GRIGNARD REACTION WITH 2,6-DIALKOXYDIHYDRO- AND -TETRAHYDROPYRANS

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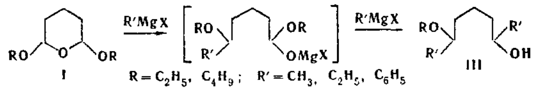
The Grignard reaction with 2,6-dialkoxytetrahydropyran and 2,6-dialkoxy-5,6-dihydro-2H-pyran has been studied. In both cases the reaction takes place with the opening of the pyran ring and the formation of alkoxy-substituted saturated or γ, δ-unsaturated alcohols.

The Grignard reaction with 2,6-dialkoxytetrahydropyran (I) and 2,6-dialkoxy-5,6-dihydro-2H-pyran (II) appeared of interest. It was found that the Grignard reaction with these compounds can take place in two directions: with the opening of the pyran ring and the formation of aliphatic alcohols, or, without the opening of the ring, with the replacement of one of the alkoxy groups by alkyl.* The second direction of the reaction would provide the possibility in the case of II of obtaining alkylakoxydihydropyrans, which are important intermediates in the synthesis of aminodeoxysugars. Compounds I and II are internal cyclic acetals of glutaraldehyde and glutaconaldehyde and, obviously, the direction of the Grignard reaction with them is determined by the difference in the reactivities of the two acetal centers. It is known that the simplest acetals do not react with organomagnesium compounds even under severe conditions (up to 150° C [2]). The majority of acetals take part in the Grignard reaction at 80–120° C with the formation of α-alkyl-substituted ethers. In α, β-unsaturated acetals, this reaction takes place under milder conditions, but at the same time is accompanied by the formation of by-products (γ-alkyl-substituted vinyl ethers [3]).

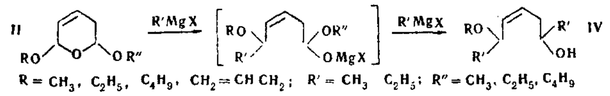
Like the lower aliphatic acetals, 2-ethoxytetrahydropyran does not take part in the Grignard reaction [1]. However, on treatment with a Grignard reagent 2-phenoxytetrahydropyran gives a satisfactory yield of the corresponding 2-alkyltetrahydropyran [4]. It is obvious that this is not due to the higher reactivity of the acetal center in the pyran ring (C_2), but is explained in the same way as the cleavage of phenol ethers by a Grignard reagent [5]. If there is a double bond in the α, β-position, the acetal group is activated. 2-Ethoxy-5,6-dihydro-2H-pyran reacts almost quantitatively with a Grignard reagent: a 2-alkyl-5,6-dihydro-2H-pyran is formed (50–60%), and the ring opens with the formation of ethoxy-substituted unsaturated alcohols (20–30%) [1].

We have found that the presence of two alkoxy groups in tetrahydro- and dihydropyrans makes the acetal centers more reactive and the pyran ring less stable than in monoalkoxy-substituted pyrans. The Grignard reaction with 2,6-dialkoxytetrahydropyrans (I) takes place with the opening of the pyran ring and the consumption of two equivalents of the Grignard reagent; alkoxy-substituted alcohols (III) are the sole reaction products (according to gas-liquid chromatography). The ratio of the reactants and different temperature conditions affect the yield of the alcohols III but do not change the direction of the reaction; in ethereal solution the alcohols III are obtained with a yield of 20–25%, and in benzene solution with a yield of about 80%.



$R = C_2H_5, C_4H_9$; $R' = CH_3, C_2H_5, C_6H_5$

The acetal center is activated still further if the ring has a double bond: 2,6-dialkoxy-5,6-dihydro-2H-pyrans (II) react with a Grignard reagent under the usual conditions (in ether). Alkoxy-substituted unsaturated alcohols (IV) are formed in high yield as the sole reaction products (according to gas-liquid chromatography).



$R = CH_3, C_2H_5, C_4H_9, CH_2{=}CHCH_2$; $R' = CH_3$ C_2H_5; $R'' = CH_3, C_2H_5, C_4H_9$

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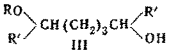
*During the completion of our work, a paper appeared in which the Grignard reaction with 2,6-diethoxytetrahydropyran was studied [1].

It was natural to assume that the reaction first affects the acetal center in the position α,β to the double bond and gives γ,δ-unsaturated alcohols. To prove this, the reaction was carried out with compounds II which had different alkoxy groups: the alcohol formed retained the alkoxy group adjacent to the double bond. Thus, from the action of methylmagnesium iodide with three alcohols II with the same R groups (CH_3) but different R' groups (CH_3, C_2H_5, and C_4H_9), the same unsaturated alcohol IV (R = R' = CH_3) was obtained.

