SYNTHESIS OF *m*-DIOXANS

By GY. SCHNEIDER and Ö. KOVÁCS
Institute of Organic Chemistry József Attila University, Szeged
and

M. CHINORAI
Vernish- and Paint Factory, Budapest

(Received May 5, 1964)

A number of 1,3-dioxan derivatives have been prepared by means of various methods.

In connection with the preparation of condensed trimethylene oxide [1], moreove with the study of γ-neighbouring group effect [2], greater amounts of stereochemically pure cis- and trans-2-hydroxy-methylcyclohexanol (A—1 and B—1) were required, respectively. The cis and trans isomers, however, beind accessible through the application of various synthesis methods, are always contaminated, usually with the other modification, too. For this reason some simple procedure has been looked for to separate the isomers, or to purify them, respectively. In the course of our preliminary experiments it has been observed that there is a preparatively useful difference in the physical constants of the benzal derivatives (C—1 and D—1) of the two modifications (A—1 and B—1). On this basis the two isomers might be separated from one another and from accompanying materials, as well, simply

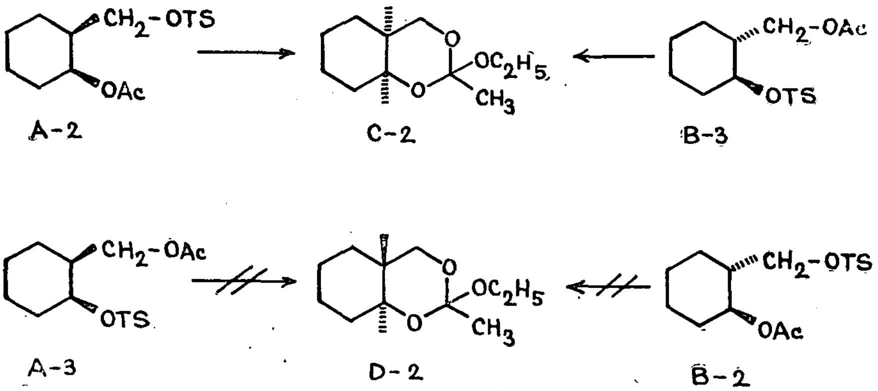


Fig. 1

by distillation, subsequent mild acidic hydrolysis resulting in the recovery of the diol (A—1 and B—1), respectively [3]. On the other hand, it has been shown [2] that ethanolysis of both cis-2-p-toluenesulphonyloxymethylcyclohexyl acetate (A—2) and trans-2-acetoxymethylcyclohexyl p-tosylate (B—3), proceding presence of potassium acetate affords cis-1,3-dioxadecalin derivative (C—2), while the corresponding trans modification (D—2) could not be detected in the similar reaction of either cis-2-acetoxymethylcyclohexyl tosylate (A—3) or trans 2-p-toluenesulphonyloxymethylcyclohexyl acetate (B—2).

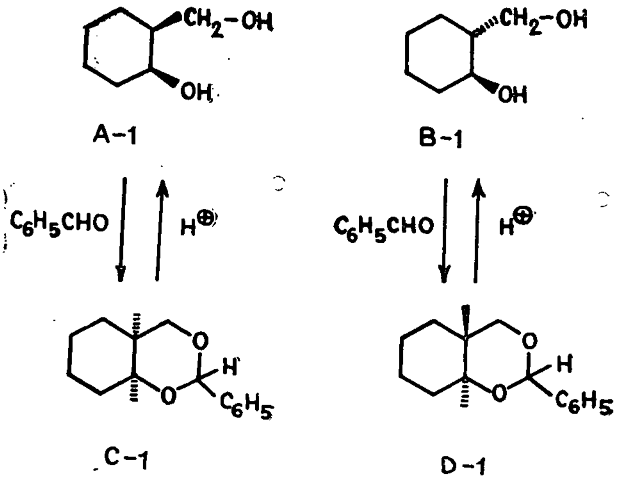


Fig. 2

On basis of the foregoing it has been assumed that the difference originating in the molecular structure of cis and trans-1,3-dioxadecalin derivatives (C—1, D—1, C—2, D—2) appears also in the reactivity of these compound pairs, from the numerical data of which conclusions might be drawn concerning the conformation of the bicyclic compound examined, moreover the configuration of the starting 1,3-diol. Such kind of investigations is known in the case of the 1,3-dioxolan derivative [4—6] obtainable from cis and trans-1,2-cyclohexanediols, showing essentially greater difference in stability and reactivity, furthermore the kinetics of hydrolysis of 1,3-dioxolan and 1,3-dioxan derivatives, available from aliphatic 1,2- and 1,3-diols has been studied as well [7—11].

