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Reaction of Epoxides. IV.1) Addition of 2,3-Epoxypropyl Phenyl Ether to Oximes and Hydrazones

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Reaction of 2,3-epoxypropyl phenyl ether with equivalents of aromatic aldoximes and hydrazones in which the difunctional group, the carbon-nitrogen double bond adjacent to the active hydrogen group, is involved in the molecule was attempted in the presence of Lewis acid catalyst. In the result, the 1:1 adduct formed by the addition of the epoxide to the active hydrogen group was obtained as the only product, no trace of any cycloaddition product of the epoxide to the carbon-nitrogen double bond being isolated. The structure of the adduct was also discussed.

β-Hydroxyethylation of a number of compounds involving the active hydrogen atom, alcohols, thiols, phenols, amines and active methylene compounds, with epoxides has hitherto been widely investigated. Cycloaddition of epoxides to several compounds, in which a carbon-nitrogen double bond is involved, such as Schiff bases,1,3) nitriles,4a,b) isocyanates,5a,b) isothiocyanates6a,b) and carbodiimides,7a,b) has also been well known. In continuation of our studies on the reaction of epoxides, we attempted to react epoxides with oximes and hydrazones in which a carbon-nitrogen double bond adjacent to an active hydrogen group is involved in the molecule. This paper deals with the reaction between 2,3-epoxypropyl phenyl ether and aromatic aldoximes or phenylhydrazones.

Regarding the reaction of epoxides with oximes, Bachmann8) has already reported that the hydroxy group of the ketoximes undergoes β-hydroxyethylation with a few simple

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1) Part III: M. Furukawa, K. Nagato, Y. Kojima and S. Hayashi, *Chem. Pharm. Bull.* (Tokyo), 20, 2262 (1972).
2) Location: *Oe-hon-machi, Kumamoto.*
3) R. Oda, M. Okano, S. Tokiura and A. Miyano, *Bull. Chem. Soc. Japan*, **35**, 1216 (1962).
4) *a*) R. Oda, M. Okano, S. Tokiura and F. Misumi, *Bull. Chem. Soc. Japan*, **35**, 1219 (1962); *b*) M. Taguchi and K. Nagano, *Chem. Abstr.*, **71**, 124477w (1969).
5) *a*) K. Gulbins and K. Hamann, *Angew. Chem.*, **70**, 705 (1958); *b*) G.P. Speranza and W.J. Peppel, *J. Org. Chem.*, **23**, 1922 (1958).
6) *a*) G.A. Razuvaev, A.N. Egorochkin, V.S. Etlis and A.P. Sineokov, *Izv. Akad. Nauk SSSR. Ser. Khim.*, **1963**, 1518 (*Chem. Abstr.*, **59**, 13789c (1958)); *b*) V.S. Etlis, A.P. Sineokov and G.A. Razuvaev, *ibid.*, **1964**, 737 (*Chem. Abstr.*, **61**, 3112a (1964)).
7) *a*) K. Gulbins and K. Hamann, *Chem. Ber.*, **94**, 3287 (1961); *b*) K. Gulbins, M. Roth and K. Hamann, *Angew. Chem.*, **73**, 434 (1961).
8) G.B. Bachmann and T. Hokama, *J. Am. Chem. Soc.*, **81**, 4223 (1959).

epoxides in the presence of sodium or lithium ethoxide, though no unequivocal veidence for the structure is provided. The reaction of aldoximes with styrene oxide in the similar conditions, however, gives styrene glycol and benzonitriles, which were probably formed through the β-hydroxyethyl ether of the aldoximes. Kliegel[9] has also shown that oximes reacted with epoxides in the similar conditions to give not only 2-hydroxyethyl ether of the oximes but also nitrones.

Expecting 1,3-dipolar cycloaddition to the carbon-nitrogen double bond of oximes, we attempted to carry out the reaction of 2,3-epoxypropyl phenyl ether[10a,b] with *syn*-benzaldoximes possessing a substituent group in the *para* position of the benzene ring in the presence of Lewis acid which is generally used in the cycloaddition of epoxides to a carbon-nitrogen double bond. The reaction was carried out by stirring a solution of equivalent amounts of 2,3-epoxypropyl phenyl ether and *syn*-benzaldoximes in dry benzene containing a small amount of stannic chloride catalyst at room temperature for about 30 hours. The resulting product was confirmed to be 1:1 aldoxime–epoxide adduct by the elemental analysis and the mass spectrum in which the corresponding molecular ion was observed as the abundant peak. By this result, the following compounds (I—IV), in which a position isomer due to the orientation of the cleavage of the epoxide ring is involved, are possible for the structure of the adduct.

