Carbohydrate Research, 83 (1980) 243–248
Elsevier Scientific Publishing Company, Amsterdam – Printed in The Netherlands

FORMATION OF DIALKOXYPHOSPHINYLALKYLIDENE DERIVATIVES OF GALACTITOL BY TRANSACETALATION REACTIONS*

SHAUL YANAI, MORDEHAI HALMANN, AND DAVID VOFSI
The Weizmann Institute of Science, Rehovot (Israel)

(Received August 16th, 1979, accepted for publication, October 15th, 1979)

ABSTRACT

Transacetalation reactions of galactitol with 2,2-dialkoxyethylphosphonates gave the expected 1,3 4,6-diacetal as the minor product, but the major product was a 1,3 4,5 derivative With a 3,3-diethoxypropylphosphonate, the 1,3 4,6-diacetal became the major product The influence of the dialkoxyphosphinyl substituent on the acetal linkage is shown to be stereoelectronic

INTRODUCTION

We have described[1-3] the synthesis and hydrolysis of a series of acyclic and cyclic phosphonoacetals The latter compounds are remarkably stable towards hydrolysis[2] We now report on phosphonoacetals of galactitol, as part of a study of the use of these and similar compounds[4] as monomers for the synthesis of flame-retardant polyols and polyurethanes[5,6]

Galactitol reacts with aldehydes[7-9] to give 1,3 4,6-cyclic acetal derivatives containing two β-rings in accord with the established rules[10,11] Transacetalation reactions also yield the expected product, as illustrated by the acid-catalysed reaction between galactitol and chloroacetaldehyde diethyl acetal[12]

We have studied transacetalation reagents of the general formula $(RO)_2P(O)$-$(CH_2)_nCH(OEt)_2$, where R is Et or Me and n is 1 or 2 The reactions were catalysed by strong mineral acids at room temperature and with thermodynamic control for the formation of the di(phosphonoacetal) products

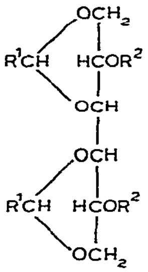
RESULTS AND DISCUSSION

Acyclic phosphonoacetaldehyde dialkyl acetals are stable towards hydrolysis at low concentrations[1] of acid and transacetalation reactions therefore require relatively high concentrations of mineral acids The reactions were monitored by t l c

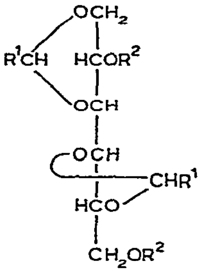
Galactitol reacted with diethyl 2,2-diethoxyethylphosphonate, to give two products that were isolated and characterised as the crystalline 1,3 4,6- (**1**) and the

---

*Phosphonated Acetals, Part IV For Part III, see ref 3 syrupy 1,3 4,5-di-*O*-(2-diethoxyphosphinylethylidene)-DL-galactitol (**4**) The diacetate **2** and dibenzoate **3** of **1** were crystalline, but the corresponding derivatives (**5** and **6**) of **4** were syrups



1—3 7 8



4—6

1—6 $R^1 = CH_2P(O)(OEt)_2$
1 4 $R^2 = H$
2 5 $R^2 = Bz$
3 6 $R^2 = Ac$
7 $R^1 = CH_2P(O)(OMe)_2$ $R^2 = H$
8 $R^1 = CH_2CH_2P(O)(OEt)_2$ $R^2 = H$

Periodate-oxidation measurements revealed that **1** did not possess vicinal hydroxyl groups The ^{1}H-n m r spectrum of **1** was suggestive of a 1,3-dioxane system, and this inference was confirmed by comparison of the ^{13}C-n m r spectrum of **1** with that of 1,3 4,6-di-*O*-chloroethylidenegalactitol[12]

Compound **4** also did not consume periodate, and the ^{1}H-n m r. spectrum was suggestive of a 1,3-dioxane system (δ 4 86) and a 1,3-dioxolane system (δ 5 29) Hydrolysis of methylated **4** gave a syrupy product that consumed 1 8–1 93 mol of periodate, but yielded no formaldehyde Therefore the acetal rings in **4** occupied positions 1, 3, 4, and 5 On the basis of the Barker and Bourne rules[11], a seven-membered ring is excluded and a 1,3 4,5 distribution of the cyclic acetals is assigned

