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Synthesis of the Fungicide Propiconazole a Systemic Foliar Fungicide.

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Synthesis of the fungicide propiconazole a systemic foliar fungicide.

By

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Submitted to the Dublin Institute of Technology in fulfilment of the Degree of Master of Philosophy

This work was carried out in the Department of Chemistry in the Dublin Institute of Technology, Kevin Street, Dublin 8 under the supervision of Dr. P. Mulligan and in Agriguard Ltd., School of Chemical Sciences D.C.U., Glasnevin Dublin 9 under the direction of Dr. Nigel M^c Sweeney and Mr. B. Parker.

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March 2000

Declaration

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Signature Hazel Delaney Date 1/12/2000

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"For my Mother"

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Introduction

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Abstract

Propiconazole, 1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxol-2-yl]methyl]-1H-1,2,4-triazole, commerically known as "Tilt" is a systemic foliar fungicide for cereals and is widely used in agriculture. The aim of this project was to develop an economically feasible process for the production of propiconazole and to maximise the yields of the intermediates in the developed process. Processes investigated included the original Ciba-Geigy process. In addition an investigation into the synthesis and characterisation of the impurities formed, and reported to be formed in each step of the reaction process was carried out and seven of the reported impurities were synthesised. One impurity was shown not to be present in the reaction process. In addition a new impurity was identified, synthesised and characterised.

The synthesis of propiconazole was initiated with ethanone-1-(2,4-dichlorophenyl) which under-went a condensation reaction with 1,2-pentanediol to yield 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl. 1,3-Dioxolane-2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl was then brominated in dichloromethane to yield 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-bromomethyl-4-*n*-propyl. Finally 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-bromomethyl-4-*n*-propyl under-went nucleophlic substitution with a sodium triazole salt in dimethyl-sulphoxide at 160°C for 16hrs to yield propiconazole in 45% yield. The final phase of the project involved the scale up of the reaction process in order to evaluate any problems that might result in an industrial scale up.

1.1 General introduction

Crop failures, blights and famines have been recorded in agriculture throughout history. Early farmers accepted these natural disasters as an inevitable part of life. Indeed many people believed that the crop failures were the direct result of black magic and dark curses. For centuries mysteriously failed crop harvests were shrouded in superstitious beliefs and blame apportioned to local witches or goblins. Crop failures were also attributed to retribution from the Gods.

UN population estimates predicted that on the twelfth of October 1999 there would be six billion human beings on the planet. In less than 200 years the world population has grown from one billion to six billion people[1]. The reason for this rapid population growth is the breaking of the balance between the birth and death rates. UN projections predict a slow down in population growth in the next fifty years as the result of the widespread use of birth control. A century from now the world's population will probably reach 10-15 billion people[1]. Pessimists predict catastrophes before ever reaching this number. Optimists believe that the planet can accommodate a much larger population. The survival of the human race depends not only on population control but also on the better management of our resources.

In 1845 when potato blight made a dramatic appearance in Western Europe, the discipline of plant pathology did not exist[2]. The blight spread rapidly through Belgium, the Netherlands, France and Ireland and resulted in the loss of approximately half the entire potato crop. The blight reappeared the following year in Ireland and destroyed the entire potato crop. At that time the potato was the staple food in Ireland and the blight was directly responsible for the deaths of over one million people through starvation and disease. Another one million people died on emigrant ships to America and Canada.

In 1914 LR Jones stated that[3] " it required the plague of the potato disease and the example of the Irish famine finally to focus attention upon the fundamental problem, the relation of the mildew to the sick potato plant, of the smut and the rust fungi to the infected grain, the problem of parasitism ".

In 1845 the majority of the scientific community believed that plant disease was the result of external factors such as climatic and weather changes or perhaps even a general over propagation of the potato plant. A few scientists after observing the development of small fungi on dead plants speculated that the blight itself was actually caused by the fungus. This theory was easily dismissed as fungi had frequently been observed growing on dead matter and the fungi were attributed to the result of plant disease rather than the cause. In 1853 Anton De Barry published work which confirmed[4] " that Brand fungi do not arise from the cell content or from the secretion of diseased cells, that they are not the consequence but the cause of pathological process ". Finally there was agreement among the scientific community that fungi were in fact the cause of plant disease and not just a symptom. The emphasis then shifted, to research into treatment of plant disease.

In 1882 the French botanist Millardet observed that a mixture of copper sulphide, lime and water discouraged the development of downy mildew on grapevines[5]. Millardet called this mixture Bordeaux mixture and it is still used today as a contact fungicide. The development of the railroads and the need to protect and maintain the wooden railway ties, stimulated research into other chemical treatments. Products developed for this purpose-contained creosote and salts of copper, mercury, and zinc[6]. Important advances in the development of agrochemicals occurred as a by-product of the scientific research undertaken during the war years. Organo-mercurials were introduced in 1913, as seed dressings and the 1930's signalled the birth of synthetic organic pesticides. The majority of organic fungicides developed at that time belonged to one of the following chemical classes, dithiocarbamates, chlorobenzene and related compounds, phenols, quinones and dicarboximides.

The mid-ninteen sixties marked the development of systemic fungicides. Many of these new compounds had a common mode of action. One of the most important classes of compounds developed were the ergosterol biosynthesis inhibitors (EBI's). These compounds are nitrogen-containing hetrocycles and members of this class include morpholines, piperazines, imidazoles and triazoles. All of these classes of compounds with the exception of the morpholines interfere specifically with the carbon-14 demethylation reactions in ergosterol biosynthesis (see section 1.6). All the fungicides listed in table 1.1.1 have this common biochemical mode of action[7].

Chemical class	Name	Use
Imidazole	Imazalil	Agrochemical fungicide
Imidazole	Fenapanil	Agrochemical fungicide
Imidazole	Propchloraz	Agrochemical fungicide
Imidazole	Miconazole	Medical purposes
Imidazole	Ketoconazole	Medical purposes
Imidazole	Clotrimazole	Medical purposes
Imidazole	Isconazole	Medical purposes
Pyrimidine	Fenarimol	Agrochemical fungicide
Pyrimidine	Nuarimol	Agrochemical fungicide
Pyrimidine	Buthiobate	Agrochemical fungicide
Pyrimidine	Pyrifenox	Agrochemical fungicide
Triazole	Triadimefon	Agrochemical fungicide
Triazole	Triadimenol	Agrochemical fungicide
Triazole	Propiconazole	Agrochemical fungicide
Triazole	Etaconazole	Agrochemical fungicide
Triazole	Diniconazole	Agrochemical fungicide
Triazole	Biteranol	Agrochemical fungicide
Triazole	Diclobutrazole	Agrochemical fungicide
Triazole	Flutraifol	Agrochemical fungicide
Triazole	Fusilazole	Agrochemical fungicide
Triazole	Myclobutanil	Agrochenical fungicide
Triazole	Penconazole	Agrochemical fungicide
Triazole	Terconazole	Medical purposes
Piperazine	Triforine	Agrochemical fungicide

Table 1.1.1 Fungicides that inhibit sterol C-14 demethylation.

Agricultural fungicides are chemicals that are used to prevent or minimise crop losses caused by phytopathogenic fungi[8]. Approximately 150 different fungicides are now in use with an end-user market value of $6 billion dollars (figure 1.1.1)[9]. Fungicides account for 20% of the world pesticide market (table 1.1.2)[9]. Western Europe has the highest intensity of fungicide usage with a total of 40% of the world's fungicides being applied to only 8% of the world's agricultural land.

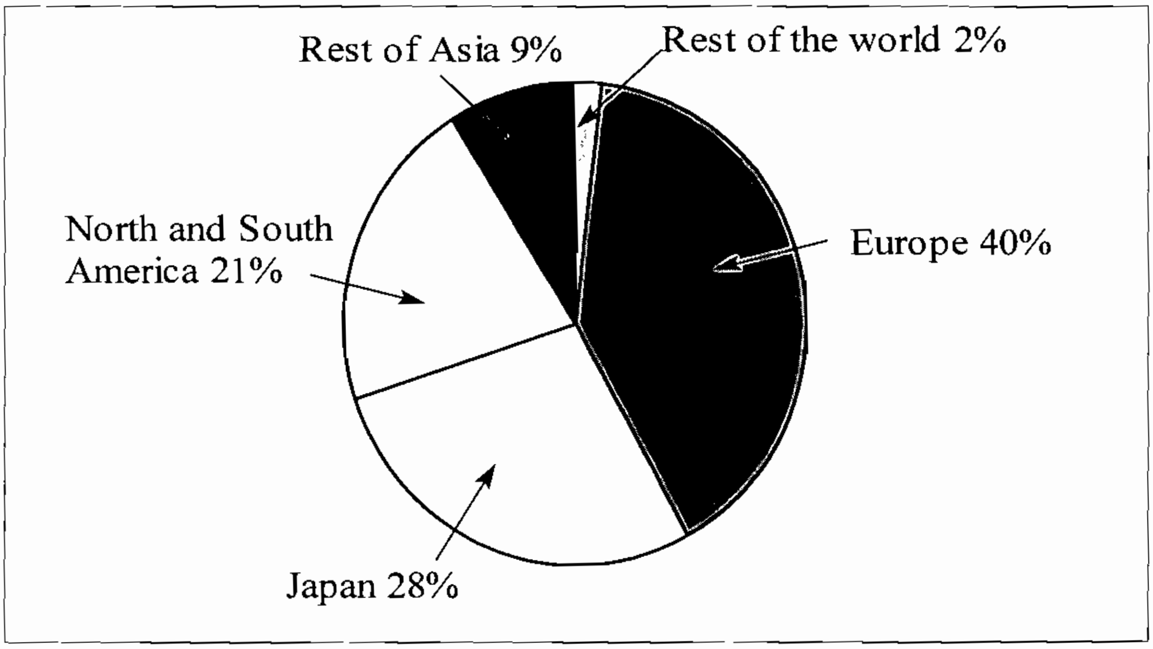


Figure 1.1.1 Regional fungicide markets.

All of the compounds, which have been recently introduced, are systemic compounds. The most commercially successful class of systemic fungicides developed to-date are the triazole fungicides and in the early nineties, in a period of shrinking EU markets the triazole fungicides increased in absolute sales (table 1.1.3)[9].

	1960	1970	1980	1990	1995
Total pesticide sales ($ million)	850	2700	11600	26150	30300
Fungicides sales ($ million)	340	594	2181	5550	5848
% of total	40.0	22.2	18.8	21.2	19.3

Table 1.1.2 Development of the world fungicide market and pesticide market from 1960-1995.

Group	1990	1995
Benzimidazoles	673	430
Triazoles	1172	1385
Substituted anilides	638	680
Organophosphorus	232	205
Morpholines	366	295
Other systemics	818	880
Total	3899	3875

Table 1.1.3 Recent sales ($ million) of systemic fungicides.

1.2 Classification and formulation of fungicides

Fungicides may be classified according to their (1) systemic properties and/or by (2) their biochemical mode of action.

(1) Systemic properties refer to the different extents which the active ingredient in the fungicide formulation can be transported and translocated through the plant.

Non-systemic fungicide: the fungicide does not have the ability to appreciably penetrate the plant tissues and consequently cannot be transported and translocated through the plant[10].

Loco-systemic fungicide: this type of fungicide possesses an entirely local contact action in the area of application and also in the immediate surrounding area of application[10]. A loco-systemic fungicide cannot be transported and translocated throughout the entire plant.

Systemic fungicide: this type of fungicide has the ability to penetrate right through the leaf cuticle and can be transported and translocated in the xylem and phloem of the plant [10]. A systemic fungicide theoretically provides complete plant protection. Systemic or loco-systemic fungicides tend to be site specific as they generally only have one or two biochemical targets within the organism. Non-systemic fungicides such as mercury seed dressings tend to have multiple biochemical targets within the organism (table 1.2.1).

(2) Biochemical mode of action is the second mode of classification of fungicides and this type of classification generally covers fungicides from the same chemical families, which have the same or similar biochemical sites of action in fungi.

One classification of modes of action of fungicides leads to three main groups. These three groups are (1) inhibitors of energy production by blocking SH-groups, the glycolysis/citrate cycle or the respiratory chain, (2) inhibitors of the biosyntheses of proteins, nucleic acids, cell walls and membrane lipids and (3) those which induce indirect effects which induce changes in the host/fungal pathogen interactions[11].

Multiple sites of action	Site(s) of action uncertain	Site-specific
Copper and tin compd.	Dicarboximides	Dinitrocompounds
Mercurials		Benzimidazoles
Dithiocarbamates		Oxathiins
Phthalimides		Morpholines
Phthalonitriles		C-14 demethylation inhibitors
		Hydroxyaminopyrimidines
		Antibiotics
		Phenylamides
		Organophophosphorus compounds
		Miscellaneous

Table 1.2.1 Site(s) of action of fungicides.

Furmidge defined formulation as[12], " a vehicle which allows the active ingredient to be transported to its site of action in the biological system that is to be modified or destroyed ". The effectiveness of a pesticide is often due to the method of formulation and the type of formulation is often influenced by the method of application. A pesticide may be applied in the vapour, liquid or solid phase[13]. Many companies formulate the same product in a number of different formulations.

The choice of method of application and formulation is influenced by factors such as climatic variations and economic considerations. Spraying is generally considered a superior method of application to dusting, however in countries where drought or water shortages are prevalent, dusting has been adopted as the preferred method of application. In more recent years technological developments in spraying techniques have resulted in further developments of formulations. Conventional spraying techniques require approximately 100-400 litres of fluid per hetarce whereas only ultra low volume techniques (ULV) require only 1-5 litres per hetacre[14].

In the dry state the active ingredient may be formulated as a dust or as granules[15]. Granular application is generally employed for ground level application. A dust is prepared by the impregnation of a sorptive substance by a concentrated solution of the active ingredient. The solvent is then evaporated off and the powder diluted down with a large bulk of the sorptive substance. The most suitable sorptive substances are generally clays (usually kaolinite or attapulgite) or silica (usually talc, diatomite or pumice).

When a pesticide is applied as a liquid it is formulated as an emulsifiable concentrate (EC), as a wetable powder (WP) or as a suspended concentrate (SC). Formulation as an EC is the most common method of formulation when the active ingredient is insoluble in water. The active ingredient is formulated in a suitable organic solvent with the addition of non-ionic emulsifying agents. The EC is then diluted down with water to form a milky emulsion and sprayed within twenty-four hours. A wetable powder (WP) is formulated by grinding down the active ingredient with an inert inorganic mineral diluent e.g. talc or clay to give a fine powder. If the active ingredient is a liquid an adsorbent filter is used before grinning down to form the powder. Wetting agents and more inorganic mineral diluent are often added. The third type of liquid formulation is a suspended concentrate (SC). The solid active ingredient is suspended in a small quantity of liquid (usually an oil or water) and is blended with an inert dust diluent, ethylene glycol, wetting and dispersing agents. The result is a smooth paste, which can then be diluted down with water before spraying. Newer developments in formulation techniques include slow release formulations in the form of slow release strips or mircocapsules[16].

1.3 Plant and Fungi physiology

1.3.1 The structure of the plant

A plant consists of the root system and the shoot system as illustrated in figure 1.3.1[17]. The root penetrates the soil and the root hairs absorb various minerals from the soil that are necessary for plant nutrition. The root is also responsible for anchoring the plant in the soil. The shoot consists of the stem and the leaves. The leaves of the plant are where photosynthesis takes place. Flowers, fruit etc. are all positioned on the stem. Although the root system and the shoot system have very different functions they both contain the same three types of plant tissue, (1) vascular tissue, (2) ground tissue and (3) dermal tissue.

There are a variety of cells present in plant tissues. Parenchyma cells are close to spherical and do not contain cell walls till maturity. Parenchyma cells can be found throughout the plant in leaves, stems and roots. Parenchyma cells contain a nucleus at maturity and so are referred to as living cells. Collenchyma are also living cells at maturity and are elongated and have unevenly thick cell walls. The primary function of both these cell types is support. Sclerenchyma cells contain thick cell walls and are unliving at maturity. There are two types of Sclerenchyma cells, fibres, which are elongated, and strands which are not. The function of these cells is to strengthen the plant tissues in which they occur. The vascular tissues consist of xylem and phloem. Vascular tissue is embedded within the ground tissue of the plant. Xylem consists of tracheids and vessels, which form a continuous system running throughout the entire plant[18]. Xylem is the principal water conducting tissue in plants but also transports dissolved minerals in the water that has been taken up through the roots. Phloem is the principal food conducting tissue. Phloem contains sieve cells, which do not contain a nucleus at maturity but each cell is accompanied by a living cell (Parenchyma cell) which is called a companion cell. Dermal tissue forms the outer protective covering of the plant. Epidermal cells are flat cells, which are often coated with a thick layer of cuticle. Epidermal cells cover all parts of the plant from root to shoot. Trichomes and guard cells are also contained in dermal tissues. Two guard cells accompany each stoma and they regulate the gaseous exchange through the stoma. Trichromes are outgrowths of the epidermis of the plant and their function is the regulation of heat and water within the plant. Root hairs also occur at the base of the root.

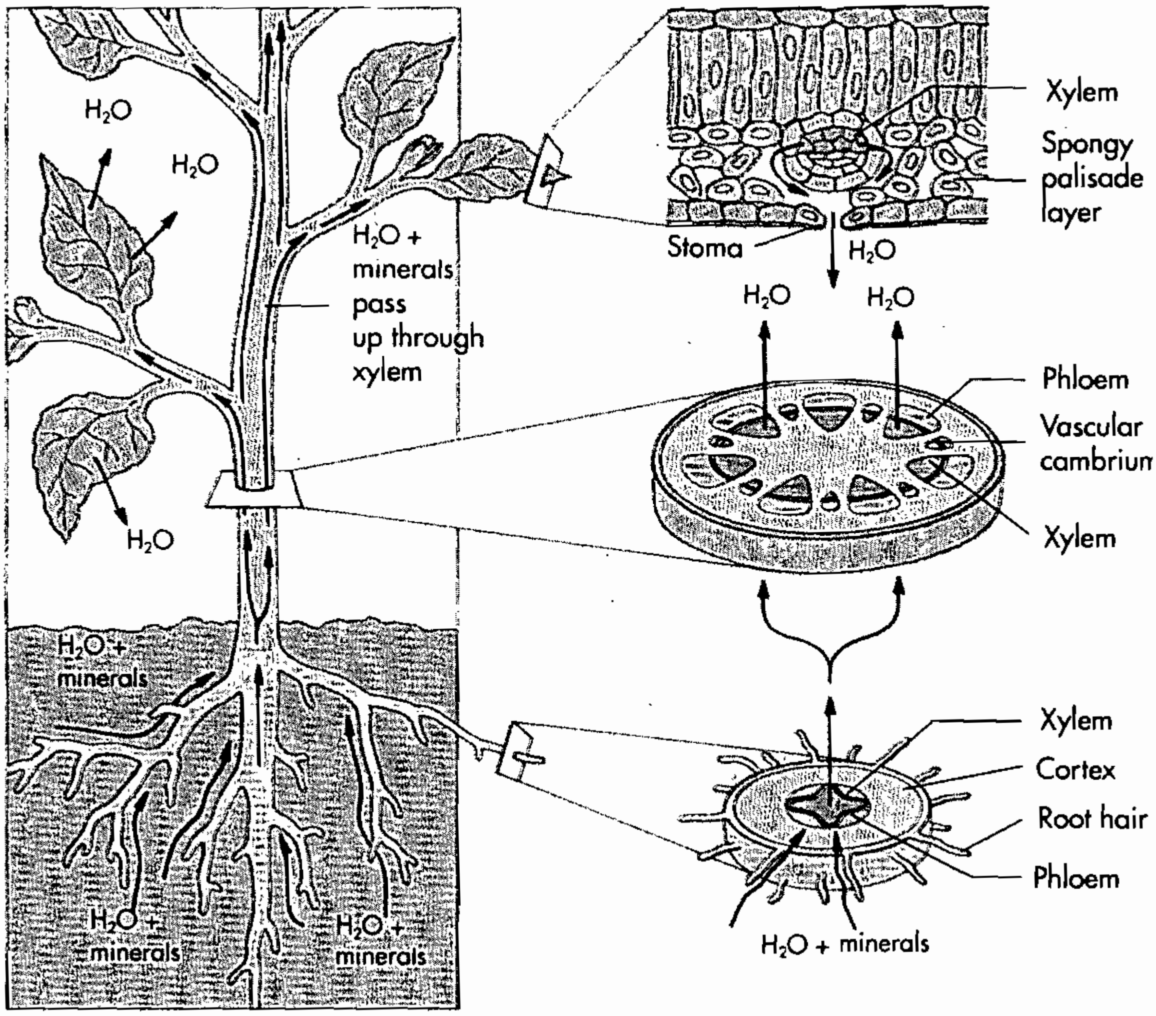


Figure 1.3.1 Diagram of flow of materials into, out of and within the plant.

1.3.2 Cellular Respiration

Cellular respiration is the oxidation of food molecules to obtain energy[19]. This energy is produced in the form of adenosine triphoshate (ATP). Cells use ATP to drive chemical reactions by providing the necessary activation energy required, to power movement, to grow and any other energy-requiring process that cells carry out. Cells can synthesise ATP in two ways, either by substrate level phosphorylation or by chemiosmotic synthesis.

$$\boxed{C_6H_{12}O_6 + 6O_2 \longrightarrow 6CO_2 + 6H_2O + \text{Energy}}$$

Scheme 1

There are three consecutive stages in cellular respiration (1) glycolysis, (2) oxidation of pyruvate and the reactions of the citric acid cycle, (3) electron transport and oxidative phosphorylation. There are ten reactions involved in glycolysis. Three reactions are responsible for the priming of the glucose molecule. The investment of two ATP molecules changes glucose into a compound, which can be readily cleaved into two phosphorylated carbon units. Cleavage and rearrangement then results in two three-carbon molecules. One is glyceraldehyde-3-phosphate (G3P) and the other will form G3P, which is then oxidised and the electrons produced are donated to a coenzyme called nicotinamide adenine dinucleotide (NAD^+), which forms NADH. The last four reactions covert G3P to pyruvate and generate two molecules of ATP for each of the two pyruvate molecules. Glycolsis does not require oxygen and this method of respiration is anaerobic. If oxygen is present the next stage is the oxidation of pyruvate, which consists Acetyl-CoA is also formed by the breakdown of proteins, fats and lipids.

The citric acid cycle consists of eight reactions that the cell uses to extract electrons to drive the synthesis of ATP (figure 1.3.2)[19]. In the first reaction acetyl-CoA undergoes an irreversible condensation reaction with oxalo-acetic acid to form citric acid. Before the oxidation reaction begins citric acid must first be converted to isocitric acid. In the first energy-yielding step, isocitric acid undergoes an oxidative decarboxylation reaction in which isocitric acid is first oxidised, yielding a pair of electrons that reduce a molecule of NAD^+ to NADH. The reduced carbohydrate intermediate is then decarboxylated by splitting off the central carbon as a CO_2 molecule, yielding α-ketoglutaric acid which then undergoes oxidative decarboxylation. The fragement left after the removal of CO_2 results in the formation of succinyl-CoA by reaction with a molecule of coenzyme A. In this reaction a pair of electrons are also abstracted which reduce a molecule of NAD^+ to NADH. In reaction five the bond linking the succinyl group to the CoA carrier molecule is a high energy ester linkage and this bond is cleaved and the energy is use to drive the phosphorylation of guanosine diphosphate (GDP) which is then converted to guanosine triphosphate (GTP) and then to ATP. The four carbon fragment remaining is succinic acid and in reaction six it is oxidised to fumaric acid. The free energy change in this reaction is small so a different electron receptor, flavin adenine dinucleotide (FAD^+), is used. In reduced form $FADH_2$ contributes electrons directly to the electron transport network of the membrane. In the final two reactions a water molecule is added to fumaric acid forming malic acid which is then oxidised to form oxaloacetic and two electrons which convert NAD^+ to NADH. Oxaloactic acid is then free to bind to another molecule of acetyl-CoA and the cycle is reinitiated.

The third and final stage involves coupled processes of electron transport and oxidative phosphorylation. Adenine diphosphate (ADP), is converted to high energy ATP by the release of the energy from the transfer of electrons to oxygen which in turn is converted to water. Glycolysis takes place in the cytoplasm, whereas the citric acid cycle and oxidative phosphorylation occur in the mitochondria.

If no oxygen is available after glycolysis, then anaerobic respiration in the form of fermentation occurs and with yeast, this anaerobic respiration can result in the formation of ethanol as shown in scheme 2. A similar process in animals results in the formation of lactic acid.

$$\text{organic molecule} + \text{NADH} \longrightarrow \text{reduced organic molecule} + \text{NAD}^+$$

Scheme 2

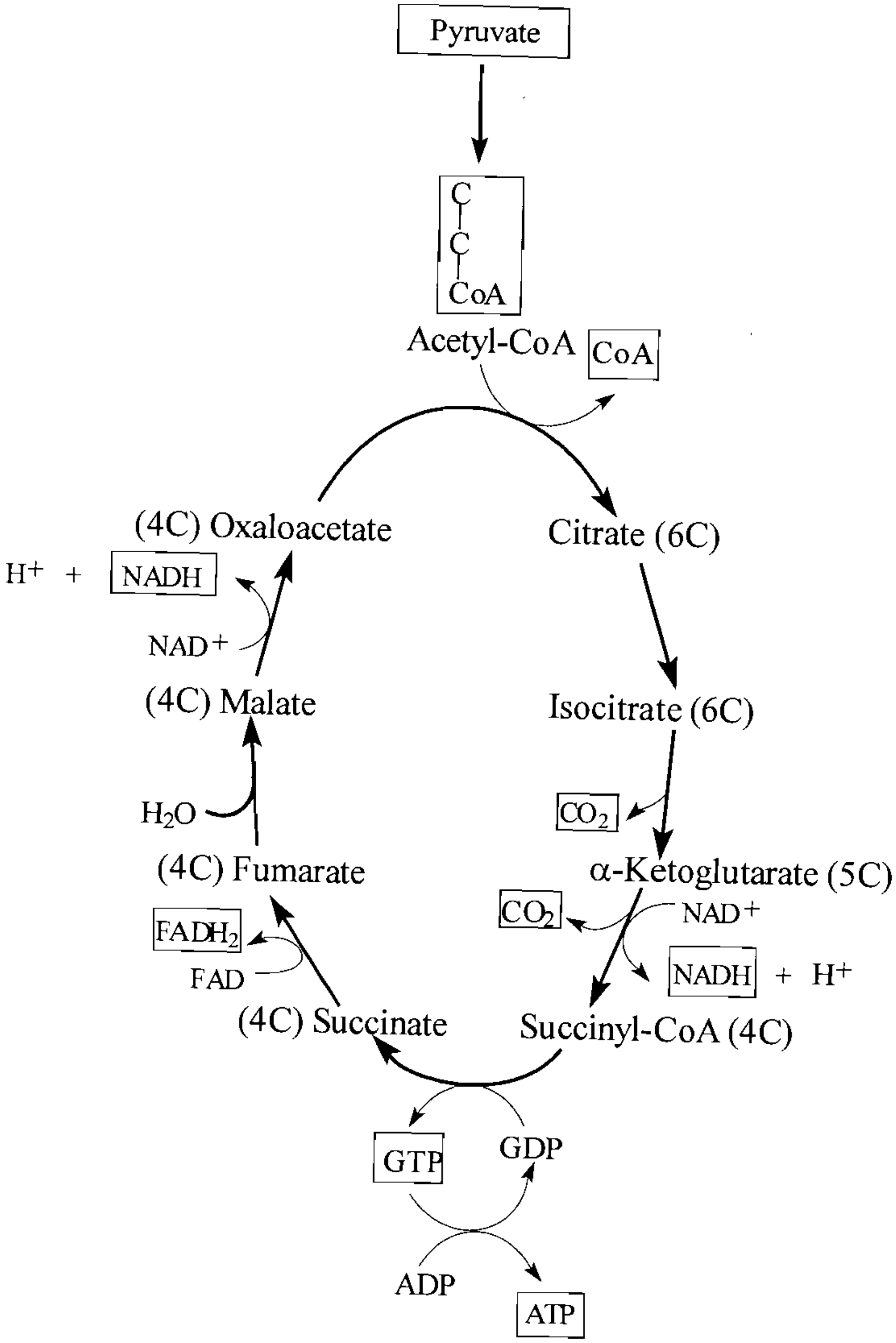


Figure 1.3.2 The citric acid cycle.

1.3.3 Photosynthesis

Green plants algae and some bacteria have the ability to harvest the Sun's energy to make their own food, such organisms are called autotrophs (self-feeders). All other organisms on the planet, including humans, are either directly or indirectly dependent on these autotrophs for energy in the form of food. Photosynthesis is the name given to a series of complex events and chemical process which allows these autrophs to harness the Sun's energy. The overall process of photosynthesis can be simplified by the following equation in scheme 3.

$$\underset{\substack{\text{atmospheric}\\\text{carbon dioxide}}}{6CO_2} + \underset{\substack{\text{water}\\\text{vapor}}}{12H_2O} \xrightarrow{\text{light}} \underset{\text{sugar}}{C_6H_{12}O_6} + \underset{\text{water}}{6H_2O} + \underset{\substack{\text{oxygen from}\\\text{orginal water}\\\text{molecules}}}{6O_2}$$

Scheme 3

The first process is the chemosmotic generation of ATP. These reactions require sunlight and are referred to as the light phase reactions. The next process is the utilisation of the ATP in a series of enzyme–catalysed reactions in order to drive the formation of organic molecules from atmospheric carbon dioxide. These reactions are referred to as the dark phase reactions of photosynthesis as they do not require sunlight and can occur anytime.

Plants have a two-stage photocenter as illustrated in figure 1.3.3. Photosystem 1 is thought to have evolved in groups of green and purple bacteria over three billion years ago, while photosystem 2 originated in the cyanobacteria approximately 2.8 billion years ago. Evolution is responsible for grafting photosystem 2 onto photosystem 1. Photosystem 2 acts first. A photon of light strikes a pigment molecule in photosystem 2 and excites an electron. This electron is passed along a chain of membrane-bound electron carriers including the cyctochromes. The energy supplied by the photon is used to transport protons across a membrane and the resulting proton gradient drives the chemiosmotic synthesis of ATP. The spent electron then passes on to photosystem 1. A photon of light also hits photosystem 1. The pigment of photosystem 1, P_{700} then passes a second high-energy electron to a reducing complex. This reducing complex then drives the synthesis of NADPH. The pigment of photosystem 2, P_{680} must then be regenerated, as the photosynthetic process was initiated by donation of an electron from this molecule.

The loss of this electron turned P_{680} into a powerful oxidant, which proceeds to acquire an electron from a Z-protein. The Z-protein is then a powerful electron acceptor and catalyses a series of reactions that split water into electrons (which are passed on to P_{680}), H^+ ions and OH radicals. The OH radicals recombine to form water and oxygen gas[20].

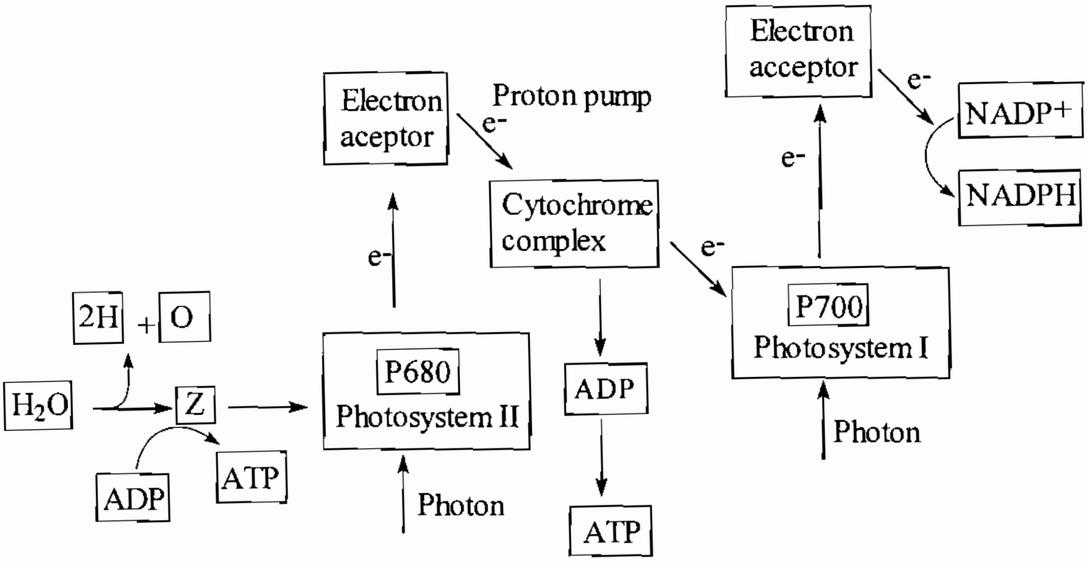


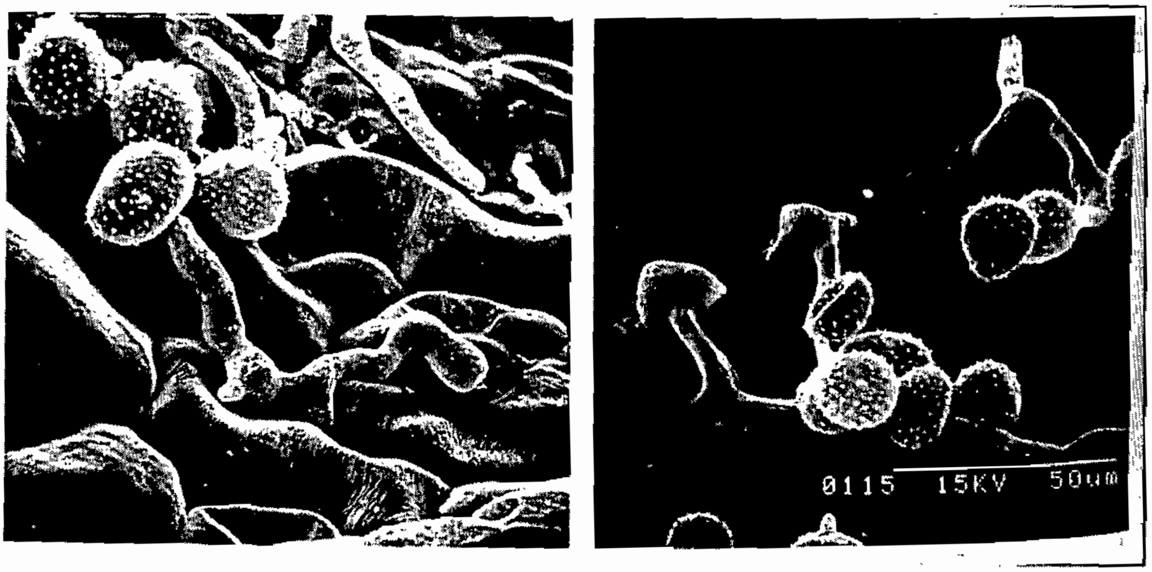
Figure 1.3.3 The two-stage photocentre.

1.3.4 Structure and classification of fungi

A few species of fungi, such as yeast consist of a single cell however most species are multi-celluar organisms[21]. Fungi consist of filaments or threads called hyphae. As a fungus grows, hyphae branch out to form an extensive mass called a mycelium. In many species of fungi hyphae are divided by crosswalls or partial cell walls that separate the hyphae into individual cells. These crosswalls are called septa. The cell walls of most fungi are composed of chitin. Chitin is a much stronger material than cellulose which forms the cell walls in plant cells. Chitin is also found in the external skeletons of lobsters, crabs, insects and spiders. As fungi do not contain chlorophyll they are either saprophytic or parasitic in nature. Saprophytic fungi are fungi that grow on putrefying or decaying organic matter. Parasitic fungi are organisms that live on a host organism (usually a plant) and derive nutrients from it. Parasitism may be regarded as a form of predation. Plant pathogens are generally parasitic in nature. Fungi obtain nutrients through extra cellular digestion. In this process food is digested outside the cells of the fungus. The fungus releases a digestive chemical through its hyphae that breaks down the organic substrate into smaller molecules. Once digested the transformed substrate molecules are absorbed through the hyphae. This digestive process of fungi causes spoilage of food e.g. the moulding of bread.

Reproduction in fungi is by means of spores and is mainly asexual. There are three main divisions of fungi, Zygomycota, Ascomycota and Bassidomycota. Fungi classification is based on the method of sexual reproduction or by the method of infection of the host plant. Zygomyceta are the smallest of the three groups with only about six hundred named species. Members of this class include bread moulds and other fungi found on decaying organic material. Ascomycota is the largest group, with over sixity thousand species already discovered. Yeast, common moulds, truffles and powdery mildews are just some of these species. The majority of serious plant pathogens are also included in this class. Ascomycota spores are airborne and favour dry conditions for infection. Airborne fungal spores fall on the plant leaves, germinate into hyphae and grow around the edge of the leaf towards the stomata on the underside. The stoma of the leaf are surrounded by ridges and when fungal hypha encounter these ridges they balloon out growing into a stomatal infection structure and grow rapidly into the stomata (figure 1.3.4)[22].

The third division is Bassidomycota. Members of this class include mushrooms, toadstools, and puffballs and jelly fungi. This class also includes many rusts and smuts. Basidiomycetes generally infect the host plant via the seeds or through the soil e.g. onion smut. Basidiomycetes reproduce sexually whereas, Zygomycota, Ascomycota can reproduce sexually but more usually reproduce asexually. Another category of fungi is the Deuteromycetes or the Fungi Imperfecti. These fungi have lost the ability to reproduce sexually and they are grouped together. Many fungi grouped in this category are airborne and prefer damp conditions for the infection of the host plant e.g. Botrytis grey mould. Oomycetes include water moulds, slime moulds, downy mildews and late potato blight. Oomycetes infect plants via the aqueous phase.



(a) **(b)**

Figure 1.3.4 Stomatal infection of fungi under an electron microscope.

(a) Hypha growing down into a stoma on a bean leaf.

(b) Fungus producing infection structures.

