SYNTHESIS, THREE-DIMENSIONAL STRUCTURE, AND STEREOCHEMISTRY OF EPOXIDATION OF 1-CHLORO-2-METHYLENECYCLOHEXANE

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There is interest in the characteristics of the chemical and conformational behavior of six-membered rings containing an exocyclic double bond and an electronegative substituent attached to an adjacent atom [1, 2]. Previous studies of the isomeric carenyl chlorides [3] have shown that given an identical conformation for the six-membered ring in these compounds, they can differ in the orientation of the Cl atom, which may be one of the factors responsible for their different behavior in epoxidation reactions. In order to exclude any possible influence due to the cyclopropane fragment in these reactions, in the present paper we have examined the structure and epoxidation stereochemistry of a six-membered ring analog of carenyl chlorides, namely, 1-chloro-2-methylenecyclohexane (VI). Based on an analysis of the data reported for the synthesis of (VI) [4-8], and comparison with our own results, we conclude that the physical constant data reported previously for (VI) [4, 5] refer to a mixture of structurally different chlorides. The other reports [6-8] did not contain any characteristic data which would enable us to assess the homogeneity or purity of (VI). We have carried out the synthesis of (VI) starting from (I) via two reaction schemes: a) POCl\_-induced dehydration in pyridine of (III), which was obtained by the reaction of (II) with HCl in ether, and b) direct chlorination of (I) with chlorine bleach according to [8].



Treatment of (II) with HCl resulted in the formation of the isomeric chlorohydrins (III) and (IV), in a l.l:l ratio, which were difficult to separate chromatographically on SiO<sub>2</sub> due to their similar  $R_f$  values. For this reason, the mixture was worked up with Ac<sub>2</sub>O/Py, which converted (IV) to its acetate (V) with a greater  $R_f$  value. Treatment of (III) with POCl<sub>3</sub> in pyridine gave a mixture of two products in a 1:2 ratio, which were characterized by their PMR spectra as (VI) and (VII). Compound (VI) was formed in smaller amounts in this reaction.

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Chlorination of (I) with chlorine bleach in aqueous  $CH_2Cl_2$  in the presence of  $CO_2$  (dry ice) according to [8] also led to the formation of (VI) and (VII) as the main products (35 and 45%, respectively in the reaction mixture). (III) was also detected in the reaction mixture, just as was observed previously [8]. Dichloride (VIII) and, in trace amounts, 1-methylcyclohexan-6-ol (IX) were also detected. Compound (VI) was isolated by distillation. Upon chromatography of the fraction containing (VI) and (VII) on  $Al_2O_3$ , (VII) was converted to (IX), and (VI) could be separated from it by elution with pentane. However, an impurity, probably a rearrangement product, chloromethylcyclohexene [8], appeared as a result.

Epoxidation of (VI) with peracetic acid (PAA) gave two products in a 3:1 ratio, which on the basis of their IR and PMR spectra, as well as elemental analyses, correspond to the isomeric epoxides (X) and (XI). Structural assignments of (X) and (XI) relative to the product epoxides were made based on their reaction with LiAlH4. The epoxide formed from (VI) gave (III) as the predominant product, while reduction of the minor epoxide resulted in the formation of (XII), which was also synthesized independently from (XIII). According to GLC analysis compound (X) contains an impurity (ca. 7%) corresponding, based on elemental analysis, to the product of epoxidation of (VII), which was present in small amounts in (VI) (cf. Experimental). The retention times of main epoxidation products of (VII) and of the impurity in (X) were also identical, confirming the assignment of the latter as 1,2-epoxy-1-methy1-6-chlorocyclohexane.

There is literature data concerning the stereochemistry of epoxidation of methylenecyclohexanes containing an OH group [9] or alkyl substituents [10] in the  $\alpha$ -position. Kinetic data were used in [9] based on model compounds in which the presence of a t-Bu group in the 4-position fixed the OH group adjacent to the double bond in either an axial or equatorial orientation. It is assumed that the stereochemistry of the reaction (cis:trans = 1.1:1) is determined primarily by the conformational equilibrium involving the unsaturated alcohol, in which, furthermore, the form with an equatorial hydroxyl group is assumed to predominate. This approach is valid since the transition state in epoxidation reactions is structurally similar to the reagents [11]. The stereochemical results obtained in the epoxidation of a methylenecyclohexane derivative with an isopropyl substituent in the  $\alpha$ -position have been explained in an analogous manner [10]. In this regard, therefore, we have examined the three-dimensional structure of (VI).