The time of the reaction and the nature and the concentration of the catalyst

TABLE I

INFLUENCE OF THE CATALYST ON THE RELATIVE YIELDS (%) OF THE PRODUCTS IN THE PHOSPHONO-ACETALATION OF GALACTITOL WITH CONC AQUEOUS ACIDS AT ROOM TEMPERATURE

Product	*HCl*			*HBr*	
	24 h	*48 h*	*7 days*	*24 h*	*72 h*
1	8 2	13 4	20 4	34 6	36 2
4	91 8	86 6	79 6	65 4	63 8

influenced the yields and ratio of **1** and **4** (see Table I) In the presence of conc hydrochloric acid, the yield of **1** increased with time at the expense of **4**, but after 7 days, the ratio of **1** to **4** was no more than 1 4 On the other hand, in the presence of ~48% hydrobromic acid, the ratio of **1** and **4** stabilised at 1 2

The reaction of galactitol with dimethyl 2,2-diethoxyethylphosphonate gave a crystalline diacetal which did not consume periodate, on the basis of n m r and m s data, it was correlated with **1** and assigned the structure 1,3 4,6-di-*O*-(2-dimethoxyphosphinylethylidene)galactitol (**7**) Similarly, galactitol and diethyl 3,3-diethoxypropylphosphonate gave a crystalline, major product that was assigned the structure 1,3 4,6-di-*O*-(3-diethoxyphosphinylpropylidene)galactitol (**8**)

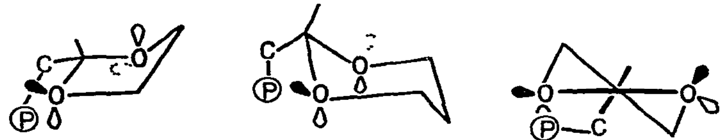
The data in Table I show that the expected 1,3 4,6-diacetal is not the major product Although the yield of **1** can be increased by increasing the reaction time, the major product is **4**

When trifluoroacetic acid was added to a solution of 2,3 4,5-di-*O*-butylidene-galactitol in $CDCl_3$ and the reaction was followed by n m r spectroscopy, a high-field triplet at δ 4 6, characteristic for the proton on the acetal carbon of a six-membered ring, rapidly appeared[13] This observation suggested an expansion of the five- to six-membered rings, and the product was the 1,3 4,6-diacetal Compound **4** was stable under the above conditions, even after 24 h

The formation of the *α-threo* ring in **4** may reflect steric or electronic influences A decrease in the bulk of the phosphonic ester groups from ethyl to methyl did not result in the 1,3 4,6 derivative (**7**) becoming the major product A steric influence of the dialkoxy group was not observed in the kinetic behaviour of the acid-catalysed hydrolysis of the phosphonoacetals[1]

Moving the dialkoxyphosphinyl substituent away from the acetal linkage, by insertion of a methylene group, caused the predicted acetal **8** to become the major product (72%) This finding suggests that the influence of the phosphoryl group is responsible for the formation[3] of the unexpected five-membered ring in **4**

The foregoing data are suggestive of a selective reaction with stereoelectronic control Such a mechanism was proposed by Deslongchamps[14] who showed that, for orthoesters, orthoamides, and acetals, selective formation and cleavage of C–O or C–N bonds is controlled by the lone-pair orbitals (on the other heteroatoms) that are antiperiplanar to that bond Recent *ab initio* calculations[15] support this view



a
envelope form

b
chair form

c
twisted form

Fig 1 Envelope conformer (a) for phosphonoacetal 1,3-dioxolane system, and the chair (b) and twist (c) conformers for 1,3-dioxane systems

