AN INVESTIGATION OF REACTIONS DIRECTED TOWARDS THE SYNTHESIS OF 2-METHYL-2-(METHYLTHIO)PROPANAL OXIME

THESIS

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by

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Dedicated to my parents

Abstract

The processes leading to the formation of 2-methyl-2-(methylthio)propanal oxime, known industrially as aldicarb oxime, have been studied. The three stages of the synthesis, *viz.*, chlorination, thiomethylation and oximation have been thoroughly investigated, with the aim of optimising the yield and purity of aldicarb oxime. Attention has been focused on the chlorination step, and the effects of altering various conditions have been determined; the reaction has been carried out in the absence and presence of heat, solvent and buffer, and the extent of chlorine addition has also been varied. These studies have led to some improvement in the yield for this step.

Several simple and inexpensive methods for purifying contaminated batches of aldicarb oxime have also been examined. Possible aldicarb oxime contaminants, identified by GLC and GC-MS analysis, have been synthesised for use as chromatographic and spectroscopic standards, and confirmation of the presence of a number of these contaminants has been achieved.

Aldehyde trimers have been found to be the primary contaminants present in aldicarb oxime and the thermal stability of these trimers, their corresponding monomers and aldicarb oxime itself has been studied using variable temperature ^{1}H NMR spectroscopy.

Novel pyridine derivatives, with potential as aldicarb analogues, have been synthesised and characterised using spectroscopic methods.

Contents

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1. Introduction

1.1 Synthetic pesticides - a survey

1.1.1 Historical overview of pesticides

A 'pesticide' or economic poison, is defined under the United States Federal Insecticide, Fungicide and Rodenticide Act of 1947 as 'any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any insects, rodents, nematodes, fungi, or weeds, or any other forms of life declared to be pests; and any substance or mixture of substances intended for use as a plant regulator, defoliator or desiccant.[1] A pest is defined as 'forms of plant and animal life and viruses when they exist under circumstances that make them injurious to plants, man, domestic animals, other useful vertebrates, useful invertebrates or other articles or substances'.[2]

The need to control pests has been necessary ever since the development of agriculture approximately 10 000 years ago. With this development came the establishment of permanent homes and the need to store food. Early pest control methods were based largely on superstition and mysticism, and successful methods arose as a result of trial and error. As early as 2500 B.C. the Sumarians were using sulphur to control mites and insects[3] and Homer noted its use as a fumigant in 950 B.C.[4] The Chinese were culturing silkworms as early as 4700 B.C. and they realised the importance of pest control long before the West. They used wood ash and chalk for the control and prevention of indoor pests and pests encountered during storage, and mercury and arsenic compounds to control such pests as body lice.[5]

However, pest control methods in Europe failed to advance much until the Renaissance and the subsequent agricultural revolution. They still relied very heavily on religion and superstition. An example of this is illustrated by the treatment of cutworms in Berne, Switzerland in 1476. The cutworms were taken to court,

pronounced guilty, excommunicated by the archbishop and then banished![5] Discoveries in the 17th century about the origin of pests and the nature of their life cycles was the beginning of true pest control. Botanical insecticides such as derris, pyrethrin and nicotine were introduced or rediscovered in Europe around this time. In the mid to late 18th century agriculture became more commercial; crops were grown in rows, crop rotation was practised and manure was used. The first pest control literature began to appear in the early 1800's. However, the largest single cause of crop disaster was weather induced, either directly through, for example, droughts and floods, or indirectly through diseases such as scab or rust which favour high humidity. Perhaps, the worst agricultural disaster recorded was the Irish Potato Famine of 1845-1849.[4] The entire potato crop was destroyed, literally overnight, by a fungal disease, leading to the death of over 1 million people.

Advances in pest control in the latter part of the last century and the beginning of this century were slow, although entomology was advancing rapidly. The role of insect vectors in diseases such as malaria, the plague, typhoid fever and yellow fever was discovered and it was realised that the spread of disease could be limited by controlling these insects.[5] Good farming methods such as weeding, fertilisation, crop rotation and planting at times when pest outbreaks could be avoided were thought to be the key to pest control. It was only in the 1930's that the modern era of chemical control by synthetic organic compounds slowly began with the introduction of compounds such as the thiocyanates, dinocap, methyl bromide and napthalene.[6]

Research on the development of new pesticides became a top priority as a result of pressures introduced by the outbreak of World War II. As much of the war took place in the tropics, vector-borne diseases such as malaria, typhus, dengue and sleeping sickness were a threat to the war efforts of both sides. The contribution made by compounds such as DDT and organophosphates, *e.g.* parathion, to the outcome of the war should not be underestimated.[7,8]

The industry has shown explosive growth since then, and it is predicted that this will continue. However, the use of chemicals for pest control has disadvantages as will be

discussed, and the trend is now towards integrated pest control, whereby many methods are combined so as to cause as little disruption to ecosystems and the environment as possible. These methods include good agricultural practices, genetic manipulation, and the use of pheromones, insect pathogens and selective insecticides.[9]

1.1.2 Factors influencing pesticide choice

Pesticides fall into three major classes based on their target species,[10,11] *viz.*,; i) insecticides for killing insects; ii) fungicides for destroying fungi; and iii) herbicides for killing weeds. There are also minor classes such as acaricides for killing ticks, defoliants for removing unwanted plant leaves, desiccants for dealing with unwanted plant tops, and nematicides and rodenticides for dealing with nematodes and rodents respectively. Overlap between classes can occur.

Pesticides may also be placed in three general classes on the basis of their mode of action: - stomach poisons (systemic); contact poisons (non-systemic); and fumigants. Many pesticides fall into more than one class.[12]

The earliest pesticides were mostly contact poisons, discovered by trial and error. Such poisons do not penetrate plant tissues, and are thus not translocated within the plant. They may provide protection against infection for the plant, but once the fungus is established, they cannot destroy it. As they do not penetrate the plant, any new growth is left unprotected. They are applied to the surface, and remain there for a few days or weeks to carry out their action. Their decomposition is dependant on: the nature of the pesticide, the weather conditions and temperature, the light intensity and the application surface type.[13]

Most modern pesticides, however, are systemic. After application, they penetrate into the tissue of the plant, dissolve in the sap and are translocated by the plant's vascular system thus killing sap sucking insects and fungi. As most systemic pesticides can

only flow upwards, they must be applied to healthy plants that are unaffected by drought conditions or physical abnormalities, which might affect sap flow.[14] Moreover, there is a danger of the host plant being affected, so care must be taken to ensure that the pesticide used exhibits selective toxicity.

The selectivity of a pesticide, (meaning that a susceptible insect is killed and a tolerant one is saved) arises from one of five factors:[15]

1. A susceptible insect may be brought into contact with the pesticide because of a behavioural pattern that an unsusceptible insect does not possess. For example, insects that do not feed on plants will be unaffected by systemic pesticides.
2. A tolerant insect may come into contact with the pesticide, but may not take it up as rapidly or efficiently as a susceptible insect.
3. The pesticide may be taken up by a tolerant insect, but instead of being transported to the site of action, ends up being in regions where it is harmless.
4. A tolerant insect may have a method of rendering the pesticide harmless by appropriate metabolism, or by being unable to convert it from an inactive to an active form.
5. A tolerant insect may not possess a site of action that is affected by the pesticide.

1.1.3 Pesticide Toxicity

When the toxicity of pesticides is considered, it must be borne in mind that any substance, even sodium chloride, can be toxic if it is absorbed in excessive amounts [*e.g.* 3320 milligrams per kilogram body mass (mg/kg) for sodium chloride].[16] Pesticide dose ranges are generally of the order 0.1-25 mg/kg.[17] A broad knowledge of both the toxicity of the chemical and the hazards associated with exposure are essential for pesticide users. 'Hazard' is the probability that injury will result from the use of the chemical. It is a function of the toxicity of the pesticide, the concentration, the formulation and the amount of exposure.[18] 'Toxicity' is the inherent ability of the chemical to produce injury or death. It is measured by oral, dermal and inhalation studies on test organisms.[18] A compound can be extremely toxic in its concentrated

form, but when diluted in a formulation that does not penetrate the skin easily and used by experienced applicators with the correct equipment, it can pose very little hazard. Relative toxicity varies, depending on the age, sex and nutritional state of the potential victim, and the formulation of the pesticide.[19]

The toxicity value of a compound would probably be best expressed as a human toxicity rating, but since it is not possible to obtain ratings based on human exposures, most toxicity ratings are based on animal exposures. Toxicity is usually expressed as an LD_{50} value.[20] This represents the dose that is lethal to 50% of the test population. There should be at least 10 animals in the test, and rats and mice, or sometimes rabbits, are generally used. The LD_{50} is expressed as mg/kg body weight of the animal. Exposure of the animal can be oral (in the food), dermal or intravenous. The smaller the LD_{50} the more toxic the chemical. Dermal values are often less than oral values, while intravenous values are often higher. LD_{50} values are only expressed in terms of a single dosage, and thus give little information regarding possible cumulative effects of the chemical. Organochlorine compounds accumulate to toxic amounts in the body with repeated exposure to small amounts. Organophosphorus compounds condition the body upon repeated intake of small doses, so that later exposure, even to a very small dose, can cause acute poisoning. Toxicities can also be expressed as LC_{50} values which represent the toxicity of a compound present in the air as a dust, mist, gas or vapour. It is generally expressed as μg/L, or ppm in the case of a gas or vapour.[20] Toxicities can be graded as shown in Table 1.[20,21]

Table 1 Toxicity Ratings of Pesticides

Classification	**Labelling**	**Oral LD_{50} (mg/kg)**	**Dermal LD_{50} (mg/kg)**	**Inhalation LC_{50} (µg/l)**
Highly hazardous	POISON, EXTREMELY TOXIC	0-50	0-200	0-2 000
Moderately hazardous	POISONOUS	50-500	200-2 000	2 000-20 000
Slightly hazardous	CAUTION	500-5 000	2 000-20 000	over 20 000
Relatively non-hazardous	no marking	over 5 000	over 20 000	-

Toxicity is most singularly influenced by dosage. Almost all of the safety measures regarding the use of pesticides are aimed at reducing the dosage absorbed by anyone coming in contact with the pesticide. Exposure does not always occur during actual use, but is often due to poor storage, incorrect labelling, failure to recognise toxicity and the use of empty pesticides containers for food and drink. These are problems often exacerbated by illiteracy. The route of exposure is also important. On a hot day, volatilisation of the pesticide may be rapid, and the resulting increase in concentration of the compound in the air may lead to poisoning by inhalation or absorption through the skin. Absorption through the skin is the most common route of poisoning thus care must be taken to ensure that the correct protective clothing is worn.[22] This usually includes: - overalls covering the entire body, or a waterproof rainsuit if the pesticide is to be applied as a mist; a hat, preferably a waterproof one that offers neck protection as well; gloves, either natural rubber or polyethylene in cases where the pesticide causes the rubber to disintergrate; waterproof footgear, preferably rubber boots; eye protection, a full face shield or even a respirator mask if indicated on the pesticide label. All protective clothing should be thoroughly washed after each use.[22,23] Limiting exposure to 5 hours daily, and 5 days weekly is an

important factor in reducing the cumulative effects of overdosage, especially of those pesticides having a narrow safety margin.[23]

For a pesticide to be acceptable for use, it must satisfy two safety criteria:[23]

1. The concentration required for pest control must not be hazardous to the operator. The safety margin must be high to allow for differing field conditions and different levels of operator efficiency.
2. Any effects of absorption experienced during one day's application must be toxicologically insignificant at the beginning of the following day's operation.

Even a small amount of impurity in a pesticide, especially an organophosphorus compound, can influence its biological activity. Impurities are either introduced during manufacture, or form during storage as a result of interaction between the active ingredients and the diluents. As pesticide patents expire, they may be manufactured by companies with little experience in pesticide formulation, with a resultant increase in toxic impurities.[23]

Modern synthetic organic pesticides are developed through collaboration between organic chemists and biologists. Potential candidates are scanned for pesticidal activity at concentrations of 500 ppm, then at increasingly lower concentrations down to about 10 ppm. Compounds showing promise are then subjected to further stringent testing, the compound in question being tested against a range of economically important insects, a range of plant pathogenic fungi, a range of weeds and other pests such as slugs, rats and mites.[24] Once the compound has shown promise, a range of structural analogues are designed, both in an effort to enhance activity and to find out as much as possible about the mode of action. Generally, only one chemical in ten-thousand tested is finally marketed as a pesticide.[25] The development of pesticides has been characterised by an increase in potency, targeted mainly at the neurotransmitters, although other areas of particular interest are the processes of growth and development and hormone-mediated processes. The increase in potency is illustrated in Figure 1.[26]

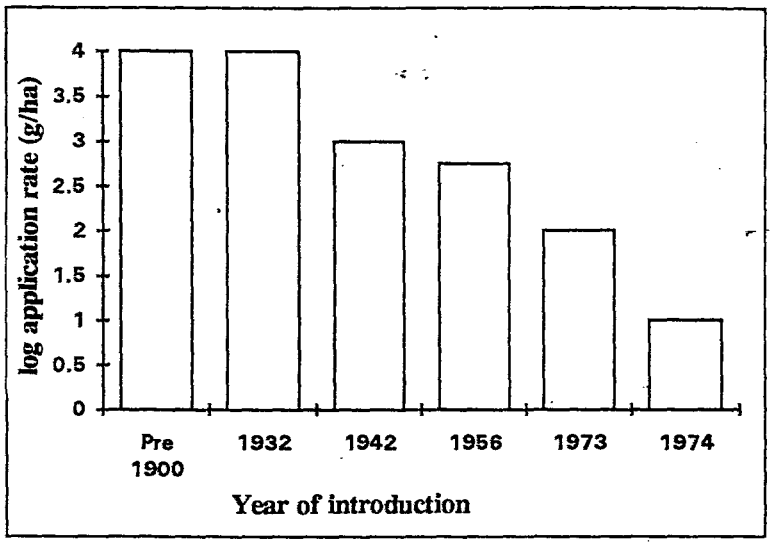


Figure 1 Increase in potency of commercial pesticides

1.1.4 Formulation of Commercial Pesticides

The optimum performance of a pesticide depends largely on the formulation. Formulation involves conversion of the highly concentrated pesticidal active ingredient into a convenient-to-use product, usually packaged at application concentrations for the end user in a form that can easily be handled by the application machinery.[27] In some cases, use of a pesticide 'precursor' that is more stable and physicochemically better suited for delivery to the site of action may be advantageous. This precursor is then chemically or metabolically altered to deliver the active ingredient over the required timespan. An example is metham-sodium, which is used in soil fumigation. It is applied as an aqueous solution which allows greater initial penetration and slower release of the volatile active compound, methyl isothiocyanate, thus ensuring that it remains in the soil for longer (see Figure 2).[28]

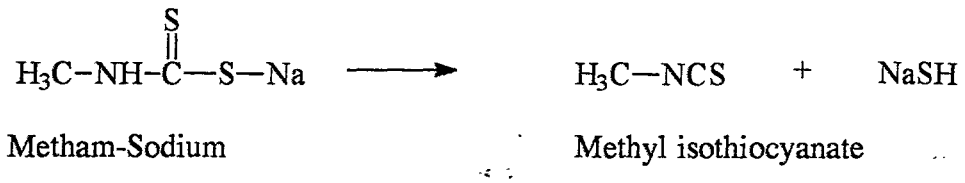


Figure 2 Use of Pesticide Precursors

Formulation generally involves: - i) blending, whereby the active ingredients are mixed with inert ingredients; ii) particle size reduction procedures such as milling; and iii) coating operations, if seeds and granules are involved.[23] Formulation is a means of stabilising the active ingredient and minimising the hazards associated with its use. A single pesticide is often available in many different formulations. The insecticide, Diazinon, for example, is available as 25 or 48% emulsifiable concentrates, a 4% dust, 25 or 50% wettable powders and 5, 10 or 14% granules.[29] Factors influencing choice of formulation are: - the habits of the pest; the effectiveness of the pesticide against the pest; the nature of the application surface (plant, animal or inanimate); the application machinery; and the dangers of drift or runoff.[30]

There are three types of formulation: solvent-based; water-based and solid-based.[27,30] In a solvent-based formulation, either a solvent or a solvent-water emulsion serve as a carrier medium for the active ingredient; a water-based formulation may be a suspension or an emulsion. Both solvent- and water-based formulations may be applied directly either as liquids, or as aerosols. To prepare a solid-based formulation, the active ingredient is blended with or adsorbed onto an inert carrier, such as sand or clay. Common solid-based formulations are wettable powders, dusts, granules and pellets. Encapsulated, granular and other slow release formulations minimise hazards associated with the pesticide.

As indicated below, various formulation and preparation materials may be used.
For **dry formulations**, sulphur, silicon oxide, lime, gypsum, talc, prophyllite, kaolins, attapulgite and volcanic ash are used. **Liquid formulations** invlove solvents

such as xylenes, kerosenes, methyl isobutyl ketone, amyl acetate, and chlorinated solvents; propellants such as carbon dioxide and nitrogen; and also wetting and dispersing agents, deodorants, masking agents and emulsifiers.[27]

Adjuvants are also often added to improve the efficiency of the pesticide. An adjuvant is defined as 'a substance added to a prescription to aid the operation of the main ingredient'.[31] Adjuvants, which usually comprise solvents or co-solvents, surfactants, solubilisers, buffering agents and film formers, enhance activity, prolong action and improve the physical characteristics of the pesticide.[31]

Chemical pesticides appear to have provided a highly successful method of pest control, but because of their success and widespread use, a number of problems have arisen. These include:[8] - i) the possibility of the pest developing resistance to the pesticide; ii) poor selectivity; iii) the development of secondary pest problems; iv) their often transient efficacy, necessitating repeated applications; v) their performance may be weather dependent.; and vi) unwanted persistance leading to environmental pollution, as was pointed out as early as 1963 in Rachel Carson's controversial book 'Silent Spring'.[32] The future success of using chemicals can only be assessed by considering all the advantages and disadvantages associated with their use. Advantages include the following:[8] - i) in the absence of resistance, they are highly effective in reducing pest populations to very low levels; ii) they exhibit rapid and effective action; iii) they are readily available; and iv) they are easy to apply.

1.1.5 Classification of pesticides

1.1.5.1 Miscellaneous pesticides

1.1.5.1.1 Inorganic Compounds

The earliest pesticides were mainly inorganic. Compounds containing arsenic, lead, calcium, barium and mercury were the principal insecticides, while sulphur and copper were used for their fungicidal action.[33] Paris Green, a copper aceto-arsenate, of approximate composition $Cu_4(CH_3CO_2)_2(AsO_2)_2$, was used successfully in the United States to control the Colorado beetle on potatoes as early as 1867. This insecticide kills leaf-eating insects and its selectivity depends on the feeding habits of the insect and the placement of the poison.[34,35] The three forms in which arsenic compounds were available, *viz.*, calcium arsenate, Paris Green and lead arsenate, offer little choice in selectivity; they are generally non-systemic poisons and their differences are largely based on the solubility, stability, and physical qualities of the compound.[33] The general use of arsenicals has declined greatly because of the dangers, both environmental and toxicological, associated with their use. Lead arsenate, however, is still used to a limited extent because of its action against the codling moth.[36]

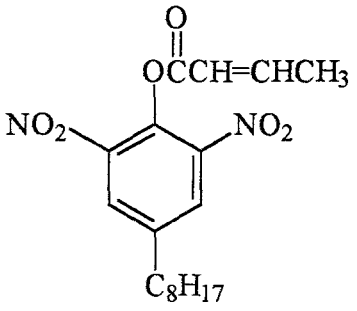
The toxicological action of sodium fluoride against insects has been known since 1842. It is used in bait against cockroaches, ants and earwigs. However, because of its solubility, it is limited to indoor use. Sodium hexafluorosilicate (Na_2SiF_6) and native cryolite (Na_3AlF_6) are generally preferred because of their greater insolubility and persistance.[36]

Borax is still widely used to kill cockroaches which are very suspicious insects and are repelled by most insecticides and formulations. Thus, although borax is not as toxic as many other modern chemicals (based on an LD_{50} rating), it is often used because it is one of the few insecticides of which they are not suspicious.[35,36]

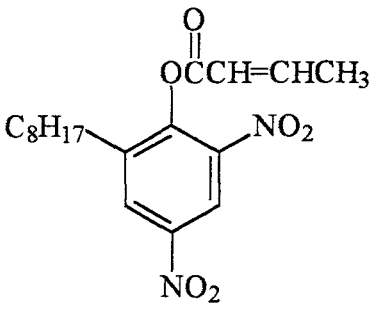
1.1.5.1.2 Dinitrophenols

Substituted dinitrophenols and their derivatives have been widely used as herbicides, fungicides and insecticides. They were first used in France in 1933 with the introduction of 2-methyl-4,6-dinitrophenol (DNOC) as a selective herbicide in cereals.[37] It is highly explosive, extremely toxic (oral LD_{50} for rats 25 mg/kg[38]) and very easily absorbed through the skin. Consequently its use and that of related compounds has been limited.

It has been found that, while 2,4-dinitro-6-alkylphenol derivatives are acaricidal, 2,6-dinitro-4-alkylphenol derivatives tend to be fungicidal. A 70:30 mixture of 2,6-dinitro-4-octylphenyl crotonate (dinocap-4) and 2,4-dinitro-6-octylphenyl crotonate (dinocap-6) has been used to control powdery mildews.[39]



Dinocap-4



Dinocap-6

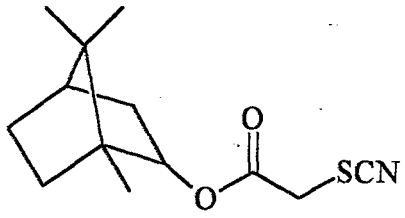
1.1.5.1.3 Thiocyanates

Thiocyanates were first used in the early 1930's and are obtained by the action of sodium thiocyanate on an alkyl halide. They are all insecticidal and have the general formula R-S-CN.[40] They all show rapid 'knockdown action', and are also ovicidal against a number of insect eggs. Their action is thought to be partly due to *in vivo* liberation of the cyanide ion inside the insect's body. However, the rapid knockdown is a result of other factors. The use of thiocyanates was not fully exploited because

they were overshadowed by the dramatic success of organochlorine compounds. In any event, their potential is limited because they cause skin irritation and also damage the leaves of many crops.[40,41,42]

Lethane was the first significant thiocyanate formulation. It was introduced in 1936 in the United States and comprises mainly a compound of molecular formula $C_4H_9OC_2H_4SCN$.

The only commercially successful thiocyanate, used at present, is thanite, a thiocyanic ester of isoborneol. It is used in sprays to control flies, bedbugs, and mosquitoes. Its use on foodstuffs, however, is prohibited in many countries.[40]



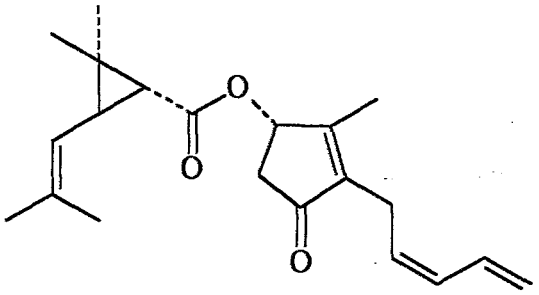
Thanite

1.1.5.2 Pyrethroids

The earliest reported use of pyrethroids is in 1851, when the insecticidal action of dried, powdered *Chrysanthemum roseum* and *Chrysanthemum carneum* flowers was noted by Koch.[43] Today, almost all natural pyrethrin extracts come from *Chrysanthemum cinerariaefolium.* The flowers are dried, and the pyrethrins extracted in organic solvents such as ethylene dichloride. Synergists, such as methylene-dioxyphenyl derivatives or piperonyl butoxide, are often added to increase the stability.

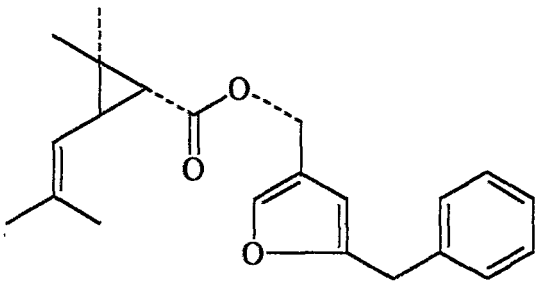
Naturally occuring pyrethrins, *e.g.* pyrethrin, have extremely rapid knockdown activity against a wide range of insects, and because of the ease with which they are

metabolised into non-toxic products, their mammalian toxicity is negligible. They decompose rapidly on exposure to air and light, thus their persistence is low. They are used for control of household and public health pests and also for treating expensive food crops prior to harvest. However, their instability, the relatively high cost involved in extraction, and the problems associated with ensuring a constant supply of plant material have limited their use, and stimulated the search for synthetic pyrethroids. Progress in the synthesis, however, has been slow due to their molecular and stereochemical complexity.

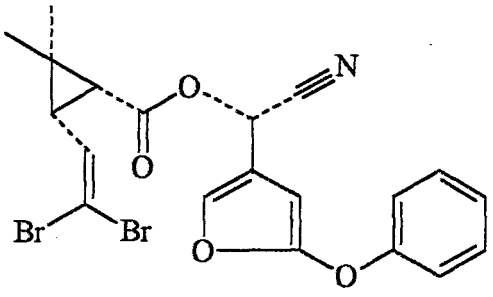


Pyrethrin 1

Bioresmethrin and resmethrin are interesting synthetic pyrethroids because they are more active than the naturally occuring compounds, but are even safer to humans. Bioresmethrin, for example, is 40 000 times less toxic for mammals (on a weight- for-weight basis) than it is for houseflies. Recently, a class of photostable synthetic pyrethroids with very high activity has been discovered. Deltamethrin, for example, is the most potent insecticide available against many insect species.



Bioresmethrin



Deltamethrin

Pyrethroid insecticides are highly lipophilic esters of alcohols and acids; at least two centres in the molecule must possess appropriate chirality for the molecule to be insecticidally active. Their volatility and aqueous solubility are low. They pose little environmental threat because of the ease with which they are metabolised by ester hydrolysis and oxidation.

It is thought that pyrethroids act on the nervous system, probably by disrupting axionic conduction.[43,44]

1.1.5.3 Organochlorine pesticides

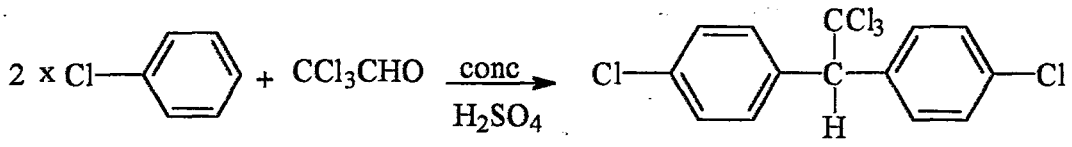
This class encompasses a wide range of compounds. It includes some of the best known pesticides as well as some which have given rise to the worst problems. It was once the most extensively used class, but is now rapidly losing importance, and has been overshadowed by other classes. Although the structures vary widely, they have several properties in common, in particular:[45] i) they all appear to affect axonal transmission in the insect nervous system; ii) they are relatively chemically inert; and iii) they are all lipophilic, which means that they can easily be absorbed by fatty tissues of organisms, and by the soil. Organochlorines are generally non-systemic in plants, and are mostly stomach and contact poisons. Because of their stability they are relatively persistent, which is a particular advantage in soil poisons. However it is this persistence, as well as their lipophilicity, that has brought about the environmental hazards associated with their use. There are three principal groups within this class:

1. DDT and related compounds
2. Cyclodienes
3. Lindane

1.1.5.3.1 DDT and related compounds

Although dichlorodiphenyltrichloroethane or DDT [1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane] was first synthesised in 1874 by Zeider,[41] it was not until 1939 that Dr Paul Müller of the Geigy company discovered its insecticidal action, for which he was awarded a Nobel Prize.[45] Compared to other pesticides available at the time, DDT was far superior because of its low mammalian toxicity (oral LD_{50} for rats 113-118 mg/kg),[46] high persistence, chemical and photochemical stability, low vapour pressure, potent action, ease of synthesis and handling, and low cost.[45]

DDT is prepared by the condensation of chloral and chlorobenzene in the presence of concentrated sulphuric acid (see Scheme 1).[47]



DDT

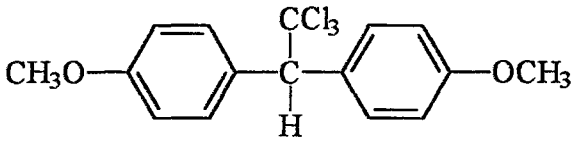
Scheme 1

The crude product contains, in addition to the desired 4,4′-compound (ca 80%), about 20% of the 2,4′-isomer, and trace amounts of the 2,2′-isomer. The melting point of the isomer mixture is not clearly defined. Technical grade DDT was described by the DDT Committee of the Manufacturing Chemists' Association of the United States as the product having a melting point above 88°C, and purified DDT as that product having a minimum melting point of 103°C.[48] Pure DDT can easily be obtained by recrystallisation from ethanol to give a white powder with m.p. 108°C.[41] DDT was introduced and manufactured as a pesticide in 1942, with production in the United States peaking at approximately 81.3 million kilograms in 1963.[49] However, with its extensive use, a number of problems emerged.[45,50] The first of these was resistance.

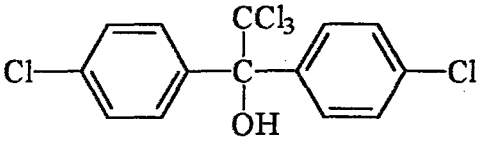
The first case, involving resistance to the house fly was reported in Sweden in 1946.[50] Within 20 years most major agricultural pests exhibited resistance. DDT also leads to secondary pest outbreaks. This occurs when the levels of a plant-feeding species, not previously a pest, suddenly surge to damaging levels because their natural enemies have been destroyed by the use of a pesticide. Related to this is the problem of target pest resurgence. Use of the pesticide is initially effective, but because it kills the pest, its predators and parasites are severely affected, and usually die from lack of food. Any pests surviving the pesticide now have no natural enemies to restrict their growth, and they surge to even higher levels.

Although DDT has been so widely used, little is known about its precise mode of action. It is thought to act on the nervous system, and its toxicity probably involves the transmission of nerve impulses by upsetting ion channels in nerve membranes.[41]

A number of DDT analogues have been prepared. The 4,4′ substitution appears to be related to the activity. The only commercially successful analogue made by varying the aromatic substituents is methoxychlor, which is more easily degraded and, unlike DDT, is not stored in body fat. Dicofol, an analogue in which the aliphatic portion is modified, is an effective, non-systemic acaricide which is used on a wide range of crops. It has weak insecticidal activity.[51,52]



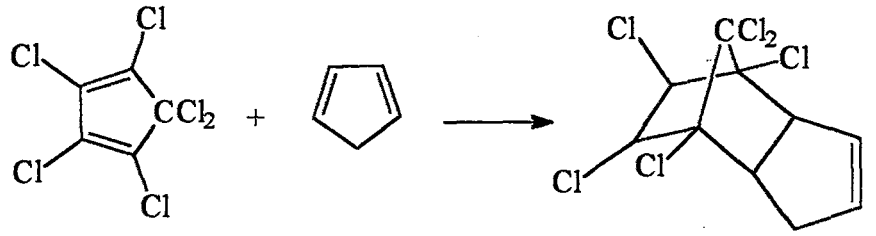
Methyoxychlor



Dicofol

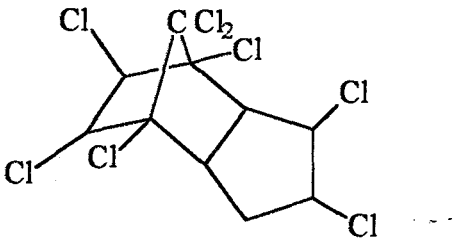
1.1.5.3.2 The cyclodienes

Cyclopentadiene derivatives constitute a class of highly reactive contact insecticides formed *via* Diels-Alder cycloaddition reactions of 1,1,2,3,4,5-hexachlorocyclopentadiene.[53] They were first synthesised in 1945, one of the earliest such compounds being chlordane.[53,54] The insecticidal properties of chlordane were described by Kearns *et al*. in 1946 [54] and its formation is shown in Scheme 2.[53]



1,1,2,3,4,5-hexachloro-cyclopentadiene

Chlordene



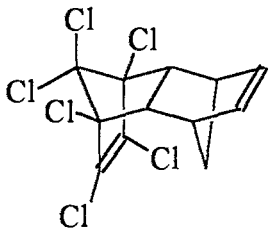
Chlordane

Scheme 2

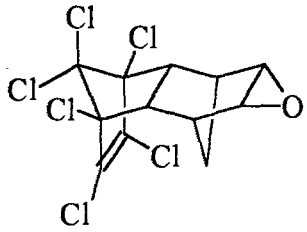
These compounds are potent contact and stomach poisons, and often also have fumigant action. They are very stable and have extreme persistence properties which, together with their lipophilicity, make them environmentally undesirable.

The stereochemistry of these compounds is complex. The most important members of the group contain four fused rings and are derived from 1,1,2,3,4,5-hexachlorocyclopentadiene. Two of the most significant of these compounds are dieldrin

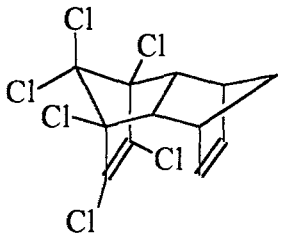
[(1*R*,4*S*,5*S*,8*R*)-1,2,3,4,10,10-hexachloro-1,4,4a,5,6,7,8,8a-octahydro-6,7-epoxy-1,4:5,8-dimethanonaphthalene], and aldrin [(1*R*,4*S*,5*S*,8*R*)-1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-1,4:5,8-dimethanonaphthalene] named after Diels and Alder respectively.[55] Their insecticidal action was first reported in 1949.[56] The reaction of cyclopentadiene with acetylene affords dicycloheptadiene. This is condensed with hexachlorocyclopentadiene to produce two isomers *viz.*, aldrin and isodrin. Epoxidation with hydrogen peroxide affords endrin from isodrin, and dieldrin from aldrin. Aldrin, dieldrin and endrin are active as general contact insecticides. They are highly lipophilic and are very good soil insecticides. The mammalian toxicity of these compounds is higher than that of DDT, their oral LD_{50} values for rats being 67, 46 and 17.5 mg/kg respectively.[57]



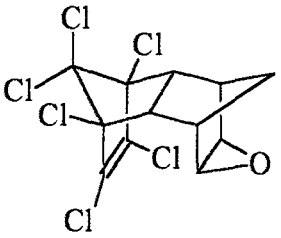
Aldrin



Dieldrin



Isodrin



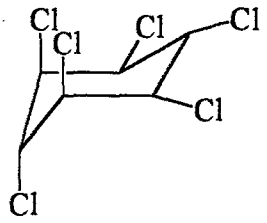
Endrin

As with DDT, not much is known about the precise mode of action of these compounds. Symptoms of exposure are consistent with nervous system poisoning. They are not widely used anymore for various reasons, *viz.*, their high toxicity, their easy absorption through the skin, their persistence in the environment, their indiscriminate action against beneficial insects as well as harmful ones, and their accumulation in body fats. They have, in fact, been withdrawn from use in most countries.[53]

1.1.5.3.3 Lindane

Lindane has very similar properties to DDT and was first synthesised by Michael Faraday in 1825.[58] It was developed as a pesticide shortly after DDT. It has been known at times as BHC (benzenehexachloride) and HCH (hexachlorocyclohexane). It is a stomach poison and contact insecticide with a wide spectrum of activity. It is more volatile than DDT and more water soluble than most organochlorines. As it is also more rapidly degraded it is less of an environmental hazard, and is very effective as a seed dressing against soil insect attack.

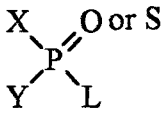
Hexachlorocyclohexane is manufactured by treating benzene with chlorine at low temperature in the absence of catalysts but in the presence of a mercury arc light. The reaction affords 1,2,3,4,5,6-hexachlorocyclohexane, with little contamination by the intermediate products. The crude product is crystalline and has a musty smell. There are several structural isomers but the gamma isomer having three adjacent axial and three adjacent equatorial chlorine atoms has 100-1 000 times more insecticidal activity than the other isomers, and accounts for almost all the activity in the crude hexachlorocyclohexane mixture. The purified form of γ-HCH is known as lindane. The oral LD_{50} of lindane for rats is 88-91 mg/kg.[59] This insecticide is thought to act by disrupting axionic conduction in the nervous system.[58,59]



Lindane

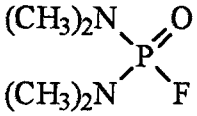
1.1.5.4 Organophosphorus pesticides

Organophosphorus compounds form a large, well-recognised class. They are easy to synthesise and many thousands exist, with over 100 in regular use as pesticides.[60] They exhibit a wide range of activities, and there is a suitable compound for almost every pest problem. A great deal of research continues to be focused on this area, and more is known about their mode of action and structure-activity relationships than almost any other pesticide class. The class is chemically very well defined, with all active compounds having the following general structure,

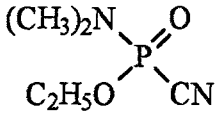


in which X and Y are usually alkyl or alkoxy (especially methyl, ethyl, methoxy or ethoxy) or, sometimes, alkylamino groups, while substituent L is usually an acidic moiety and is sometimes referred to as the leaving group because it is much less strongly bonded to the phosphorus than X or Y and is easily cleaved by alkaline hydrolysis. The co-ordinate bond to oxygen (or sulphur) satisfies the valency of the central phosphorus.[60]

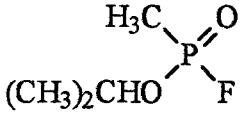
The earliest investigations into organophosphorus compounds were during the second World War, when their potential as nerve gases was realised. Some of the first compounds used were tetramethylphosphorodiamide fluoride (dimefox) which is still used as a systemic insecticide, and the highly toxic nerve gases tabun and sarin, which are no longer used because of their toxicity.[61]



Dimefox



Tabun



Sarin

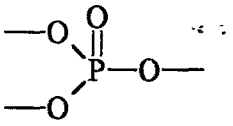
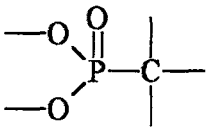
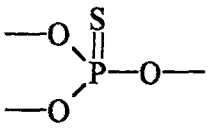
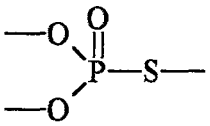
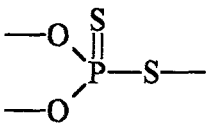
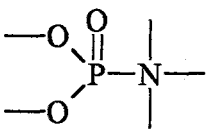
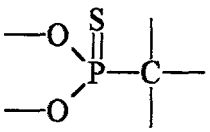
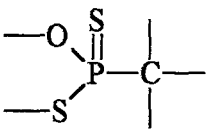
The nature of the substituents determines which type of reactions, *viz.*, hydrolysis, oxidation or isomerism, these compounds will undergo, and thus influences their biological activity and persistence. Hydrolysis can occur chemically or enzymatically and the rate is influenced by the electrophilicity of the substituents. P=O compounds are more readily hydrolysed than P=S compounds. Enzymatic hydrolysis may result in compounds that are less biologically active than the parent compound. Hydrolysis is thus is an important detoxification reaction in living organisms. Isomerism occurs readily, especially the conversion of a P=S (thiono) compound to a P=O (thiolo) one, *e.g.* the conversion of parathion to *S*-ethyl parathion as shown below.

