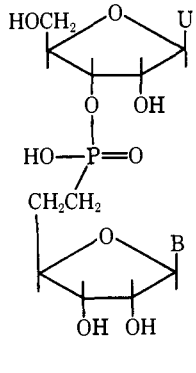
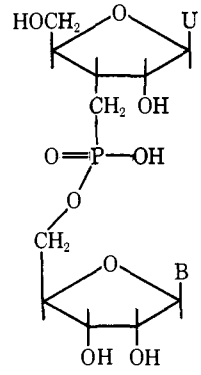


7a, B = uracil
b, B = adenine



8a, B = uracil
b, B = adenine

dinucleoside phosphates. Acetylation of **1b** with acetic anhydride in the presence of excess tetraethylammonium acetate[9] gave the 2′,3′-di-*O*-acetyl derivative in 82% yield and the latter was condensed with 2′,5′-di-*O*-(4-methoxytetrahydropyran-4-yl)uridine[10] in the presence of DCC. Treatment of the product with ammonium hydroxide followed by 80% acetic acid removed the protecting groups and gave the dinucleoside phosphonate $UpCH_2U$[11] (**7a**) as its sodium salt in 78% yield following ion-exchange chromatography: $\lambda_{max}^{H_2O}$ 261 mμ ($\epsilon_{(p)}$ 21,200). Similarly, by condensation of the acetyl derivative of **1b** with 2′,5′-di-*O*-(4-methoxytetrahydropyran-4-yl)uridine, $UpCH_2A$ (**7b**) was obtained in 50% yield with λ_{max} 259 mμ ($\epsilon_{(p)}$ 24,200). Since **7a** and **7b** cannot be cleaved by spleen phosphodiesterase, the purity of the 3′,6′-phosphono ester was confirmed by nmr spectroscopy. Thus, the spectrum of **7b** in D_2O showed C_6H of the uracil ring as a sharp doublet ($J_{5,6}$ = 8 Hz) at 7.78 ppm while mixtures of the 2′,6′- and 3′,6′-phosphono esters prepared as above from 5′-*O*-*p*-nitrobenzoyluridine showed C_6H as a pair of doublets at 7.74 and 7.77 ppm, respectively. The nmr spectrum of **7a** showed the two C_6 protons as sharp doublets at 7.65 and 7.85 ppm. By careful time averaging[12] the purity of the 3′,6′ ester bonds in **7a** and **7b** was shown to be at least 98%.

The reactions of the triethylammonium salts of **2a** and **2b** with DCC in *tert*-butyl alcohol–DMF mixtures at 80° for 1 hr led to quantitative formation of the 2′,3′-cyclic phosphonates (**6a** and **6c**) which were isolated as their calcium salts. **6a** had a comparable stability to adenosine 2′,3′-cyclic phosphate being 50% hydrolyzed by 0.1 *M* hydrochloric acid in 35 min at 23°.[13]

Treatment of **2b** with dihydropyran in dioxane–DMF in the presence of trifluoroacetic acid gave the 2′,5′-bistetrahydropyranyl derivative which was isolated as its calcium salt in 73% yield. Condensation of the latter as its pyridinium salt with 2′,3′-*O*-anisylideneuridine using DCC in pyridine followed by removal of the protecting groups with 80% acetic acid at 23° for 24 hr gave UCH_2pU (**8a**) in 56% yield as its calcium salt following chromatography on DEAE-Sephadex: $\lambda_{max}^{H_2O}$ 262 mμ ($\epsilon_{(p)}$ 18,500). Hydrolysis of **8a** with 1 *N* sodium hydroxide at 23° for 15 hr gave equal amounts of **2b** and uridine. Similarly, condensation of the tetrahydropyranyl derivative of **2b** with 2′,3′-*O*-anisylidene-N^6-benzoyladenosine[14] gave UCH_2pA (**8b**) in 54% yield: $\lambda_{max}^{H_2O}$ 260 mμ ($\epsilon_{(p)}$ 23,400).

Synthesis of further derivatives of **1** and **2** and enzymatic studies on these compounds will be described shortly.

(9) In the absence of excess acetate ion roughly 15% of the 2′-*O*-acetyl 3′,6′-cyclic phosphonate was formed.