Fig 1 attempts to relate these requirements to the preferred conformations of 1,3-dioxolane and 1,3-dioxane systems, and also considers the tendency for maximum p_π–d_π bonding of tetracoordinated phosphorus[16] The flexible 1,3-dioxolane system (Fig 1a) can preserve an envelope conformation[17] satisfying the proposed[14] stereoelectronic requirements, and allow maximum π-bonding interaction If the stable, chair conformation of the six-membered ring (Fig 1b) is considered, the lone pairs of the ring oxygens are forced into the synclinal (gauche) conformation, when an attempt is made to increase the π-bonding for phosphorus In order to maximise π-bonding and achieve the antiperiplanar requirement, the twist conformation shown in Fig 1c is required Support for these arguments is given by the ^{31}P-n m r chemical-shift data The total occupation of the d_π orbitals of phosphorus has a dominating influence affecting the chemical shift[18] Thus, the extra p_π–d_π interaction suggested by Fig 1a has already been measured[2] for the dioxolane ring (δ_P —25 9) as compared to Fig 1b for the dioxane-ring system (δ_P —26 4) The corresponding chemical shift for **1** was —26 5, and for **5**, —25 8 and —25 0 Thus, Fig 1c is suggested as the conformation of **1**.

In the foregoing transacetalation reactions, the polar phosphoryl group is rapidly protonated in the acidic media, and the proton is shared with an alkoxy oxygen through a hydrogen bond[1] The stabilised carboxonium ion which is developed is forced to react with a more acidic, secondary hydroxyl group Ring closure to give an *α-threo-* or *β*-ring acetal is a compromise between the stereoelectronic requirements imposed by the presence of the phosphorus substituent and other stereochemical preferences

EXPERIMENTAL

T l c was performed on precoated, silica-gel (60 F_{254}, Merck) plates with 1-butanol–acetic acid–water (6 3 1), and detection with sodium periodate–benzidine[19a] (for 1,2-diols) and ammonium molybdate–perchloric acid[19b] (for phosphonates) N m r spectra ($CDCl_3$, internal Me_4Si for ^{1}H, external 85% H_3PO_4 for ^{31}P) were recorded with Varian (A-60 and T-60) and Bruker instruments (HFX-90, WH-90, and WH-270) I r spectra were recorded with Perkin–Elmer Infracord 137 and 237B instruments, for 0 05M solutions in chloroform or for KBr (0 5–1 %) pellets Mass spectra (70 eV) were obtained by using a Varian–Mat 731 instrument with a direct-inlet probe at 270°

1,3 4,6-Di-O-(2-diethoxyphosphinylethylidene)galactitol (**1**) — Galactitol (4 g, 22 mmol) was stirred at room temperature with hydrochloric acid (10 ml) for ~30 min Diethyl 2,2-diethoxyethylphosphonate[1] (11 55 g, 45 5 mmol) was added and, after 7 days, the reaction was stopped by neutralisation with 2 5M NaOH to pH 7 with external cooling The diacetals were extracted with chloroform, and the dried extract was concentrated Treatment of the colourless, syrupy residue with ether gave **1** (2 25 g, 20 5%), m p 174–176°, R_F 0 48, ν_{max}^{KBr} 3320 (OH), 1200, 1240 (P=O), 1000, 1040 (P-O-Et), and 1400 cm^{-1} (O-C-O), $\nu_{max}^{CHCl_3}$ 3585 and 3650 (respectively, hydrogen-bonded and free OH), and 3420 cm^{-1} (OH) (Found C, 42 4, H, 7 0, P, 12 2 $C_{18}H_{36}O_{12}P_2$ calc C, 42 7, H, 7 1, P, 12 25) ^{1}H-N m r (270 MHz) δ 1 32 (t, 12 H, J 7 04 Hz, 4 Me), 2 23 (dd, 4 H, $J_{H H}$ 4 99, $J_{P H}$ 18 49 Hz, 2 PCH_2), 3 67 (s, 2 H, 2 OH), 4 10 (quin, 8 H, $J_{H,H}$ 7 04, $J_{P,H}$ 7 92 Hz, 4 OCH_2C), 3 88, 3 92, 3 99, 4 11, 4 15 (8 H, skeleton protons), and 5 0 (2 t, 2 H, $J_{H H}$ 4 99, $J_{P H}$ 11.74 Hz, acetal protons), ^{13}C-n m r (22 63 MHz) δ 16 53, 16 27 (Me), 35 78, 29 52 (PCH_2), 61 97, 61 71 ($POCH_2$), 61 89 (C-2,5), 72 16 (C-1,6), 76 43 (C-3,4), and 97 54 (acetal C), ^{31}P-n m r (109 3 MHz) δ —26 5 Mass spectrum *m/e* 506 (M^+, 1), 505 (M^+ —1, 4 2), 223 [$(EtO)_2P(O)CH_2CHOCH_2CH{=}O^+$, 100], 283 (48), 355 [($M^+$ — $CH_2P(O)$-$(OEt)_2$, 6 5], 253 ($M^+/2$, 4 6), and 447 (M^+ — 59, 10 6)

