SYNTHESIS AND STEREOCHEMISTRY OF α,β,α',β'-DIEPOXY KETONES

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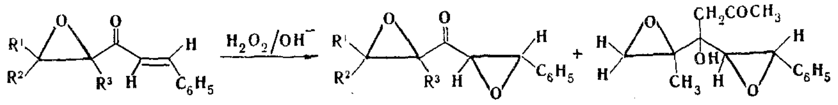
Diastereomeric α,β,α',β'-diepoxy ketones and the products of their condensation with acetone were synthesized by oxidation of cinnamoyloxiranes with alkaline hydrogen peroxide. It is shown that the acidic hydrolysis of 2-methyl-1,2,4,5-diepoxy-3-pentanones leads to ketones of the tetrahydropyran and tetrahydrofuran series. The stereochemistry of the hydrolysis products was confirmed by chemical transformations and spectroscopy.

The synthesis of aryl-aliphatic diepoxy ketones by epoxidation of β-arylacrylyloxiranes has been reported [1]; however, their stereochemistry and chemical transformations were not discussed. In addition, it is known that the acidic hydrolysis of aliphatic diepoxy ketones leads to tetrahydropyranones [2-4] and that tetrahydropyranones or tetrahydrofuranones are formed in the acetolysis of keto diepoxides of the steroid series [5]; Kamernitskii and coworkers [5] attribute the latter fact to the regioselectivity of opening of the epoxy ring. In order to synthesize aryl-aliphatic diepoxy ketones and to ascertain their stereochemistry and the structural specificity and stereospecificity of the acid hydrolysis of diastereomeric diepoxy ketones, in the present research we studied the products of alkaline epoxidation of β-arylacrylyloxiranes Ia-d.

We found that the oxidation of the E isomers of epoxy ketones Ia-d with alkaline hydrogen peroxide in a methanol–acetone system leads to mixtures of two diastereomeric keto diepoxides IIa, b and Va, b with a trans configuration of the aryl-substituted epoxy ring that differ with respect to the configuration of the chiral center of the epoxide ring, which is not involved in the oxidation. The trans configuration of the epoxy ring was confirmed by the data from the PMR spectra (Table 1) [6]. It was shown that the degree of stereoselectivity of the reaction increases when there is a substituent attached to the α-carbon atom of the epoxy ring in starting unsaturated epoxy ketones Ia, c; this is evidently associated with the steric hindrance in the cyclization of the intermediate β-hydroperoxy enolate [7].



I a-d II-V a, b VI a,b

Ia, IIa, b $R^1=R^2=H$, $R^3=CH_3$; Ib, IIIa, b $R^1=R^2=CH_3$, $R^3=H$; Ic, IVa, b $R^1=R^3=CH_3$, $R^2=H$; Id, Va, b $R^1=R^3=H$, $R^2=CH_3$

The ratio of the acetone and methanol used as the solvents in the reaction has a substantial effect on the yields of keto diepoxides IIa, b. The oxidation of cinnamoyloxirane Ia in acetone leads to dioxides IIa, b, which, under alkaline catalysis conditions, undergo aldol condensation with acetone to give a mixture of diastereomeric diepoxy ketols VIa, b. The formation of only two diastereomeric diepoxy ketols VIa, b is probably associated with the reversibility of the addition of acetone to the carbonyl group of ketones IIa, b. Compounds VIa, b were also obtained in a separate experiment by condensation of keto diepoxides IIa, b with acetone in an alkaline medium. The structures of diepoxy ketols VIa, b were confirmed by spectroscopy and chemical means by retroaldolization with the liberation of acetone.

It seemed of interest to determine the relative configuration of the aryl-substituted epoxy ring, which is primarily formed in the course of the oxidation, with respect to the

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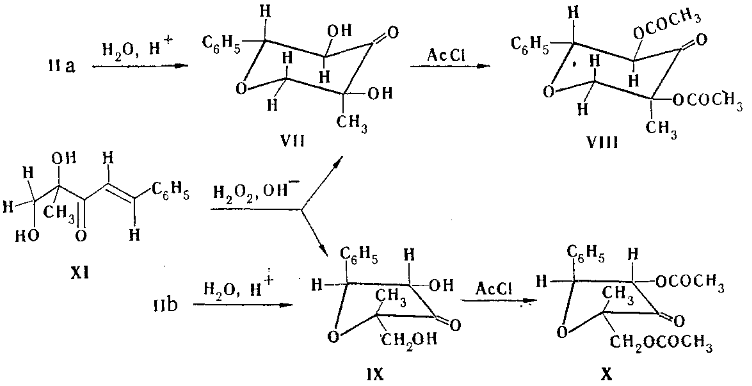
TABLE 1. Physicochemical and Spectral Characteristics of II-XI

