REGIOSPECIFIC SYNTHESIS OF 2-SUBSTITUTED 4-METHYL-3,6-DIHYDRO-2H-PYRANS

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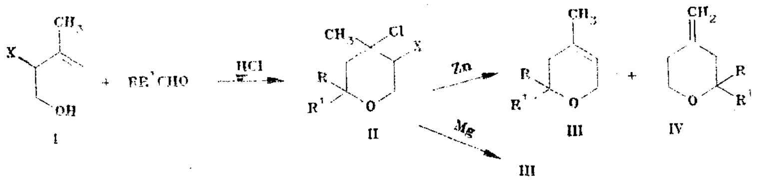
The chloroalkylation of 3-halo-2-methyl-1-buten-4-ols was used to synthesize 4,5-dihalo-4-methyl-2-substituted tetrahydropyrans, which were converted regiospecifically to 3,6-dihydropyrans by reaction with magnesium. A similar reaction with zinc dust gave mixtures of 3,6- and 5,6-dihydropyrans.

The known methods for the synthesis of dihydropyrans [1-6] generally lead to mixtures of 3,6- and 5,6-dihydropyrans, and reliable physicochemical characteristics of most individual dihydropyrans are therefore unavailable. We have previously reported [7] that individual 5,6-dihydropyrans can be synthesized in good yields by dehalogenation of 3-bromo-4-chloro-4-methyl-2-substituted tetrahydropyrans with zinc dust in alcohol.

The present communication is devoted to the development of the regiospecific synthesis of 3,6-dihydro-2H-pyrans via a similar scheme [7] of transformations: allylcarbinol → 4,5-dihalotetrahydropyran → 3,6-dihydropyran. Of the possible schemes for the preparation of tetrahydropyrans II from allylcarbinols [8], a method involving the synthesis by means of 3-methyl-3-butenal seemed of greatest interest, since the step involving the oxidation of 2-methyl-1-buten-4-ol to isopropenylacetaldehyde was previously developed in [9]. However, it was found that the isomeric β,β-di-methylacrolein rather than isopropenylacetaldehyde is formed under the described conditions. It might be assumed that the high (with respect to acid) reactivity of the isopropenyl group leads to its facile isomerization to an isobutenyl group. This sort of isomerization was described in [10] in the analogous oxidation of 2-methyl-1-buten-4-ol under milder conditions. It should, however, be noted that our attempts to oxidize 1-bromo-2-methyl-1-buten-4-ol, the multiple bond of which should not have undergone protonation and isomerization so readily, were also unsuccessful — the reaction mixture underwent resinification.

The most suitable synthone for the regiospecific synthesis of 3,6-dihydropyrans was found to be isopropenyloxirane [12], the addition to which of hydrogen chloride and bromide led to halohydrins I. The latter readily form dihalotetrahydropyrans II by cycloalkylation with aldehydes and ketones in the presence of hydrogen chloride.



Ia, IIa-f X=Cl; Ib, IIg-k X=Br; IIa–d, f–i, IIIa–d, IVa–d,f R=H; IIe,j, IIIe, IVe R=$(CH_2)_5$; IIb; IIIf, IVf R=C_6H_5; IIa—IVa $R^1=CH_3$; IIb,g, IIIb, IVb $R^1=i\text{-}C_3H_7$; IIc,n, IIIc, IVc $R^1=C_3H_7$; IId, i, IIId, IVd $R^1=i\text{-}C_4H_9$; IIf $R^1=C_6H_5$

In contrast to the isomeric 3,4-dihalo-2-substituted 4-methyltetrahydropyrans [7], dihalides II react with zinc powder with a high degree of regioselectivity: in addition to 3,6-dihydropyrans III, 3-5% 4-methyltetrahydropyrans IV in the case of dichlorides and 0.5-1% IV in the case of chlorobromides are also formed. The identification of IV for IVb was

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TABLE 1. 4-Methyl-4-chloro-5-halo-2-R-tetrahydropyrans IIa-k

