ACTA CHEMICA SCANDINAVICA 12 (1958) 63—67

Cis- and *Trans*-2,5-Dimethoxy-2,5-dihydrofuran *

JØRGEN TORMOD NIELSEN, NIELS ELMING ** and NIELS CLAUSON-KAAS

Centrallaboratoriet, Sadolin & Holmblad A/S, Copenhagen, Denmark

2,5-Dimethoxy-2,5-dihydrofuran was separated into the *cis* and the *trans* isomer by fractional distillation. Hydrogenation gave the corresponding *cis* and *trans* isomers of 2,5-dimethoxytetrahydrofuran.

The two isomers of 2,5-dimethoxy-2,5-dihydrofuran were *cis*-hydroxylated. Only one *cis*-3,4-dihydroxy-2,5-dimethoxytetrahydrofuran was isolated in each case. The corresponding diacetates were prepared. Attempts to resolve *d,l-cis*-3,4-dihydroxy-*trans*-2,5-dimethoxytetrahydrofuran into the *d*- and the *l*-form by chromatography failed. Attempts to carry out the optical resolution *via* the *l*-menthoxyacetates were also unsuccessful.

2,5-Dimethoxy-2,5-dihydrofurans, prepared by methoxylation of furans, are usually mixtures of the *cis* and the *trans* isomers [1,2]. The same applies to 2,5-dimethoxytetrahydrofurans, which are prepared from the dihydrofurans by catalytic hydrogenation. In one case, *viz.* the derivatives of 2-acetamidomethylfuran, the pair of isomers has been separated [2]. In general, however, these cyclic acetals are used as intermediates for the preparation of 1,4-dicarbonyl compounds and are therefore not separated since both isomers give the same dicarbonyl compounds on acid hydrolysis.

The parent 2,5-dimethoxy-2,5-dihydrofuran has now been separated into the pure isomers by fractional distillation. Hydrogenation gave the corresponding pure 2,5-dimethoxytetrahydrofurans. *Cis*-hydroxylation with potassium permanganate gave only one *cis*-3,4-dihydroxy-2,5-dimethoxytetrahydrofuran from each isomer. The hydroxylation reaction therefore gives no information as to the *cis-trans* relationship between the isomers. Neither did an investigation of the infrared spectra, dipole measurements of the dimethoxydihydrofurans, chromatography of the *cis*-glycols on D-lactose and on starch or the preparation of acetates and *l*-menthoxyacetates of the *cis*-glycols enable us to solve the problem of the *cis-trans* relationship. The reactions are shown in Fig. 1.

* Presented (N.E.) before the Division of Organic Chemistry at the XVIth International Congress of Pure and Applied Chemistry, Paris, France, August 1957.

** Present address: A/S PHARMACIA, Copenhagen, Denmark.

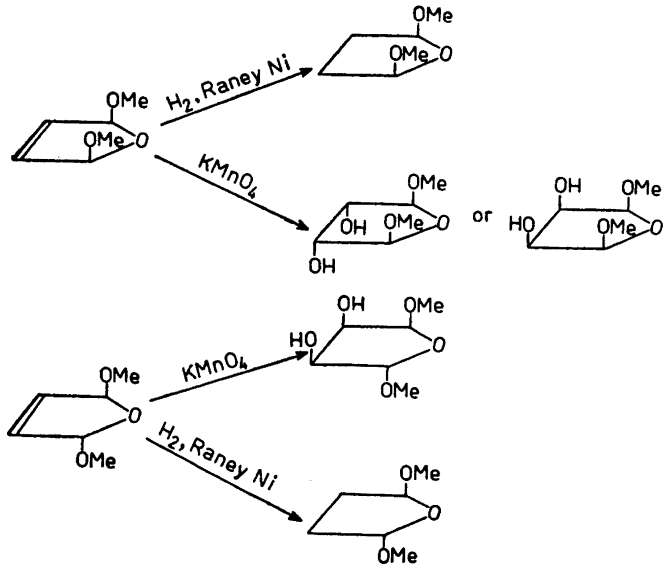

Fig. 1.

It is interesting to observe that there is a marked difference in the yields (44 and 17 %, respectively) of the two *cis*-glycols. Actually the present experiments were initiated by the desire to improve the yields of the hydroxylation reaction of dimethoxydihydrofurans, since a good general procedure for this reaction might open a simple route for the preparation of certain carbohydrates from furans.