1.4 Uptake, transport and side effects of systemic fungicides in the plant.

A xenobiotic is a chemical foreign to a plant[23]. Many herbicides, fungicides and insecticides are systemic xenobiotics. Once a xenobiotic has entered a plant it may move in the direction of the transpiration stream or move with the flow of photosynthetic products to "sinks" or in both directions as illustrated in figure 1.4.1. These three patterns of movement are termed apoplastic, symplastic and ambimobile[24]. Transportation in the symplast is synonymous with transportation in the protoplasts, plasmadesmota and phloem sieve cells. Long distance phloem transport is symplastic. The apoplast is the non-living part of the plant and consists of cell walls, cuticles and xylem tracheids and vessels. Long distance xylem transport is apopolastic. Establishment of the fungicide in the plant tissues involves the uptake of the fungicide through the leaves, roots, seeds or fruits of the plant. The fungicide is then transported a short distance in the parenchyma or, long distance in the flow of solutions in the xylem and phloem. Xylem transport is determined by the potential gradient of water between the roots and the shoots. Xenobiotics are generally absorbed with water through the root hairs and are transported and translocated to areas where there is a high rate of transpiration such as the tips and margins of the leaves. Xylem-mobile substances do not undergo any downward movement from expanded leaves. Translocation occurs only to a limited extent in organs like fruits and young leaves where the rate of transpiration is small. Factors that effect the rate of transpiration and hence transportation in the xylem include relative humidity, temperature, light and phytohormones. Phloem transport is accomplished by the physiological gradient between sites of photosynate production and export. Transport is generally from photosynthetic sources such as green leaves to growing or storing organs. If phloem-mobile substances are applied to the roots only small amounts will be transported to the upper parts of the plant whereas ambimobile compounds show distribution patterns of xylem-systemic xenobiotics.

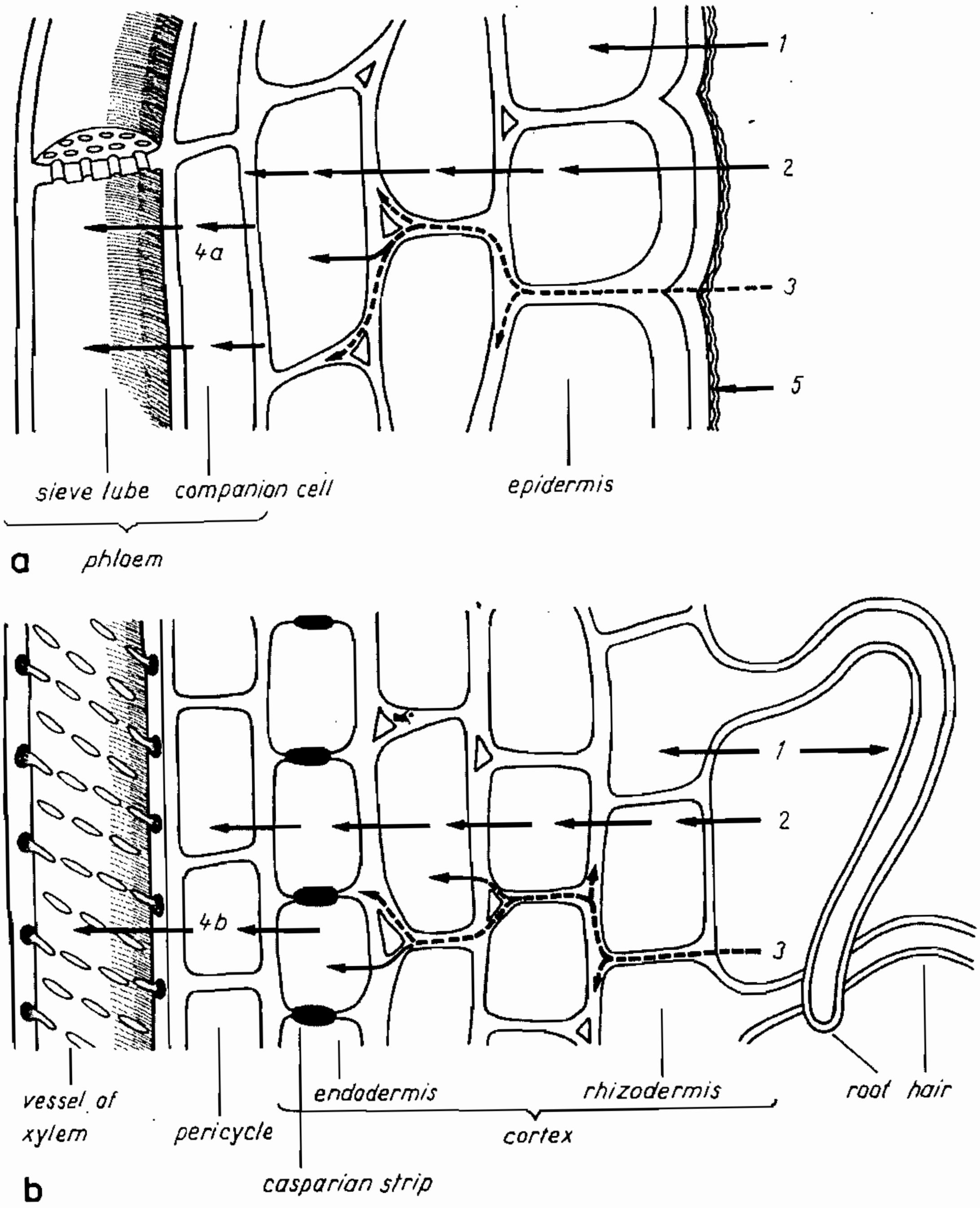
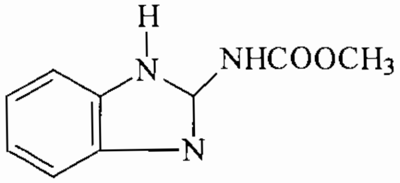


Figure 1.4.1 The pathway of xenobiotic substances in plant tissues by penetrating (a) the leaf or (b) the root surface. (1) Uptake in outer cells, (2) symplastic transport, (3) apoplastic transport, (4a) absorption in sieve tubes, (4b) transfer to vessels, (5) absorption in the cuticular layers.

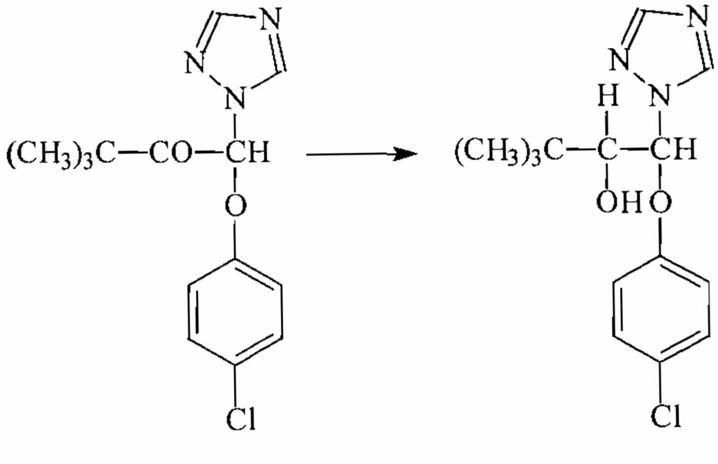
In order for a xenobiotic to be systemic within a plant, it must fulfil certain physiological factors[25]. The xenobiotic must be selective within the plant cells, affecting only the target pathogen. An example of this selective toxicity is the herbicide carbenzim[26]. Carbenzim **(1)**, figure 1.4.2 possesses selective activity for the microtublin protein of fungi and not for the mirotubulin* protein of plants.



(1)

Figure 1.4.2

When a xenobiotic enters the symplast of the plant it is subjected to metabolism within the cells of the plant. The xenobiotic must therefore be metabolically stable without being too rapidly degraded. In the case of some pesticides, metabolic transformations can make the pesticide more toxic to the pathogen in question. An example of such a fungicide is triadimefon **(2)**, which is reduced to the corresponding alcohol triadimenol **(3)** in the plant as illustrated in scheme 4[27]. Triadimenol **(3)** is the more fungitoxic of the two compounds.



(2) **(3)**

Scheme 4

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* Microtuble-[MICRO+TUBLE] a small hollow, cyclinderical structure found in the cytoplasm of nearly all eukarytic cells. Microtubles function as a cellular skeleton and are also involved in cell movement.

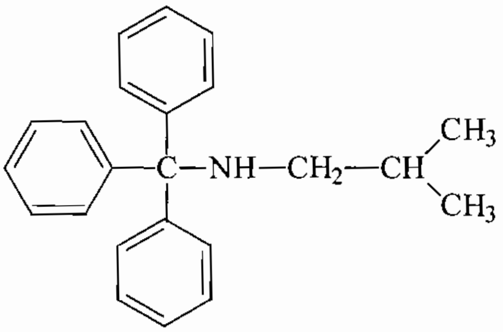
Many systemic xenobiotics contain the same functional groups. Phloem systemic compounds are generally acids and if the acid group is removed, the compound is no longer a phloem systemic compound. Xylem-systemic compounds do not have such structural requirements, but the addition of an acid group to a xylem systemic compound results in ambimobile derivatives. Finally a xenbiotic must have the correct hydrophlic-lipophlic balance in order to pass through plant membranes.

Fungicide resistance may be defined as the stable, inheritable adjustment by a fungus to a fungicide, resulting in a less than normal sensitivity to that fungicide[28]. The main side effects associated with the use of azole fungicides are **(1)** the development of fungi resistance to the new systemic fungicides and **(2)** growth retardant sensitivity to that fungicide. Problems with fungicide resistance did not really exist before the development of systemic fungicides. Fungicide resistance is often due to a single gene mutation in the fungus resulting in a slightly changed target site. If the fungicide has only one target sight and this has been altered then fungicide resistance becomes a problem. Conventional fungicides in existence before 1960 were nearly all multi-site inhibitors and so the development of resistance in these fungicides would have required many simultaneous gene mutations. Today problems of fungicide resistance are generally overcome by the use of two fungicides that do not show cross-resistance.

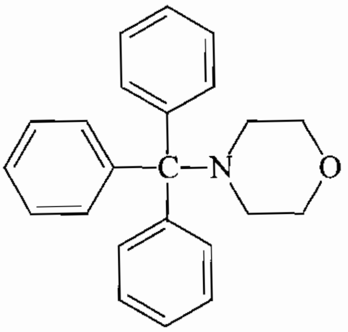
Distinct plant growth regulatory effects have been reported in both monocotyledonous and dicotyledonous since the first use of systemic fungicides. Monococotyledonous and dicotyledonous are two different classes of flowering plants and these growth regulatory effects have been observed to be more pronounced in dicotyledonous than in monocotyledonous[29]. Growth regulatory side effects include shorter shoots and internodes and/or darker greener leaves. There are two possible explanations for these growth regulatory side effects. The primary target of many of these fungicides are reactions that depend on cytochrome P-450. These reactions assist the conversion of kaurene to kaurenoic acid in the gibberellin biosynthesis pathway[29]. In some cases plant growth side effects have been reversed by the application of gibberellic acid. Another possible explanation for these plant growth side effects is that some fungicides have been shown to inhibit demethyl-sterol synthesis in plants (section 1.6).

1.5 Triazole fungicides

Work on N-substituted imidazoles and triazoles began in the mid-nineteen sixties. It was know that tropylium compounds cycloheptatriene derivatives and some N-trityl-amines such as **(4)** had biological activity[30]. Examples of this biological activity include N-trityl-morpholine **(5)** which was developed by Shell as a molluscide for water snails and is illustrated in figure 1.5.1. Other examples of compounds exhibiting biological activity include some triphenylmethane dyestuffs that are active against certain endoparasites. In addition naturally occurring tropolone derivatives were also shown to exhibit biological activity[30].



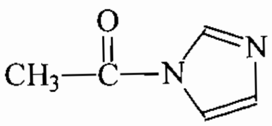
Molluscicide (ICI) (4)



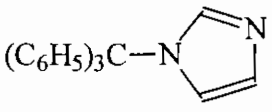
Molluscicide (Frescon, Shell) (5)

Figure 1.5.1

Researchers speculated that the carbonium ions formed by azole compounds could interfere in the metabolic processes of biological systems. Many structural variations of the 1-trityl-imidazole skeleton such as (6) and (7) illustrated in figure 1.5.2 were synthesised and their biological activities studied. The imidazole or 1H-1,2,4-triazole ring system was found to be a necessary structural requirement for the exhibition of optimal biological activity[30].



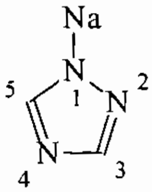
N-acetyl-imidazole (6)



N-trityl-imidazole (7)

Figure 1.5.2

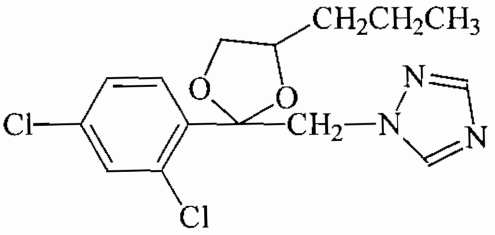
An azole fungicide is formed by the nucleophlic substitution of a precursor compound with a 1,2,4-triazole salt and this can occur at the N-1 or the N-4 position on the triazole ring **(8)**, figure 1.5.3.



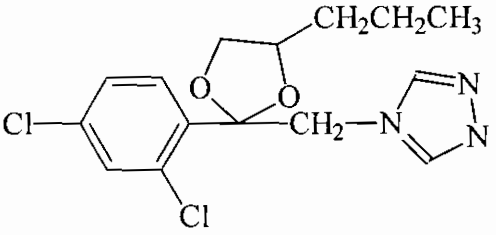
(8)

Figure 1.5.3

If substitution occurs at the N-4 position the result is a remarkable decrease in biological activity compared to the more common substitution at the N-1 position. An example of this type of reduced biological activity is the fungicide propiconazole **(9)**, where although N-1 substitution **(9)** is prevalent some N-4 substitution does occurs and results in a much less active geometrical isomer **(10)** as illustrated in figure 1.5.4. The reason for this remarable decrease in biological activity is believed to be due to the binding of the triazole fungicide to a cytochrome P-450 complex (section 1.6). Other studies on the effect of different substitution on phenyl rings revealed that dichloro-substitution at the 2 and 4 positions was another necessary structural requirement for optimum biological activity[31].



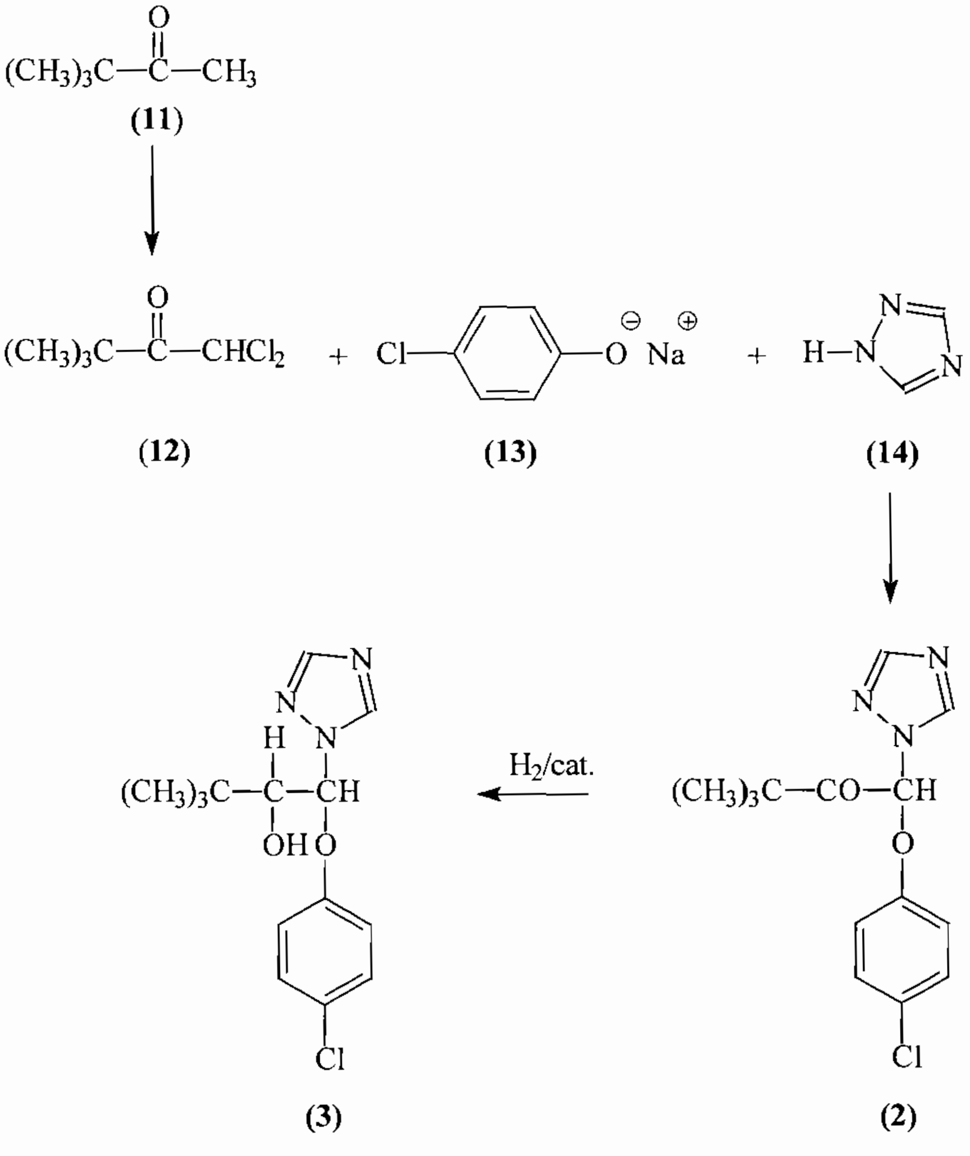
(9)



(10)

Figure 1.5.4

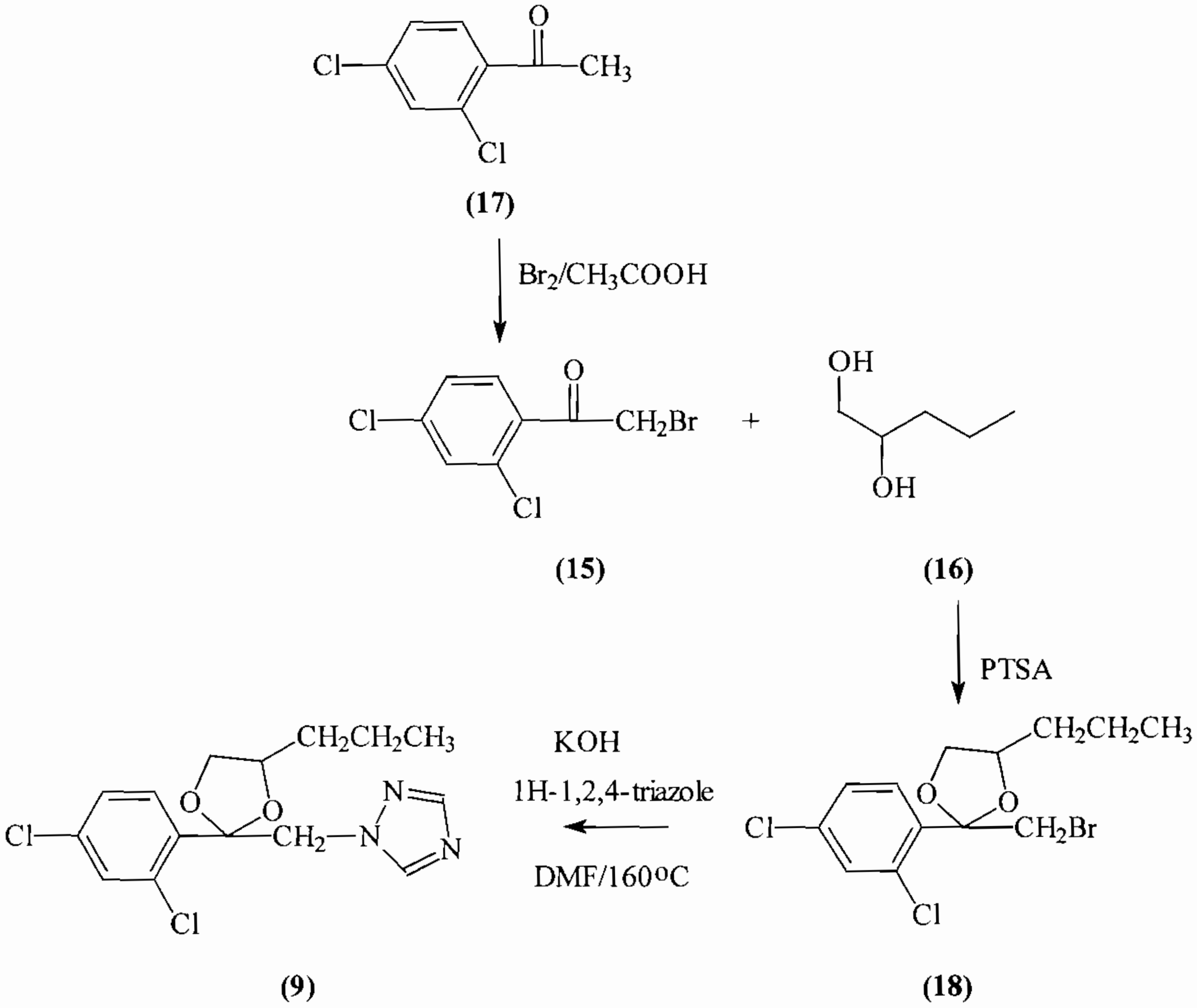
Triadimefon **(2)** 1-(4-chlorophenoxy)-3,3-dimethyl-1-(1H-1,2,4-triazole-1-yl)-2-butanone was reported in 1973 and was the first broad-spectrum systemic triazole fungicide to be developed[32]. Triadimefon **(2)** is synthesised by the dichlorination of pinacolone **(11)** to yield **(12)** followed by substitution with sodium *p*-chlorophenoxide **(13)** and triazole **(14)** as illustrated in scheme 5. Triadimefon **(2)** consists of a racemic mixture of two optical isomers and is used as a foliar spray for the control of powdery mildew and rust diseases of cereal coffee, grapes, stone fruit and vegetables. Soon after the development of triadimefon, it was discovered that triadimefon was reduced to the corresponding alcohol triadimenol **(3)**, β-(4-chlorophenoxy)-α-(1,1-dimethylethyl)-1H-1,2,4-triazole-1-ethanol in the plant[27]. Triadimenol **(3)** is more fungitoxic than triadimefon. Triadimenol (**3**) is used as a seed treatment for the control of powdery mildew, rust diseases and also for Rhynchosporium secalis on barely. As a foliar fungicide triadimenol is used to control powdery mildew in grapes, vegetables, hops sugar beet, and tobacco. Bayer was the company responsible for the development of these fungicides.



Scheme 5

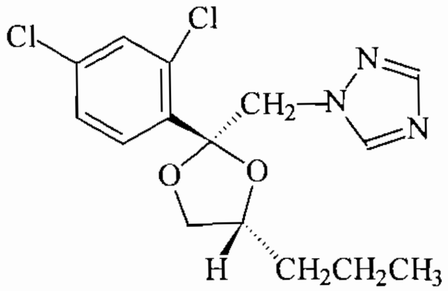
Propiconazole (**9**), 1-[[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-yl]-methyl]-1H-1,2,4-triazole, the subject of this thesis, was first reported in 1979[31, 33-37]. Propiconazole is chemically classified as an azolymethyl-dioxolane fungicide and is produced by ketalization of ethanone-2-bromo-1-(2,4-dichlorophenyl) (**15**) with 1,2-pentanediol (**16**), followed by nucleophlic substitution with a 1,2,4-triazole (**14**) in the presence of a base in dimethyl formamide at 160°C as illustrated in scheme 6.

Propiconazole **(9)** is a broad-spectrum foliar fungicide used to control a range of cereal disease, including powdery mildew, rust and net blotch. It is also used against various diseases of turf, rice, peanuts, pecans, maize, stone fruit and other crops. Propiconazole was developed by Ciba-Geigy AG and trade names include Tilt®, Desmel® and Radar® and is one of the most commercially successful fungicides developed to date.



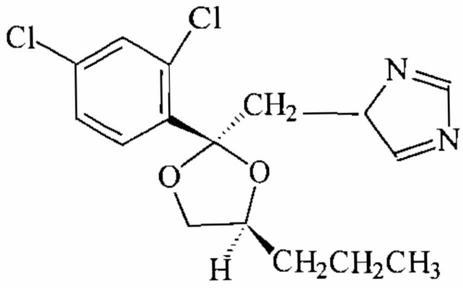
Scheme 6

Propiconazole **(9)** contains two chiral centres and therefore exists as four steroisomers, comprising of two diasteroisomeric pairs of enantiomers as illustrated in figure 1.5.5. These steroisomers do not have the same biological activity. The two S-isomers **(9a)** and **(9b)** were found to have significantly higher biological activity than the two R-isomers **(9c)** and **(9d)**. The **(9a)** and **(9b)** enatiomers were also found to have a greater biological activity than the racemic mixture of the four isomers. Fungicides are generally formulated as a racemic mixture of the active ingredient. In the case of etaconazole **(19)**, an ethyl analogue of propiconazole the racemic mixture of etaconazole was found to be equally as active as the two-diasteromeric pairs of enatiomers[38].



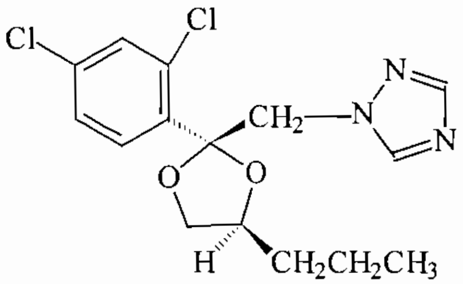
(2S, 4R)

(9a)



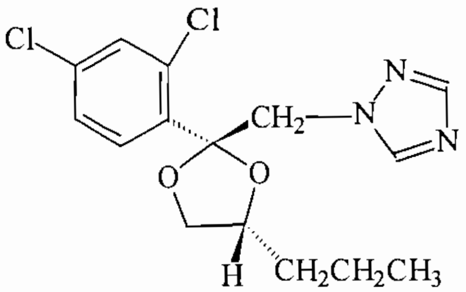
(2S, 4S)

(9b)



(2R, 4S)

(9c)

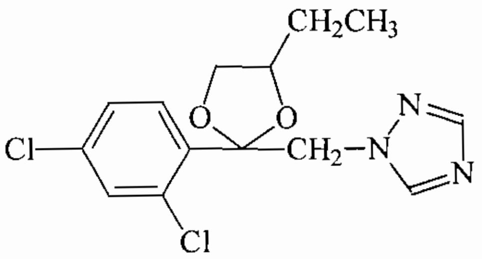


(2R, 4R)

(9d)

Figure. 1.5.5

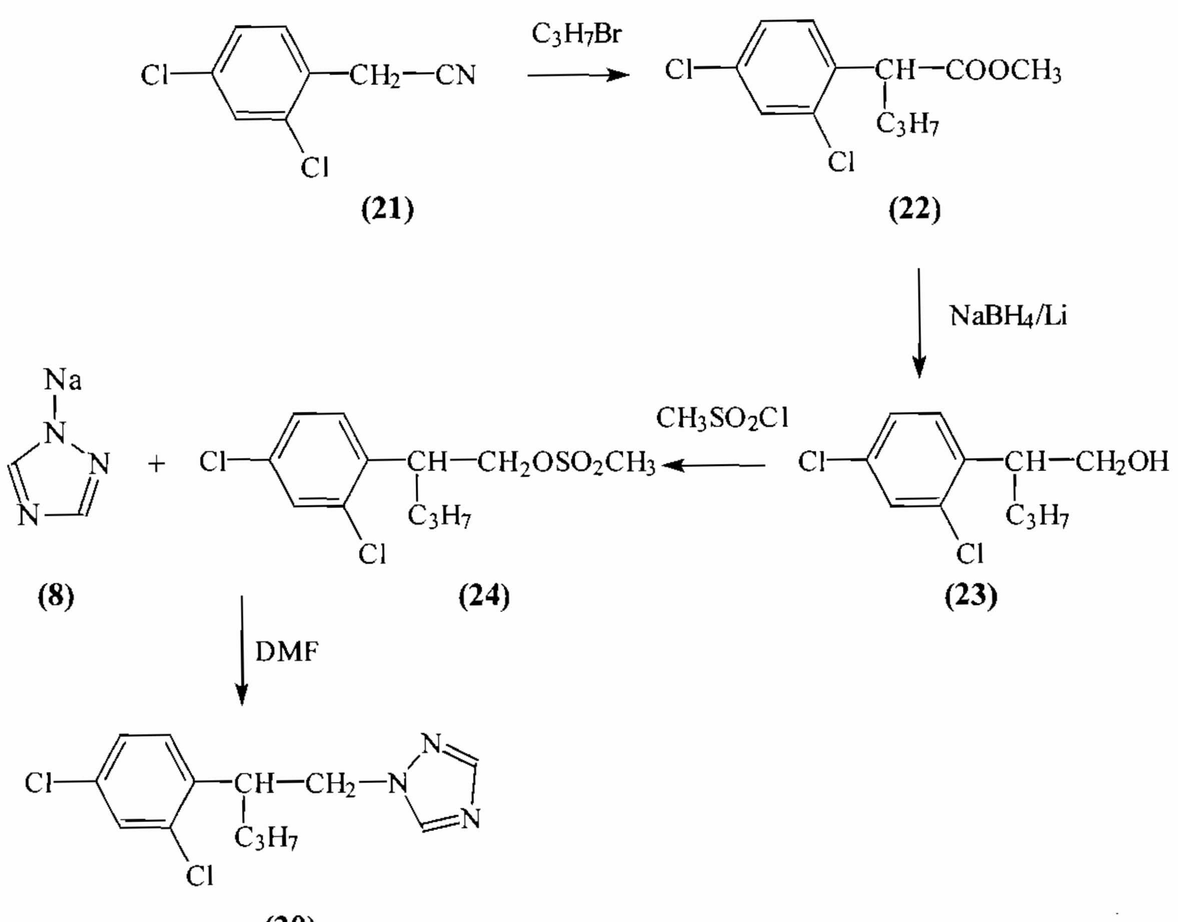
Etaconazole **(19)**, 1-[[2-(2,4-dichlorophenyl)-4-ethyl-1,3-dioxolan-2-yl]methyl]-1H-1,2,4-triazole, figure 1.5.6 is used for the control of powdery mildew on apples, grapes, vegetables and roses. Tradenames for etaconazole include Vangard® and Sonax®[39].



(19)

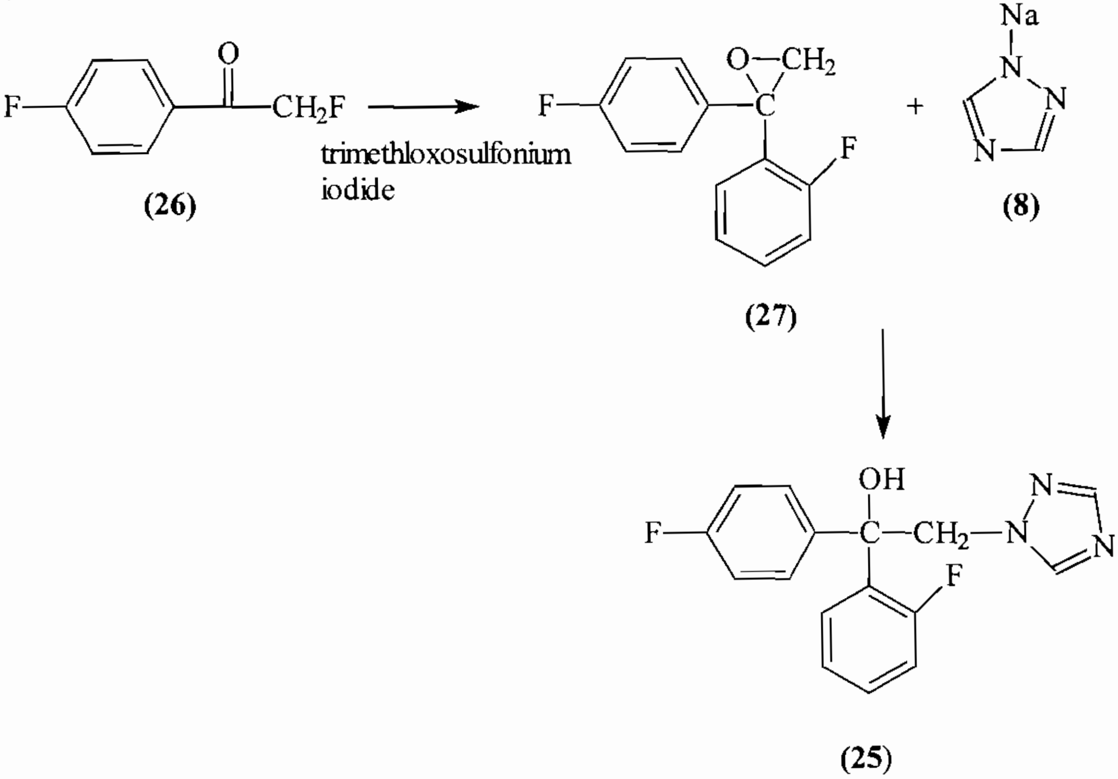
Figure 1.5.6

Penconazole **(20)** 2-(2,4-dichlorophenyl)-pentyl-1H-1,2,4-triazole was reported in 1981 and is used as a foliar fungicide to control powdery mildew of pome fruit, grapes, stone fruit, tobacco and vegetables, scab of apples and pears and black rot of grapes[40]. Penconazole **(20)** is produced by the alkylation of 2,4-dichlorophenyl-acetonitrile **(21)** with bromopropane, followed by conversion of the nitrile to the acetate **(22)**. Reduction with lithium aluminium hydride gives the corresponding alcohol **(23)**, which is first reacted with methanesulfonyl chloride to yield **(24)**. Finally **(24)** is reacted with a sodium triazole salt **(8)**. The synthesis of penconazole is illustrated in scheme 7. Ciba-Geigy AG developed the synthesis of penaconazole and trade names include Topas® and Topaze®.



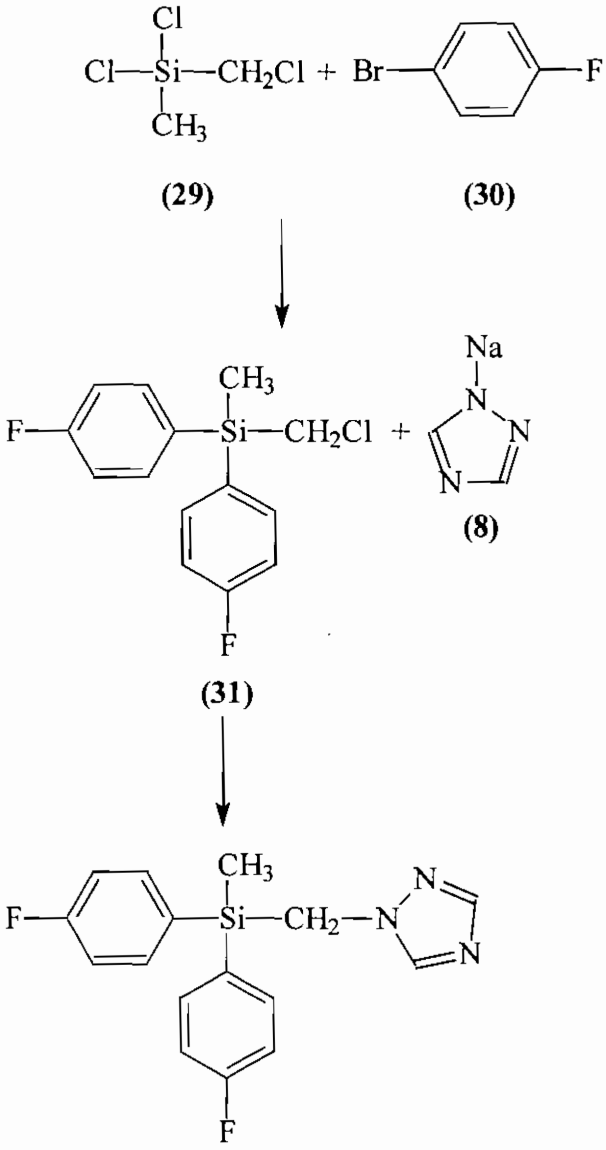
Scheme 7

Flutriafol **(25)**, (RS)-2,4'-difluro-α-(1H-1,2,4-triazol-1-ylmethyl)-benzhydryl alcohol is a colourless solid and was reported in 1980[41]. It is used as a foliar fungicide for the control of diseases such as powdery mildew, rust, Rhynchosporium secalis, Helminthosporium and is also employed as a seed treatment on cereals. Flutriafol is produced by reaction of 2,4'-flurobenzophenone **(26)** with the trimethyloxosulfonium iodide and the resulting epoxide **(27)** is then reacted with the 1,2,4-triazole salt **(8)** in a suitable solvent as illustrated in scheme 8. Flutriafol was developed by ICI and has a variety of trade names, including Impact® and Vincit®.



Scheme 8

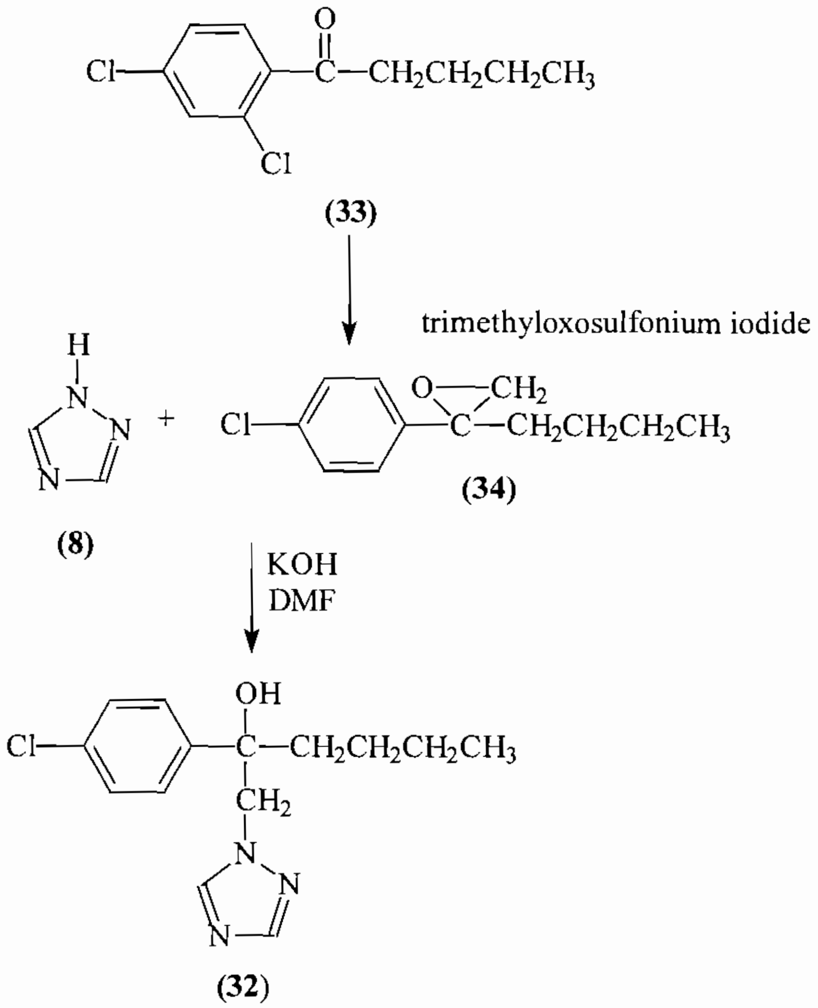
Flusilazole **(28)**, bis(4-flurophenyl)methyl-(1H-1,2,4-triazol[-1-yl]methyl)silane was reported in 1983 and is a broad-spectrum foliar fungicide, which is used for the control of powdery mildew, rust, and leaf spot diseases of cereals[42]. Flusilazole is produced by the addition of butyllithium to a solution of chloromethyldichlorosilane **(29)** and 1-bromo-4-flurobenzene **(30)** to yield **(31)** and subsequent reaction with the triazole **(8)** as illustrated in scheme 9. Du Pont markets Flusilazole under a variety of trade names, which include Punch®, Nustar®, Olymp® and Triumph®.



