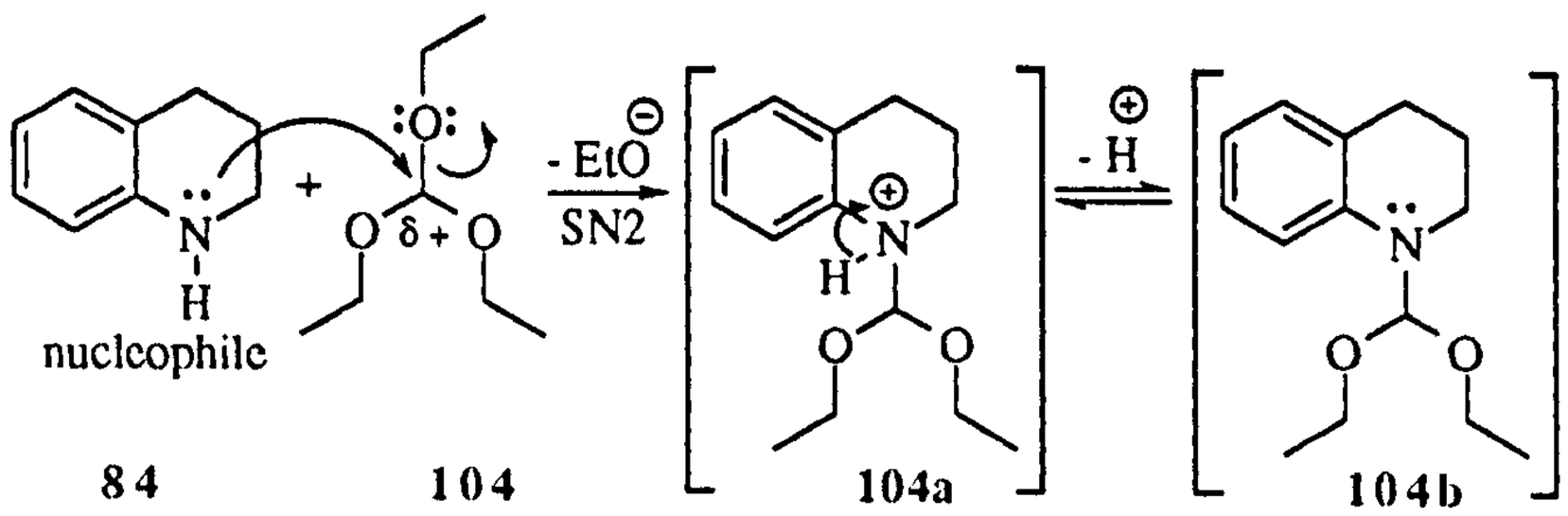


84 **104** **105** **106**

91 **104** **105** **107**

Scheme 43

The orthoformate carbon in triethyl orthoformate (**104**) is highly reactive and participates in a number of bond-forming reactions [117]. All the intermediates shown in both stages (**Scheme 44**) are proposed intermediates as they were not isolated. The lone pair of electrons on the heterocyclic nitrogen **84** nucleophilically attacks the orthoformate carbon in **104** in an S_N2 substitution process to form a protonated quaternary ammonium ion (**104a**). Loss of a proton from this species gives **104b**, as shown in **Scheme 44** (stage 1).



84 **104** **104a** **104b**

+ EtOH

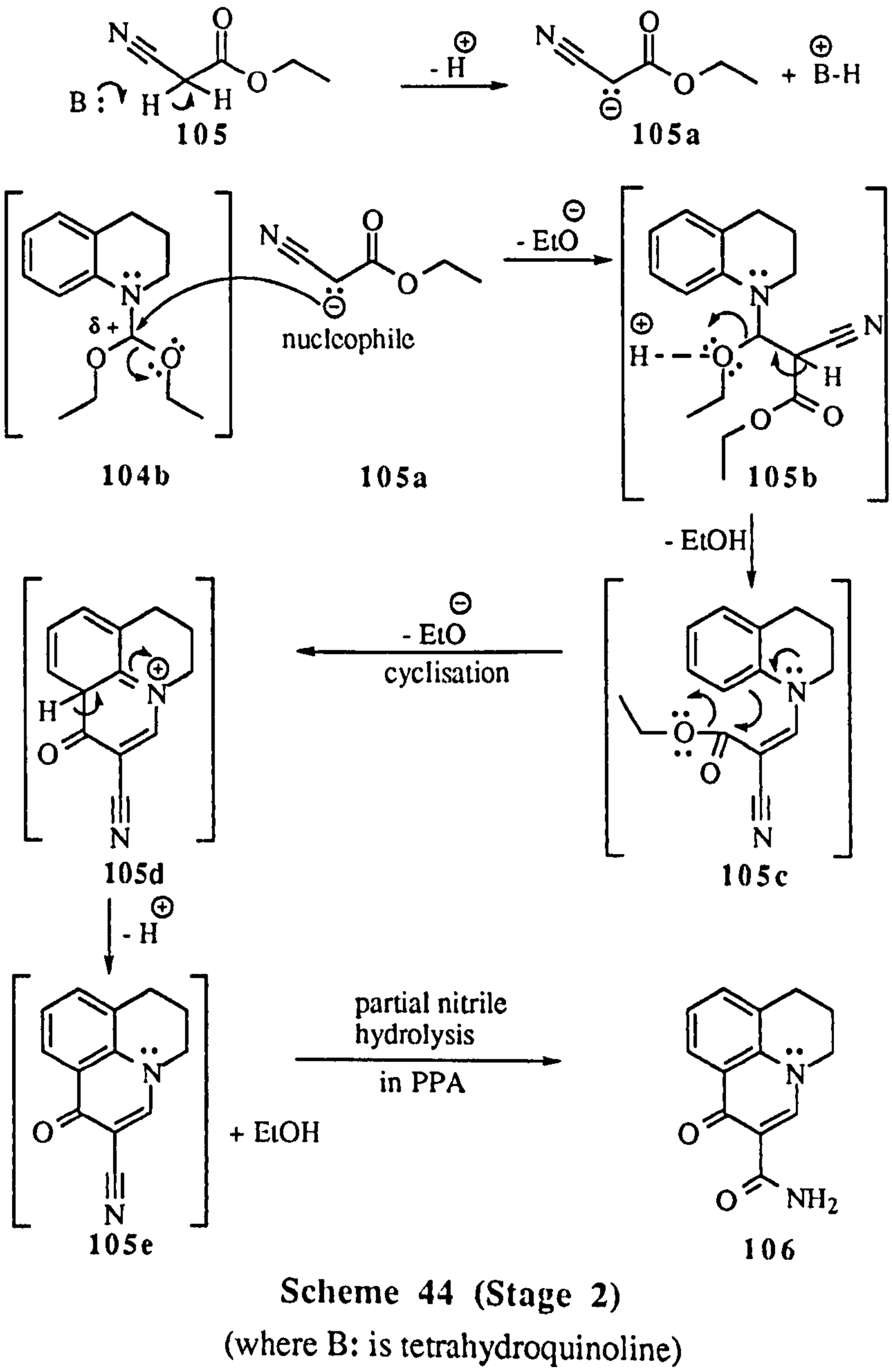
Scheme 44 (Stage 1)

In the second stage, the acidic hydrogens α to the nitrile and carbonyl groups in ethyl cyanoacetate (**105**) are removed by base (tetrahydroquinoline) to form the carbanion **105a** which in turn attacks the orthoformate carbon in **104b** in a Knoevenagel-type condensation process [118] to form **105c** by acid-catalysed loss of ethanol in **105b**. Cyclisation using polyphosphoric acid gives **105d** and **105e** via

elimination of the second molecule of ethanol . Subsequent hydrolysis of the nitrile group in acidic solution yields the corresponding amide **106**, as shown in **Scheme 44** (stage 2).

Although nitriles are reported to hydrolyse more slowly than either esters or amides [119], under these reaction conditions this process occurs readily. Usually, hydrolysis of nitriles requires more severe conditions [119] and therefore the amide **106** would be converted into the corresponding carboxylic acid. However, carboxylic acid formation was not observed probably due to the presence of excess PPA which causes the concentration of free water to be very low. This may account for the reaction stopping at the amide stage.

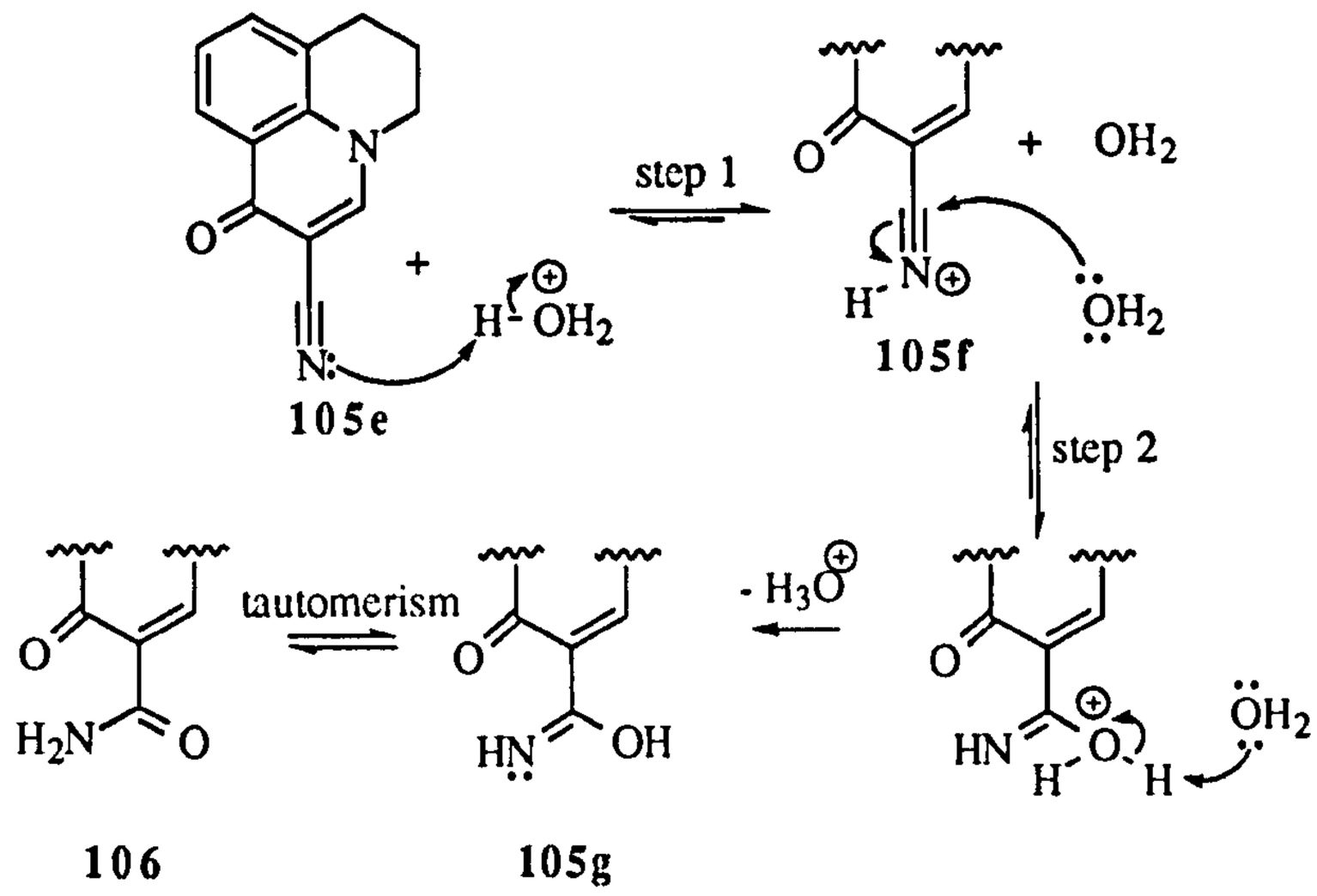
Compounds **106** and its analogue **107** were isolated, as the amides, as confirmed by proton NMR, mass spectrometry and infra-red evidence.



Scheme 44 (Stage 2)

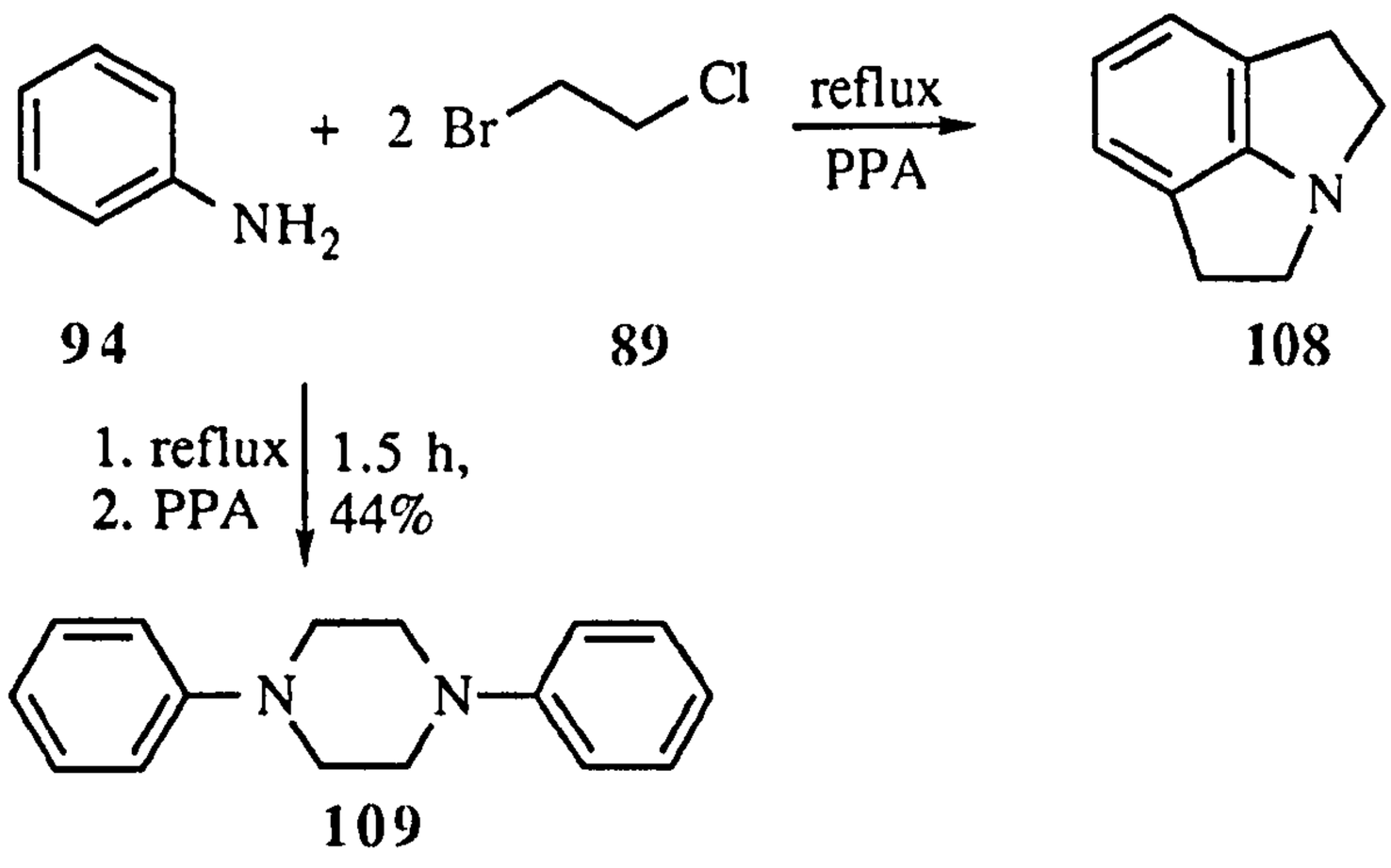
(where B: is tetrahydroquinoline)

The mechanism of nitrile hydrolysis in acidic solution is illustrated in **Scheme 45** and involves an attack by the weakly nucleophile water on this electrophilic nitrile carbon, followed by the loss of a proton to give an intermediate imidic acid (**105g**). The imidic acid tautomerises to the amide **106**.



Scheme 45

Since 1-bromo-3-chloropropane has been used [46, 48, 120] to synthesise julolidine from aniline, by analogy, aniline (**94**) and 1-bromo-2-chloroethane (**89**) were reacted in an attempted synthesis of **108**, 1,2,4,5-tetrahydro-pyrrolo[3,2,1-*hi*]-indole (**Scheme 46**). Instead, *N*,*N*-diphenylpiperazine (**109**) was obtained when aniline (**94**) and two equivalents of 1-bromo-2-chloroethane (**89**) were reacted. The reaction failed to give the desired product (**108**) probably due to increased strain resulting from two 5-membered rings fused to the benzene ring, and perhaps the poor nucleophilic strength of the intermediate nitrogen.



94 89 108

109

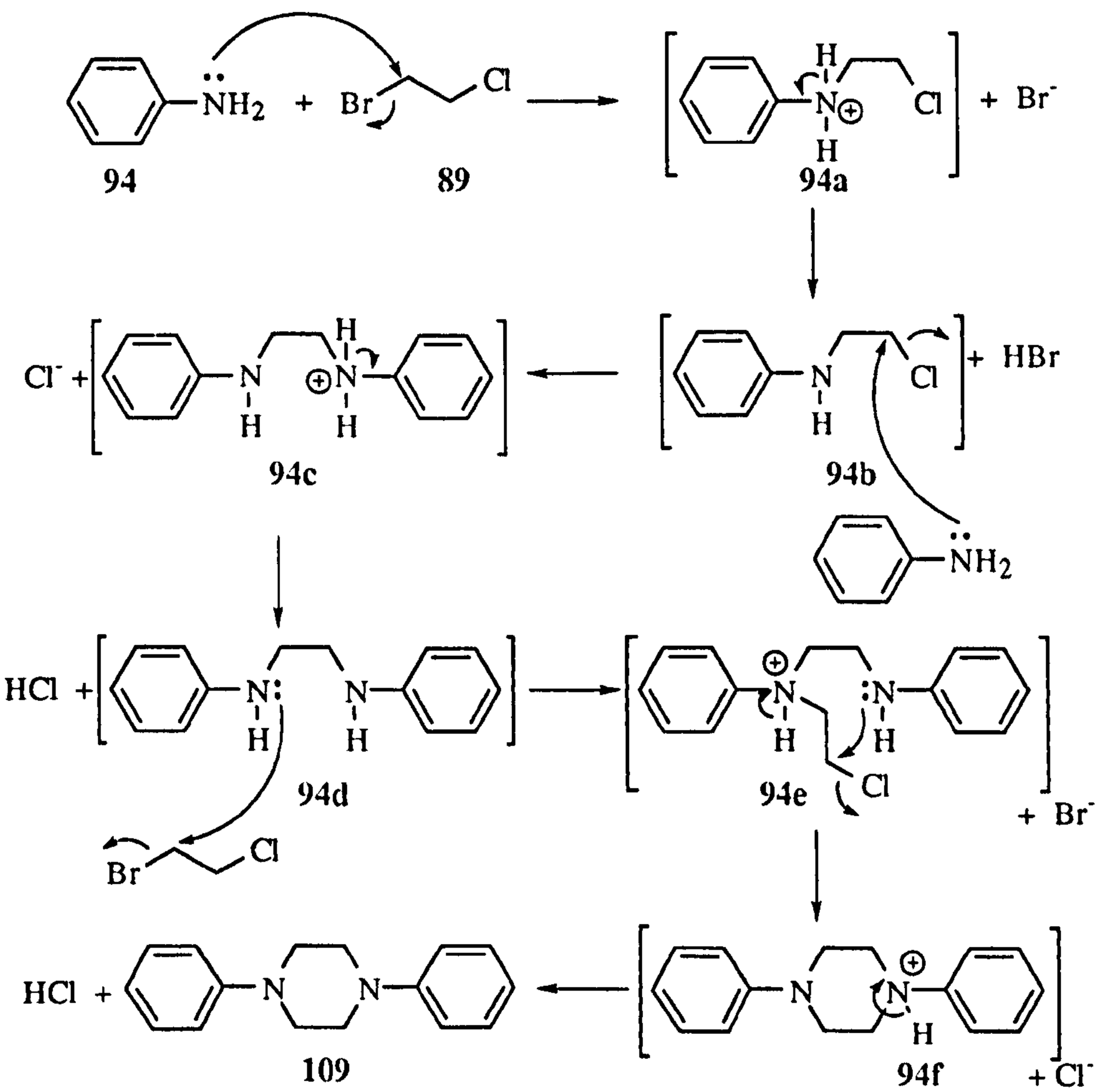
Scheme 46

Although dimer **109** has been prepared in a number of ways [120-127], our method may offer a novel route to the *N*,*N*-disubstituted piperazines in a one-pot

synthesis starting from relatively simple reagents using the right stoichiometry.

The mass spectrometric results confirmed the presence of the dimer with a peak at m/z 238 (70%) corresponding to the molecular ion, whilst the proton NMR showed a singlet at 3.27 ppm (due to the four equivalent sets of methylene protons) and three signals as expected in the aromatic region.

The proposed mechanism of formation of **109** is outlined in **Scheme 47** and involves S_N2 nucleophilic attack on **89** by the lone pair on the aniline nitrogen to form **94a** (bromine is displaced in preference to chlorine since it is a better leaving group). Assuming that some unreacted aniline is still present in the mixture, it attacks the carbon of the methylene group attached to chlorine in **94b** to form **94c** (or the process happens simultaneously in one step to give **94c**). The nucleophilic substitution process is repeated to give **94e** and intra-molecular cyclisation gives the salt of the dimer (**94f**), which probably existed as the salt in the reaction mixture. In the basification stage during the work-up, the dimer (**109**) was precipitated out.



Scheme 47

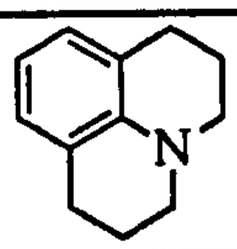
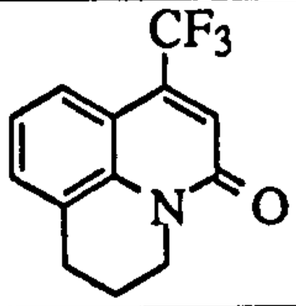
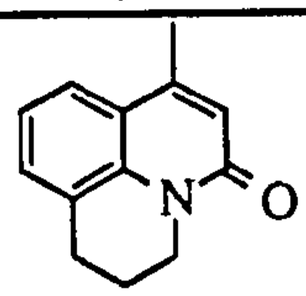
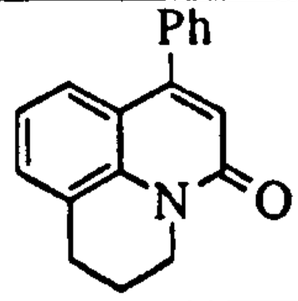
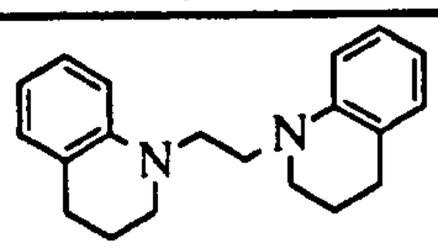
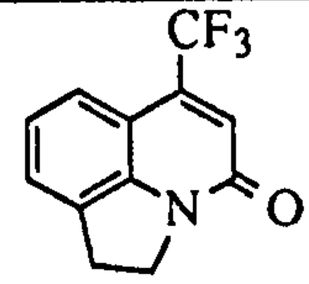
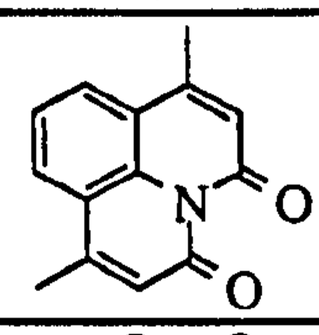
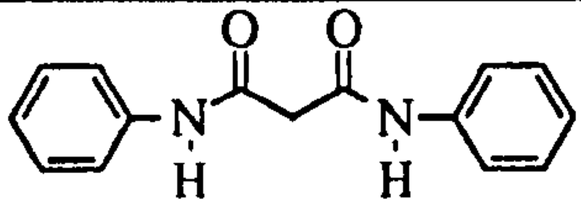
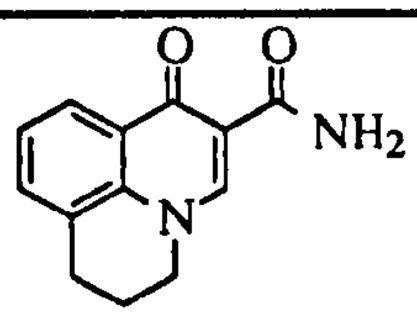
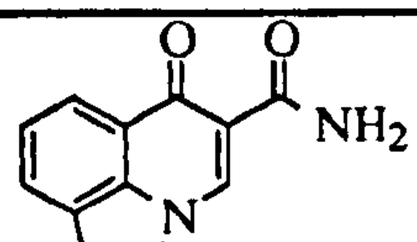
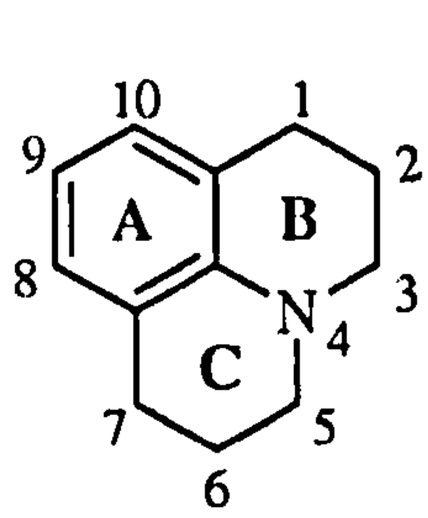
Structure	No	Yield (%)
	36	25 (46, 48)
	88a	52
	88b	57 (63)
	88c	47
	90	65 (110-111)
	93	42
	96	4
	99	55 (113)
	106	43
	107	40
	109	54 (127a)

Table 13

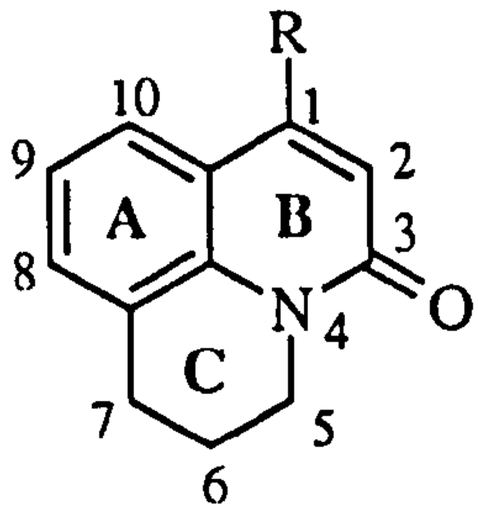
The compounds successfully synthesised in this study are listed in Table **13** along with their respective yields. As far as we are aware all the compounds are novel, except compounds **36, 88b, 90, 99** and **109**. From the table there appears to be no significant correlations between the electronic effects of the substituents and the percentage yields. Yields are based on isolated and recrystallised products.

4.20 NMR spectral analyses of quinolizine and some of its derivatives

The numbering systems for the compounds listed in Table **13** (and also discussed in the Introduction) are shown in Chart **1**.

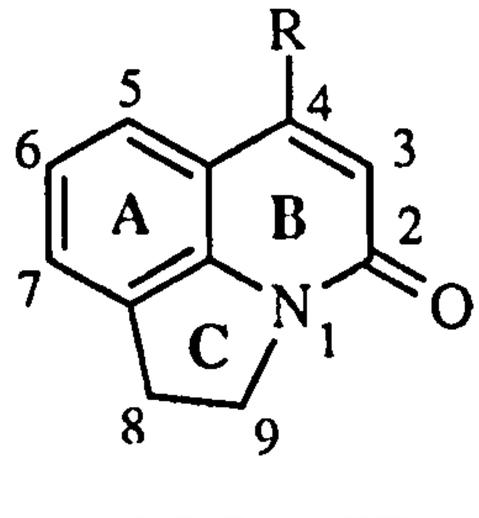


36

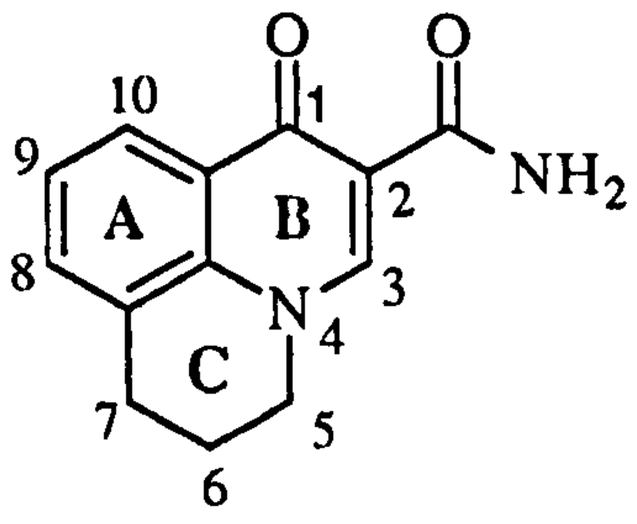


88

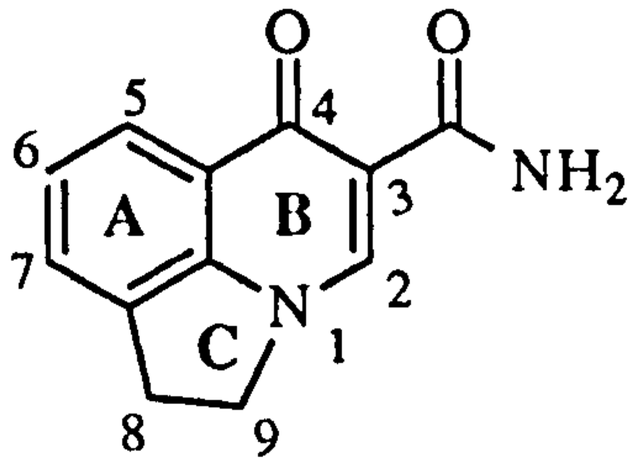
a $R = CF_3$
b $R = CH_3$
c R = Ph
96 see Scheme **39**



93 $R = CF_3$



106

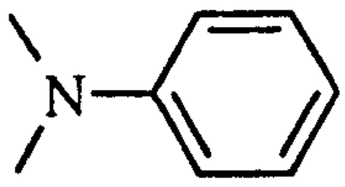


107

Chart 1

The ^1H NMR, mass, and infra-red spectra of julolidine (**36**) synthesised in this study were consistent with those of an authentic commercial sample. Two sets of the axial/equatorial trimethylene hydrogens (carbons-1, -2, -3 and -5, -6, -7) thus showed vicinal coupling constants of 6.0 Hz. This observation was also supported by the HETCOR experiment. The protons of the methylene groups attached to nitrogen appeared as a triplet at 3.57-3.66 ppm (*J* 6.0 Hz), as do those joined directly to the aromatic ring, at 3.00-3.06 ppm (*J* 6.0 Hz). The protons of C-2 and C-6 methylene groups produced a quintet at 2.23-2.33 ppm (*J* 6.0 Hz). Similarly, the julolidine dimer **36a** formed as a by-product (see **Scheme 35**) showed typical cyclic methylene

signals with no evidence of axial/equatorial splittings suggesting that the cyclic rings are probably more flexible than its monomer. The ease of oxidation of the dimer **36a** at position-9 probably suggests an unusually great availability of electrons at that position [105]. The lone pair of the nitrogen in julolidine is perpendicular to the plane of the aromatic ring and overlaps well with the π system of the ring [128]. Therefore, to allow more efficient conjugation with the aromatic nucleus the heterocyclic nitrogen is sp^2 hybridised [128] compared to, for example, the nitrogen atom in the *N*,*N*-dimethylaniline **110** which is sp^3 hybridised. This explanation is offered by Hallas *et al* [128] who noted a reduced intensity of the second band in the electronic absorption spectra of julolidine compared with that of *N*,*N*-dimethylaniline. Hallas further observed that π-interaction of the amino-nitrogen atom with the aromatic ring is also brought about by the methylene bridges in the julolidine ring system [52, 77, 128].



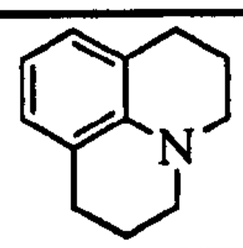
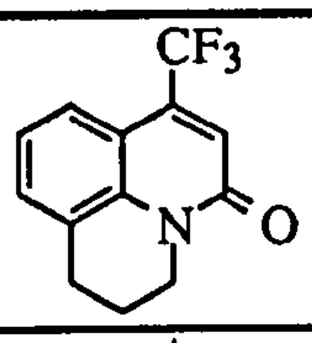
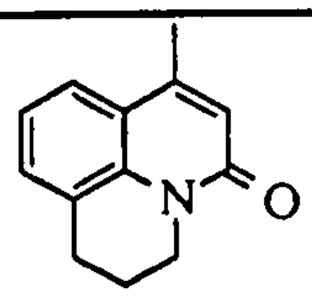
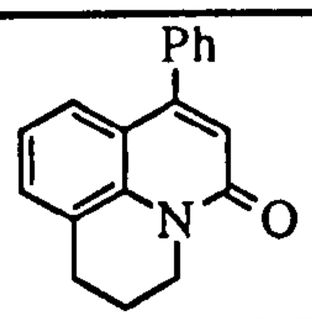
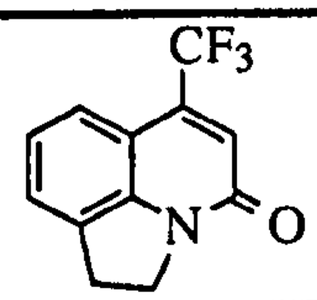
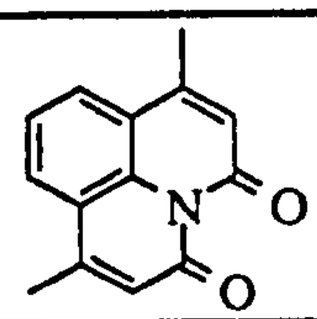
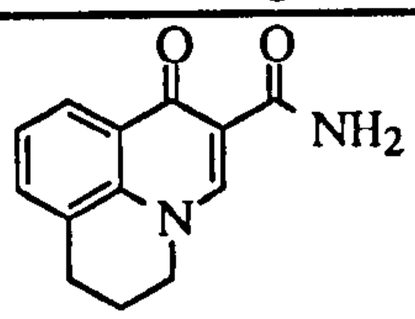
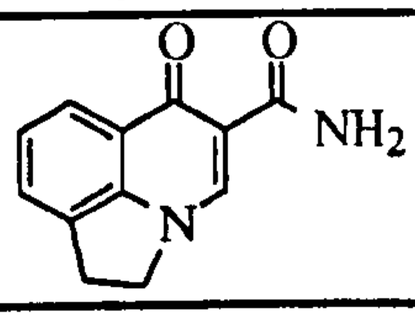
110

It is useful to understand the electronic nature of the lone pair on the heterocyclic nitrogen in julolidine in terms of interactions to form analogous julolidine dimers and dyes via coupling reactions.

A more detailed explanation and understanding of the crystal structure and electronic behaviour of the nitrogen lone pair is given by R. Dunlop *et al* [129]. From crystal structure data he observed that the heterocyclic nitrogen atom in the julolidine skeleton (in his case, with a nitroso substituent in position-9) deviates by 0.05 Å from the plane defined by the C-3, C-5 and C-12 carbon atoms. However, this small deviation from planarity does not significantly inhibit the delocalisation of the nitrogen lone pair. Thus in julolidine, the aromatic ring is planar with two fused cyclic six-membered rings having slightly distorted 'envelope' conformations (C-2 and C-5 slightly displaced from the plane of the aromatic ring) [129].

The chemical shifts of hydrogens present in these compounds are summarised in Table **14**.

Protons on:- (ppm)

Structures	No	C-1	C-2	C-3	C-5	C-6	C-7	C-8	C-9	C-10
	**36**	3.01-3.06	2.23-2.33	3.57-3.62	3.57-3.62	2.23-2.33	3.01-3.06	7.17-7.19	7.32-7.35	7.17-7.19
	**88a**	–	7.09	–	4.07-4.11	1.98-2.08	2.96-3.00	7.60-7.64	7.27-7.34	7.53-7.56
	**88b**	–	6.50	–	3.99-4.04	1.94-2.01	2.92-2.97	7.59-7.62	7.14-7.20	7.37-7.39
	**88c**	*	*	*	*	*	*	*	*	*
	**93**	–	–	6.95	7.45-7.49	7.22-7.31	7.52-7.55	3.37-3.43	4.28-4.35	–
	**96**	**	**	**	**	**	**	**	**	**
	**106**	–	–	8.74	4.34-4.38	2.07-2.17	3.01-3.10	7.58-7.62	7.38-7.42	8.13-8.18
	**107**	–	8.98	–	7.85-7.93	7.51-7.59	7.39-7.45	3.52-3.55	4.65-4.76	–

* difficult to assign due to high noise levels on the base line

** compound insoluble in standard NMR solvents

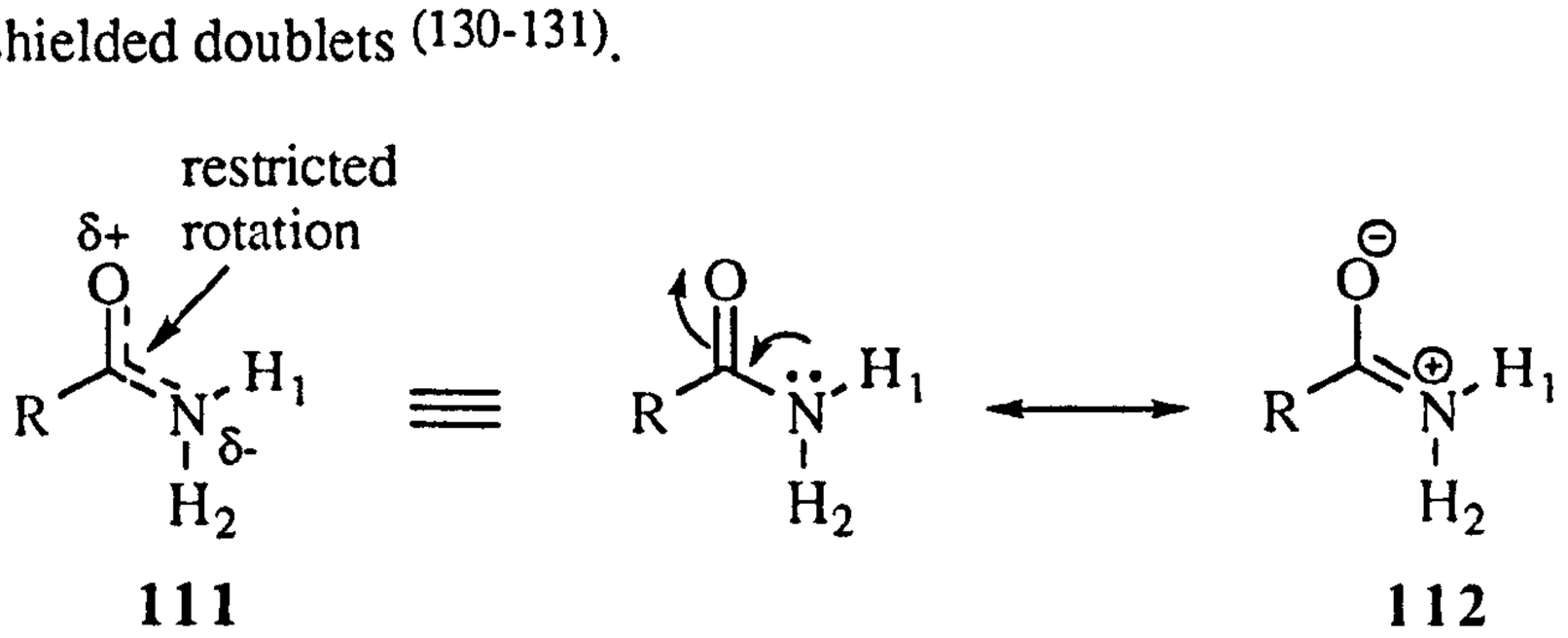
Table 14

The triplet signals of the C-(5)-H_2 alkyl atoms of ring C adjacent to the heteroatom, in compounds **88a-b** and **106** were, as expected, shifted further downfield than other alkyl CH_2 atoms of ring C in the same compounds, due to the electronic influences of the heteroatom. Similarly, in compounds **93** and **107**, the C-(9)-H_2 alkyl atoms of ring C which are adjacent to the heteroatom, were more

deshielded compared to other alkyl CH_2 atoms of the same compounds.

Generally, replacing the R group at positions C-1 in compounds **88a-c** and **106**, or at position C-4 in compound **93**, influenced the chemical shifts of the aromatic hydrogens of ring **A**. The benzylic CH_2 triplet at C-7 of ring C in compounds **88a** and **88b** was more shielded compared to the signal at position C-8 of compounds **93** and **107** and this was perhaps due to the presence of ring strain in the 5-membered analogues causing these protons to be deshielded. Otherwise replacing the R group at positions C-1 and C-4 with the carbonyl group and introducing an amide group at positions C-2 and C-3 in compounds **106** and **107** respectively, caused small shifts in the positions of the benzylic proton resonances, as expected. Initially, the cyclic ring **C** in compounds **93** and **107** was thought to be rigid because of the expected overall strain in the molecules but the proton NMR experiments, surprisingly, showed no such evidence of axial/equatorial splittings of the cyclic methylene protons. The absence of geminal coupling between methylene hydrogens suggests sufficient flexibility in the cyclic ring **C**, on the NMR time scale.

One of the obvious properties of the amide group was observed in the proton NMR spectra of compounds **106** and **107**. Due to the restricted rotation about the C-N bond in **111**, due to the partial double bond character (**112**) (**Scheme 48**), resulted in non-equivalence of the two hydrogens on the nitrogen atom producing two sets of deshielded doublets [130-131].



111 **112**

Scheme 48

The vinylic proton at C-2 (in compounds **88a, 88b** and **107**) and C-3 (in compounds **93** and **106**) was found to be uniquely deshielded in the range of 6.50-8.50 ppm. This position was sensitive to electronic effects from adjacent substituent R and was therefore influenced by changes in the nature of the substituent R, and subsequent introduction of the amide group. Introducing the amide group at positions C-2 and C-3 in compounds **106** and **107** respectively, caused a sharp downfield shift of this proton, in contrast to compounds **88a-b** and **93**. Although there is no definitive resonance range for vinylic protons in these types of compounds reported in the literature, the shift is expected to be downfield, almost in the aromatic region, due to the extensive conjugation with the adjacent fused phenyl ring, the electronegativity

of the substituent R adjacent to this proton, and perhaps the anisotropy [121, 132] effects of the amide group. The term anisotropic indicates a magnetic field which is not isotropic, i.e. non uniform [133]. Therefore, all groups which have π electrons generate anisotropic fields and protons falling within the anisotropic area are shielded and those falling outside the area are deshielded [133-135]. The magnitude of the anisotropic field diminishes with distance [134].

The deshielding of the vinylic protons in **106** and **107** could also be attributed to the sp^2 hybridisation effects of the carbon atom concerned. In an sp^2-1*s* C-H bond, the carbon atom has more *s* character, which effectively makes it more electronegative than an sp^3 carbon [136]. The reason for an sp^2 carbon being more electronegative is due to the *s* orbitals holding the electrons closer to the nucleus compared to carbon *p* orbitals. This causes the electrons in the sp^2 carbon to be held more tightly, thus resulting in less shielding for the H nucleus than in an sp^3-1*s* bond [136].

Comparing compounds **88a** and **93**, the trifluoromethyl (CF_3) group in **93** splits the C-3 vinylic proton into a doublet by long range ^{19}F-coupling, giving a coupling constant (^4J) of 1.0 Hz (see spectrum no. 68, appendix). In the carbon-13 spectrum of the same compound, the carbon of the trifluoromethyl group is split into a quartet ($^1J_{C\text{-}F}$ = 271 Hz) [137], and the C-4 carbon is also split into a quartet ($^2J_{C\text{-}F}$ = 31 Hz) [137] due to the adjacent CF_3 group (see spectrum no. 69, appendix). In compound **88a**, no such ^{19}F long range coupling was observed in the proton spectrum. However, in the carbon-13 NMR spectrum of **88a**, evidence of splitting due to fluorine coupling was observed but it proved difficult to assign all the four lines due to background interference in this spectrum (see spectrum no. 64, appendix).

The ^{1}H and ^{13}C NMR spectra of compounds **90, 99** and **109** (not listed in Table **14**), were consistent with the structures proposed (see **Schemes 37, 41** and **46** respectively).

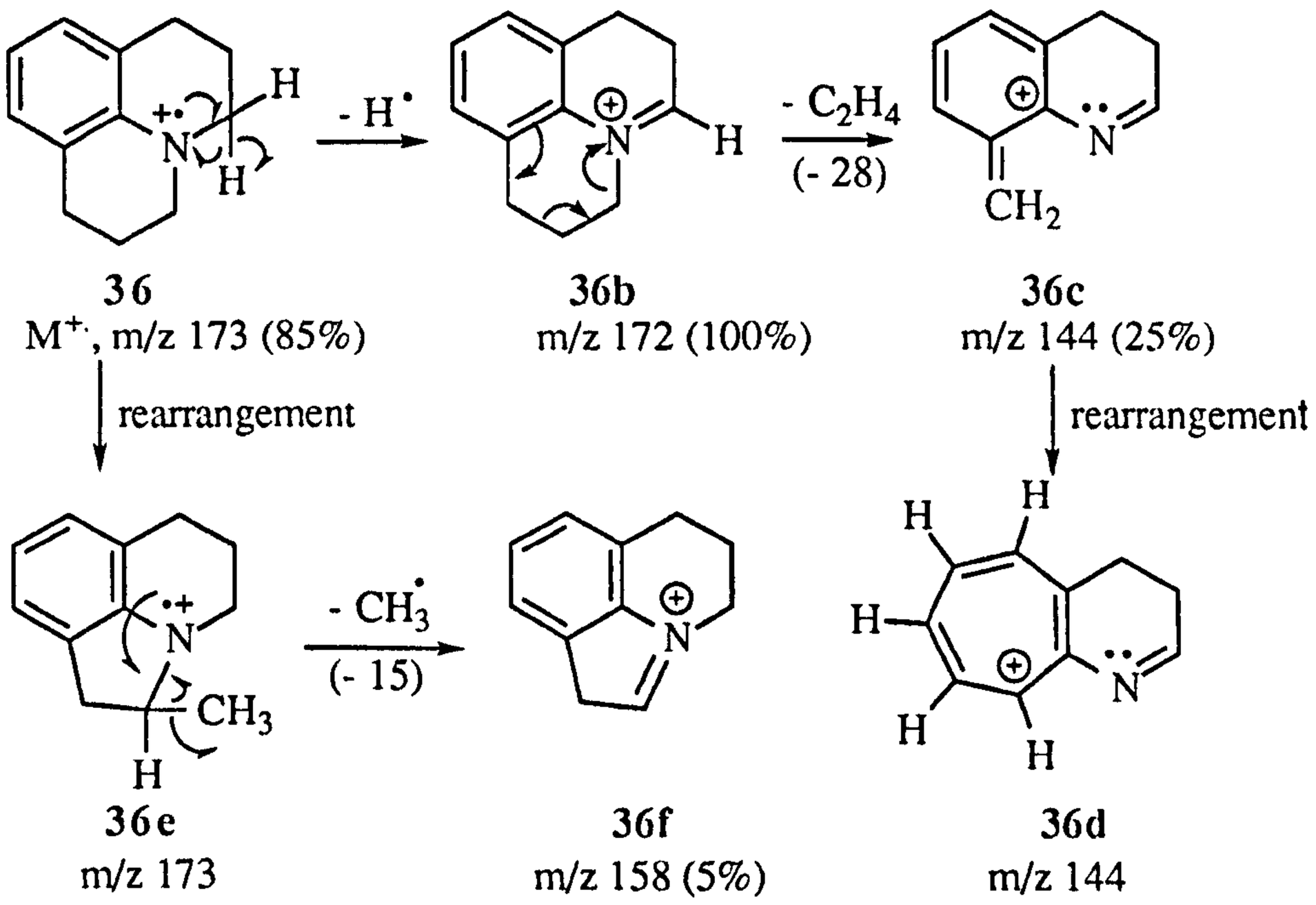
4.30 Mass Spectrometric analyses of quinolizine derivatives

Two major fragments of importance in the mass spectra of quinolizine derivatives arise by expulsion of hydrogen and methyl radicals from the molecular ion. It must be emphasised that where a methyl substituent is present at the 4-position (compound **88b**, see Table **14**), there is ambiguity in terms of the loss of a methyl radical. In this case, loss of a methyl radical can occur in two possible ways, either directly from the 4-position, or via a proposed rearrangement of ring C of julolidines. In compound **88a**, where a methyl substituent is absent at the 4-position, a methyl radical can only be eliminated via the rearrangement process.

In julolidine (**36**), the methyl radical is eliminated via rearrangement to the indonyl species **36e**. Although methyl loss in the parent ring compound julolidine is a

minor process, hydrogen abstraction and subsequent ethene elimination were major processes in **36**, as shown in **Scheme 49**. Hydrogen abstraction from the molecular ion of julolidine (**36**) produces a stable, quaternised nitrogen-containing ion, **36b**, as the base peak. It is an intense ion because it is conjugated with the aromatic ring and is symmetrical. Loss of ethene from the base peak by a retro Diels-Alder gives **36c**, which rearranges to the more stable tropylium ion **36d** with m/z 144 (25%). The second major fragmentation process involves the loss of a methyl radical via an intermediate rearrangement [138] form (**36e**) to give the ion at m/z 158 (**36f**).

The spectrum of the isolated 9,9'-bijulolidyl dimer (**36a**) formed in the same reaction (see **Scheme 36**) was consistent with the structure showing the molecular ion at m/z 344 (100%). The even mass supports the presence of two nitrogens in the structure. The molecule proved to be very stable as only a few weak fragment ions were observed. The peak at m/z 171.5 suggests a doubly charged species (see spectrum no. 16, appendix).



36 — $M^{+\cdot}$, m/z 173 (85%) — rearrangement → **36e** m/z 173

36b — m/z 172 (100%) — - $CH_3^{\bullet}$ (- 15) → **36f** m/z 158 (5%)

36c — m/z 144 (25%) — rearrangement → **36d** m/z 144

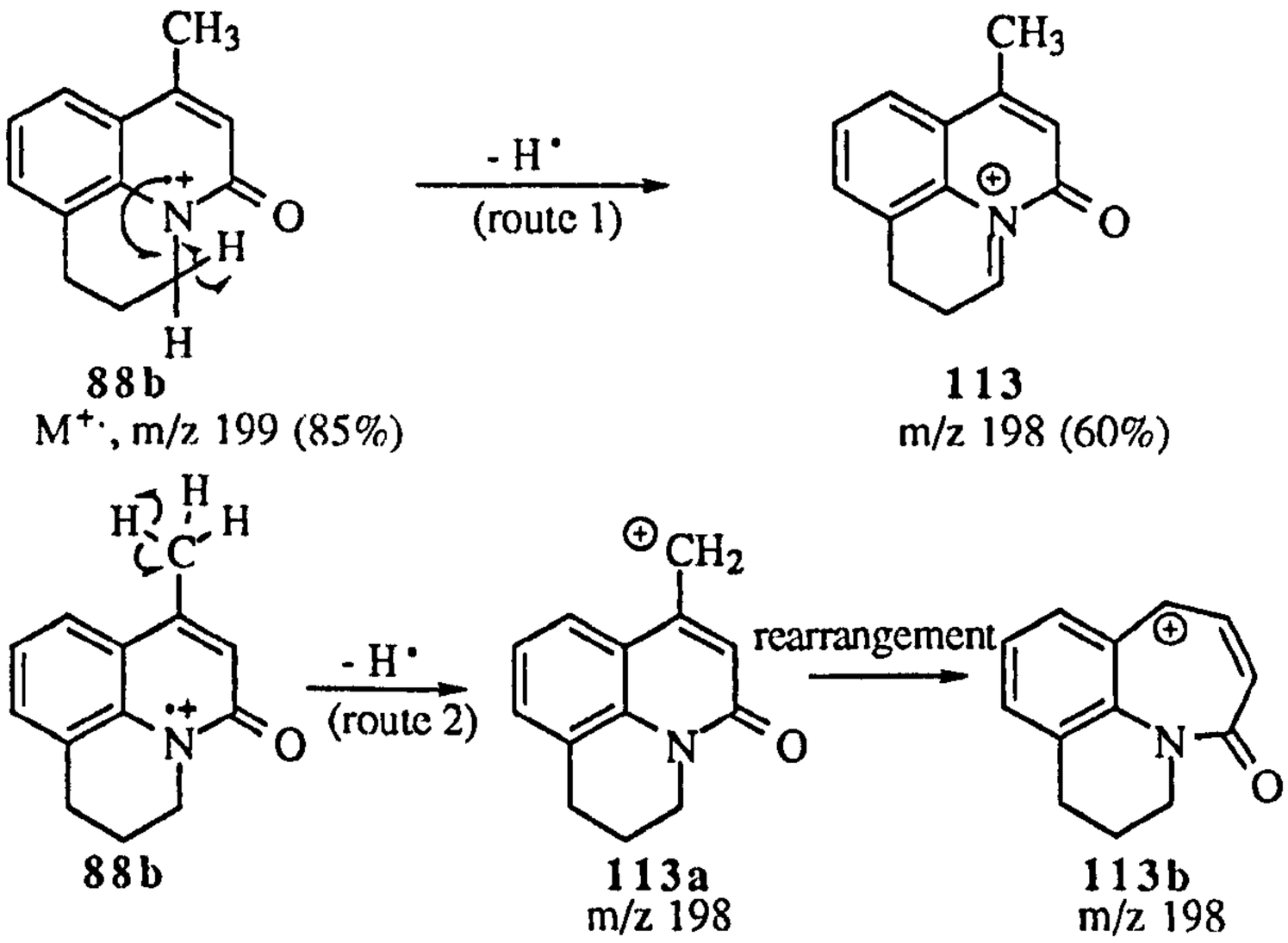
Scheme 49

The spectrum of 1-methyl-5,6-dihydro-3*H*,5*H*-benzo[ij]quinolizin-3-one (**88b**) showed interesting results since hydrogen abstraction is followed by a loss of the methyl radical. Two possible routes for the loss of a hydrogen radical are outlined in **Scheme 50**. Route 1 shows the loss of hydrogen from ring **C** in **88b** to produce a quaternary nitrogen heterocycle **113**. Route 2 shows the loss of a hydrogen radical from the methyl group at position 4 of the molecular ion **88b** to give **113a**. This (M-H) fragment rearranges to a more stable tropylium ion **113b** in which the carbon of

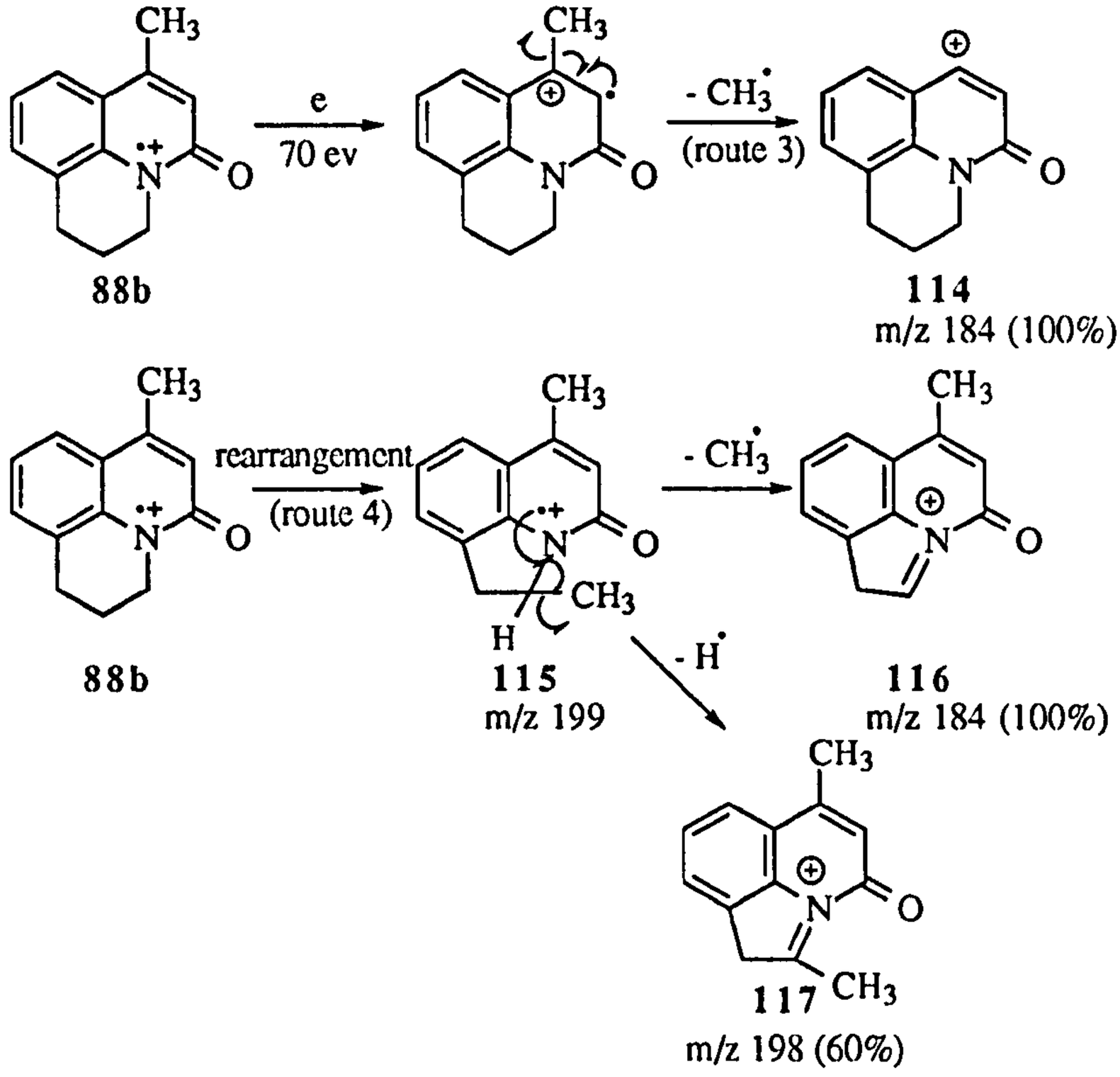
the original methyl group becomes equivalent to the ring carbon atoms. A similar type of fragmentation has also been suggested by Djerassi *et al* (138).

Loss of a methyl radical from **88b** could also proceed via two possible fragmentation pathways as shown in **Scheme 50a**. In route 3 one of the methyl substituents is lost as a fragment from the molecular ion **88b** to give the stable species **114** as the base peak at m/z 184. Alternatively, route 4 envisages the loss of a methyl radical to form **116** as the base peak at m/z 184. Furthermore, loss of a hydrogen radical from ion **115** is also possible, producing the quaternary nitrogen species **117**.

There is a certain amount of ambiguity in these fragmentation processes as there is a lack of evidence to support which pathway actually occurs. Isotopic labelling experiments with deuterium could be investigated. Thus, route 4 is arbitrarily assumed to be the most likely route for the loss of methyl radicals. Since no deuterated analogues were available (within the time constraints of the project) this point could not be substantiated. The loss of a molecule of HCN is also present but is a relatively minor process (ion at m/z 171 (4% intensity)). This is in contrast to quinolines which readily fragment by this route.



Scheme 50



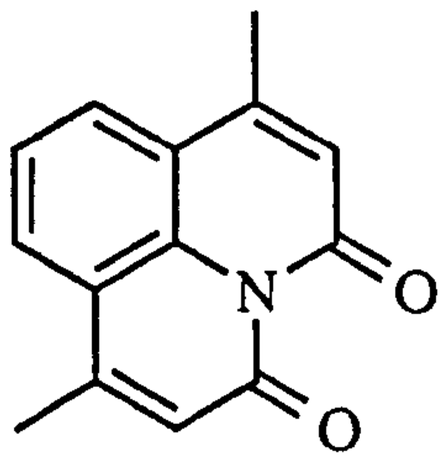
Scheme 50a

There is a similarity observed between the spectra of compounds **88a** and **88b** (see Table **14**). The methyl analogue **88b** shows major fragmentations involving loss of hydrogen and methyl radicals from the molecular ion but in the trifluoro analogue **88a** the methyl expulsion can only occur via the rearrangement process (as shown in route 4, **Scheme 50**). The loss of hydrogen radical proceeds as described in **Scheme 50** (routes 1 or 4). Compound **88a** shows a typical, but minor loss of a fluorine radical from the trifluoromethyl group to give a peak at m/z 234 (5%). A second possible loss of hydrogen radical is also observed from ion m/z 252 to give ion m/z 251 (8%) in a minor process (see spectrum no. 66, appendix). In **88a**, the loss of HCN was not observed. Similarly, analogue **88c** (Table **14**), which has a phenyl group attached to C-4, eliminated hydrogen and methyl radicals in the same fashion as compound **88a**.

In the 5-membered ring analogue **93**, methyl loss was not observed, and thus this suggests that the methyl loss occurs from the 6-membered ring in the quinolizine ring system via the rearrangement process. However, where a methyl substituent is present in the system, it is not clear whether the methyl loss occurs as the substituent from the position at C-1, or via the indonyl species (rearrangement). Other common losses from **93** include hydrogen and fluorine radicals to give ions m/z 238 (100%) and 220 (5%), respectively (see spectrum no. 72, appendix). The peak at m/z 190

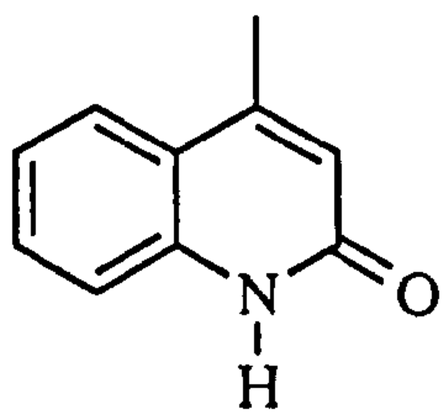
(15%) is highly unusual from this molecule since it suggests a loss of 49 mass units which cannot be identified easily.

The spectrum of compound **96** indicated it to be a mixture of the actual product and its mono adduct **96a** (see Figure **14**). The base peak at m/z 159 seemed to indicate the mono adduct due to its stability (see spectrum no. 72, appendix). A hydrogen radical fragmented from the molecular ion **96** in the same way as previously described. Methyl loss from **96** was not detected, but the mono-adduct **96a** showed a minor loss of a methyl radical from the 4-position to give the ion at m/z 144. Since the loss was weaker in intensity to other methyl losses, it seems to suggest that the methyl loss from the 4-position is not greatly favoured, and thus further supports the rearrangement mechanism postulated above.



96

$M^{+\cdot}$, m/z 225 (60%)



96a

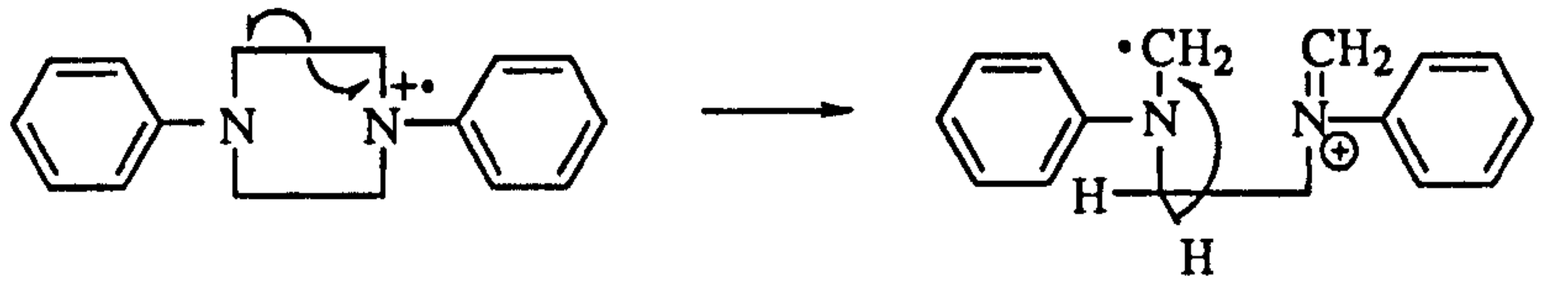
m/z 159 (100%)

Figure 14

The *N*,*N*^{1}-diphenylpiperazine dimer **109** (see **Scheme 46**) showed a loss of a methyl radical via hydrogen transfer through species **109a** and **109b** to give a quaternary nitrogen ion **118** as illustrated in **Scheme 51**. The fragment ion **119** is generated directly from the molecular ion **109** by the loss of a C_2H_4N radical via aryl arrangement [139]. The ring cleavage of the molecular ion **109** (path 2) and the subsequent rearrangement with the transfer of the *N*-bonded aryl group afforded the ion 119. Species **120** (path 3) was produced by the loss of $C_6H_5NCH_3$ radical from the molecular ion **109**. The base peak is at m/z 105, species **121** (path 4), and is due to $C_6H_5NCH_2^{+\cdot}$. This ion results from the retro-Diels-Alder decomposition of the molecular ion **109**, which in turn probably rearranges to a more stable tropylium ion as shown. Species **119** may lose $C_6H_5NCH_2$ as a neutral fragment to give ion **122** at m/z 91 (path 5), which may rearrange to a stabilised tropylium species.

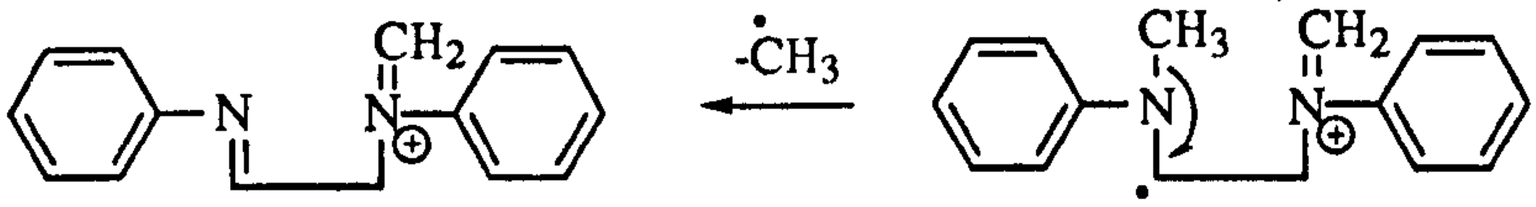
This fragmentation behaviour of *N*',*N*'-diphenylpiperazine (**109**) resembles that of piperazine and its derivatives [140], but the M-1 ions were not observed, as expected in the *N*',*N*'-diarylpiperazines [139-140].

Path 1



109
$M^{+\cdot}$, m/z 238 (70%)

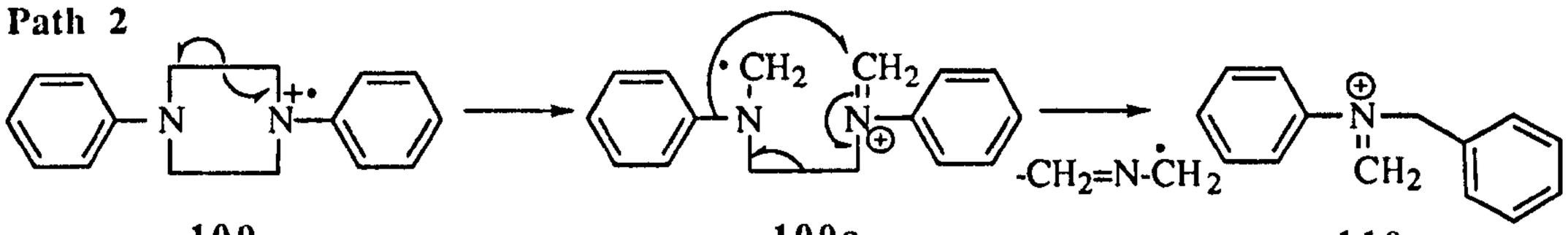
109a
m/z 238



118
m/z 223 (5%)

109b
m/z238

Path 2

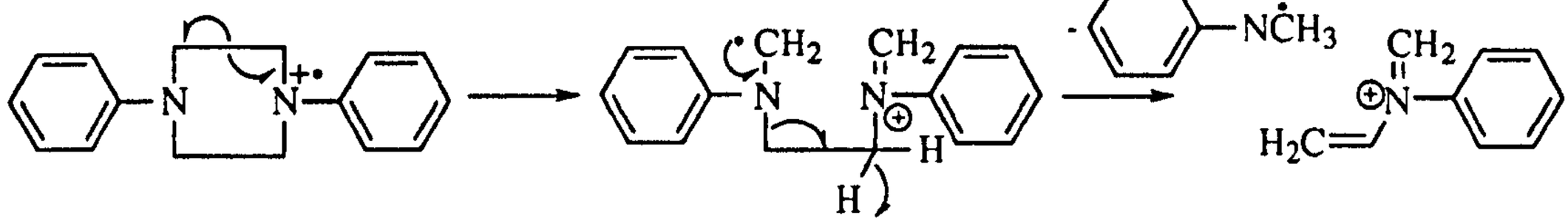


109
$M^{+\cdot}$, m/z 238 (70%)

109a
m/z 238

119
m/z 196 (5%)

Path 3

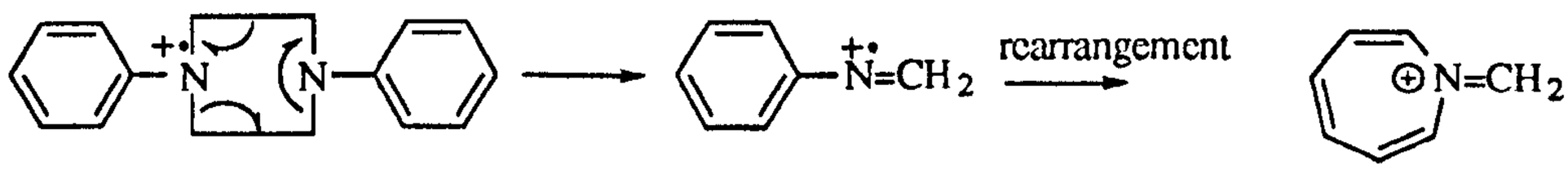


109
$M^{+\cdot}$, m/z 238 (70%)

109a
m/z 238

120
m/z 132 (45%)

Path 4

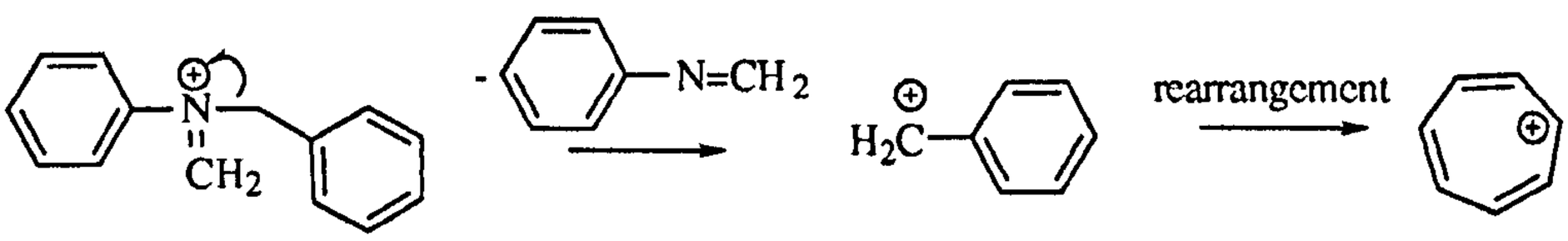


109
$M^{+\cdot}$, m/z 238 (70%)

121
m/z 105 (100%)

121
m/z105 (100%)

Path 5



119
m/z. 196 (5%)

122
m/z. 91 (19%)

122
m/z. 91 (19%)

Scheme 51

4.40 IR spectral analysis of quinolizine and some of its derivatives

The most characteristic infrared absorption bands of the quinolizines are the carbonyl (C=O) and amide (C=O) stretching frequencies and these are summarised in Table **15**.

No	Cyclic (C=O) stretch (cm^{-1})	Amide (C=O) stretch (cm^{-1})
88a	1661	-
88b	1645	-
88c	1658	-
93	1625	-
96	1633	-
106	~1660	1650
107	1653	1610

Table 15

Since the carbonyl stretching frequency is sensitive to the nature of the attached groups, the range of values given in Table **15** may be explained by a consideration of inductive and mesomeric effects, which operate in opposite ways to influence the carbonyl stretching frequency. An electronegative element attracts the electrons between the carbon and oxygen atoms through its electron-withdrawing effects, so that the C=O bond becomes stronger. A higher frequency (higher energy) absorption then results. Also, the unpaired electrons on a heteroatom can conjugate with the carbonyl group, resulting in increased single bond character and a lowering of the C=O absorption frequency [141]. Thus, from the results summarised in Table **15**, it is observed that the C=O stretching frequencies are lower than expected for ketones (around 1715 cm^{-1}). Conjugation effects in a molecule results in delocalisation of the π-electrons in the C=O bonds. This conjugation increases the single bond character of the C=O bond and, hence, lowers its force constant, resulting in a lowering of the frequency of carbonyl absorption. Thus, for instance the presence of an electron-donating group such as CH_3 in compound **88b** resulted in a lowering of the C=O stretching frequency to 1645 cm^{-1}, and as expected [142], the introduction of an additional electron-donating group in compound **96** resulted in further lowering of the frequency to 1633 cm^{-1}; (CH_3 is only very weakly +M, by hyperconjugation). Conversely, introducing an electron-withdrawing group such as CF_3 in compound **88a** resulted in a shift to higher carbonyl frequency (1661 cm^{-1}).