The molar Kerr constant (mK) was measured for (VI) and compared with the theoretically calculated values for chair forms containing an axial (VIA) and equatorial (VIB) orientation of the Cl atom. The experimental dipole moment value ( $\mu$ ) of 2.20 D and standard bond polar-izability parameters [3] were used in these calculations. Comparison of the theoretically calculated mK values for (VIA) and (VIB) (9•10<sup>-12</sup> and 294·10<sup>-12</sup>, respectively) with the experimentally determined value of 26•10<sup>-12</sup> indicates that form (VIA) strongly predominates in (VI); the mK value corresponds to a concentration of (VIA) equal to 0.95. Analysis of the half-width of the methine proton signal in the PMR spectrum of (VI) in CCl4, under condi-

tions used to measure the electrooptical properties [1], also supports the fact that form (VIA) predominates. The magnitude of  $W_{1/2}$  is equal to 10 Hz, which according to the limiting parameters in [1] corresponds to a two-fold greater population of the axial form, which is consistent with NMR data for oxygen-containing substituents, although the Kerr effect indicates an even greater preponderance of the axial orientation for the C-Cl bond. This also agrees with the previously stated assumption [1] concerning the axial favored-tendency of a halogen atom (Br). The observed stereochemistry of the epoxidation of (VI) thus appears to be the result of reactions of molecules in the form (VIA). The Cl atom directs the approach of the epoxidizing reagent to the opposite side of the double bond (from the anti-side). An axial Me group in the a-position [10] exerts a relatively small effect on the stereochemistry of epoxidation of a methylenecyclohexane derivative. This leads us to hypothesize that the observed direction of attack in (VI) is the consequence not only of the steric influence of Cl atom (which hinders approach from this side), which was used previously to explain the different stereochemical results obtained in the epoxidation of isomeric carenyl chlorides [3].

Information concerning the structure of spiroepoxycyclohexanes is limited to the following. In the case of the methylenecyclohexane epoxide, the conformation with a pseudo-axial orientation of the C-CH<sub>2</sub> bond has been shown to predominate [12, 13]. In the case of the isomeric epoxides of  $\alpha$ -Me and  $\alpha$ -i-Pr substituted methylenecyclohexanes, the orientation of the alkyl substituent, equatorial for Me and axial for i-Pr [13], is the determining factor. The structures of (X) and (XI) were established based on their polarity and polarizability data via measurements of µ and mK. The following bond moment values were used in calculating theoretical µ values: 1.94 D for the epoxy fragment and 2.18 D for the C-Cl bond. Theoretical mK values were calculated using bond anisotropic polarizability parameters from [3]. The experimental and theoretical values of  $\mu$  and mK for each of the two chair forms of (X) and (XI) are given in Table 1. The experimental value for (X) was calculated taking into account the presence of an impurity (XI) by measuring the µ value (1.20 D) and mK (28.10<sup>-13</sup>) for an independently synthesized sample of 1,2-epoxy-1-methy1-6-chlorocyclohexane. It is apparent that the properties of the latter are practically superimposable with those of (X), so that the results of the conformational studies seem to be completely insensitive to the presence of the impurity. Analysis of the data in Table 1 leads to the unequivocal conclusion that for both of the isomers (X) and (XI) the experimental mK values are similar to the calculated values for the chair form featuring an axial orientation for the Cl atom. For (XI) the value of mK corresponds to a concentration of conformer (XIA) of 0.94, while the dipole moment values for the two forms are practically superimposible. In the case of isomer (X) excellent agreement was obtained in determining the concentration of conformer (XA) by the dipole moment (0.88) and Kerr effect methods (0.90). The use of NMR for the conformation analysis of chloroepoxides in analogy with [1] requires information concerning the limiting parameters (width of the multiplet for the methine proton W or the half height  $W_1/2$ ) for the axial and equatorial forms, which can be different for the two isomers. There is no data concerning unsymmetrically substituted cyclohexanes. However, the results obtained in [1] suggest that the magnitudes of W and  $W_1/2$  depend on the size of the ring which is spiro-annelated with the substituted cyclohexane fragment, but are practically insensitive to replacement of C atoms by 0. To a first approximation, therefore, the characteristics of spirocyclopropanes analogous to (X) and (XI) may be used. The experimental values of  $W_1/2$  in CC14, 7 Hz for (X) and 9 Hz for (XI), would thus correspond to a concentration of the axial form of  $0.8 \pm 0.1$  in both cases, which is in excellent agreement with the data obtained using electrooptical methods.