Parathion *S*-Ethyl Parathion

This affords a compound which is more susceptible to hydrolysis and a more active acetylcholinesterase inhibitor. The greater electronegativity of oxygen relative to sulphur means that the phosphorus becomes more electron deficient, and, hence, more susceptible to nucleophilic attack. This isomerism is slow at room temperature, but in the organism it may be enzyme catalysed, resulting in a more lethal compound. This is known as 'lethal synthesis'.[60,61]

Organophosphorus compounds act by inhibiting acetylcholinesterase, an important enzyme responsible for hydrolysing acetylcholine, the principal compound in conduction of nerve impulses across a synapse.[60,61] The broad classes of organophosphorus compounds are summarised in Table 2.[62]

Table 2 Classification of Organophosphorus Pesticides

Class	Structure	Example
Phosphates		dichlorvos
Phosphonates		butonate
Phosphorothionates		cyanophos
Phosphorothiolate		omethoate
Phosphorothiolothionate		methidathion
Phosphoroamidate		phosfolan
Phosphonothionate		cyanofenphos
Phosphonothiolothionate		mecarphon

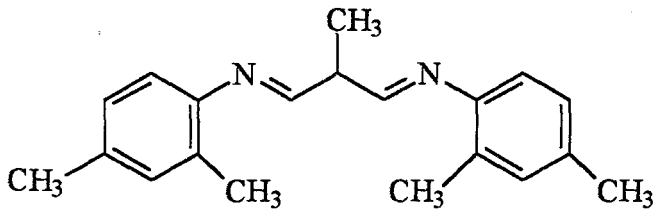
1.1.5.5 Formamidine derivatives

Several compounds belonging to the chemical class of formamidines (derivatives of $NH{=}CHNH_2$) have been found to exhibit interesting insecticidal and acaricidal activity.[63,64]

Formamidines seem to be more effective at controlling insects rather than exhibiting direct lethal action. They induce behavioural effects at much lower doses than are required for killing, *e.g.*, the lethal dose for an adult cockroach is 700 mg/kg, whereas only 0.5 mg/kg can affect it. These effects include disruption of locomotor activity, greater excitability at each stage of insect growth and even death, usually from disruption of feeding or reproduction cycles.

They appear to have two modes of action, *viz.*, disruption of membrane ion channels and induction of agonistic effects at octopamine junctions by blocking octopamine receptors.[63,64]

Amitraz is a formamidine used in the control of the eggs and larvae of several insect pests and also against animal ectoparasites. It has an oral LD_{50} for rats of 800 mg/kg.[65]

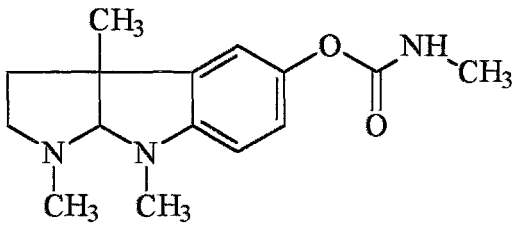


Amitraz

1.1.5.6 Carbamates

The success of the organophosphorus compounds stimulated the search for other organic compounds possessing acetylcholinesterase inhibition activity. One naturally

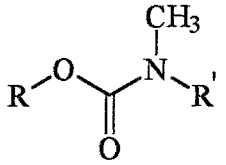
occuring compound, physostigmine, present in the calabar bean, was known to owe its physiological activity to the presence of the phenylmethylcarbamate moiety.[66]



Physostigmine

Physostigmine has a low toxicity to insects because of its high degree of ionisation at pH 7, which makes penetration of the insect cuticle difficult. The development of insecticidal carbamates originated from attempts to attach a lipophilic group to the *N*-methyl moiety, thus conferring sufficient stability to the molecule without decreasing its affinity for the enzyme. The earliest studies on the insecticidal properties of carbamates were carried out in 1954[67] but, although thousands of carbamates were screened, only about 20 of these are marketed commercially as pesticides. The earliest carbamate pesticides were introduced in 1956.[68]

Substituent and stereochemical effects appear to have a greater effect on the insecticidal activity of carbamates than is the case for organophosphorus compounds. The active carbamates have the general structure shown below. These compounds have low lipid solubility and are unable to penetrate the sheath surrounding the insect



R = Carbocyclic group, heterocyclic group or oxime derivative

R′ = H,CH_3

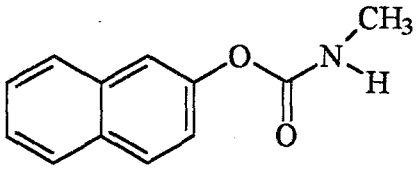
nervous system. Carbamates, like organophosphorus pesticides, act by inhibiting acetylcholinesterase but, whereas organophosphorus compounds phosphorylate the enzyme, carbamates appear to compete with acetylcholine for active sites.[69] Carbamates are also susceptible to hydrolysis which, in theory, can involve either ester or amide hydrolysis. It appears that the ester is the more vulnerable moiety.

There are three subgroups in this class:[70]

1. aryl methyl carbamates
2. heterocyclic monomethyl and dimethyl carbamates
3. *N*-methyl carbamate derivatives of oximes

1.1.5.6.1 Aryl methyl carbamates

An example of this class is carbaryl which is probably the most widely used carbamate pesticide. It is a contact pesticide with a broad spectrum of activity as an insecticide and a nematicide. It has an oral LD_{50} for rats of 850 mg/kg[71] which is large relative to other carbamates. It is often used as a DDT substitute because it biodegrades and does not accumulate in food chains. Consequently, it is less of an environmental hazard than DDT. Other members of this group are propoxur and methiocarb.[70]

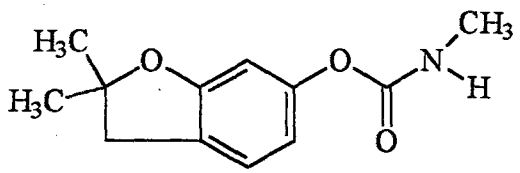


Carbaryl

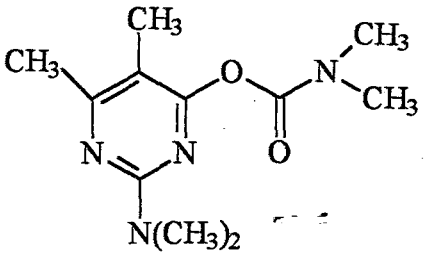
1.1.5.6.2 Heterocyclic monomethyl and dimethyl carbamates

These were the first useful carbamates. The two best known members of this class are carbofuran (a monomethyl carbamate) and pirimicarb (a dimethyl carbamate). Carbofuran is primarily an insecticide, with an oral LD_{50} for rats of 8-14 mg/kg.[72] Pirimicarb is one of the few insecticidal *N*-dimethylcarbamates. It is a fast acting

aphicide and is a contact pesticide as well as a fumigant; it has an oral LD_{50} for rats of about 147 mg/kg.[73]



Carbofuran

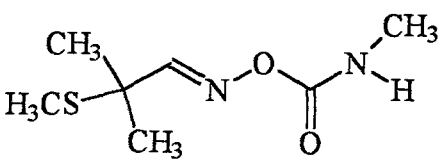


Pirimicarb

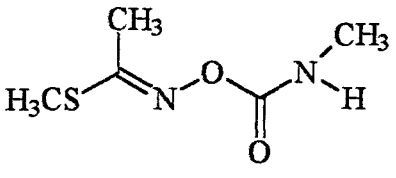
In neither of these subgroups (aryl methyl carbamates and heterocyclic mono-and dimethyl carbamates) can the activity be attributed to structural analogy with acetylcholine. The ring structure, however, seems to be important, conferring a number of properties on the molecule which facilitate insecticidal activity. These properties include sufficient lipophilicity to penetrate the insect membrane, stability in the haemolymph, ability to fit onto the enzyme, and an adequate rate of carbamylation of the enzyme.[70]

1.1.5.6.3 N-*Methyl carbamate derivatives of oximes*

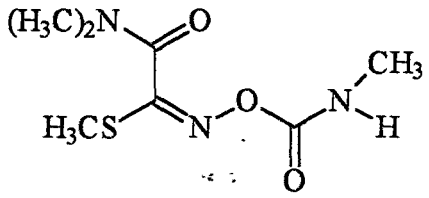
Members of this group best represent attempts to design compounds that both resemble acetylcholine and are also sufficiently lipophilic to be able to penetrate their site of action in the insect. This explains their very high mammalian and insecticidal toxicity. They are ester-like compounds, formed by carbamylation of the OH group of oximes. The three most important members are aldicarb **1**, methomyl **2** and oxamyl **3**.



Aldicarb **1**

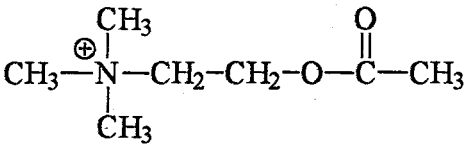


Methomyl **2**

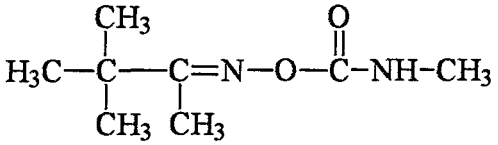


Oxamyl **3**

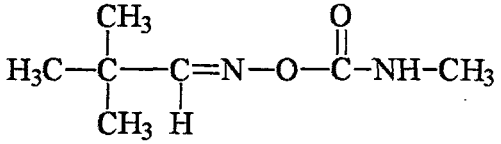
Aldicarb **1** was developed as a result of modification of *O*-(methylcarbamoyl)oximes.[74] Both butanone and acetone *O*-(methylcarbamoyl)oximes were known to possess insecticidal activity, although they were only weak cholinesterase inhibitors. Various *O*-(methylcarbamoyl)oximes, resembling acetylcholine **4** and thus able to interact with both the anionic and esteratic sites of the enzyme, were synthesised in an attempt to enhance insecticidal activity. Two compounds, *viz.*, trimethylacetaldehyde *O*-(methylcarbamoyl)oxime **5** and *tert*-butyl methyl ketone *O*-(methylcarbamoyl)oxime **6** were used as starting points. The quarternary carbon atom in each of these molecules is analogous to the trimethyl substituted nitrogen atom of acetylcholine **4**, and the interatomic distance from the carbonyl carbon to the quarternary carbon is approximately 5.6 Å in both compounds, while the analagous distance in acetylcholine **4** is approximately 5.9 Å.



Acetylcholine **4**

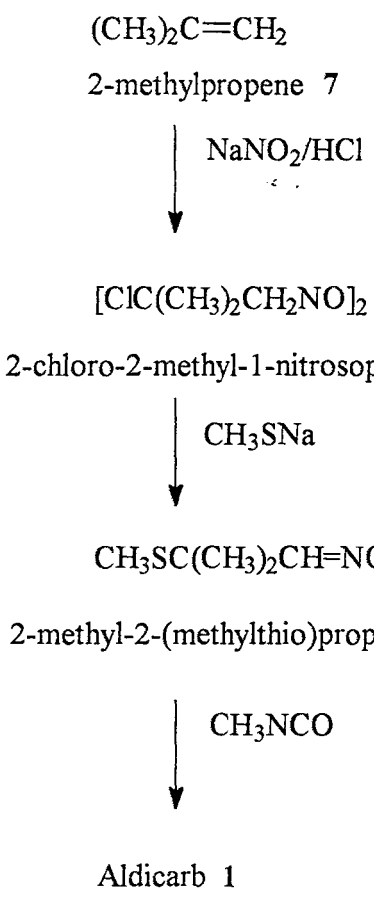


tert-butyl methyl ketone
O-(methylcarbamoyl)oxime **6**



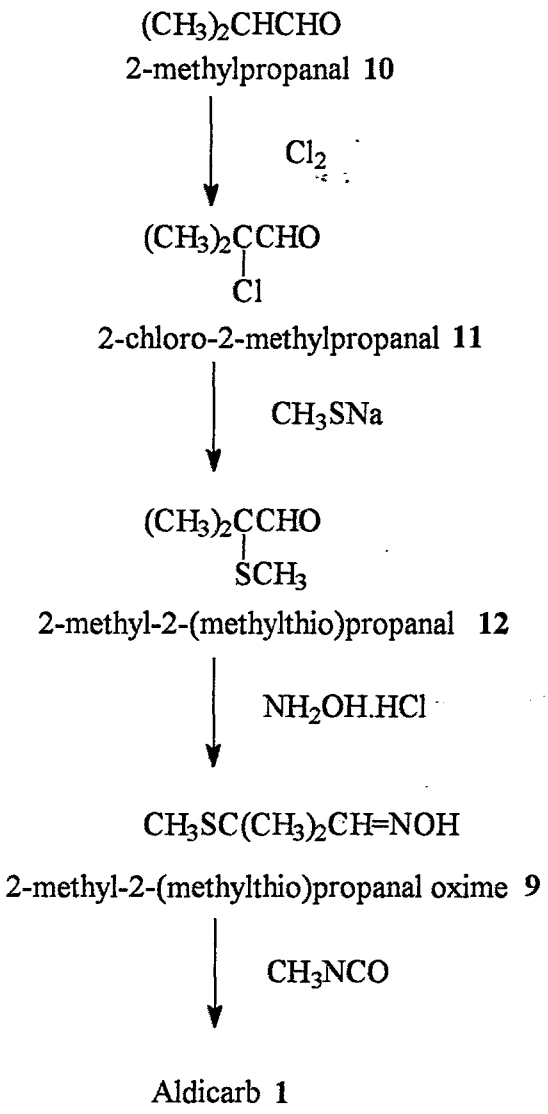
trimethylacetaldehyde
O-(methylcarbamoyl)oxime **5**

The trimethylacetaldehyde *O*-(methylcarbamoyl)oxime **5** showed a marked increase in enzyme inhibition compared to butanone and acetone *O*-(methylcarbamoyl)oxime. The *tert*-butyl methyl ketone *O*-(methylcarbamoyl)oxime **6**, however, failed to exhibit insecticidal properties. Further studies showed that although trimethyl substitution at the quarternary carbon was important, one of the methyl groups could be replaced by a larger group such as an allyl group, without a decrease in enzyme inhibition. This did, however, result in a decrease in insecticidal activity. Attention was then focused on increasing insecticidal activity. Analogues of **5** with the same basic skeleton were synthesised but an electron-withdrawing group was substituted for one of the 2-methyl groups in order to increase the affinity for the anionic site of the enzyme. This substitution was also found to increase the spectrum of activity and, in many cases, it also induced systemic properties. The combination of two methyl groups and a methylthio group was found to afford optimal insecticidal activity; in addition, this compound **1**, systematically named 2-methyl-2-(methylthio)propanal *O*-[(methylamino)carbonyl]oxime was stable under laboratory conditions unlike many of the other analogues synthesised. Compound **1**, also known as 2-methyl-2-(methylthio)-propionaldehyde *O*-(methylcarbamoyl)oxime) or aldicarb, was subjected to stringent field and laboratory tests and is the active ingredient in the insecticides marketed as Temik® and UC 21149. It is nonflammable, noncorrosive and relatively soluble in water and organic solvents. Aldicarb **1** was originally synthesised as shown in Scheme 3.[74,75,76]



Scheme 3 Preparation of aldicarb **1**

2-Chloro-2-methyl-1-nitrosopropane dimer **8** (prepared by reacting 2-methylpropene **7** with sodium nitrite and hydrochloric acid) is reacted with an ethanolic solution of methyl mercaptan and sodium hydroxide to form 2-methyl-2-(methylthio)propanal oxime **9**. This oxime is treated with methyl isocyanate to afford 2-methyl-2-(methylthio)propanal *O*-(methylamino)carbonyl oxime (aldicarb) **1**.[74,77] However, the dimer **8** has been found to be unstable and explosive at high temperatures,and yields are not always good.[77] An alternative method, shown in Scheme 4, whereby 2-chloro-2-methylpropanal **11** (prepared by chlorination of 2-methylpropanal **10**) is thiomethylated and subsequently oximated to form 2-methyl-2-(methylthio)propanal oxime **9**, is also widely used.[77,78]

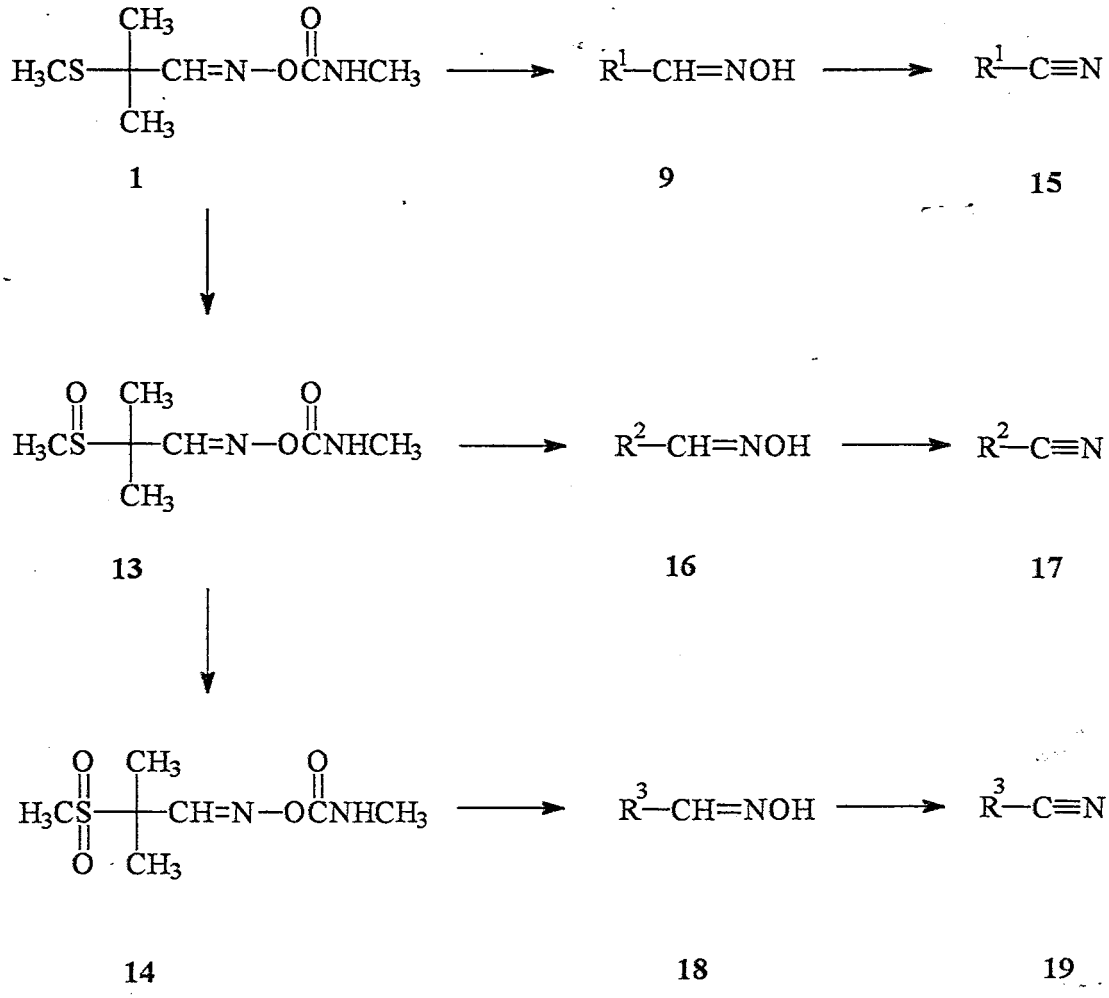


Scheme 4 Alternative preparation of aldicarb 1[±]

Aldicarb is rapidly oxidised *in vivo,* and also in the presence of an oxidising agent,to the sulphoxide **13**, and more slowly, to the sulphone **14**.[79] The oral toxicities of aldicarb **1** and aldicarb sulphoxide **13** are similar, and that of the sulphone **14** is approximately one twenty-fifth of this. The degradation of aldicarb is shown in

[±] Industrially 2-methylpropanal **10**, 2-chloro-2-methylpropanal **11** and 2-methyl-2-methylthiopropanal **12** are known as IBA (isobutyraldehyde), CIBA (α-chloroisobutyraldehyde), and ADO (aldicarb oxime) respectively.

Scheme 5.[79] Further degradation to a number of non-toxic alcohol, amide and acid derivatives occurs.

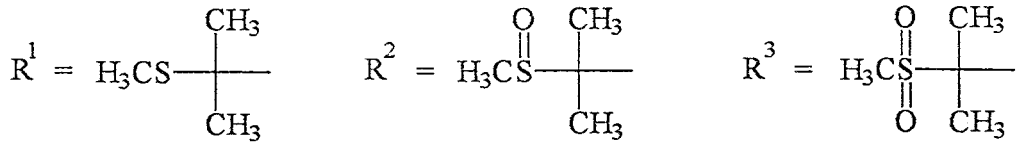


1 9 15

13 16 17

14 18 19

Where:

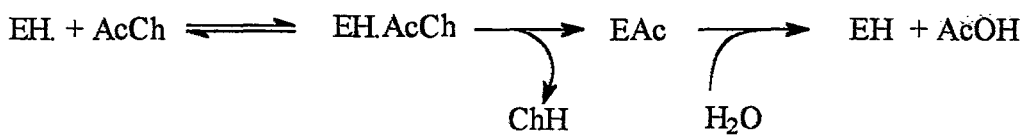


Scheme 5 Degradation of aldicarb 1

Aldicarb 1 is one of the most potentially toxic insecticides currently in use. It has an oral LD_{50} of 0.93 mg/kg for rats.[79] In order to limit the health and environmental

hazards associated with the use of aldicarb **1**, it is only available commercially as a granular formulation (Temik®) with large (14/40 mesh) granules, containing 5-15% active ingredient adsorbed onto gypsum granules. A bonding agent incorporated into the formulation helps limit the dustiness which originates due to abrasion during shipping. It has also been found that the dermal toxicity of aldicarb **1** itself is higher if the skin is moist. This toxicity is reduced by formulation: the toxicity by dermal exposure of Temik ® is 500 times less than that of technical aldicarb **1**.[74,79]

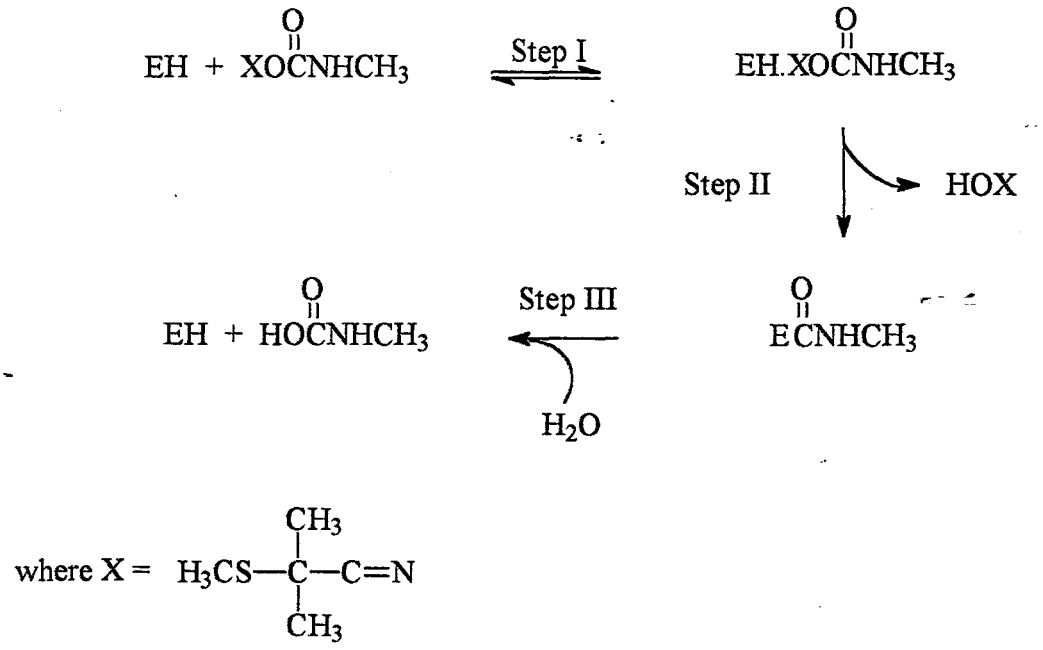
The toxicity of aldicarb **1**, and of this class in general, arises from the ability of these pesticides to rapidly and reversibly inhibit acetylcholinesterase, the enzyme responsible for breaking down acetylcholine **4**. Enzyme inhibition occurs because of the ability of aldicarb to mimic acetylcholine **4**. The mechanism of acetylcholinesterase activity can be represented as shown in Scheme 6.[80]



Scheme 6

Where EH represents the enzyme; AcCh, acetylcholine **4**; EH.AcCh the reversible intermediate enzyme-substrate complex; EAc the acetylated enzyme; ChH, choline; and AcOH acetic acid.

When an inhibitor such as aldicarb **1** is present, the inhibitor forms a reversible complex with the enzyme and carbamylates it, with release of a leaving group (HOX), as shown in Scheme 7.[75]



Scheme 7

The carbamylation step and the subsequent loss of the carbamyl group, which occurs on addition of water, are several magnitudes of order slower (correspomding to a half life of ca 30-40min) than the corresponding process when acetylcholine **4** occupies the enzyme. Once the enzyme is decarbamylated, it is free to react with acetylcholine **4**. This means that once a person is removed from exposure, recovery begins within a few minutes and is complete within a matter of hours. Although enzyme inhibition is reversible with respect to the enzyme, it is irreversible with respect to aldicarb **1** - once cleaved from the enzyme, the modified fragment is unable to inhibit acetylcholinesterase. The rate-limiting step for enzyme inhibition is the carbamylation of the enzyme (Step II, Scheme 7), in fact it is thought that the strength of aldicarb **1** as an inhibitor is not due to strong binding with the enzyme, but rather as a result of its high carbamylation rate. Aldicarb sulphoxide **13** has been shown to be 23 times more effective as an inhibitor than aldicarb, and 60 times more effective than aldicarb sulphone **14**; it is thought to be the primary species responsible for the cholinergic effects arising from aldicarb exposure because it is so rapidly formed in the body.[75.78.80]

Inhibition of the enzyme results in accumulation of acetylcholine **4** at synaptic and myoneural junctions. Onset of cholinergic dysfunction occurs when 60-90% of the enzyme has been inhibited. Acute poisoning can cause death by respiratory failure. Onset of symptoms of over-exposure is rapid and includes dilation of the pupils, nausea, vomiting, laboured respiration, convulsions and muscle spasms, the severity depending on the route of exposure, and the dose. However, because the inhibition is so rapidly reversible, recovery from sublethal doses is rapid, even without antidote. Atropine, administered as atropine sulphate is the most effective antidote, as it antagonizes the parasympathetic effects.[79,81] Aldicarb **1** exposure has been shown to have no long-term or irreversible effects and it does not cause mutations,cancer or birth defects.

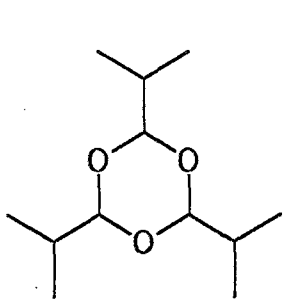
Aldicarb **1** is applied as granules below the surface of moist soil, or in an area where rainfall or irrigation is expected because moisture releases the active ingredient from the gypsum carrier granules. Aldicarb **1** provides protection for up to 12 weeks after application, although degradation begins almost immediately after application.[75,79,82] The oxidation to the sulphoxide **13** is rapid, but the half-lives of the non-carbamate oxime and nitrile hydrolysis products (**16** and **18;** and **17** and **19** respectively) varies from 0.5-36 months. However, because of the low toxicity of these products (oral LD_{50} values ranging from 350 to 8 600 mg/kg) relative to aldicarb **1**, aldicarb sulphoxide **13** and aldicarb sulphone **14**, and the fact that they further degrade to non-toxic alcohols, acids and aldehydes, they are of little concern. The complete degradation of aldicarb **1** has been shown to be a complex process involving chemical hydrolysis, microbes and heterogeneous catalysts, and is influenced by temperature, pH, the presence of oxygen and the type of soil.[82-88] The use of aldicarb **1** in South Africa is summarised in Table 3.[89]

Table 3 Use of aldicarb **1** in South Africa.[89]

Crop	**Protection against**
Bananas	nematodes
Citrus	nematodes, rust mite
Coffee	leaf miner
Cotton	aphids, thrips, nematodes
Grapes	nematodes
Macadamias	stinkbugs
Maize	ground weevils, nematodes
Flowers, Lawns	nematodes
Peas	aphids
Plums	aphids
Potatoes	nematodes
Sugar cane	nematodes
Tobacco	aphids, nematodes, tobacco red mite
Tomatoes	nematodes

1.2 Aims of the present investigation

Aldicarb oxime **9** is manufactured by Sanachem at their Berlin industrial site. From here it is sold to be converted into aldicarb **1** by reaction with methyl isocyanate. When the plant was put into operation, it was found that not only were the yields of aldicarb oxime very poor, but the purity of the product was below standard. Gas chromatographic analysis (see Figure 3) at the plant revealed a number of unidentified impurities in the final reaction mixture, most of which appeared to originate in the chlorination stage and were then carried through the entire process. It was thought that trimers 2,4,6-triisopropyl-1,3,5-trioxane **20** and 2,4,6-tris(2-chloro-2-methyl-ethyl)-1,3,5-trioxane **21** were the primary contaminants. Preliminary GC-MS studies[90] provided tentative identification of a number of the possible impurities and the basis for a fuller investigation.



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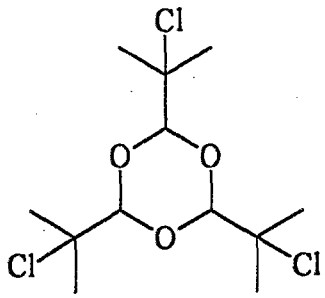

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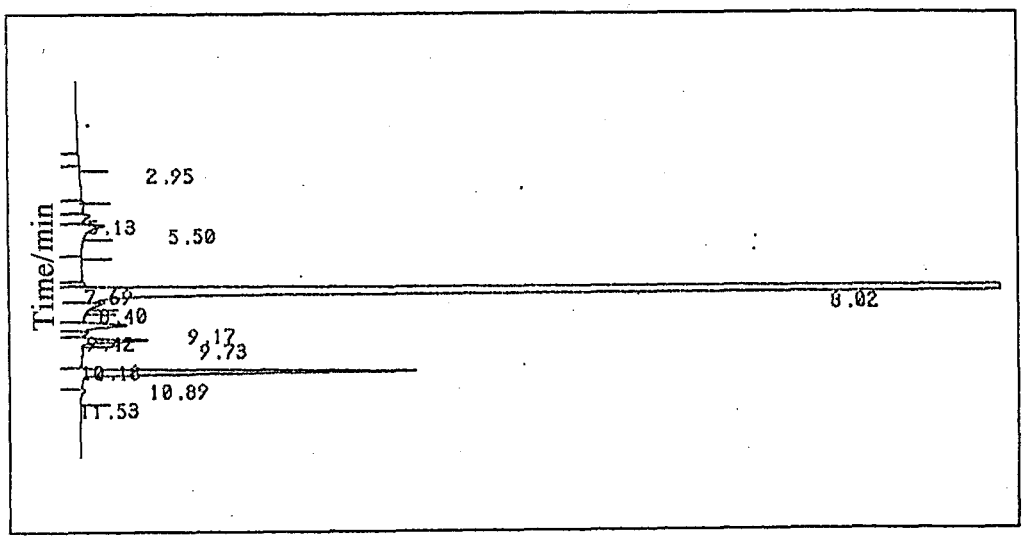


Figure 3 Gas chromatogram of aldicarb oxime **10** final reaction mixture

Aims of the present project have included:

1. Optimisation of aldicarb oxime **10** yields and purification procedures.
2. An investigation of α-halogenation of various aldehydes.
3. Synthesis of possible aldicarb oxime **10** contaminants.
4. Chromatographic and spectroscopic studies using synthetic standards to identify aldicarb oxime contaminants.
5. An investigation of the thermal stability of aldicarb oxime **10** and the kinetics of aldehyde trimerisation.
6. Synthesis of novel aldicarb **1** analogues.

2. Discussion

The synthetic aspects of the project are covered in section 2.1. In synthesis of aldicarb oxime **9**, attention is focused on the optimisation of yields (section 2.1.1.1) and attempts at removing the impurities present at the final stage (section 2.1.1.2). As the chlorination of 2-methylpropanal **10** appears to be the stage at which the principal impurities arise, optimisation of this step was desirable. The chlorination of a range of aldehydes having replaceable α-hydrogens is covered in section 2.1.2.2, while attempts to optimise the chlorination of 2-methylpropanal **10**, by varying the reaction conditions, are discussed in section 2.1.2.3; as a comparison, the synthesis of 2-bromo-2-methylpropanal **22** is also discussed (section 2.1.2.1).

Based on earlier work and a consideration of the reaction conditions, the formation of various products as aldicarb oxime **9** contaminants can be postulated. In section 2.1.3 the synthesis of these compounds is discussed and section 2.2 deals with the GC-MS and NMR studies carried out in order to compare the synthetic standards to the impurities present in the final aldicarb oxime **9** reaction mixture.

The synthesis of a range of compounds with potential as precursors for possible aldicarb **1** analogues is dealt with in section 2.1.4.

Variable temperature NMR studies (section 2.3) were used to investigate the stability of aldicarb oxime **9**, over a wide temperature range, and the kinetics of the trimerisation of 2-methylpropanal **10** and 2-chloro-2-methylpropanal **11**. These results are discussed in sections 2.3.1 and 2.3.2 respectively.

2.1 Synthetic studies

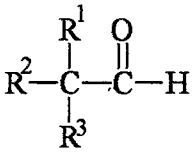
2.1.1 Aldicarb oxime synthesis

2.1.1.1 Optimisation studies

Sanachem manufacture aldicarb oxime **9** by the process outlined in Scheme 4 (pg. 31) The low overall yields of approximately 50% were primarily a result of the problems experienced in the chlorination of 2-methylpropanal **10**. The thiomethylation and oximation steps proceeded cleanly and in good yield; the purity of the aldicarb oxime **9** produced was, however, dependent on the purity of the 2-chloro2-methylpropanal **11** used.

The optimisation of the chlorination is discussed in detail in section 2.1.2.3. Once relatively pure 2-chloro-2-methylpropanal **11** was obtained in good yield, attention was focused on the thiomethylation and the oximation stages, both of which proceed cleanly and need little optimisation.

Kirrman *et al.*[91] describe the synthesis of α-(methylthio)aldehydes of the form



where R^1, R^2 and R^3 are alkyl groups,

in 55-80% yields by reacting sodium thiomethylate with α-chloroaldehydes in dry ether. The synthesis of these α-(methylthio)aldehydes has also been achieved using thiols in the presence of pyridine.[77] Besides the low yields, the problems associated with working with dry ether and the contamination of pyridine (which prevents recycling) mean that both of these methods are industrially unsuitable. A patent[77] lodged by Allied Chemical Corporation in 1974 describes the synthesis of similar α-(alkylthio)aldehydes in aqueous medium in yields of 85-100%. By using an aqueous medium, the need for recycling the solvent is eliminated. Oximation of

α-(alkylthio)aldehydes occurs readily in almost quantitative yield, and the overall yields of the α-(alkylthio)aldehyde oximes ranged from 50-90%; the production of 2-methyl-2-(methylthio)propanal oxime **9** from 2-methylpropanal **10** is reported in 67% overall yield. Oximation of 2-methylpropanal **10** prior to chlorination resulted in subsequent halogenation of the azomethine carbon in preference to the α-carbon.[77]

It is essential to use freshly prepared 2-chloro-2-methylpropanal **11** for the thiomethylation step because the aldehyde tends to trimerise rapidly on standing. On an industrial scale, the 2-chloro-2-methylpropanal **11** is distilled directly into a reactor containing sodium thiomethylate. In the present investigation, freshly prepared 2-chloro-2-methylpropanal **11** was neutralised by titration with sodium hydroxide, and then added dropwise into a solution of sodium thiomethylate. Distillation of the 2-methyl-2-(methylthio)propanal **13** prior to oximation was found not to improve the purity of the product markedly.