The amide carbonyl absorption band was similar in intensity to that of the ketones but was subject to much greater variations, (compounds **106** and **107** in Table **15**). In these compounds the resonance effect [143] (structure **112**, **Scheme 48**) is dominant since nitrogen is less electronegative than oxygen and more readily back-donates its unshared electrons, resulting in an absorption frequency lower than that of the ketone group (**107**, Table **15**). There was no significant difference in stretching frequencies between the cyclic ketone carbonyl group and the amide carbonyl group in **106**, as there was an overlap between 1660 and 1630 cm^{-1}. Usually primary amides display an overlap of their amide I carbonyl and amide II (primary or secondary amino bending) bands [144] in the region of 1650-1515 cm^{-1}. The nature of the R group had little effect upon the amide II band in this study. A broad, weak band in the 700-600 cm^{-1} region in the spectrum of compound **107** was observed from the out-of-plane N-H wagging. The same was not clearly observed in the analogue **106**. Two N-H stretching bands were observed in the primary amide compounds **106** and **107** from symmetrical and asymmetrical N-H stretching in the 3400-3300 cm^{-1} region. The primary amide N-H stretch in **107** was appreciably higher (3441 cm^{-1}) compared to **106** (3354 cm^{-1}) due to greater ring strain in the former, a 5-membered ring analogue [142]. This phenomenon can prove useful in distinguishing between four, five, and larger membered ring amides, although does not offer conclusive proof. The C-N stretching bands in compounds **106** and **107** were also observed in the 1400-1300 cm^{-1} region [145].

Compounds **88a-c**, **93** and **96** showed aromatic C-H stretches of medium intensities at around 3400 cm^{-1}. This is higher than expected and is probably due to the complexity (the availability of the nitrogen lone pair orthogonal to the benzene ring) of these type of molecules.

In summary, the NMR study of these compounds revealed a unique, deshielded vinylic proton in the range 6.50-8.50 ppm which was sensitive to the electronic influences of the functional groups attached. The mass spectrometry results indicated the loss of a methyl radical via rearrangement to an indonyl species. Where a methyl group was present in the molecule, there was a cetain amount of ambiguity as to which pathway was occurring. In the FT-IR analyses, differences between the carbonyl stretching frequencies of the cyclic ketone and the amide groups were explicable in terms of the electronic effects of the attached groups.

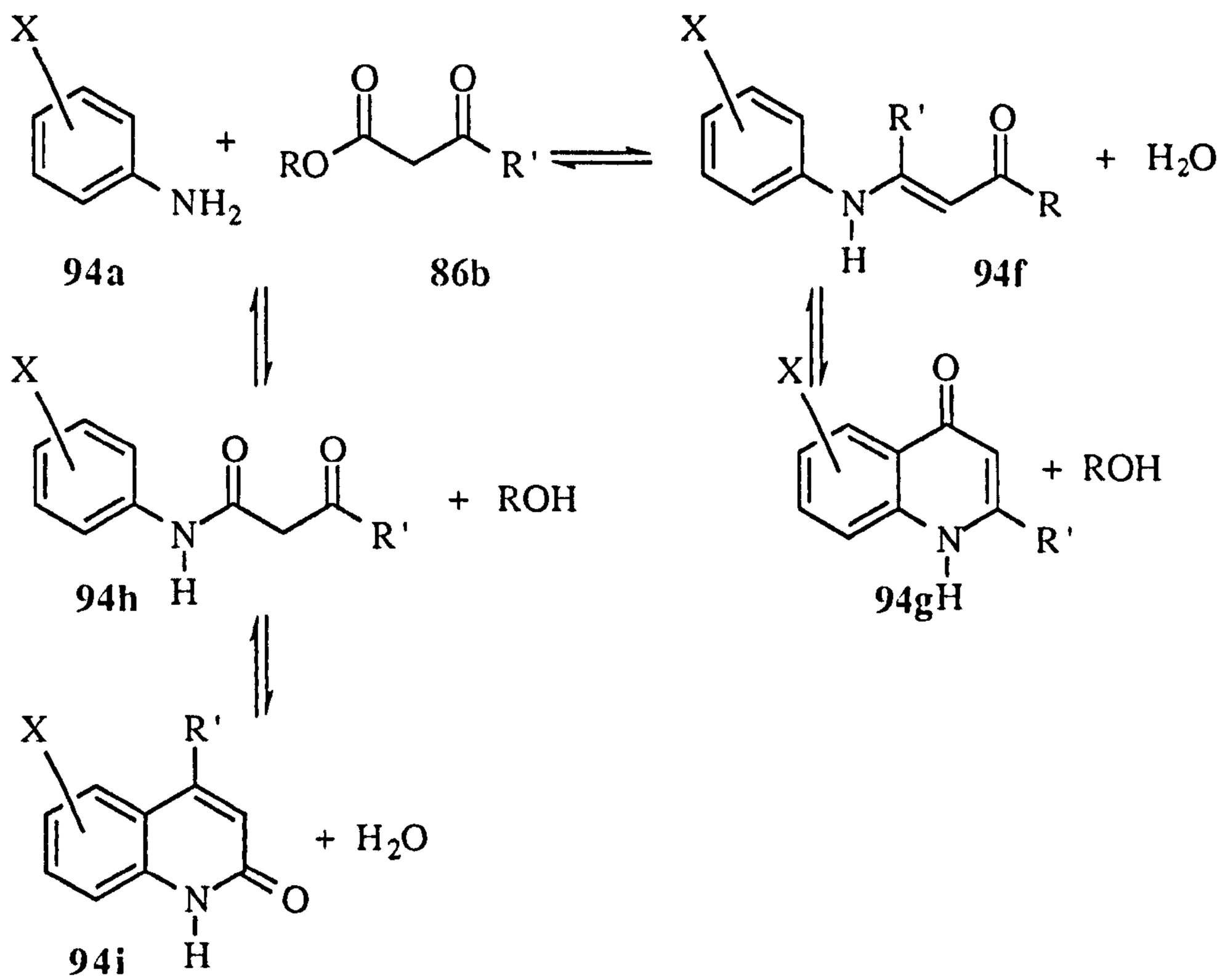
5.0 Quinolinones

Alkaloids containing the quinoline ring structure play a very important role in medicine [146]. Although extensive research has been carried out in this area, there is still plenty of scope for the synthesis of new, interesting and promising broad-spectrum drugs.

Since many quinoline compounds are potent antiparasitic agents [147-149] this suggested the synthesis of a range of novel substituted quinolinones for screening for biological activity, particularly against malaria and leishmania.

To synthesise quinolinone derivatives, the Conrad-Limpach-Knorr [150] synthesis was chosen, as a range of substituted quinolinones could be readily obtained by varying the substituents in the β-ketoesters, and in the aromatic amines. Also, these substituted quinolinones could be used as precursors for further cyclisations to yield the corresponding, substituted julolidines.

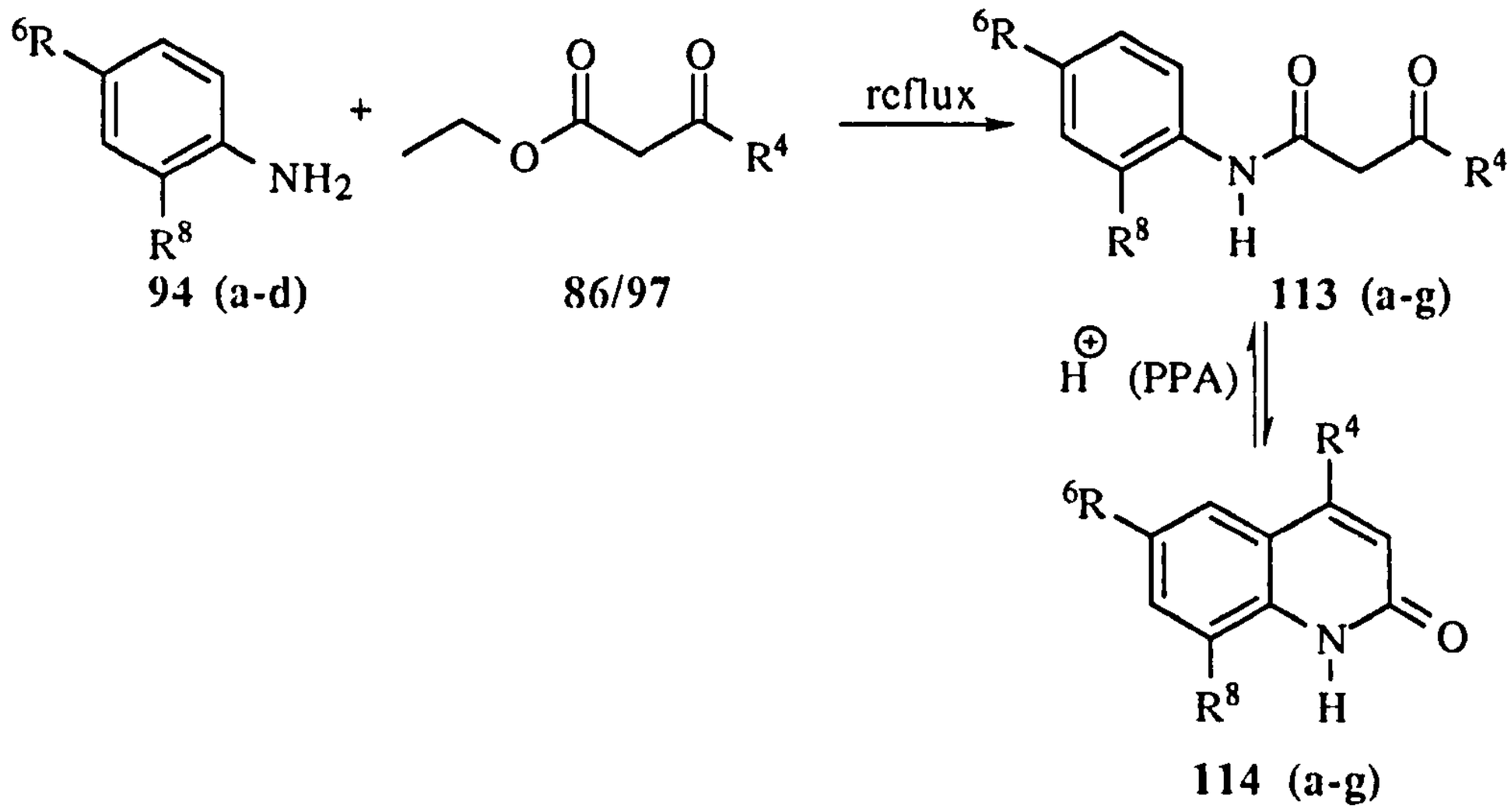
The Conrad-Limpach-Knorr synthesis involves a reaction between an aromatic amine (an aniline **94**) and a β-ketoester **86b**, potentially giving a mixture of two regioisomeric products (**94g** and **94i**), as outlined in **Scheme 52**.



Scheme 52

Thus when Hauser *et al* [137] heated ethyl acetoacetate (**86b**, R = C_2H_5; R' = CH_3) with aniline (**94a**, X = H), 2-methyl-4-quinolone (**94g**, R' = CH_3; X = H) and 4-methyl-2-quinolone (**94i**, R' = CH_3; X = H) were obtained as outlined in **Scheme**

52. To obtain the crotonates (**94f**, R = C_2H_5; R' = CH_3), the two reagents are heated with an acid catalyst, the reaction then proceeding at the temperature of boiling methylene chloride or benzene [83]. At higher temperatures, without an acid catalyst, anilides (**94h**, R' = CH_3) are formed. Hauser and his team [151] thought that the reaction was thermodynamically controlled and that the products were readily interconvertable, to give the regioisomers **94g** and **94i**. However, when Afsah [63] synthesised functionalised julolidines, the products obtained were regiospecific. In the current synthetic work, Afsah's [63] method was followed to give regiospecific substituted quinolinones in yields of 12 to 86%. The reaction scheme is outlined in **Scheme 53** where aromatic amines (and substituted aromatic amines) were heated under reflux with various substituted β-ketoesters to initially form the intermediate amides through nucleophilic addition-elimination processes. These amides (without isolation) were subjected to acid-catalysed cyclisation using polyphosphoric acid (PPA) in a Friedel-Crafts intramolecular cyclisation to give the desired substituted quinolinones. The substituents are summarised in Table **16**.



Scheme 53

94	R^6	R^8	86/97	R^4	113	R^4	R^6	R^8	114	R^4	R^6	R^8
94a	H	H	86a	CF_3	113a	CF_3	H	H	114a	CF_3	H	H
94a	H	H	86c	Ph	113b	Ph	H	H	114b	Ph	H	H
94b	Cl	H	86b	CH_3	113c	CH_3	Cl	H	114c	CH_3	Cl	H
94b	Cl	H	97	OC_2H_5	113d	OC_2H_5	Cl	H	114d	OH	Cl	H
94c	Cl	Cl	86b	CH_3	113e	CH_3	Cl	Cl	114e	CH_3	Cl	Cl
94c	Cl	Cl	97	OC_2H_5	113f	OC_2H_5	Cl	Cl	114f	OH	Cl	Cl
94d	CH_3	H	97	OC_2H_5	113g	OC_2H_5	CH_3	H	114g	OH	CH_3	H

Table 16

Results for these reactions are summarised in Table **17**.

Aniline (**94**)	Ketoester (**86/97**)	Intermediate amides (**113**)	quinolinones (**114**)	% Yield	mp (°C)
94a	**86a**	*N*-(phenyl)-3-oxo-4-trifluoromethyl-propanamide (**a**)	4-Trifluoromethyl-1,2-dihydroquino-lin-2-one (**a**)	67	221-225[152]
94a	**86c**	*N*-(phenyl)-3-oxo-4-phenylpropana-mide (**b**)	4-Phenyl-1,2-di-hydroquinolin-2-one (**b**)	86 [153]	258-260 (lit.260-261) [154]
94b	**86b**	*N*-(4-chlorophenyl)-3-oxo-propanamide (**c**)	6-Chloro-4-methyl-1, 2-dihydroquino-lin-2-one (**c**)	59	269-271[155]
94b	**97**	*N*-(4-chlorophenyl) -3-oxo-4-ethoxy-propananamide (**d**)	6-Chloro-4-hydroxy -1,2-dihydroquino -lin-2-one (**d**)	27*	320-326[156]
94c	**86b**	*N*-(2, 4-dichloro-aniline)-3-oxopro-panamide (**e**)	6, 8-Dichloro-4-methyl-1,2-dihydro -quinolin-2-one (**e**)	41	270-274[157]
94c	**97**	*N*-(4-dichloroani-line-3-oxo-4-etho-xypropanamide (**f**)	6,8-Dichloro-4-hydroxy-2-dihydro quinolin-2-one (**f**)	36*	300-304
94d	**97**	*N*-(4-methylaniline) -3-oxo-4-ethoxy-propanamide (**g**)	4-Hydroxy-6-meth-yl-1, 2-dihydroqui-nolin-2-one (**g**)	22*	318-320[158]

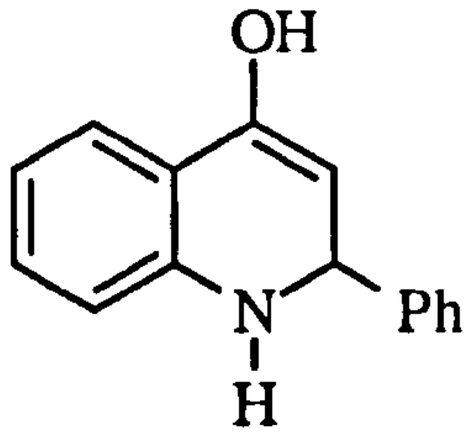
* mixture of tautomers

Table 17

Compounds **114d**, **114f** and **114g** are tautomers in the ratio 5:1, 10:1 and 4:1 for enol : keto forms, respectively (by NMR, and TMS as the internal standard). There is no apparent relationship evident between the percentage yields of substituted quinolinones obtained and any steric or electronic effects of the substituents. However, in terms of their melting points, compounds **114d**, **114f** and **114g** have higher melting points then the rest of the compounds probably due to the presence of hydroxyl groups which participate in inter-molecular hydrogen bonding.

4-Phenyl-1,2-dihydroquinolin-2-one **114b** (Table **17**) was first synthesised in 1899 by Camps [159] using acetyl-*o*-amidobenzophenone. Other workers [153, 160] have also prepared **114b** in 35-43% yields. Knorr [161] reported that, like the

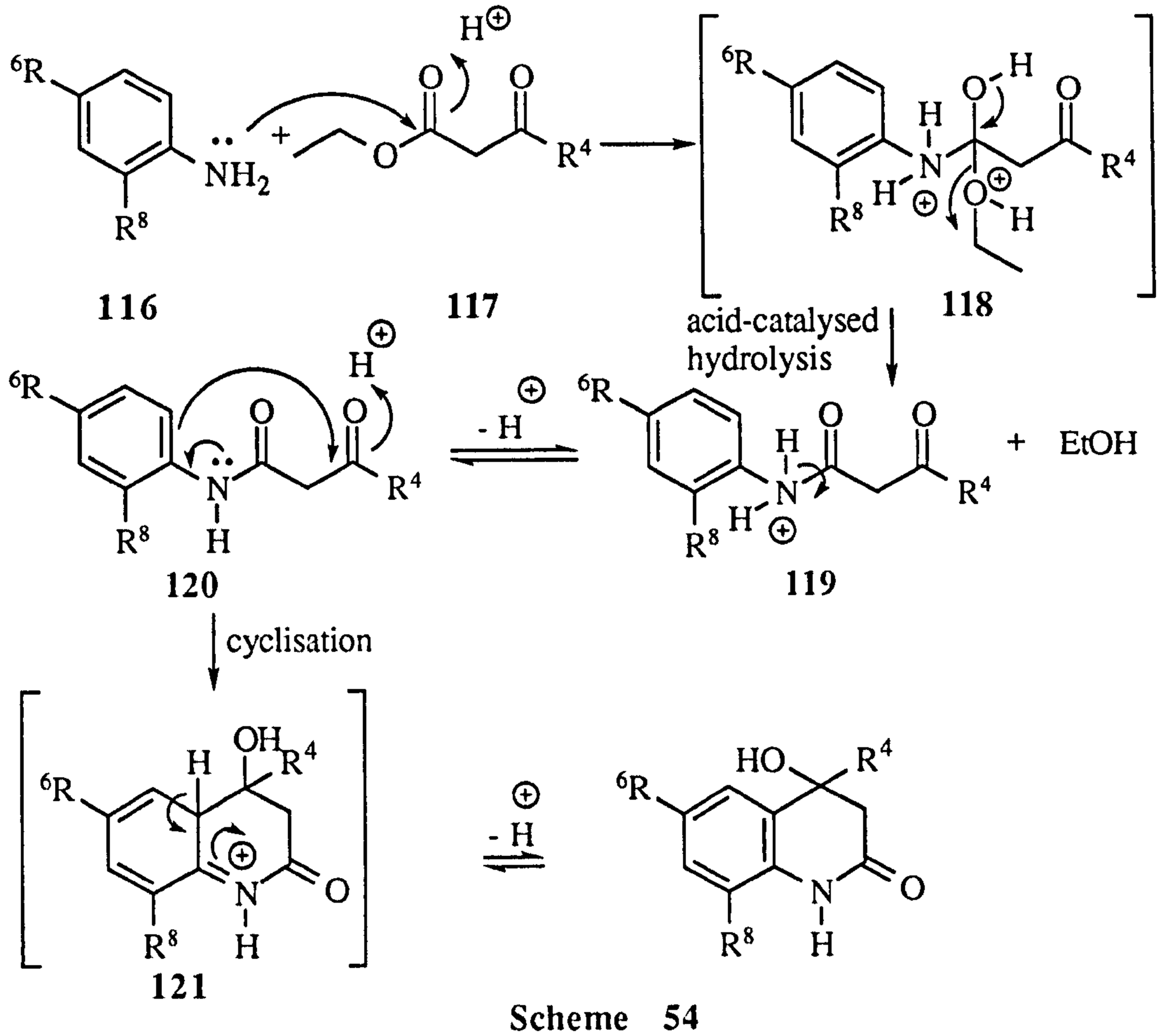
crotonate, the anilide from aniline and ethyl benzoylacetate produced 2-phenyl-4-hydroxyquinoline **115** on cyclisation, which is the enol form of the corresponding quinolinone.



115

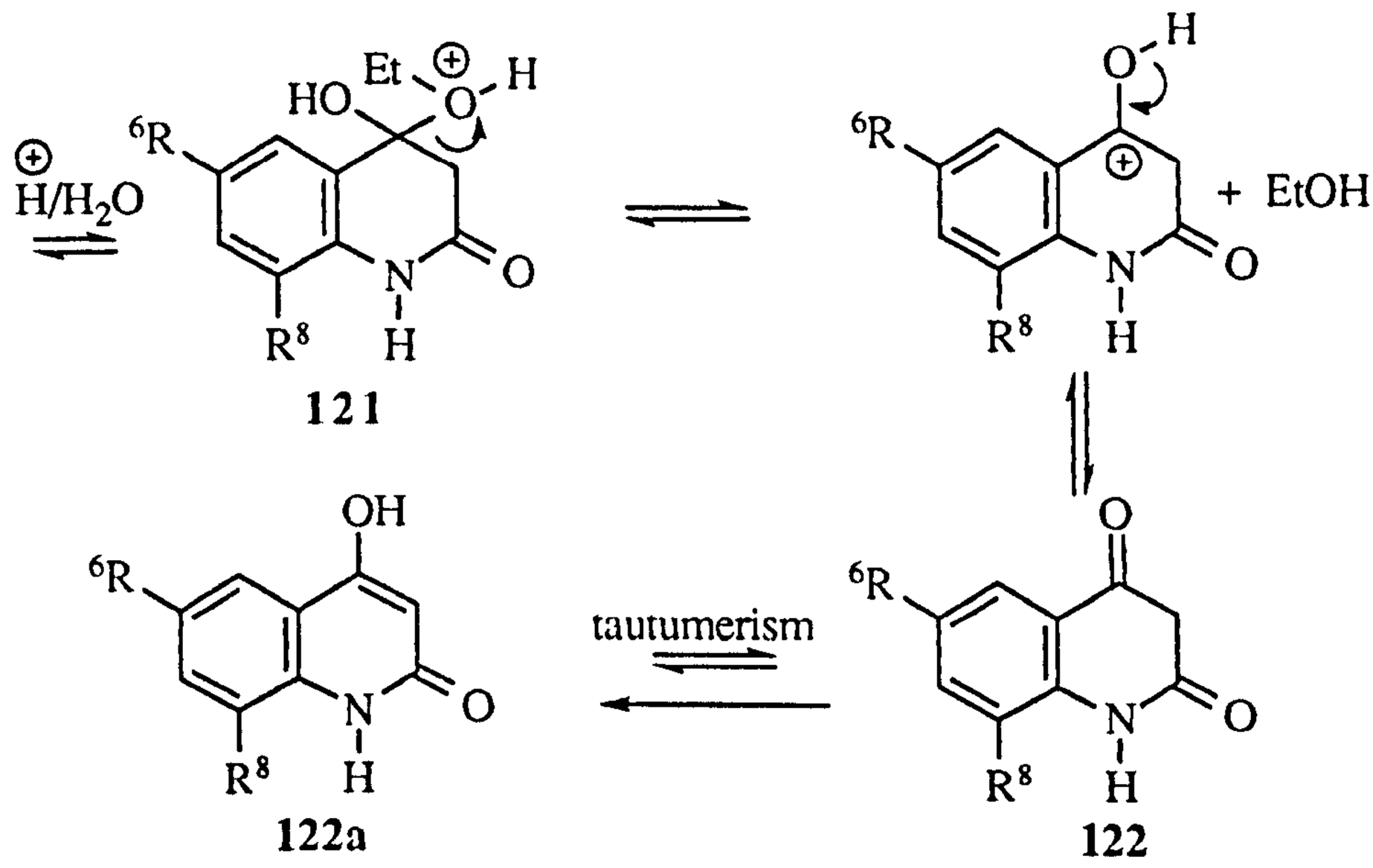
However, in the present synthesis, it was found that heating aniline **94a** and ethyl benzoylacetate **86c** at 150-160º C, followed by cyclisation produced **114b**, presumably via the anilide **113b**, (which was not isolated, see Table **17**). This result is in agreement with that of Hauser *et al* (151). The present method of preparing 4-phenyl-2-quinolinone **114b**, or its enol form, 4-phenyl-2-hydroxyquinolone, and indeed other substituted quinolinone derivatives in this series appears much more convenient than that carried out previously by Camps (159) using acetyl-*o*-amidobenzophenones.

A generalised mechanistic pathway in the syntheses of these quinolones is outlined in **Scheme 54** and is similar to the one proposed previously for julolidines (see **Scheme 42**). It involves a nucleophilic addition-elimination process whereby the lone pair of the anilino nitrogen in **116** attacks the carbon atom of the carbonyl group in the β-ketoester (**117**) to give the intermediate **118**. Since the reaction occurs in polyphosphoric acid, i.e. strongly acidic conditions, then this nucleophilic attack is acid-catalysed. Oxy-anion species are not expected to exist to any great extent in polyphosphoric acid and therefore under these conditions, would be present as hydroxyl groups. Thus **118** probably exists as the hemi acetal. Under acidic conditions, **118** undergoes a standard acid-catalysed hydrolysis of a hemiacetal back to the ketone **119** (162). Loss of a proton from **119** gives **120**. Intramolecular electrophilic aromatic substitution (S_E Ar) (Friedel-Crafts cyclisation) produces the intermediate **121**. This mechanism applies to both types of reaction as shown in **Scheme 54.**



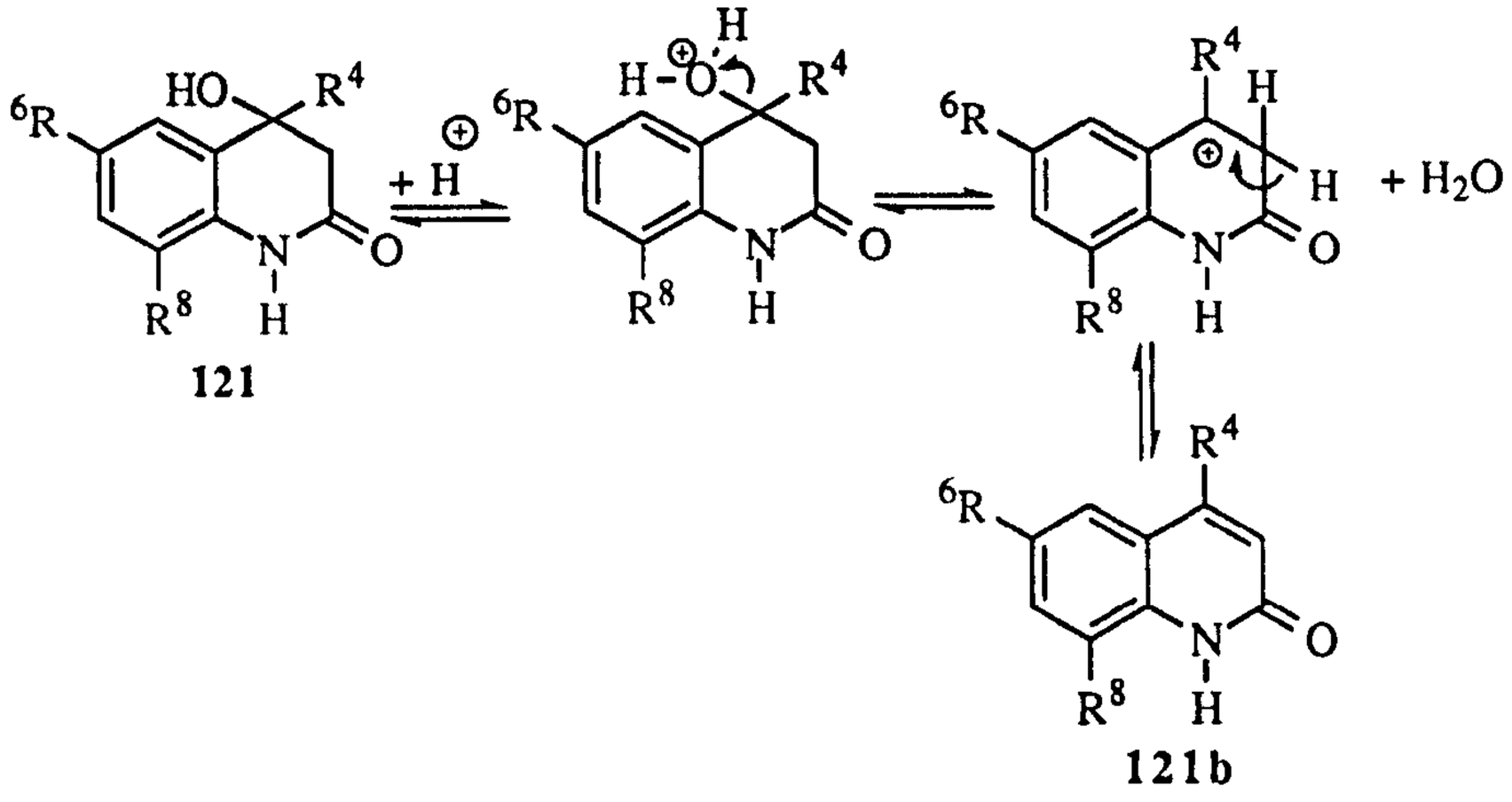
Scheme 54

At this stage two different reactions occur, depending on the nature of R^4. Firstly, when R^4 = OEt, a hemiacetal is formed, (**121**), which is hydrolysed to give the ketone **122**, which then tautomerises to the enol (**122a**), as shown in **Scheme 55**. The enol form is the major tautomer favoured.



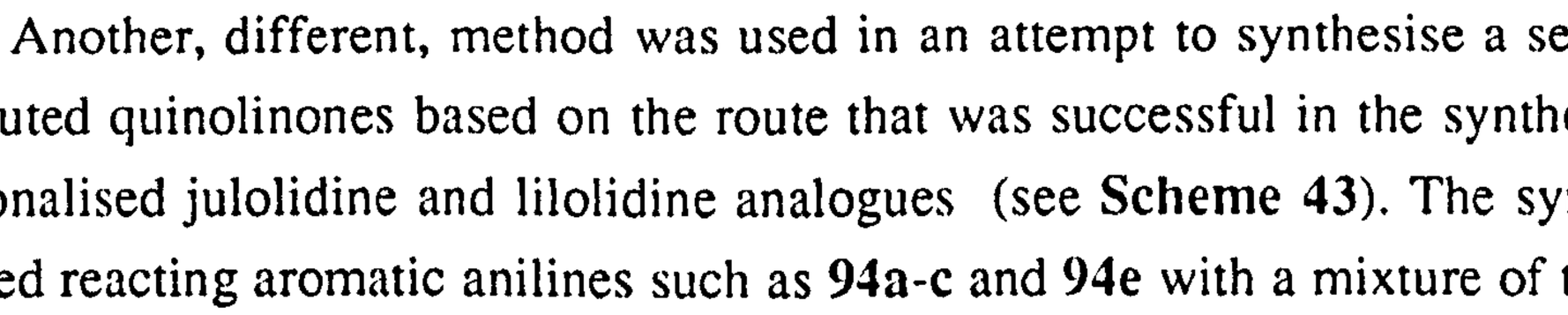
Scheme 55

Secondly, when $R^4 = CF_3$, Ph or CH_3, **121** is then simply a benzylic secondary alcohol dehydrating in polyphosphoric acid to give the corresponding substituted quinolinone **121b**, as outlined in **Scheme 56**. In this instance, other groups (i.e. CF_3, Ph, CH_3) cannot be protonated, therefore, only water can be eliminated thus retaining aromaticity in the molecule. The formation of **121b** is driven by the aromaticity of 2-pyridinone systems (the same driving force which favours the formation of enol **122a**, (see **Scheme 55**)).



Scheme 56

Another, different, method was used in an attempt to synthesise a series of substituted quinolinones based on the route that was successful in the syntheses of functionalised julolidine and lilolidine analogues (see **Scheme 43**). The synthesis involved reacting aromatic anilines such as **94a-c** and **94e** with a mixture of triethyl orthoformate (**104**) and ethyl cyanoacetate (**105**), followed by cyclisation using polyphosphoric acid *in situ*, in an attempt to produce the corresponding quinolinones **123a-d**, as outlined in **Scheme 57**. This method is potentially versatile and introduces a nitrile function on the 3-position which could be partially hydrolysed to the amide function, or fully hydrolysed to the corresponding acid function.



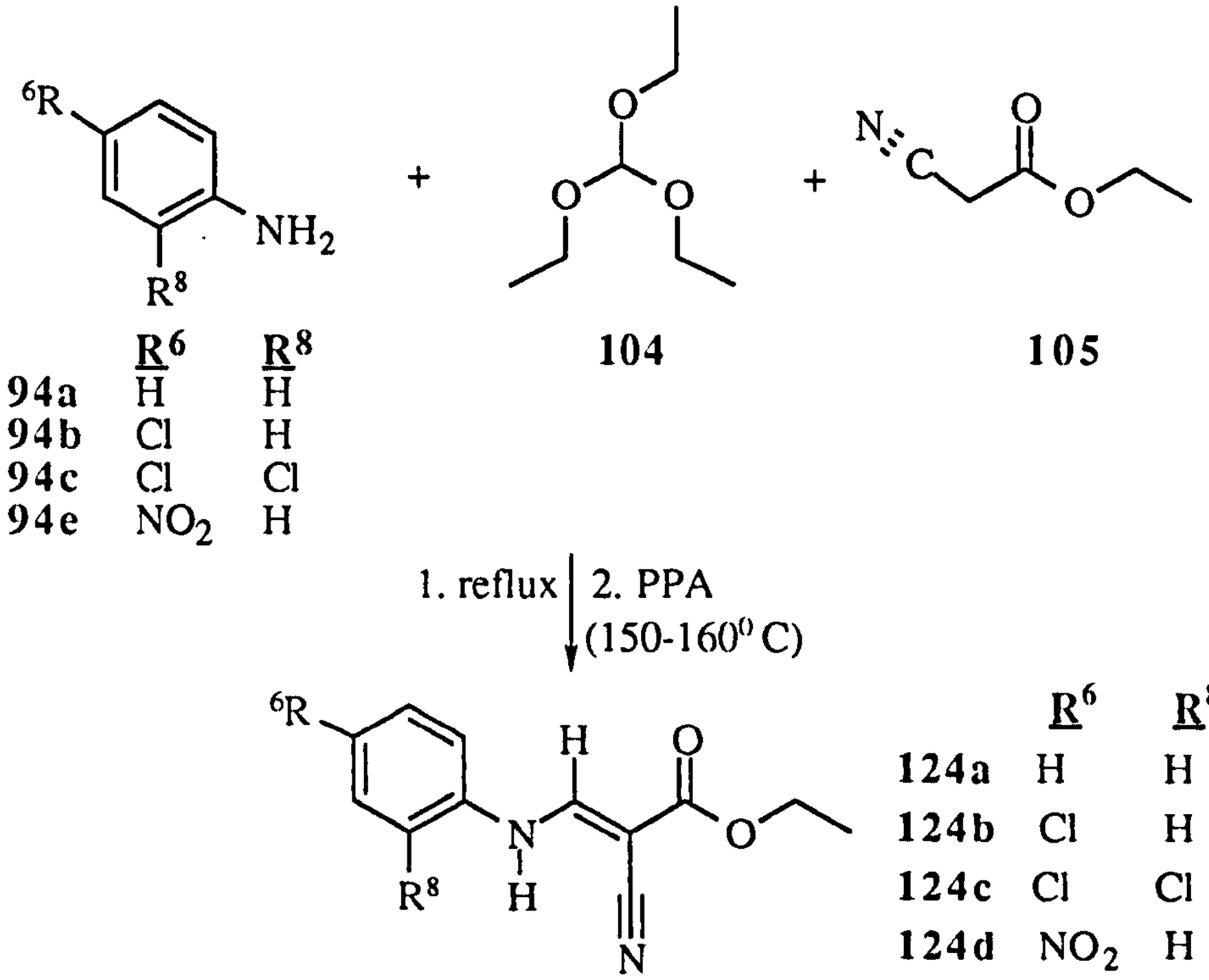
	R^6	R^8
94a	H	H
94b	Cl	H
94c	Cl	Cl
94e	NO_2	H

104 **105**

	R^6	R^8
123a	H	H
123b	Cl	H
123c	Cl	Cl
123d	NO_2	H

Scheme 57

These reactions, however, proved to be unsuccessful. Instead, when the products were isolated and analysed, they were found to be the corresponding nitrile esters **124a-d**, as outlined in **Scheme 58**. Interestingly, the nitrile group in position-3 was not hydrolysed (as expected) under the acidic conditions, probably due to these nitriles being α, β unsaturated. The results obtained are summarised in Table **18**. These esters are novel compounds. Product **124d** was found to be a mixture of the expected product (**124d**), and the starting material, **94e**.



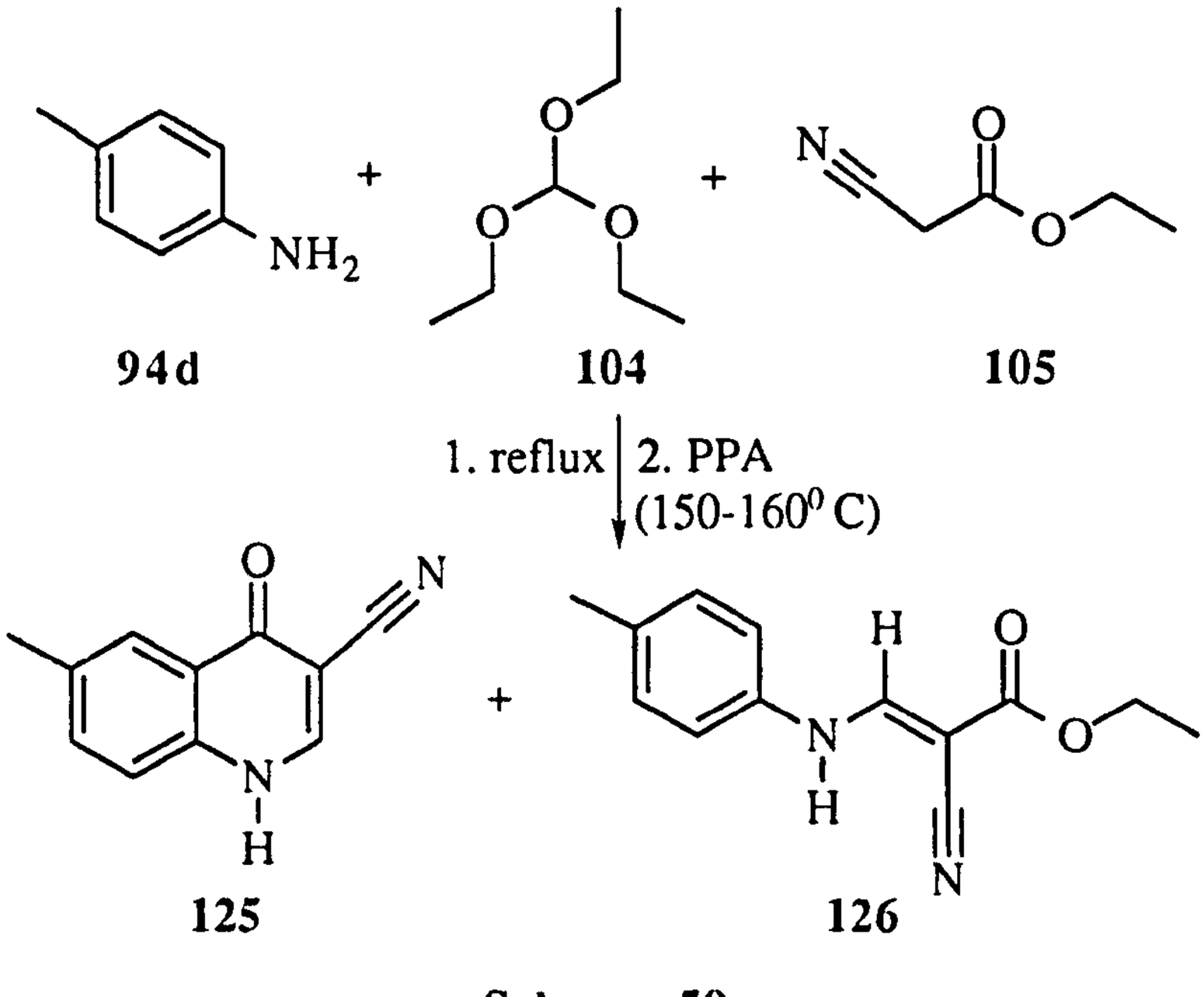
Scheme 58

Aniline (**94**)	R^6	R^8	Ester (**124**)	% yield	mp (°C)
a	H	H	Ethyl(*E*)-2-cyano-3-(*N*-phenyl-amino)-prop-2-enoate (**a**)	91	105-108 (163)
b	Cl	H	Ethyl (*E*)-2-cyano-3-(*N*-4-chloro-phenylamino)prop-2-enoate (**b**)	41	134-136
c	Cl	Cl	Ethyl (*E*)-2-cyano-3-(*N*-2,4-dichloro-phenylamino)prop-2-enoate (**c**)	53	166-168
e	NO_2	H	Ethyl (*E*)-2-cyano-3-(*N*-4-nitro-phenylamino)prop-2-enoate (**d**)	92*	220-222

* a mixture.

Table 18

On the other hand, when *p*-toluidine (**94d**) was reacted with triethyl orthoformate (**104**) and ethyl cyanoacetate (**105**) as previously described, a mixture of products was formed, namely, 3-cyano-6-methyl-1,4-dihydroquinolin-4-one (**125**) and ethyl (*E*)-2-cyano-3-(*N*-4-methylphenylamino)prop-2-enoate (**126**) in the ratio 4:1 respectively, as shown in **Scheme 59**. This mixture of products was confirmed by spectral analysis. By integration of their ^{1}H NMR spectrum, the yields were 58% and 42% for **125** and **126**, respectively.



94d **104** **105**

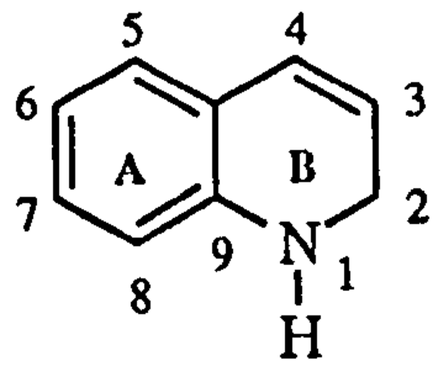
125 **126**

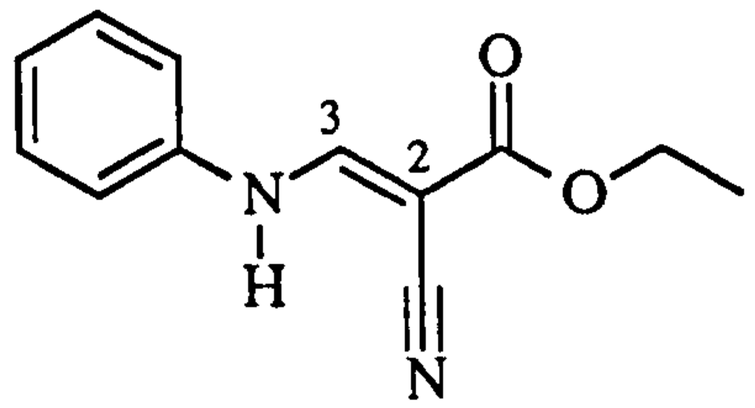
Scheme 59

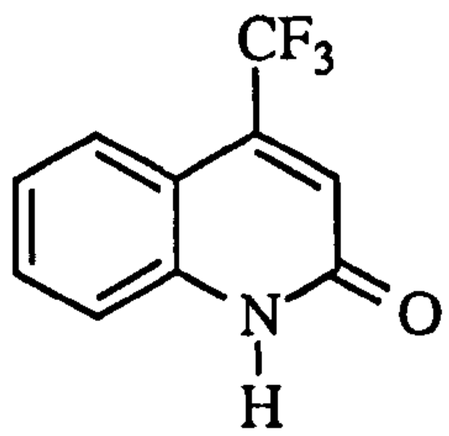
All the products summarised in Tables **17** and **18** were analysed spectroscopically and their spectra were found to be consistent with the structures proposed. These compounds show interesting features in terms of their proton and carbon-13 NMR spectra, and their mass spectra, and are discussed in the following sections.

5.10 Interpretation of the NMR spectra of the quinolinones and the nitrile esters

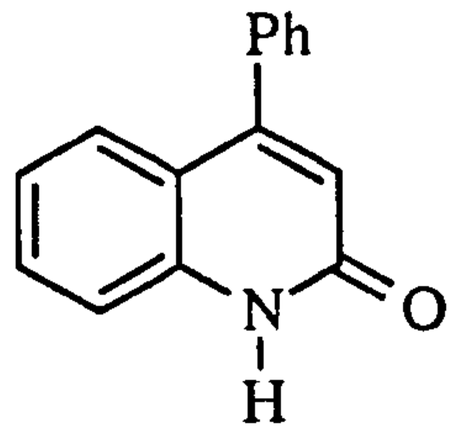
Although the nomenclature of these compounds is covered in the Introduction, for reference purposes, Chart **2** summarises the numbering of the atoms and the proposed structures of the compounds, and is referred to in the following discussions.



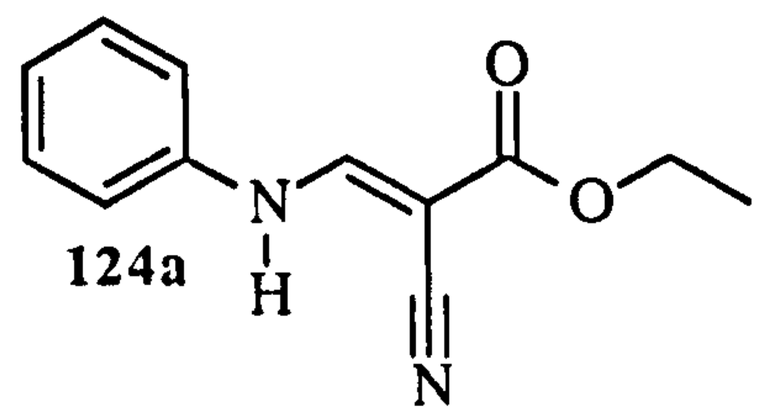




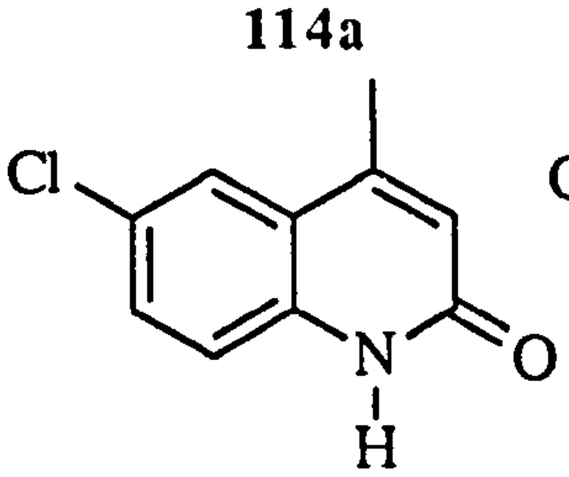
114a



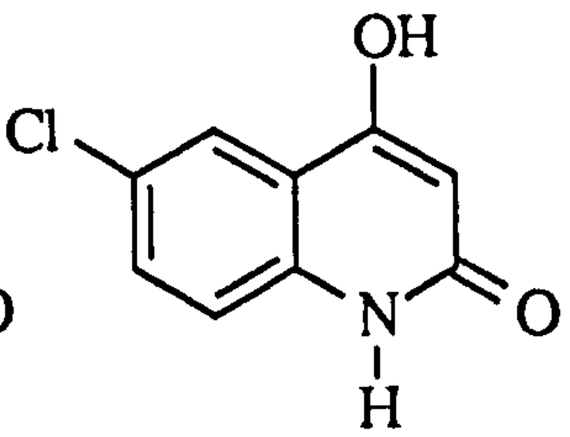
114b



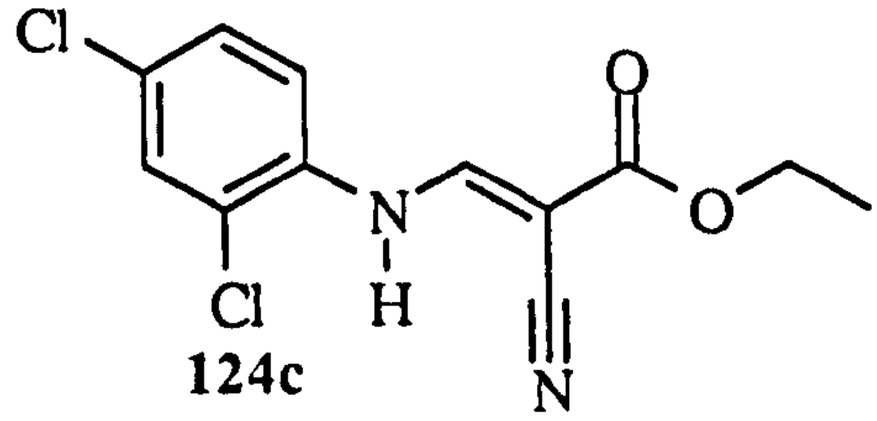
124a



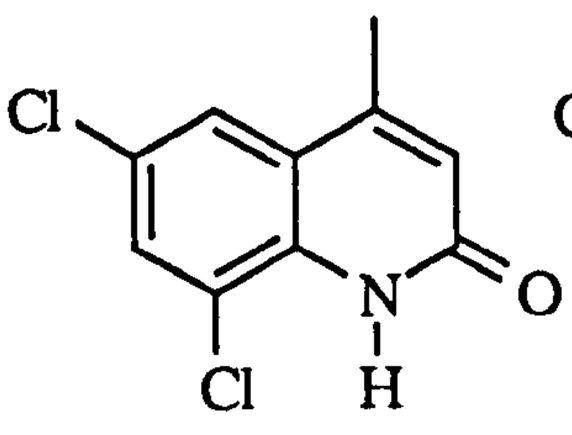
114c



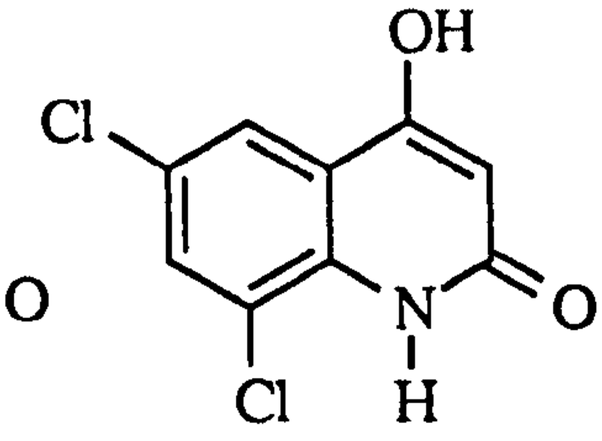
114d



124b

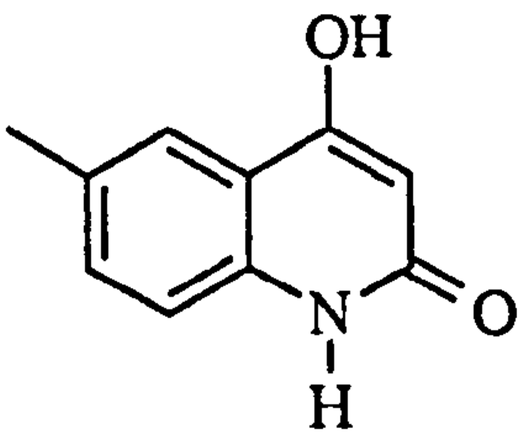


114e

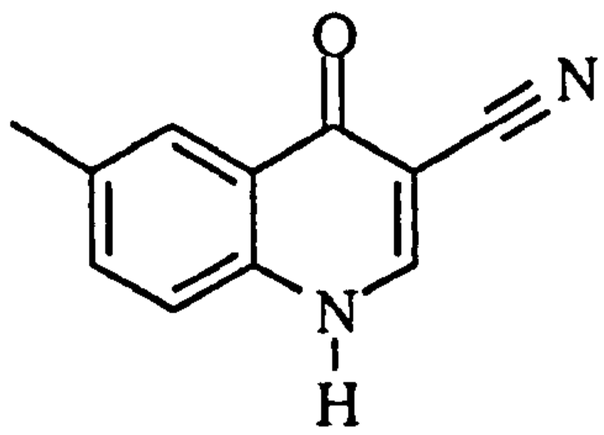


114f

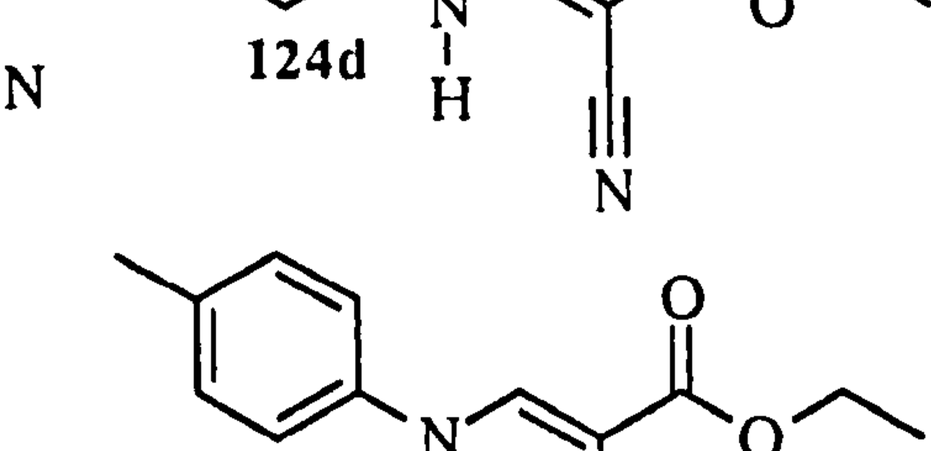
124c



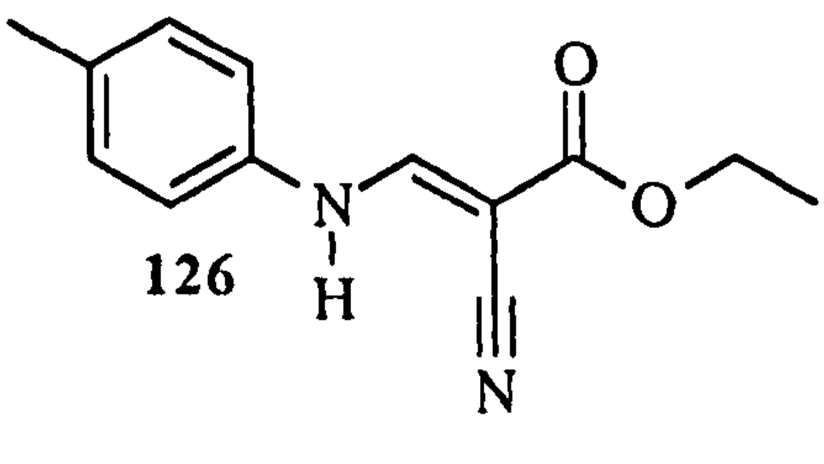
114g



125



124d



126

Chart 2

The proton shifts (in ppm) from the ^1H NMR spectra of the quinolinones are summarised in Table **19.**

114	N-H	2-H	3-H	4-H	5-H	6-H	7-H	8-H
a	7.07	-	6.99	-	7.98-8.01	7.64-7.68	7.85-7.88	8.20-8.23
b	7.96	-	6.45	-	7.82-7.85	7.69-7.77	7.38-7.44	8.14-8.18
c	5.47	-	6.20	-	7.97-7.98	-	7.72-7.73	7.68-7.69
d	*	-	5.82	11.42 (OH)	7.73-7.74	-	7.52-7.57	7.28-7.31
f	10.66	-	5.91	11.89 (OH)	7.82-7.83	-	7.75-7.76	-
g	*	-	5.85	11.22 (OH)	7.72	-	7.31-7.35	7.18-7.21

* hidden under the aromatic proton signals

Table 19

The unique, deshielded proton signal at position-3 in these quinolinones was influenced by changes in the electronic and perhaps, the anisotropic effects [133, 164] of the substituent groups. Electron-withdrawing groups like trifluoromethyl on the aromatic ring withdraw electrons from the nucleus causing an area of low electron density. Consequently, a relatively low magnetic field is needed to cause deshielding effects in the NMR. For an electron-donating group like the methyl, the opposite effect is present [165]. On the other hand, for chlorine the +M effect is almost the same as the -I effect thus counter-balancing the electron-donating and withdrawing effects. Hence it is difficult to predict the shielding and deshielding effects in NMR (for oxygen the +M is far greater than -I).

A large variation in N-H resonances amongst these quinolinones can be attributed to possible changes in sample concentrations or operating temperature variations. Broad N-H peaks were observed in the proton spectra due to the electrical quadrupole moment (Q) [131, 166-167] of the nitrogen nucleus, which enables the nitrogen to flip rapidly among its three spin states since nitrogen has a spin quantum number (*I*) of 1 [166]. The peak broadening depends on the rate of exchange of the proton on the nitrogen atom. In these structures it is not possible to distinguish between a slow, or intermediate rate of exchange because of the absence of adjacent C-H protons to the heteroatom.

In compounds **114d** and **114g** (**Chart 2**), the N-H peaks were difficult to observe since they were superimposed on the aromatic peaks. However, this was verified by deuterium exchange when the total integration area of the aromatic region collapsed to approximately three quarters of the intensity present in the spectra of the non-deuterated samples. The O-H signals were clearly observed in **114d** and **114g** at 11.42 and 11.22 ppm, respectively (Table **19**). All the N-H and O-H protons exchanged in deuterium oxide (D_2O) to give the corresponding deuterated species.

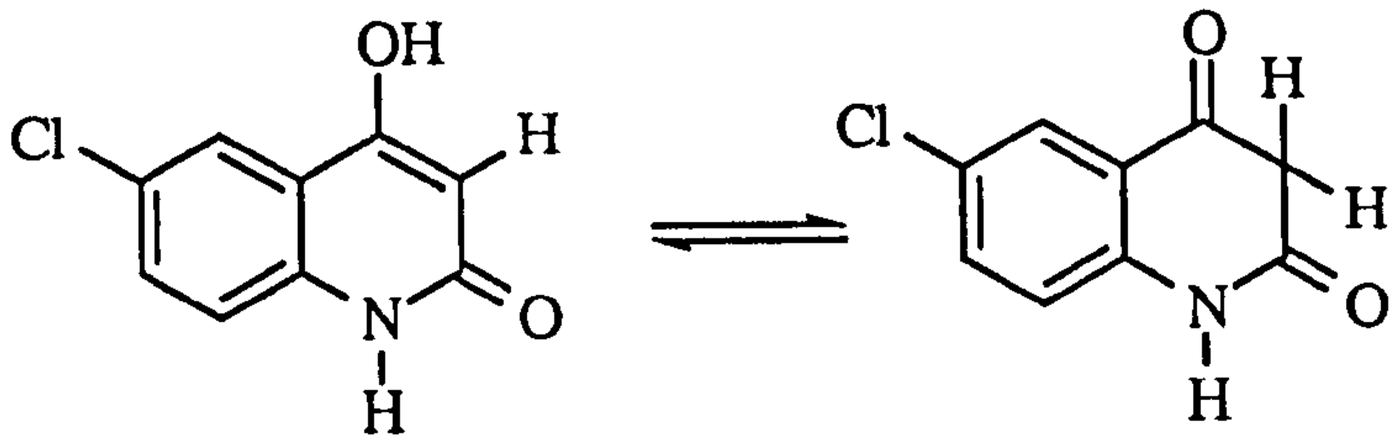
The proton NMR spectrum of the mixture of products (**125** and **126**, **Scheme 59**) showed the presence of cyclised 4-quinolinone (**125**) and the nitrile ester (**126**). The following is a tentative explanation of the proton spectrum as there is some difficulty in assigning all the signals correctly for this mixture of products.

The spectrum shows the presence of a strong ethyl signal, a triplet and a quartet due to the ester **126**. The ethyl signal coupling pattern is more complex than expected, with overlapping of a second ethyl group due to the ethanol solvent used during recrystallisaton. The proton at position-3 showed coupling with the adjacent amino proton (*J* 13.82 Hz) and this coupling disappeared in the deuterium experiment, thus confirming the presence of an exchangeable amino group adjacent to the vinyl group in the structure. Although it is not entirely evident from the proton spectrum of the mixture, its carbon-13 spectrum clearly indicates the presence of a mixture of both compounds (i.e. **125** and **126**) due to the large number of quaternary carbon signals present.

The fluorine-19 spectrum of compound **114a** showed a singlet at -61.99 ppm indicating the presence of the trifluoromethyl group [168]. It is interesting to note that unlike its analogue **93** (see **Scheme 38**), there was no evidence of long range ^{19}F-coupling to the vinylic protons at positions-3. In the carbon-13 spectrum of **114a** it proved difficult to identify the C-F coupling due to high background interferences.

For the quinolinones present as mixtures of their keto-enol tautomers (i.e. **114d**, **114f** and **114g**), the enol forms were identified by integration as the major components in the proton spectra. The enol : keto tautomer ratios are summarised in Chart **3**.

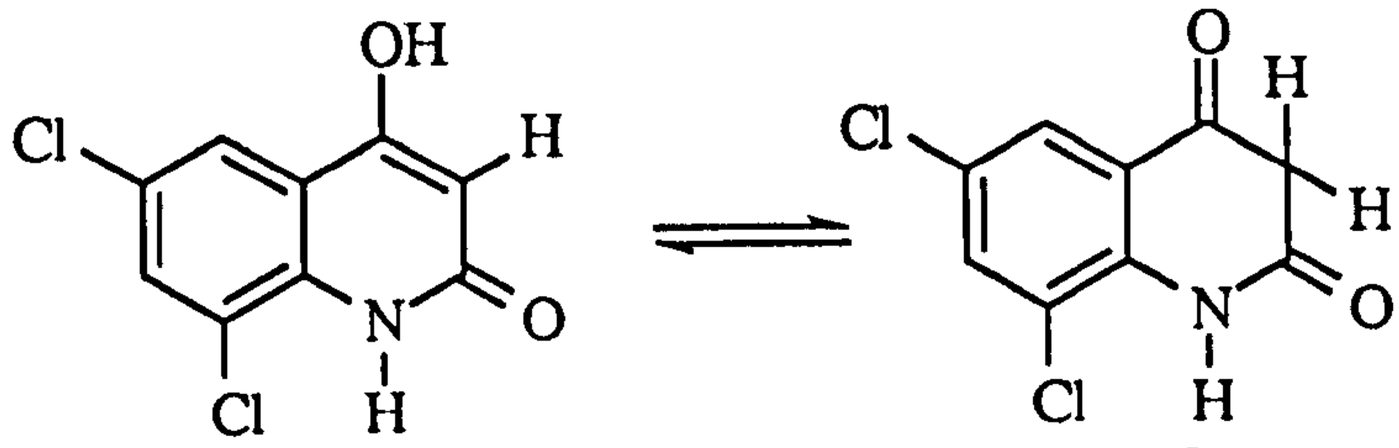
114d



vinyl-H ppm (δ) 5.82 | -OH δ 11.42 | CH_2 δ 2.42

enol ⇌ keto
5 : 1

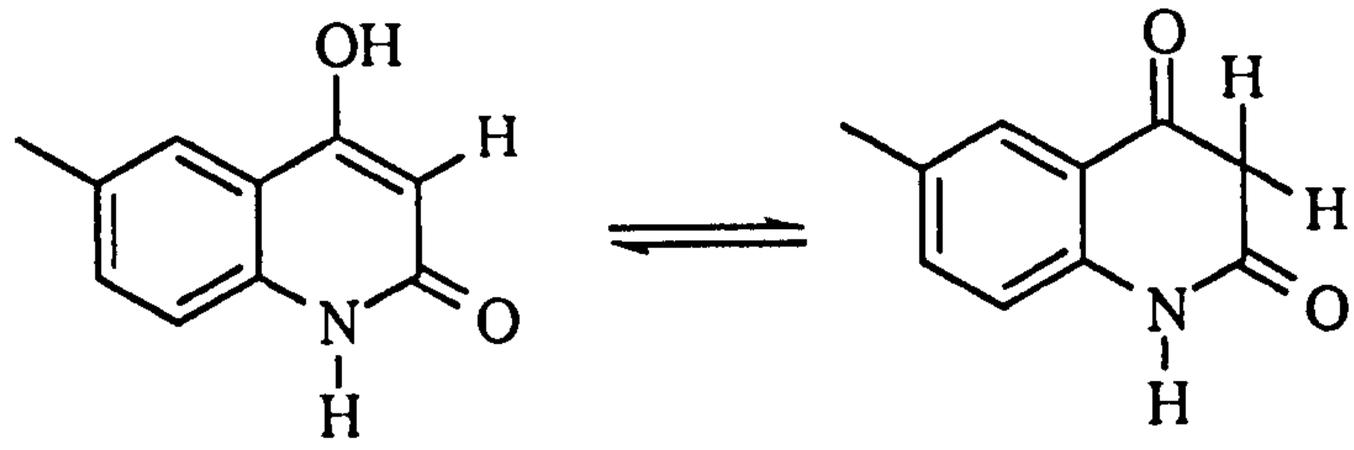
114f



vinyl-H δ 5.91 | -OH δ 11.89 | CH_2 δ 2.11

enol ⇌ keto
10 : 1

114g



vinyl-H δ 5.85 | -OH δ 11.22 | CH_2 δ 2.57

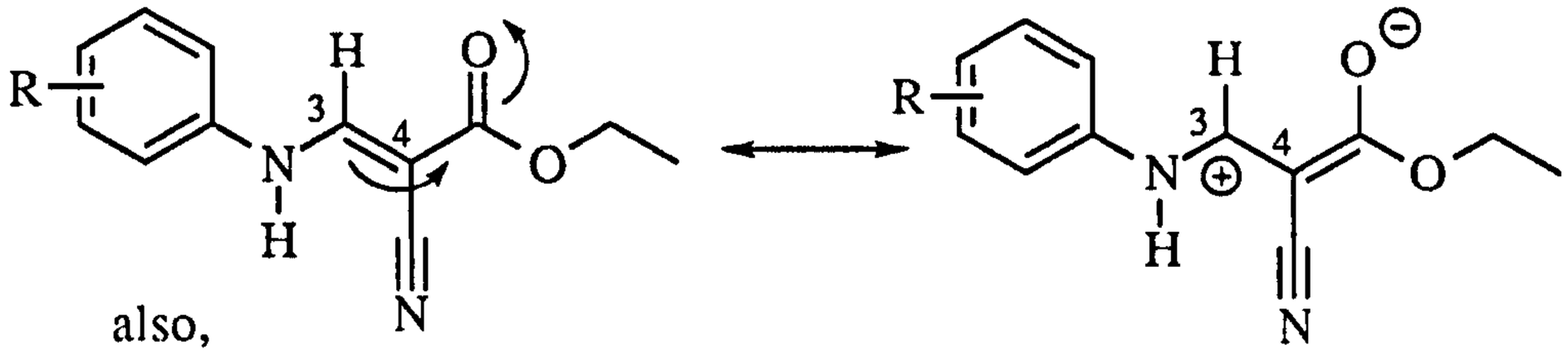
Chart 3

The ratios of the tautomers (in the NMR solvents only) is influenced more by the solvent than any electronic effects. This may be quite different in the solid state. The enol forms were favoured in the NMR solvents due to the presence of aromaticity in the molecules. The enol forms satisfy the Huckel's rule [169] for aromaticity as π electrons delocalise through the empty *p*-orbitals on the C of the carbonyl when it is polarised. Similarly, the OH group in **114f** resonates at a slightly higher ppm (11.89 ppm) compared to **114d** (11.42 ppm) due to the presence of the two chlorine groups on the aromatic ring.

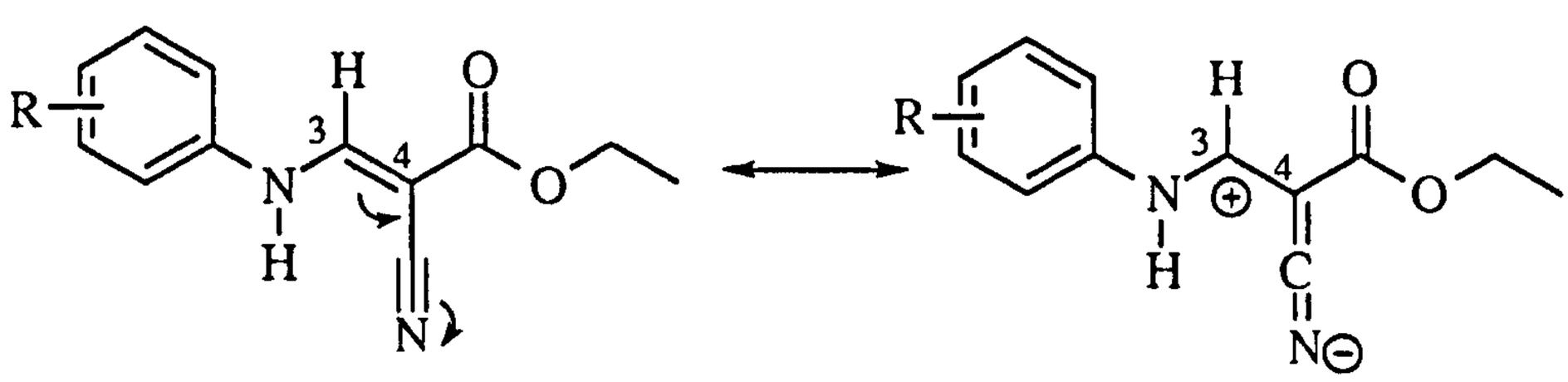
Compound **114e** was insoluble in the standard solvents so its proton and carbon-13 NMR spectrum could not be obtained. However, its mass spectrum showed the molecular ion at m/z 227 as the base peak.

The NMR spectral data was consistent with the proposed structures of the esters **124a-d**, the distinguishing feature being the highly deshielded vinylic protons at position-3 (see Table **20**). This shift is more deshielded compared to the previously mentioned vinylic proton shifts of the quinolinones due to the stronger electron with-drawing effects of the adjacent carbonyl and nitrile groups via electron delocalisation

(as shown in **Scheme 60**), resulting in a lower electron density at position-3 [170].



also,



Scheme 60

Esters **124a-d** (see **Chart 2**) have been drawn in their (*E*)-configurations. These compounds could also adopt the (*Z*)-configuration, but it is highly unlikely due to increased steric hindrance. Unfortunately, in this case, NMR spectroscopy cannot prove their configurations as there is no other vinyl hydrogen at C_4. However, proton chemical shifts were calculated to give an estimation of (*E*) or (*Z*)-configurations. The values were calculated using equation **4** [165], the standard equation used to work out the configuration of alkenes. The results obtained were compared with the observed values from the corresponding proton spectra and are summarised in Table **20**.

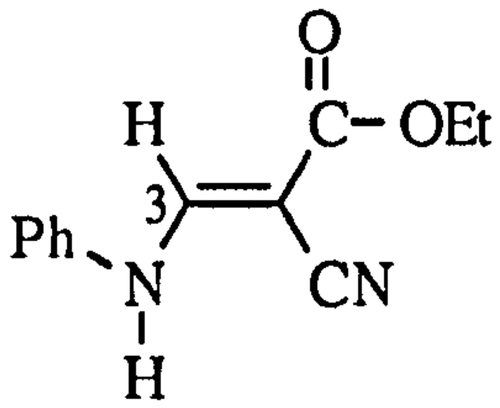
$$\delta H = 5.25 + Z_{gem} + Z_{cis} + Z_{trans} \quad \text{(eq. 4)}$$

124	Calculated for H *trans* to CN (ppm)	Calculated for H *cis* to CN (ppm)	Observed value (δ H ppm)
a	7.98	7.63	8.68-8.73
b	7.98	7.63	8.33
c	7.98	7.63	8.28-8.33
d	7.98	7.63	8.40 *

* a tentative assignment (mixture)

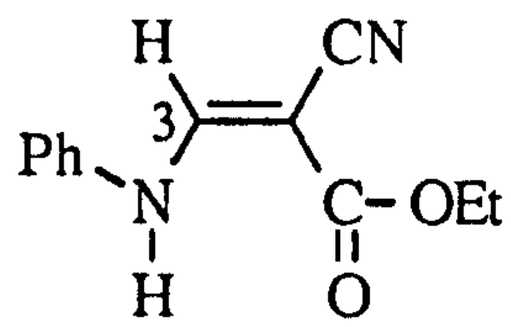
Table 20

Below is the application of equation **4**, employing compound **124a** as an example.