The electronegative Cl atom in both of the isomers (X) and (XI) thus seems to exert an anomalously high axial tendency, which cannot be explained based on steric interaction alone.

## EXPERIMENTAL

IR spectra were measured on a UR-10 spectrophotometer, PMR spectra on a Varian T-60 spectrometer for CCl4 solutions relative to TMS. Fractional distillation was carried out on a column with an 8 theoretical plate efficiency. Chromatography was done using Chemapol A (100/ 160 mu silica gel. The composition of the distillation and chromatography fractions were monitored by GLC. The following columns were used: in the case of haloolefins, VKZh-94, 15% on Inertone AW-DMCS and 10% Carbowax 20M on chromosorb; for haloepoxides, 15% tris( $\beta$ -cyanoethoxy)propane on Chromosorb, 3 × 2500, 90-150°C. Dipole moments and Kerr constants were measured at 25°C in CCl4 solutions, methylcyclohexene (I) was prepared as in [14], 2-chlorocyclohexanone (XIII) according to [15].

TABLE 1

Compound	μ.D	m <sup>K-10-12</sup>	Experimental
(XA) (XB)	0.39 3.19	2 309	$\mu = 1,17 D_{,m} K = 31 \cdot 10^{-12}$
(XIA) (XIB)	3.65 3.50	$-9 \\ 255$	$\mu = 3.35 D_{m} K = 7.10^{-12}$

<u>Methylcyclohexene Oxide (II)</u>. To 10.4 g of (I) in 25 ml CH<sub>2</sub>Cl<sub>2</sub> containing 30 g Na<sub>2</sub>CO<sub>3</sub> at 20°C was added 25 ml of a solution of PAA in CH<sub>2</sub>Cl<sub>2</sub> (0.36 g of PAA per 1 ml of solution). The reaction mixture was maintained at 20°C for 24 h, and the precipitate was removed, washed with CH<sub>2</sub>Cl<sub>2</sub> and the filtrate was washed with 20% KOH, H<sub>2</sub>O, and dried over Na<sub>2</sub>SO<sub>4</sub>. The residue remaining after CH<sub>2</sub>Cl<sub>2</sub> evaporation (9.6 g) was distilled. Yield 8.6 g of (II), bp 62-63°C (55 mm),  $n_D^{2°}$  1.4430.

Reaction of HCl with Methylcyclohexene Oxide (II). To a solution of 2.85 g (II) in 75 ml ether at 13°C was added dropwise a solution of 2 g HCl in 10 ml ether. After 2 h the mixture was washed with 5% Na<sub>2</sub>CO<sub>3</sub>, H<sub>2</sub>O, and dried over Na<sub>2</sub>SO<sub>4</sub>. The residue (3.3 g) was chromatographed on 155 g SiO<sub>2</sub> with petroleum ether—ether (1:1) eluent. Isolated: 1) chlorohydrin (IV), 0.28 g, 1.4873. IR spectrum ( $\nu$ , cm<sup>-1</sup>): 660, 1080, 3470. PMR spectrum ( $\delta$ , ppm): 1.53 s (3H, 1-CH<sub>3</sub>), 3.6 m (1H, HC<sup>2</sup>); 2) chlorohydrin (III), 0.6 g, n<sub>2</sub><sup>-0</sup> 1.4870. IR spectrum ( $\nu$ , cm<sup>-1</sup>): 710, 1112, 3430. PMR spectrum ( $\delta$ , ppm): 1.21 s (3H, 1-CH<sub>3</sub>), 3.9 m (1H, HC<sup>2</sup>); 3) 1.62 g of a mixture of (III) and (IV).