Compound	bp, deg C (mm)	n_D^{20}	d_4^{20}	PMR, δ, ppm	Found, %			Empirical formula	Calculated, %			Yield, %
					C	H	Hal		C	H	Hal	
IIa	83—87 (11,5)	1,4802	1,1635	1,21—1,30 (3H, m, CH_3); 1,70 and 1,75 (3H, s, Z,E-CCl—CH_3); 2,14—2,21 (2H, m, CH_2); 3,37—3,57 (1H, m, CHCl); 3,78—4,09 (3H, m, CH_2O+CHO)	46,1	6,8	38,4	$C_7H_{12}Cl_2O$	45,9	6,6	38,8	60
IIb	76—80 (2,5)	1,4805	1,1379	0,82 [6H, d in m form , J=6,2 Hz, $(CH_3)_2$]; 1,20—1,33 (1H, m, CH); 1,68 and 1,74 (3H, c, Z,E-CH_3); 2,06—2,23 (2H, m, CH_2); 2,98—3,39 (1H, m, CHCl); 3,45—4,13 (3H, m., CH_2O+ +CHO)	51,4	7,6	33,4	$C_9H_{16}Cl_2O$	51,2	7,6	33,7	70
IIc	76—82 (2)	1,4795	1,1191	0,74—1,54 (7H, m, C_3H_7); 1,70 and 1,80 (3H, s, Z,E-CH_3); 2,01—2,19 (2H, m, CH_2); 3,35—3,54 (1H, m, CHCl); 3,75—4,09 (3H, m, CH_2O+ +CHO)	51,5	7,6	33,4	$C_9H_{16}Cl_2O$	51,2	7,7	33,7	87
IId	73—76 (2,5)	1,4760	1,0734	0,89 [6H, d, J=6,2 Hz, $(CH_3)_2$]; 1,22—1,59 (3H, m CH_2+CH- isobutyl); 1,69 and 1,79 (3H, s, Z,E-CH_3); 2,09—2,18 (2H, m, CH_2); 3,31—3,54 (1H, m., CHCl); 3,75—4,07 (3H, m, CH_2O+ +CHO)	53,5	8,3	31,2	$C_{10}H_{18}Cl_2O$	53,3	8,0	31,6	89
IIe	99—103 (2,5)	1,5075	1,1363	1,32—1,57 [10H, m, $(CH_2)_5$]; 1,70 (3H, s, CH_3); 1,97 (2H, s, CH_2); 3,36—3,80 (1H, m, CHCl); 3,91—4,10 (2H, m, CH_2O)	55,9	7,9	29,6	$C_{11}H_{18}Cl_2O$	55,7	7,7	30,0	80
IIf	130—138 (2,5)	1,5482	1,2016	1,76 and 1,82 (3H, s, Z,E-CH_3); 2,21—2,42 (2H, m CH_2); 3,41—3,56 (1H, m, CHCl); 3,91—4,09 (3H, m, CH_2O+CHO); 7,32 (5H, s, C_6H_5)	58,6	5,9	28,7	$C_{12}H_{14}Cl_2O$	58,8	5,8	29,0	80
IIg	76—78 (2)	1,4992	1,3356	0,83 and 0,97 [6H, d, J=6,2 Hz, $(CH_3)_2$]; 1,74 and 1,81 (3H, s, Z,E-CH_3); 2,22—2,28 (2H,m, CH_2); 3,45—3,65 (1H, m, CHBr); 3,87—4,29 (3H, m., CH_2O+CHO)	42,4	6,6	44,8*	$C_9H_{16}BrClO$	42,3	6,3	45,2	83
IIh	72—73 (1,5)	1,4979	1,3310	1,02—1,80 (7H, m, C_3H_7); 2,01 and 2,09 (3H, s, Z,E-CH_3); 2,26—2,62 (2H, m, CH_2); 4,03—4,31 (1H, m, CHBr); 4,50—5,12 (3H, m, CH_2O+ +CHO)	42,5	6,5	44,9	$C_9H_{16}BrClO$	42,3	6,3	45,2	65
IIi	88—90 (2,5)	1,4929	1,2879	0,91 [6H, d in m form , J=6,2 Hz, $(CH_3)_2$]; 1,22—1,74 (3H, m CH_2+CH isobutyl .); 1,73 and 1,79 (3H, s, Z,E-CH_3); 2,12—2,24 (2H, m, CH_2); 3,45—3,65 (1H, m, CHBr); 3,86—4,25 (3H, m, CH_2O+CHO)	44,4	6,9	42,5	$C_{10}H_{18}BrClO$	44,5	6,7	42,9	81
IIj	111—114 (2,5)	1,5255	1,3380	1,30—1,64 [10H, m, $(CH_2)_5$]; 1,76 (3H, s, CH_3); 2,03 and 2,05 (2H, s, CH_2); 3,48—3,64 (1H, m, CHBr); 3,85—4,35 (2H, m, CH_2O)	47,1	6,2	40,8	$C_{11}H_{18}BrClO$	46,9	6,4	41,0	80
IIk	150—152 (3,5)	1,5665	1,4169	1,75 and 1,80 (3H, s, Z,E-CH_3); 2,25—2,44 (2H, m, CH_2); 3,60—3,78 (1H, m, CHBr); 3,86—4,25 (3H, m, CH_2O+CHO); 7,27 (5H, s, C_6H_5)	49,9	4,5	39,5	$C_{12}H_{14}BrClO$	49,7	4,8	39,9	67

*Overall halogen.

