PRINS REACTION WITH CYCLOPENTENE AND SYNTHESIS OF HYDROXYMETHYL-2-CYCLOPENTENE

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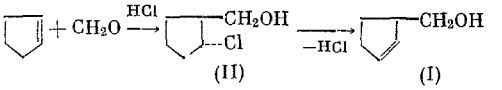
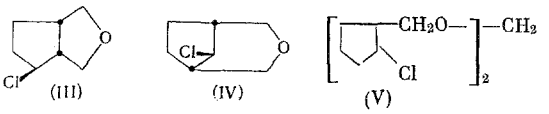
The behavior of cyclohexene in the Prins reaction has been studied well [1], whereas the behavior of cyclopentene (CP) in this reaction has been studied inadequately. Such a study is important in order to develop a synthesis for hydroxymethyl-2-cyclopentene (I), which serves as the starting compound in the preparation of substituted thiapentalanes as described in [2]:



(II) (I)

1-Hydroxymethyl-2-chlorocyclopentane (II) was obtained [3] as the sole product in the reaction of CP, CH_2O and HCl. Recently it was shown [4] that chloro-substituted 3-oxabicyclooctanes (III) and (IV) and formal (V) are formed when gaseous HCl is added to a mixture of CP, paraform and CH_2Cl_2:



The methanolysis of (V) gave alcohol (II) as a mixture of two isomers in a 4:1 ratio. By analogy with cyclohexene (stereospecific trans-addition) the main component of the mixture was assigned the trans-configuration. In [5, 6] it was concluded that the Prins reaction with CP is stereospecific for the reason that only the trans-glycols were detected in the addition products of the elements of CH_2O and CH_3COOH after saponification. The stereospecific nature of the Prins reaction with cyclohenene is explained [1] by the formation of the nonclassical ion. However, according to [7], the CP molecule is incapable of forming the nonclassical carbation and, consequently, nonstereospecific reaction could be expected in the given case. Since in the formation of 1, 2-disubstituted cyclopentanes, like the glycols and chlorocarbinols, an important role is played by steric hindrance, which favors trans-addition, a study of the configuration of 1, 2-disubstituted cyclopentanes, in which both substituents enter into one cyclic grouping, is of great interest. The most suitable object for this are the cyclic formals (1, 3-dioxanes) that are obtained by the Prins reaction directly from CP, and not by the formylation of the corresponding cis- and trans-glycols [8, 9]. The formation and properties of 4-methyl-4, 5-trimethylene-1, 3-dioxane (VI) and 4, 5-trimethylene-1, 3-dioxane (VII) were discussed in [10-13], but a conclusion regarding their configuration and the stereodirectivity of the Prins reaction was not made.

We studied the reaction of CP and CH_2O in the presence of hydrochloric acid. From the reaction products we isolated the cyclic formal, 4, 5-trimethylene-1, 3-dioxane (VII), the chloro-substituted 3-oxabicyclooctanes (III) and (IV), and 1-hydroxymethyl-2-chlorocyclopentane (II) and its formal (V). Dioxane (VII) represented a mixture of two isomers (VIIa) and (VIIb) in a 2:1 ratio, which were separated by preparative GLC and converted to the corresponding glycols.

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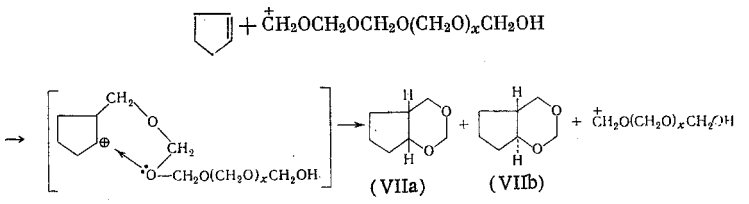
Three groups of signals can be isolated in the NMR spectra of the isomeric dioxanes (VIIa) and (VIIb): the unresolved signals upfield (δ ranging from 1.5 to 1.8 ppm), corresponding to the seven protons of the hydrocarbon ring, the signals in the region of δ 3-4 ppm, which correspond to the three protons of the dioxane ring at 4-C and 6-C, and an AN quadruplet with $\delta \sim 4.7$ ppm, which corresponds to the two protons of the dioxane ring at 2-C. The 7:3:2 ratio of the protons is corroborated by the ratio of the integral intensities.