(10) D. P. L. Green, T. Ravindranathan, C. B. Reese, and R. Saffhill, *Tetrahedron*, **26**, 1031 (1970).

(11) We shall use standard abbreviations for oligonucleotides except that the ester oxygen replaced by a methylene group is so indicated.

(12) The capable assistance of Dr. M. Maddox is gratefully acknowledged.

(13) For further kinetic data see M. R. Harris, D. A. Usher, H. P. Albrecht, G. H. Jones, and J. G. Moffatt, *Proc. Natl. Acad. Sci. U. S.*, **63**, 246 (1969).

(14) S. Chladek and J. Smrt, *Collect. Czech. Chem. Commun.*, **29**, 214 (1964).

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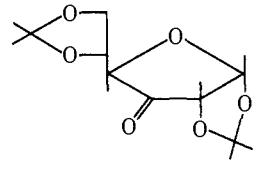
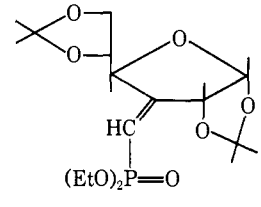
3′-Deoxy-3′-(dihydroxyphosphinylmethyl)nucleosides. Isosteric Phosphonate Analogs of Nucleoside 3′-Phosphates

Sir:

Previous work from these laboratories has led to syntheses of isosteric[1] and nonisosteric[2] phosphonate analogs of nucleoside 5′-phosphates. We now describe a synthetic route to 3′-deoxy-3′-(dihydroxyphosphinylmethyl)nucleosides (**9**) which are isosteric analogs of nucleoside 3′-phosphates. In view of the instability of 3′-ketonucleosides[3] under basic conditions and the lack of reactivity of suitable, less basic reagents such as diphenyl triphenylphosphoranylidenemethylphosphonate[4] toward ketones, we preferred a route to the title compounds *via* the common, versatile carbohydrate intermediate **6**. Accordingly, 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (**1**)[5] was condensed in tetrahydrofuran with tetraethyl methylenediphosphonate[6] in the presence of 1 equiv of *n*-butyllithium giving the vinyl phosphonate **2**[7] in 81% yield



1



2

with bp 136–140° (10^{-3}mm); $[\alpha]^{22}D$ +127.6° (*c* 0.88, MeOH). The nmr spectrum (pyridine-d_5) indicated

(1) G. H. Jones and J. G. Moffatt, *J. Amer. Chem. Soc.*, **90**, 5337 (1968).

(2) (a) L. Yengoyan and D. H. Rammler, *Biochemistry*, **5**, 3629 (1966); (b) D. H. Rammler, L. Yengoyan, A. V. Paul, and P. C. Bax, *ibid.*, **6**, 1828 (1967).

(3) (a) A. F. Cook and J. G. Moffatt, *J. Amer. Chem. Soc.*, **89**, 2697 (1967); (b) U. Brodbeck and J. G. Moffatt, *J. Org. Chem.*, in press.

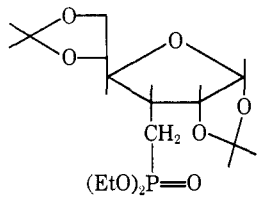
(4) G. H. Jones, E. K. Hamamura, and J. G. Moffatt, *Tetrahedron Lett.*, 5731 (1968).

(5) W. A. Szarek, J. S. Jewell, I. Szczerek, and J. K. N. Jones, *Can. J. Chem.*, **47**, 4473 (1969).

(6) W. S. Wadsworth and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961).

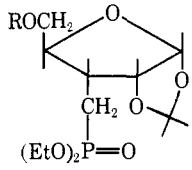
(7) All new compounds gave satisfactory elemental analyses and 100-MHz nmr spectra.

the presence of a single geometrical isomer, the vinyl proton appearing as a doublet of triplets at 6.28 ppm with $J_{P,H}$ = 14 Hz and allylic couplings to C_2H and C_4H of 1.5 Hz. Extensive glc analysis indicated the presence of roughly 5% of a second compound with very similar retention time. Catalytic reduction of **2** using 10% palladium on carbon was, as expected, stereospecific and gave the D-allophosphonate **3** in 98% yield with bp 163–168° (3 × 10^{-3}mm), $[\alpha]^{22}D$