First the relative rates of hydrolysis of acetals and ketals, obtainable from A—1 and B—1, were intended to be examined. To this the derivative had to be selected, which might be measured kinetically the best, that is to say, the suitable oxo-component. Since we had had some experience in the field of aliphatic 1,3-propanediols [12], this compound class was chosen as model to study the above viewpoints. Thus in the course of our experiments some formals, acetals and ketals of the basic compound, 1,3-propanediol, moreover of its derivatives, *e. g.* 2,2-dimethyl-, 2,2-diethyl-, and 2-ethyl-2-n-butyl-1,3-propanediol, of pentaerythritol and of 1,3-butanediol were prepared, respectively.

Preparation of the formals and acetals followed the usual procedure [13], the diol and the oxocomponent were reacted in beneze (Method A), or in ether (Method B) in the presence of sulphuric acid (A), or dry hydrogen chloride (B), respectively. The acetonals and the aromatic acetals were prepared in benzene solution in the presence of catalytic amount of p-toluenesulphonic acid (Method C), or sulphuric acid (Method D), with the simultaneous removal of water formed by means of azeotropic distillation. Some acetals (XX, XXIV, XXXIII, XXXVIII) were obtained through transacetalation (Method E) [4, 14]. In the preparation of the acetals of furfural (VI, XVIII) p-toluenesulphonic acid was used as catalyst to avoid the partial polymerization of the oxo-component. The preparation of the mono and diacetals of pentaerythritol (XXVIII—XXXII, XXXVII—XLII) was accomplished in benzene -dioxan mixture, because of the polar character of the starting tetraol. The ketal of cyclopentanone (XII) smoothyl hydrolyses even under the effect of carbon dioxide dissolved in the water; the phenomenon has been explained by **Brown** and coworkers [15] with the I-strain principle. In the case of preparation of compound XI more than catalytic amount of sulphuric acid was applied in order to complete the reaction.

In the D—1 and D—2 conformational equilibrium of derivatives $R_1 = R_2$, $R_3 \neq R_4$ (II, IV—VII, X, XI, XIV—XVIII, XX, XXXIII, XXXVI) one of the conformers containing the more bulky group at carbon atom C_2 in equatorial position is preponderant [16—18], owing to the interaction of the axial hydrogens being in meta position relatively to ieach other at carbon atoms C_4 and C_6. The same does not hold true to derivative XXI ($R_1 \neq R_2$, $R_3 = R_4$), because of the absence of meta axial hydrogens. On the other hand, compound XXIV ($R_1 \neq R_2$, $R_3 \neq R_4$) exists in two diastereoisomeric forms [4, 19], the separation of which is to be reported in a later publication.

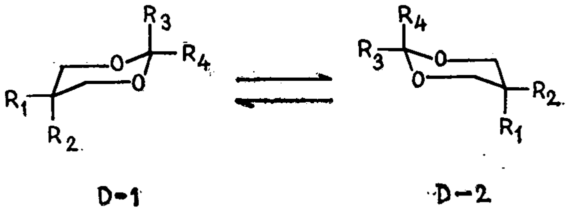
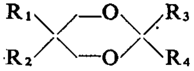


Fig. 3

At about the time of completion of the experiments [20] the authors got knowledge of the publications of **Rondestvedtnek** [19] and **Conrad** and coworkers [21], respectively, dealing with similar topic and reporting the preparation of some of the compounds occuring also in the present paper, accomplished in partly different way from those applied by us. The physical constants given there are in good agreement with the values found by us.

