

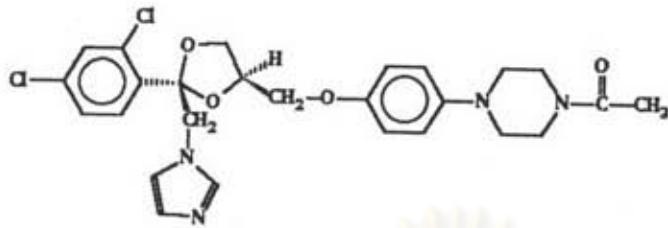
CHAPTER I

INTRODUCTION

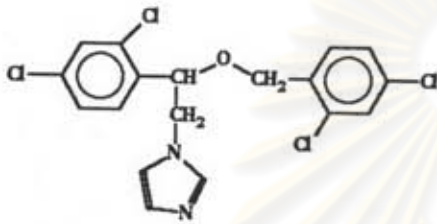
Although it has long been recognized by reliable pharmaceutical manufacturers that the potency of a drug is very important at the time it is administered to the patient, the environment of the drug is altered by changes in the storage conditions (e.g. temperature, humidity, light intensity, etc.) that can affect to the stability of the drug. Drug instability in pharmaceutical products may be attributed to physical and chemical changes. Physical changes can be detected by alterations in appearance, color, odor, taste, dissolution rate or disintegration time of the formulation, whereas chemical changes, which are not self evident, may only be ascertained through chemical analysis. So a accelerated stability testing in physical and chemical stability for a new pharmaceutical preparation is also necessary. A accelerated stability of the drug in general includes the investigation of the effect of temperature, humidity and light on the stability of the drug (Lin and Lachman, 1969). For example, many drugs are known to be photolabile when they are exposed to natural or artificial light such as nifedipine (Berson and Brown, 1955), hydrocortisone, prednisolone, methylprednisolone (Hamlin et al., 1960), chlorpromazine (Felmeister and Dischler, 1964), clonazepam (Wad, 1986), tamoxifen (Wilson and Ruenitz, 1993), fenofibrate (Vargas, Rivas, and Canudas, 1993).

Ketoconazole is an imidazole derivative antifungal drug structurally related to the earlier compounds in this series, such as miconazole and econazole (Figure 1). However, retaining a similar broad-spectrum of antifungal activity, it differs from the earlier members of this group in that it can be administered orally for a wide variety of treatment of superficial or deep fungal infection (Heel et al., 1982; Borgers and Bossche, 1982; Graybill and Craven, 1983). Ketoconazole has been widely used clinically in the treatment of fungal disease. In Thailand, the drug is available for oral use as a 200 mg tablet and for topical use as 2% cream and shampoo.

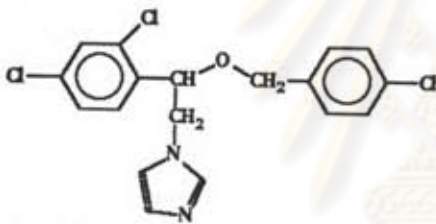
It was reported that ketoconazole is a photosensitive drug because its manufacturing procedure and its storage condition should be protected from light (McEvoy, ed., 1989). Some studies about the stability of ketoconazole and other imidazole derivative antifungals have been reported, nevertheless, there was no report about photochemical stability study of ketoconazole (Kumer et al., 1991; Oyler et al., 1991; Nishikawa and Fujii, 1991; Holmes and Aldous, 1991; Akbuga and Ermantas, 1992). In 1991, Kumer and workers reported the stability of ketoconazole in an ethanolic solution which were placed in glass bottles stored either at room temperature or at 8 °C for 29 days. It was found that no statistically significant difference between or among the test solutions over time. In 1992, Akbura and Ermantas reported the effects of temperature and moisture on the physical properties of ketoconazole tablets. In addition, it was found that disintegrant type and storage condition (moisture, temperature) have an importance on the physical stability (disintegration time and dissolution time) of