124a

trans (H/CN), or (*E*-isomer)



124a

cis (H/CN), or (*Z*-isomer)

Applying equation **4**, the calculated position-3 proton chemical shift for the *trans*-isomer is as follows:

Base value	5.25
Ph-N-H	1.17 (conjugated alkyl or aryl-N. (Z_{gem}))
NC	0.55 (Z_{trans})
COOEt	<u>1.01</u> (conjugated RO_2C. (Z_{cis}))
δ H =	7.98

Using the same equation (**4**) the calculated position-3 proton chemical shift for the *cis*-isomer is as follows:

Base value	5.25
Ph-N-H	1.17 (conjugated alkyl or aryl-N. (Z_{gem}))
NC	0.75 (Z_{cis})
COOEt	<u>0.46</u> (conjugated RO_2C. (Z_{trans}))
δ H =	7.63

Similarly, vinyl δ H values are calculated for compounds **124b-d** (see Table **20**). The reason for having the same calculated values for different analogues is due to the value 1.17, which remains unchanged when using substituted aryl-N as the R group [165].

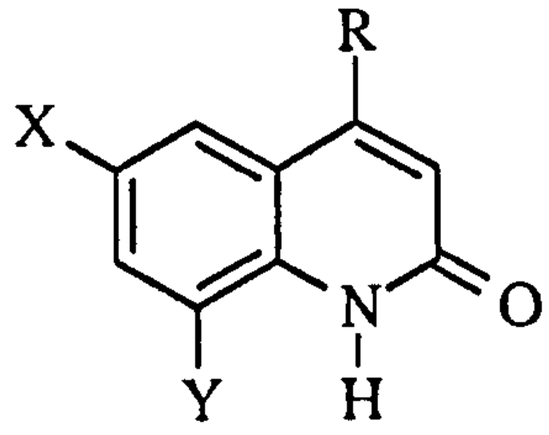
From Table **20**, the observed values from the proton spectra are 'closer' to the *trans* calculated values and thus may suggest that the compounds probably adopt the (*E*)-configurations. Clearly, some allowance for the substituents on the aryl ring needs to be made, as this is a serious limitation on the application of this equation. This observation is supported by Bottomley *et al* [171] where compound **124a** has been identified as the *trans* isomer from the proton spectrum.

The proton NMR of **124d** was not conclusive, but its mass spectrum showed the presence of the molecular ion at m/z 261, as the base peak.

5.20 Interpretations of the Mass spectra of the quinolinones and the nitrile esters

Their mass spectra were consistent with the proposed structures of the quinolinones (**114a-g**) and the esters (**124a-d**). Neutral molecules such as hydrogen cyanide (HCN), carbon monoxide (CO) and aldehyde group (HC=O), hydrogen radical (H·), ethyne (C_2H_2), as well as ketene (CH_2=C=O, from the keto-form) were some of the typical losses observed, common to these types of heterocyclic compounds [172-173]. These losses occurred mainly from the heterocyclic ring. McLafferty rearrangements were observed in the aryl substituted esters **124a-d** via loss of the neutral ethene molecule (CH_2=CH_2) from the ethoxy group [174] (see **Scheme 64**).

The results obtained are summarised in Table **21** and some possible fragmentation pathways for these molecules are described below.



114

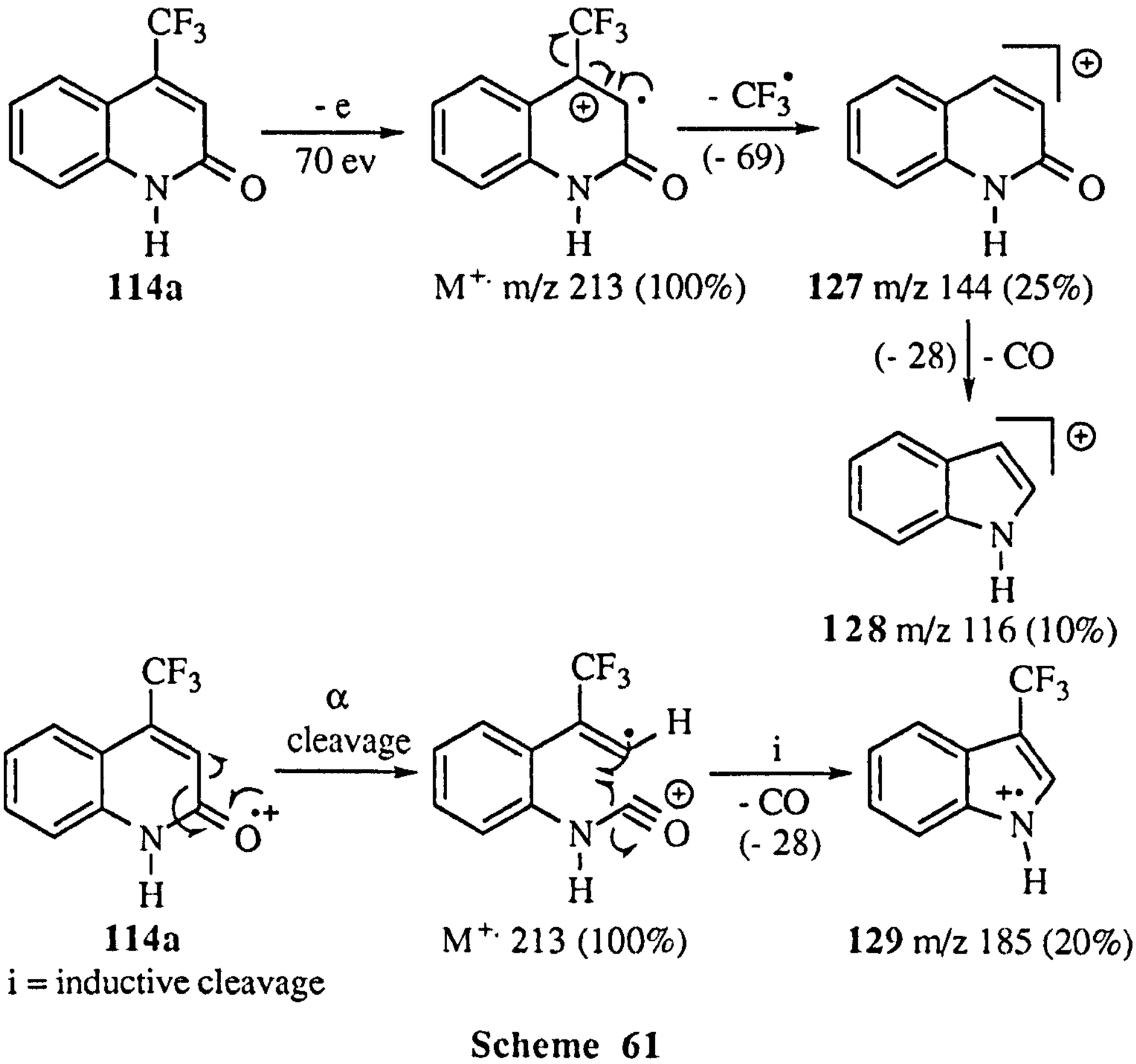
114	R	X	Y	M+· (base peak)	Loss of R	Loss of CO	Loss of CH_2CO	Loss of X/Y
a	CF_3	H	H	213	144	185 116	-	-
b	Ph	H	H	221	-	193	-	-
c	Me	Cl	H	193/195	178/180	165/167	-	158 (X)
d	OH	Cl	H	195/197	-	-	153/155	-
e	Me	Cl	Cl	227/229/231	-	199/201 /203	-	192/194 (X)
f	OH	Cl	Cl	229/231/233	-	201/203 /205	187/189 /191	-
g	OH	Me	H	175	-	-	133	-

Table 21

The extent of loss of the carbon monoxide molecule from the molecular ions is more dominant compared to the loss of the R groups, or hydrogen cyanide, as shown in Table **21**. The preferred loss of carbon monoxide is probably driven by the

formation of the stable indonyl species. All the quinolinones gave their molecular ions as the base peaks in their mass spectra (as expected for aromatic systems).

Compound **114a** loses the very stable trifluoromethyl radical from its molecular ion, to give ion **127** at m/z 144, followed by the loss of carbon monoxide, to give an indole **128** at m/z 116, as shown in **Scheme 61**. This fragmentation is similar to the one mentioned by Djerassi *et al* in respect of alkyl pyridinones displaying the expected expulsion of carbon monoxide to give the corresponding pyrrole ions [175]. Compound **114a** also loses carbon monoxide directly from the molecular ion, firstly by ring opening (α cleavage), followed by inductive cleavage to give the trifluoromethyl indole ion **129** at m/z 185. The loss of carbon monoxide shown in **Scheme 61** is representative of all the compounds mentioned in this section.



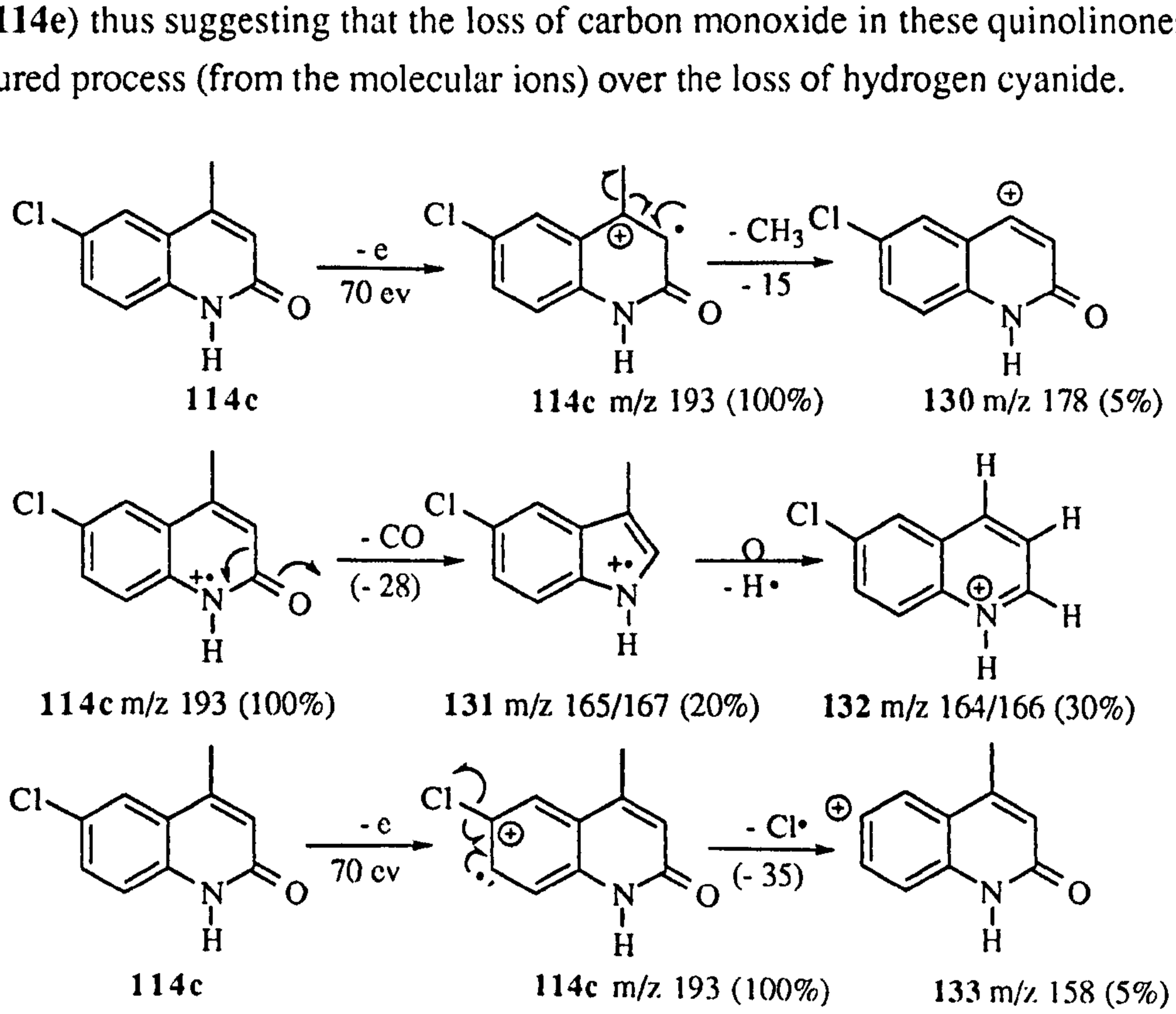
Scheme 61

Compounds **114a** and **114b** showed similar fragmentation patterns, except that in compound **114b**, the loss of the R group (R = Ph) was not observed because it is a bulky group. Instead, the preferred losses were the hydroxyl radical from the enol form to give the ion at m/z 204, and hydrogen atom to form ion at m/z 220. Although loss of a hydrogen atom is observed, it is difficult to rationalise a feasible fragmentation. Deuterium experiments could be carried out to determine the site of loss

of the hydrogen atom, but in the absence of any further studies the structure is not obvious. In compound **114b**, the ion at m/z 193 (table **21**) is formed via two different routes. The first route involves the loss of carbon monoxide from the molecular ion ($M^{+\cdot}$ 221) and the second route involves the loss of hydrogen cyanide from m/z 220. In contrast to compound **114b**, the loss of hydrogen cyanide is not observed in its analogue **114a**.

It seems that the methyl loss in these quinolinones occurs as a very minor process similar to that previously described for julolidine compounds (see **Schemes 49** and **50**). For instance, molecular ion **114c** ($M^{+\cdot}$193/195) loses a methyl radical to give the ion **130** at m/z 178 in 5% intensity as outlined in **Scheme 62**. However, in the analogue **114e** this is not observed even though this compound has a methyl group in position-4. Extrusion of carbon monoxide from the molecular ion **114c** gives the ion **131** at m/z 166/167 in 3:1 ratio, followed by the loss of hydrogen radical and ring expansion to a more stable six-membered system **132** [176] at m/z 164/166. An expected loss of the chlorine radical from species **114c** is observed to give the ion **133** at m/z 158, but only as a minor process. Similarly, in species **114e** ($M^{+\cdot}$ 227/229/231), the loss of carbon monoxide and chlorine radical is also observed to give the ions at m/z 199/201/203 and 192/194, respectively in the ratio 10:6:1 [177].

The loss of hydrogen cyanide is not observed in either compound (i.e. **114c** and **114e**) thus suggesting that the loss of carbon monoxide in these quinolinones is a favoured process (from the molecular ions) over the loss of hydrogen cyanide.



114c → **114c** m/z 193 (100%) → **130** m/z 178 (5%)

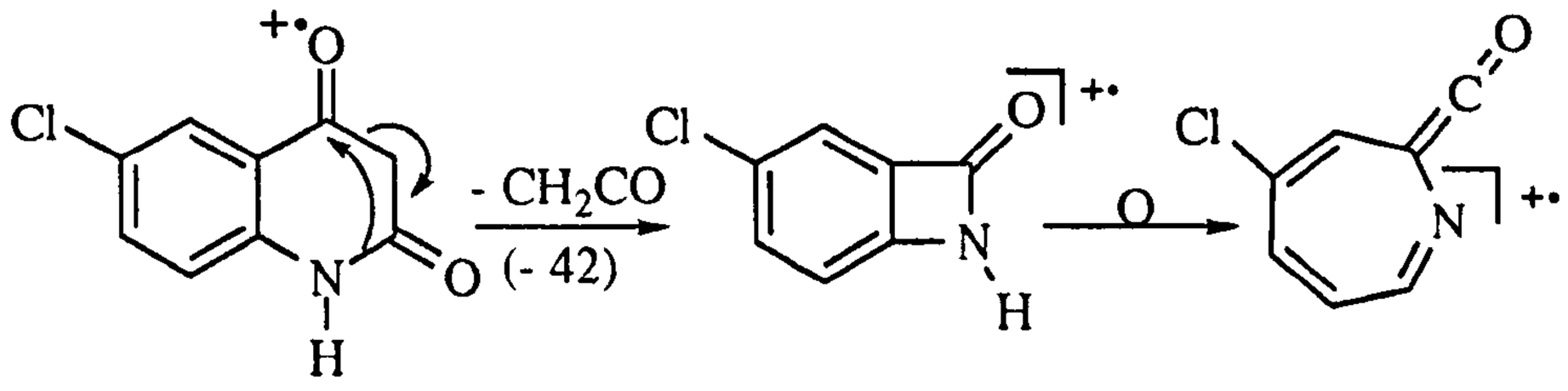
114c m/z 193 (100%) → **131** m/z 165/167 (20%) → **132** m/z 164/166 (30%)

114c → **114c** m/z 193 (100%) → **133** m/z 158 (5%)

Scheme 62

Compounds **114d** and **114g-f** were detected predominantly as the molecular ions in their corresponding keto forms (see Table **21**) since loss of a ketene group was observed from their molecular ions. The fragmentation pathway for the elimination of the ketene group in compound **114d** is shown in **Scheme 61** and is applicable to compounds **114g-f**.

The ketene molecule (CH_2CO) is eliminated from the molecular ion of **114d** ($M^{+\cdot}$ 195) to afford the ion **134** at m/z 153, a highly strained radical cation, via retro-Diels-Alder [178]. This is a typical fragmentation of cyclic α, β-unsaturated ketones. This ion **134** then rearranges to a more stable azatropylium ion **135**. The loss of carbon monoxide from this ion was also detected to give the ion at m/z 125.



114d $M^{+\cdot}$, m/z 195 (100%) **134** m/z 153 (85%) **135** m/z 153 (85%)

Scheme 61

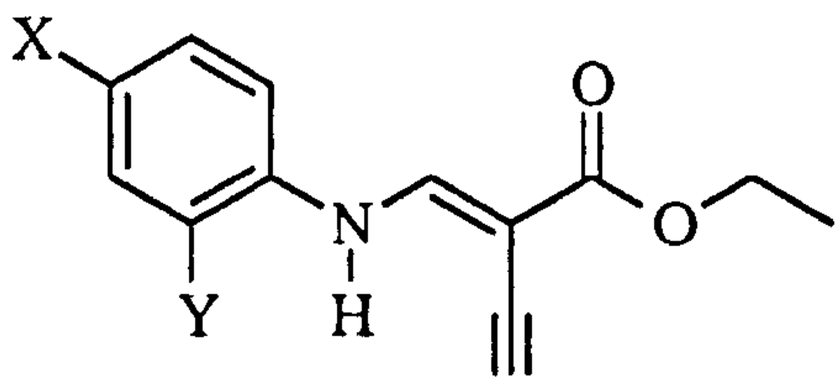
In contrast to compound **114d**, the loss of carbon monoxide in **114f** occurred directly from the molecular ion to give the ions at m/z 201/203/205 (see Table **21**), indicating that the compound was behaving like a phenol, where ($M^{+\cdot}$ - CO) loss is common [179].

The mass spectrum of the mixture of products, 3-cyano-6-methyl-1*H*,4*H*-quinolin-4-one **125** and ethyl (*E*)-2-cyano-3-(*N*-4-methylphenylamino)prop-2-enoate **126** (see **Scheme 59**) showed **126** as the molecular ion at $M^{+\cdot}$ 230. McLafferty rearrangement gave the ion at m/z 202 via the loss of an ethene molecule from the molecular ion. The base peak at m/z 184 is compound **125**, formed either via the elimination of ethanol from the molecular ion **126**, or it is detected in the spectrum as a separate compound.

In summary, the extent of the loss of carbon monoxide versus the substituent group, or hydrogen cyanide, is observed in these quinolinones. The substituents on the aromatic rings do not influence any particular order of losses and thus the elimination is driven by aromaticity, and the stability of the resulting ions. The loss of the methyl group in **114c** was favoured in minor form as was the loss of the chlorine radical from the aromatic ring in **114e**. Where R = OH (i.e. compounds **114d** and **114f**), the keto forms were the major components detected in the mass spectra, the ketene group being eliminated via retro-Diels-Alder. This was followed by ring expan-

sion, leading to the more stable azatropylium ions.

The mass spectrometry results obtained for the nitrile esters **124a-d** were consistent with the structures proposed [180], the typical groups lost included ethene (by the McLafferty rearrangement), ethanol, the carbethoxy group and hydrogen cyanide. The results are summarised in Table **22**.



124 (a-d)

The presence of substituents on the aromatic ring did not influence the extent of the loss of ethene, or indeed any other groups mentioned in Table **22**. The esters behaved in a similar way, except compound **124d**, where the molecular ion was observed as the base peak, and the loss of hydrogen cyanide was not detected.

Compound **124c** is selected as an example to illustrate the fragmentation pathways (and is representative of the other compounds **124a-b** and **d**), as shown in **Scheme 64**.

The base peaks in the mass spectra of compounds **124a-c** arose either from the transfer of aromatic hydrogen onto the keto group **136** with subsequent elimination of ethanol and cyclisation to give species **137**, or the process occurred in two steps, i.e. firstly, elimination of an ethoxy radical from the molecular ion to give species **138**, followed by the loss of a hydrogen atom to give species **137** [181]. It is interesting to note that species **137** is an analogue of the previously mentioned mixtures of products (**125**, outlined in **Scheme 59**), but it is probably cyclising in the gas phase.

Typical McLafferty rearrangements [131] of ethyl esters were observed in compounds **124a-d** (Table **22**). The ion **139** at m/z 256/258/260 was formed from the molecular ion **124c** as a result of this rearrangement via loss of an ethene molecule from β-cleavage with transfer of a γ-hydrogen atom, as shown in **Scheme 64**. As expected, loss of hydrogen cyanide was observed from the base peak (quinolinone structure) in compounds **124a-c** [182].

124	X	Y	$M^{+\cdot}$	$M^{+\cdot}$ due to loss of C_2H_4 (McL)	$M^{+\cdot}$ due to loss of $C_2H_5O\cdot$	$M^{+\cdot}$ due to loss of C_2H_5OH (base peak)	$M^{+\cdot}$ due to loss of HCN	Other losses
a	H	H	216	188	171	170	116 (143 -HCN)	143 ($M^{+\cdot}$ - CO_2Et)
b	Cl	H	250/252	222/224	205/207	204/206	177 (204 -HCN)	-
c	Cl	Cl	284/286/ 288	256/258 /260	239/241 /243	238/240/ 242	211/213/ 215 (238 -HCN)	-
d	NO_2	H	261 (base peak)	233	216	215 (65%)	-	188 ($M^{+\cdot}$ - CO_2Et) 142 ($M^{+\cdot}$ - NO_2)

(McL) McLafferty rearrangement

Table 22

Scheme 64

5.30 Interpretations of Infra-red spectral analyses of the quinolinones and the nitrile esters

FT-IR results offered good evidence for particular functional groups, thus providing further support to the proposed structures.

The most characteristic infra-red bands of these compounds were the carbonyl (C=O) and vinylic (C-H) stretching frequencies and these are summarised in Table **23** for the quinolinones and in Table **24** for the nitrile esters.

114	Vinyl (C-H) str. (cm^{-1})	N-H bend (Amide II) (cm^{-1})	Carbonyl (C=O) (Amide I) str. (cm^{-1})
a	2924	1577	1625
b	2923	1593	1642
c	2922	1600	1650
d	2924	~1600	1652
e	2921	1587	1632
f	2924	~1595	1645
g	2922	~1604	1660
125 **126**	2921	–	1625 (ketone) 1672 (ester)

Table 23

124	Vinyl (C-H) str. (cm^{-1})	Ester carbonyl (C=O) str. (cm^{-1})
a	2925	1683
b	2923	1630
c	2982	1675
d	2990	1689

Table 24

The unique vinyl C-H stretching frequencies listed in Table **23** further supported the formation of these quinolinones. This C-H stretch is not influenced by the electronic properties of the substituent groups of the compounds listed in Tables **17** and **18** and as a consequence, there is very little variation in the frequency of absorption in these compounds.

In compound **124d**, the vinylic C-H absorbs at much higher wave numbers (2990 cm^{-1}) compared to the rest of the compounds due to the strong electron-withdrawing (- I and -M) effects of the nitro group.

The position of the carbonyl (C=O) stretching band was also influenced by the electronic effects of the substituents, conjugation effects, and ring strain (167). Extended conjugation in compound **114b** due to the phenyl ring results in delocalisation of the π - electrons of the C=O group, thus reducing the double bond character of the C-O bond (183), causing absorption at lower frequency than most other compounds in this series (see Table **23**). However, there are exceptions, such as compounds **114a, 114e** and **124b**, where the carbonyl frequency happens to be lower than that of compound **114b**. We can offer no obvious reasons as to why this occurs.

The IR spectrum of 4-quinolinone **125** and the nitrile ester **126** (see **Scheme 59**), showed two carbonyl peaks. The peak at 1625 cm^{-1} represents the ketone carbonyl group (lit. 1635-1655 cm^{-1}) (183) and at 1672 cm^{-1}, the ester carbonyl group (lit. 1700 cm^{-1}) (144).

It was impossible in our experience to distinguish between keto-enol forms using the IR spectral results as no obvious O-H stretches were observed for compounds **114d, 114f**, or **114g** since the region around 3400 cm^{-1} also corresponds to the secondary amine stretch (185). The OH peaks are probably present but they may be hidden under the NH peak region. However, the associated N-H bands were weaker and frequently sharper than that of the corresponding O-H bands. Thus, the presence of strong amide I and amide II bands may suggest that these compounds probably exist as amides (i.e regioselective) rather than their corresponding alcohols. It was also difficult to confirm the cyclic CH_2 stretch of the keto forms since there was an overlap with the aromatic C-H stretches in the region of 3200-3000 cm^{-1}.

Other miscellaneous peaks included nitrile (CN) stretches in the region of 2200-2220 cm^{-1} in the nitrile esters **124a-d** (lit. 2240-2222 cm^{-1}) (145). Conjugation with the aromatic system in these nitrile esters reduced the frequency of absorption of CN stretches and enhanced the intensity of the peak (145).

In summary, the NMR results showed quite clearly, the keto : enol tautomerism present in compounds **114d, 114f-g**, while the esters **124a-d** are suspected to be in their (*E*)-configurations, also backed on NMR evidence.

Mass spectrometric analyses of the quinolinone derivatives showed conventional losses of hydrogen cyanide and carbon monoxide molecules, whilst the McLafferty rearrangements were observed in the esters.

As expected, the FT-IR results showed the carbonyl stretching frequencies of the esters to be higher than those of the quinolinones.

6.0 GENERAL CONCLUSIONS

A series of novel compounds were prepared successfully in a one-pot method, and their structures characterised by spectroscopic and micro analyses. Some of the compounds were subjected to biological evaluation and the results are summarised in the appendix.

The future work would very much depend on the biological data, and based on the results, more target syntheses on promising lead compounds could be pursued to optimise biological activities.

7.0 FUTURE WORK

Trifluralins

This class of compounds not only possess anti-leishmanial properties but are also potent herbicides. Clearly the next library of compounds would depend on the biological results. One of the interesting chemistry to pursue would be the thermal cyclisation of the *ortho*-aryldiamine to the phenazine compound in a one-pot synthesis. A route to compounds containing the phenazine ring skeleton starting from relatively cheap materials such as substituted ortho-aryldiamines could be explored and their biological and pharmacological properties studied.

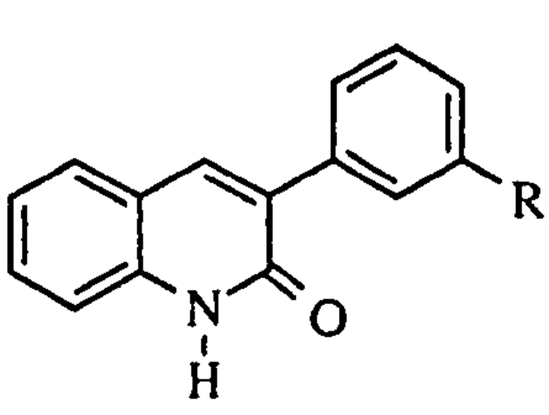
Julolidines/lilolidines and their related compounds

Various substituted anilines, tetrahydroquinolines and indolines can be used as starting materials to give the corresponding functionalised julolidines and lilolidines via 1-bromo-3-chloropropane and 1-bromo-2-chloroethane respectively. Substituted β-ketoesters could also be used to build a library of related compounds.

Another route to tetrahydroquinolines is via the widely used benzotriazole methodology [191]. Hydroquinolines can be synthesised successfully by the reaction of benzotriazolyl-derivatives of the indolines or tetrahydroquinolines with electron-rich alkenes and p-toluenesulphonic acid as a catalyst. This approach may produce a library of novel tetrahydroquinolines and its related compounds with potential biological and pharmacological properties.

Quinolinones

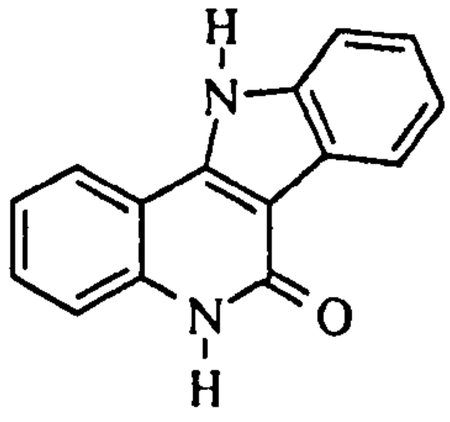
Study could be extended to synthesise a broader range of substituted quinolinones containing the parent lactam ring moiety. Structural classes such as phenyl quinolinones (**140**), dihydro-indolo quinolinones (**141**), bromo-furo quinolinoes (**142**) and benzopyrano quinolinoes (**143**) can be explored. Recent literature indicates that these type of compounds may have potential antimalarial properties [192].



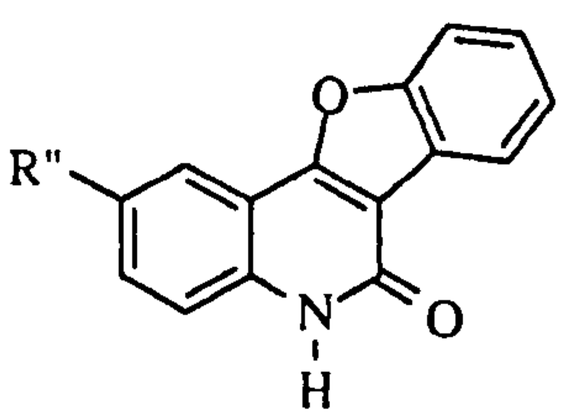
140

R = OCH_2COOH

R = OCH_2CH_2OH

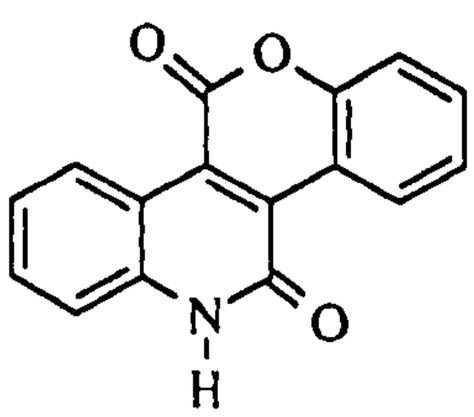


141



142

R" = H, OH, Br/Cl



143

8.0 EXPERIMENTAL

GENERAL

Source of chemicals

Starting materials were obtained from Aldrich Chemical Company and Lancaster Synthesis.

Solvents

Solvents used in the reactions were purified according to the methods of Perrin and Armarego [186].

NMR spectroscopy

NMR spectra were recorded on a BRUKER AC-250 nuclear magnetic resonance spectrometer. Spectrometer frequency was 250 MHz for proton NMR, (equivalent to field strength of 5.87 TELSA), 62.896 MHz for carbon-13 and DEPT spectra. Internal standard for proton and carbon-13 was tetramethyl silate (TMS). Fluorine-19 spectrometer frequency was 235.36 MHz and the internal standard was fluorotrichloromethane ($CFCl_3$).

Mass spectrometry

Spectra were recorded on a VG MICROMASS 7070H, operated at 70 eV electron energy. Source temperature was 200-250 degrees. Scan time was 3 seconds/decade from 750-720 Daltons (mass units).

For chemical ionisation (CI) experiments the instrument was operated at 50 eV electron energy, and ammonia was used as the ionizing reagent.

FT-IR spectroscopy

The instrument used was a GALAXY™, series 5000 FT-IR spectrometer GL-7020. Spectra were recorded by a plotter type HP 7440 Colourpro. The majority of the samples were prepared as KBr discs. Where samples were liquids, they were run as thin films between sodium chloride plates.

Thin Layer Chromatography (TLC)

This was carried out on silica gel 60 plates using chloroform as the eluting solvent, unless otherwise stated. Visualisation was carried out either at 254 nm under UV light or in iodine tank.

Melting point

The instrument used was a Gallenkamp melting point apparatus and the melting points recorded were uncorrected.

Microanalysis

This was sub-contracted to MEDAC LTD, Brunel Science Centre, Egham, Surrey.

Symbols used in the text

^{1}H NMR Proton nuclear magnetic resonance

^{13}C NMR Carbon-13 nuclear magnetic resonance

^{19}F NMR Fluorine-19 nuclear magnetic resonance

D_2O Deuterated proton NMR

(DMSO) Dimethylsulphoxide

(DMSO-d_6) hexa deuterated dimethylsulphoxide

(TMS) Tetramethylsilane

($CDCl_3$) Dueterated chloroform

(m) multiplet

(q) quartet

(t) triplet

(d) doublet

(s) singlet

(*o*) ortho

(*m*) meta

(*p*) para

(*J*) Coupling constant

(δ) Chemical shift in parts per million

(Hz) Hertz

(DEPT) Distortionless Enhancement by Polarisation Transfer*

(HETCOR) Heteronuclear chemical shift correlation$^{\Delta}$

(COSY) Correlated spectroscopy$^{\Delta\Delta}$

IR Infra red

υ Frequency (cm^{-1})

str. stretch

KBr Potassium bromide

def deformation

symm symmetric

asymm asymmetric

MS Mass spectrometry

m/z mass to charge ratio (in amu)

$M^{+\cdot}$ radical cation

McL McLafferty rearrangement

FAB Fast atom bombardment**

TLC Thin layer chromatography

DMF Dimethyl formamide

Miscellaneous

Ar (in mass spectrometry) = $C_7H_2N_2O_4F_2$, m/z 216.

PPA Polyphosphoric acid

mp melting point

Al. Alkyl (or aliphatic)

Ar. Aryl (or aromatic)

Ph Phenyl

Et Ethyl

Me Methyl

h (or hrs) hours

* This technique differentiates between CH, CH_2 and CH_3 using the improved sensitivity of polarisation transfer [187] and provides the quickest way of determining the ^{13}C-^{1}H multiplicities.

** This technique directs fast moving, neutral, atoms onto a metal plate coated with the sample and is commonly used for organic salts.

Δ Heteronuclear chemical shift correlation (HETCOR) experiment correlates the peaks of an ^{1}H spectrum with the peaks of a ^{13}C spectrum. It shows specific protons attached

to each ^{13}C. The ^{1}H spectrum is presented on the vertical axis and the ^{13}C broadband-decoupled spectrum is presented on the horizontal axis. The ^{1}H-^{13}C correlation is shown by a crosspeak contour at the intersection of a horizontal line drawn from a proton peak or a multiplet and a vertical line drawn from a ^{13}C peak.

ΔΔ Correlated spectroscopy (COSY) is a three-dimensional plot showing the ^{1}H-^{1}H connectivity as a contour plot. COSY spectra can be obtained to reveal all the coupling relationships in a molecule, including long-range coupling.

Trifluralin [2,6-dinitro-(*N*,*N*-dipropylamino-4-trifluoromethyl)benzene] (3) [15]

1-Chloro-2,6-dinitro-4-trifluoromethylbenzene (2.71 g; 0.01 moles) dissolved in dry toluene (50 ml) was added dropwise to a srirred solution of dipropylamine (1.01 ml) and triethylamine (2.05 ml) under nitrogen. The mixture was heated under reflux for 3 h, filtered, washed with water (2 x 20 ml) and air dried to give the title compound (3.22 g; 96 %) as yellow needles, mp 44-45° C (from ethanol) [15] . ^{1}H NMR ($CDCl_3$) δ 0.86-0.92 (6H, t, *J* 3.4 Hz, 2 x CH_3), 1.55-1.69 (4H, m, *J* 3.5 Hz, 2 x CH_2), 2.95-3.00 (4H, t, *J* 3.4 Hz, 2 x CH_2 at N), 8.07 (2H, s, 2 x Ar. CH at C-3/C-5). ^{13}C NMR ($CDCl_3$) δ 2 x C of CH_3 (11.12), 2 x C of CH_2 (20.76), 2 x C of CH_2-N, (54.06), C-1 (141.26), C-2/C-6 (145.33), C-3/C-5 (126.75), C-4 (121.14-121.71, (quartet), *J* 36.0 Hz), CF_3 (~117.00-138.00, (quartet),*J* 272 Hz).^{19}F NMR ($CDCl_3$) (-62.69) [12]. MS, m/z 335 ($M^{+\cdot}$, 10%, $C_{13}H_{16}N_3O_4F_3$), 306 (100%, $M^{+\cdot}$ - C_2H_5), 290 (15%, 306 - O), 264 (75%, 290 - C_2H_2), 248 (10%, 264 - O), [335 (10%), 306 (100%), 290 (15%), 264 (75%), 248 (10%), 159 (5%), 145 (5%), 71 (5%)]. IR (KBr) υ 3445 (N-H str.), 3069 (Ar. C-H str.), 2975 (Al. C-H str.), 1625 (N-H bend, secondary), 1537 (NO_2 asymm. str.), 1288 (NO_2, O-H bonded, symm. str.), 1132 (C-F str.), 710 (CF_3 str.). R_f ($CHCl_3$) 0.27.

Potassium 4-chloro-3,5-dinitrobenzene sulphonate (6)

Chlorobenzene (2.05 ml, 0.02 mole), concentrated sulphuric acid (12.25 ml) and fuming sulphuric acid (2.04 ml) were stirred and heated on a steam bath for 2 h and cooled to room temperature. Potassium nitrate (6.98 g, 0.069 mole) was added in two portions to the clear solution. The temperature during the addition was held at 40-60° C. The solution was heated to 110-115° C for 20 h. The hot contents were poured onto crushed ice (200 g) and the yellow precipitate was filtered and recrystallised from boiling water (100 ml). The insoluble material was removed by decantation and filtration of the hot solution. The filtrate was cooled to 5-10° C for 12 h to give the title compound (4.2 g, 66%) as yellow needles, mp>300° C (from water).

The product was used in the next step without further purification.

potassium 4-(*N*,*N*-dipropylamino)-3,5-dinitrobenzene sulphonate (7)

Potassium 4-chloro-3,5-dinitrobenzenesulphonate (0.98 g, 3.06 x 10^{-3} mole), dipropylamine (0.31 ml, 0.23 g, 2.27 x 10^{-3} mole), triethylamine (0.31 ml) and toluene (30 ml) were stirred and heated under reflux for 4 h, cooled and filtered to give the crude title compound (1.13 g, 95%), as orange needles, mp 199-200° C.
The product was used in the next step without further purification.

2,6-dinitro-4-(*N*,*N*-dipropylamino)benzenesulphonyl chloride (8)

Distilled thionyl chloride (0.3 ml, 0.41 g, 3.46 x 10^{-3} mole) was added dropwise to potassium 4-(*N*,*N*-dipropylamino)-3,5-dinitrobenzene sulphonate (1.1 g, 2.86 x 10^{-3} mole) and the reaction mixture was heated under reflux for 3.5 h on a steam bath. The product was not isolated from the reaction mixture and was used to prepare compound **68** (see later pages).

Synthesis of Julolidine (36): formation of julolidine and 9,9'-bijulolidyl (36a).

The title compound was prepared by the method of Glass and Weissberger [46] on a 0.20 molar scale to give julolidine (**36**) (8.69 g, 25%) as cream needles, mp 38-42° C (from heptane) (Lit 40° C) [120, 188], and 9,9'-bijulolidyl (**36a**) (0.77 g, 2%) as pink needles, mp 190-194° C (from water) (Lit 206° C) [105].

Julolidine (36):

^{1}H NMR (MeOH-d_4) δ 2.23-2.33 (4H, m, *J* 6.0 Hz, 2 x cyclic CH_2 at C-2/C-6), 3.00-3.06 (4H, t, *J* 6.0 Hz, 2 x benzylic CH_2 at C-1/C-7), 3.29-3.31 (MeOH), 3.57-3.62 (4H, t, *J* 6.0 Hz, 2 x cyclic CH_2 at C-3/C-5), 4.88 (broad peak, water in MeOH), 7.17-7.19 (2H, d, *J* 8.0 Hz, 2 x Ar. C-H at C-8/C-10), 7.29-7.35 (1H, dd, *J* 8.0, 8.0 Hz, Ar. C-H at C-9). ^{13}C NMR (MeOH) δ C-1/C-7 (26.34), C-2/C-6 (20.91), C-3/C-5 (54.43), C-8/C-10 (129.66), C-9 (130.26), C-11/C-13 (133.02), C-12 (133.55). MS, m/z 173 ($M^{+\cdot}$, 85%, $C_{12}H_{15}N$), 172 (100%, $M^{+\cdot}$ - H), 144 (25%, $C_{10}H_{10}N$), 158 (5%, $C_{11}H_{12}N$), [173 (85%), 172 (100%), 158 (5%), 144 (25%), 130 (8%), 115 (8%), 91 (7%), 77 (8%)]. IR (KBr) ϑ 3432 (Ar. C-H str.), 2924 (Al. C-H asymm. str.), 2849 (Al. C-H symm. str.), 1469 (C=C skeletal str.), 891-807 (CH_2 rocking) cm^{-1}.

9,9'-Bijulolidyl (36a):

^{1}H NMR ($CDCl_3$) δ 1.94-2.03 (8H, m, *J* 6.0 Hz, 4 x cyclic CH_2 at C-2/C-2'/C-6/C-6'), 2.77-2.82 (8H, t, *J* 6.0 Hz, 4 x benzylic CH_2 at C-1/C-1'/C-7/C-7'), 3.09-3.11 (8H, t, *J* 6.0 Hz, 4 x cyclic CH_2 at C-3/C-3'/C-5/C-5'), 6.94 (4H, s, 4 x Ar. C-H at C-8/C-8'/C-10/C-10'). ^{13}C NMR ($CDCl_3$) δ C-1/C-1'/C-7/C-7' (27.76), C-2/C-2'/

C-6/C-6' (22.32), C-3/C-3'/C-5/C-5' (50.14), C-8/C-8'/C-10/C-10' (124.95), C-9/C-9' (129.62), C-11/C-11'/C-13/C-13' (121.75), C-12/C-12' (141.48). MS, m/z 344 ($M^{+\cdot}$, 100%, $C_{24}H_{28}N_2$), 342 (10%, $C_{24}H_{26}N_2$), 172 (25%, $C_{12}H_{14}N$), 171 (20%, $C_{12}H_{13}N$), 157 (10%, $C_{11}H_{11}N$), [344 (100%), 342 (10%), 172 (25%), 171 (20%), 157 (10%), 71 (8%), 57 (9%), 43 (9%)]. IR (KBr) ϑ 3442 (Ar. C-H str.), 2924 (Al. C-H asymm. str.), 2830 (Al. C-H symm. str.), 1608 (C=C skeletal str.), 1495-1459 (C-H bending vibrations) cm^{-1}.

N^1,N^2-di-(2,6-dinitro-4-trifluoromethylphenyl)-1,2-ethylenediamine (65a) [84]

1-Chloro-2,6-dinitro-4-trifluoromethylbenzene (5.41 g, 0.02 mole) was dissolved in dry toluene (40 cm^3) and added dropwise to a stirred solution of ethylenediamine (0.67 ml, 0.60 g, 0.01 mole) and triethylamine (2.05 ml, 1.49 g, 0.01 mole) under nitrogen. The mixture was heated under reflux for 3 h, filtered, washed with water (2 x 20 ml) and air dried to give the title compound (1.7 g, 32%) as yellow needles, mp 204-206° C (from methanol) (Lit. 199.5-199.6° C, from ethanol) [84]. ^1H NMR (acetone-d_6) δ 3.55 (4H, s, 2 x Al. CH_2), 8.53 (4H, s, 4 x Ar. CH at C-3/C-3'/C-5/C-5'), 8.56 (2H, s, 2 x NH). ^{13}C NMR (acetone-d_6) δ C of 2 x CH_2-NHAr (47.48), C-1/C-1' (139.18), C-2/C-2'/C-6/C-6' (142.39), C-3/C-3'/C-5/C-5' (129.64) , C-4/C-4' (116.63-117.12, (quartet), J 35.66 Hz) , CF_3 (117.27-125.85, (quartet), J 270.53 Hz). ^{19}F NMR (DMSO-d_6) δ (-59.90). MS, m/z 509 (11 %, $M^{+\cdot}$, $C_{16}H_{10}N_6O_8F_6$ - F), 264 (100%, $M^{+\cdot}$ - CH_2NHAr), 235 (30%, 264 - CH_2NH), [509 (11%), 264 (100%), 235 (30%), 217 (32%), 185 (20%), 159 (35%), 71 (10%), 43 (12%)]. IR (KBr) υ 3347 (N-H str.), 3069 (Ar. C-H str.), 2877 (Al. C-H str.), 1640 (N-H bend, secondary), 1536 (NO_2 asymm. str.), 1291 (NO_2, O-H bonded, symm. str.), 1125 (C-F str.), 730 (CF_3 str.). R_f ($CHCl_3$) 0.16.

The following compounds were prepared by the method described above.

N^1,N^2-di-(2,6-dinitro-4-trifluoromethylphenyl)-1,3-propylenediamine (65b) [84]

1-Chloro-2,6-dinitro-4-trifluoromethylbenzene (5.41 g, 0.02 mole) and 1,3-propylenediamine (0.74 ml, 0.64 g, 8.68 x 10^{-3} mole) were reacted to give the title compound (3.85 g, 71%) as yellow needles, mp 171-174° C (from methanol) (Lit. 175.6-176.2° C, from ethanol) [84]. ^1H NMR and ^{13}C NMR (sample was insoluble to obtain good spectra). MS, m/z 523 (50%, $M^{+\cdot}$, $C_{17}H_{12}N_6O_8F_6$ - F), 278 (100%, 523 - CH_2NHAr.), 250 (5%, 278 - C_2H_4). [523 (50%), 278 (100%), 250 (5%), 232 (10%), 217 (10%), 187 (10%), 159 (10%), 105 (10%)]. IR (KBr) υ 3289 (N-H str., coupled doublet, asymm. and symm.), 3104 (Ar. C-H str.), ~ 2900 (Al. C-H str.), 1639 (N-H bend, secondary), 1538 (NO_2 asymm. str.), 1291 (NO_2, O-H bonded, symm. str.),

1137 (C-F str.), 763 (CF_3 str.). R_f ($CHCl_3$) 0.54.

N^1,N^2-di-(2,6-dinitro-4-trifluoromethylphenyl)-1,4-diaminobutane (65c)

1-Chloro-2,6-dinitro-4-trifluoromethylbenzene (5.41 g, 0.02 mole) and 1,4-diaminobutane (0.89 ml, 0.78 g, 8.85 x 10^{-3} mole) were reacted to give the title compound (2.92 g, 53%) as yellow needles, mp 193-195° C (from methanol). ^1H NMR ($CDCl_3$) δ 1.87 (4H, d, *J* 3.49 Hz, 2 x Al. CH_2), 3.14 (4H, d, *J* 7.1Hz, 2 x Al. CH_2 at NHAr), 8.53 (4H, s, 4 x Ar. CH at C-3/C-3'/C-5/C-5'), 8.65 (2H, s, 2 x NH). ^{13}C NMR (acetone-d_6) δ C of 2 x CH_2 (27.64) , C of 2 x CH_2-NHAr (46.89) , C-1/C-1' (138.72) , C-2/C-2'/C-6/C-6' (142.34), C-3/C-3'/C-5/C-5' (129.70), C-4/C-4' (126.02), CF_3 (difficult to assign due to background noise). ^{19}F NMR (DMSO-d_6) δ (-59.79). MS, m/z 537 (12%, $M^{+\cdot}$, $C_{18}H_{14}N_6O_8F_6$ - F), 487 (5%, $M^{+\cdot}$ - CF_3), 322 (12%, $ArNH(CH_2)_4NH_2$ (monomer)), 264 (30%, $M^{+\cdot}$ - $(CH_2)_2NH_2$), 235 (98%, $C_7H_2N_2O_4F_3$), 71 (100%), [537 (12%), 487 (5%), 322 (12%), 264 (30%), 248 (45%), 235 (98%), 71 (100%), 69(35%)]. IR (KBr) υ 3353 (N-H str.), 3063 (Ar. C-H str.), 2965 (Al. C-H str.), 1639 (N-H bend, secondary), 1542 (NO_2 asymm. str.), 1294 (NO_2, O-H bonded, symm. str.), 1130 (C-F str.), 724 (CF_3 str.). R_f ($CHCl_3$) 0.16.

Anal. Calcd. for $C_{18}H_{14}N_6O_8F_6$: C, 38.86; H, 2.54; N, 15.10.
Found: C, 38.94; H, 2.67; N, 15.07.

N^1,N^2-di-(2,6-dinitro-4-trifluoromethylphenyl)-1,5-diaminopentane (65d)

1-Chloro-2,6-dinitro-4-trifluoromethylbenzene (5.41 g, 0.02 mole) and 1,5-diaminopentane (1.03 ml, 0.89 g, 8.80 x 10^{-3} mole) were reacted to give the title compound (3.88 g, 68%) as yellow needles, mp 130-134° C (from methanol). ^1H NMR ($CDCl_3$) δ 1.49-1.57 (2H, m, *J* 6.72 Hz, Al. CH_2), 1.71-1.83 (4H, m, *J* 7.15 Hz, 2 x Al. CH_2), 3.02-3.09 (4H, q, *J* 6.81 Hz, 2 x Al. CH_2 at NHAr), 8.41 (4H, s, 4 x Ar. CH at C-3/C-3'/C-5/C-5'), 8.64 (2H, s, 2 x NH). ^{13}C NMR ($CDCl_3$) δ C of 2 x CH_2 (23.84), C of 2 x CH_2 (29.49), C of 2 x CH_2-NHAr (46.19), C-1/C-1' (137.50), C-2/C-2'/C-6/C-6' (142.50), C-3/C-3'/C-5/C-5' (129.10), C-4/C-4' and CF_3 (difficult to assign due to background noise). ^{19}F NMR (DMSO-d_6) δ (-59.84). MS, m/z 551 (18%, $M^{+\cdot}$, $C_{19}H_{16}N_6O_8F_6$ - F), 501 (2%, $M^{+\cdot}$ - CF_3), 335 (8%, $M^{+\cdot}$ - $C_7H_2N_2O_4F_3$), 235 (100%, $C_7H_2N_2O_4F_3$), [551 (18%), 501 (2%), 335 (8%), 264 (70%), 248 (55%), 235 (100%), 85 (60%), 55 (40%)]. IR (KBr) υ 3342 (N-H str.), ~ 3100 (Ar. C-H str.), 2924 (Al. C-H str.), 1640 (N-H bend, secondary), 1544 (NO_2 asymm. str.), 1274 (NO_2, O-H bonded, symm. str.), 1131 (C-F str.), ~ 700 (CF_3 str.). R_f ($CHCl_3$) 0.29.

Anal. Calcd. for $C_{19}H_{16}N_6O_8F_6$: C, 43.50; H, 4.09; N, 4.27.
Found: C, 43.33; H, 4.11; N, 4.27.

N^1,N^2-di-(2,6-dinitro-4-trifluoromethylphenyl)-1,6-diaminohexane (65e)

1-Chloro-2,6-dinitro-4-trifluoromethylbenzene (5.41 g, 0.02 mole) and 1,6-diaminohexane (1.16 ml, 1.02 g, 8.73 x 10^{-3} mole) were reacted to give the title compound (1.43 g, 25%) as yellow needles, mp 157-160° C (from methanol). ^{1}H NMR ($CDCl_3$) δ 1.41-1.46 (4H, m, *J* 3.63 Hz, 2 x Al. CH_2), 1.71-1.76 (4H, m, *J* 3.13 Hz, 2 x Al. CH_2), 3.00-3.07 (4H, m, *J* 4.93 Hz, 2 x Al. CH_2) 8.40 (4H, s, 4 x Ar. CH at C-3/C-3'/C-5/C-5'), 8.66 (2H, s, 2 x NH). ^{13}C NMR ($CDCl_3$) δ C of 2 x CH_2 (26.17), C of 2 x CH_2 (29.74), C of 2 x CH_2-NHAr. (46.37), C-1/C-1' (137.22), C-2/C-2'/C-6/C-6' (141.35), C-3/C-3'/C-5/C-5' (129.16), C-4/C-4' and CF_3 (difficult to assign due to background noise). ^{19}F NMR (DMSO-d_6) δ (-59.77). MS, m/z 565 (10%, $M^{+\cdot}$, $C_{20}H_{18}N_6O_8F_6$ - F), 349 (5%, $M^{+\cdot}$ - $C_7H_2N_2O_4F_3$), 264 (100%, $C_8H_5N_3O_4F_3$), 235 (80%, 264 - CH_2NH), [565 (10%), 349 (5%), 316 (18%), 264 (100%), 248 (70%), 235 (80%), 69 (30%), 55 (48%)]. IR (KBr) υ 3330 (N-H str.), 3103 (Ar. C-H str.), 1643 (N-H bend, secondary) 1545 (NO_2 asymm. str.), 1291 (NO_2, O-H bonded, symm. str.), 1126 (C-F str.), 730 (CF_3 str.). R_f ($CHCl_3$) 0.30.
Anal. Calcd. for $C_{20}H_{18}N_6O_8F_6$: C, 41.11; H, 3.10; N, 14.37.
Found: C, 41.10; H, 3.18; N, 14.24.

N^1,N^2-di-(2,6-dinitro-4-trifluoromethylphenyl)-1,10-diaminodecane (65f)

1-Chloro-2,6-dinitro-4-trifluoromethylbenzene (5.41 g, 0.02 mole) and 1,10-diaminodecane (1.72 g, 9.98 x 10^{-3} mole) were reacted to give the title compound (3.56 g, 55%) as yellow needles, mp 109-110° C (from ethanol). ^{1}H NMR ($CDCl_3$) δ 1.29-1.37 (12H, m (broad), 6 x Al. CH_2), 1.65-1.73 (4H, dd, *J* 7.02, 7.02 Hz, 2 x Al. CH_2), 2.99-3.06 (4H, dt, *J* 6.82, 6.82 Hz, 2 x Al. CH_2 at NHAr.), 8.40 (4H, s, 4 x Ar. CH at C-3/C-3'/C-5/C-5'), 8.66 (2H, s, 2 x NH). ^{13}C NMR ($CDCl_3$) δ C of 2 x CH_2 (26.58), C of 2 x CH_2 (28.95), C of 12 x CH_2 (29.12), C of 2 x CH_2-NHAr. (29.96), C-1/C-1' (137.21), C-2/C-2'/C-6/C-6' (141.49), C-3/C-3'/C-5/C-5' (129.09), C-4/C-4' (115.78-116.35, (quartet), *J* 36.29 Hz), CF_3 (115.76-124.66, (quartet), *J* 271.52 Hz). ^{19}F NMR (DMSO-d_6) (-59.79). MS, m/z 621 (20%, $M^{+\cdot}$,$C_{24}H_{26}N_6O_8F_6$ - F), 623 (18%, $M^{+\cdot}$ - OH), 605 (40%, $M^{+\cdot}$ - F - O), 390 (10%, $M^{+\cdot}$ - ArNH), 264 (61%, $C_8H_5N_3O_4F_3$), 248 (100%, $C_8H_5N_3O_3F_3$), [621 (20%), 623 (18%), 605 (40%), 390 (10%), 264 (61%), 248 (100%), 69 (32%), 55 (55%)]. IR (KBr) υ 3318 (N-H str.), 3310 (Ar. C-H str.), 2927 (Al. C-H str.), 1639 (N-H bend, secondary), 1549 (NO_2 asymm. str.), 1292 (NO_2, O-H bonded, symm. str.),

1148 (C-F str.), 727 (CF_3 str.). R_f ($CHCl_3$) 0.19.

Anal. Calcd. for $C_{24}H_{26}N_6O_8F_6$: C, 43.93; H, 2.95; N, 15.49.
Found: C, 43.61; H, 3.03; N, 15.52.

N^1,N^2-di-(2,6-dinitro-4-trifluoromethylphenyl)-1,12-diaminododecane (65g)

1-Chloro-2,6-dinitro-4-trifluoromethylbenzene (5.41 g, 0.02 mole) and 1,12-diaminododecane (1.99 g, 9.93 x 10^{-3} mole) were reacted to give the title compound (5.85 g, 88%) as yellow needles, mp 98-100° C (from ethanol). ^1H NMR ($CDCl_3$) δ 1.26-1.37 (16H, m (broad), 8 x Al. CH_2), 1.65-1.76 (4H, m, *J* 7.06 Hz, 2 x Al. CH_2), 2.98-3.06 (4H, dt, *J* 4.99, 4.99 Hz, 2 x Al. CH_2 at NHAr.), 8.40 (4H, s, 4 x Ar. CH at C-3/C-3'/C-5/C-5'), 8.66 (2H, s, 2 x NH). ^{13}C NMR ($CDCl_3$) δ C of 2 x CH_2 (26.59), C of 2 x CH_2 (28.99), C of 6 x CH_2 (29.27), C of 6 x CH_2 (29.31), C of 2 x CH_2-NHAr. (46.75), C-1/C-1' (137.18), C-2/C-2'/C-6/C-6' (141.47), C-3/C-3'/C-5/C-5' (129.14), C-4/C-4' (115.75-116.33, (quartet), *J* 36.17 Hz), CF_3 (115.90-124.64, (quartet), *J* 271.65 Hz). ^{19}F NMR (DMSO-d_6) δ (-59.76). MS, m/z 651 (5%, $M^{+\cdot}$, $C_{26}H_{30}N_6O_8F_6$ - OH), 649 (5%, $M^{+\cdot}$ - F), 633 (20%, $M^{+\cdot}$ - F - O), 433 (22%, $M^{+\cdot}$ - Ar.), 418 (21%, $M^{+\cdot}$ - ArNH), 404 (5%, $M^{+\cdot}$ - $ArNHCH_2$), 264 (45%, 404 - $(CH_2)_{10}$), 248 (100%, $C_8H_5N_3O_3F_3$), 69 (25%, CF_3), [651 (5%), 649 (5%), 633 (20%), 433 (22%), 418 (21%), 404 (5%), 264 (45%), 248 (100%)]. IR (KBr) υ 3352 (N-H str.), 3063 (Ar. C-H str.), 2925 (Al. C-H str.), 1638 (N-H bend, secondary), 1542 (NO_2 asymm. str.), 1278 (NO_2, O-H bonded, symm. str.), 1136 (C-F str.), 725 (CF_3 str.). R_f ($CHCl_3$) 0.37.

Anal. Calcd. for $C_{26}H_{30}N_6O_8F_6$: C, 46.71; H, 4.52; N, 12.56.
Found: C, 46.69; H, 4.62; N, 12.24.

N^1,N^2-di-(2,6-dinitro-4-trifluoromethylphenyl)piperazine (65h)

1-Chloro-2,6-dinitro-4-trifluoromethylbenzene (5.41 g, 0.02 mole) and 1,4-diaminopiperazine (0.89 g, 0.01 mole) were reacted to give the title compound (4.51 g, 81%) as yellow needles, mp 226-228° C (from methanol) (Lit. 243.3-243.4° C, from ethanol) [84]. ^1H NMR (DMSO-d_6) δ 3.12 (8H, s, 4 x CH_2), 8.62 (4H, s, 4 x CH at C-3/C-3'/C-5/C-5'). ^{13}C NMR (DMSO-d_6) δ C of 4 x CH_2 (50.13), C-1/C-1' (139.85), C-2/C-2'/C-6/C-6' (147.08), C-3/C-3'/C-5/C-5' (126.17), C-4/C-4' and CF_3 (difficult to assign due to background noise). ^{19}F NMR (DMSO-d_6) δ (-59.80). MS, m/z 554 (100%, $M^{+\cdot}$, $C_{18}H_{12}N_6O_8F_6$), 535 (50%, $M^{+\cdot}$ - F), 524 (10%, $M^{+\cdot}$ - NO), 507 (40%, $M^{+\cdot}$ - HNO_2), 69 (20%, CF_3). [554 (100%), 535 (50%), 524 (10%), 507 (40%), 291 (75%), 260 (20%), 69 (20%)]. IR (KBr) υ. R_f ($CHCl_3$) 0.19.

N^1,N^2-di-(2,6-dinitro-4-trifluoromethylphenyl)-1,3-cyclohexane*bis*-(methylamine) (65i)

1-Chloro-2,6-dinitro-4-trifluoromethylbenzene (5.41 g, 0.02 mole) and 1,3-cyclohexane*bis*(methylamine) (1.43 g, 0.01 mole) were reacted to give the title compound (3.16 g, 52%) as yellow needles, mp 190-192° C (from methanol). The following is a tentative assignment since 1, 3-cyclohexane*bis*(methylamine) is a mixture of cis/trans isomers. ^{1}H NMR ($CDCl_3$) δ 0.74-0.99 (2H, m, *J* 11.80 Hz, cyclic CH_2 at C-5), 1.25-1.88 (6H, m (broad), 3 x cyclic CH_2 at C-2/C-4/C-6), 2.18 (2H, s, 2 x cyclic CH at C-1/C-3), 2.86-2.91 (4H, m, *J* 4.83 Hz, 2 x bridged CH_2), 8.42 (4H, s, 4 x Ar. CH at C-3'/C-5'), 8.69 (2H, s, 2 x NH). ^{13}C NMR ($CDCl_3$) δ C-1/C-3 (38.07), C-2 (34.69), C-4/C-6 (30.16), C-5 (24.88), 2 x bridged methylene C (52.75), C-1' (137.21), C-2'/C-6' (141.54), C-3'/C-5' (129.25), C-4' and CF_3 (difficult to assign due to background noise). ^{19}F NMR (DMSO-d_6) δ (-59.80). MS, m/z 591 (10%, $M^{+\cdot}$, $C_{22}H_{20}N_6O_8F_6$ - F), 375 (2%, $M^{+\cdot}$ - Ar.), 342 (12%, 591 - ArNH), 264 (100%, $C_8H_5N_3O_4F_3$), 248 (80%, $ArNHCH_2$), 235 (45%, $C_7H_2N_2O_4F_3$), [591 (10%), 375 (2%), 342 (12%), 264 (100%), 248 (80%), 235 (45%), 95 (75%), 69 (15%)]. IR (KBr) υ 3346 (N-H str.), 3099 (Ar. C-H str.), 2935 (Al. C-H str.), 1640 (N-H bend, secondary), 1533 (NO_2 asymm. str.), 1297 (NO_2, O-H bonded, symm. str.), 1123 (C-F str.), 727 (CF_3 str.). R_f ($CHCl_3$) 0.44.

Anal. Calcd. for $C_{22}H_{20}N_6O_8F_6$: C, 43.29; H, 3.30; N, 13.76.
Found: C, 43.34; H, 3.49; N, 13.46.

N^1,N^2-di-(2,6-dinitro-4-trifluoromethylphenyl)-1,2-diaminocyclohexane (65j)

1-Chloro-2,6-dinitro-4-trifluoromethylbenzene (5.41 g, 0.02 mole) and 1,2-diaminocyclohexane (1.15 ml, 1.07 g, 9.38 x 10^{-3} mole) were reacted to give the title compound (3.92 g, 67%) as yellow needles, mp 264-265° C (from methanol). ^{1}H NMR ($CDCl_3$) and ^{13}C NMR showed a mixture of stereoisomers due to the amine (cis/trans). MS, m/z 563 (10%, $M^{+\cdot}$, $C_{20}H_{16}N_6O_8F_6$ - F), 347 (8%, $M^{+\cdot}$ - Ar.), 235 (100%, $C_7H_2N_2O_4F_3$), 69 (15%, CF_3), [563 (10%), 347 (8%), 330 (10%), 300 (25%), 264 (5%), 235 (100%), 69 (15%), 55 (40%)]. IR (KBr) υ 3321 (N-H str.), 3097 (Ar. C-H str.), 2934 (Al. C-H str.), 1642 (N-H bend, secondary), 1544 (NO_2 asymm. str.), ~1290 (NO_2, O-H bonded, symm. str.), 1134 (C-F str.), ~ 700 (CF_3 str.). R_f ($CHCl_3$) 0.63.

Anal. Calcd. for $C_{20}H_{16}N_6O_8F_6$: C, 41.25; H, 2.77; N, 14.42.
Found: C, 41.31; H, 2.93; N, 14.41.

N^1,N^2-di-(2,6-dinitro-4-trifluoromethylphenyl)diethylenetriamine (65k)

1-Chloro-2,6-dinitro-4-trifluoromethylbenzene (5.41 g, 0.02 mole) and diethylene-triamine (1.03 ml, 0.98 g, 9.53 x 10^{-3} mole) were reacted to give the title compound (4.13g, 73%) as yellow needles, mp 132-136° C (from methanol). ^{1}H NMR (DMSO-d_6) δ 2.78-2.80 (4H, t, *J* 5.57 Hz, 2 x CH_2 at $NHCH_2$), 2.96-2.99 (4H, t, *J* 5.84 Hz, 2 x CH_2 at NHAr.), 3.17-3.19 (2H, s, 2 x NH at CH_2), 3.36 (2H, s, 2 x NH at Ar.), 8.53 (4H, s, 4 x Ar. CH at C-3/C-3'/C-5/C-5'). ^{13}C NMR (DMSO-d_6) δ 2 x C-NHAr. (45.41), 2 x C-$NHCH_2$ (46.89), C-1/C-1' (137.03), C-2/C-2'/C-6/C-6' (140.99), C-3/C-3'/C-5/C-5' (128.76), C-4/C-4' (112.61-114.30, (quartet), *J* 35.54 Hz), CF_3 (113.08-124.83, (quartet), *J* 271.21 Hz). ^{19}F NMR (DMSO-d_6) δ (-59.78). MS, m/z 552 (31%, $M^{+\cdot}$, $C_{18}H_{15}N_7O_8F_6$ - F), 307 (100%, $M^{+\cdot}$ - $ArNHCH_2$), 264 (10%, 307 - $NH(CH_2)_2$), 172 (8%, 264 - 2 x NO_2), [552 (31%), 307 (100%), 264 (10%), 244 (70%), 172 (8%), 105 (5%), 69 (8%), 56 (60%)]. IR (KBr) υ 3323 (N-H str.), 3211 (Ar. C-H str.), ~ 2900 (Al. C-H str.), 1639 (N-H bend, secondary), 1544 (NO_2 asymm. str.), ~ 1290 (NO_2, O-H bonded, symm. str.), 1121 (C-F str.), ~ 720 (CF_3 str.). R_f ($CHCl_3$) 0.37.

Anal. Calcd. for $C_{18}H_{15}N_7O_8F_6$: C, 39.05; H, 2.67; N, 15.07.
Found: C, 38.99; H, 2.78; N, 15.03.

N^1,N^2-di-(2, 6-dinitro-4-trifluoromethylphenyl)-1,2-phenylenediamine (65l)

1-Chloro-2,6-dinitro-4-trifluoromethylbenzene (5.41 g, 0.02 mole) and 1,2-phenyl enediamine (1.08 g, 9.99 x 10^{-3} mole) were reacted to give the title compound (1.02 g, 58%) as needles, mp 252-254° C (from methanol). ^{1}H NMR (DMSO-d_6) δ 6.72-6.77 (2H, d (*m* - coupled), *J* 8.06, J_m 2.07 Hz, 2 x Ar. CH at C-3/C-6), 6.96-7.14 (2H, dd (*m* - coupled), *J* 8.07, 8.07, J_m 2.07 Hz, 2 x Ar. CH at C-4/C-5), 8.61 (4H, s, 4 x Ar. CH at C-3'/C-5'), 9.68 (2H, s, 2 x NH). ^{13}C NMR (DMSO-d_6) δ C-1/C-2 (134.96), C-3/C-6 (129.46), C-4/C-5 (114.52), C-1' (140.88), C-2'/C-6' (141.22), C-3'/C-5' (128.32), C-4' (117.85-119.53, (quartet), *J* 35.35 Hz), CF_3 (116.00-128.93, (quartet), *J* 272.0 Hz). ^{19}F NMR (DMSO-d_6) δ (-60.12). MS, m/z 576 (30%, $M^{+\cdot}$, $C_{20}H_{10}N_6O_8F_6$), 557 (10%, $M^{+\cdot}$ - F), 529 (100%, $M^{+\cdot}$ - HNO_2), 482 (80%, 529 - HNO_2), 452 (9%, 482 - NO), 406 (5%, 452 - NO_2), 337 (10%, 406 - CF_3), [576 (30%), 557 (10%), 529 (100%), 482 (80%), 452 (9%), 406 (5%), 337 (10%), 296 (35%)]. IR (KBr) υ 3304 (N-H str.), 3105 (Ar. C-H str.), 1638 (N-H bend, secondary), 1542 (NO_2 asymm. str.), ~ 1300 (NO_2 , O-H bonded, symm. str.), 1129 (C-F str.), 757 (CF_3 str.). R_f ($CHCl_3$) 0.41.

Anal. Calcd. for $C_{20}H_{10}N_6O_8F_6$: C, 41.68; H, 1.75; N, 14.58.
Found: C, 41.86; H, 1.95; N, 14.59.

N^1,N^2-di-(2,6-dinitro-4-trifluoromethylphenyl)-1,3-phenylenediamine (65m)

1-Chloro-2,6-dinitro-4-trifluoromethylbenzene (5.41 g, 0.02 mole) and 1,3-phenyl enediamine (1.08 g, 9.99 x 10^{-3} mole) were reacted to give the title compound (4.00 g, 70%) as yellow needles, mp 264-266° C (from methanol). ^{1}H NMR (DMSO-d_6) δ 6.71-6.75 (2H, d (*m* - coupled), *J* 8.05, J_m 2.09 Hz, 2 x Ar. CH at C-4/C-6), 6.94-6.95 (1H, s (*m*-coupled), J_m 1.99 Hz, Ar. CH at C-2), 7.07-7.13 (1H, dd, *J* 8.07, 8.07 Hz, Ar. CH at C-5) 8.16 (4H, s, 4 x Ar. CH at C-3'/C-5'), 9.67 (2H, s, 2 x NH). ^{13}C NMR (DMSO-d_6) δ C-1/C-3 (134.95), C-2 (118.98), C-4/C-6 (129.48), C-5 (114.50), C-1' (140.90), C-2'/C-6' (141.25), C-3'/C-5' (128.28), C-4' (118.42-119.58, (quartet), *J* 35.36 Hz), CF_3 (difficult to assign due to background noise). ^{19}F NMR (DMSO-d_6) δ (-60.15). MS, m/z 576 (100%, $M^{+\cdot}$, $C_{20}H_{10}N_6O_8F_6$), 557 (22%, $M^{+\cdot}$ - F), [576 (100%), 557 (25%), 542 (10%), 512 (18%), 496 (35%), 465 (20%), 449 (22%), 390 (10%)]. IR (KBr) υ 3355 (N-H str.), 3091 (Ar. C-H str.), 1641 (N-H bend, secondary), 1537 (NO_2 asymm. str.), 1279 (NO_2, O-H bonded, symm. str.), 1136 (C-F str.), ~ 750 (CF_3 str.). R_f ($CHCl_3$) 0.50.

Anal. Calcd. for $C_{20}H_{10}N_6O_8F_6$: C, 41.68; H, 1.75; N, 14.58.
Found: C, 41.81; H, 1.96; N, 14.54.

N^1,N^2-di-(2,6-dinitro-4-trifluoromethylphenyl)-1,4-phenylenediamine (65n)

1-Chloro-2,6-dinitro-4-trifluoromethylbenzene (5.41 g, 0.02 mole) and 1,4-phenyl enediamine (1.08 g, 9.99 x 10^{-3} mole) were reacted to give the title compound (2.54 g, 45%) as yellow needles, mp 316-318° C (from methanol). ^{1}H NMR (DMSO-d_6) δ 7.05 (4H, s, 4 x Ar. CH at C-2/C-3/C-5/C-6), 8.57 (4H, s, 4 x Ar. CH at C-3'/C-5'), 9.79 (2H, s, 2 x NH). ^{13}C NMR (DMSO-d_6) δ C-1/C-4 (135.86), C-1' (136.56), C-2'/C-6' (140.52), C-3'/C-5' (128.46), C-4' and CF_3 (difficult to assign due to background noise). ^{19}F NMR (DMSO-d_6) δ (-60.04). MS, m/z 576 ($M^{+\cdot}$, 100%, $C_{20}H_{10}N_6O_8F_6$), 557 (12%, $M^{+\cdot}$ - F), 341 (8%, $M^{+\cdot}$ - $C_7H_2N_2O_4F_3$), 249 (10%, 341 - 2 x NO_2). [576 (100%), 557 (12%), 341 (8%), 249 (10%), 221 (5%), 159 (5%), 108 (5%), 69 (5%)]. IR (KBr) υ 3289 (N-H str.), ~ 3100 (Ar. C-H str.), 1633 (N-H bend, secondary), 1550 (NO_2 asymm. str.), 1272 (NO_2, O-H bonded, symm. str.), 1125 (C-F str.), ~ 750 (CF_3 str.). R_f ($CHCl_3$) 0.25.

Anal. Calcd. for $C_{20}H_{10}N_6O_8F_6$: C, 41.68; H, 1.75; N, 14.58.
Found: C, 41.88; H, 1.98; N, 14.57.