Compound	mp, °C	IR spectrum, ν, cm^{-1}	PMR spectrum, δ, ppm (J, Hz)	Found, %		Empirical formula	Calc., %		Yield, % (a/b ratio)
				C	H		C	H	
IIa	60—61	1720 (C=O)	1,48 s (3H); 2,80 d, 3,02 d (2H, J=5,0); 3,70 d, 3,84 d (2H, J=1,5); 7,15 s (5H)	70,4	5,0	$C_{12}H_{12}O_3$	70,6	5,9	62 (1,7/1)
IIb	59—60		1,48 s (3H); 2,90 d, 3,23 d (2H, J=5,0); 3,52 d, 3,90 d (2H, J=1,5); 7,4—7,7 m (5H)	70,4	6,0				
IIIa	68—69	1720 (C=O)	1,28 s (3H); 1,12 s (3H); 3,40 s (1H); 3,52 d, 3,75 d (2H, J=2,0); 7,08 s (5H)	71,4	6,4	$C_{13}H_{14}O_3$	71,5	6,5	85 (1/1)
IIIb	103—104		1,42 s (3H); 1,32 s (3H); 3,30 s (1H); 3,50 d, 4,10 d (2H, J=2,0); 7,20 s (5H)	71,4	6,3				
IVa	Oil	1715 (C=O)	1,44 s (3H); 1,33 d (3H); 3,20 q (1H); 3,80 s (2H); 7,26 s (5H)	71,6	6,3	$C_{13}H_{14}O_3$	71,5	6,5	51 (1,4/1)
IVb	55—56		1,41 s (3H); 1,38 d (3H); 3,42 q (1H); 3,60 d, 3,90 d (2H, J=2,0); 7,5—7,8 m (5H)	71,7	6,4				
Va	113—114	1720 (C=O)	1,42 d (3H); 3,29 m (2H); 3,60 d, 4,02 d (2H, J=1,8); 7,25 s (5H)	70,4	5,8	$C_{12}H_{12}O_3$	70,6	5,9	54 (1,2/1)
Vb	68—70		1,38 d (3H); 3,32 m (2H); 3,50 d, 4,10 d (2H, J=1,8); 7,5—7,8 m (5H)	70,4	5,7				
VIa	90—92	1700 (C=O), 3400 s (OH), 3520 w(OH)	1,38 s (3H); 2,20 s (3H); 2,48 d, 2,74 d (2H, J=5,0); 2,56 s (2H); 2,88 d, 4,02 d (2H, J=1,5); 4,52 s (1H); 7,20 s (5H)	68,5	6,8	$C_{15}H_{18}O_4$	68,7	6,9	18
VIb	In a mixture		1,36 s (3H); 2,20 s (3H); 2,44 d, 2,75 d (2H, J=5,0); 2,55 s (2H); 2,95 d, 4,02 d (2H, J=1,5); 4,15 s (1H); 7,18 s (5H)	—	—				
VII	86—89 128—129	1705 (C=O)	1,65 s (3H); 3,53 d, 4,19 d (2H, J=10,8); 4,16 d, 4,50 d (2H, J==9,5); 3,25 s (1H); 5,55 s (1H)	64,6	6,5	$C_{12}H_{14}O_4$	64,8	6,4	49
VIII	115—116	1720 (C=O), 1740 (C=O), 1745 (C=O)	1,80 s (3H); 2,02 s (3H); 2,17 s (3H); 4,03 d, 4,53 d (2H, J=10,8); 4,79 d, 5,50 d (2H, J=9,5)	62,6	5,7	$C_{16}H_{18}O_6$	62,7	5,9	80
IX	92—93	1780 (C=O), 3580 (OH), 3610 (OH)	1,10 s (3H); 3,39 s (2H); 3,96 d, 4,95 d (2H, J=8,4); 7,1—7,4 m (5H)	65,0	6,2	$C_{12}H_{14}O_4$	64,8	6,4	51
X	Oil	1780 (C=O), 1740 (C=O), 1745 (C=O)	1,23 s (3H); 1,83 s (3H); 2,00 s (3H); 3,78 d, 4,20 d (2H, J=13,5); 4,92 s (2H); 7,18 s (5H)	62,6	6,0	$C_{16}H_{18}O_6$	62,7	5,9	75
XI	84—86	1680 (C=O), 3480 (OH), 3570 (OH)	1,26 s (3H); 3,36 s (3H); 4,16 s (H); 7,23 d, 7,66 d (2H, J=16,0); 7,36 s (5H)	69,7	6,8	$C_{12}H_{14}O_3$	69,9	6,8	81

