Phosphite triesters of methyl alpha-D- and methyl beta-D-ribopyranoside

Recueil des Travaux Chimiques des Pays-Bas
Journal of the Royal Netherlands Chemical Society

Rec. trav. chim. **96** 293-322 (1977)/RTCPA3-96 (12) 293-322 (1977)/december 1977

Phosphite triesters of methyl α-D- and methyl β-D-ribopyranoside

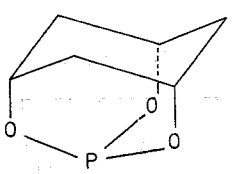
A. C. Bellaart*, H. M. Buck*, P. A. Leclercq and L. J. M. van de Ven****

Laboratories of Organic Chemistry and Instrumental Analysis**, Eindhoven University of Technology, Eindhoven, The Netherlands*
(Received May 31st, 1977)

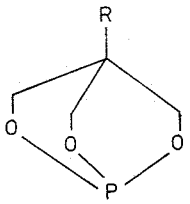
Abstract. The phosphites of methyl α-D- and methyl β-D-ribopyranoside were prepared from the corresponding methylglycosides according to the method of *Stetter* and *Steinacker*[1]. The mass spectra of the isomeric phosphites, which are markedly different, and the NMR spectral data are in agreement with the proposed structures.

Introduction

Several cyclic phosphites have already been prepared, but the synthesis of cyclic phosphites from sugar derivatives has not yet been reported. *Stetter* and *Steinacker*[1] prepared 1-phospha-2,8,9-trioxa-adamantane (I) by treating *cis*-1,3,5-cyclohexanetriol with phosphorus trichloride and by using pyridine as an acid acceptor. *Verkade* and *Reynolds*[2]



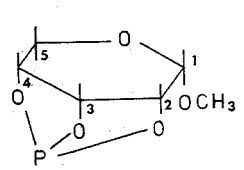
I



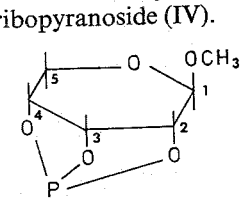
II

reported the synthesis of 4-methyl-1-phospha-2,6,7-trioxa-bicyclo[2.2.2]octane (II, R=CH_3) using a modification of their synthetic method.

Wadsworth and *Emmons*[3] prepared compounds of the type II (R=CH_3, CH_3CH_2, $HOCH_2$, CH_3COOCH_2, CH_2=$=C(CH_3)COOCH_2$ and $CH_3(CH_2)_3CH(CH_2CH_3)$-$COOCH_2$) using either of two procedures: transesterification of a trialkyl phosphite with, or addition of phosphorus trichloride to, the appropriate triol at 0°. Using the synthetic method of *Stetter* and *Steinacker*[1] we have prepared the heretofore unknown phosphite triesters of methyl α-D-ribopyranoside (III) and methyl β-D-ribopyranoside (IV).



III



IV

The compounds III and IV are very hygroscopic and hydrolyse readily when exposed to moisture, into phosphorus acid and methyl α-D-, or methyl β-D-ribopyranoside, respectively, but they are stable to aerial oxidation. Unlike bicyclic phosphites of the type II, compounds III and IV do not give the *Arbusov* reaction when heated at 170° with benzyl chloride for twelve hours[3].

Results

Mass spectra

The mass spectra of III and IV are presented in Figures 1 and 2, respectively.

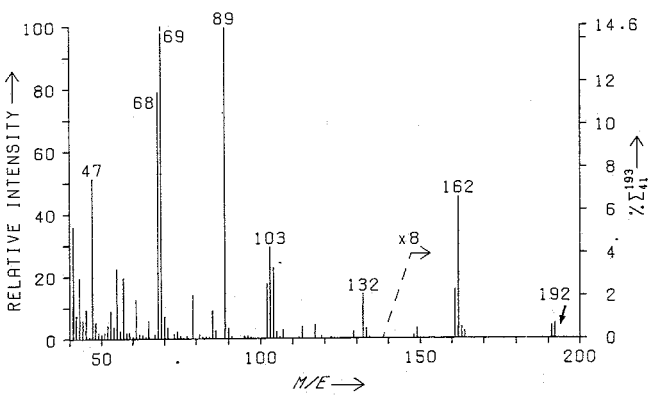


Fig. 1. Mass spectrum of III.