***N*-(2,6-dinitro-4-trifluoromethylphenyl)aminobenzene (67a)** (86)

1-Chloro-2,6-dinitro-4-trifluoromethylbenzene (2.71 g, 0.01 mole) and aniline (0.94 ml, 0.96 g, 0.01 mole) were reacted to give the title compound (1.59 g, 49%) as

yellow needles, mp 102-104° C (from methanol) (Lit. 121-122° C, from toluene) (86). ^{1}H NMR (DMSO-d_6) δ 7.08-7.14 (3H, m, J 12.68, J_m 1.22 Hz, 3 x Ar. CH at C-3/C-4/C-5), 7.24-7.33 (2H, d (*m*-coupled), J 12.63, J_m 1.25 Hz, 2 x Ar. CH at C-2/C-6), 8.58 (2H, s, 2 x CH at C-3'/C-5'), 9.79 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ C-1 (139.66), C-2/C-6 (120.22), C-3/C-5 (124.89), C-4 (128.34), C-1' (135.89), C-2'/C-6' (140.55), C-3'/C-5' (129.00), C-4' (116.86-117.99, (quartet), J 35.35 Hz), CF_3 (difficult to assign due to high background levels). ^{19}F NMR (DMSO-d_6) δ (-60.06). MS m/z 327 (100%, $M^{+\cdot}$, $C_{13}H_8N_3O_4F_3$), 308 (10%, $M^{+\cdot}$ - F), 235 (30%, $M^{+\cdot}$ - C_6H_6N), 216 (10%, 308 - 2 x NO_2). [327 (100%), 308 (10%), 282 (20%), 264 (12%), 247 (15%), 235 (30%), 216 (10%), 77 (35%)]. IR (KBr) υ 3331 (N-H str.), 3069 (Ar. C-H str.), 1637 (N-H bend, secondary), 1531 (NO_2 asymm. str.), 1124 (C-F str.), 756 (CF_3 str.). R_f ($CHCl_3$) 0.75.

4-Methyl-1-[*N*-(2,6-dinitro-4-trifluoromethylphenyl)amino]benzene (67b)

1-Chloro-2,6-dinitro-4-trifluoromethylbenzene (2.71 g, 0.01 mole) and *p*-toluidine (1.07 ml, 1.04 g, 9.72 x 10^{-3} mole) were reacted to give the title compound (0.93 g, 68%) as yellow needles, mp 138-140° C (from methanol). ^{1}H NMR (DMSO-d_6) δ 2.26 (3H, s, CH_3 at C-4), 6.99-7.03 (2H, d, J 8.51 Hz, 2 x Ar. CH at C-2/C-6), 7.08-7.11 (2H, d, J 8.38 Hz, 2 x Ar. CH at C-3/C-5), 8.56 (2H, s, 2 x CH at C-3'/C-5'), 9.77 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ C of CH_3 (20.39), C-1 (137.03), C-2/C-6 (120.58), C-3/C-5 (128.51), C-4 (134.40), C-1' (136.37), C-2'/C-6' (140.15), C-3'/C-5' (129.47), C-4' (116.78-118.24, (quartet), J 35.43 Hz), CF_3 (difficult to assign due to high background levels). ^{19}F NMR (DMSO-d_6) δ (-60.01). MS m/z 341 (100%, $M^{+\cdot}$, $C_{14}H_{10}N_3O_4F_3$), 322 (10%, $M^{+\cdot}$ - F), 294 (18%, $M^{+\cdot}$ - HNO_2), 248 (42%, 294 - NO_2), 179 (10%, 248 - CF_3). [341 (100%), 322 (10%), 294 (18%), 278 (5%), 261 (15%), 248 (42%), 179 (10%), 77 (10%)]. IR (KBr) υ 3335 (N-H str.), 3101 (Ar. C-H str.), 2923 (Al. C-H str.), 1643 (N-H bend, secondary), 1544 (NO_2 asymm. str.), 1132 (C-F str.), 730 (CF_3 str.). R_f ($CHCl_3$) 0.68.

Anal. Calcd. for $C_{14}H_{10}N_3O_4F_3$: C, 49.28; H, 2.95; N, 12.31.
Found: C, 49.30; H, 2.98; N, 12.28.

4-Methoxy-1-[*N*-(2,6-dinitro-4-trifluoromethylphenyl)amino]benzene (67c) (86)

1-Chloro-2,6-dinitro-4-trifluoromethylbenzene (2.71 g, 0.01 mole) and *p*-anisidine (1.23 g, 0.01 mole) were reacted to give the title compound (2.64 g, 74%) as yellow needles, mp 133-135° C (from methanol) (Lit. 137-138° C, from toluene) (86). ^{1}H NMR (DMSO-d_6) δ 3.74 (3H, s, CH_3 at C-4), 6.84-6.86 (2H, d, J 8.99 Hz, 2 x Ar. CH at C-2/C-6), 7.08-7.12 (2H, d, J 8.96 Hz, 2 x Ar. CH at C-3/C-5), 8.53 (2H, s,

2 x CH at C-3'/C-5'), 9.81 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ C of CH_3O (55.21), C-1 (137.31), C-2/C-6 (114.18), C-3/C-5 (128.57), C-4 (157.02), C-1' (132.37), C-2'/C-6' (139.66), C-3'/C-5' (123.19), C-4' (116.07-118.64, (quartet), *J* 35.47 Hz), CF_3 (~ 116.10-129.0, (quartet), *J* 271.58 Hz). ^{19}F NMR (DMSO-d_6) δ (-60.09). MS m/z 357 (100%, $M^{+\cdot}$, $C_{14}H_{10}N_3O_5F_3$), 342 (10%, $M^{+\cdot}$ - CH_3), 338 (8%, $M^{+\cdot}$ - F), 310 (10%, $M^{+\cdot}$ - HNO_2), 264 (5%, 310 - NO_2), 250 (18%, $M^{+\cdot}$ - C_7H_7O). [357 (100%), 342 (10%), 338 (8%), 323 (10%), 310 (10%), 295 (10%), 264 (5%), 250 (18%)]. IR (KBr) υ 3298 (N-H str.), 3096 (Ar. C-H str.), 2924 (Al. C-H str.), 1638 (N-H bend, secondary), 1511 (NO_2 asymm. str.), 1140 (C-F str.), ~ 720 (CF_3 str.). R_f ($CHCl_3$) 0.66.

4-Chloro-1-[*N*-(2,6-dinitro-4-trifluoromethylphenyl)amino]benzene (67d)

1-Chloro-2,6-dinitro-4-trifluoromethylbenzene (2.71 g, 0.01 mole) and *p*-chloroaniline (1.27 g, 0.01 mole) were reacted to give the title compound (3.37 g, 93%) as yellow needles, mp 98-104° C (from water). ^{1}H NMR (DMSO-d_6) δ 7.13-7.17 (2H, d, *J* 8.84 Hz, 2 x Ar. CH at C-2/C-6), 7.31-7.35 (2H, d, *J* 8.53 Hz, 2 x Ar. CH at C-3/C-5), 8.59 (2H, s, 2 x CH at C-3'/C-5'), 9.81 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ C-1 (135.74), C-2/C-6 (122.01), C-3/C-5 (128.51), C-4 (139.03), C-1' (128.45), C-2'/C-6' (141.01), C-3'/C-5' (129.02), C-4 (117.70-119.39, (quartet), *J* 35.47 Hz), CF_3 (116.09-133.00, (quartet), *J* 271.95 Hz). ^{19}F NMR (DMSO-d_6) δ (-60.33). MS m/z 361 (100%, $M^{+\cdot}$, $C_{13}H_7ClN_3O_4F_3$), 342 (5%, $M^{+\cdot}$ - F), 314 (10%, $M^{+\cdot}$ - HNO_2), 268 (18%, 314 - NO_2), 250 (5%, $M^{+\cdot}$ - C_6H_4Cl). [361 (100%), 342 (5%), 314 (10%), 268 (18%), 281 (15%), 250 (5%), 234 (20%), 111 (15%)]. IR (KBr) υ 3295 (N-H str.), 3090 (Ar. C-H str.), 1637 (N-H bend, secondary), 1532 (NO_2 asymm. str.), 1131 (C-F str.), 728 (CF_3 str.). R_f ($CHCl_3$) 0.57.

Anal. Calcd. for $C_{13}H_7ClN_3O_4F_3$: C, 43.17; H, 1.95; N, 11.61.
Found: C, 43.36; H, 1.99; N, 11.60.

2,4-Dichloro-1-[*N*-(2,6-dinitro-4-trifluoromethylphenyl)amino]benzene (67e)

1-Chloro-2,6-dinitro-4-trifluoromethylbenzene (2.71 g, 0.01 mole) and 2,4-dichloroaniline (1.62 g, 0.01 mole) were reacted to give the title compound (0.87 g, 22%) as needles, mp 150-151° C (from methanol). ^{1}H NMR ($CDCl_3$) δ 6.86-6.89 (1H, d, *J* 8.62 Hz, Ar. CH at C-6), 7.15-7.19 (1H, d (*m*-coupled), *J* 8.64, J_m 2.29 Hz, Ar. CH at C-5), 7.52-7.53 (1H, s (*m*-coupled), J_m 2.25 Hz, Ar. CH at C-3), 8.51 (2H, s, 2 x CH at C-3/C-5), 9.82 (1H, s, NH). ^{13}C NMR (difficult to assign all the peaks due to background noise). ^{19}F NMR (DMSO-d_6) δ (-60.13). MS, m/z

395/397/399 (100%, $M^{+\cdot}$, $C_{13}H_6Cl_2N_3O_4F_3$), 376/378/380 (10%, $M^{+\cdot}$ - F), 360/362 (10%, $M^{+\cdot}$ - Cl), 303 (30%, $M^{+\cdot}$ - 2 x NO_2), 234 (10%, $M^{+\cdot}$ - $C_6H_4Cl_2N$). [395/397/399 (100%), 376/378/380 (10%), 360/362 (10%), 303 (30%), 268 (35%), 249 (5%), 234 (10%), 69 (65%)]. IR (KBr) υ 3321 (N-H str.), 3092 (Ar. C-H str.), 1639 (N-H bend, secondary), 1538 (NO_2 asymm. str.), 1117 (C-F str.), 727 (CF_3 str.). R_f ($CHCl_3$) 0.19.

Anal. Calcd. for $C_{13}H_6Cl_2N_3O_4F_3$: C, 39.42; H, 1.53; N, 10.60. Found: C, 39.41; H, 1.73; N, 10.55.

2,5-Dichloro-1-[*N*-(2,6-dinitro-4-trifluoromethylphenyl)amino]benzene (67f)

1-Chloro-2,6-dinitro-4-trifluoromethylbenzene (2.71 g, 0.01 mole) and 2,5-dichloroaniline (1.62 g, 0.01 mole) were reacted to give the title compound as a crude oil. ^1H and ^{13}C NMR (shows a complex mixture of **67f** and possibly some starters). MS (shows a mixture) m/z 395/397/399 (20%, $M^{+\cdot}$, $C_{13}H_6Cl_2N_3O_4F_3$), 270/272 (100%, $C_7H_2ClN_2O_4F_3$), 161/163/165 (25%, $C_6H_5Cl_2N$). IR (KBr) υ 3459 (N-H str.), 3083 (Ar. C-H str.), 1637 (N-H bend), 1542 (C=C str.), 1124 (C-F str.). R_f ($CHCl_3$) crude 0.66.

2,4,5-Trichloro-1-[*N*-(2,6-dinitro-4-trifluoromethylphenyl)amino]-benzene (67g)

1-Chloro-2,6-dinitro-4-trifluoromethylbenzene (2.71 g, 0.01 mole) and 2,4,5-trichloroaniline (2.03 g, 0.01 mole) were reacted to give the title compound (0.19 g, 35%) as a mixture. The following is a tentative assignment. ^1H NMR (DMSO-d_6) δ 7.08 (1H, s, CH at C-2), 7.35 (1H, s (broad), NH), 7.48 (1H, s, CH at C-5), 8.67 (2H, s, 2 x CH at C-3'/C-5'). ^{13}C NMR (shows a mixture). ^{19}F NMR (DMSO-d_6) δ (-60.15). MS (shows a mixture) m/z 429/431/433 (30%, $M^{+\cdot}$, $C_{13}H_5Cl_3N_3O_4F_3$), 270/272 (70%, $C_7H_2ClN_2O_4F_3$ - starting material), 395/397/399 (30%, $C_6H_3Cl_2$ - dichloro compound), 195/197/199 (100%, $C_6H_2Cl_3NH_2$ - starting material). IR (KBr) (a mixture).

***N*-morpholino-(2,6-dinitro-4-trifluoromethylphenylamine) (67h)** [85]

1-Chloro-2,6-dinitro-4-trifluoromethylbenzene (2.71 g, 0.01 mole) and morpholine (0.87 ml, 1.26 g, 0.01 mole) were reacted to give the title compound (3.05 g, 95%) as yellow needles, mp 142-144° C (from toluene) (Lit. 139-140° C) [85]. ^1H NMR ($CDCl_3$) δ 3.13-3.16 (4H, t, *J* 4.53 Hz, 2 x CH_2 at C-3/C-5), 3.77-3.81 (4H, t, *J* 4.74 Hz, 2 x CH_2 at C-2/C-6), 8.08 (2H, s, Ar. CH at C-3'/C-5'). ^{13}C NMR ($CDCl_3$) δ 2 x C at C-3/C-5 (50.99), 2 x C at C-2/C-6 (66.28), C-1' (140.49), C-2'/C-6' (146.37),

C-3'/C-5' (126.05), C-4' (119.89-120.14, (quartet), *J* 35.98 Hz), CF_3 (125.14-128.55, (quartet), *J* 286.55 Hz). ^{19}F NMR (DMSO-d_6) δ (-60.37). MS, m/z 321 (35%, $M^{+\cdot}$, $C_{11}H_{10}N_3O_5F_3$), 304 (65%, $M^{+\cdot}$ - OH), 302 (15%, $M^{+\cdot}$ - F), 291 (10%, $M^{+\cdot}$ - NO), 69 (10%, CF_3). [321 (35%), 304 (65%), 302 (15%), 291 (10%), 228 (10%), 200 (25%), 159 (30%), 69 (10%)]. IR (KBr) υ 3080 (Ar. C-H str.), 2885 (Al. C-H str.), 1542 (NO_2 asymm. str.), 1139 (C-F str.), 713 (CF_3 str.). R_f ($CHCl_3$) 0.42.

2-[*N*-(2,6-dinitro-4-trifluoromethylphenyl)amino]benzotrifluoride (67i)

1-Chloro-2,6-dinitro-4-trifluoromethylbenzene (2.71 g, 0.01 mole) and 2-amino-benzotrifluoride (1.41 g, 8.75 x 10^{-3} mole) were reacted to give the title compound (2.95 g, 75%) as an oil. ^1H NMR ($CDCl_3$) δ 4.16 (1H, s (broad), NH), 6.72-6.79 (2H, m, *J* 4.73 Hz, 2 x CH at C-3/C-4), 7.23-7.26 (1H, dd, *J* 4.73, 4.73 Hz, CH at C-5), 7.31-7.42 (1H, d, *J* 4.73 Hz, CH at C-6), 8.27 (2H, s, 2 x CH at C-3'/C-5'). ^{13}C NMR (background noise, hence difficult to assign all the peaks). ^{19}F NMR (DMSO-d_6) δ (-61.16, CF_3 at C-1), (-61.08, CF_3 at C-4). MS, m/z 395 ($M^{+\cdot}$, 100%, $C_{14}H_7N_3O_4F_6$), 376 (10%, $M^{+\cdot}$ - F), 348 (10%, $M^{+\cdot}$ - HNO_2). [395 (100%), 376 (10%), 348 (10%), 310 (10%), 283 (30%), 264 (10%), 252 (10%), 69 (10%)]. IR (KBr) υ 3432 (N-H str.), 3083 (Ar. C-H str.), 1625 (N-H bend, secondary), 5551 (NO_2 asymm. str.), 1119 (C-F str.), 720 (CF_3). R_f ($CHCl_3$) 0.17.

Anal. Calcd. for $C_{14}H_7N_3O_4F_6$: C, 38.82; H, 1.63; N, 11.60.
Found: C, 39.00; H, 1.52; N, 11.55.

2-Methyl-4-[*N*-(2,6-dinitro-4-trifluoromethylphenyl)amino]quinoline (67j)

1-Chloro-2,6-dinitro-4-trifluoromethylbenzene (2.71 g, 0.01 mole) and 4-amino-2-methylquinoline (1.58 g, 0.01 mole) were reacted to give the title compound (2.01 g, 51%) as pale yellow needles, mp > 270° C (from methanol). ^1H NMR (DMSO-d_6) δ 2.31 (3H, s, CH_3), 5.76 (1H, s, CH at C-3), 7.34-7.40 (1H, t (*m*-coupled), *J* 7.06 Hz, CH at C-7), 7.53-7.56 (1H, d (*m*-coupled), *J* 8.17 Hz, CH at C-8), 7.65-7.72 (1H, t (*m*-coupled), *J* 7.03, J_m 1.40 Hz, CH at C-6), 8.16-8.19 (1H, d (*m*-coupled), *J* 8.12, J_m 1.07 Hz, CH at C-5), 8.56 (2H, s, 2 x CH at C-3'/C-5'). ^{13}C NMR (DMSO-d_6) δ C of CH_3 (19.24), C-2 (120.91), C-3 (99.59), C-4 (144.75), C-5 (118.49), C-6 (125.53), C-7 (125.59), C-8 (123.85), C-9 (157.72), C-10 (148.88), C-1' (138.64), C-2'/C-6' (143.98), C-3'/C-5' (131.69), C-4' (118.49-120.62, (quartet), *J* 34.91 Hz), CF_3 (~ 117-129, (quartet), *J* 271.77 Hz). ^{19}F NMR (DMSO-d_6) δ (-59.86). MS, m/z 392 (60%, $M^{+\cdot}$, $C_{17}H_{11}N_4O_4F_3$), 371 (5%, $M^{+\cdot}$ - F), 362 (10%, $M^{+\cdot}$ - NO), 346 (5%, $M^{+\cdot}$ - NO_2), 328 (100%, 358 - NO), 300 (30%, $M^{+\cdot}$ - 2 x NO_2). [392 (60%), 371 (5%), 362 (10%), 346 (5%), 358 (100%), 312 (40%), 300 (30%), 69 (22%)]. IR

(KBr) υ 3401 (N-H str.), 3100 (Ar. C-H str.), ~ 1600 (N-H bend, secondary), 1550 (NO_2 asymm. str.), 1131 (C-F str.), ~ 720 (CF_3). R_f ($CHCl_3$) 0.03.

Anal. Calcd. for $C_{17}H_{11}N_4O_4F_3$: C, 53.51; H, 4.51; N, 4.97.
Found: C, 53.32; H, 4.49; N, 5.02.

4-(*N*,*N*-dipropylsulphamoyl)-2,6-dinitro-1-(*N*,*N*-dipropylamino) benzene (68)

Dipropylamine (0.19 ml, 0.14 g, 1.39 x 10^{-3} mole) was added dropwise to 2,6-dinitro-4-(*N*,*N*-dipropylamino)benzenesulphonyl chloride (8) in toluene (20 ml). The reaction was heated under reflux, under argon, for 4h, poured onto crushed ice (100 g) and extracted with ethyl acetate (50 ml). The extract was washed with brine (50 ml) dried ($MgSO_4$), and evaporated *in vacuo* to give the title product as yellow-orange needles (1.01 g, 87%), mp 199-200° C. ^{1}H NMR (DMSO-d_6) δ 0.76-0.82 (6H, t, *J* 7.0 Hz, 2 x CH_3 at f), 0.88-0.94 (6H, t, *J* 7.0 Hz, 2 x CH_3 at a), 1.36-1.51 (4H, m, *J* 7.0 Hz, 2 x CH_2 at e), 1.53-1.66 (4H, m, *J* 7.0 Hz, 2 x CH_2 at b), 2.82-2.85 (4H, t, *J* 7.0 Hz, 2 x CH_2 at d), 2.88-2.91 (4H, t, *J* 7.0 Hz, 2 x CH_2 at c), 8.11 (2H, s, 2 x Ar. CH at C-3/C-5). ^{13}C NMR (DMSO-d_6) δ 2 x C of CH_3 at a (10.94), 2 x C of CH_2 at b (20.81), 2 x C of CH_2 at c (54.05), 2 x C of CH_2 at d (48.26), 2 x C of CH_2 at e (18.96), 2 x C of CH_3 at f (10.79), C-1 (143.07), C-2/C-6 (146.56), C-3/C-5 (125.43), C-4 (137.04). MS (compound was involatile to give a mass spectrum under normal (CI) conditions). IR (KBr) υ 3147 (Ar. C-H str.), 2967 (Al. C-H str.), 1537 (NO_2 asymm. str.), 1459 (C-H bend), 1238 (NO_2, O-H bonded, symm. str.), 1048 (SO_2 str.), 750 (C-NO_2 str.), 627 (S-N str.). R_f ($CHCl_3$) 0.78.

Anal. Calcd. for $C_{18}H_{30}N_4O_6S$: C, 50.22; H, 7.02; N, 13.01.
Found: C, 50.10; H, 7.02; N, 13.05.

N^{10}-(2,6-dinitro-4-trifluoromethylphenyl)-2-trifluoromethyl-4-nitro-5, 10-dihydrophenazine (79)

Two equivalents of 1-chloro-2,6-dinitro-4-trifluoromethylbenzene (27.0 g; 0.05 mole) and one equivalent of 1,2-phenylenediamine (5.39 g; 0.025 mole) were mixed in excess anhydrous toluene (100 ml). Two equivalents of triethylamine (10.10 ml) were added and the reaction mixture was heated under reflux for 5 h, filtered and washed with water (500 ml) to give the title compound (23.49 g; 81%) as purple needles, mp 237-239° C (from methanol). ^{1}H NMR (DMSO-d_6) δ 5.84-5.88 (1H, d (*m* - coupled), J_o 7.9, J_m 0.9 Hz, CH at C-9), 6.11-6.12 (1H, s (*m* - coupled), J_m 1.6 Hz, CH at C-1), 6.54-6.60 (1H, dd (*m* - coupled), J_o 7.7, 7.7, J_m 1.2 Hz, CH at C-7), 7.04-7.08 (1H, d (*m* - coupled), J_o 7.8, J_m 1.4 Hz, CH at C-6), 7.55-7.56 (1H, s (*m* - coupled), J_m 0.9 Hz, CH at C-3), 9.13 (2H, s, 2 x CH at C-3'/C-5'), 9.74 (1H, s, NH). ^{13}C NMR (DMSO-d_6) δ C-1 (110.13), C-1' (126.37), CF_3 at C-2 (difficult to assign due

to overlaping peaks), C-2 (~130.00), C-2'/C-6' (149.98), C-3 (116.34), C-3'/C-5' (129.21), C-4 (129.57), C-4' (~119.51), CF_3 at C-4' (difficult to assign due to overlaping peaks), C-6 (116.81), C-7 (124.02), C-8 (124.67), C-9 (112.61), C-11 (~129.90), C-12 (131.32), C-13 (136.08), C-14 (136.34). ^{19}F NMR (DMSO-d_6) δ (-61.53, CF_3 at C-2), (-61.17, CF_3 at C-4'). MS, m/z 529 ($M^{+\cdot}$, 100%, $C_{20}H_9N_5O_6F_6$), 510 (10%, $M^{+\cdot}$ - F), 482 (70%, $M^{+\cdot}$ - HNO_2), 436 (5%, 482 - NO_2), 390 (20%, 436 - NO_2), 321 (20%, 390 - CF_3), [529 (100%), 510 (10%), 482 (70%), 436 (5%), 390 (20%), 321 (20%), 294 (10%), 265 (10%)]. IR (KBr) υ 3456 (N-H asymm. str.), 3315 (N-H symm. str.), 3127 (C-H str.), 1558 (NO_2 asymm. str.), 1432 (C-H bend), 1335 (NO_2, O-H bonded, symm. str.), 1122 (C-F str.). R_f (methanol/toluene, 5:1) 0.32.

Anal. Calcd. for $C_{20}H_9N_5O_6F_6$: C, 45.38; H, 1.71; N, 13.22.
Found: C, 45.60; H, 1.40; N, 13.44.

1-Trifluoromethyl-6,7-dihydro-3*H*,5*H*-benzo[ij]quinolizin-3-one (88a)

1,2,3,4-Tetrahydroquinoline (1.90 ml, 2.02 g, 0.015 mol) and ethyl trifluoroacetoacetate (2.19 ml, 2.76 g, 0.015 mol) were heated under reflux for 2 h. Polyphosphoric acid (40.19 g) was added and the mixture was heated at 150° C for 1.5 h to give the title compound (1.97g, 52%) as brown needles, mp 117-120° C (from methanol/water). ^1H NMR (DMSO-d_6) δ 1.98-2.08 (2H, m, *J* 6.0 Hz, CH_2 at C-6), 2.96-3.00 (2H, t, *J* 6.0 Hz, benzylic CH_2 at C-7), 4.07-4.11 (2H, t, *J* 6.0 Hz, cyclic CH_2 at C-5), 7.09 (1H, s, vinyl CH at C-2), 7.27-7.34 (1H, t, *J* 8.0 Hz, Ar. CH at C-9), 7.53-7.56 (1H, d (*m*-coupled), *J* 8.0, J_m 2.0 Hz, Ar. CH at C-10), 7.60-7.64 (1H, d (*m*-coupled), *J* 8.0, J_m 2.0 Hz, Ar. CH at C-8). ^{13}C NMR (DMSO-d_6) δ C-1 (135.00), C-2 (120.43), C-3 (158.79), C-5 (42.34), C-6 (19.62), C-7 (26.95), C-13 (124.95), C-8 (131.24), C-9 (122.51), C-10 (122.41), C-11 (126.06), C-12 (137.13). ^{19}F (DMSO-d_6) δ (- 61.58). MS, m/z 253 ($M^{+\cdot}$, 85%, $C_{13}H_{10}F_3NO$), 252 (57%, M - H), 238 (100%, $C_{12}H_7F_3NO$), [253 (85%), 252 (57%), 238 (100%), 190 (5%), 155 (5%), 120 (5%), 77 (5%), 44 (2%)]. IR (KBr) ϑ 3442 (Ar. C-H str.), 2924 (vinyl C-H str.), 2853 (N-CH_2 str.), 1661 (C=O str.), 1587 (C=C str.), 1472 (C-H def.), 1283-1136 (C-F str.), ~720 (CF_3) cm^{-1}.

Anal. Calcd. for $C_{13}H_{10}NOF_3$: C, 61.66; H, 3.98; N, 5.53.
Found: C, 61.61; H, 3.92; N, 5.20.

1-Methyl-6,7-dihydro-3*H*,5*H*-benzo[ij]quinolizin-3-one (88b)

The title compound was prepared by Afsah's method [63] to give (1.69 g, 57%) as needles, mp 128-130° C (from benzene/petroleum ether 40-60°) (Lit 130° C) [120]. ^1H NMR (DMSO-d_6) δ 1.94-2.01 (2H, m, *J* 6.0 Hz, CH_2 at C-6), 2.42 (3H, s, CH_3), 2.92-2.97 (2H, t, *J* 6.0 Hz, benzylic CH_2 at C-7), 3.99-4.04 (2H, t, *J* 6.0 Hz, CH_2 at

C-5), 6.50 (1H, s, vinyl CH at C-2), 7.14-7.20 (1H, t, *J* 8.0 Hz, Ar. CH at C-9), 7.37-7.39 (1H, d (*m* -coupled), *J* 8.0,J_m 2.0 Hz, Ar. CH at C-10), 7.59-7.62 (1H, d (*m* -coupled), *J* 8.0, J_m 2.0 Hz, Ar. CH at C-8). ^{13}C (DMSO-d_6) δ C-2 (119.23), C-3 (161.23), C-5 (41.42), C-6 (20.11), C-7 (27.06) C-13 (124.83), C-8 (129.82), C-9 (121.22), C-10 (123.11), C-11 (120.00), C-12 (146.24), C-1 at CH_3 (18.49). MS, m/z 199 ($M^{+\cdot}$, 90%, $C_{13}H_{13}NO$), 198 (60%, $M^{+\cdot}$ - H), 184 (100%, $C_{12}H_{10}NO$). IR (KBr) ϑ 3441 (Ar. C-H str.), 2929 (vinyl C-H str.), 2820 (N-CH_2 str.), 1645 (C=O str.), 1548 (C=C str.) cm^{-1}.

1-Phenyl-6,7-dihydro-3*H*,5*H*-benzo[ij]quinolizin-3-one (88c)

1,2,3,4-Tetrahydroquinoline (2.02 ml, 2.02 g, 0.015 mol) and ethyl benzoyl acetate (2.59 ml, 2.88 g, 0.015 mol) were heated under reflux for 2 h. Polyphosphoric acid (40.61 g) was added and the mixture was heated at 150° C for 1.5 h to give the title compound (1.84 g, 47%) as needles, mp > 350° C (from water). NMR results were poor due to high distortion levels. MS, m/z 261 ($M^{+\cdot}$, 100%, $C_{18}H_{15}NO$), 260 (50%, $M^{+\cdot}$ - H), 246 (95%, $C_{17}H_{12}NO$), [261 (100%), 260 (50%), 246 (95%), 230 (10%), 217 (10%), 133 (10%), 105 (20%), 77 (10%)]. IR (KBr) ϑ 3427 (Ar. C-H str.), 2602 (vinyl C-H str.), 1658 (C=O str.), ~ 1600 (overlap, C=C skeletal stretch/condensed systems), 924 (C-H out-of-plane bending) cm^{-1}.

Anal. Calcd. for $C_{18}H_{15}NOF$: C, 58.91; H, 4.21; N, 5.11.
Found: C, 59.00; H, 4.22; N, 5.20.

Synthesis of Lilolidine (37): formation of 1,2-di-(1,2,3,4-tetrahydro-quinolin-1-yl)ethane (90) [110]

Attempted preparation by the method of Glass and Weissberger [46] gave (**90**) (9.49 g, 65%) as colourless needles, mp 148-149° C (from heptane) (Lit. 147° C) [110] when 1,2,3,4-tetrahydroquinoline (6.30 ml, 6.68 g, 0.05 mole) and 1-bromo-2-chloroethane (21.15 ml, 36.44 g, 0.25 mole) were reacted. ^1H NMR ($CDCl_3$) δ 1.87-1.99 (4H, m, *J* 6.0 Hz, 2 x cyclic CH_2 at C-3), 2.71-2.76 (4H, t , *J* 6.0 Hz, 2 x benzylic CH_2), 3.31-3.36 (4H, t, *J* 6.0 Hz, 2 x cyclic CH_2 at C-2), 3.47 (4H, s, 2 x Al. CH_2), 6.54-6.57 (2H, d (*m* -coupled), *J* 9.0 Hz, 2 x Ar. CH at C-5), 6.56-6.66 (2H, t (*m* -coupled), *J* 9.0 Hz, 2 x Ar. CH at C-6), 7.02-7.05 (2H, d, *J* 8.0 Hz, 2 x Ar. CH at C-8), 7.08-7.22 (2H, t (*m* -coupled), *J* 8.0 Hz, 2 x Ar. CH at C-7). ^{13}C NMR ($CDCl_3$) δ C-2 (48.33), C-3 (26.99), C-4 (50.21), C-5 (129.32), C-6 (127.26), C-7 (110.12), C-8 (115.65), C-9 (145.08), C-10 (122.25), C-at CH_2 (22.29). MS, m/z 292 ($M^{+\cdot}$, 12%, $C_{20}H_{24}N_2$), 146 (100%, $M^{+\cdot}$ - $C_{10}H_{12}N$), 131 (9%, $C_9H_{10}N$), [292 (12%), 146 (100%), 131 (9%), 117 (5%), 91 (10%), 69 (12%), 55 (12%), 44 (5%)]. IR (KBr) ϑ 3432 (Ar. C-H str.), 2927 (Al. C-H asymm.str.), 2851 (N-CH_2 str.), 1598 (C=C str.), 1454 (CH_2 asymm. bend) cm^{-1}.

4-Trifluoromethyl-1,8-dimethylene-1,2-dihydroquinolin-2-one (93)

Indoline (1.68 ml, 1.79 g, 0.015 mol) and ethyl trifluoroacetoacetate (2.19 ml, 2.76 g, 0.015 mol) were heated under reflux for 2 h. Polyphosphoric acid (41.08 g) was added and the mixture was heated at 150° C for 5.40 h to give the title compound (1.51 g, 42%) as tan-coloured needles, mp 160-165° C (from methanol). ^{1}H NMR (DMSO-d_6) δ 3.37-3.43 (2H, t, *J* 8.0 Hz, benzylic CH_2 at C-8), 4.28-4.35 (2H, t, *J* 8.0 Hz, CH_2 at C-9), 6.95 (1H, s (long range ^{19}F coupling), *J* 1.0 Hz, vinyl CH at C-3), 7.22-7.31 (1H, dd, *J* 7.0, 7.0 Hz, Ar. CH at C-6), 7.45-7.49 (1H, d (*m*-coupled and long range ^{19}F coupling), *J* 7.0, J_m 1.0 Hz, Ar. CH at C-5), 7.52-7.55 (1H, d (*m*-coupled), *J* 7.0, J_m 1.0 Hz, Ar. CH at C-7). ^{13}C NMR (DMSO-d_6) δ C-4 (134.80-135.30 (quartet) *J* 31 Hz), C-3 (122.25), C-2 (157.75), C-9 (46.99), C-8 (26.69), C-10 (111.14), C-7 (126.58), C-6 (123.91), C-5 (120.35), C-12 (132.09), C-11 (142.99), CF_3 (115.50-139.05 (quartet) *J* 271 Hz). ^{19}F (DMSO-d_6) δ (- 62.19). MS, m/z 239 ($M^{+\cdot}$, 75%, $C_{12}H_8F_3NO$), 238 (100%, $M^{+\cdot}$ - H), [239 (75%), 238 (100%), 190 (15%), 141 (8%), 118 (7%), 90 (4%), 77 (4%), 44 (2%)]. IR (KBr) ϑ 3441 (Ar. C-H str.), 2923 (vinyl C-H str.), 1625 (C=O str.), 1149 (CF_3 str.) cm^{-1}.

Anal. Calcd. for $C_{12}H_8NOF_3$: C, 60.26; H, 3.37; N, 5.85.
Found: C, 60.32; H, 3.39; N, 5.82.

1,7-Dimethyl-3*H*,5*H*-benzo[ij]quinolizin-3,5-dione (96)

Aniline (1.36 ml, 1.39 g, 0.015 mol) and two equivalents of ethyl acetoacetate (3.82 ml, 3.90 g, 0.03 mol) were heated under reflux for 2 h. Excess polyphosphoric acid (80.06 g) were added and the mixture was heated at 150° C for 1.5 h to give the title compound (0.13 g, 4%) as brown needles, mp 203-205° C (from benzene/petroleum ether 40-60°). NMR results were poor due to insufficient sample availability. MS, m/z 225 ($M^{+\cdot}$, 60%, $C_{14}H_{11}NO_2$), 159 (100%, $C_{10}H_9NO$), [225 (60%), 209 (5%), 180 (5%), 159 (100%), 131 (30%), 130 (60%), 93 (40%), 77 (50%)]. IR (KBr) ϑ 3423 (Ar. C-H str.), 2922 (vinyl C-H str.), 2853 (N-CH_2 str.), 1633 (C=O str.) cm^{-1}.

Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22.
Found: C, 74.68; H, 4.96; N, 6.21.

Formation of N^1,N^2-diphenylmalonamide (99) in the attempted synthesis of 1,7-dicarbonyl-3*H*,5*H*-benzo[ij]quinolizin-3,5-dione (98)

Aniline (9.11 ml, 9.31 g, 0.10 mol) and two equivalents of diethylmalonate (32.08 ml, 33.83 g, 0.20 mol) were heated under reflux for 2h. Excess polyphosphoric acid (80.88 g) was added and the mixture was heated at 150° C for 1.5 h to give the title compound (13.96 g, 47%) as pink needles, mp 214-216° C (from methanol) (113). ^{1}H NMR (DMSO-d_6) δ 3.43-3.50 (2H, d, *J* 18.0 Hz, CH_2), 7.03-7.09 (2H, t (*m* -

coupled), *J* 8.0 Hz, J_m 1.0 Hz, 2 x Ar. CH at C-4), 7.29-7.36 (4H, t (*m* -coupled), *J* 8.0, J_m 1.0 Hz, 4 x Ar. CH at C-3), 7.61-7.65 (4H, d (*m* -coupled), *J* 7.0, J_m 1.0 Hz, 4 x Ar. CH at C-2), 10.20 (2H, s, 2 x NH). ^{13}C (DMSO-d_6) δ C-1/C-1' (138.87), 2 x C-2/C-2' (128.68), 2 x C-3/C-3' (119.02), C-4/C-4' (123.32), 2 x C at (C=O) (165.36), C at CH_2 (45.86). MS, m/z 254 ($M^{+\cdot}$, 55%, $C_{15}H_{14}N_2O_2$), 135 (50%, $M^{+\cdot}$ - PhNCO), 120 (10%, PhNHCO), 93 (100%, $PhNH_3$), [254 (55%), 135 (50%), 120 (10%), 93 (100%), 77 (22%), 65 (15%), 43 (8%)]. IR (KBr) ϑ 3450 (secondary amide N-H str.), 3273 (Ar. C-H str.), 2926 (Al. C-H str.), 1648 (C=O str.), 1598 (Ar. C=C str.), 1444 (CH_2 def.) cm^{-1}.

2-Carbamoyl-6,7-dihydro-1*H*,5*H*-benzo[ij]quinolizin-1-one (106)

1,2,3,4-Tetrahydroquinoline (1.90 ml, 2.02 g, 0.015 mol), triethylorthoformate (2.49 ml, 2.22 g, 0.015 mol) and ethylcyanoacetate (1.60 ml, 1.69 g, 0.015 mol) were heated under reflux for 2 h. Polyphosphoric acid (40.0 g) was added and the mixture was heated at 150° C for 1.5 h to give the title compound (1.46 g, 43%) as olive coloured needles, mp 271-273° C (from water). ^{1}H NMR (DMSO-d_6) δ 2.07-2.17 (2H, m, *J* 6.0 Hz, CH_2 at C-6), 3.01-3.10 (2H, t, *J* 6.0 Hz, benzylic CH_2 at C-7), 4.34-4.38 (2H, t, *J* 6.0 Hz, CH_2 at C-5), 7.38-7.42 (1H, t, *J* 8.0 Hz, Ar. CH at C-9), 7.45-7.48 (1H, d, *J* 5.0 Hz, amide N<u>H</u>, D_2O exchanged), 7.58-7.62 (1H, d (*m* -coupled), *J* 8.0, J_m 2.0 Hz, Ar. CH at C-8), 8.13-8.18 (1H, d (*m* -coupled), *J* 8.0, J_m 2.0 Hz, Ar. CH at C-10), 8.74 (1H, s, vinyl CH at C-3), 9.34-9.36 (1H, d, *J* 5.0 Hz, amide N<u>H</u>, D_2O exchanged). ^{13}C (DMSO-d_6) δ C-1 (175.55), C-2 (110.47), C-3 (147.19), C-5 (52.04), C-6 (20.53), C-7 (26.04), C-8 (131.83), C-9 (123.68), C-10 (124.35), C-11 (127.01), C-12 (136.55), C-13 (128.22), C of amide (165.65). MS, m/z 228 ($M^{+\cdot}$, 100%, $C_{13}H_{12}N_2O_2$), 212 (40%, $M^{+\cdot}$ - NH_2), 211 (25%, $M^{+\cdot}$ - OH), 185 (95%, 212 - HCN), 184 (30%, $M^{+\cdot}$ - $CONH_2$), 156 (20%, 184 - CO), [228 (100%), 212 (40%), 211 (25%), 185 (95%), 184 (30%), 156 (20%), 128 (10%), 77 (10%).] IR (KBr) ϑ 3354 (primary amide N-H str.), 2929 (vinyl C-H str.), ~ 1660 (cyclic C=O str.), 1650 (primary amide C=O str.), 1603 (benzene ring), 1548 (C=C str.) cm^{-1}.

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27.
Found: C, 68.42; H, 5.59; N, 12.26.

3-Carbamoyl-1,8-dimethylene-1,4-dihydroquinolin-4-one (107)

Indoline (1.68 ml, 1.79 g, 0.015 mol), triethylorthoformate (2.49 ml, 2.22 g, 0.015 mol) and ethylcyanoacetate (1.59 ml, 1.69 g, 0.015 mol) were heated under reflux for 2 h. Polyphosphoric acid (41.56 g) was added and the mixture was heated at 150° C for 2 h to give the title compound (1.28 g, 40%) as tan-coloured needles, mp 226-230° C (from methanol). ^{1}H NMR (DMSO-d_6) δ 3.52-3.55 (2H, t, benzylic CH_2

at C-8), 4.65-4.76 (2H, t, *J* 8.0 Hz, CH_2 at C-9), 7.39-7.45 (1H, d (*m* -coupled), *J* 8.0, J_m 1.0 Hz, Ar. CH at C-7), 7.51-7.59 (1H, dd, *J* 8.0, 8.0 Hz, Ar. CH at C-6), 7.71-7.74 (1H, d, *J* 9.0 Hz, NH of amide, D_2O exchanged),7.85-7.93 (1H, d (*m* -coupled), *J* 8.0, J_m 1.0 Hz, Ar. CH at C-5), 8.84-8.87 (1H, d, *J* 9.0 Hz, NH of amide, D_2O exchanged), 8.98 (1H, s, vinyl CH at C-2). ^{13}C (DMSO-d_6) unable to assign peaks conclusively due to high noise levels in the spectrum. MS, m/z 214 ($M^{+\cdot}$, 70%, $C_{12}H_{10}N_2O_2$), 198 (40%, $M^{+\cdot}$ - NH_2), 171 (100%, $M^{+\cdot}$ - $CONH_2$), 77 (25%, Ph), [214 (70%), 198 (40%), 171 (100%), 118 (60%), 91 (35%), 77 (25%), 55 (50%), 51 (25%)]. IR (KBr) ϑ 3441 (amide N-H str.), ~ 2900 (Ar. C-H str.), ~ 2800 (Al. C-H str.), 1653 (amide C=O str.), 1610 (C=O str.), 1542 (C=C str.) cm^{-1}.

Anal. Calcd. for $C_{12}H_{10}N_2O_2$: C, 35.72; H, 2.23; N, 10.80.

Found: C, 34.91; H, 2.73; N, 10.25.

Formation of *N*,*N*-diphenylpiperazine (109) in the attempted synthesis of 1,2,4,5-Tetrahydro-pyrrolo[3,2,1-*hi*]indole (108)

1,2,3,4-Tetrahydroquinoline (6.28 ml, 6.66 g, 0.05 mol) and 1-bromo-2-chloro-ethane (8.32 ml, 14.34 g, 0.10 mol) were heated under reflux for 2 h. Polyphosphoric acid (40.00 g) was added and the reaction mixture was heated at 150° C for 3 h to give the title compound as colourless needles (25.88 g, 44%), mp 158-160° C (from water) (Lit 166° C) [127a] . ^1H NMR (DMSO-d_6) δ 3.27 (8H, s, 4 x CH_2), 6.78-6.84 (2H, t (*m*-coupled), *J* 8.0, J_m 2.0 Hz, 2 x Ar. CH at C-4), 6.98-7.02 (4H, d (*m*-coupled), *J* 8.0, J_m 2.0 Hz, 4 x Ar. CH at C-2), 7.21-7.29 (4H, dd (*m*-coupled), *J* 8.0, 8.0, J_m 2.0 Hz, 4 x Ar. CH at C-3). ^{13}C NMR (DMSO-d_6) δ C of CH_2 (48.25), C-1 (150.85), C-2/2' (128.88), C-3/3' (115.56), C-4/4' (119.03). MS, m/z 238 ($M^{+\cdot}$, 70%, $C_{16}H_{18}N_2$), 223 (5%, $M^{+\cdot}$ - $CH_3\cdot$), 196 (8%, 223 - C_2H_3), 119 (9%, 223 - Ph), 105 (100%, $M^{+\cdot}$ - PhC_3H_6N). IR (KBr) ϑ 3433 (Ar. C-H str.), 2959 (Al. C-H str.), 2831 (N-CH_2 str.), 1597 (C=C skeletal str.), 1446 (CH_2 asymm. bending), 1028-939 (CH_2 rocking) cm^{-1}.

4-Trifluoromethyl-1,2-dihydroquinolin-2-one (114a) [152]

Aniline (1.36 ml, 1.39 g, 0.015 mol) and ethyl trifluoroacetoacetate (2.19 ml, 2.76 g, 0.015 mol) were heated under reflux for 2 h. Polyphosphoric acid (40.00 g) was added and the mixture was heated at 150° C for 1.5 h to give the title compound (0.69 g, 20%) as colourless needles, mp 221-225° C (from water) (Lit. 245-246° C, from methanol) [152]. ^1H NMR (DMSO-d_6) δ 6.99 (1H, s, vinyl CH at C-3), 7.07 (1H, s, N-H), 7.64-7.68 (1H, t (*m* -coupled), *J* 5.0 Hz, Ar. CH at C-6), 7.85-7.88 (1H, t (*m* -coupled), *J* 7.0 Hz, Ar. CH at C-7), 7.98-8.01 (1H, d, *J* 8.0 Hz, Ar. CH at C-5), 8.20-8.23 (1H, d, *J* 9.0 Hz, Ar. CH at C-8). ^{19}F (DMSO-d_6) δ (- 61.99). ^{13}C NMR results were poor due to very high distortion levels. MS, m/z 213 ($M^{+\cdot}$, 100%,

$C_{10}H_6F_3NO$), 185 (20%, $M^{+\cdot}$ - CO), 144 (25%, $M^{+\cdot}$ - CF_3)116 (10%, 185 - CF_3), [213 (100%), 185 (20%), 165 (20%), 144 (25%), 116 (10%), 89 (12%), 77 (5%), 44 (5%)]. IR (KBr) ϑ 3434 (secondary amide N-H / Ar. C-H str. overlap), 2924 (vinyl C-H str.), 1625 (C=O str.), 1577 (C=C str.), ~ 1145 (C-F str.) cm^{-1}.

4-Phenyl-1,2-dihydroquinolin-2-one (114b)

Aniline (1.36 ml, 1.39 g, 0.015 mol) and ethyl benzoylacetate (2.59 ml, 2.88 g, 0.015 mol) were heated under reflux for 2 h. Polyphosphoric acid (41.0 g) was added and the mixture was heated at 150° C for 1.5 h to give the title compound (2.85 g, 86%) as brown needles, mp 258-260° C (from methanol) (Lit. 260-261° C) [154]. ^1H NMR (DMSO-d_6) [189] δ 6.45 (1H, s, vinyl CH at C-3), 7.38-7.44 (1H, t (*m* -coupled), *J* 7.5, J_m 1.0 Hz, Ar. CH at C-7), 7.60-7.63 (3H, t, *J* 3.0 Hz, 2 x Ar. CH at C-13; 1 x Ar. CH at C-14 (superimposed)), 7.69-7.77 (1H, t (*m* -coupled), *J* 7.0, J_m 1.5 Hz Ar. CH at C-6), 7.82-7.85 (1H, d (*m* -coupled), *J* 6.0, J_m 1.0 Hz, Ar. CH at C-5), 7.88-7.99 (2H, d (*m* -coupled), *J* 6.0, J_m 1.0 Hz, 2 x Ar. CH at C-12), 7.96 (1H, s, N-H), 8.14-8.18 (1H, d (*m* -coupled), *J* 8.0, J_m 1.0 Hz, Ar. CH at C-8). ^{13}C NMR (DMSO-d_6) δ C-2 (174.87), C-3 (106.25), C-4 (133.36), C-5 (119.26), C-6 (133.36), C-7 (124.17), C-8 (124.41), C-9 (151.42), C-10 (140.33), C-11 (123.12), C-12 (127.69), C-13 (129.01), C-14 (130.84). MS [170], m/z 221 ($M^{+\cdot}$, 100%, $C_{11}H_{11}NO$), 220 (25%, $M^{+\cdot}$ - H), 204 (10%, $M^{+\cdot}$ - OH), 193 (45%, $M^{+\cdot}$ - CO), [221 (100%), 220 (25%), 204 (10%), 193 (45%), 165 (18%), 97 (10%), 83 (5%), 77 (5%)]. IR (KBr) ϑ 3440 (N-H / Ar. C-H str. overlap), 2923 (vinyl C-H str.), 1642 (C=O str.), 1594 (C=C str.), 1500 (aromatic ring), 1057 (C-O str.) cm^{-1}.

6-Chloro-4-methyl-1,2-dihydroquinolin-2-one (114c)

4-Chloroaniline (1.91 g, 0.015 mol) and ethyl acetoacetate (1.91 ml, 1.95 g, 0.015 mol) were heated under reflux for 2 h. Polyphosphoric acid (41.52 g) was added and the reaction mixture was heated at 150° C for 22 h to give the title compound (0.44 g, 15%) as brown needles, mp 269-271° C (from ethanol) (Lit. 289-291° C, from aqueous ethanol) [155]. ^1H NMR (DMSO-d_6) δ 2.43 (3H, s, CH_3), 5.47 (1H, s (broad), N-H), 6.20 (1H, s, vinyl CH at C-3), 7.68-7.69 (1H, d, *J* 8.0 Hz, Ar. CH at C-8), 7.72-7.73 (1H, d (*m* -coupled), *J* 8.8, J_m 2.4 Hz, Ar. CH at C-7), 7.97-7.98 (1H, s (*m* -coupled), J_m 2.3 Hz, Ar. CH at C-5). ^{13}C NMR (DMSO-d_6) δ C at CH_3 (19.50), C-2 (174.04), C-3 (108.09), C-4 (124.31), C-5 (131.96), C-6 (151.68), C-7 (123.32), C-8 (120.45), C-9 (138.39), C-10 (128.09). MS, m/z 193 ($M^{+\cdot}$, 100%, $C_{10}H_8ClNO$), 178 (5%, $M^{+\cdot}$ - CH_3), 166 (25%, $M^{+\cdot}$ - HCN), 158 (5%, $M^{+\cdot}$ - Cl), [193 (100%), 178 (5%), 166 (25%), 158 (5%), 130 (10%), 102 (5%), 75 (5%), 43 (5%)]. IR (KBr) ϑ 3437 (amide N-H str.), 2922 (vinyl C-H str.), 2853 (CH_3 str.), 1650 (C=O str.), ~ 1600 (C=C str.), ~ 890 (C-Cl str.) cm^{-1}.

Anal. Calcd. for $C_{10}H_8ClNO$: C, 62.03; H, 4.16; N, 7.23.
Found: C, 62.33; H, 4.11; N, 7.27.

6-Chloro-4-hydroxy-1,2-dihydroquinolin-2-one (114d)

4-Chloroaniline (1.90 g, 0.015 mol) and diethylmalonate (2.40 ml, 2.28 g, 0.015 mol) were heated under reflux for 2 h. Polyphosphoric acid (41.72 g) was added and the reaction was heated at 150°C for 46 h to give the title compound (0.79 g, 27%) as brown needles, mp 320-326° C (from ethanol) (Lit. 302° C, from DMF) [156]. ^1H NMR (DMSO-d_6) δ 5.82 (1H, s, vinyl CH at C-3), 7.28-7.31 (1H, d, *J* 9.0 Hz, Ar. CH at C-8), 7.52-7.57 (1H, d (*m* -coupled), *J* 9.0, J_m 2.0 Hz, Ar. CH at C-7), 7.73-7.74 (1H, s (*m* -coupled), J_m 2.0 Hz, Ar. CH at C-5), 11.42 (1H, s (broad), OH at C-4). ^{13}C NMR (DMSO-d_6) δ C-2 (163.23), C-3 (99.00), C-4 (161.25), C-5 (130.60), C-6 (125.05), C-7 (121.62), C-8 (116.99), C-10 (116.15). MS, m/z 195 ($M^{+\cdot}$, 100%, $C_9H_6ClNO_2$), 166 (10%, $M^{+\cdot}$ - CHO), 153 (85%, $M^{+\cdot}$ - CH_2=C=O), 126 (30%, C_6H_5ClN), [195 (100%), 166 (5%), 153 (85%), 139 (10%), 126 (30%), 102 (5%), 75 (15%), 63 (20%)]. IR (KBr) ϑ 3428 (amide N-H str.), 2924 (vinyl C-H str.), 1652 (cyclic C=O str.), ~1600 (amide C=O str.), 817 (C-Cl str.) cm^{-1}.

6,8-Dichloro-4-methyl-1,2-dihydroquinolin-2-one (114e) [157]

2,4-Dichloroaniline (2.40 g, 0.015 mol) and ethyl acetoacetate (1.91 ml, 1.95 g, 0.015 mol) were heated under reflux for 2 h. Polyphosphoric acid (41.76 g) was added and the mixture was heated at 150° C for 5.45 h to give the title compound (1.40 g, 41%) as colourless needles, mp 270-274° C (from ethanol) (Lit. 235-236.6° C, from ethanol) [157]. NMR results were unobtainable due to the sample's insolubility in standard NMR solvents. MS, m/z 227 ($M^{+\cdot}$, 100%, $C_{10}H_7Cl_2NO$), 198 (35%, $M^{+\cdot}$ - CHO), 192 (10%, $M^{+\cdot}$ - Cl), 164 (12%, 192 - CO), 128 (8%, 164 - HCl), [227 (100%), 198 (35%), 192 (10%), 164 (12%), 128 (8%), 82 (9%), 67 (12%)]. IR (KBr) ϑ 3407 (N-H str.), 2924 (vinyl C-H str.), 1632 (C=O str.), 1587 (C=C str.), 1373 (CH_3 symm. def.), ~ 840 (C-Cl str.) cm^{-1}.

6,8-Dichloro-4-hydroxy-1,2-dihydroquinolin-2-one (114f)

2,4-Dichloroaniline (2.40 g, 0.015 mol) and diethylmalonate (2.40 ml, 2.28 g, 0.015 mol) were heated under reflux for 2 h. Poylphosphoric acid (40.56 g) was added and the mixture was heated at 150° C for 3 h to give the title compound (1.23 g,36%) as colourless needles, mp 300-304° C (from acetone). ^1H NMR (DMSO-d_6) 5.91 (1H, s, vinyl C-H at C-3), 7.75-7.76 (1H, s (*m* -coupled), J_m 2.4 Hz, Ar. CH at C-7), 7.82-7.83 (1H, s (*m* -coupled), J_m 2.0 Hz, Ar. CH at C-5), 10.66 (1H, s (broad), N-H), 11.89 (1H, s (broad), OH). ^{13}C NMR (DMSO-d_6) δ C-2 (162.86), C-3 (99.56), C-4 (160.97), C-5 (130.26), C-6 (119.59), C-7 (121.09), C-8 (125.03), C-9 (134.59)

C-10 (117.64). MS, m/z 229 ($M^{+\cdot}$, 100%, $C_9H_5Cl_2NO_2$), 201 (10%, $M^{+\cdot}$ - CO), 187 (90%, $M^{+\cdot}$ - CH_2=C=O), 161 (60%, $C_6H_5NCl_2$), [229 (100%), 201 (10%), 187 (90%), 161 (60%), 149 (50%), 69 (52%), 57 (95%), 43 (80%)]. IR (KBr) ϑ 3413 (N-H str.), 2921 (vinyl C-H str.), 1645 (C=O), ~ 820 (C-Cl str.) cm^{-1}.

Anal. Calcd. for $C_9H_5Cl_2NO_2$: C, 46.99; H, 2.19; N, 6.09.
Found: C, 46.93; H, 2.15; N, 6.04.

4-Hydroxy-6-methyl-1,2-dihydroquinolin-2-one (114g)

p -Toluidine (1.61 g, 0.015 mol) and diethylmalonate (2.40 ml, 2.28 g, 0.015 mol) were heated under reflux for 2 h. Polyphosphoric acid (40.93 g) was added and the mixture was heated at 150° C for 4.5 h to give the title compound (0.58 g, 22%) as yellow needles, mp 318-320° C (from water) (Lit. >300° C, from DMF) (158). ^{1}H NMR (DMSO-d_6) (158) δ 2.35 (3H, s, CH_3), 3.67 (2H, s (broad), H_2O), 5.85 (1H, s, vinyl CH at C-3), 7.18-7.21 (1H, d, *J* 8.0 Hz, Ar. CH at C-8), 7.31-7.35 (1H, d (*m* -coupled), *J* 9.5, J_m 2.0 Hz, Ar. CH at C-7), 7.72 (1H, s (*m* -coupled), J_m 2.0 Hz, Ar. CH at C-5), 11.22 (2H, s (broad), O-H/N-H). ^{13}C NMR (DMSO-d_6) δ C-2 (163.41), C-3 (98.05), C-4 (162.25), C-5 (131.90), C-6 (114.78), C-7 (122.02), C-8 (114.99), C-9 (137.04), C-10 (130.80), C of CH_3 (20.38). MS, m/z 175 ($M^{+\cdot}$, 100%, $C_{10}H_9NO_2$), 133 (80%, $M^{+\cdot}$ - CH_2=C=O), 104 (30%, 133 - CHO), [175 (100%), 149 (5%), 133 (80%), 104 (22%), 91 (25%), 77 (20%), 51 (18%)]. IR (KBr) ϑ 3432 (N-H str.), 2922 (Ar. C-H str.), 2859 (vinyl C-H str.), 1660 (C=O str.), 1604 (C=C str.), 1317 (C-N str.) cm^{-1}.

Ethyl (*E*)-2-cyano-3-(*N*-phenylamino)prop-2-enoate (124a)

Aniline (1.36 ml, 1.39 g, 0.015 mol), triethylorthoformate (2.49 ml, 2.22 g, 0.015 mol) and ethyl cyanoacetate (1.59 ml, 1.69 g, 0.015 mol) were heated under reflux for 2 h. Polyphosphoric acid (42.16 g) was added and the mixture was heated at 150° C for 2 h to give the title compound (2.94 g, 91%) as pale yellow needles, mp 105-108° C (from methanol) (Lit. 105-107° C). ^{1}H NMR (DMSO-d_6) δ 1.22-1.31 (3H, t, *J* 7.0 Hz, CH_3), 4.15-4.29 (2H, q, *J* 7.0 Hz, CH_2), 7.16-7.23 (1H, dd (*m* -coupled), *J* 5.0, 5.0, J_m 1.0 Hz, Ar. CH at C-8), 7.38-7.42 (2H, dd, *J* 5.0, 5.0 Hz, 2 x Ar. CH at C-7), 7.47-7.50 (2H, d (*m* -coupled), *J* 8.0, J_m 2.0 Hz, 2 x Ar. CH at C-6), 8.33 (1H, s, vinyl CH), 8.52 (1H, s, N-H). ^{13}C NMR (DMSO-d_6) δ C-1 (164.54), C-2 (73.41), C-3 (152.37), C-5 (138.66) C-6 (129.43), C-7 (117.77), C-8 (124.79), C at CH_2 (60.25), C at CH_3 (14.14). MS, m/z 216 ($M^{+\cdot}$, 95%, $C_{12}H_{12}N_2O_2$), 188 (9%, $M^{+\cdot}$ - C_2H_4), 171 (35%, $M^{+\cdot}$ - $C_2H_5O\cdot$), 170 (100%, $M^{+\cdot}$ - C_2H_5OH), 143 (42%, $M^{+\cdot}$ - CO_2Et), 116 (18%, 143 - HCN), [216 (95%), 188 (9%), 170 (100%), 143 (42%), 116 (18%), 104 (60%), 77 (42%), 51 (20%)]. IR (KBr) ϑ 3443 (N-H/C-H str. overlap), 2923 (vinyl C-H str.), 2213 (CN str.), 1630 (C=O str.), 1379 (CH_3

symm. bending), 1320 (Ar. C-N str.), 1249 (C-O-C asymm. str.), 1168 (C-O str.), ~ 720 (CH_2 rocking) cm^{-1}.

Ethyl (*E*)-2-cyano-3-(*N*-4-chlorophenylamino)prop-2-enoate (124b)

4-Chloroaniline (1.91 g, 0.015 mol), triethylorthoformate (2.49 ml, 2.22 g, 0.015 mol) and ethyl cyanoacetate (1.59 ml, 1.69 g, 0.015 mol) were heated under reflux for 2 h. Polyphosphoric acid (40.04 g) was added and the mixture was heated at 150° C for 2 h to give the title compound (1.51 g, 41%) as yellow needles, mp 134-136°C (from methanol). ^1H NMR (DMSO-d_6) δ 1.23-1.31 (3H, t, *J* 7.0 Hz, CH_3), 4.16-4.22 (2H, q, *J* 8.0 Hz, CH_2), 7.42-7.45 (2H, d, *J* 9.0 Hz, 2 x Ar. CH at C-6), 7.49-7.51 (2H, d, *J* 10.0 Hz, 2 x Ar. CH at C-7), 8.28-8.33 (1H, d, *J* 14.0 Hz, vinyl CH), 8.42-8.47 (1H, d, *J* 14.0 Hz, N-H). MS, m/z 250/252 ($M^{+\cdot}$, 68%, $C_{12}H_{11}ClN_2O_2$), 222/224 (10%, $M^{+\cdot}$ - CO), 205/207 (25%, $M^{+\cdot}$ - $C_2H_5O\cdot$), 204/206 (100%, $M^{+\cdot}$ - C_2H_5OH), 177 (20%, 204 - HCN), [250 (68%), 222 (10%), 204 (100%), 177 (20%), 138 (45%), 111 (20%), 99 (7%), 75 (15%)]. IR (KBr) ϑ 3439 (N-H str.), 3212 (Ar. C-H str.), 2982 (vinyl C-H str.), 2211 (CN str.), 1675 (C=O str.), 1639 (C=C str.), 1245 (C-O-C asymm. str.), 1151 (C-O str.), 785 (C-Cl bend) cm^{-1}.

Anal. Calcd. for $C_{12}H_{11}ClN_2O_2$: C, 57.50; H, 4.42; N, 11.17.
Found: C, 57.44; H, 4.42; N, 11.09.

Ethyl (*E*)-2-cyano-3-(*N*-2,4-dichlorophenylamino)prop-2-enoate (124c)

2,4-Dichloroaniline (2.43 g, 0.015 mol), triethylorthoformate (2.49 ml, 2.22 g, 0.015 mol) and ethyl cyanoacetate (1.60 ml, 1.69 g, 0.015 mol) were heated under reflux for 2 h. Polyphosphoric acid (40.26 g) was added and the mixture was heated at 150° C for 1 h to give the title compound (2.26 g, 53%) as recrystallised yellow mixture, mp 166-168° C (from ethanol). ^1H NMR (DMSO-d_6) δ 1.26-1.31 (3H, t, *J* 7.0 Hz, CH_3), 4.21-4.31 (2H, q, *J* 7.0 Hz, CH_2), 7.45-7.49 (1H, d (*m*-coupled), *J* 9.0, J_m 2.0 Hz, Ar. CH at C-9), 7.73-7.74 (1H, s (*m*-coupled), J_m 2.0 Hz, Ar. CH at C-7), 7.83-7.86 (1H, d, *J* 9.0 Hz, Ar. CH at C-10), 8.68-8.73 (1H, d, *J* 13.0 Hz, vinyl CH at C-3), 11.09-11.14 (1H, d, *J* 14.0 Hz, N-H). ^{13}C NMR (DMSO-d_6) δ C-1 (116.57), C-2 (75.98), C-3 (152.96), C-5 (122.80), C-6 (134.17), C-7 (128.48), C-9 (118.13), C-10 (129.09), C of CH_2 (60.98), C of CH_3 (14.01). MS, m/z 284/286/288 ($M^{+\cdot}$, 62%, $C_{12}H_{10}Cl_2N_2O_2$), 256/258/260 (10%, $M^{+\cdot}$ - CO), 239/241/243 (20%, $M^{+\cdot}$ - $C_2H_5O\cdot$), 238 (100%, $M^{+\cdot}$ - C_2H_5OH), 211/213/215 (20%, 238 - HCN), [284 (62%), 256 (10%), 238 (100%), 211 (20%), 172 (58%), 145 (18%), 109 (17%), 45 (38%)]. IR (KBr) ϑ 3432 (N-H str.), 2925 (vinyl C-H str.), 2218 (CN str.), 1683 (C=O str. of 'enol' form), 1631 (C=C str.), 1259 (C-O-C asymm. str.), 784 (C-Cl str.) cm^{-1}.

Anal. Calcd. for $C_{12}H_{10}Cl_2N_2O_2$: C, 51.73; H, 4.04; N, 11.21.
Found: C, 51.42; H, 4.08; N, 11.14.

Ethyl (*E*)-2-cyano-3-(*N*-4-nitrophenylamino)prop-2-enoate (124d)

p -Nitroaniline (2.07 g, 0.015 mol), triethylorthoformate (2.49 ml, 2.22 g, 0.015 mol) and ethyl cyanoacetate (1.59 ml, 1.69 g, 0.015 mol) were heated under reflux for 0.5 h. Polyphosphoric acid (40.06 g) was added and the mixture was heated at 150° C for 4 h to give the title compound (3.59 g, 92%) as bright yellow needles, mp 220-222° C (from ethanol). ^{1}H NMR (DMSO-d_6) A mixture: not possible to assign all the peaks conclusively. ^{13}C NMR (DMSO-d_6) A mixture: not possible to assign all the peaks conclusively. MS (attributable to **124d**), m/z 261 ($M^{+\cdot}$, 100%, $C_{12}H_{11}N_3O_4$), 233 (20%, $M^{+\cdot}$ - C_2H_4), 216 (20%, $M^{+\cdot}$ - $C_2H_5O\cdot$), 215 (65%, $M^{+\cdot}$ - C_2H_5OH), 188 (30%, $M^{+\cdot}$ - $CO_2C_2H_5$), 142 (30%, 188 - NO_2), [261 (100%), 233 (20%), 215 (65%), 188 (30%), 142 (30%), 115 (20%), 103 (15%), 76 (17%)]. IR (attributable to **124d**) (KBr) ϑ ~ 3400 (N-H str.), 3084 (Ar. C-H str.), 2990 (vinyl C-H str.), 2213 (CN str.), 1689 (C=O str.), 1629 ($C_6H_5NO_2$?), 1594 (C=C str.), 1379 (NO_2 symm. str.), 1314-1112 (C-O-C asymm. and symm. str.), 848 (C-N str.) cm^{-1}.
Anal. Calcd. for $C_{12}H_{11}N_3O_4$ (**124d**): C, 55.17; H, 4.24; N, 16.08.
Found: C, 55.11; H, 4.23; N, 16.03.

3-Cyano-6-methyl-1,4-dihydroquinolin-4-one (125) and Ethyl (*E*)-2-cyano-3-(*N*-4-methylphenylamino)prop-2-enoate (126)

p -Toluidine (1.61g, 0.015 mol), triethylorthoformate (2.49 ml, 2.22 g, 0.015 mol) and ethyl cyanoacetate (1.59 ml, 1.69 g, 0.015 mol) were heated under reflux for 0.5 h. Polyphosphoric acid (40.64 g) was added and the mixture was heated at 150° C for 2 h to give 1.83 g of a yellow mixture of the title compound and Ethyl (*E*)-2-cyano-3-(*N*-4-methylphenylamino)prop-2-enoate (**126**) (58% : 42% based on ^{1}H NMR analysis). ^{1}H NMR (DMSO-d_6) A mixture: not possible to assign all the peaks conclusively. ^{13}C NMR (DMSO-d_6) A mixture: not possible to assign all the peaks conclusively. MS (attributable to **126**), m/z 230 ($M^{+\cdot}$, 75%, $C_{13}H_{14}N_2O_2$), 202 (5%, $M^{+\cdot}$ - C_2H_4), 184 (100%, $M^{+\cdot}$ - C_2H_5OH), 157 (20%, 184 - HCN), 142 (10%, 157 - CH_3), [230 (75%), 202 (5%), 184 (100%), 157 (20%), 142 (10%), 130 (8%), 118 (42%), 91 (27%)]. IR (attributable to **126**) (KBr) ϑ 3229 (N-H str.), 2986 (Ar. C-H str.), 2991 (vinyl C-H str.), 2213 (CN str.), 1672 (C=O str.), 1626 (C=C str.), 1450 (CH_3 asymm. bending), 1250 (C-O-C asymm. str.) cm^{-1}.

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APPENDIX

RAPID COMMUNICATIONS IN MASS SPECTROMETRY, VOL. 11, 201–205 (1997)

Electron Impact Induced Elimination of HNO_2 from Trifluralin–Phenylenediamine Dimers — an *ortho*-Effect Resulting from a π–π Interaction Persisting into the Vapour Phase†

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In this paper we attempt to explain the two neutral HNO_2 losses observed from the *ortho* isomer of the title compounds in terms of a minimum energy conformation which we suggest persists into the vapour phase. This is supported to some extent by preliminary molecular modelling studies. The 'splitpin' shape of the *ortho* molecule brought about by π–π stack interactions brings the nitrated rings together in a favourable orientation, allowing hydrogen transfer processes to occur.

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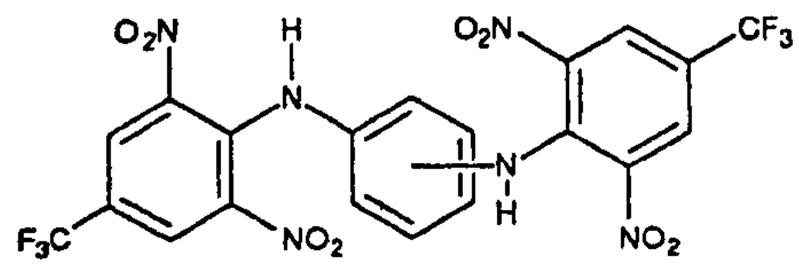
No. of Figures: 5 No. of Tables: 1 No. of Refs: 6

Trifluralin (2,6-dinitro-(*N*,*N*-dipropyl-4-trifluoromethyl)benzene) is a potent herbicide[1] that has recently been shown to selectively inhibit proliferation and differentiation of various protozoa such as *Leishmania mexicana*[2] and *Plasmodium falciparum*[3], apparently because it binds to *Leishmania* microtubulin in preference to host tubulin. Our work has involved synthesizing several novel N^1,N^2-bis(2,6-dinitro-4-trifluoromethylphenyl)diamine type dimers[1] related to trifluralin with the aim of both probing putative drug-receptor interactions and screening them against *Leishmaniasis* or other tropical diseases such as malaria and trypanosomiasis in both animals and humans.



Scheme 1. N^1,N^2-bis(2,6-dinitro-4-trifluoromethylphenyl)diamine type dimers (1)

In the course of this work we made all three of the trifluralin adducts of the diphenylene diamines, the formulae of which are shown on Figs. 1, 2 and 3, by reacting 1-chloro-2,6-dinitro-4-trifluoromethylbenzene with the appropriate diamine. Whereas the most general features of the electron impact (EI) mass spectra of these diamine compounds are losses of 16 (O), 30 (NO), 46 (NO_2) and 19 (F) mass units in various sequences, the *ortho*-phenylenediamine derivative alone showed intense ions resulting from two successive losses of 47 mass units, thought to be due to HON=O, followed by minor conventional NO, NO_2 and F losses, even though the possibility of similar HON=O elimination exists in all three isomers.

EXPERIMENTAL

The mass spectra were determined using a VG Analytical (Floats Road, Altrincham, Manchester, UK) 70–250 MS, with a DEC PDP 11/24 data system, at 70eV and a source temperature of ~200 °C. Samples were admitted by a direct insertion probe heated to 250–300 °C. High resolution measurements were made at a resolving power of ~10 000, using a calibration with perfluorokerosene.

All materials used were of the highest purity commercially available from both Lancaster Synthesis (Eastgate, Lancashire, UK) and Aldrich Chemical Co. (Gillingham, Dorset, UK). Thin-layer chromatography (TLC), was carried out on pre-coated silica gel 60 plates and substances were detected using a UV light source (254 nm).

The diphenylenediamine adducts were prepared as follows: 4-chloro-3,5-dinitrotrifluoromethylbenzene (5.41g) was dissolved in dry toluene (40cm^3) and added dropwise to a stirred solution of the diphenylenediamine (1.08g) and triethylamine (2.05 cm^3) under nitrogen. The mixtures were heated for 4–5 h, until TLC showed that the reaction was complete, then cooled, filtered, washed with water, air-dried and recrytallized from methanol. The 1,2-adduct (58% yield), had a m.p. of 252–254 °C; the 1,3-adduct (70% yield) a m.p. of 264–266 °C, and the 1,4-adduct (45% yield) a m.p. of 316–318°C. Fourier-transform infra-red spectroscopy was performed using a Mattson (Maddison, Wisconsin, USA) Galaxy series FT-IR 5000 instrument using a 1% compound/KBr mixture compressed into flats under vacuum. This analysis and ^{1}H, ^{13}C, Distortionless Enhancement by Polarization Transfer (DEPT), and deuterium oxide exchange NMR spectra (Brucker Spectrospin, Coventry, UK; 250 MHz FT Aspect 2000) were consistent with the expected structures.

Molecular modelling studies were performed on a Silicon Graphics Indy workstation and used the MM2* forcefield of MacroModel Version 4.0[4] to predict global energy minimum conformations of the three isomers. Systematic conformational searching was performed at 15–30° intervals.