chiral center present in the molecule, i.e., to ascertain the diastereo-differentiating capacity of alkaline hydrogen peroxide in the reaction with cinnamoyloxiranes. It is known that the acidic hydrolysis of chalcone oxides [8] and the electrophilic opening of the epoxy ring of cinnamoyloxirane Ia [9] proceed regioselectively with retention of the configuration of the α-carbon atoms. As a result of the acidic hydrolysis of diastereomers IIa, b one might therefore have expected the formation of two 3,5-dihydroxytetrahydro-4-pyranones that differ with respect to the configuration of the chiral $C_{(3)}$ center; the relative configuration of the $C_{(3)}$ and $C_{(5)}$ atoms in the cyclization product is identical to the relative configuration of the chiral centers of diepoxy ketones IIa, b.

In fact, the acidic hydrolysis of diepoxy ketone IIa in aqueous dioxane leads to 3,5-dihydroxytetrahydro-4-pyranone (VII). In the IR spectrum of VII the position of the νOH absorption band at 3520 cm^{-1} does not change when the solution is diluted to 10^{-3} mole/liter, which constitutes evidence for the existence of intramolecular hydrogen bonds between the hydroxy groups and the oxygen atom of the carbonyl group. In the PMR spectrum of 3,5-dihydroxytetrahydropyranone VII the observed spin-spin coupling constant (J = 10.3 Hz) is characteristic for the vicinal protons in the six-membered ring in the chair conformation and corresponds to interaction of the axially oriented 6-H proton with the axial 5-H proton. The configuration of the $C_{(3)}$ atom was assigned on the basis of a comparison of the chemical shifts of the protons of tetrahydropyran ring VII and its diacetate VIII. The shift of the signals of the geminal protons attached to the $C_{(2)}$ atom to weak field as a consequence of the deshielding effect of the ester group corresponds to an equatorial orientation of the 3-OH group [10]. A comparison of the chemical shift of the 3-CH_3 protons with the chemical shifts of the methyl protons in analogous heterocyclic systems [11] also provides evidence for the axial orientation of the 3-CH_3 group in dihydroxytetrahydropyranone VII.



The presence of a hydrogen atom in the α position relative to the carbonyl group does not exclude the possibility of enolization, and solvolysis product VII may then be the result of thermodynamic control of the cyclization, which casts doubt upon correlation of the configuration of the C_5 atom of dihydroxytetrahydropyranone VII with the configuration of the C_2 atom of keto diepoxide IIa. A study of deuterium exchange at C_5 in VII by means of PMR spectroscopy demonstrated the absence of isotopic substitution under acidic hydrolysis conditions. In addition, it is known that epoxy ketones are not epimerized in acidic media [12]; in the case of diepoxy ketones IIa, b epimerization also does not take place in alkaline media. Thus the relative configuration of the $C_{(3)}$ and $C_{(5)}$ atoms of dihydroxytetrahydropyranone VII is SR(RS), which corresponds to the RR(SS) configuration of the aryl-substituted epoxide ring in IIa. The RRR(SSS) relative configuration was assigned to diepoxy ketone IIb on the basis of this fact. A comparison of the differences in the chemical shifts of the vicinal protons of IIa-Va and IIb-Vb make it possible, in analogy with IIa, b, to assign the SRR(RSS) relative configuration to diastereomers IIIb-Vb and the RRR(SSS) relative configuration to diastereomers IIIb-Vb.