Oximation of the α-(alkylthio)aldehydes may be achieved using an aqueous solution of hydroxylamine sulphate and ammonia gas to regulate the pH,[77,78] or by using equimolar, aqueous solutions of hydroxlamine hydrochloride and sodium hydroxide (the procedure employed by Sanachem). If hydroxylamine sulphate and ammonia gas are used, the by-product of the reaction is ammonium sulphate which may be used as fertiliser. However, a disadvantage of this method arises from difficulties in removing the ammonium sulphate from the organic layer;[92] although most of it is removed in the aqueous layer during a phase separation, an appreciable quantity may remain as an emulsion in the organic layer. During subsequent distillation of the oxime product **10,** the liquid gradually becomes supersaturated in ammonium sulphate, which then crystallises out on the surface of the reactor, thereby forcing periodic shutdowns so that the reactor may be cleaned. As these shutdowns may sometimes occur as often as several times a week, a significant decrease in productivity occurs. Passing the crude product through a bed of solid ammonium sulphate, known as mascagnite [$(NH_4)_2SO_4$], has been reported[92] to agglomerate the ammonium sulphate emulsion into droplets which may then be removed by phase

separation This has been found to decrease the ammonium sulphate content of the final product by as much as 95%.

Using the procedures followed by Sanachem aldicarb oxime **9** was prepared in 69% overall yield from 2-methylpropanal **10** after distillation (compared to 45% at the factory laboratory). The almost quantitative yields reported[77] for the thiomethylation and oximation steps were not achieved (see Table 4). Possible reasons for the reduced yield are:- i) the fact that 2-methyl-(2-methylthio)propanal was dried overnight over molecular sieves, where some loss of product would have occurred due to absorption; ii) instead of hydroxylamine sulphate and ammonia gas, hydroxylamine hydrochloride and sodium hydroxide were used and the oximation may not have been as efficient; and iii) in the reported procedure,[77] using hydroxylamine sulphate and ammonia gas, the product was not distilled whereas, in fact, slight losses could be expected during distillation of the oxime **9** obtained.

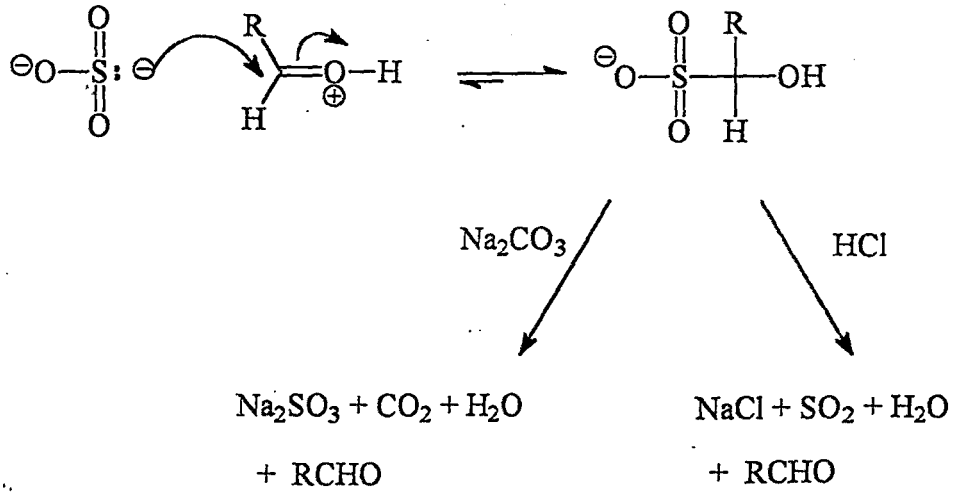
Table 4 Yields of aldicarb oxime **9** synthesis

Compound	Yield/%	Overall yield % (based on 2-methylpropanal **10**)
2-chloro-2-methylpropanal **11**	85	85
2-methy2-(methylthio)propanal **12**	89	76
aldicarb oxime **10**	91	69

2.1.1.2 Purification of aldicarb oxime

Various simple and relatively inexpensive methods for purifying crude aldicarb oxime **9** were explored. These included the use of sodium bisulphite, activated charcoal, silica and alumina and steam distillation.

Aldehydes, methyl and cyclic (generally seven-membered rings and smaller) ketones (most other ketones are too sterically hindered), α-keto esters, and isocyanates form addition products upon treatment with sodium bisulphite.[93] The reaction is typically carried out by dissolving the aldehyde (dissolved in ethanol if it is water-insoluble) in a large excess of a cold, saturated solution of sodium bisulphite; alternatively 75% ethanol may be added to a freshly prepared saturated aqueous sodium bisulphite solution, followed by adding the aldehyde directly to this solution. The sulphite anion, SO_3^{2-}, acts as the nucleophile and, because it is present as an anion in solution and is a sufficiently powerful nucleophile, neither base nor acid catalysis is necessary for the reaction to proceed. The bisulphite addition complex may be isolated as a crystalline sulphonic acid salt, which has the properties of an ionic metal compound, *viz.*, it is water-soluble, and may be salted out by the common ion effect. Bisulphite addition compounds are often used as a method of separating, for example, aldehydes from liquid hydrocarbons and other water-insoluble liquid compounds. The reaction is reversible with the equilibrium favouring the free carbonyl compound; therefore the aldehyde can be regenerated by dissolving the adduct in a minimal amount of cold concentrated hydrochloric acid or aqueous sodium bicarbonate to destroy or neutralise any free sodium bisulphite. The liberated aldehyde is either precipitated or is obtained by extraction with ether or by steam distillation. The overall reaction sequence is shown in Scheme 8. [93,94,95,96]



Scheme 8

The predominant impurities present in aldicarb oxime **9** are the trimers 2,4,6-triisopropyl-1,3,5-trioxane **20** and 2,4,6-tris(2-chloro-2-methylethyl)-1,3,5-trioxane **21**, which are expected to exist in equilibrium with the aldehyde monomers. The free aldehydes should form addition compounds with bisulphite, thus removing them from solution, and shifiting the equilibrium in favour of the free aldehyde. However, several attempts to purify aldicarb oxime **9** by this method produced disappointing results, presumably because the equilibrium lies in favour of the trimer and little free aldehyde exists in solution. Heating a solution of aldicarb oxime **9** and sodium bisulphite in a minimal volume of water for several hours under reflux resulted in a dramatic deterioration in the quality of aldicarb oxime **9**, whereas stirring a solution overnight at room temperature resulted in only a slight deterioration.

Activated charcoal (also known as decolourising carbon), most commonly used as a decolourising agent, also has a chromatographic function. Impurities may be adsorbed onto the charcoal by passing a cold solution of the organic substance dissolved in ethanol through a funnel containing a small amount of charcoal supported on a cotton wool plug.[97,98] Silica gel and alumina are both commonly used in chromatographic separations and as catalytic supports for numerous organic reactions.[99100,101] The possibility of removing some of the contaminants from aldicarb oxime **9** by stirring a sample of aldicarb oxime **9** with either alumina, silica or charcoal was therefore investigated.

The results of gas chromatographic and ^{1}H NMR analyses of samples subjected to these purification procedures as well as bisulphite are presented in Table 5. GLC was used to calculate the amount of aldicarb oxime **9** present in the sample and ^{1}H NMR to examine the ratio of trimers present relative to aldicarb oxime **9**. Alumina and charcoal appeared to be the most promising methods of purification.

Table 5 Analytical data for aldicarb oxime 9 samples after purification procedures.

	Purification Method				Results of Analysis	
	Sodium Bisulphite	Alumina	Silica	Charcoal	%ADO [a]	Trimers:ADO [b]
5					90.2	0.080
5.1	X				88.4	0.081
5.2		X			93.3	0.080
5.3			X		89.5	0.081
5.4				X	93.3	0.079

a. Determined by GLC analysis
b. The integral ratios of trimers relative to ADO were determined using ^{1}H NMR spectroscopy.

Steam distillation is often used to separate and purify organic compounds.[102] The substance (which may be dissolved in water) is volatilised by the passage of steam; as long as the compound has a vapour pressure of at least 5-10mm at 100°C, it will distill along with the steam, at temperatures well below the boiling point of water, and in many cases, below the boiling point of the organic substance as well. Many high-boiling compounds may thus be purified by means of a low temperature, atmospheric pressure distillation. Separation of the desired organic compound is also possible in many cases, *viz.*, i) from non-volatile tarry substances which may have formed as by-products of the reaction, ii) from dissolved inorganic salts in an aqueous mixture, iii) from a mixture that would otherwise be difficult to separate, such as an emulsion, iv) from compounds that are not steam-volatile, and v) from reaction by-products that are more steam-volatile than the desired compound.

A compound with the molecular formula $C_6H_{14}S_2$, thought to be the dithioacetal of 2-methylpropanal, has been detected in the gaseous form during a steam distillation.[103] As this is one of the impurities present in aldicarb oxime 9, it was hoped that it and other volatile compounds could be removed in this manner. Steam distillation of the

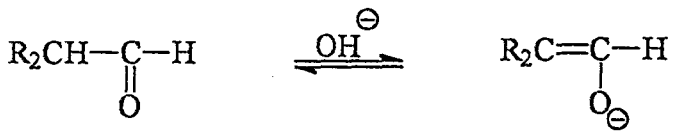
crude aldicarb oxime **9** mixture, however, did not result in an appreciable improvement in the quality of aldicarb oxime **9**. This was determined by analysis of ^{1}H NMR spectra of aldicarb oxime **9** before and after the distillation.

2.1.2 Halogenation Studies

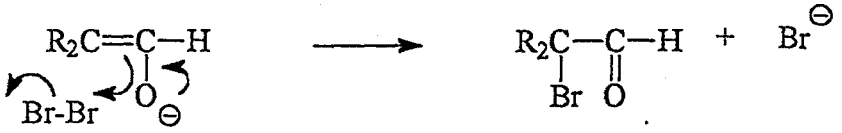
Aldehydes and ketones can be successfully halogenated in the α-position with chlorine, bromine and iodine.[104] The reaction is generally not successful with fluorine unless specialised reagents and conditions are used.

The general mechanism of halogenation is well established;[104] it is actually the enol or enolate ion that is halogenated, not the aldehyde itself. The reaction can be acid or base catalysed, the purpose of the catalyst being to provide a small amount of enol or enolate, but catalysis is not always necessary as there is generally a trace of acid or base present which is enough to catalyse the reaction. With acid catalysis, it is possible to stop the reaction after the introduction of only one halogen but, in a base catalysed reaction, if there are two or more replaceable α-hydrogens, such selectivity is not possible because the acidity of the remaining hydrogens is increased as a result of the electron-withdrawing effect of the halogen. The mechanisms for base- and acid-catalysed halogenation are shown in Scheme 9 and Scheme 10 respectively.[104]

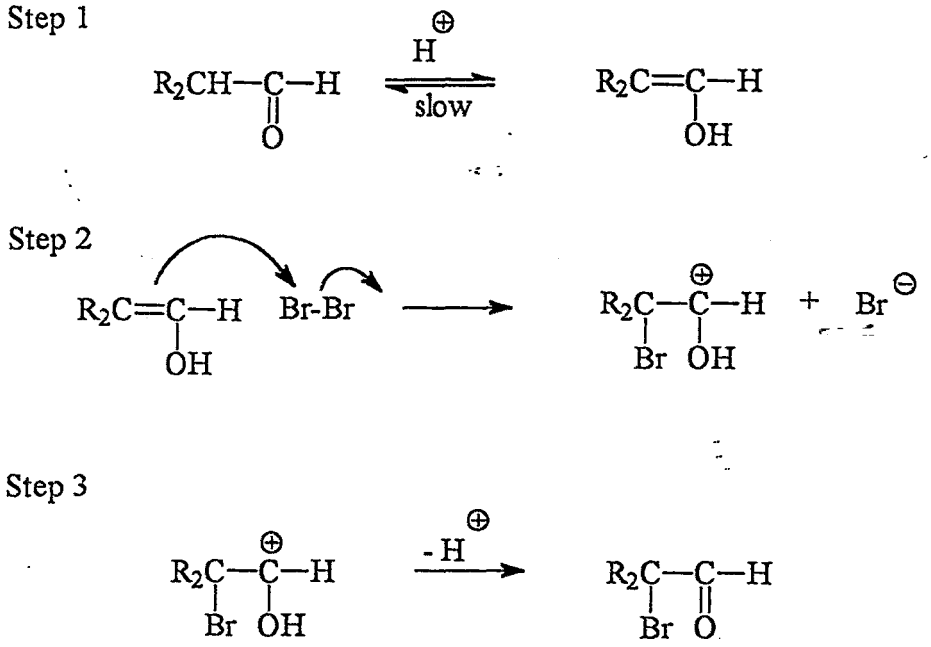
Step 1



Step 2



Scheme 9 Base catalysed α-halogenation

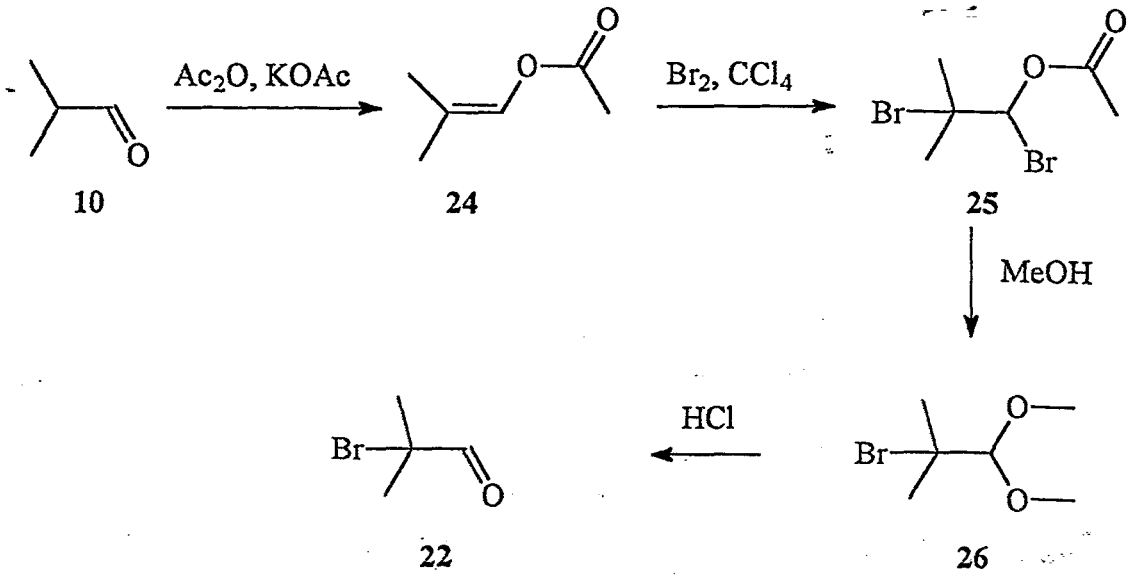


Scheme 10 Acid catalysed α-halogenation

2.1.2.1 Bromination of 2-methylpropanal

2-Bromoaldehydes are highly reactive and are difficult to obtain by direct bromination of the corresponding aldehyde.[105] Early methods of preparation were based on replacement reactions, involving lengthy, complex procedures and drastic conditions; the yields were very low and the methods often limited in applicability.[106] In 1944 Bedoukian[106] reported the synthesis of 2-bromoaldehydes by addition reactions. As indicated above it is actually the enol form of the aldehyde which undergoes addition and, while aldehydes do not exist in any appreciable quantity in the enolic form, stable enol acetates are readily prepared by refluxing the aldehyde with acetic anhydride in the presence of a catalyst such as potassium acetate. Filachione[107] reported the synthesis of bromoacetaldehyde acetal by adding bromine to vinyl acetate in the presence of methanol; these bromoacetals could be hydrolysed readily to produce the desired 2-bromoaldehydes. Vinyl acetate is, in fact, the enol acetate of acetaldehyde, and the applicability of the reaction to higher aldehydes was examined.

The production of 2-bromo-2-methylpropanal **22** by this method is shown in Scheme 11.[106] The method was also found to give adequate yields with low boiling aldehydes (*e.g.* acetaldehyde), branched aldehydes (*e.g.* 2-methylpropanal **10**), high boiling aldehydes (*e.g.* heptaldehyde) and aromatic aldehydes with replaceable α-hydrogens, (*e.g.* 2-phenylethanal).



Scheme 11

Other methods for α-bromination of aldehydes include: i) dissolving the aldehyde in carbon disulphide in the presence of calcium carbonate and adding bromine dropwise (the yield of 2-bromo-2-methylpropanal **22** thus prepared was 35%);[108] ii) the use of *N*-bromosuccinimide, a highly regioselective reagent for bromination α to a carbonyl group, a C≡C triple bond or a benzene ring;[109] iii) formation and subsequent bromination of the enamine of the aldehyde;[110] and iv) bromination of silyl enol ethers, followed by spontaneous β-cleavage[111,112] - an efficient and regioselective process. Silyl enol ethers of aldehydes are readily prepared either by reaction of the aldehyde with chlorotrimethylsilane in dimethylformamide, in the presence of triethylamine, or by reaction of the aldehyde with lithium diisopropylamide, followed by the addition of chlorotrimethylsilane in dimethoxyethane. Silyl enol ethers can be brominated by using 1 equivalent of bromine either in pentane at -75°C or in

tetrachloromethane at -20°C, or by using 1 equivalent of *N*-bromosuccinimide in tetrachloromethane at reflux or in tetrahydrofuran at 0°C. Using this approach 2-bromoaldehydes are generally obtained in 70-90% yield, although 2-bromo-2-methylpropanal **22** was only obtained in 51% yield; the lower yield, in this case, being attributed to the volatility of the product, causing loss during distillation.[111] α-Bromoaldehydes may also be prepared by reaction of organoboranes with 2-bromoacrolein.[105] The reaction involves 1,4-addition of the organoborane to the conjugated acrolein system to produce an enol borinate which, upon hydrolysis with water affords the free aldehyde. The resulting highly reactive 2-bromoaldehydes were converted to the corresponding diethyl acetals for storage and analysis.

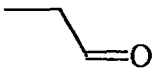
In the present study, 2-bromo-2-methylpropanal **22** was prepared in approximately 21% yield following the enol acetate route.[106] Upon standing, 2-bromo-2-methylpropanal **22** formed a white solid. A portion of this was recrystalised from hexane and upon analysis was found to be the trimer of 2-bromo-2-methylpropanal **26**. This observation is consistent with the literature reports.[108] The monomeric 2-bromo-2-methylpropanal **22** was recovered by distillation.

2.1.2.2 Chlorination of aldehydes

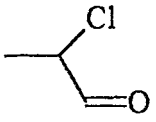
In 1904 Kohlschütter[113] observed that acetone could be chlorinated by cupric chloride, a reagent which much later (1967) was also found to be very effective in chlorinating aldehydes.[114] The products of the reaction vary, depending on the reaction conditions. Non-aqueous solvents lead to extensive acid-catalysed side reactions due to the action of copper salts, acting as Lewis acids, or of HCl present as a by-product. Water-alcohol or water-acetone mixtures, however, give 2-chloroaldehydes in yields of greater than 90%; for example, refluxing 2-methylpropanal **10** and $CuCl_2$ under nitrogen in a 2:1 acetone-water mixture for 1.5 hours afforded 2-chloro-2-methylpropanal **11** in 96% yield. Sulphuryl chloride[108,115] is also an effective chlorinating agent, although yields of only 50-60% are obtained.

Chlorination using chlorine gas is carried out in either the vapour or the liquid phase. The chlorination of compounds provides a convenient method of introducing functionality into a molecule by the subsequent displacement or elimination of chlorine.[116] On an industrial scale, the use of chlorine gas has the basic economic disadvantage that for every molecule of chlorine reacting, a molecule of hydrogen chloride is produced, and only if this HCl can be recycled, does chlorination with gaseous chlorine compete with alternative processes. The HCl produced during the chlorination of 2-methylpropanal **10** at the Sanachem plant, although not of high enough purity to be sold, is used very successfully to lower the pH of the factory effluent from 12 to approximately 7.

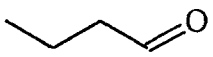
Chlorination of a range of aldehydes with replaceable α-hydrogens was undertaken. These aldehydes included propanal **27**, butanal **28**, 2-methylpropanal **10** and 2-phenylethanal **29**. These aldehydes and the desired 2-chloro derivatives are shown below.



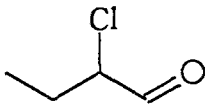
Propanal **27**



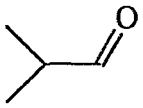
2-Chloropropanal **30**



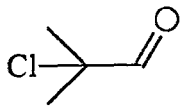
Butanal **28**



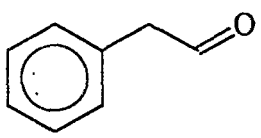
2-Chlorobutanal **31**



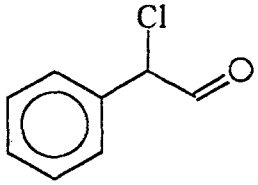
2-Methylpropanal **10**



2-Chloro-2-methylpropanal **11**



2-Phenylethanal **29**



2-Chloro-2-phenylethanal **32**

Monochlorination of aldehydes **27**, **28** and **29**, using chlorine gas was complicated by the presence of more than one replaceable α-hydrogen and none of the monochloro compounds **30**, **31**, and **32** respectively could be obtained by this route. ^{1}H NMR spectroscopy of the products obtained by bubbling chlorine gas through solutions of the aldehyde in chloroform until a permanent green colour was obtained (an indication of complete chlorination of 2-methylpropanal **10**) revealed, in each case, a complex mixture. Further chlorination only increased the compexity of the products, as shown by the ^{1}H NMR spectrum recorded after the chlorination of butanal **28** (see Figure 4).

2.1.2.3 Optimisation of chlorination of 2-methylpropanal

Sanachem produce 2-chloro-2-methylpropanal **11** by bubbling chlorine through a solution of 2-methylpropanal **10** in $CHCl_3$. The reaction is carried out at reflux temperature (*ca.* 70°C). An in-depth investigation into the chlorination was conducted in an attempt to optimise the procedure. Initial reactions were complicated by the lack of an accurate flow meter; a soap bubble flow meter was used but an accurate and consistent flow of chlorine gas proved difficult to achieve and, after addition of the supposed theoretical quantity of chlorine, ^{1}H NMR spectroscopy consistently revealed the presence of unchlorinated 2-methylpropanal **10**. These difficulties were overcome once an Edwards rotameter was obtained, and chlorine was added until a permanent green colour indicated that the chlorination had gone to completion. The chlorination was repeated under a range of different conditions, *viz.*, i) varying the extent and manner of chlorine addition; ii) with and without solvent ($CHCl_3$); iii) with and without heating; and iv) with and without a buffer. The effects of varying reaction conditions are recorded in Table 6. In most cases, the addition of chlorine was *via* a dip tube, the end of which was under the surface of the liquid to ensure chlorine addition in the liquid phase. An alternative procedure[77] whereby the chlorine is added in the gaseous phase, *i.e.* above the surface of the liquid, was attempted, but was found to drastically decrease the quality of the 2-chloro-2-methylpropanal **11**, so much so that an accurate assessment of the yield was not possible. It was found that solvent is not necessary for the chlorination to proceed; in

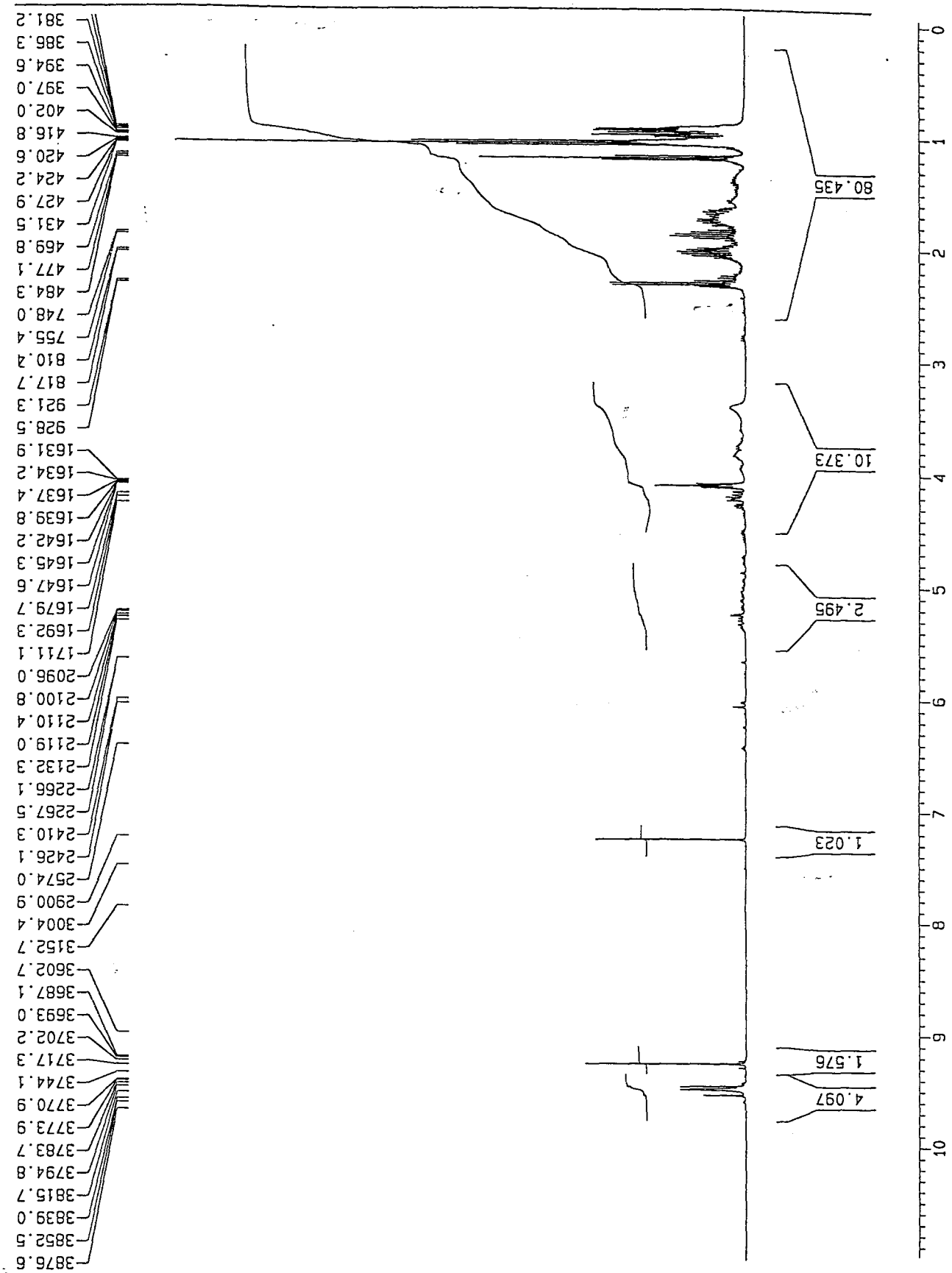


Figure 4 400MHz ^{1}H NMR spectrum of mixture obtained from chlorination of butanal **28.**

fact, the most promising results were obtained in the absence of solvent. This is very attractive commercially, as the cost of the solvent, as well as the cost of recycling it are removed. However, the reaction temperature needs to be monitored carefully at the beginning of the reaction as it rises upon addition of chlorine. It was also found that, in the presence of solvent, heating is not necessary for efficient chlorination. In the absence of external heat and solvent, the reaction mixture solidified rapidly, and after approximately 30 minutes, the reaction had to be halted. ^{1}H NMR analysis of the solid product showed it to be the trimer 2,4,6-tris(2-chloro-2-methylethyl)-1,3,5-trioxane **21**. The effect of heating 2-methylpropanal **10** to reflux before the addition of chlorine was also investigated. It was found not to improve the purity of the product. Replacement of a hydrogen atom by a chlorine atom generates HCl, which was shown by subsequent ^{1}H NMR experiments to catalyse trimer formation (see Section 2.3.2), it was hoped that addition of a buffer such as Na_2CO_3 would neutralise the HCl as it was formed and thus minimise the trimerisation. First attempts at using such a buffer involved bubbling the chlorine through a well-stirred solution of 2-methylpropanal **10** and Na_2CO_3 dissolved in water. This resulted in the formation of a large amount of NaCl precipitate which hindered stirring of the reaction. In later attempts water (in excess of the theoretical quantity needed to dissolve the amount of NaCl generated) was used to dissolve the Na_2CO_3, and this solution was added dropwise over the first 30 minutes of the reaction. In all attempts however, the buffer was found not to improve the yields. Washing the crude product three times with saturated brine had a beneficial effect on the purity of the 2-chloro-2-methylpropanal **11**. Distillation of the reaction mixture could be omitted without affecting the purity of the product. Retrieval of all the product by distillation was difficult; even though the boiling point of 2-chloro-2-methylpropanal **11** is low (90°C); the distillation was very slow and usually had to be halted because no more product could be collected. This led to significant loss of product, and the distillate was often little cleaner than the crude material.

The yields quoted in Table 6 represent the percentage conversion of 2-methylpropanal **10** to 2-chloro-2-methylpropanal **11**; these were obtained from ^{1}H NMR integral values, and are yields of distilled product unless otherwise noted. The chlorination in

the absence of solvent was repeated several times and consistent yields of *ca.* 85% of the undistilled product were achieved. The improvement in the chlorination step in indicated in Figures 5 and 6.

Table 6 Summary of optimisation studies of the chlorination of 2-methylpropanal **10**; the reaction conditions used in each case are indicated by a cross.

	Solvent	Heating	Buffer	Green colour	Yields (%)	Notes
6.1	X	X			27	
6.2	X		X			1
6.3	X		X		1	2
6.4	X		X		4.6	
6.5	X	X		X	14	
6.6	X			X	47	3
6.7						4
6.8		X		X	83	5
6.9		X		X	41	6
6.10		X		X	58	7
6.11		X		X		8

Notes:

1. Na_2CO_3 was used as a buffer. The large amount of precipitated sodium chloride, which was formed, hindered stirring and the reaction was halted after 30 minutes.
2. Na_2CO_3 was used as a buffer, but it was dissolved in an excess of water and the solution was added dropwise over the first 30 minutes of the reaction.
3. The quoted yield is for distilled material.
4. A white solid, found to be the 2,4,6-tris(2-chloro-2-methylethyl)-1,3,5-trioxane **21** formed after 30 minutes and the reaction was halted.
5. ^1H NMR analysis of crude 2-chloro-2-methylpropanal **11** shows it is very clean. The quoted yield is for undistilled material.

6. Chlorine was added to a refluxing solution of 2-methylpropanal **10**. ^{1}H NMR analysis prior to distillation revealed the presence of trimers. Although the yield was low the distillate was very clean.
7. The 2-chloro-2-methylpropanal **11** was washed with brine. This resulted in a cleaner product, but the yield was low because of mass loss.
8. Chlorine was added above the level of the liquid. The yield could not be assessed.

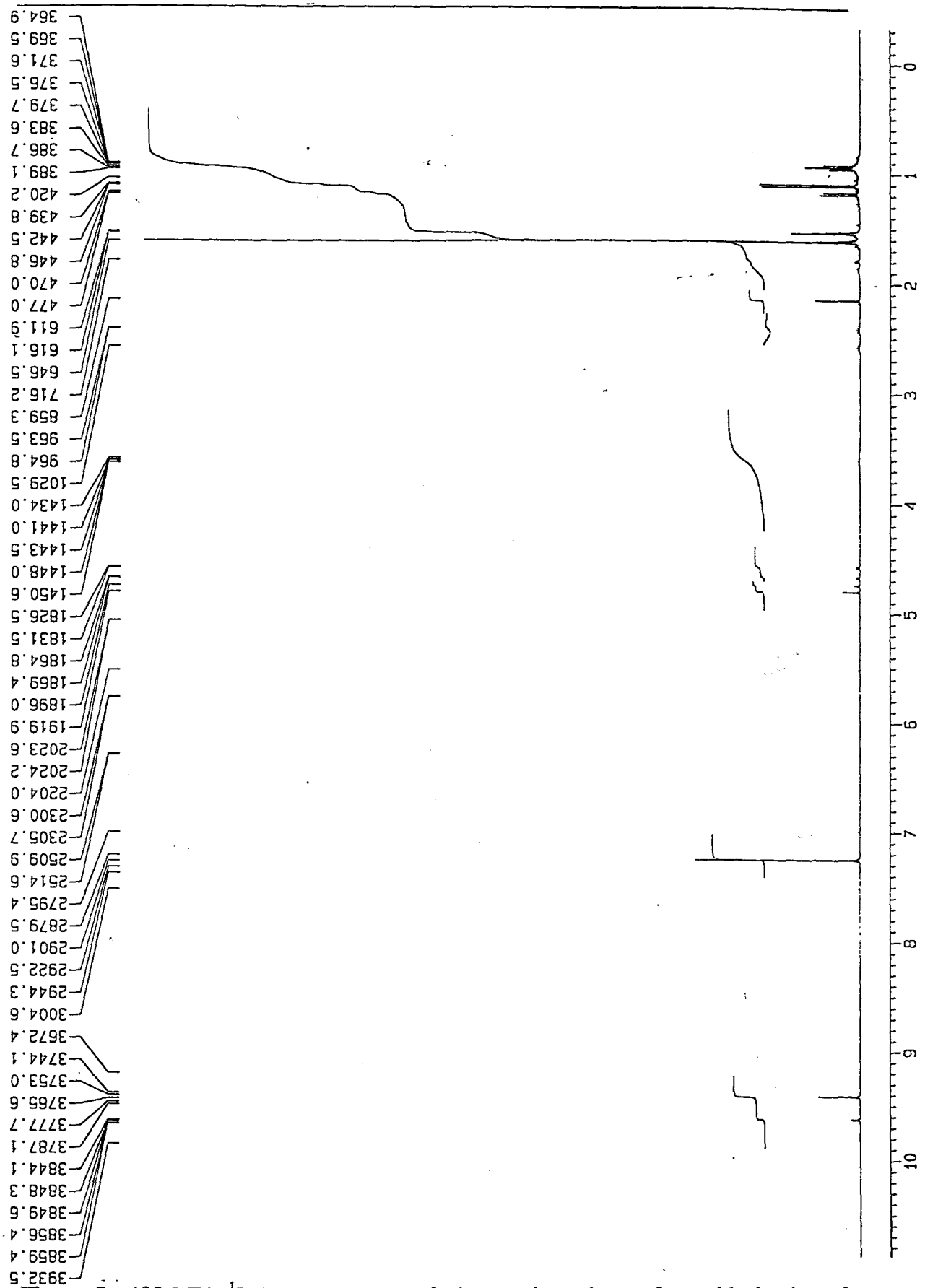


Figure 5 400 MHz ^{1}H NMR spectrum of the reaction mixture from chlorination of 2-methylpropanal **10**; entry 1 (Table 6))

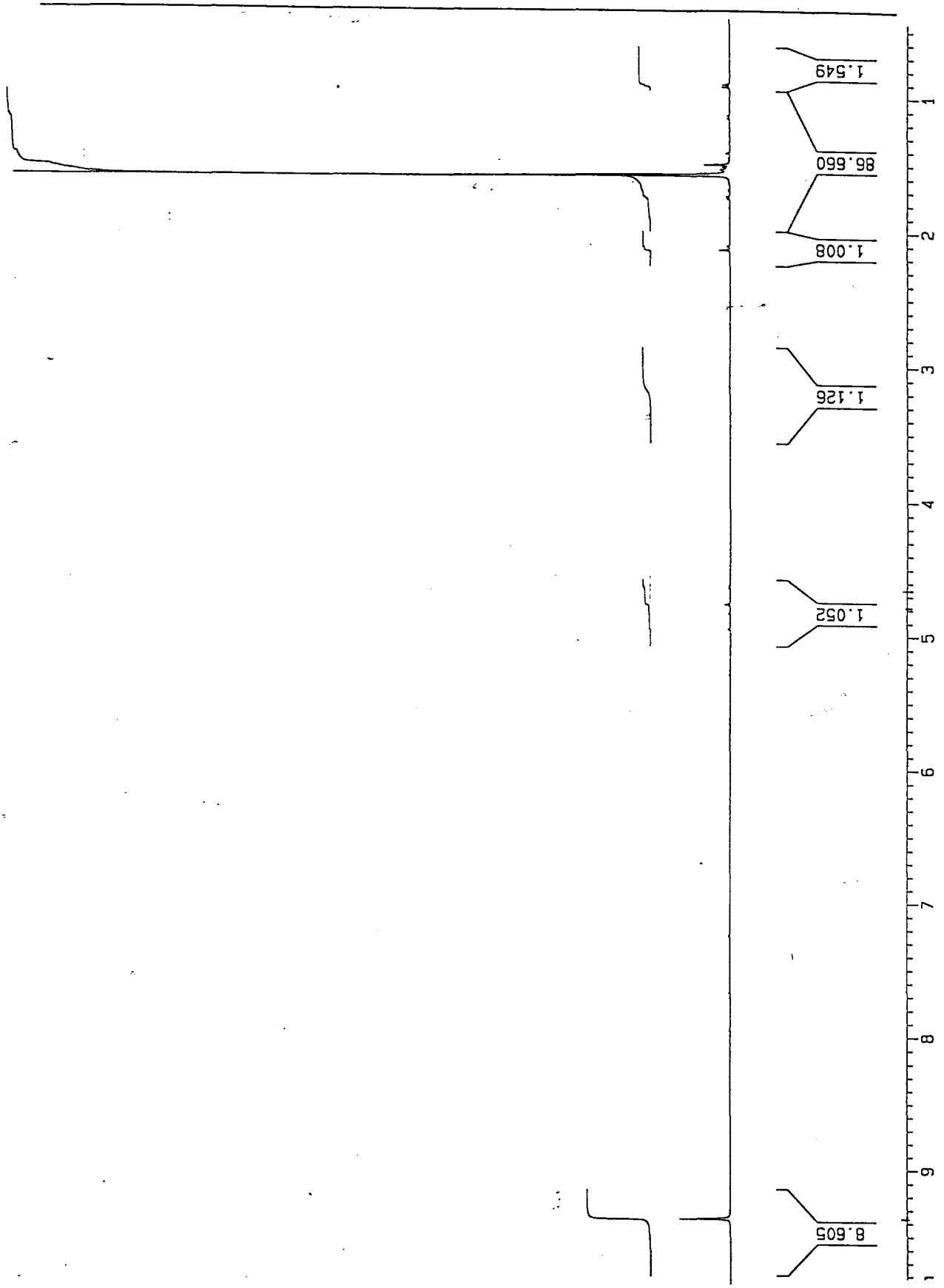
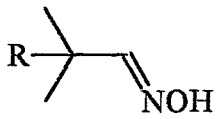


Figure 6 400 MHz ^{1}H NMR spectrum of the reaction mixture from chlorination of 2-methylpropanal **10**; entry 8 (Table 6)

2.1.3 Preparation of possible aldicarb oxime contaminants

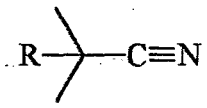
From the results of preliminary GC-MS studies and a consideration of reaction conditions, the possible formation of a number of impurities was postulated. These included the oximes, nitriles, trimers, thioacetals and aldol condenstaion products detailed below. These compounds were therefore synthesised for use as chromatographic and spectroscopic standards for the analysis of the crude aldicarb oxime **9**.