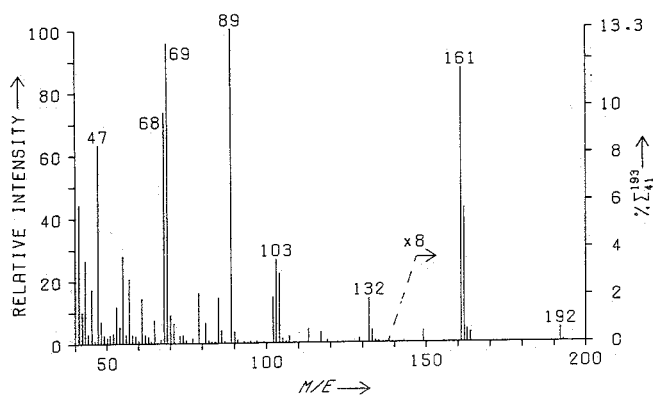
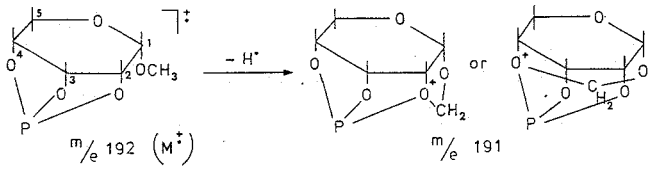


Fig. 2. Mass spectrum of IV.

[1] *H. Stetter* and *K. H. Steinacker*, Ber. **85**, 451 (1952).
[2] *J. G. Verkade* and *L. T. Reynolds*, J. Org. Chem. **25**, 663 (1960).
[3] *W. S. Wadsworth* and *W. D. Emmons*, J. Am. Chem. Soc. **84**, 610 (1962).

Significant differences between the otherwise similar spectra occur at *m/e* 191 ($M_{\bullet}^{+} - H^{\bullet}$) and *m/e* 161 ($M_{\bullet}^{+} - CH_3O^{\bullet}$). The facile loss of $H^{\bullet}$ from the molecular ion of III might be rationalized by the following mechanism:



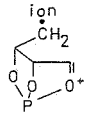
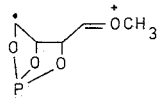
Scheme 1

Sterically, this mechanism probably leads to the formation of a five-membered ring involving the O(2), although the formation of a seven-membered ring with O(4) is possible too. The formation of six-membered rings involving the O(3) or P is sterically not feasible.

The decreased intensity of the ion at *m/e* 161 in the spectrum of III as compared with IV is easily explained by the elimination of $H^{\bullet}$ from the α-methoxy group as proposed above, thus inhibiting the formation of the ($M_{\bullet}^{+} - CH_3O^{\bullet}$) ion.

The prominent peaks in both mass spectra may be assigned to the following ions:

m/e	ion
47	PO^+
68	$C_4H_4O^{+\bullet}$
69	$C_4H_5O^+$
89	
103	

m/e	ion
132	
161	
162	

NMR spectra

The NMR spectral results are collected in Tables I and II. For III the proton signals (Table I) near δ = 4.35 and δ = 3.70, which form an AB-type quadruplet with additional splittings and J_{AB} = 13.5 Hz, are assigned to the protons on C(5). Irradiation of the broad multiplet near δ = 4.00 leads to collapsing of the triplets in the doublet of triplets at δ = 5.07. Thus the signal near δ = 4.00 belongs to H(2) and H(4) and the signal at δ = 5.07 is due to H(3). The remaining broad singlet at δ = 4.50 should be H(1).

For IV the doublet of triplets at δ = 5.03 is assigned to H(3) and the doublet at δ = 5.01 to H(1). The broad singlet at δ = 3.96 (3 protons) is coming from H(5) and H(2), because the remaining signal at δ = 3.80 is rather complex and should therefore be H(4).

The ^{13}C resonances (Table II) are assigned by their multiplicities and by selective decoupling of the protons. Despite the fact that it was impossible to distinguish between C(2) and C(4), differentiation between chemical shifts and *J*(PC) coupling constants was achieved by measuring the spectra at 25.15 MHz and at 22.63 MHz.