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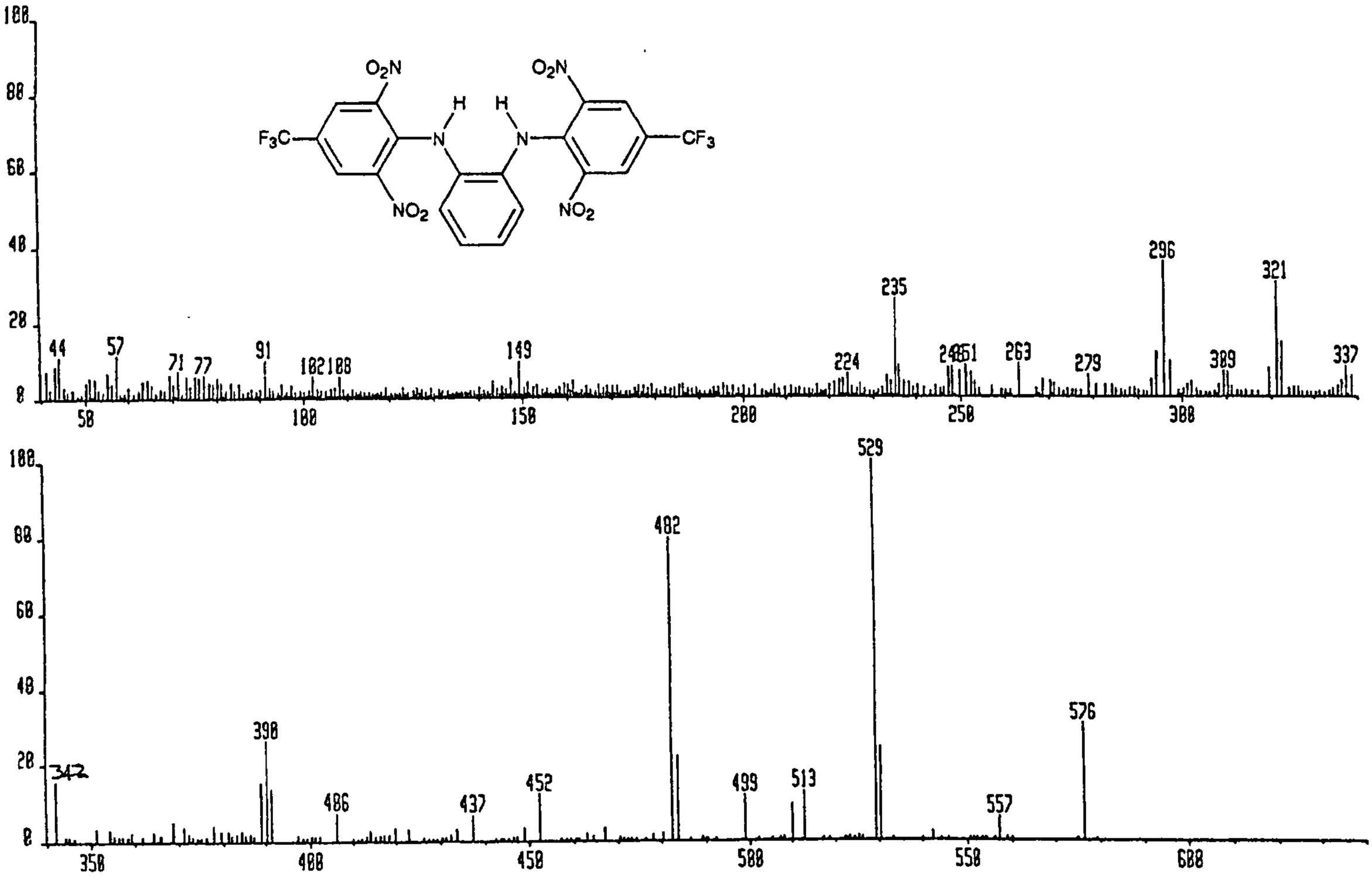


Figure 1.

RESULTS AND DISCUSSION

The EI mass spectra of the *ortho*-, *meta*- and *para*-phenylenediamine adducts of 2,6-dinitro-4-trifluoromethylbenzene are shown in Figs 1, 2 and 3 respectively. It is immediately apparent that the *meta* and *para* derivatives give intense stable molecular ions with restricted losses of O, OH, F, NO and NO_2 neutral fragments, as expected for aromatic nitro compounds and a trifluoromethyl group.[5] There is some evidence for α-cleavage at the imino groups with either hydrogen transfer or self-protonation to yield the $M^{+\cdot}$ ions of the

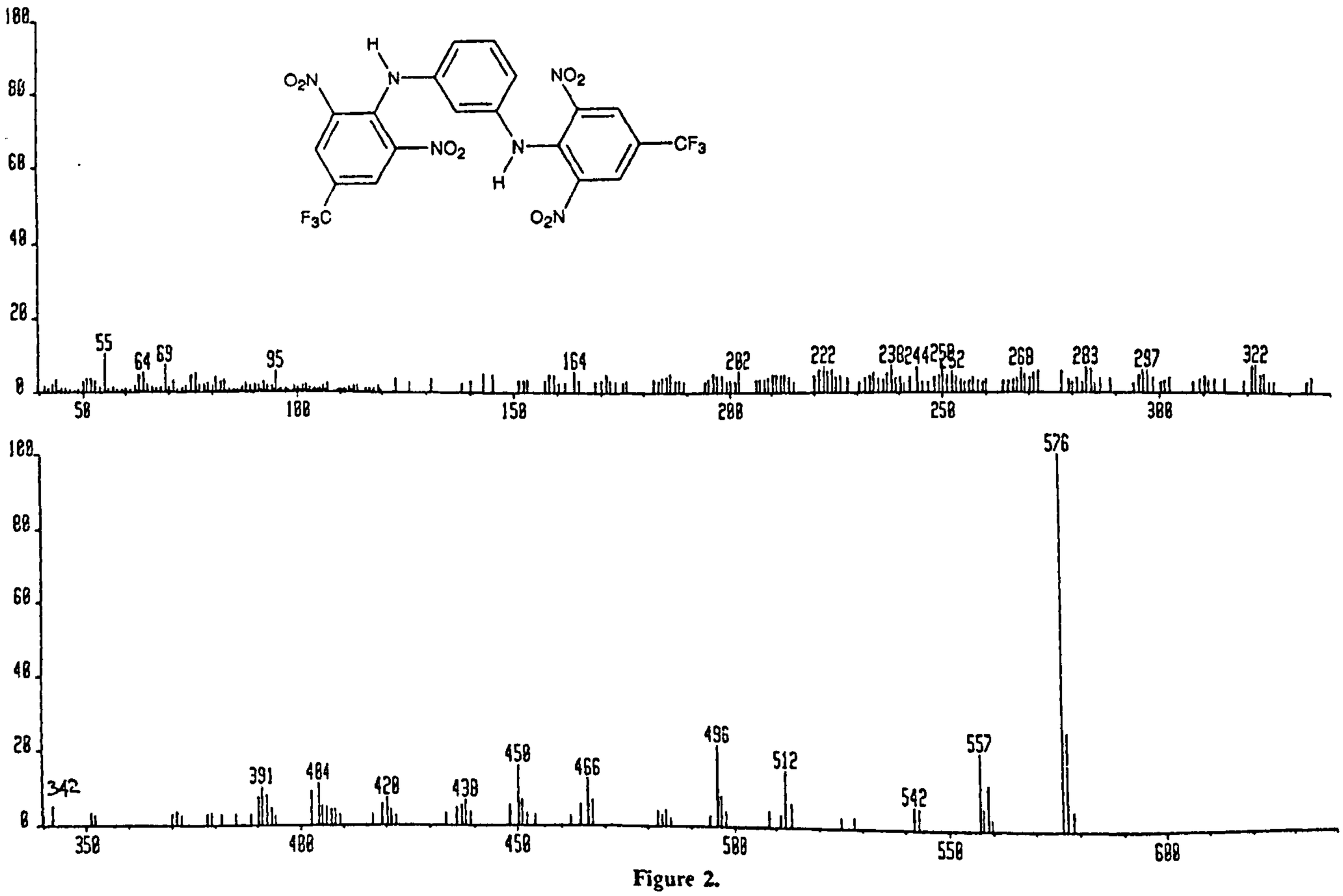


Figure 2.

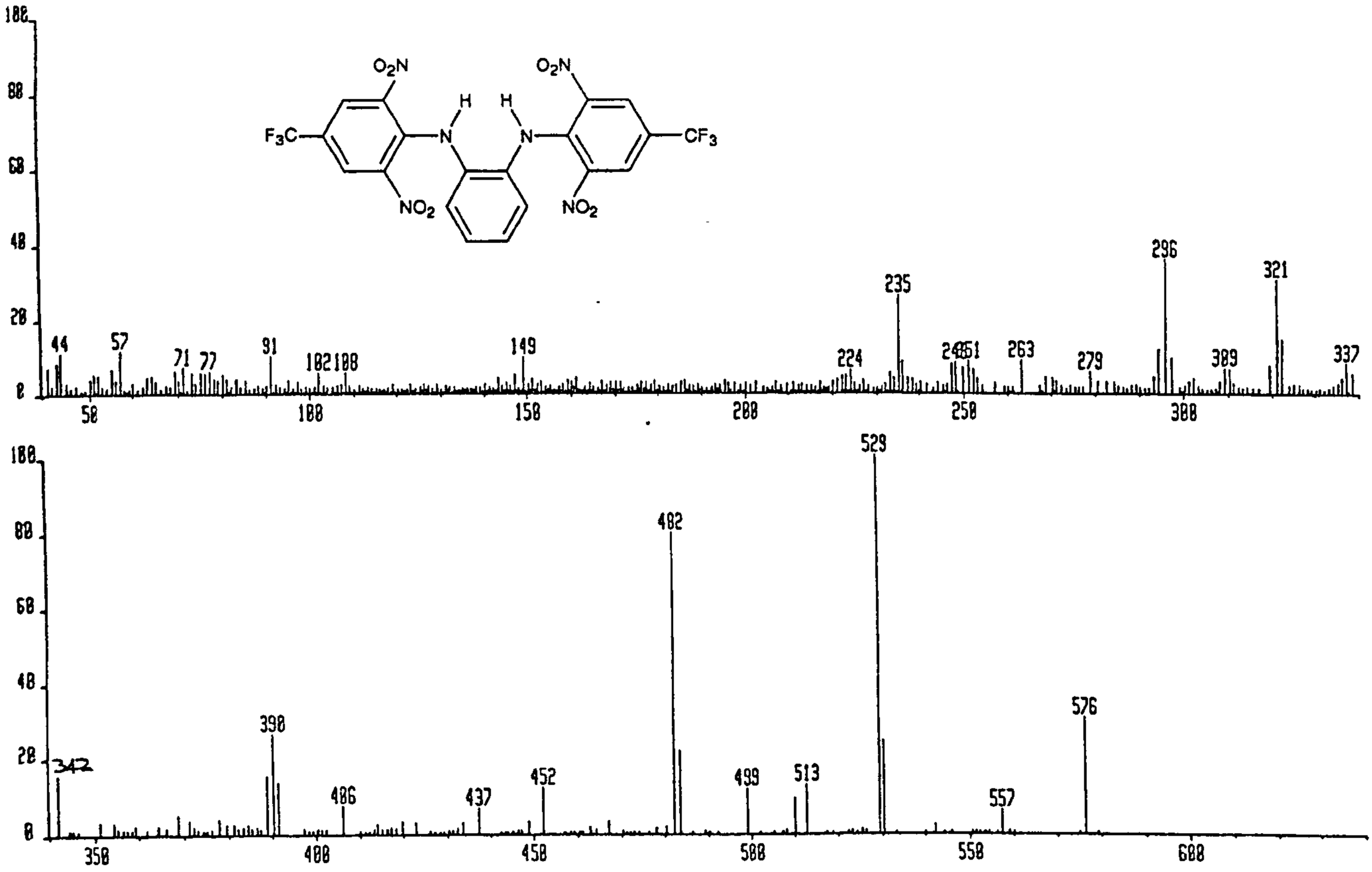
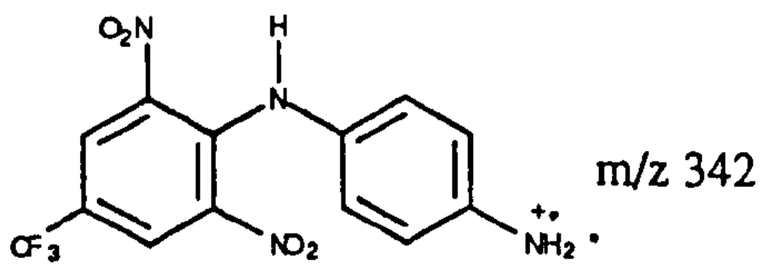


Figure 3.

mono-trifluorodinitrobenzene adduct of *m/z* 342 in all three spectra; this ion could also be due to an impurity of the mono-adduct, though these are twice recrystallized samples.



Scheme 2.

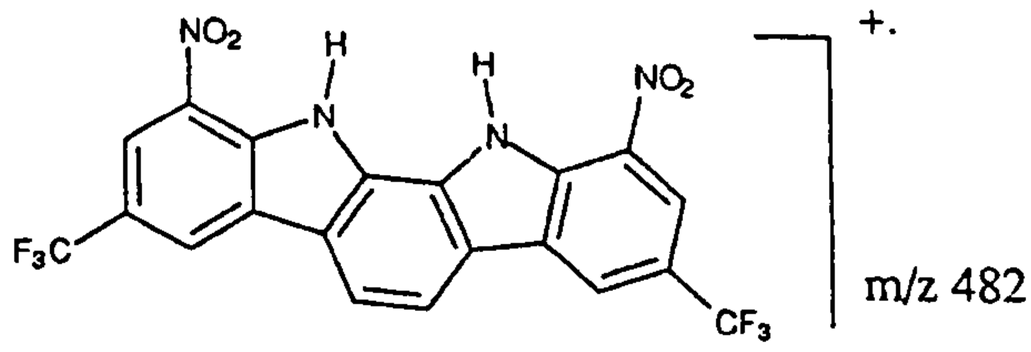
The spectrum of the *ortho*-bis-trifluorodiphenylenediamine adduct, by contrast is very distinctive (Fig. 1). About 25% $M^{+\bullet}$-ion is seen, but the base peak is *m/z* 529 $[M–HNO_2]^{+\bullet}$ and the ion of *m/z* 482, resulting from consecutive loss of the elements a HNO_2 is of 80% relative abundance. Since we are aware of few, if any, literature reports of HNO_2 losses from aromatic nitro compounds (loss of $HO^{\bullet}$ is common[5]), we have confirmed these processes by high resolution mass measurements on *m/z* 576, 529 and 482 (see Table 1).

Since the *ortho* compound shows the HNO_2 losses and the *meta* and *para* isomers do not, it is tempting to ascribe them to an *ortho* effect and leave it at that. However, it is perfectly possible to devise novel pentacyclic structures for the (M–2 HNO_2) ions by elimination of both *ortho* hydrogens of the diamino

Table 1.

Formula	Measured mass	Theoretical mass
$C_{20}H_{10}N_6O_8F_6$	576.0445	576.04643
$C_{20}H_9N_5O_6F_6$	529.0471	529.04570
$C_{20}H_8N_4O_4F_6$	482.0455	482.04497

rings and a nitro group from each trifluralin ring in all three isomers. An example of such a structure is:



Scheme 3.

In the case of the *meta* isomer this leads to two structures depending on whether the 2,4- or 4,6-hydrogens are involved. There is no obvious reason why the *ortho*-phenylenediamine derived ion should be so intrinsically more stable than those of the *meta* and *para* isomers as to cause its domination of the mass spectrum to the extent observed.

Simple ball and stick models and molecular modelling of the un-ionized isomers showed that three possible factors might be involved. In the *ortho* isomer the preferred conformation was a hairpin shape brought about by π–π stack interactions, bringing the nitrated rings together in a favourable orientation for single-electron transfer (SET) processes to occur. In the *meta* isomer steric overcrowding arising from the nitro groups of the two trifluralin rings could inhibit the transfer of the 2-hydrogen, though not the 4- and 6-hydrogens, while the *para* isomer's shape would not allow close approach of the nitro oxygens to the 2-hydrogen positions.

More sophisticated molecular modelling using MacroModel Version 4.0 sheds further light. Figure 4 shows the global minimum energy conformers with the key H — O distances in Ångstrom units. The sum of the van

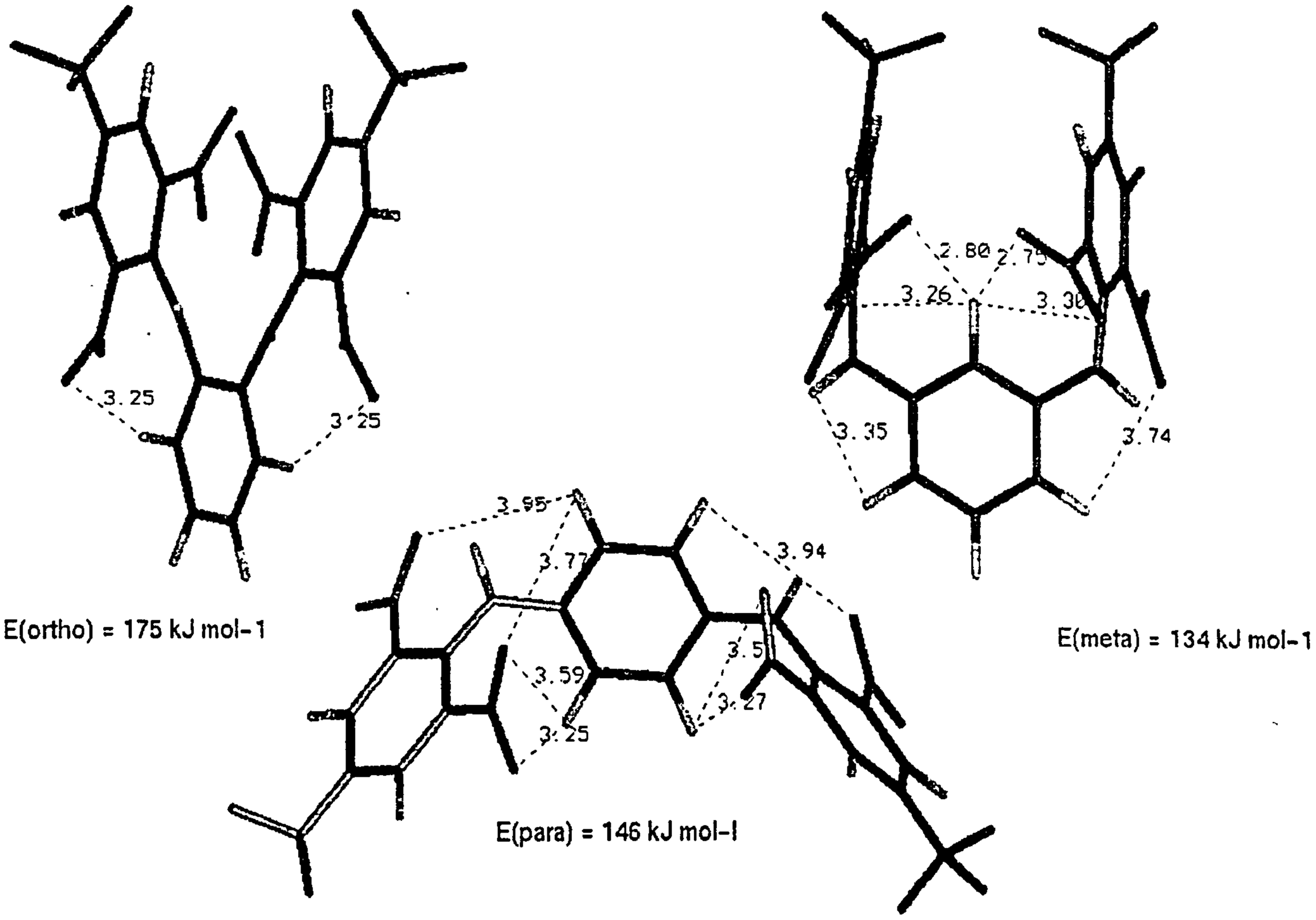


Figure 4. Global minimum energy conformers of the *o*-, *m*- and *p*-isomers

der Waals covalent radii for H and O is about 2.7 Å; thus, it is reasonable to assume that in those conformers where the *ortho* hydrogens and the nitro oxygens can approach one another to this extent hydrogen transfer could occur, but that transfer would be difficult or impossible where this distance was significantly larger.

The interesting points about these results are that the *meta* isomer has the lowest energy at 134 kJ mol^{-1} and the closest H—O approach, to the 2-hydrogen, at 2.75–2.80 Å. In the *ortho* isomer, which has the highest energy by some margin, the closest H—O distance is 3.25 Å, similar to that for the *para* isomer which has an intermediate energy of 146 kJ mol^{-1}. H—O distances to the 4- and 6-hydrogens in the *meta* isomer are also in the 3.3–3.8 Å range which would appear to rule out the involvement of facile SET processes. So, if these conformers were maintained in the gas phase, and after ionization, only the *meta* isomer appears to be able to

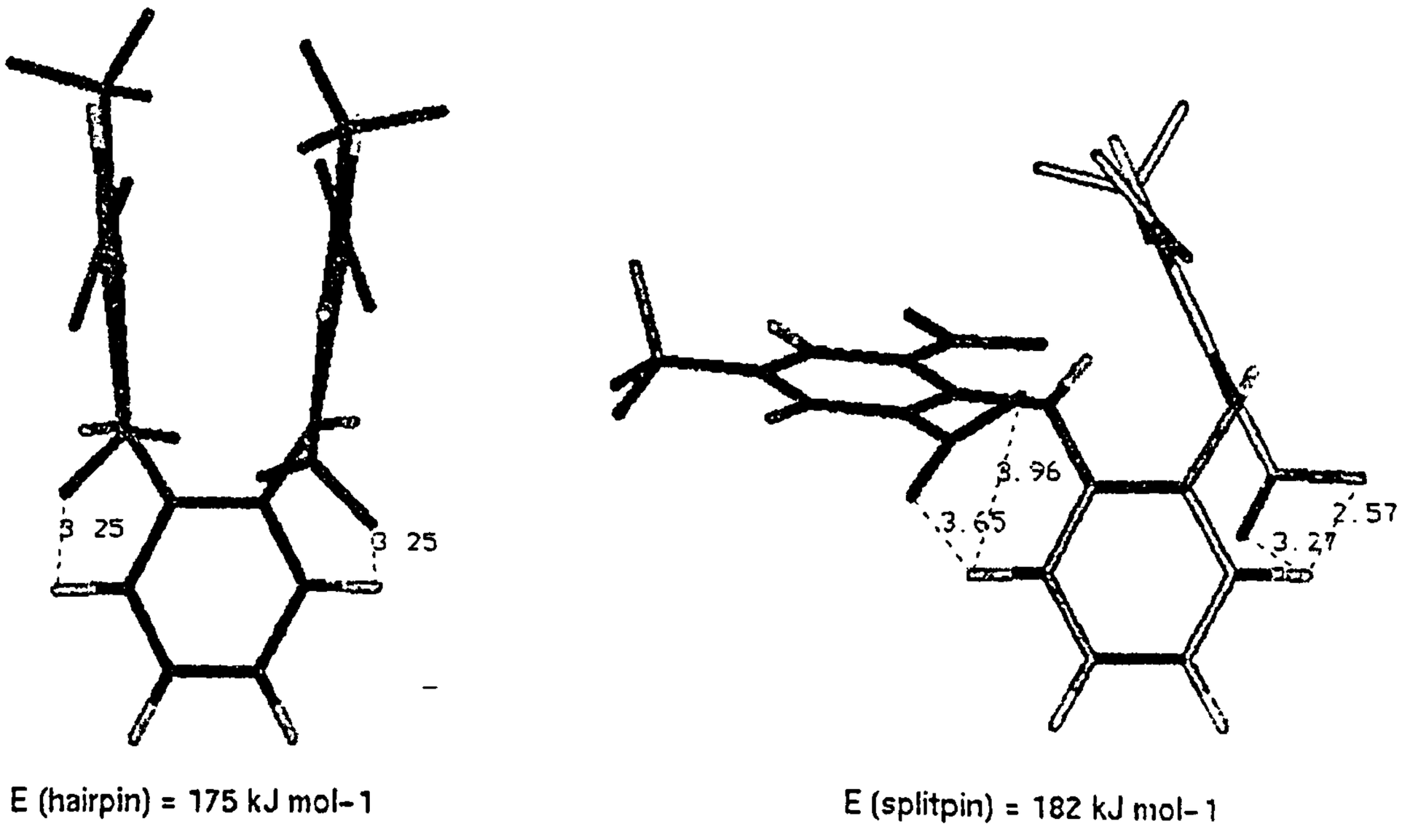


Figure 5. Closest H—O contacts in low energy conformers of the *ortho* isomer.

allow an *ortho* hydrogen to approach sufficiently close to a nitro oxygen to transfer and give rise to the HNO_2 fragment. If hydrogens as far away as 3.25 Å could transfer. all three isomers would lose HNO_2.

Using the MacroModel Modelling package, it is possible to search for conformations, among the hundreds generated, that have a stipulated distance between selected atoms. When this approach was used it revealed that the next higher energy conformer of the *ortho* isomer, with an energy of 182 kJ mol^{-1}, had a closest H–O contact to the 2-hydrogens of 2.57 Å, suitable for hydrogen transfer to occur. This conformer is no longer symmetrical, one of the legs of the hairpin being bent away from the other. Thus, it resembles the splitpin used to secure a wheel to an axle, and we call this the 'splitpin' conformation, as shown in Fig. 5.

We believe the explanation of the facile elimination of two HNO_2 fragments from the *ortho*-phenylenediamine adduct is that the splitpin conformation persists into the vapour phase, and the higher energy of this conformer, with its suitable van der Waals H—O distance of closest approach, promotes the SET processes leading to the formation of the highly stabilized pentacyclic azacyle molecular ion of *m/z* 482 shown in Scheme 3.

The *para* isomer is more stable and the minimum contact is too long for hydrogen transfer and, while for the *meta* isomer although the conformer is quite stable, the approach to the 2-hydrogen is too hindered by the other nitro group and the transition state may lack the necessary planarity. All other H—O distances are too long.

Modelling of the ground state conformations is clearly not conclusive and we intend to carry out further molecular orbital modelling studies on the molecular ions themselves. It would also be interesting to attempt to prepare the azacycles from the three adducts using radical-mediated cyclization, in the expectation that only the *ortho* compound will lead to the pentacyclic product which is related to the heterocyclic portion of several anticancer drugs including K-252a, staurosporine and rebeccamycin.[6]

Acknowledgements

We are grateful for the patience and practical skills of Mr D. Clarke and Mr P. A. Arnold in acquiring the NMR and mass spectra respectively for this study, and to Ms. W. Moule for the preliminary modelling studies.

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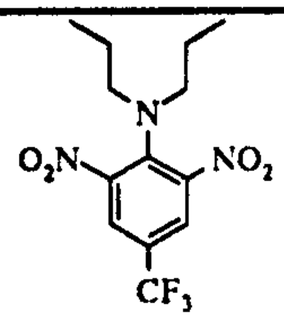
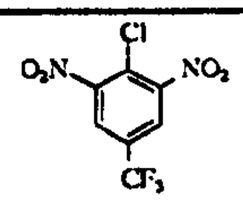
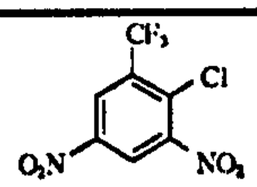
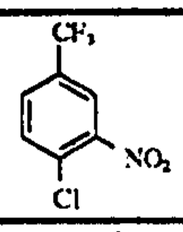
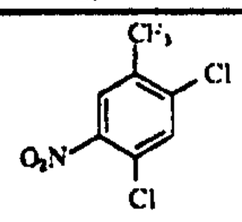
Screening for antimalarial activity

The following procedure was carried out and the results provided by Dr. Dascombe [190] and his group at University of Manchester.

Plasmodium berghi was maintained by serial passage in MF1 mice and was injected intravenously into experimental male mice, 18-25 g, in doses of 2×10^7 parasitized erythrocytes/animal. Control mice were injected with 0.2 mL of normal mouse blood diluted to the same extent with 0.85% saline. All animals were treated topically with an alcoholic solution of monosulphiram (2.5%) to prevent infection by *Eperythrozoon coccoides*.

In a blind study, putative antimalarials were injected subcutaneously into groups of 5-6 mice using sterile, peroxide-free olive oil and dimethylsulphoxide as vehicle (24:1, dose volume 10 mL kg^{-1}). Some compounds required the addition of 5% water or Tween 80, or both, to facilitate carriage of the chemical; for all compounds tested a concurrent control malaria group received the appropriate vehicle. Mice were treated on the day of inoculation, approximately 3 hours after being infected then twice daily (am and pm) for the next two days at 2-7 dose levels (range 2.5-200 mg kg^{-1}). Seventy-two hours after inoculation, body weights and colonic temperatures were measured and blood smears taken for the determination of parasitaemia which was assessed as the percentage of erythrocytes containing Leishman-positive bodies. The antimalarial activities of the compounds were assessed as the reduction in parasitaemia compared with that in concurrent vehicle-treated mice (Student's *t*-test); their relative potencies were assessed by calculating the dose (mg kg^{-1} s.c) which would, in this three day supression test, inhibit blood parasite counts to half of those in vehicle-treated mice (ID50). The results are summarised in Table **25**. Visual observation of the general autonomic and behavioural states of the mice was made throughout the experimental period.

Drug	Structure	Dose (mg kg^{-1} s.c)	% Difference control parasitaemia x +/- sem	Antimalarial P (probability)	Survival survivors/ starters
Trifluralin		25	-11 +/- 11	NS	5/5
		50	-16 +/- 16	NS	5/5
		100	-13 +/- 10	NS	5/5
		200	-13 +/- 8	NS	4/4
Chloralin		12.5	-29 +/- 14	NS	4/5
		25	-21 +/- 7	P < 0.1	4/10
		50	-51 +/- 9	P < 0.05	7/10
		100*	-70 +/- 6	P < 0.05	3/5
		200	-	-	0/5
2-chloro-3,5-dinitrobenzotri-fluoride		12.5	-34 +/- 12	NS	2/5
		25	-14 +/- 8	NS	4/10
		100	-	-	0/5
4-chloro-3-nitro-benzotrifluoride		50	-2 +/- 10	NS	5/5
		100	-15 +/- 16	NS	5/5
2,4-dichloro-5-nitrobenzotri-fluoride		25	-22 +/- 11	NS	5/5
		50	-2 +/- 4	NS	5/5
		100	-5 +/- 13	NS	5/5

NS = not significant

s.c = subcutaneous injections

* = once then 4 x 50 mg dose

Table 25

The results indicate that trifluralin in this three day-suppression test was not antimalarial in doses upto 200 mg kg^{-1} s.c twice daily. Chloralin was found to be toxic (zero survival at 200 mg kg^{-1} s.c) and was also acutely toxic to 100 mg kg^{-1} s.c which necessited reduction in dose in this group, to 50 mg kg^{-1} s.c for subsequent days' treatment. However, the drug had antimalarial activity since the results showed significant reduction in parasitaemia.

2-chloro-3,5-dinitrobenzotrifluoride, an analogue of chloralin readily bought, was toxic at 100 mg kg^{-1} s.c with no survivors. Hence reduction in dose levels to 25 and 12.5 mg kg^{-1} still caused some deaths. There is indication that latter dose may be

antimalarial but the group remaining (2 survivours from 5) suggests too small for statistical significance.

4-chloro-3-nitrobenzotrifluoride and 2,4-dichloro-5-nitrobenzotrifluoride were not toxic and also not antimalarial as there was 100% survival rate.

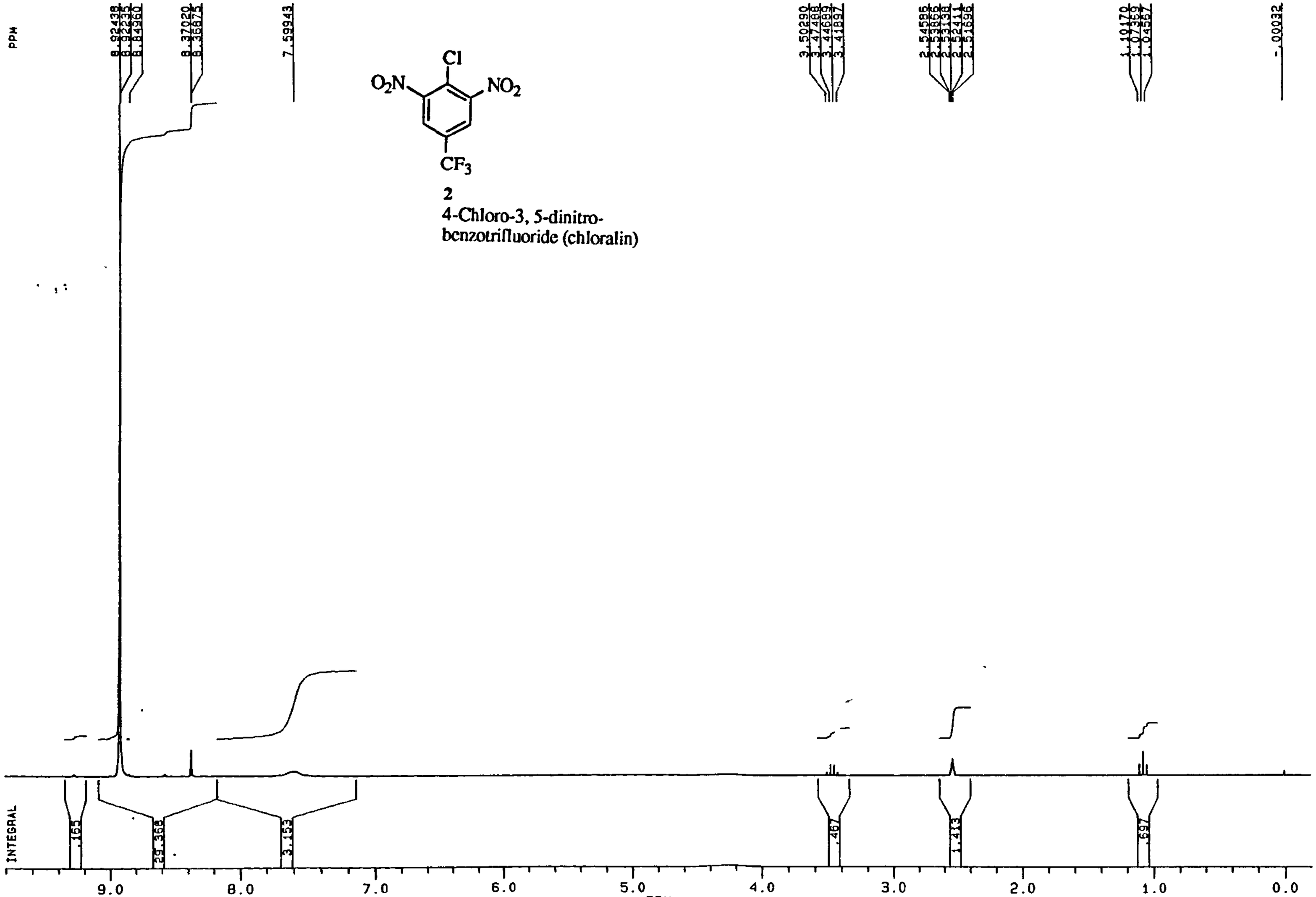
A separate study was performed by Dr. Bell and his team at Trinity College, Dublin, Ireland. They reported some very preliminary results on the antimalarial activity of compound **65b**. It was found to be consistent with that reported by Dascombe *et al* on trifluralin (on a molar basis).

Compounds **65c, 65e, 65f** and **65g** were not fully soluble in DMSO at suitable concentrations (> 5 mM), hence results are not available as yet. However, these results should be treated with caution as they are from a single experiment.

In summary, the data in table **25** is consistent with chloralin being the active (toxic and antimalarial) component of trifluralin. The researchers (Dascombe *et al*) were unable to separate toxicity from the antimalarial effect of the chloralin analogue, 2-chloro-3,5-dinitrobenzotrifluoride, hence the profile reported. The remaining two compounds (i.e. 4-chloro-3-nitrobenzotrifluoride and 2,4-dinitro-5-nitrobenzotrifluoride) lacked toxophore/pharmacophore associated with chloralin and/or 2-chloro-3,5-dinitrobenzo-trifluoride, hence full survival rate observed.

SPECTRUM NO. 1

4-CHLORO-3, 5-DINITROBENZOTRIFLUORIDE (RECRYST.)



2
4-Chloro-3, 5-dinitro-
benzotrifluoride (chloralin)

BRUKER

JN250S.111
AU PROG:
X00.AU
DATE 25-6-96
TIME 15:50

SOLVENT DMSO
SF 250.134
SY 100.0
O1 5540.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305

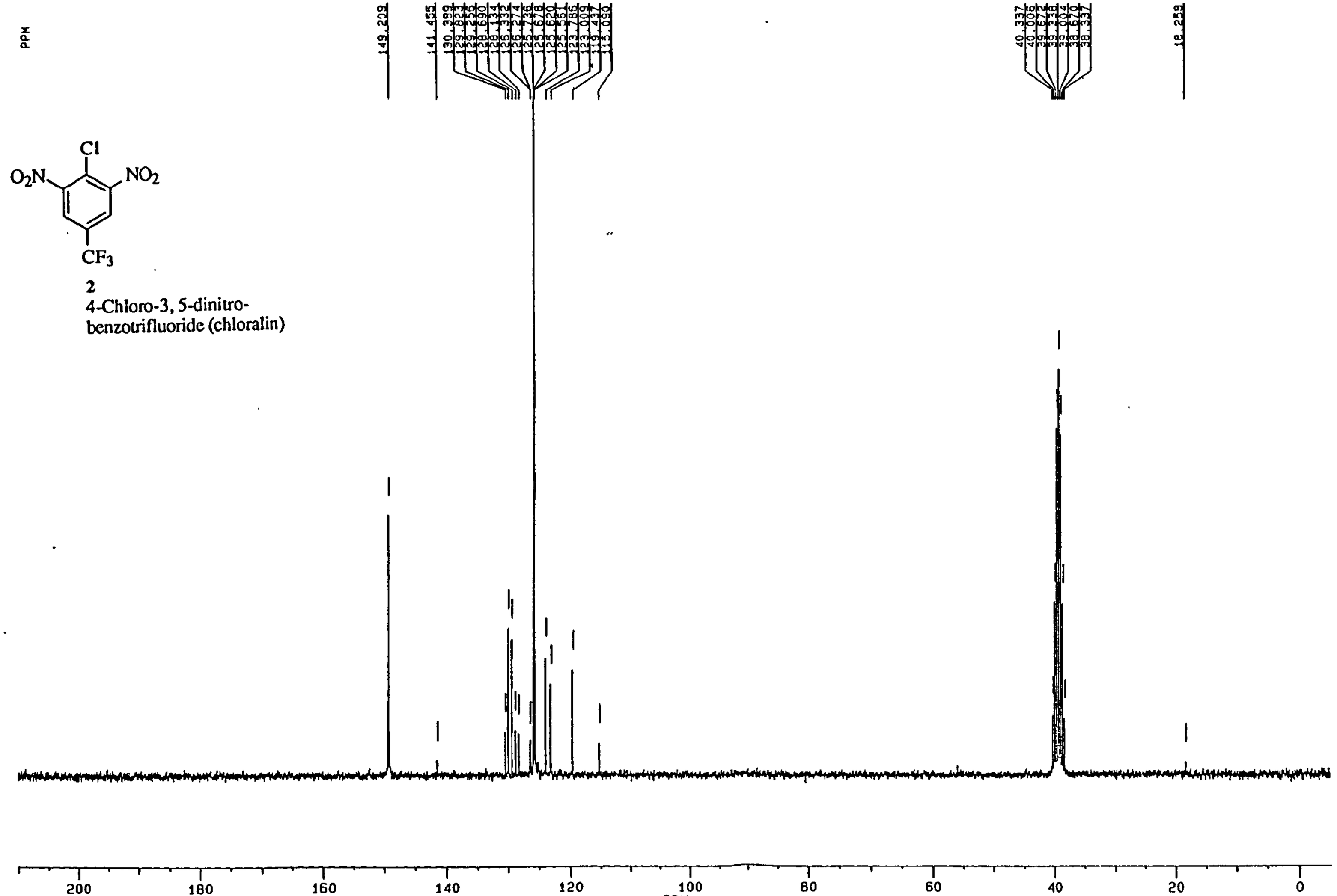
PW 0.0
RD 0.0
AQ 3.277
RG 20
NS 96
TE 297

O2 0.0
DP 63L PO

LB .200
CX 35.00
CY 18.00
F1 9.801
F2 -.199
HZ/CM 71.463
PPM/CM .286
SR 4030.60

SPECTRUM NO. 2

4-CHLORO-3, 5-DINITROBENZOTRIFLUORIDE (RECRYST.)



2
4-Chloro-3, 5-dinitro-benzotrifluoride (chloralin)

BRUKER

JN251S.111
AU PROG:
X02.AU
DATE 25-6-96
TIME 16:36

SOLVENT DMSO
SF 62.896
SY 62.0
O1 2596.000
SI 65536
TD 65536
SW 15625.000
HZ/PT .477

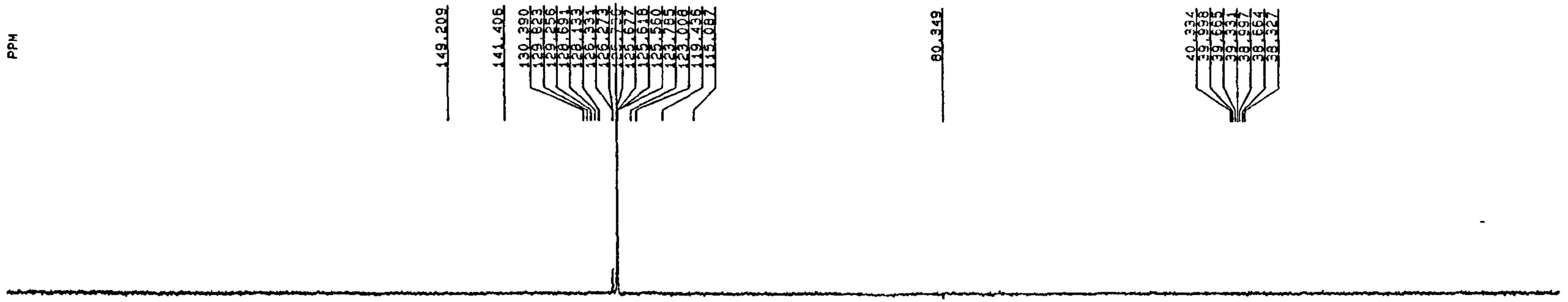
PW 0.0
RD 0.0
AQ 2.097
RG 400
NS 800
TE 297

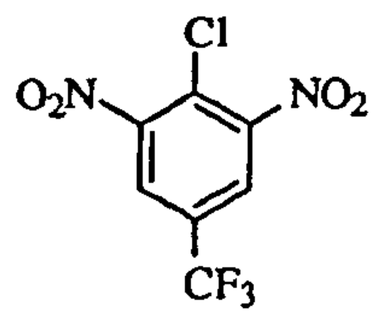
O2 5270.000
DP 18L DO

LB 1.000
CX 35.00
CY 18.00
F1 210.010
F2 -4.989
HZ/CM 386.361
PPM/CM 6.143
SR -3710.17

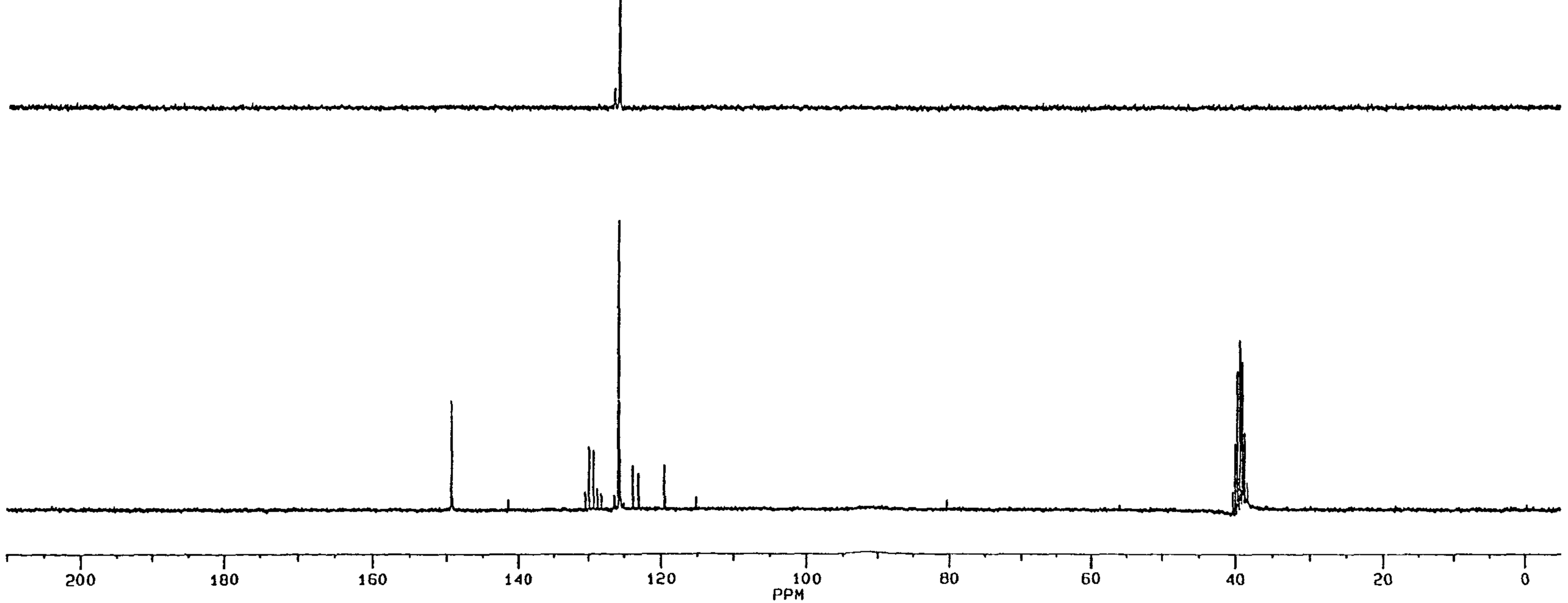
SPECTRUM NO. 3

4CHLORO-3, 5-DINITROBENZOTRIFLUORIDE (RECRYST.)





2
4-Chloro-3, 5-dinitro-
benzotrifluoride (chloralin)



BRUKER

JN252S.111
AU PROG:
X02.AU
DATE 25-6-96
TIME 17:12

SOLVENT DMSO
SF 62.896
SY 62.0
O1 2596.000
SI 65536
TD 65536
SW 15625.000
HZ/PT .477

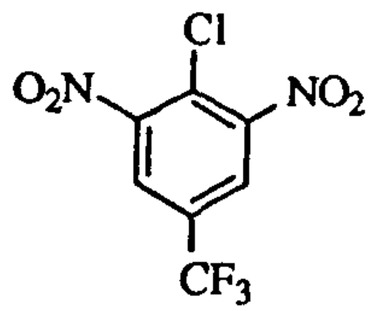
PW 0.0
RD 0.0
AQ 2.097
RG 640
NS 600
TE 297

O2 5270.000
DP 18L DO

LB 1.000
CX 35.00
CY 6.50
F1 210.010P
F2 -4.989P
HZ/CM 386.361
PPM/CM 6.143
SR -3710.17

SPECTRUM NO. 4

4-CHLORO-3, 5-DINITROBENZOTRIFLUORIDE (RECAYST.)



2
4-Chloro-3, 5-dinitro-
benzotrifluoride (chloralin)

BRUKER

F19JN26.F001
DATE 27-6-96
TIME 12:00

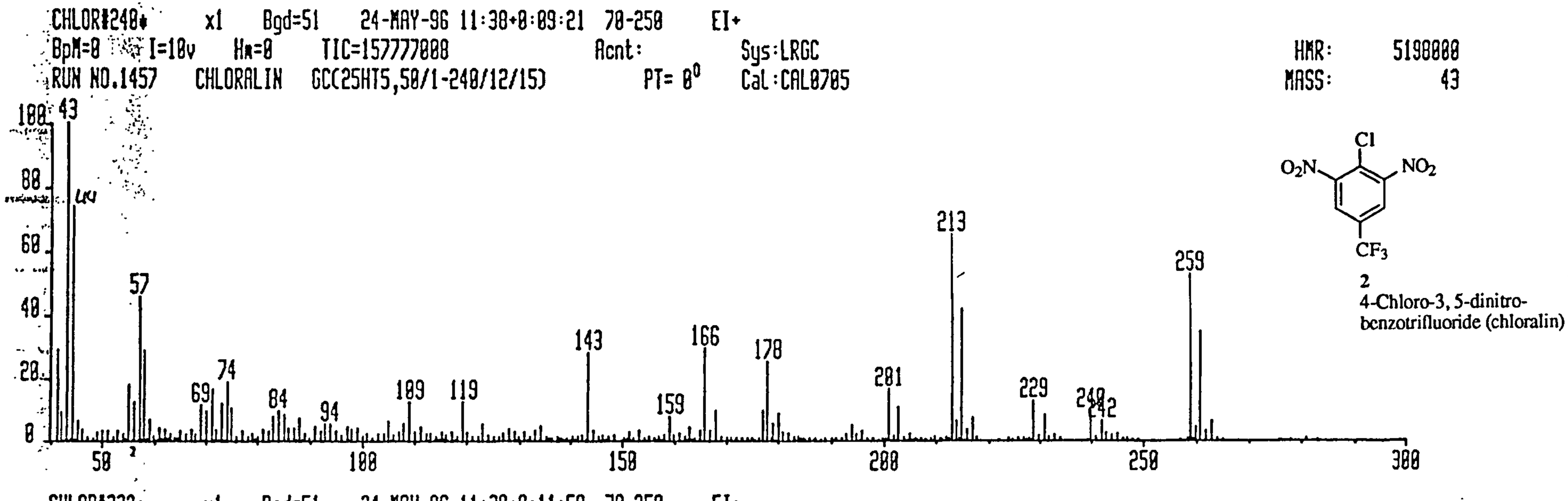
SOLVENT DMSO
SF 235.361
SY 85.0
O1 -4565.186
SI 32768
TD 32768
SW 35714.286
HZ/PT 2.180

PW 6.0
RD 0.0
AQ .459
RG 10
NS 128
TE 297

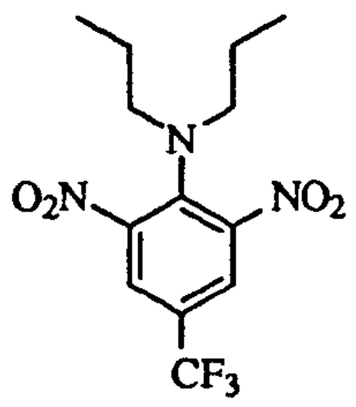
O2 6043.000
DP 18L PO

LB 0.0
CX 35.00
CY 18.00
F1 10.012P
F2 -99.989P
HZ/CM 739.709
PPM/CM 3.143
SR 11016.22

SPECTRUM NO. 5

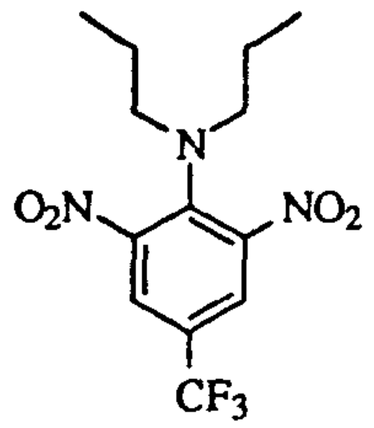


SPECTRUM NO 6

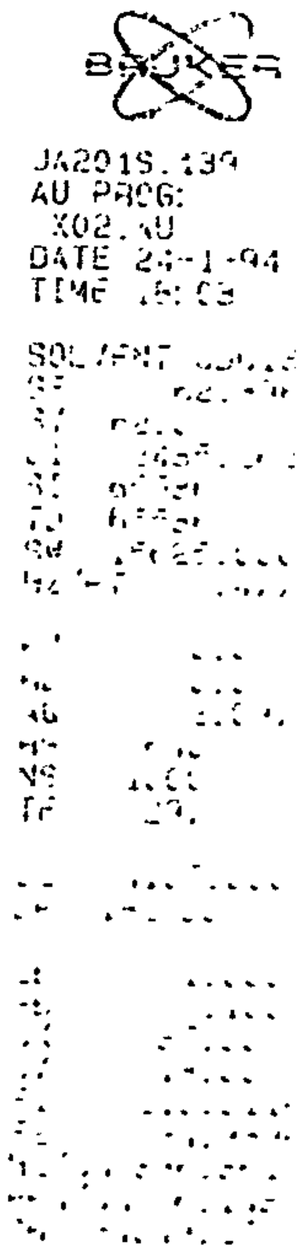


3
2, 6-Dinitro-(*N*, *N*-dipropyl-4-trifluoromethyl)benzene

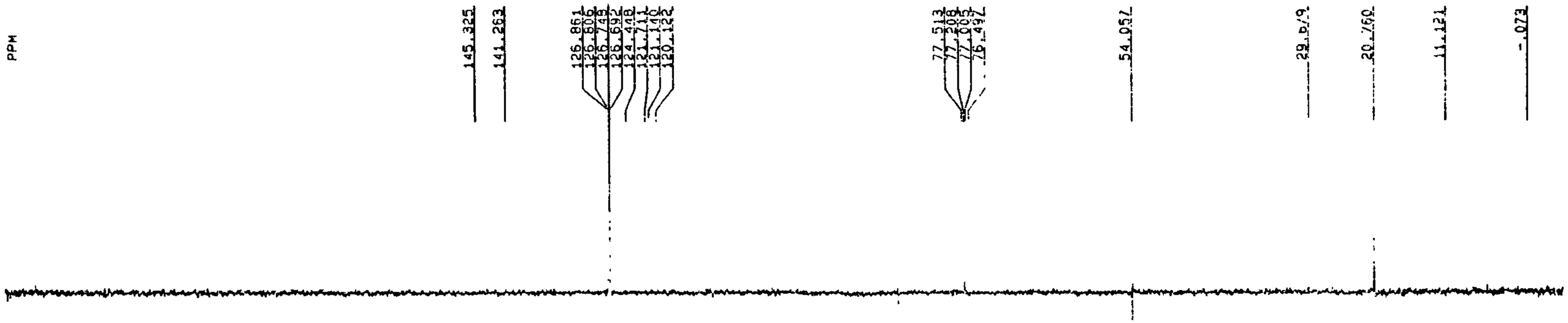
SPECTRUM NO. 7

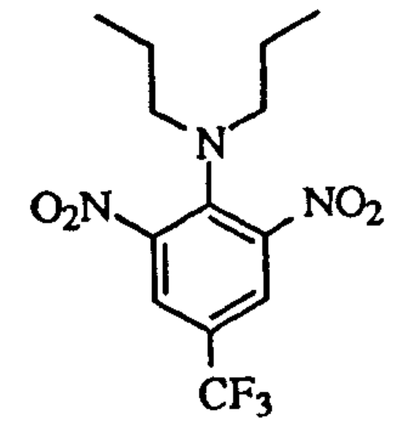


3
2, 6-Dinitro-(*N*, *N*-dipropyl-
4-trifluoromethyl)benzene

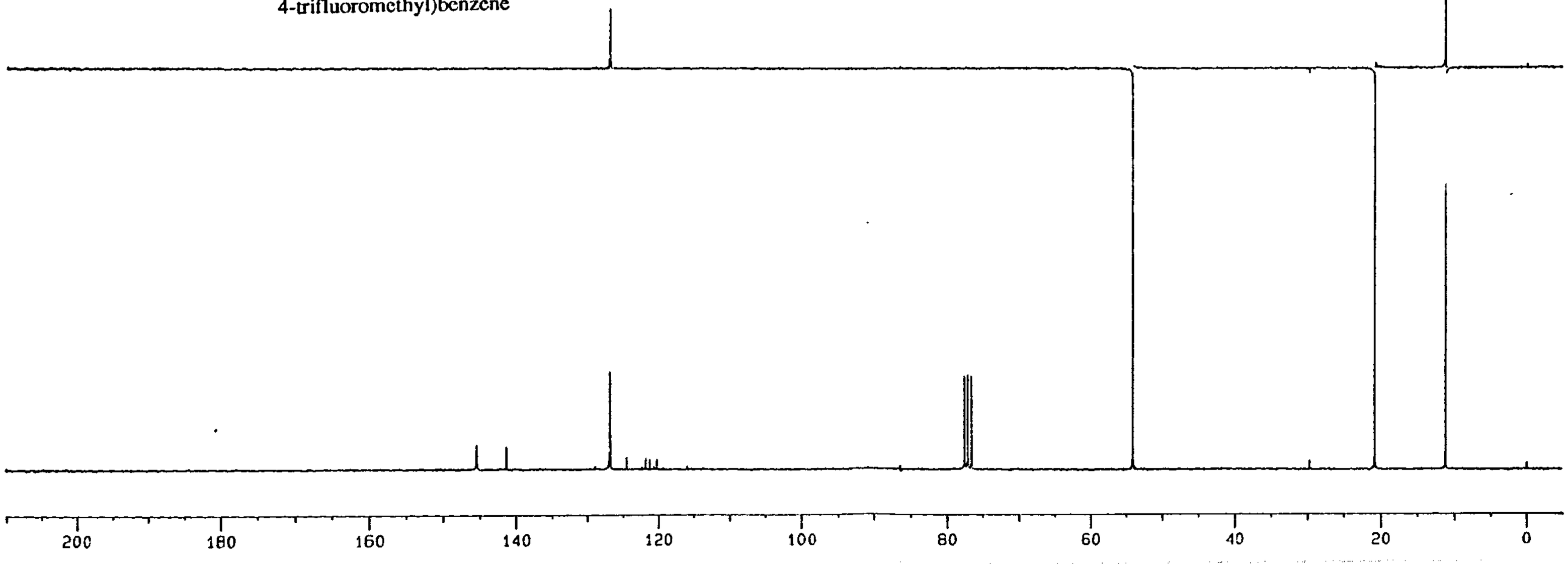


SPECTRUM NO. 8





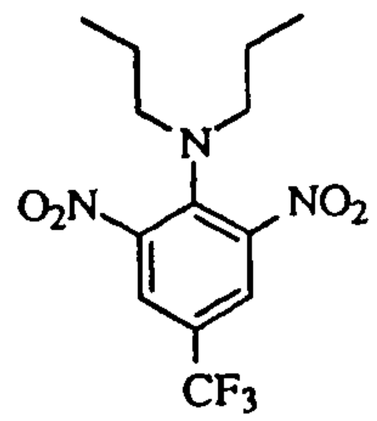
3
2, 6-Dinitro-(*N*, *N*-dipropyl-
4-trifluoromethyl)benzene



BRUKER

```
JA202S.139
AU PROG:
 X02.AU
DATE 24-1-94
TIME 19:01

SOLVENT CDCl3
SF      62.896
SY   62.0
01    2435.262
SI   65536
TD   65536
SW   15625.000
HZ/PT     .477

PW        0.0
RD        0.0
AG        2.097
RG        400
VS        1000
TE        297

D2     4105.000
DE     18L 00

LB        1.000
GB         .100
CX       35.00
CY        6.50
F1     210.011
F2      -4.969
HZ/CM 386.361
PPM/CM  6.143
SR    -4044.96
```

SPECTRUM NO. 9



3
2, 6-Dinitro-(*N*,*N*-dipropyl-
4-trifluoromethyl)benzene

PPM .0020 -62.6737

BRUKER

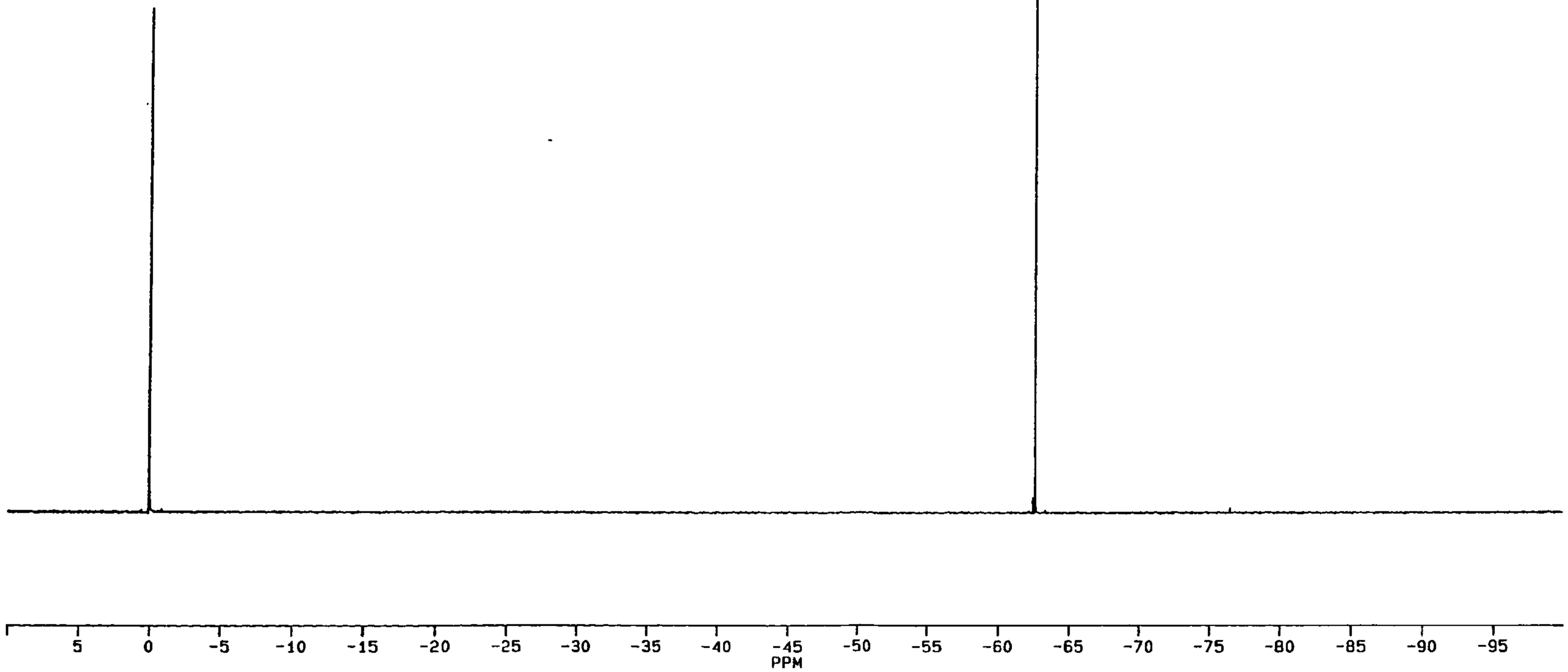
F19JAN9.F002
DATE 9-1-96
TIME 11:46

SOLVENT CDCl3
SF 235.360
SY 85.0
O1 -4565.186
SI 32768
TD 32768
SW 35714.286
HZ/PT 2.180

PW 6.0
RD 0.0
AQ .459
RG 64
NS 64
TE 297

O2 6043.000
DP 18L PO

LB 0.0
CX 35.00
CY 18.00
F1 10.021
F2 -99.980
HZ/CM 739.709
PPM/CM 3.143
SR 10144.29

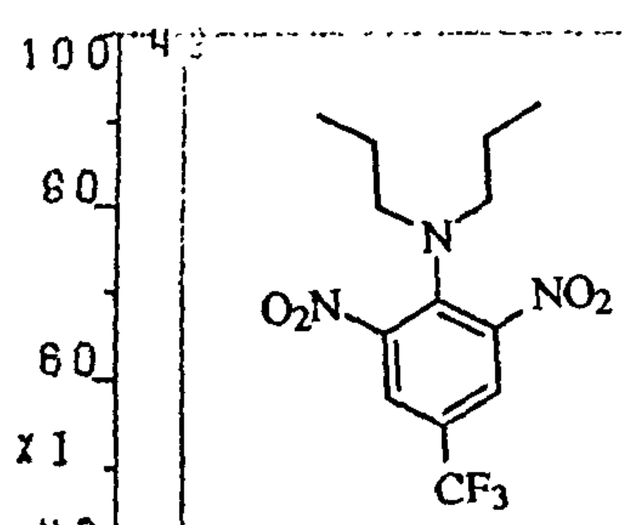


SPECTRUM NO. 10

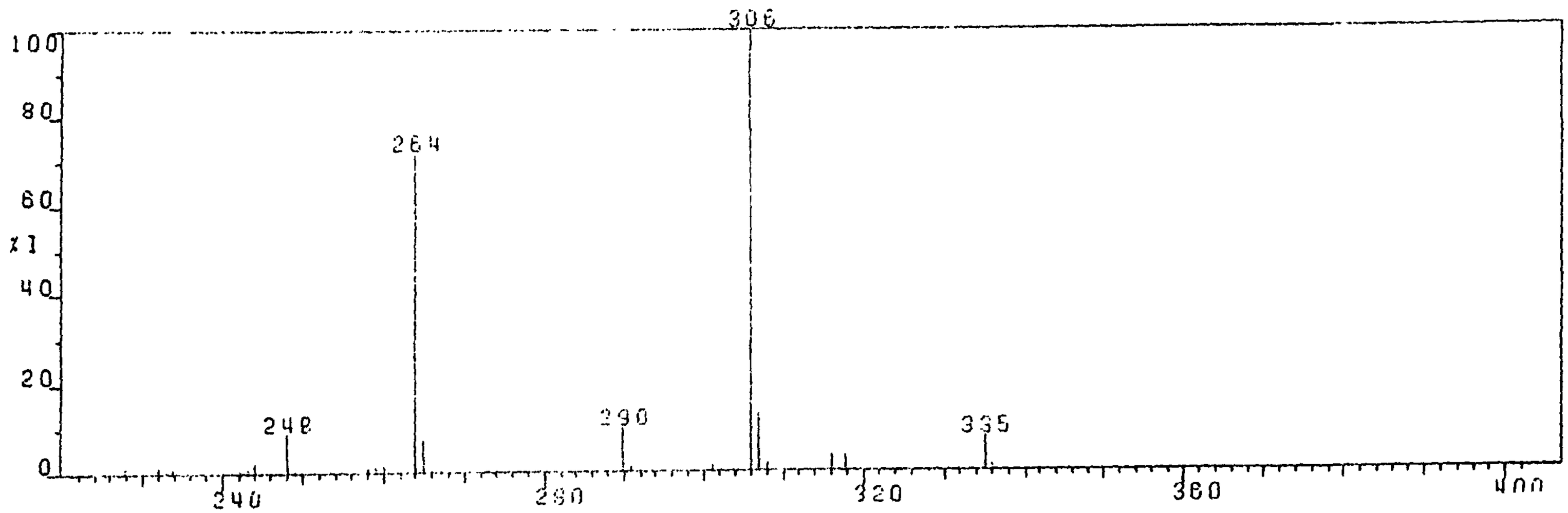
PROBE

RES10 . S 08-SEP-94 CAL:2H1109 STA: BG SCAN = 0
PROBE MS RUN NO. 14

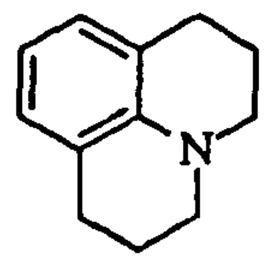
1: 7



3
2, 6-Dinitro-(*N*,*N*-dipropyl-
4-trifluoromethyl)benzene



SPECTRUM NO. 11



36
2, 3, 6, 7-Tetrahydro-*1H*, *5H*-benzo[ij]quinoline

BRUKER

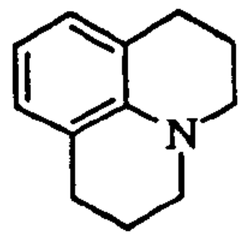
AP100S.206
AU PROG:
X00.AU
DATE 11-4-95
TIME 18:21

SOLVENT MeOH
SF 250.13
SY 100.0
O1 5351.00
SI 32768
TD 32768
SW 5000.00
HZ/PT .30

PW 0.0
RD 0.0
AQ 3.27
RG 10
NS 96
TE 297

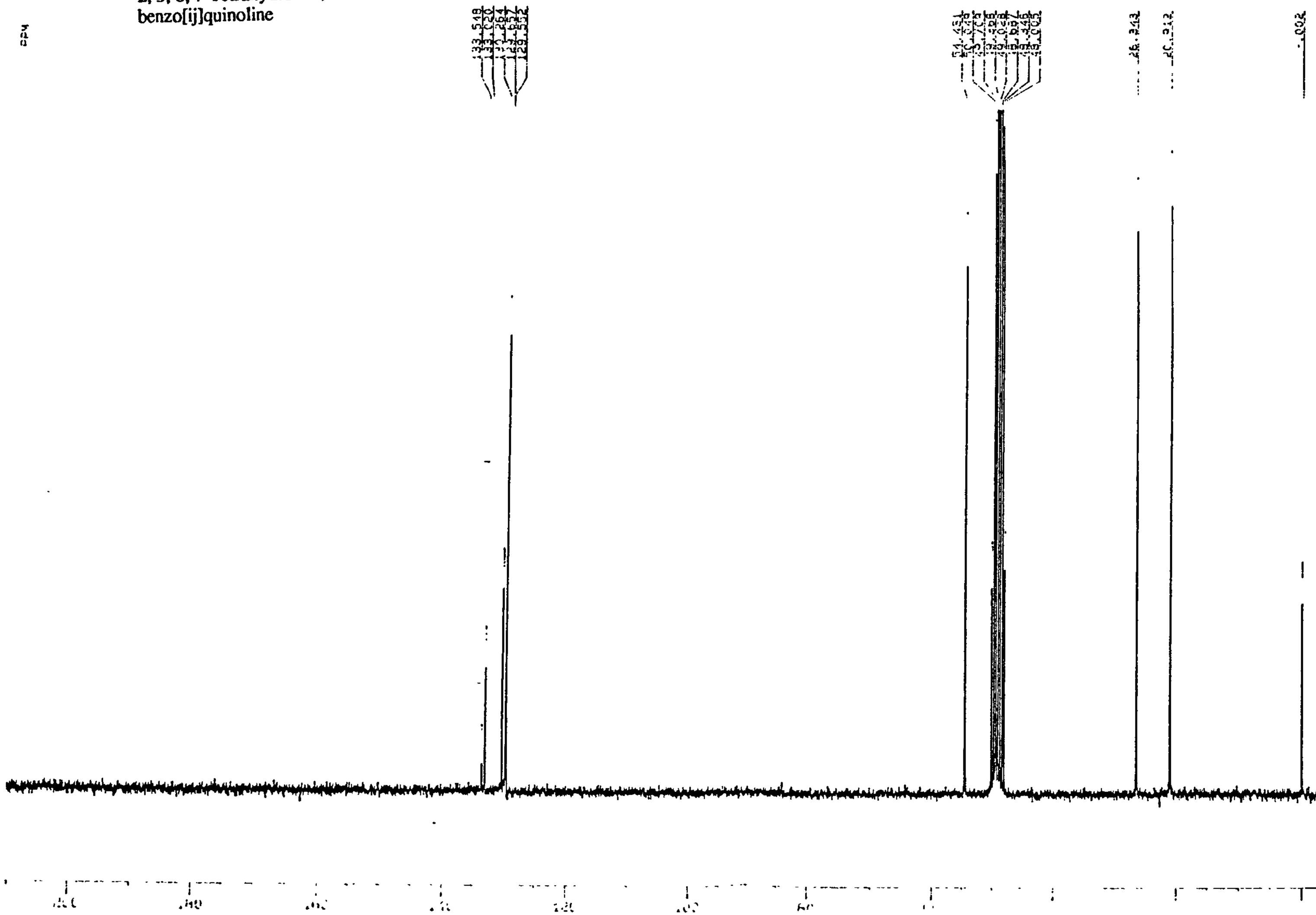
O2 0.0
DP 63L PO

LB .200
GB .100
CX 35.00
CY 18.00
F1 9.80
F2 -.199
HZ/CM 71.463
PPM/CM .286
SR 3840.99



SPECTRUM NO. 12

36
2, 3, 6, 7-Tetrahydro-*1H*, *5H*-benzo[ij]quinoline



BRUKER

AP101S.208
AU PROG:
X02.AU
DATE 11-4-95
TIME 19:19

SOLVENT MeOH
SF 62.896
SY 62.0
01 2404.000
SI 65536
TD 65536
SW 15625.000
HZ/PT .477

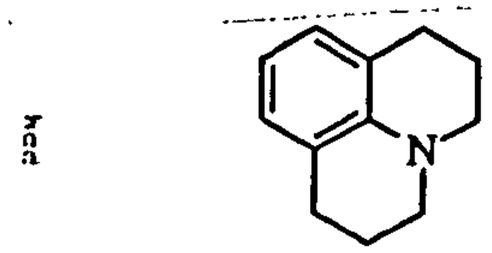
PW 0.0
RD 0.0
AG 2.097
RG 640
NS 1000
TE 297

02 5100.000
DP 18L DO

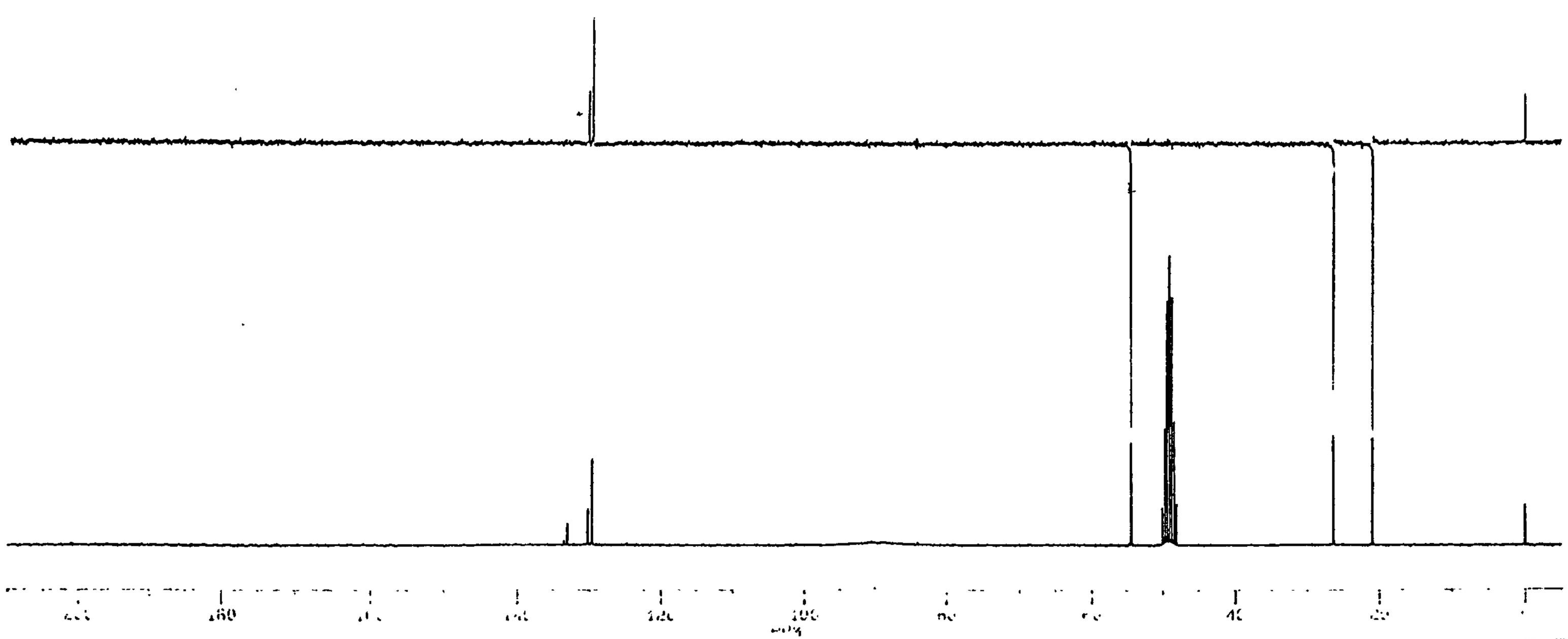
LB 1.000
GB .100
CX 35.00
CY 5.00
F1 210.011P
F2 -4.989P
HZ/CM 386.361
PPM/CM 6.143
SR -3685.01

SPECTRUM NO. 13

(RECRYST.)



