(V) bromide at the temperature necessary for synthesis (*ca.* 100°) keeps the yield very low and that separation of the trimer and tetramer is very difficult to achieve.[2-5] We have found, however, that under proper conditions, phosphorus(III) bromide, bromine, and ammonium bromide react in *sym*-tetrachloroethane or *sym*-tetrabromoethane to yield the mixed phosphonitrilic bromides in yields as high or higher than the best reported for the chlorides.[6] To some extent, the latter solvent is the less effective since it suffers partial conversion to pentabromoethane.

In a typical reaction, 350 g. of bromine was added over a period of 4 days to a mixture of 300 g. of phosphorus(III) bromide and 250 g. of ammonium bromide in 450 ml. of *sym*-tetrachloroethane maintained at 110–120°. The temperature was then increased slowly and the mixture was held at 145–155° for 2–3 days. After cooling, the unused ammonium bromide was removed by filtration, and the solvent was evaporated (35–40° at 2 mm.). The resulting crude product was separated from oily homologs and sublimed *in vacuo* (130–160° at 0.05–0.5 mm.) to recover the trimeric and tetrameric phosphonitrilic bromides. The yield was 112.5 g., or 50%.[7] The trimer is present in considerably greater quantity than the tetramer.

However, if *sym*-tetrabromoethane is used as solvent and the temperature is increased, the tetramer predominates. Thus with the same quantities of reagents but with the temperature maintained at 160–175° for several days after addition of the bromine, 58.5 g. (25.7% of theoretical) of sublimed phosphonitrilic bromide containing over 50% of the tetramer was obtained, together with larger quantities of the higher homologs and some 30 g. of pentabromoethane.

Fractional sublimation was used to effect gross separation into trimer-rich (90–100° at 0.025 mm.) and tetramer-rich (130–150° at 0.025 mm.) fractions. Final separation then was achieved by chromatography using an aluminum oxide column or fractional crystallization from organic solvents.

Reaction in either solvent at still higher temperatures converts increasing quantities of the lower polymers to rubber-like substances comparable in appearance and properties to the phosphonitrilic chloride rubbers. At above 350°, these materials lose their elasticity, become brittle, and become quite stable toward boiling acids or alkalies.

In the chloride system, the monomeric adduct $PNCl_2 \cdot PCl_5$ has been obtained only by treating the trimer with phosphorus(V) chloride at 250° in a sealed tube or by allowing phosphorus(III) chloride to react with tetrasulfur tetranitride.[8] In the bromide system, the corresponding adduct $PNBr_2 \cdot PBr_5$ is isolated easily by stopping the reaction after addition of bromine and while the system is still at the lower temperature. Rapid removal of ammonium bromide by filtration, followed by cooling the remaining brown solution to 0°, gives large quantities of the crystalline, orange compound.

Anal. Calcd. for P_2NBr_7: N, 2.21; P, 9.75; Br, 88.04. Found: N, 2.41; P, 10.29; Br, 89.39.

This adduct is more stable than phosphorus(V) bromide, but it decomposes slowly on standing and hydrolyzes within a matter of minutes in water. It is insoluble in the ordinary organic solvents, but phosphorus(V) oxytrichloride, bromoform, *o*-dichlorobenzene, *sym*-tetrachloroethane, and *sym*-tetrabromoethane dissolve it with decomposition. The compound gives a distinctive X-ray diffraction pattern. When heated in *sym*-tetrachloroethane, it polymerizes to small quantities of the trimer and tetramer and large quantities of the higher homologs.

Solubility, infrared, nuclear magnetic resonance, X-ray diffraction, and chemical data will be discussed in a subsequent paper.

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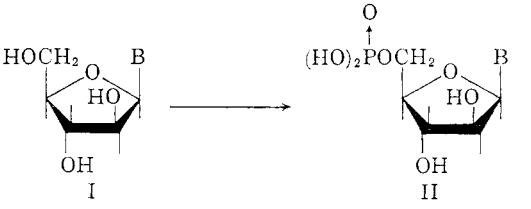
(2) A. Besson, *Compt. rend.*, **114**, 1479 (1892).
(3) W. Grimme, Dissertation, Münster (1926).
(4) H. Bode, *Z. anorg. Chem.*, **252**, 113 (1943).
(5) N. L. Paddock and H. T. Searle: "Advances in Inorganic Chemistry and Radiochemistry" (H. J. Emeléus and A. G. Sharpe, Eds.), Academic Press, New York, N. Y., Vol. I, 1959, p. 350.
(6) M. Yokoyama, *J. Chem. Soc. Japan*, **80**, 1189 (1959).
(7) Yield in the corresponding chloride system is 35–40%.[6]
(8) W. L. Groeneveld, J. H. Visser and A. M. J. H. Seuter, *J. Inorg. Nucl. Chem.*, **8**, 245 (1958).

