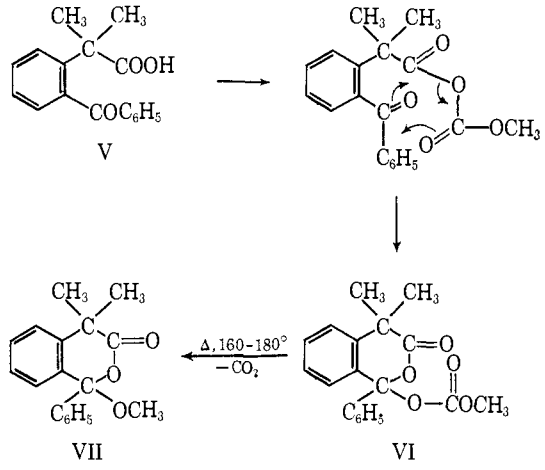
described, which may be predicted by changing the atoms involved in the bicyclic path. Some of these are under study in these laboratories.



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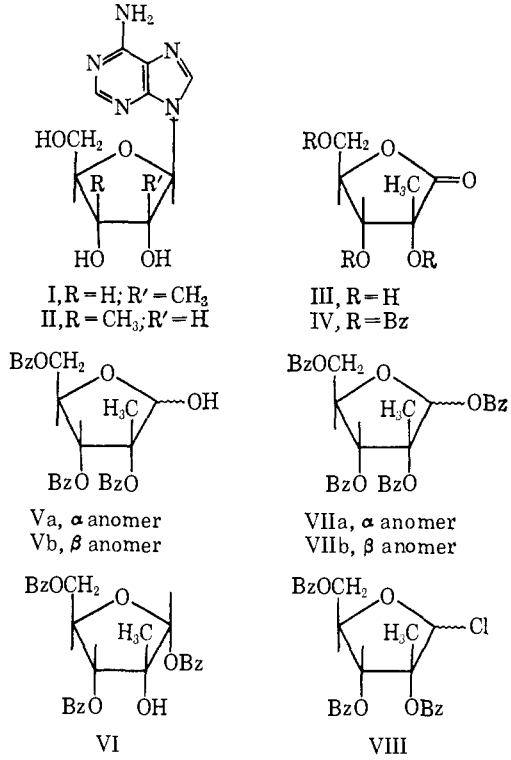
Branched-Chain Sugar Nucleosides. A New Type of Biologically Active Nucleoside

Sir:

It has been proposed[1] that the therapeutic value of a number of biologically active adenosine analogs is limited by their facile conversion into the less active inosines through the action of adenosine deaminase. Hence, adenosine analogs resistant to the action of adenosine deaminase are of interest. We wish to report two new adenine nucleosides, 2′-C-methyladenosine (I) and 3′-C-methyladenosine (II),[2] which have biological activity as measured by their ability to inhibit the growth of KB cells in culture and at the same time show a marked resistance to the action of adenosine deaminase. These compounds are the first examples of nucleosides containing branched-chain sugars.

The cytotoxicity of the 2′- and 3′-C-methyladenosine against KB cells in culture was determined by the method of Gitterman and co-workers.[3] As measured by protein determination, the inhibitory effect of both 2′-C-methyladenosine and 3′-C-methyladenosine was between 65 and 80% at a concentration of 10 μg/ml. The activity of calf intestine adenosine deaminase with I and II was compared with that observed with adenosine. Deamination was determined spectrophotometrically by the change in absorption at 265 mμ. 3′-C-Methyladenosine was not measurably deaminated over a period of 10 min under conditions where adenosine was completely deaminated in 2.5 min. The rate of deamination of 2′-C-methyladenosine was $^1/_{25}$ that observed when adenosine was the substrate.

For the synthesis of 2′-C-methyladenosine (I), a suitable derivative of the hitherto undescribed 2-C-methyl-D-ribofuranose was required. 2-C-Methyl-D-ribono-γ-lactone (α-D-glucosaccharinic acid lactone, III)[4] was a convenient starting material. The lactone III, after conversion into its 2,3,5-tri-O-benzoyl derivative (IV) [mp 140–141°; λ_{max}^{Nujol} 5.56 μ (lactone), 5.70, 5.79 (ester); $[\alpha]_D$ −79° (*c* 1, $CHCl_3$)], was reduced with bis(3-methyl-2-butyl)borane (disiamylborane)[5] to produce an anomeric mixture of 2,3,5-tri-O-benzoyl-2-C-methyl-D-ribofuranose (V) as the main product. The mixture of Va and Vb was not separated. When their separation was attempted by chromatography on acid-washed alumina, a complete rearrangement to 1,3,5-tri-O-benzoyl-2-C-methyl-α-D-ribofuranose (VI) ($[\alpha]_D$ +92° (*c* 1, $CHCl_3$)) resulted. The same rearrangement occurred, but only to a slight extent, during chromatography of the reduction products on silica gel. Benzoylation of the mixed anomers of V with benzoyl chloride in pyridine produced 1,2,3,5-tetra-O-benzoyl-2-C-methyl-α(β)-D-ribofuranose. Following chromatography, one of the anomers (presumably β),