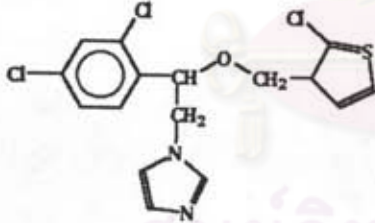
Ketoconazole



Miconazole



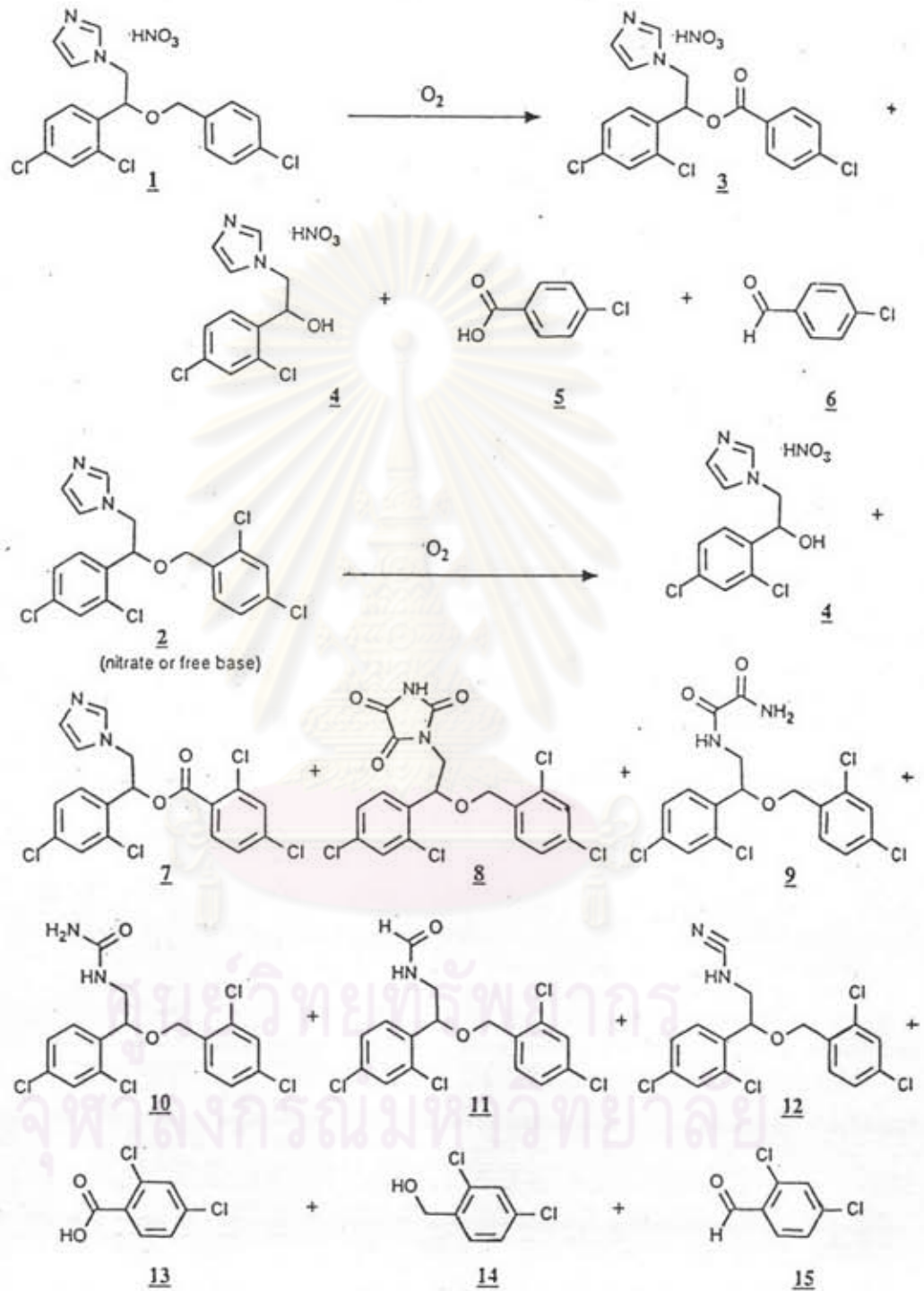
Econazole



Tioconazole

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย

Figure 1 : The chemical structure of imidazole derivative antifungal drugs.



Scheme 1 : The autoxidation products of econazole and miconazole.

ketoconazole tablets . In 1991 , Oyler and his colleagues reported the degradation products of econazole nitrate (1) and miconazole nitrate (2). Both of them were heated to 77 °C in 90% ethanol in the presence of oxygen and 2,2'- azobis(2-methylpropionitrile) (AIBN) for 5 hours. The degradation products of (1) and (2) were compounds 3-6 and compounds 4, 7-15 , respectively (Scheme 1).

To investigate the photochemical degradation products of ketoconazole , light stress stability studies was performed to simulate the condition that is likely to occur during long term storage period . In this study , raw material of ketoconazole in various organic solvents were irradiated with 254 nm UV lamp at room temperature in the presence of oxygen .

The purpose of this study was to identify the photodegradation products of ketoconazole , elucidate their structures based on spectroscopic data, and propose the possible mechanism of its photolysis in order to find out the possible way for protecting its degradation and increase the stability of its pharmaceutical products.

ศูนย์วิทยทรัพยากร
จุฬาลงกรณ์มหาวิทยาลัย