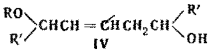
The IR spectra of all the alcohols III are completely similar; they each have a symmetrical absorption band at 3620 cm^{-1}. The IR spectra of all the alcohols IV are also similar, but in addition to a strong absorption band at 3630 cm^{-1} they each have a weaker band at 3595 cm^{-1} which is obviously due to the presence of a hydrogen bond between O—H group and the π electrons of the double bond. The difference between the IR spectra of alcohols III and IV is similar to that observed between corresponding saturated and γ,δ-unsaturated alcohols [6].

EXPERIMENTAL

6-Ethoxyheptan-2-ol (IIIa). To a solution of methylmagnesium iodide prepared from 1.8 g (0.07 mole) of magnesium and 10.7 g (0.07 mole) of methyl iodide in 50 ml of absolute ether was added 5 g (0.03 mole) of 2,6-diethoxytetrahydropyran in 15 ml of absolute ether. Then 35 ml of absolute benzene was added, the ether was distilled off, and the reaction mixture was heated in a boiling water bath for 5 hr. It was decomposed with a solution of ammonium chloride and extracted with ether, and the extract was dried with magnesium sulfate. This gave 3.8 g of IIIa (table).


$(RO)(R')CH(CH_2)_3CH(R')(OH)$

III


$(RO)(R')CHCH{=}CHCH_2CH(R')(OH)$

IV

Initial compound			Compound produced			Bp, °C (mm)	n_D^{20}	d_{20}^{20}	MR_D		Empirical formula	Found, %		Calculated %		Yield, %
	R	R″		R	R′				found	calculated		C	H	C	H	
Ia	C_2H_5		IIIa	C_2H_5	CH_3	48—50 (1)	1.4311	0.8894	46.66	46.93	$C_9H_{20}O_2$	67.2; 67.1	12.9; 12.7	67.4	12.6	78.5
Ia	C_2H_5		IIIb	C_2H_5	C_2H_5	44—46 (0.8)	1.4388	0.8906	55.97	56.17	$C_{11}H_{24}O_2$	69.9; 70.0	12.5; 12.7	70.1	12.8	75
Ia	C_2H_5		IIIc	C_2H_5	C_6H_5	145—147 (0.3)	1.5439	1.0406	86.24	85.91	$C_{19}H_{24}O_2$	80.5; 80.4	8.4; 8.7	80.2	8.5	37.5
Ib	C_4H_9		IIId	C_4H_9	C_2H_5	78—80 (0.8)	1.4417	0.8820	64.98	65.40	$C_{13}H_{28}O_2$	71.9; 72.2	12.9; 13.0	72.1	13.0	68
IIa	CH_3	C_2H_5	IVa*	CH_3	CH_3	86—87 (9)	1.4460	0.9234	41.66	41.84	$C_8H_{16}O_2$	66.4; 66.4	10.9; 11.0	66.6	11.2	71
IIb	C_2H_5	C_2H_5	IVb	C_2H_5	CH_3	90—91 (9)	1.4470	0.9095	46.48	46.46	$C_9H_{18}O_2$	68.2; 68.2	11.3; 11.3	68.3	11.4	73.5
IIb	C_2H_5	C_2H_5	IVc	C_2H_5	C_2H_5	62—63 (1)	1.4519	0.9046	55.54	55.70	$C_{11}H_{22}O_2$	70.8; 70.7	12.0; 11.7	70.9	11.9	78
IIc	C_4H_9	C_4H_9	IVd	C_4H_9	CH_3	61—62 (0,2)	1.4486	0.8887	55.78	55.70	$C_{11}H_{22}O_2$	70.8; 70.7	11.7; 11.8	70.9	11.9	68
IId	$CH_2{=}CHCH_2$	C_4H_9	IVe	$CH_2{=}CHCH_2$	C_2H_5	73—74 (0.06)	1.4615	0.9168	59.41	59.84	$C_{12}H_{22}O_2$	72.2; 72.3	11.0; 10.9	72.6	11.2	71.5

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*The same alcohol was obtained from both 2,6-dimethoxy-5,6-dihydro-2H-pyran and 6-butoxy-2-methoxy-5,6-dihydro-2H-pyran.

Alcohols IIIb, c, and d were obtained similarly.

3-Ethoxynon-4-en-7-ol (IVc). To a solution of ethylmagnesium bromide prepared from 3.7 g (0.15 mole) of magnesium and 16.5 g (0.15 mole) of ethyl bromide in 75 ml of absolute ether was slowly added 10 g (0.06 mole) of 2,6-diethoxy-5,6-dihydro-2H-pyran (IIb) in 20 ml of absolute ether. The mixture was heated to a gentle boil for 5 hr. After the usual working up, 8.4 g of IVc (table) was obtained.

Alcohols IVa, b, d, and e were obtained similarly.

On a gas-liquid chromatogram, all the alcohols III and IV gave a single peak (PEGA/Celite, 130° C).

The IR spectra of alcohols III were taken in 0.01 N CCl_4 solutions and those of alcohols IV in 0.01 N and 0.005 N CCl_4 solutions on a UR-10 instrument.

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