As was shown for the hydrindans and decalins [14-16], in the NMR spectra the trans-isomers of these compounds give broader (at times partially split) signals than do the cis-isomers. This difference was explained by the difficulty of the conformational transformations of the trans-isomers when compared with the cis-isomers. When applied to the bicyclic dioxanes this can refer to the signals of the protons of the hydrocarbon ring (except the 4-C proton), since the signals downfield are related to the protons of the dioxane ring. In contrast to the similar signal in the spectrum of (VIIb), the NMR signal of the hydrocarbon ring of isomer (VIIa) is narrower and is almost unsplit. In the spectrum of (VIIa), the same as in the spectrum of cis-4, 5-tetramethylene-1, 3-dioxane, in contrast to the spectra of the trans-isomers, the signals from the 4-C and 6-C protons of the dioxane ring merge into unsymmetrical, not completely resolved doublets, which makes their detailed analysis difficult.

As a result, the data of the NMR spectra corroborate the fact that isomer (VIIa), which is formed in larger amount, is the previously uninvestigated cis-4, 5-trimethylene, 1, 3-dioxane, while isomer (VIIb) is the trans-4, 5-trimethylene-1, 3-dioxane, the spectral characteristics of which correspond to the literature data [17, 18].

In addition, it should be indicated that the centers of the AB quadruplets from the 2-C protons respectively have chemical shifts of 4.65 and 4.75 ppm, and an absolute value of the geminal spin–spin coupling constant $|J_{2gem}| = 6.2 \pm 0.2$ Hz. The $|J_{2gem}|$ value for a large number of other dioxanes is of the same order of magnitude [17, 19]. The difference in the chemical shifts of these protons δ_{ae} is equal to 0.32 for (VIIa) and 0.44 ppm for (VIIb), i.e., the nonequivalence of the 2-C protons is also retained in the cis-isomer.

The nonstereospecific nature of the Prins reaction with CP can be explained by the formation of the open carbcation (VIII) during the addition of the protonated polymeric HC_2O molecule [1, 8, 20, 21]:

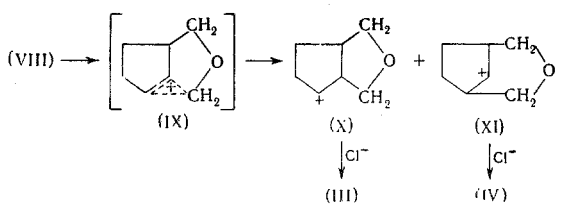


In view of the data obtained by us it seems erroneous to conclude that the free carbcation is absent during the addition of CH_2O and CH_3COOH to the double bond of the cyclopentene ring [5] on the basis that only the trans-glycol was isolated as a reaction result.

The predominant formation of cis-dioxane (VIIa) is explained by steric factors. The above said is apparently also valid as regards the 1-alkylcyclopentenes* and cyclopentadiene. Thus, an examination of the NMR spectrum of 4-methyl-4, 5-trimethylene-1, 3-dioxane (VI), given in [10], shows that this compound represents the cis-isomer, since the narrow, unsplit lines in the spectrum testify to an averaging of the signals of the axial and equatorial protons of the dioxane ring, which can be explained only by its rapid inversion. Another theory expressed in [10] as an alternative, namely that the molecule of dioxane (VI) has a planar conformation, lacks either chemical or spectral justification.

Using the GLC method, it was shown in our study that the chloro-substituted 3-oxabicyclooctanes (III) and (IV) are formed in a 1:1 ratio, and not a 2:1 ratio as indicated in [4]. The divergence is explained by the fact that in [4] the fraction with bp 84-86° (15 mm) was analyzed, whereas bicyclooctane (IV) boils at 77° (15 mm), and as a result a substantial portion of it was lost. The formation of chlorides (III) and

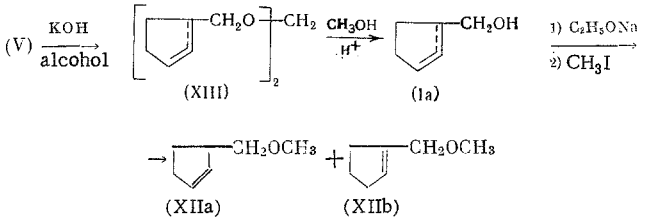
* The nonstereospecific nature of the Prins reaction with 1-methylcyclohexene was shown in [21].