The reason why these investigations have been extended besides the above to the synthesis of 1,3-dioxans and within them to 1,3-dioxadecalins and 1,3-hydrindans, the latters being to be published in the future, is that according to recent literary data these derivatives are useful for the preparation of valuable intermediates, thus for instance their catalytic isomerization gives rise to β-alkoxyaldehydes [22], their perioxide oxidation to diol monobenzoates [23, 24], their bromination to bromobenzoates [23], and their reduction ($LiAlH_4 + BF_3$, or $LiAlH_4 + AlCl_3$) to diol monoethers [24], respectively.

Table I



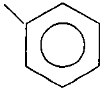
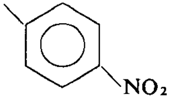
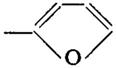
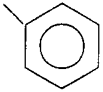
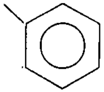
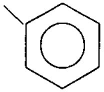
Nr.	R₁	R₂	R₃	R₄	Mp.:	Bp.:	n_d^{25}	Formula	Calcd %		Found %		Method
I.	H	H	H	H	104°		–	$C_4H_8O_2$	54,53	12,49	54,60	12,55	A
II.	H	H	CH_3	H		107°	1,4120	$C_5H_{10}O_2$	58,81	11,76	58,70	11,79	B
III.	H	H	CH_3	CH_3		125°	1,4159	$C_6H_{12}O_2$	62,08	10,42	61,90	10,30	C
IV.	H	H		H	50°		–	$C_{10}H_{12}O_2$	73,15	7,36	73,32	7,45	D
V.	H	H		H	111,5°		–	$C_{10}H_{11}O_4N$	57,41	5,30	57,50	5,49	D
VI.	H	H		H		102°/2 Hgmm	1,4885	$C_8H_{10}O_3$	62,35	6,54	62,53	6,52	C
VII.	H	H		$-CH_3$	57°		–	$C_{11}H_{14}O_2$	74,14	7,91	74,25	8,05	D
VIII.	H	H			112°		–	$C_{16}H_{16}O_2$	79,97	6,71	79,82	6,85	D
IX.	CH_3	CH_3	H	H		126°	1,4190	$C_6H_{12}O_2$	62,08	10,42	61,02	10,30	A

Table I (contd.)

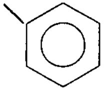
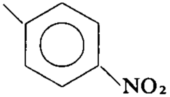
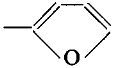
Nr.	R_1	R_2	R_3	R_4	Mp.: Bp.:	n_d^{25}	Formula	Calcd %		Found %		Method
X.	CH_3	CH_3	CH_3	H	58–60°/52 Hgmm	1,4134	$C_7H_{14}O_2$	64,58	10,84	64,50	10,83	B
XI.	CH_3	CH_3	$-CCl_3$	H	129°	–	$C_7H_{11}Cl_3O_2$	36,00	4,75	36,05	4,90	D
XII.	CH_3	CH_3	$-(CH_2)_4-$		103°/36 Hgmm	1,4520	$C_{10}H_{18}O_2$	70,55	10,66	70,60	10,52	C
XIII.	CH_3	CH_3	$-(CH_2)_5-$		116°/34 Hgmm	1,4610	$C_{11}H_{20}O_2$	71,69	10,94	71,50	10,86	C
XIV.	CH_3	CH_3	C_2H_5	H	76°/54 Hgmm	1,4227	$C_8H_{16}O_2$	66,61	11,19	66,90	11,15	B
XV.	CH_3	CH_3	C_3H_7	H	91°/20 Hgmm	1,4510	$C_{10}H_{20}O_2$	69,72	11,71	69,51	11,65	B
XVI.	CH_3	CH_3		H	120°/4 Hgmm	1,5010	$C_{12}H_{16}O_2$	74,96	8,39	74,82	8,35	D
XVII.	CH_3	CH_3		H	48°	–	$C_{12}H_{15}NO_4$	60,84	6,37	60,65	6,38	D
XVIII.	CH_3	CH_3		H	107°/12 Hgmm	1,4558	$C_{10}H_8O_3$	64,48	9,74	64,25	9,67	C
XIX.	CH_3	CH_3	CH_3	CH_3	143°	1,4178	$C_8H_{16}O_2$	66,63	11,18	66,36	10,98	C
XX.	C_2H_5	C_2H_5	CH_3	H	70°/5 Hgmm	1,4205	$C_9H_{18}O_2$	68,33	11,46	68,42	11,55	B; E
XXI.	C_2H_5	C_2H_5	CH_3	CH_3	198°	1,4241	$C_{10}H_{20}O_2$	69,75	11,70	69,80	11,76	C

Table I (contd.)

