SYNTHESIS AND THREE-DIMENSIONAL STRUCTURE OF 4-HYDROXY-4-METHYL-3-CHLORO-6-ALKYLTETRAHYDROPYRANS

A. A. Gevorkyan, P. I. Kazaryan,
and O. V. Avakyan

UDC 547.281.412.723'
811:07:542.953

A method has been developed for the preparation of 4-hydroxy-4-methyl-3-chloro-6-alkyltetrahydropyrans based on the cycloalkylation of 4-hydroxy-2-methyl-3-chloro-1-butene with aldehydes. Dehydrochlorination of these compounds furnished the corresponding oxiranes of the tetrahydropyran series. The chlorine atoms in these newly synthesized chlorotetrahydropyranols have been found to favor equatorial positions.

Cycloalkylation of allylcarbinols to give tetrahydropyran derivatives has been widely used for the preparation of fragrances and biologically active reagents, as well as to resolve questions concerning electrophilic addition reactions, etc. [1-3]. Due to the difficulties inherent in the separation and assignment of configuration of the stereoisomers obtained in this manner, however, the mechanism and stereochemistry of this reaction have not been studied in detail. We have obtained a wide series of data based on our investigation of the cycloalkylation of 4-hydroxy-2-methyl-3-chloro-1-butene (I) with aldehydes.

In the presence of 50% sulfuric acid chlorohydrins of the tetrahydropyran series II are obtained as mixtures of cis and trans isomers (6:4) in total yields of 60-80%. The assignment of structures to compounds A and B based on the array of possible isomers A-D was made by comparison of the relative reactivities of the isomers with respect to basic reagents and also with respect to acylation with acetic anhydride (an OH_e is more easily acylated, and chlorohydrins containing a trans-functional group arrangement are more easily dehydrochlorinated to the corresponding oxides). Thus, treatment of compound IIa with base results in the disappearance of only one of the isomers, that with the high-field methyl group absorption (in its PMR spectrum), to give 4-methyl-6-isopropyl-3,4-epoxytetrahydropyran (IIIa), whereas the isomer with the weak field methyl group signal (in its PMR spectrum) can be isolated in pure form from the reaction mixture (A, R = i-Pr). This can be explained in terms of the axial orientation of the hydrogen atom of the CH_XCl fragment (J_{AX} = 8 Hz) in this isomer. The isomer with the high-field methyl group absorption also undergoes preferential acylation with acetic anhydride.

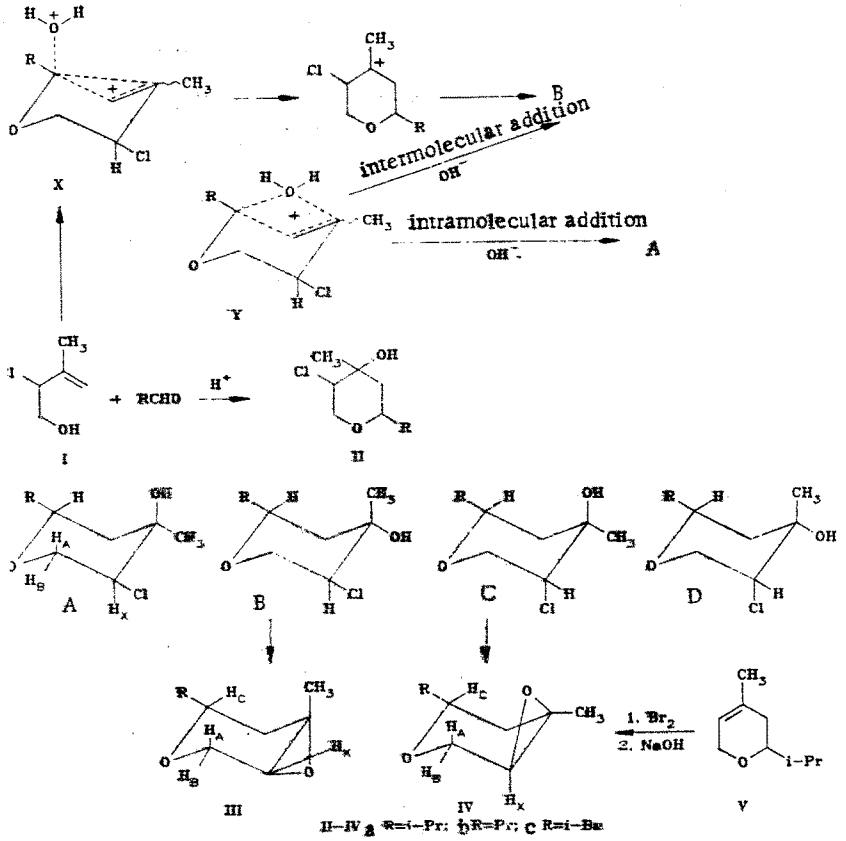
Treatment with base would be expected to effect facile and selective reaction of the isomers containing a trans-orientation of the chlorine atom and hydroxyl group, namely, compounds B and C, rather than isomers A and D, in which these functional groups are arranged in a cis-orientation (ae and ea). With respect to acylation, isomers B and D, which have sterically more accessible hydroxyl groups, would be expected to be more reactive. For these reasons, the compound in the mixture under investigation which was shown to be more reactive, should be regarded as isomer B. It is further assumed that dehydrochlorination of this compound occurs via the conformer with a diaxial arrangement of the chlorine atom and hydroxyl group. Without this assumption, it is difficult to perceive why chlorohydrin B can be completely converted, after only several hours stirring, to its oxide, whereas the e,e-bromohydrin with a similar structure requires many tens of hours under analogous conditions [4].