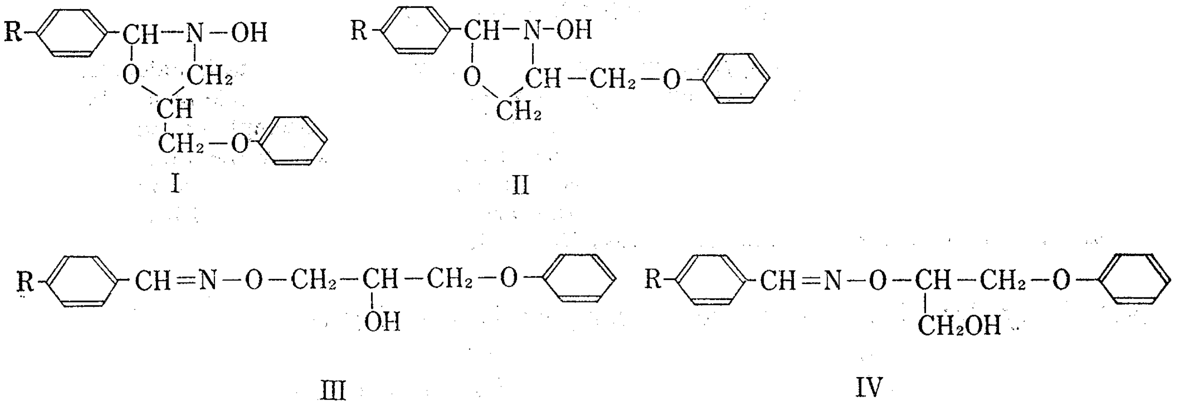

Chart 1

Among these possible structures, I and II are presumed to be unstable and immediately stabilized with elimination of water or by conversion into nitrone,[9] as shown in the following shceme. However, the adduct was stable and the mass spectrum did not show the frag-

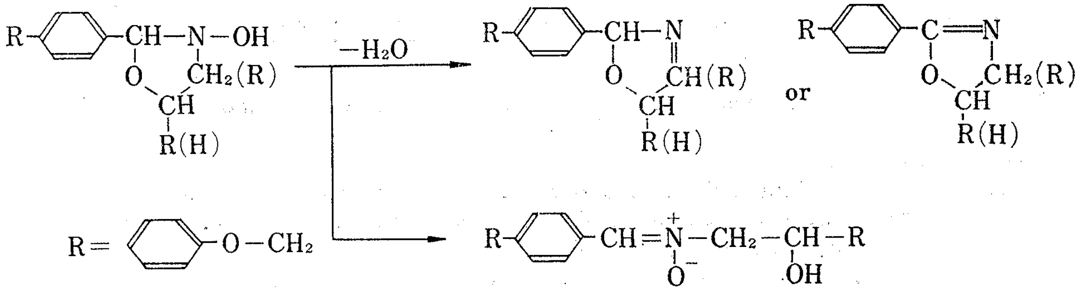

Chart 2

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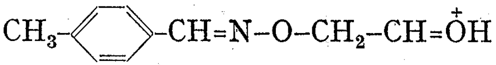
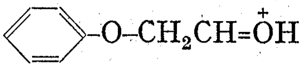
9) W. Kliegel, *Ann.*, **733**, 192 (1970).

10) *a*) Y. Iwakura and S. Izawa, *J. Org. Chem.*, **29**, 379 (1964); *b*) Y. Iwakura, S. Izawa and F. Hayano, *J. Poly. Scie.*, **4**, 751 (1966).

ment peak corresponding to the elimination of water from the molecular ion. The nuclear magnetic resonance (NMR) spectrum indicated the different pattern from that of nitrone[9] and a singlet assignable to the methylidene hydrogen was observed at near τ 1.80, which was almost same for the methylidene hydrogen of *syn*-benzaldoxime. Therefore, the adduct would be III or IV. When R is the methyl group, the mass spectrum of III might exhibit a fragment ion corresponding to  or  at *m*/*e* 178 or 137 respectively. On the other hand, the mass spectrum of IV should indicate the fragmentation characteristic to primary alcohols at *m*/*e* 31 due to $CH_2=\overset{+}{O}H$. The adduct