Scheme 1

(IV) can be explained by Scheme 1. Carbcation (VIII) is converted via the intramolecular cleavage of a proton and protonation (see [1]) to the classical cations (X) and (XI) (since the formation of specifically such cations is characteristic for CP). It is not excluded that, together with the intermediate ion (IX), a compound with a double bond in the cyclopentane ring is formed.

The addition of Cl^- occurs from the side that is opposite to the oxygen-containing ring, as a result of which only the trans-chloro-substituted cis-3-oxabicyclooctanes are formed (see [4]). The stereochemistry of the main reaction product, namely 1-hydroxymethyl-2-chlorocyclopentane (II), was ascertained by converting it to hydroxymethyl-2-cyclopentene (I) and its methyl ether (XIIa):



We established that the end product (XII) consists of 90% of methyl-2-cyclopentenyl methyl ether (XIIa) and 10% of methyl-1-cyclopentenyl methyl ether (XIIb). Since the dehydrochlorination of secondary chlorides by alcoholic caustic solution proceeds by an E_2 mechanism, the starting 1-hydroxymethyl-2-chlorocyclopentane [(or its formal (V)] should consist of 90% of the trans-1-hydroxymethyl-2-chlorocyclopentane and 10% of the cis-isomer. The high stereoselectivity of the formation of the trans-isomer (II) from carbcation (VIII) is explained by the steric difficulty of forming the cis-form. The yields of the 1-hydroxymethyl-2-chlorocycloalkanes (or of their formals) and the chloro-substituted 3-oxabicyclanes (and their ratio) are quite close for cyclopentene and cyclohexene, whereas the yields of the cyclic formals are sharply different, and specifically 1% for cyclopentene and 17% for cyclohexene.

METHOD

The analytical and preparative GLC was run by I. V. Cherepanova and F. V. Kozlova on PVKh-1 and PKhV-2 chromatographs; the IR spectra were taken on Unicam SP-200 and UR-20 spectrophotometers. The NMR spectra were taken on a Varian T-60 spectrometer in CCl_4 relative to HMDS.

Reaction of Cyclopentene and Formaldehyde in the Presence of Hydrochloric Acid. Paraform (150 g) was dissolved in 850 ml of conc. HCl at 60-70°C. The solution was cooled to 20°, 264 ml of CP was added, and the mixture was stirred at 20-25° for 1 h, and then at 40-45° for 3 h. The mixture was then diluted with an equal volume of saturated NaCl solution and extracted with ether. The ether was distilled off to give 330 g of an oil as residue. The aqueous acid layer was neutralized with 20% NaOH solution and then extracted with ether to give an additional 30 g of substance. The product (360 g) was distilled through a column with an efficiency of 15 theoretical plates. The following fractions were obtained: A) bp 50-70° (15 mm), 8 g; B) bp 70-90° (15 mm), 56 g; C) bp 90-103° (15 mm), 60 g; residue, bp > 103° (15 mm), 178 g. The methods used to treat each fraction, the yields and the characteristics of the obtained compounds are given below.

4, 5-Trimethylene-1, 3-dioxanes [cis-(VIIa) and trans-(VIIb)]. Fraction A (24 g) was mixed with an equal volume of heptane and refluxed with Na for 2 h, filtered, and the treatment with Na was repeated. After a double distillation through a column (8 theoretical plates) we obtained 9 g (0.8% when based on CP) of pure 4, 5-trimethylene-1, 3-dioxane (VII) (based on the GLC data, a mixture of the cis- and trans-isomers in a 2:1 ratio) as a colorless liquid bp 60-61° (15 mm); d_4^{20} 1.0530; n_D^{20} 1.4620 [12-13]. The

chromatographic separation* of the mixed isomers gave: cis-(VIIa) (retention time 33 min, bp 60° (15 mm); d_4^{20} 1.0575; n_D^{20} 1.4620. Found: C 65.56; H 9.55%; MR 33.32. $C_7H_{12}O_2$. Calculated: C 65.59; H 9.44%; MR 33.48; trans-(VIIb) (retention time 43 min, bp 62° (15 mm); d_4^{20} 1.0528; n_D^{20} 1.4610. Found: C 65.77; H 9.26%; MR 33.41. $C_7H_{12}O_2$. Calculated: C 65.59; H 9.44%; MR 33.48).