The oxides are formed as mixtures of isomers in a 9.5:0.5 ratio (according to GLC), and it is not possible to exclude the presence of small amounts of isomer C in these mixtures. It is feasible that, due to similar chemical environments, the methyl group absorption in the PMR spectrum of this isomer exhibits the same chemical shift value as one of the other

---

Institute of Organic Chemistry, Academy of Sciences of the Armenian SSR, Erevan. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1457-1460, November, 1986. Original article submitted July 2, 1985.

 0009-3122/86/2211-1174$12.50



isomers (A and B), and that the hydroxyl group is also similar to that in chlorohydrins A or B with respect to its chemical behavior.

In order to obtain evidence for these assumptions, we have carried out an independent synthesis of oxide IV based on bromination of 4-methyl-2-isopropyl-3,6-dihydro-2H-pyran (V) [5, 6] (in 83% yield based on starting dihydropyran), which resulted in a compound identical with the minor component of the mixture of oxides obtained from chlorohydrin IIa. We have further ruled out the possibility of the formation of oxides from chlorohydrin A; the chloride was recovered unchanged after a sample of A was refluxed with sodium tert-butoxide for 60 h.

In the mixture of chlorotetrahydropyranols obtained via cylcoalkylation, the main products (ca. 90%) appear to be isomers with equatorial chlorine atoms. A similar effect was found in the cycloalkylation of 4-hydroxy-2,4-dimethyl-1-butene with acetaldehyde [7]. It follows, therefore, that in the cycloalkylation of allylcarbinols with aldehydes, the bulkiest substituents in positions 2, 3, and 6 (but not 4) of the resulting tetrahydropyran rings favor the equatorial positions. Apparently, the substituents in the transition state pseudo-ring arrange themselves in the energetically more favorable equatorial positions, and stabilization of the incipient tetrahydropyranyl carbocation by means of the hydroxyl group, as has been proposed previously [2], occurs via intramolecular assistance. As a result, cis-addition to the double bond predominates.

Analysis of literature data [2, 3, 7] reveals that this cycloalkylation scheme is operative in those cases where equilibrium among the isomers does not exist. In cases where the transition state V can be stabilized by the hydroxyl group by means of an intermolecular interaction, a chlorohydrin with an equatorial hydroxyl group is formed. In the present case, the chlorine atom apparently retards the cleavage process of the hemiacetal C-OH linkage, which hinders intermolecular interaction. This occurs despite the relatively large separation between the chlorine atom and the reactive site, as evidenced by the fact that 4-hydroxy-2-methyl-3-chloro-1-butene (I) reacts much more slowly in cycloalkylation than does 4-hydroxy-2-methyl-1-butene; if a mixture of the reagents is maintained for a long period of time, or heated, a significant portion of compound I is recovered unchanged, whereas 4-hydroxy-2-methyl-1-butene reacts completely under the same conditions (6 h, 25°C) [2].