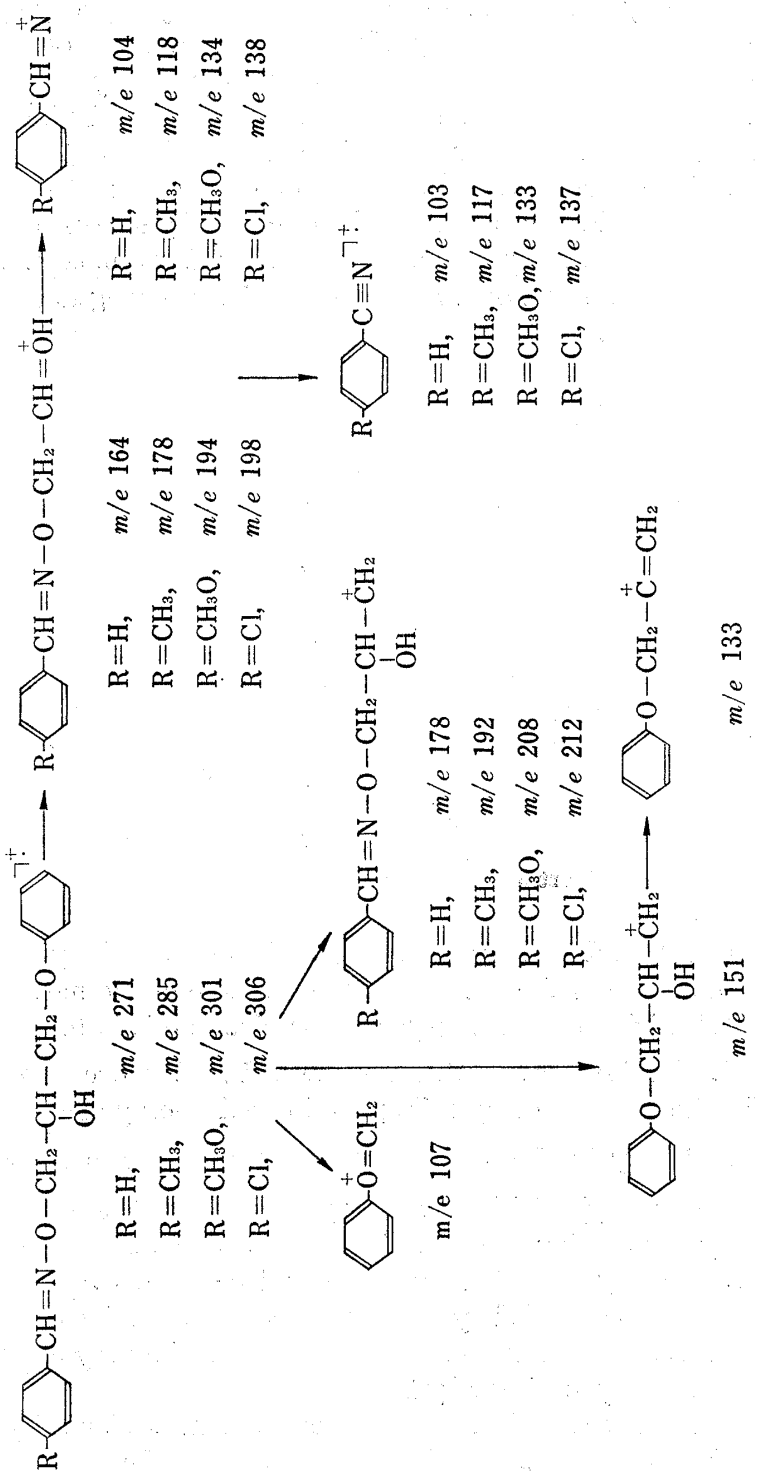


Chart 3

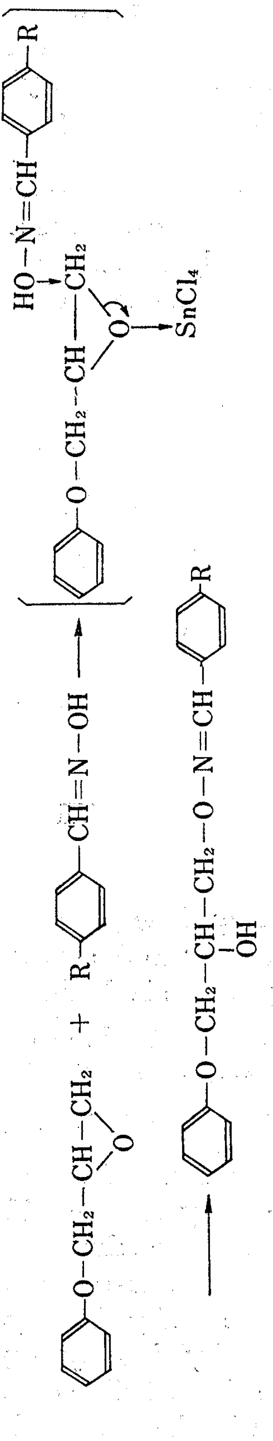
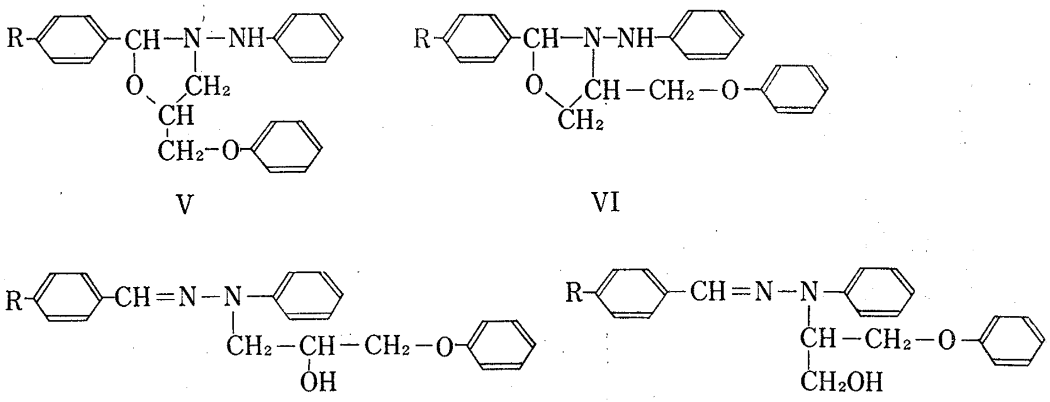


Chart 4

exhibited a fragment ion at *m/e* 178 as an abundant peak (70% intensity), no trace of any fragment ion peak at *m/e* 31 being observed. Analogously, when R is hydrogen, methoxy and chlor groups, the similar peaks were observed at *m/e* 164, 194 and 198, respectively, as the abundant peak. On the basis of these results, it is reasonable to consider that the structure of III is more likely for the adduct. The possible fragmentation is as follows.

The formation of III is presumed to occur by the nucleophilic attack of the hydroxy group of the aldoxime to the positive 1,3-dipolar methylene group formed by the cleavage of the epoxide ring which was catalyzed with Lewis acid.

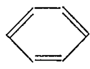
Aromatic aldehyde-hydrazones may be expected to show behaviors analogous to those of aromatic aldoximes toward epoxides, because of the structural similarity. Thus, the reaction between 2,3-epoxypropyl phenyl ether and some aromatic aldehyde-phenylhydrazones was attempted. The reaction was carried out by adding a small amount of stannic chloride catalyst to a solution of equivalent amounts of 2,3-epoxypropyl phenyl ether and aromatic aldehyde-phenylhydrazones in dry carbon tetrachloride below 10° during 40—60 minutes in a nitrogen stream and then by stirring for additional 5—6 hours at 20—25°. In some cases, during or after addition of the catalyst, the isolation of the product from the reaction mixture was observed. The product was confirmed to be 1:1 hydrazone–epoxide adduct by the elemental analysis and the mass spectrum which exhibited the molecular ion as an abundant peak. Similarly to the case of aromatic aldoximes, the following four structures (V—VIII) are possible for the adduct.



V VI

VII VIII

Chart 5

Among these possible structures, V and VI may be anticipated to show a fragment ion corresponding to the elimination of aniline in the mass spectrum, because of the most facile cleavage of the N–N linkage. VIII might exhibit a fragment ion characteristic to primary alcohols at *m/e* 31 due to $CH_2{=}\overset{+}{O}H$. In the mass spectrum of the adduct, however, no these peaks were observed. Instead, the peak corresponding to ionized methylideneaniline, -N=CH_2, which is anticipated only in the mass spectrum of VII, was observed at *m/e* 105 as an abundant peak (90% intensity). This result suggests that the structure of VII is more likely for the adduct. By considering the abundant peaks observed in the mass spectrum of the adduct, the plausible fragmentation process would be as follows.