36
2, 3, 6, 7-Tetrahydro-*1H*, *5H*-benzo[ij]quinoline



BRUKER

AP102S.208
AU PROG:
X02.AU
DATE 11-4-95
TIME 20:19

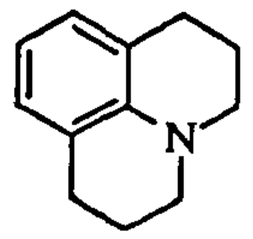
SOLVENT MeOH
SF 62.896
SY 62.0
01 2404.000
SI 65536
TD 65536
SW 15625.000
HZ/PT .477

PW 0.0
RD 0.0
AQ 2.097
RG 640
NS 1000
TE 297

02 5100.000
DP 18L DO

LB 1.000
GB .100
CX 35.00
CY 6.50
F1 210.011P
F2 -4.989P
HZ/CM 386.361
PPM/CM 6.143
SR -3885.00

SPECTRUM NU-14

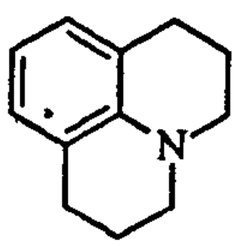


36
2, 3, 6, 7-Tetrahydro-*VI*, *5H*-benzo[ij]quinoline

BRUKER

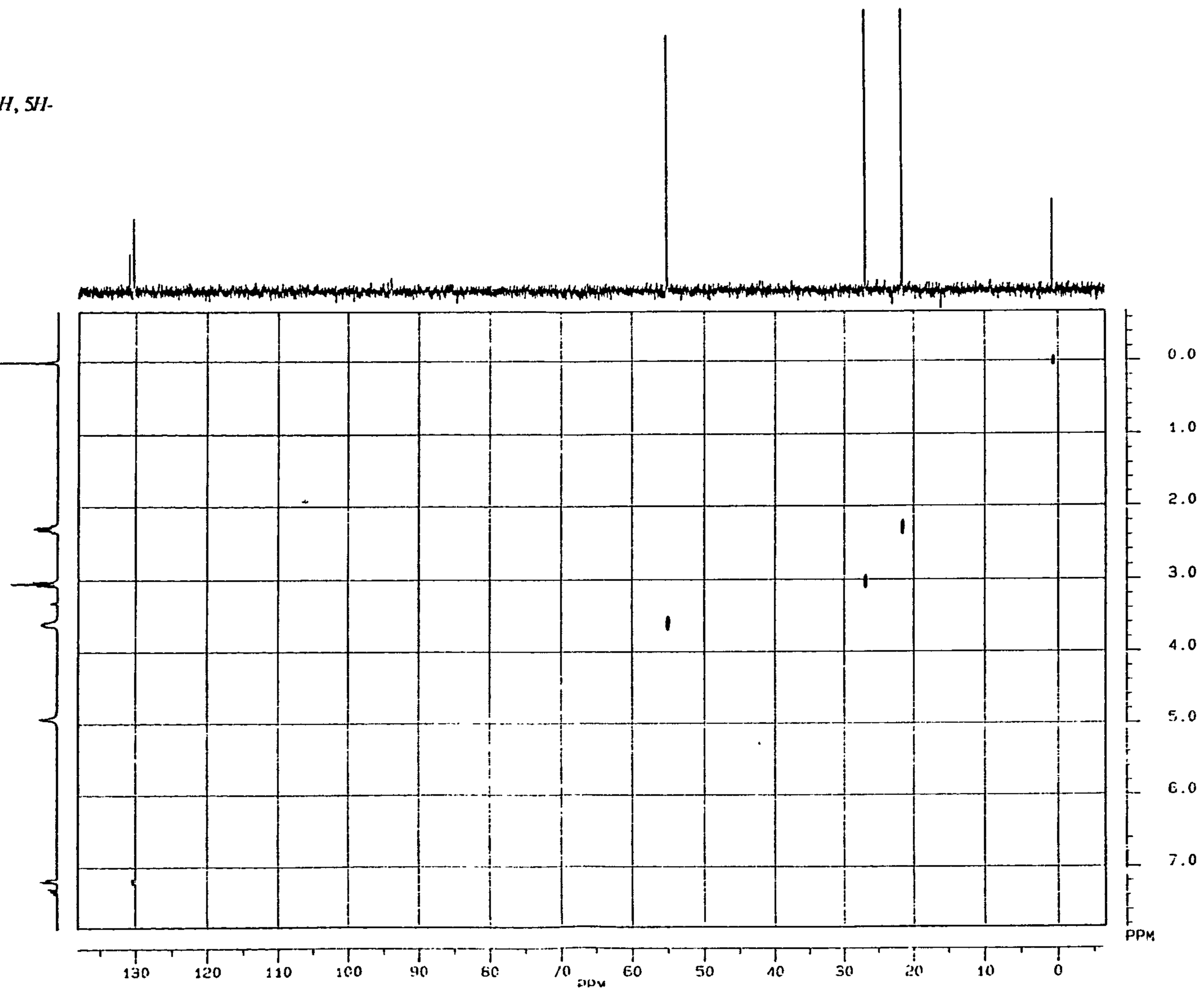
```
AP121125.SMX
F1 PROJ:
 PROJH1.001
F2 PROJ:
 PROJH1.001
AU PROG:
 Z27.AU
DATE 13-4-95

SI2   1024
SI1    512
SW2  2145.923
SW1  1072.961
NDO       1

WDW2      S
WDW1      S
SSB2      0
SSB1      0
MC2       M
PLIM ROW:
F1        7.870P
F2        -.709P
AND COLUMN:
F1        7.870P
F2        -.709P

D1      .8630000
P1         9.20
RGA
RD      0.0
PW         0.0
DE       293.60
NS          16
DS           2
D0      .0000030
P3         4.60
NE          128
IN      .0004660
```

SPECTRUM NO. 15



36
2, 3, 6, 7-Tetrahydro-*1H*, *5H*-benzo[ij]quinoline

(RECRYST.)



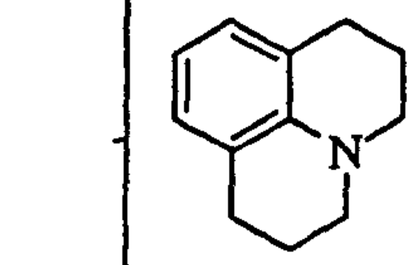
BRUKER

AP124125.SMX
F1 PROJ:
PROJH1.001
F2 PROJ:
PROJX.001
AU PROG:
Z28.AU
DATE 13-4-95

SI2	2048
SI1	512
SW2	9090.909
SW1	1067.006
NDO	2
WDW2	S
WDW1	S
SSB2	0
SSB1	0
MC2	M
PLIM ROW:	
F1	138.019P
F2	-6.520P
AND COLUMN:	
F1	7.839P
F2	-.693P
D1	.9520000
S3	0H
P1	9.50
D0	.0000030
P6	10.60
D2	.0037000
P5	5.30
D4	.0018500
S2	18H
RGA	
RD	0.0
PW	0.0
DE	71.30
NS	32
DS	2
P9	85.00
NE	128
IN	.0002345

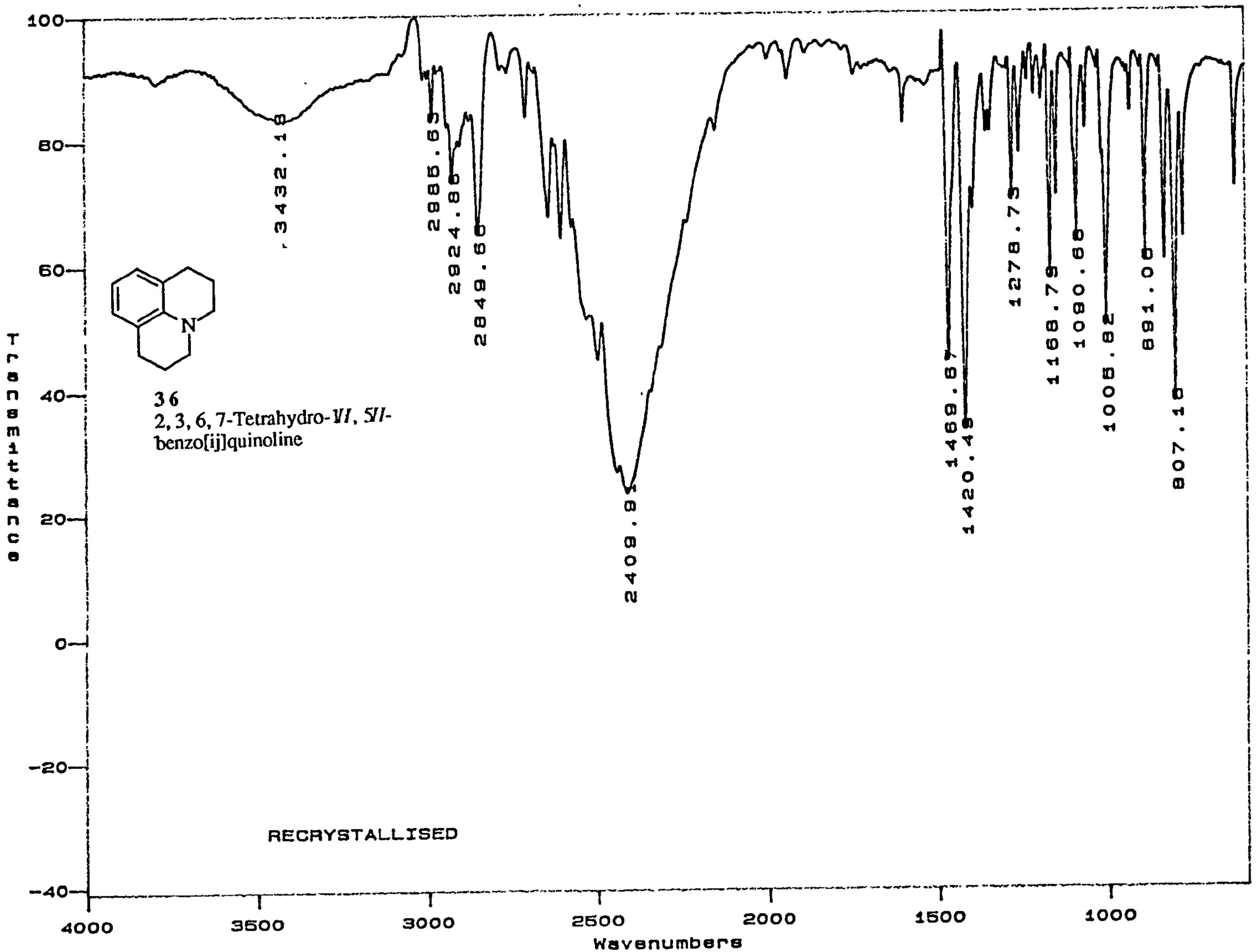
SPECTRUM NO. 16

RES441. 9 10-APR-95 CAL:2C0604 STA: BG SCAN = 0
PROBE MS RUN NO. 1302 1:15

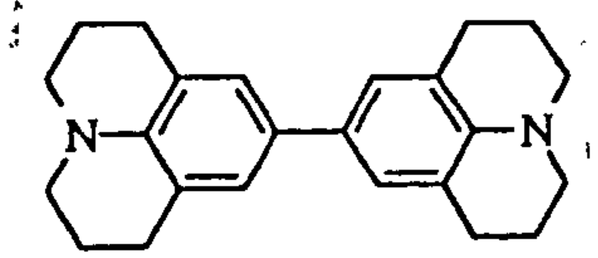


36
2, 3, 6, 7-Tetrahydro-*1H*, *5H*-benzo[ij]quinoline

SPECTRUM NO. 17



36
2, 3, 6, 7-Tetrahydro-*1H*, *5H*-benzo[ij]quinoline



36a
9, 9'-Bijulolidyl

SPECTRUM NO. 18

PPM

7.23031
7.17512
6.93877

3.40720
3.38654
3.36319
3.27563
3.25456
3.23035
3.13907
3.11727
3.09143
3.05055
3.02647
2.86674
2.81969
2.79364
2.76745
2.74642
2.53645

2.03487
2.00948
1.99926
1.98617
1.97413
1.96407
1.93784
1.62459

1.34059
1.31622
1.25362

.23559
.07301
.01381
.00033
-.00033
-.01299

INTEGRAL
.99
35.14
44.40
4.35
.75
9.20

BRUKER

AP130S.131
AU PROG:
X00.AU
DATE 13-4-95
TIME 13:47

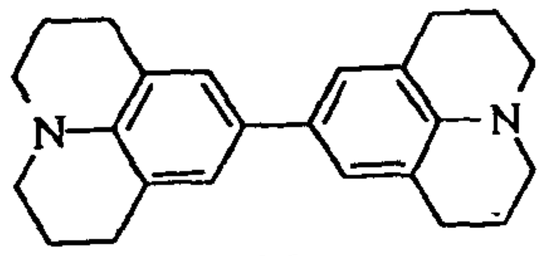
SOLVENT CDC13
SF 250.133
SY 100.0
O1 4358.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305

PW 0.0
RD 0.0
AQ 3.277
RG 10
NS 96
TE 297

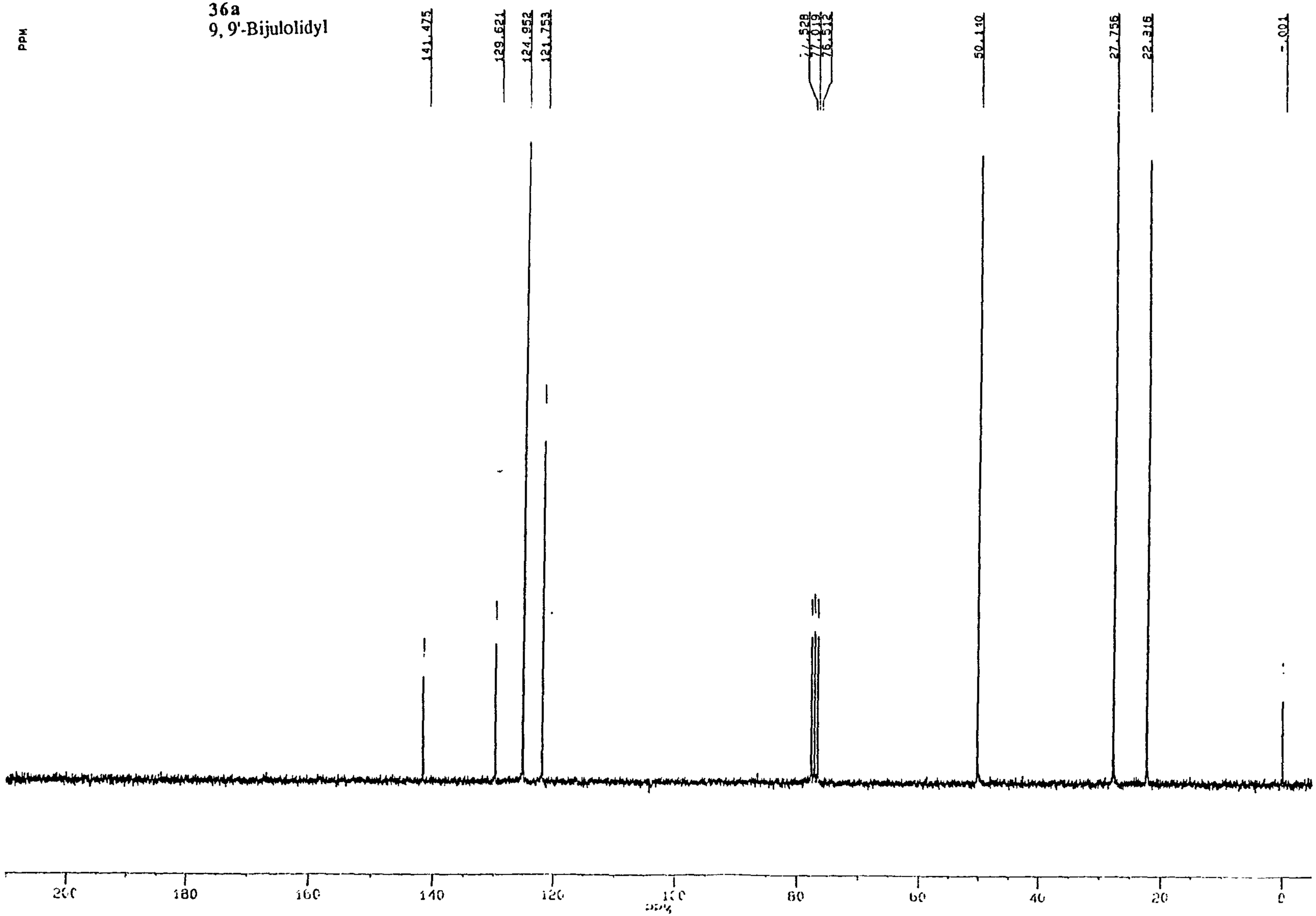
O2 0.0
DP 63L PO

LB .200
GB .100
CX 35.00
CY 18.00
F1 9.801P
F2 -.199P
HZ/CM 71.463
PPM/CM .286
SR 2861.72

SPECTRUM NO. 19



36a
9, 9'-Bijulolidyl



AP131S.131
AU PROG:
X02.AU
DATE 13-4-95
TIME 14:44

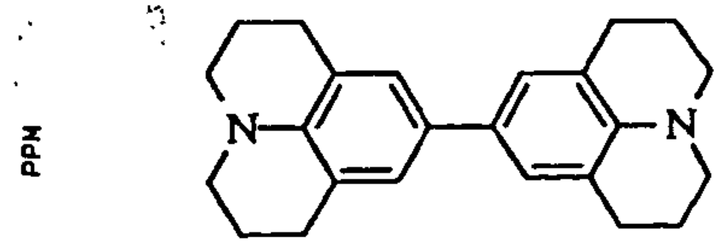
SOLVENT CDCl3
SF 62.896
SY 62.0
O1 2435.262
SI 65536
TD 65536
SW 15625.000
HZ/PT .477

PW 0.0
RD 0.0
AQ 2.097
RG 640
NS 1000
TE 297

O2 4105.000
DP 18L DO

LB 1.000
GB .100
CX 35.00
CY 18.00
F1 210.011P
F2 -4.989P
HZ/CM 386.361
PPM/CM 6.143
SR -4043.05

SPECTRUM NO. 20



36a
9, 9'-Bijulolidyl

BRUKER

AP132S.131
AU PROG:
X02.AU
DATE 13-4-95
TIME 15:41

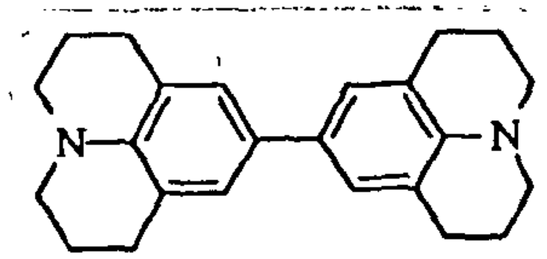
SOLVENT CDCl3
SF 62.896
SY 62.0
01 2435.262
SI 65536
TD 65536
SW 15625.000
HZ/PT .477

PW 0.0
RD 0.0
AQ 2.097
RG 640
NS 1000
TE 297

02 4105.000
DP 18L DO

LB 1.000
GB .100
CX 35.00
CY 6.50
F1 210.01
F2 -4.989
HZ/CM 386.36
PPM/CM 6.14
SR -4043.05

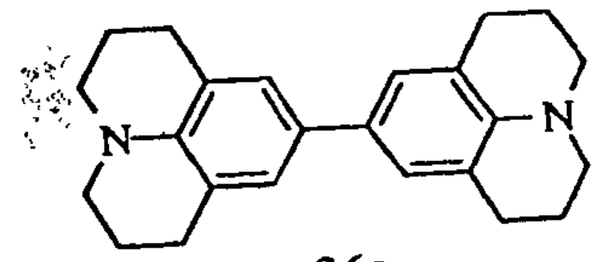
SPECTRUM NO. 21



36a
9,9'-Bijulolidyl

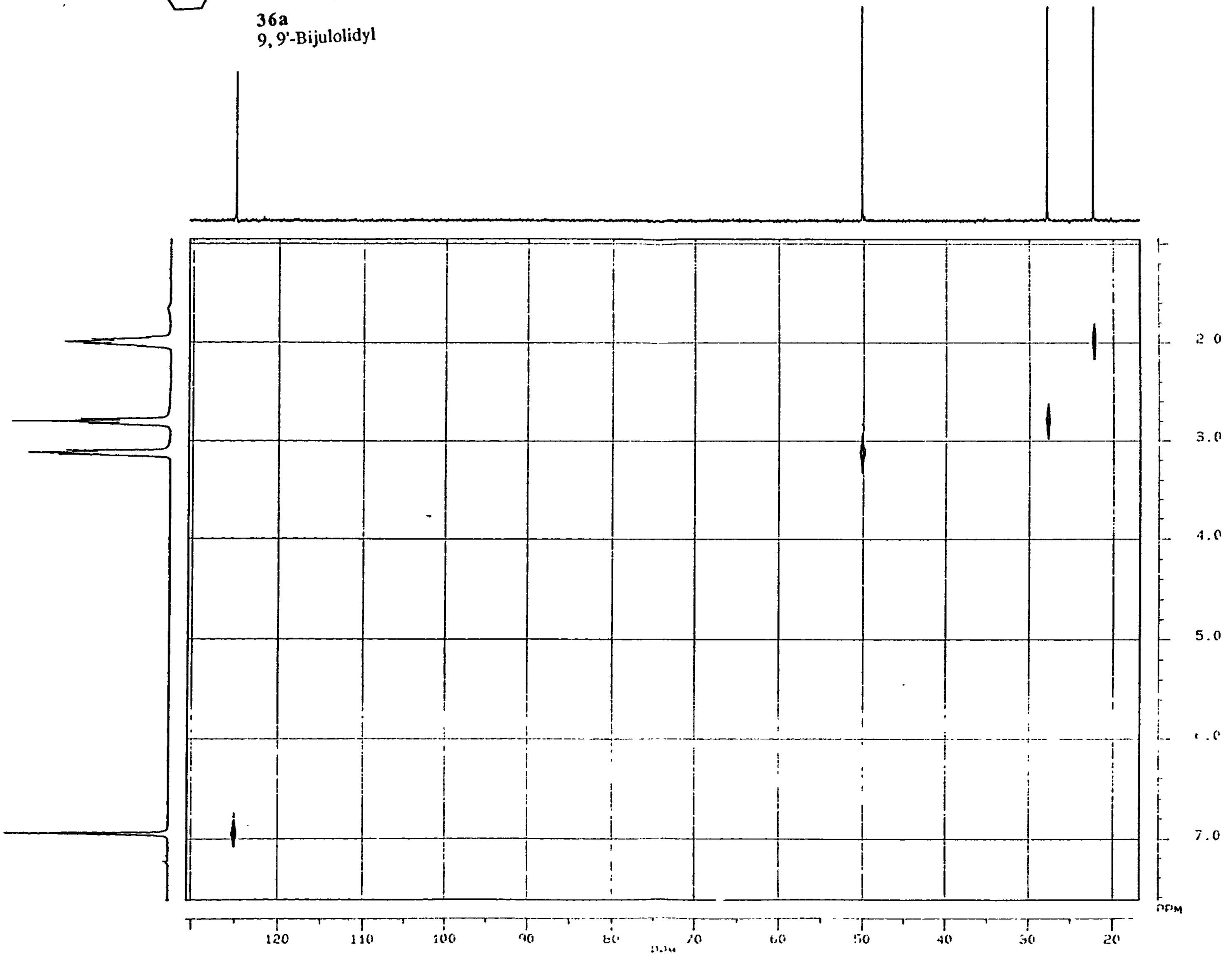
BRUKER

```
AP136131.SMX
F1 PROJ:
 PROJH1.001
F2 PROJ:
 PROJH1.001
AU PROG:
 Z27.AU
DATE 13-4-95

SI2   1024
SI1    512
SW2  1700.680
SW1   850.340
NDO      1

WDW2     S
WDW1     S
SSB2     0
SSB1     0
MC2      M
PLIM ROW:
F1        7.639P
F2         .840P
AND COLUMN:
F1        7.639P
F2         .840P

D1       .9030000
P1          9.20
RGA
RD       0.0
PW           0.0
DE        370.00
NS             8
DS             2
DO       .0000030
P3          4.60
NE           128
IN       .0005880
```



36a
9, 9'-Bijulolidyl

SPECTRUM NO. 22

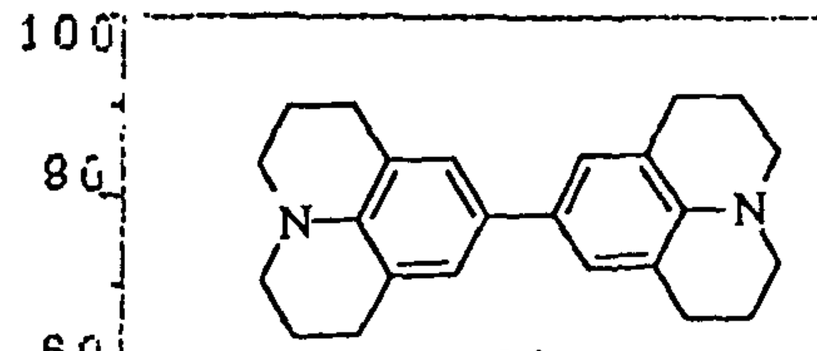


BRUKER

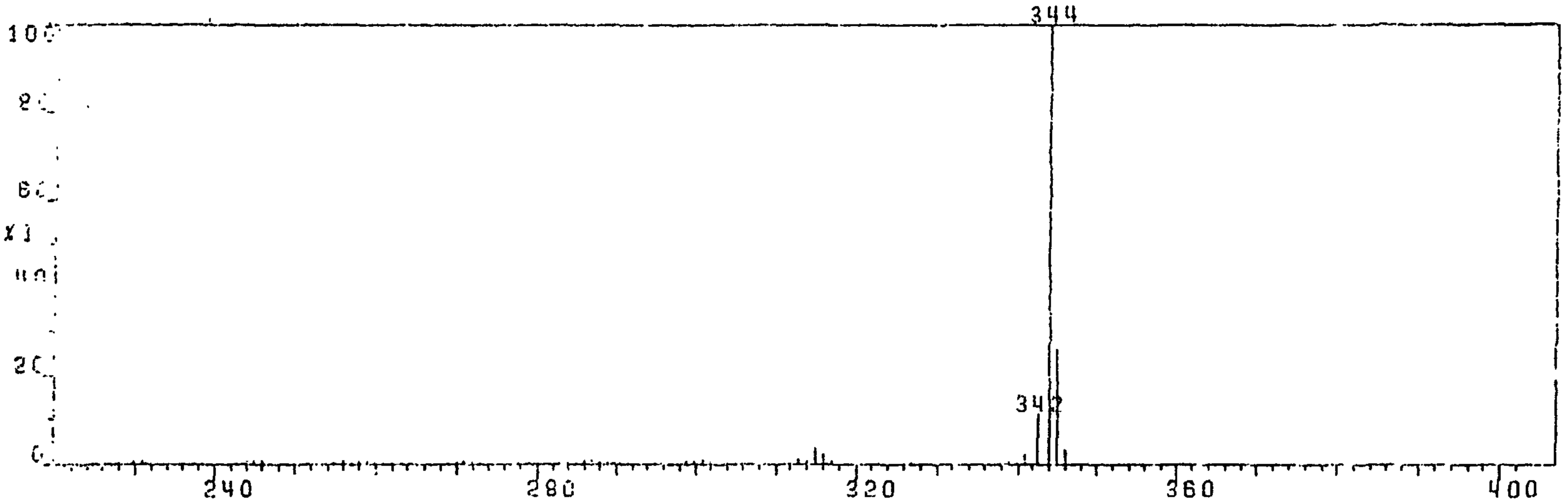
```
AP139131.SMX
F1 PROJ:
 PROJH1.001
F2 PROJ:
 PROJX.001
AU PROG:
 Z28.AU
DATE 13-4-95

SI2   2048
SI1    512
SW2  7142.857
SW1   835.282
NDO      2

WDW2     Q
WDW1     Q
SSB2     4
SSB1     4
MC2      M
PLIM ROW:
F1     130.451P
F2      16.885P
AND COLUMN:
F1       7.623P
F2        .945P

D1     .9300000
S3     0H
P1        9.50
D0     .0000030
P6       10.60
D2     .0037000
P5        5.30
D4     .0018500
S2    18H
RGA
RD     0.0
PW        0.0
DE       90.00
NS         32
DS          2
P9       85.00
NE         128
IN     .0002993
```

SPECTRUM NO. 23

RES514. 3 04-MAY-95 CAL:2C2604 STA: BG SCAN = 0
PROBE MS RUN NO. 1417 0:28

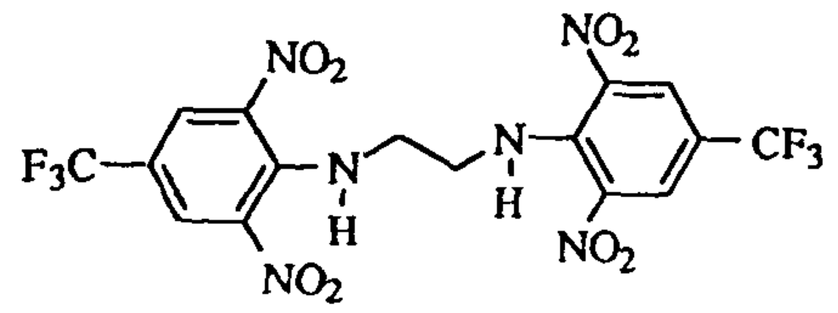


36a
9, 9'-Bijulolidyl



SPECTRUM NU. 24

RECRYSTALLISED



65a

N^1,N^2-di-(2, 6-dinitro-4-trifluoromethyl-phenyl)-1, 2-ethylenediamine

BRUKER

AP260S.211
AU PROG:
X00.AU
DATE 26-4-94
TIME 9:24

SOLVENT Aceto
SF 250.13
SY 100.0
O1 5653.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305

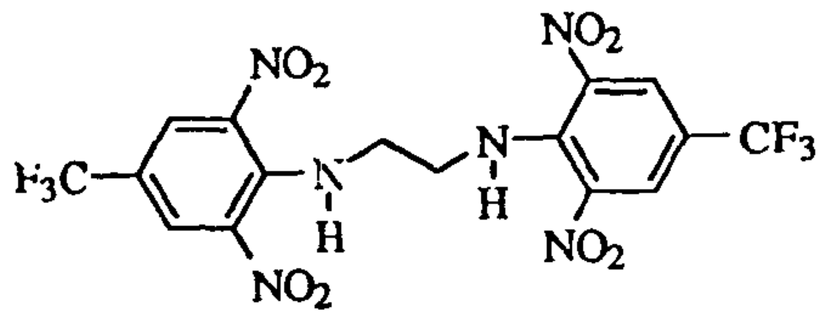
PW 0.0
RD 0.0
AQ 3.277
RG 20
NS 256
TE 297

O2 0.0
DP 63L PO

LB .200
GB .100
CX 35.00
CY 18.00
F1 9.801
F2 -.199
HZ/CM 71.463
PPM/CM .286
SR 4151.84

SPECTRUM NO. 25

RECRYSTALLISED [WITH D20]



65a

N^1,N^2-di-(2, 6-dinitro-4-trifluoromethyl-phenyl)-1, 2-ethylenediamine

BRUKER

AP260S.414
AU PROG:
X00.AU
DATE 27-4-94
TIME 0:21

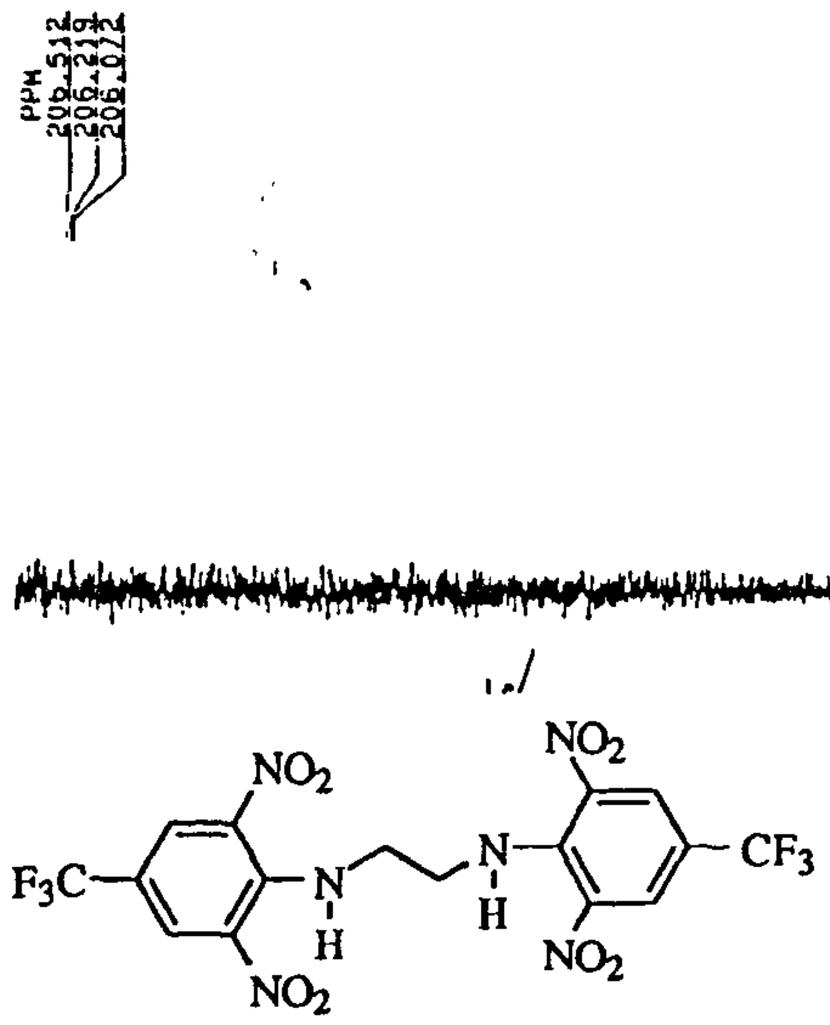
SOLVENT Aceton
SF 250.134
SY 100.0
01 5653.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305

PW 0.0
RD 0.0
AQ 3.277
RG 20
NS 256
TE 297

02 0.0
DP 63L PO

LB .200
GB .100
CX 35.00
CY 18.00
F1 9.801P
F2 -.199P
HZ/CM 71.463
PPM/CM .286
SR 4140.85

RECRYSTALLISED SPECTRUM NO 26



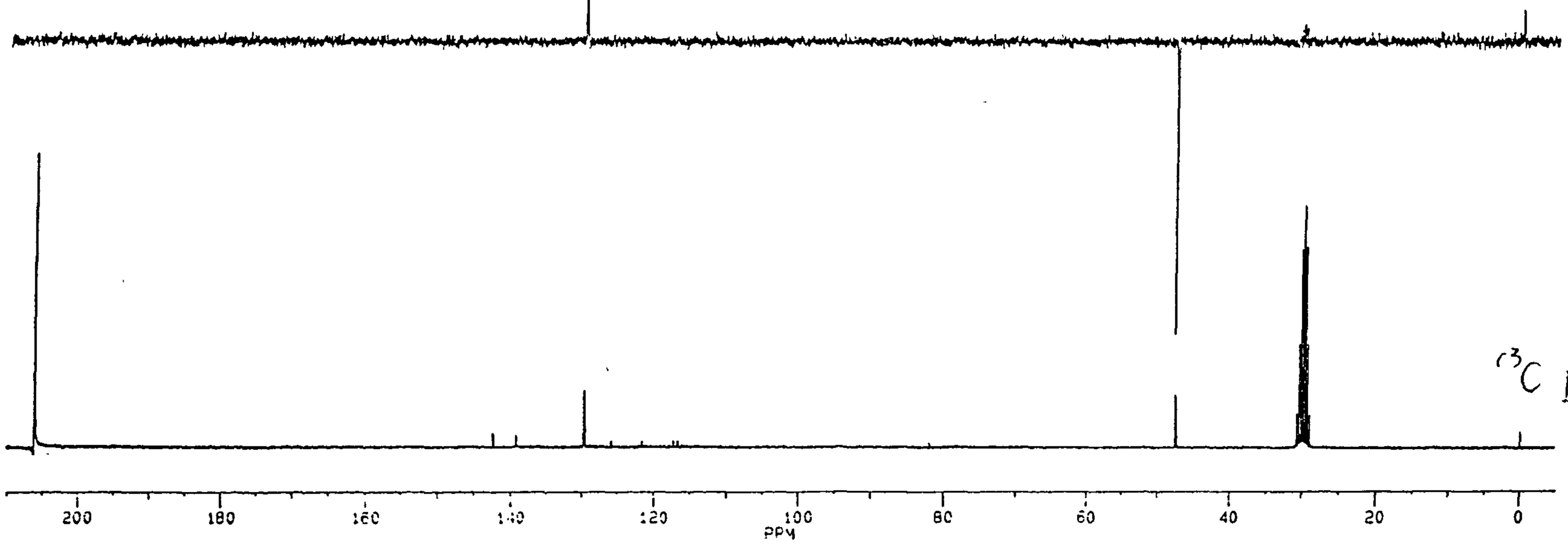
65a

N^1,N^2-di-(2, 6-dinitro-4-trifluoromethyl-phenyl)-1, 2-ethylenediamine

Dept 90.

Dept 135


```
AP252S.211
AU PROG:
 X02.AU
DATE 25-4-94
TIME 19:04

SOLVENT Aceton
SF      62.896
SY      62.0
O1    2547.000
SI      65536
TD      65536
SW    15625.000
HZ/PT     .477

PW        0.0
RD        0.0
AQ      2.097
RG        400
NS       1000
TE        297

O2    5400.000
DP    18L 00

LB        1.000
GB         .100
CX        35.00
CY         6.50
F1     210.010P
F2      -4.989P
HZ/CM 386.361
PPM/CM  6.143
SR   -3771.09
```

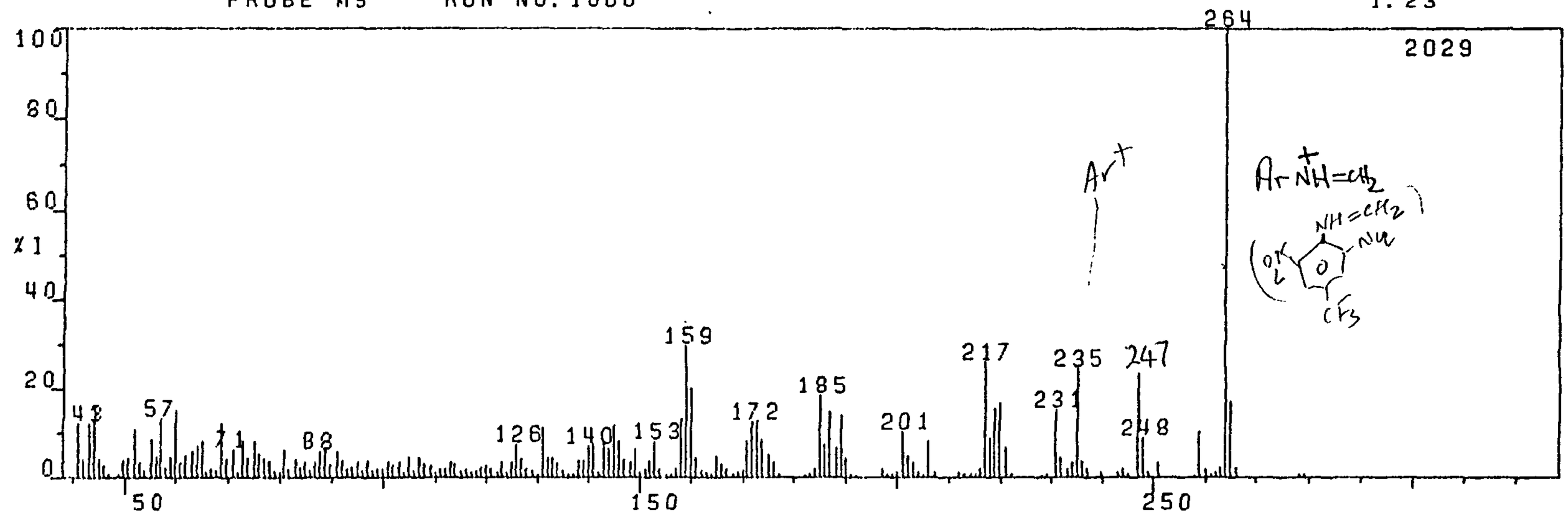


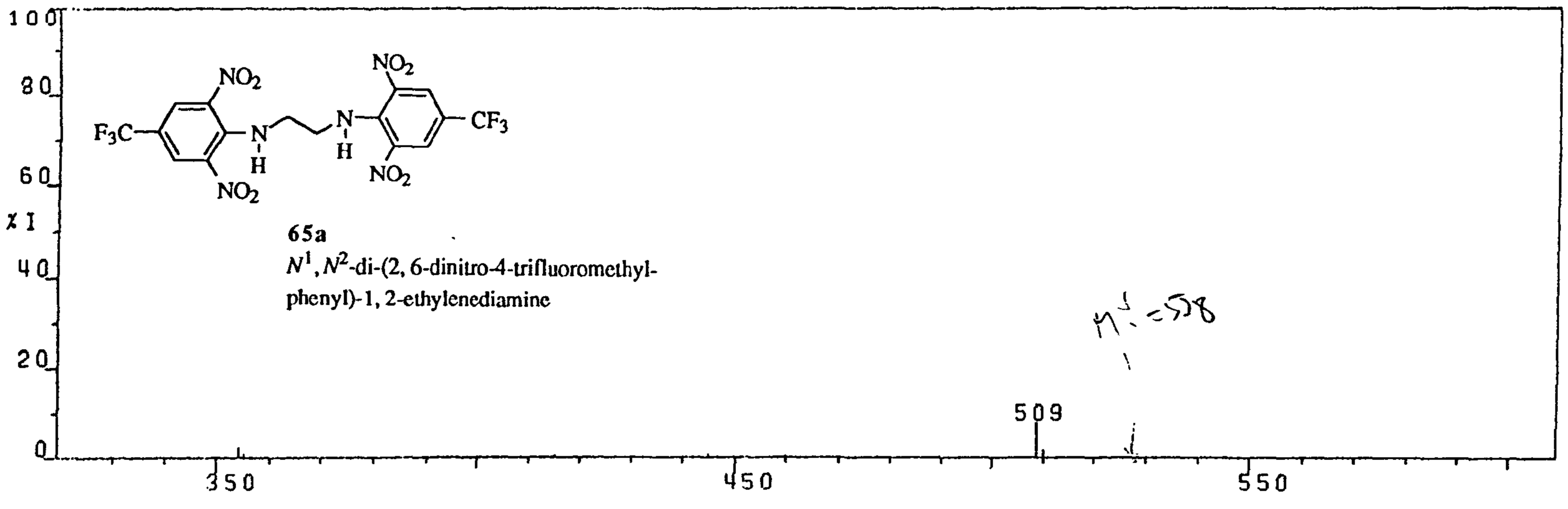
^{13}C fully decouple

Probe: Source temp. Spectrum No. → 10 ↙ Calibration ↓ Status ↓ Background scan. SPECTRUM NO. 27

File NO. →RES487 10 25-MAY-94 CAL:2H1005 STA: BG SCAN = 6
PROBE MS RUN NO. 1660

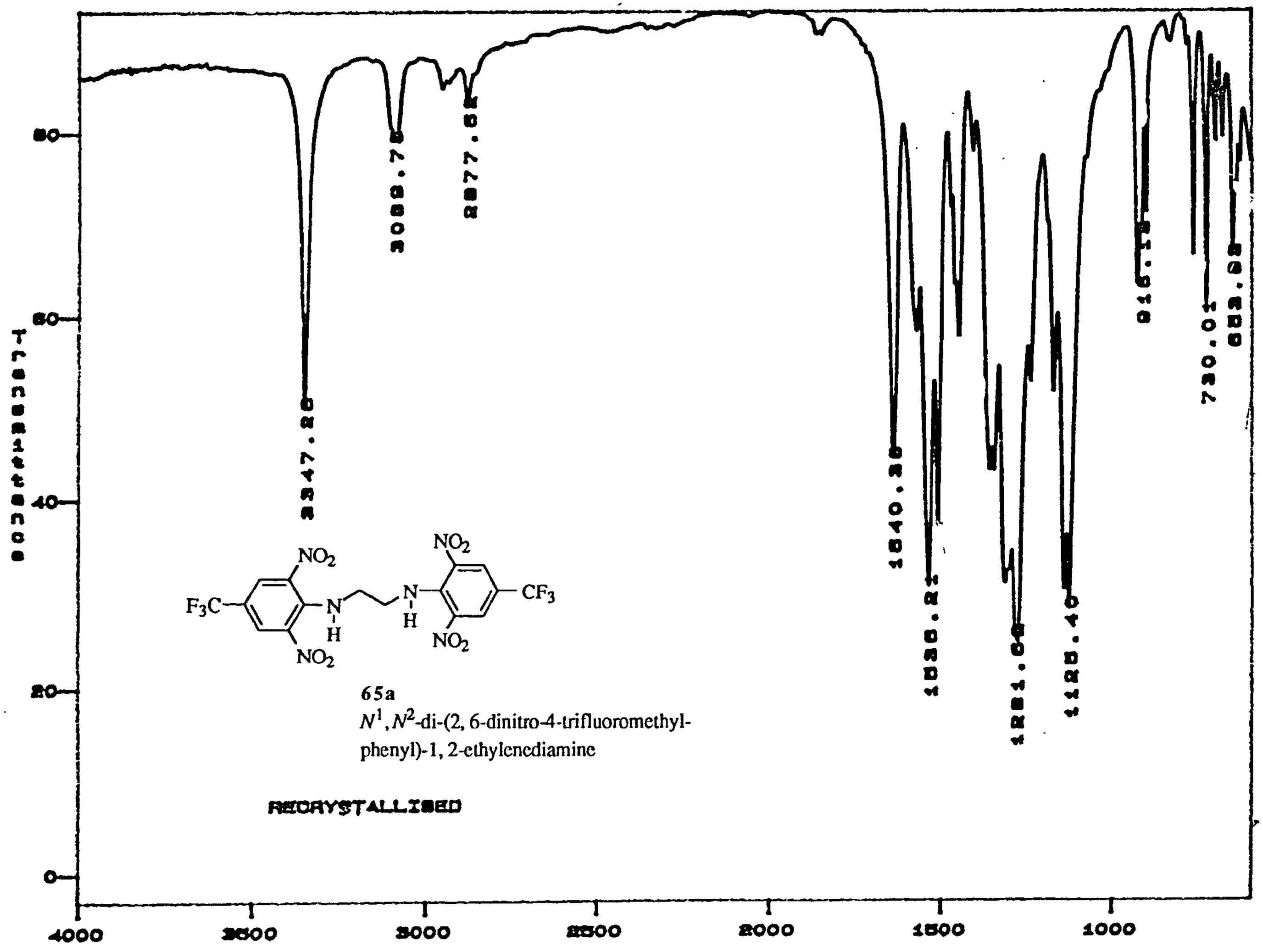
1:23





65a
N^1,N^2-di-(2, 6-dinitro-4-trifluoromethyl-phenyl)-1, 2-ethylenediamine

SPECTRUM NU. 28



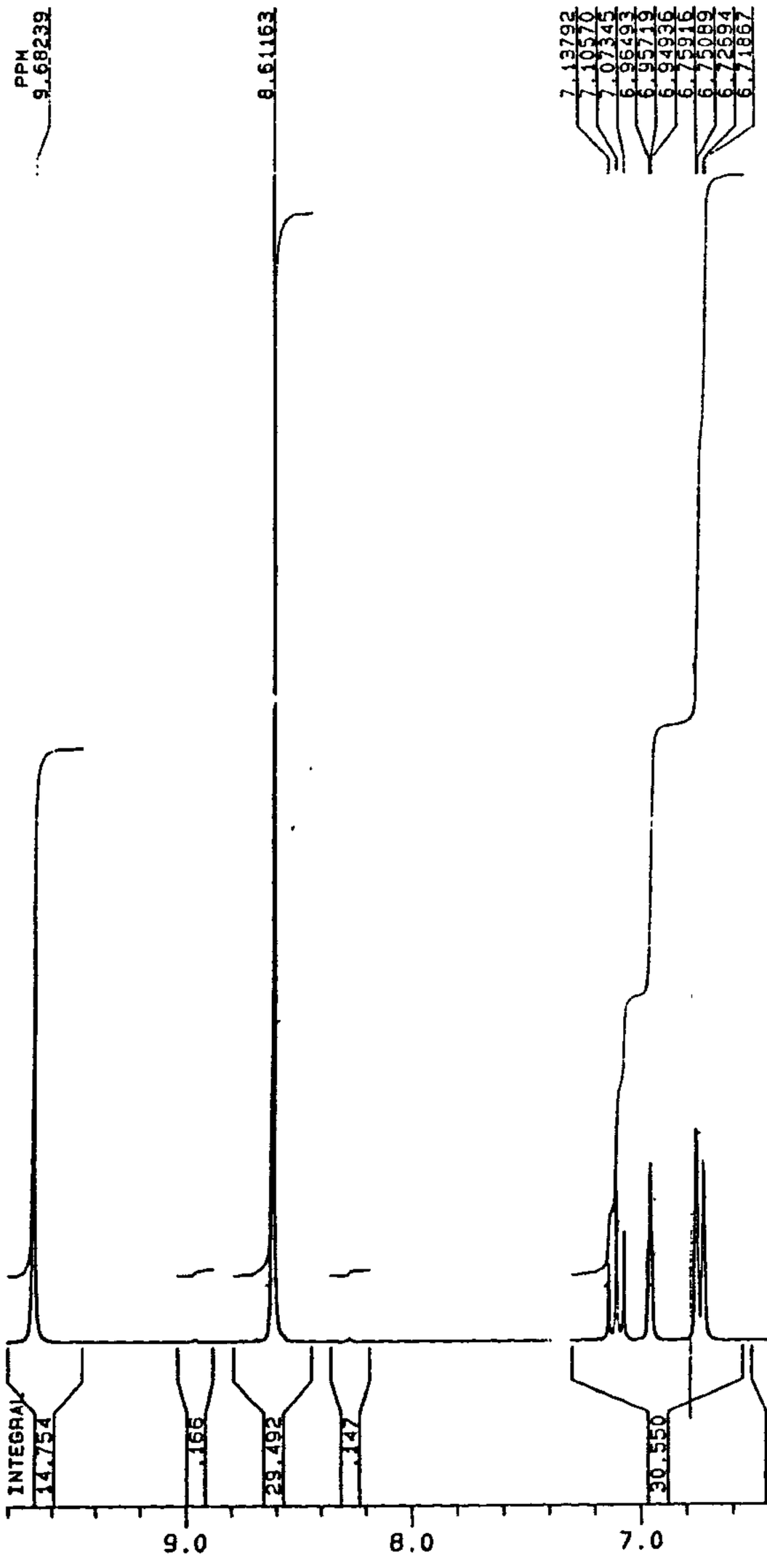
65a

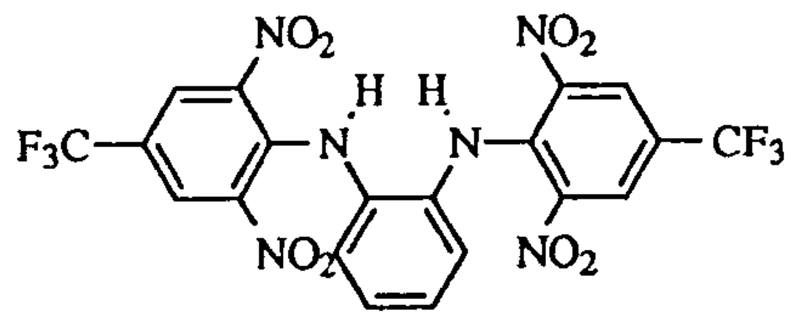
N^1,N^2-di-(2, 6-dinitro-4-trifluoromethyl-phenyl)-1, 2-ethylenediamine

RECRYSTALLISED

SPECTRUM NO. 29

(RECRYST X1)





651

N^1,N^2-di-(2, 6-dinitro-4-trifluoromethyl-phenyl)-1, 2-phenylenediamine

BRUKER

DEC20S.126
AU PROG:
XOO.AU
DATE 3-12-94
TIME 1:34

SOLVENT DMSO
SF 250.134
SY 100.0
O1 5540.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305

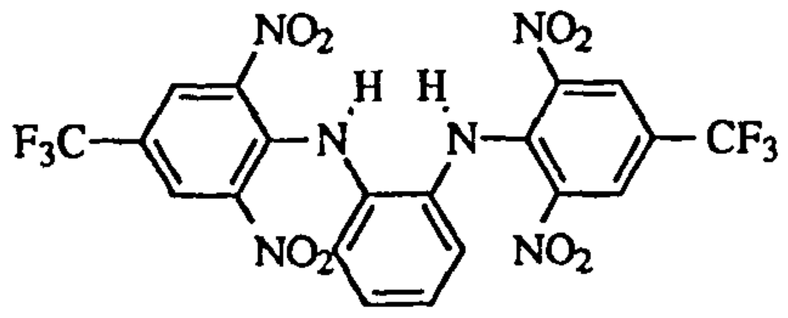
PW 0.0
RD 0.0
AQ 3.277
RG 32
NS 96
TE 297

O2 0.0
DP 63L PO

LB .200
GB .100
CX 35.00
CY 18.00
F1 9.801P
F2 -.199P
HZ/CM 71.463
PPM/CM .286
SR 4037.01

SPECTRUM NO 30

(RECRYST X1) (WITH D2O)



651

N^1,N^2-di-(2, 6-dinitro-4-trifluoromethyl-phenyl)-1, 2-phenylenediamine

BRUKER

DEC50S.160
AU PROG:
X00.AU
DATE 7-12-94
TIME 1:38

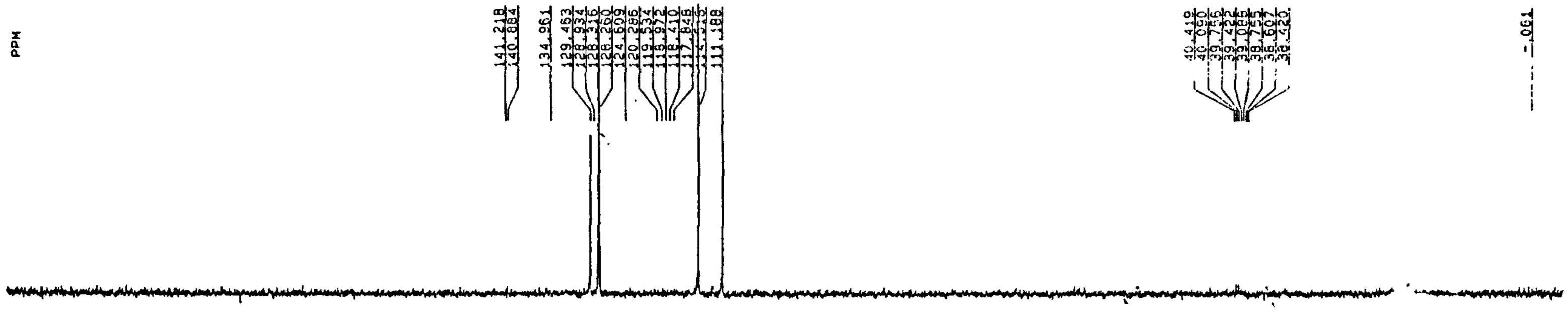
SOLVENT DMSO
SF 250.134
SY 100.0
01 5540.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305

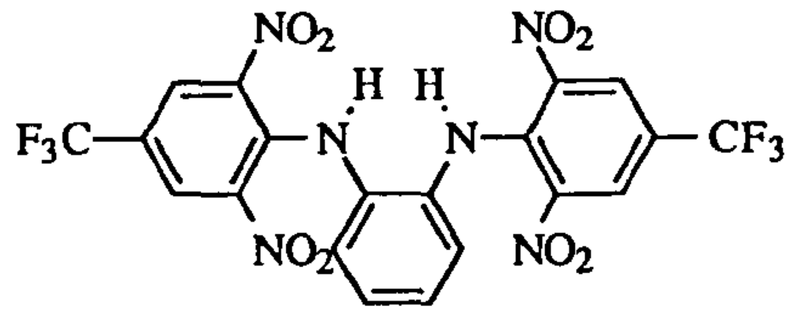
PW 0.0
RD 0.0
AQ 3.277
RG 40
NS 96
TE 297

02 0.0
DP 63L PO

LB .200
GB .100
CX 35.00
CY 18.00
F1 9.801P
F2 -.199P
HZ/CM 71.463
PPM/CM .286
SR 4030.91

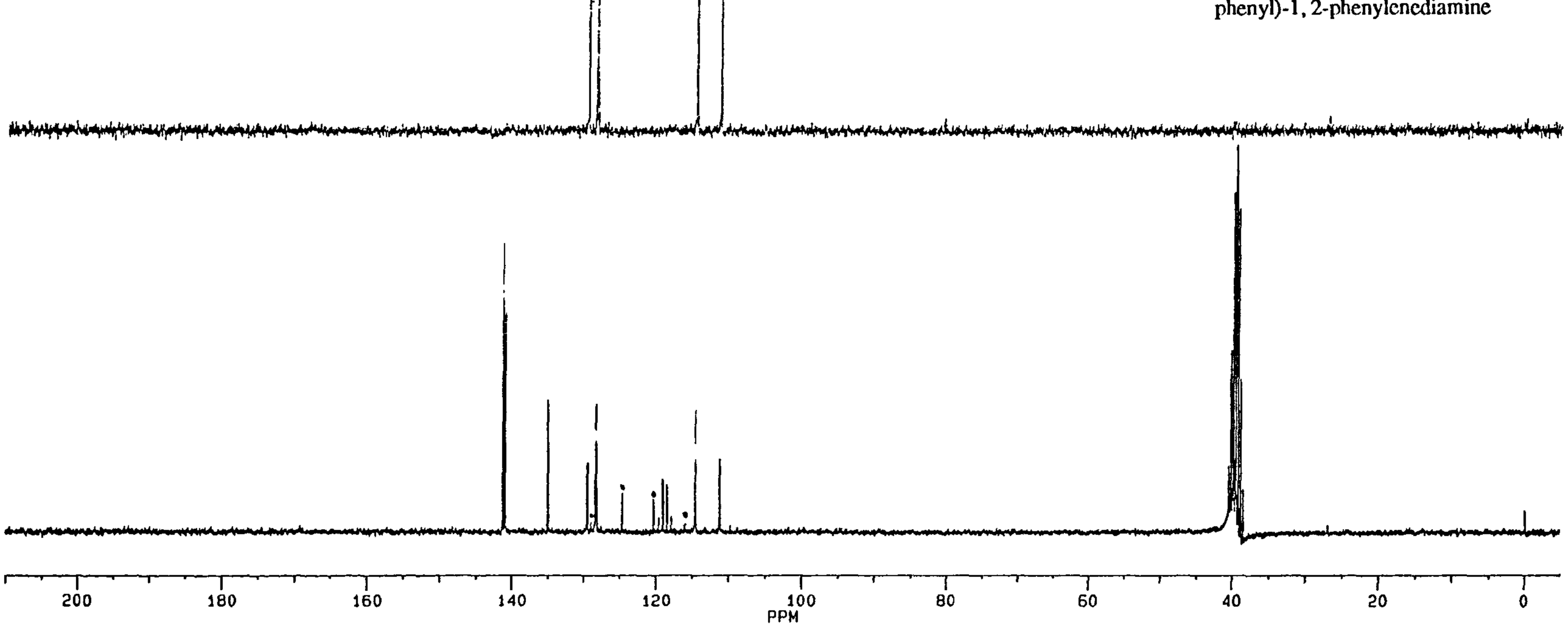
(RECRYST X1) SPECTRUM NO. 31





651

N^1,N^2-di-(2, 6-dinitro-4-trifluoromethyl-phenyl)-1, 2-phenylenediamine



BRUKER

DEC22S.126
AU PROG:
X02.AU
DATE 3-12-94
TIME 3:25

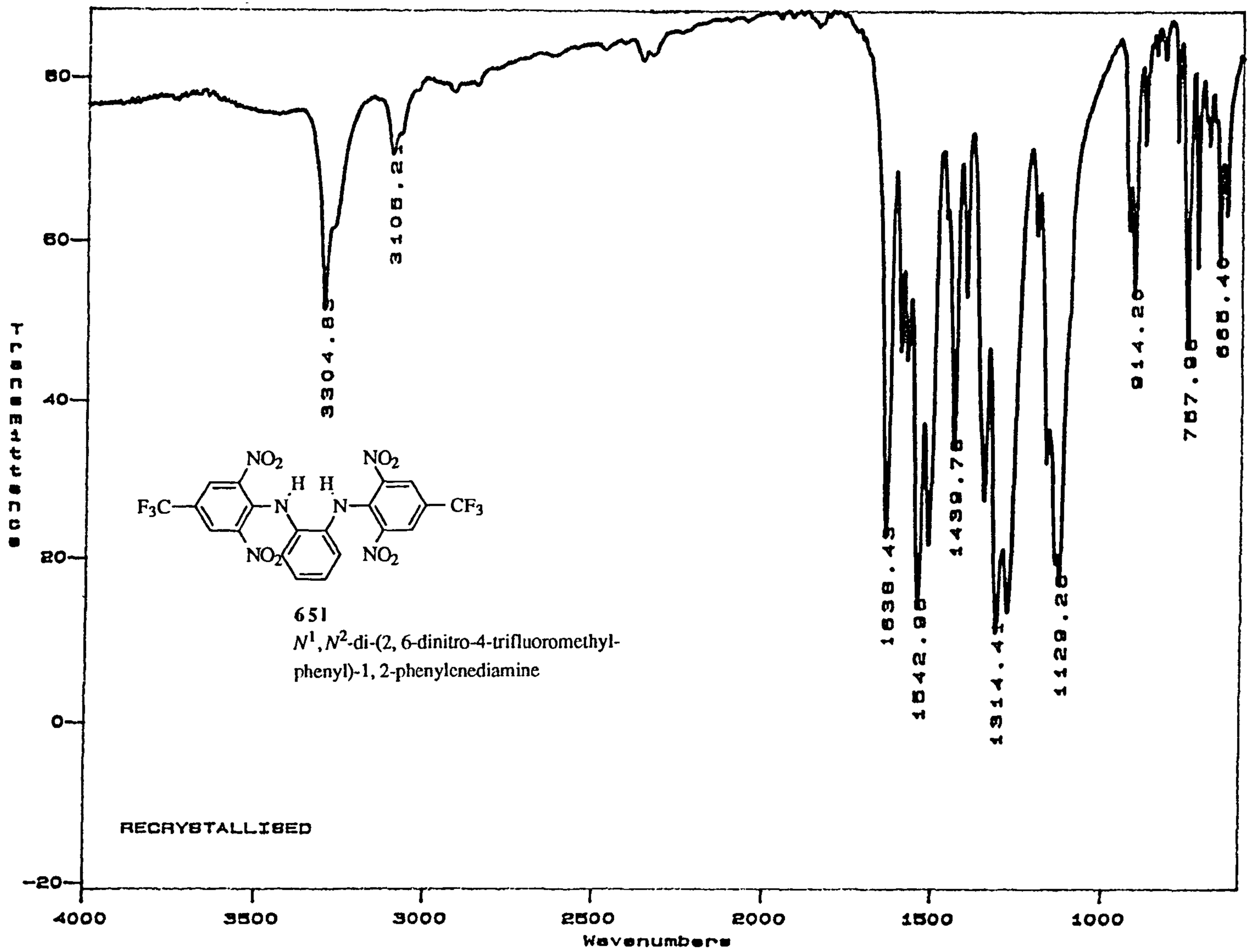
SOLVENT DMSO
SF 62.896
SY 62.0
01 2596.000
SI 65536
TD 65536
SW 15625.000
HZ/PT .477

PW 0.0
RD 0.0
AQ 2.097
RG 640
NS 1000
TE 297

02 5270.000
DP 18L DO

LB 1.000
GB .100
CX 35.00
CY 6.50
F1 210.010
F2 -4.989
HZ/CM 386.361
PPM/CM 6.143
SR -3710.17

SPECTRUM NO.32

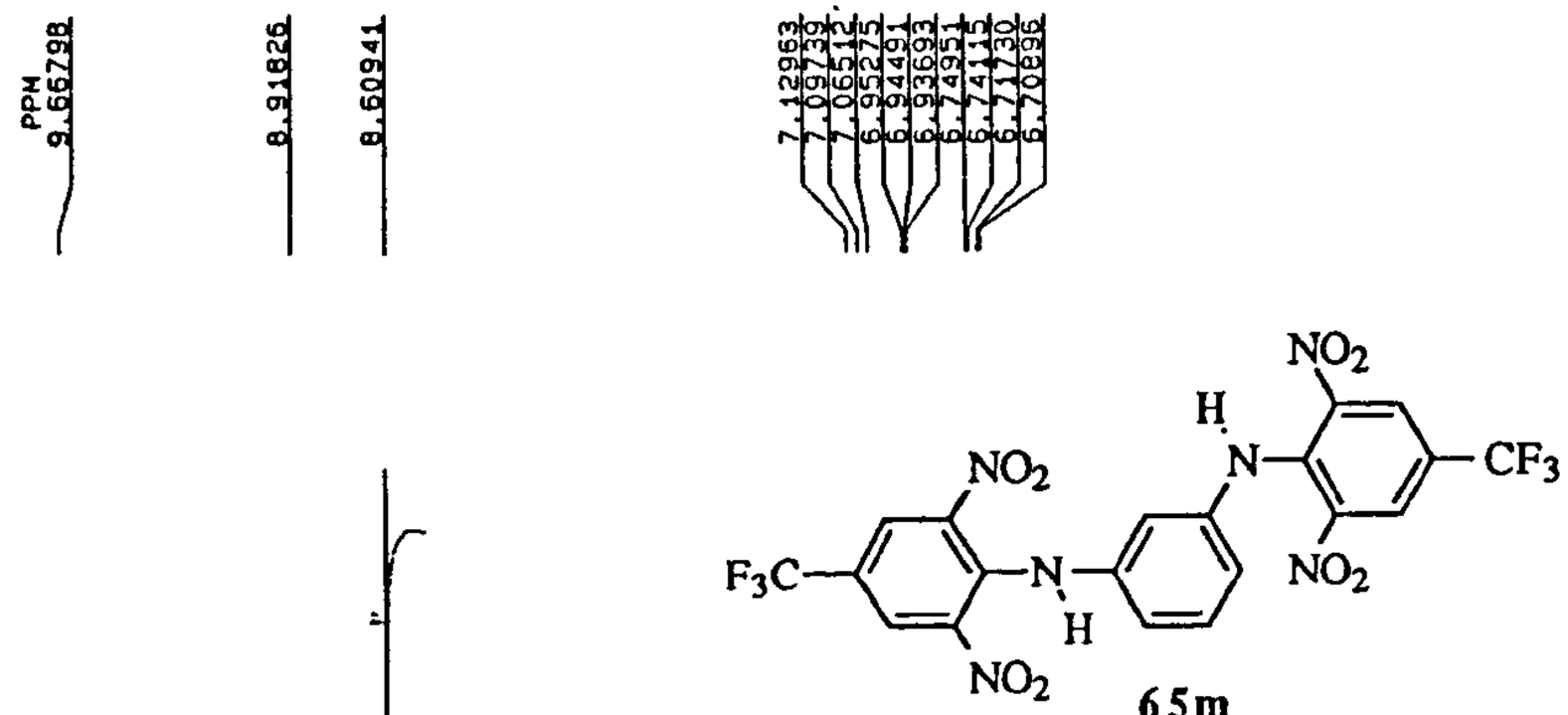


651

N^1,N^2-di-(2, 6-dinitro-4-trifluoromethyl-phenyl)-1, 2-phenylenediamine

SPECTRUM NO. 33

(RECRYST X1)



65m

N^1, N^2-di-(2, 6-dinitro-4-trifluoromethyl-phenyl)-1, 4-phenylenediamine

PPM
9.66798
8.91826
8.60941
7.12963
7.09739
7.06515
6.95272
6.94491
6.93693
6.74951
6.74112
6.71730
6.70896
3.34917
3.16788
2.51697
2.50991
2.50268
2.49542
2.48824
2.46924
2.30016
.23472
.01319
.00000
-.01316

INTEGRAL
6.480
.338
12.835
3.387
3.316
6.699
15.611
.048
.058
12.414
.337
.133
14.877

9.0 8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0.0
PPM

BRUKER

DEC20S.125
AU PROG:
XOO.AU
DATE 2-12-94
TIME 21:41

SOLVENT DMSO
SF 250.134
SY 100.0
O1 5540.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305

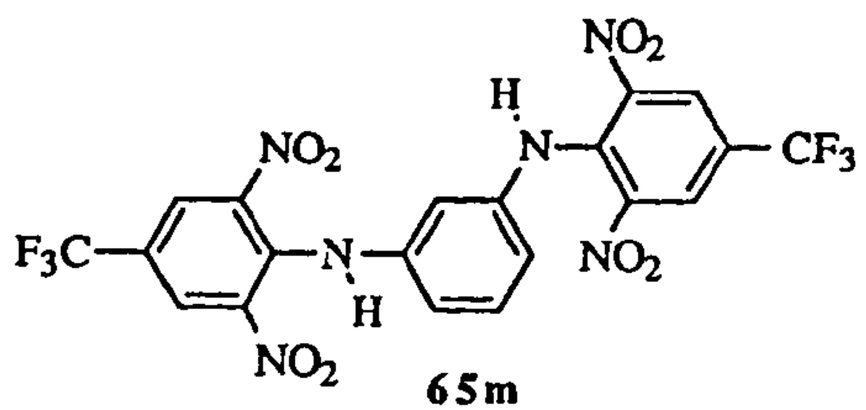
PW 0.0
RD 0.0
AQ 3.277
RG 64
NS 96
TE 297

O2 0.0
DP 63L PO

LB .200
GB .100
CX 35.00
CY 18.00
F1 9.801P
F2 -.199P
HZ/CM 71.463
PPM/CM .286
SR 4037.31

SPECTRUM NO. 34

(RECRYST. X1) [WITH D2O]



65m

N^1,N^2-di-(2, 6-dinitro-4-trifluoromethyl-phenyl)-1, 4-phenylenediamine

BRUKER

DEC50S.146
AU PROG:
X00.AU
DATE 5-12-94
TIME 17:22

SOLVENT DMSO
SF 250.13
SY 100.0
O1 5540.00
SI 32768
TD 32768
SW 5000.00
HZ/PT .30

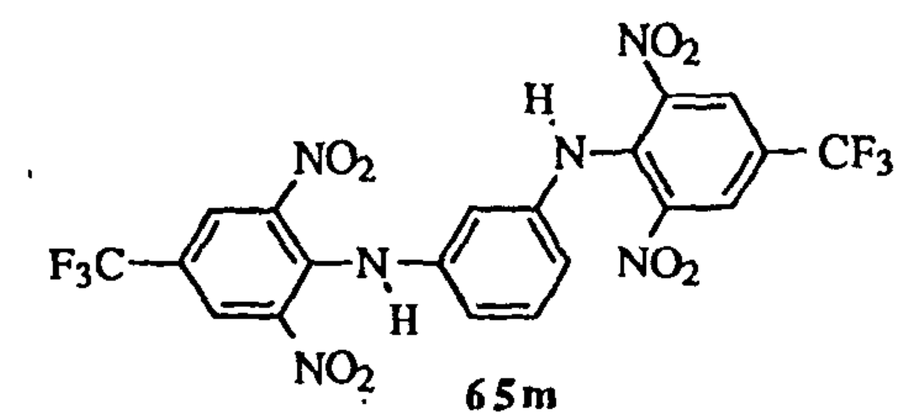
PW 0.0
RD 0.0
AQ 3.27
RG 40
NS 96
TE 297