Acylation of chlorohydrins (III) and (IV). To a mixture of (III) and (IV) (1.12 g) in 35 ml pyridine at 20°C was added 1.6 g of acetic anhydride. After 24 h the reaction mixture was poured into H<sub>2</sub>O and extracted with ether; the ether extract was washed with 3.5% HCl and H<sub>2</sub>O, and dried over Na<sub>2</sub>SO<sub>4</sub>. The residue (1.34 g) remaining after ether removal was chromatographed on 40 g Al<sub>2</sub>O<sub>3</sub> with petroleum ether ether (10:1 and 4:1) eluent. Yield 0.49 g of chloroacetate (V),  $n_{D}^{2^{\circ}}$  1.4625. IR spectrum (v, cm<sup>-2</sup>): 680, 1240, 1740. PMR spectrum ( $\delta$ , ppm): 1.53 s (3H, 1-CH<sub>3</sub>), 2.02 s (3H, OCH<sub>3</sub>), 4.8 m (1H, HC<sup>2</sup>), and 0.37 g of chlorohydrin (III).

Reaction of Methylcyclohexene (I) with Chlorine Bleach. To 10 g of (I) in 250 ml CH<sub>2</sub>Cl<sub>2</sub> at 0°C was added with stirring 35 g of technical chlorine bleach (35%); 25 ml H<sub>2</sub>O was then added in portions and over 2 h dry ice was added (about 60 g) at 0-8°C; the solution was layered and the precipitate was washed with CH<sub>2</sub>Cl<sub>2</sub>. Solutions from four identical experiments were washed with H2O and a saturated NaCl solution, and dried over Na2SO4. Fractionation of the residue remaining after CH<sub>2</sub>Cl<sub>2</sub> removal (49.3 g) gave: 1) 4.2 g with bp 30-52°C (14 mm), 2) 18.8 g with bp 50-54°C (14 mm), 3) 7.3 g with bp 54-68°C (14 mm). Distillation of fraction 2 gave 8.06 g of product, bp 50.5-51°C (15 mm), which contained 70% (VI). Fractionation of 70 g of the mixture obtained in an analogous manner from 60 g of (I) gave: 1) 2.7 g with bp 45-61°C (22 mm), 2) 30.9 g with bp 61°C (22 mm), and 3) 8.7 g with bp 64°C (15 mm). Distillation of fraction 2 gave 7.2 g of product with bp 39°C (10 mm), containing 70% (VI). Repeat fractionation of the fractions with bp 50.5-51°C (15 mm) and 39°C (10 mm) (15.17 g) gave 2.34 g of (VI) with bp 54°C (18 mm),  $n_D^{2^\circ}$  1.4876. The sample contains 6-7% of (VII). IR spectrum (v, cm<sup>-1</sup>): 670, 900, 1440, 1645, 3080. PMR spectrum ( $\delta$ , ppm): 4.47 m (1H, HC<sup>1</sup>), 4.70 m and 4.87 m (2H, H<sub>A</sub> and H<sub>B</sub>, C<sup>7</sup>). Found: C 64.66; H 8.41%. C<sub>7</sub>H<sub>11</sub>Cl. Calculated: C 64.37; H 8.49%. Yield 2.18 g of 6-chloro-1-methylcyclohexene (VII), bp 54°C (18 mm), n 2° 1.4897. IR spectrum (v, cm<sup>-1</sup>): 810, 1220, 1450. PMR spectrum (ô, ppm): 4.30 m (1H, HC<sup>6</sup>), 5.50 m (1H, HC<sup>2</sup>). From 5 g of the first distillation product fraction with bp  $64^{\circ}C$  (15 mm) was isolated by chromato-graphy on 185 g Al<sub>2</sub>O<sub>3</sub> with pentane 0.9 g of (VIII),  $n_D^{2\circ}$  1.4890. PMR spectrum (8, ppm): 1.60 s (3H, 1-CH<sub>3</sub>), 4.10 m (1H, HC<sup>2</sup>). Found: C 50.82; H 7.23%. C<sub>3</sub>H<sub>12</sub>Cl<sub>2</sub>. Calculated: C 50.32; H 7.24%.