Oximes



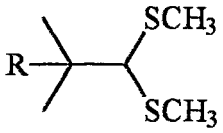
R	Compound
H	**33**
Cl	**34**

Nitriles



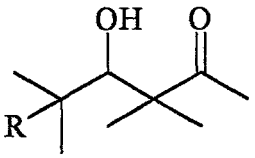
R	Compound
H	**35**
H_3CS	**36**

Thioacetals



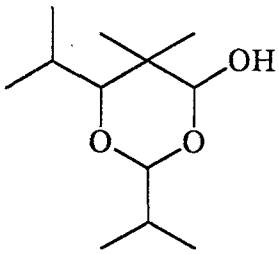
R^1	Compound
H	**37**
Cl	**38**

Aldols



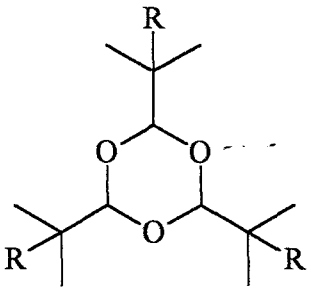
R	Compound
H	**39**
Cl	**40**

Aldol Trimer



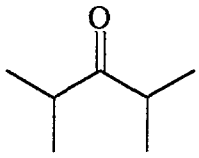
41

Trimers



R	Compound
H	**20**
Cl	**21**

2,4-Dimethyl-3-pentanone

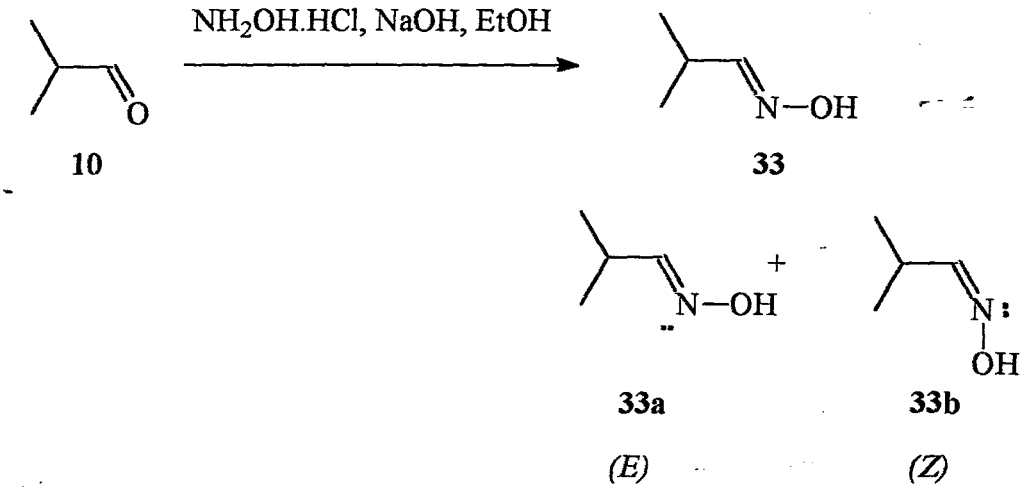


42

2.1.3.1 Oximes

Aldehydes and ketones both condense readily with hydroxylamine to give oximes. These are usually crystalline compounds with sharp melting points, and can thus be used as a means of identifying the parent aldehyde or ketone. They also provide a convenient route, *via* reduction, to primary amines.[117] Hydroxylamine is usually available as a salt, most commonly the sulphate or the hydrochloride. The free base is liberated from an aqueous solution of the salt by treatment with sodium hydroxide or sodium acetate.

2-methylpropanal oxime **33** was prepared readily and in good yield by treating an ethanolic solution of 2-methylpropanal **10** with hydroxylamine hydrochloride in the presence of sodium hydroxide, as shown in Scheme 12.



Scheme 12

Aldoximes and certain ketoximes can exist in two stereoisomeric forms (*E* and *Z*) differing in configuration about the C=N bond.[118,119] In some cases when the products are crystalline, one of the stereoisomers may be formed in greater amounts than the other and the mixture may be purified by recrystallisation. The *anti-* or *E-*isomer is the thermodynamically favoured product. 2-methylpropanal oxime **33**, however, was isolated as a liquid and the ^{1}H NMR spectrum (see Figure 7) clearly revealed the presence of both stereoisomers. No attempts were made to separate the stereoisomers, which gave a single spot on TLC.

Various attempts, summarised in Scheme 13, were made to obtain the crystalline 2-chloro-2-methylpropanal oxime **34**.[120] Although the presence of the oxime could be confirmed using infra-red spectroscopy (ν_{max} 1690-1640 cm^{-1}), the product could not be isolated. A crystalline solid was obtained after standing at 4°C for several weeks, but this was found to be the trimer of 2-chloro-2-methylpropanal **21**. A method[121] whereby the oxime **34** was synthesised by chlorinating 2-methylpropanal oxime **33** reports obtaining the product as an oil. The difficulty experienced in synthesising the

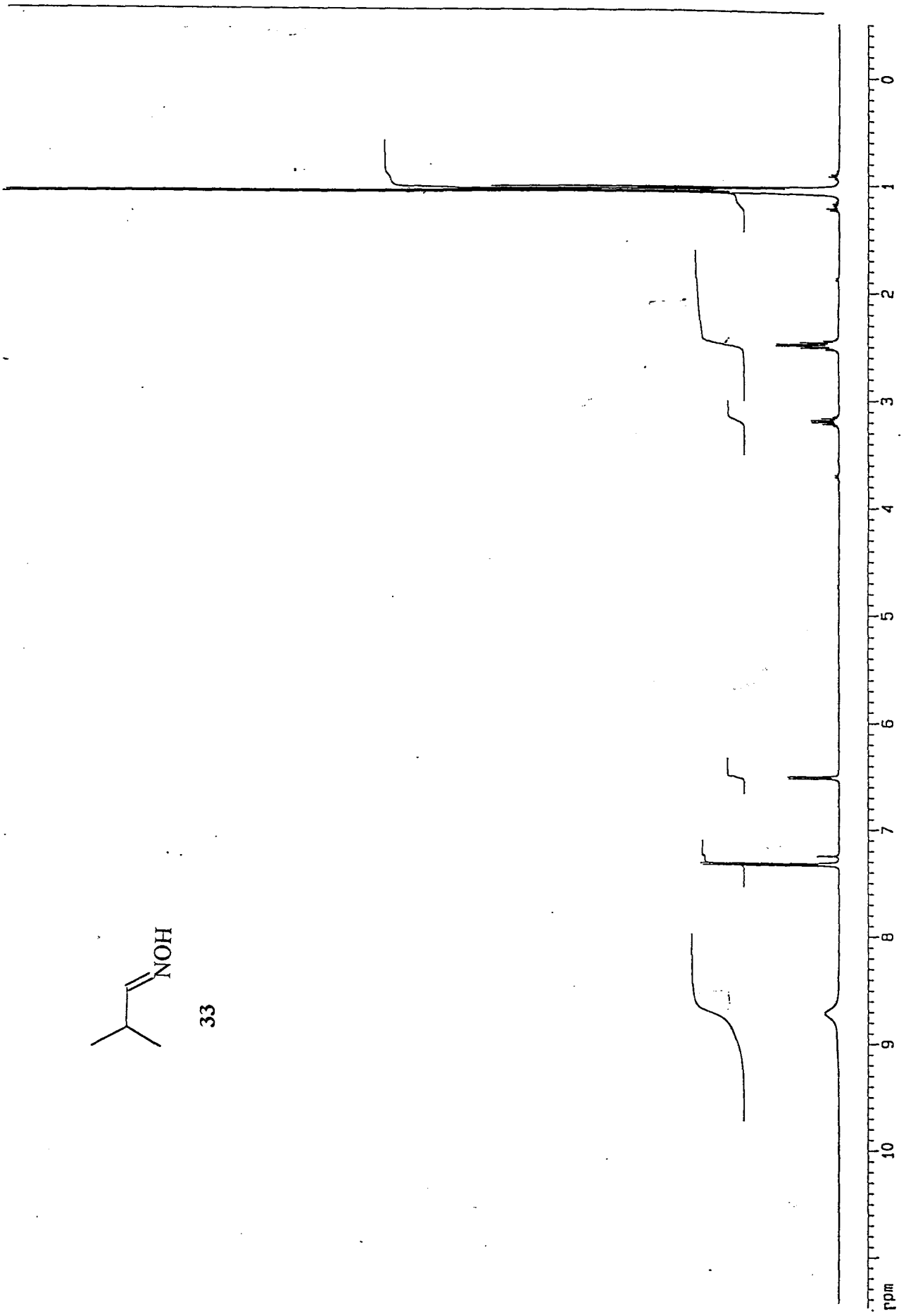
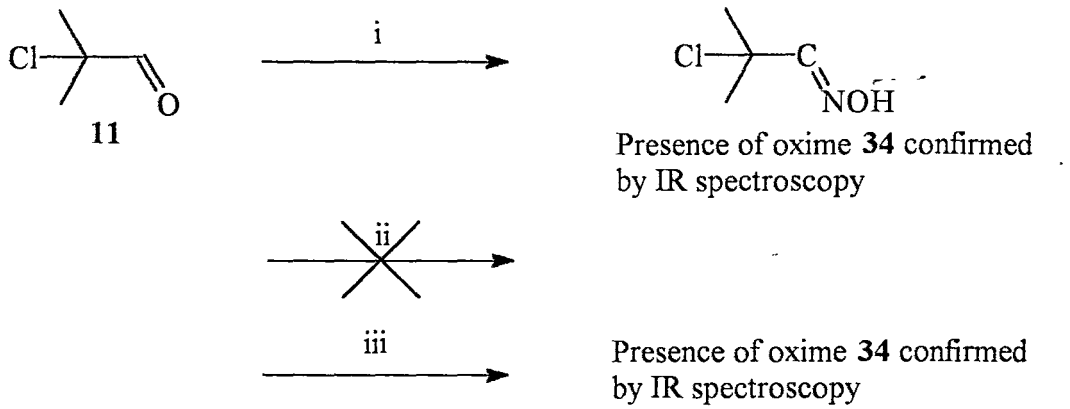


Figure 7 400 MHz ^{1}H NMR spectrum of 2-methylpropanal oxime **33** in $CDCl_3$.

oxime **34** suggests that it does not form easily under the reaction conditions and, as no evidence for the presence of the oxime **34** was found in the GC-MS analysis of the final aldicarb oxime **9** reaction mixture, it was thought to be an unlikely impurity.



Reagents: i) $NH_2OH.HCl$, NaOH, EtOH r.t.

ii) $NH_2OH.HCl$, NaOAC, H_2O, r.t.

iii) $NH_2OH.HCl$, NaOH, H_2O, 0°C

Scheme 13 Attempted synthesis of 2-chloro-2-methylpropanal oxime **34**.

2.1.3.2 Nitriles

Aliphatic nitriles are commonly prepared by one of four methods:[122] - i) displacement reactions of alkyl halides with cyanide ion; ii) displacement reactions of arylsulphonylhydrazones with cyanide ion; iii) cyanoethylation; and iv) dehydration of aldoximes and amides.

Displacement of halide from alkyl halides, using cyanide ion, is a method of extending the carbon chain by one carbon atom. The cyano group can subsequently be hydrolysed to a carboxylic acid or reduced to an amino group. The classic procedure involves heating the alkyl halide, usually the bromide or chloride, with either sodium cyanide or potassium cyanide in methanolic or ethanolic solution.[122] Yields for this

reaction are not always good because the alkyl halide substrate is not always soluble in water or polar solvents whilst the nucleophile (the cyanide anion) is water soluble, but insoluble in organic solvents;[123] formation of the isonitrile is also sometimes observed. (If the isonitrile is specifically desired, it can be produced by using silver cyanide).[124] The solubility problem can be overcome by use of a dipolar aprotic solvent such as hexamethylphosphoramide (HMPA) or a mixture of HMPA and a crown ether such as 18-crown-6, which dissolves both of the reacting species.[125] Phase transfer catalysts may also be used to transfer the nucleophile into the organic phase. Common phase transfer catalysts for this type of reaction are quarternary ammonium salts (*e.g.* tetraethylammonium cyanide),[125] phosphonium salts (*e.g.* hexadecyltributylphosphonium bromide[126]), cryptands and crown ethers.[127] Complementary to the use of phase transfer catalysts is the use of a catalytic support, such as alumina, in a solid-liquid biphase reaction; an example is the reaction between 1-bromooctane and sodium cyanide to produce 1-cyanooctane. This is known as triphase catalysis.[99]

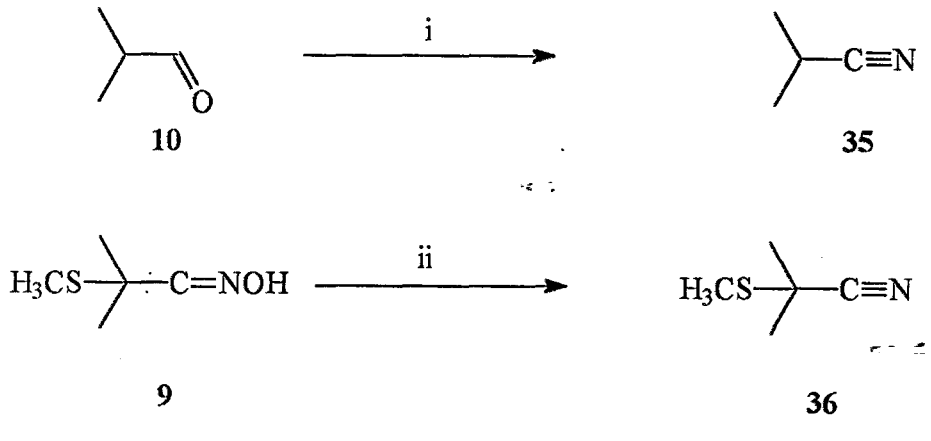
The use of arylsulphonylhydrazones is convenient when an aldehyde or ketone is more readily available as a starting material than the corresponding alkyl halide. The 2,4,6-triisopropylbenzenesulphonyl hydrazone is prepared from the carbonyl compound and then gently refluxed with potassium cyanide to afford the nitrile.[128]

Cyanoethylation is a means of introducing a three carbon unit (a 2-cyanoethyl group) from which a range of polyfunctional compounds can subsequently be prepared. An example is the reaction of acrylonitrile with diethylmalonate to produce diethyl (2-cyanoethyl)malonate. Sodium ethoxide is used as a base.[122]

The most logical method for the preparation of 2-methylpropanenitrile **35** and 2-methyl-2-(methylthio)propanenitrile **36** was dehydration of the corresponding oximes. Dehydration of aldoximes occurs under milder conditions than the corrseponding dehydration of amides and a wide range of dehydrating agents have been reported in recent literature. However, some of these are not readily available, are dangerous to work with or have complicated work-up procedures. Some successful

reagents include:- phosphorous pentoxide;[129] 4,6-diphenyl-2-(methylthio)pyrilium tetrafluoroborate,[130] a general reagent applicable to alkyl, aryl, alkaryl and heteroaryl aldoximes, with yields varying from 72-93%; clay (montmorillonite KSF)[131] which is readily available, convenient to use and simple to work up, and affords yields ranging from 65-86%; trifluoroacetic anhydride and pyridine,[132] a versatile combination which is especially useful if the parent oxime has a *trans* (E)-configuration. *Trans* oximes are often more difficult to dehydrate than the corresponding *cis* (Z)-isomers, but, by varying the substrate-base molar ratio, 90% conversion of the (E)-isomer has been observed; copper acetate monohydrate in refluxing acetonitrile[133] is effective for dehydrating both alkyl and aryl aldoximes in good yield (80-98%); chlorosulphonyl isocyanate[134] - a very mild and effective method giving yields of 75-86%; and disubstituted hydrogen phosphonates which, in the presence of a tertiary amine and tetrachloromethane,[135] react cleanly, the geometry of the oxime apparently having little effect on the reaction.

Two other methods involve the one-step conversion of aldehydes into nitriles, either by refluxing a solution of the aldehyde and hydroxylamine hydrochloride in formic acid for 30-60 min,[136] or refluxing a solution of the aldehyde, hydroxylamine hydrochloride and a few drops of hydrochloric acid in 95% ethanol for 6 hours.[137] Both methods quote very good yields (>90%) The oxime is generated *in situ* and dehydrated without isolation. These methods were, in fact, used for the synthesis of 2-methylpropanenitrile **35** and 2-methyl-2-(methylthio)propanenitrile **36** as shown in Scheme 14. Since compound **9** is already an oxime, it was refluxed in formic acid alone. Although the presence of each nitrile was confirmed using infra-red spectroscopy (ν_{max} 2260-2240 cm^{-1}), isolation was difficult. The formic acid procedure used to prepare 2-methyl-2-(methylthio)propanenitrile required neutralisation using a 5% sodium hydroxide solution. The volume required to neutralise the solution was large relative to the organic layer, which further complicated isolation.



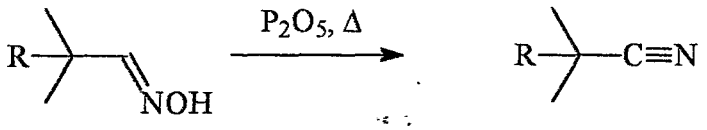
Reagents:

i) $NH_2OH.HCl$, HCl, EtOH, Δ

ii) HCOOH

Scheme 14

One of the classic dehydrating agents is phosphorus pentoxide (P_2O_5), mentioned above. However, its use does have several disadvantages, *viz.*, the reaction is carried out at elevated temperatures which may be unsuitable for thermosentsitive systems; the nitrile must be sufficiently volatile to allow isolation by distillation; the avidity of P_2O_5 for water makes it unpleasant to work with; and the extensive charring that occurs during the reaction makes cleaning of glassware difficult. Use of a supported phosphorus pentoxide reagent (supplied by E. Merck as 'Sicapent'®) has been reported as a means of overcoming some of these difficulties.[138] Residues are easily removed from the glassware after work-up, and the dehydration occurs readily at moderate temperatures. This method was also attempted for the synthesis of 2-methyl-propanenitrile **35**, but because of the large volume solvent necessary to facilitate stirring of the reaction mixture, isolation of the product proved difficult. The dehydration of both oximes was finally was achieved using phosphorus pentoxide (Scheme 15).[129,139] Although yields of 2-methylpropanenitrile **35** were only in the region of 50%, the product was very clean, and no further purification was necessary. The dehydration of 2-methyl-2-(methylthio)propanionitrile **36** was a far more vigorous reaction and the product was not as clean; further purification using preparative thin layer chromatography was therefore necessary.



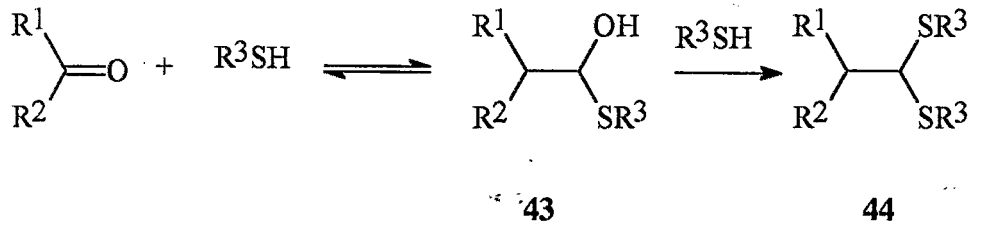
Compound	R	Compound
33	H	**35**
9	H_3CS	**36**

Scheme 15

2.1.3.3 Thioacetals

Thioacetals and dithioacetals constitute one of the most useful classes of compounds in organo-sulphur chemistry.[140] They are classically prepared by protic acid or Lewis acid catalysed condensation of an aldehyde or ketone with a thiol, as shown in Scheme 16.[141,142] Carbonyl compounds react more readily with thiols than with the corresponding alcohols; this is because of the greater nucleophilicity of sulphur relative to oxygen.[143] Lower members of the thiol class have extremely offensive odours, but this diminishes as the carbon content increases.[144] The name 'thioacetal' has long been used, following the convention in the oxygen series (the acetals) and systematic names are seldom used.[±] Thus compound **43** is trivially named a half-mercaptal [systematically, it is a 1-(alkylthio)alkanol or an α-hydroxyalkyl sulphide], and **44** is a thioacetal or a mercaptal [systematically, 1-(alkylthio)alkylsulphide].[142]

[±] Older papers refer to acetals and hemiacetals derived from ketones as ketals and hemiketals respectively; this has since been abandoned (IUPAC Rule C-331.1) and they are now all referred to as acetals and hemiacetals.



Scheme 16

The synthetic utility of thioacetals can largely be attributed to the fact that they are more stable under acidic and basic conditions than their oxygen analogues. They are widely used as nucleophilic carbon monoxide equivalents, or carbonyl synthons.[142] (A synthon is defined as 'a structural unit within a molecule that can be formed and/or assembled by known or conceivable synthetic operations'.[145]) They are useful carbonyl protecting groups and are reagents which bring about 'umpolung',[142,143] a reversal of the polarity of the carbonyl group; they thus convert an electrophilic centre into a nucleophilic one. Thioacetals are particularly useful as protecting groups in steroid synthesis,[140,146] and as intermediates in the conversion of aldehydes to chain-extended hydrocarbons.[145,147] The thiol protecting group is readily removed under mild conditions using $HgCl_2$.[142,145]

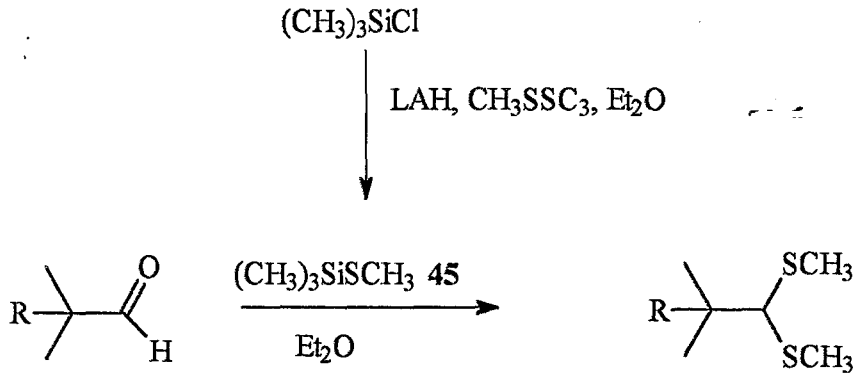
Because the first step of the thioacetalisation is reversible (see Scheme 16) the conditions necessary for high yields are often severe. Lewis acids, long used in the preparation of thioacetals, include $ZnCl_2$,[148] boron trifluoride-diethyl ether complex[149], and, more recently, $AlCl_3$,[150] which has been found to be an extremely efficient reagent, especially for thioacetalisation of aromatic ketones which are generally less reactive. However, carbonyl compounds containing an α-hydrogen only give yields in the region of 50%, while carbonyl compounds capable of a high degree of enolisation give vinyl sulphides, the elimination products of the thioacetal. The use of two other Lewis acids, $TiCl_4$ and $FeCl_3$, have thus been investigated.[147] $FeCl_3$ was found to be inferior to $AlCl_3$, but $TiCl_4$ was found to be an excellent catalyst, affording carbonyl compounds with α-hydrogens in yields in excess of 95% and even highly enolisable compounds in near quantitative yields. Other more recent

methods include:- tetrachlorosilane ($SiCl_4$),[140] a mild and selective catalyst showing excellent chemoselectivity (99%); polyphosphoric acid trimethylsilyl ester (PPSE),[151] an efficient reagent which is not affected by the presence of functional groups such as phenol or carboxylic acid; silica gel treated with thionyl chloride,[100] a very effective, highly selective catalyst for thioacetalisation of aldehydes, its selectivity making it especially useful when both aldehydes and ketones are present; and H-Y and H-mordenite zeolites.[152]

The catalytic properties of zeolites is thought to be due to their shape selectivity as well as their acidity and thermal stability, and their potential in synthetic organic chemistry is largely unexplored. A wide range of dithioacetals have been prepared in good yield using H-Y and H-mordenite zeolites;[152] the workup procedure is very simple and the catalyst can easily be regenerated by heating. H-Y zeolite is superior to H-mordenite, especially in the case of sterically hindered ketones and other bulky substrates, and particularly good yields were obtained compared to more conventional methods. In addition to $BF_3.Et_2O$ mentioned earlier, other compounds containing boron have been found to be useful reagents in the synthesis of thioacetals. These include:- alkylthioborates,[153] reagents which are readily prepared and provide a mild, effective route to cyclic ethylene thioacetals at room temperature; and orthothioboric esters,[154] obtained by the action of mercaptans on boron sulphide, which react with aldehydes and ketones to form the corresponding thioacetals. The reaction proceeds at room temperature in neutral medium and is general for both aromatic and aliphatic substrates. Efficient deoxygenative thioacetal formation in almost quantitative yield using tributylphosphine under mild conditions has also been reported[155] but, owing to difficulties experienced in obtaining tributylphosphine, this method was not attempted.

The method finally chosen to prepare compounds **37** and **38** was one which appeared to give the best yields for lower aliphatic aldehydes,[146,156] *viz.*, the use of trimethyl(methylthio)silane. In this approach, the affinity of silicon for oxygen is exploited; chlorotrimethylsilane is used to prepare trimethyl(methylthio)silane **45**, a reagent which reacts spontaneously at 0°C with a wide range of aldehydes and ketones. The rate of thioacetalisation is proportional to the polarity of the solvent,

and solvents such as benzene, acetonitrile, dichloromethane and diethyl ether can be used; diethyl ether was the solvent chosen for the preparation of compounds **37** and **38** *via* the route outlined in Scheme 17.



R	Compound	R
H	**10**	
Cl	**11**	
	37	H
	38	Cl

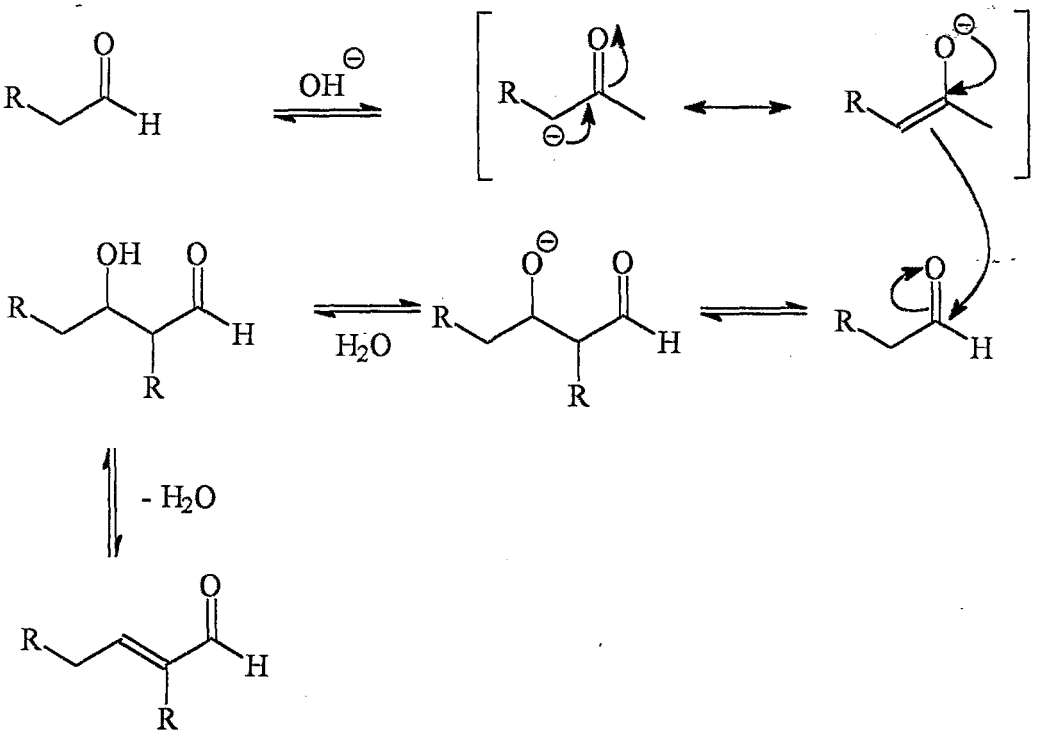
Scheme 17

The formation of 2-methylpropanal dithioacetal **37** was confirmed by NMR and mass spectroscopic analysis. The crude product, isolated as an oil, was not purified; two spots were detected by TLC, and the presence of unreacted 2-methylpropanal **10** was also evident in the NMR spectra. There was no evidence for the formation of the corresponding hemiacetal. The attempted synthesis of the 2-chloro-2-methylpropanal dithioacetal **38** by this method, however, proved to be unsuccessful.

2.1.3.4 Aldol products

The aldol reaction involves the base-catalysed addition of an aldehyde or a ketone to the carbonyl group of another aldehyde or ketone to form a β-hydroxycarbonyl compound (an aldol). Alkali metal hydroxides are the most commonly used bases,

although stronger bases such as aluminium *t*-butoxide may also be employed.[157, 158] The reaction is sometimes referred to as the aldol condensation; strictly speaking this is not correct, as condensation implies formation of the α,β-unsaturated dehydration product, not the aldol itself. The dehydration often occurs spontaneously to form a double bond in conjugation with the carbonyl double bond. In many cases, it is the dehydrated product that is isolated, and extreme care must be taken if the aldol is the desired product. Isolation of the aldol product can be achieved by carrying out the reaction at or below room temperature, followed by careful distillation under reduced pressure; when the reaction is carried out at elevated temperatures the α,β-unsaturated dehydration product is typically obtained. All steps in the reaction are reversible, but the equilibrium generally favours the aldol product in the case of unhindered aldehydes, and the starting materials in the case of sterically hindered aldehydes and ketones. The mechanism of the base-catalysed reaction is shown in Scheme 18.[157,158,159] The reaction may also be catalyed by dilute mineral acid.[160]



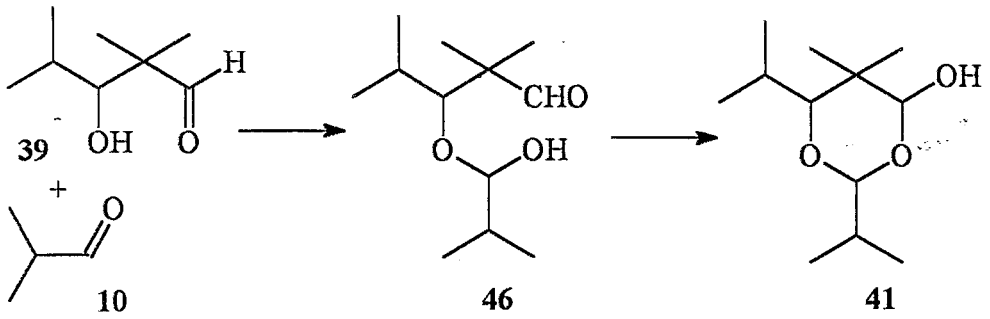
Scheme 18

The reaction may occur between two molecules of the same aldehyde or ketone, two molecules of different aldehydes or ketones or between an aldehyde and a ketone, and is one of the most fundamental and versatile tools in synthetic organic chemistry.[161,162] However, the crude product frequently contains di-, poly- and self-condensation products, and separation of the mixture is usually difficult.[161] In addition, in mixed aldol reactions (between different aldehydes or ketones) two self-condensation products may form as well as the two 'crossed' products, and these reactions are generally of little synthetic utility unless one of the carbonyl compounds has no α-hydrogen and can only act as as a carbanion acceptor.[158,163] These difficulties may be obviated and the reaction may be made regioselective by effecting a directed aldol reaction. This is achieved by preforming the enol derivative, the most common of which is a silyl enol ether, which is then reacted with the aldehyde or ketone in the presence of a catalyst such as $TiCl_4$; this is known as the Mukaiyama reaction.[161] It is applicable to all common aldehydes and ketones and affords the cross-aldol addition product in excellent yield. The reaction is regiospecific to the olefinic α-carbon of the silyl enol ether.[161] Various other catalysts may be used and, at high pressure, the reaction may even proceed in the absence of catalyst.[162] Basic ion exchange resins are very effective at converting two molecules of the same aldehyde to the aldol,[157] and the formation of aldols has also been reported using $POCl_3$ at -15°C.[164] However the yields obtained using this method are low and at higher temperatures $POCl_3$ catalyses polymerisation.

The two faces of the carbonyl group in all aldehydes except formaldehyde are prochiral and, in most cases, the aldol condensation creates two new chiral centres and four stereoisomers are possible- a *syn* (*erythro*) pair and an *anti* (*threo*) pair. Diastereosolectivity and enantioselectivity may be achieved by the judicious choice of reagent systems.[157, 159]

In the present investigation, 3-hydroxy-2,2,4-trimethylpentanal **39**, the aldol formed from the self-condensation of 2-methylpropanal **10**, was synthesised. Due to the presence of the two methyl groups in the α-position, dehydration to a conjugated product is not possible. However, it can condense further with another molecule of

2-methylpropanal **10**, with or without catalyst, to form 2,4-diisopropyl-5,5-dimethyl-6-hydroxy-1,3-dioxane **41**;[165,166,167] this compound was, in fact, isolated upon reacting 2-methylpropanal **10** with sodium hydroxide at room temperature (see Scheme 19). The aldol **39** and the uncyclised trimer **46**, however, were not isolated. Reaction of 2-methylpropanal **10** with potassium hydroxide in the presence of dibutylamine, afforded a white crystalline product which formed in the condenser during distillation. This compound was shown (by the absence of hydroxyl and carbonyl peaks in the IR spectrum and by ^{1}H and ^{13}C NMR spectroscopy) to be the trioxane trimer **20** of 2-methylpropanal **10**. The formation of this compound is discussed in Section 2.1.3.5 Reaction of equimolar quantities of 2-methylpropanal **10** and 2-chloro-2-methylpropanal **11** afforded an oil which, upon NMR analysis, was found to contain a mixture of unreacted aldehydes and trioxane trimers.



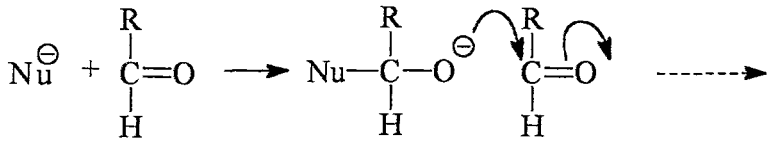
Scheme 19

2.1.3.5 Aldehyde Trimers

Due to the strong polarity of the carbonyl double bond of aldehydes, these compounds can be incorporated into polymer chains through anionic or cationic polymerisations.[166,167] Formaldehyde may be polymerised with weak nucleophiles and electrophiles but higher aldehydes require strong acids and bases for polymerisation to occur.[168] Polyaldehydes are very unstable and equilibrium between polymerisation and depolymeristion is easily reached. End-capping of the unstable hydroxyl and

alkoxide ends to form stable ether and ester ends substantially increases the stability of the polymer.[168,169,170] In anionic polymerisation studies carried out in THF at -78°C on chloro- and methyl trisubstituted acetaldehydes and 2-methylpropanal **10**, it was found that substitution of chlorine for methyl groups in the aldehyde increases the stability of the polymer relative to the monomer.[170]

Anionic initiators produce polymers of higher aldehydes if polymerisation is carried out at low temperatures. Initiators include:- alkali metals, *e.g.* lithium, sodium and potassium sand; alkali metal alkoxides, *e.g.* lithium triphenylmethoxide; soluble hydrides *e.g.* lithium aluminium hydride; organometallic compounds *e.g.* butyllithium and Grignard reagents; and sodium naphthalene.[168,169,171] No side reactions occur under anionic polymerisation conditions. (This is not the case for cationic polymerisation, as will be discussed.) Studies on the effects of solvent on the polymerisation of 2-methylpropanal **10** have shown yields of polymer to be greater in hydrocarbon solvents.[171,172] Several detailed mechanisms have been proposed for anionic polymerisation[168] and the basic mechanism for initiation is shown in Scheme 20. Propagation proceeds by attack of the nucleophilic alkoxide ion on a new monomer.