A solution of **1** (40 mg) in 15mM $NaIO_4$ (10 ml) was incubated at 35° in the dark[20]. Aliquots of 1 ml were withdrawn at intervals and diluted to 250 ml, and the absorbance was checked at 223 nm, in comparison with appropriate blanks The periodate consumption was 0 04 (3 h), 0 07 (20 h), and 0 1 mol (4 days)

The 2,5-dibenzoate (**2**) of **1** had m p 165–166° (from methanol–ether) (Found P, 8 5 $C_{32}H_{44}O_{14}P_2$ calc P, 8 7)

The 2,5-diacetate (**3**) of **1** had m p 152–154° (from methanol–ether) (Found C, 44 3, H, 6 2, P, 10 1 $C_{22}H_{40}O_{14}P_2$ calc C, 44 7, H, 6 8, P, 10 5)

*1,3 4,5-Di-O-(2-diethoxyphosphinylethylidene)-*DL*-galactitol* (**4**) — The syrup remaining after the isolation of **1** described above was eluted from a column of silicic acid (300 g) with chloroform followed by chloroform–methanol (9 1), to give **4** as a syrup (8 85 g, 79 6%), n_D^{25} 1 4605, R_F 0 23 (Found P, 12 3) ^{1}H-N m r (60 MHz) δ 1 35 (t, 12 H, J 7 Hz, 4 Me), 2 09, 2 36 (dd, 4 H, $J_{H,H}$ 4, $J_{P,H}$ 18 Hz, 2 PCH_2), 3 31 (s, 2 H, 2 OH), 3 33–4 0 (m, 8 H, sugar protons), 4 06 (quin, 8 H, J 7 Hz, 4 $POCH_2$), 4 86 (m, 1 H, 1,3-dioxane acetal protons), and 5 29 (m, 1 H, 1,3-dioxolane acetal proton), ^{13}C-n m r δ 16 18, 16 44 (Me), 29 26, 28 59, 35 56, 34 82 (PCH_2), 57 78 (C-6), 62 23, 61 92 ($POCH_2$), 62 66 (C-2), 74 48 (C-1), 77 46 (C-3), 79 62 (C-4), 80 91 (C-5), 97 31 (1,3-dioxane C), and 100 03 (1,3-dioxolane C), ^{31}P-n m r δ —25 06, —25 68 Mass spectrum *m/e* 506 (0 31), 505 (1 31), 355 (7 48), 283 (12 73), 253 (9 9), 475 (M^+ — 31, 2 11), and 223 (26 07) Periodate consumption 0 22 (3 h), 0 35 (48 h), 0 38 (48 h), and 0 38 mol (4 days)

The 2,6-dibenzoate (**5**) and 2,6-diacetate (**6**) of **4** were syrups To a solution of **4** (1 73 g) in *N,N*-dimethylformamide (20 ml) were added silver oxide (5 g) and methyl iodide (5 ml) The mixture was stirred at room temperature overnight and then filtered, and insoluble material was washed with *N,N*-dimethylformamide (5 ml) The combined filtrate and washings were concentrated and the residue was remethylated as described above A solution of the product (1 9 g) in water (100 ml) was boiled under reflux for 20 h in the presence of Amberlite IRC-50 (H^+) ion-exchange resin (5 g), filtered, and concentrated, to give a yellow–brown syrup (930 mg) that did not contain phosphorus The periodate consumption of this oil was 1 8 (3 h) and 1 93 mol (24 h), no formaldehyde was liberated[21]

