

## INVESTIGATIONS IN THE FIELD OF DIOLS AND CYCLIC ETHERS. V

### Preparation of 2-monosubstituted derivatives of tetrahydropyran

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In the course of studying the contact catalytic transformations of cyclic ethers in the gas-phase, investigation of tetrahydropyran derivatives was also undertaken. The present communication reports a modified synthesis of 2-monosubstituted six-membered cyclic ethers, required for the experiments.

In the course of the study of the contact catalytic and vapour-phase transformations of cyclic ethers, their isomerisation to oxo-compounds has also been studied [1, 2, 3]. In the present paper we report our work on the synthesis of 2-monosubstituted derivatives of tetrahydropyran, required for the above experiments. During our syntheses we have also dealt with the preparation of 2-monosubstituted derivatives of tetramethylene oxide. Oxetane derivatives are synthesized by the alkaline ring closure of 1,3-chloroacetates in a yield of about 70%. The preparation of cyclic ethers by the intramolecular dehydration of 1,3-diols has not been successful up to now.

The study of literature shows that the first attempts to synthesize tetrahydropyran derivatives applied directly the intramolecular water cleavage reaction of diols. The dehydration of diols in the presence of sulphuric acid first was examined in a more detailed manner by FRANKE and his coworkers [4, 5, 6, 7]. They have described the syntheses of some 2-monosubstituted tetrahydropyran derivatives.

A remarkable progress in the development of the synthesis of 2-monosubstituted tetrahydropyran derivatives was brought by a completely new method of synthesizing dihydropyran, elaborated and published in 1933 by PAUL [8]. He prepared 2,3-dihydropyran from a very cheap and easily obtainable starting substance, i. e. from furfural, by hydrogenation under pressure. This way he first got tetrahydrofurfuryl alcohol and from it 2,3-dihydropyran in one step. The novelty in this method was the obtainment of the compound in a continuous system on aluminum oxide catalyst, at 380°C. After elaborating the large-scale synthesis of 2,3-dihydropyran, PAUL had studied its chemical transformations and 2-bromotetrahydropyran was prepared by addition of hydrogen bromide [9, 10] to the 2,3-dihydro compound, and the reaction of the

2-bromo derivative with the GRIGNARD reagent resulted in corresponding 2-alkyl- and aryl-derivatives, respectively [11, 12].

After this short introduction we give a report on the literature of the synthesis of 2-monosubstituted tetrahydropyran. FRANKE [6] had also prepared 2-methyltetrahydropyran by the intramolecular dehydration of diol, however, the exact description of the synthesis was given only by PAUL in 1938 [13]. He started from 2-( $\alpha$ -furyl)-methyl carbinol, which is prepared in two steps from furfurool. He got 2-methyl-5,6-dihydropyran by dehydration, and its hydrogenation resulted in 2-methyltetrahydropyran. PAUL prepared the compound also from 2-bromotetrahydropyran [14], and by the method above mentioned [3]. The required compound was synthesized by COLONGE and LASFARGUES [15] by the isomerisation of hexen-5-ol-1 with phosphoric acid, in a yield of 72%. COLONGE and GIRANTET according to their paper, published this year, prepared 2-methyltetrahydropyran in the following way: 2-furancarboxylic-acid-methylester was converted to 5-methyl-2-carbomethoxy furan by a FRIEDEL—CRAFTS reaction. By a two step reduction of RANEY Ni and with lithium aluminum hydride, 2-oxymethyl-5-methyl furan was obtained and from this 2-methyl tetrahydropyran prepared in the known way by intramolecular dehydration and hydrogenation on RANEY Ni. Other derivatives were also synthesized in the same way, they will be referred to at the corresponding place. They prepared 2-ethyl tetrahydropyran from 2-bromotetrahydropyran with ethylmagnesiumbromide [11, 14, 13] with a yield of 76% [12].

2-n-propyltetrahydropyran was also prepared from 2-bromotetrahydropyran and n-propylmagnesiumbromide [11, 14, 13] with 86% yield [12]. FRANKE [6] synthesized it, too, from diol by dehydration.

2-i-propyltetrahydropyran was prepared by COLONGE and GIRANTET by the way already described [16].

2-n-butyltetrahydropyran was prepared by PAUL [14], BELSKII and SHUIKIN [3] from 2-bromotetrahydropyran by the GRIGNARD reaction; FRANKE and LIEBERMAN [5, 6] prepared it from diol by dehydration with sulphuric acid, while SMITH, NORTON and BALLARD applied the hydrogenation of dihydropyran derivatives formed by the dien type condensation of acrolein and hexene-1. 2-t-butyltetrahydropyran was synthesized by COLONGE and GIRANTET [16].

2-n-amyltetrahydropyran was prepared by the dehydration of diol with sulphuric acid in a yield of 62% [6, 18].