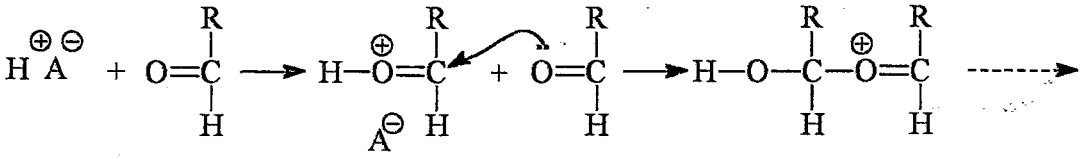
where Nu is a nucleophile

R is an alkyl group

Scheme 20

Initiators for cationic polymerisation include BF_3-etherate, γ-alumina, silica, mineral acids, trifluoro- and trichloroacetic acid, and Lewis acids such as $AlCl_3$.[168,169] Addition of a strong mineral acid to acetaldehyde at room temperature results in a vigourous, highly exothermic reaction to form the trimer, paraldehyde.[168,173] The

equilibrium favours the trimer (88%). If the reaction is carried out at -10 to -30°C, a tetramer is also formed in amounts of 5-10%. At temperatures of -40°C and below, the polyacetaldehyde forms and, only at temperatures below -80°C, can the formation of the undesired trimer and tetramer be avoided. Strict temperature control is therefore necessary to prepare polyaldehydes in the presence of cationic initiators, as any local temperature rises will lead to the formation of the trimer.[168] The proposed mechanism of cationic initiation by protic acids is shown in Scheme 21. The process is initiated by electrophilic attack of the proton on the carbonyl oxygen of the aldehyde monomer to afford an oxonium ion. Propagation occurs by nucleophilic attack of the carbonyl oxygen of the aldehyde monomer on the electrophilic terminal carbon atom next to the oxonium ion, thus forming a new oxonium ion which can further be attacked on the terminal carbon atom.

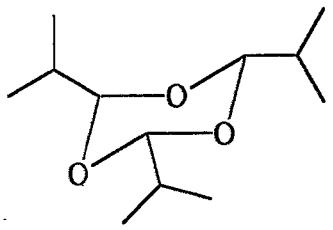


where R is an alkyl group

Scheme 21

2,4,6-Triisopropyl-1,3,5-trioxane **20** can be prepared in 80%yield by gently stirring 2-methylpropanal **10** with an oxide of either Zr, Sn or Ti,[174] or by stirring 2-methylpropanal **10** for 4 hours in the presence of either 55-58% H_2SO_4 or 80% H_3PO_4 to afford the trimer **20** in 90% yield.[175] 2-Chloro-2-methylpropanal **11** rapidly trimerises in the presence of a trace of acid to form 2,4,6-tris(2-chloro-2-methylethyl)-1,3,5-trioxane **21**.[108] In the present study, a solution of 2-methyl-propanal **10** was found to spontaneously trimerise upon standing at room temperature and exposed to oxygen for several weeks. Stoppered flasks containing 2-chloro-2-methylpropanal **11** were found to trimerise rapidly at or below room temperature.

In principle, substituted 1,3,5-trioxanes can exist in either a boat or a chair form, although it has been determined experimentally, by X-ray diffraction and IR measurements, that the chair form is more stable.[176] Four geometrical isomers of the chair form are possible; two *cis-trans* isomers in which two of the three R groups can be axial or equatorial, and two *cis-cis* isomers in which the three R groups are either axial or equatorial. Due to unfavourable steric interactions however, the axial form of the *cis-cis* isomer is unlikely, and the equatorial form is therefore the expected form. The isomeric forms of the trimer can be differentiated by analysis of their ^{1}H NMR spectra.[176] For example, the *cis-cis* isomer of 2,4,6-triisopropyl-1,3,5-trioxane **20** (Figure 8) has three equivalent O-CH-O protons, twelve equivalent methyl protons and three equivalent isopropyl protons, which is reflected by three signals in the ^{1}H NMR spectrum (see Figure 9). The ^{1}H NMR spectrum of the *cis-trans* isomer would contain three signals for the two equivalent groups and three signals half as intense for the other protons. Clearly, both 2,4,6-triisopropyl-1,3,5-trioxane **20** and 2,4,6-tris(2-chloro-2-methylethyl)-1,3,5-trioxane **21** (the ^{1}H NMR spectrum of which is shown in Figure 10) are the *cis-cis* isomers.



2,4,6-triisopropyl-1,3,5-trioxane **20**

Figure 8

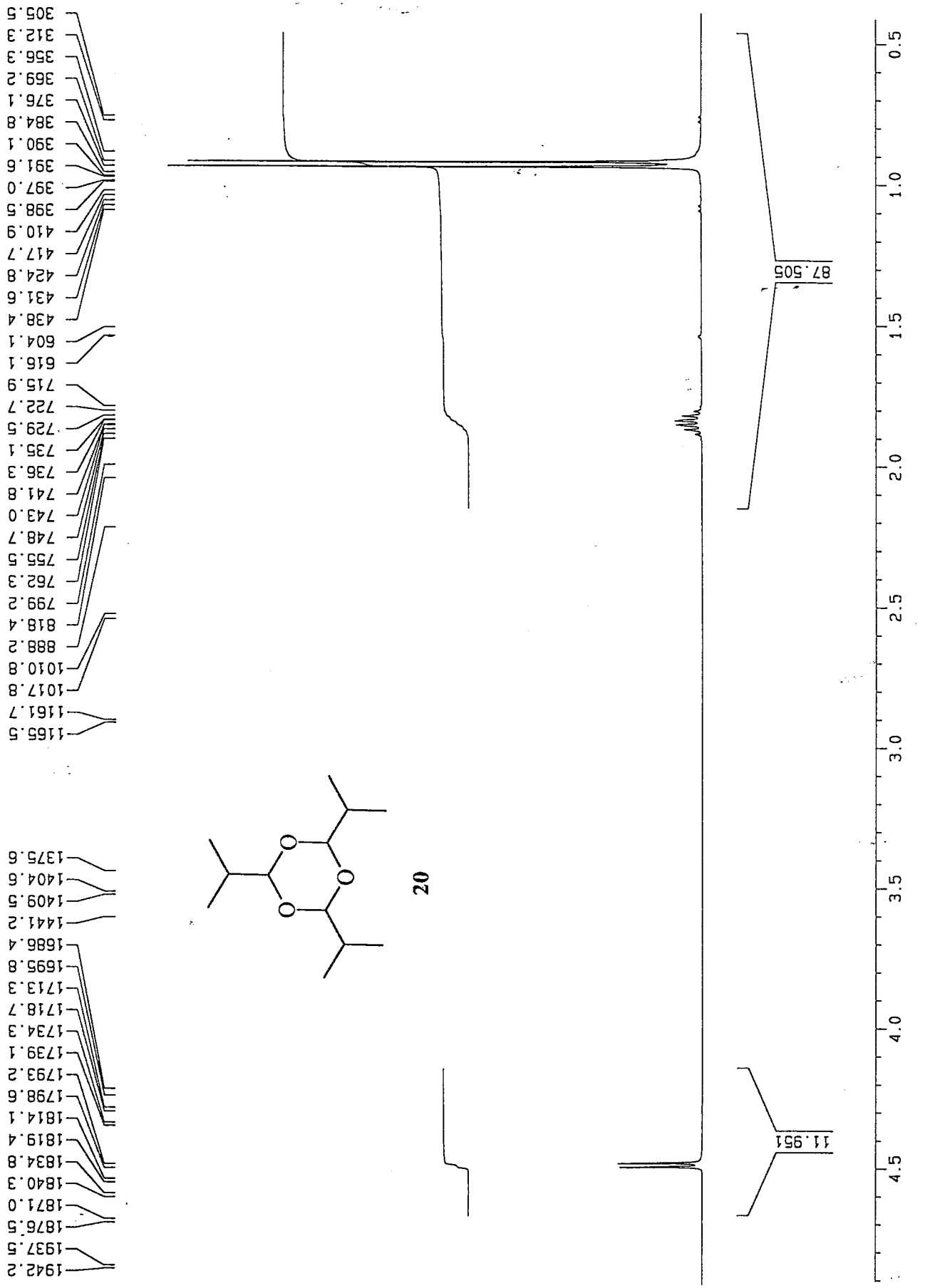


Figure 9 400Mhz ^{1}H NMR spectrum of 2,4,6-triisopropyl-1,3,5-trioxane **20**

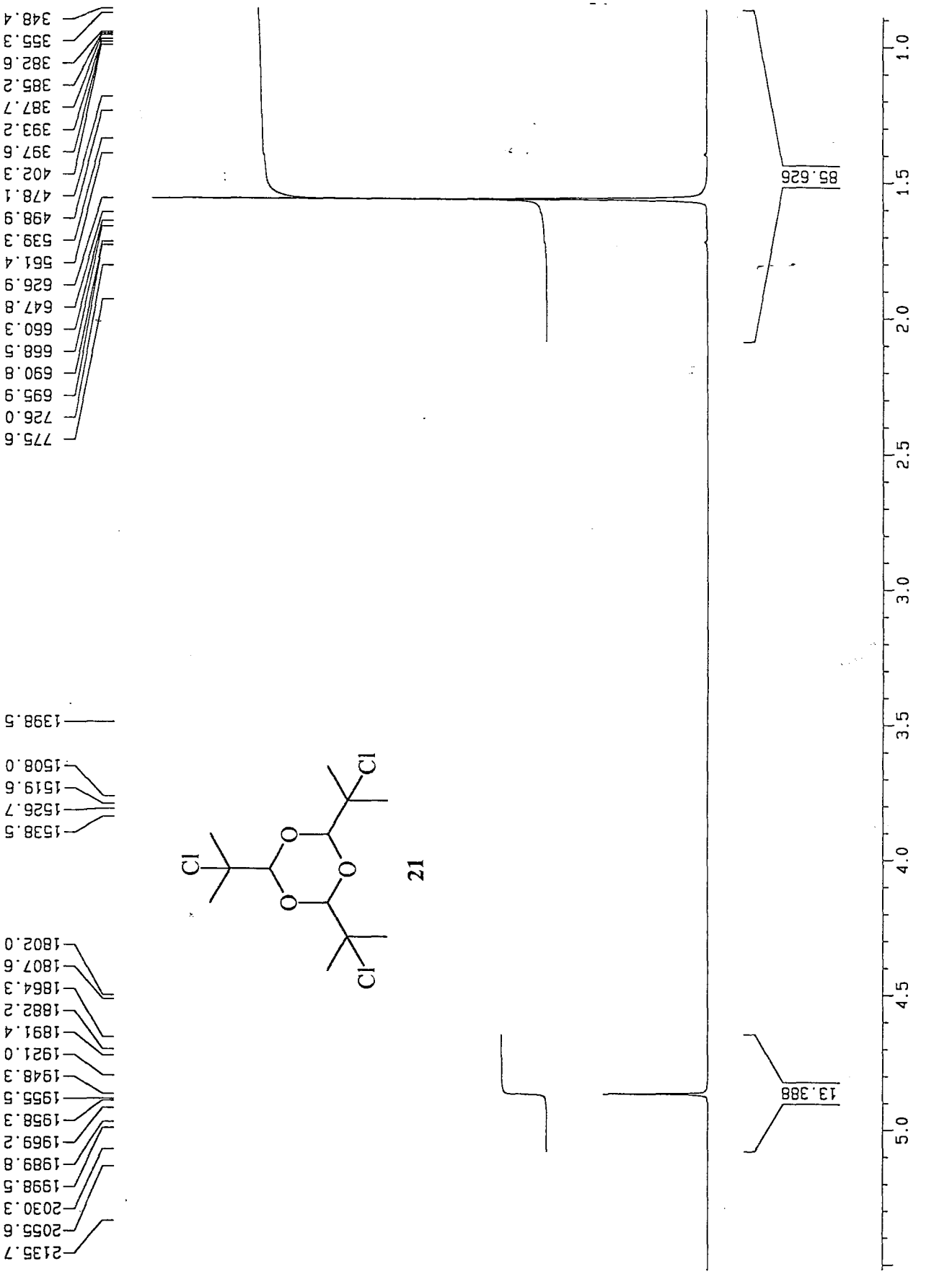
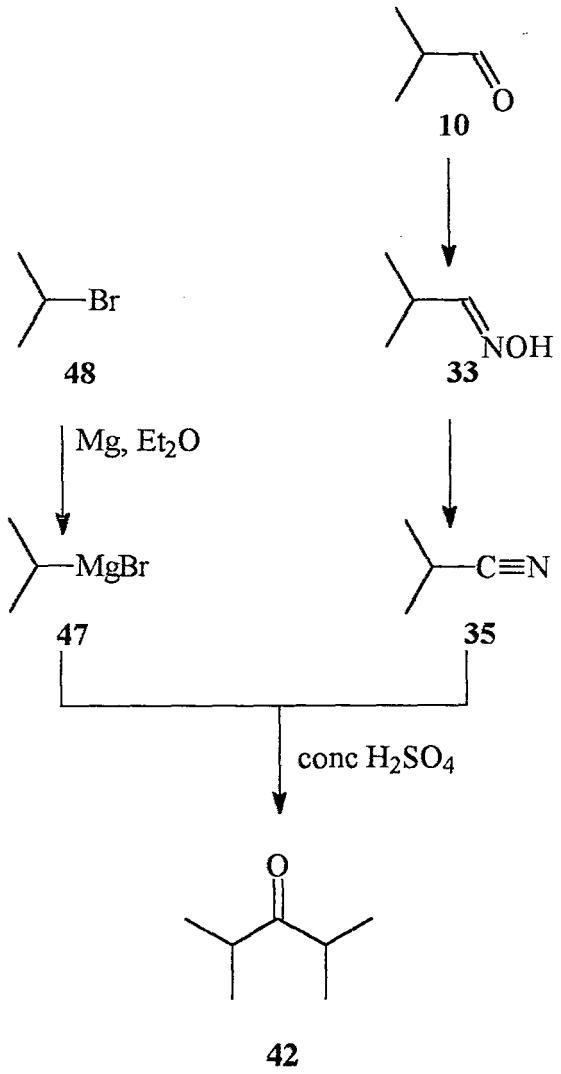


Figure 10 400Mhz ^{1}H NMR spectrum of 2,4,6-tris(2-chloro-2-methylethyl)-1,3,5-trioxane **21**

2.1.3.6 2,4-Dimethyl-3-pentanone

Aliphatic ketones can readily be synthesised *via* several routes. A previously reported method[177] was chosen to prepare 2,4-dimethyl-3-pentanone **42** (see Scheme 22). This approach involved reaction of a Grignard reagent **47**, generated from 2-bromopropane **48** with 2-methylpropanenitrile **35** to afford 2,4-dimethyl-3-pentanone **42** in 32% yield.

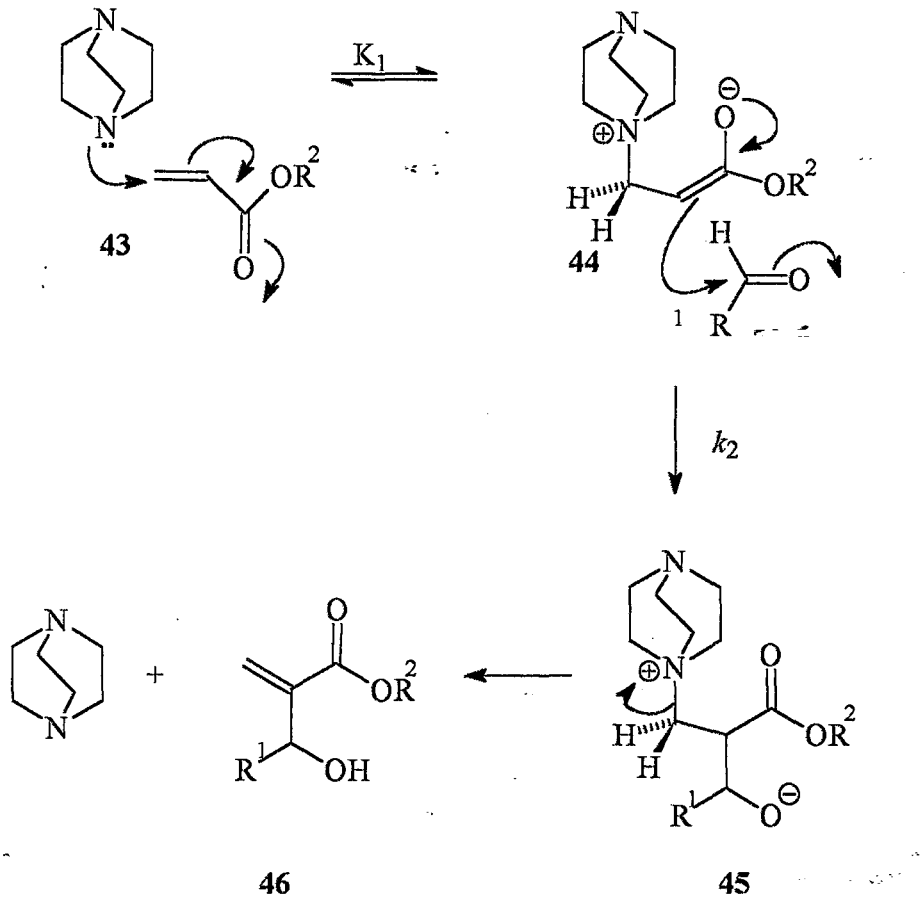


Scheme 22

2.1.4 Novel aldicarb analogues

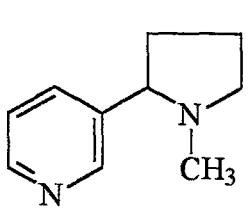
The Baylis-Hillman reaction is widely employed in organic synthesis, especially for the production of natural product intermediates such as necic acid synthons.[178] The reaction provides a convenient method of constructing a bond in the α-position of activated alkenes. Baylis and Hillman first described the reaction in 1972;[179] they reacted various aldehydes with α,β-unsaturated amides, esters, ketones and nitriles. The reactions, which are usually conducted at room temperature, are catalysed by cyclic tertiary amines and are typically very slow. Acrylate esters are the most common α,β-unsaturated systems employed, although acrylonitrile, methyl vinyl ketone, diethyl vinyl phosphonate, phenyl vinyl sulphone and acrolein are also used. 1,4-Diazabicyclo[2.2.2]octane (DABCO) is the most common catalyst, but other tertiary amines have also been successful, *e.g.* 3-hydroxyquinuclidine which dramatically accelerates the reaction, permitting a reduction in reaction time from days to hours.[180]

The addition-elimination mechanism which has been proposed for the Baylis-Hillman reaction is shown in Scheme 23.[181] Nucleophilic attack of the tertiary amine on the α,β-unsaturated system **43** forms a short-lived dipolar enolate **44**, which attacks the aldehyde to form an intermediate **45** in the rate-determining step of the reaction. Rapid proton transfer and elimination of the catalyst then affords the final coupled product **46**.

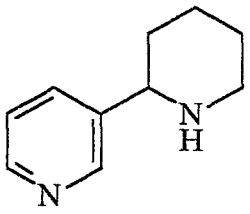


Scheme 23

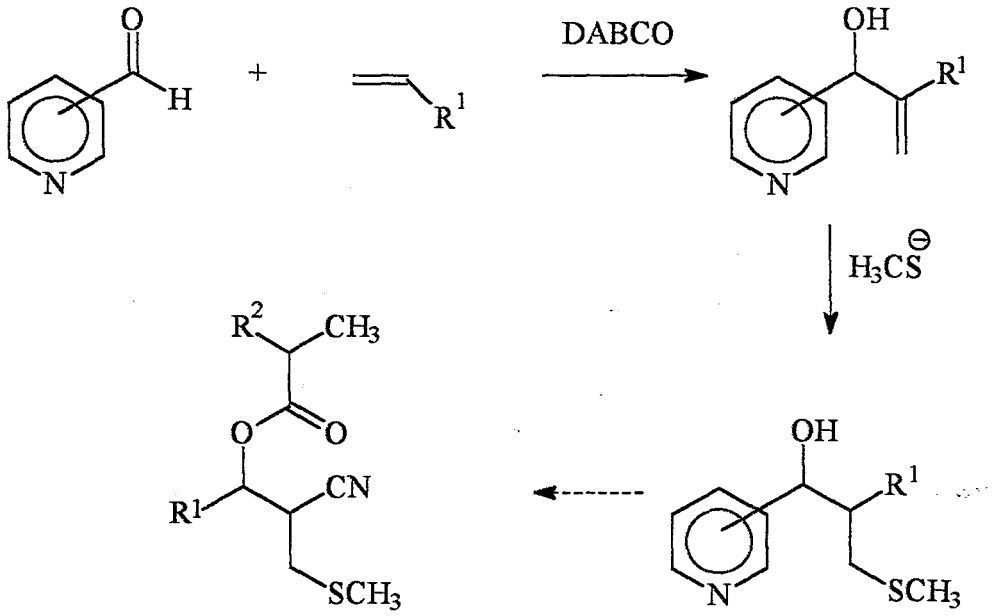
In the present study the Baylis-Hillman reaction provided access to novel aldicarb analogues (Scheme 24). Acrylonitrile and methyl acrylate were reacted with pyridine-carboxaldehydes under Baylis-Hillman conditions to prepare a range of hydroxyalkyl derivatives **47**, **48**, **49** (Scheme 25, Table 7), thiomethylation of which afforded a range of aldicarb analogue precursors **50** and **51** (Scheme 26). These compounds, like aldicarb, contain a thiomethyl group. Compound **50** also possesses a hydroxyl group which may be carbamylated to produce the corresponding carbamate. Moreover, the presence of the pyridyl moiety makes these compounds somewhat analagous to nicotine **52** and 3-(2-piperidyl)pyridine **53**, both of which are insecticidal.[182]



Nicotine **52**



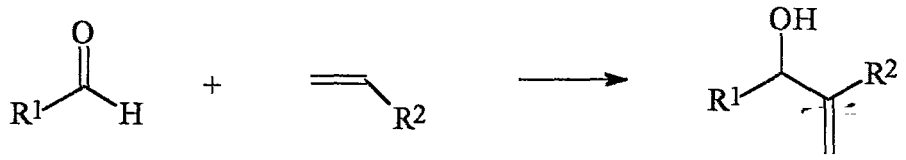
Neonicotine **53**



Scheme 24

The formation of Baylis-Hillman products can be monitored using ^{1}H NMR spectroscopy, by observing the disappearance of the aldehyde proton peak and the change in the vinylic protons of the acrylate substrate. Formation of the hydroxyalkyl products **47** and **48** was slow and even after several days the presence of starting material was detected. However, crystals of 3-hydroxy-2-methylene-3-(3-pyridyl)propanenitrile **49** formed in a matter of hours, and the reaction mixture, when left standing over the course of a week, formed a thick, tarry precipitate which finally became a dark brown solid, which was insoluble in most organic solvents. This particular reaction was therefore only allowed to run for four hours before work-up. Compounds **47** and **48** were viscous oils whereas **49** was crystalline. The products

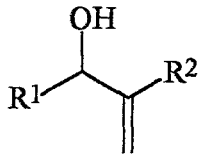
were all fully characterised by spectroscopic (^{13}C and ^{1}H NMR) and elemental analysis (high resolution ms). The presence of the nitrile group in compounds **48** and **49** was also confirmed by IR spectroscopy. The results of this stage are presented in Table 7.



R^1		R^2		R^1	R^2	
pyr-2	**55**	CO_2Me	**57**	pyr-2	CO_2Me	**47**
pyr-3	**56**	CN	**58**	pyr-2	CN	**48**
				pyr-3	CN	**49**

Scheme 25

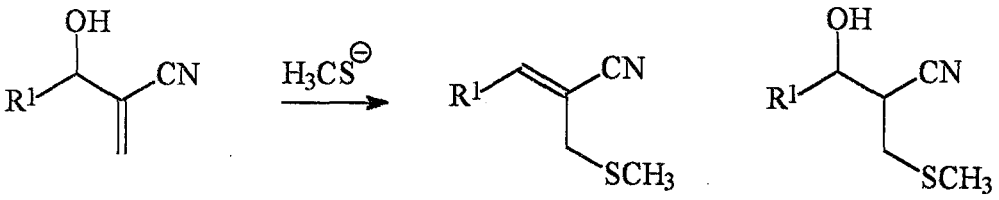
Table 7 Characterisation of Baylis-Hillman products



R^1	R^2	Compound	High Resolution MS Data			m.p	Yield
			Found	Molecular Formula	Calculated	°C	%
pyr-2	CO_2Me	**47**	193.0743	$C_{10}H_{11}NO_3$	193.0739	-	79
pyr-2	CN	**48**	160.0624	$C_9H_8N_2O_2$	160.0636	-	74
pyr-3	CN	**49**	160.0628	$C_9H_8N_2O_2$	160.0636	92-94	30

Thiomethylation of the α,β-unsaturated intermediates **47**, **48** and **49** was expected to occur readily to afford the corresponding 3-hydroxy-2-(methylthiomethyl)-3-

pyridylpropanenitriles and methyl 3-hydroxy-2-(methylthiomethyl)-3-pyridyl-propanoate. This thiomethylation was achieved by reacting the Baylis-Hillman products **47**, **48** and **49** at 35°C with a 21% aqueous solution of sodium thiomethylate (as shown in Scheme 26), and monitoring the course of the reaction by TLC. The reaction could also be monitored using ^{1}H NMR spectroscopy, by following the disappearance of the vinylic proton signals and the appearence of the thiomethyl signal (see Figures 11 and 12).



R^1			R^1	
pyr-2	**48**		pyr-2	**50**
pyr-3	**49**	**51**	pyr-3	

Scheme 26

Methyl 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate **47** appeared to be consumed during the course of the reaction (as monitored by TLC), but difficulties were experienced in isolating the product and NMR spectroscopy revealed that hydrolysis of the ester had occurred. 3-Hydroxy-2-methylene-3-(2-pyridyl)propanenitrile reacted readily to afford the expected 3-hydroxy-2-(methylthiomethyl)-3-(2-pyridyl)-propanenitrile product **50**; however, 3-hydroxy-2-methylene-3-(3-pyridyl)-propanenitrile **49** afforded the corresponding, conjugated, dehydrated derivative **51**

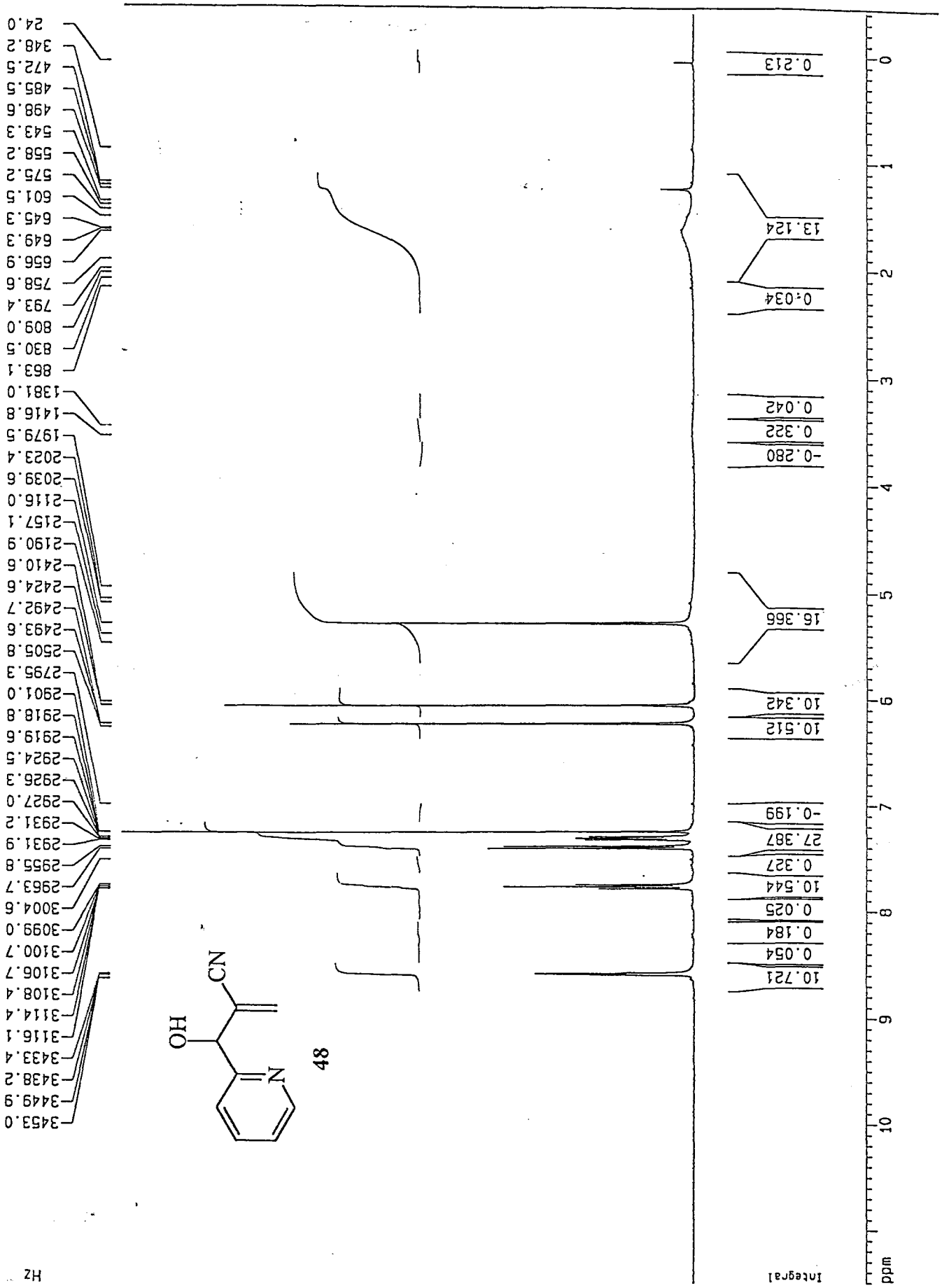


Figure 11 400MHz ^{1}H NMR spectrum of 3-hydroxy-2-methylene-3-(2-pyridyl)-propanenitrile **48**

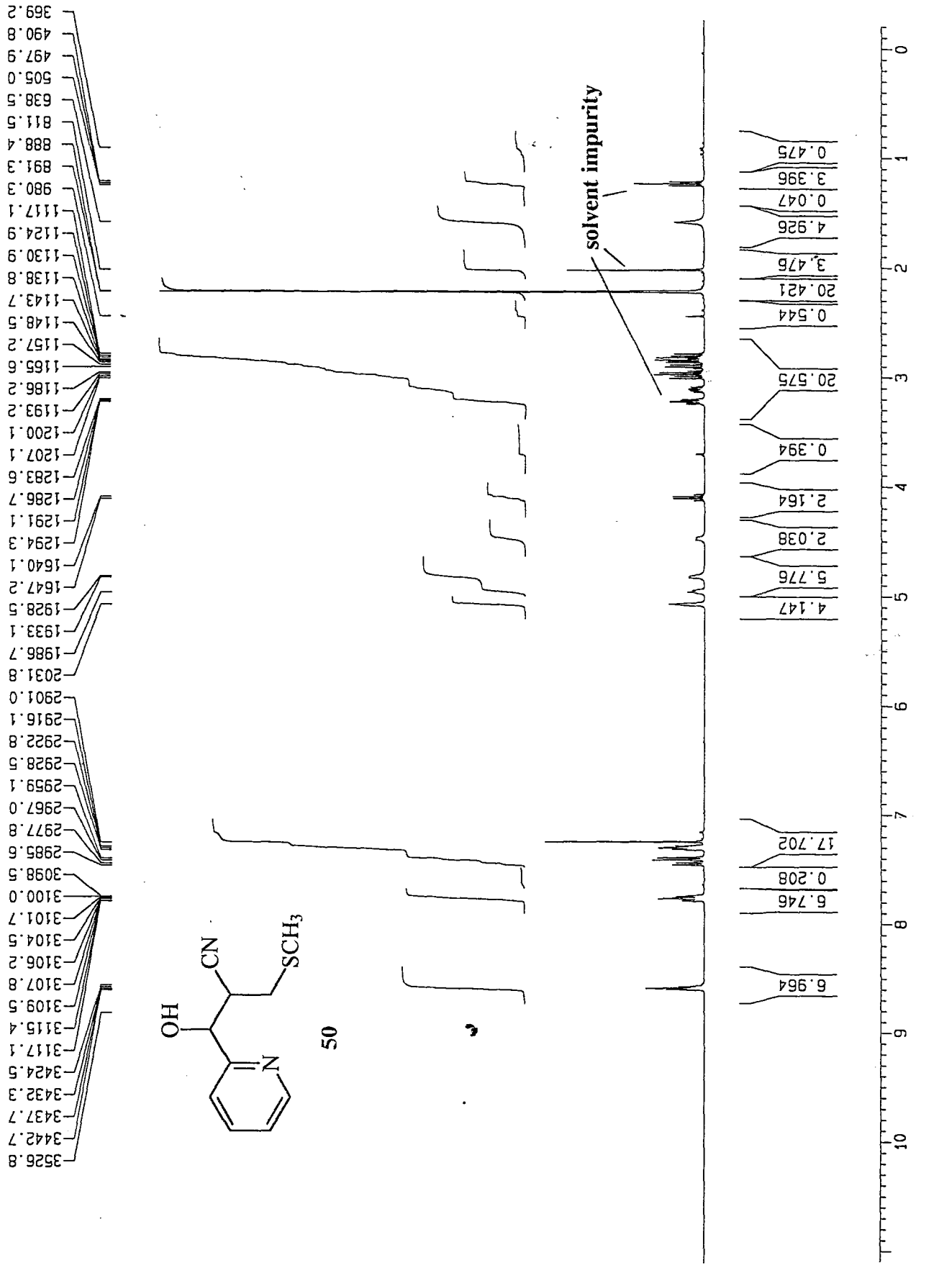


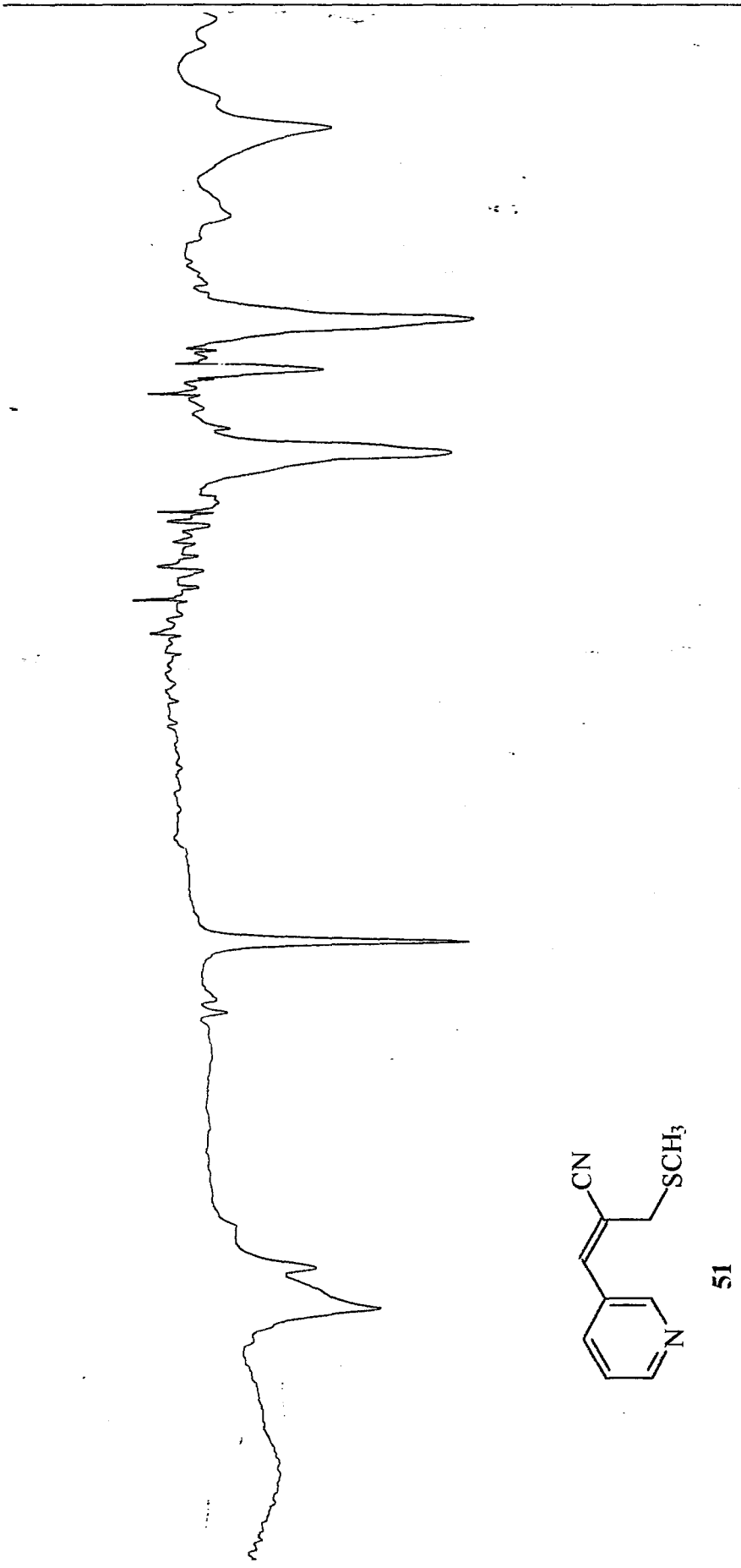
Figure 12 400MHz ^{1}H NMR spectrum of 3-hydroxy-2-(methythiomethyl)-3-(2-pyridyl)propanenitrile **50**.

instead of the hydroxy compound. This was proved by the disappearance of the hydroxy peak in the IR spectra, as well as by NMR spectroscopy (see Figure 13). Compound **50** possesses 2 chiral centres, and the presence of diastereomers was detected in the ^1H NMR spectrum (see Figure 12). However, the spectra for compound **51** indicates the presence of vinyl protons and shows no evidence of chirality. The absence of a hydroxyl group in this compound precludes its direct carbamylation to an aldicarb analogue. The results of the thiomethylation step are presented in Table 8.