VIIa, was isolated as a crystalline solid [mp 159–160°; λ_{max}^{Nujol} 5.72 and 5.80 μ (ester); $[\alpha]_D$ + 68° (*c* 1, $CHCl_3$); τ^{CDCl_3} 2.90 (singlet, H-1) and 4.02 ppm (doublet, H-3) ($J_{3,4}$ = 7.3 cps)]; the other (presumably α) was obtained as a pure syrup [λ_{max}^{neat} 5.76 μ (ester); $[\alpha]_D$ +68° (*c* 1, $CHCl_3$); τ^{CDCl_3} 3.12 (singlet, H-1) and 4.30 ppm (broad singlet, H-3, half-width 4–5 cps)]. The tentative anomeric configurational assignments of VIIa and VIIb are based on the observation that VIIa (β) was much more easily converted, in ethereal hydrogen chloride, into the chloro sugar VIII than was VIIb (α). The more rapid conversion of the β anomer into the chloro sugar is to be expected because of the predicable anchimeric effect

(1) G. A. LePage and I. G. Junga, *Cancer Res.*, **25**, 46 (1965).
(2) For a description of the synthesis of II see E. Walton, F. W. Holly, and R. F. Nutt, Winter Meeting of the American Chemical Society, Phoenix, Ariz., Jan 1966, Abstract 37C.
(3) C. O. Gitterman, R. W. Burg, G. E. Boxer, D. Meltz, and J. Hitt, *J. Med. Chem.*, **8**, 664 (1965).
(4) E. Peligot, *Compt. Rend.*, **89**, 918 (1879).
(5) The reduction of several nonbranched, acylated hexono-γ-lactones has been described by P. Kohn, R. H. Samaritano, and L. M. Lerner, *J. Am. Chem. Soc.*, **86**, 1457 (1964).

of the 2-aryloxy moiety, an effect which is not operative in the α anomer. The same chloro sugar VIII was obtained from either VIIa or VIIb. Reaction of VIII with chloromercuri-6-benzamidopurine gave 9-(2,3,5-tri-O-benzoyl-2-C-methyl-β-D-ribofuranosyl)-6-benzamidopurine (IX) as an amorphous solid. The blocked intermediate IX was purified by chromatography on silica gel. Removal of the benzoyl blocking groups from IX in the methanolic sodium methoxide gave crystalline 2'-C-methyladenosine (II);[6] mp 257–258°; $\lambda_{max}^{H_2O}$ mμ ($\epsilon \times 10^{-3}$) 258 at pH 1 (15.1), 260 at pH 7 (15.1), 260 at pH 13 (14.9); $\tau^{\text{deuteriopyridine}}$ 3.10 (singlet, H-1') and 4.93 ppm (doublet, H-3') ($J_{3',4'} = 8.8$ cps); $[\alpha]_D$ −21° (*c* 0.5, H_2O); $[\phi]$ −2500° at λ_{278}, $[\phi]$ +10,000° at λ_{247} (*c* 5.16×10^{-3}, H_2O).[7]

(6) The product was assigned the β-anomeric configuration on the basis of the "*trans*" rule and the optical rotational data.

(7) We wish to thank Dr. J. J. Wittick of these laboratories for the ORD determination. Nmr spectra were measured with a Varian A-60 spectrometer.

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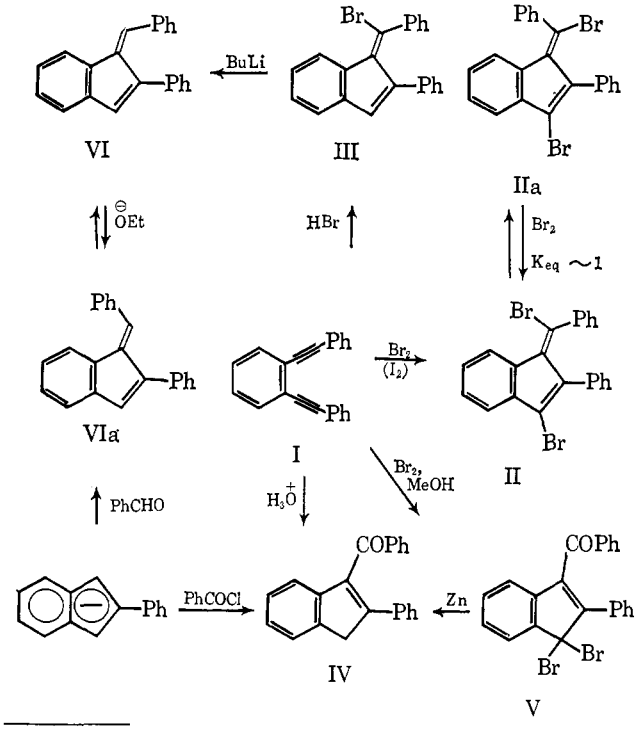
An Example of Alkyne–Alkyne Interaction