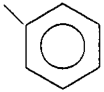
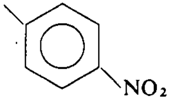
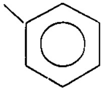
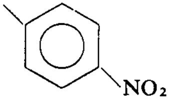
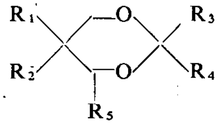
Nr.	R_1	R_2	R_3	R_4	Mp.: Bp.:	n_d^{25}	Formula	Calcd %		Found %		Method
XXII.	C_2H_5	C_2H_5		H	143°/3 Hgmm	1,5075	$C_{14}H_{20}O_2$	76,43	9,16	76,48	9,30	D
XXIII.	C_2H_5	C_2H_5		H	92°	–	$C_{14}H_{19}O_4N$	63,38	7,21	63,40	7,35	D
XXIV.	C_4H_9	C_2H_5	CH_3	H	94°/5 Hgmm	1,4270	$C_{11}H_{22}O_2$	70,99	11,91	70,81	11,98	B; E
XXV.	C_4H_9	C_2H_5	CH_3	CH_3	120°/20 Hgmm	1,4282	$C_{12}H_{24}O_2$	71,96	12,07	77,00	12,15	C
XXVI.	C_4H_9	C_2H_5		H	172°/4 Hgmm	1,5029	$C_{15}H_{24}O_2$	76,25	10,24	76,30	10,28	D
XXVII.	C_4H_9	C_2H_5		H	54°	–	$C_{15}H_{23}O_4N$	64,11	8,25	64,20	8,14	D
XXVIII.	CH_2-OH	CH_2-OH	CH_3	CH_3	135°	–	$C_8H_{16}H_4$	54,73	8,61	54,65	8,55	C
XXIX.	CH_2-OH	CH_2-OH	CH_2-Cl	H	114°	–	$C_7H_{13}O_4Cl$	42,76	6,66	42,70	6,58	B
XXX.	CH_2-OH	CH_2-OH	C_3H_7	H	70°	–	$C_9H_{18}O_4$	56,84	9,47	56,70	9,52	B
XXXI.	CH_2-OH	CH_2-OH	C_4H_9	H	82°	–	$C_{10}H_{20}O_4$	58,82	9,80	58,76	9,85	B
XXXII.	CH_2-OH	CH_2-OH	$-(CH_2)_5-$		123°	–	$C_{11}H_{20}O_4$	61,11	9,25	61,25	9,30	C

Table II



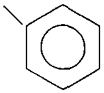
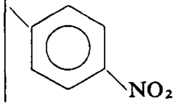
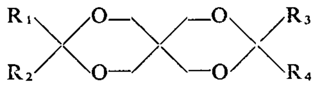
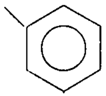
Nr.	R_1	R_2	R_3	R_4	R_5	Mp.: Bp.:	n_d^{25}	Formula	Calcd. %		Found		Method
									C	H	C	H	
XXVIII.	H	H	CH_3	H	CH_3	118°	1,4039	$C_6H_{12}O_2$	62,02	10,42	62,10	10,50	B E
XXIX.	H	H	CH_3	CH_3	CH_3	129°	1,4190	$C_7H_{14}O_2$	64,56	10,85	64,56	10,80	C
XXX.	H	H		H	CH_3	105°/5 Hgmm	1,5161	$C_{11}H_{14}O_2$	74,14	7,91	74,20	7,81	D
XXXI.	H	H		H	CH_3	104°C	–	$C_{11}H_{13}O_4N$	59,19	5,87	59,10	5,91	D

