

## Ozonolysis of Five-Membered Heterocycles

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The relative reaction rate of five-membered heterocycles with ozone was evaluated. These relative rates were correlated to the highest bond order value in the corresponding ring, calculated by the convenient HMO method. From this correlation, the reactivity of heterocycles with ozone was able to be predicted. Also it was concluded that the predominant product in the ozonolysis of five-membered heterocycles containing an oxygen atom was the corresponding carboxylic acid, while nitrogen heterocycles gave the corresponding amide.

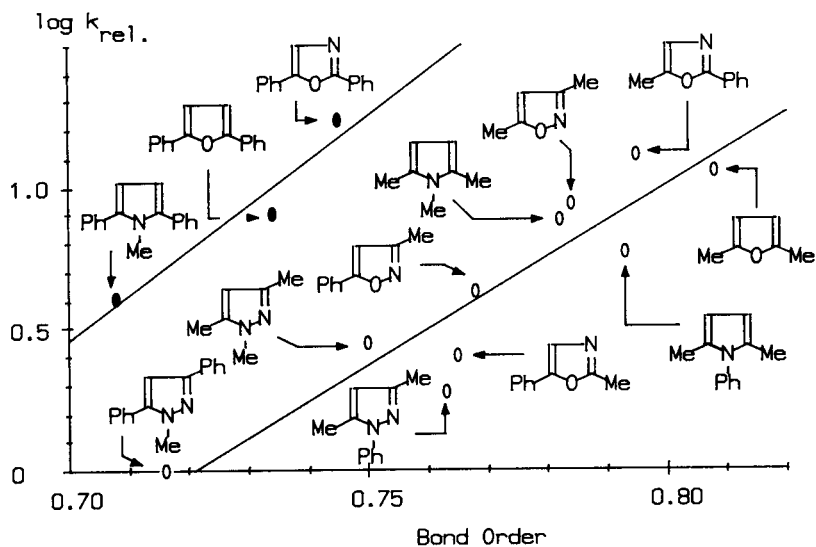
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Five-membered heterocycles having two double bonds in the ring indicate different aromaticity depending on either the kind or the position of hetero atoms. Bird reported that the index of the aromatic character of five-membered heterocycles was estimated about half as much as that of benzene [1]. This estimation suggested that these heterocycles showed either an aromatic or a double bond character. Since the ozonolysis of an olefinic double bond is typical electrophilic addition, we investigated the ozonolysis of various five-membered heterocycles, such as 1,2,5-trisubstituted pyrroles, 1,3,5-trisubstituted pyrazoles, 2,5-disubstituted furans, 3,5-disubstituted isoxazoles and 2,4,5-trisubstituted oxazoles. Also we investigated the ozonolysis products of these heterocycles.

The relative rates of ozonolysis of these heterocycles were determined by the measurement of the decrease of the starting material under competitive conditions at  $-78^\circ$  in dichloromethane. Due to the lowest reactivity of

1-methyl-3,5-diphenyl pyrazole (**2a**), the relative reaction rates of these heterocycles were evaluated based on that of **2a**. When the most stable conformations were calculated by the Force Field method, these heterocycles were found to be almost planar structures, even these having a phenyl substituent group. This calculated prediction indicated that the HMO calculation should be the most suitable method for the estimation of double bond character. Especially, the bond orders of the HMO calculation should be the most convenient parameter to evaluate double bond character. It is well-known that a bond having a higher bond order value indicates more double bond character. Therefore, a plot of the highest bond order in the five-membered heterocycles *vs* the logarithm of the relative rate of ozonolysis gave two straight lines (Scheme I). One line consisted of the substituted 2,5-diphenyl heterocycles, and the other consisted of the remaining heterocycles. This result indicates that the reactivity of these hetero-

Scheme I

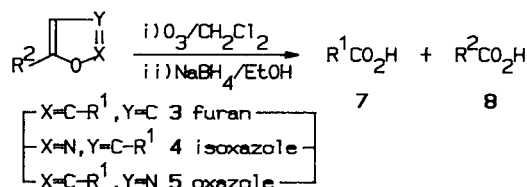


cycles with ozone correlates with the higher value of the bond order, and that the reactivity of five-membered heterocycles to ozone should be predictable from simple molecular orbital calculations.

White *et al.* reported that ozonolysis of 2,5-diphenylfuran proceeded *via* 1,2- and 1,4-addition of ozone to the reactive diene moiety of furan [2]. Although either the type of solvent or the reaction temperature affected the competition between the two types of reactions, the 1,2-addition products were predominant. From this fact, ozonolysis of five-membered heterocycles should mainly proceed *via* a 1,2-addition of ozone to the diene system in the ring. Actually when the five-membered heterocycles were treated with excess ozone-oxygen stream in dichloromethane at  $-78^\circ$ , followed by treatment with sodium borohydride in ethanol, the products *via* a 1,2-addition of ozone were mainly obtained. In the cases of the five-membered heterocycles containing nitrogen atom, the corresponding amide was exclusively obtained (Table I). For example, 1-phenyl-3,5-dimethylpyrazole (**2b**) was treated with ozone and then treated with sodium borohydride to give acetanilide in a 55% yield *via* *N-N* bond cleavage. Similarly, 1-methyl-2,5-diphenylpyrrole (**1a**) gave *N*-methylbenzamide in a 67% yield, which was attributable to the 2- or 5-phenyl group. On the other hand, the five-membered heterocycles having an oxygen atom instead of a nitrogen atom yielded the corresponding carboxylic acid in the reaction with excess ozone-oxygen stream (Table II). When 2,5-diphenylfuran (**3a**) was treated with excess ozone, benzoic acid was obtained in a 112% yield. This result suggested that the products were attributable to both 2- and 5-substituted groups. Similarly, 2,5-diphenyloxazole (**5a**) gave benzoic acid in a 166% yield. Further ozonolysis of 2-methyl-5-phenyl- or 2-phenyl-5-methyloxazole (**5b** or **5c**) offered benzoic acid and acetic acid, which was detected by  $^1\text{H-nmr}$  and gas chromatography. These results suggested that both 2- and