POTENTIAL ANTICANCER AGENTS.[1] XL. SYNTHESIS OF THE β-ANOMER OF 9-(D-ARABINOFURANOSYL)-ADENINE

Sir:

Recent studies by Pizer and Cohen[2] have shown some unique, highly surprising, and very useful substrate properties of 1-(β-D-arabinofuranosyl)-uracil (I, B = uracil). This compound is phosphorylated to the nucleotide (II, B = uracil) by the enzyme that phosphorylates deoxyuridine *but not uridine*. Secondly, II (B = uracil) is methylated to the thymine nucleotide (II) by the enzyme that converts deoxyuridylic acid to thymidylic acid, an enzyme that will *not* methylate



uridylic acid. Finally, nucleoside phosphorylase will not rupture the arabinosyl-uracil bond under conditions in which the ribosyl and deoxyribosyl nucleosides of uracil are cleaved,[2] in contrast to its action on the important anticancer agent, 5-

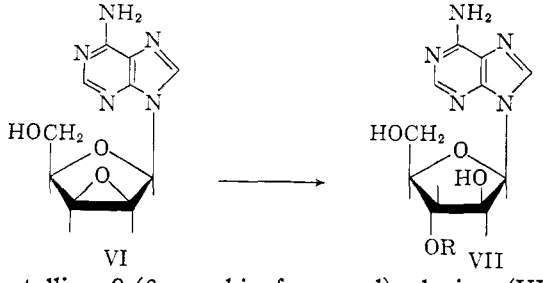
(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. SA-43-ph-1892. The opinions expressed in this paper are those of the authors and are not necessarily those of the Cancer Chemotherapy National Service Center. For the preceding paper in this series, *cf.* A. Benitez, O. P. Crews, Jr., L. Goodman and B. R. Baker, *J. Org. Chem.*, **25**, in press (1960).
(2) L. I. Pizer and S. S. Cohen, Abstr. 136th Meeting, Am. Chem. Soc., 1959, p. 9-C.

fluorodeoxyuridine,[3] which is *cleaved in vivo* with resultant decrease in biological activity.[4,5] Since nucleosides derived from β-D-arabinofuranose (I) have many of the substrate properties of 2'-deoxynucleosides, except cleavage of the base, nucleosides such as I with a fraudulent base could have useful anticancer properties.

Chemical formation of a nucleoside from 2,3,5-tri-O-acetyl-D-arabinofuranosyl bromide with the properly substituted adenine gave the *alpha*-anomer of 9-(D-arabinofuranosyl)-adenine[6] with the now predictable[7] C_1C_2-*trans* configuration. By a presumably general method that should have considerable utility for synthesis of the desired fraudulent-base nucleosides of Type I, this Communication reports the first synthesis of a 9-(D-arabinofuranosyl)-purine with the *beta*-configuration.

9-(3',5'-O-Isopropylidene-β-D-xylofuranosyl)-adenine (III)[8] with methanesulfonyl chloride in pyridine gave 9-(3',5'-O-isopropylidene-2'-O-methanesulfonyl-β-D-xylofuranosyl)-adenine (IV), m.p. 212°, in 63% yield (Found for $C_{14}H_{19}N_5O_6S$: C, 43.4; H, 4.95; N, 18.1). Deacetonation of IV with 90% aqueous acetic acid at 100° for 6 hours gave a 60% yield of 9-(2'-O-methanesulfonyl-β-D-xylofuranosyl)-adenine (V), m.p. 171–172° (Found for $C_{11}H_{15}N_5O_6S$: C, 38.4; H, 4.43; N, 20.2; S, 9.01). Treatment of V in refluxing methanolic sodium methoxide for 12 minutes resulted in an 87% yield, after purification via the picrate of VI, of the very water-soluble anhydronucleoside VI, m.p. 205–206° (Found for $C_{10}H_{11}N_5O_3$: C, 48.2· H, 4.50· N, 27.9).

