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Reaction of Epoxides. VI.[1] Reaction of 2,3-Epoxypropyl Aryl Ether with Ethyl-N-phenylformimidate and N,N′-Diphenylformamidine

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The reactions of 2,3-epoxypropylaryl ether with ethyl-N-phenylformimidate (I) and with N,N′-diphenylformamidine (II) were examined. It was found that the reactions gave the same product, N-(2-hydroxy-3-aryloxypropyl)-N-phenylformamide (III).

Keywords——epoxide; C-N double bond; 2,3-epoxypropyl aryl ether; ethyl N-phenylformimidate; N,N′-diphenylformamidine; N-(2-hydroxy-3-aryloxypropyl)-N-phenylformamide; cycloaddition

A number of cycloaddition reactions of epoxides to C-N double and triple bonds have hitherto been widely investigated and we also examined a criss-cross cycloaddition[1] of epoxides to aromatic aldazines. As a series of studies on the reaction of epoxides, we examined the reactions of 2,3-epoxypropyl aryl ether[3] with ethyl-N-phenylformimidate (I)[4] and N,N′-diphenyl formamidine (II).[5]

When 2,3-epoxypropyl phenyl or *p*-tolyl ether was heated with I in the presence of anhydrous stannic chloride catalyst under reflux, a corresponding product was obtained. The

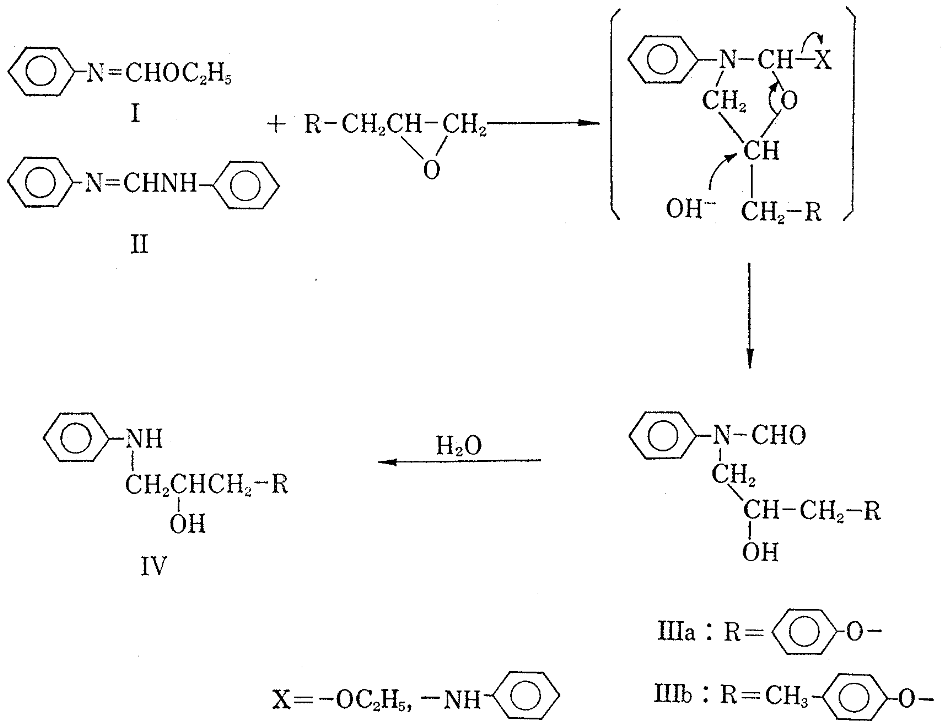

Chart 1

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[1] Part V: M. Furukawa, M. Sugita, Y. Kojima and S. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **22**, 1468 (1974).

[2] Location: *5-1 Oe-hon-machi, Kumamoto 862, Japan.*

[3] G. Van Zyl, *J. Am. Chem. Soc.*, **75**, 5002 (1953).