(28)

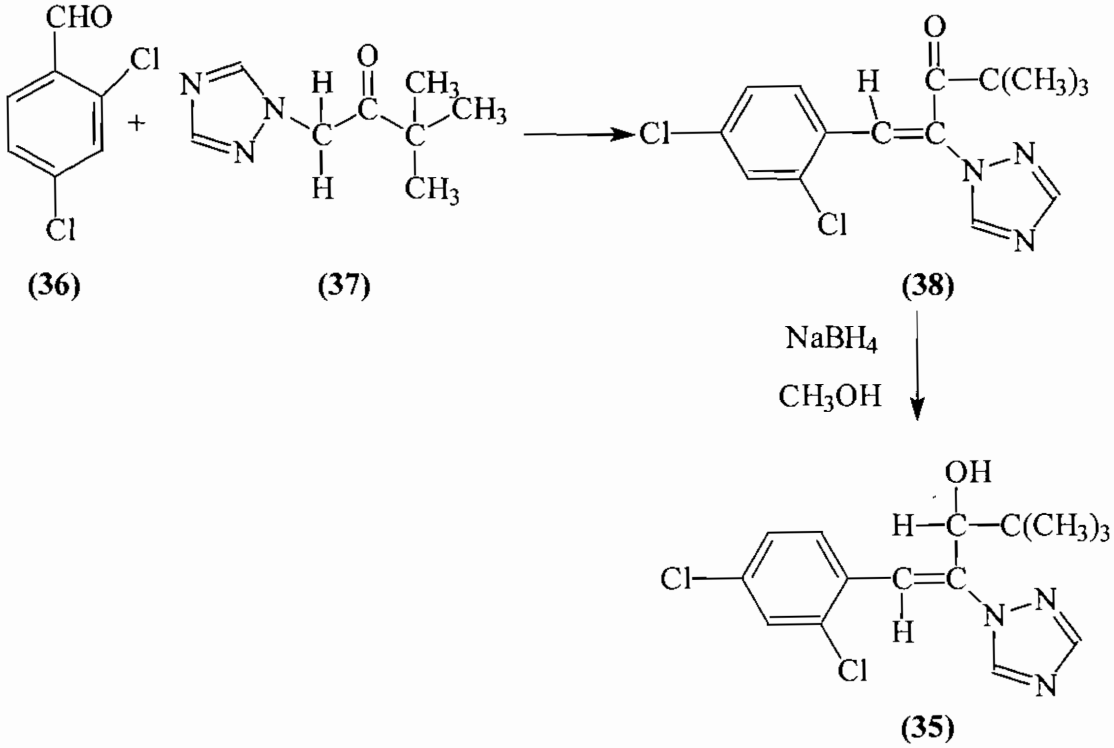
Scheme 9

Hexaconazole **(32)**, (RS)-2-(2,4-dichlorophenyl)-1-(1H-1,2,4-triazol-1-yl)hexan-2-ol was reported in 1980 and is being developed as a broad-spectrum foliar fungicide[43]. It is used for the control of powdery mildew and black rot of grapes. Hexaconazole may be produced by reaction of 1-(2,4-dichlorophenyl)pentan-2-one **(33)** with trimethyloxosulfonium iodide, followed by the ring opening of the resulting epoxide **(34)** with 1H-1,2,4-triazole **(14)** in the presence of a base as illustrated in scheme 10. Hexaconazole (**32**) is being developed by ICI UK and trade names for the compound include Anvil® and Meteor®.



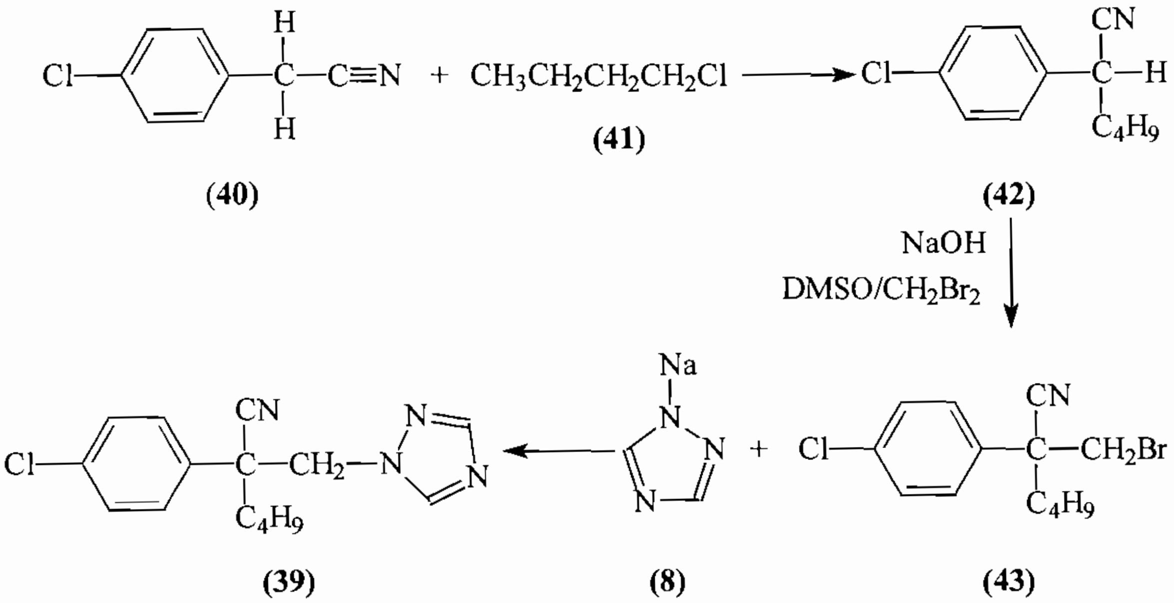
Scheme 10

Diniconazole **(35)**, β-(2,4-dichlorophenyl)-methylen-α-(1,1-dimethylethyl)-1H-1,2,4-triazol-1-ethanol was reported in 1981 and is produced by the condensation of 2,4-dichlorobenzaldehyde **(36)** and triazolpinacolone **(37)** to yield **(38)**, followed by photochemical isomerization of the E-Z mixture to the E isomer and reduction with sodium borohydride, as illustrated in scheme 11[44]. Diniconazole **(35)** was developed as a foliar spray and a seed treatment. As a foliar spray it controls leaf spot, rust, and white mould of groundnuts, powdery mildew of apples, grapes and small grain cereals, and rust diseases of apples and cereals. Sumitomo (Japan) developed diniconazole **(35)** under the trade name Spotless®.



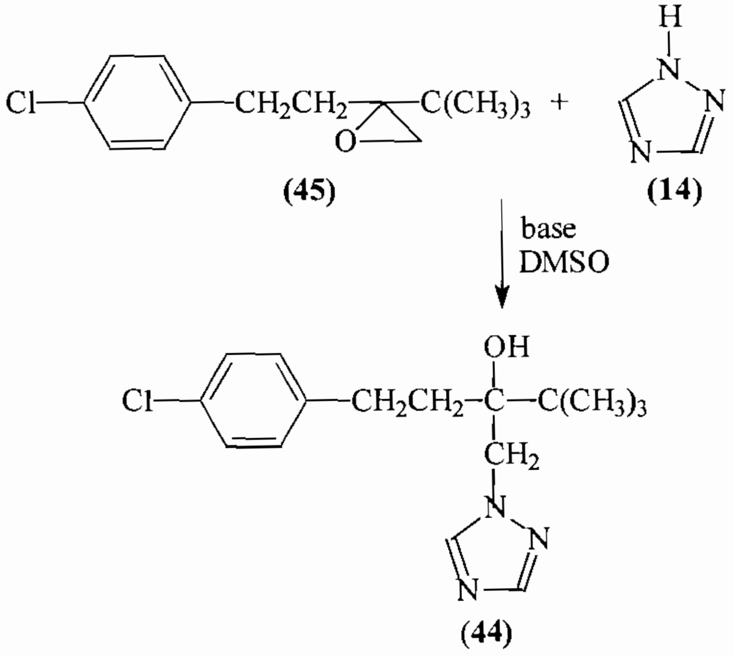
Scheme 11

Myclobutanil **(39)**, α–butyl-α'-(4-chlorophenyl)-1H-1,2,4-triazol-1-propane-nitrile was also reported in 1985[45]. Rohm & Haas were responsible for the development of this compound as an agricultural fungicide under the trade name Systhane®. Myclobutanil acts against powdery mildew and scab of apples, as well as black rot and powdery mildew of grapevines. Myclobutanil is produced by alkylation of 4-chlorophenyl-acetonitrile **(40)** with 1-chloro-butane **(41)** to yield **(42)**, followed by treatment with dibromomethane and sodium hydroxide to yield **(43)**. Finally reaction of (**43**) and the triazole **(8)** in dimethyl sulfoxide yields myclobutanil **(39)** as illustrated in scheme 12.



Scheme 12

Tebuconazole **(44)**, α-[2-(4-chlorophenyl)-ethyl]-α-(1,1-dimethylethyl)-1H-1,2,4-triazole-1-ethanol was reported in 1981 and is used as a foliar spray and seed treatment[46]. It is an effective seed treatment against bunts and smuts on cereals. Tebuconazole **(44)** is produced by the reaction of 2-t-butyl-2-(4-chlorophenylethyl)oxirane **(45)** with triazole **(14)** in the presence of a base as illustrated in scheme 13. Bayer FRG developed tebuconazole and trade names include Folicur® and Raxil®.



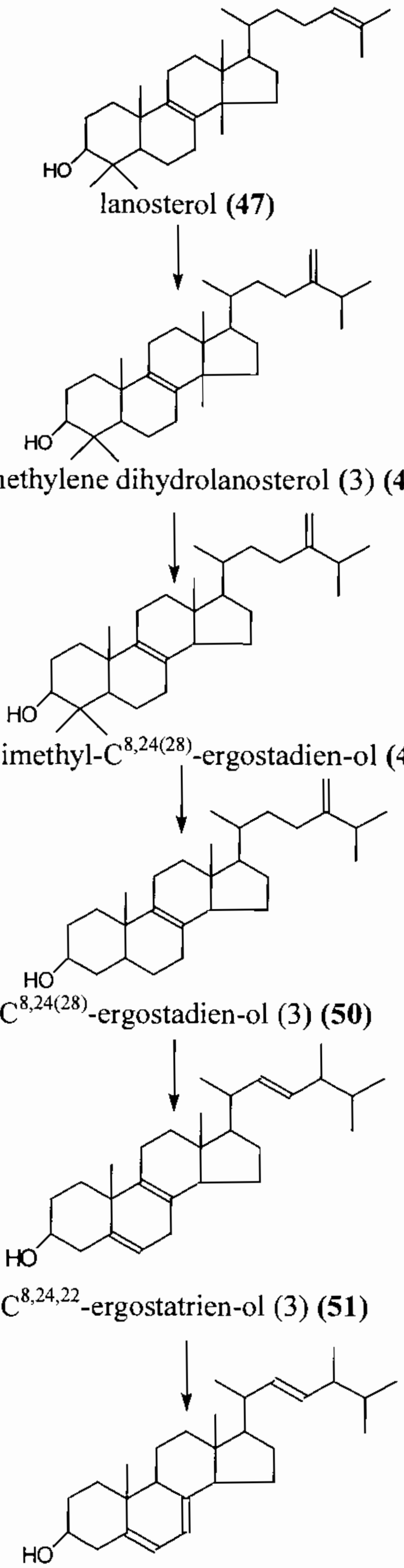
Scheme 13

1.6 Biochemical mode of action of ergosterol biosynthesis inhibitors

Azole fungicides belong to a group of fungicides, which inhibit the biosynthesis of membrane lipid by interfering with the biosynthesis of ergosterol **(46)**. Sterols are responsible for the stabilisation of phospholid phases in membranes. Changes in sterol content induce changes in the overall membrane stability and can also effect the activity of some membrane bound enzymes. One fundamental difference between plants and fungi is that the sterol responsible for membrane stabilisation in plants is cholesterol whereas in fungi cholesterol is replaced by ergosterol **(46)**. The last common intermediate in the synthesis of these two sterols is lanosterol **(47)** as illustrated in scheme 14.

In ergosterol biosynthesis, side chain alkylation of lanosterol **(47)** normally takes place to build 24-methylenedihydrolanosterol **(48)** which is the substrate for the demethylation reactions at C-14. The C-14-demethylation reactions have been studied in detail and it is an oxidative demethylation catalysed by a cytochrome P450-system[47]. The first step in this reaction is the hydroxylation of the C-14-methyl group to form the C-14-hydroxymethyl derivative **(49)**. A second hydroxylation and loss of water lead to the C-14-formyl intermediate **(50)**, which is hydrolysed a third time to form the corresponding carboxylic acid. Decarboxylation does not directly take place but proceeds instead by abstraction of a proton from C-15, followed by elimination and formation of a C-14 double bond. The NADPH-dependent reduction of the C-14-double bond finishes the demethylation reaction. Subsequent demethylation at C-4 then takes place twice, followed by a dehydrogenation reaction in the C-5 position and isomerisation to **(51)**.

The absence of oxygenated intermediates during the C-14 demethylation reactions indicates that the first oxygenation step which is catalysed by a cytochrome P-450 enzyme, is the primary site of action of the SDIs (sterol demethylation inhibitors). It is believed that the SDIs may interact with a specific form of the microsomal cytochrome P-450 that is involved in the biosynthesis of ergosterol. Research into the azole fungicides has shown reduced quantities of ergosterol and a build up of intermediate sterols in the ergosterol biosynthesis pathway showing that ergosterol biosynthesis is being inhibited. No sterol intermediates are found beyond the C-14 demethylation reactions.



lanosterol **(47)**

24-methylene dihydrolanosterol (3) **(48)**

4,4-dimethyl-$C^{8,24(28)}$-ergostadien-ol **(49)**

$C^{8,24(28)}$-ergostadien-ol (3) **(50)**

$C^{8,24,22}$-ergostatrien-ol (3) **(51)**

ergosterol **(46)**

Scheme 14 Ergosterol biosynthesis in yeasts, derenatophytes and bacteria.

Imidazole and triazole fungicides block cytochrome P-450 complexes by the binding of the hetrocyclic nitrogen atom of the fungicide to the protohaem iron atom thus excluding oxygen, the natural sixth ligand. However since not all nitrogen hetrocycles are equally good inhibitors of sterol 14-demethylation, it is clear that the rest of the molecule has an important bearing on the binding of the fungicide to the cyctochrome P-450. It was postulated that that the non-N-hetrocyclic part of the molecule binds to the lipophilic binding site of cyctochrome P-450 which is normally occupied by the 14α-methyl sterol as illustrated in figure 1.6.1[48].

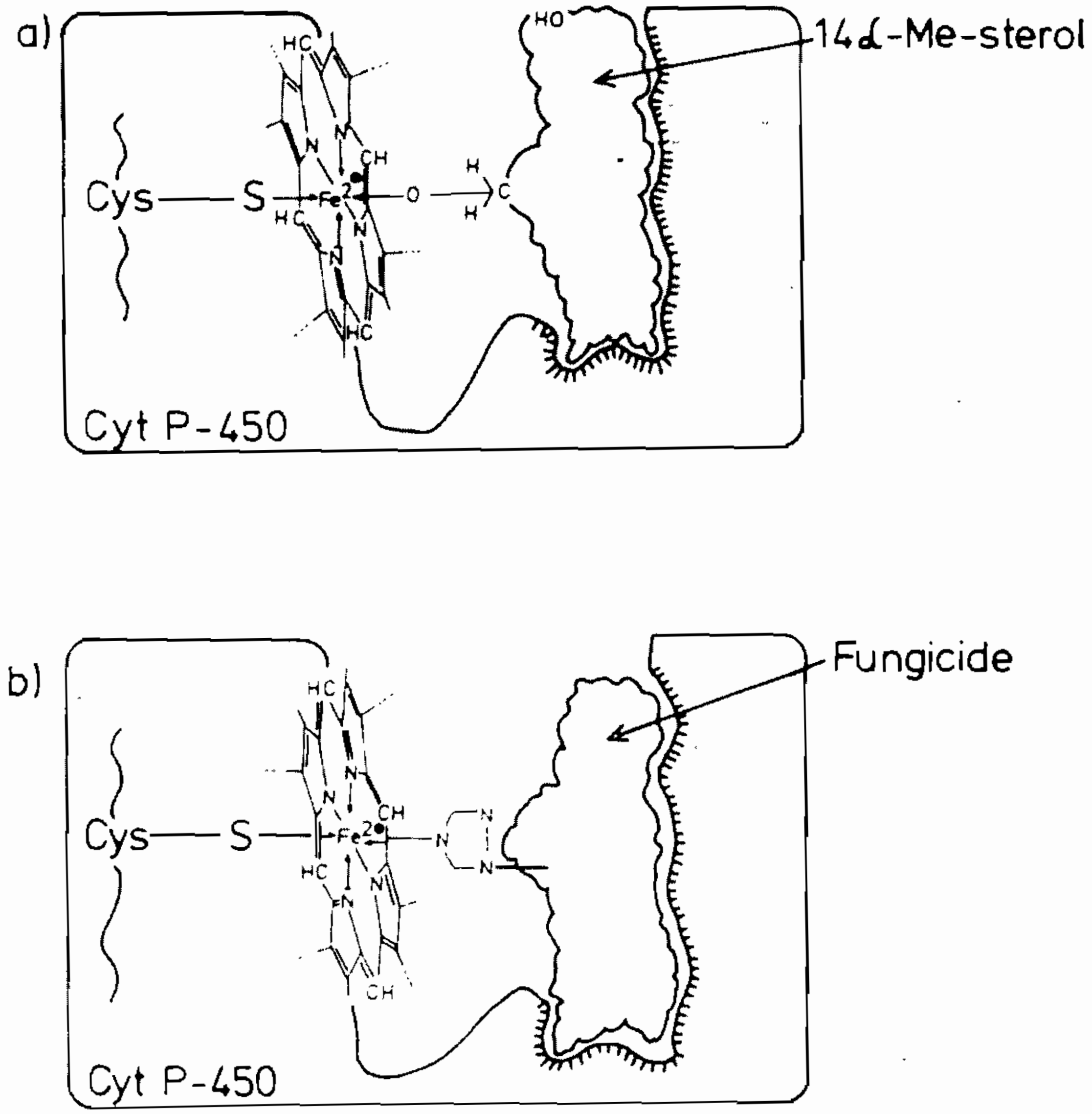
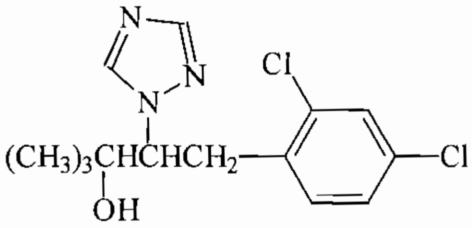


Figure 1.6.1 Binding of a triazole fungicide to the haem of cyctochrome-P450.

Studies have also revealed a correlation between fungicide binding and biological activity. The more toxic isomers (2R, 3R) of diclobutrazole **(52)**(illustrated in figure 1.6.2) exhibit a greater affinity for binding to the haem of cytochrome P-450 than the less biologically active (2S, 3S) isomer[49].



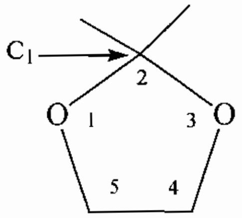
(52)

Figure 1.6.2

1.7 Chemistry of 1,3-dioxolanes

1.7.1 Introduction

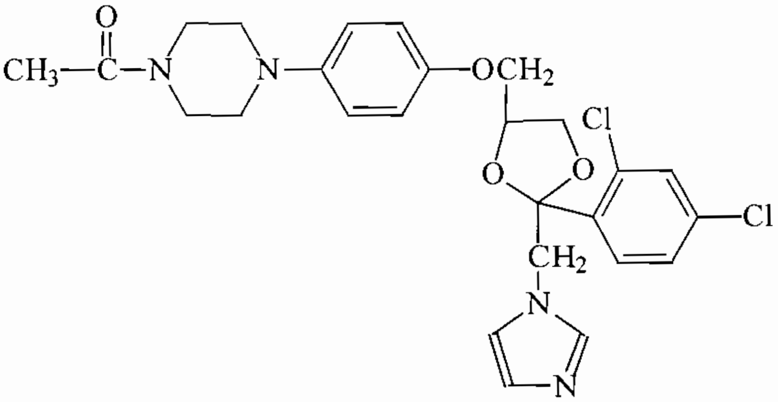
The 1,3-dioxolane ring system **(53)** is illustrated in figure 1.7.1 and is present in some of the most effective and successful anti-fungal agents developed to date including etaconazole **(19)**, propiconazole **(9)** and ketconazole (54). Propiconazole **(9)** and etaconazole **(19)** are two agrochemical fungicides developed by Janssen[33,39].



(53)

Figure 1.7.1

Ketconazole **(54)**, figure 1.7.2 is a broad spectrum, orally active antifungal agent used to treat a variety of anti-fungal infections[50]. Although the 1,3-dioxolane ring **(53)** system does not appear to be fungitoxic, the 1,3-dioxolane ring system has been shown to have muscarinic activity[51].



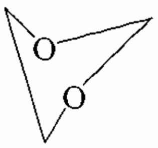
(54)

Figure 1.7.2

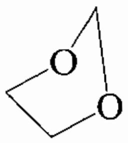
The 1,3-dioxolane ring **(53)** is a five membered hetroaromatic ring containing two oxygen atoms in the 1 and 3 positions. ^{13}CNMR studies show significant deshielding of the C-1 and this is attributed to the adjacent oxygen atoms[52].

^{1}HNMR studies have shown that progressive rotation (pseudorotation), between various half chair and envelope conformers alternating around the ring, was taking place.

There is a small energy barrier between the conformers and the half-chair and envelope forms are the two lowest energy conformers (figure 1.7.3)[53].



Half chair conformer (55)



Envelope conformer (56)

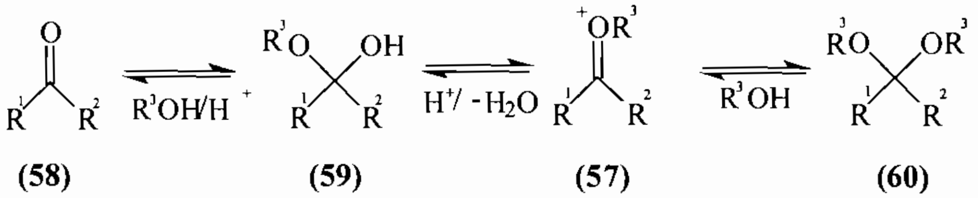
Figure 1.7.3

The free energy differences between the cis and trans isomers of compounds containing the 1,3-dioxolane ring structure **(53)** are very small and such small energy differences are explained in terms of a highly flexible ring[54]. 1,3-Dioxolanes are cyclic acetals and some of the main methods of acetal synthesis are discussed in the following section 1.7.2.

1.7.2 Synthesis of acetals

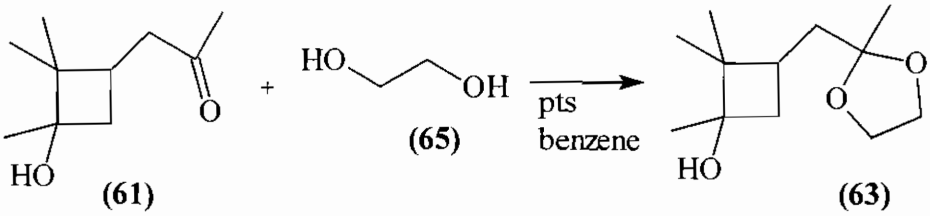
(i) From aldehydes and ketones with alcohols and protic or Lewis acid catalysts

Aldehydes and ketones react with alcohols under acidic conditions to form acetals and water in an equilibrium process which proceeds via an oxonium ion **(57)** as illustrated in scheme 15.



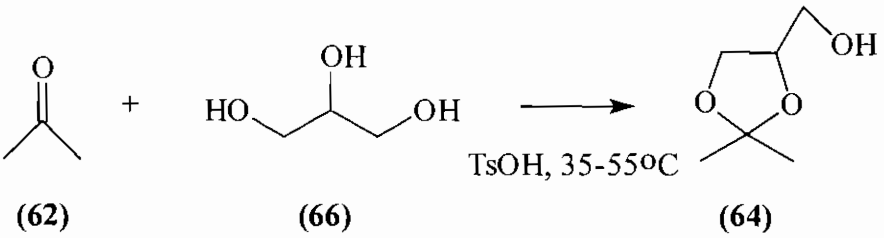
Scheme 15

The most common method employed for acetal formation involves heating an aldehyde or ketone with an alcohol or diol in an inert solvent such as benzene, toluene or xylene with the removal of water by azeotropic distillation with a Dean & Stark apparatus[55]. Examples of this type of reaction are illustrated in scheme 16 and 17 where the ketones **(61)** and **(62)** are converted to the cyclic acetals **(63)** and **(64)**[56,57]. Another possibility is the removal of water using a dehydrating agent such as molecular sieves, calcium sulphate, copper sulphate or alumina.



pts = *p*-toulenesulphonic acid

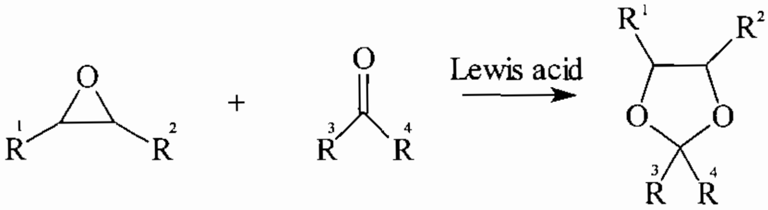
Scheme 16



Scheme 17

(ii) From aldehydes and ketones with epoxides

Hydrolysis of an epoxide **(67)** under acidic conditions produces a diol which can react with aldehydes and ketones **(68)** to form cyclic acetals **(69)**. These cyclic acetals are known as 1,3-dioxolanes **(69)** and can also be formed by direct condensation of epoxides with aldehydes and ketones in the presence of Lewis acids as illustrated in scheme 18[58].

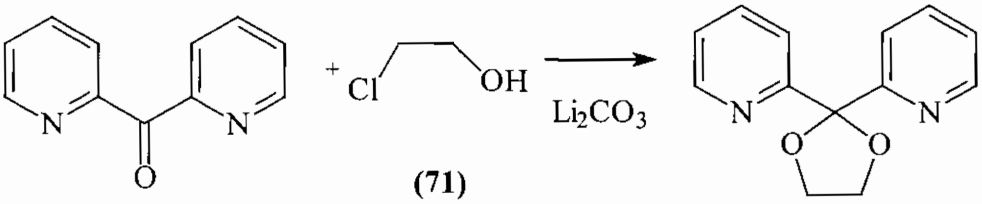


(67) **(68)** **(69)**

Scheme 18

(iii) From aldehydes and ketones under basic or neutral conditions

Carbonyl derivatives whose carbonyl group is flanked by electron-withdrawing groups readily form hemiacetals but are usually difficult to convert into acetals. In acidic conditions the electron-withdrawing groups have a destabilising effect towards carbonium ion formation. Aldehydes and ketones may form acetals by the alkylation of the intermediate hemiacetals formed in situ under basic conditions[59]. An example of this type of reaction is illustrated in scheme 19 where **(70)** is reacted with **(71)** to give the ketal **(72)**.

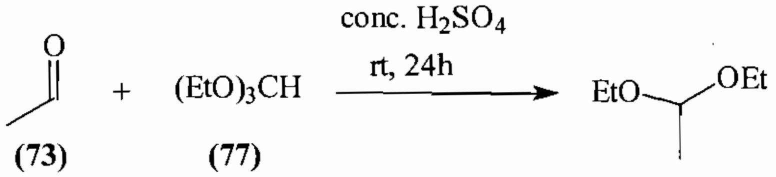


(70) **(71)** **(72)**

Scheme 19

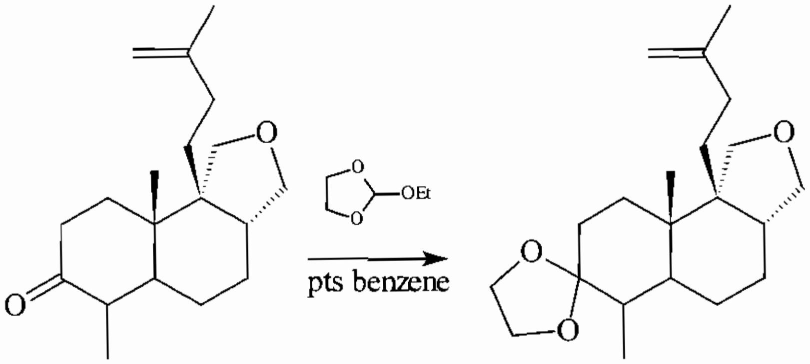
(iv) From aldehydes and ketones with orthoformates

Ortho esters undergo acid-catalysed reactions with aldehydes **(73)** and ketones **(74)** to form acetals **(75)** and **(76)** as illustrated in schemes 20 and 21[60,61]. The presence of an alcohol accelerates the reaction. This reaction has been widely employed in steroid chemistry and is sometimes more selective than conventional procedures[62].



(73) (77) (75)

Scheme 20



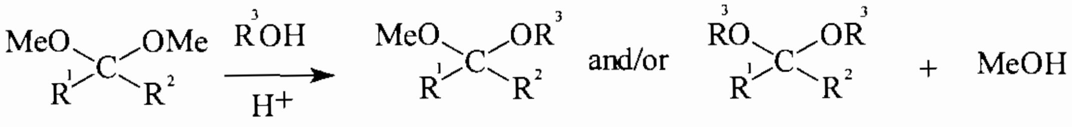
(74) (76)

pts = *p*-toulenesulphonic acid

Scheme 21

(v) From acetals with alcohols

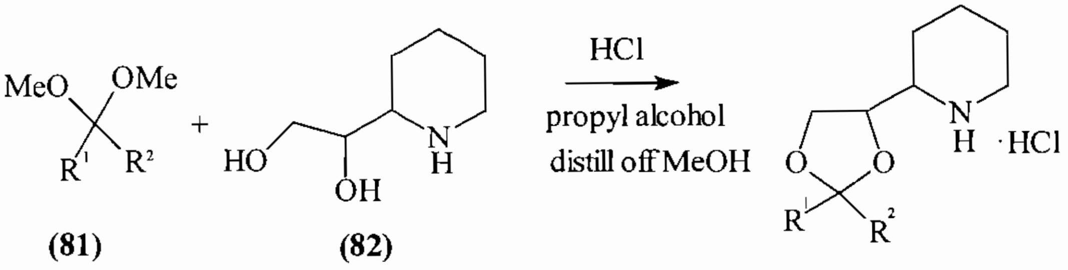
When the alkoxy groups of acetals formed from low boiling alcohols are exchanged under acidic conditions with higher boiling alcohols, the equilibrium is displaced by the removal of the lower boiling alcohol by distillation as illustrated in scheme 22. Control of the reaction conditions allows the formation of mixed acetals **(78)**, but it is often necessary to separate this from the symmetrical acetal **(79)** which is formed exclusively in the presence of an excess of the alcohol R^3OH. The use of excess of starting acetal **(80)** allows the unsymmetrical acetal to be isolated in good yield at room temperature[63].



(80) (78) (79)

Scheme 22

Cyclic acetals are formed in good yields from methyl acetals with diols and this method also allows the preparation of aromatic acetals which could not have been prepared from the corresponding ketones. 2,2-Dimethoxypropane **(81)** and analogous compounds are widely used in synthesis for the protection of diols **(82)** as cyclic acetals **(83)** as illustrated in scheme 23[64].



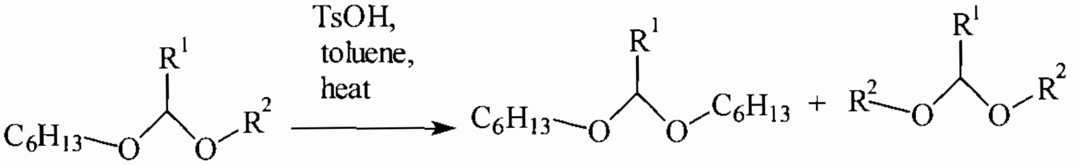
(81) **(82)** **(83)**

R^1, R^2 = H, alkyl, aryl

Scheme 23

(vi) From acetals by acetal interchange

Methoxymethyl ethers or ethoxyethyl ethers undergo acetal interchange when heated in the presence of an acid to afford formaldehyde or acetaldehyde acetals. The equilibrium is displaced by evaporation of the volatile acetal co-product **(84)** as illustrated in scheme 24[65].



(85) **(86)** **(84)**

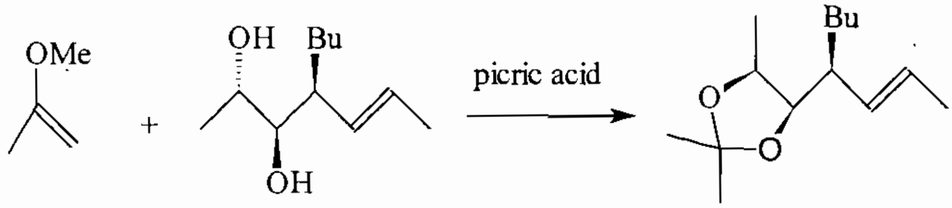
R^1 = H, R^2 = Me, 78%

R^1 = Me, R^2 = H, 69%

Scheme 24

(vii) From enol ethers and alcohols by acid catalysis

Protection of diols **(87)** is commonly achieved by their reaction with enol ethers such as 2-methoxypropene **(88)** to form cyclic acetals **(89)** as illustrated in scheme 25[66]. This method is widely used in the synthesis of natural products[67].

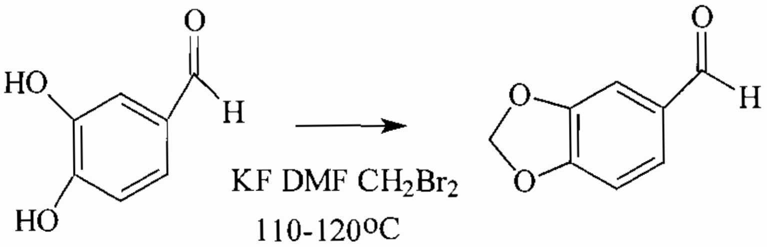


(88) **(87)** **(89)**

Scheme 25

(viii) From gem-dihalides by alkylation

Dihalomethanes undergo displacement with alcohols, diols (symmetrical and unsymmetrical) and phenols to provide acetals of formaldehyde. Phase transfer catalysts are often employed and generally give the best yields as illustrated in scheme 26 where **(90)** is converted to **(91)**[68].



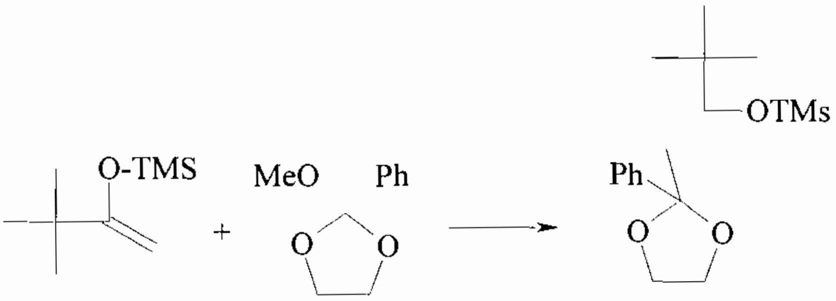
(90) **(91)**

Scheme 26

(ix) From orto esters and nucleophiles with enolate derivatives

Lithium enolates, silyl enol ethers and enamines react with orthoformates in the presence of a Lewis acid to form monoprotected 1,3-dicarbonyl derivatives.

This reaction has been extended to prepare cyclic acetals of ketones and an example is illustrated in scheme 27 where **(92)** and **(93)** react to form the ketal **(94)**[69].

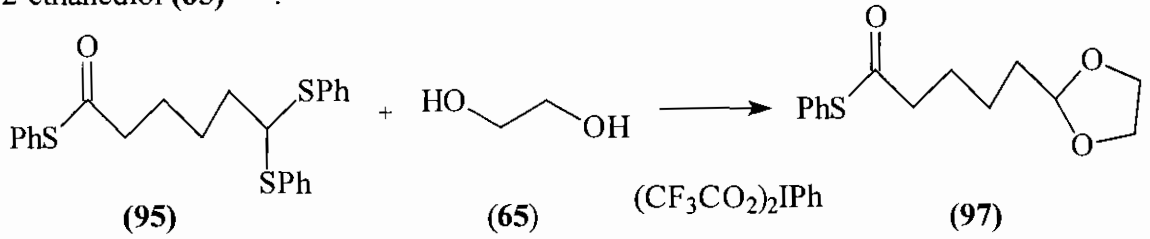


(92) **(93)** **(94)**

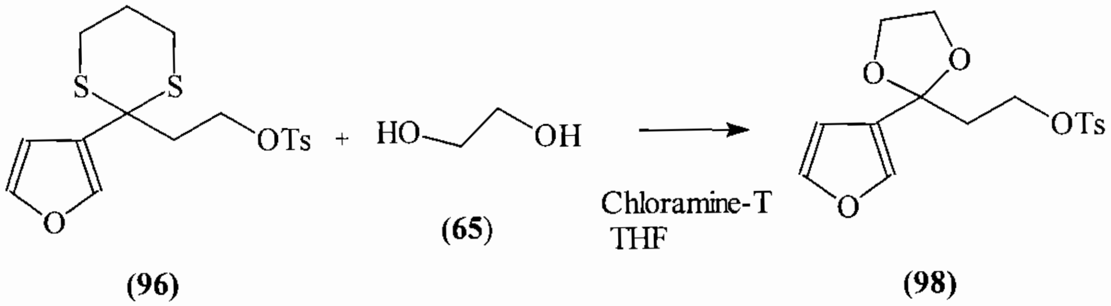
Scheme 27

(x) From dithioacetals

Finally the alcoholysis of dithioacetals induced by thiophilic metals, such as mercury(II), copper(II) or silver(I), or by S-alkylation or oxidation is a potentially nonacidic procedure for acetal formation and some examples are shown in schemes 28 and 29 where **(95)** and **(96)** are converted to the ketals **(97)** and **(98)** utilising 1,2-ethanediol **(65)**[70,71].