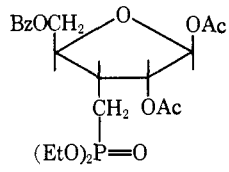


3

+51.8° (*c* 0.5, $CHCl_3$). No sign of the corresponding D-gluco isomer could be detected by glc and the allo configuration of **3** was confirmed both by subsequent transformations (*e.g.*, **7** → **9**) and by its nmr spectrum ($CDCl_3$) which showed C_2H as a triplet ($J_{1,2} = J_{2,3}$ = 4 Hz) at 4.77 ppm.[8] Selective acidic hydrolysis of the 5,6-acetonide followed by periodate oxidation and borohydride reduction of the resulting aldehyde gave 3-deoxy-3-(diethoxyphosphinylmethyl)-1,2-*O*-isopropylidene-α-D-ribofuranose (**4a**) in 75% yield with bp 90° (bath temperature) (10^{-3}mm); $[\alpha]^{22}D$ +79.4° (*c* 0.26, MeOH). Benzoylation of **4a** gave the 5-*O*-benzoyl derivative **4b** as a syrup with $[\alpha]^{22}D$ +49.7° (*c* 0.2, $CHCl_3$) which was treated with acetic anhydride–acetic acid containing 2% sulfuric acid giving a 65% yield of the crystalline 1,2-di-*O*-acetate **5**[9] with mp 79°; $[\alpha]^{22}D$ 0.1° (*c* 0.1, $CHCl_3$); nmr ($CDCl_3$) 6.08 ppm (br s, 1, C_1H). Treatment of **5** with ether saturated with hydrogen chloride at 0° for 3 days gave the glycosyl chloride **6** as a syrup.



4a, R = H
b, R = benzoyl



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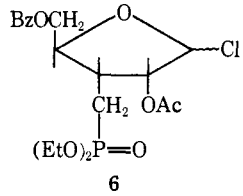
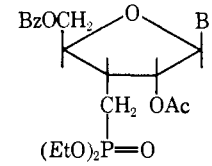


6

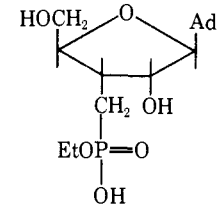
Condensation of **6** with chloromercuri-6-benzamidopurine in toluene under reflux gave chromatographically homogeneous 9-[2-*O*-acetyl-5-*O*-benzoyl-3-deoxy-3-(diethoxyphosphinylmethyl)-β-D-ribofuranosyl]-6-benzamidopurine (**7a**) in 63% yield: $[\alpha]^{22}D$ +13.3° (*c* 0.13, MeOH); λ_{max}^{MeOH} 279 (ε 19,700). The β configuration of **7a** was confirmed by its ORD spectrum (negative Cotton effect)[10] and by its nmr spectrum ($CDCl_3$) which showed $C_1'H$ as a singlet at 6.02 ppm.[11] The preparation of **7a** was also achieved by the fusion of **5** with 6-benzamidopurine at 160° for 30 min in the presence of di-*p*-nitrophenylphosphoric acid[12] but the product (53%) was contaminated by a small amount of its α anomer that was difficult to remove. In similar ways, the mercury salts of N^4-acetylcytosine, thymine, and 6-chloropurine were condensed with **6** giving the β-nucleoside derivatives **7b**, **7c**, and **7d** in yields of 60, 21, and



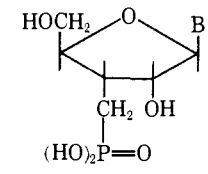
7a, B = N^6-benzoyladenine
b, B = N^4-acetylcytosine
c, B = thymine
d, B = uracil
e, B = 6-chloropurine

60%. Also, condensation of **6** with bis-*O*-(trimethylsilyl)uracil in the presence of mercuric oxide and mercuric chloride[13] gave the uridine derivative **7d** in 59% yield. In all cases the β configuration was confirmed by ORD and nmr studies.