1,3 4,6-Di-O-(2-dimethoxyphosphinylethylidene)galactitol (**7**) — The reaction of dimethyl 2,2-diethoxyethylphosphonate and galactitol, as described above for **1**, gave 7, m p 191–192° (from ethanol), R_F 0 54 (Found C, 37 5; H, 6 55, P, 13 8 $C_{14}H_{28}O_{12}P_2$ calc C, 37 3, H, 6 2, P, 13 8) ^{1}H-n m r (270 MHz) δ 2 23, 2 30 (dd, 4 H, $J_{H,H}$ 4 69, $J_{P,H}$ 18 49 Hz, 2 PCH_2), 3 68 (s, 2 H, 2 OH), 3 73, 3 77 (d, 12 H, $J_{P,H}$ 11 15 Hz, 4 Me), 3 90, 3 94, 4 00, 4 13, 4.18 (m, 8 H, A_2BB', sugar-skeleton protons), and 5 03 (2 t, 2 H, $J_{H\,H}$ 4 69, $J_{P\,H}$ 13 20 Hz, 1,3-dioxane acetal protons)

1,3 4,6-Di-O-(3-diethoxyphosphinylpropylidene)galactitol) (**8**) — The reaction of diethyl 3,3-diethoxypropylphosphonate (5 5 g) with galactitol (1 8 g), as described above for **1**, gave **8** (3 8 g, 72%), m p 91–92° (from ethanol), R_F 0 60 (Found P, 11 4 $C_{16}H_{32}O_{12}P_2$ calc P, 11 6) Mass spectrum m/e 534 (M^+, 1 22), 533 ($M^+ - 1$, 4 58), 475 ($M^+ - 59$, 7 01), 369 [$M^+ - EtO_2P(O)CH_2CH_2$, 34 73], 297 (37 52), and 237 (100)

ACKNOWLEDGMENT

We thank Mrs Varda Katzir for technical assistance

REFERENCES

1 M Halmann, D Vofsi, and S Yanai, *J Chem Soc , Perkin Trans 2*, (1976) 1210–1213
2 S Yanai, D Vofsi, and M Halmann, *J Chem Soc , Perkin Trans 2*, (1978) 511–516
3 S Yanai, D Vofsi, and M Halmann, *J Chem Soc , Perkin Trans 2*, (1978) 517–519
4 K C Frisch and J E Kresta, *Am Chem Soc Symp Ser* , 41 (1977) 238–255
5 J N Lyons, *The Chemistry and Uses of Fire Retardants*, Wiley–Interscience, New York, 1970
6 M Lewin, S M Atlas, and E M Pearce (Eds), *Flame Retardant Polymeric Materials*, Plenum Press, New York, Vol 1, 1975, Vol 2, 1978
7 R M Hann, W T Haskins, and C S Hudson, *J Am Chem Soc* , 64 (1942) 986–987
8 T G Bonner, E J Bourne, D Lewis and L Yuceer, *Carbohydr Res* , 33 (1974) 1–8
9 W T Haskins, R M Hann, and C S Hudson, *J Am Chem Soc* , 64 (1942) 132–136
10 R M Hann and C S Hudson, *J Am Chem Soc* , 66 (1944) 1909–1912
11 S A Barker and E J Bourne, *J Chem Soc* , (1952) 905–909
12 H B Sinclair and W J Wheadon, *Carbohydr Res* , 4 (1967) 292–297
13 L Yuceer, Ph D Thesis, University of London, 1973, pp 37–39
14 P Deslongchamps, *Heterocycles*, 7 (1977) 1271–1317
15 G Wipff, *Tetrahedron Lett* , (1978) 3269–3270
16 R F Hudson, *Pure Appl Chem* , 9 (1964) 371–386
17 W E Willy, G Binsch, and E L Eliel, *J Am Chem Soc* , 92 (1970) 5394–5402
18 J R Van Wazer and J H Letcher, in M Grayson and E J Griffith (Eds), *Topics in Phosphorus Chemistry*, Vol 5, Interscience, New York, 1967, pp 179–180
19 E Stahl, *Thin Layer Chromatography*, Springer, Berlin–Heidelberg, 2nd edn , 1969, (*a*) p 885, (*b*) p 886
20 G O Aspinall and R J Ferrier, *Chem Ind (London)*, (1957) 1216
21 A C Corcoran and I H Page, *J Biol Chem* , 170 (1947) 165–171