Sir:

In marked contrast with its behavior on reaction with iron pentacarbonyl or on irradiation,[1] *o*-bis(phenylethinyl)benzene[2] (I) exhibits pronounced interaction between its triple bonds when confronted with electrophilic, nucleophilic, or radical reagents.

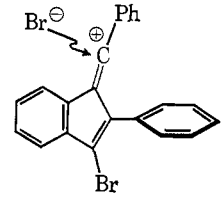
Addition of bromine to I in chloroform affored a single yellow-orange dibromide II, mp 139–141°.[3]



(1) E. Müller, M. Sauerbier, and J. Heiss, *Tetrahedron Letters*, 2473 (1966).

(2) Mp 51–52°; from bromination–dehydrobromination of *o*-distyrylbenzene.

Comparison of its ultraviolet spectrum (λ_{max}^{EtOH} 247 mμ (log ϵ 4.22), 277 (4.19), 340 (4.12)) with those of similar[4] benzofulvenes of known or herein determined structure points to the presence of this π system in II and eliminates from consideration 2,3-diphenylnapthalene or 1,2-dibenzylidenebenzocyclobutene[5] derivatives. The bromination satisfies the standard criteria of a concerted stereoselective reaction. Competitive bromination of I and tolane produces II exclusively; no tolane dibromide could be detected. Equilibration of II with an orange isomer, IIa, mp 114–117°, λ_{max}^{EtOH} 250 mμ (ϵ 4.18), 274 (4.19), and 337 (4.10), $K_{eq} \sim 1$, could be achieved by allowing II to stand in chloroform containing small amounts of bromine, but IIa could not be detected as a primary product of the bromination. Both stereoisomeric diiodides could be isolated on iodination of I. They closely resembled II spectrally. On the basis of recent work[6–8] on resonance-stabilized vinyl cations, II is assigned the stereochemistry arising from least hindred attack of bromide ion on ion VII.



VII

Reaction of I with hydrogen bromide in chloroform or hydrobromic acid in acetic acid affords a single hydrobromide, III, mp 144–145°, λ_{max}^{EtOH} 252 mμ (ϵ 4.34), 274 (4.38), and 339 (3.99). Reaction of III with butyllithium in ether at 0° followed by protonation gave diphenylbenzofulvene VI. Fulvene VI was identified as the less stable of the two isomers produced on *t*-butoxide-catalyzed condensation of 2-phenylindene and benzaldehyde. The two isomers, VI, mp 129–131°, and VIa, an oil, could be separated by chromatography and interconverted on being allowed to stand with potassium ethoxide in ethanol; VIa was considerably the more stable. Their sterochemistry is assigned from the consideration of models. Hydration of I could be effected by acetic acid–sulfuric acid. The product, IV, mp 92–93°, was identical with that arising from lithium 2-phenylindenide and benzoyl chloride. The rate constant for hydration of I in aqueous 95% ethanolic sulfuric acid (1:1:2) at 48.9° ($k = 2.04 \times 10^{-5}$ sec^{-1}) was 36 times that ($k = 5.68 \times 10^{-7}$ sec^{-1}) for hydration of tolane under the same conditions. Bromination of I in methanol gave, in addition to starting material and a 12% yield of II, a 72% yield of dibromo ketone V, mp 116–117°. Brief reaction of V with zinc in acetic acid gave IV. Both IV and V are considered as arising from facile electrophilic attack on alkoxy- and acetoxyfulvene precursors.

(3) All new compounds have been characterized by elemental analysis and afford the various spectra appropriate for the assigned structure.

(4) N. Campbell, P. S. Davidson, and M. G. Heller, *J. Chem. Soc.*, 993 (1963).

(5) A. T. Blomquist and V. J. Hruby, *J. Am. Chem. Soc.*, **86**, 5041 (1964).

(6) C. A. Grob, J. Csapilla, and G. Cseh, *Helv. Chim. Acta*, **47**, 1590 (1964).

(7) C. A. Grob and G. Cseh, *ibid.*, **47**, 194 (1964).

(8) D. S. Noyce, M. A. Matesich, O.P., M. D. Schiavelli, and P. E. Peterson, *J. Am. Chem. Soc.*, **87**, 2295 (1965).