TABLE 2. Characteristics of IIIa-f

Compound	bp, deg C (mm)	n_D^{20}	d_4^{20}	δ, ppm (J, Hz)						Found,%		Empirical formula	Calc., %		Yield, %
				=CH	CH_2O	C*H	CH_2	CH_3	R	C	H		C	H	
IIIa	125—127 (680)	1,4433	0,8901	5,44 m (1)	4,10 sext (2,8)	3,41—3,74 m	1,86 m	1,68 dd (1)	1,12 & 1,22 s	75,1	10,5	$C_7H_{12}O$	75,0	10,7	45[a]
IIIb	55 (12,5)	1,4496	0,8787	5,36 br	4,05 sext (2,8)	2,91—3,24 m	1,86 m	1,68 dd (1,2)	0,88 & 0,92 d (6,5)	77,2	11,3	$C_9H_{16}O$	77,1	11,4	52[b], 67[c]
IIIc	61 (12,5)	1,4492	0,8146	5,36 m	4,05 sext (2,8)	3,21—3,50 m	1,73 m	1,66 dd (1)	0,92 (3H, m, CH_3), 1,31 (4H, m CH_2CH_2)	77,2	11,4	$C_9H_{16}O$	77,1	11,4	64, 70
IIId	72—74 (12)	1,4517	0,8819	5,37 m	4,02 sext (2,8)	3,20—3,57 m	1,82 m	1,66 br	0,90 [6H, d, $J=6$ Hz $(CH_3)_2$] 1,12—1,49 (3H, m $CH+CH_2$)	77,8	11,6	$C_{10}H_{18}O$	77,9	11,7	53, 75
IIIe	53—54 (2,5)	1,4855	0,9613	5,35	3,97 sext (2,8)	—	1,31—1,76 [15H, m, $CH_2+CH_3+(CH_2)_5$]			79,4	10,6	$C_{11}H_{18}O$	79,5	10,8	61, 80
IIIf	80 (2,5)	1,5380	1,0230	5,42 br	4,23 m	4,45 m	2,06 m	1,70 dd (1)	7,25 br	82,7	8,0	$C_{12}H_{14}O$	82,8	8,1	70, 70

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[a] Splitting out by magnesium from the dichloro derivative. [b] Splitting out by magnesium from the bromo chloro derivative. [c] Splitting out by zinc from the bromo chloro derivative.

carried out by comparison with a genuine sample [13]; in the remaining cases identification was realized from data from gas-liquid chromatography (GLC) and from the presence of vinyl protons in the PMR and IR spectra. When zinc is replaced by magnesium, the reaction proceeds regiospecifically: only 3,6-dihydropyrans III are formed in 52-70% yields.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in CCl_4 were obtained with a Perkin-Elmer spectrometer (60 MHz) with hexamethyldisiloxane (HMDS) as the internal standard. Gas-liquid chromatography (GLC) was accomplished with an LKhM-8MD chromatograph with a catharometer and 200 cm and 300 cm columns packed with 10% PEG-20M on Inerton AW-HMDS, 5% SE-30 on Chromaton A-AW-HMDS, and 5% APM on Chromaton NAW; the carrier-gas (helium) flow rate was 40-60 ml/min, and the temperature was 140-180°C.

2-Methyl-3-chloro-1-buten-4-ol (Ia). A 13.2-g (0.1 mole) sample of the $HCl \cdot OEt_2$ complex was added dropwise at 0°C to 8.4 g (0.1 mole) of isopropenyloxirane [12], after which the mixture was stirred for another 2 h. The ether was removed by distillation, and the residue was distilled *in vacuo* to give 6.7 g (55.6%) of Ia with bp 66-68°C (13 mm), n_D^{20} 1.4730, and d_4^{20} 1.0938. IR spectrum: 1652 (C=C), 3086 (=CH_2), and 3330-3452 cm^{-1} (OH). PMR spectrum: 3.79 (2H, d, J = 6.2 Hz, CH_2OH), 3.60 (1H, s, OH), 4.49 (1H, t, J = 6.2 Hz), 1.84 (3H, d, J = 1 Hz, CH_3), and 5.21 and 5.10 ppm (2H, J = 1.2 Hz, =CH_2).

2-Methyl-3-bromo-1-buten-4-ol (Ib). A mixture of 8.4 g (0.1 mole) of isopropenyloxirane, 20.3 g (0.12 mole) of 48% hydrobromic acid, 11.9 g (0.1 mole) of KBr, and 20 ml of benzene was stirred at 0°C for 2 h, after which the liquid was decanted, neutralized with solid sodium carbonate, and extracted with ether. The extract was dried with $MgSO_4$ and distilled to give 9.9 g (60%) of Ib with bp 74-76°C (10 mm), n_D^{20} 1.5112, and d_4^{20} 1.4417. IR spectrum: 1640 (C=C), 3090 (=CH_2), and 3340-3400 cm^{-1} (OH). PMR spectrum: 1.88 (3H, br, CH_3), 3.50 (1H, s, OH), 3.74 [2H, d, J = 8 Hz, CH_2(OH], 4.56 (1H, t, J = 8 Hz), and 5.04 and 5.20 ppm (2H, m, J = 1 Hz, =CH_2).