Support for the structure VII was also provided by the NMR spectrum. A singlet assignable to the methylidene hydrogen was observed at near τ 2.40 which was similarly exhibited for the methylidene hydrogen of benzaldehyde–phenylhydrazone.

The distinct difference between III and VII inspite of their structural similarity was observed in the mass and infrared (IR) spectra. In the mass spectrum, the cleavage be-

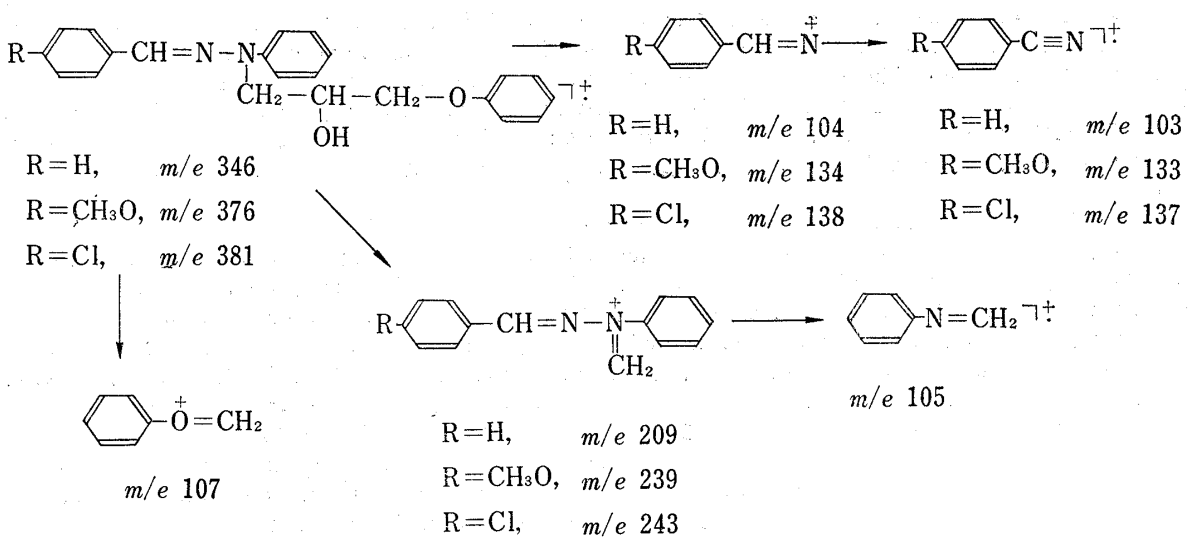


Chart 6

tween the oxygen atom and the methylene group in III was apparently observed, whereas the cleavage between the nitrogen atom and the methylene group in VII was not observed at any rate. In the IR spectrum, the absorption assignable to the hydroxy group in III exhibited a shift to lower frequency, whereas the absorption due to the hydroxy group in VII was observed in the normal region. Such a difference in the IR spectrum can be explained by the difference of the steric structure between III and VII. III would readily undergo the formation of intramolecular hydrogen bond between the hydroxy group and the nitrogen atom, because of the *syn*-form. However, the formation of the similar hydrogen bond would be difficult in VII by the steric interference with the bulky benzene ring, because of the *anti*-form of VII. The formation of hydrogen bond shifts the absorption of the hydroxy group to a lower frequency.