2-t-amyltetrahydropyran was synthesized also by the above authors in the already known method [16].

Tetrahydropyran substituted at the position 2 with a phenyl radical was first prepared by PAUL, by means of the GRIGNARD reaction of 2-bromotetrahydropyran with phenylmagnesiumbromide [11, 12, 14]. SMITH and his coworkers got to the compound in question by the condensation of acrolein with styrene followed by hydrogenation [17]. Data in literature on the syntheses and main physical constants of 2-monosubstituted tetrahydropyran derivatives are summarized in Table I.

In the course of study of the contact catalytic transformations of cyclic ethers in the gas-phase, experiments were carried out with six-membered cyclic ethers, too.

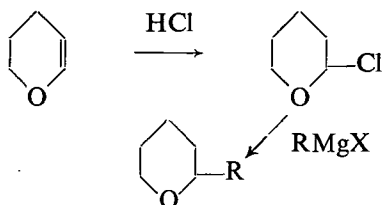
The present paper reports the synthesis of 2-monosubstituted tetrahydropyran, required for our experiments. From the study of data available in the literature it can be stated that the preparation in laboratory of the compounds in question can

Table I  
Data in literature on the preparation and physical constants of 2-monosubstituted tetrahydropyrans

No	Name	Yield in %	Boiling point °C (mm)		d gr/cm <sup>3</sup>	n <sub>D</sub> (t°C)	References
1.	2-methyl-THP	—	104—6	(770)	0,866 $\frac{1}{5}$ <sup>3</sup>	1,42355 (13)	13 1938
2.	2-methyl-THP	—	101—103	(758)	0,868 <sup>11</sup>	1,42175	14 1938
3.	2-methyl-THP	—	101—102	(750)	0,8570 $\frac{20}{4}$	1,4187 (20)	3 1959
4.	2-methyl-THP	72	103	(750)	0,852 $\frac{20}{4}$	1,418 (20)	15 1962
5.	2-methyl-THP	—	101—2	(750)	0,851 $\frac{25}{4}$	1,4160 (25)	16 1962
6.	2-ethyl-THP	—	128—9	(770)	0,865 $\frac{15}{20}$	1,42885 (15)	11 1934
7.	2-ethyl-THP	76	128—9	(770)	0,865 $\frac{15}{5}$	1,42885 (15)	12 1935
8.	2-ethyl-THP	—	128—9	(773)	0,869 <sup>10</sup>	1,42985	14 1938
9.	2-ethyl-THP	—	128—9	(752)	0,8566 $\frac{20}{4}$	1,4245 (20)	3 1959
10.	2- <i>n</i> -propyl-THP	—	152—3	(760)	0,860 $\frac{15}{5}$	1,43256 (15)	11 1934
11.	2- <i>n</i> -propyl-THP	86	152—3	(760)	0,860 $\frac{15}{5}$	1,43256 (15)	12 1935
12.	2- <i>n</i> -propyl-THP	—	153—4	(768)	0,866 <sup>9</sup>	1,43407	14 1938
13.	2- <i>n</i> -propyl-THP	—	152—3	(745)	0,8552 $\frac{20}{4}$	1,4290 (20)	3 1959
14.	2- <i>i</i> -propyl-THP	—	142,5	(750)	0,857 $\frac{25}{4}$	1,4308 (25)	16 1962
15.	2- <i>n</i> -butyl-THP	—	175—7		—	—	5 1922
16.	2- <i>n</i> -butyl-THP	—	64	(14)	0,865 <sup>10</sup>	1,43818	14 1938
17.	2- <i>n</i> -butyl-THP	—	63—5	(14)	—	1,4368 (20)	17 1951
18.	2- <i>n</i> -butyl-THP	—	176—7	(750)	0,8570 $\frac{20}{4}$	1,4350 (20)	3 1959
19.	2- <i>t</i> -butyl-THP	—	157	(750)	0,857 $\frac{25}{4}$	1,4350 (25)	16 1962
20.	2- <i>n</i> -amyl-THP	62	84	(14)	—	—	6 1929
21.	2- <i>n</i> -amyl-THP	—	73,7—74	(10)	—	—	18 1935
22.	2- <i>n</i> -amyl-THP	—	198,5—200,5	(747)	—	—	18 1935
23.	2- <i>t</i> -amyl-THP	—	103	(71)	0,880 $\frac{25}{4}$	1,4515 (25)	16 1962
24.	2-phenyl-THP	—	113	(11)	1,020 $\frac{15}{20}$	1,53191 (15)	11 1934
25.	2-phenyl-THP	74	113	(11)	1,02 $\frac{18}{15}$	1,5319 (18)	12 1935
26.	2-phenyl-THP	—	111—2	(10)	1,0229 <sup>11</sup>	1,53183	14 1938
27.	2-phenyl-THP	—	105—6	(10)	1,0145 <sup>20</sup>	1,5273. (20)	17. 1951