Table III



Nr.	$R_1=R_3$	$R_2=R_4$	Mp.: Bp.:	n_d^{25}	Formula	Calcd. % C	Calcd. % H	Found C	Found H	Method
XXXVII.	H	H	50°	–	$C_7H_{12}O_4$	52,50	7,50	52,47	7,52	A
XXXVIII.	CH_3	H	45°	–	$C_9H_{16}O_4$	57,40	8,57	57.42	8,59	B; E
XXXIX.	CH_3	CH_3	116°	–	$C_{11}H_{20}O_4$	61,07	9,33	61,02	9,45	C
XL.	C_2H_5	H	152°/10 Hgmm	1,4520	$C_{11}H_{20}O_4$	61,07	9,33	59,84	9,22	B
XLI.	C_3H_7	H	95°	–	$C_{13}H_{24}O_4$	63,88	9,90	63,94	9,98	B
XLII.		H	160°	–	$C_{22}H_{20}O_4$	73,08	6,41	73,15	6,52	D

Experimental

a) 1,3-Propanediol, b. p.: 214° $n_D^{25} = 1{,}4390$
b) 2,2-Dimethylpropanediol, m. p.: 206°
c) 2,2-Diethylpropanediol, m. p.: 60,5°
d) 2-Methyl-2-propylporpanediol, m. p.: 56,6°
e) 2-Ethyl-2-butylpropanediol, m. p.: 43,8°
f) 1,3-Butanediol, b. p.: 106° /15 mm., $n_D^{25} = 1{,}4398$ Chemische Werke HÜLS A. G./MARL.

Preparation of formals Method A

A 10% benzene solution of 1,2 moles of paraformaldehyde and 1 mole of 1,3-propanediol derivatives was treated with catalytic amount of concentrated sulphuric acid. The mixture was kept at the temperature of boiling water-bath for 6 hours. After cooling the acid and the unreacted diol were removed by washing the solution with water and subsequently with 10% sodium hydrogencarbonate solution, the organic phase was dried over anhydrous magnesium sulphate and the solvent evaporated. The residue was subjected to fractionated distallition.

Preparation of acetals (Method B)

1,2 Moles of acetaldehyde was added to a 10% solution of 1 mole 1,3-propanediol derivatives in ether with ice-cooling. Then dry hydrogen chloride gas was introduced to the solution for one hour. The reaction mixture was allowed to warm up to room temperature and washed subsequently with water, 10% sodium hydrogencarbonate solution and water again. The organic phase was dried over anhydrous magnesium sulphate and evaporated. The residue was distilled fractionately.

Preparation of acetonals (Method C)

1,2 Moles of acetone, a 10% solution of 1 mole of 1,3-propanediol derivative in benzene and catalytic amount of p-toluenesulphonic acid were placed in the lower container of a Soxhlet apparatus. The upper part of the apparatus was provided with a jacket containing anhydrous calcium chloride. The reaction mixture in the Soxhlet apparatus was refluxed for 24 hours by means of and infrared lamp. The reaction mixture was subsequently washed with water, 10% sodium hydrogencarbonate solution and water again. The benzene phase was dried over anhydrous magnesium sulphate and evaporated. The residue was fractionately distilled.

Preparation of aromatic acetals (Method D)

1,2 Moles of the aromatic aldehyde or ketone component was refluxed with 1 mole of 1,3-propanediol component in 10% benzene solution in the presence of catalytic amount of sulphuric acid in an apparatus fitted with a water-separatory device. Subsequent fitted with a water-separatory device. Subsequent to the distillation out of the necessary amount of water, the reaction mixture was washed until neutral, dried, and the solvent removed. The residue was either distilled or crystallized.

Transacetalation (Method E)

1 Mole of 1,3-propanediol derivative was refluxed with 5 moles of acetaldehyde diethylacetal in the presence of catalytic amount of benzoyl chloride for 6 hours. In order to complete the reaction, the theoretical amount of ethanol was distilled out of the reaction mixture by means of a Vigreux column. Then absolute ether was added to the solution and the mixture washed with 10% sodium hydrogencarbonate solution and water until neutral. Following the removal of ether and excess diethylacetal the product was fractionated.