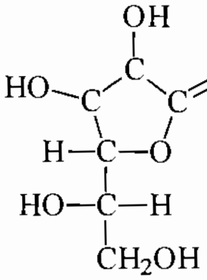
Scheme 28



Scheme 29

1.7.3 Carbonyl-protection

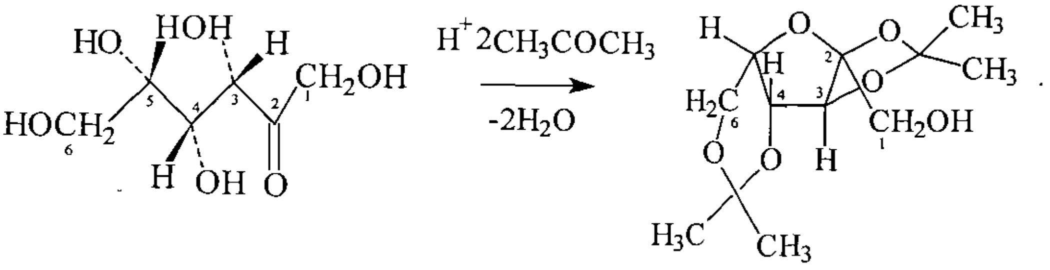
In the course of complex syntheses carbonyl groups often must be protected against nucleophilic attack. To achieve this the carbonyl functions are often transformed into acetals, thioacetals, hydrazones, oximes or cyanohydrins. The carbonyl function is desensitised towards attack under neutral and basic conditions and the protecting group can be easily removed. The oxygen acetals and ketals are readily cleaved by acidic hydrolysis and are stable to oxidants and heavy metal ions. As a rule 1,3-dioxolanes are more stable than acyclic acetals. 1,3-Dioxolanes derived from ketones also hydrolyse faster than the corresponding 1,3-dioxolanes derived from aldehydes. Both dioxanes and dioxolanes are stable to strong nucleophiles and bases and organometallic reactions can be performed on compounds protected in this way. An example of carbonyl-protection involving 1,3-dioxolanes is the synthesis of vitamin C **(99)** figure 1.7.4[72].



(99)

Figure 1.7.4

At an early stage in the synthesis of vitamin C **(99)**, the primary alcohol group at C-I of the sugar sorbose **(100)** must be selectively oxidised to a carboxylic acid without affecting the OH groups at carbons C-3 through C-6. On acid catalysed reaction with excess propanone, the hydroxyl groups at C-2 and C-3 are blocked as a five member cyclic acetal and those at C-4 and C-6 are protected as a six membered acetal ring as illustrated in scheme 30. Potassium permanganate then converts the unprotected CH_2OH(C-1) into CO_2H.



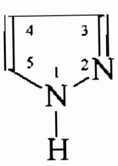
(100) (101)

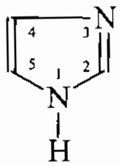
Scheme 30

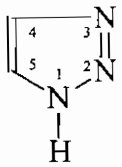
1.8 Chemistry of triazoles

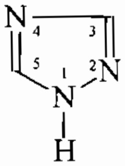
1.8.1 Introduction

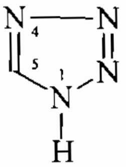
Azole compounds may be regarded as being formally derived from pyrrole or indole by the replacement of one or more of the annular carbons by nitrogen atoms. The parent compounds of the azole class are pyrazole **(102)**, imidazole **(103)**, 1,2,3-triazole **(104)**, 1,2,4-triazole **(14)**, tetrazole **(105)**, indazole **(106)**, benzimidazole **(107)** and benzoltriazole **(108)** as illustrated in figure 1.8.1.

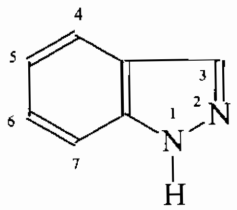

(102)


(103)


(104)


(14)


(105)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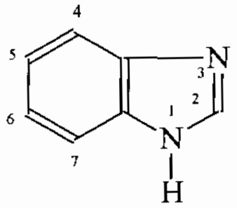
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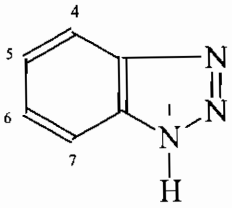
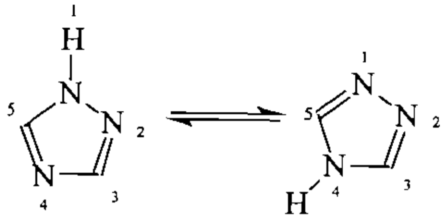

(108)

Figure 1.8.1

Interest in the azole class of compounds has been stimulated because of their applications in industry and agriculture and because of their biological and analytical importance. 1,2,3-Triazoles **(104)** are used as light stabilisers and as optical brightening agents. 1,2,4-Triazoles **(14)** have found applications as herbicides, plasticisers, adhesives and in the photographic industry[73]. The triazole rings **(14)** and **(104)** are planar 6π–electron aromatic systems with distortions of the π-system induced by the annular nitrogens. Simple 1,2,4-triazoles **(14)** are cyclic hydrazidines with H or some other subsituent on either a hydrazide nitrogen as on **(109)** or an amide nitrogen as on **(110)**. The prefixes 1H and 4H are used to distinguish between **(109)** and **(110)** and structures **(109)** and **(110)** are tautomers (scheme 31)[74] .

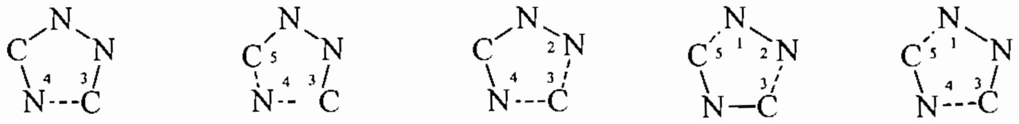


(109) **(110)**

Scheme 31

1.8.2 Synthesis of 1,2,4-triazoles

The methods of synthesis of 1,2,4-triazoles include: (i) the formation of the 3,4-bond, (ii) formation of the 3,4- and 4,5-bonds, (iii) formation of the 2,3- and 3,4-bonds, (iv) formation of the 1,5- and 2,3-bonds and (v) formation of the 1,5- and 3,4-bonds as illustrated in figure 1.8.2[75].

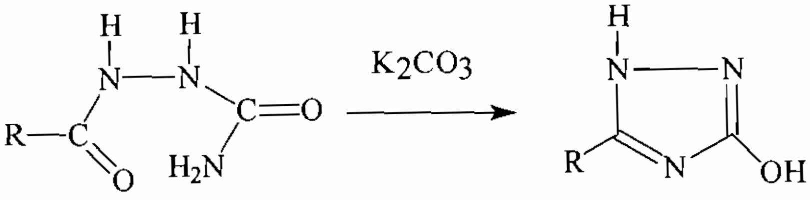


(i) **(ii))** **(iii)** **(iv)** **(v)**

Figure 1.8.2

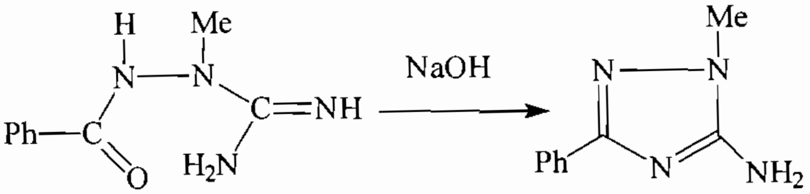
(i) Formation of 3,4-bond

The intramolecular condensation in alkaline medium of acyl derivatives of, semicarbazides such as **(111)** and **(112)** produces 1,2,4-triazoles **(113)** and **(114)** as illustrated in schemes 32 and 33.



(111) **(113)**

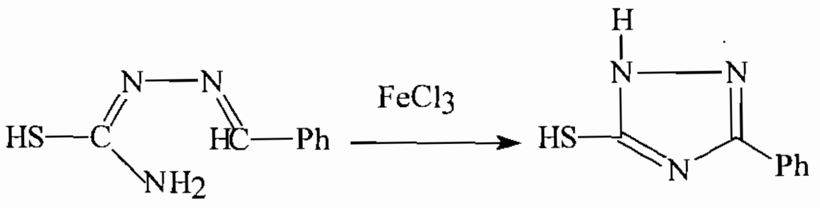
Scheme 32



(112) **(114)**

Scheme 33

In acidic conditions acylthiosemicarbazides tend to be transformed into thiadiazoles rather than triazoles but there are some examples of successful synthesis of the triazole ring system. The oxidative cyclisation of benzaldehyde thiosemicarbazone **(115)** gives rise to a mercaptotriazole **(116)** as illustrated in scheme 34.

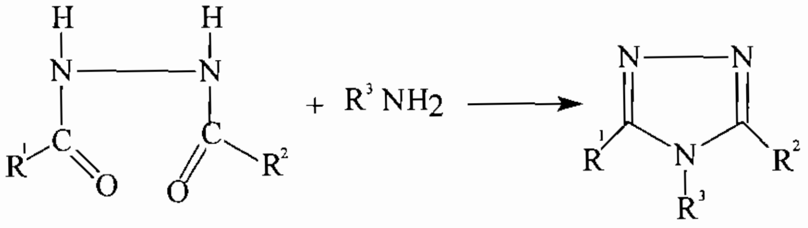


(115) **(116)**

Scheme 34

(ii) Formation of the 3,4- and 4,5-bonds

An example of method (ii) is provided by the intermolecular condensation of diacyl-hydrazines **(117)** with amines as illustrated in scheme 35. This method leads to the synthesis of 4-substituted 1,2,4-triazoles **(118)**. Cyclisation may be thermally promoted or induced by a dehydrating agent.

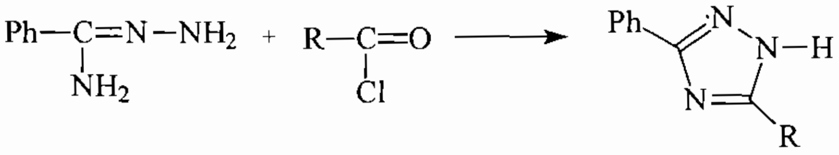


(117) **(118)**

Scheme 35

(iii) Formation of the 2,3- and 3,4- bonds

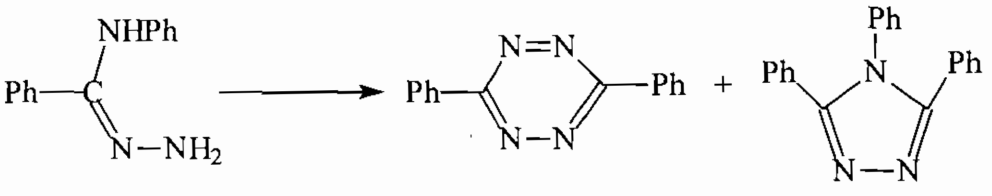
The 2,3- and 3,4-bonds form when amidrazones **(119)** or hydrazidines cyclise with carbonyl compounds such as acid chlorides **(120)** or anhydrides as illustrated in scheme 36.



(119) **(120)** **(121)**

Scheme 36

Phenyl-benzimidrazone **(122)** self-condenses to form a mixture of diphenyltetrazine **(123)** and 3,4,5-triphenyl-1,2,4-triazole **(124)** as illustrated in scheme 37.

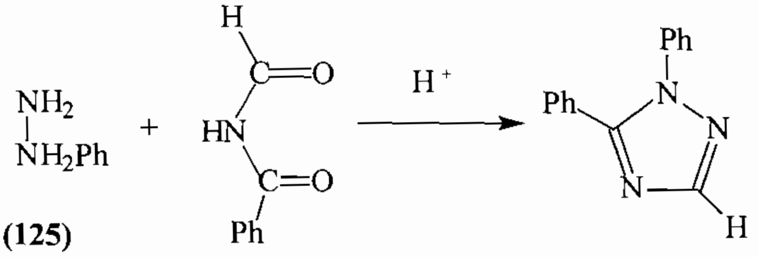


(122) **(123)** **(124)**

Scheme 37

(iv) Formation of the 1,5- and 2,3- bonds

The Einhorn-Brunner reaction of hydrazines **(125)** with diacyl amines **(126)** in mildly acid conditions gives rise to 1,2,4-triazoles **(127)** as illustrated in scheme 38[75]. The reaction has the advantage that unsymmetrical diacylamines do not produce mixtures of isomeric triazoles. The corresponding thioacyl or imino-compounds will also take part in the reaction.

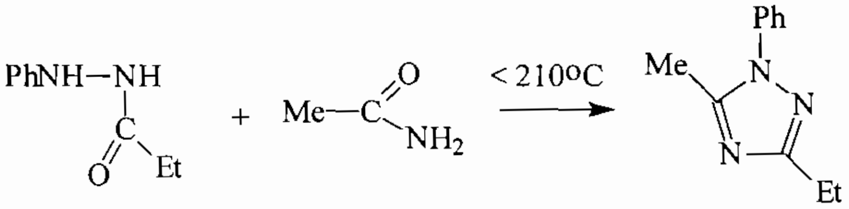


(125) **(126)** **(127)**

Scheme 38

(v) Formation of the 1,5- and 3,4- bonds

The formation of the 1,5- and 3,4-bonds is demonstrated by the Pellizzari reaction[75] where hydrazides **(128)** and amides **(129)** are heated at high temperature in the absence of solvent to produce 1,2,4-triazoles **(130)** as illustrated in scheme 39. Complications involving this method include concurrent dehydration of the amide and sometimes aryl inter-change between amide and hydrazide.

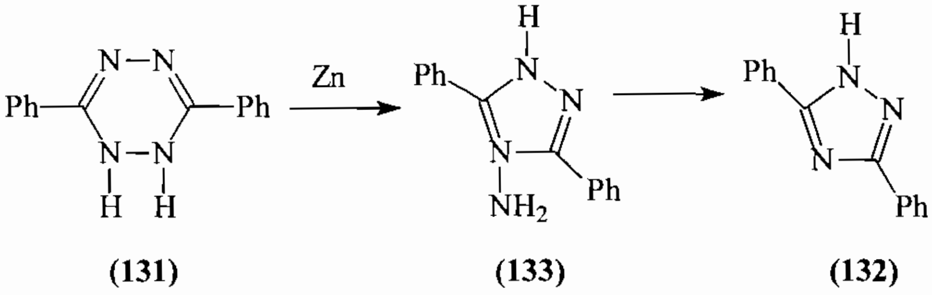


(128) **(129)** **(130)**

Scheme 39

(vi) Molecular rearrangements

Besides the ring synthesis methods mentioned above, 1,2,4-triazoles may be formed as the result of molecular rearrangements. Ring contractions of tetrazines and the pyrolysis of 5-subsituted tetrazoles can result in the formation of 1,2,4-triazoles. The conversion of diphenyl-tetrazine **(131)** into 3,5-diphenyltriazole **(132)** by reduction occurs in two stages with **(133)** formed in an intermediate step as illustrated in scheme 40[76].

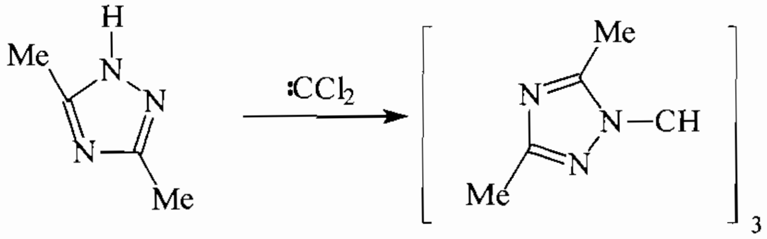


Scheme 40

1.8.3 Reactivity of the 1,2,4-triazole ring

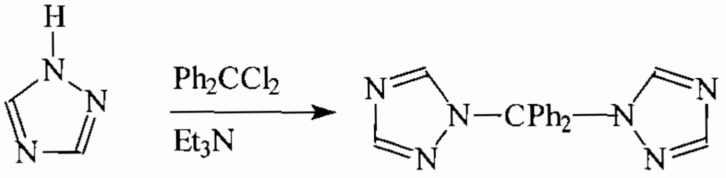
(i) Stability of the triazole ring

The triazole ring is thermally stable to approximately 300°C. On heating the ring remains unaffected but the subsituents on the ring and their location may undergo changes[77]. Unlike the pyrazoles and imadazole rings the triazole ring does not undergo ring expansion and attempted ring expansions have resulted in the formation of tristriazoles **(134)** or bistriazoles **(135)** as illustrated in schemes 41 and 42.[78].



(136) **(134)**

Scheme 41

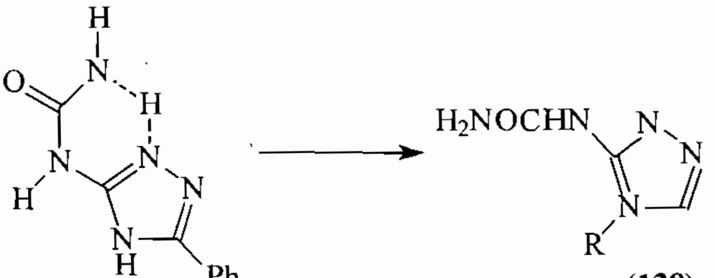


(14) **(135)**

Scheme 42

(ii) Electrophlic attack at nitrogen

There are three main types of reactions, which occur on the ring nitrogens. These reactions are alkylations, arylations and acylations. Alkylation of NH on the triazole ring introduces substituents at the N-1 position rather than the N-4 position suggesting a preference for the N-1 position. Alkylation of simple 1,2,4-triazoles at N-4 is very rare although it has been observed[79]. An example of N-4 alkylation is illustrated in scheme 43. 3-Phenyl-5-ureido-1,2,4-triazole **(137)** is methylated or benzylated to give **(138)**. Alkylation at N-4 occurs because of internal hydrogen bonding within the molecule pre-empting the favoured N-1 site.



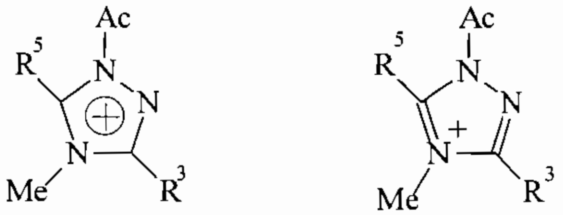
(137) (138)

R=Me, $PhCH_2$

Scheme 43

Active aromatic halides and 2 or 4-pyridyl halides can be used for the N-arylation of 1,2,4-triazole. This type of reaction is often best achieved by the Ullmann reaction where a preference for annular arylation on the N-4 position is observed[80].

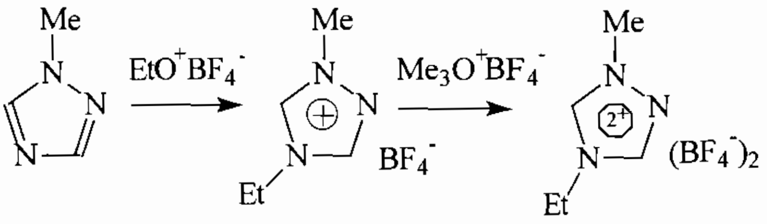
Quaternisation also occurs with arylation and triazoles with alky, aryl or acyl substituents on N-1 or on N-4 may be quaternised. The mesomeric distribution of the positive charge on triazolium compounds can be represented by **(139)** or by the equivalent formula **(140)**, which denotes the site where quaternisation has taken place is illustrated in figure 1.8.3.



(139) (140)

Figure 1.8.3

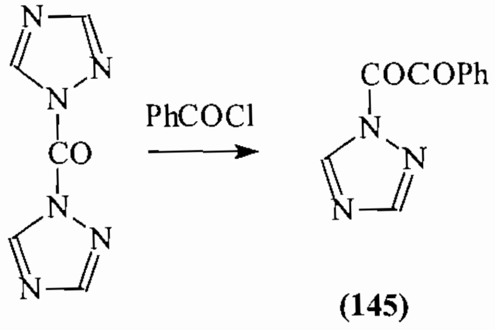
The motivation behind quaternisation is to maximise the distance between subsituents on the annular N. A triazole which is substituted on N-1 will therefore be quaternised on N-4. Quaternisation of 4-aminotriazoles at N-1 follows the rule that predicts attack on N-centres of maximum separation. Diquaternisation is also possible **(141)**[81]. This time there is a mesomeric distribution of two charges over the ring as illustrated in scheme 44.



(142) (143) (141)

Scheme 44

Acylations are generally carried out by the reaction of anhydrides or acyl halides with triazolates or the treatment of triazoles in inert solvents with acyl halides. N,N-Carbonyl-ditriazole **(144)** is formed exothermically by acylation at N-1. An example of a transacylation reaction is illustrated in scheme 45. The transacylation reaction is between N,N-carbonyl-ditriazole **(144)** and benzoyl chloride to afford 1-benzoyl- triazole **(145)**[82].

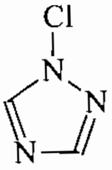


(144)

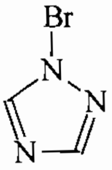
(145)

Scheme 45

In general electrophilic halogenation of 1,2,4-triazoles is used as a preparative method for the preparation of C-halo triazoles. N-Chloro-1,2,4-triazole **(146)** can however be chlorinated in aqueous potassium hydrogen carbonate solution where an excess of chlorine in alkaline solution allows the formation of 1,3-dichloro and 1,3,5-trichloro-triazoles[83]. Reaction of potassium triazolate with bromine at 0°C affords N-bromotriazole **(147)**. If the triazole is 3,5-disubstitued, N-bromotriazole **(147)** (figure 1.8.4) is formed, otherwise C-bromination occurs[84].



(146)

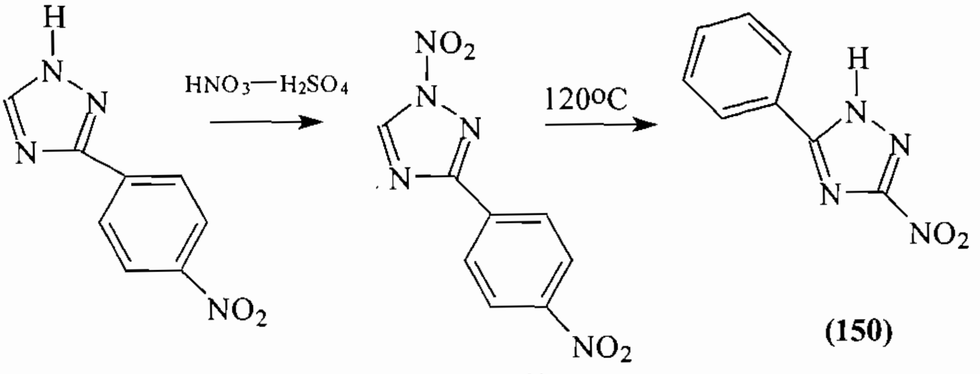


(147)

Figure 1.8.4

(iii) Electrophilic attack at carbon

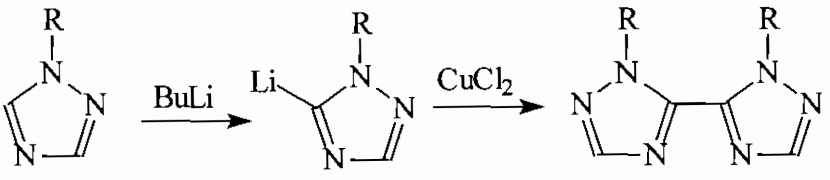
Nitration of triazole and its C-monoalkyl derivatives is not possible. Aryl triazoles can be nitrated on the benzene ring but 3-*p*-nitrophenyltriazole **(148)** in which the benzene ring is deactivated is nitrated to afford the N-nitro derivative **(149)**. The N-nitro derivative **(149)** then rearranges to the C-nitro compound **(150)** at 120°C as illustrated in scheme 46[85].



(148) **(149)** **(150)**

Scheme 46

Although N-substituted triazoles generally form triazolates on reaction with metalating agents, lithiation of 1-(2-pyridyl)-1,2,4-triazole **(152)** provides a method for the formation of bistriazoles such as **(153)** as, illustrated in scheme 47[86].



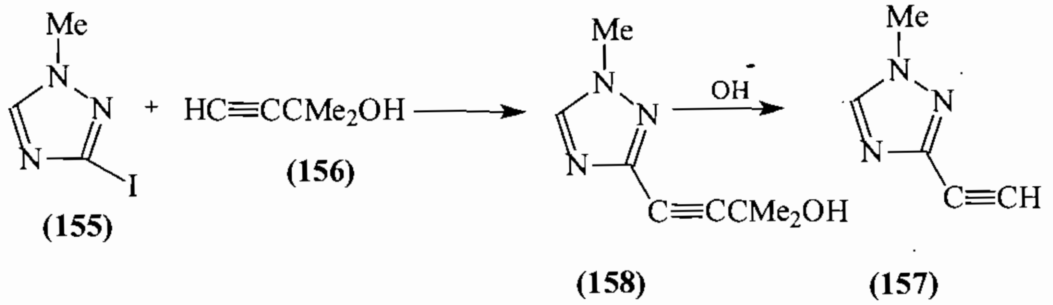
(152) **(154)** **(153)**

R = 2-pyridyl

Scheme 47

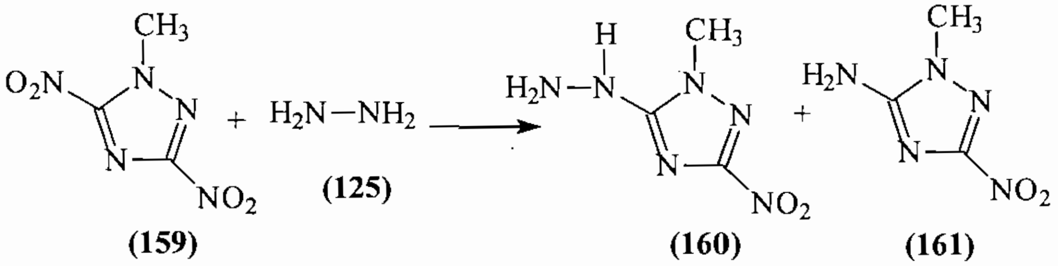
(iv) Nucleophlic attack at carbon

The main types of nucleophlic reactions are exchange reactions involving anionic subsituents and also reactions involving the generation of a transient carbonium ion. Many triazole derivatives are accessible by the exchange of 3- or 5-halo, hydroxy, alkoxy, aryloxy, alkylthio, amino or cynano groups[87-90]. 3-Iodo-1-methyl-1,2,4-triazole **(155)** reacts with 2-methylbut-3-yn-2-ol **(156)** to afford 3-ethynyl-1-methyl-1,2,4-triazole **(157)** via **(158)** as illustrated in scheme 48.



Scheme 48

Triazoles can readily exchange the nitro groups of nitro and dinitro triazoles and nitrotriazolinones[91,92]. The reaction of 1-methyl-3,5-dinitro-1,2,4-triazole **(159)** with hydrazine **(125)** affords 5-hydrazino-1-methyl-3-nitro-1,2,4-triazole **(160)** but reduction of a nitro group by the same reagent also affords 5-amino-1-methyl-3-nitro-1,2,4-triazole **(161)** as illustrated in scheme 49.[93].



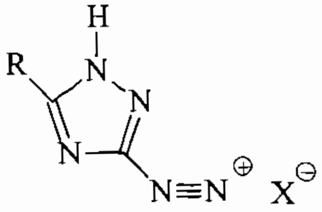
Scheme 49

Diazonium salts are very important synthetic intermediates. When a primary aromatic amine such as aniline **(162)**, dissolved or suspended in cold mineral acid, is treated with sodium nitrite, a diazonium salt **(163)** is formed as shown in scheme 50[94,95].

$$\underset{\textbf{(162)}}{Ar{-}NH_2} + NaNO_2 + 2HX \xrightarrow{\text{cold}} \underset{\textbf{(163)}}{Ar{-}N_2^+ X^-} + Na_2X + 2H_2O$$

Scheme 50

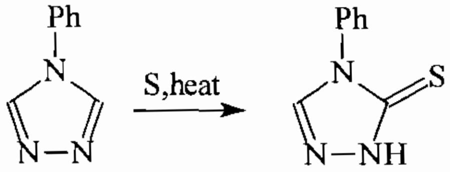
At room temperature in conc. hydrochloric acid diazonium salts such as **(163)** derived from triazoles are unstable and their decomposition products include chlorotriazoles[96].



(163)

Figure 1.8.5

Direct oxidative thiation can be accomplished by heating sulphur with triazole **(164)** but a subsituent on nuclear nitrogen is required as illustrated in scheme 51[97].



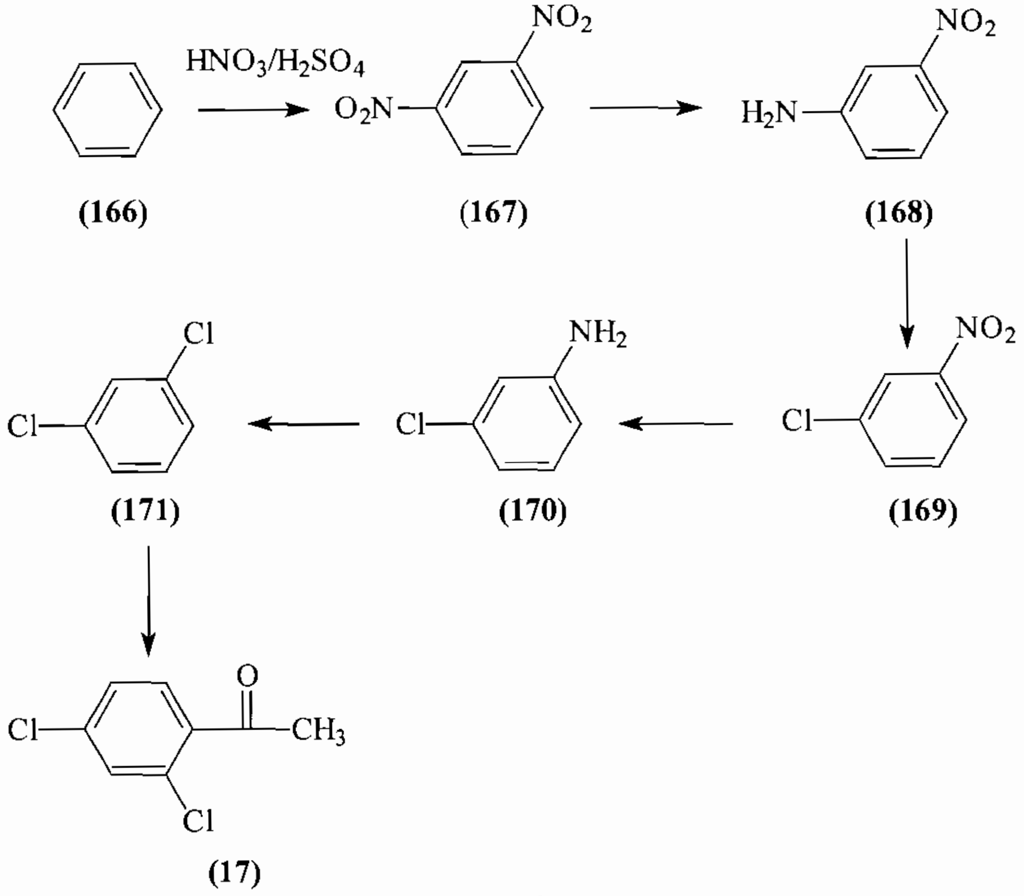
(164) **(165)**

Scheme 51

1.9 Review of the synthesis of propiconazole and intermediates

1.9.1 Synthesis of starting materials

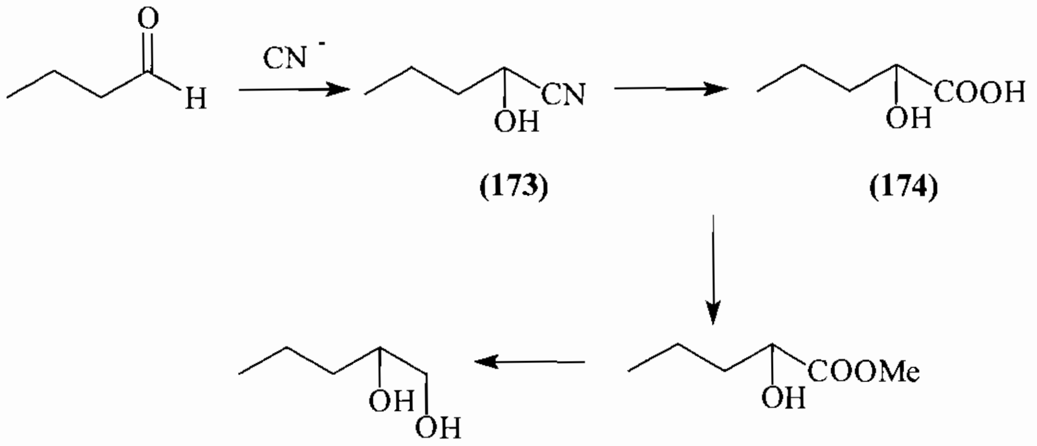
There are three important reagents required for the synthesis of propiconazole **(9)**, ethanone-1-(2,4-dichlorophenyl)**(17)**, 1,2-pentanediol **(16)** and 1H-1,2,4-triazole **(14)**. These three reagents are commercially available. Ethanone-1-(2,4-dichlorophenyl)**(17)** may be synthesised, according to scheme 52. Benzene (**166**) is nitrated with nitric acid/sulphuric acid to give m-dinitro benzene **(167)**. This is then be reduced to yield m-nitroaniline **(168)** using sodium sulphide. The amino group is then diazotized and chlorinated to yield m-nitro-chloro benzene **(169)**. Further reduction yields 3-chloro aniline **(170)** which is again diazotized and chlorinated to yield m-dichloro-benzene **(171)** which undergoes a Friedel-Crafts acylation reaction by reaction with ethanoyl bromide to yield the desired product ethanone-1-(2,4-dichlorophenyl)**(17)**[35].



Scheme 52

1,2-Pentanediol **(16)** is synthesised as illustrated in scheme 53, via 2-hydroxy-valeronitrile **(172)**, which was prepared by the cyanohydrin synthesis from butanal.

2-Hydroxy-valeronitrile **(173)** was then hydrolysed to 2-hydroxy-valeric acid **(174)**, which was then treated with diazomethane to yield the ester **(175)** which was then reduced with lithium aluminium hydride to yield 1,2-pentanediol **(16)**[30, 34].

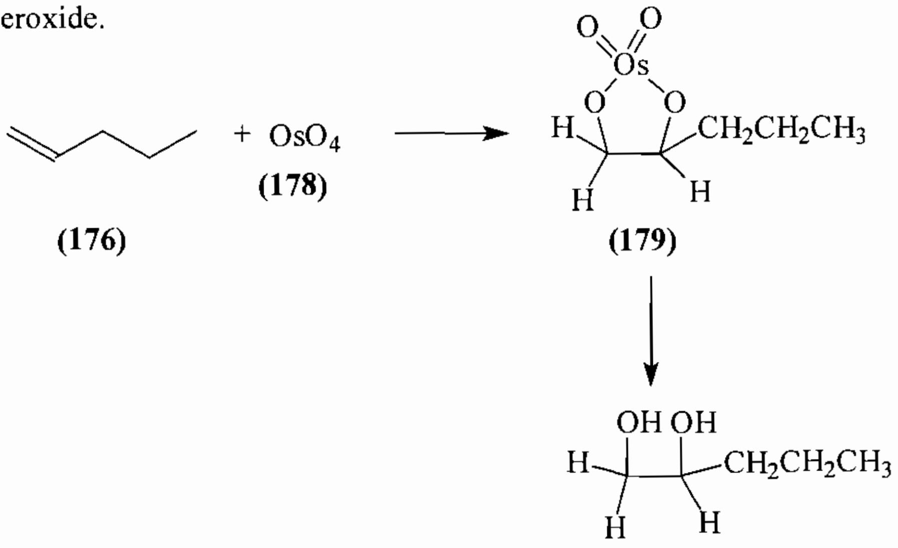


(173) **(174)** **(16)** **(175)**

Scheme 53

Other possible synthesis of 1,2-pentanediol **(16)** include the 1,2-dihydroxylation of pentene **(176)** or the reduction of 2-oxo-pentanal **(177)**[98]. Potassium permanganate is a well-known dihydroxylating agent, although this reagent does not generally give good yields of diols[99].

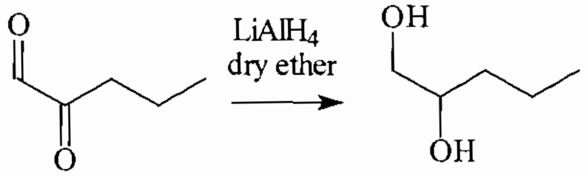
The cis-hydroxylation of alkenes by osmium tetroxide **(178)** to form 1,2-diols is one of the most reliable synthetic transformations as illustrated in scheme 54[100]. There is however problems of toxicity and cost associated with the reagent and the reagent is most often used catalytically in the stoichiometric presence of a co-oxidant such as t-butyl hydroperoxide.



(176) **(178)** **(179)** **(16)**

Scheme 54

2-Oxo-pentanal **(177)** can be reduced with a suitable reducing agent such as lithium aluminium hydride or sodium borohydride to yield 1,2-pentanediol **(16)** as illustrated in scheme 55[101,102].