be carried out in the simplest, quickest and most profitable method starting from dihydropyran, which can be obtained in very large quantity. The corresponding cyclic ether can be obtained more easily by the dehydration of 1,5-diols, but the preparation of the starting material is rather lengthy. In the synthesis we have applied PAUL's basic conception. As it is known, PAUL had prepared 2-bromotetrahydropyran from dihydropyran by adding HBr, and the C—Br bond, which is easy to polarize, enters a reaction with the GRIGNARD reagent, and this results in the corresponding 2-substituted tetrahydropyran derivative.

Our synthesis differs so that we have started from 2-chlorotetrahydropyran, the preparation of which is already described in literature [19—22]. The addition of hydrogen chloride to dihydropyran can be performed much more easily than the addition of hydrogen bromide. Hydrogen chloride gas is easier to obtain than hydrogen bromide, and the purification of the latter from bromide is rather complicated. The preparation of the compounds was carried out according to the following scheme:



R = methyl, ethyl, n-propyl, i-propyl, n-butyl, t-butyl, c-hexyl, phenyl and benzyl.

In the course of choosing (and improving) this process the following considerations were taken besides the forementioned facts: the 2-positioned chlorine atom of cyclic ethers (of ethers in general) can be easily polarized due to the well known reasons, thus it easily reacts. The chemical properties of the chlorine atom at the position 2 in the tetrahydrofuran series were far-reachingly discussed [23, 24]. It a report has been published recently on its reaction with the GRIGNARD reagent [25].

2-chlorotetrahydropyran is an instable compound, it decomposes even if allowed to stand. Its purification by distillation brings therefore great losses. It is purposeful to carry out the synthesis so that after the calculated amount of hydrogen chloride had dissolved the formed 2-chlorotetrahydropyran should be added dropwise (without any purification) direct to the dry etheric solution of the formerly prepared GRIGNARD reagent.

### Experimental

*Dihydropyran* was BDH product. B. p. 85—86°C;  $d_4^{20}$ : 0,918;  $n_D^{20}$ : 1,4400.

*2-chlorotetrahydropyran*. 1000 ml three-necked bottle was equipped with a stirrer, a gas-inlet tube and a thermometer. The third hole was closed with a tube containing anhydrous calcium chloride. 252 g dihydropyran (3 mole) was measured into the bottle and the content cooled with a mixture of ice and NaCl. Calculated amount of hydrogen chloride (105 g), dried with concentrated sulphuric acid and calcium chloride was introduced with stirring, at a rate that the temperature had not risen above 0°C. The time required for the introduction of hydrogen chloride was about 2—3 hours.

In order to determine the physical constants of the obtained product, it was redistilled. B. p.: 54–55°C (26 mm);  $n_D^{24}$ : 1,4660.

*2-alkyl, c-alkyl, aryltetrahydropyran.* The corresponding GRIGNARD reagents were prepared from 3 mole of metallic magnesium and 3 mole of R—X according to the methods described in Organic Syntheses. The following halogenides were applied in the preparation of the GRIGNARD reagent: methyl iodide, ethyl bromide, *n*-propyl bromide, *i*-propyl bromide, *n*-butyl bromide, *t*-butyl chloride, *c*-hexyl chloride, bromobenzol and benzyl chloride.

To the dry etheric solution of the corresponding GRIGNARD reagent, cooled with ice-NaCl mixture, dry etheric solution of crude 2-chlorotetrahydropyran, prepared from dihydropyran, was added dropwise, under intensive stirring in a ratio of 1:1. To avoid decomposition of 2-chlorotetrahydropyran a double walled dropping funnel, cooled with icy water, was used. The time of addition is about two hours. After introduction the mixture it was allowed to stand at room temperature and stirred for two hours, then 1000 ml 5% acetic acid was added dropwise to it, under further stirring. The layers thus formed were separated. The aqueous layer was extracted twice with ether. The combined organic phases were washed with saturated aqueous sodium hydrocarbonate and dried over dry  $K_2CO_3$ . After removing of the ether, it was fractionated. The yield, calculated for dihydropyran was generally 65–85%.

Physical constants of the formed 2-monosubstituted tetrahydropyran derivatives are given in Table II.

