When the hydroxyfulvene **7** was allowed to stand in oxalyl chloride solution at room temperature for 12 hr it was converted to the highly reactive, yellow chloride **8**, mp 126–127° (88%), ultraviolet absorptions at 234 (ε 5010), 314 (ε 10,300), 327 (ε 9700), and 343 mμ (ε 5140) in pentane. Condensation with lithium di(*trans*-1-propenyl)cuprate (**10**)[8] in ether solution at −25° gave a purple reaction mixture which was chromatographed on silicic acid. Elution with chloroform followed by crystallizations from chloroform–hexane gave the orange fulvoplumierin (**1**) (27%), mp 148–150°. Infrared,[2] ultraviolet,[2] and nuclear magnetic resonance[3] spectra of synthetic and natural fulvoplumierin were indistinguishable.

Acknowledgment. We are indebted to the National Institutes of Health for financial support.

(8) Prepared by the method of G. M. Whitesides, J. San Fillipo, Jr., C. P. Casey, and E. J. Panek, *J. Am. Chem. Soc.*, **89**, 5302 (1967). Lithium dimethylcopper has been condensed with a vinyl bromide by E. J. Corey and G. H. Posner, *ibid.*, **89**, 3911 (1967). Analogous coupling reactions were performed by H. O. House and W. F. Fischer (unpublished), while G. M. Whitesides and J. San Fillipo, Jr. (unpublished), have condensed vinyl cuprates with alkyl halides. We are indebted to the latter investigators for much unpublished information.

(9) National Institutes of Health Predoctoral Fellow, 1966–present.

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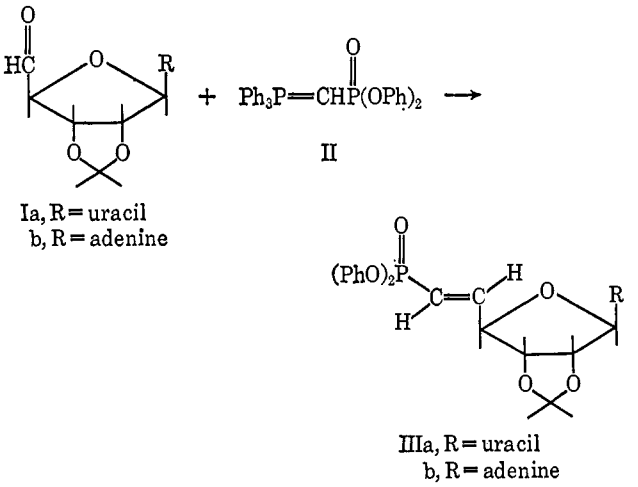
The Synthesis of 6′-Deoxyhomonucleoside-6′-phosphonic Acids[1]

Sir:

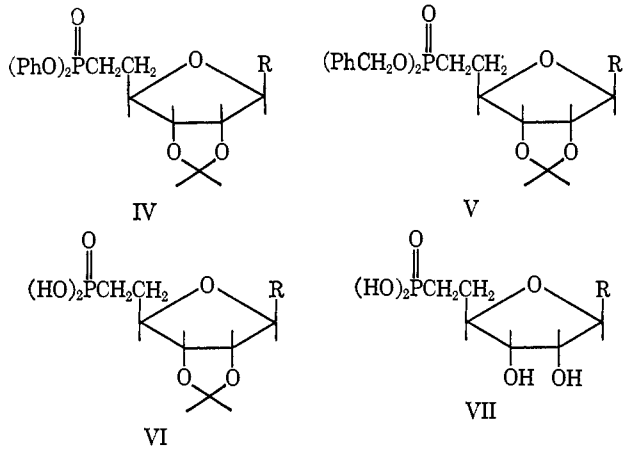
We have recently been involved in a general program on the utility, as synthetic intermediates, of nucleoside derivatives containing aldehydo[2] and keto[3] functions in the sugar moiety. In a separate paper[4] we describe the synthesis of the stabilized Wittig reagent diphenyl triphenylphosphoranylidenemethylphosphonate (II) and we here describe the reaction of this compound with protected nucleoside 5′-aldehydes (I) leading to 6′-deoxyhomonucleoside-6′-phosphonic acids.