Table 8 Results of thiomethylation

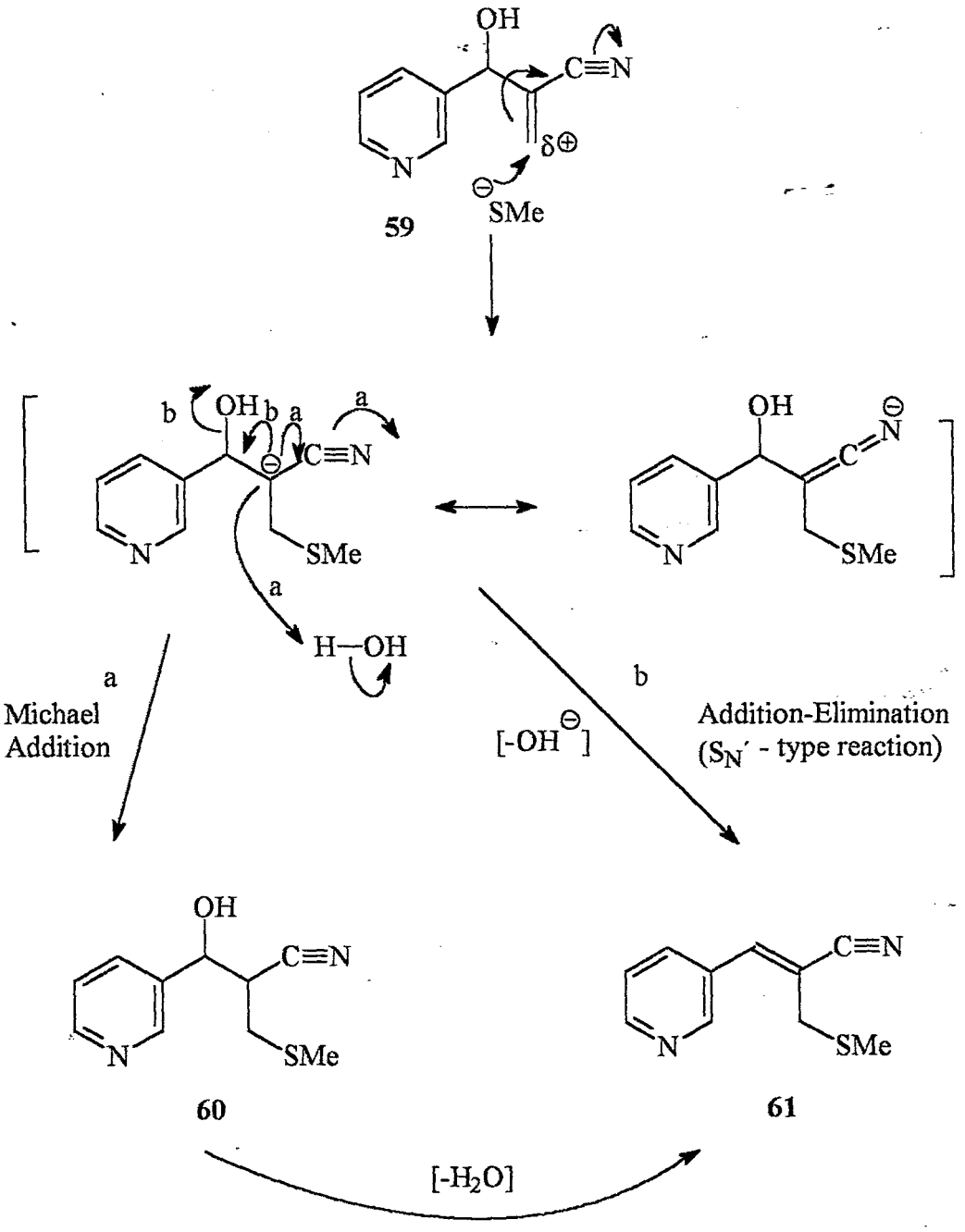
R^1	Compound	High Resolution MS Data			Yield
		Found	Molecular Formula	Calculated	%
pyr-2	**50**	208.0667	$C_{10}H_{12}N_2OS$	208.0670	38
pyr-3	**51**	190.0554	$C_{10}H_{11}N_2S$	190.0565	54

Formation of the dehydration product can be rationalised from a consideration of the mechanistic options. At least two possible mechanisms for the thiomethylation step can be can be proposed (see Scheme 27). Route (a) involves Michael addition to an α,β-unsaturated system **59** to form the hydroxy compound **60**, protonation (the proton being provided by the aqueous medium), followed by elimination of water then affords the conjugated product **61**. Route (b) is an addition-elimination reaction which affords the conjugated product **61** directly. Further investigations are necessary in order to establish the mechanism unambiguously.



51

Figure 13 IR spectrum of 2-(methylthiomethyl)-3-(3-pyridyl)-2-propenenitrile **51**.


OH
C≡N
δ⊕
N
SMe
59
b
OH
b
a
a
C≡N
N
SMe
OH
N
C
SMe
a
H—OH
a
Michael
Addition
b
[-OH⊖]
Addition-Elimination
(SN′ - type reaction)
OH
C≡N
N
SMe
60
C≡N
N
SMe
61
[-H2O]

Scheme 27

2.2 Analysis of aldicarb oxime impurities

2.2.1 Gas chromatography-mass spectrometry (GC-MS)

Crude aldicarb oxime **9** and the various synthetic standards were analysed by gas chromatography and by both low- and high-resolution mass spectrometry. The presence or absence of possible contaminants was confirmed by comparing the mass spectra of standards with those of all the components present in aldicarb oxime **9**. The identity of contaminants was further confirmed by spiking aldicarb oxime **9** with the standards and comparing gas chromatograms of the spiked and unspiked samples.

High resolution mass spectrometric analysis was attempted for all the synthetic standards. However, 2-methylpropanal oxime **33**, 2-methylpropanenitrile **35** and 2-methyl-2-(methylthio)propanenitrile **36** appeared to decompose on analysis, precluding high resolution analysis, although the presence of these compounds was confirmed by low resolution spectra. This observation is not unusual, especially in the case of aliphatic nitriles which are known to undergo skeletal rearrangement, and the molecular ion is often weak or non-existent.[183] Furthermore, in a previous study of the degradation products of aldicarb,[88] the difficulties in detecting nitriles have also been attributed to their decomposition.

Figure 14 shows a GLC trace of crude aldicarb oxime **9**. Low resolution mass spectrometric analysis was performed on the components labelled 1 to 12. In addition, selected fragments from component 7 (the low resolution mass spectrum of which is shown in Figure 15) were subjected to elemental analysis using high resolution mass spectroscopy, the results of which are recorded in Table 9.

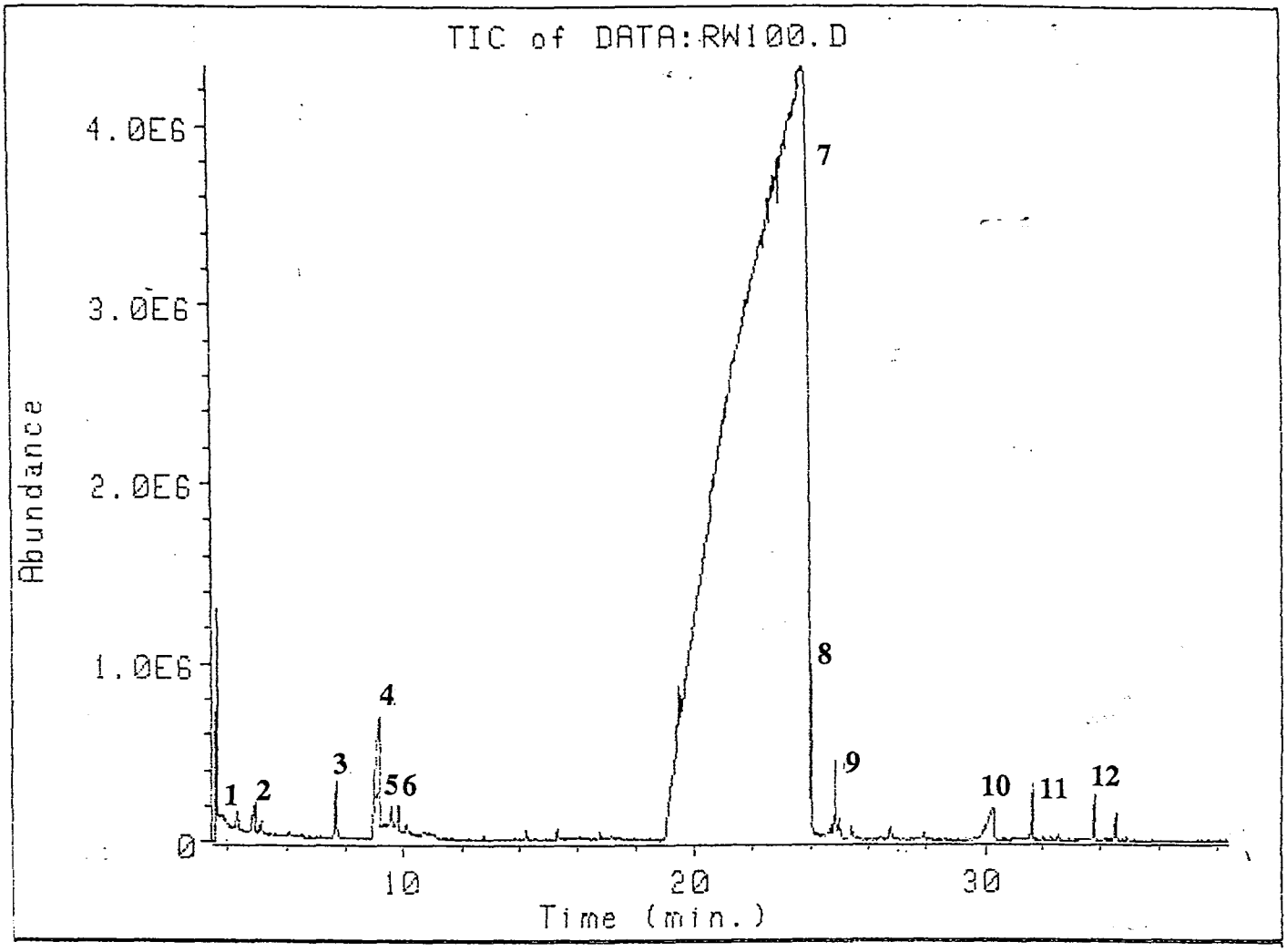


Figure 14 GLC trace of crude aldicarb oxime **9**

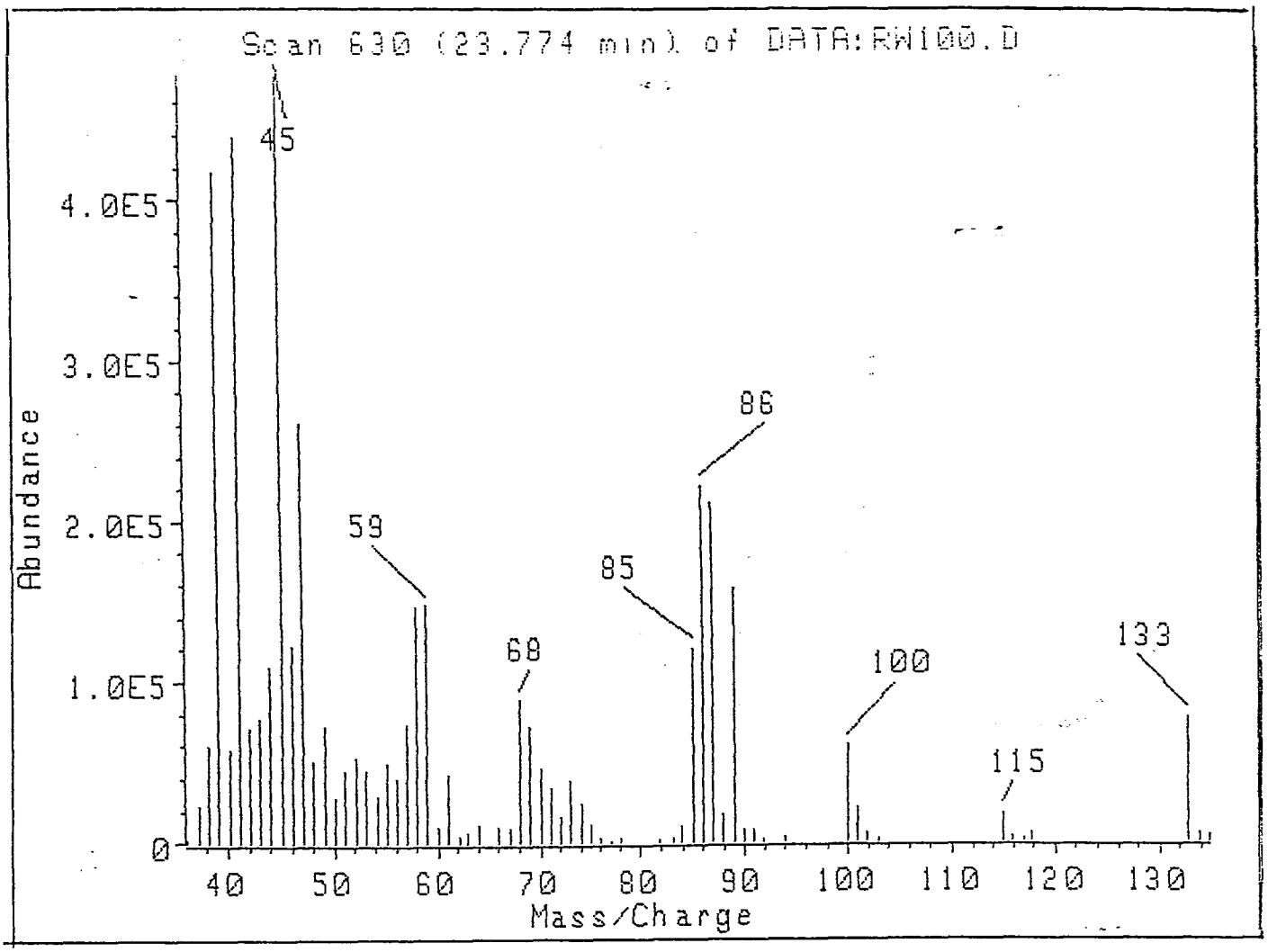


Figure 15 Mass spectrum of component 7

Table 9 High resolution MS data (*m/z*) for aldicarb oxime **9** (component 7)

Peak	Found	Molecular Formula	Calculated
133	133.0556	$C_5H_{11}NOS$	133.0561
115	115.0466.	C_5H_9NS	115.0455
100	100.0217	C_4H_6NS	100.0221
87	87.0675	C_4H_9NO	87.0684
86	86.0595	C_4H_8NO	86.0606
85	85.0532.	C_4H_7NO	85.0528
73	73.0642.	C_4H_9O	73.0653
68	68.0503	C_4H_6N	68.0500

The fragmentation patterns of components 1-12 (Figure 14) were examined and compared to those obtained for the synthetic standards.. As an example, the low resolution mass spectrum of component 12 is shown in Figure 16. The analysis outlined in Scheme 28 permits assignment of component 12 as the trimer of 2-chloro-2-methylpropanal. Assignment of the structures of components 1-12 is shown in Table 10.

No evidence of 2-chloro-2-methylpropanal oxime **34** and 2,4-dimethyl-3-pentanone (*m/z* 114) was detected, inducating their absence as contaminants in the aldicarb oxime **9** sample.

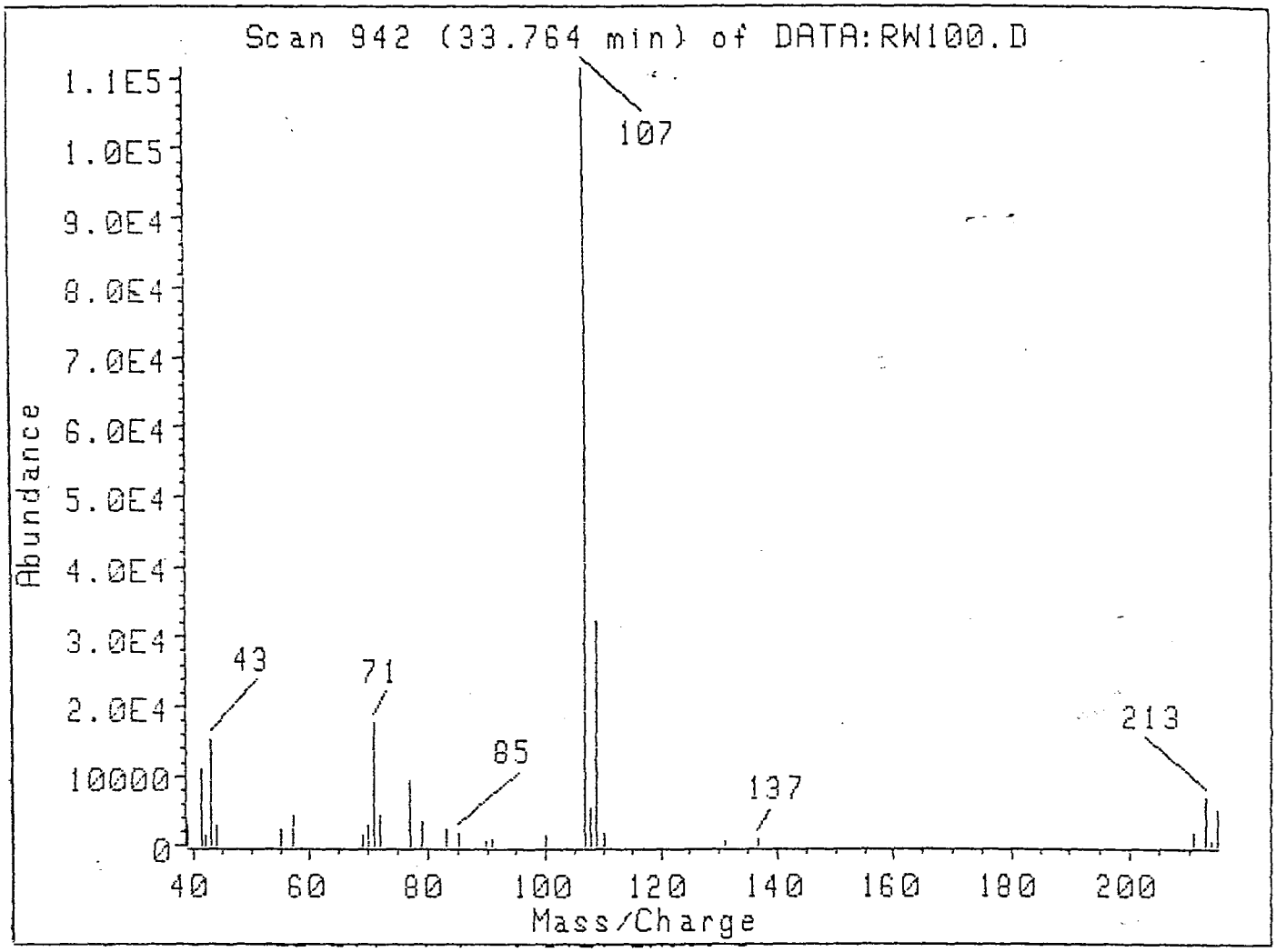
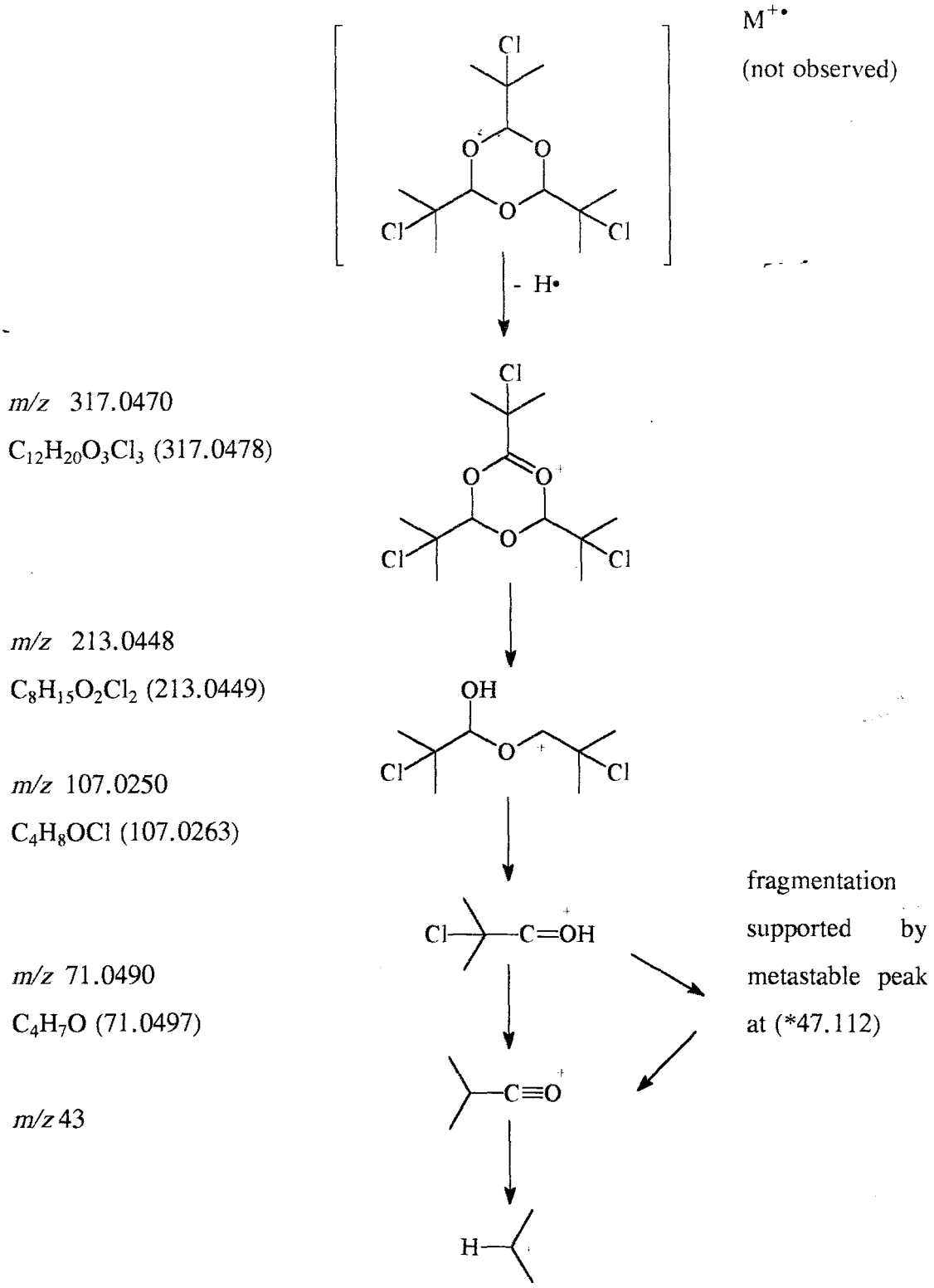
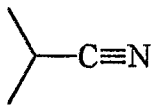
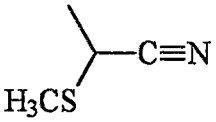
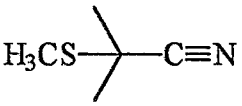
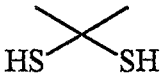
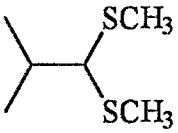
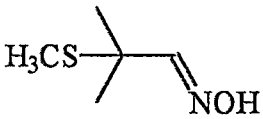
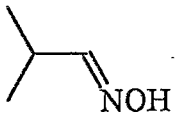
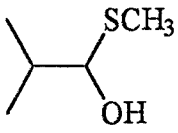


Figure 16 Low resolution mass spectrum of component 12 of aldicarb oxime **9**



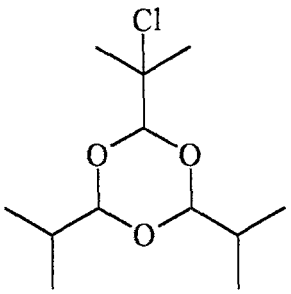
Scheme 28 Mass fragmentation of component 12; for high resolution data, the observed m/z values are followed, in parentheses, by the calculated value.

Table 10 Structural assignments for components 1-12 in 'crude' aldicarb oxime **9**

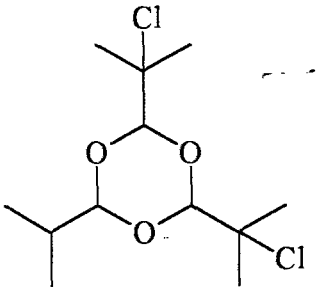
Component	Possible Structure	Evidence
1	CH_3SSCH_3	MS,
2		MS, comparison with synthetic standard, NMR
3		MS,
4		MS, comparison with synthetic standard, NMR
5		MS
6		MS, comparison with synthetic standard, elemental analysis
7		MS, comparison with synthetic standard, elemental analysis, nmr
8		MS, comparison with synthetic standard, elemental analysis, NMR
9		MS
10,11	note[a]	
12	See Scheme 28	

a. Components 10, 11 and 12 all show the same fragmentation pattern. The presence of 2,4,6-tris(2-chloro-2-methylethyl)-1,3,5-trioxane **21** (component 12) was confirmed by high resolution mass spectrometry. However, in the case of

component 10 and 11 the molecular ion was not detected. In a previous study[90] chemical ionisation methods were used to detect the presence of the mixed trimers **62** and **63** [*m/z* 168 ($m+1+NH_3$] and [*m/z* 302 ($M+1+NH_3$) respectively]. These compounds would give rise to the same fragmentation patterns and it is possible that they constitute components 10 and 11.



62



63

2.3 Variable temperature NMR studies

2.3.1 Aldicarb oxime stability

The thermal stability of aldicarb oxime **9** over a wide temperature range was investigated using variable temperature ^{1}H NMR spectroscopy. A sample of the oxime **10** was dissolved in DMSO-d_6 and spectra were recorded at 15 minute intervals at temperatures ranging from 303K to 421K. The temperature profile of the experiment is shown in Figure 18. Stackplots generated from each temperature series show that little degradation of the oxime is apparent (see Figure 17). The only significant changes in the spectra were the temperature dependant broadening of the oxime OH signal and shift upfield of the water peak. A plot of aldicarb oxime **9** relative to the solvent signal (see Figure 18) show minor concentration fluctuations which are attributed to experimental error. In other words, aldicarb oxime **9** appears to be thermally stable under these conditions

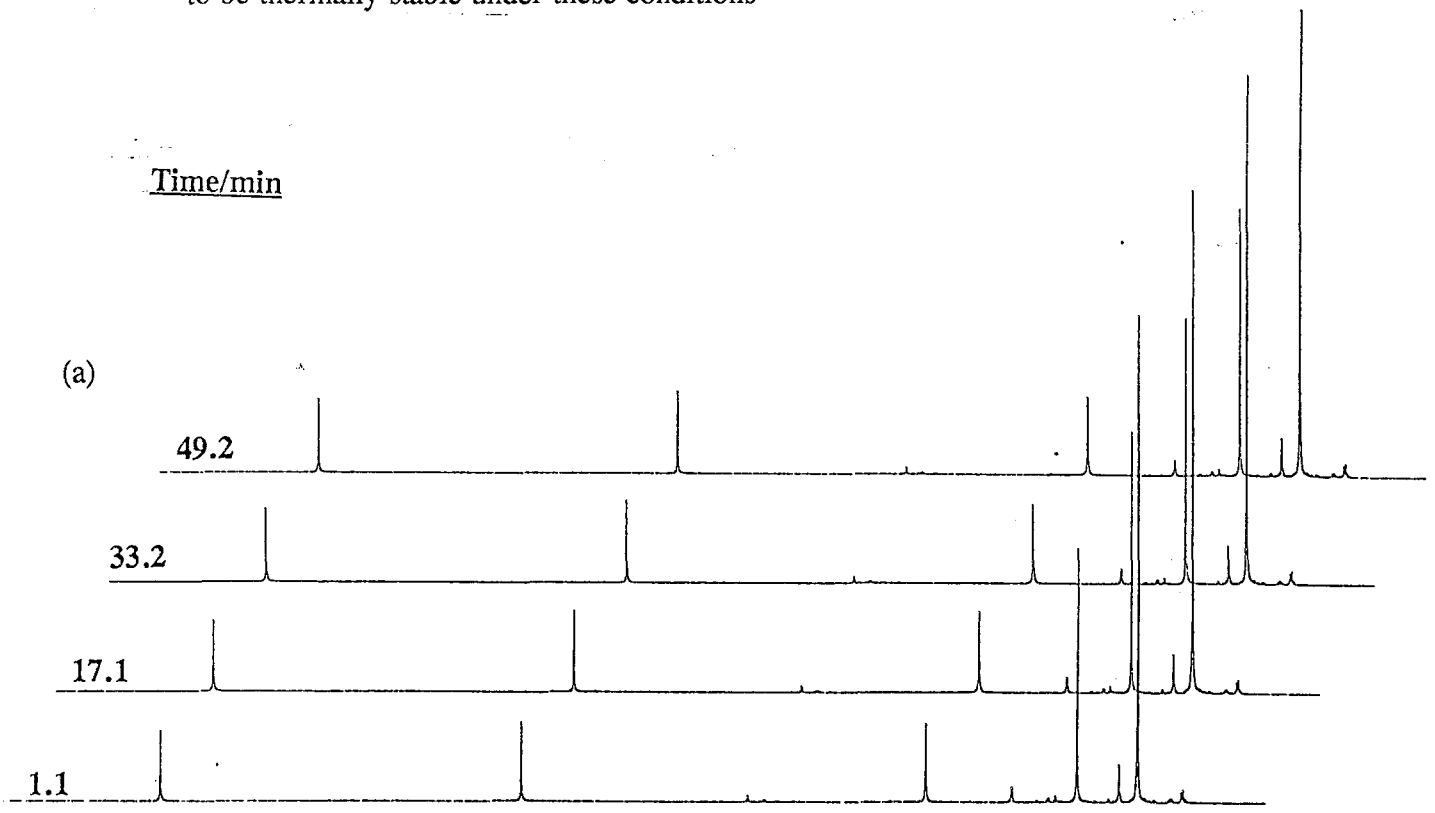


Figure 17 400MHz ^{1}H NMR spectra recorded at 15 minute intervals at (a) 303K

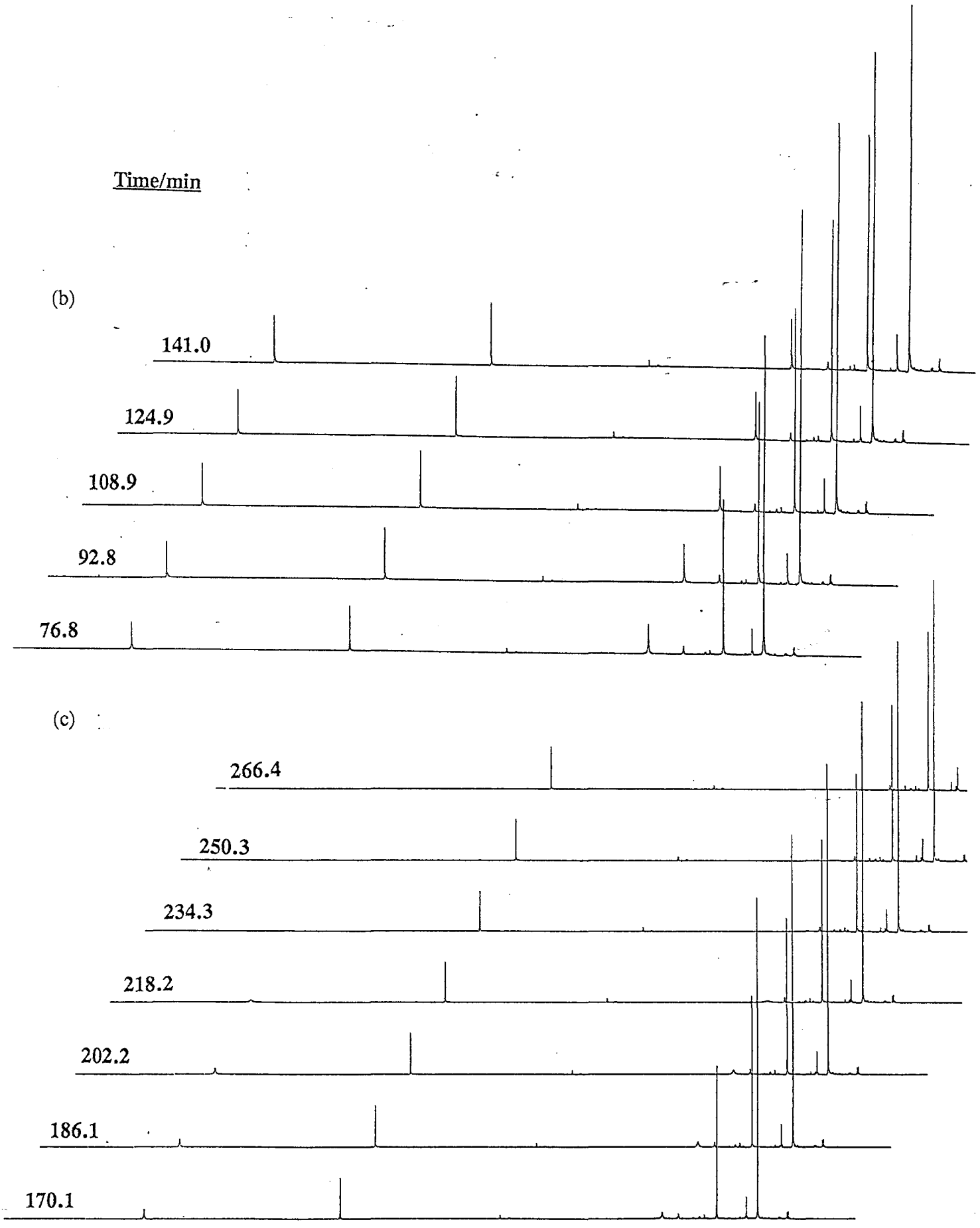


Figure 17 400MHz ^{1}H NMR spectra recorded at 15 minute intervals at (b) 366K and (c) 421K

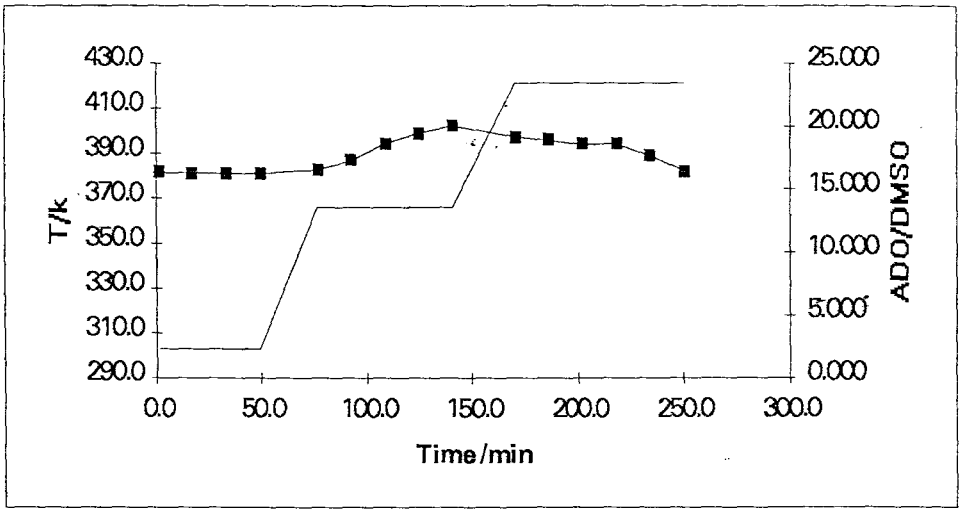


Figure 18 Concentration of aldicarb oxime **9** relative to DMSO during thermal stability experiment

2.3.2 Aldehyde trimerisation

In the industrial synthesis of 2-chloro-2-methylpropanal **11**, chlorination is effected in boiling chloroform in an attempt to minimise trimerisation. Consequently, it was decided to explore the influence of temperature on 2-methylpropanal **10**, 2-chloro-2-methylpropanal **11** and their corresponding trimers 2,4,6-triisopropyl-1,3,5-trioxane **20** and 2,4,6-tris(2-chloro-2-methylethyl)-1,3,5-trioxane **21**. These compounds were subjected to numerous variable temperature NMR experiments. The stability of each trimer was assessed by refluxing the trimer in $CDCl_3$ for several hours. A sample was removed every 30 minutes and analysed by ^1H NMR spectroscopy. Neither trimer showed any evidence of degradation under these conditions. An investigation of stability at high temperatures was not possible because both trimers are insoluble in DMSO-d_6.