The acidic hydrolysis of diepoxide IIb in aqueous dioxane leads 4-hydroxy-2-hydroxymethyl-5-phenyltetrahydro-3-furanone (IX) to the structure of which was confirmed spectrally and chemically. The formation of the alternative 4-hydroxy-2-hydroxybenzyl-4-methyltetrahydro-3-furanone structure is excluded, since cyclization product IX is not dehydrated when it is refluxed in benzene in the presence of p-toluenesulfonic acid. In the IR spectrum of IX the stretching vibrations of the carbonyl group are observed at 1780 cm^{-1} (which is characteristic for furanones [13]), and the hydroxy absorption region contains two bands, one of which

(3610 cm^{-1}) corresponds to the vibrations of a free hydroxy group, while the other (3580 cm^{-1}) corresponds to the vibrations of a hydroxy group that participates in the formation of an intramolecular hydrogen bond. The transoid orientation of the vicinal 4-H and 5-H protons in tetrahydrofuranone IX is confirmed by the magnitudes of the changes in the chemical shifts of these protons when dihydroxy ketone IX is converted to its diacetate X (Table 1). A comparison of the chemical shifts of the protons of these compounds with the chemical shifts of the protons of the two diastereomeric 2-chloromethyl-2-methyl-5-phenyltetrahydro-3-furanones obtained in [9] indicates the cisoid orientation of the methyl and phenyl groups in IX and X.

Thus the acidic hydrolysis of keto diepoxides II proceeds stereospecifically with cyclization of diastereomer IIa to tetrahydropyranone VII and cyclization of diastereomer IIb to tetrahydrofuranone IX. This provides a basis for the assumption that the hydrolysis of diepoxy ketones II takes place through the formation of intermediate 1,2-dihydroxy-2-methyl-5-phenyl-4,5-epoxy-3-pentanones, which, depending on the relative configuration of the chiral centers, undergo cyclization to tetrahydropyranone VII or tetrahydrofuranone IX. The isolation of VII and IX from the complex mixture of products of oxidation of 1,2-dihydroxy-2-methyl-5-phenyl-4-penten-3-one (XI) with alkaline hydrogen peroxide serves as a confirmation of this.

EXPERIMENTAL

The IR spectra of 10^{-1} and 10^{-3} mole/liter solutions of the compounds in $CHCl_3$ and CCl_4 (layer thicknesses 0.01 cm and 1.00 cm) were recorded with a Specord 75 IR spectrometer. The PMR spectra of solutions in CCl_4 and $CHCl_3$ were obtained with a Varian HA-100 spectrometer with hexamethyldisiloxane as the internal standard.

2-Methyl-5-phenyl-1,2,4,5-diepoxy-3-pentanones (IIa, b). A solution of 0.24 g (0.006 mole) of sodium hydroxide in 10 ml of water was added to a cooled (0°C) solution of 7.52 g (0.04 mole) of epoxy ketone Ia in 150 ml of acetone—methanol (1:2), and 20 ml of 30% H_2O_2 solution was then added slowly with stirring while maintaining the temperature at ~5°C. The reaction was carried out for 2.5 h, after which the mixture was diluted with water and extracted with ether, and the excess H_2O_2 was decomposed with MnO_2. The extract was dried with potassium carbonate, the ether was partially evaporated, and hexane was added. The precipitated mixture of diastereomers IIa, b was separated by crystallization from ether—petroleum ether (1:2).

2,3,5,6-Diepoxy-4-hexanones (III-V). A 15-ml sample of 30% H_2O_2 solution was added in the course of 1.5 h to a cooled (to 0°C) solution. Of 0.05 mole of epoxy ketone Ib-d in 50 ml of methanol, and the reaction mixture was worked up as described above. Keto diepoxides IIIa, b were separated by crystallization from ether. Diastereomers Va, b were separated by crystallization from petroleum ether—ether. Compounds IVa, b were separated by chromatography on silica gel [elution with petroleum ether—ether (1:1)], and diastereomer IVa was crystallized from ether—petroleum ether (1:5).

3-Acetonyl-3-hydroxy-2-methyl-5-phenyl-1,2,4,5-diepoxypentanes (VIa, b). A 0.16-g (0.04 mole) sample of sodium hydroxide was added at 5°C to a solution of 7.52 g (0.04 mole) of epoxy ketone Ia in 25 ml of acetone, after which 15 ml of 30% H_2O_2 solutions was added slowly with stirring. The reaction was carried out for 1 h, after which the mixture was worked up by the usual method. Compounds IIa, b and VIa, b were separated by chromatography on silica gel [elution with petroleum ether—ether (1:1)]. Diepoxy ketone VIb was crystallized from hexane—ether (3:1).