TABLE 1. Properties of Synthesized Compounds

Compound	bp, °C (pressure, mm)	n_D^{20}	d_4^{20}	PMR, ppm	Found, %			Molecular formula	Calc., %			Yield, %
					C	H	Cl		C	H	Cl	
IIa	72—73 (3)	1,4785	1,1021	0,89 [6H, m, J=6,3 Hz, $(CH_3)_2$]; 1,34 and 1,39 (3H, s, CH_3, $a:e$=40:60); 1,52—1,96 [3H, m, CH_2+**CH**$(CH_3)_2$]; 2,70 (1H, s, OH); 2,96—3,18 (1H, m, CHCl); 3,72—4,11 (3H, m, CH_2O+CHO)	56,3	9,1	18,2	$C_9H_{17}ClO_2$	56,1	8,8	18,4	80
IIb	76—77 (3)	1,4773	1,0992	0,91 (3H, m CH_3); 1,21—1,92 (6H, m, CH_2+**CH_2CH_2**CH_3); 1,33 and 1,37 (3H, s, CH_3, $a:e$=35:65); 3,04 (1H, s, OH); 3,01—3,09 (1H, m, CHCl); 3,77—4,20 (3H, m, CH_2O+ +CHO)	56,2	9,2	18,5	$C_9H_{17}ClO_2$	56,1	8,8	18,7	72
IIc	82—84 (3)	1,4750	1,0744	0,82 [6H, d, J=6 Hz $(CH_3)_2$]; 1,31 and 1,35 (3H, s, CH_3, $a:e$=40:60); 1,19—1,91 [5H, m, CH_2+**CH_2CH**$(CH_3)_2$]; 2,67 (1H, m, OH); 3,11—3,48 (1H, m CHCl); 3,74—4,10 (3H, m, CHO+CH_2O)	58,4	9,0	17,5	$C_{10}H_{19}ClO_2$	58,1	9,2	17,2	76
A	75—76 (3,5)	1,4760	1,1023	0,88 and 0,95 [6H, d, J=7 Hz, $(CH_3)_2$]; 1,38 (3H, s, CH_3); 1,54—1,92 [3H, m, CH_2+**CH**$(CH_3)_2$]; 2,85 (1H, m, OH); 3,05 and 3,15 (1H, dd, J_{AX}=8 Hz, J_{BX}=3 Hz, CHCl); 3,65—4,21 (3H, m, CH_2O+CHO)	56,2	9,0	18,3	$C_9H_{17}ClO_2$	56,1	8,8	18,4	—
IIIa	46—47 (3)	1,4522	0,9807	0,89 [6H, m, J=7 Hz, $(CH_3)_2$]; 1,35 (3H, s, CH_3); 1,48—1,82 [3H, m, CH_2+$CH(CH_3)_2$]; 2,62—2,82 (1H, m, H_C); 2,89 (1H, s, H_X); 3,67 and 4,11 (2H, J_{AB}=12,5 Hz, H_AH_B)	69,3	10,2	—	$C_9H_{16}O_2$	69,2	10,3	—	62
IV	74 (14)	1,4449	0,9738	0,67 and 0,78 [6H, d, J=7 Hz, $(CH_3)_2$]; 1,29 (3H, s, CH_3); 1,35—1,92 [3H, m, CH_2+**CH**$(CH_3)_2$]; 2,77—2,88 (1H, m, H_C); 2,96 (1H, d, J_{XB}=4 Hz, H_X); 3,68 and 4,03 (2H, ABX system, J_{BX}=4 Hz, J_{AB}=13 Hz, CH_2O)	69,0	9,9	—	$C_9H_{16}O_2$	69,2	10,3	—	83
IIIb	50 (3)	1,4535	0,9689	0,93 (3H, m CH_3); 1,12—1,69 (6H, m, CH_2+**CH_2CH_2**CH_3); 1,30 (3H, s, CH_3); 2,32—2,57 (1H, m, H_C); 2,71 (1H; s H_X); 3,61 and 4,08 (2H, J_{AB}=12,2 Hz H_AH_B)	69,1	10,2	—	$C_9H_{16}O_2$	69,2	10,3	—	63
IIIc	58—59 (3)	1,4545	0,9660	0,86 [6H, d, J=7 Hz, $(CH_3)_2$]; 1,01—1,79 [6H, m $(CH_3)_2$**CH**CH_2+CH_2]; 1,30 (3H, s, CH_3); 1,72 (1H, s, H_X); 2,93—3,22 (1H, m, H_C); 3,64 and 4,09 (2H, J_{AB}= =12,2 Hz, H_AH_B)	70,6	10,8	—	$C_{10}H_{18}O_2$	70,6	10,6	—	63

EXPERIMENTAL

PMR spectra were recorded on a Perkin Elmer R-12 (60 MHz) and Tesla BS-497 (100 MHz) spectrometer in CCl_4 or $CDCl_3$ (versus HMDS as internal standard). The purities of the synthesized compounds were assessed using GLC on an LKhM-8MD chromatograph equipped with a catharometer detector and a 2 or 3 m long column filled with 10% PEG-20M on AW-HMDS inertone or 5% SE-30 on N-AW-HMDS chromatone; the rate of helium gas flow was 40-60 ml/min, the temperature 100-230°C.