Treatment of 2′,3′-O-isopropylideneuridine with dicyclohexylcarbodiimide and dimethyl sulfoxide in the presence of pyridinium trifluoroacetate led to the formation of the 5′-aldehyde Ia in high yield. This material was not isolated,[5] but rather was treated directly with II in DMSO at 37° for 20 hr. Chromatography on silicic acid then gave the crystalline α,β-unsaturated phosphonate IIIa in 58% yield, mp 146–147°.[6]

The 100-MHz nmr spectrum of IIIa showed the $C_{6'}$ proton as an octet at 6.13 ppm with $J_{6',5'}$ = 17 Hz, $J_{H,P}$ = 21 Hz, and $J_{6',4'}$ = 1.5 Hz. The $C_{5'}$ proton was located within the aromatic envelope. These data are consistent with a *trans* configuration for the vinyl phosphonate.[7] Hydrogenation of IIIa in methanol using a 5% palladium on barium sulfate catalyst proceeded readily and gave IVa in quantitative yield as a white foam with the expected nmr and ultraviolet spectra. Alkaline hydrolysis readily cleaved one phenyl ester and, following acidic removal of the isopropylidene group, the second could be removed enzymatically using the phosphodiesterase from *Crotalus adamanteus* venom[8] giving the free phosphonic acid VIIa.



Removal of the ester groups was, however, more readily achieved on a preparative scale by reaction of the diphenyl ester IVa with 4 equiv of sodium benzoxide in dimethyl sulfoxide at 20° for 5–15 min. Such treatment led to almost instantaneous transesterification with formation of the dibenzyl ester Va which was isolated in 83% yield by chromatography on silicic acid. Palladium-catalyzed hydrogenolysis of the benzyl esters of Va was rapid and gave the free phosphonic acid VIa which was treated with water at 100° for 1 hr to remove the isopropylidene groups, giving crystalline 6′-deoxy-



(1) This trivial nomenclature stresses the relationship of these compounds with the essentially isosteric nucleoside 5′-phosphates. Systematically they may be referred to as 5′-deoxy-5′-(dihydroxyphosphinylmethyl)nucleosides or as derivatives of phosphonic acids, *e.g.*, VIIa, being [1-(5′,6′-dideoxy-β-D-*ribo*-hexofuranosyl)uracil]-6′-phosphonic acid.

(2) (a) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **85**, 3027 (1963); (b) K. E. Pfitzner and J. G. Moffatt, *ibid.*, **87**, 5661 (1965).

(3) A. F. Cook and J. G. Moffatt, *ibid.*, **89**, 2697 (1967).

(4) G. H. Jones and J. G. Moffatt, in preparation.

(5) See G. H. Jones, J. P. H. Verheyden, and J. G. Moffatt, XXIst International Congress of Pure and Applied Chemistry, Prague, 1967, Abstract N-26, for the problems associated with chromatographic isolation.

(6) All crystalline products have given satisfactory elemental analyses.

(7) C. E. Griffin and T. D. Mitchell, *J. Org. Chem.*, **30**, 1935 (1965); L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Inc., New York, N. Y., 1959, p 85.

(8) The close analogy between the homonucleoside phosphonates and natural nucleotides is emphasized by this enzymatic reaction which proceeded at roughly 20% the rate found using monophenyluridine 5′-phosphate.

homouridine-6′-phosphonic acid (VIIa), mp 198–199° (from ethanol), in 84% yield from Va; $\lambda_{max}^{H_2O}$ 263 mμ (ε 10,000). The product was homogeneous by paper chromatography and electrophoresis under a variety of conditions and behaved much like uridine 5′-phosphate. The over-all yield of crystalline VIIa from 2′,3′-O-isopropylideneuridine was 41%.

In a similar series of reactions 2′,3′-O-isopropylideneadenosine-5′-carboxaldehyde (Ib, prepared *in situ*[2a]) was treated with II to give the unsaturated phosphonate ester IIIb in 33% yield. This product was obtained as a foam which has resisted crystallization. Catalytic hydrogenation of IIIb was extremely slow and incomplete even after prolonged treatment with several portions of fresh catalyst. Reduction was readily achieved using 5 equiv of diimide generated from potassium azodicarboxylate and acetic acid in pyridine.[9] The resulting saturated phosphonate IVb was obtained as needles, mp 135–136° (from benzene), in 69% yield. Transesterification with sodium benzoxide as above gave the dibenzyl ester Vb, mp 127–128°, in 75% yield, and subsequent catalytic hydrogenolysis rapidly removed both ester groups, giving the isopropylidenephosphonic acid VIb as a syrup in essentially quantitative yield. Conditions necessary for the removal of the isopropylidene group inevitably led to some hydrolysis of the glycosidic bond with release of adenine. Following treatment of free acid VIb in water at 100° for 70 min, the mixture was purified by ion-exchange chromatography on DEAE-Sephadex (HCO_3^-), giving the monotriethylammonium salt of VIIb in 62% yield. Acidification of a solution of the latter in aqueous ethanol gave crystalline 6′-deoxyhomoadenosine-6′-phosphonic acid (VIIb), mp 170–172° dec, $\lambda_{max}^{H_2O}$ 259 mμ (ε 14,000).