3,5-Dihydroxy-3-methyl-6-phenyltetrahydro-4-pyranone (VII) and 4-Hydroxy-2-hydroxymethyl-5-phenyltetrahydro-3-furanone (IX). A few drops of hydrochloric acid were added to a solution of 2.04 g (0.01 mole) diepoxy ketone IIa or IIb in 20 ml of aqueous dioxane (1:1). After 72 h, the solvent was partially evaporated with a film evaporator, and the mixture was diluted with water and extracted with ether. The extract was dried with sodium sulfate, the ether was removed, and tetrahydropyranone VII was crystallized from hexane—ether (2:1), and tetrahydrofuranone IX was crystallized from petroleum ether—ether (1:1).

3,5-Diacetoxy-3-methyl-6-phenyltetrahydro-4-pyranone (VIII) and 4-Acetoxy-2-acetoxymethyl-5-phenyltetrahydro-3-furanone (X). A 2.22-g (0.01 mole) sample of tetrahydropyranone VII or tetrahydrofuranone IX was dissolved in 5 ml of acetyl chloride, and the solution was allowed to stand for 2 h. It was then diluted with a tenfold volume of water and extracted with ether. The extract was washed with sodium bicarbonate solution and dried with potassium carbonate. The ether was removed by distillation, and acetates VIII and X were crystallized from ether–hexane (1:1).

1,2-Dihydroxy-2-methyl-5-phenyl-4-penten-3-one (XI). A 1-ml sample of concentrated sulfuric acid was added to a solution of 9.4 g (0.05 mole) of monoepoxide Ia in 100 ml of aqueous dioxane (1:1), and the mixture was refluxed for 4 h. The dioxane was evaporated, and the residue was diluted with water and extracted with ether. The extract was dried with magnesium sulfate, the ether was partially evaporated, and petroleum ether was added to give 8.4 g of keto diol XI.

Retroaldolization of 3-Acetonyl-3-hydroxy-2-methyl-5-phenyl-1,2,4,5-diepoxypentane (VI). A 0.3-ml sample of a 20% solution of sodium hydroxide in methanol was added to a solution of 0.4 g (0.0015 mole) of diepoxy ketols VIa, b in 30 ml of methanol, and the mixture was refluxed for 45 min. The solvent was removed by distillation into a receiver containing 0.5 g of 2,4-dinitrophenylhydrazines and 6 ml of 85% phosphoric acid in 4 ml of ethanol, as a result of which, acetone 2,4-dinitrophenylhydrazone, with mp 127-128°C (from methanol), precipitated.

Condensation of Diepoxy Ketones IIa and IIb with Acetone. A solution of 0.4 g (0.01 mole) of sodium hydroxide in 2 ml of water was added to 2.04 g (0.01 mole) of diepoxy ketone IIa, b in 25 ml of acetone, and the mixture was allowed to stand for 1 h. The acetone was evaporated, and the residue was diluted with water and extracted with ether. The extract was dried with potassium carbonate, the ether was evaporated, and the residue was separated by chromatography on silica gel [elution with petroleum ether–ether (1:4)]. In addition to the products of opening of the epoxy rings, diepoxy ketols VIa, b were isolated in 33% yield.

Deuterium Exchange of Diepoxides IIa, b. A 0.4-g (0.002 mole) sample of diepoxy ketone IIa or IIb was dissolved in a mixture of CD_3OD and $(CD_3)_2SO$ (1:1), and 0.016 g of CD_3ONa was added. The reaction was carried out for 5 h, after which D_2O was added, and the mixture was extracted with benzene. The extract was dried with potassium carbonate, the benzene was evaporated, and the PMR spectrum was recorded, from which it was determined that 46% deuterium exchange had occurred; epimerization of IIa, b was not observed.

Oxidation of 1,2-Dihydroxy-2-methyl-5-phenyl-4-penten-3-one (XI). A solution of 0.3 g of sodium hydroxide in 5 ml was added to a cooled (to 0°C) solution of 3.06 g (0.015 mole) of diol XI in 30 ml of methanol–acetone (1:2), after which 10 ml of 30% H_2O_2 was added slowly with stirring at no higher than 5°C. After 5 h, the mixture was worked up as described above. The ether was evaporated, and the residue was chromatographed on silica gel [elution with petroleum ether–ether (1:3)] to give VII and IV in 8% yield.

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