Data of all compounds prepared during this investigation are given in Tables 1—5 of the experimental part. It will be noted that the low boiling isomer of 2,5-dimethoxy-2,5-dihydrofuran on hydrogenation gives the high boiling isomer of 2,5-dimethoxytetrahydrofuran.

EXPERIMENTAL

Microanalyses by E. Boss, K. Glens and P. Hansen

2,5-Dimethoxy-2,5-dihydrofurans (I and II). Technical 2,5-dimethoxy-2,5-dihydrofuran (175 g, n_D^{25} 1.4321), prepared by electrolysis [3], was separated into the two isomers by distillation through a 50 cm packed column [4] under 90 mm. It was inferred from the infrared spectra that the purity of the isomers was higher than 95 %. Data of the two isomers are given in Table 1.

Table 1. Data of 2,5-dimethoxy-2,5-dihydrofurans.

	C	H	OCH_3	B.p.$_{90}$ °C	n_D^{25}	Yield, % of distilland
$C_4H_4O(OCH_3)_2$ (130.1) requires	55.4	7.8	47.7			
I	55.6	7.7	47.2	96.0	1.4318	54
II	55.5	7.8	47.6	98.5	1.4331	40

The dielectric constants of dilute benzene solutions of identical concentrations of the isomers were found to be identical within the experimental error.

2,5-Dimethoxytetrahydrofurans (III and IV). This pair of isomers was prepared by catalytic hydrogenation of the pure *cis-* and *trans*-2,5-dimethoxy-2,5-dihydrofurans as described previously [5]. Their data (Table 2) were in agreement with those recorded on samples obtained by fractional distillation of technical 2,5-dimethoxytetrahydrofuran through a 50 cm packed column under 100 mm.

Table 2. Data of 2,5-dimethoxytetrahydrofurans.

	C	H	OCH_3	B.p.$_{760}$ °C	n_D^{25}	Yield %
$C_4H_6O(OCH_3)_2$ (132.2) requires	54.5	9.2	47.0			
III (prepared from I)	54.6	9.2	46.3	147	1.4148	80
IV (prepared from II)	54.7	9.2	46.7	144	1.4158	81

Cis-*3,4-dihydroxy-2,5-dimethoxytetrahydrofurans (V and VI).* I and II were *cis*-hydroxylated by a modification of the method previously described [6]. Powdered potassium permanganate (30.0 g, 0.19 mole) was added in small portions during 1.3 h with vigorous stirring to a solution of 2,5-dimethoxy-2,5-dihydrofuran (26.0 g, 0.20 mole) in water (100 ml) and acetone (100 ml). The temperature was kept at −18° to −21°. The resultant suspension was stirred for 1 h at −20° and the manganese dioxide removed by centrifugation and washed twice with water. The turbid solution was filtered and the filtrate concentrated in a vacuum to about 50 ml. Potassium carbonate (10 g) was added and the solution continuously extracted with ether overnight. The reaction products were isolated by distillation in a vacuum. Their data are given in Table 3.

Table 3. Data of *cis*-3,4-dihydroxy-2,5-dimethoxytetrahydrofurans.

	C	H	OCH_3	B.p.$_{0.1}$ °C	n_D^{25}	M.p. °C	Yield %
$C_4H_6O_3(OCH_3)_2$ (164.2) requires	43.9	7.4	37.8				
V (prepared from I)	43.9	7.4	37.9	109−110	1.4569	34-36	44
VI (prepared from II)	43.9	7.4	37.9	85−87	1.4600	67-69	17

V and VI were crystallized from ether [m.p's 34−36° and 67−69°, respectively (Hershberg apparatus, corr.)]. Another crystallization did not change the m.p's. By evaporation of the mother liquors white crystalline residues having the same m.p's were obtained.

V and VI are therefore believed to be pure isomers. This was also indicated by the infrared spectra.

VI is apparently identical with the product (b.p.$_2$ 130°, n_D^{25} 1.4600, m.p. 65−67°) obtained by Sheehan and Bloom [7] by distillation through a semi-micro fractionating column of their crude product (b.p.$_2$ 106−132°).

Since V or VI must be *d,l-cis*-3,4-dihydroxy-*trans*-2,5-dimethoxytetrahydrofuran it was attempted to resolve V and VI by chromatography on D-lactose using the technique described by Prelog and Wieland [8], but no resolution was observed. Experiments using starch as the adsorbing agent as described by Krebs, Wagner and Diewald [9] were also unsuccessful.