2-Alkyl-4-hydroxy-4-methyl-3-chlorotetrahydropyrans (IIa-c). A mixture of 12 g (0.1 mole) of 4-hydroxy-2-methyl-3-chloro-1-butene, 0.1 mole of aldehyde, and 2 ml of 50% H_2SO_4 was stirred at 50°C for 25 h. The mixture was neutralized with dry sodium hydroxide, extracted with ether, dried over $MgSO_4$, then concentrated to remove solvent and distilled under vacuum (see Table 1).

2-Alkyl-4-methyl-3,4-epoxytetrahydropyrans (IIIa-c). A mixture of 0.1 mole of compound II, 0.2-0.3 mole 50% aqueous KOH, and triethylbenzylammonium chloride (2% by weight of combound II) was stirred at 70°C for 45 h. The mixture was extracted with ether, dried over $MgSO_4$, concentrated to remove the ether, and distilled under vacuum (Table 1; yield data was calculated based on the amount of unreacted isomer).

2-Isopropyl-4-methyl-3,4-epoxytetrahydropyran (IV). A flask cooled to −40°C was charged with 25 ml DMF and 5.6 g (0.035 mole) bromine was added dropwise with stirring; the temperature was lowered to −65°C and 4.9 g (0.035 mole) 2-isopropyl-4-methyl-3,6-dihydro-2H-pyran was added and the mixture was stirred for 30 min. The temperature was raised to −40°C, 1.3 g of ice was added, and the mixture was stirred an additional 30 min; water (25 ml) was then added slowly to the reaction mixture, which quickly raised the temperature to 20°C. The organic layer was separated, the aqueous layer was extracted with ether, and then the combined ether layers were dried over $MgSO_4$, concentrated to remove ether and excess DMF, and the residue was treated dropwise with 12 ml of 50% aqueous KOH at 20°C and then heated to 45°C for 3 h. The mixture was cooled, extracted with ether, dried over $MgSO_4$, concentrated to remove ether, and distilled under vacuum (see Table 1).

Reaction of Compound IIa with Acetic Anhydride. A mixture of 9.9 g (0.05 mole) of chlorohydrin IIa, 2.6 g (0.025 mole) of acetic anhydride, and 0.2 g p-toluenesulfonic acid was heated for 10 min at 40°C, and then the PMR spectrum of the mixture was recorded. This process was then repeated after 10 min. It was noted that the high field signal due to the axial methyl group (1.34 ppm) gradually disappeared.

Reaction of Chlorohydrin A (R = i-Pr) with Sodium tert-Butoxide. A mixture of 3.8 g (0.025 mole) of compound A, 1.15 g (0.05 mole) sodium, and 12 ml tert-butyl alcohol was heated at 75°C for 60 h. Excess alcohol was removed, 3 ml of water was added, and the mixture was extracted with ether. Yield, 3.5 g of A was recovered unchanged.

LITERATURE CITED

1. P. I. Kazayan, A. A. Gevorkyan, Sh. O. Badanyan, A. S. Arakelyan, and A. A. Manukyan, Arm. Khim. Zh., 27, 35 (1974).
2. A. A. Gevorkyan, A. S. Arakelyan, and P. I. Kazaryan, Khim. Geterotsikl. Soedin., No. 12, 1611 (1982).
3. A. A. Gevorkyan, Dissertation, Erevan (1978).
4. E. Eliel, N. Allinger, S. Angyal, and H. Morrison, Conformational Analysis, Interscience New York (1965).
5. P. I. Kazaryan, O. V. Avakyan, S. V. Avakyan, and A. A. Gevorkyan, Khim. Geterotsikl. Soedin., No. 9, 1189 (1985).
6. N. M. Khizantsyan, Dissertation, Erevan (1984).
7. D. Tavernier, M. Anteunis, and N. Hosten, Bull. Soc. Chim. Belg., 85, 151 (1976).