(177) **(16)**

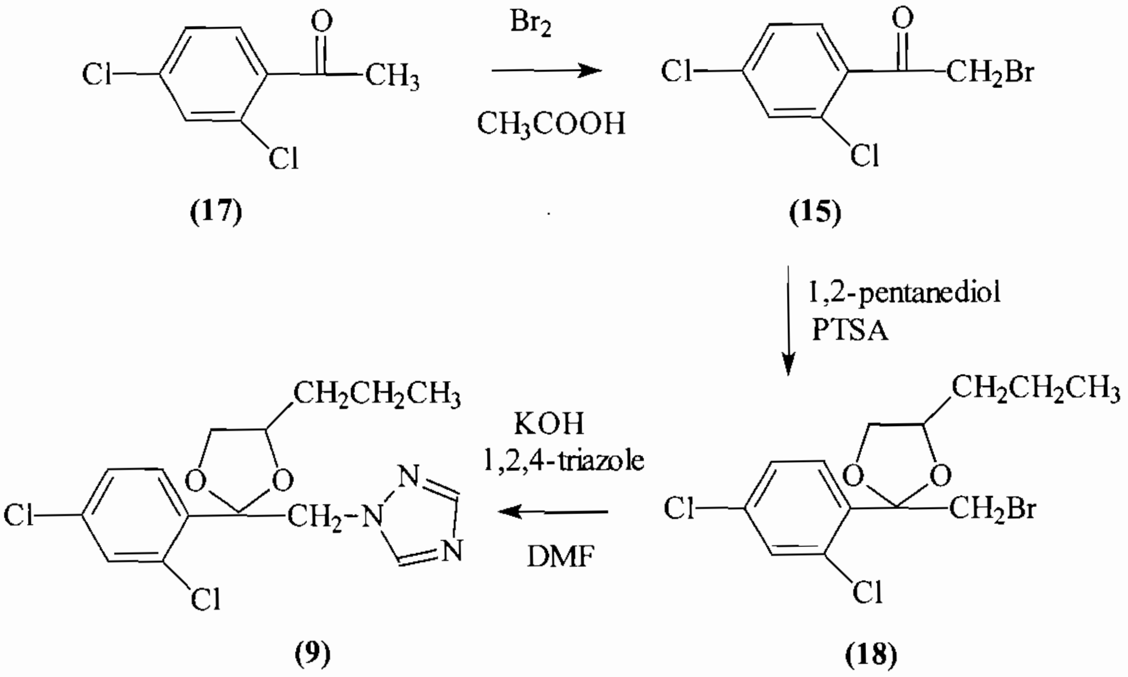
Scheme 55

1H-1,2,4-Triazole **(14)** is readily available, having been around for quite a long time and there are numerous pathways to the synthesis of triazoles (section 1.8.2).

1.9.2 Synthesis of propiconazole

(i) Ciba-Geigy patent

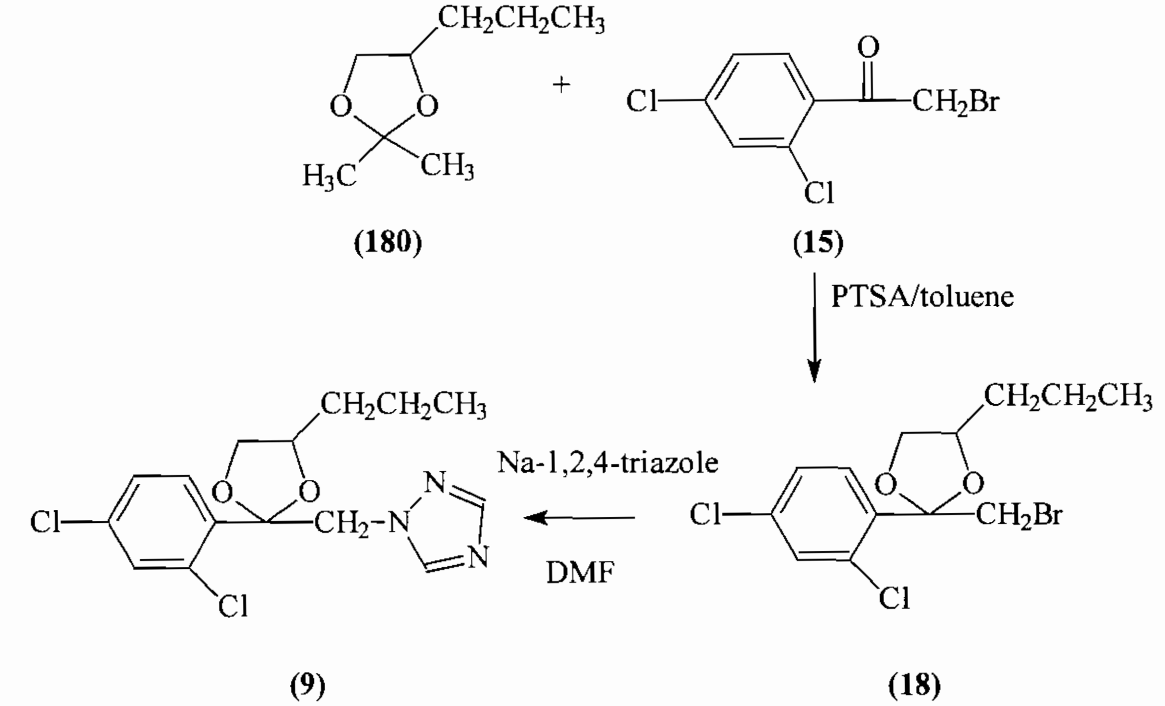
Propiconazole **(9)** was first synthesis by Janssen pharmaceuticals in Belgium in 1978[33]. Ciba-Geigy AG. later, developed propiconazole as an agricultural fungicide. The Ciba-Geigy patent is a three-step process and is illustrated in scheme 56. The first step involves the bromination of the starting material ethanone-1-(2,4-dichlorophenyl)**(17)** to yield ethanone-2-bromo-1-(2,4-dichlorophenyl)**(15)** when bromination is carried out in an acidic solvent. The second step is a condensation reaction with azeotropic removal of water from the reaction of ethanone-2-bromo-1-(2,4-dichlorophenyl)**(15)** and 1,2-pentanediol **(16)** to afford the ketal, 1,3 dioxolane-2-(2,4 dichlorophenyl)-2-bromomethyl-4-*n*-propyl **(18)**, which is the precursor to propiconazole **(9)**. The final step is a nucleophlic substitution reaction of **(18)** with 1H-1,2,4-triazole **(14)** in the presence of a base in dimethylformamide at 160°C to yield propiconazole **(9)** in approximately 73% yield. Other syntheses following the Ciba-Geigy patent include the synthesis of ^{14}C-labelled propiconazole and the synthesis of stereo-specific enatiomers of propicoazole in order to quantify biological activity[34,35].



Scheme 56

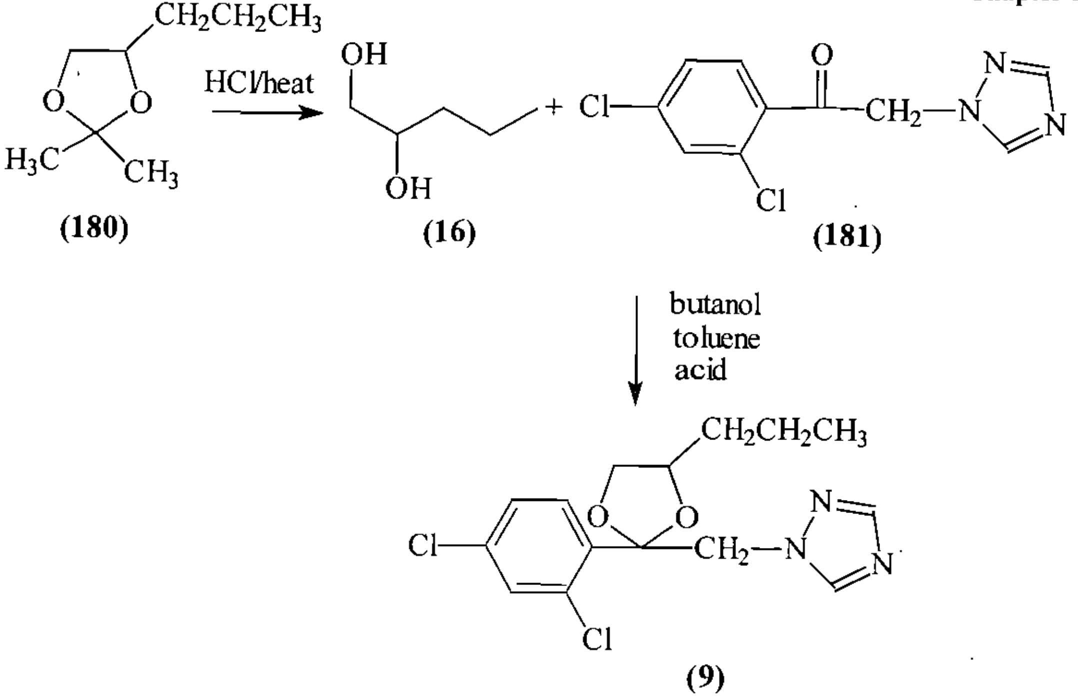
(ii) Colle & Camamagi patent

The Colle & Camamagi patent was filed in 1986 in South Africa and describes two variations of a process for the preparation of propiconazole **(9)**[37]. In the first variation of the process (scheme 57) the ketal 1,3-dioxolane-2-dimethyl-4-*n*-propyl **(180)** undergoes a transketalisation reaction with the ethanone-2-bromo-1-(2,4-dichlorophenyl)**(15)**. The catalyst is sulphuric acid or *p*-toluene-sulphonic acid and the reaction is carried out at temperatures in the range of 60°-140°C. The intermediate formed is 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-bromomethyl-4-*n*-propyl **(18)** which is then reacted with the alkali-metal salt of 1H-1,2,4-triazole **(8)** in a dipolar aprotic solvent for 16hrs to yield propiconazole **(9)**.



Scheme 57

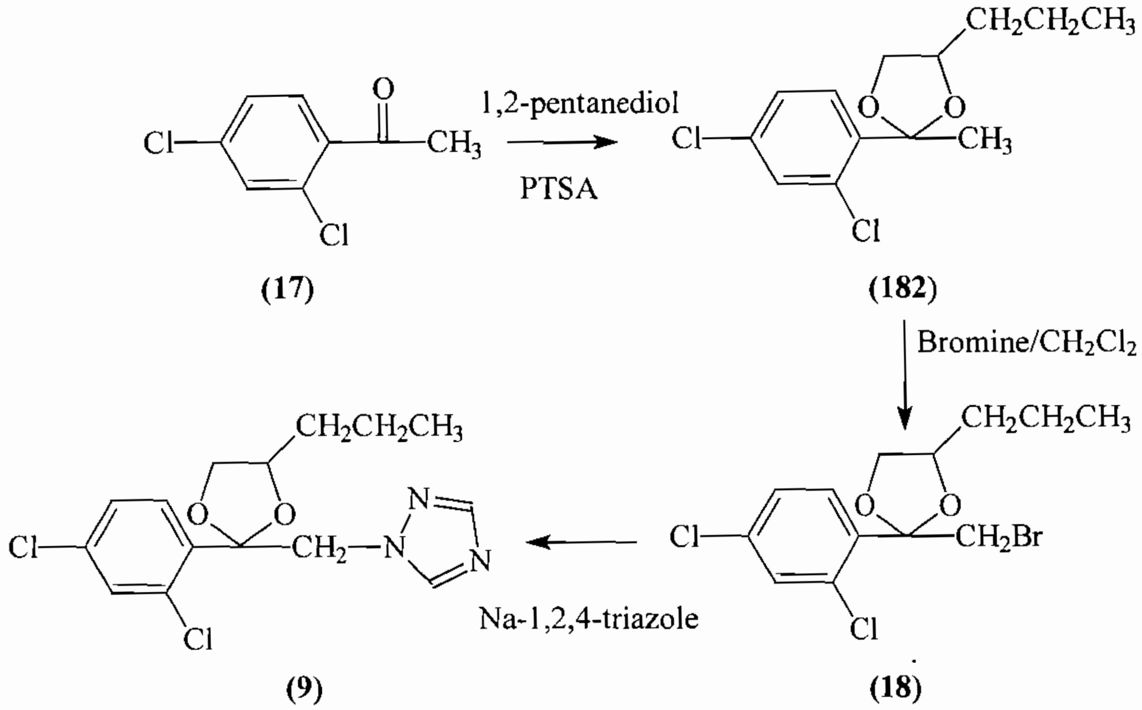
A variation of this process is illustrated in scheme 58. In this process the ketal 1,3-dioxolane-2-dimethyl-4-*n*-propyl **(180)** is hydrolysed with an aqueous mineral acid at various temperatures and the diol **(16)** was obtained and was reacted with the ketone **(181)** to yield propiconazole **(9)**. This reaction consists of refluxing the reactants for several hours, while azeotropically removing water in a suitable solvent such as toluene or xylene, preferably in the presence of an alcohol and a strong acid.


CH2CH2CH3
O
O
H3C
CH3
(180)
HCl/heat
OH
OH
(16)
+
Cl
O
CH2
N
N
N
Cl
(181)
butanol
toluene
acid
CH2CH2CH3
Cl
O
O
CH2
N
N
N
Cl
(9)

Scheme 58

(iii) Agriguard technical bulletin

A technical bulletin from Agriguard Ltd. proposes the following synthesis of propiconazole (scheme 59), without any reaction procedures^{36}. Step one is the ketalisation of ethanone-1-(2,4-dichlorophenyl)**(17)** to yield 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl **(182)**. This ketal **(182)** is then brominated to yield 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-bromomethyl-4-*n*-propyl **(18)** followed by nucleophlic substitution with the potassium or sodium salt of 1,2,4-triazole **(8)** to yield propiconazole **(9)**.



Scheme 59

1.9.3 Conclusion

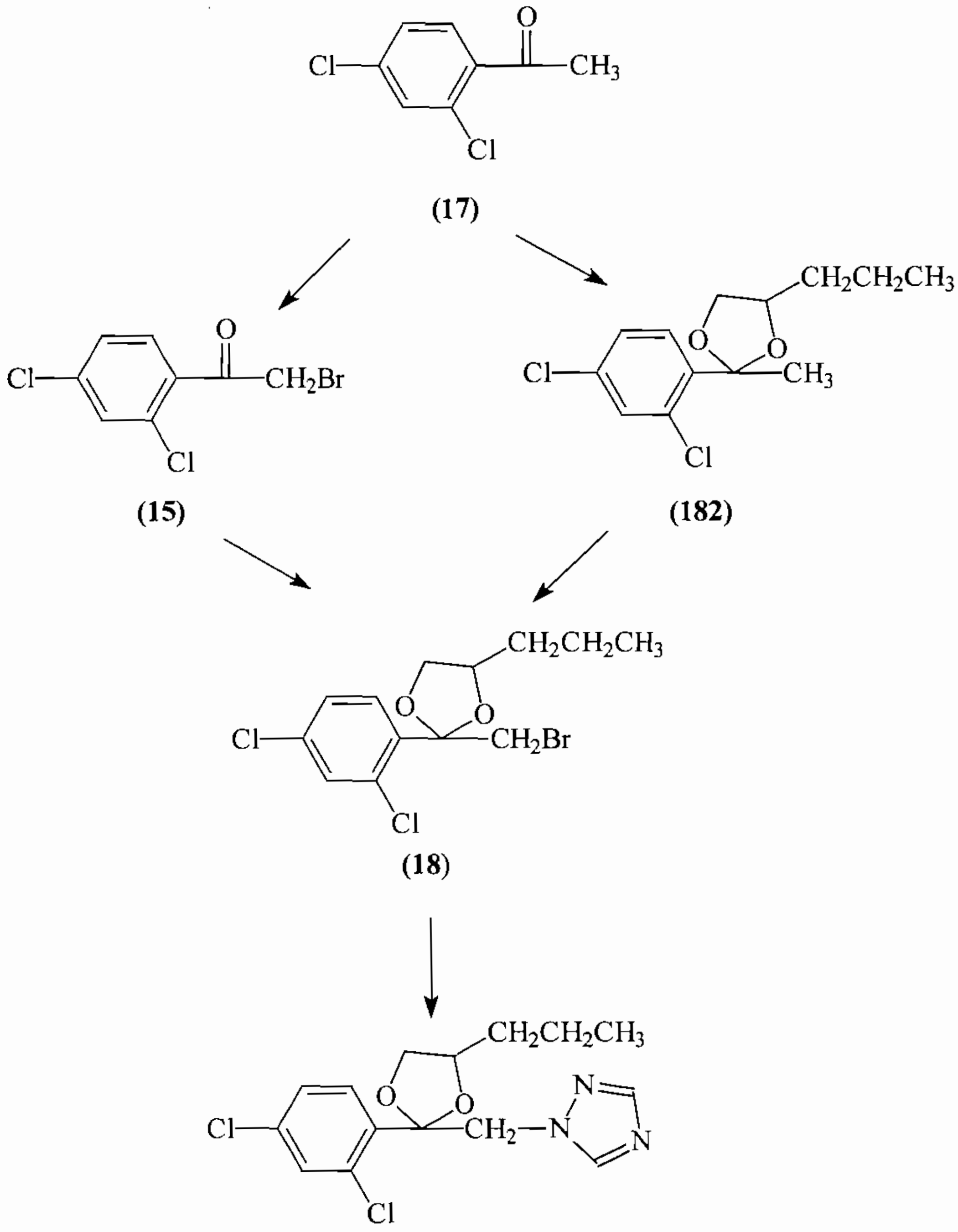
Of the four possible synthetic routes discussed above two were chosen for the investigation of the synthesis of propiconazole **(9)**. The first was the Ciba-Geigy route and the second was the route proposed in the Agriguard technical bulletin[33,36]. The Ciba-Geigy route was chosen because this route was already in existence and is therefore known to be economically feasible and it was therefore possible to compare process yields with the literature yields. Another reason to choose these two processes is that both the Ciba-Geigy process and the process outlined in the Agriguard technical bulletin utilised the same commercial available starting material ethanone-1-(2,4-dichlorophenyl)**(17)**.

Chapter 2

Disscussion

2.1 Synthesis of propiconazole

Propiconazole **(9)** was synthesised from ethanone-1-(2,4-dichlorophenyl)**(17)** in a three stage process via 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-bromomethyl-4-*n*-propyl **(18)** as illustrated in scheme 60[31,33-37].



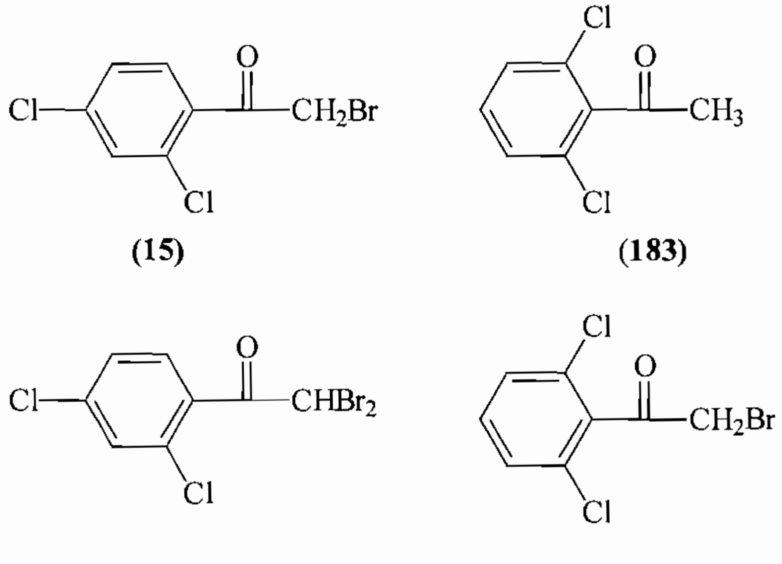
Scheme 60

Ethanone-1-(2,4-dichlorophenyl)**(17)** was brominated to yield ethanone-2-bromo-1-(2,4-dichlorophenyl)**(15)** which then underwent a condensation reaction with 1,2-pentanediol **(16)** in the presence of an acid catalyst to yield 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-bromomethyl-4-*n*-propyl **(18)**[31,33-35]. An alternative preparation of **(18)** involved the conversion of ethanone-1-(2,4-dichlorophenyl)**(17)** to 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl **(182)** by condensation with 1,2-pentanediol **(16)** followed by bromination in dichloromethane at 35°C[36].

In the final stage 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-bromomethyl-4-*n*-propyl **(18)** underwent a nucleophilic substitution reaction with the sodium or potassium salt of 1H-1,2,4-triazole **(8)** to yield 1-[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-ylmethyl]-1H-1,2,4-triazole (propiconazole)**(9)**. The process outlined by Ariguard was then scaled-up to 2-litres in order to try and evaluate any problems that might occur from a future industrial scale-up. Propiconazole **(9)** and the intermediate products were isolated and characterised by boiling points, NMR, FTIR and GC-MS.

2.2 Synthesis of ethanone-2-bromo-1-(2,4-dichlorophenyl) from ethanone-1-(2,4-dichlorophenyl)

Ethanone-1-(2,4-dichlorophenyl)**(17)** was brominated using bromine in acetic acid in a 1:2 mole ratio of ethanone-1-(2,4-dichlorophenyl)**(17)** to bromine. Hydrogen bromide gas was produced as a by-product of the reaction. The product yield was 75%, while the reported yield was 75%[31,33-35,103,104]. This reaction was monitored on GC-MS and the product **(15)** had a retention time of 15:51 minutes. Three impurities ethanone-1-(2,6-dichlorophenyl)**(183)**, ethanone-2,2-dibromo-1-(2,4-dichlorophenyl)**(184)** and ethanone-2-bromo-1-(2,6-dichlorophenyl)**(185)**, figure 2.2.1 were identified on GC-MS. The retention times of these impurities were 9:52, 19:38 and 15:36 minutes respectively. The starting material ethanone-1-(2,4-dichlorophenyl)**(17)** was also identified and had a retention time of 10:17 minutes. The mole ratio of ethanone-1-(2,4-dichlorophenyl)**(17)** to bromine was altered to 1:2.05 in order to try and optimise the yield of the desired product **(15)**. The result was the formation of more of the ethanone-2,2-dibromo-1-(2,4-dichlorophenyl)**(184)** impurity.



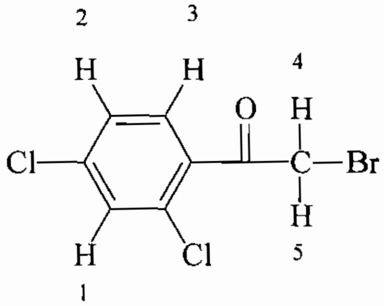
(15) **(183)**

(184) **(185)**

Figure 2.2.1

Spectral analysis of the product **(15)** revealed the presence of carbonyl stretching (C=O) at 1700.0cm^{-1} in the infrared, whereas the starting material ethanone-1-(2,4-dichlorophenyl)**(17)** had carbonyl stretching present at 1696.2cm^{-1}. The ^{1}HNMR spectra of **(15)**(figure 2.2.2) had the expected integration of 3:2 protons, three aromatic protons and two hydrogens on the bromomethyl group. A CH$_2$Br peak was present at δ4.503ppm

(2H, s, H-4, H-5) and there were three sets of peaks at 7.543-7.573ppm (1H, d, J=8.37Hz, H-3), 7.461-7.478ppm (1H, d, J=1.97Hz, H-1), 7.340-7.374ppm (1H, dd, J=1.97, 8.37Hz, H-2).

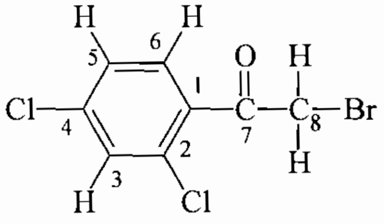


(15)

Figure. 2.2.2

The signals from H-1 and H-3 were doublets as both H-1 and H-3 were coupled with H-2. The signal from H-2 was a double doublet as H-2 was coupled to both H-1 and H-3.

There were eight peaks in the ^{13}CNMR spectra (figure 2.2.3) as there were eight carbons in different chemical enviroments present in the molecule. The following peaks were present on ^{13}CNMR at 192.69ppm (C=O, C-7), six peaks due to the aromatic carbons at 138.51ppm (C-4), 134.17ppm (C-1), 132.41ppm (C-2), 131.47ppm (C-3), 130.00ppm (C-6), 127.55ppm (C-5) and a peak at 34.52ppm (CH_2Br, C-8).



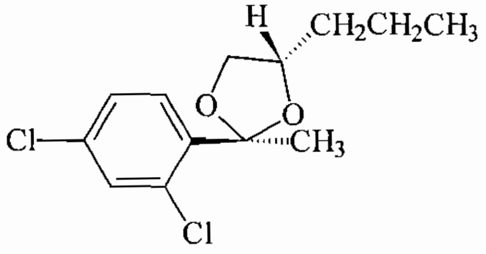
(15)

Figure 2.2.3

2.3 Synthesis of 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl from ethanone-1-(2,4-dichlorophenyl)

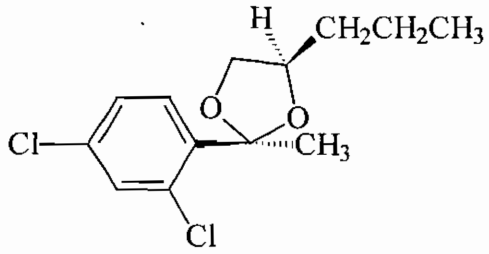
Ethanone-1-(2,4-dichlorophenyl)(**17**) in toluene underwent a condensation reaction with 1,2-pentanediol (**16**) using an acid catalyst with a mole ratio of 1:1.1. The catalyst was *p*-toluenesulphonic and the water formed as a by-product of the reaction was removed using a Dean & Stark apparatus[105]. The crude product was washed with 10% sodium carbonate solution in order to remove any traces of the acid catalyst. 1,3-Dioxolanes are stable compounds but they are sensitive to acids and may hydrolyse back to the ketone from which they were derived in the presence of an acid. For similar reasons anhydrous sodium sulphate was chosen as the most suitable drying agent as magnesium sulphate was not suitable for use with compounds sensitive to acid. The final product yield was 80%.

The progress of the reaction was monitored by the quantity of water driven off or by monitoring the disappearance of the carbonyl stretching of ethanone-1-(2,4-dichlorophenyl (**17**) at 1696.2cm^{-1} in the infrared. The reaction was also monitored on GC-MS and the retention times for ethanone-1-(2,4-dichlorophenyl)(**17**) and 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl (**182**) were 10:17 and 18:05 minutes respectively. Only one peak was present for each of these compounds although two peaks were expected for 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl (**182**) as this compound contained two chiral centres and had four enatiomers as illustrated in figure 2.3.1.



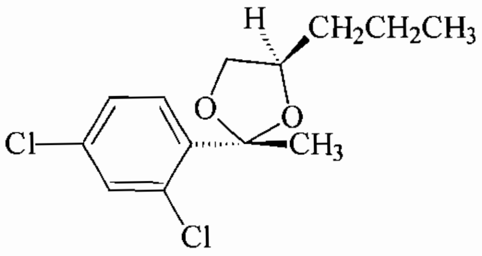
(2S, 4R)

(182a)



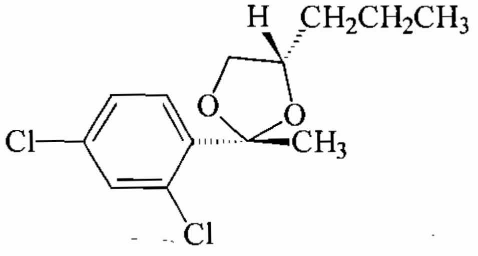
(2S, 4S)

(182b)



(2R, 4S)

(182c)

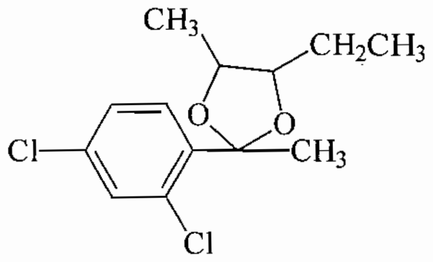


(2R, 4R)

(182d)

Figure. 2.3.1

Six impurity peaks were identified on the GC-MS with retention times 9:52, 10:17, 16:21, 16:25, 17:06, 17:26 minutes respectively. The first two peaks were identified as ethanone-1-(2,6-dichlorophenyl)(**183**) and ethanone-1-(2,4-dichlorophenyl)(**17**)(figure 2.2.1) and the other four impurity peaks were identified as 1,3-dioxolane-2-(2,4-dichlorophenyl)-2,5-dimethyl-4-ethyl (**186**)(figure 2.3.2).



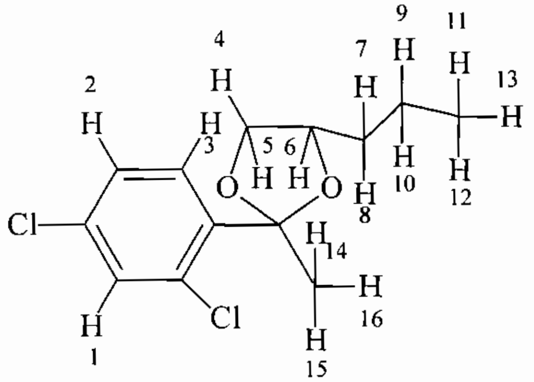
(186)

Figure 2.3.2

Spectral analysis of the main product (**182**) (distilled fraction with a boiling point range of 130-132^{0}C, 3.5mmHg) revealed that there was no carbonyl stretching band present at 1696.2cm^{-1} in the infrared indicating that no unreacted ethanone-1-(2,4-

dichloroacetophenone)(**17**) remained and the four strong characteristic ring stretching bands of 1,3-dioxolane[106] appeared at 1196, 1149, 1096 and 1031cm^{-1}.

The ^{1}HNMR spectrum (figure 2.3.3) had the expected integration of 3:3:3:4:3. The following peaks were present 7.569-7.649ppm (1H, dd, J=8.37Hz, H-3), 7.379-7.400ppm (1H, d, J=1.97Hz, H-1), 7.192-7.299ppm (1H, dd, J=1.97, 8.37Hz, H-2), 4.149-4.268ppm, 3.819-3.915ppm, 3.575-3.635ppm, 3.301-3.350ppm (3H, 4m, H-4, H-5, H-6), 1.725, 1.793ppm (3H, 2s, H-14, H-15, H-16), 1.260-1.724ppm (4H, m, H-7, H-8, H-9, H-10), 0.890-0.981ppm (3H, dt, J=7.14Hz, H-11, H-12, H-13).



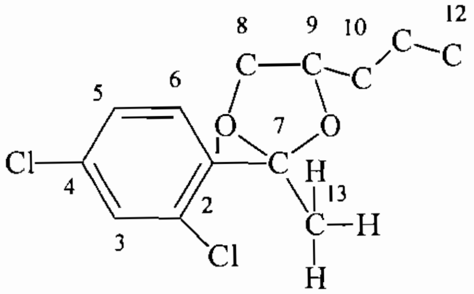
(182)

Figure 2.3.3

Unlike H-1 and H-2, H-3 was located in a different magnetic environment in each of the diasteromers figure 2.3.1. H-1 and H-2 happened to be in the same magnetic environment and showed only one signal. The ratio of the two signals for H-3 was 1:2, implying that the ratio of diasteromers was 1:2. The four multiplets from the three hydrogens on the dioxolane ring H-5, H-6, H-7 were the result of overlap between doublets and multiplets integrating for 2H and 1H. These multiplets 4.149-4.268ppm, 3.301-3.350ppm and 3.819-3.915ppm, 3.575-3.635ppm, were also present in the same 1:2 diasteromeric ratio as the signals from H-3. The methyl group H-14, H-15, H-16 consisted of two singlets at 1.725ppm and 1.793ppm representing the two sets of diasteromers again in the ratio of 1:2 as before. Similarly two triplets were present between 0.890-0.981ppm representing H-11, H-12, H-13. The signals from the four remaining hydrogens in the propyl group H-7, H-8, H-9, H-10 were more complicated and a complex multiplet from 1.260-1.724ppm was the result.

The following peaks were present in the ^{13}CNMR (figure 2.3.4), 141.50ppm (C-4), 140.39ppm (C-4), 134.67ppm (C-1), 134.54ppm (C-1), 133.54ppm (C-2), 133.46ppm

(C-2), 131.51ppm (C-3), 131.35ppm (C-3), 130.20ppm (C-6), 129.76ppm (C-6), 127.67ppm (C-5), 127.62ppm (C-5), 108.61ppm (C-7), 108.57ppm (C-7), 77.75ppm (C-9), 76.58ppm (C-9), 70.43ppm (C-8), 69.87ppm (C-8), 36.27ppm (C-13), 36.09ppm (C-13), 26.27ppm (C-10), 26.18ppm (C-10), 19.95ppm (C-11), 19.69ppm (C-11), 14.33ppm (C-12).



(182)

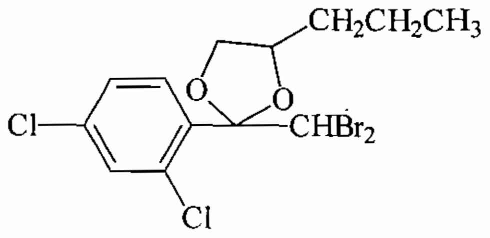
Figure 2.3.4

Diasteromers were clearly present, as there was two sets of splitting with slightly different chemical shifts present for each carbon. The molecule contained thirteen carbon atoms and a total of twenty-five lines were present. Only one peak was present for C-12 although two peaks were expected, this was the result of the two C-12 peaks overlapping so they appeared as only one peak. The absence of C-1 and C-7 on the DEPT spectra confirmed that these carbon atoms were quaternary carbons. DEPT spectra also identified as expected four CH_3, six CH_2, and four CH groups. The C-9 and C-8 carbons produced signals at 77.75ppm, 76.58ppm 70.43ppm 69.87ppm, due to their proximity to the oxygen atoms on the 1,3-dioxolane ring. Similarly C-13 a methyl group, produced two signals at 36.27ppm and 36.09ppm also pulled downfield due to the nearby oxygens. The C-10, C-11, C-12 carbons were pulled downfield by proximity to the 1,3-dioxolane ring.

2.4 Synthesis of 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-bromomethyl-4-*n*-propyl from ethanone-2-bromo-1-(2,4-dichlorophenyl)

Ethanone-2-bromo-1-(2,4-dichlorophenyl)**(15)** underwent a condensation reaction with 1,2-pentanediol **(16)** to form 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-bromomethyl-4-*n*-propyl **(18)** similar to the condensation reaction between ethanone-1-(2,4-dichlorophenyl)**(17)** and 1,2-pentanediol **(16)**. The reaction was catalysed with *p*-toluenesulphonic acid although other catalysts such as hydrochloric acid may also have been used and a Dean and Stark apparatus was employed for the removal of the water. The product yield was 78%, while the reported yield was 78%[31,33-36].

This reaction was monitored using infrared spectroscopy by monitoring the disappearance of the carbonyl stretching frequency of ethanone-2-bromo-1-(2,4-dichlorophenyl)**(15)** at 1700.0cm^{-1}. The reaction was also monitored on GC-MS and the retention times for ethanone-2-bromo-1-(2,4-dichlorophenyl)**(15)** and 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-bromomethyl-4-*n*-propyl **(18)** were 15:51 and 23:21, 23:31 minutes respectively. On GC-MS two peaks with identical mass spectra and molecular ions of m/z 353 were present for 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-bromomethyl-4-*n*-propyl **(18)** corresponding to the two diasteromeric pairs of enantiomers. Unlike 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl **(182)** the diasteromers were easily resolved due to the additional effect of the heavy bromine atom on the methyl group. Eight impurities, namely ethanone-1-(2,4-dichlorophenyl)**(17)**, ethanone-1-(2,6-dichlorophenyl)**(183)**, ethanone-2-bromo-1-(2,4-dichlorophenyl)**(15)**, ethanone-2,2-dibromo-1-(2,4-dichlorophenyl)**(184)**, ethanone-2-bromo-1-(2,6-dichlorophenyl)**(185)**(figure 2.2.1), 1,3-dioxolane-2-(2,4-dichlorophenyl)-2,5-dimethyl-4-ethyl **(186)**(figure 2.3.2), 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl **(182)** and 2-(2,4-dichlorophenyl)-2,2-dibromomethyl-4-*n*-propyl-1,3-dioxolane **(187)**(figure 2.4.1) were identified on GC-MS. The retention times for these impurities were 9:17, 10:17, 15:51, 19:38, 15:36, 16:21, 16:25, 17:06, 17:26, 18:05, and 26:16, 26:32 minutes respectively.

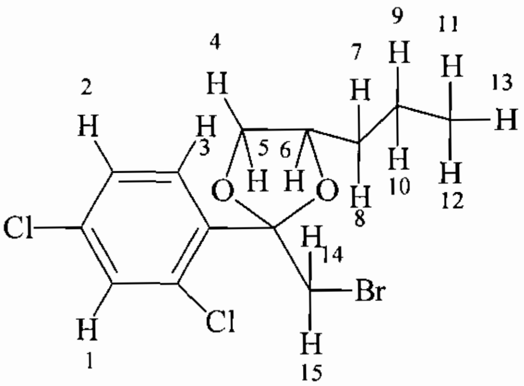


(187)

Figure 2.4.1

Spectral analysis of the main product **(18)** revealed the following characteristic 1,3-dioxolane ring stretching bands at 1189, 1141, 1105 and 1062cm^{-1} in the infrared spectrum.

The ^{1}HNMR spectrum had the expected integration of 3:5:4:3 (figure 2.4.2). The following peaks were present, 7.59-7.74ppm (1H, dd, J=8.37Hz, H-3), 7.15-7.39ppm (1H, d, J=1.97Hz, H-1), 7.22-7.26ppm (1H, dd, J=1.97, 8.37Hz, H-2), 4.37-4.41ppm, 4.28-4.32ppm, 3.95-4.04ppm, 3.70-3.78ppm 3.41-3.46ppm, (3H, 5m, H-4, H-5, H-6), 3.91ppm, 3.87ppm, 3.85ppm, 3.82ppm (2H, dd, J=11.3Hz, H-14, H-15), 1.27-1.85ppm (4H, m, H-7, H8, H-9, H-10), 0.89-0.99ppm (3H, dt, J=7.14Hz, H-11, H-12, H-13).