4-Chloro-4-methyl-5-halo-2-R-tetrahydropyrans IIa-k. A 0.1-mole sample of halohydrin Ia, b, 0.1 mole of the carbonyl compound, and 30 ml of chloroform were placed in a flask cooled to 0°C, and dry hydrogen chloride was passed through the mixture for 2-5 h. The mixture was then neutralized with sodium carbonate and extracted three times with ether. The extract was dried with $MgSO_4$, the solvents were removed by distillation, and the residue was distilled to give IIa-k (Table 1) in the form of cis and trans isomers in approximately equal amounts.

4-Methyl-2-R-3,6-dihydro-2H-pyrans IIIa-f. A) A mixture of 0.1 mole of II, 0.2-0.3 mole of zinc dust, and 40 ml of ethanol was heated at 70-80°C for 25-30 h, after which it was filtered to remove the resulting precipitate. The precipitate was washed several times with ether and combined with the filtrate, and the solvents were removed by distillation under low vacuum. The residue was treated with a saturated solution of sodium carbonate and extracted three times with ether. The extract was dried with $MgSO_4$, the ether was removed by distillation, and the residue was distilled in vacuo to give dihydropyrans III (Table 2). IR spectrum: 1680, 1640 (C=C); 3080 cm^{-1} (=CH_2).

B) A 20-ml sample of absolute ether and 0.5 ml of ethyl bromide (to start the reduction) were added to 0.2 mole of magnesium turnings, after which another 50 ml of ether was added, and the mixture was treated with a solution of 0.1 mole of dihalides II in 30 ml of ether at such a rate that the mixture refluxed gently. The mixture was then heated at 35°C for 3 h, after which the resulting precipitate was removed by filtration and washed with ether. The filtrate was treated with a saturated solution of ammonium chloride and dried with $MgSO_4$. The ether was removed by distillation, and the residue was distilled to give dihydropyrans IIIa-f (Table 2). IR spectrum: 1680 cm^{-1} (C=C).

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NEW DATA ON THE REACTION OF 1,3-DIARYL-3-(2-OXOCYCLOHEXYL)-1-PROPANONES WITH HYDROGEN SULFIDE AND METHANOL

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The stereochemical aspects of the reaction of 1-aryl- and 1,3-diaryl-substituted 3-(2-oxo-cyclohexyl)-1-propanones with hydrogen sulfide and methanol have been discussed. A mechanism is proposed for the formation of trans, trans-1-methoxy-3,5-diaryl-2-thia(oxa)bicyclo-[4.4.0]dec-3-enes.

1-Aryl- and 1,3-diaryl-3-(2-oxocyclohexyl)-1-propanones (I-IV) react with hydrogen sulfide and methanol under conditions of acid catalysis to form bicyclic thioacetals [1]. By analogy with 2-methoxy-2,4-diphenylhexahydrochromene [2] the latter were erroneously considered to be derivatives of 2-methoxyhexahydrothiochromene [1]. Study of the structure of these compounds by PMR [3] and x-ray diffraction [4] showed that they are trans, trans-1-methoxy-3,5-diaryl-2-thiabicyclo[4.4.0]dec-3-enes (VII-X); this caused us to reconsider the reaction mechanism that we had previously proposed [1].

Continuing our work on the bicyclic thioacetals, we have studied the composition and structure of the products of the reaction of the 1,5-diketones I-VI with methanol and hydrogen sulfide at 10-15°C, and have also obtained data on the structure of the starting dicarbonyl compounds. The structural assignments were based on ^{13}C NMR analysis.

It was established that under the conditions described, 1,3-diaryl-3-(2-oxocyclohexyl)-1-propanones (I-IV) form trans-1-methoxy-2-phenyl- (VII) and trans, trans-1-methoxy-3,5-diaryl-2-thiabicyclo[4.4.0]dec-3-enes (VIII-X). The monoaryl-substituted 1,5-diketone I gave, along with trans-thioacetate VII, a small amount of cis-isomer XI. In tests with diaryl substituted 1,5-diketones, cis-thioacetals were not found. Under the same conditions when both hydrogen sulfide and methanol were present in the reaction mixture, 1,5-diketones V and VI reacted with only one of the nucleophiles, viz., methanol, to form trans, trans-1-methoxy-3,5-diaryl-2-oxabicyclo[4.4.0]dec-3-enes (XII, XIII).

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