Discussion

The decreased basicity resulting from molecular constraint in the phosphite triesters III and IV explains the absence of quaternization of phosphorus *via* the *Arbusov* reaction. From CNDO/2 and protonation studies of a number of phosphite triesters *Verkade*, *Buck* et al.[4] showed that the proton induces enlargement of the OPO angles, consequently the ring POC angles would diminish. This results in more sp^3 character of the oxygen thus lowering its tendency for π-donation to phosphorus. Therefore, compounds of type III and IV are weakly basic. On the other hand, the

[4] *L. J. Vande Griend, J. G. Verkade, J. F. M. Pennings* and *H. M. Buck*, J. Amer. Chem. Soc. **99**, 2459 (1977).

Table I ^1H *chemical shifts*[a] *and coupling constants*[b].

Compound	Solvent	H(1)	H(2)	H(3)	H(4)	H(5)	H(5′)	OCH_3
III	$CDCl_3$	4.50 s	3.90–4.05 m	5.07 d of t $J_{23} = J_{34} = 3.5$ ^3J(POCH) = 15.2	3.90–4.05 m	4.35 d of d $J_{55'} = 13.5$ $J_{45} = 2.0$	3.70 d of t $J_{45'} = 1.0$ ^4J(POCCH) = 1.0	3.62 s
IV	$CDCl_3$	5.01 d $J_{12} = 2.0$	3.96[c]	5.03 d of t $J_{23} = J_{34} = 3.0$ ^3J(POCH) = 15.2	3.80 m	3.96[c]	3.96[c]	3.47 s

[a] δ-values in ppm with respect to TMS; s = singlet, d = doublet, t = triplet, m = multiplet.
[b] In Hz.
[c] Broadened singlet.

Table II ^{13}C *and* ^{31}P *chemical shifts*[a] *and* $^{13}C-^{31}P$ *coupling constants*[b].

Compound	Solvent	C(1)	C(2)	C(3)	C(4)	C(5)	OCH_3	P
III	$CDCl_3$	99.69 (1.4)	73.53[d] (1.0)	75.85 (5.2)	70.88[d]	62.77	58.49	116.08
IV	$CDCl_3$	97.08	70.43[d] (0.9)	72.00 (5.2)	70.38[d] (0.7)	57.11 (0.7)	55.77	116.87
IV hydrolysed	H_2O	102.60	69.21	71.46	68.73	64.32	57.26	5.02[c]
Me-β-D-ribopyranoside	H_2O	102.69	69.34	71.59	68.81	64.40	57.26	

[a] ^{13}C shifts in δ-values with respect to external TMS; ^{31}P shifts in δ-values with respect to H_3PO_4.
[b] Values between braquets are $J(^{13}C^{31}P)$ coupling constants in Hz.
[c] Due to $HP(O)(OH)_2$; *J*(PH) = 674 Hz.
[d] Assignments to C(2) and C(4) may be interchanged.

absence of π-delocalization of oxygen to phosphorus may explain the fast hydrolysis of III and IV into methyl α-D-ribopyranoside and methyl β-D-ribopyranoside, respectively. The increased basicity of the ester oxygen upon increased constraint catalyzes the nucleophilic attack of water on phosphorus with retention of configuration of the sugar moiety. It seems reasonable to assume that we are dealing with high-energy phosphites. One of the most fascinating observations for this supposition is based on the mass spectra which are fully presented under Results. The fact that for III the peak at *m/e* 191 corresponds with the proposed configuration as described in Scheme 1, leads to the assumption that the phosphite triester III (and IV) cannot be described as a pure chair configuration. X-ray diffraction measurements are in progress to elucidate both configurations unambiguously.

Experimental

All m.p.s were determined in a Buchi m.p. apparatus (designed by Tottoli) and are uncorrected. Electron impact mass spectra were produced with an AEI MS-12 magnetic sector instrument under the following conditions: 70 eV electron energy, 500 μ A trap current, 4 kV accelerating voltage. The samples III and IV were analysed after direct introduction and evaporation at 150° and 80°, respectively, at a source temperature of 250°. Coherent wave ^{1}H and pulsed ^{13}C and ^{31}P NMR spectra were run on a Varian HA-100 and/or a Bruker HX-90 spectrometer interfaced with a Digilab FTS-NMR-3 pulsing and data system. Samples were contained in 5 mm or 10 mm tubes for ^{13}C and ^{31}P measurements equipped with concentric capillaries containing the lock substance and/or the reference.