Treatment of **7a** with methanolic ammonium hydroxide for 24 hr at 22° removed the N^6-benzoyl group and gave two acid-stable monoanions, presumably **8** and its 5′-*O*-benzoate. Further treatment with 1 *N* sodium hydroxide at 22° followed by ion-exchange chromatography on DEAE Sephadex gave the triethylammonium salt of 3′-deoxy-3′-(dihydroxyphosphinylmethyl)-adenosine (**9a**) in 87% yield from **7a**. Acidification of a



8



9a, B = adenine
b, B = cytosine
c, B = thymine
d, B = uracil

solution of this salt in aqueous ethanol gave crystalline free acid **9a** with mp 198–205° dec in 94% yield: $[\alpha]^{22}D$ −12.3° (*c* 0.16, H_2O); $\lambda_{max}^{H_2O}$ 258 mμ (ε 14,900). The ease of hydrolysis of both phosphonate ester groups is, of course, a consequence of the presence of the cis vicinal 2′-hydroxyl function. Similar alkaline treatments of **7b–d** gave the corresponding nucleotide analogs (**9b–d**) which were isolated by ion-exchange chromatography.

(8) R. J. Abraham, L. D. Hall, L. Hough, and K. A. McLauchlan, *J. Chem. Soc.*, 3699 (1962).
(9) In another preparation crystalline **5** was obtained in an overall yield of 44% from **1** without purification of the intermediates.
(10) (a) R. T. Emerson, R. J. Swan, and T. L. V. Ulbricht, *Biochemistry*, **6**, 843 (1967); (b) T. Nishimura, B. Shimizu, and I. Iwai, *Biochem. Biophys. Acta*, **157**, 221 (1968).
(11) T. D. Inch, *Annu. Rev. NMR (Nucl. Magn. Resonance) Spectrosc.*, **2**, 35 (1969).
(12) T. Hashizume and H. Iwamura, *Tetrahedron Lett.*, 3095 (1965).
(13) E. Wittenburg, *Chem. Ber.*, **101**, 1095 (1968).

The conversion of some of these compounds into other derivatives of biological interest is the subject of the accompanying communication.[14]

(14) G. H. Jones, H. P. Albrecht, N. P. Damodaran, and J. G. Moffatt, *J. Amer. Chem. Soc.*, **92**, 5510 (1970).

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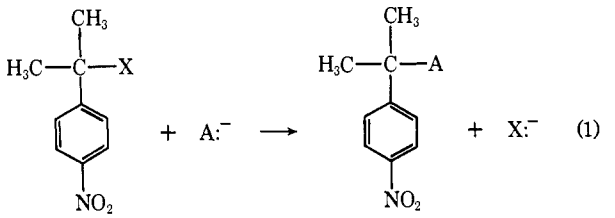
New and Facile Substitution Reactions at Tertiary Carbon. Entrainment

Sir:

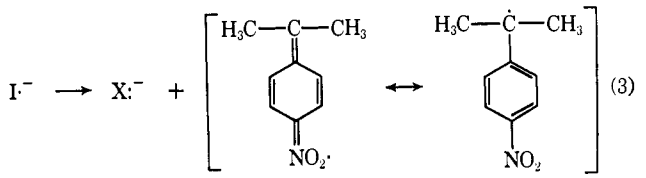
A number of examples of a new type of substitution at a tertiary carbon are now known.[1] Many of these reactions involve *p*-nitrocumyl chloride (Ia) and α,p-



Ia, X = Cl
Ib, X = NO_2

dinitrocumene (Ib) which undergo substitution by a variety of anions and amines according to eq 1;[1] a chain mechanism, described by eq 2–5 has been proposed.[1]

$$I + A:^- \longrightarrow I\cdot^- + A\cdot \quad (2)$$



$$III + A:^- \longrightarrow II\cdot^- \quad (4)$$

$$II\cdot^- + I \longrightarrow II + I\cdot^- \quad (5)$$

If these reactions are, indeed, chain processes, then the anions which react most rapidly may well do so because they enter into the initiation step (eq 2) with the greatest facility. In other words, the anions which react most readily with Ia, and with Ib, are those which find it easiest to transfer one electron to the *p*-nitrocumyl system and, thereby, produce the chain carrying *p*-nitrocumyl radicals (eq 2 and 3). Conversely, according to this hypothesis, those anions which react slowly are the ones which have difficulty entering into the initiation step (eq 2).

The mechanism of eq 2–5 assigns not one, but two, roles to the anion. In the chain-propagating sequence (eq 4) the anion adds to the *p*-nitrocumyl radical in a manner reminiscent of the first stage of the Michael reaction;[2] since this is part of a chain-propagating sequence it should be a rapid process.