Diacetates of cis-*3,4-dihydroxy-2,5-dimethoxytetrahydrofurans (VII and VIII).* V (328 mg) was dissolved in a mixture of pyridine (3 ml) and acetic anhydride (3 ml) and

the mixture left standing overnight. Evaporation followed by crystallization from ether gave 346 mg of VII (white crystals).

VI (1.26 g) was acetylated as described above and the reaction product isolated by distillation. The yield was 1.47 g of VIII (colorless, viscous liquid, which did not crystallize on standing or by treatment with various solvents). Data of the two isomers are given in Table 4.

Table 4. Data of diacetates of *cis*-3,4-dihydroxy-2,5-dimethoxytetrahydrofurans.

	C	H	OCH_3	$COCH_3$	B.p.$_{0.1}$ °C	n_D^{25}	M.p. °C	Yield %
$C_4H_4O_3(OCH_3)_2(COCH_3)_2$ (248.2) requires	48.4	6.5	25.0	34.7				
VII (prepared from V)	48.5	6.7	24.7	34.5			97–98	70
VIII (prepared from VI)	48.2	6.7	24.7	34.4	90–92	1.4431		77

VII is apparently identical with the diacetate (m.p. 97–99°) reported by Zeile and Heusner [10].

l-Menthoxyacetates of cis*-3,4-dihydroxy-2,5-dimethoxytetrahydrofurans (IX, X and XI).* When treated with one mole of *l*-menthoxyacetyl chloride in pyridine V gave 33 % of a mono-*l*-menthoxyacetate (IX) and 53 % of its di-*l*-menthoxyacetate (X). Under the same conditions VI gave only its di-*l*-menthoxyacetate (XI) (yield 83 %).

Cis-3,4-dihydroxy-2,5-dimethoxytetrahydrofuran (1.35 g, 0.0082 mole) was dissolved in pyridine (10 ml) and *l*-menthoxyacetyl chloride (1.92 g, 0.0082 mole) was added dropwise with cooling at 10–15°. The mixture was left standing at room temperature overnight. Water (5 ml) was added and the mixture continuously extracted with ether for 2 h. The ether extract was washed once with a little water, dried with magnesium sulfate and distilled in a vacuum. Data of the *l*-menthoxyacetates are given in Table 5.

Table 5. Data of *l*-menthoxyacetates of *cis*-3,4-dihydroxy-2,5-dimethoxytetrahydrofurans.

	C	H	OCH_3	B.p.$_{0.05}$ °C	n_D^{25}	Yield %
$C_{16}H_{26}O_5(OCH_3)_2$ (360.4) requires	60.0	9.0	17.2			
IX (prepared from V)	59.5	9.0	17.2	175–185	1.4699	33
$C_{28}H_{46}O_7(OCH_3)_2$ (556.7) requires	64.7	9.4	11.2			
X (prepared from V)	64.3	9.4	11.8	230–235	1.4712	53
XI (prepared from VI)	64.7	9.3	11.5	222–226	1.4731	83

IX, X and XI did not crystallize on standing or by treatment with various solvents. Attempts to prepare a crystalline acetate of IX failed. Only an oil was obtained. It was therefore not possible to separate any diastereomeric forms by fractional crystallization.

Acknowledgment. We are indebted to our colleagues, Professor Børge Bak and Mr. Daniel Christensen for measuring and interpreting the infrared spectra and the dielectric constants.

REFERENCES

1. Clauson-Kaas, N. and Limborg, F. *Acta Chem. Scand.* **6** (1952) 551.
2. Clauson-Kaas, N. and Tyle, Z. *Acta Chem. Scand.* **6** (1952) 667.
3. Clauson-Kaas, N., Limborg, F. and Glens, K. *Acta Chem. Scand.* **6** (1952) 531.
4. Clauson-Kaas, N. and Limborg, F. *Acta Chem. Scand.* **8** (1954) 1579.
5. Clauson-Kaas, N., Li, S. O. and Elming, N. *Acta Chem. Scand.* **4** (1950) 1233.
6. Clauson-Kaas, N. (to Kemisk Værk Køge A/S). Danish patent 78381 (filed July 5, 1951).
7. Sheedan, J. C. and Bloom, B. M. *J. Am. Chem. Soc.* **74** (1952) 3825.
8. Prelog, V. and Wieland, P. *Helv. Chim. Acta* **27** (1944) 1127.
9. Krebs, H., Wagner, J. A. and Diewald, J. *Chem. Ber.* **89** (1956) 1875.
10. Zeile, K. and Heusner, A. *Chem. Ber.* **87** (1954) 439.

Received September 19, 1957.