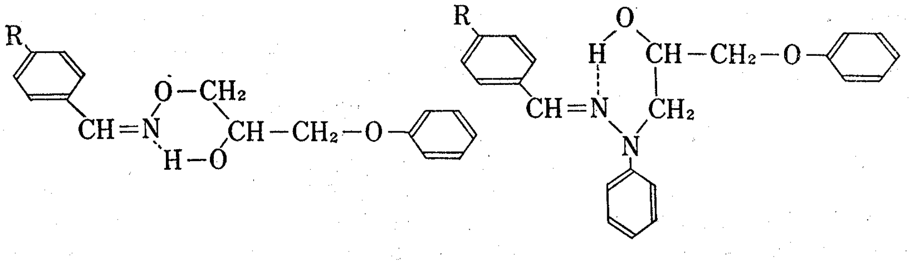


Chart 7

Experimental

***syn*-Benzaldoxime O-2-Hydroxy-3-phenoxypropyl Ether (IIIa, R=H)**——To a solution of 2.42 g (0.02 mole) of *syn*-benzaldoxime and 3.0 g (0.02 mole) of 2,3-epoxypropyl phenyl ether in 50 ml of dry benzene was added with stirring a solution of 0.52 g (0.002 mole) of stannic chloride in 20 ml of dry benzene during 15—20 min and the mixture was stirred for additional 26 hr at room temperature. The solution was washed with 50 ml of water and the separated benzene layer was dried over Na_2SO_4, and distilled to remove benzene under reduced pressure. The residue solidified on cooling was recrystallized from benzene to give 0.7 g (13%) of colorless needles melting at 148.3—148.5°. *Anal.* Calcd. for $C_{16}H_{17}O_3N$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.81; H, 6.22; N, 5.05. Mass Spectrum *m/e*: 271 (M^+). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3238 (OH). NMR ($CDCl_3$) τ: 6.20—5.25 (5H, m, CH_2CHCH_2), 3.25—2.45 (10H, m, aromatic hydrogens), 1.85 (1H, s, CH=N).

***syn*-*p*-Tolualdoxime O-2-Hydroxy-3-phenoxypropyl Ether (IIIb, R=CH_3)**——A solution of 0.37 g (0.0014 mole) of stannic chloride in 10 ml of dry benzene was added with stirring in 15 min at room temperature into a solution of 1.9 g (0.014 mole) of *syn*-*p*-tolualdoxime and 2.1 g (0.014 mole) of 2,3-epoxypropyl phenyl ether in 40 ml of dry benzene. The mixture was stirred for additional 26 hr at room temperature and washed with 50 ml of H_2O. The benzene layer separated was dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residue solidified at room temperature was recrystallized from benzene to give 0.6 g (15%) of colorless needles melting at 147—148°. *Anal.* Calcd. for $C_{17}H_{19}O_3N$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.48; H, 6.58; N, 4.94. Mass Spectrum *m/e*: 285 (M^+). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3180 (OH), 1255 (–O–). NMR ($CDCl_3$) τ: 7.65 (3H, s, CH_3), 6.15—5.15 (5H, m, CH_2CHCH_2), 3.25—2.55 (9H, m, aromatic hydrogens), 1.96 (1H, s, CH=N).

***syn-p*-Methoxybenzaldoxime O-2-Hydroxy-3-phenoxypropyl Ether (IIIc, R=CH_3O)**——To a solution of 4.5 g (0.03 mole) of *syn-p*-methoxybenzaldoxime and 4.5 g (0.03 mole) of 2,3-epoxypropyl phenyl ether in 60 ml of dry benzene was added with stirring a solution of 0.8 g (0.003 mole) of stannic chloride in 20 ml of dry benzene during 15 min at room temperature. The mixture was stirred for additional 32 hr at room temperature. Resulted precipitates were collected by filtration and recrystallized from MeOH to give 2.2 g (24%) of colorless plates melting at 162—162.5°. *Anal.* Calcd. for $C_{17}H_{19}O_4N$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.47; H, 6.47; N, 4.74. Mass Spectrum *m/e*: 301 (M^+). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3180 (OH), 1266 (–O–).

***syn-p*-Chlorobenzaldoxime O-2-Hydroxy-3-phenoxypropyl Ether (IIId, R=Cl)**——To a suspension of 7.8 g (0.05 mole) of *syn-p*-chlorobenzaldoxime and 7.5 g (0.05 mole) of 2,3-epoxypropyl phenyl ether in 80 ml of dry benzene was added with stirring a solution of 1.3 g (0.005 mole) of stannic chloride in 20 ml of dry benzene during 20 min at room temperature. The suspension gradually became clear and then precipitates were deposited again. After stirring for additional 18 hr at room temperature, the precipitates were collected by filtration and recrystallized from EtOH to give 6.7 g (44%) of colorless plates melting at 162—162.5°. *Anal.* Calcd. for $C_{16}H_{16}O_3NCl$: C, 62.95; H, 5.29; N, 4.59. Found: C, 62.77; H, 5.18; N, 4.70. Mass Spectrum *m/e*: 306 (M^+). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3180 (OH), 1249 (–O–).