This point of view leads to the prediction that *p*-nitrocumyl radicals (III) can be intercepted not only by the anions used to produce them but, also, by other anions; that is to say, even those anions which react slowly with *p*-nitrocumyl chloride are able to compete for the *p*-nitrocumyl radicals (eq 4). It follows, then, that a catalytic amount of a reactive nucleophile should be capable of inducing the reaction of a less reactive (or nonreactive) nucleophile with *p*-nitrocumyl chloride (Ia) or α,p-dinitrocumene (Ib). As will be seen from the sequel, this prediction is amply fulfilled.

One of our more dramatic examples of entrainment involves α,p-dinitrocumene and sodium azide which, in the dark, do not react at all after 48 hr. In contrast, the lithium salt of 2-nitropropane reacts readily with α,p-dinitrocumene, the reaction being 87% complete in 3 hr. When α,p-dinitrocumene (1 mol) is treated with sodium azide (2 mol) in the presence of the lithium salt of 2-nitropropane (0.1 mol) all the α,p-dinitrocumene is consumed after 3 hr and a 97% yield of pure *p*-nitrocumyl azide is obtained. Thus, the 2-nitropropane anion transforms sodium azide from a reagent which does not react to one which reacts completely.

The reaction of α,p-dinitrocumene with sodium benzenesulfinate provides another clear example of entrainment. In the dark the reaction proceeds only

Table I. Reactions of α,p-Dinitrocumene Entrained by the Lithium Salt of 2-Nitropropane[a]

Anion	Mol % $(CH_3)_2CNO_2^-$ [b]	Time, hr	% reaction	R anion;[c] % yield
$(CH_3)_2CNO_2^-$		3	87	$RC(CH_3)_2NO_2$; 71
N_3^-		48	0	RN_3; 0
N_3^-	5	3	100	RN_3; 97
$C_6H_5SO_2^-$		96	8	$RSO_2C_6H_5$; 8
$C_6H_5SO_2^-$	5	4	100	$RSO_2C_6H_5$; 95[d]
$C_6H_5SO_2^-$	0.8	4	77	$RSO_2C_6H_5$; 75
$^-CH(CO_2C_2H_5)_2$		12	26	$RCH(CO_2C_2H_5)_2$; 26[e]
$^-CH(CO_2C_2H_5)_2$	5	12	53	$RCH(CO_2C_2H_5)_2$; 51[e,f]

[a] In the dark in hexamethylphosphoramide (HMPA). [b] Relative to anion. [c] R = *p*-nitrocumyl. [d] $RC(CH_3)_2NO_2$ also formed; 1% yield. [e] By nmr. [f] $RC(CH_3)_2NO_2$ also formed; 2% yield.

Table II. Reactions of *p*-Nitrocumyl Chloride Entrained by the Lithium Salt of 2-Nitropropane[a]

Anion	Mol % $(CH_3)_2CNO_2^-$ [b]	Time, min	% reaction	R anion;[c] % yield
$(CH_3)_2CNO_2^-$		90	85	$RC(CH_3)_2NO_2$; 53
NO_2^-		90	0	RNO_2; 0
NO_2^-	5	90	100	RNO_2; 93[d]
$C_6H_5SO_2^-$		15	18	$RSO_2C_6H_5$; 18[e]
$C_6H_5SO_2^-$	5	15	100	$RSO_2C_6H_5$; 96[e,f]
Quinuclidine[g]		36[h]	0[i]	[R quinuclidine]$^+$; 0
Quinuclidine[g]	7	36[h]	79	[R quinuclidine]$^+$; 63[j]

[a] In the dark in HMPA. [b] Relative to anion. [c] R = *p*-nitrocumyl. [d] $RC(CH_3)_2NO_2$ also formed; 3% yield. [e] By nmr. [f] $RC(CH_3)_2NO_2$ also formed; 4% yield. [g] In DMSO. [h] Hours. [i] *Cf.* ref 4. [j] $RC(CH_3)_2NO_2$ also formed; 8% yield.

(1) N. Kornblum and F. W. Stuchal, *J. Amer. Chem. Soc.*, **92**, 1804 (1970).

(2) N. Kornblum, R. E. Michel, and R. C. Kerber, *ibid.*, **88**, 5663 (1966).