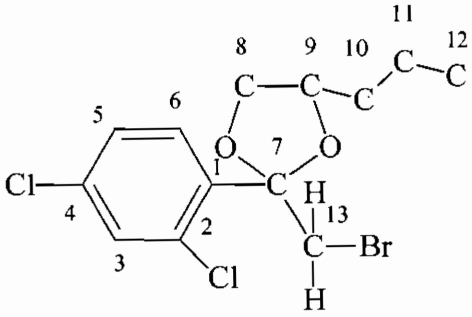


(18)

Figure 2.4.2

The ^{1}HNMR spectrum of this compound was very similar to the spectrum of 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl **(182)**. Once again the seven hydrogens on the propyl side-chain gave signals of two triplets H-11, H-12, H-13 and a complex multipet H-7, H-8, H-9, H-10. A similar splitting pattern was also observed on the phenyl ring where once again H-3 was in a different magnetic environment in the diasteromers and gave two signals whereas H-1 and H-2 gave only one signal. The ratio of diasteromers was approximately 1:2. The two singlets present at 1.725, 1.793ppm in

1,3-dioxolane-2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl **(182)** were no longer present. The non-equivalent geminal H-14 and H-15 had a large coupling constant of 11.3Hz yielding two sets of overlapping double doublets. It was not possible to integrate the doublets due to the overlap with the multiplets from the three dioxolane ring hydrogens (H-4, H-5, H-6) but integrating over this region from 3.70ppm to 4.41ppm gave an integration of five protons corresponding to the three dioxolane hydrogens (H-4, H-5, H-6) and the two hydrogens from the bromomethyl group (H-14, H-15). The following peaks were present in the ^{13}CNMR (figure 2.4.3) spectra, 137.74ppm (C-4), 137.03ppm (C-4), 135.68ppm (C-1), 135.58ppm (C-1), 133.64ppm (C-2), 133.54ppm (C-2), 131.56ppm (C-3), 131.46ppm (C-3), 131.40ppm (C-6), 131.31ppm (C-6), 127.81ppm (C-5), 127.72ppm (C-5), 107.72(C-7), 107.59(C-7), 79.36(C-9), 77.71(C-9), 71.42(C-8), 71.18(C-8), 36.88(C-13), 36.68(C-13), 35.73(C-10), 35.13(C-10), 19.68(C-11), 19.64(C-11), 14.25(C-12), 14.21(C-12).



(18)

Figure. 2.4.3

The carbon spectrum of **(18)** was very similar to the spectrum of 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl **(182)** with the exception that C-13 was a bromomethyl group and was pulled downfield by the bromine atom and had two signals at 36.88 and 36.68ppm. Overall the addition of the bromine resulted in all the signals being shifted downfield.

2.5 Synthesis of 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-bromomethyl-4-*n*-propyl from 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl

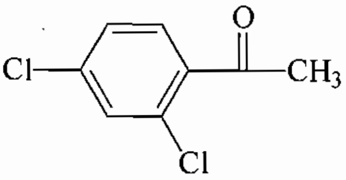
1,3-Dioxolane-2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl (**182**) was brominated using bromine in dichloromethane at 35°C in a ratio of one mole of 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl (**182**) to two moles of bromine to yield 1,3-dioxolane -2-(2,4-dichlorophenyl)-2-bromomethyl-4-*n*-propyl (**18**) in a 80% yield. This reaction was monitored on GC-MS and the retention times for 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl (**182**) and the product 1,3-dioxolane-2-(2,4-dichloro- phenyl)-2-bromomethyl-4-*n*-propyl (**18**) were 18:05 and 23:21, 23:31 minutes respectively. The MS confirmed that the two peaks with retention times of 23:21 and 23:31 minutes were diasteromers as the peaks had identical mass spectra including molecular ion peaks at 353m/e and a base peak at 259m/e.

Spectral analysis of the product (**18**) revealed the following characteristic 1,3-dioxolane ring stretching bands at 1189, 1141, 1105 and 1062cm^{-1} in the infrared spectrum. The ^{1}HNMR spectrum (figure 2.4.2) had the expected integration of 3:5:4:3 and the following peaks were present 7.59-7.74ppm (1H, dd, J=8.37Hz, H-3), 7.15-7.39ppm (1H, d, J=1.97Hz, H-1), 7.22-7.26ppm (1H, dd, J=1.97, 8.37Hz, H-2), 4.37-4.41ppm, 4.28-4.32ppm, 3.95-4.04ppm, 3.70-3.78ppm 3.41-3.46ppm, (3H, 5m, H-4, H-5, H-6), 3.91ppm, 3.87ppm, 3.85ppm, 3.82ppm (2H, dd, J=11.3Hz, H-14, H-15), 1.27-1.85ppm (4H, m, H-7, H8, H-9, H-10), 0.89-0.99ppm (3H, dt, J=7.14Hz, H-11, H-12, H-13). The following peaks were present in the ^{13}CNMR (figure 2.4.3), 137.76ppm (C-4), 137.04ppm (C-4), 135.69ppm (C-1), 135.59ppm (C-1), 133.66ppm (C-2), 133.55ppm (C-2), 131.57ppm (C-3), 131.47ppm (C-3), 131.40ppm (C-6), 131.31ppm (C-6), 127.81ppm (C-5), 127.72ppm (C-5), 107.72ppm (C-7), 107.59ppm (C-7), 79.36ppm (C-9), 77.71ppm (C-9), 71.42ppm (C-8), 71.18ppm (C-8), 36.88ppm (C-13), 36.68ppm (C-13), 35.73ppm (C-10), 35.13ppm (C-10), 19.68ppm (C-11), 19.58ppm (C-11), 14.25ppm (C-12), 14.21ppm (C-12).

^{1}HNMR, IR and GC-MS confirmed that the product 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-bromomethyl-4-*n*-propyl (**18**) prepared from ethanone-2-bromo-1-(2,4-dichlorophenyl)(**15**) was identical with the product (**18**) prepared from 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl (**182**).

2.6 Synthesis of 1-[2-(2,4-dichlorophenyl)-4-*n*-propyl-1,3-dioxolan-2-ylmethyl]-1H-1,2,4-triazole (propiconazole)

This step was common to both of the processes investigated[33,36]. 1,3-Dioxolane-2-(2,4-dichlorophenyl)-2-bromomethyl-4-*n*-propyl **(18)** underwent a nucleophilic substitution reaction with a 1,2,4-triazole potassium or sodium salt **(8)** at 160°C for 15-16hrs. in an aprotic solvent. The product yield was 70% while the reported yield was 70%[31,33-36]. This reaction was monitored on GC-MS and the retention times for 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-bromomethyl-4-*n*-propyl **(18)** and 1-[2-(2,4-dichlorophenyl)-4-*n*-propyl-1,3-dioxolan-2-ylmethyl]-1H-1,2,4-triazole (propiconazole)**(9)** were 23:21, 23:31 and 27:49, 28:02 minutes respectively. The MS confirmed that the two peaks with retention times of 27:49 and 28:02 minutes were diasteromers of propiconazole **(9)**. In total eleven impurities were identified at trace levels in the technical product as illustrated in figure 2.6.1. These impurities are discussed further in section 2.7.



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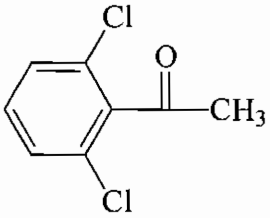

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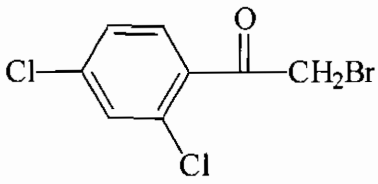

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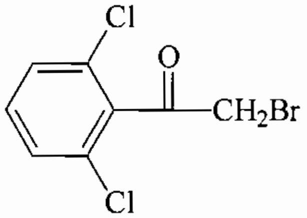

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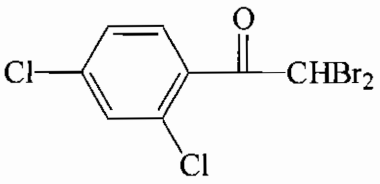

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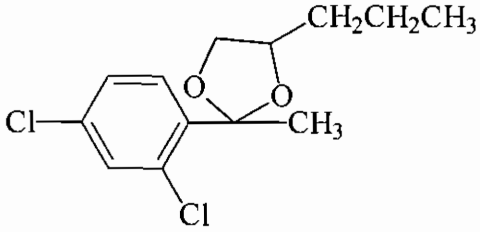

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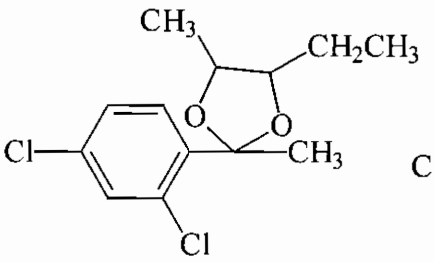

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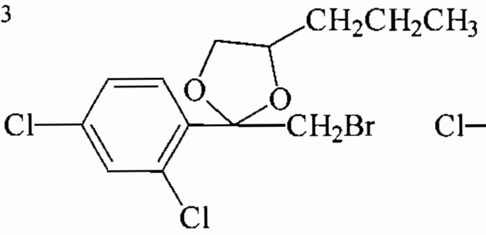

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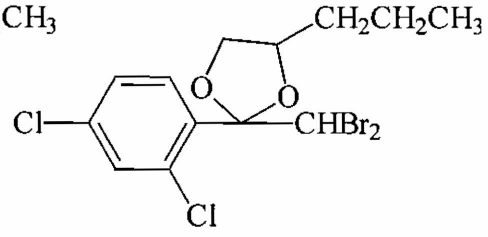

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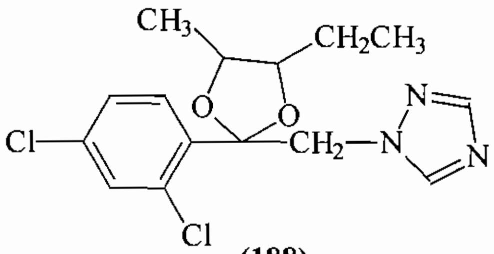

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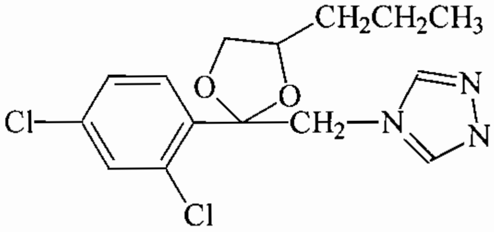
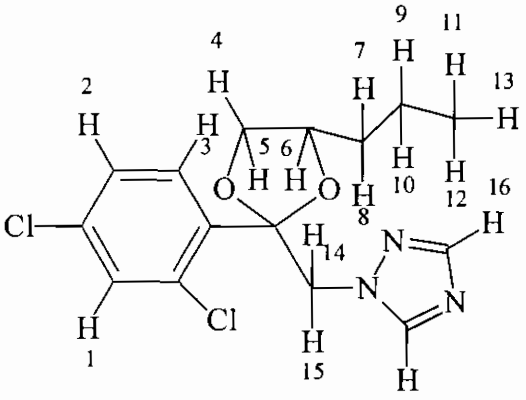


(9)

Figure. 2.6.1

Although the Ciba-Geigy process employed N,N-dimethyl-formamide as the solvent, dimethyl-sulphoxide was chosen, as it is safer to the environment[107]. The triazole salt **(8)** can either be purchased directly or either prepared using potassium or sodium hydroxide and 1H-1,2,4-triazole **(14)** at 45°C in dimethyl-sulphoxide in a mole ratio of 1:1.2. The salt formed when all the potassium hydroxide had been completely dissolved and was used in situ. A commercially available sodium 1H-1,2,4-triazole salt **(8)** was also used and this reduced the reaction time to 15hrs. Spectral analysis of the product **(9)** revealed the following characteristic 1,3-dioxolane ring stretching bands at 1209, 1137, 1105, 1049cm^{-1} in the infrared spectrum.

The ^{1}HNMR spectra (figure 2.6.2) had the expected integration of 2:3:2:3:4:3. The following peaks were present, 8.16, 8.19ppm (1H, 2s, H-16), 7.89,7.90ppm (1H, 2s, H-17), 7.52-7.58ppm (1H, dd, J=8.37Hz, H-3), 7.43-7.74ppm (1H, d, J=1.97Hz, H-1), 7.20-7.24ppm (1H, 2dd, 1.97, 8.86Hz, H-2), 4.78ppm, 4.73ppm, 4.70ppm, 4.69ppm (2H, 2dd, J=14.3Hz, H-14, H-15), 3.87-4.00ppm (m), 3.68-3.76ppm (m), 3.31-3.36ppm (m), 3.14-3.20ppm (t, J=8.12Hz), (3H, H-4, H-5, H-6), 1.21-1.90ppm (4H, m, H-7, H-8, H-9, H-10), 1.19-1.54ppm (3H, dt, J=7.1Hz, H-11, H-12, H-13).

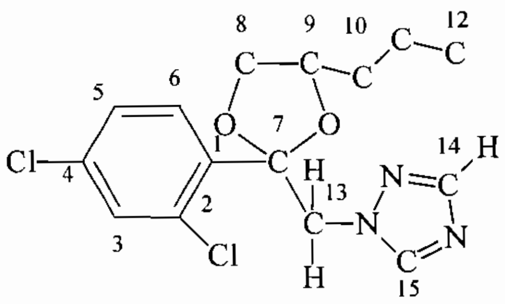


(9)

Figure 2.6.2

The triazole ring in propiconazole (**9**) contains hydrogens H-16, H-17 and these hydrogens appeared as singlets[34]. Two singlets are present for each hydrogen due to the existence of diasteromers. The H-14 and H-15 hydrogens are non-equivalent with large coupling constants of 14.3Hz yielding two sets of double doublets overlapping at 4.78ppm, 4.73ppm, 4.70ppm and 4.69ppm. The doublets at 4.78 and 4.69ppm represented one diasteromer and the signals at 4.73 and 4.70ppm represented the other. These peaks were down field from the dioxolane signals due to the proximity of the nitrogen atoms on the triazole ring and also the proximity of the 1,3-dioxolane ring. As expected these four overlapping signals integrated for two hydrogens. Similar to the splitting pattern of 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl (**182**) the three dioxolane ring hydrogens in propiconazole (**9**) H-4, H-5, H-6 gave three multiplets and one triplet. These four signals consisted of overlapping doublets and multiplets and integrated for two and one hydrogens. Once again the signals showed a 1:2 diasteromer ratio. The propyl side chain gave a complex multiplet for H-7, H-8, H-9, H-10 at 1.21-1.90ppm and two triplets for H-11, H-12, H-13 at 1.19-1.54ppm. On the phenyl ring both H-3 and H-2 are in different magnetic environments than H-1 in the two diasteromers and the result was that there was only one signal for H-1 and two signals for H-3 and H-2. The diasteromer ratio was 1:2.

The following peaks were present in the ^{13}CNMR as illustrated in figure 2.6.3, 151.73ppm (C-14), 151.64ppm (C-14), 145.98ppm (C-15), 145.85ppm (C-15),137.59ppm (C-4), 136.84ppm (C-4), 135.81ppm (C-1), 134.68ppm (C-1), 134.01ppm (C-2), 133.94ppm (C-2), 131.65ppm (C-3), 131.46ppm (C-3), 131.05ppm (C-6), 130.77ppm (C-6), 127.92ppm (C-5), 127.82ppm (C-5), 107.83ppm (C-7), 107.77ppm (C-7), 78.84ppm (C-9), 77.56ppm (C-9), 70.83ppmm (C-8), 70.78ppm (C-8), 54.84ppm (C-13), 54.68ppm (C-13), 35.56ppm (C-10), 35.34ppm (C-10), 19.67ppm (C-11), 19.58ppm (C-11), 14.16ppm (C-12), 14.12ppm (C-12).



(9)

Figure 2.6.3

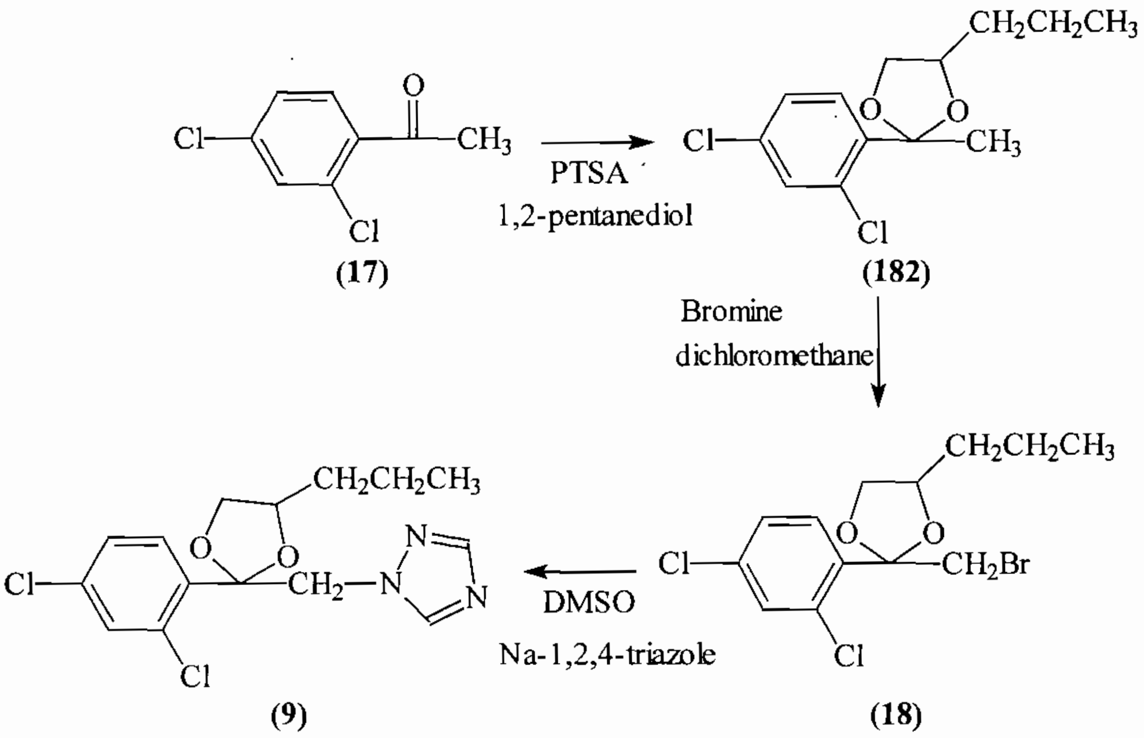
The carbon spectra was similar to the other 1,3-dioxolane derivatives **(182)** and **(18)**, however two additional carbon atoms C-14, C-15 from the triazole ring were present and this resulted in four signals at 151.73ppm, 151.64ppm, 145.98ppm and 145.85ppm representing the two sets of diasteromers. Overall the effect of the triazole ring was to pull the signals of all the carbon atoms downfield particularly C-13 which lay in close proximity to the triazole ring and had two signals at 54.84ppm and 54.68ppm. Diasteromers were also clearly present as each carbon produced two signals. DEPT spectra indentified 2CH_3, 8CH_2, and 12CH groups. The absence of four signals in the DEPT spectra indicated two quaternary carbons[108].

2.7 Scale-up of the reaction process

Table 2.7.1 summarises the product yields from the two alternative processes. These results indicated that the process outlined by Agriguard was the process with the highest overall yield from ethanone-1-(2,4-dichlorophenyl)**(17)** 45% compared to 41% with the Ciba-Geigy process[31,33-36]. The results of the scale up of the Agriguard process (scheme 61) are illustrated in table 2.7.2.

Ciba-Geigy process	**Scale (g)**	**Yield (g)**	**Yield (%)**	**Lit. (%)**
Stage 1	10	10.20	72	76
	25	26.58	75	
	50	53.20	75	
Stage 2	10	10.56	80	80
	25	26.08	79	
	50	52.83	80	
Agriguard process	**Scale (g)**	**Yield (g)**	**Yield (%)**	**Lit. (%)**
Stage 1	10	11.64	80	-
	25	29.10	80	
	100	119.31	82	
	200	238.62	82	
Stage 2	10	9.78	76	-
	25	25.75	80	
	100	102.98	80	
	200	205.93	80	
Stage 3 Common to both processes	10	5.31	70	70
	100	67.62	70	
	200	137.18	68	

Table 2.7.1 Comparison of process yields



Scheme 61

Step	Scale (g)	Yield (g)	Yield (%)
1	250g	290	80
2	285	277	76
3	270	135.6	51

Table 2.7.2 2-litre scale-up process yields.

The synthesis of propiconazole **(9)** was scaled up to a 2-litres process, requiring 250g of ethanone-1-(2,4-dichlorophenyl)**(17)** and a number of difficulties were encountered.

Ethanone-1-(2,4-dichlorophenyl)**(17)** was converted to 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl **(182)**(290 g) following the procedure outlined in section 2.3. A 2-litre flask with 900cm^3 of solvent was required. No major problems were encountered with the scale up of the first stage of the process. NMR and GC-MS were used to confirm the purity of the product. The final product yield was 290g, 80% and this product was carried through to step two of the reaction process.

1,3-Dioxolane-2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl **(182)**(285g) was brominated in a 3-litre reaction flask using bromine (165.8 g) with dichloromethane (600g) to yield 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-bromomethyl-4-*n*-propyl (**18**). A three-litre reaction flask was utilised due to the build-up of pressure from the hydrogen bromide gas produced as a by-product of the reaction. An efficient fume cupboard was required for this reaction as a great quantity of hydrogen bromide gas (approximately 168 g) was produced. Even though the system was well sealed the hydrogen bromide gas had a corrosive effect on the metallic stirring motor unit. During fractional distillation the product bumped and had to be redistilled. The bumping was attributed to a large amount of product condensing through a narrow necked condenser. The final pure product fraction yielded (75%) of 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-bromomethyl-4-*n*-propyl (**18**)(277 g). The yield was slightly less then the 80% yield expected and this was attributed to the difficulties experienced during distillation.

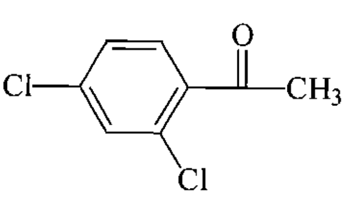
1,3-Dioxolane-2-(2,4-dichlorophenyl)-2-bromomethyl-4-*n*-propyl (**18**)(270 g) underwent nucleophilic substitution with a commercially available sodium 1,2,4-triazole salt (**8**)(84.2 g) in 1-litre of dimethyl-sulphoxide. The reaction was monitored by GC-MS and the reaction had gone to completion after 20hrs. The reaction time was 4hrs longer than expected and this was attributed to the greater volume of solvent, reagents and difficulties in heating to and maintaining the contents of the reaction flask at 160°C. The dimethyl sulphoxide was removed under vacuum and the mixture was very dark making the work-up difficult. The solution was extracted with diethyl ether and water and the diethyl ether extracts were combined and dried over anhydrous sodium sulphate. This extraction was time consuming on this large scale and one and a half litres of diethyl ether were required for the extraction. Further problems arose during distillation where several attempts had to be made to distill the product even though a mechanical stirrer and fractionating column was used. The product was an extremely thick viscous oil and as the product distilled, problems were encountered with the remaining solid inorganic waste clogging up the still head. This problem did not arise when the crude product was distilled on a smaller scale. The remaining crude product was divided into three smaller volumes and distilled to yield 135.6 g of product in 51% yield. The low yield was attributed to problems with the distillation.

One and a half litres of aqueous waste was produced and this waste contained some unreacted sodium triazole (**8**), sodium bromide and traces of dimethyl sulphoxide. The sodium triazole salt (**8**) was potentially dangerous to a marine environment and on a larger industrial scale could result in fish kills and a waste treatment procedure of aqueous waste will be required for industrial production. The trace dimethyl sulphoxide could easily be removed by distillation from the aqueous fraction.

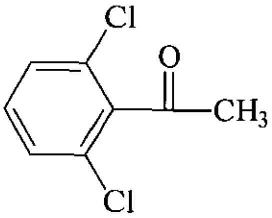
2.8 Synthesis of impurities

Propiconazole **(9)** was synthesised in a three-stage reaction process[33,36]. Although two different synthetic routes were investigated, the same starting materials were employed with the result that the same impurities were present in both processes. The impurities in each step of the reaction process were discussed in relation to the Agriguard process. Twelve impurities were reported to form during the course of the reaction process and these impurities are illustrated in figure 2.8.1[36]. Two of these impurities **(182)** and **(18)** were reaction intermediates. The starting material for the process was ethanone-1-(2,4-dichlorophenyl)**(17)** and according to supplier specification was 96% pure. The main impurity was an undesired isomer ethanone-1-(2,6-dichlorophenyl)**(183)** which was formed during the Friedel Crafts reaction utilised in the synthesis of **(17)**. Commercial standards were readily available for both of these impurities so it was not necessary to synthesise them. 1,3-Dioxolane-2-(2,4-dichlorophenyl)-2,5-dimethyl-4-ethyl **(186)** was formed from 2,3-pentanediol **(189)**, an impurity present in 1,2-pentanediol **(16)**. Traces of ethanone-1-(2,4-dichlorophenyl)**(17)**, ethanone-1-(2,6-dichlorophenyl)**(183)**, 1,3-dioxolane -2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl **(182)** and 1,3-dioxolane-2-(2,4-dichlorophenyl)-2,5-dimethyl-4-ethyl **(186)** were brominated and formed ethanone-2-bromo-1-(2,4-dichlorophenyl)**(15)**, ethanone-2,2-dibromo-1-(2,4-dichlorophenyl)**(184)** and ethanone-2-bromo-1-(2,6-dichlorophenyl)**(185)**, 1,3-dioxolane-2-(2,4-dichlorophenyl)-2,2-dibromomethyl-4-*n*-propyl **(187)** and 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-bromomethyl-4-ethyl-5-methyl **(190)**.

1,3-Dioxolane-2-(2,4-dichlorophenyl)-2-bromomethyl-4-ethyl-5-methyl **(190)** underwent a nucleophilic substitution reaction with the triazole salt **(8)** and formed 1-[2-(2,4-dichlorophenyl)-4-ethyl-5-methyl-1,3-dioxolan-2-ylmethyl]-1H-1,2,4-triazole **(188)**. 1,3-Dioxolane-2-(2,4-dichlorophenyl)-2-bromomethyl-4-*n*-propyl **(18)** underwent nucleophlic substitution on the 4-postion of the triazole ring resulting in the formation of 4-[2-(2,4-dichlorophenyl)-4-ethyl-5-methyl-1,3-dioxolan-2-ylmethyl]-1H-1,2,4-triazole **(10)**, a structural isomer of propiconazole with reduced biological activity see figure 2.8.1[31].



(17)



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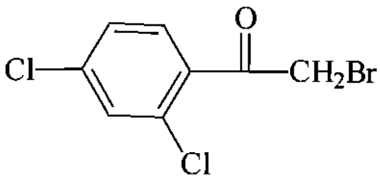

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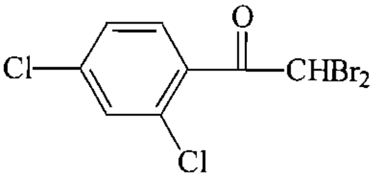

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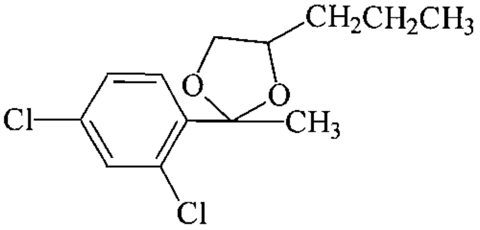

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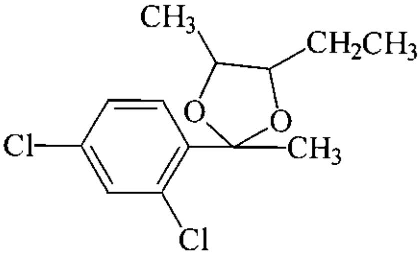
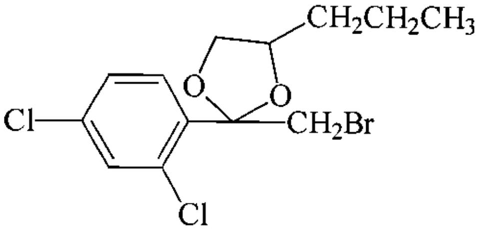


(186)



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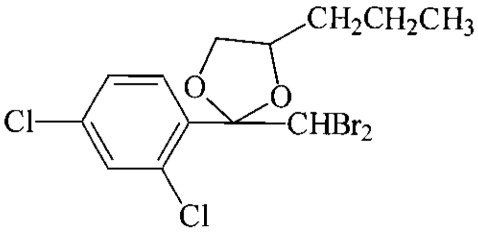

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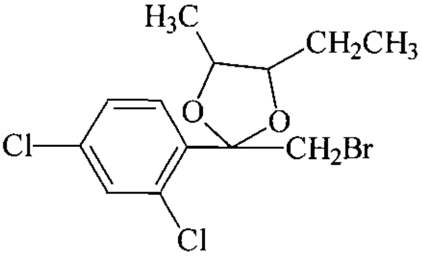

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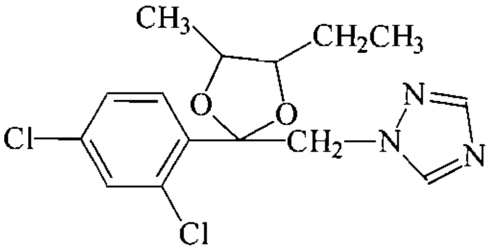

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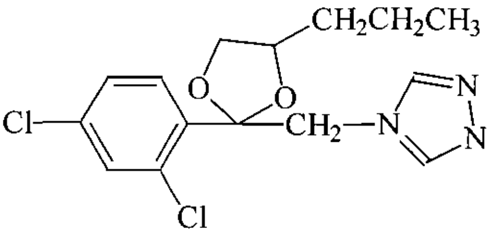
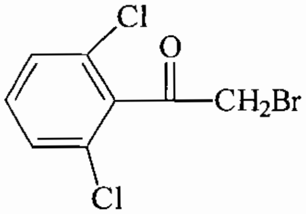


(10)

Figure 2.8.1

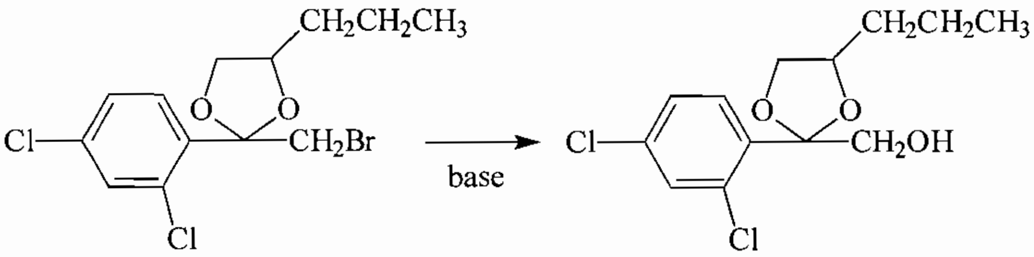
Ethanone-2-bromo-1-(2,6-dichlorophenyl)**(185)** figure 2.8.2, had not been previously identified as an impurity in the reaction process.



(185)

Figure 2.8.2

Finally one impurity reported in the technical propiconazole was eliminated by the use of a commercially available sodium triazole salt **(8)** as opposed to preparing the salt without isolation from 1,2,4-triazole **(14)** and potassium or sodium hydroxide in an aprotic solvent. 1,3-Dioxolane-2-(2,4-dichlorophenyl)-2-bromomethyl-4-*n*-propyl **(18)** was reacted in the presence of a base such as sodium hydroxide to form 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-hydroxymethyl-4-*n*-propyl **(191)** as illustrated in scheme 62.



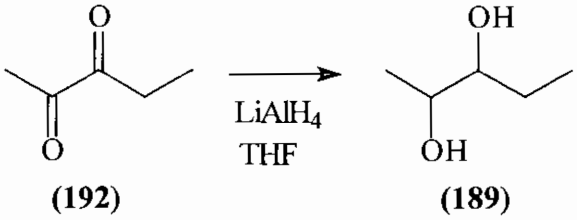
(18) **(191)**

Scheme 62

A commercialy available sodium triazole salt **(8)** was used and no evidence of impurity **(191)** was found.

2.9 Synthesis of 2,3-pentanediol from 2,3-pentanedione

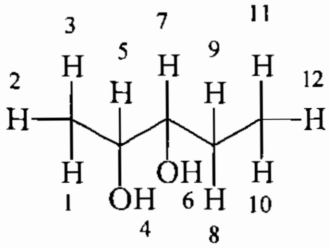
2,3-Pentanediol **(189)** was present as an impurity in.1,2-pentanediol **(16)** and resulted in the formation of two impurities **(186)** and **(188)** figure 2.8.1. 2,3-Pentanediol **(189)** was prepared by the reduction of 2,3-pentanedione **(192)** using lithium aluminium hydride in dry tetrahydrofuran as illustrated in scheme 63[109].



Scheme 63

The product yield was 36% and the lower than expected yield may have been due to solubility problems. A high product yield was not necessary as the objective was merely to obtain a sample of 2,3-pentanediol **(189)** to prepare a synthetic standard of the impurity 1,3-dioxolane-2-(2,4-dichlorophenyl)-2,5-dimethyl-4-ethyl **(186)** for analysis and for registration purposes.

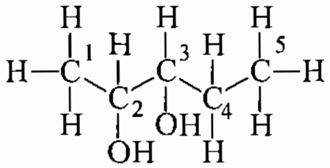
Spectral analysis of the product **(189)** revealed the presence of a broad hydroxyl stretching band at 3390cm^{-1} in the infrared spectrum and there was no trace of carbonyl stretching (C=O) present at 1700cm^{-1} as in the diketone **(192)**. ^{1}HNMR of the 2,3-pentanediol **(188)**(figure 2.9.1) had an integration of 4:2:3:3. The four hydrogens on the C-2 and C-3 appeared to have overlapping signals and this multiplet integrated for four protons. The following peaks were identified at 3.151-3.850ppm (4H, m, H-4, H-5, H-6, H-7), 1.222-1.650ppm (2H, m H-8, H-9) and 1.10-1.21ppm (3H, m, H-1, H-2, H-3) and 0.935-1.200ppm (3H, m, H-10, H-11, H-12). A D_2O shake was carried out and as expected the integration changed to 2:2:3:3 by the disappearance of two protons from 3.151-3.850ppm (4H, m, H-4, H-5, H-6, H-7) confirming the presence of the two interchangeable hydrogens in the two hydroxyl groups.



(189)

Figure 2.9.1

The ^{13}CNMR spectrum (figure 2.9.2) consisted of ten lines as **(189)** contains two chiral centres C-2, C-3 and hence existed as four enatiomers, two diasteromeric pairs. These diasteromers were not chemically equivalent so they displayed slightly different chemical shifts. The following peaks were present in the ^{13}CNMR spectra, 76.14ppm (C-3), 75.82ppm (C-3), 69.41ppm (C-2), 69.07ppm (C-2), 25.51ppm (C-4), 24.68ppm (C-4), 19.09ppm (C-1), 18.66ppm (C-1), 10.43ppm (C-5) and 10.26ppm (C-5).

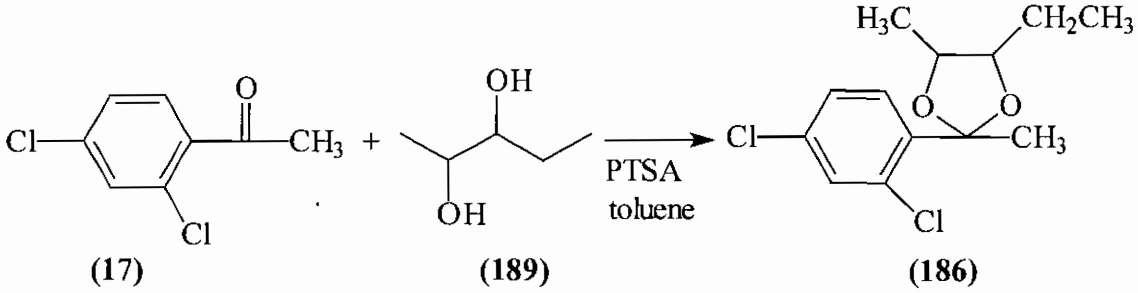


(189)

Figure 2.9.2

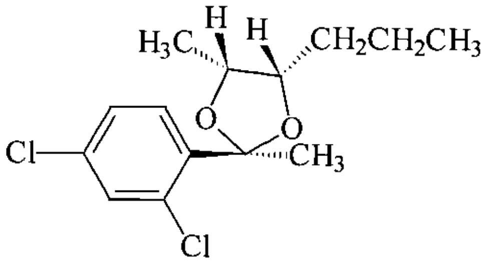
2.10 Synthesis of 1,3-dioxolane-2-(2,4-dichlorophenyl)-2,5-dimethyl-4-ethyl from ethanone-1-(2,4-dichlorophenyl)

1,3-Dioxolane-2-(2,4-dichlorophenyl)-2,5-dimethyl-4-ethyl **(186)** was prepared by a condensation reaction involving ethanone-1-(2,4-dichlorophenyl)**(17)** in toluene with 2,3-pentanediol **(189)** using an acid catalyst as illustrated in scheme 64[105].



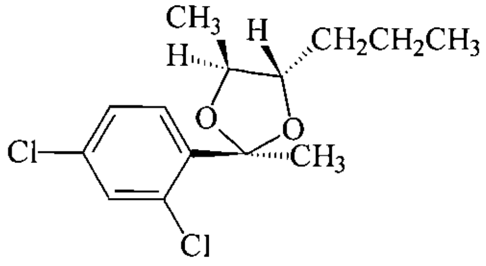
Scheme 64

A Dean & Stark apparatus removed the water formed as a by-product of the reaction and the product yield was 66%. The reaction was monitored using infrared spectroscopy by the disappearance of the carbonyl stretching of ethanone-1-(2,4-dichlorophenyl)**(17)** at 1696.2cm^{-1}. This reaction was also monitored on GC-MS and the retention times for ethanone-1-(2,4-dichlorohenyl)**(17)** and 1,3-dioxolane-2-(2,4-dichlorophenyl)-2,5-dimethyl-4-ethyl **(186)** were 10:17 **(17)** and 16:21, 16:25, 17:06, 17:26 minutes **(186)** respectively. There were four peaks on the GC-MS representing 1,3-dioxolane-2-(2,4-dichlorophenyl)-2,5-dimethyl-4-ethyl **(186)**, indicated a diasteromer ratio of aproximately 2:2:3:1. The four diasteromers are therefore present in different quantities. 1,3-Dioxolane-2-(2,4-dichlorophenyl)-2,5-dimethyl-4-ethyl **(186)** has three sterochemical centres and therefore eight enatiomers. Four diasteromeric pairs of enatiomers were possible as illustrated in figure 2.10.1.