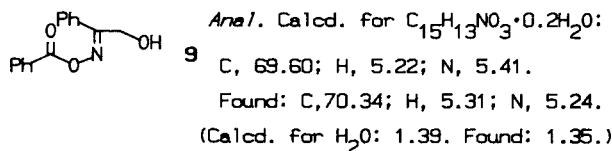
5-substituent of oxazole could be attributable to the products of ozonolysis. From these results, these heterocycles gave the corresponding 1,2-addition products by the treatment with excess ozone in good yields. In conclusion, the reaction of the five-membered heterocycles with excess ozone should be synthetically useful.

Table II



entry	X=, Y=	R <sup>1</sup>	R <sup>2</sup>	Yield (%)		
				7	8	
1	X=C-R <sup>1</sup> , Y=C	3a	Ph	Ph	112	
2	X=N, Y=C-R <sup>1</sup>	4a	Ph	Ph	-	(a)
3	X=N, Y=C-R <sup>1</sup>	4b	Me	Ph	-	59
4	X=C-R <sup>1</sup> , Y=N	5a	Ph	Ph	166	
5	X=C-R <sup>1</sup> , Y=N	5b	Me	Ph	(b)	65
6	X=C-R <sup>1</sup> , Y=N	5c	Ph	Me	77	(b)

(a) **4a** was treated with excess ozone-oxygen stream at room temperature to give **9** in a 12% yield. (b) Acetic Acid was detected by  $^1\text{H-nmr}$  and gc.



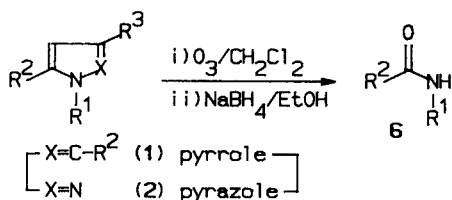
## EXPERIMENTAL

Melting points were measured on a Yanagimoto Micro Melting Point Apparatus, and are uncorrected. The ir spectra were measured on a Jasco IRA-1 Infrared spectrophotometer. The  $^1\text{H-nmr}$  and  $^{13}\text{C-nmr}$  spectra were recorded on a Hitachi R-24 and Jeol-100 spectrometer using tetramethylsilane as an internal standard. The gc was recorded on a Shimadzu GC-4CM gas chromatography by using SE-30 (2 m) column. Flash column chromatography was carried out on a silica gel (230-400 mesh, Merck). The bond orders of the five-membered heterocycles were calculated by the HMO method based on Kikuchi's parameters [3].

## Materials.

1-Methyl-2,5-diphenylpyrrole (**1a**), 1-phenyl-2,5-dimethylpyrrole (**1b**) and 1,2,5-trimethylpyrrole (**1c**) were prepared according to the Paal-Knorr method [4]. 1-Methyl-3,5-diphenylpyrazole (**2a**), 1-phenyl-3,5-dimethylpyrazole (**2b**), 1,3,5-trimethylpyrazole were prepared by Aumers's method [5]. 2,5-Diphenylfuran (**3a**) was prepared by Lutz's method [6]. 3,5-Diphenylisoxazole (**4a**), 3-methyl-5-phenylisoxazole (**4b**) and 3,5-dimethylisoxazole were prepared by Claisen's method [7]. 2-Methyl-5-phenyloxazole (**5b**) and 5-methyl-2-phenyloxazole (**5c**) were prepared by Gabriel's method [8]. These compounds had physical con-

Table I



entry	X=	No.	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Yield
						<b>6</b>
1	C-R <sup>2</sup>	<b>1a</b>	Me	Ph	H	67
2	C-R <sup>2</sup>	<b>1b</b>	Ph	Me	H	39
3	N	<b>2a</b>	Me	Ph	Ph	12
4	N	<b>2b</b>	Ph	Me	Me	55

stants and spectra identical with literature values. 2,5-Dimethylfuran (**3b**) and 2,5-diphenyloxazole (**5a**) were commercially available.

#### Evaluation of the Relative Rate in Ozonolysis of the Five-membered Ring Heterocycles.

The five-membered heterocycles (0.25 mmole) were dissolved in 20 ml of dry dichloromethane with the reactive standard compound (such as tetrahydrocarbazole or *trans*-stilbene) (100 mg) and stearic acid methyl ester (50 mg) as the unreactive standard compound. Ozone-oxygen stream (<1.0 equivalent of the starting material) was bubbled into the solution, and the decrease of the starting material and the reactive compound in the reaction mixture was monitored by gas chromatography.

#### General Ozonolysis of Five-membered Heterocycles.

To the five-membered heterocycles (1 mmole) dissolved in 50 ml of dry dichloromethane, ozone-oxygen stream was bubbled at  $-78^{\circ}$ . When the reaction mixture became blue, the bubbling of ozone was stopped, and excess ozone in the solution was released by bubbling of nitrogen. After sodium borohydride (4 mmoles) in ethanol (10 ml) was added, the solution was allowed to stand overnight at room temperature, and extracted

with dichloromethane. The organic layer was washed with water, dried over anhydrous magnesium sulfate, and the solvent was removed *in vacuo*. By flash column chromatography on silica gel with chloroform-acetone-ethanol mixture (100:10:2 (v/v)), the products were isolated.

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