[4] R.M. Roberts and P.J. Vogt, "Organic Synthesis," Coll. Vol. IV, ed. by N. Rabjohn, John Wiley and Sons, Inc., New York, 1963, p. 464.

[5] R. Kuhn, *Chem. Ber.*, **87**, 272 (1953).

mass spectrum of the product exhibited the abundant molecular ion peak corresponding to the 1 : 1 imidate–epoxide adduct with loss of the ethoxy group, and elemental analysis was also in agreement with the adduct. In the infrared (IR) spectrum of the product, characteristic absorptions assignable to hydroxy and carbonyl groups were observed. The nuclear magnetic resonance (NMR) spectrum showed a characteristic singlet of the formyl proton near τ 1.6.

The same product was also obtained by the reaction of 2,3-epoxypropyl aryl ether with N,N′-diphenylformamidine (II). The reaction was achieved by stirring of II with the 2,3-epoxypropyl aryl ether in the presence of anhydrous stannic chloride catalyst.

On considering these results, it is reasonable to presume that the structure of III depicted in Chart 1 is the most likely for the product

Furthermore, the products (III) were hydrolysed with hydrochloric acid. In the IR spectra of the products, the absorption of carbonyl group disappeared and an absorption of NH group was newly observed at 3200 cm^{-1}. The mass spectra of the products exhibited the molecular ion peak corresponding to the loss of formyl group. The structure of the products were established by comparison with the authentic sample of N-(2-hydroxy-3-aryloxypropyl)aniline prepared by the method of Smith.[6]

It is considered that the reaction takes place through dipolar cycloaddition of the epoxy group to the C-N double bond and the ethoxy or anilino group is eliminated. The attack of the hydroxy anion to the oxazolidine ring affords III finally.

Experimental

All the melting points were determined on a Yanagimoto micro melting point apparatus and were uncorrected. IR and NMR spectra were measured on a JASCO IRA-1 Grating Infrared Spectrometer and JEDL High Resolution NMR Instrument C-60H at 60 MHz, respectively. Mass spectra were determined at 75 eV on a JEOL-01SG Mass Spectrometer.

Reactions of Ethyl-N-phenylformimidate (I) with 2,3-Epoxypropyl Phenyl or *p*-Tolyl Ethers (Method A)——A suspension of anhydrous $SnCl_4$ (0.3 g) in benzene (20 ml) was added dropwise into a solution of ethyl-N-phenylformimidate (I) (0.1 mol) and 2,3-epoxypropyl phenyl or *p*-tolyl ether (0.1 mol) in benzene (40 ml) at 10 ° during 20 min and the reaction mixture was refluxed for 6 hr. After cooling to room temperature, the reaction mixture was washed with 1 N NaOH and then water. The benzene layer was dried over anhydrous sodium sulfate and benzene was evaporated. The residue was washed with *n*-hexane and dissolved in a small amount of ether. The precipitates deposited on cooling were collected by filtration and recrystallized from a mixture of benzene and *n*-hexane (or from ether) to give N-(2-hydroxy-3-phenoxy or *p*-tolyloxypropyl)-N-phenylformamide (III).

Reactions of N,N′-Diphenylformamidine (II) with 2,3-Epoxypropyl Phenyl or *p*-Tolyl Ethers (Method B)——A suspension of anhydrous $SnCl_4$ (0.3 g) in tetrachloromethane (20 ml) was added dropwise into a solution of N,N′-diphenylformamidine (II) (0.1 mol) and 2,3-epoxypropylphenyl or *p*-tolyl ether (0.1 mol) in tetrachloromethane (40 ml) at 10 ° during 20 min and the reaction mixture was stirred for 12 hr at room temperature. The post-treatment was accomplished in the same manner of the method A and product III was obtained.

These results are summarized in TableI.