When VI was heated at reflux with sodium benzoate in N,N-dimethylformamide (DMF) containing 5% water for 6 hours, a 54% crude yield of



crystalline 9-(β-D-arabinofuranosyl)-adenine (VII, R = H),[9] m.p. 257° after recrystallization, $[\alpha]^{27}D$ −5° (0.25% in water),[10] could be isolated as a hemihydrate (Calcd. for $C_{10}H_{13}N_5O_4 \cdot 0.5H_2O$: C, 43.5; H, 5.11; N, 25.4. Found: C, 43.9; H, 4.81; N, 25.5). The arabinoside (VII, R = H) was readily separable from the isomeric 9-(β-D-xylofuranosyl)-adenine[8] on paper chromatography in three solvent systems, and the crude product showed only a trace of this isomeric xyloside. The very predominant opening of VI at C_3 follows the usual pattern.[11]

The conversion of VI to VII (R = H) could also be effected in comparable yield with sodium acetate in 95% DMF but could only be obtained in trace amounts (as shown by paper chromatography) by the reaction of sodium benzoate in diethylene glycol dimethyl ether containing 5% water, under the same conditions of time and temperature as in the DMF reactions. One of the usual reagents for opening sugar epoxides, namely, potassium hydroxide,[12] caused cleavage of VI to adenine and no VII (R = H) was formed. With sodium acetate in boiling acetic acid containing acetic anhydride, VI was recovered unchanged after deacetylation.

These results suggest that a complex between DMF and the carboxylate salts is formed which enhances the nucleophilicity of the latter; this Communication, then, adds another important example of the utility of the DMF–sodium benzoate reagent.[13]

(3) R. Duschinsky, E. Pleven, J. Malbica and C. Heidelberger, Abstr. 132nd Meeting, Am. Chem. Soc., 1957, p. 19-C; M. Hoffer, R. Duschinsky, J. J. Fox and N. Yung, THIS JOURNAL, **81**, 4112 (1959), and references therein.

(4) S. S. Cohen, J. G. Flaks, H. D. Barner, M. R. Loeb and J. Lichtenstein, *Proc. Natl. Acad. Sci.*, **44**, 1004 (1958).

(5) N. K. Chaudhuri, K. L. Mukherjee and C. Heidelberger, *Biochemical Pharmacology*, **1**, 328 (1959).

(6) N. W. Bristow and B. Lythgoe, *J. Chem. Soc.*, 2306 (1959).

(7) B. R. Baker in G. E. W. Wolstenholm and C. M. O'Conner, "The Chemistry and Biology of Purines," J. and A. Churchill Ltd., London, 1957, p. 120.

(8) B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 966 (1957).

(9) In the original conversion of VI to VII, a sodium methoxide treatment was included in the processing to convert any VII (R = Bz) that may have been formed to VII (R = H). In later experiments which omitted the sodium methoxide treatment, paper chromatography of the crude product showed that only traces, if any, of the 3'-O-benzoate of VII could have been present. Evidently the first-formed benzoate VII (R = Bz) is hydrolyzed to VII (R = H) in the slightly alkaline medium.

(10) Compound VII (R = H) is only slightly soluble in water and the $[\alpha]D$ value reported in this Communication is subject to a large uncertainty. The value is being redetermined in a better solvent but the present value affords a comparison with the α-anomer which had m.p. 208° and $[\alpha]^{27}D$ +69° (1.1% in water) as the anhydrous compound.[1]

(11) For further discussion of this point, see (a) C. D. Anderson, L. Goodman and B. R. Baker, THIS JOURNAL, **81**, 898 (1959), and (b) R. E. Schaub and M. J. Weiss, *ibid.*, **80**, 4683 (1958).

(12) G. J. Robertson and W. Whitehead, *J. Chem. Soc.*, 319 (1940).

(13) (a) E. J. Reist, R. R. Spencer and B. R. Baker, *J. Org. Chem.*, **24**, 1618 (1959); (b) E. J. Reist, L. Goodman and B. R. Baker, THIS JOURNAL, **80**, 5775 (1958).

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HIGHLY STRAINED BICYCLIC SYSTEMS. III. THE STEREOCHEMISTRY AND REARRANGEMENT OF THE 1,5,5-TRIMETHYLBICYCLO[2,1,1]HEXANE-6-CARBOXYLIC ACIDS[1]

Sir:

The demonstration by Horner and Spietschka that photolysis of diazocamphor (I) leads to a 1,5,5-trimethylbicyclo[2,1,1]hexane-6-carboxylic acid (II)[2] (equation 1), has opened the way to the synthesis of a variety of interesting bicyclic systems.[3] One important feature of this work which remained to be clarified was the stereochemistry of the product. In studying a related

(1) The support of this work by the National Science Foundation and the Alfred P. Sloan Foundation is gratefully acknowledged.

(2) L. Horner and E. Spietschka, *Chem. Ber.*, **88**, 934 (1955).

(3) See, for example, J. Meinwald and P. G. Gassman, Abstracts of Papers presented at the April 1959 meeting of the American Chemical Society in Boston, p. 14-O. A fuller account of this work will soon appear in THIS JOURNAL.