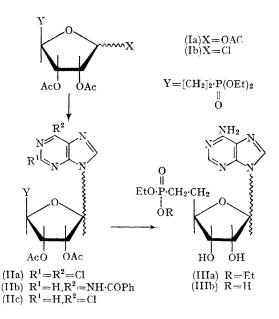
## The Synthesis of Phosphonic Acid Analogues of Purine Ribonucleotides: an Exception to the *trans* Rule

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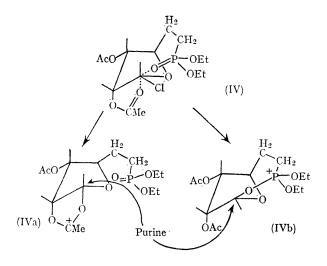
FUSION of 1,2,3-tri-O-acetyl-5,6-dideoxy-6-di-O-ethylphosphono-1)-ribo-hexofuranose (Ia) (prepared from 1,2:5,6-di-Oisopropylidene-a-D-allofuranose<sup>1</sup> by selective hydrolysis, oxidation, reaction with tetraethyl methylenediphosphonate,<sup>2</sup> catalytic reduction, acetolysis, and acetylation) with 2,6-dichloropurine gave 2,6-dichloro-9-(2,3-di-O-acetyl-5,6-didcoxy-6-di-O-ethylphosphono-D-ribo-hexofuranosyl)purine (IIa) as an anomeric mixture containing slightly more  $\alpha$ - than  $\beta$ -anomer. A similar result was obtained with 6-chloropurine, but the  $\alpha$  :  $\beta$  ratio was even higher. In general fusion of glycosyl acetates with an acetoxy-group at C(2) gives predominantly the trans- or, in the case of ribose derivatives,  $\beta$ -anomer,<sup>3</sup> although a trace of the  $\alpha$ anomer has been detected in a number of cases,<sup>4</sup> and at least one exception to this general statement has been recorded.<sup>5</sup> On the other hand, the reaction of heavy metal salts of purines and pyrimidines with glycosyl halides contairing an acyloxy-group at C(2) gives primary the trans-anomer and no true exceptions to this rule<sup>6</sup> have previously been reported.7 Consequently, 1,2,3-tri-Oacetyl-5,6-dideoxy-6-di-O-ethylphosphono-D-ribo-hexofuranose (Ia) was converted in the usual manner into 2,3-di-O-acetyl-5,6-dideoxy-6-di-O-ethylphosphono-D-ribo-hexo-

furanosyl chloride (Ib), which was treated with the chloromercuri-derivative of N-benzoyladenine. This reaction also gave an anomeric mixture (IIb), but in this case the  $\alpha:\beta$  ratio was about 2:1. Kissmann and Baker<sup>7</sup> obtained a small amount of  $\alpha$ -anomer in the reaction of 1,2,3-tri-Oacetyl-5-deoxy-D-ribofuranosyl chloride and chloromercuri-N-benzoyladenine, but this anomer was not formed when chloromercuri-6-chloropurine was used. The reaction of (Ib) with chloromercuri-6-chloropurine, however, gave an anomeric mixture (IIc) with  $\alpha:\beta$  1.5:1. The reason for



the unusual behaviour of this glycosyl halide is not yet clear. Other glycosyl halides with relatively bulky groups

at C(5) react with chloromercuri-N-benzoyladenine to give only one anomer, assumed to be the  $\beta$ -(trans)-anomer<sup>8</sup> on the basis of the trans rule.<sup>6</sup> It seems unlikely that the present result is due to steric interference alone. There



may be interaction between the oxygen of the diethyl phosphonate group and C(1) (IVb) that results in the predominant formation of the  $\alpha$ -anomer.<sup>†</sup>

Since the anomeric mixtures were difficult to separate by any of the usual procedures, the anomer ratios were estimated from the 1H n.m.r. spectra of the reaction mixtures. The C(1') proton signal of a *cis*-furanosylpurine occurs downfield from that of the corresponding transfuranosylpurine.4b Treatment of the anomeric mixture (IIb) with methanolic sodium methoxide at reflux for 30 min. gave 9-(5,6-dideoxy-6-di-O-ethylphosphono- $\alpha,\beta$ ribo-hexofuranosyl)adenine (IIIa). The a-anomer of (IIb), separated from the mixture by silica gel chromatography, was converted by treatment with methanolic ammonia (18 hr.; 100°) into a separable mixture of 9-(5,6-dideoxy-6di-O-ethylphosphono- $\alpha$ -D-ribo-hexofuranosyl)adenine [ $\alpha$ -

(IIIa)] and 9-[5,6-dideoxy-6-(O-ethylphosphono)-a-D-ribohexofuranosyl]adenine  $\lceil \alpha - (IIIb) \rceil$ .

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† A Stuart-Briegleb model of this sugar indicates that such interaction would involve no steric strain.

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 <sup>2</sup> W. S. Wadsworth, jun., and W. D. Emmons, J. Amer. Chem. Soc., 1961, 83, 1733.
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have described variations of the method.
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<sup>5</sup> L. Pichat, P. Dufay, and Y. Lamorre, Compt. rend., 1964, 259, 2453.
<sup>6</sup> B. R. Baker, Ciba Foundation Symposium Chem. Biol. Purines, 1957, 120.
<sup>7</sup> H. M. Kissman and B. R. Baker, J. Amer. Chem. Soc., 1957, 79, 5594, reported a case in which a α: β anomer ratio of 3:19 was obtained. At this time they stated "it should be emphasized that experience to date indicates that anomers having the C(1)-C(2) cis configuration are not often observed; and when they are observed, they are present in only minor quantities." Since that time the universally applicable. [G. T. Rogers and T. L. Y. Ulbricht cis configuration are not often observed; and when they are observed, they are present in only minor quantities." Since that time the *trans* rule, with the addition related above, has appeared to be universally applicable. [G. T. Rogers and T. L. V. Ulbricht, J. Chem. Soc. (C), 1968, 1929, have reported that the reaction of the silver salt of hypoxanthine gives an α: β ratio of 1:4.] <sup>8</sup> E. J. Reist, R. R. Spencer, and B. R. Baker, J. Org. Chem., 1958, 23, 1958; R. F. Nutt and E. Walton, J. Medicin. Chem., 1968, 11, 151. 11, 15ľ.