Table I. N-(2-Hydroxy-3-phenoxy or *p*-tolyloxypropyl)-N-phenylformamide IIIa, b

Product	mp (°C)	Method	Yield (%)	Formura	Analysis (%)					
					Calcd.			Found		
					C	H	N	C	H	N
IIIa	81—82	A B	39 25	$C_{16}H_{17}NO_3$	70.83	6.32	5.16	70.73	6.34	5.10
IIIb	82—83	A B	36 23	$C_{17}H_{19}NO_8$	71.56	6.71	4.91	71.49	6.56	4.73

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[6] L.H. Smith, *J. Med. Chem.*, **20**, 1254 (1973).

Hydrolysis of N-(2-Hydroxy-3-aryloxypropyl)-N-phenylformamide (IIIa,b)——N-(2-hydroxy-3-phenoxy or *p*-tolyloxypropyl)-N-phenylformamide was hydrolysed in 4 N HCl under reflux for 12 hr. The solution was extracted with ether twice and the aqueous layer was evaporated. The residue was treated with 6 N NaOH and extracted with ether. The extract was evaporated and the residue was recrystallized from ethanol to give N-(2-hydroxy-3-phenoxy or *p*-tolyloxypropyl)aniline(IVa,b). IVa; *Anal.* Calcd. for $C_{15}H_{17}NO_2$: C, 74.05: H, 7.04: N, 5.76. Found: C, 74.39: H, 7.12: N, 5.57. IVb; *Anal.* Calcd. for $C_{16}H_{19}NO_2$: C, 74.68: H, 7.44: N, 5.44. Found: C, 74.34: H, 7.55: N, 5.99.

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Hemin-Catalyzed Peroxidation Test for Rapid Evaluation of Antioxidant Activity

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A rapid method for evaluating antioxidant activity was developed. By this method as many as twenty samples can be evaluated simultaneously. Moreover, the procedure is facile and gives quick result. The test system consisted of linoleate emulsion dispersed in phosphate buffer (pH 7.0) containing hemin. The rapid oxygen uptake due to hemin-catalyzed oxidation of linoleic acid was manometrically measured with a Gilson differential respirometer. The rate of decrease in the oxygen uptake was used for evaluating antioxidant activity of samples. The activity of browning products formed by the reaction between amino acid and sugar was determined by this method, and the results were compared with those obtained by the active oxygen method.

Keywords——antioxidant evaluation; oxygen uptake; linoleic acid; hemin; browning product; tocopherol

A number of methods have been known for evaluating oxidative stability of fatty materials and antioxidant activity.[2] The Schaal oven test, the active oxygen method (AOM) and many procedures measuring oxygen uptake are typical methods widely used. However, these conventional methods are time consuming and laborious.

Hamilton and Tappel[3] developed a polarographic, hemoglobin catalyzed oxygen uptake method for determining antioxidant activity. Berner *et al.*[4] modified this method to determine activity in animal fats. Cort[5] also published a paper describing a similar procedure to screen compounds having antioxidant activity and to study synergism using safflower oil as substrate. In these methods, the rate of oxygen uptake was measured with an oxygen analyzer. Thus, only one sample can be determined with one instrument although time required for the test is very short. So, we attempted to develop a new system which can evaluate many samples simultaneously in a short time. As a result, very efficient method was developed. The procedure consists of a hemin peroxidation system and the amount of oxygen consumption in the system is measured manometrically with a Gilson differential respirometer

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[1] Location: *16-89, Kashima-3-chome, Yodogawa-ku, Osaka, 532, Japan.*

[2] E.R. Sherwin, *J. Am. Oil Chemists' Soc.*, **45**, 632A (1968).

[3] J.W. Hamilton and A.L. Tappel, *J. Am. Oil Chemists' Soc.*, **40**, 52, (1963).

[4] D.L. Berner, J.A. Conte, and G.A. Jacobson, *J. Am. Oil Chemists' Soc.*, **51**, 292 (1974).

[5] W.M. Cort, *Food Technology*, *Oct.* p. 60, (1974).