O2 0.0
DP 63L PO

LB .20
GB .10
CX 35.00
CY 18.00
F1 9.80
F2 -.19
HZ/CM 71.46
PPM/CM .28
SR 4029.99

SPECTRUM NO. 35

(RECRYST X1)



65m

N^1,N^2-di-(2, 6-dinitro-4-trifluoromethyl-phenyl)-1, 4-phenylenediamine

BRUKER

DEC21S.125
AU PROG:
X02.AU
DATE 2-12-94
TIME 22:36

SOLVENT DMSO
SF 62.89
SY 62.0
O1 2596.00
SI 65536
TD 65536
SW 15625.00
HZ/PT .47

PW 0.0
RD 0.0
AQ 2.09
RG 400
NS 1000
TE 297

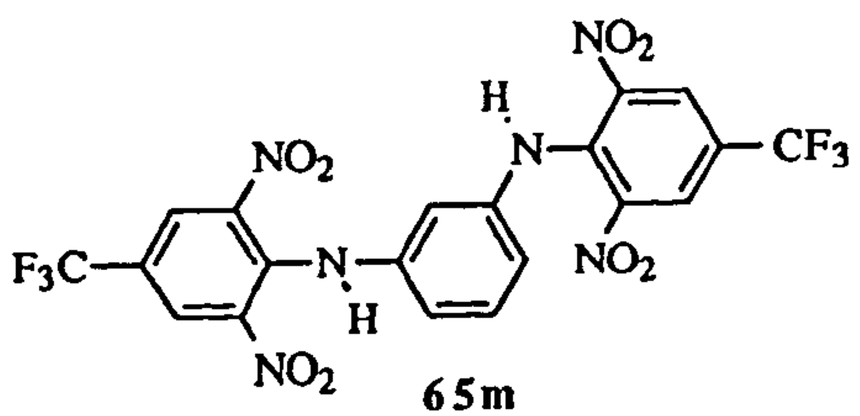
O2 5270.00
DP 18L DO

LB 1.00
GB .10
CX 35.00
CY 18.00
F1 210.01
F2 -4.98
HZ/CM 386.36
PPM/CM 6.14
SR -3711.13

(RECRYST X1) SPECTRUM NO. 36

PPM

141.246
140.897
134.942
129.472
128.276
114.499
111.164
40.447
40.114
39.780
39.447
39.113
38.780
38.446
.002



65m

N^1,N^2-di-(2, 6-dinitro-4-trifluoromethyl-phenyl)-1, 4-phenylenediamine

BRUKER

DEC22S.125
AU PROG:
X02.AU
DATE 2-12-94
TIME 23:33

SOLVENT DMSO
SF 62.896
SY 62.0
O1 2596.000
SI 65536
TD 65536
SW 15625.000
HZ/PT .477

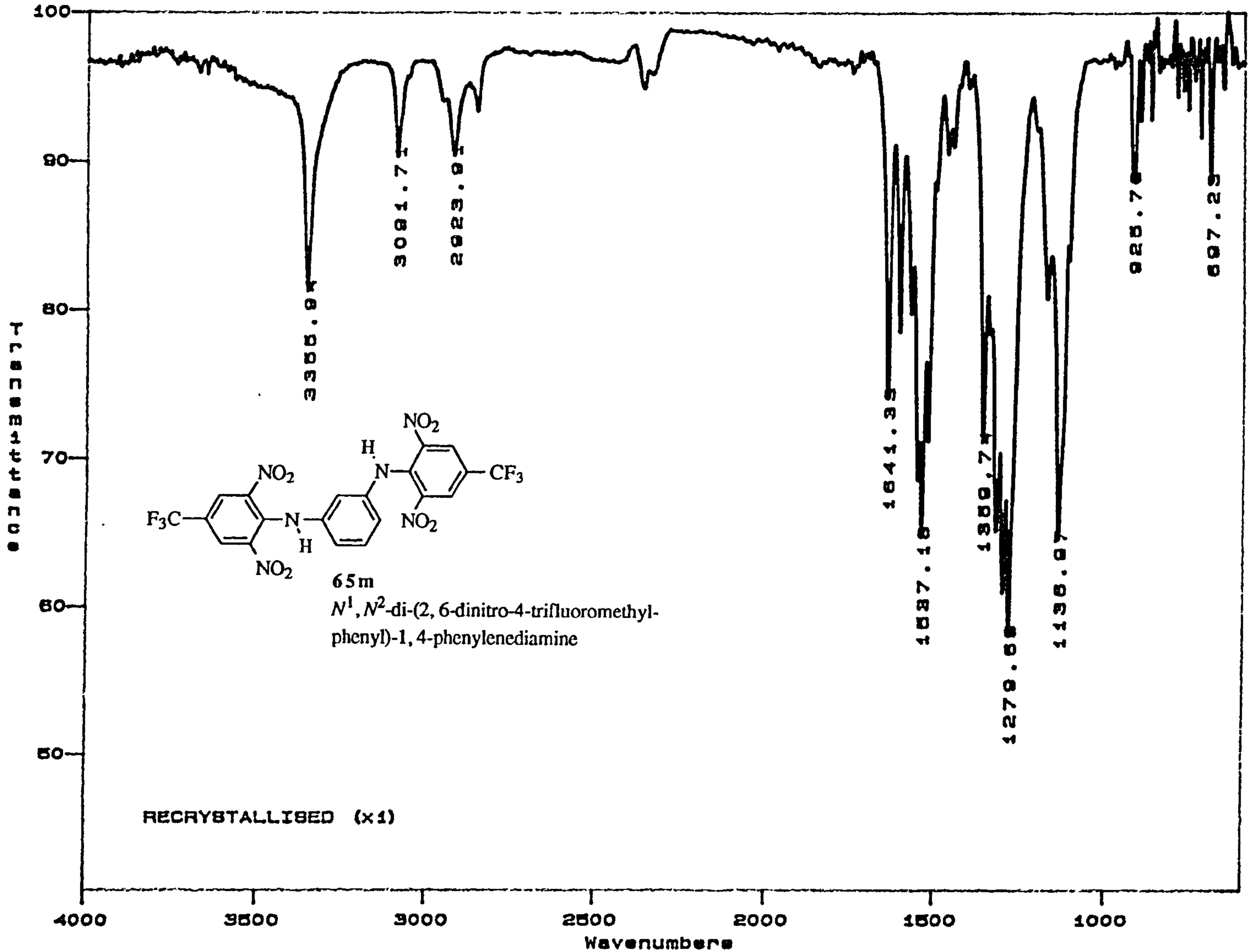
PW 0.0
RD 0.0
AQ 2.097
RG 400
NS 1000
TE 297

O2 5270.000
DP 18L DO

LB 1.000
GB .100
CX 35.00
CY 6.50
F1 210.010P
F2 -4.989P
HZ/CM 386.361
PPM/CM 6.143
SR -3711.13

200 180 160 140 120 100 80 60 40 20 0
PPM

SPECTRUM NO. 37

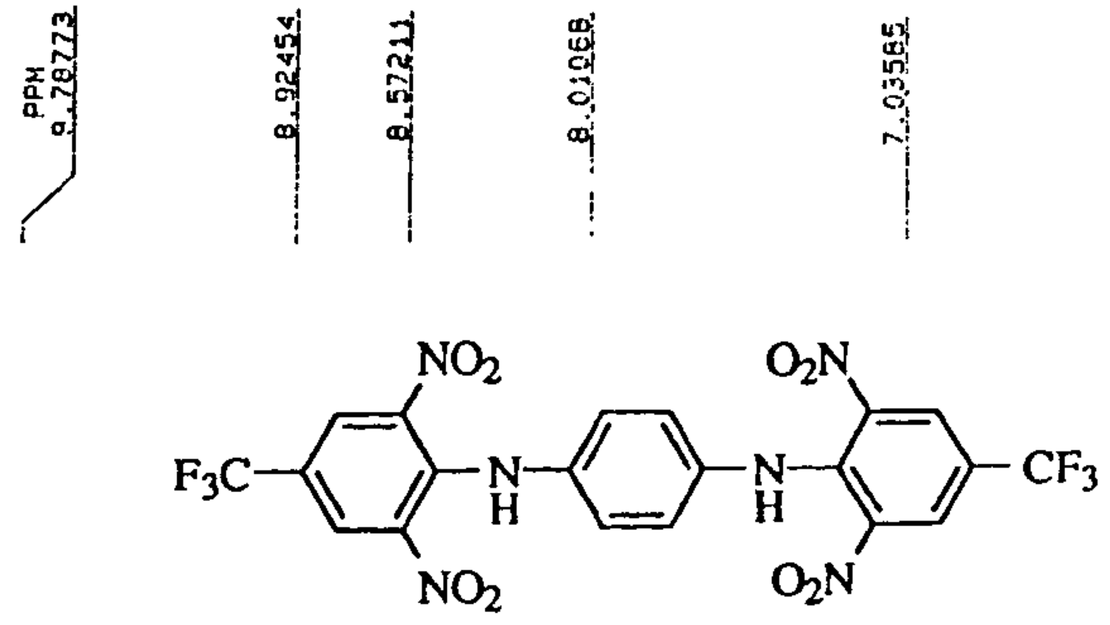


65m

N^1, N^2-di-(2, 6-dinitro-4-trifluoromethyl-phenyl)-1, 4-phenylenediamine

SPECTRUM NO. 38

(RECRYST X1)



65n

N^1,N^2-di-(2, 6-dinitro-4-trifluoromethyl-phenyl)-1, 4-phenylenediamine

BRUKER

DEC20S.142
AU PROG:
X00.AU
DATE 5-12-9
TIME 0:00

SOLVENT DMS
SF 250.1
SY 100.0
01 5540.0
SI 32768
TD 32768
SW 5000.0
HZ/PT .3

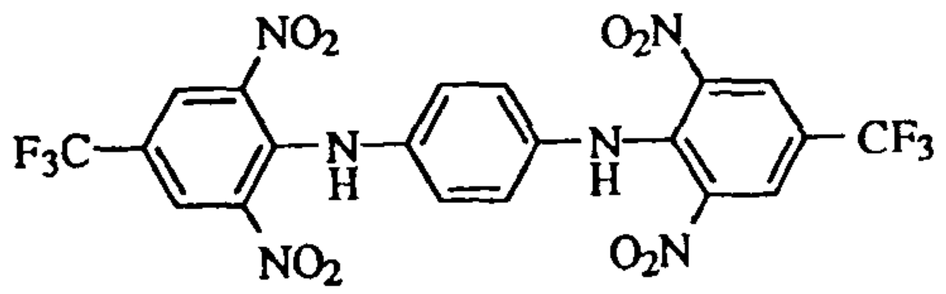
PW 0.0
RD 0.0
AQ 3.2
RG 40
NS 96
TE 297

O2 0.0
DP 63L PO

LB .20
GB .10
CX 35.00
CY 18.00
F1 9.80
F2 -.19
HZ/CM 71.46
PPM/CM .28
SA 4036.70

SPECTRUM NO. 39

(RECRYST. X1) (WITH D2O)



65n

N^1,N^2-di-(2, 6-dinitro-4-trifluoromethyl-phenyl)-1, 4-phenylenediamine

BRUKER

DEC60S.109
AU PROG:
XQQ.AU
DATE 7-12-94
TIME 9: 44

SOLVENT DMSO
SF 250.134
SY 100.0
O1 5540.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305

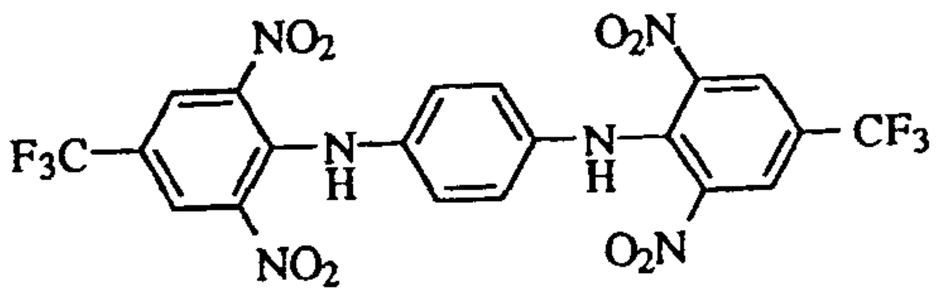
PW 0.0
RD 0.0
AQ 3.277
RG 40
NS 96
TE 297

O2 0.0
DP 63L PO

LB .200
GB .100
CX 35.00
CY 18.00
F1 9.801P
F2 -.199P
HZ/CM 71.463
PPM/CM .286
SR 4029.07

SPECTRUM NO 40

(RECRYST X1)



65n

N^1,N^2-di-(2, 6-dinitro-4-trifluoromethyl-phenyl)-1, 4-phenylenediamine

BRUKER

DEC21S.142
AU PROG:
X02.AU
DATE 5-12-94
TIME 0:57

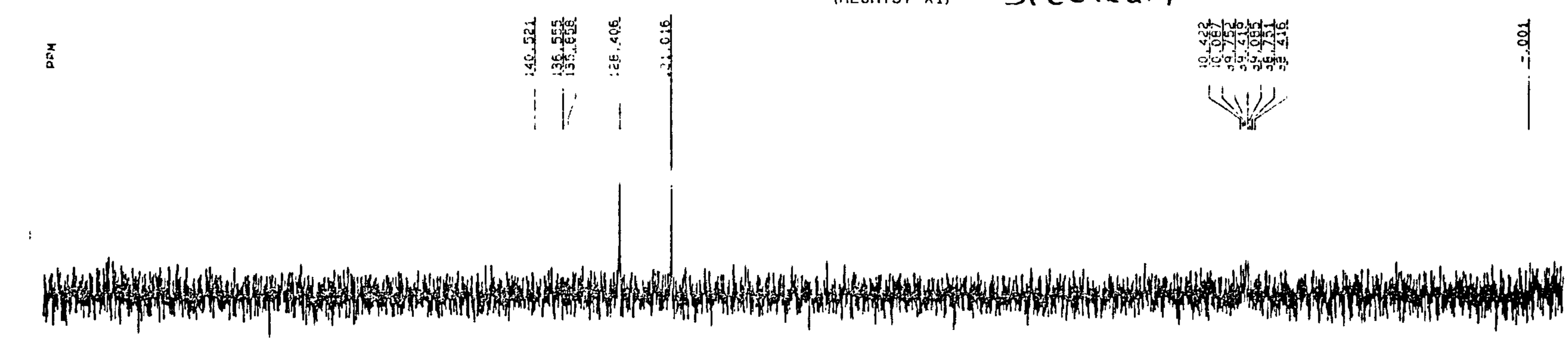
SOLVENT DMSO
SF 62.896
SY 62.0
01 2596.000
SI 65536
ID 65536
SW 15625.000
HZ/PT .477

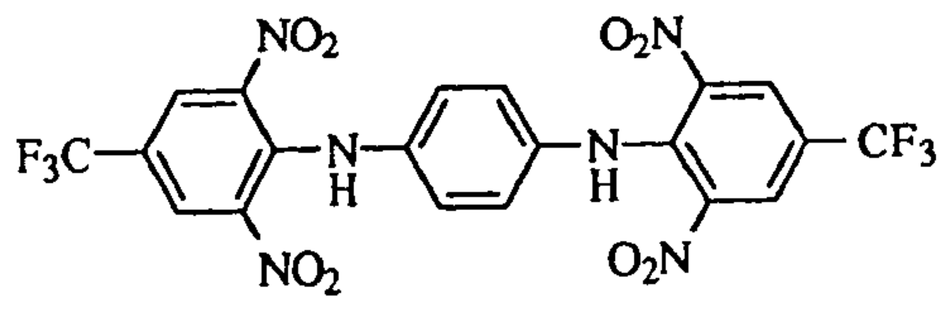
PW 0.0
RD 0.0
AG 2.097
RG 400
NS 1000
TE 297

02 5270.000
DP 18L D0

LB 1.000
GB .100
CX 35.00
CY 18.00
F1 210.010
F2 -4.989
HZ/CM 386.361
PPM/CM 6.143
SR -3710.65

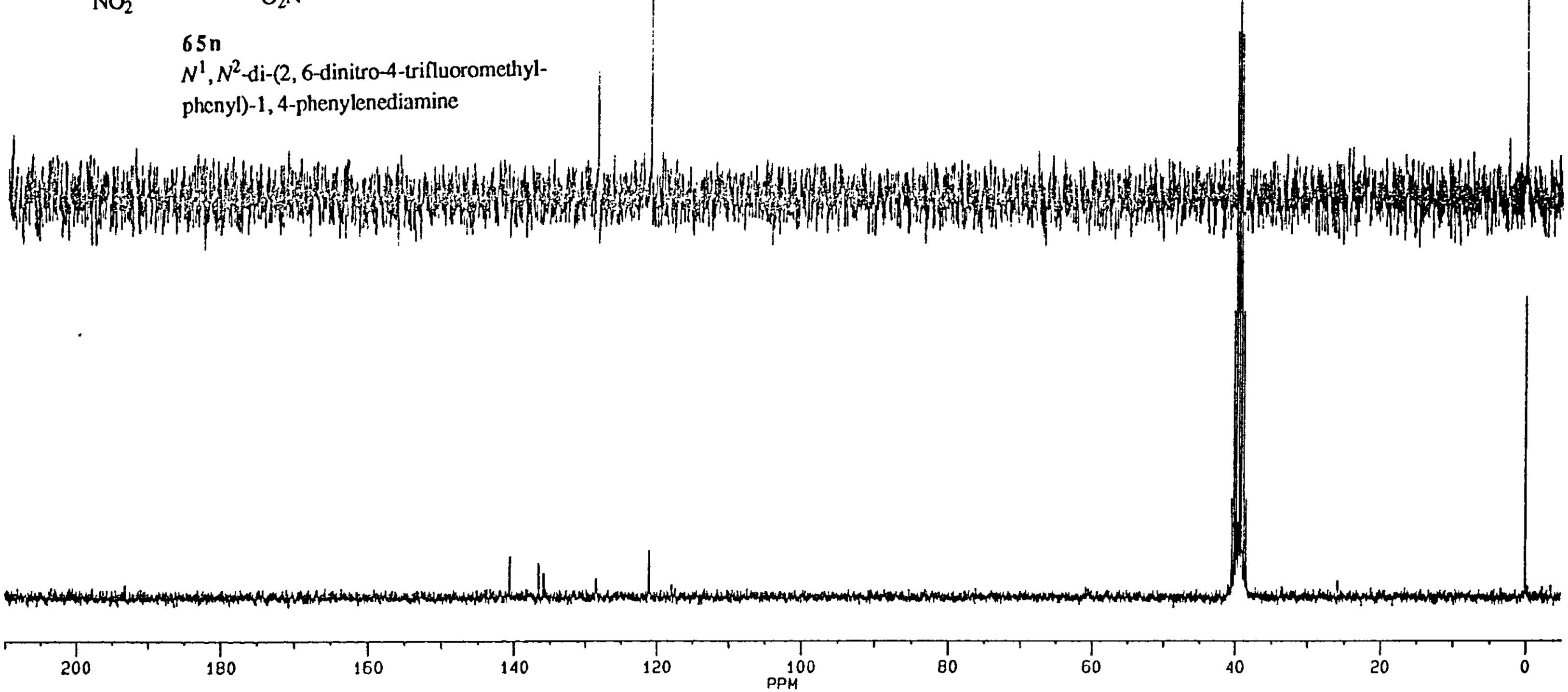
(RECRYST X1) SPECTRUM NO. 41





65n

N^1, N^2-di-(2, 6-dinitro-4-trifluoromethyl-phenyl)-1, 4-phenylenediamine



BRUKER

DEC22S.142
AU PROG:
X02.AU
DATE 5-12-94
TIME 1:54

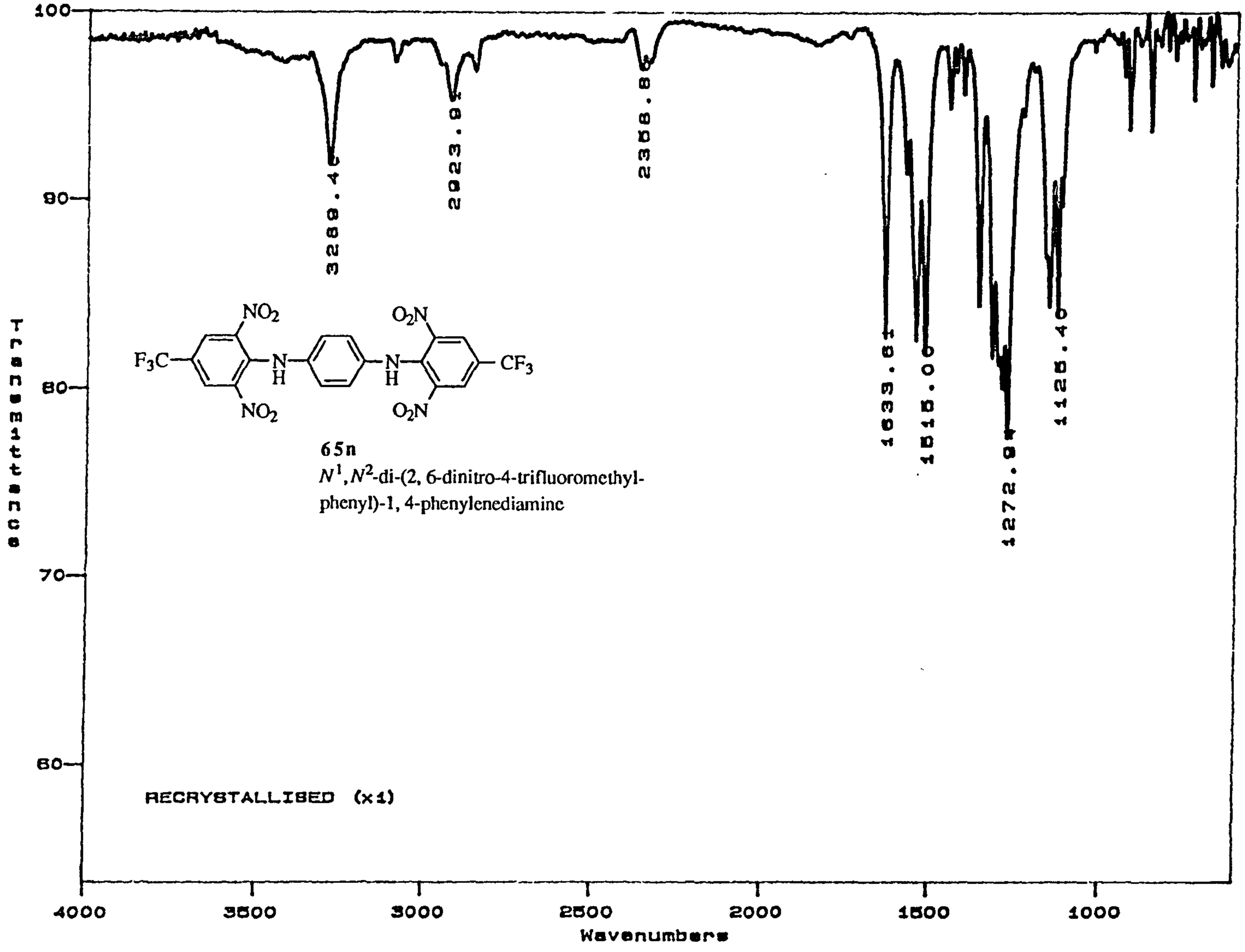
SOLVENT DMSO
SF 62.896
SY 62.0
01 2596.000
SI 65536
TD 65536
SW 15625.000
HZ/PT .477

PW 0.0
RD 0.0
AQ 2.097
RG 320
NS 1000
TE 297

02 5270.000
DP 18L D0

LB 1.000
GB .100
CX 35.00
CY 6.50
F1 210.010
F2 -4.989
HZ/CM 386.361
PPM/CM 6.143
SR -3710.65

SPECTRUM NO. 42

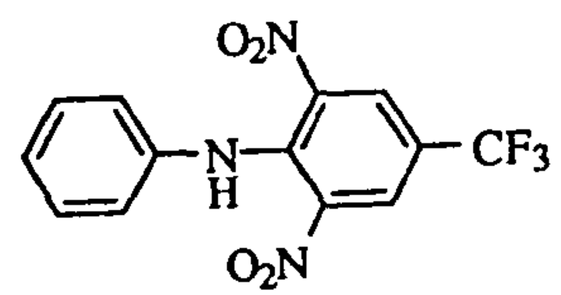


65n

N^1,N^2-di-(2, 6-dinitro-4-trifluoromethyl-phenyl)-1, 4-phenylenediamine

SPECTRUM NO. 43

RECRYSTALLISED



67a
1-[*N*-(2, 6-dinitro-4-trifluoro-methyl)amino]benzene

BRUKER

MR111S.219
AU PROG:
X00.AU
DATE 12-3-96
TIME 2:16

SOLVENT DMSO
SF 250.13
SY 100.0
O1 5540.00
SI 32768
TD 32768
SW 5000.00
HZ/PT .30

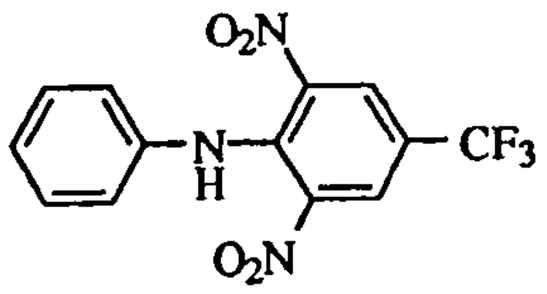
PW 0.0
RD 0.0
AQ 3.27
RG 20
NS 96
TE 297

O2 0.0
DP 63L PO

LB .20
CX 35.00
CY 18.00
F1 9.80
F2 -.19
HZ/CM 71.46
PPM/CM .28
SR 4037.31

SPECTRUM NO 44

RECRYSTALLISED [WITH D2O]



67a
1-[*N*-(2, 6-dinitro-4-trifluoro-methyl)amino]benzene

BRUKER

MR130S.140
AU PROG:
X00.AU
DATE 13-3-96
TIME 13:32

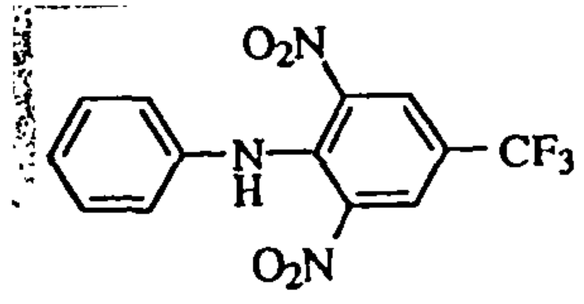
SOLVENT DMSO
SF 250.134
SY 100.0
O1 5540.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305

PW 0.0
RD 0.0
AQ 3.277
RG 20
NS 96
TE 297

O2 0.0
DP 63L P0

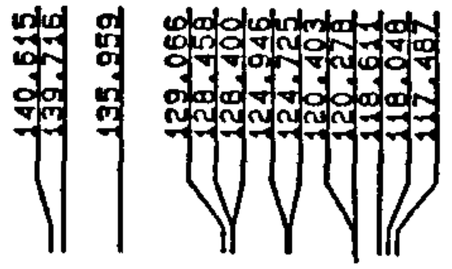
LB .200
CX 35.00
CY 18.00
F1 9.801P
F2 -.199P
HZ/CM 71.463
PPM/CM .286
SR 4028.16

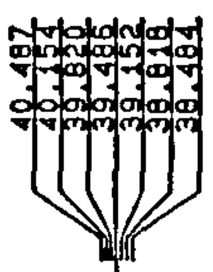
SPECTRUM NO. 45

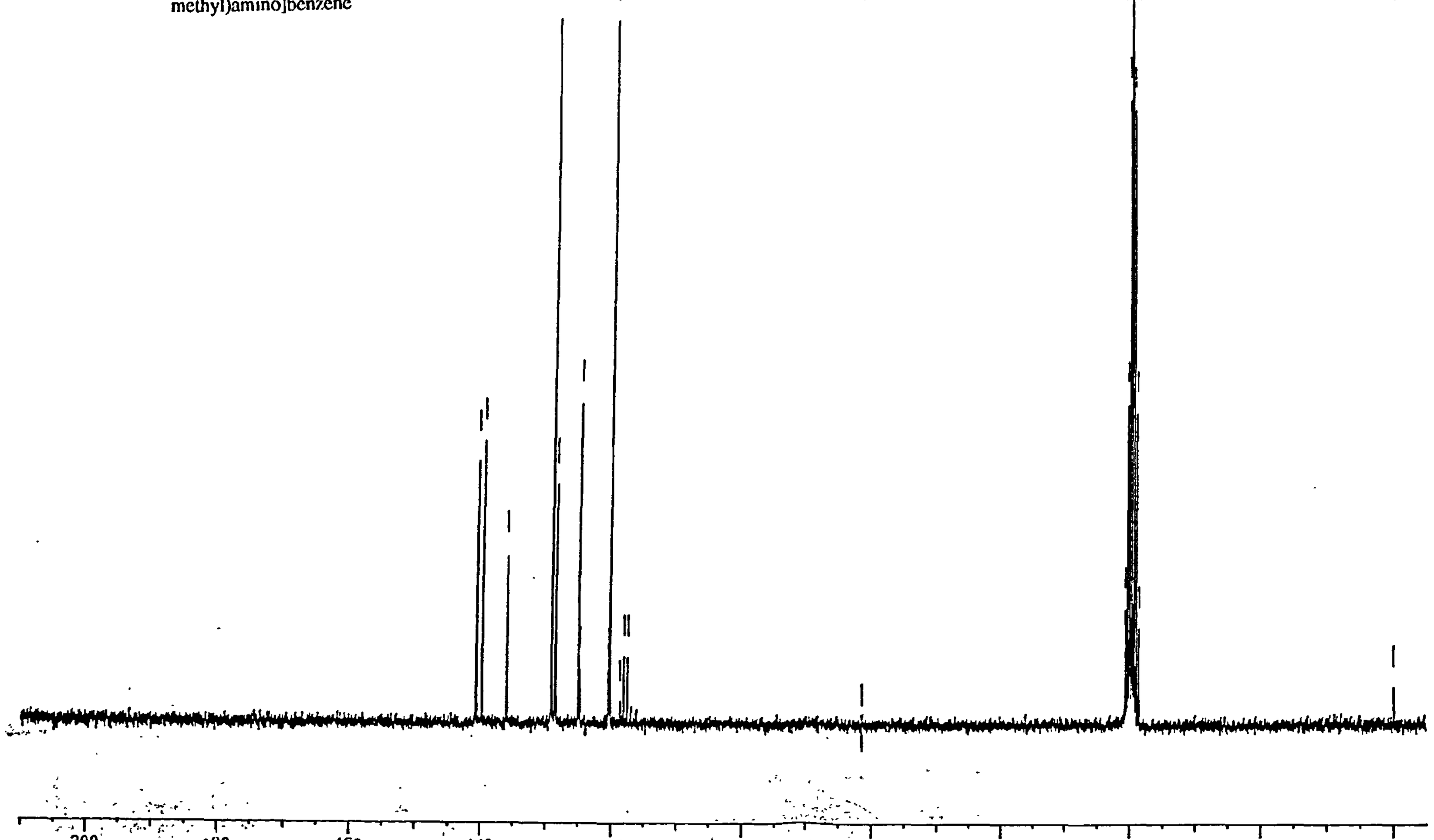


67a
1-[*N*-(2, 6-dinitro-4-trifluoro-methyl)amino]benzene

RECRYSTALLISED







BRUKER

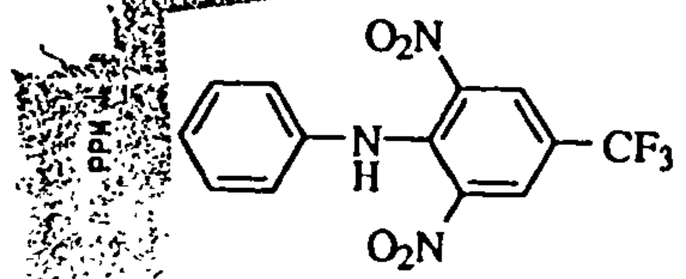
MR110S.219
AU PROG:
X02.AU
DATE 12-3-96
TIME 2:07

SOLVENT DMSO
SF 62.896
SY 62.0
01 2596.000
SI 65536
TD 65536
SW 15625.000
HZ/PT .477

PW 0.0
RD 0.0
AQ 2.097
RG 640
NS 1000
TE 297

02 5270.000
DP 18L DO

LB 1.000
CX 35.00
CY 18.00
F1 210.010P
F2 -4.989P
HZ/CM 386.361
PPM/CM 6.143
SR -3713.99



67a
1-[*N*-(2, 6-dinitro-4-trifluoro-methyl)amino]benzene

SPECTRUM NO. 46

RECRYSTALLISED

BRUKER

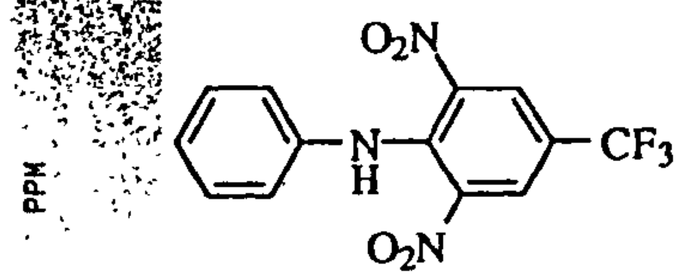
MR112S.219
AU PROG:
X02.AU
DATE 12-3-96
TIME 3: 11

SOLVENT DMSO
SF 62.896
SY 62.0
O1 2596.000
SI 65536
TD 65536
SW 15625.000
HZ/PT .477

PW 0.0
RD 0.0
AQ 2.097
RG 640
NS 1000
TE 297

O2 5270.000
DP 18L D0

LB 1.000
CX 35.00
CY 6.50
F1 210.010P
F2 -4.989P
HZ/CM 386.361
PPM/CM 6.143
SR -3710.17



67a
1-[*N*-(2, 6-dinitro-4-trifluoro-methyl)amino]benzene

SPECTRUM NO. 47

-60.0516

BRUKER

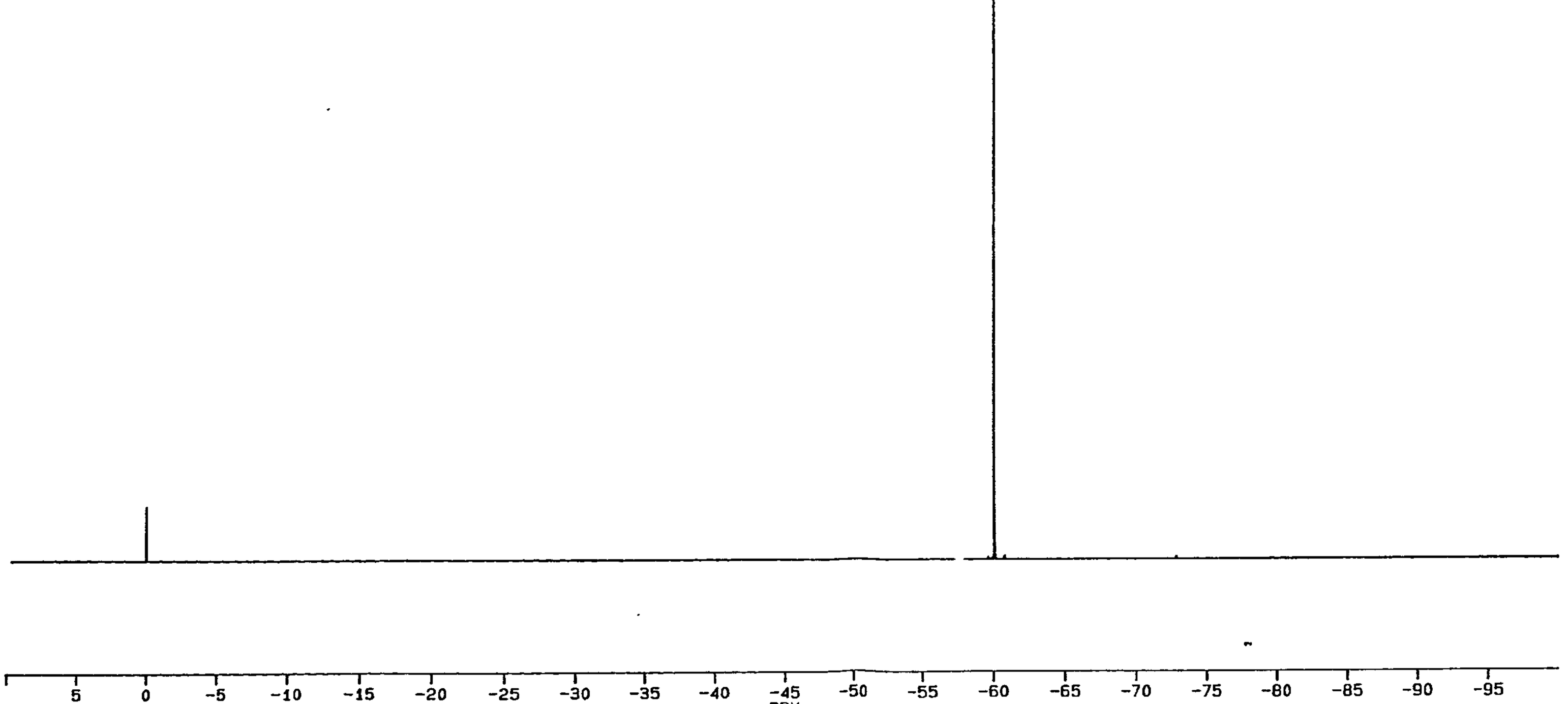
F19AP11.F008
DATE 11-4-96
TIME 12: 10

SOLVENT DMSO
SF 235.361
SY 85.0
01 -4565.186
SI 32768
TD 32768
SW 35714.286
HZ/PT 2.180

PW 6.0
RD 0.0
AQ .459
RG 160
NS 512
TE 297

02 6043.000
DP 18L PO

LB 0.0
CX 35.00
CY 18.00
F1 10.012P
F2 -99.979P
HZ/CM 739.646
PPM/CM 3.143
SR 11022.76

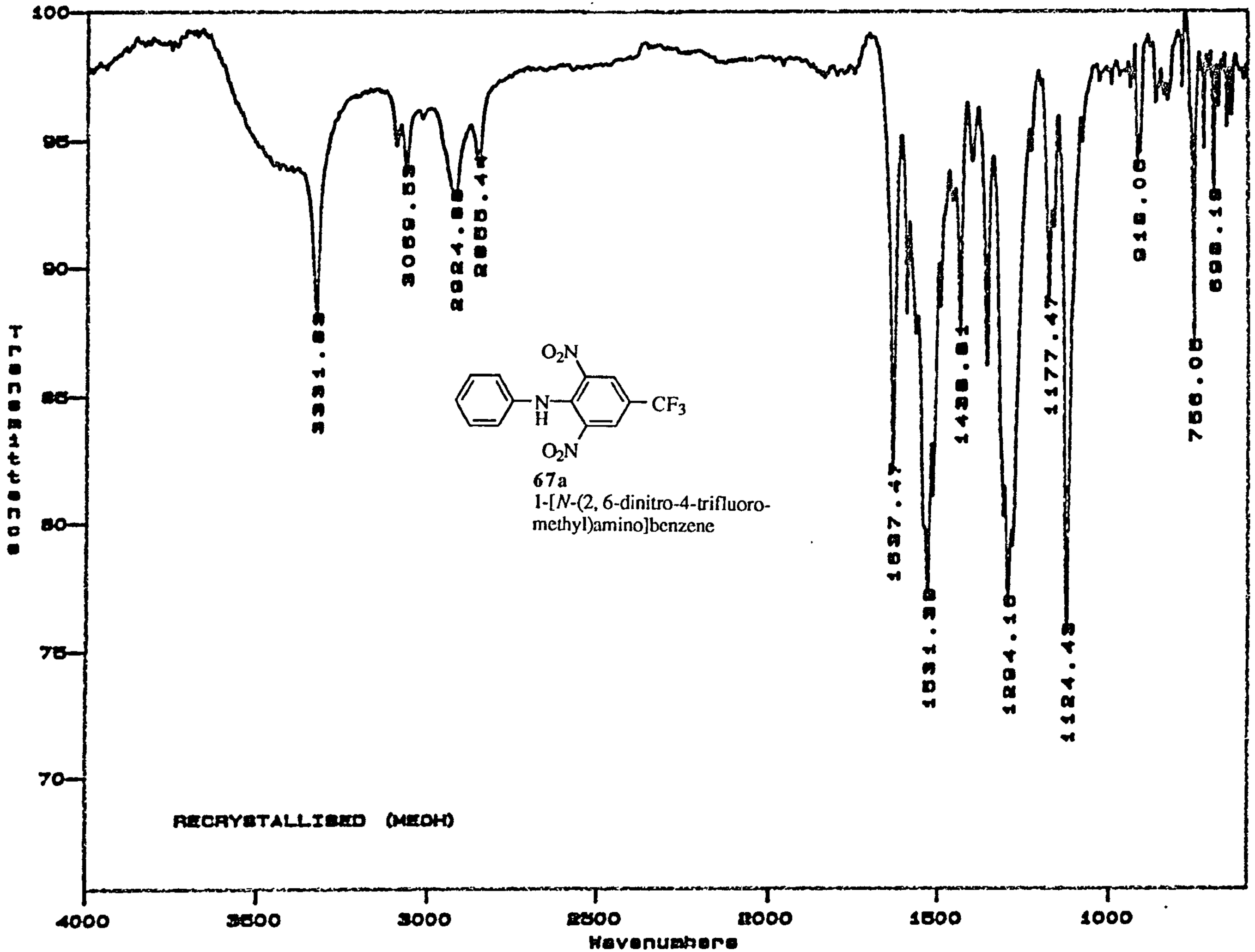


SPECTRUM NO. 48

Bpm=0 I=972mV Ha=0 TIC=76419000 Acnt: Sys:LRP HMR: 6370000
RUN NO.1698 PT= 0° Cal:CAL1485 MASS: 327

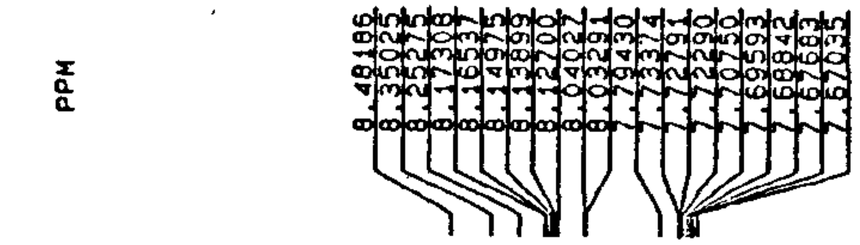
67a
1-[*N*-(2, 6-dinitro-4-trifluoro-methyl)amino]benzene

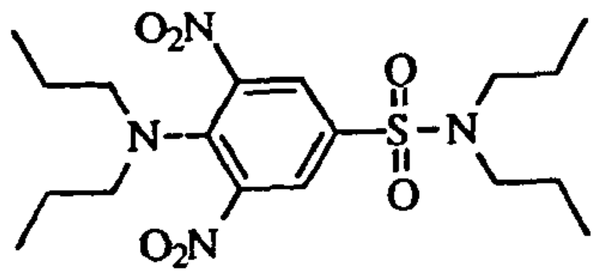
SPECTRUM NO. 49



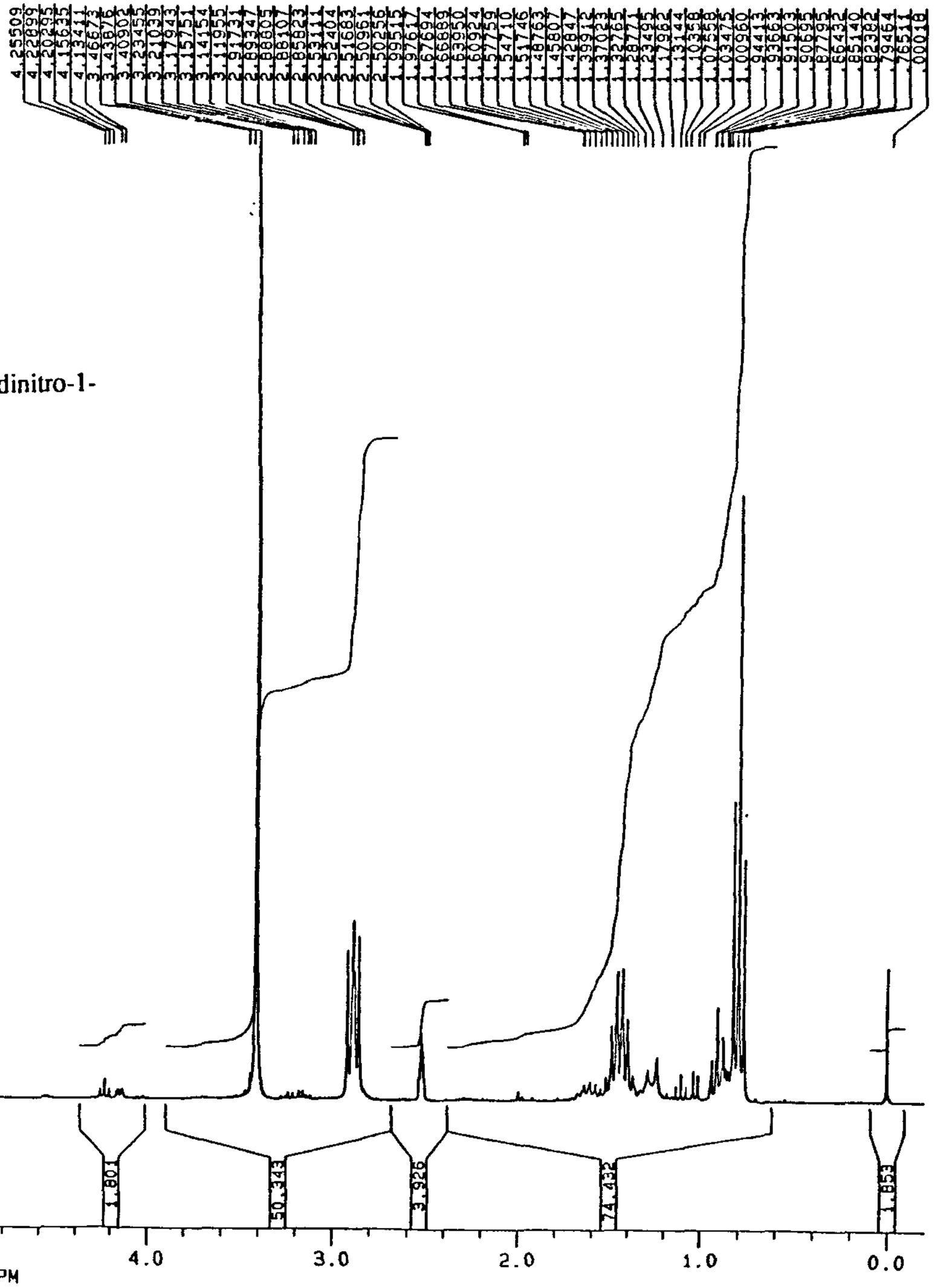
67a
1-[*N*-(2, 6-dinitro-4-trifluoro-methyl)amino]benzene

SPECTRUM NU. 50





68
4-(*N*,*N*-dipropylsulphamoyl)-2, 6-dinitro-1-(*N*,*N*-dipropylamino)benzene



BRUKER

JNE30S.130
AU PROG:
XOO.AU
DATE 4-6-94
TIME 5:27

SOLVENT DMSO
SF 250.134
SY 100.0
O1 5540.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305

PW 0.0
RD 0.0
AQ 3.277
RG 10
NS 96
TE 297

O2 0.0
DP 63L PO

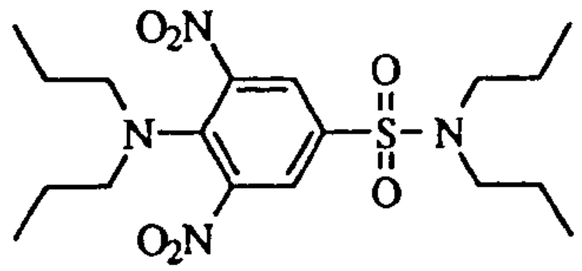
LB .200
GB .100
CX 35.00
CY 18.00
F1 9.801P
F2 -.199P
HZ/CM 71.463
PPM/CM .286
SR 4033.96

SPECTRUM NO. 51

PPM

149.142
148.375
146.469
142.795
137.066
131.379
128.532
125.467
125.071

80.469
80.450
64.896
54.006
48.249
40.392
40.255
40.117
39.724
39.390
39.056
38.722
38.390
29.896
29.680
28.249
22.273
20.774
18.911
13.740
13.404
10.900
10.744
10.663
-.057



68
4-(*N*,*N*-dipropylsulphamoyl)-2, 6-dinitro-1-(*N*,*N*-dipropylamino)benzene

BRUKER

JNE32S.130
AU PROG:
X02.AU
DATE 4-6-94
TIME 7:23

SOLVENT DMSO
SF 62.896
SY 62.0
01 2596.000
SI 65536
TD 65536
SW 15625.000
HZ/PT .477

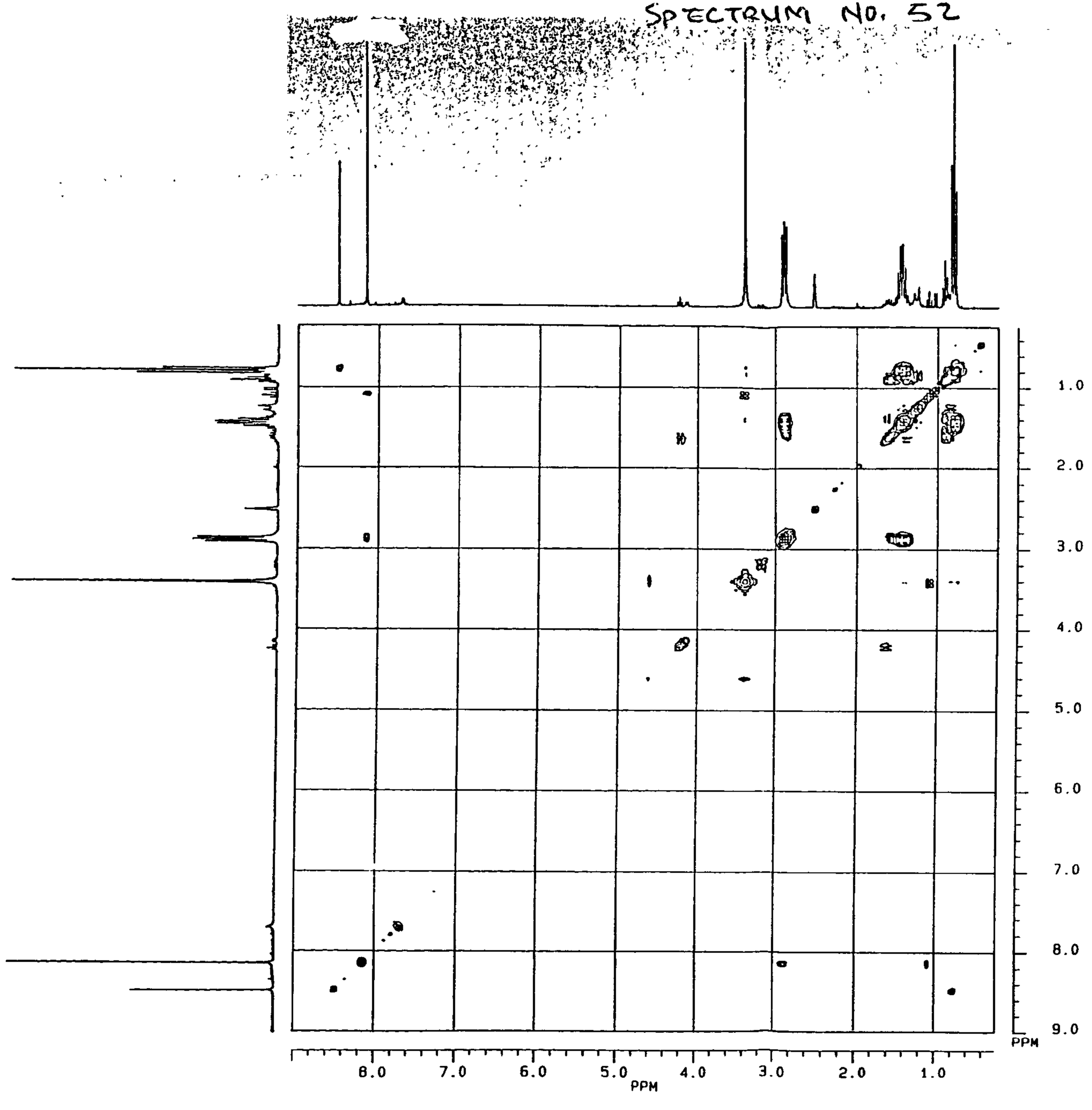
PW 0.0
RD 0.0
AQ 2.097
RG 640
NS 1000
TE 297

02 5270.000
DP 18L D0

LB 1.000
GB .100
CX 35.00
CY 6.50
F1 210.010P
F2 -4.989P
HZ/CM 386.361
PPM/CM 6.143
SR -3710.17

200 180 160 140 120 100 80 60 40 20 0
PPM

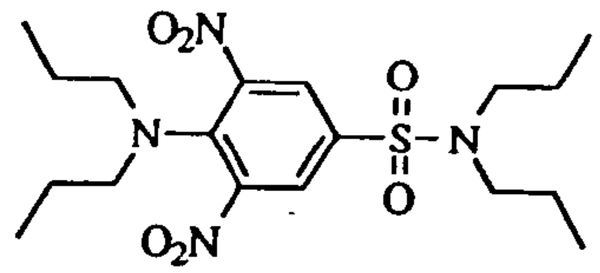
SPECTRUM NO. 52



BRUKER

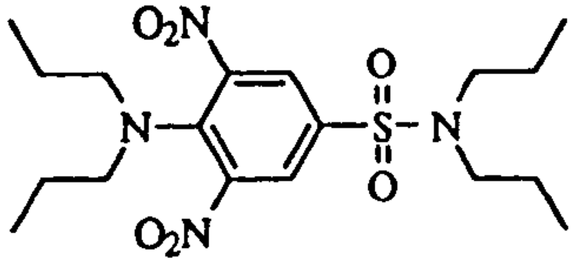
JNE36130.SMX
F1 PROJ:
PROJH1.001
F2 PROJ:
PROJH1.001
AU PROG:
Z27.AU
DATE 4-6-94

SI2	1024
SI1	512
SW2	2192.982
SW1	1096.491
ND0	1
WDW2	S
WDW1	S
SSB2	0
SSB1	0
MC2	M
PLIM ROW:	
F1	9.000P
F2	.232P
AND COLUMN:	
F1	9.000P
F2	.232P
D1	.8680000
P1	9.20
RGA	
RD	0.0
PW	0.0
DE	287.50
NS	8
DS	2
D0	.0000030
P3	4.60
NE	128
IN	.0004560



68
4-(*N*, *N*-dipropylsulphamoyl)-2, 6-dinitro-(*N*, *N*-dipropylamino)benzene

SPECTRUM NO. 53.



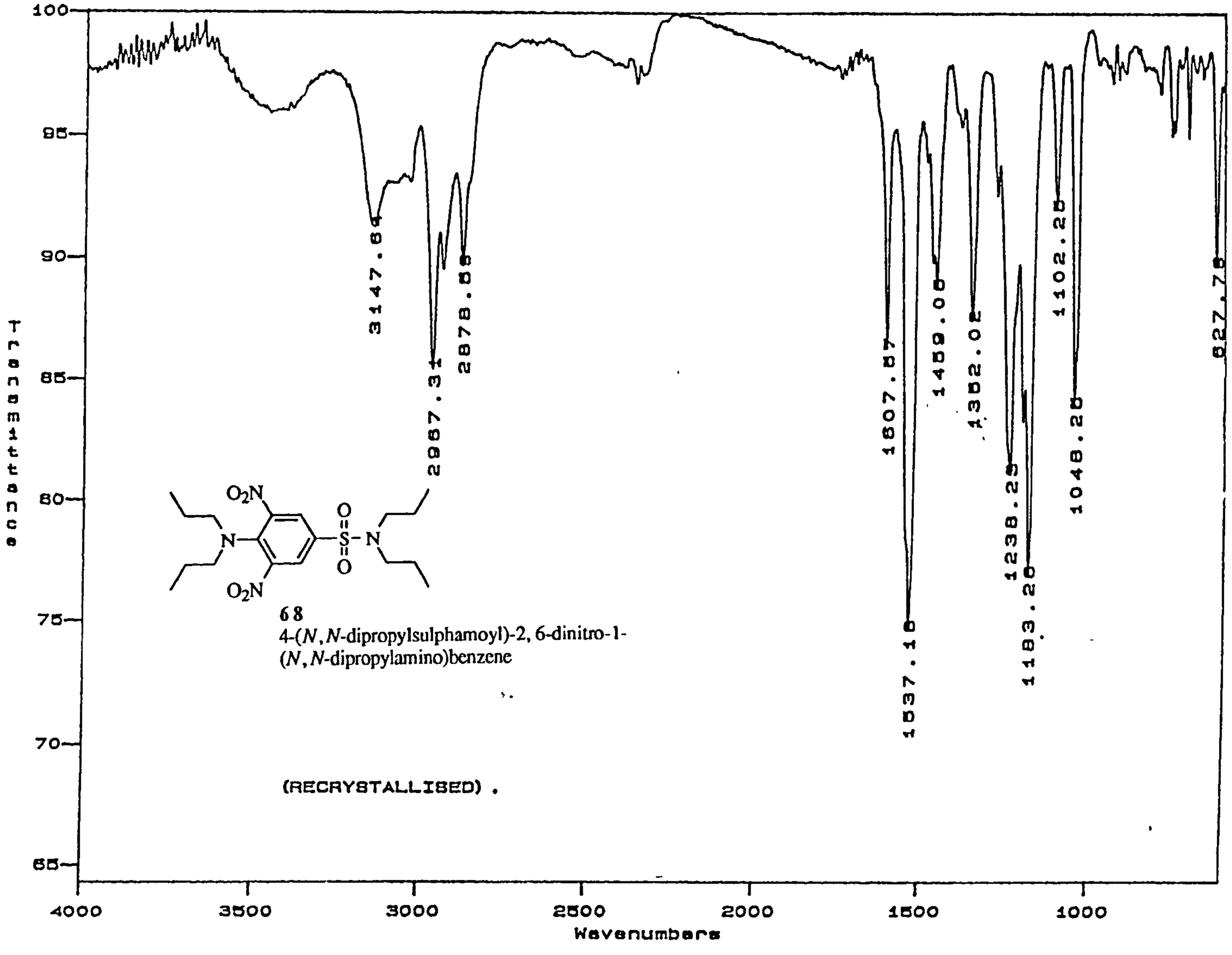
68
4-(*N*, *N*-dipropylsulphamoyl)-2, 6-dinitro-1-(*N*, *N*-dipropylamino)benzene

BRUKER

JNE36130.SMX
F1 PROJ:
PROJH1.001
F2 PROJ:
PROJH1.001
AU PROG:
Z27.AU
DATE 4-6-94

SI2	1024
SI1	512
SW2	2192.982
SW1	1096.491
NDO	1
WDW2	S
WDW1	S
SSB2	0
SSB1	0
MC2	M
PLIM ROW:	
F1	4.445P
F2	.661P
AND COLUMN:	
F1	4.445P
F2	.661P
D1	.8680000
P1	9.20
AGA	
RD	0.0
PW	0.0
DE	287.50
NS	8
DS	2
D0	.0000030
P3	4.60
NE	128
IN	.0004560

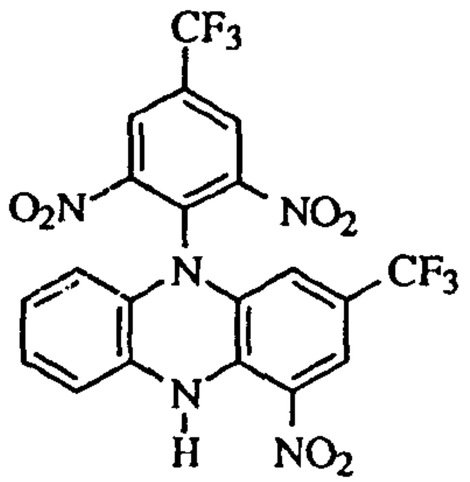
SPECTRUM NU- 54



68
4-(*N*,*N*-dipropylsulphamoyl)-2, 6-dinitro-1-(*N*,*N*-dipropylamino)benzene

(RECRYSTALLISED) .

SPECTRUM NO. 55



79

N^{10}-(2, 6-dinitro-4-trifluoromethylphenyl)-2-trifluoromethyl-4-nitro-5, 10-dihydrophenazine

BRUKER

DE160S.122
AU PROG:
X00.AU
DATE 16-12-96
TIME 11:35

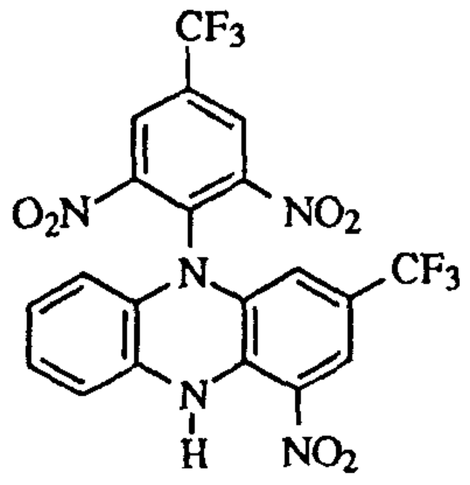
SOLVENT DMSO
SF 250.134
SY 100.0
O1 5540.000
SI 32768
TD 32766
SW 5000.000
HZ/PT .305

PW 0.0
RD 0.0
AQ 3.277
RG 40
NS 96
TE 297

O2 0.0
DP 63L PO

LB .200
CX 35.00
CY 18.00
F1 9.801P
F2 -.199P
HZ/CM 71.463
PPM/CM .286
SR 4036.09

SPECTRUM NO. 56



79

N^{10}-(2, 6-dinitro-4-trifluoromethylphenyl)-2-trifluoromethyl-4-nitro-5, 10-dihydrophenazine

BRUKER

DE121S.308
AU PROG:
X02.AU
DATE 14-12-96
TIME 14:41

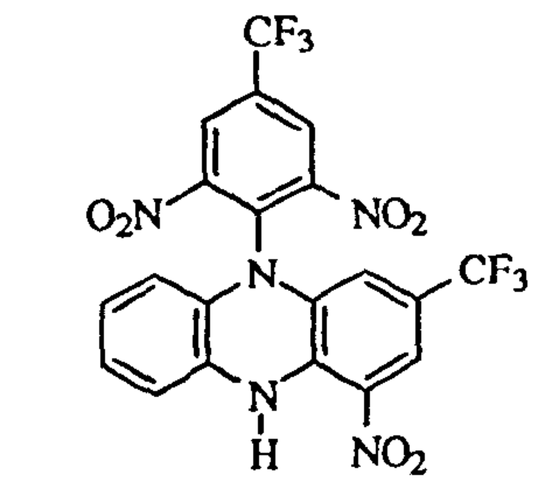
SOLVENT DMSO
SF 62.896
SY 62.0
01 2596.000
SI 65536
TD 65536
SW 15625.000
HZ/PT .477

PW 0.0
RD 0.0
AQ 2.097
RG 640
NS 1000
TE 297

02 5270.000
DP 18L DO

LB 1.000
CX 35.00
CY 18.00
F1 210.010P
F2 -4.989P
HZ/CM 386.361
PPM/CM 6.143
SR -3710.17

SPECTRUM NO 57



79

N^{10}-(2, 6-dinitro-4-trifluoromethylphenyl)-2-trifluoromethyl-4-nitro-5, 10-dihydrophenazine

BRUKER

DE161S.122
AU PROG:
X02.AU
DATE 16-12-96
TIME 12:32

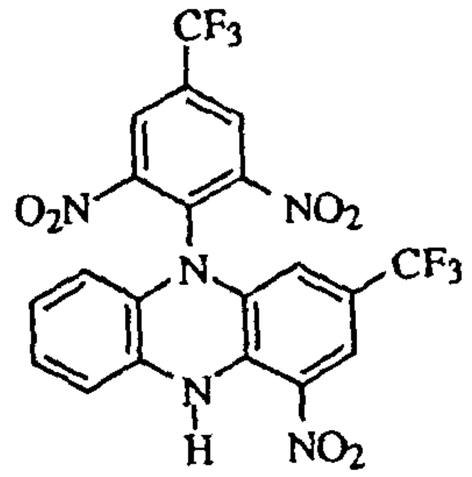
SOLVENT DMSO
SF 62.896
SY 62.0
01 2596.000
SI 65536
TD 65536
SW 15625.000
HZ/PT .477

PW 0.0
RD 0.0
AQ 2 097
RG 640
NS 1000
TE 297

02 5270.000
DP 18L D0

LB 1.000
CX 35.00
CY 6.50
F1 210.010P
F2 -4.989P
HZ/CM 386.361
PPM/CM 6.143
SR -3713.51

SPECTRUM NU. 58



79

N^{10}-(2, 6-dinitro-4-trifluoromethylphenyl)-2-trifluoromethyl-4-nitro-5, 10-dihydrophenazine

PPM

.0026

-61.1733
-61.5287
-61.6731

BRUKER

F19JA16F.001
DATE 16-1-97
TIME 14:27

SOLVENT DMSO
SF 235.361
SY 85.0
01 -4565.186
SI 32768
TD 32768
SW 35714.286
HZ/PT 2.180

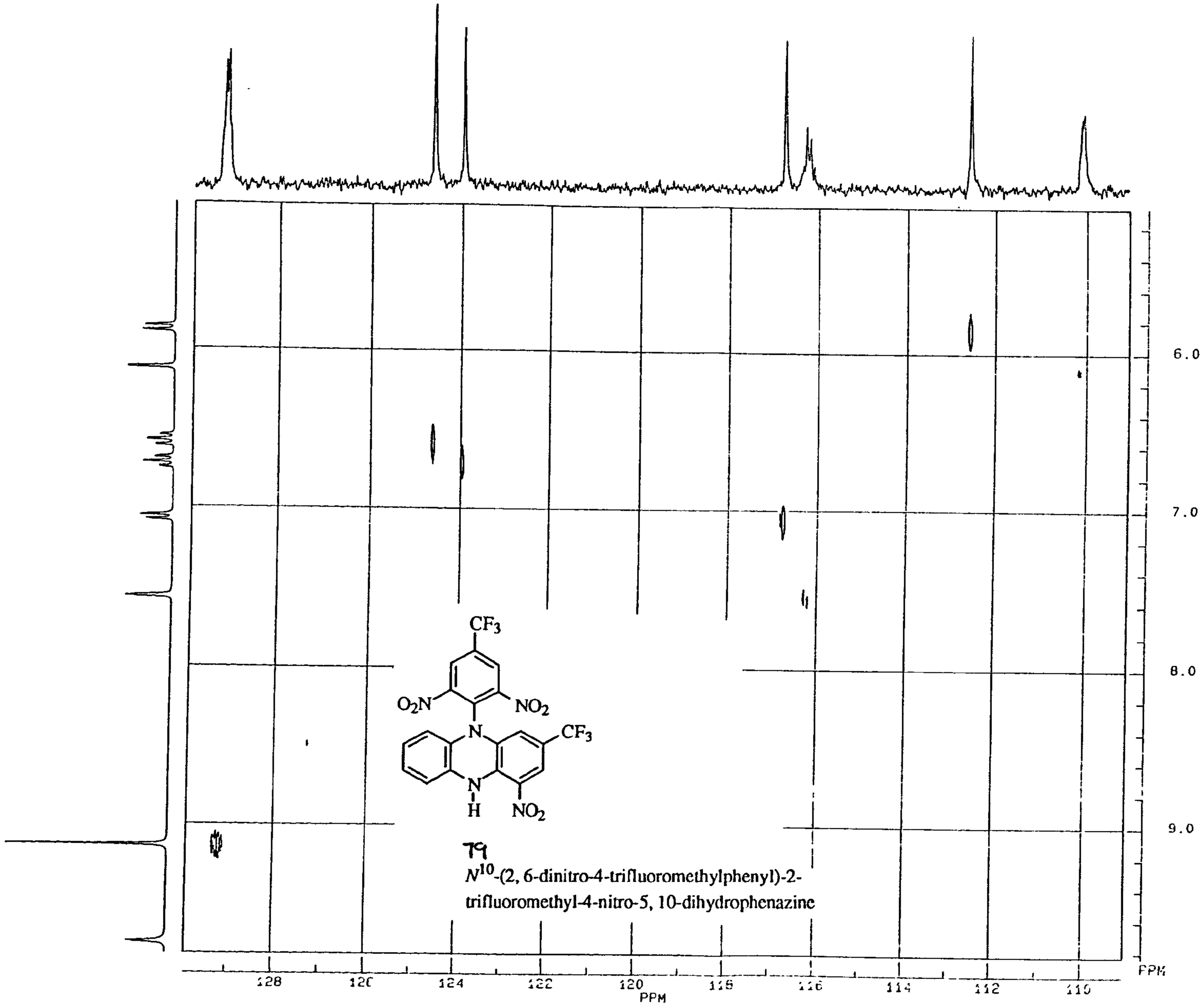
PW 6.0
RD 0.0
AQ .459
RG 800
NS 128
TE 297

02 6043.000
DP 18L P0

LB 0.0
CX 35.00
CY 18.00
F1 10.012P
F2 -99.989P
HZ/CM 739.709
PPM/CM 3.143
SR 11029.30

5 0 -5 -10 -15 -20 -25 -30 -35 -40 -45 -50 -55 -60 -65 -70 -75 -80 -85 -90 -95

SPECTRUM NO. 59



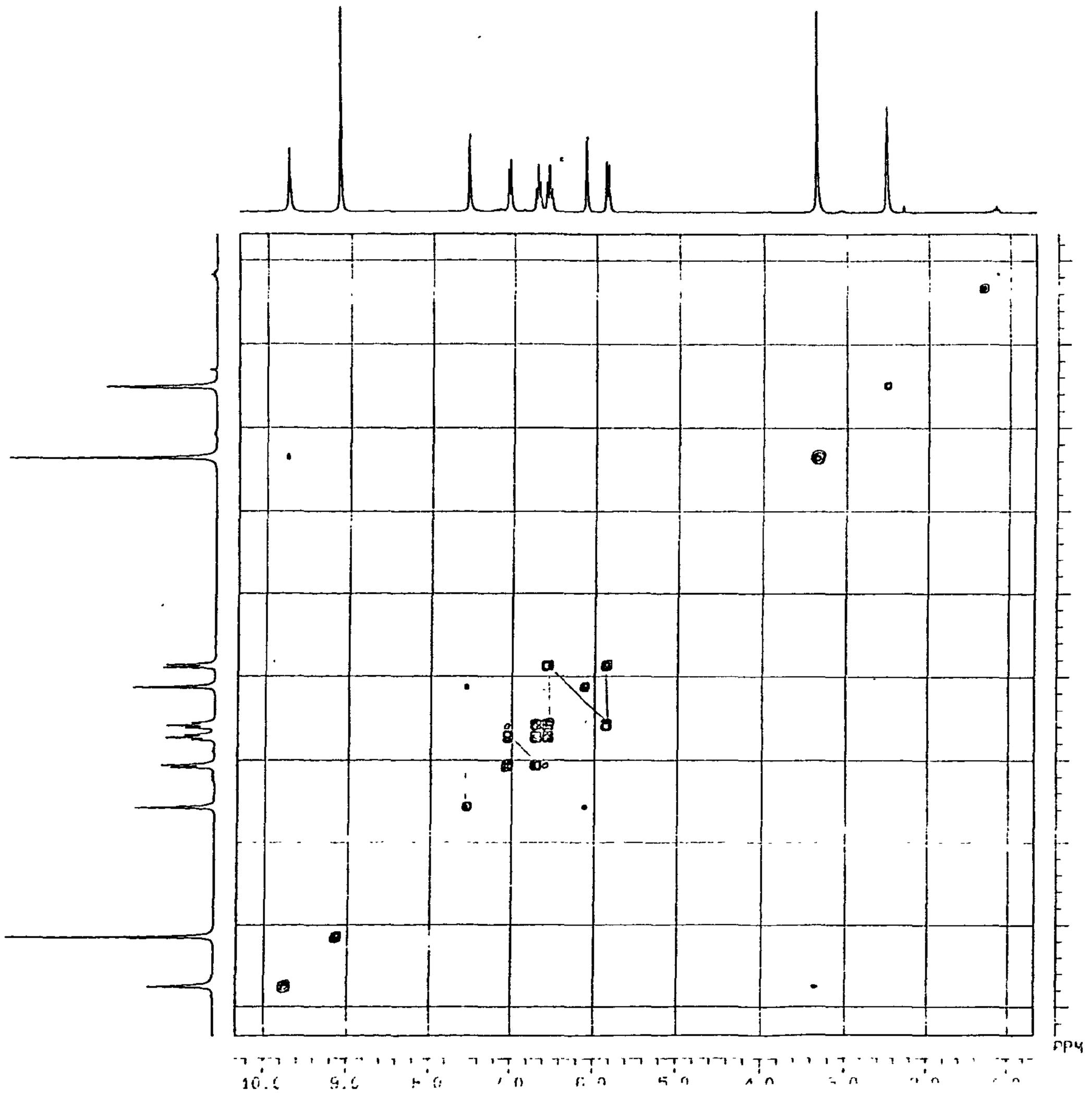
79

N^{10}-(2, 6-dinitro-4-trifluoromethylphenyl)-2-trifluoromethyl-4-nitro-5, 10-dihydrophenazine