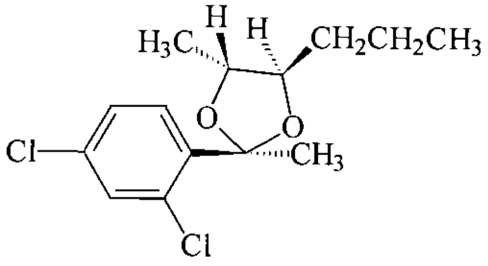
(2S, 4R, 5R)

(186a)



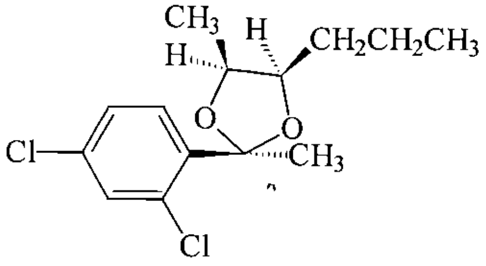
(2S, 4R, 5S)

(186b)



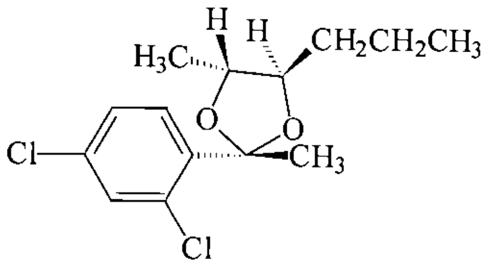
(2S, 4S, 5R)

(186c)



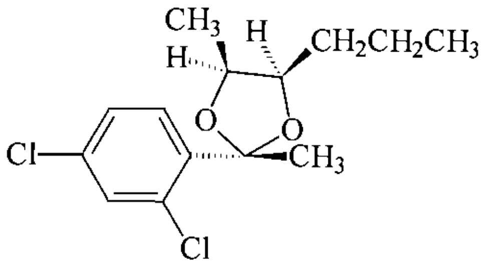
(2S, 4S, 5S)

(186d)



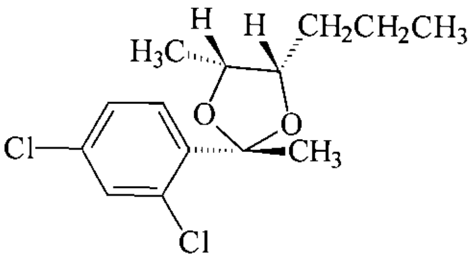
(2R, 4S, 5R)

(186e)



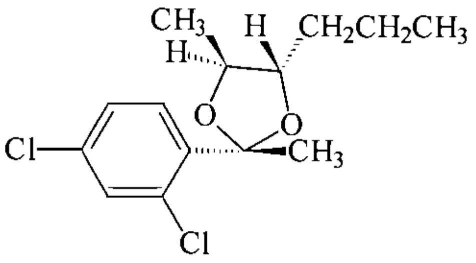
(2R, 4S, 5S)

(186f)



(2R, 4R, 5R)

(186g)

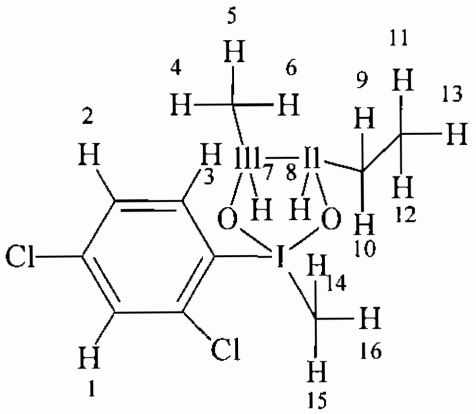


(2R, 4R, 5S)

(186h)

Fig. 2.10.1

Spectral analysis of the product **(186)** revealed the presence of four characteristic 1,3-dioxolane ring stretching vibrations at 1201, 1163, 1096 and 1031cm^{-1} in the infrared. The ^{1}HNMR spectra (figure 2.10.2) had the expected integration of 3:2:3:5:3 and exhibited the following peaks, 7.08-7.72ppm (3H, m, H-3, H-1, H-2), 4.28-4.42ppm 3.910-4.15ppm, 3.73-3.90ppm, 3.42-3.72ppm, 3.17-3.32ppm (2H, 5m, H-7, H-8), 1.64-1.74ppm (3H, m, H-14, H-15, H-16), 1.22-1.62ppm (2H, m, H-9, H-10), 1.06-1.20ppm (3H, m, H-4, H-5, H-6), 0.83-1.04ppm (3H, m, H-11, H-12, H-13).

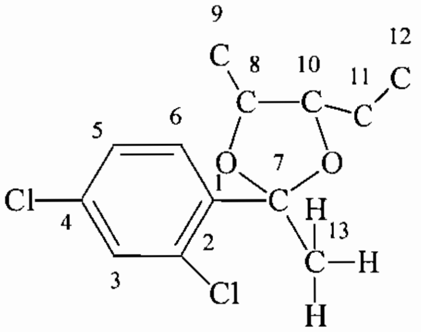


(186)

Figure 2.10.2

On the phenyl ring H-1, H-2 were located in the same magnetic enviroment but H-3 was located in a different magnetic environment in different diasteromers and the result was only one signal for H-1 and H-2 and two signals for H-3. The two hydrogens on the dioxolane ring H-7, H-8 gave a signal of five complex multiplets resulting from the overlap of doublets and quartets of the four sets of diasteromers. These five multiplets integrated for two hydrogens. Compared to the other 1,3-dioxolane derivatives the spectrum of this compound **(186)** and splitting patterns were far more complex due to the presence of four sets of diastereomers representing the eight enantiomers illustrated in figure 2.10.1. The methyl and ethyl side chains gave rise to three complex multiplets at 1.22-1.62ppm, integrating for five hydrogens (H-4, H-5, H-6, H-9, H-10), 0.83-1.04ppm integrating for three hydrogens (H-11, H-12, H-13) and at 1.64-1.74ppm represented the methyl group H-14, H-15, H-16. Unlike 1,3-dioxolane-2-(2,4-dichlorohenyl)-2-methyl-4-*n*-propyl **(182)** it was not possible to figure out the ratio of the four diastereomers from integration as the spectrum was too complex.

The ^{13}CNMR spectrum gave a clearer picture of the molecule and as expected four sets of splitting were present for each carbon, indicating four sets of diasteromers. The following peaks were present (figure 2.10.3), 142.91ppm (C-4), 141.93ppm (C-4), 141.84ppm (C-4), 140.99ppm (C-4), 134.58ppm (C-1), 134.51ppm (C-1), 134.34ppm (C-1), 133.63ppm (C-2), 133.51ppm (C-2), 133.41ppm (C-2), 133.10ppm (C-2), 131.84ppm (C-3), 131.51ppm (C-3), 131.42ppm (C-3), 131.04ppm (C-3), 130.25ppm (C-6), 130.00ppm (C-6), 129.74ppm (C-6), 129.36ppm (C-6), 128.40ppm (C-5), 127.61ppm (C-5), 127.53ppm (C-5), 107.79ppm (C-7), 107.71ppm (C-7), 107.44ppm (C-7), 107.10ppm (C-7), 85.45ppm (C-10), 84.62 ppm (C-10), 81.18ppm (C-10), 80.35ppm (C-10), 78.25ppm (C-8), 77.77ppm (C-8), 75.22ppm (C-8), 74.61ppm (C-8), 27.28ppm (C-13), 27.02ppm (C-13), 26.93ppm (C-13), 26.52ppm (C-13), 26.08ppm (C-11), 25.39ppm (C-11), 23.33ppm (C-11), 22.90ppm (C-11), 18.12ppm (C-9), 17.75ppm (C-9), 16.02ppm (C-9), 15.27ppm (C-9), 11.17ppm (C-12), 10.99ppm (C-12), 10.78ppm (C-12), 10.64ppm (C-12).



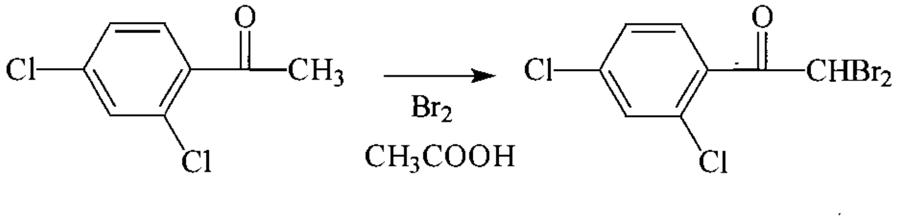
(186)

Figure 2.10.3

The carbon spectrum was very similar to 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl **(182)**. Fours sets of peaks were present for each carbon atom compared to two sets of peaks for each carbon in the spectra of **(182)**. Only three peaks were identified for the C-1 and C-12 carbons although four peaks were expected for each of them. One of the four peaks may have overlapped with another peak making it appear as though there was only three peaks present. DEPT spectra confirmed the presence of 12CH_3, 4CH_2 and 16CH groups. Eight lines corresponding to the two quaternary carbons C-1 and C-7 were absent as expected from the Dept spectra.

2.11 Synthesis of ethanone-2,2-dibromo-1-(2,4-dichlorophenyl) from ethanone-1-(2,4-dichlorophenyl)

Ethanone-1-(2,4-dichlorophenyl)**(17)** was brominated in acetic acid to form ethanone-2,2-dibromo-1-(2,4-dichlorophenyl)(**184**) as illustrated in scheme 65. The stoichiometry of the reaction was 4:1 and the product yield was 66%[110].

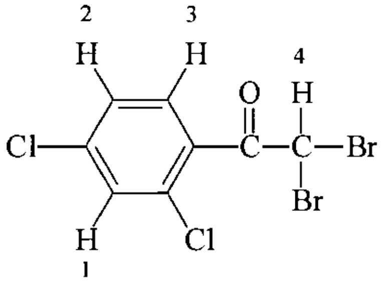


(17) **(184)**

Scheme 65

This reaction was monitored on GC-MS and the retention times for ethanone-1-(2,4-dichlorophenyl)(17) and ethanone-2,2-dibromo-1-(2,4-dichlorophenyl)(**184**) were 10:17 and 19:38 minutes respectively.

Spectral analysis of the product (**184**) revealed the presence of a carbonyl stretching (C=O) at 1719.0cm^{-1}. The ^{1}HNMR spectrum (figure 2.11.1) had the expected integration of 3:1. The spectrum exhibited the following peaks 7.584-7.618ppm (1H, d, J=8.37Hz, H-3), 7.483-7.500ppm (1H, d, J=1.97Hz, H-1), 7.356-7.395ppm (1H, dd, J=1.97, 8.37Hz, H-2) and 6.735 (1H, s, H-4) ppm.

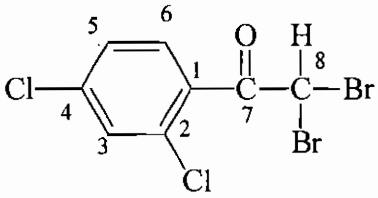


(184)

Figure 2.11.1

H-1 and H-3 each gave a signal of a doublet but H-2 gave a signal of a double doublet as H-2 was coupled to both H-1 and H-3. As expected there were eight signals on the carbon spectra.

The following peaks were present in ^{13}CNMR spectra (figure 2.11.2), 187.66ppm (C=O, C-7), 138.88ppm (C-4), 132.25ppm (C-1), 132.15ppm (C-2), 131.78ppm (C-3), 130.49ppm (C-6), 127.71ppm (C-5), and 41.63ppm (CHBr$_2$, C-8).



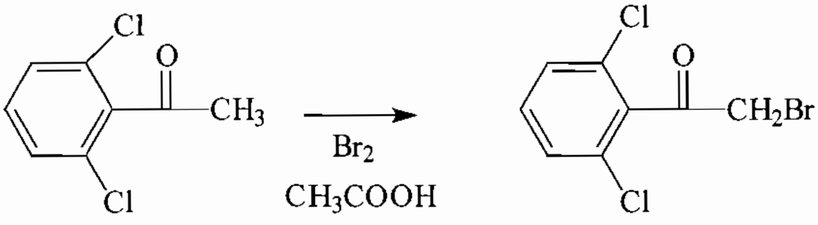
(184)

Figure 2.11.2

In ethanone-2-bromo-1-(2,4-dichlorophenyl)**(15)** C-8 had a chemical shift of 34.52ppm and the addition of the second bromine atom resulted in a further downfield shift to 41.63ppm for C-8.

2.12 Synthesis of ethanone-2-bromo-1-(2,6-dichlorophenyl) from ethanone-1-(2,6-dichlorophenyl)

Ethanone-2-bromo-1-(2,6-dichlorophenyl)**(185)** was prepared by the bromination of ethanone-1-(2,6-dichlorophenyl)**(183)** in acetic acid. The stoichiometry of the reaction was 2:1. Hydrogen bromide gas was produced as a by-product of the reaction and the yield of product was 69%[103].

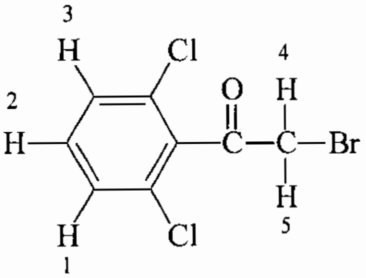


(183) **(185)**

Scheme 66

This reaction was monitored by GC-MS and the retention times for ethanone-1-(2,6-dichlorophenyl)**(183)** and ethanone-2-bromo-1-(2,6-dichlorophenyl)**(185)** were 9:52 and 15:36 minutes respectively.

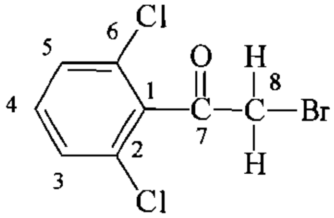
Spectral analysis of the product **(185)** revealed the presence of a carbonyl stretching at 1715cm^{-1} whereas in ethanone-1-(2,6-dichlorophenyl)**(183)** the carbonyl stretching was at 1709cm^{-1}. In the ^{1}HNMR (figure 2.12.1) the integration as expected was 3:2. The spectrum exhibited the following peaks at 7.258-7.409ppm (3H, m, H-3, H-1, H-2) and 4.445ppm (2H, s, CH_2Br).



(185)

Figure 2.12.1

The ^{13}CNMR spectrum (figure 2.12.2) exhibited the following peaks at 192.75.2ppm (C=O, C-7), 136.64ppm (C-1), 131.54ppm (C-2, C-6), 131.12ppm (C-3, C-5), 128.23ppm (C-4) and 35.23ppm (CH_2Br, C-8). The non protonated C-6 and C-2 carbons gave weaker signals than the C-5, C-4 and C-3 carbons.

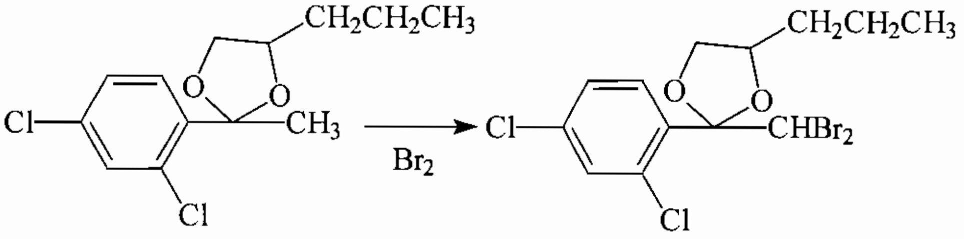


(185)

Figure 2.12.2

2.13 Synthesis of 1,-dioxolane-2-(2,4-dichlorophenyl)-2,2-dibromomethyl-4-*n*-propyl from 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl.

1,3-Dioxolane-2-(2,4-dichlorophenyl)-2,2-dibromomethyl-4-*n*-propyl **(187)** was prepared by the bromination of 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl **(182)** using bromine in dichloromethane at 35°C as illustrated in scheme 67. The stiochiometric ratio was 4:1 and four moles of bromine were required to produce one mole of product. The product yield was 60%.

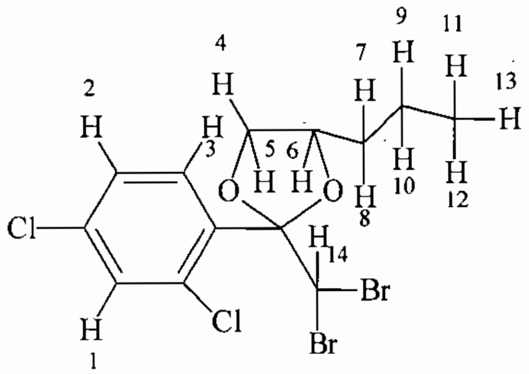


(182) **(187)**

Scheme 67

This reaction was monitored on GC-MS and the retention times for 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl **(182)** and 1,3-dioxolane-2-(2,4-dichlorophenyl)-2,2-dibromomethyl-4-*n*-propyl **(187)** were 18:05 and 26:16, 26:32 minutes respectively. Two peaks with identical mass and molecular ion at m/e 432 were present for 1,3-dioxolane-2-(2,4-dichlorophenyl)-2,2-dibromomethyl-4-*n*-propyl **(187)** indicating the presence of diasteromers.

Spectral analysis of the product **(187)** revealed the following characteristic 1,3-dioxolane stretching bands present at 1195, 1151, 1104, 1063cm^{-1} in the infrared spectrum. The ^{1}HNMR spectrum (figure 2.13.1) had the expected integration of 3:1:3:4:3 with the following peaks present at 7.67-7.74ppm (1H, dd, J=8.37Hz, H-3), 7.40-7.41ppm (1H, d, J=1.97Hz, H-1), 7.24-7.28ppm (1H, dd, J=1.97, 8.37Hz, H-2), 6.42, 6.16ppm (1H, 2s, H-14), 4.60-4.67ppm, 4.44-4.50ppm, 4.14-4.18ppm, 3.88-3.93ppm, 3.51-3.56ppm (3H, 5m, H-4, H-5, H-6), 1.20-1.96ppm (4H, m, H-7, H-8, H-9, H-10), 0.90-1.10ppm (3H, dt, J=7.14Hz, H-11, H-12, H-13).

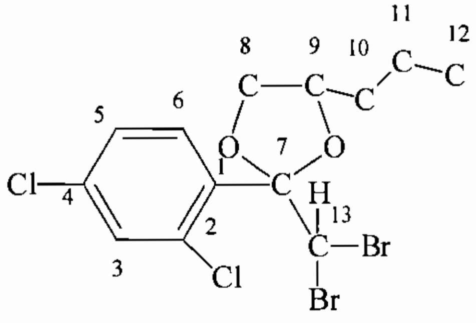


(187)

Figure 2.13.1

On the phenyl ring H-1 and H-2 each had one signal, H-3 however was located in a different magnetic environment in each of the diasteromers and showed two signals. The ratio of the two signals for H-3 was 1:2, implying a diasteromeric ratio of 1:2. The five multipets 4.60-4.67ppm, 4.44-4.50ppm, 4.14-4.18ppm, 3.88-3.93ppm, 3.51-3.56ppm integrated for the three hydrogens H-5, H-6, H-7 and these multiplets were the result of overlap between doublets and multiplets. Two singlets were present at 6.42, 6.16ppm integrating for one hydrogen and represented H-14. Two triplets were present between 0.90-1.10ppppm representing H-11, H-12, H-13. The signals from the four remaining hydrogens in the propyl group H-7, H-8, H-9, H-10 were more complicated and exhibited a complex multiplet from 1.20-1.96ppm.

The ^{13}CNMR spectrum (figure 2.13.2) exhibited the following peaks at 136.36ppm (C-4), 136.10ppm (C-4), 136.03ppm (C-1), 135.68ppm (C-1), 133.13ppm (C-2), 133.01ppm (C-2), 132.64ppm (C-3), 132.52ppm (C-3), 131.55ppm (C-6), 131.45ppm (C-6), 127.80ppm (C-5), 127.76ppm (C-5), 109.12ppm (C-7), 108.89ppm (C-7), 81.08ppm (C-9), 78.75ppm (C-9), 72.88ppm (C-8), 72.25ppm (C-8), 49.66ppm (C-13), 48.96ppm (C-13), 35.84ppm (C-10), 34.22ppm (C-10), 19.78ppm (C-11), 19.59ppm (C-11), 14.25ppm (C-12), 14.16ppm (C-12).



(187)

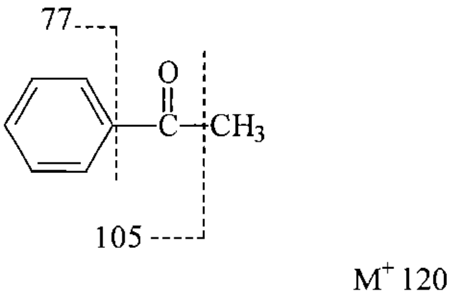
Figure 2.13.2

A total of twenty-six signals for thirteen carbons were present on the ^{13}CNMR and this was further evidence of the presence of diastereomers. The C-13 carbon in **(187)** had chemical shifts of 49.66ppm and 48.96ppm, compared to chemical shifts of 36.88ppm and 36.68ppm in 1,3-dioxolane-2(2,4-dichlorophenyl)-2-bromo-4-*n*-propyl **(18)**, the mono-bromo derivative. As expected the Dept spectra identified 2CH_3, 6CH_2 and 10CH groups and four signals were absent from the Dept spectra indicating the presence of two diastereometric quaternary carbons at C-1 and C-7.

2.14 Fragmentation patterns of propiconazole, intermediates and impurities.

(i) Fragmentation of alkyl-aryl and alkylhalo-aryl-ketones

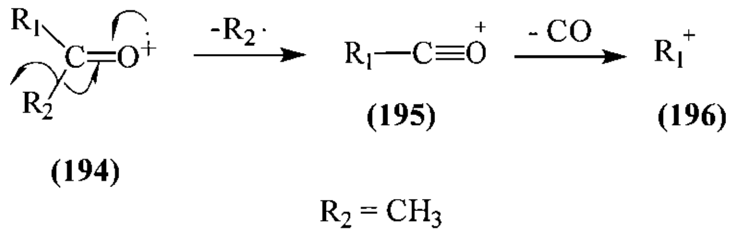
The breakdown of acetophenone **(193)** figure 2.14.1, had been shown by deuterium labelling to occur by successive loss of a methyl radical and carbon monoxide with m/e 105 and m/e 77. Alternatively α-fission of the phenyl-carbonyl bond resulted in a peak at m/e 43 (CH_3CO^+)[111].



(193)

Figure 2.14.1

The general fragmentation behaviour of substituted acetophenones follows that of acetophenone except that the extent of the phenyl-carbonyl bond cleavage is affected by the nature of the substituent. The fragmentation of the dichloroacetophenones occurred by successive loss of a methyl radical m/e 173 and of carbon monoxide m/e 145 as illustrated in scheme 68[111].



Scheme 68

The breakdown of the alkyl-aryl-ketones, ethanone-1-(2,4-dichlorophenyl)(17), ethanone-1-(2,6-dichlorophenyl)**(183)** and the alkylhalo-aryl-ketones, ethanone-2-bromo-1-(2,4-dichlorophenyl)(15), ethanone-2,2-dibromo-1-(2,4-dichlorophenyl)**(184)** and ethanone-2-bromo-1-(2,6-dichlorophenyl)**(185)** is illustrated in the type of electron impact (EI) mass spectra fragmentation patterns shown in figure 2.14.2.

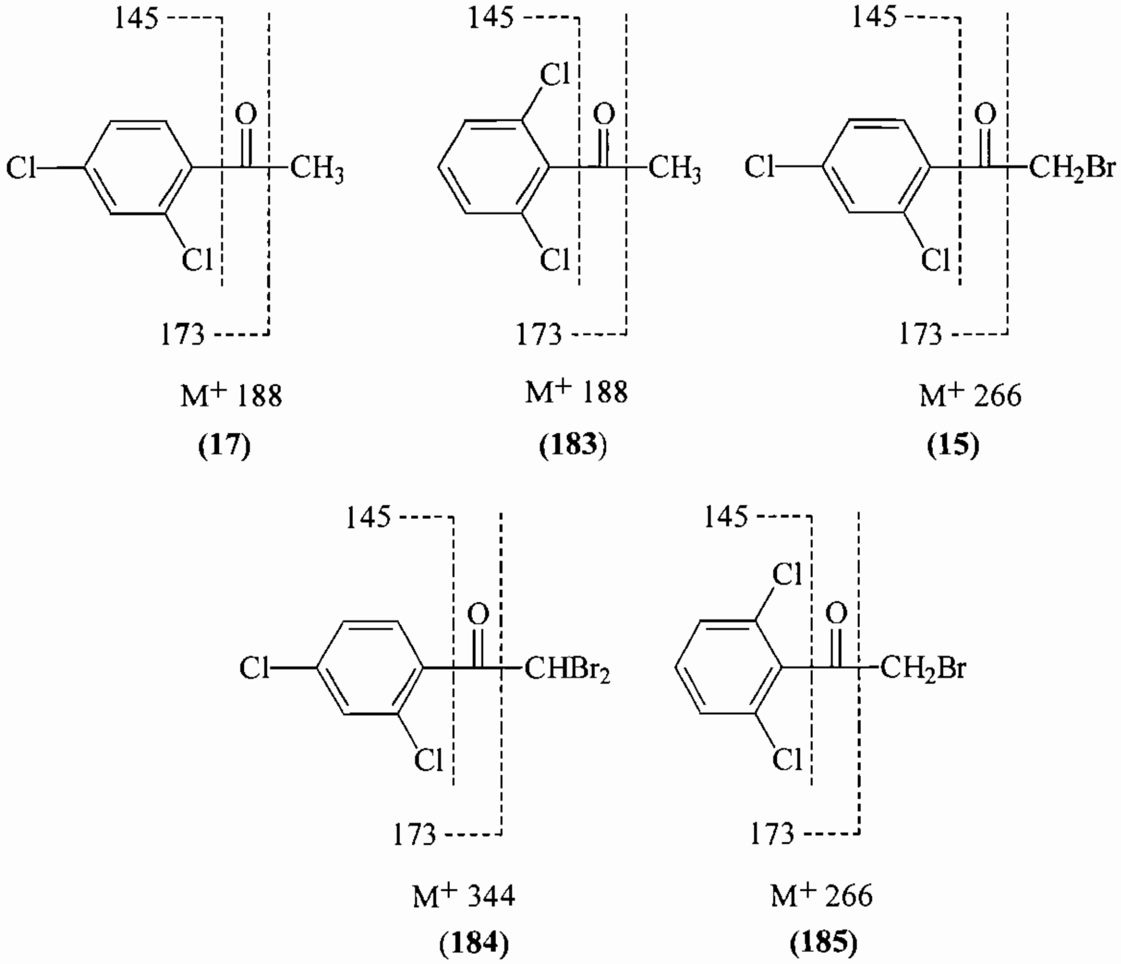


Figure 2.14.2

The peak at m/e 173 corresponds to structures **(195)**. Ethanone-1-(2,4-dichlorophenyl)**(17)** and ethanone-1-(2,6-dichlorophenyl)**(183)** both contain two chlorine atoms. Chlorine consists of two isotopes ^{35}Cl and ^{37}Cl which are present in the ratio 3:1 approximately. An isotopic pattern for a compound containing two chlorine atoms is illustrated in figure 2.14.3. The peaks are spaced two mass units apart.

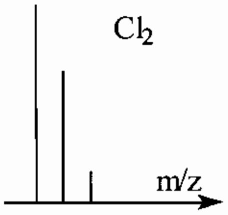


Figure 2.14.3

Ethanone-2-bromo-1-(2,4-dichlorophenyl)**(15)** and ethanone-2-bromo-1-(2,6-dichlorophenyl)**(185)**, both contain two chlorine atoms. However they also contain one bromine atom each. Bromine also has two isotopes ^{79}Br and ^{81}Br present in a 1:1 isotope ratio.

This combination of bromine and chlorine isotope affects the isotopic pattern as illustrated in figure 2.14.4. Once again all the peaks are two mass units apart[111].

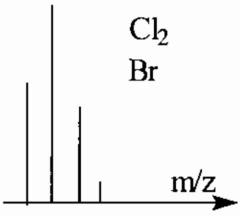


Figure 2.14.4

Ethanone-2,2-dibromo-1-(2,4-dichlorophenyl)**(184)** contains two chlorine atoms and two bromine atoms and the result is the isotopic pattern are illustrated in figure 2.14.5.

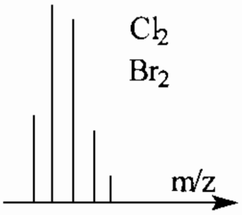
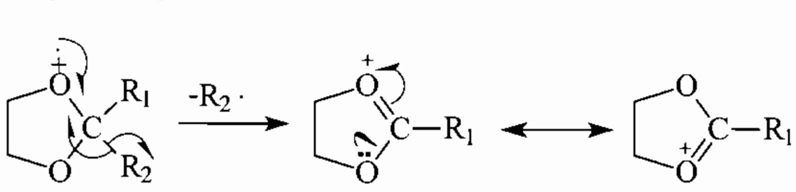


Figure 2.14.5

(ii) Fragmentation of 2-alkyl-aryl- and 2-alkylhalo-aryl-1,3-dioxolanes derivatives.

2,2-Alkyl-aryl-dioxolanes have a very characteristic fragmentation pattern consisting in the loss of a substituent on C-2, which results in the formation of a resonance stabilised oxonium ion as illustrated in scheme 69. The peak at m/e 259 was the result of the loss of the alkyl or alkylhalide substituents on C-2[112].

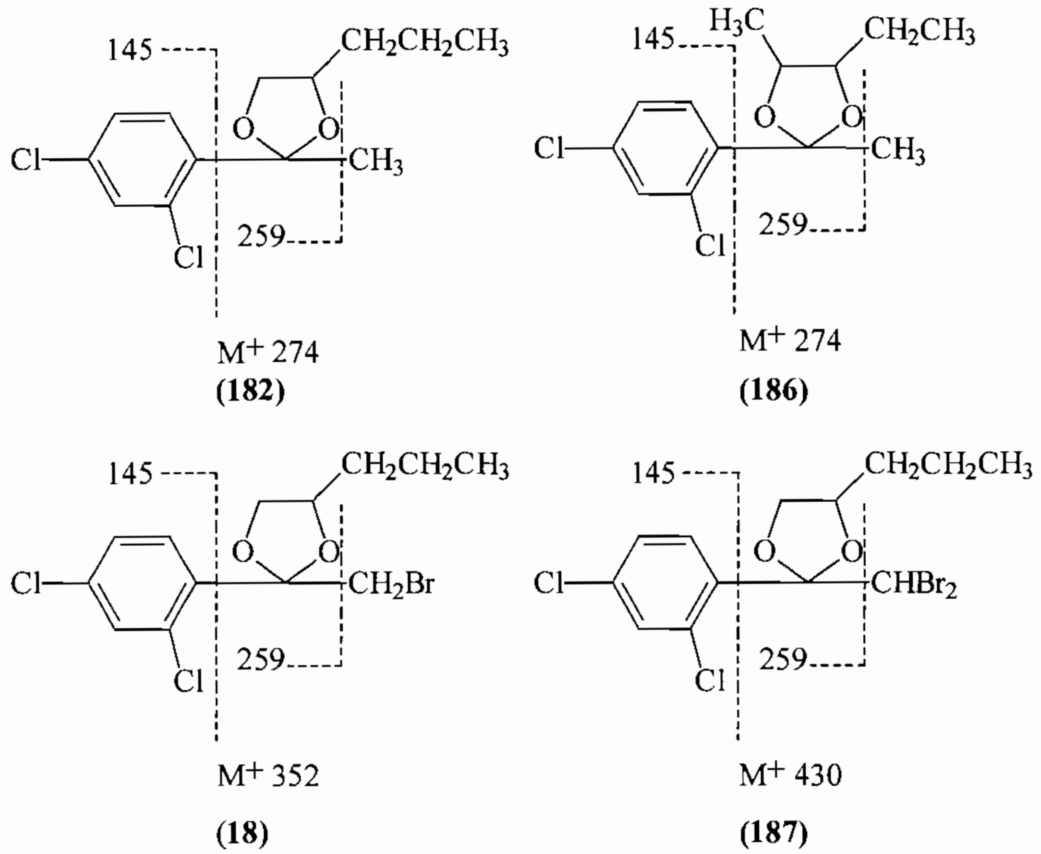


(197) **(198)** **(199)**

Scheme 69

Theoretical (EI) fragmentation patterns for the four 1,3-dioxolane compounds, 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl **(182)**, 1,3-dioxolane-2-(2,4-dichlorophenyl)-2,5-dimethyl-4-ethyl **(186)**, 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-

bromomethyl-4-*n*-propyl **(18)** and 1,3-dioxolane-2-(2,4-dichlorophenyl)-2,2-dibromomethyl-4-*n*-propyl **(187)** are illustrated in figure 2.14.6. These compounds all contain isotopic patterns similar to those illustrated in figures. 2.14.3, 2.14.4 and 2.14.5.



M+ 274 **(182)**

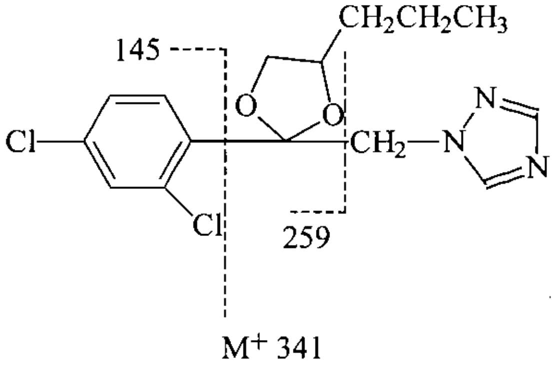
M+ 274 **(186)**

M+ 352 **(18)**

M+ 430 **(187)**

Figure 2.14.6

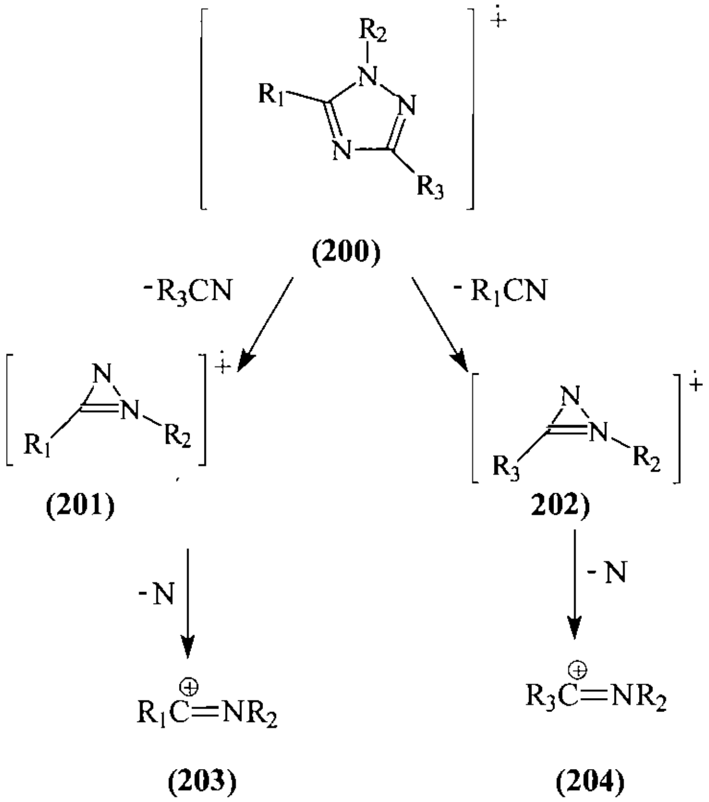
All of the 1,3-dioxolane derivative synthesised including propiconazole **(9)**(figure 2.14.7) have a peak at m/e 259 and this peak corresponds to structures **(198)** and **(199)**. Propiconazole (9) was classified as an azolymethyl-dioxolane fungicide and a theoretical fragmentation pattern for propiconazole is illustrated in figure 2.14.7. Propiconazole **(9)** and the synthetic starting material ethanone-1-(2,4-dichlorophenyl) were both in the GC-MS existing library of know compounds. Isotopic patterns similar to figure 2.14.3, indicated the presence of two chlorine isotopes in the mass spectrum of propiconazole. Isotope effects due to nitrogen can be ignored as the ^{15}N isotope of nitrogen has only a 0.36 percent abundance compared to the ^{14}N isotope. The most prominent fragment ion was still m/e 259 and a molecular ion was identified at 341m/e.



(9)

Figure 2.14.7

A general fragmentation pattern for 1,2,4-triazole derivatives **(200)** is illustrated in scheme 70. Fragmentation of various 1,2,4-triazole derivatives occurs by two predominant pathways involving the loss of RCN originating from both C_3 and C_5 positions[113,114]. The resulting diazirinium radical cation **(201)** and **(202)** had been observed to lose a nitrogen atom to give a nitrilium ion **(203)** and **(204)** whose substitution pattern was dependent upon the original substituents in the nucleus. In the case of the 1,2,4-triazole ring in propiconazole **(9)** the R_2 and R_3 subsituents were both hydrogens and the result was the same nitrilium ion **(203)** and **(204)** regardless of the fragmentation pattern.