Table II.  
Physical properties of 2-monosubstituted tetrahydropyrans

No	R	Formula	Molecular weight	Boiling point C° (Hgmm)	
1.	methyl	$C_6H_{12}O$	100,16	102–3	(752)
2.	ethyl	$C_7H_{14}O$	114,18	127–8	(751)
3.	<i>n</i> -propyl	$C_8H_{16}O$	128,21	152–3	(746)
4.	<i>i</i> -propyl	$C_8H_{16}O$	128,21	144–5	(752)
5.	<i>n</i> -butyl	$C_9H_{18}O$	142,23	176–7	(750)
6.	<i>t</i> -butyl	$C_9H_{18}O$	142,23	157–8	(752)
7.	<i>c</i> -hexyl	$C_{11}H_{20}O$	168,27	122–4	(30)
8.	phenyl	$C_{11}H_{14}O$	162,22	106–8	(10)
9.	benzyl	$C_{12}H_{16}O$	176,25	130–5	(10)

$d_4^{20}$ g/cm <sup>3</sup>	$n_D^{20}$	$R_{M,D}$		C%		H%	
		found	calctd.	found	calctd.	found	calctd.
0,856	1,4186	29,52	29,66	—	71,95	—	12,08
0,856	1,4245	34,07	34,08	73,28	73,62	12,22	12,35
0,855	1,4294	38,69	38,86	74,71	74,97	12,31	12,58
0,860	1,4315	38,63	38,86	74,82	74,97	12,25	12,58
0,857	1,4352	43,32	43,51	75,68	75,98	12,60	12,75
0,860	1,4361	43,25	43,51	75,92	75,98	12,62	12,75
0,932	1,4729	50,62	50,60	78,32	78,51	11,76	11,98
1,020	1,5300	49,13	49,06	81,29	81,43	8,53	8,69
1,030	1,5408	53,76	53,71	82,12	81,76	8,81	9,15

\* \* \*

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## References

- [1] *Shuikin, N. I., I. F. Belskii*: Doklady Akad. Nauk S. S. S. R. **120**, 548 (1958).
- [2] *Shuikin, N. I., I. F. Belskii*: Doklady Akad. Nauk S. S. S. R. **127**, 815 (1959).
- [3] *Belskii, I. F., N. I. Shuikin*: Doklady Akad. Nauk S. S. S. R. **127**, 91 (1959).
- [4] *Franke, A., F. Lieben*: Monatsh. **35**, 1431 (1914).
- [5] *Franke, A., O. Liebermann*: Monatsh. **43**, 589 (1922).
- [6] *Franke, A.*: Monatsh. **53/54**, 577 (1929).
- [7] *Franke, A., A. Kroupa*: Monatsh. **69**, 167 (1936).
- [8] *Paul, R.*: Bull. Soc. chim. France **53**, 1492 (1933).
- [9] *Paul, R.*: Bull. Soc. chim. France **1**, 1397 (1934).
- [10] *Paul, R.*: Compt. rend. **198**, 375 (1934).
- [11] *Paul, R.*: Compt. rend. **198**, 1246 (1934).
- [12] *Paul, R.*: Bull. Soc. chim. France **2**, 311 (1935).
- [13] *Paul, R.*: Bull. Soc. chim. France **5**, 919 (1938).
- [14] *Paul, R.*: Compt. rend. **206**, 1028 (1938).
- [15] *Colonge, J., P. Lasfargues*: Bull. Soc. chim. France **1962**, 177.
- [16] *Colonge, J., A. Girantet*: Compt. rend. **254**, 498 (1962).
- [17] *Smith, C. W., D. G. Norton, S. A. Ballard*: J. Amer. Chem. Soc. **73**, 5274 (1951).
- [18] *Franke, A., A. Kroupa, O. Schmid*: Monatsh. **66**, 406 (1935).
- [19] *Lamant, M.*: Bull. Soc. chim. France **20**, 920 (1953).
- [20] *Riobé, O., L. Gouin*: Compt. rend. **243**, 1424 (1956).
- [21] *Gouin, L.*: Compt. rend. **245**, 2302 (1957).
- [22] *Zelinski, R., J. Louvar*: J. Org. Chem. **23**, 807 (1958).
- [23] *Reppe, W.* u. Mitarbeitern: Annalen **596**, 86 (1956).
- [24] *Gross, H.*: Angew. Chem. **72**, 268 (1960).
- [25] *Gross, H.*: Chem. Ber. **95**, 83 (1962).

ИЗУЧЕНИЕ ХИМИЧЕСКИХ ПРЕВРАЩЕНИЙ ДИОЛОВ И  
ОРГАНИЧЕСКИХ ОКИСЕЙ. V

ПРИГОТОВЛЕНИЕ 2-ОДНОЗАМЕЩЕННЫХ ПРОИЗВОДНЫХ  
ТЕТРАГИДРОПИРАНА

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При изучении контактно-каталитических превращений циклических соединений в газовой фазе, авторы изучали также производных тетрагидропирана. Настоящая работа дает отчет о модифицированном синтезе 2-однозамещенных шестичленных органических окисей нужных для экспериментов.