BRUKER

```
JA132128.SMX
F1 PROJ:
 PROJH1.001
F2 PROJ:
 PROJX.001
AU PROG:
 Z28.AU
DATE 13-1-97

SI2   2048
SI1    512
SW2   1347.709
SW1   1217.137
NDO      2


WDW2     G
WDW1     G
SSB2     4
SSB1     4
MC2      M
PLIM ROW:
F1     129.904P
F2     109.084P
AND COLUMN:
F1       9.822P
F2       5.070P

D1     .3057000
S3     0H
P1       9.50
D0     .0000030
P6      10.60
D2     .0037000
P5       5.30
D4     .0018500
S2     18H
RGA
RD     0.0
PW       0.0
DE     466.00
NS       32
DS        2
P9       85.00
NE       128
IN     .0002054
```

SPECTRUM NU. 60

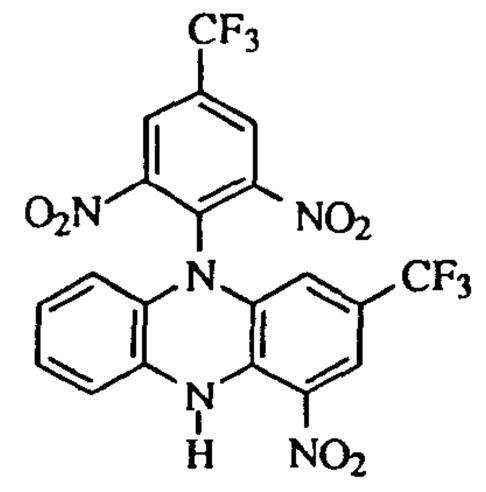


DE181154.SMX
F1 PROJ:
PROJH1.001
F2 PROJ:
PROJH1.001
AU PROG:
Z27.AU
DATE 19-12-96

SI2 1024
SI1 512
SW2 2415.459
SW1 1207.729
ND0 1

WDW2 S
WDW1 S
SSB2 0
SSB1 0
MC2 M
PLIM ROW:
F1 10.326P
F2 .669P
AND COLUMN:
F1 10.326P
F2 669P

D1 .8900000
P1 9.20
RGA
RD 0.0
PW 0.0
DE 261.50
NS 8
DS 2
D0 .0000030
P3 4.60
NE 128
IN .0004140

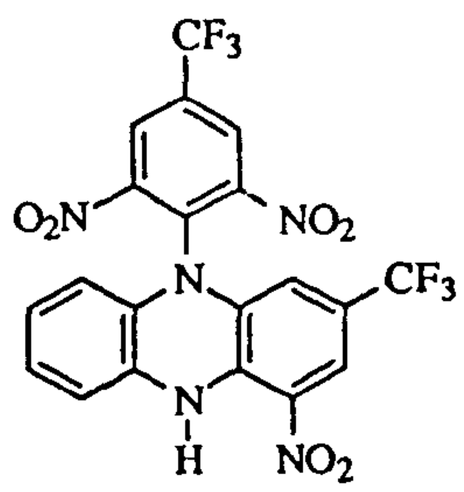


79

N^{10}-(2, 6-dinitro-4-trifluoromethylphenyl)-2-trifluoromethyl-4-nitro-5, 10-dihydrophenazine

SPECTRUM NO. 61

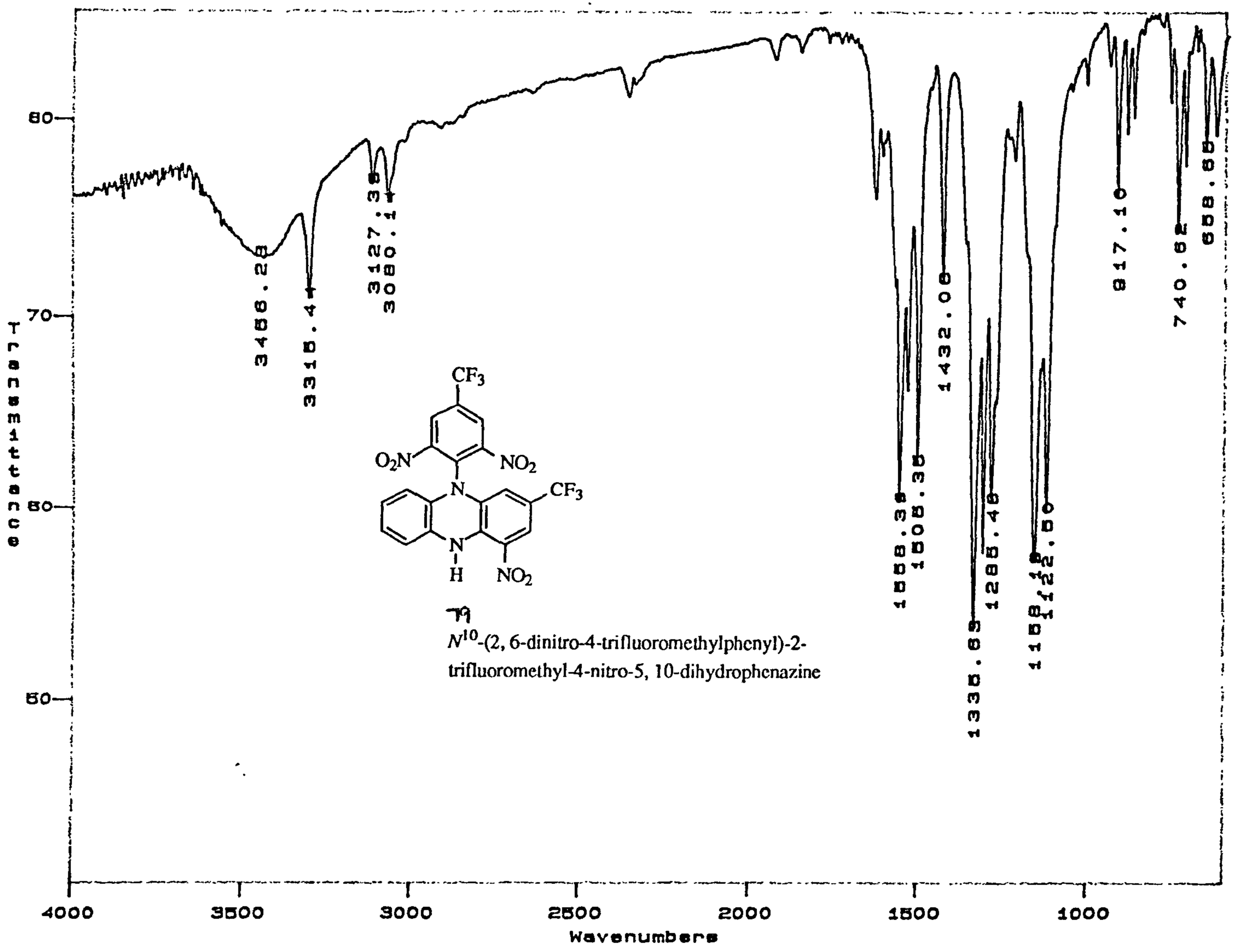
RES380#38 x1 Bgd=30 21-JAN-97 14:51+0:03:46 70-250 EI+
BpM=0 I=9.9v Hm=0 TIC=390772992 Acnt: Sys:LRP HMR: 65017
RUN NO.679 SAMPLE: PT= 0° Cal:CAL0801 MASS:



79

N^{10}-(2, 6-dinitro-4-trifluoromethylphenyl)-2-trifluoromethyl-4-nitro-5, 10-dihydrophenazine

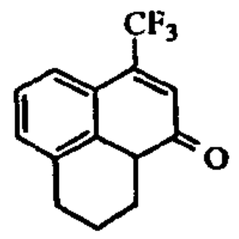
SPECTRUM NO-62



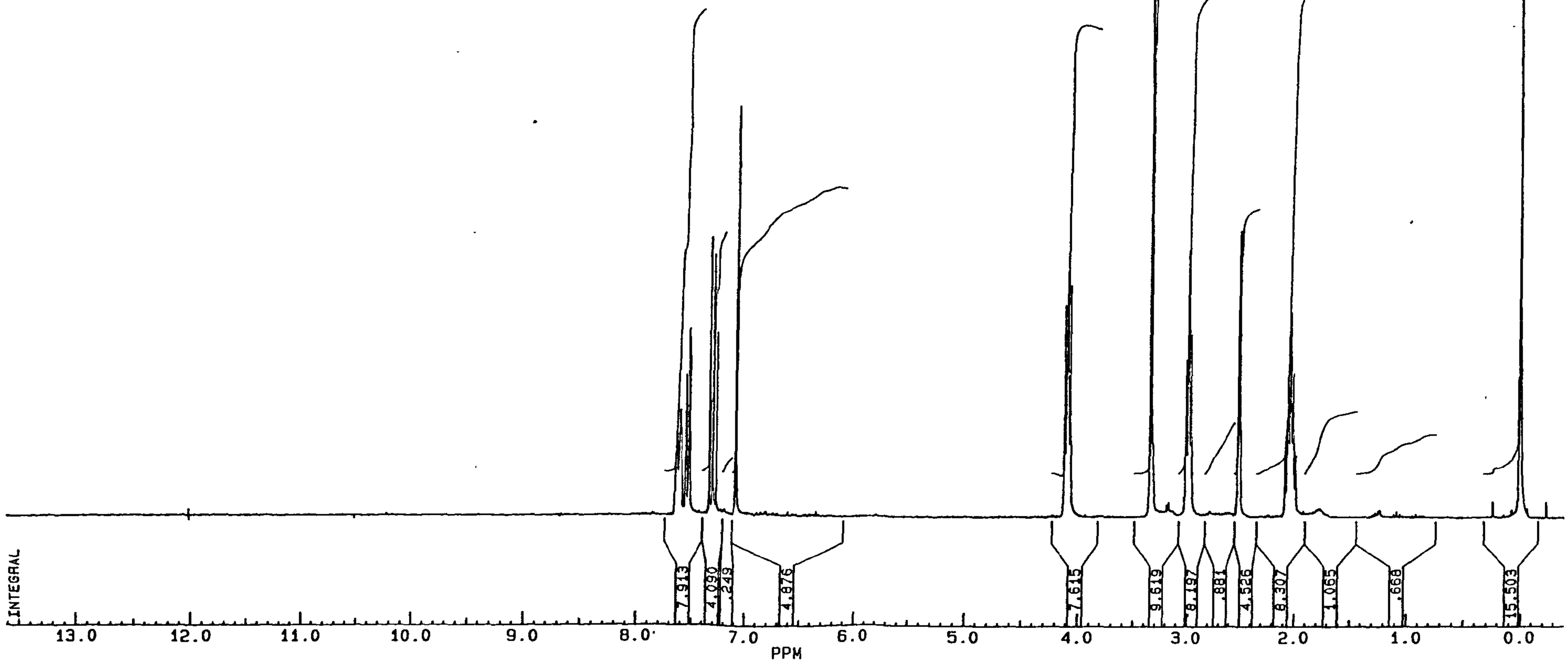
79

N^{10}-(2, 6-dinitro-4-trifluoromethylphenyl)-2-trifluoromethyl-4-nitro-5, 10-dihydrophenazine

SPECTRUM NO 63



88a
1-Trifluoromethyl-6, 7-dihydro-
3*H*, 5*H*-benzo[ij]quinolizin-3-one



BRUKER

MAY81S.137
AU PROG:
X00.AU
DATE 9-5-96
TIME 20:00

SOLVENT DMSO
SF 250.134
SY 100.0
01 5540.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305

PW 0.0
RD 0.0
AQ 3.277
RG 40
NS 96
TE 297

02 0.0
DP 63L PO

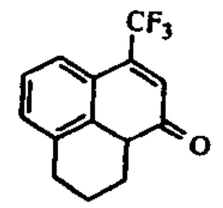
LB .200
CX 35.00
CY 0.0
F1 13.601P
F2 -.399P
HZ/CM 100.054
PPM/CM .400
SR 4037.01

SPECTRUM NU 64

PPM

158.794
137.138
131.241
126.070
125.553
125.411
125.326
120.431
113.214

48.349
40.470
40.135
39.802
39.468
39.134
38.801
38.466
25.959
19.628
.006



88a
1-Trifluoromethyl-6, 7-dihydro-
3H, 5H-benzo[ij]quinolizin-3-one

BRUKER

MAY80S.137
AU PROG:
X02.AU
DATE 9-5-96
TIME 19:50

SOLVENT DMSO
SF 62.896
SY 62.0
O1 2596.000
SI 65536
TD 65536
SW 15625.000
HZ/PT .477

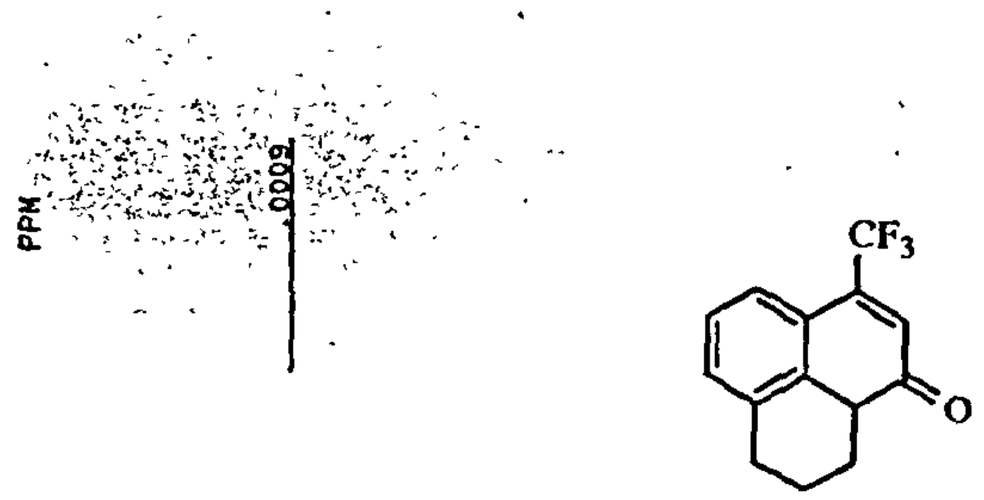
PW 0.0
RD 0.0
AQ 2.097
RG 640
NS 1000
TE 297

O2 5270.000
DP 18L DO

LB 1.000
CX 35.00
CY 15.00
F1 210.010
F2 -4.989
HZ/CM 386.361
PPM/CM 6.143
SR -3712.08

200 180 160 140 120 100 80 60 40
PPM

SPECTRUM NO. 65



88a
1-Trifluoromethyl-6, 7-dihydro-
3*H*, 5*H*-benzo[ij]quinolizin-3-one

-61.5577

BRUKER

F19MY15.F001
DATE 15-5-96
TIME 8:44

SOLVENT DMSO
SF 235.361
SY 85.0
O1 -4565.186
SI 32768
TD 32768
SW 35714.286
HZ/PT 2.180

PW 6.0
RD 0.0
AQ .459
RG 100
NS 128
TE 297

O2 6043.000
OP 18L PO

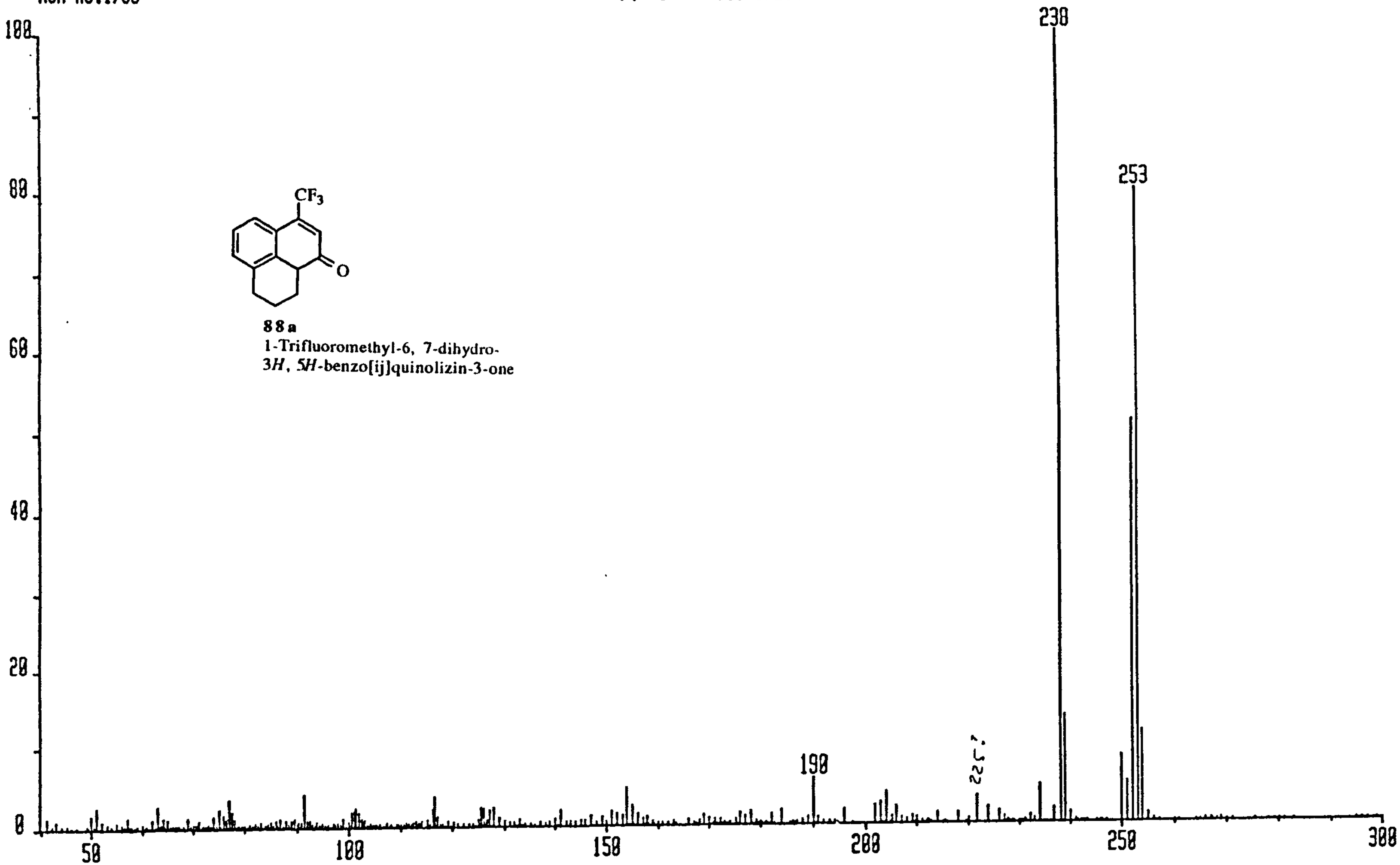
LB 0.0
CX 35.00
CY 18.00
F1 10.012F
F2 -99.979F
HZ/CM 739.646
PPM/CM 3.143
SA 11018.40

5 0 -5 -10 -15 -20 -25 -30 -35 -40 -45 -50 -55 -60 -65 -70 -75 -80 -85 -90 -95
PPM

SPECTRUM NO. 66

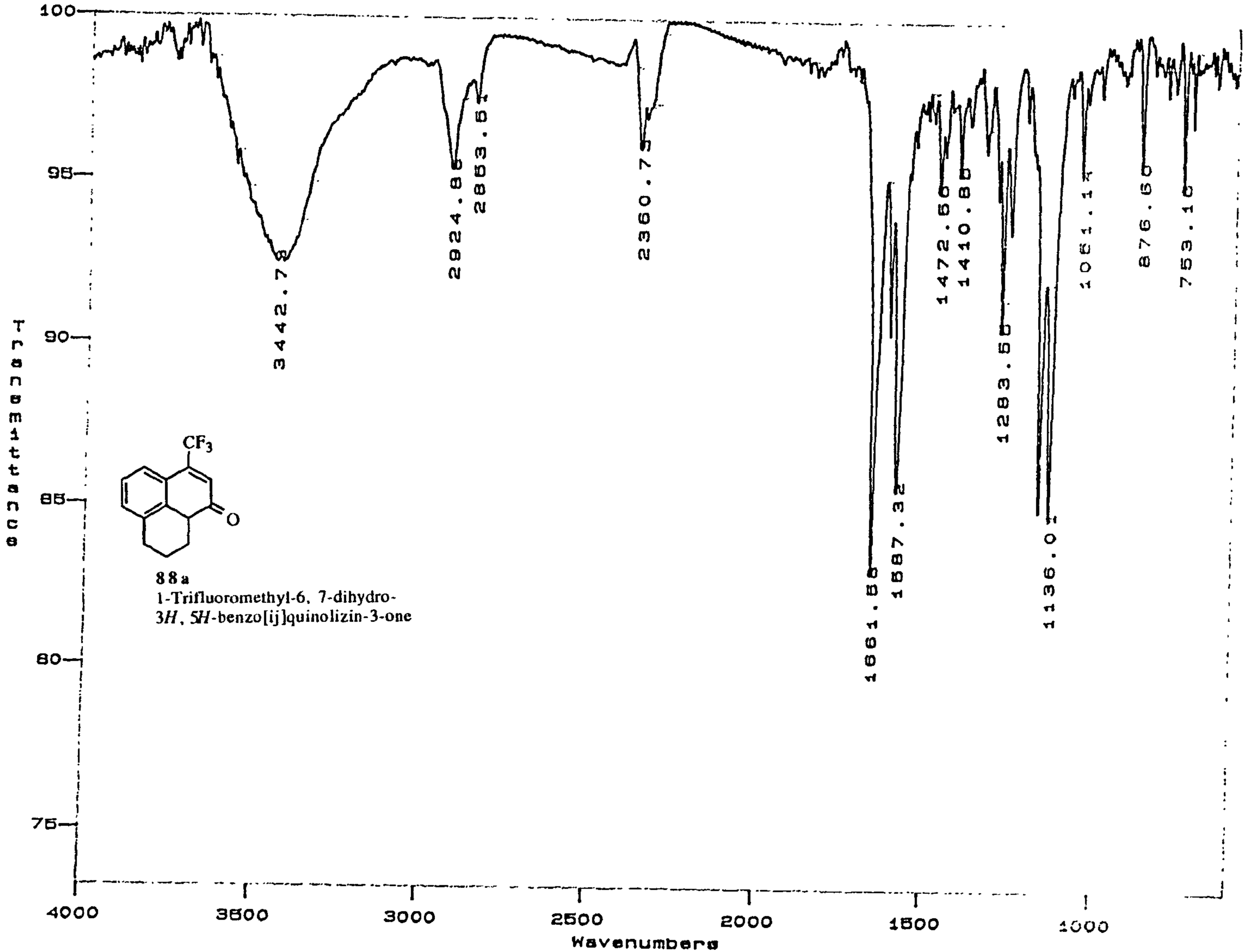
RES679#7# x1 Bgd=1 3-JUL-96 12:09+0:01:00 70-250 EI+
BpM=0 I=4.8v Hm=0 TIC=123110000 Acnt: Sys:LRP
RUN NO.1700 PT= 0° Cal:CAL1405

HMR: 26066000
MASS: 238



88a
1-Trifluoromethyl-6, 7-dihydro-
3*H*, 5*H*-benzo[ij]quinolizin-3-one

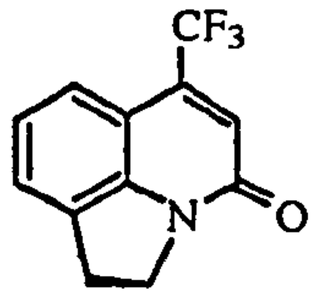
SPECTRUM NO. 67



88a
1-Trifluoromethyl-6, 7-dihydro-
3*H*, 5*H*-benzo[ij]quinolizin-3-one

SPECTRUM NO 68

(WITH D2O)



93
4-Trifluoromethyl-1, 8-dimethylene-
1, 2-dihydroquinolin-2-one

BRUKER

AU230S.411
AU PROG:
X00.AU
DATE 23-8-96
TIME 12:01

SOLVENT DMSO
SF 250.134
SY 100.0
O1 5540.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305

PW 0.0
RD 0.0
AQ 3.277
RG 10
NS 64
TE 297

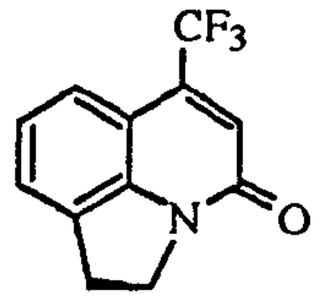
O2 0.0
DP 63L PO

LB .200
CX 35.00
CY 18.00
F1 9.801P
F2 -.199P
HZ/CM 71.463
PPM/CM .286
SR 4020.22

INTEGRAL

PPM

SPECTRUM NO. 69



93
4-Trifluoromethyl-1, 8-dimethylene-
1, 2-dihydroquinolin-2-one

157.752
142.985
135.303
134.790
132.087
129.235
126.581
125.769
125.170
124.715
123.911
122.245
122.163
122.078
121.891
120.442
120.414
116.995
111.138
79.401
46.993
40.529
40.193
39.860
39.526
39.192
38.858
38.524
26.692
-.002

BRUKER

AU210S.156
AU PROG:
X02.AU
DATE 22-8-96
TIME 21:18

SOLVENT DMSO
SF 62.896
SY 62.0
01 2596.000
SI 65536
TD 65536
SW 15625.000
HZ/PT .477

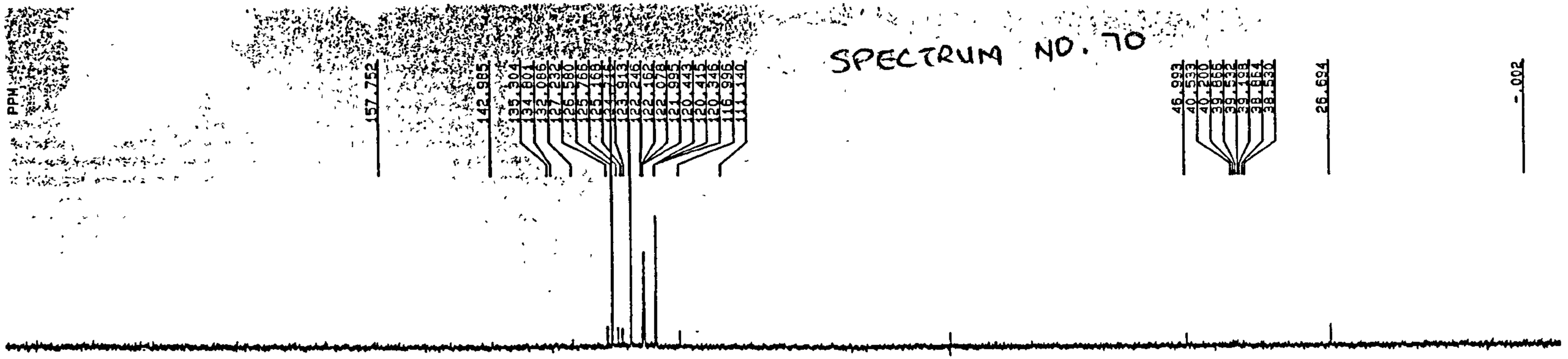
PW 0.0
RD 0.0
AQ 2.097
RG 640
NS 897
TE 297

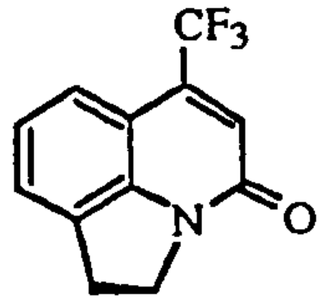
02 5270.000
DP 18L D0

LB 1.000
CX 35.00
CY 18.00
F1 210.010P
F2 -4.989P
HZ/CM 386.361
PPM/CM 6.143
SR -3719.23

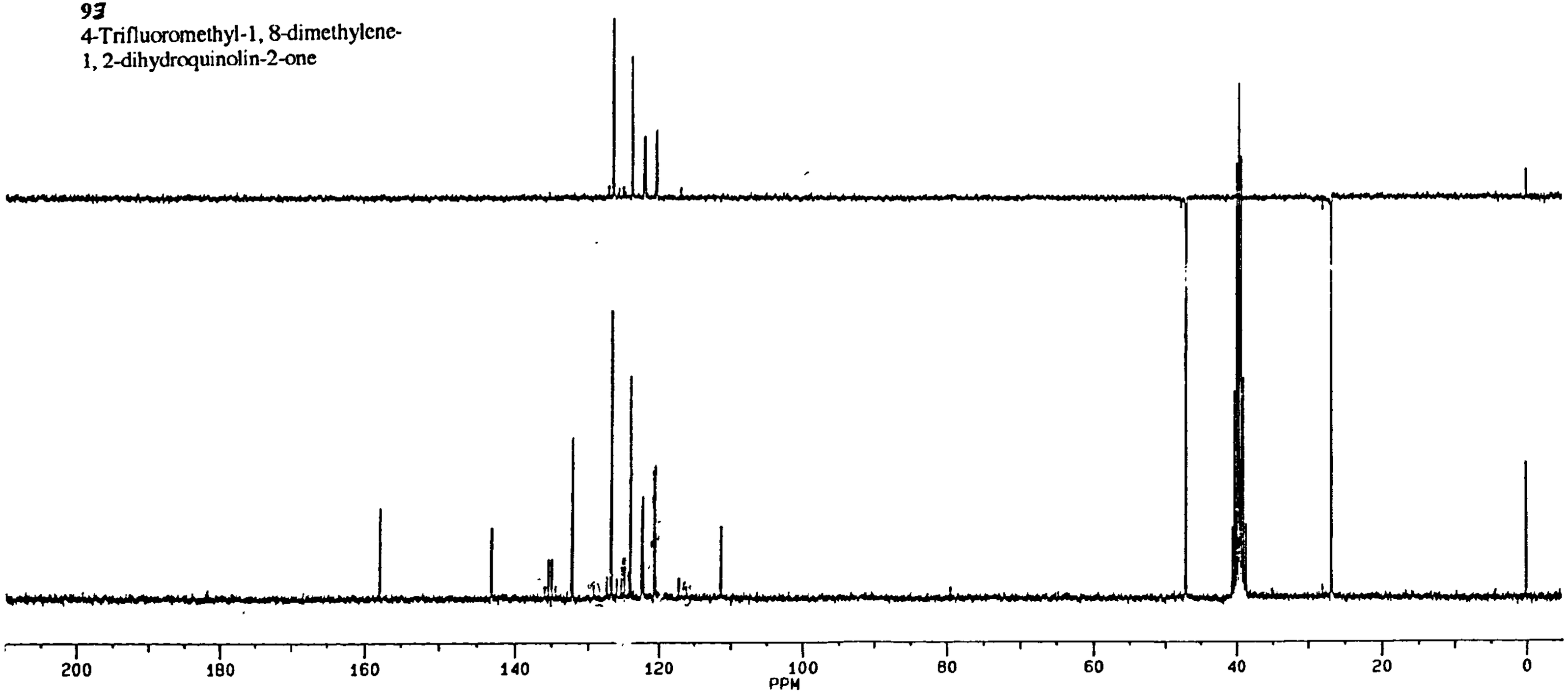
200 180 160 140 120 100 80 60 40 20 0
PPM

SPECTRUM NO. 70





9j
4-Trifluoromethyl-1, 8-dimethylene-
1, 2-dihydroquinolin-2-one



BRUKER

AU211S.156
AU PROG:
X02.AU
DATE 22-8-96
TIME 22: 14

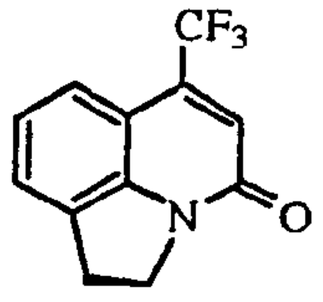
SOLVENT DMSO
SF 62.896
SY 62.0
O1 2596.000
SI 65536
TD 65536
SW 15625.000
HZ/PT .477

PW 0.0
RD 0.0
AQ 2.097
RG 800
NS 1000
TE 297

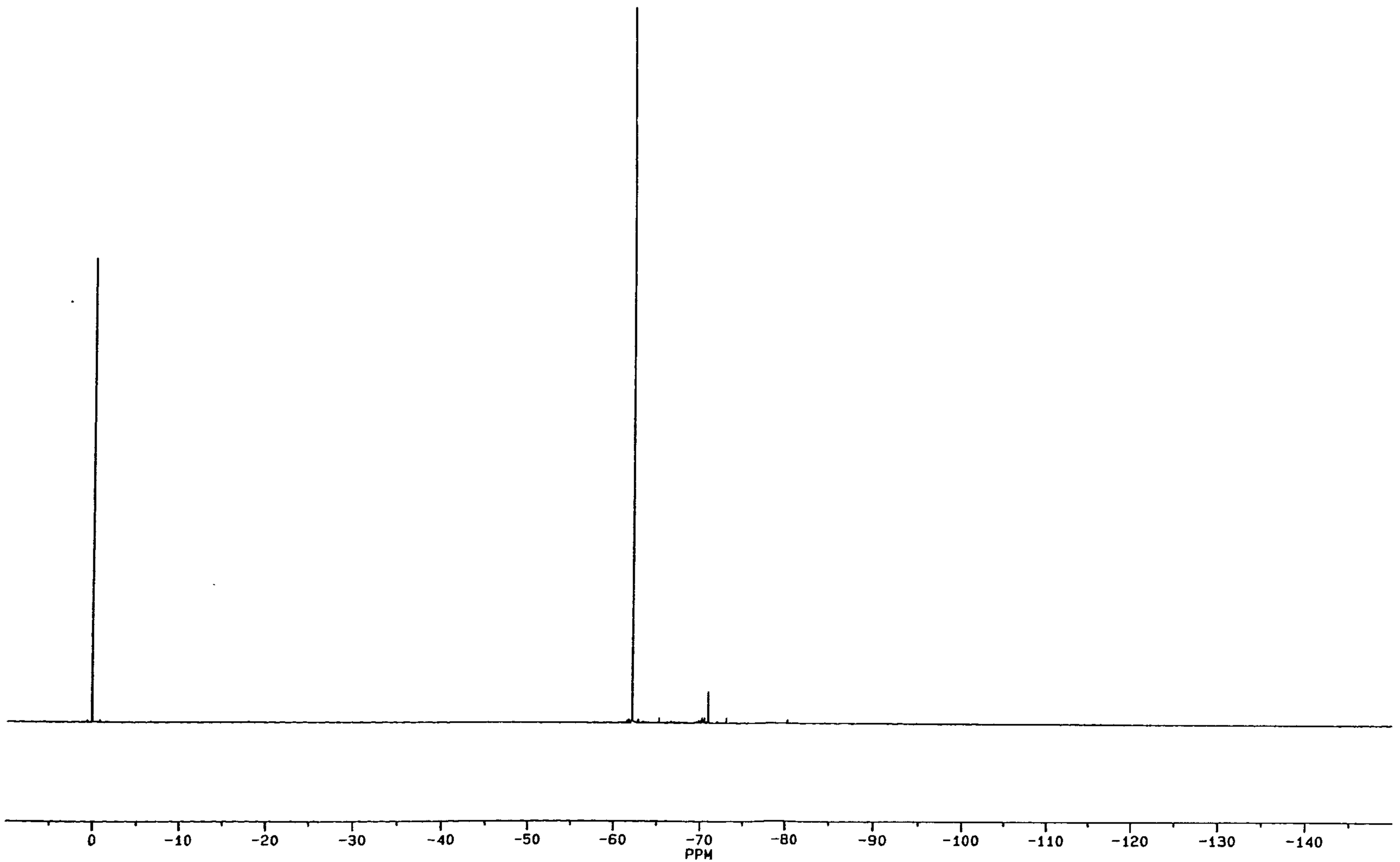
O2 5270.000
DP 18L DO

LB 1.000
CX 35.00
CY 6.50
F1 210.010P
F2 -4.989P
HZ/CM 386.361
PPM/CM 6.143
SR -3719.23

SPECTRUM NO. 71



93
4-Trifluoromethyl-1, 8-dimethylene-
1, 2-dihydroquinolin-2-one



BRUKER

AP290S.129
AU PROG:
X03.AU
DATE 29-4-97
TIME 9:24

SOLVENT DMSO
SF 235.361
SY 85.0
01 -4565.186
SI 32768
TD 32768
SW 41666.667
HZ/PT 2.543

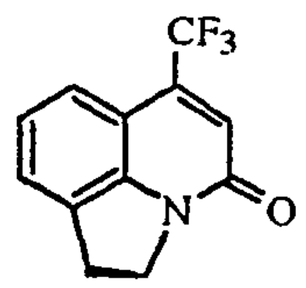
PW 0.0
RD 0.0
AQ .393
RG 100
NS 128
TE 297

02 6043.000
DP 18L PO

LB .300
CX 35.00
CY 18.00
F1 10.016P
F2 -149.998P
HZ/CM 1.076E3
PPM/CM 4.572
SR 11021.67

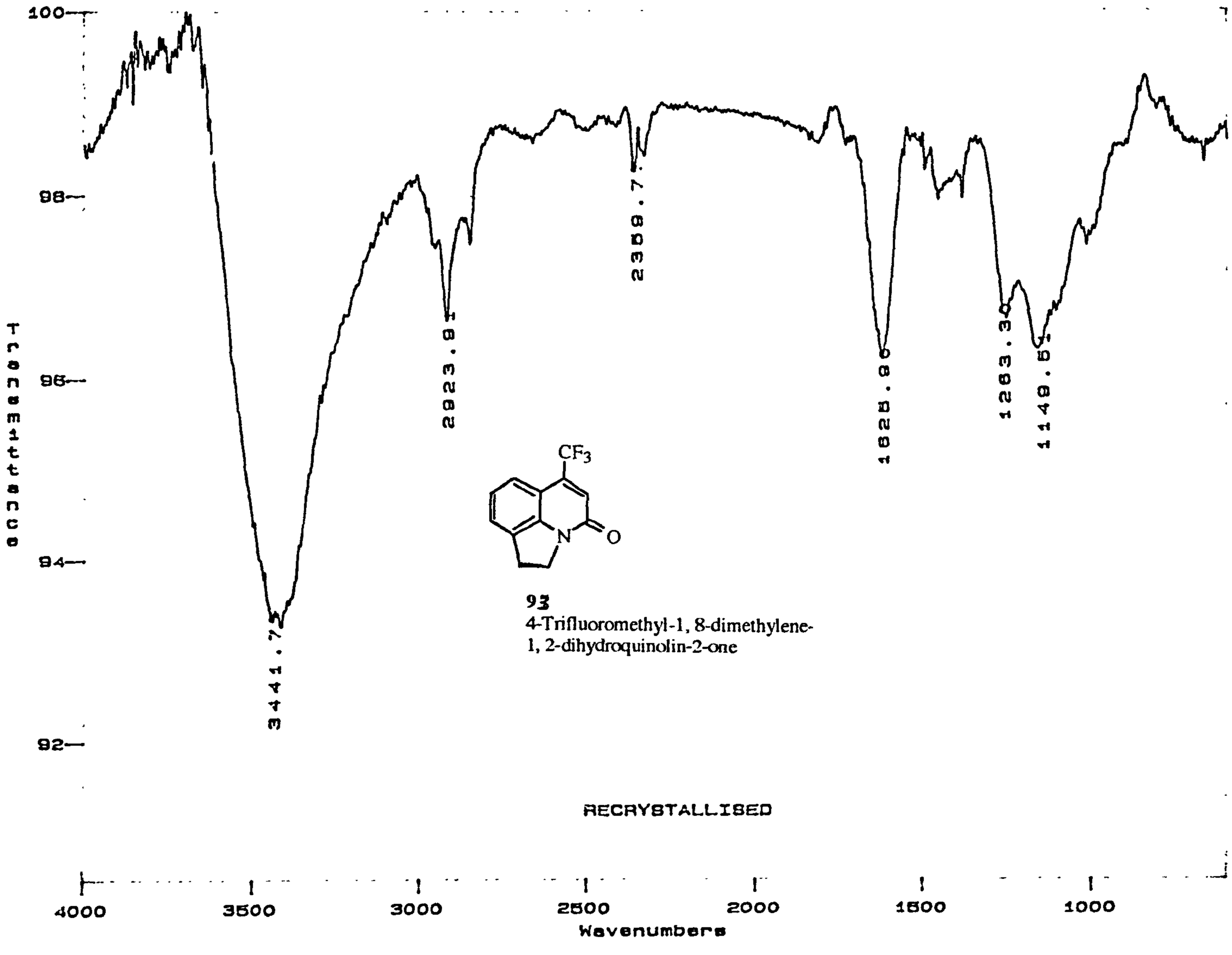
SPECTRUM NO. 72

RES877#9* x1 Bgd=1 30-AUG-96 15:19+0:01:08 70-250 EI+
BpM=0 I=5.7v Hz=0 TIC=148333088 Acnt: Sys:LRP HMR:
RUN NO.2848 PT= 0° Cal:CAL2908 MASS:



93
4-Trifluoromethyl-1, 8-dimethylene-
1, 2-dihydroquinolin-2-one

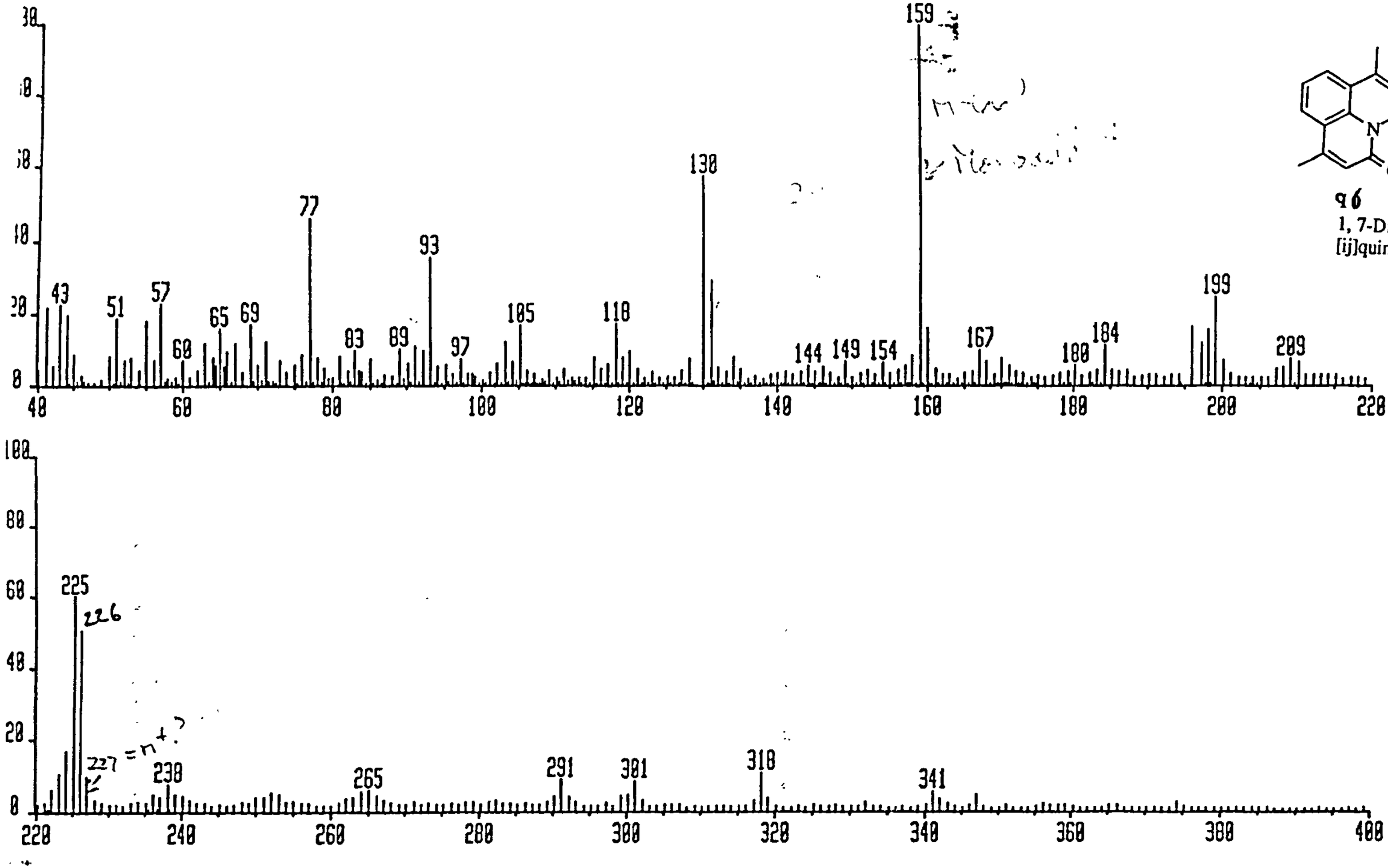
SPECTRUM NO. 73



93
4-Trifluoromethyl-1, 8-dimethylene-1, 2-dihydroquinolin-2-one

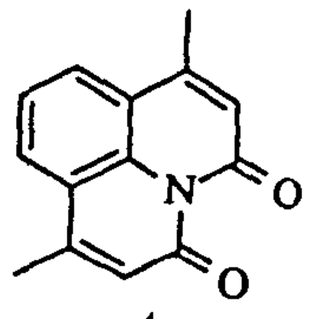
RES659#26♦ x1 Bgd=9 2-JUL-96 15:35+0:02:49 70-250 EI+
BpM=0 I=546mv Hm=0 TIC=70033000 Acnt: Sys:LRP HMR: 3419000
RUN NO.1760 PT= 0° Cal:CAL1485 MASS: 159

SPECTRUM NO. 74



96

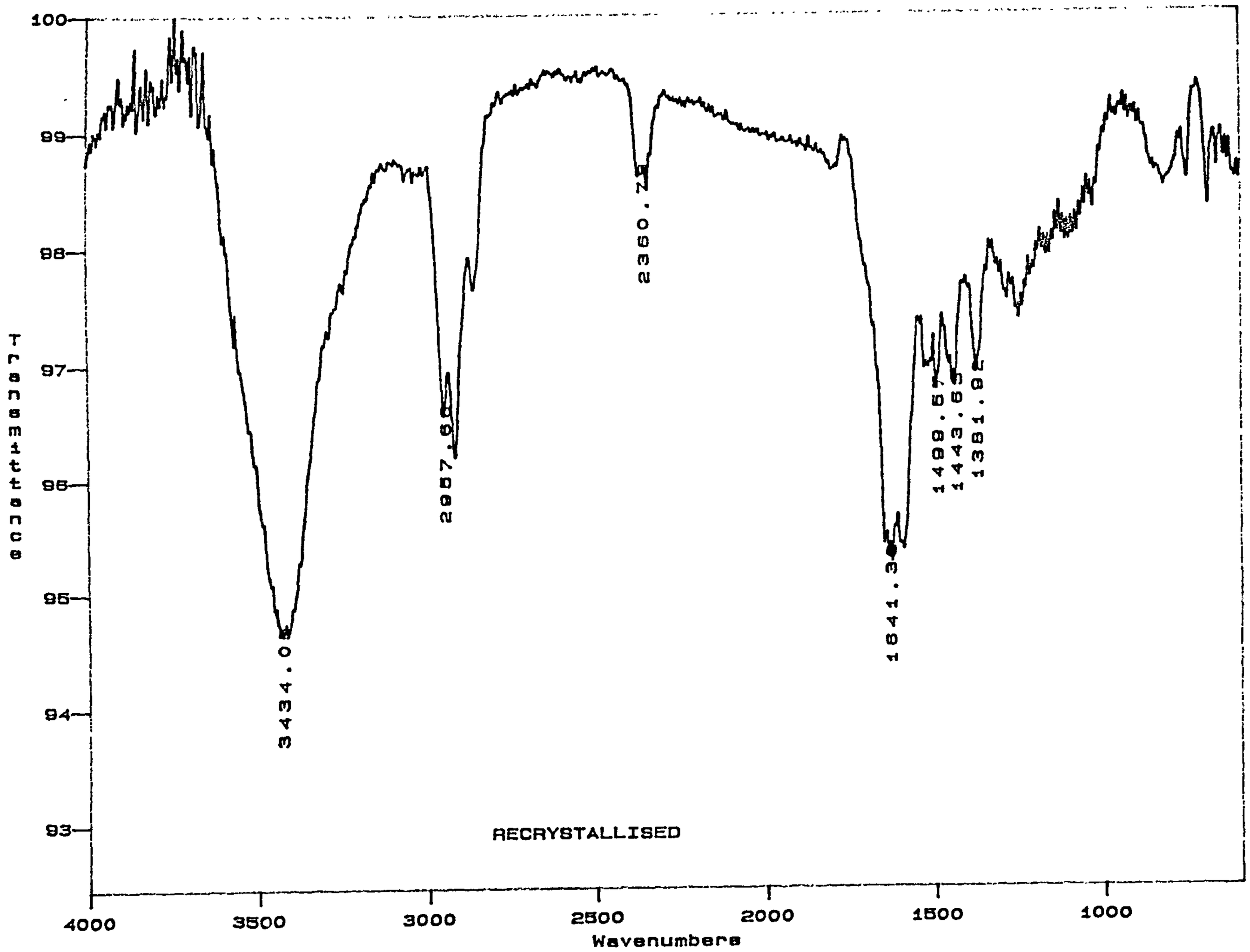
1, 7-Dimethyl-3*H*, 5*H*-benz
[ij]quinolizin-3, 5-dione



96

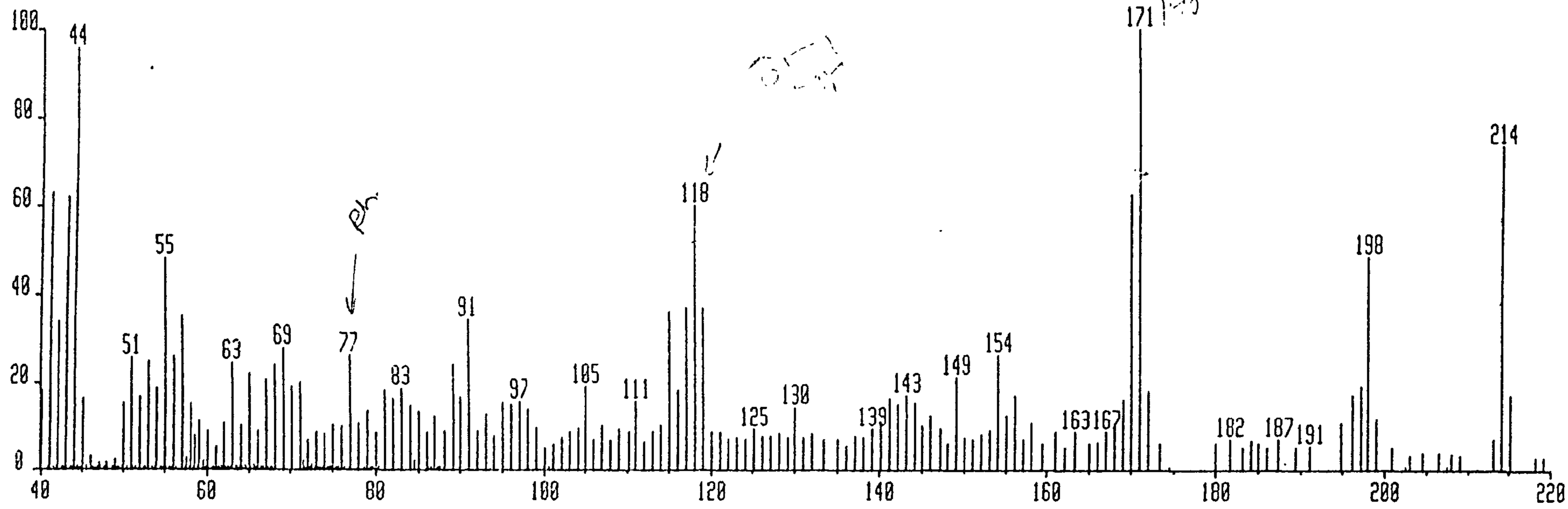
1, 7-Dimethyl-3*H*, 5*H*-be
[ij]quinolizin-3, 5-dione

SPECTRUM NO. 75

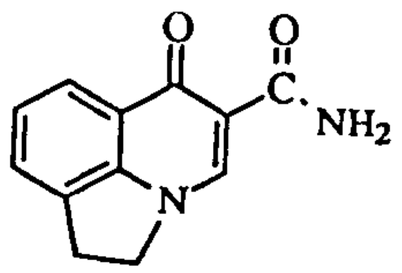


SPECTRUM NO. 76

RES228#38 x1 Bgd=11 7-NOV-96 16:22:0 03 43 70-250 EI+
BpM=0 I=1.4v Hm=0 TIC=172559008 Acnt Sys:LRP HMR: 5591
RUN NO.374 PT= 0° Cal:CAL0411 MASS:

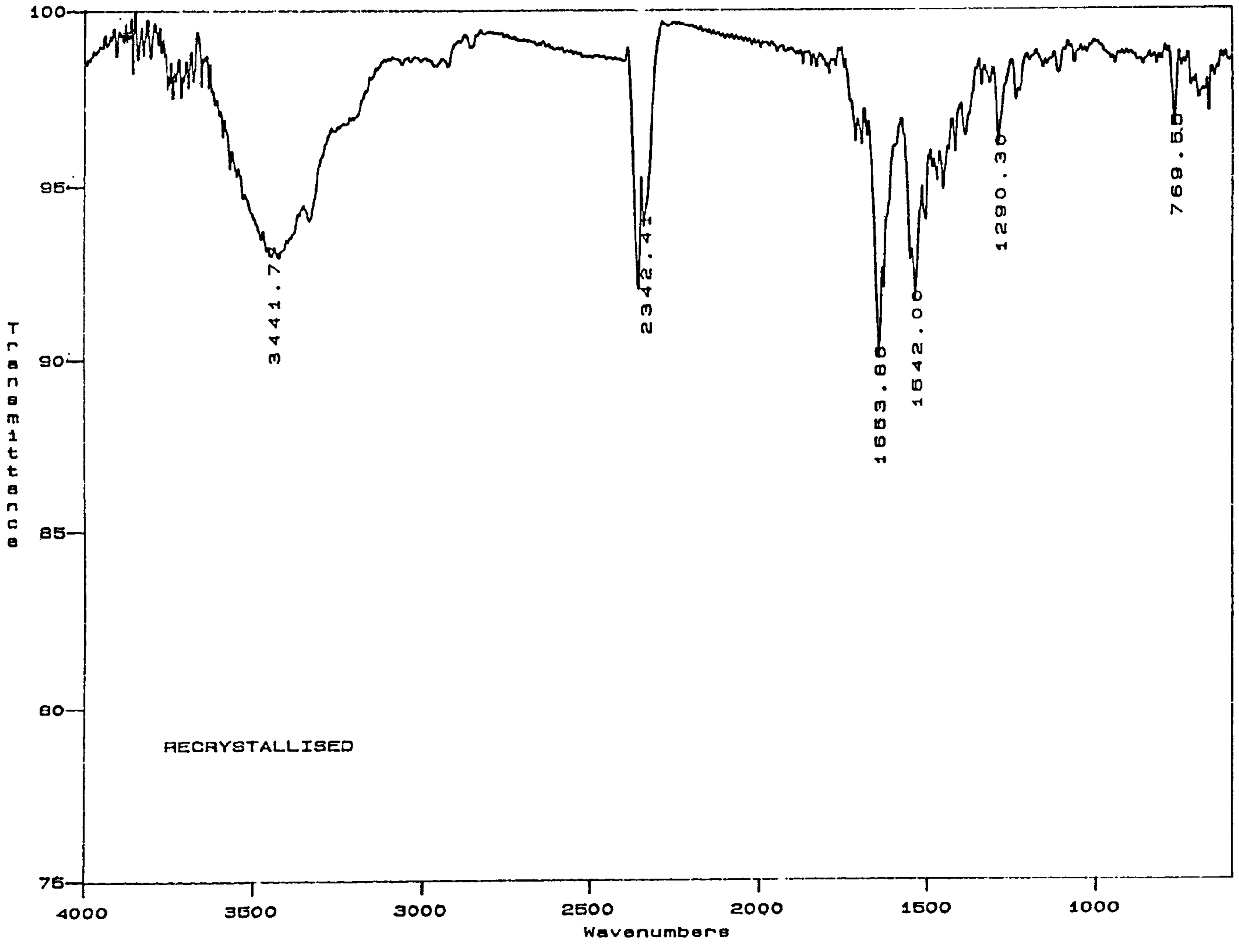


107
3-Carbamoyl-1, 8-dimethylene-
1, 4-dihydroquinolin-4-one

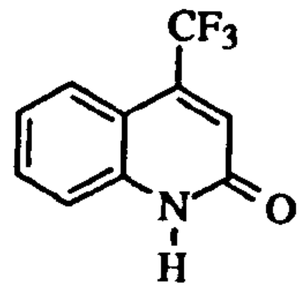


107
3-Carbamoyl-1, 8-dimethyl-
1, 4-dihydroquinolin-4-one

SPECTRUM NO. 77



RECRYST. SPECTRUM NO. 78



11ɬa
4-Trifluoromethyl-1, 2-dihydroquinolin-2-one

PPM -.0011 -61.9894 -65.9738

BRUKER

F19MY15.F016
DATE 15-5-96
TIME 13:53

SOLVENT DMSO
SF 235.361
SY 85.0
O1 -4565.186
SI 32768
TD 32768
SW 35714.286
HZ/PT 2.180

PW 6.0
RD 0.0
AQ .459
RG 80
NS 128
TE 297

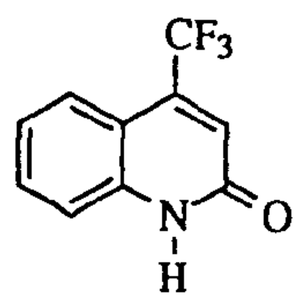
O2 6043.000
DP 18L PO

LB 0.0
CX 35.00
CY 15.00
F1 10.030P
F2 -99.961P
HZ/CM 739.646
PPM/CM 3.143
SR 11022.76

5 0 -5 -10 -15 -20 -25 -30 -35 -40 -45 -50 -55 -60 -65 -70 -75 -80 -85 -90 -95
PPM

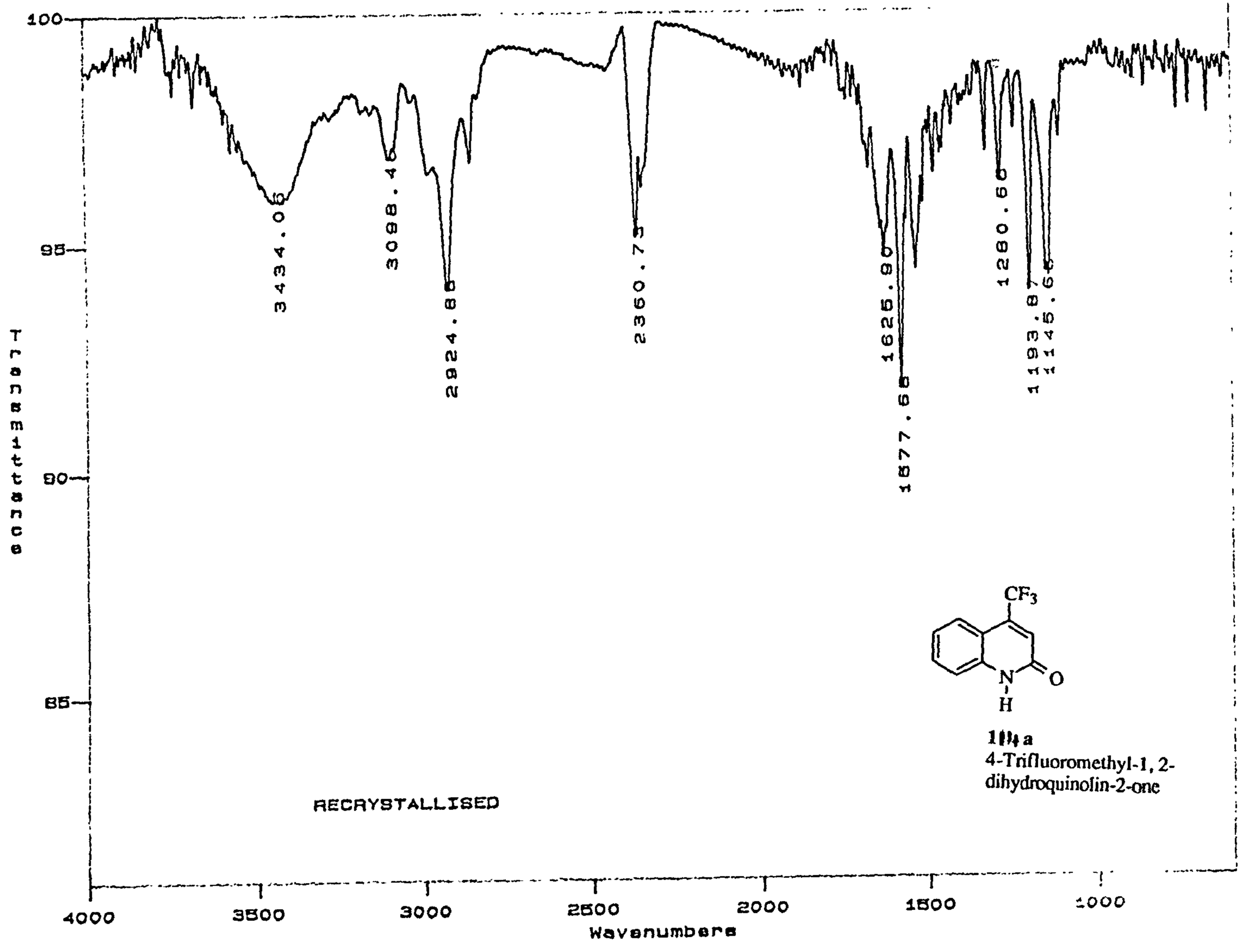
SPECTRUM NO. 79

RES682114 x1 Bgd=1 3-JUL-96 14:18+0:01:40 70-250 EI+
BpM=0 I=9.7v Xm=0 TIC=190271008 Acnt: Sys:LRP HMR: 63773000
RUN NO.1783 PT= 0° Cal:CAL1405 MASS: 213



114a
4-Trifluoromethyl-1, 2-dihydroquinolin-2-one

SPECTRUM NO. 80



11a
4-Trifluoromethyl-1, 2-dihydroquinolin-2-one

SPECTRUM NO. 81

RECRYST.

PPM

8.52282
8.46779
8.32543

7.50445
7.49349
7.46904
7.41777
7.39928
7.38356
7.35474
7.22418
7.20908
7.20554
7.18098
7.17250
7.15606
7.13770

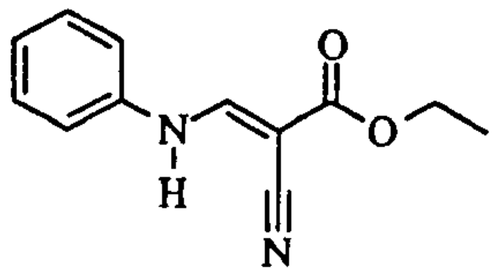
4.27868
4.25029
4.23244
4.18564
4.16824
4.13994

3.35444

2.52023
2.51328
2.50612
2.49844
2.49190

1.30087
1.23251
1.14434
1.12596

0.01233
0.00048
-0.01346



12a
Ethyl (*E*)-2-cyano-3-(*N*-phenyl-amino)prop-2-enoate

INTEGRAL

5.653
29.161
11.650
16.422
6.206
17.106
6.475

9.0
8.0
7.0
6.0
5.0
4.0

BRUKER

JL310S.221
AU PROG:
X00.AU
DATE 3-8-96
TIME 2:07

SOLVENT DMSO
SF 250.134
SY 100.0
O1 5540.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305

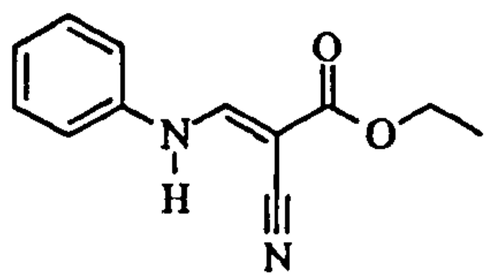
PW 0.0
RD 0.0
AQ 3.277
RG 40
NS 96
TE 297

O2 0.0
DP 63L PO

LB .300
CX 35.00
CY 18.00
F1 9.601P
F2 -.199P
HZ/CM 71.463
PPM/CM .286
SR 4035.48

SPECTRUM NO. 82

RECRYST. [WITH D2O]



12ja
Ethyl (*E*)-2-cyano-3-(*N*-phenyl-amino)prop-2-enoate

BRUKER

AUG50S.141
AU PROG:
X00.AU
DATE 6-8-96
TIME 4:59

SOLVENT DMSO
SF 250.134
SY 100.0
O1 5540.000
SI 32768
TD 32768
SW 5000.000
HZ/PT .305

PW 0.0
RD 0.0
AQ 3.277
RG 20
NS 96
TE 297

O2 0.0
DP 63L PO

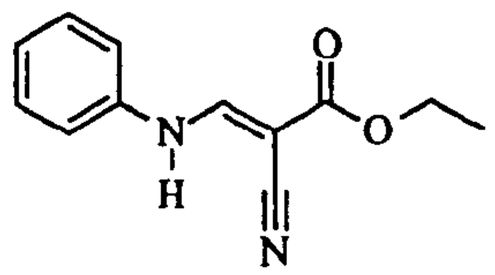
LB .200
CX 35.00
CY 18.00
F1 9.801P
F2 -.199P
HZ/CM 71.463
PPM/CM .286
SR 4027.24

SPECTRUM NO. 83.

RECRYST.

PPM

166.253
164.535
153.399
153.169
152.952
139.660
138.656
129.434
125.062
124.785
117.917
117.769
115.794
79.881
74.404
73.410
60.382
60.248
40.439
40.705
40.472
39.772
39.438
39.104
38.770
38.436
14.236
14.138
.001



12ɥa
Ethyl (*E*)-2-cyano-3-(*N*-phenyl-amino)prop-2-enoate

BRUKER

JL311S.221
AU PROG:
X02.AU
DATE 3-8-96
TIME 3:02

SOLVENT DMSO
SF 62.896
SY 62.0
O1 2596.000
SI 65536
TD 65536
SW 15625.000
HZ/PT .477

PW 0.0
RD 0.0
AQ 2.097
RG 640
NS 1000
TE 297

O2 5270.000
DP 18L D0

LB 1.000
CX 35.00
CY 18.00
F1 210.010P
F2 -4.989P
HZ/CM 386.361
PPM/CM 6.143
SR -3711.13

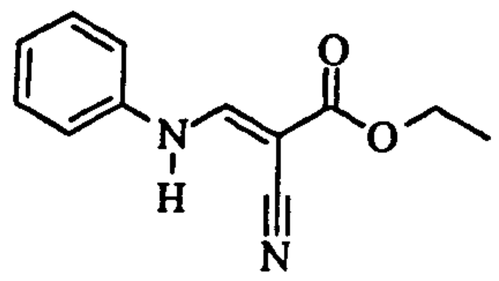
200 180 160 140 120 100 80 60 40 20 0

SPECTRUM NO. 84

RECRYST.

PPM

154.533
153.399
152.368
139.661
138.655
129.434
125.060
124.761
117.810
117.768
115.791
79.739
74.405
73.411
60.381
60.247
40.439
40.105
39.773
39.441
39.104
38.770
38.437
14.233
14.136
-.001



124a
Ethyl (*E*)-2-cyano-3-(*N*-phenyl-amino)prop-2-enoate

200 180 160 140 120 100 80

BRUKER

JL312S.221
AU PROG:
X02.AU
DATE 3-8-96
TIME 3:56

SOLVENT DMSO
SF 62.896
SY 62.0
O1 2596.000
SI 65536
TD 65536
SW 15625.000
HZ/PT .477

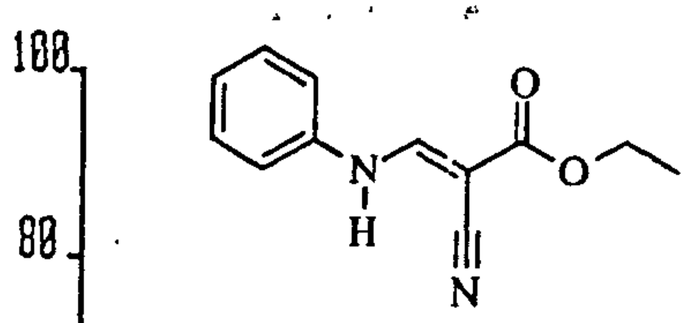
PW 0.0
RD 0.0
AQ 2.097
RG 800
NS 1000
TE 297

O2 5270.000
DP 18L D0

LB 1.000
CX 35.00
CY 6.50
F1 210.010P
F2 -4.989P
HZ/CM 386.361
PPM/CM 6.143
SR -3711.13

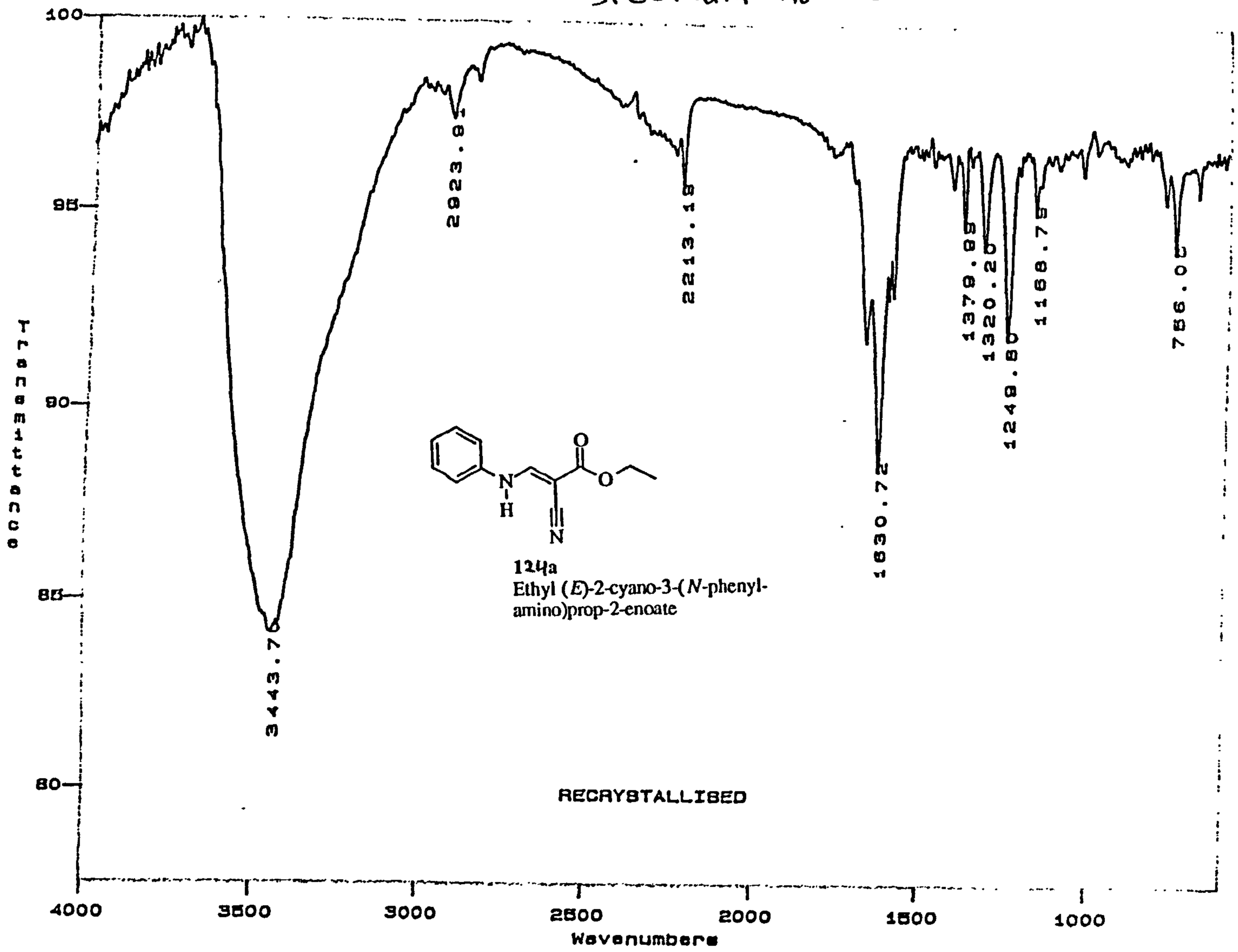
SPECTRUM NO. 85

RES858#9 x1 Bgd=1 29-AUG-96 13:12+0:01:09 70-250 EI+
BpM=0 I=5.3v Hm=0 TIC=220986000 Acnt: Sys:LRP
RUN NO.2018 PT= 0° Cal:CAL2908
HMR: 347
MASS:



124a
Ethyl (*E*)-2-cyano-3-(*N*-phenyl-amino)prop-2-enoate

SPECTRUM NO. 86.



124a
Ethyl (*E*)-2-cyano-3-(*N*-phenyl-amino)prop-2-enoate