trans-8-Chloro-cis-3-oxabicyclo[3.2.1]octane (IV) and trans-6-chloro-cis-3-oxabicyclo[3.3.0]octane (III). The distillation of fraction B through a column (15 theoretical plates) gave 50 g (11%) of a colorless oil with bp 75-82° (15 mm). Based on the GLC data, the oil consists of equal amounts of trans-8-chloro-cis-3-oxabicyclo[3.2.1]octane (IV) and trans-6-chloro-cis-3-oxabicyclo[3.3.0]octane (III). Preparative GLC (164°, carrier gas He, 120 ml/min) gave: trans-(IV) (retention time 42 min, colorless liquid with a characteristic camphor odor, bp 77° (15 mm); d_4^{20} 1.1661; n_D^{20} 1.4948. Found: Cl 24.64%; MR 36.65. $C_7H_{11}ClO$. Calculated: Cl 24.23%; MR 36.66) and trans-(III) (retention time 51 min, colorless liquid, bp 81° (15 mm); d_4^{20} 1.1545; n_D^{20} 1.4890. Found: Cl 24.45%; MR 36.62. $C_7H_{11}ClO$. Calculated: Cl 24.23%; MR 36.66).

1-Hydroxymethyl-2-chlorocyclopentane Formal (V). The distillation of 178 g of the residue with bp > 103° (15 mm) gave 148 g (35%) of crude formal (V) as an oil with bp 128-137° (2 mm).

Methanolysis of 1-Hydroxymethyl-2-chlorocyclyclopentane Formal (V). A mixture of 34 g of formal (V), 0.2 ml of conc. H_2SO_4 and 200 ml of methanol was refluxed for 10 h, with a periodic removal of the low-boiling fraction through a fractionating column (15 theoretical plates). At the end of reaction the mixture was neutralized with alcoholic caustic solution and then distilled through a column. We obtained 22 g (67%) of 1-hydroxymethyl-2-chlorocyclopentane (II), bp 100-103° (15 mm).

Formylation of 1-Hydroxymethyl-2-chlorocyclopentane (II). A mixture of 50 g of (II), 70 g of paraform and 200 ml of conc. HCl was stirred at 50° for 4 h, the upper layer was separated, while the lower layer was diluted with water, saturated with NaCl, and extracted with benzene. The benzene was distilled off, and the residue was added to the main product. A double distillation gave 20 g of unchanged (II), bp 70-80° (2 mm), and 22 g [70% when based on reacted (II)] of 1-hydroxymethyl-2-chloro-cyclopentane formal (V) as a colorless oil, bp 132° (2.5 mm); d_4^{20} 1.1423; n_D^{20} 1.4895.

Hydroxymethyl-2-cyclopentene Formal (XIII). Into a stainless steel autoclave were charged 48 g of formal (V) and a solution of 38 g of KOH in 100 ml of ethanol. The mixture was heated at 160° for 3 h, cooled, diluted with water, and extracted three times with ether. The ether was distilled off, and the residue was distilled through a column (8 theoretical plates). We obtained 21 g (59%) of 3-hydroxymethylcyclopentene formal (XIII) (contaminated with ~10% of the 1-hydroxymethylcyclopentene formal) as a colorless oil, bp 90° (2.5 mm); d_4^{20} 0.9806; n_D^{20} 1.4803. Found: C 74.95; H 9.43%; MR 60.37. $C_{13}H_{20}O_2$. Calculated: C 74.96; H 9.68%; MR 60.41.

Hydroxymethyl-2-cyclopentene (I). The methanolysis of 16.5 g of formal (XIII) was run in the presence of 0.3 g of p-toluenesulfonic acid in the same manner as the methanolysis of (V). After a double distillation we obtained 12.4 g (80%) of (I) with bp 160° (760 mm) and 66° (15 mm); d_4^{20} 0.9604; n_D^{20} 1.4737 [22].