A sample containing both 2-methylpropanal **10** and its trimer, 2,4,6-triisopropyl-1,3,5-trioxane **20**, dissolved in $CDCl_3$, was kept in the NMR probe and maintained at a temperature of 324K. ^1H NMR spectra were recorded at 15 minute intervals; a

representitive spectrum is shown in Figure 20. The experiment was repeated using a similar sample of 2-chloro-2-methylpropanal **11** and its trimer, 2,4,6-tris(2-chloro-2-methylethyl)-1,3,5-trioxane **21** (Figure 21). The integral ratios of monomer to trimer were calculated for each spectrum, and the results were plotted as shown in Figure 19 and Figure 22. Although the changes in the monomer to trimer ratios are very small, the concentration of trimer increases relative to monomer in both cases. These observations raise questions concerning the need to effect chlorination of 2-methylpropanal **10** at elevated temperature. In fact, chlorination of 2-methylpropanal **10** in chloroform at room temperature was found to result in the formation of very few trimers (see section 2.1.2.3). However, similar analysis of a mixture of all four compounds (**11**, **12**, **21** and **22**) leads to somewhat different conclusions (see Figure 23). At elevated temperatures, 2-methylpropanal trimer **20** disappeared entirely whereas the ratios of 2-chloro-2-methylpropanal **11**, and its trimer **21** remained relatively constant while 2-methylpropanal **10** increased slightly. The overall changes are, of course, very small and might be attributable to experimental error. Further research is clearly needed to resolve the apparent anomalies.

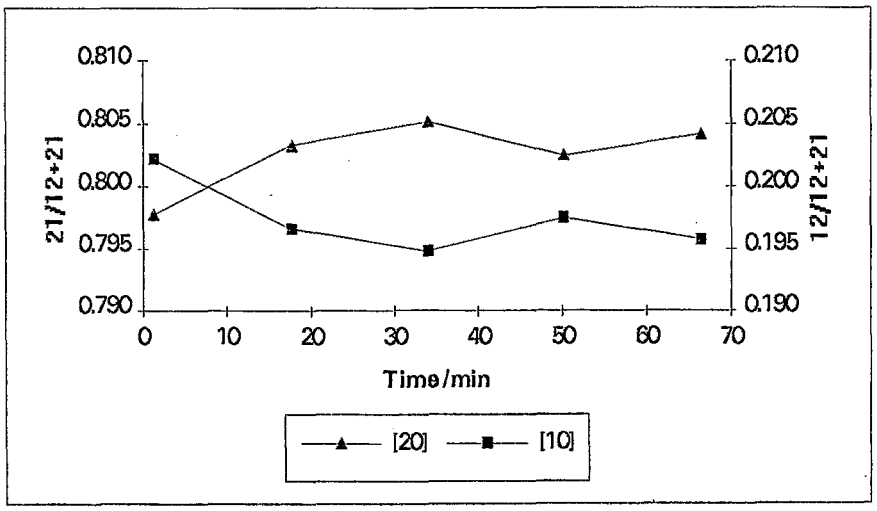


Figure 19 Relative concentrations of 2-methylpropanal **10** and its trimer **20** during thermal stability experiment

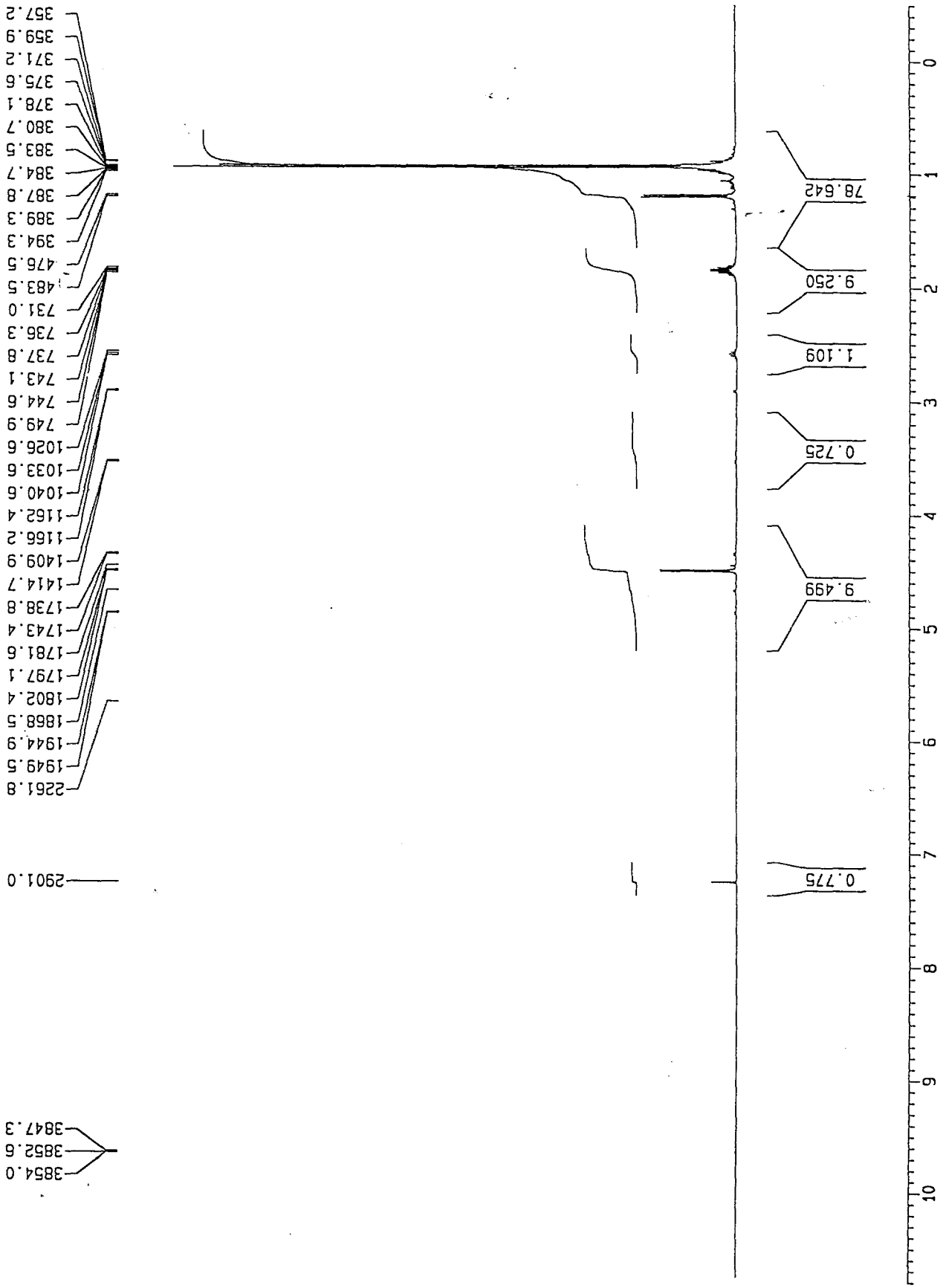


Figure 20 400MHz ^{1}H NMR spectrum of a mixture of 2-methylpropanal **10** and its trimer **21** in $CDCl_3$ at 324K

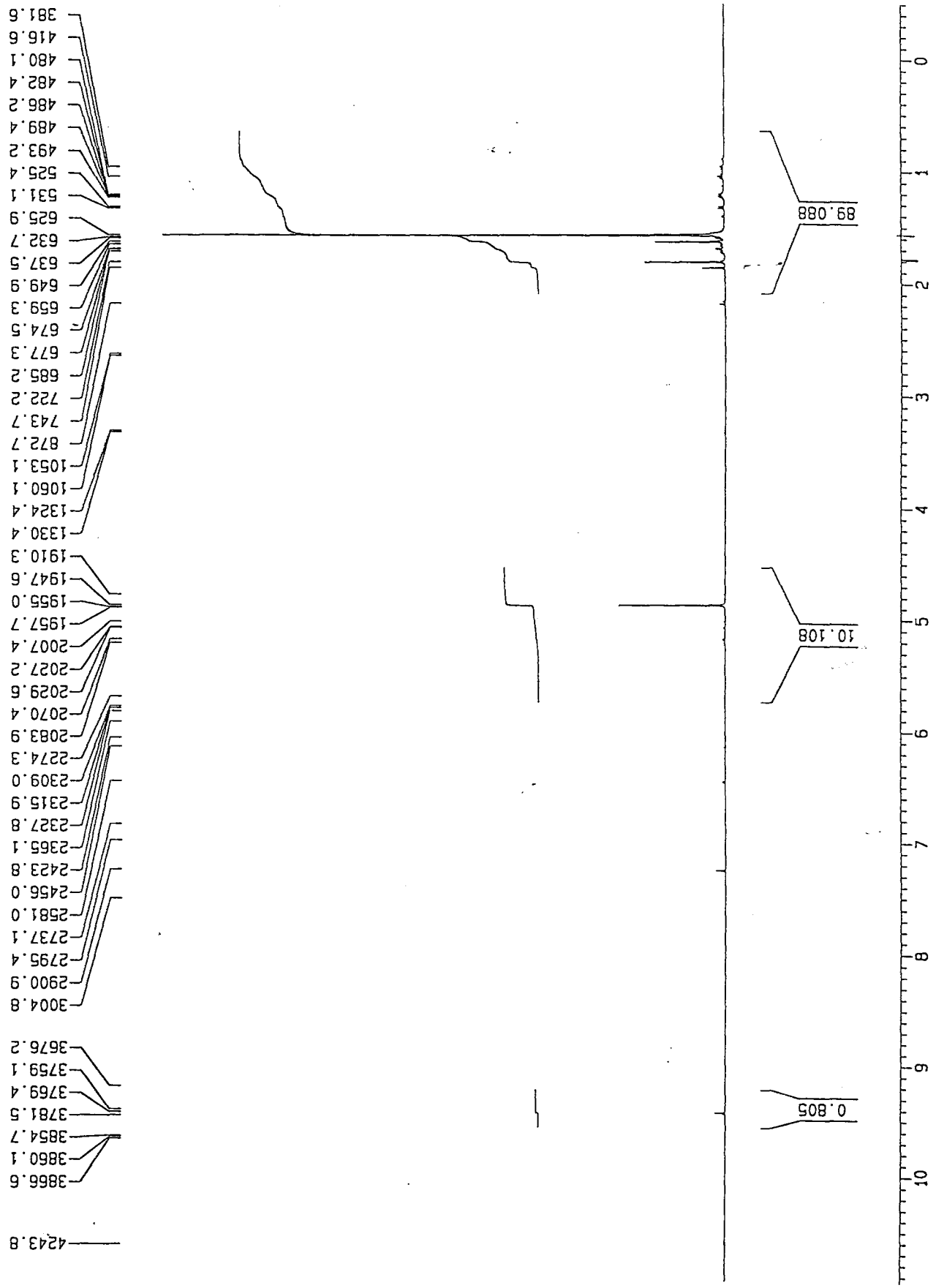


Figure 21 400MHz ^{1}H NMR spectrum of a mixture of 2-chloro-2-methylpropanal **11** and its trimer **22** in $CDCl_3$ at 324K

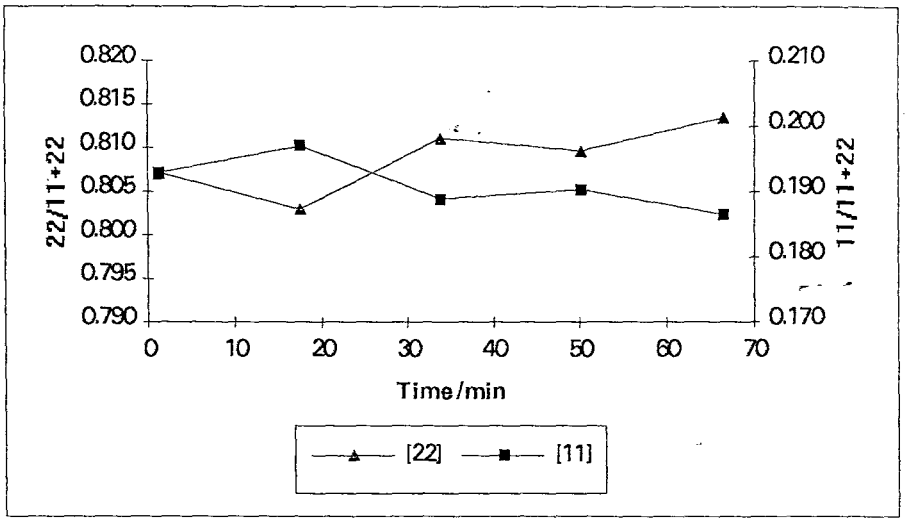


Figure 22 Relative concentrations of 2-chloro-2-methylpropanal **11** and its trimer **21** during thermal stability experiment.

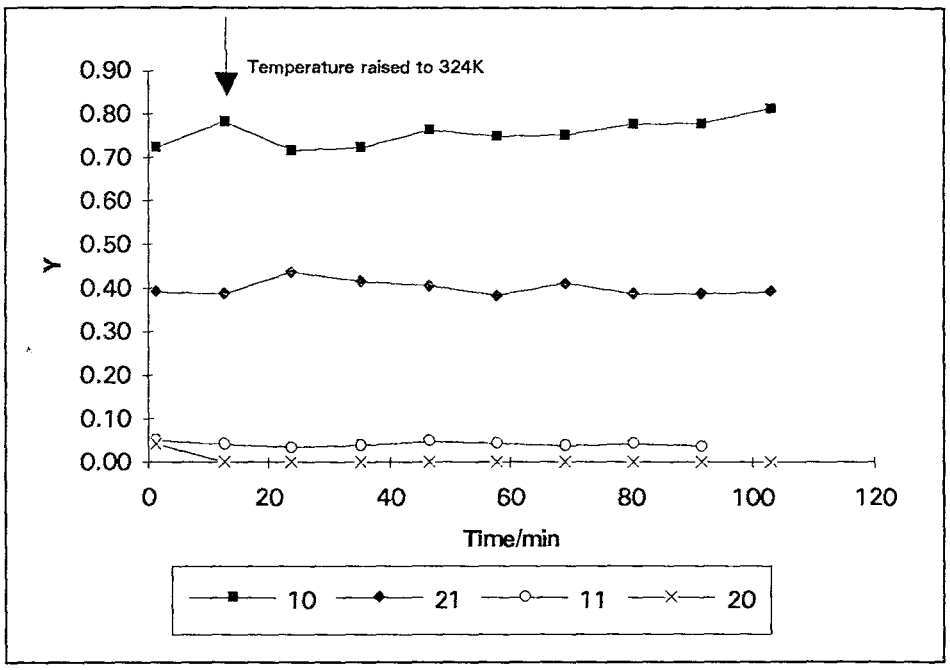


Figure 23 Relative concentration of compounds **11**, **12**, **20** and **21** in $CDCl_3$ at 324K

As trimerisation is known to be catalysed by acid,[108] the effects of adding HCl as well as *p*-toluenesulphonic acid to a solution of 2-methylpropanal **10** dissolved in $CDCl_3$

were investigated, and a similar analysis was carried out on a sample of 2-chloro-2-methylpropanal **11** dissolved in $CDCl_3$. In all cases, the trimer formation was instantaneous and determination of the kinetics of trimerisation was not possible. At elevated temperatures, the trimer propartions remained realtively constant.

2.4 Conclusions

The results of this investigation have led to an improvement in the yields and purity of aldicarb oxime and have provided insights into the formation of by-products, present as contaminants, in the final product. The optimisation of the chlorination step was found to be the key to increasing the overall yield. The chlorination has been shown to occur efficiently either by heating the reaction mixture gently in the absence of solvent or, without external heating, in the presence of solvent. Simple adsorption methods involving the use of alumina and activated charcoal, have shown some potential for purifying contaminated batches of aldicarb oxime.

GC-MS analysis of crude aldicarb oxime indicated the presence of various contaminants. These included oximes, nitriles, disulphides, thioacetals and aldehyde trimers. A number of these compounds were synthesised as chromatographic and spectroscopic standards, providing further confirmation of their presence as aldicarb oxime contaminants.

In a series of variable temperature ^{1}H NMR analyses, aldicarb oxime was found to be thermally stable over the temperature range investigated, and the changes in the aldehyde monomer:trimer ratios, as a function of temperature, have been shown to be very small. In the presence of acid, however, the trimers were observed to form rapidly.

A range of novel compounds as potential precursors for aldicarb analogues have been successfully synthesised *via* the Baylis-Hillman reaction between pyridine carboxaldehydes and methyl acrylate (or acrylonitrile) in the presence of DABCO. Both hydroxy and dehydrated products were obtained. These compounds were fully characterised using various spectroscopic techniques.

Aspects of this project which warrant further research include:

1. Further investigation of the kinetics of trimerisation of 2-methylpropanal and 2-chloro-2-methylpropanal in order to resolve observed anomalies.
2. Optimisation of the purification procedures using activated charcoal and alumina.
3. Elucidation of the mechanism of the formation of the thiomethylated compounds formed from the Baylis-Hillman products.

3. Experimental

3.1 General

Melting points were determined using a Kofler hot stage apparatus and are uncorrected. NMR spectra were run on a Bruker AMX400 spectrometer, using $CDCl_3$ unless otherwise specified. Spectra were calibrated against solvent signals ($CDCl_3$: 7.25ppm for ^1H and at 77.0ppm for ^{13}C, DMSO-d_6: 2.50ppm for ^1H and at 39.5ppm for ^{13}C).

IR spectra were recorded on a Beckman IR 4260 or a Perkin-Elmer 180 spectrometer using liquid films or KBr discs.

GLC analyses were performed on a Hewlett Packard 5980A gas chromatograph using a flame ionisation detector. Low-resolution mass spectra were obtained using a Hewlett Packard 5988A mass spectrometer, and high-resolution mass spectra using a Kratos double-focusing magnetic sector instrument.

Thin layer chromatography (TLC) was performed on precoated Merck Silica gel F_{254} plates; compounds were visualised by exposure to iodine vapour or by examination under UV light. Flash chromatography was carried out using Merck silica gel [particle size 0.040-0.063mm(230-400 mesh)].

Diethyl ether was dried initially by stirring over calcium hydride then distilled from sodium wire under nitrogen, using benzophenone as an indicator.[94]

3.2 Synthetic procedures

3.2.1 Halogenation studies

2-Methylpropanal enol acetate (**23**).[106] -

A mixture of 2-methylpropanal (**10**) (28.80g, 0.40mol), acetic anhydride (61.20g, 0.60mol) and potassium acetate (4.80g, 0.05mol) was refluxed for 11 hours in a 250ml round-bottomed flask. The mixture was then cooled, washed three times with equal volumes of water to remove any traces of acid, and finally with 5% aqueous sodium carbonate. The resulting oil was dried (anhydrous magnesium sulphate). Fractional distillation of the residue afforded 2-methylpropanal enol acetate (**23**) (34.62g, 76%), b.p. 119-122°C (lit.,[106] 124-126°C); δ_H(400MHz; $CDCl_3$) 1.62 (6H, d, CH_3), 2.1 (3H, s, CH_3O) and 6.8 (1H, s, C=CH).

2-Bromo-2-methylpropanal dimethyl acetal (**24**).[106]-

A solution of 2-methylpropanal enol acetate (**23**) (34g, 0.30mol) in carbon tetrachloride (90ml) was cooled in an ice bath and bromine (15.46ml, 0.30mol) in carbon tetrachloride (16ml) was added dropwise, with constant stirring. The temperature of the reacton was maintained below 10°C. Methanol (70ml) was added to the mixture, which was left to stand, with occasional stirring, at room temperature for 2d and then diluted with water (300ml). The separated oil was dried (anhydrous magnesium sulphate), and fractionated in the presence of a small amount of sodium carbonate to give 2-bromo-2-methylpropanal dimethyl acetal (**24**) (30.20g, 51.4%), b.p. 66-70°C, *ca.* 25 mmHg (lit.,[106] 52-54°C, 10mm); δ_H(400MHz; $CDCl_3$) 1.70 (6H, s, CH_3), 3.55 (6H, s, CH_3O) ,and 4.21 [1H, s, $(CH_3)_2BrCH$].

2--Bromo-2-methylpropanal (**26**).[106]-

A mixture of 2-bromo-2-methylpropanal dimethyl acetal (**24**) (30.15g) and concentrated hydrochloric acid (30ml) was distilled gently. A mixture of 2-bromo-2-methylpropanal (**26**), methanol and water was collected. Redistillation of the organic layer gave 2-bromo-2-methylpropanal (**26**) (12.68g, 55%), b.p. 112-113°C. (Lit.,[106]

113-115°C); δ_H(400MHz;$CDCl_3$) 1.75 (6H, s, CH_3), 9.25 (1H, s, CHO). Upon standing, a white crystalline solid formed, which was found to be the trimer of (**26**) m.p. 128-129°C (from hexane) (lit.,[108] 129-130°C), δ_H(400MHz; $CDCl_3$) 1.74 (18H, s, CH_3) and 4.91 (3H, s, 4.90).

3.2.1.1 General Procedure for aldehyde chlorination

The chlorination of propanal (**27**), butanal (**28**), 2-methylpropanal (**20**) and 2-phenyl-ethanal (**29**) was carried out using the following general procedure unless otherwise indicated. The aldehyde was dissolved in $CHCl_3$ in a 100 ml three-necked round-bottomed flask fitted with a thermometer **b**, a double-jacketed condenser **c** connected to two scrubbers to neutralise the HCl gas evolved (the first one **d** empty and the second **e** containing a 20% NaOH solution and methyl red as an indicator) and a dip tube **f** for the chlorine gas, the end of the tube lying below the level of the liquid. Chlorine flow was regulated by means of a rotameter **g** and an empty trap **h** was placed between the rotameter and the reaction vessel to prevent suck-back to the cylinder **i.** Figure 24 is a schematic diagram of the apparatus used. Chlorine was bubbled through the stirred (**j**) reaction mixture at a rate of *ca.* 80ml per minute for the required time. The temperature rose on addition of the chlorine. After reaction, the mixture was cooled and analysed by ^{1}H NMR spectroscopy.

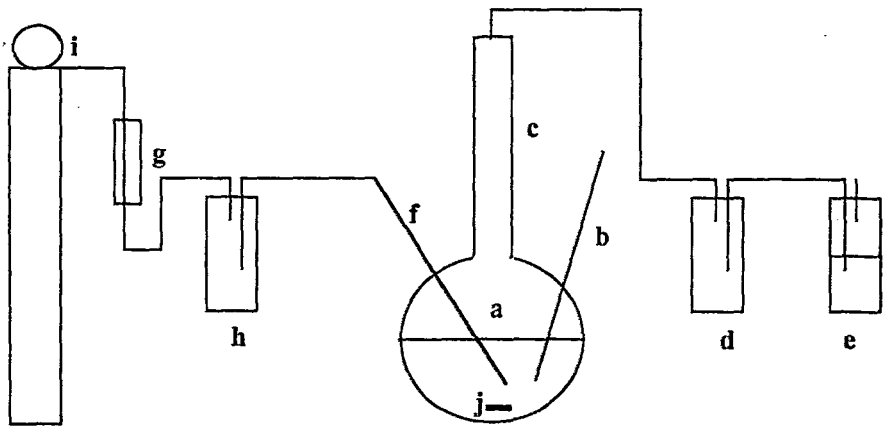


Figure 24 Schematic representation of chlorination apparatus

2-Chloropropanal (**30**).-

Method 1. Propanal (**27**) (10g, 0.17mol) was dissolved in $CHCl_3$ (15ml) and chlorinated using the general procedure. ^1H NMR spectroscopic analysis revealed the formation of numerous compounds in addition to the monochloro compound (**30**) which was not isolated from the mixture.

Method 2. The above procedure was repeated using propanal (**27**) (10g, 0.17mol) but omitting the solvent. ^1H NMR spectroscopy of the sample obtained revealed no improvement in the purity of the product.

2-Chlorobutanal (**31**).-

Method 1. The general procedure was followed using butanal (15g, 0.21mol) and bubbling in the chlorine over 75min. The reaction mixture was cooled and distilled. ^1H NMR analysis of the fraction with b.p. 60°C/*ca.* 15mmHg revealed a complex mixture of numerous aldehydes, indicationg that more than one chlorinated compound had formed.

Method 2. The general procedure was followed using butanal (**28**) (10g, 0.14mol) and $CHCl_3$ (15ml) and bubbling in the chlorine over 45 minutues. ^1H NMR analysis of the sample revealed no improvement on the previous method.

2-Chloro-2-phenylethanal (**32**).-

2-Phenylethanal (**29**) (distilled prior to use to remove diethyl phthalate present as a stabiliser; 10g, 0.08mol) was dissolved in $CHCl_3$ (15ml) and chlorinated following the general procedure. Chlorine was introduced over 30 minutes. ^1H NMR analysis revealed a complex mixture from which the monochloro compound (**32**) could not be isolated.

2-Chloro-2-methylpropanal (**11**).-

2-methylpropanal (**10**) was purified prior to use by shaking with aqueous 10% sodium carbonate to remove any traces of acid. The organic layer was washed with water,

dried (anhydrous magnesium sulphate) and fractionally distilled, collecting the fraction boiling between 61and 63°C.[94] Chlorination of 2-methylpropanal (**11**) was carried out following the general procedure. Flow regulation in the initial chlorinations was carried out using a soap-bubble flow meter and some difficulties were encountered in achieving a consistent gas flow. These difficulties were obviated when a rotameter was obtained. In each experiment, a 1.1% molar excess of chlorine was added at a rate of *ca.* 80ml/min to 2-methylpropanal **10** (33.02g, 0.46mol). The boiling point of 2-chloro-2-methylpropanal is 90°C[r22], however, where solvent was used, product was collected in the range 65-70°C. The conditions and results for each of the methods used are listed below.

Method 1. 2-Methylpropanal (**10**) was dissolved in $CHCl_3$ (50ml). After bubbling in the chlorine for approximately 30min, the reaction mixture was heated to maintain a gentle reflux (65-70°C). The crude mixture was analysed using ^1H NMR spectroscopy. The presence of 2-methylpropanal (**10**) {δ_H[400MHz; $CDCl_3$] 1.06 (6H, d, CH_3), 2.35 (1H, m, CH_3CH) and 9.58 (1H, d, CHO)}; the corresponding trimer, 2,4,6-triisopropyl-1,3,5-trioxane (**20**) {δ_H[400MHz; $CDCl_3$] 0.93 (18H, d, CH_3), 1.84 (3H, m, CH_3CH) and 4.50 (3H, d, OCHO)} and the trimer of 2-chloro-2-methylpropanal (**11**), 2,4,6-tris(2-chloro-2-methyl)ethyl-1,3,5-trioxane (**21**) {1.55 (18H, s, CH_3) and 4.88 (3H, s, OCHO)} were detected in addition to the desired 2-chloro-2-methylpropanal (**11**) in 26% yield; δ_H(400MHz; $CDCl_3$) 1.55 (6H, s, CH_3) and 9.36 (1H, s, CHO).

Method 2. 2-Methylpropanal (**10**) was added to a mixture of $CHCl_3$ (50ml) and Na_2CO_3 (28.9g, 0.27mol) in water (90ml). The reaction was not heated and after bubbling Cl_2 through the mixture for 30min, the reaction had to be halted as a result of the formation of a large amount of white precipitate which hindered stirring.

Method 3. 2-Methylpropanal (**10**) was dissolved in $CHCl_3$ (50ml) and a solution of Na_2CO_3 (28.9g) in water (120ml) was added dropwise throughout the course of the reaction to dissolve the precipitated sodium chloride as it formed. ^1H NMR analysis

of the crude mixture revealed the presence of the same products as in method 1. 2-Chloro-2-methylpropanal (**11**) was present in 1% yield.

Method 4. 2-Methylpropanal (**10**) was dissolved in $CHCl_3$ (50ml) and the mixture was heated as in method 1. A solution of Na_2CO_3 (28.9g) in water (120ml) was added dropwise over the first half-hour of the reaction to dissolve the precipitated sodium chloride as it formed. After distillation, the yield of 2-chloro-2-methyl-propanal (**11**) was 5%.

Method 5. 2-Methylpropanal (**10**) was dissolved in $CHCl_3$ (50ml) and heated as in method 1. From this reaction onwards, chlorine was added until a permanent dark green colour was obtained. After distillation, 2-chloro-2-methylpropanal (**11**) was obtained in 14% yield.

Method 6. 2-Methylpropanal (**10**) was dissolved in $CHCl_3$ (50ml) and the reation was not heated. After distilation 2-chloro-2-methylpropanal (**11**) was obtained in 47% yield.

Method 7. No solvent was used and the reaction mixture was not heated. After 30 minutes the mixture solidified into white, needle-like crystals and the reaction had to be halted. The crystalline product was shown to be 2,4,6-tris(2-chloro-2-methylethyl)-1,3,5-trioxane (**21**), the trimer of 2-chloro-2-methylpropanal (**11**), m.p. 104-106°C (lit.,[108] 106-107°C); δ_H (400MHz; $CDCl_3$) 1.56 (18H, s, CH_3), and 4.83 (3H, s, OCHO).

Method 8. No solvent was used, and the reaction mixture was heated as in method 1. ^1H NMR analysis of the crude reaction revealed very few impurities and the yield of 2-chloro-2-methylpropanal (**11**) was 83%. Distillation of the residue was found not to significantly improve the purity of the product.

Method 9. No solvent was used and 2-methylpropanal (**10**) was brought to reflux before any chlorine was added. Thereafter, the reaction was maintained at reflux. Distillation of the residue afforded 2-chloro-2-methylpropanal (**11**) in 41% yield.

Method 10. The conditions of method 8 were followed and the crude product was washed with saturated saturated aqueous NaCl (3 x 50ml). 2-Chloro-2-methyl-propanal (**11**) was obtained in 58% yield and ^{1}H NMR analysis showed the washed product to be cleaner than the unwashed product.

Method 11. Chlorine was introduced in the absence of solvent above the surface of 2-methylpropanal (**10**), and the reaction was heated at reflux. The product was analysed by ^{1}H NMR spectroscopy and was shown to contain a number of unidentified impurities.

2-Methyl-2-(methylthio)propanal (**12**).-

A 21% solution of sodium thiomethylate (35.65g, 0.10mol CH_3SNa) was added to a three-necked round-bottomed flask fitted with a thermometer, a pressure-equalising dropping funnel and a reflux condenser attached to three scrubbers [the first one empty, the second containing a 5% NaOH solution and the third sodium hypochlorite. Freshly prepared 2-chloro-2-methylpropanal (**11**) (11.29g, 0.10mol) was added dropwise, with stirring, over a period of 15min. The reaction mixture was then heated to 35°C and stirred for 30min, cooled and transferred to a separating funnel. The organic layer was separated, dried overnight (3 Å molecular sieves) and distilled to afford 2-methyl-2-(methylthio)propanal (**12**) as a yellow oil (11.19g, 89%), b.p. 138-140°C (lit.,[78] 140-141°C); δ_H(400MHz; $CDCl_3$) 1.3 (6H, s, CH_3), 1.79 (3H, s, CH_3S) and 9.07 (1H, s, CHO).

2-Methyl-2-(methylthio)propanal oxime (**9**).[184]-

A warm solution of hydroxylamine hydrochloride (7.09g, 0.10mol) dissolved in water (15ml) was added dropwise to a solution of 2-methyl-2-(methylthio)propanal (**12**) (10g, 85mmol) in absolute ethanol (50ml) contained in a 250ml round-bottomed flask. The resulting solution was stirred thoroughly and a cold solution of sodium hydroxide

(4.0g, 0.1mol) dissolved in water (10ml) was added dropwise. The reaction mixture was stirred at room temperature for 2h, the resulting precipitate was filtered off and the filtrate was washed with saturated aqueous NaCl (2 x 20ml) and the product extracted with ethyl acetate (2 x 20ml). The combined extracts were dried (anhydrous magnesium sulphate), the solvent removed *in vacuo* and the residue distilled to afford 2-methyl-2-(methylthio)propanal oxime (**9**) as a clear oil (10.23g, 91%), b.p. 78-81°C/4mmHg (lit.,[74] 82-83°C/8mmHg); ν_{max} (thin film)/cm^{-1} 3300 (br), 2950, 2900 and 1640; δ_H(400MHz; $CDCl_3$) 1.39 (6H, s, CH_3), 1.95 (3H, s, CH_3S), 7.30 (1H, s, C*H*NOH) and 8.21 (1H, br s, NOH); δ_C(100MHz; $CDCl_3$) 11.21 (CH_3S), 25.5 (CH_3), 44.2 [$(CH_3)_2C$] and 152.3 (C=N).

3.2.2 Synthesis of possible aldicarb oxime 10 contaminants

2-Methylpropanal Oxime (**33**).[184]-

2-Methylpropanal (**10**) (21.64g, 0.30mol) was dissolved in absolute ethanol (100 ml) contained in a 250ml three-necked round-bottomed flask fitted with a thermometer, a condenser and a dropping funnel. A warm solution of hydroxylamine hydrochloride (25.02g, 0.36mol) in water (30ml) was added and the resulting solution was mixed thoroughly. A solution of sodium hydroxide (14.40g, 0.36mol) in water (20ml) was added dropwise, and a white precipitate formed immediately. The resulting slurry was stirred for several hours at room temperature. The solid was filtered off and the filtrate was washed with saturated aqueous NaCl (2 x 50ml), and then extracted with ethyl acetate (2 x 50ml). The combined extracts were dried (anhydrous magnesium sulphate) and the solvent was removed *in vacuo.* The residue was distilled to give 2-methylpropanal oxime (**33**) (22.38g, 86%), b.p. 61-64°C/ *ca.* 25mmHg. (lit.,[185] 140°C); ν_{max} (thin film)/cm^{-1} 3300 (br), 2950, 2850 and 1640. NMR spectroscopy revealed the presence of both the (*E*)- and (*Z*)- isomers; thus for the (*E*)-isomer (**33a**), δ_H(400MHz; $CDCl_3$) 1.07 [6H, d, $(CH_3)_2CH$)], 2.48 [1H, m, $(CH_3)_2CH$)], 7.33 (1H, d, C*H*=NOH) and 8.78 (1H, s, OH); δ_C(100MHz; $CDCl_3$) 19.8 (CH_3), 29.3 [$C(CH_3)_2$]) and 156.8 (C=N), and for the (*Z*)-isomer (**33b**), δ_H(400MHz; $CDCl_3$) 1.04 [6H, d, $(CH_3)_2CH$)], 3.19 [1H, m, $(CH_3)_2CH$)], 6.53 (1H, d,

C*H*=NOH) and 8.78 (1H, s, OH); δ_C(100MHz); $CDCl_3$) 19.5 (CH_3), 24.4 [*C*$(CH_3)_2$]) and 157.8 (C=N).

2-Chloro-2-methylpropanal oxime (**34**).[184]

Method 1. 2-Chloro-2-methylpropanal (**11**) (15.97g, 0.15mol) was dissolved in absolute ethanol (60ml) contained in a 250ml three-necked round-bottomed flask fitted with a thermometer, a condenser and a dropping funnel. A warm solution of hydroxylamine hydrochloride (12.51g, 0.18mol) in water (15ml) was added and the resulting solution was mixed thoroughly. A solution of sodium hydroxide (7.2g, 0.18mol) in water (12ml) was added slowly. A vigourous exothermic reaction occurred. The resulting slurry was stirred at room temperature for 24 hours. The solid was filtered off and the filtrate was washed with saturated aqueous NaCl (2 x 25ml) and the extracted with ethyl acetate (2 x 25ml). The combined extracts were dried (anhydrous magnesium sulphate) and the solvent removed *in vacuo* to afford a dark yellow oil (9.68g). The presence of traces of the required oxime (**34**) was confirmed by IR spectroscopy [ν_{max} (thin film)/cm^{-1} 1640].

Method 2.[118] 2-Chloro-2-methylpropanal (**11**) (1g, 9.4mmol) was added to a solution of hydroxylamine hydrochloride (1g, 14mmol) and sodium acetate (1.15g, 14mmol) dissolved in water (10ml), and the resulting solution was gently shaken and warmed on a water bath for 10 minutes. No crystals of the desired product (**34**) were observed.

Method 3.[117] To a solution of hydroxylamine hydrochloride (6.26g, 90mmol) in water (10ml) was added a cooled solution of sodium hydroxide (3.6g, 90mmol) and the resulting mixture cooled to below 10°C. 2-Chloro-2-methylpropanal (**11**) (7.99g, 75mmol) was added dropwise, the mixture shaken gently after each addition, and the temperature maintained below 15°C. No crystals of the desired product (**34**) were observed, although the presence of the desired oxime was detected by IR spectroscopy [ν_{max} (thin film)/cm^{-1} 1640].

2-Methylpropanenitrile (**35**).-

Method 1. [129] Phosphorous pentoxide (35g, 0.25mol) was placed in a dry 500ml 2-necked round-bottomed flask fitted with a double-jacketed condenser with a drying tube and a dropping funnel. 2-Methylpropanal oxime (**33**) (20g, 0.23mol) was added dropwise, very slowly. A vigorous exothermic reaction occurred. When all the oxime had been added, the mixture was left to stand for a few minutes to ensure complete reaction. The condenser was then replaced with a distillation apparatus and the flask was heated gently, initially at atmospheric pressure and then under vacuum (*ca.* 25mmHg) to afford 2-methylpropanenitrile (**35**) (8.33g, 49%), b.p. 100-102°C (lit.,[129] 101-103°C); ν_{max} (thin film)/cm^{-1} 3400, 2950, 2900 and 2240 ; δ_H(400MHz; $CDCl_3$) 1.31 [6H, d, $(CH_3)_2CH$] and 2.68 [IH, m, $(CH_3)_2CH$]; δ_C(100MHz; $CDCl_3$) 19.8 [$(CH_3)_2CH$], 19.9 [$(CH_3)_2C$] and 123.7 (C≡N).

Method 2.[138] 'Supported' phosphorus pentoxide (Sicapent® as supplied by Merck; 100ml), 2-methylpropanal oxime (**33**) (5g; 69mmol) and xylene (60ml) were placed in a 250ml flange flask, fitted with an overhead stirrer and a reflux condenser with drying tube. The stirred reaction mixture was heated at 100°C for 1h, and when cool, filtered under vacuum. The residual solid was washed with diethyl ether (30ml), the washings and filtrate were combined, and the ether was removed *in vacuo.* Fractional distillation affored a mixture which was shown to contain the nitrile [ν_{max} (thin film)/cm^{-1} 2240].