Satisfactory condensations of the ylide II with other ribo- and deoxyribonucleoside-5′-carboxaldehydes have also been achieved, and several 6′-deoxyhomonucleoside-6′-phosphonic acids have been converted into analogs of natural nucleoside polyphosphates, nucleoside coenzymes, and related compounds.[10] Details of these syntheses and of enzymatic studies on the resulting compounds will be described shortly.

(9) J. W. Hamersma and E. I. Snyder, *J. Org. Chem.*, **30**, 3985 (1965).
(10) Unpublished studies by U. Brodbeck, G. H. Jones, and J. G. Moffatt.

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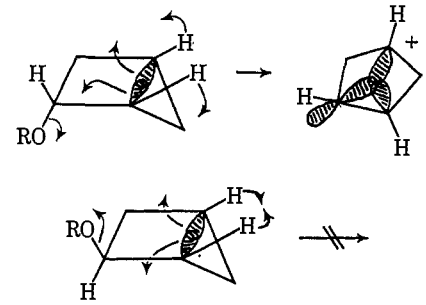
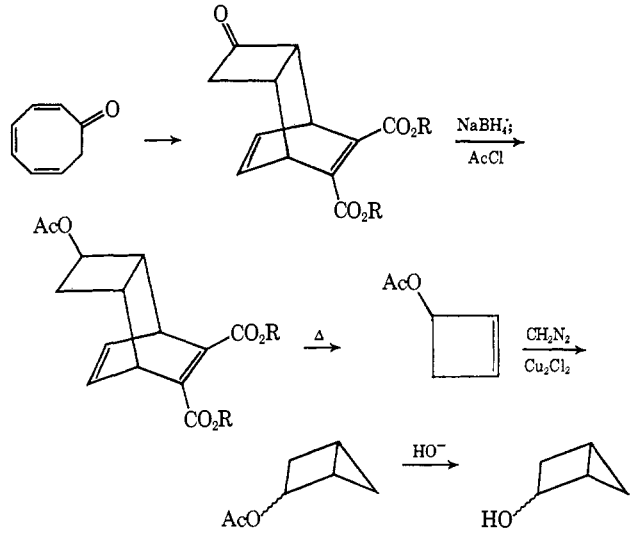
Solvolysis of Bicyclo[2.1.0]-2-pentyl Derivatives[1]

Sir:

The bicyclo[2.1.0]-2-pentyl derivatives should provide another valuable test of the cyclobutyl orbital participation scheme which we found useful in explaining the solvolytic reactions of the *cis*- and *trans*-fused bicyclo[4.2.0]-7-octyl tosylates.[2] The *endo* isomer would be expected to be quite reactive, for the required orbital rotation will relieve part of the strain caused by the central bond. The *exo* isomer would be expected to be much less reactive because the required rotation would lead to an increase in strain. Participation by one of the nonbridging cyclobutyl bonds might also be involved, but this would not lead to as much strain relief.



The alcohols were prepared by forming the Diels–Alder adduct between cyclooctatrienone and ethyl acetylenedicarboxylate,[3] followed by sodium borohydride reduction, acetylation, pyrolysis, and treatment with diazomethane catalyzed by cuprous bromide.



The mixture of epimeric alcohols could be separated with some difficulty by vpc. The assignment of configuration was made by an analysis of the nmr spectrum. The spectrum of one isomer had seven distinct multiplets, one for each of the protons. By decoupling experiments and computer simulation of the spectrum, the coupling constant of the hydrogen α to the bridgehead hydrogen was found to be 4.2 Hz.[4] In the cyclobutane ring the coupling constant between the bridgehead proton and an *endo* proton was found to be 0.5 Hz, whereas that to the *exo* proton was 4.0 Hz. Thus, the above isomer has an *endo*-hydroxy group. Similarly, the spectrum of the other isomer indicated a much smaller coupling constant to the bridgehead proton.

The rate constants and products of the solvolysis of the 3,5-dinitrobenzoates derived from the two alcohols are shown below.[5] The extrapolated rate constant for

(1) This investigation was supported by Public Health Service Grant GM12800 from the National Institute of General Medical Science.
(2) K. B. Wiberg and J. G. Pfeiffer, *J. Am. Chem. Soc.*, **90**, 5324 (1968).
(3) A. C. Cope, S. F. Schaeren, and E. R. Trumbull, *ibid.*, **76**, 1096 (1954).
(4) The analysis of the nmr spectrum was carried out by D. Barth and will be reported in detail at a later time. We thank him for supplying us with his data.
(5) Because of analytical difficulties, the solvolysis of the *endo* isomer was studied in aqueous dioxane rather than the more common aqueous acetone. The *Y* values of 80% acetone and 80% dioxane are almost the same, and so there should be a negligible difference in rate between the two solvents.