Methyl β-D-ribopyranoside and methyl α-D-ribopyranoside

Methyl β-D-ribopyranoside was prepared as described by *Jackson* and *Hudson*[5]. From 200 g of D-ribose we obtained 80 g of crystalline methyl β-D-ribopyranoside, m.p. 83–84°. The mother-liquor was distilled *in vacuo* and gave a thick, colourless syrup, b.p. 134–136/0.03 mm. This syrup exists mainly of methyl α-D-ribopyranoside, but still contains some methyl β-D-ribopyranoside. We used the crude syrup for further reactions.

Phosphite ester of methyl β-D-ribopyranoside (IV)

A 1000 ml five-necked flask was equipped with an efficient oil-sealed stirrer, two calibrated cylindrical dropping funnels, a thermometer and a drying tube filled with phosphorus pentoxide. The dropping funnels were respectively filled with a solution of methyl β-D-ribopyranoside (32.8 g = 0.2 mol) in dry redistilled pyridine (300 ml) and a solution of redistilled phosphorus trichloride (27.5 g, 0.2 mol) in dry carbon tetrachloride (300 ml) and protected with phosphorus pentoxide guard tubes. The flask now containing dry pyridine (30 ml) was cooled in a bath of ice and salt and both solutions were added at equal rates with stirring, the temperature being kept below 0°. After additions the mixture was stirred for 4 hrs at 20° and was filtered from the precipitated pyridine hydrochloride. The filtrate was evaporated and the residue was crystallized from sodium-dried hexane. The solution in hexane was cooled down to −5° and the crystals formed were filtered with suction on a Buchner funnel in a drying-box and washed with sodium-dried hexane at −5°.
Yield: 18 g of long (20–30 mm), colourless needles, m.p. 34.5–35°. The ester can be distilled in a vacuum, b.p. 82–84°/0.1 mm, and must be stored in a desiccator over phosphorus pentoxide (Found: C, 37.1; H, 4.7. Calc. for $C_6H_9O_5P$ (192.10): C, 37.51; H, 4.72).
Subsequently we obtained IV more readily and in much higher yield by transesterification of trimethyl phosphite with methyl β-D-ribopyranoside.

Phosphite ester of methyl α-D-ribopyranoside (III)

III was prepared in exactly the same way as IV. From crude methyl α-D-ribopyranoside (32.8 g, 0.2 mol) we obtained only 1 g of III as small (1–2 mm), colourless needles, m.p. 119–120° (Found: C, 37.2; H, 4.9. Calc. for $C_6H_9O_5P$ (192.10): C, 37.51; H, 4.72).
III is less soluble in hexane than IV. The solution of III in hexane must be cooled down to 10° in order to get the pure compound. On concentration of the mother-liquor and cooling to −5° we were able to isolate 1.5 g of IV.

Acknowledgement

The authors thank Mr. *H. Eding* for carrying out the microanalyses.

[5] *E. L. Jackson* and *C. S. Hudson*, J. Am. Chem. Soc. **63**, 1229 (1941).

A ^{13}C-NMR study of squalene. Part II. Functionalized squalene-like compounds.

Marianne E. van Dommelen*, Leo J. M. van de Ven, Henk M. Buck and Jan W. de Haan

Laboratories of Organic Chemistry and Instrumental Analysis, Eindhoven University of Technology, The Netherlands
(Received June 10th, 1977)

Abstract. ^{13}C-NMR chemical shifts of substituted squalenes and model compounds with a hetero-atom in δ-position to a double bond show that a steric interaction exists between the hetero-atom and the double bond. This points to the presence of "precoiled" conformations in the hetero-substituted squalenes and also in squalene itself. The nature of the interaction remains veiled, but it appears to be a general feature as is shown in a series of 2- and 3-substituted thiophenes with a double bond in the side chain.

Introduction

Recently, we investigated the behaviour of squalene (I) by means of ^{13}C-NMR in a number of media in order to check the existence of different degrees of coiling[1a]. The main target of this study was to obtain additional information regarding conformational aspects of steroid precursors. It was found that squalene itself assumes *similar time-averaged conformations* in the media tested at concentrations of

[1a] *M. E. van Dommelen, A. R. N. Wilson, J. W. de Haan* and *H. M. Buck*, Recl. Trav. Chim. Pays-Bas **94**, 206 (1975).