N-Phenyl-N-(2-hydroxy-3-phenoxypropyl)-N′-benzylidenehydrazine (VIIa, R=H)——To a solution of 9.8 g (0.05 mole) of benzaldehyde–phenylhydrazone and 8.0 g (0.055 mole) of 2,3-epoxypropylphenyl ether in 80 ml of dry CCl_4 was added with stirring a solution of 0.7 g (0.0025 mole) of stannic chloride in 20 ml of CCl_4 below 10° during 20—30 min in a nitrogen stream. After adding, the mixture was stirred for additional 6 hr at 20—25° in a nitrogen stream. The mixture was shaken with 100 ml of H_2O and weakly basified with 0.1 N potassium hydroxide solution. The CCl_4 layer was separated, dried over Na_2SO_4 and evaporated to dryness under reduced pressure. Crystal mass solidified upon cooling was recrystallized from EtOH to give 3.0 g (17%) of colorless prisms melting at 86—86.5°. *Anal.* Calcd. for $C_{22}H_{22}O_2N_2$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.19; H, 6.42; N, 8.22. Mass Spectrum *m/e*: 346 (M^+). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3360 (OH), 1249 (–O–). NMR ($CDCl_3$) τ: 7.12 (1H, OH), 6.00—5.50 (5H, m, CH_2CHCH_2), 3.10—2.25 (15H, m, aromatic hydrogens), 2.20 (1H, s, CH=N).

N-Phenyl-N-(2-hydroxy-3-phenoxypropyl)-N′-*p*-methoxybenzylidenehydrazine (VIIb, R=CH_3O)——To a solution of 11.4 g (0.05 mole) of *p*-methoxybenzaldehyde–phenylhydrazone and 8.0 g (0.055 mole) of 2,3-epoxypropyl phenyl ether in 80 ml of dry CCl_4 was added with stirring a solution of 0.7 g (0.0025 mole) of stannic chloride in 20 ml of dry CCl_4 below 10° during 1 hr in a nitrogen stream. After addition, the mixture was stirred for additional 6 hr at 20—25°. The precipitates deposited were collected by filtration and recrystallized from EtOH to give 13.0 g (69%) of colorless needles melting at 114—114.5°. *Anal.* Calcd. for $C_{23}H_{24}O_3N_2$: C, 73.38; H, 6.43; N, 7.44. Found: C, 73.08; H, 6.46; N, 7.30. Mass Spectrum *m/e*: 376 (M^+). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3290 (OH), 1255 (CH_3O), 1248 (–O–). NMR ($CDCl_3$) τ: 7.11 (1H, OH), 6.28 (3H, s, CH_3O), 6.10—5.55 (5H, m, CH_2CHCH_2), 3.25—2.50 (14H, m, aromatic hydrogens), 2.40 (1H, s, CH=N).

N-Phenyl-N-(2-hydroxy-3-phenoxypropyl)-N′-*p*-chlorobenzylidenehydrazine (VIIc, R=Cl)——To a suspension of 6.93 g (0.03 mole) of *p*-chlorobenzaldehyde–phenylhydrazone and 4.95 g (0.033 mole) of 2,3-epoxypropyl phenyl ether in 50 ml of dry CCl_4 was added with stirring a solution of 0.4 g (0.0015 mole) of stannic chloride in 30 ml of dry CCl_4 below 10° in a nitrogen stream during 40 min. After addition, stirring was continued for additional 5 hr at 20—25°. The solution was shaken with 100 ml of H_2O and weakly basified with 0.1 N potassium hydroxide solution. The CCl_4 layer was then separated, dried over Na_2SO_4 and evaporated under reduced pressure. To the residue was added 30 ml of MeOH. Precipitates deposited were collected by filtration and recrystallized from MeOH to give 9.0 g (79%) of colorless needles melting at 94.5—96°. *Anal.* Calcd. for $C_{22}H_{21}O_2N_2Cl$: C, 69.51; H, 5.84; N, 7.37. Found: C, 69.01; H, 5.35; N, 7.38. Mass Spectrum *m/e*: 381 (M^+). IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3343 (OH), 1245 (–O–). NMR ($CDCl_3$) τ: 7.37 (1H, OH), 6.05—5.45 (5H, m, CH_2CHCH_2), 3.20—2.45 (14H, m, aromatic hydrogens), 2.28 (1H, s, CH=N).

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