Preparation of pentaerythritol acetals

All the above methods were suitable for the preparation of acetals of pentaerythritol of strongly polar character with the modification that benzene-dioxan (1:1) mixture was used as solvent in the case of methods A and D, respectively.

* * *

The authors gratefully acknowledge the help of Mrs. K. LÁNG and Mrs. G. B. BOZÓKI for microanalyses and Mr. R. FERENCI for his technical assistance.

References

[1] *Kovács, Ö., Z. Tuba, I. Weisz, Gy. Schneider:* Chem. and Ind. **1961**, 1222; Izvest. Akad. Nauk SSSR, Otdel. Khim. Nauk **1962**, 130; M. Kémiai Folyóirat **69**, 37 (1963).
[2] *Kovács, Ö., Gy. Schneider, K. L. Láng:* Proc. Chem. Soc. **1963**, 374.
[3] will be later published.
[4] *Cromartie, R. I. T., Y. K. Hamied:* J. Chem. Soc. **1961**, 3622.
[5] *Fischer, F., R. Schiere:* J. prakt. Chem. **22**, 39 (1963).
[6] *Bonsignore, P. V., M. D. Hurwitz:* J. Org. Chem. **28**, 3535 (1963).
[7] *Ceder, O.:* Arkiv för Kemi **6**, 523 (1954).
[8] *Laurent, P. A., A. G. da Silva-Pinto, J. L. C. Preira:* Bull. Soc. Chim. France **1960**, 926.
[9] *Salomaa, P., A. Kankaanperä:* Acta Chem. Scand. **15**, 871, (1961); **16**, 1532 (1962).
[10] *Bender, M. L., M. S. Silver:* J. Amer. Chem. Soc. **85**, 3006 (1963).
[11] *Skrabal, A., M. Zlatewa:* Z. Phys. Chem. **119**, 305 (1925).
[12] *Schneider, Gy., M. Halmos, P. Mészáros, Ö. Kovács:* Monatshefte **94**, 426 (1963).
[13] *Klages, F.:* Acetale und ketale in Schwab, G. M.: Handbuch der Katalyse VII. 2, (Springer-Verlag, Wien, 1943) p. 305–315.
[14] *Lukes, R. M.:* J. Org. Chem. **26**, 2515 (1961).
[15] *Brown, H. C., R. S. Fletcher and R. B. Johannessen:* J: Amer. Chem. Soc. **73**, 212 (1951).
[16] *Foster, A. B., et al.:* J. Chem. Soc. **1961**, 5005, 5011; **1963**, 4157, 4161, 4167, 4171.
[17] *Fischer, F., M. Lötzsch:* J. prakt. Chem. **18**, 86 (1962).
[18] *Arbuzov, B. A., L. K. Yukdashera:* Izvest. Akad. Nauk. SSSR **1962**, 1734.
[19] *Rondestvedt C. S.:* J. Org. Chem. **26**, 2247 (1961).
[20] *Chinorai, M.:* Ph. D. Dissertation, Szeged, 1961.
[21] *Conrad, W. E., B. D. Gesner, L. A. Levasseur, R. F. Murphy, H. M. Conrad:* J. Org. Chem. **26**, 3571 (1961).
[22] *Rondestvedt, C. S., G. J. Mantel:* J. Amer. Chem. Soc. **82**, 6419 (1960); **84**, 3307, 3319 (1962).
[23] *Rieche, A., E. Schmitz, W. Schade, E. Beyer:* Chem. Ber. **94**, 2926 (1961).
[24] *Huyser, E. S., Z. Garcia:* J. Org. Chem. **27**, 2716 (1962).
[25] *Abdun-Nur, A. R., C. H. Issidorides:* J. Org. Chem. **27**, 67 (1962).

СИНТЕЗ М-ДИОКСАНОВ

Г. Шнеидер, Е. Ковач, М. Хинораи

Различными методами были синтезированы многие из 1,3-диоксандериватов.