Method 3.[137] To a solution of 2-methylpropanal (**10**) (1.0g, 14mmol) in 95% ethanol (10ml) was added hydroxylamine hydrochloride (1g, 14mmol), and concentrated hydrochloric acid (3 drops). The mixture was refluxed for 6 hours. The presence of the nitrile in the crude product was confirmed by IR spectroscopy [ν_{max} (thin film)/cm^{-1} 2240].

2-Methyl-2-(methylthio)propanenitrile (**36**).-

Method 1. [129] Phosphorous pentoxide (15g, 0.11mol) was placed in a dry 250ml 2-necked round-bottomed flask fitted with a dropping funnel and a still head, condenser

and receiver flask cooled in ice. 2-Methyl-2-(methylthio)propanal oxime (**9**) (10g, 0.08mol) was added dropwise. The reaction mixture was heated gently and when the temperature reached 90°C, a vigourous exothermic reaction occurred and a yellow oil distilled rapidly into the receiving vessel. The presence of the nitrile was confirmed by IR spectroscopy (ν_{max} (thin film)/cm^{-1} 2240), however starting material was also detected. The crude nitrile (0.1g) was purified by preparative thin layer chromatography [silica gel; ethyl acetate:hexane (3:2)] to afford 2-methyl-2-(methylthio)propanenitrile (**36**) as a pale yellow oil. ν_{max} (thin film)/cm^{-1} 2240; δ_H(400MHz; $CDCl_3$) 1.61, (6H, s, CH_3) and 2.29 (3H, s, SCH_3).

Method 2.[135] 2-Methyl-2-(methylthio)propanal oxime (**9**) (1.32g, 0.01mol) was refluxed in 96% formic acid (10g) for 30min, then allowed to cool, diluted with ice-water (100ml) and neutralised under ice cooling (5% sodium hydroxide solution). The organic layer was extracted (diethyl ether, 2 x 50ml), dried (anhydrous magnesium sulphate) and the solvent removed *in vacuo*. The presence of 2-methyl-2-(methylthio)propanenitrile (**36**) was confirmed by IR spectroscopy [ν_{max} (thin film)/cm^{-1} 2240].

Trimethyl(methylthio)silane (**45**).[146]-

Dimethyl disulphide (dried over 3Å molecular sieve; 11.78g, 0.125mol) was added, using a syringe, to a well-stirred slurry of lithium aluminium hydride (2.37g, 62.5mmol) in anhydrous diethyl ether (250ml) in a previously flame-dried, four-necked 500ml round-bottomed flask, fitted with a thermometer, a dropping funnel, a septum and a condenser attached to a N_2 line. The reaction mixture was boiled gently under reflux for 1h. Chlorotrimethylsilane (freshly distilled from calcium hydride; 34g, 0.313mol) in anhydrous diethyl ether (50ml) was added dropwise to the cool, stirred mixture. After heating the mixture under reflux for four hours followed by stirring overnight at room temperature the gelatinous precipitate of aluminium salts was slowly transformed into a granular solid, which settled on standing. The solvent was removed by distillation and the resulting dark pink liquid was distilled to afford trimethyl(methylthio)silane (**45**) (14.58g, 39%); b.p. 96-99°C (lit.,[146] 110-111°C); δ_H(400MHz; $CDCl_3$) 0.30 (9H, s, $SiCH_3$) and 1.98 (3H, s, SCH_3).

2-Methyl-1,1-bis(methylthio)propane (**37**).[146]

To a cooled (0°C) solution of 2-methylpropanal (**10**) (2.00g, 27mmol) in anhydrous diethyl ether (15ml), contained in a previously flame-dried 100 ml round-bottomed flask connected to a nitrogen line, was added dropwise trimethyl(methylthio)silane (**45**) (6.67g, 56mmol) over a period of 15 minutes. The reaction was then quenched with water (10ml), the product extracted (diethyl ether; 2 x 10ml) and dried (anhydrous magnesium sulphate). The solvent was removed *in vacuo* to afford an oil (3.01g), TLC of which showed the presence of two compounds. The presence of the thioacetal (**37**) was confirmed by ^{1}H NMR spectroscopy and high resolution mass spectroscopy: δ_H(400MHz; $CDCl_3$) 1.09 [6H, d, $(CH_3)_2CH$)], 2.06 [1H, m, $(CH_3)_2CH$], 2.13 (6H, s, (CH_3S) and 3.46 [1H, d, $(CH_3S)_2CH$] (Found: M^+ 150.0528. Calc for $C_6H_{14}S_2$: *M*, 150.0536). The presence of the hemithioacetal was not detected.

2-Chloro-2-methyl-1,1-bis(methylthio)propane (**38**). -

Attempted preparation [146]. Trimethyl(methylthio)silane (**45**) (6.67g, 56mmol) was added dropwise to a cooled (0°C) solution of freshly prepared 2-chloro-2-methylpropanal (**11**) (2.93g, 28mmol) in anhydrous diethyl ether (15ml) over a period of 15 minutes. The reaction was then quenched with water (10ml), the product extracted (diethyl ether; 2 x 10ml), dried (anhydrous magnesium sulphate) and the solvent removed *in vacuo.* ^{1}H NMR spectroscopy indicated the absence of the required thioacetal (**37**).

2,4-Diisopropyl-5,5-dimethyl-6-hydroxy-1,3-dioxane. (**41**) [186]-

2-Methylpropanal (**10**) 14.22g, 0.20mol) was added dropwise over a period of 15min to a solution of 1M NaOH (7ml) contained in a 50ml round-bottomed flask. The mixture was then cooled in an ice bath, the product extracted (diethyl ether; 2 x 15 ml), dried (anhydrous magnesium sulphate) and the solvent removed *in vacuo.* Distillation of the residue afforded 2,4-diisopropyl-5,5-dimethyl-6-hydroxy-1,3-dioxane (**41**) (6.43g, 5%), b.p. 120-122°C, *ca.* 25mmHg, (lit.,[165] 110-111°C/ 8mmHg); ν_{max} (thin film)/cm^{-1} 3500); δ_H(400MHz; $CDCl_3$) 0.89 [12H, m.

(CH_3)$_2$CH], 1.25 (6H, s, CH_3), 1.85 [2H, m, (CH_3)$_2$C*H*], 4.30 (1H, d, OC*H*), 4.41 (IH, s, OH), 4.62 (1H, s, C*H*OH) and 4.74 (1H, d, OCHO).

3-Hydroxy-2,2,4-trimethylpentanal (**39**).[165] -

A solution of 2-methylpropanal **10** (15g, 0.21mol) dissolved in diethyl ether (15ml) and dibutylamine (three drops) contained in a two-necked 100ml round-bottomed flask was cooled to below 5°C. A 10% solution of potassium hydroxide (*ca.* 20ml) was added dropwise with vigorous stirring until the temperature no longer rose on addition of the solution. The organic layer was washed three times with a 5% sulphuric acid solution, dried (anhydrous magnesium sulphate) and the solvent removed *in vacuo* and the residue was distilled. A white crystalline solid formed in the condenser during distillation. ^{1}H NMR analysis showed it to be 2,4,6-triisopropyl-1,3,5-trioxane **20**, δ_H(400MHz; $CDCl_3$) 0.93 (18H, d, CH_3), 1.84 (3H, m, CH_3C*H*) and 4.50 (3H, d, OCHO).

2-Chloro-3-hydroxy-2,4,4-trimethylpentanal (**40**).-

A mixture of 2-methylpropanal **10** (7.95g, 0.11mol) and 2-chloro-2-methylpropanal **11** (11.68g, 0.11mol) dissolved in diethyl ether (15ml) in a two-necked 100ml round-bottomed flask was cooled to below 5°C. A 10% solution of potassium hydroxide (*ca.* 20ml) was added dropwise with vigorous stirring until the temperature no longer rose on addition of the solution. The organic layer was washed three times with a 5% sulphuric acid solution, dried (anhydrous magnesium sulphate) and the solvent removed *in vacuo.* ^{1}H NMR of the oil revealed the presence of unreacted 2-methylpropanal **10**, 2-chloro-2-methylpropanal **11** as well as 2,4,6-triisopropyl-1,3,5-trioxane **20** and 2,4,6-tris(2-chloro-2-methylethyl)-1,3,5-trioxane **21**. The desired product was not detected.

2,4,6-Triisopropyl-1,3,5-trioxane (**20**).-

Crystals formed spontaneously in a sample of 2-methylpropanal **10** left standing at room temperature exposed to the atmosphere for several weeks. Recrystallisation from hexane afforded 2,4,6-triisopropyl-1,3,5-trioxane (**20**), m.p. 58-59°C, (lit.,[p91]

59°C); δ_H(400MHz; $CDCl_3$) 0.93 (18H, d, CH_3), 1.84 (3H, m, CH_3CH) and 4.50 (3H, d, OCHO); δ_C(100MHz; $CDCl_3$) 16.7 (CH_3), 32.4 (CH) and 104.8 (OCHO).

2,4,6-Tris(2-chloro-2-methyl)ethyl-1,3,5-trioxane (**21**).-

A stoppered flask containing 2-chloro-2-methylpropanal (**11**) was left standing at room temperature. Crystals formed spontaneously after approximately 2 weeks which were shown to be 2,4,6-tris(2-chloro-2-methyl)ethyl-1,3,5-trioxane (**21**), m.p. 104-106°C (lit.,[p49] 106-107°C); δ_H (400MHz; $CDCl_3$) 1.56 (18H, s, CH_3), and 4.83 (3H, s, OCHO).

2.4-Dimethyl-3-pentanone (**43**).[177]-

Magnesium turnings (4.50g, 0.19mol) were placed in a dry 2-necked round-bottomed flask fitted with a condenser and a dropping funnel and anhydrous diethyl ether (25ml) was added. 2-Bromopropane (22.52g, 0.18mol) in anhydrous diethyl ether (25ml) was added dropwise with stirring. A vigorous reaction occured. When all the 2-bromopropane had been added, the mixture was refluxed gently for 30 minutes. 2-methylpropanenitrile (**35**) (8.00g, 0.17mol) was then added dropwise to the cool, stirred mixture. The resulting gelatinous, greenish mixture was left to stand overnight. Diethyl ether (20ml) was added to loosen the precipitate, followed, cautiously, with cold 5M H_2SO_4 (20ml) and crushed ice. The resulting mixture was then poured slowly onto 5M H_2SO_4 (70ml) in crushed ice. After quenching, the mixture was steam distilled. The product was extracted with diethyl ether (2 x 30ml), dried (anhydrous magnesium sulphate) and the solvent removed *in vacuo*. Fractional distillation of the residue gave 2,4-dimethyl-3-pentanone (**43**) (6.12g, 32%); b.p. 122-124°C (lit.,[177] 123-124°C); ν_{max} (thin film)/cm^{-1} 3000, 2900 and 1725; δ_H(400MHz; $CDCl_3$) 1.08 (12H, d, CH_3) and 2.74 (2H, m, (CH); δ_C(100MHz; $CDCl_3$) 18.5 (CH_3), 39.8 (CH) and 218.2 (CO).

3.2.3 Synthesis of aldicarb analogues

Methyl 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate (**47**)[187].-

Pyridine-2-carboxaldehyde (4.3g, 39mmol) was added to a solution of methyl acrylate (3.6 ml, 40mmol) and 1,4-diazabicyclo[2,2,2]octane (DABCO) (0.206g, 1.84 mmol) in $CHCl_3$ (2ml), and the resulting mixture was left to stand in a stoppered flask at room temperature for 5d. The crude ester was chromatographed [flash chromatography on silica gel; elution with ethyl acetate:dichloromethane (1:1)] to afford methyl 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate (**47**) as a black viscous oil. (5.97g,79%); ν_{max} (thin film)/cm^{-1} 3400 and 1730; δ_H(400MHz; $CDCl_3$) 3.72 (3H, s, OCH_3), 4.80 (1H, br s, OH), 5.61 (1H, s, C*H*OH), 5.94 and 6.34 (2H, 2 x s, C=CH_2 7.19 (1H, dd, 5′-H), 7.43 (1H, d, 3′-H), 7.65 (1H, ddd, 4′-H) and 8.53 (1H, d, 6′-H); *m/z* 193 (M^+, 27%) and 176 (100%).

3-Hydroxy-2-methylene-3-(2-pyridyl)propanenitrile (**48**)[187].-

A solution of acrylonitrile (1.54g, 29mmol), pyridine-2-carboxaldehyde (2.95g, 28mmol) and (DABCO) (0.15g, 1.3mmol) in $CHCl_3$ (2ml) was stirred overnight. The solvent was removed *in vacuo,* and the crude product chromatographed [flash chromatography on silica gel; elution with ethyl acetate:dichloromethane (7:3)] to afford 3-hydroxy-2-methylene-3-(2-pyridyl)propanenitrile (**48**) as a dark viscous oil (3.32g, 74 %) (Found: M^+ 160.0624. Calc. for $C_9H_8N_2O$: *M,* 160.0636); ν_{max} (thin film)/cm^{-1} 3400, 2800 and 2200; δ_H(400MHz; $CDCl_3$) 5.28 (2H, 2 x overlapping s, OH and C*H*OH), 6.05 and 6.23 (2H, s, CH_2=C), 7.30 (1H, ddd, 5′-H), 7.40 (1H, d, 3′-H), 7.76 (1H, ddd, 4′-H), 8.58 (1H, d, 6′-H); δ_C(100MHz; $CDCl_3$) 72.8 (CHOH), 116.7 (C≡N), 121.2 (3′-C), 123.7 (5′-C) 125.9 (CH_2=*C*), 130.8(*C*H_2=C), 137.45 (4′-C), 148.5 (6′-C), 156.0 (2′-C) *m/z* 160 (M^+, 5%) and 143 (100%).

3-Hydroxy-2-methylene-3-(3-pyridyl)propanenitrile (**49**)[187].-

A mixture of pyridine-3-carboxaldehyde (2.95g, 28mmol), acrylonitrile (1.54g, 29mmol) and DABCO (0.15g, 1.3mmol) dissloved in $CHCl_3$ (2ml) was stirred at room temperature. Crystals formation was visible after 2 hours and after 4 hours the reaction was stopped, the product collected by filtration and dried to afford 3-hydroxy-2-methylene-3-(3-pyridyl)propanenitrile **49** as pale yellow crystals (1.34g, 29.88%), m.p. 92-94°C (from benzene), (Found: $\mathbf{M}^+$ 160.0628. Calc. for $C_9H_8N_2O$: *M*, 160.0636) ν_{max} (KBr)/cm^{-1} 3300 and 2200; δ_H(400MHz; $CDCl_3$); 3.47 (1H, br s, OH), 5.37 (1H, s, C*H*OH), 6.09 and 6.18 (2H, 2 x s, CH_2=C), 7.36 (1H,dd, 4'-H), 7.77 (1H, dddd, 5'-H) and 8.56 (2H, multiplet, 2'-H and 6'-H); δ_C(100MHz; $CDCl_3$) 72.1 (CHOH), 116.5 (C≡N), 123.9 (4'-C), 125.8 (CH=C), 130.4(*C*H_2=C), 134.4 (5'-C), 135.1 (3'-C), 148.1 (2'-C), 150.0 (6'-C) ; *m/z* 160 (M^+, 27%) and 108 (100%).

Methyl 3-hydroxy-2-(methylthiomethyl)-3-(2-pyridyl)propanoate (**52**).-

Methyl 3-hydroxy-2-methylene-3-(2-pyridyl)propanoate (**47**) (2.5g, 13mmol) was dissolved in THF (5ml) in a 50 ml round-bottomed flask. A 21% solution of sodium thiomethylate (4.75g, 14 mmol CH_3SNa) was added dropwise over a period of 15 minutes during which time the temperature rose from 20°C to 25°C. The flask was then heated at 35°C for 2h; the course of the reaction was monitored by TLC until no more starting material could be detected. Saturated aqueous NaCl (10ml) was added to the solution and the organic layer extracted (ethyl acetate), dried (anhydrous magnesium sulphate) and the solvent removed *in vacuo*. ^{1}H NMR analysis of the crude product did not show the presence of the thiomethyl protons and also revealed that hydrolysis of the ester had occurred.

3-Hydroxy-2-(methylthiomethyl)-3-(2-pyridyl)propanenitrile (**50**).-

3-Hydroxy-2-methylene-3-(2-pyridyl)propanenitrile (**48**) (2.5g, 0.16mol) was dissolved in THF (5ml) in a 50ml round-bottomed flask and stirred. A 21% solution of

sodium thiomethylate (4.75g, 14mmol CH_3SNa) was added dropwise over a period of 15min, during which time the temperature rose slowly from 20°C to 25°C. The temperature was then raised to 35°C for 2h; the course of the reaction was monitored by TLC until no more starting material could be detected. Saturated aqueous NaCl (10ml) was added to the mixture and the product was extracted with ethyl acetate (2 x 15ml), dried (anhydrous magnesium sulphate) and the solvent removed *in vacuo.* The oil was chromatographed [flash chromatography on silica gel; elution with dichloromethane:ethyl acetate (1:9)] to afford 3-hydroxy-2-methylene-3-(2-pyridyl)-propanenitrile (**48**) and a brown oil which was chromatographed again [flash chromatography on silica gel; elution with dichloromethane:ethyl acetate (1:1)] to afford *3-hydroxy-2-(methylthiomethyl)-3-(2-pyridyl)propanenitrile* (**50**) as a brown oil. (1.21g, 38%) (Found: M^+ 208.0667: $C_{10}H_{12}N_2OS$ requires*M*, 208.0670); ν_{max} (thin film)/cm^{-1} 3400, 2950 and 2260; δ_H(400MHz; $CDCl_3$) 2.21 (3H, s, SCH_3), 2.79-3.04 (4H, m, CH_2 SCH_3), 3.1-3.28 (2H, m, CHCN), 4.51 and 4.83 (1H, d, OH), 4.97 and 5.08 (1H, t, C*H*OH), 7.30 (1H, ddd, 5'-H), 7.40 (1H, d, 3'-H), 7.76 (1H, ddd, 4'-H) and 8.58 (1H, d, 6'-H); δ_C(100MHz; $CDCl_3$) 16.3 and 16.4 (SCH_3), 32.4 and 33.2 (CH_2SCH_3), 41.0 and 41.2 (*C*HCN), 70.7 and 71.8 (CHOH), 118.5 and 119.4 (C≡N), 120.7 and 121.8 (3'-C), 123.6 and 123.8 (5'-C), 137.2 and 137.4 (4'-C), 148.6 and 148.8 (6'-C) and 156.9 and 157.0 (2'-C); *m/z* 190 (M^+, 4.3%) and 108 (100%).

2-(Methylthiomethyl)-3-(3-pyridyl)-2-propenenitrile (**51**). -

To a stirred solution of 3-hydroxy-2-methylene-3-(3-pyridyl)propanenitrile (**49**) (1.10g, 69mmol), dissolved in THF (5ml) in a 50ml round bottomed flask was added a 21% solution of sodium thiomethylate (2.50g, 75mmol CH_3SNa) dropwise over 15min. The temperature of the reaction was then raised to 35°C for 2.5h, the disappearence of starting material being monitored by TLC. Saturated aqueous NaCl (10ml) was added to the mixture, and the product extracted with ethyl acetate (2 x 15ml), dried (anhydrous magnesium sulphate) and the solvent removed *in vacuo.* The resulting oil was chromatographed [flash chromatography on silica gel; elution wtih ethyl acetate:dichloromethane (3:2)] to afford *2-(methylthiomethyl)-3-(3-pyridyl)-2-*

propenenitrile (**51**) as a brown oil (0.71g, 54.14%), (Found: $\mathbf{M}^+$ 190.0554: requires $C_{10}H_{10}N_2S$:*M*, 190.0565); ν_{max} (thin film)/cm^{-1} 3000, 2910 and 2200; δ_H(400MHz; $CDCl_3$) 2.47 (3H, s, SCH_3), 3.51 (2H, s, CH_2SCH_3), 7.12 (1H, s, CH=C), 7.23 (1H, dd, 4′-H), 7.58 (1H, dd, 5′-H) and 8.48 (2H, m, 2′-H and 6′-H);*m/z* 190 (M^+ 72%) and 28 (100%).

3.3 GLC and GC-MS analysis

GLC analysis was performed on a Hewlett Packard 5980A gas chromatograph using a flame ionisation detector and either an Ultra-2 or an HP-1 column. Samples were dissolved in $CHCl_3$ and 0.5µl was injected for each analysis. The following operating conditions were used:

Initial temperature	50°C
Initial time	5min
Rate	10°C/min
Final temperature	200°C
Final time	10min
Injector temperature	130°C
Detector temperature	220°C

3.4 NMR studies

Variable temperature ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX400 spectrometer operating at 400MHz for ^{1}H and 100MHz for ^{13}C nuclei. The maximum possible temperature setting for samples dissolved in $CDCl_3$ was in the region of 323K and for samples dissolved in DMSO in the region of 426K.

The NMR probe temperatures were corrected by reference to a previously established calibration curve.

4. References

1. B. L. Bohmont, *The New Pesticide User's Guide*, Reston Publishing Company, Virginia, 1983, p. 93.
2. Ref. 1, p. 377.
3. M. L. Flint and R. van den Bosch, *Introduction to Integrated Pest Management*, Plenum Press, New York, 1981, p. 51.
4. R. Cremlyn, *Pesticides. Preparation and Mode of Action*, John Wiley and sons, New York, 1978, pp. 3-4.
5. Ref. 3, pp. 53-55.
6. Ref. 4, p. 5.
7. Ref. 3, pp. 68-70.
8. A. J. Burn, T. H. Coaker and P. C. Jepson, *Integrated Pest Management*, Harcourt Brace Jovanovich, Oxford, 1978, p. 114.
9. Ref. 3, pp. 78-80.
10. Ref. 4, p. 1.
11. Ref. 1, pp. 7-9
12. A. Nel, M. Krause, N. Hollings, J. Greyling and M. Dreyer, *A Guide to the Use of Pesticides and Fungicides in the Republic of South Africa*, 36th Ed., Department of Agriculture, Pretoria, 1993, p. 13.
13. J. Bot, S. Sweet, M. Krause and N. Hollings, *A Guide to the Use of Pesticides and Fungicides in the Republic of South Africa*, 33rd Ed., Department of Agriculture, Pretoria, 1988, p. 5.
14. Ref. 12, p. 3.
15. J. R. Corbett, *The Biochemical Mode of Action of Pesticides*, Academic Press, London, 1974, p. 150.
16. Ref. 13, p. 6.
17. R. D. O'Brien, *Insecticides. Action and Metabolism*, Academic Press, London, 1967, p. 1.
18. Ref. 1, pp. 363 and 390.
19. Ref. 12, p. 4.

20. Ref. 1, p. 180-183.

21. Ref. 4, p. 13.

22. Ref. 1, p. 145-150.

23. World Health Organisation Expert Committee on Vector Biology and Control, *Safe Use of Pesticides*, World Health Organisation Technical Report Series 634, Geneva, 1979.

24. Ref. 4, p. 14-15.

25. Ref. 13, p. 4.

26. Ref. 8, p. 116.

27. United States Environmental Protection Agency, *Guide to Pollution Prevention. The Pesticide Formulating Industry*, EPA/625/7-90//004, 1990.

28. Ref. 8, p. 138.

29. Ref. 1, p. 201.

30. Ref. 1, p. 203-210.

31. Ref. 1, p. 210-231.

32. R. Carson, *Silent Spring*, Hamish Hamilton Ltd, London, 1963.

33. E. R. De Ong, *Chemistry and Use of Insecticides*, Reinhold Publishing Corp., New York, 1948, p. 3.

34. M. B. Green, G. S. Hartley and T. S. West, *Chemicals for Crop Improvement and Pest Management*, 3rd Ed., Pergamon Press, Oxford, 1987, p. 69.

35. Ref. 4, p. 51.

36. Ref. 34, p. 68-69.

37. G. Hartley and T. West, *Chemicals for Pest Control*, Pergamon Press, Oxford, 1969, p. 161.

38. Ref. 1, p. 225.

39. Ref. 34, p. 175.

40. Ref. 34, p. 69-70.

41. Ref. 4, p. 52-54.

42. Ref. 37, p. 42-43.

43. Ref. 34, p. 105-107.

44. Ref. 8, p. 122-125.

45. Ref. 8, 116-119.

46. C. Worthing, *The Pesticide Manual. A World Compendium*, 6th Ed., British Crop Protection Council, 1979, p. 150.

47. Ref. 34, p. 71.

48. Manufacturing Chemists' Association of the U. S., DDT Committee, *J. Econ. Entomol.*, 1945, **38**, 516.

49. R. L. Metcalf and J. J. McKelvey, *The Future for Insecticides. Needs and Prospects*, John Wiley and Sons, New York, 1976, pp. 223.

50. Ref. 4, pp. 71-78.

51. Ref. 34, pp. 73-74.

52. Ref. 3, pp. 117-118.

53. Ref. 34, pp. 75-78.

54. C. W. Kearns, L. Ingle and R. L. Metcalf, *J. Econ. Entomol.*, 1945, **38**, 661-668.

55. Ref. 4, p. 64.

56. C. W. Kearns, C. J. Weinman and G. C. Decker, *J. Econ. Entomol.*, 1949, **42**, 127.

57. Ref. 46, pp. 6, 185 and 234.

58. Ref. 49, p. 277.

59. Ref. 8, p. 120.

60. Ref. 8, pp. 120-122.

61. Ref. 4, p. 68.

62. Ref. 15, pp. 110-126.

63. Ref. 8, pp. 126-127.

64. Ref. 34, pp. 100-104.

65. Ref. 46, 15.

66. Ref. 4, p. 96.

67. K. A. Hassal, *The Chemistry of Pesticides - their Metabolism, Mode of Action and Use in Crop Protection*, McMillan., London, 1982, p. 97.

68. Ref. 8, p. 114.

69. Ref. 67, p. 102.

70. Ref. 67, pp. 104-115.

71. Ref. 46, p. 79.

72. Ref. 46, p. 82.

73. Ref. 46, p. 432.

74. L. K. Payne Jr., H. A. Stansbury and M. H. J. Weiden, *J. Agric. Food Chem.*, 1966, **14**, 356.

75. J. F. Risher, F. L. Mink and J. F. Stara, *Environmental Health Perspectives*, 1987, **72**, 267.

76. M. H. J. Weiden, H. H. Moorefield and L. K. Payne, *J. Econ. Entomol.*, 1965, **58**, 154.

77. C.T. Mathew and H. E. Ulmer, German Patent 2 043 236, 1973.

78. J. H. Bonfield, U. S. Patent 821 898, 1977.

79. R. L. Baron and T. L. Merriam, *Rev. Environ. Contam. Toxicol.*, 1988, **105**, 1.

80. Ref. 15, pp. 127-128.

81. Ref. 1, pp. 133-134.

82. E. N. Lightfoot, P. S. Thorne, R. L. Jones, J. L. Hansen and R. R. Romine, *Environ. Toxicol. Chem.*, 1987, **6**, 377.

83. C. J. Miles, M. Trehy and R. Yost, *Bull. Environ. Contam. Toxicol.*, 1988, **41**, 838.

84. P. J. Bunyan, M. J. Van den Heuvel, P. J. Stanley and E. N. Wright, *Agro Ecosystems,*, 1981, **7**, 239.

85. R. H. Bromilov, R. J. Baker, M. A. H. Freeman and K. Görög, *Pesti. Sci.*, 1980, **11**, 37.

86. F. A. Richey Jr., W. J. Bartley and K. P. Sheets, *J. Agric. Food. Chem.*, 1977, **25**(1), 47.

87. J.H. Smelt, M. Liestra, N. W. H. Houx and A. Dekker, *Pesti. Sci.*, 1978, **9**, 293-300.

88. C. J. Miles, *Environ. Sci. Technol*, 1991, **25**, 1774.

89. Ref. 12, pp. 33, 57, 65, 70, 75, 77, 81, 99, 112, 117, 118, 138, 162, 174, 189, 193, 194, 197 and 203.

90. M. Evans, Honours Project, Rhodes University, 1992.

91. A. Kirrman, J. Cantacuzere and L. Vio, *Chem. Abstracts*, 1962, **61**, 8181a.

92. A. Mathew and D. Pickens, U. S. Patent 4 256 668, 1981.

93. J. March, *Advanced Organic Chemistry. Reactions, Mechanisms and Structure*, 4th Ed., John Wiley and Sons, New York, 1992, p. 895.

94. D.D.Perrin and W.L.F, Armarego, *Purification of Laboratory Chemicals*, 3rd Ed., Pergamon, Oxford, 1988.

95. P. Sykes, *A Guidebook to Mechanism in Organic Chemistry*, 6th Ed., Longman. John Wiley and Sons, New York. 1991. p. 215.

96. L. F. Fieser and M. Fieser, *Advanced Organic Chemistry*, Chapman and Hall Ltd., London, 1961, p. 416.

97. B. S. Furniss, A. J. Hannaford, P. W. G. Smith and A. S. Tatchell, *Vogel's Textbook of Practical Organic Chemistry*, 5th Ed., Longman, New York, 1989, p. 140.

98. F. G. Mann and B. C. Saunders, *Practical Organic Chemistry*, 4th Ed.,Longman, Singapore, 1989, p. 21.

99. S. Quici and S. L. Regen, *J. Org. Chem.*,1979, **44**, 3436.

100. Yasushiro Kamitori, Masaru Hojo, Ryoichi Masuda, Tadashi Kimura and Tatsushi Yoshida, *J. Org. Chem.*, 1986, **51**, 1427.

101. W. C. Still, M. Kahn and A. Mitra, *J. Org. Chem.*, 1978, **43**, 2923.

102. Ref. 97, p. 171.

103. Tamotsu Yokotsuka, *Chem. Abstracts*, **49**, 15163g.

104. Ref. 93, p. 587.

105. H. C. Brown, G. W. Kabalka, M. W. Rathke and M. Rogic, *J. Am. Chem. Soc.*, 1968, **91**, 4165.

106. P. Z. Bedoukian, *J. Am. Chem. Soc.*, 1944, **66**, 1325.

107. E. M. Filachione, *J. Am. Chem. Soc.*, 1939, **61**, 1705.

108. C. L. Stevens and B. T. Gillis, *J. Am. Chem. Soc.*, 1957, **79**, 3448.

109. Ref. 93, p. 695.

110. D. Barton and D. Ollis, *Comprehensive Organic Chemistry. The Synthesis and Reactions of Organic Compounds*, Pergamon Press,Oxford, **1**, 1000-1001.

111. R.H. Reuss and A.Hassner. *J. Org. Chem.*, 1974, **39**, 1785.

112. L. Blance, P Amice and J.M. Conia *Synthesis*, 1976, 194.

113. V. Kohlschütter, *Chem. Ber.*, 1904, **37**, 1153.

114. A. Lorenzini and C. Walling, *J. Org. Chem.*, 1967, **32**, 4008.

115. C. L Stevens, E. Farkas and B. Gillis, *J. Am. Chem. Soc.*, 1954, **76**, 2695.

116. J. M. Tedder, A. Nechvatal and A. H. Hubb, *Basic Organic Chemistry. Part 5. Industrial Products.*, John Wiley and Sons, London, 1975, p. 141.

117. Ref. 98, p. 93.

118. Ref. 97, p. 1259.

119. Ref. 93, p. 128.

120. *Dictionary of Organic Compounds,* 4th Ed., Eyre and Spottiswoode, London, vol 2, 1934, p. 650.

121. M. H. Benn, *Can. J. Chem*, 1964, **42**, 2393.

122. Ref. 97, p. 710.

123. Ref. 93, p. 362.

124. Ref. 98, p. 121.

125. G. Simchem and H Kobler, *Synthesis*, 1975, 606.

126. C.M. Starks, *J. Am. Chem. Soc.*, 1971, **93**, 195.

127. Ref. 93, p. 363.

128. J. Jiricny, D.M Orere and C.B Reese, *J. Chem. Soc, Perkin Trans. I*, 1980, 1487.

129. *Organic Synthesis*, John Wiley and Sons, New York, **25**, 61.

130. P. Molina, M. Alajarin and M.J. Vilaplana, *Synthesis*, 1982, 1016.

131. H.M. Meshram, *Synthesis*, 1992, 943.

132. A Carotti and F. Campagna, *Synthesis,* 1979, 56.

133. O. Attansi, P. Palma and F. Sierra-Zanetti, *Synthesis*, 1983, 741.

134. G. A.Olah, Y. D. Vankar and A. Garcia-Luna, *Synthesis*, 1979, 227.

135. P. J. Foley Jr, *J. Org. Chem.*, 1969, **34**, 2805.

136. G. A. Olah and T. Keumi, *Synthesis*, 1979, 112.

137. J. A. Findlay and C. S. Tang. *Can. J. Chem*, 1967, **45**, 1014.

138. D. A. Kaiser, P. T. Kaye, L. Pillay and G. H. P. Roos, *Synth Commun*, 1984, **14**, 883.

139. Ref. 98, p. 121.

140. B. Ku and D. Young Oh, *Synth.Commun*,1989, **19**, 433.

141. P. Kumar, R. S. Reddy, A. P. Singh and B. Pandey, *Synthesis*, 1993, 67.

142. Ref. 110, **3**, p. 57- 65.

143. Ref. 95, p. 211.

144. Ref. 97, p. 787.

145. Ref. 93, p. 474.

146. D. A. Evans, K.G. Grimm and L. K. Truesdale, *J. Am. Chem. Soc.*, 1975, **97**, 3229.

147. V. Kumar and S. Dev, *Tetrahedron. Lett*, 1983, **24**, 1289.

148. J. Romo, G. Rosenkranz and C. Djerassi, *J. Am. Chem. Soc.*, 1951, **73**, 4961.

149. L.F. Fieser, *J. Am. Chem. Soc.*, 1954, **76**, 1945.

150. B. S. Ong, *Tetrahedron. Lett*, 1980, **21**, 4225.

151. Masa-aki Kakimoto, Taskuya Seri and Yoshio Imai, *Synthesis*, 1987, 164.

152. P. Kumar, R. S. Reddy, A. P. Singh and B. Pandey, *Synthesis*, 1993, 67.

153. D. Morton and S. J. Hobbs, *J. Org. Chem.*, 1979, **44**, 656.

154. F. Bessette, J Brault and J.M Lalancette, *Can. J. Chem*, 1965, **43**, 307.

155. Masato Tazaki and Makoto Takagi, *Chem. Lett.*, 1979, 767.

156. D. A. Evans, L. K. Truesdale, K. G. Grimm and S. L. Nesbitt. *J. Am. Chem. Soc.*, 1977, **99**, 5009.

157. Ref. 93, p. 940.

158. Ref. 97, pp. 799-801.

159. Ref. 110, p. 964.

160. L. M. Baigrie, R. A. Cox, H. Slebocka-Tilk, M. Tencer and T. Tidwell, *J. Am. Chem. Soc.*, 1985, **107**, 3640.

161. T. Mukaiyama, K. Banno and K. Narasaka, *J. Am. Chem. Soc.*, 1974, **96**, 7503.

162. Y. Yamamoto and K. Maruyama, *J. Am. Chem. Soc.*, 1983, **105**, 6963.

163. Ref. 95, pg 225.

164. M. Backès *Chem. Abstracts*, 1943, **37**, 5023[6].

165. R. H. Saunders, M. J. Murray and F. F. Cleveland, *J. Am. Chem. Soc.*, 1943, **65**, 1714.

166. Itaru Mita, Isao Imai and Hirotaro Kambe, *Die Makromolekulare Chemie*, 1970, **137**, 143.

167. Z. Machácek, J. Mejzlík and J. Pác, *J. Pol. Sci.*, 1961, **52**, 309.

168. O. Vogl, *J. Macromol. Sci. (Chem.)*, 1967, **A1**, 243.

169. O. Vogl, *J. Pol. Sci.*, 1964, **A2**, 4607.

170. Itaru Mita, Isao Imai and Hirotaro Kambe, *Die Makromolekulare Chemie*, 1970, **137**, 155.

171. Itaru Mita, Isao Imai and Hirotaro Kambe, *Die Makromolekulare Chemie*, 1970, **137**, 169.

172. Itaru Mita, Isao Imai and Hirotaro Kambe, *Die Makromolekulare Chemie*, 1970, **137**, 133.

173. Ref. 96, p. 226.

174. T. Ogawa, *Chem. Abstracts*, 1979, **90**, 152247g.

175. Y. Saeki, M. Fujita T. Akiyama and Y. Ueno, *Chem. Abstracts*, 1975, **83**, 10167n.

176. J. L. Jungnickel and C. A. Reilly, *J. Mol. Spec.*, 1965, **16**, 135.

177. C. R. Hauser and W. B. Renfrow, *J. Am. Chem. Soc.*, 1937, **59**, 1823.

178. S. E. Drewes and G. H. P. Roos, *Tetrahedron*, 1988, **44**, 4653.

179. A.B. Baylis and M. E. D. Hillman, Chem. Abstracts, 1972, 77, 34174q.

180. F. Ameer, S.E. Drewes, R. Hoole, P.T. Kaye, and A. T. Pitchford, *Synth. Commun.*, 1988, **18**, 495.

181. M. L. Bode and P. T. Kaye, *Tetrahedron Lett.*, 1991, **32**, 5611.

182. H. Martin, *The Scientific Principles of Crop Protection*, Edward Arnold Publishers (Ltd.), 1595, pp. 164-165.

183. Ref. 97, p. 388.

184. L. Pillay, Honours Project, Univeristy of Natal, 1982.

185. *Dictionary of Organic Compounds*, 4th Ed., Eyre and Spottiswoode, London, vol 3, 1934, p. 1895.

186. Ref. 97, p. 802.

187. M. Bode, PhD. Thesis, Rhodes University, 1994.