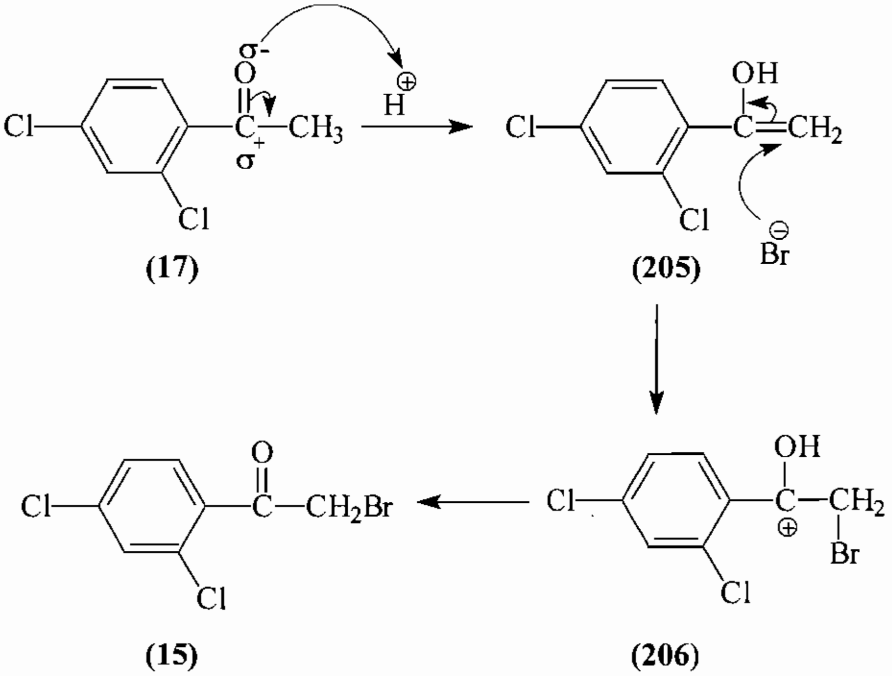


Scheme 70

2.15 Mechanisms

2.15.1 Acid catalysed bromination of ethanone-1-(2,4-dichlorophenyl)

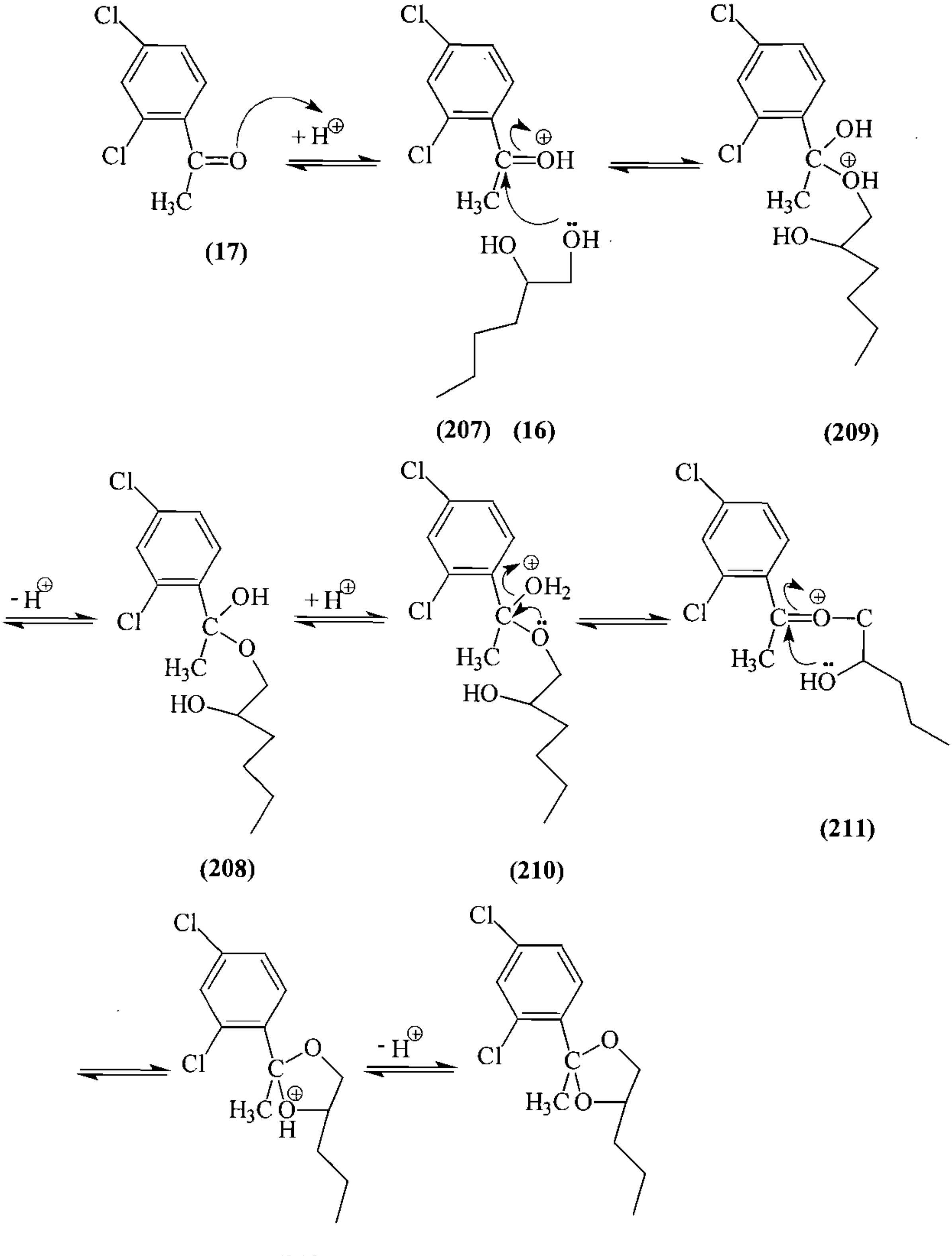
Ethanone-1-(2,4-dichlorophenyl)**(17)** was brominated at the α-positions. An acid catalyst was required and the reaction was carried out in acetic acid. The mechanism for the acid catalysed bromination of ethanone-2-bromo-1-(2,4-dichlorophenyl)**(15)** is illustrated in scheme 71. The mechanism proposes that it was not the ketone itself that was brominated but the corresponding enol or enolate ion **(205)**[115]. The purpose of the acid was to provide a small amount of enol or enolate and allowed the reaction to be easily stopped after only one bromine atom had reacted. The use of excess bromine allows the formation of di- and polybromides. A mole ratio of 4:1 moles of bromine to ethanone-1-(2,4-dichlorophenyl)**(17)** resulted in the formation of ethanone-2,2-dibromo-1-(2,4-dichloro- phenyl)**(184)**. Ethanone-2-bromo-1-(2,6-dichlorophenyl)**(185)** was formed through the acid catalysed bromination of ethanone-1-(2,6-dichlorophenyl)**(183)** through a similar mechanism.



Scheme 71

2.15.2 Addition of 1,2-pentanediol to the carbon-oxygen double bond in ethanone-1-(2,4-dichlorophenyl)

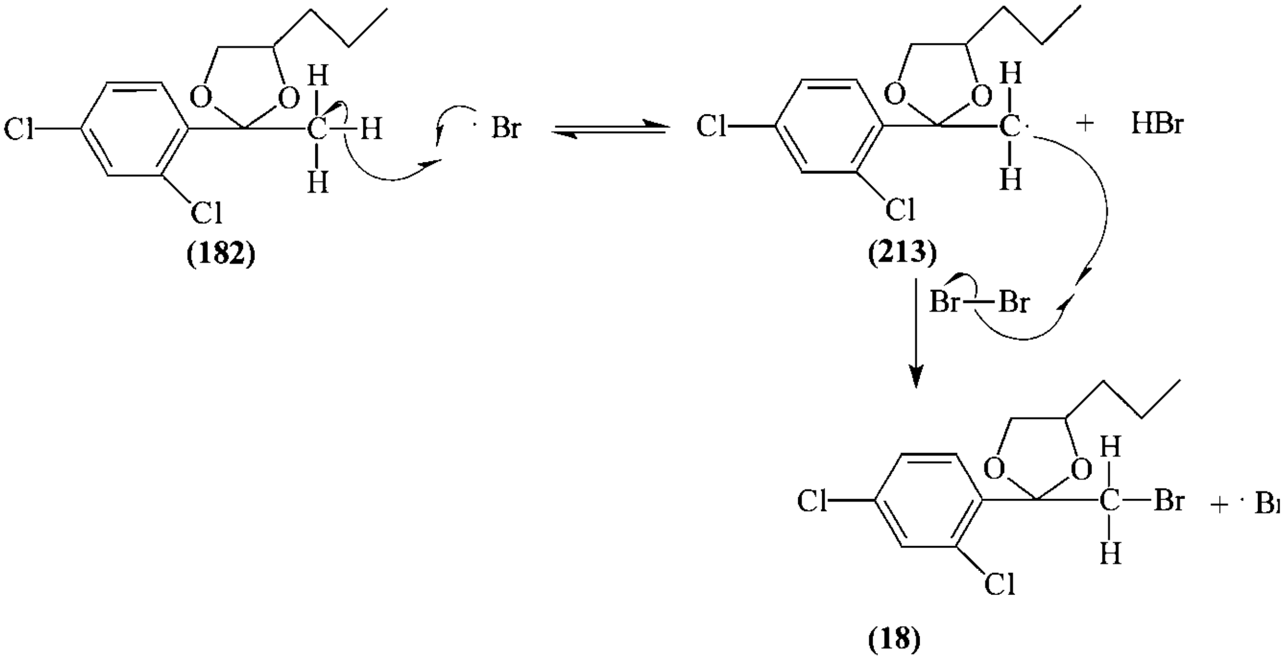
Ethanone-1-(2,4-dichlorophenyl)(**17**) underwent a condensation reaction with 1,2-pentanediol (**16**) to form the cyclic ketal 1,3-dioxolane-2-(2,4-dichlorphenyl)-2-methyl-4-*n*-propyl (**182**) as illustrated in scheme 72[116]. This reaction proceeds through the formation of the hemi-ketal (**208**). The formation of the hemi-ketal (**208**) and the formation of the cyclic ketal (**196**) are both acid catalysed reactions. 1,3-Dioxolane-(2,4-dichlorophenyl)-2,5-dimethyl-4-ethyl (**186**) and 1,3-dioxolane-(2,4-dichlorophenyl)-2-bromomethyl-4-*n*-propyl (**18**) were also formed through a similar mechanism although in the case of 1,3-dioxolane-(2,4-dichlorophenyl)-2,5-dimethyl-4-ethyl (**186**) the condenstion reaction involved 2,3-pentanediol (**188**) instead of 1,2-pentanediol (**16**).



Scheme 72

2.15.3 Free radical bromination of 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl at the α-carbon

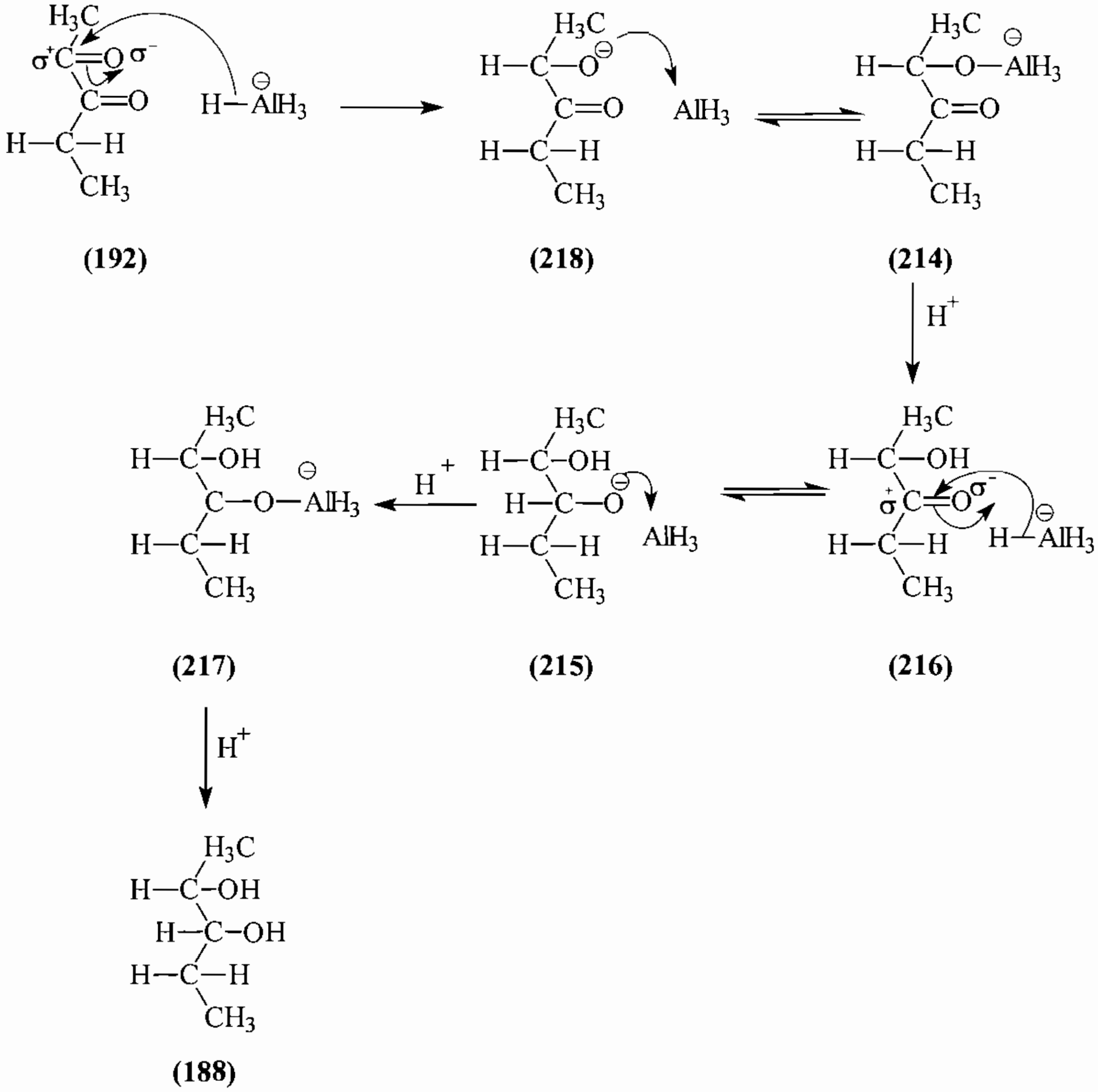
The bromination of 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl **(182)** proceeded through a free radical mechanism as illustrated in scheme 73. Both of 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-bromomethyl-4-*n*-propyl **(18)** and 1,3-dioxolane-2-(2,4-dichlorophenyl)-2,2-dibromomethyl-4-*n*-propyl **(187)** were formed through this mechanism[117].



Scheme 73

2.15.4 Reduction of 2,3-pentadione using lithium aluminium hydride

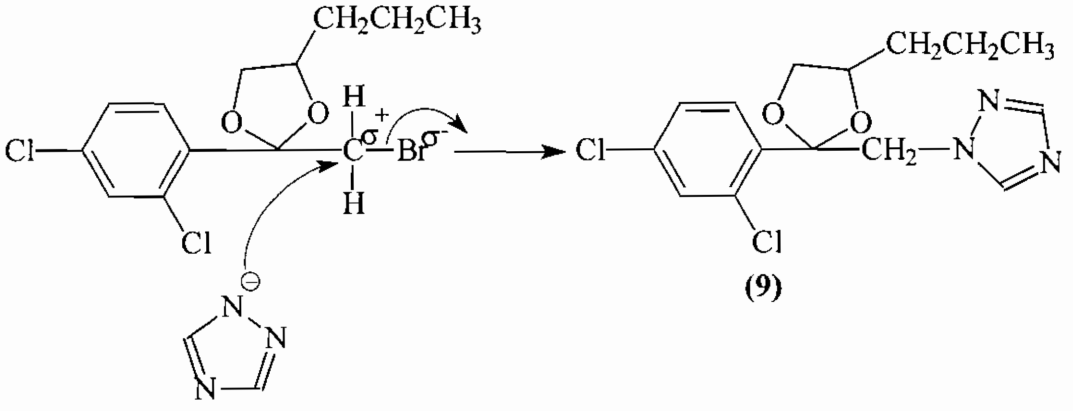
2,3-Pentadione **(192)** was reduced to yield 2,3-pentanediol **(188)** using lithium aluminium hydride in anhydrous tetrahydrofuran. The aluminium tetrahydride anion donated a hydride anion irreversibly to one of the carbonyl carbons in 2,3-pentanedione. The resulting anion then complexed with the aluminium trihydride to form **(214)** and then **(215)**. This complex **(215)** then underwent disproportionation to yield **(215)** and generate more of the aluminium tetrahydride anion. The same mechanism occurs at each of the carbonyl groups in 2,3-pentanedione **(192)** and the diol **(188)** was then formed by the protonation of **(216)** as illustrated in scheme 74[118].



Scheme 74

2.15.5 Nucleophlic substition of 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-bromomethyl-4-*n*-propyl with the 1,2,4-triazole ion

1,3-Dioxolane-2-(2,4-dichlorophenyl)-2-bromomethyl-4-*n*-propyl **(18)** was converted to 1-[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-ylmethyl]-1H-1,2,4-triazole **(9)** via a nucleophilic substitution mechanism. A 1,2,4-triazole ion from a sodium or potassium triazole **(8)** salt attacked the carbon on the bromomethyl group of 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-bromomethyl-4-*n*-propyl **(18)** and forced the bromide to leave as illustrated in scheme 75[119].



(18)

(9)

Scheme 75

2.16 Conclusion

Propiconazole **(9)**, an azolymethyl-dioxolane fungicide was successfully produced in a 41% and 45% yield from ethanone-1-(2,4-dichlorophenyl)**(17)** from two alternative processes[33,36]. Three synthetic intermediates were isolated and the Agriguard process was scaled up to a 2-litre process. Seven impurities within the reaction process were identified and characterised. Four of these impurities were synthesised.

Chapter 3
Experimental

Experimental

NMR spectra were determined with a Varian Gemini^{TM} 200MHz spectrometer, equipped with Solarius^{TM} softwwere, using deuterated chloroform, deuterated acetone, deuterium oxide or dimethylsulphoxide. The infrared spectra were recorded as neat samples with a Perkin Elmer spectrometer. GC and GC-MS spectra were obtained on a Varian Star 3400CX^{TM} gas chromatograph coupled to a Varian Star 2000^{TM} mass spectrometer using a DB5 capillary column. GC parameters involved a temperature programme of 80-300°C in increments of 8°C over 30mins and the column temperature was held at 300°C for 5mins. The MS parameters involved a mass range of 40-450m\z at 1 scan per second, over 37 minutes with a background mass of 35m\z.

The solvent system employed for the characterisation using thin layer chromatography was 50:50 toluene: hexane. The plates used were silica on alumina backing, incorporating fluorescent indicator, and were visualised by the use of either an ultra violet light source, or an iodine chamber.

3.1 2-Bromo-1-(2,4-dichlorophenyl)-ethanone

Ethanone-1-(2,4-dichlorophenyl)(20.03 g, 0.106 moles) and glacial acetic acid (20.2 g, 0.336 moles) was added to a three necked round bottom flask (500 cm^3) containing a magnetic stirring bar and fitted with a reflux condenser and a pressure equalising dropping funnel (100 cm^3). Bromine (16.99 g, 0.212 moles) was added dropwise and the colourless solution was refluxed gently. The solution changed colour to red and finally to yellow on complete addition of the bromine. The reaction flask was then placed over a water bath until all the hydrogen bromide gas had evolved. The hot solution was then poured into ice water (150 cm^3) and left stirring for 1hr. The solution was extracted with diethyl ether (2x30cm^3) separated and dried over anhydrous magnesium sulphate. After filtration the diethyl ether was removed and the crude product was distilled under vacuum to yield 2-bromo-1-(2,4-dichlorophenyl)-ethanone as a yellow liquid (21.2g, 75% yield), boiling point 129-132°C, 3mmHg (lit. bpt.155-170°C, 20mmHg)[31,34]. I.R, ν_{max} 1700.0cm^{-1} (C=O). NMR Spectra: δ_H (200MHz, $CDCl_3$) 7.543-7.573ppm (1H, d), 7.461-7.478ppm (1H, d), 7.340-7.374ppm (1H, dd), 4.503ppm (2H, s). δ_C (50MHz, $CDCl_3$) 192.69, 138.51, 134.17, 132.41, 131.47, 130.00, 127.55, 34.52ppm.

3.2 1,3-Dioxolane-2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl

Ethanone-1-(2,4-dichlorophenyl)(25 g, 0.132 moles), 1,2-pentanediol (15.10 g, 0.145 moles), toluene (35.80 g, 0.39 moles) and *p*-toluene sulphonic acid (500 mg, 2.60 mmoles) was added to a two necked round bottomed flask (100 cm^3) containing a magnetic stirring bar and fitted with a condenser, a Dean and Stark apparatus and a thermometer. The solution was refluxed with the azeotropic removal of water (2.70 g, 0.15 moles) over four hours. This solution was allowed to cool and was washed with sodium carbonate solution (10%)(2x20 cm^3), brine solution (1x20 cm^3) and water (1x20 cm^3). The product was extracted with diethyl ether and dried over anhydrous sodium sulphate. After filtration the diethyl ether and the toluene were removed and the crude product was fractionally distilled under vacuum to yield 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl as a clear viscous liquid (29.4 g, yield 81%), boiling point 130-132^{0}C, 3.5mmHg. Elemental analysis found C 56.95%, H 5.83% and Cl 25.49%, theory C 56.95%, H 5.83% and Cl 25.49%. I.R. v_{max} 1196, 1149, 1096, 1031cm^{-1}, 1,3-dioxolane ring stretching vibrations. NMR Spectra: δ_H (200MHz, $CDCl_3$) 7.569-7.649ppm (1H, dd), 7.379-7.400ppm (1H, d), 7.192-7.299ppm (1H, dd), 4.149-4.268ppm, 3.819-3.915ppm, 3.575-3.635ppm, 3.301-3.350ppm (3H, 4m), 1.725, 1.793ppm (3H, 2s), 1.260-1.724ppm (4H, m), 0.890-0.981ppm (3H, dt). δ_C (50MHz, deuterated acetone) 141.50, 140.39, 134.67, 134.54, 133.54, 133.46, 131.51, 131.35, 130.20, 129.76, 127.67, 127.62, 108.61, 108.57, 77.75, 76.58, 70.43, 69.87, 36.27, 36.09, 26.27, 26.18, 19.95, 19.69, 14.33ppm.

3.3 1,3-Dioxolane-2-(2,4-dichlorophenyl)-2-bromomethyl-4-n-propyl from ethanone-2-bromo-1-(2,4-dichlorophenyl)

Ethanone-2-bromo-1-(2,4-dichlorophenyl)(54.3 g, 0.203 moles), 1,2-pentanediol (23.28 g, 0.224 moles), toluene (173.40 g, 1.89 moles) and p-toluene sulphonic acid (500 mg, 2.6 mmoles) were added to a three necked round bottomed flask (500 cm^3) containing a magnetic stirring bar, fitted with a Dean and Stark apparatus, a condenser and a thermometer. The solution was refluxed with the azeotropic removal of water (3.8 g, 0.211 moles) over six hours. The solution in the reaction flask was left to cool and was then washed with sodium carbonate solution (10%)(2x30 cm^3), brine solution (1x30 cm^3) and water (1x30 cm^3). The product was extracted with diethyl ether and the combined diethyl ether extracts were dried over anhydrous sodium sulphate. After filtration the diethyl ether and toluene were removed and the crude product was fractionally distilled under vacuum to yield 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-bromomethyl-4-n-propyl as a pale yellow viscous liquid (56.30g, yield 78%), boiling point 163-165^{0}C, 4mmHg (lit. bpt. 125-129^{o}C, 0.1mm)[31,34]. I.R. v_{max} 1189, 1141, 1105, 1062cm^{-1}, 1,3-dioxolane ring stretching vibrations. NMR Spectra: δ_H (200MHz, $CDCl_3$) 7.59-7.74ppm (1H, dd), 7.15-7.39ppm (1H, d), 7.22-7.26ppm (1H, dd), 4.37-4.41ppm, 4.28-4.32ppm, 3.95-4.04ppm, 3.70-3.78ppm, 3.41-3.46ppm (3H, 5m), 3.91ppm, 3.87ppm, 3.85ppm, 3.82ppm (2H, dd), 1.27-1.85ppm (4H, m), 0.89-0.99ppm (3H, dt). δ_C (50MHz, deuterated acetone) 137.74, 137.03, 135.68, 135.58, 133.64, 133.54, 131.56, 131.46, 131.40, 131.31, 127.81, 127.72, 107.72, 107.59, 79.36, 77.71, 71.42, 71.18, 36.88, 36.68, 35.73, 35.13, 19.68, 19.64, 14.25, 14.21ppm.

3.4 1,3-Dioxolane-2-(2,4-dichlorophenyl)-2-bromomethyl-4-*n*-propyl from 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl

1,3-Dioxolane-2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl (105 g, 0.38 moles) and dichloromethane (161 g, 1.89 moles) was added to a three necked round bottom flask (500 cm^3), fitted with a mechanical stirrer, a pressure equalising dropping funnel (100 cm^3), a condenser and a thermometer. The reaction flask was maintained at 35°C and bromine (61.5 g, 0.77 moles) was added dropwise to the colourless solution which changed colour to red and then to yellow on complete addition of the bromine. Once all the bromine had been added the solution was heated for a further two hours until any remaining hydrogen bromide gas had evolved. This solution was allowed to cool and was washed with sodium carbonate solution (10%) (2x50 cm^3), brine solution (1x50 cm^3) and finally with water (1x50 cm^3). The product was extracted with dichloromethane and dried over anhydrous sodium sulphate. After filtration the dichloromethane and toluene were removed and the crude product was fractionally distilled under vacuum to yield 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-bromomethyl-4-n-propyl as a pale yellow viscous liquid (108.0 g, yield 80%), boiling point 165-167°C, 4.5mmHg (lit. bpt. 125-129°C , 0.1mmHg)[31,34]. I.R. ν_{max} 1189, 1141, 1105, 1062cm^{-1}, 1,3-dioxolane ring stretching vibrations. NMR Spectra: δ_H (200MHz, $CDCl_3$) 7.59-7.74ppm (1H, dd), 7.15-7.39ppm (1H, d), 7.22-7.26ppm (1H, dd), 4.37-4.41ppm, 4.28-4.32ppm, 3.95-4.04ppm, 3.70-3.78ppm 3.41-3.46ppm (3H, 5m), 3.91ppm, 3.87ppm, 3.85ppm, 3.82ppm (2H, dd), 1.27-1.85ppm (4H, m), 0.89-0.99ppm (3H, dt). δ_C (50MHz, deuterated acetone) 137.76, 137.04, 135.69, 135.59, 133.66, 133.55, 131.57, 131.47, 131.40, 131.31, 127.81, 127.72, 107.72, 107.59, 79.36, 77.71, 71.42, 71.18, 36.88, 36.68, 35.73, 35.13, 19.68, 19.58, 14.25 , 14.21ppm.

3.5 1-[2-(2,4-Dichlorophenyl)-4-propyl-1,3-dioxolan-2-ylmethyl]-1H-1,2,4-triazole (propiconazole)

Sodium triazolide (11.60 g, 0.127 moles) in dimethyl sulphoxide (90.99 g, 1.17 moles) was added to a four-necked reaction flask (500 cm^3) fitted with a mechanical stirrer, a condenser, a pressure equalising dropping funnel (100 cm^3) and a thermometer. 1,3-dioxolane-2-(2,4-dichlorophenyl)-2-bromomethyl-4-*n*-propyl (35.41 g, 0.1 moles) was added to the dropping funnel in dimethyl sulphoxide (45.45 g, 0.58 moles) and added slowly to the reaction flask. The reaction flask was heated to 160°C and maintained at 160°C for sixteen hours. The solution turned dark brown and was left to cool and stand overnight. The dimethyl sulphoxide (150 g, 1.92 moles) was removed and the product was filtered to remove solid inorganic waste and the filtrate extracted with diethyl ether (5x50 cm^3) and water (5x50 cm^3). The diethyl ether extracts were combined, washed with sodium carbonate solution (10%), (2x30 cm^3), brine solution (1x30 cm^3), water (2x50 cm^3) and dried over anhydrous sodium sulphate. After filtration the diethyl ether was removed and the crude product was fractionally distilled under vacuum to yield 1-[2-(2,4-dichlorophenyl)-4-propyl-1,3-dioxolan-2-ylmethyl]-1H-1,2,4-triazole as a dark orange viscous oil (23.98 g, yield 70%), boiling point 223-227°C, 8mmHg (lit. bpt. 156-160°C , 0.1mmHg)[31,34]. I.R. v_{max} 1209, 1137, 1105, 1049cm^{-1}, 1,3-dioxolane ring stretching vibrations. NMR Spectra: δ_H (200MHz, CDCl$_3$), 8.19, 8.16 (1H, 2s), 7.88, 7.90ppm (1H, 2s), 7.52-7.58ppm (1H, dd), 7.43-7.74ppm (1H, d), 7.20-7.24ppm (1H, 2dd), 4.78ppm, 4.73ppm, 4.70ppm, 4.69ppm (2H, 2dd), 3.87-4.00ppm, 3.68-3.76ppm, 3.31-3.36ppm, 3.14-3.20ppm (3H, 4m), 1.20-1.90ppm (4H, m), 1.19-1.54ppm (3H, dt). δ_C (50MHz, deuterated acetone) 151.73, 151.64, 145.98, 145.85, 137.59, 136.84, 135.81, 135.68, 134.01, 133.94, 131.65, 131.46, 131.05, 130.77, 127.92, 127.82, 107.83, 107.77, 78.84, 77.56, 70.83, 70.78, 54.84, 54.68, 35.56, 35.34, 19.67, 19.58, 14.16, 14.12ppm.

3.6 2,3-Pentanediol

Lithium aluminium hydride (7.00 g, 0.184 moles) was added through a solid addition funnel to a four necked reaction flask (1000 cm^3), fitted with a mechanical stirrer, a double surface condenser, a pressure equalising dropping funnel, and a thermometer. Tetrahydrofuran (227.00 g, 3.15 moles) was used to transfer the last traces of lithium aluminium hydride into the reaction flask. Drying tubes containing calcium chloride were attached to the condenser and the dropping funnel. The solution was stirred for ten minutes until most of the lithium aluminium hydride had dissolved. 2,3-Pentanedione (16.67 g, 0.163 moles) in tetrahydrofuran (113.50 g, 1.58 moles) was added through a dropping funnel to a flask containing lithium aluminium hydride in tetrahydrofuran so that the solution in the flask refluxed gently. As the reaction proceeded the mixture became viscous and two further portions of THF (2x50 cm^3) were added to the flask. The reaction was left stirring for a further ten minutes. Ethyl acetate (18.84 g; 0.21 moles) was added rapidly to the reaction flask in order to decompose any remaining lithium aluminium hydride. The solution in the flask was left to cool and the sludge was then filtered through a sintered glass funnel. The filtrate was extracted with diethyl ether and dried over anhydrous sodium sulphate. After filtration the diethyl ether and the tetrahydrofuran were removed to afford the crude product. The solid residue from the filtration was dissolved in 20% sulphuric acid and this solution was extracted with diethyl ether (6x100 cm^3) and dried over anhydrous sodium sulphate. After filtration the diethyl ether was removed to yield more of the crude product. The two fractions of crude product were combined and distilled under vacuum to yield 2,3-pentanediol as a pale yellow viscous liquid (6.06 g, yield 36%), boiling point 69-70°C, 2.5mmHg (lit. bpt. 58-59°C, 0.5mmHg)[98]. I.R. v_{max} 3390cm^{-1} (O-H, broad), NMR Spectra: δ_H (200MHz, $CDCl_3$) 3.151-3.850ppm (4H, m), 1.222-1.650ppm (2H, m) 1.10-1.21ppm (3H, m) and 0.935-1.02ppm, (3H, m). δ_C (50MHz, DMSO) 76.14, 75.82, 69.41, 69.07, 25.51, 24.68, 19.09, 18.66, 10.43, 10.26ppm.

3.7 1,3-Dioxolane-2-(2,4-dichlorophenyl)-2,5-dimethyl-4-ethyl

Ethanone-1-(2,4-dichlorophenyl)(3.43 g, 0.018 moles), 2,3-pentanediol (2.08 g, 0.02 moles), p-toluene sulphonic acid (100 mg, 0.5 mmoles) and toluene (34.68 g, 0.38 moles) were added to a two necked round bottom flask (50 cm^3) containing a magnetic stirring bar, fitted with a Dean and Stark apparatus and a condenser. The reaction flask was refluxed with the azeotropic removal of water (3.80 g, 0.211 moles) over six hours. The solution was allowed to cool and was washed with sodium carbonate solution (10%) (2x10 cm^3), brine solution (1x10 cm^3) and with water (1x10 cm^3). The product was extracted with diethyl ether and the ethereal extracts were combined and dried over anhydrous sodium sulphate. After filtration the diethyl ether and toluene were removed and the crude product was fractionally distilled under vacuum to yield 1,3-dioxolane-2-(2,4-dichlorophenyl)-2,5-dimethyl-4-ethyl as a pale yellow viscous liquid (3.21 g, yield 65%), boiling point 130-132^{0}C, 3.5mmHg. Elemental analysis found C 56.80%, H 5.97% and Cl 25.88, theory C 56.76, H 5.81% and Cl 25.80%. I.R. v_{max} 1201, 1163, 1096, 1031cm^{-1}, 1,3 dioxolane ring stretching vibrations. NMR Spectra: δ_H (200MHz, $CDCl_3$) 7.08-7.72ppm (3H, m), 4.28-4.42ppm 3.910-4.15ppm, 3.73-3.90ppm, 3.42-3.72ppm, 3.17-3.32ppm (2H, 5m), 1.64-1.74ppm (3H, m), 1.22-1.62ppm (2H, m), 1.06-1.20ppm (3H, m), 0.83-1.04ppm (3H, m). δ_C (50MHz, deuterated acetone) 142.91, 141.93, 141.84, 140.99, 134.58, 134.51, 134.34, 133.63, 133.51, 133.41, 133.10, 131.84, 131.51, 131.42, 131.04, 130.25, 130.00, 129.74, 129.36, 128.40, 127.61, 127.53, 107.79, 107.71, 107.44, 107.10, 85.45, 84.62, 81.18, 80.35, 78.25, 77.77, 75.22, 74.61, 27.28, 27.02, 26.93, 26.52, 26.08, 25.39, 23.33, 22.90, 18.12, 17.75, 16.02, 15.27, 11.17, 10.99, 10.78, 10.64ppm

3.8 Ethanone-2,2-dibromo-1-(2,4-dichlorophenyl)

Ethanone-1-(2,4-dichlorophenyl)(5.10 g, 0.027 moles) in glacial acetic acid (5.30 g, 0.088 moles) was added to a three-necked round bottom flask (250 cm^3) containing a magnetic stirrer, fitted with a condenser and a pressure equalising dropping funnel. Bromine (8.50 g, 0.106 moles) was added slowly to the colourless solution in the flask and refluxed gently. The solution changed colour to red and then to yellow on complete addition of the bromine. The reaction flask was placed over a water bath and heated until all the hydrogen bromide gas had evolved and the solution was a dark orange colour. The hot solution was then poured into ice water (150 cm^3) and left stirring for one hour. The product was then extracted with diethyl ether (2x35 cm^3) and dried over anhydrous magnesium sulphate. After filtration the diethyl ether was removed and the crude product was distilled under vacuum to yield ethanone-2,2-dibromo-1-(2,4-dichlorophenyl) as a dark yellow liquid (6.21 g, yield 66%), boiling point 157-159° 7mmHg (lit. bpt. 130-132°C, 0.5mmHg)[103,104]. I.R. ν_{max} 1719.0cm^{-1} (C=O). NMR Spectra: δ_H (200MHz, $CDCl_3$) 7.584-7.618ppm (1H, d), 7.483-7.500ppm (1H, d), 7.356-7.395ppm (1H, dd), 6.735ppm (1H, s). δ_C (50MHz, $CDCl_3$) ppm 187.66, 138.88, 132.25, 132.15, 131.78, 130.49, 127.71, 41.63ppm.

3.9 Ethanone-2-bromo-1-(2,6-dichlorophenyl)

Ethanone-1-(2,6-dichlorophenyl)(1.50 g, 7.9 mmoles) and glacial acetic acid (5 g, 0.083moles) were added to a two necked round bottomed flask (100 cm^3) containing a magnetic stirring bar, fitted with a reflux condenser and a dropping funnel (50 cm^3). Bromine (1.26 g, 0.016moles) was added slowly to the colourless solution in the flask and refluxed gently. The solution changed colour to red and then to yellow on complete addition of the bromine. Once all the bromine had been added the reaction flask was then placed over a water bath until all the hydrogen bromide gas had evolved. The hot solution was then poured into ice water (25 cm^3) and left stirring for thirty minutes. The solution was extracted with diethyl ether (2x10 cm^3), separated and the combined ethereal extracts were dried over anhydrous magnesium sulphate. After filtration the diethyl ether was removed and the crude product was distilled under vacuum to afford ethanone-2-bromo-1-(2,6-dichloro- phenyl) as a yellow liquid (1.46 g, yield 69%), boiling point 135-137°, 5mmHg (lit. bpt.85-90°C, 0.1mmHg)[104,110]. I.R. ν_{max} 1715.7cm^{-1} (C=O). NMR Spectra: δ_H (200MHz, CDCl$_3$) 7.258-7.409ppm (3H, m), 4.445ppm (2H, s). δ_C (50MHz, CDCl$_3$) 192.75, 136.64, 131.54, 131.12, 128.23, 35.23ppm.

3.10 1,3-Dioxolane-2-(2,4-dichlorophenyl)-2,2-dibromomethyl-4-*n*-propyl

1,3-Dioxolane-2-(2,4-dichlorophenyl)-2-methyl-4-*n*-propyl (49.50 g, 0.180 moles) in dichloromethane (100 g, 1.18 moles) was added to a three necked round bottomed flask (500 cm^3), fitted with a mechanical stirrer, a pressure equalising dropping funnel, a condenser and a thermometer. The reaction flask was maintained at 37°C and bromine (58 g, 0.73 moles) was added to the colourless solution which changed colour to brown on complete addition of the bromine. The solution was heated for a further two hours until all the hydrogen bromide gas had evolved. This solution was then left to cool and stand overnight and was washed with sodium carbonate solution (10%) (2x30 cm^3), brine solution (1x50 cm^3), water (1x50 cm^3) and dried over anhydrous sodium sulphate. After filtration the dichloromethane was removed and the crude product was fractionally distilled under vacuum to yield 1,3-dioxolane-2-(2,4 dichlorophenyl)-2,2-dibromomethyl-4-*n*-propyl as a viscous brown liquid (46.75 g, yield 60%), boiling point 175-178°C, 4mmHg. Elemental analysis found C 37.59% H 3.23%, Cl 16.42% and Br 37.44%, theory C 36.40%, H 3.23%, Cl 16.39% and Br 36.95%. I.R. ν_{max} 1195, 1151, 1104, 1063cm^{-1}, 1,3-dioxolane ring stretching vibrations. NMR Spectra: δ_H (200MHz, $CDCl_3$) 7.67-7.74ppm (1H, dd), 7.40-7.41ppm (1H, d), 7.24-7.28ppm (1H, dd), 6.42, 6.16ppm (1H, 2s), 4.60-4.67ppm, 4.44-4.50ppm, 4.14-4.18ppm, 3.88-3.93ppm, 3.51-3.56ppm (3H, 5m), 1.20-1.96ppm (4H, m), 0.90-1.10ppm (3H, dt). δ_C (50MHz, deuterated acetone) 136.36, 136.10, 136.03, 135.68, 133.13, 133.01, 132.64, 132.52, 131.55, 131.45, 127.80, 127.76, 109.12, 108.89, 81.08, 78.75, 72.88, 72.25, 49.66, 48.96, 35.84, 34.22, 19.78, 19.59, 14.25, 14.16ppm.

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