Methyl-2-cyclopentenyl Methyl Ether (XIIa). To 11 g of hydroxymethyl-2-cyclopentene was added a solution of sodium ethylate, obtained from 4.6 g of Na and 50 ml of ethanol, followed by the addition of 50 ml of heptane, after which the mixture of solvents was distilled off as completely as possible. The residue was treated with 15 ml of CH_3I and 20 ml of hexane and the whole was refluxed for 5 h. Then the excess CH_3I and hexane were distilled off, the residue was decomposed with water, and the reaction product was distilled through a column (8 theoretical plates). We obtained 6 g (48%) of compound (XII) as a volatile liquid with bp 47-50° (40 mm); d_4^{20} 0.8782; n_D^{20} 1.4405. Found: C 75.00; H 10.85%; MR 33.69. $C_7H_{12}O$. Calculated: C 74.95; H 10.78%; MR 33.37. Preparative GLC (9 m × 8 mm column filled with 15% ethylene glycol adipate deposited on INZ-600, 132°, carrier gas He) gave the pure methyl-2-cyclopentenyl methyl ether (XIIa) (90%; d_4^{20} 0.8787; n_D^{20} 1.4400; found MR 33.64, calculated MR 33.37. Infrared spectrum: band at 1615 cm^{-1}, (corresponding to the isolated double bond) and methyl ether (XIIb) (10%; IR spectrum: band at 1650 cm^{-1}, and the 1615 cm^{-1} band is absent [23]).

* A PKhV-2 chromatograph designed by SKB AN SSSR; ethylene glycol adipate (15%) deposited on Spherochrome; 151°; carrier gas = He; velocity = 95 ml/min. The length and diameter of the columns were: 1 m × 14 mm, 1 m × 12 mm, 4 m × 8 mm, 1 m × 6 mm.

Methanolysis of cis-4, 5-trimethylene-1, 3-dioxane (VIIa). The methanolysis of 10 g of dioxane (VIIa) in the presence of 0.5 g of p-toluenesulfonic acid was run in the same manner as described above. The reaction time was 14 h. We obtained 6.5 g (71%) of cis-1-hydroxymethyl-2-hydroxycyclopentane as an oil, bp 100° (4.5 mm); d_4^{20} 1.0844; n_D^{20} 1.4835 [6-7].

Methanolysis of trans-4, 5-trimethylene-1, 3-dioxane (VIIb). The methanolysis of 6 g of dioxane (VIIb) in the presence of 0.4 g of p-toluenesulfonic acid was run in the same manner as described above. The reaction time was 1 h. We obtained 3.9 g (72%) of trans-1-hydroxymethyl-2-hydroxycyclopentane as a viscous oil, bp 111° (4.5 mm); d_4^{20} 1.0843; n_D^{20} 1.4835.

Replacement of Chlorine by Hydrogen in trans-6-chloro-cis-3-oxabicyclo[3.3.0]octane (III). To a solution of 6.2 g of trans-(III) in 80 ml of methanol was added 9 g of Na as described in [4]. We obtained 2.6 g (55%) of cis-3-oxabicyclo[3.3.0]octane as a colorless liquid, bp 61° (40 mm); d_4^{20} 0.9644; n_D^{20} 1.4603. Found: C 75.10; H 11.05%; MR 31.87. $C_7H_{12}O$. Calculated: C 74.95; H 10.78%; MR 32.06. The purity of the obtained compound was confirmed by GLC.

Replacement of Chlorine by Hydrogen in trans-8-chloro-cis-3-oxabicyclo[3.2.1]octane (IV). The reduction of 18 g of trans- (IV) was run in the same manner as above. We obtained 6 g (44%) of cis-3-oxabicyclo[3.2.1]octane as a waxy colorless substance that had the odor of camphor and sublimed easily, mp ~100° (in a sealed capillary). The purity of the obtained compound was confirmed by GLC.

CONCLUSIONS

1. The reaction of cyclopentene, formaldehyde and hydrochloric acid gives a mixture of the cis- and trans-4, 5-trimethylene-1, 3-dioxanes (0.8%) in a 2:1 ratio, trans-6-chloro-cis-3-oxabicyclo[3.3.0]octane (5.5%), trans-8-chloro-cis-3-oxabicyclo[3.2.1]-octane (5.5%), and the cis- and trans-1-hydroxymethyl-2-chlorocyclopentanes (or their formals) in a 1:9 ratio.

2. The dehydrochlorination of the mixed 1-hydroxymethyl-2-chlorocyclopentane formals and subsequent methanolysis lead to the formation of the hydroxymethyl-1- and -2-cyclopentenes in a 1:9 ratio.

3. The Prins reaction with cyclopentene proceeds nonstereospecifically, which is explained by the formation of the free carbcation in the first step.

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