<u>Reaction of (III) with POCl</u>. To 0.43 g (III) in 1 ml pyridine was added 0.37 g POCl<sub>3</sub> in 10 ml pyridine. After 24 h the mixture was worked up as in the acylation reaction above. After removal of the ether 0.44 g of a mixture of (VI), (VII), and (III), in a 1:2:4 ratio, was obtained.

Epoxidation of 1-Chloro-2-methylenecyclohexane (VI). To 1.2 g (VI) in 10 ml chloroform was added 6.7 ml of ether.\* After 3 days ether was added to the mixture, which was then washed \*As in Russian original - Editor.

with 4% KOH, H<sub>2</sub>O, and dried over Na<sub>2</sub>SO<sub>4</sub>. The residue was chromatographed on 30 g silica gel with petroleum ether-ether (9:1 and 4:1) eluent. Yield 0.75 g of (X),  $n_D^{2^\circ}$  1.4780. IR spectrum (v, cm<sup>-4</sup>): 680, 820, 825, 1280, 1440, 1450, 3040. PMR spectrum ( $\delta$ , ppm): 2.7 m (2H, H<sub>2</sub>C<sup>7</sup>), 3.53 m (1H, HC<sup>2</sup>), and 0.22 g (XI),  $n_D^{2^\circ}$  1.4855. IR spectrum (v, cm<sup>-1</sup>): 820, 870, 1170, 1440, 1450. PMR spectrum ( $\delta$ , ppm): 2.6 m (2H, H<sub>2</sub>C<sup>7</sup>), 3.83 m (1H, HC<sup>2</sup>).

<u>Reaction of Epoxide (X) with LiAlH</u>. To 0.1 g of (X) in 1 ml ether was added 1 ml of 1.3 M LiAlH<sub>4</sub> solution in ether. The reaction mixture was poured into water, washed with 3.5% HCl and H<sub>2</sub>O, and dried over MgSO<sub>4</sub>. The residue after ether removal was identified based on PMR spectral comparison with an authentic sample of (III).

<u>2-Chloro-1-methylcyclohexanol (XII)</u>. a) In an analogous manner, treatment of 0.12 g of (XI) with LiAlH. gave 0.08 g of (XII),  $n_D^{25}$  1.4756. IR spectrum (v, cm<sup>-1</sup>): 720, 1105, 3480. PMR spectrum ( $\delta$ , ppm): 1.21 s (3H, 1-CH<sub>3</sub>), 3.97 m (1H, HC<sup>2</sup>). Found: C 57.05; H 9.31%. C<sub>7</sub>H<sub>13</sub>-OC1. Calculated: C 57.57; H 8.81%. b) Treatment of 15.2 g (XIII) with MeMgI (from 4 g Mg) followed by chromatography of a portion of the mixture (2 g) on Al<sub>2</sub>O<sub>3</sub> (activity II grade) with petroleum ether-ether (4:1) eluent gave 0.9 g of (XII).

<u>1,2-Epoxy-1-methyl-6-chlorocyclohexane.</u> To 2.8 g (VII) in 40 ml chloroform was added 8 ml of PAA solution in chloroform (0.26 g per 1 ml); the mixture was maintained 5 days at 20°C, washed with 5% KOH and water, and dried over MgSO<sub>4</sub>. The residue (2.7 g) after solvent removal was chromatographed with petroleum ether-ether (10:1) eluent. Yield 1.0 g of product,  $n_D^{2^5}$  1.4712, bp 90°C (10 mm). PMR spectrum ( $\delta$ , ppm): 1.35 s (3H, 1-CH<sub>3</sub>), 2.90 m (1H, HC<sup>6</sup>), and 4.02 m (1H, HC<sup>2</sup>).

## CONCLUSIONS

1. Epoxidation of 1-chloro-6-methylenecyclohexane occurs stereoselectively, leading to the formation of two stereoisomeric epoxides, with the trans-isomer predominating.

2. 1-Chloro-2-methylenecyclohexane and its isomeric epoxides exist predominantly in a conformation with an axial orientation of the C-Cl bond.

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