–OH absorption near 3.0 μ. The dimesylate, 3.2 g. (7.5 mmoles), was treated with excess sodium azide in 2-methoxyethanol as described for the preparation of VI, affording 2.09 g. (87%) of a yellow oil whose infrared spectrum showed little or no sulfonate ester absorption. The diazide, 2.0 g. (6.23 mmoles), was reduced with excess sodium borohydride in isopropyl alcohol to furnish 1.54 g. (92%) of a sirup whose infrared spectrum showed the absence of covalent azide absorption. Acetylation of 1.50 g. of the amine mixture in pyridine containing triethylamine afforded 1.57 g. (79%) of a yellow crystalline solid whose analysis showed it to be deficient in nitrogen and to contain excess sulfur as calculated for the diamide mixture. Chromatography of 1.50 g. of the solid over silicic acid gave 0.12 g. of a fraction eluted with ethyl acetate which appeared to be mostly dibenzyl disulfide and 1.27 g. of material eluted with methanol whose infrared spectrum indicated it to be a mixture of the diamides XIII and XIV, $[\alpha]^{24.5}D$ +29.8°.

Anal. Calcd. for $C_{17}H_{24}N_2O_4S$: C, 57.9; H, 6.86; N, 7.95; S, 9.10. Found: C, 57.5; H, 6.80; N, 7.24, 7.30, S, 8.63.

Methyl 2,5-Diacetamido-2,3,5-trideoxy-α-D-*threo*-pentofuranoside (XVIII).—A stirred mixture of 1.00 g. (2.83 mmoles) of XIII, approximately 12 g. of Raney nickel[11] (thoroughly washed with dioxane), and 50 ml. of dioxane was heated at reflux for 4.5 hr., then was cooled, and filtered through Celite with adequate washing. The filtrate and the washings were evaporated *in vacuo* leaving 0.75 g. (115%) of a sirup whose infrared spectrum showed the absence of benzyl absorption near 14.3 μ. Four recrystallizations of the residue using first benzene–petroleum ether (30–60°), then ethyl acetate afforded 0.23 g. (35%) of the analytical sample, m.p. 127–132°; $[\alpha]^{24.5}D$ +32°; λ_{max}^{Nujol} 3.03, 3.27 and 6.43 (NH), 6.09 μ (amide C=O).

Anal. Calcd. for $C_{10}H_{18}N_2O_4$: C, 52.2; H, 7.88; N, 12.2. Found: C, 52.1; H, 7.88; N, 12.4.

Methyl 3,5-Diacetamido-2,3,5-trideoxy-α-D-*threo*-pentofuranoside (XIX).—Desulfurization of 1.08 g. (3.06 mmoles) of XIV using the conditions described for preparation of XVIII gave, after four recrystallizations of the residue from ethyl acetate, 0.11 g. (15%) of the analytical sample, m.p. 200–206°; $[\alpha]^{26}D$ +172° (1% in dimethyl sulfoxide); λ_{max}^{Nujol} 3.04, 3.22, 6.39 (NH), 6.05 μ (amide C=O); there was no S-benzyl absorption at 14.3 μ.

Anal. Calcd. for $C_{10}H_{18}N_2O_4$: C, 52.2; H, 7.88; N, 12.2. Found: C, 52.5; H, 7.87; N, 12.0.

Acknowledgment.—The authors wish to thank Dr. Peter Lim and his group for the infrared spectral data, optical rotations, thiol titrations, n.m.r. spectra, and paper chromatography, and Mr. O. P. Crews and staff for the large-scale preparation of intermediates.

(11) Sponge nickel catalyst, Davison Chemical Co., Cincinnati 29, Ohio.

Syntheses with Partially Benzylated Sugars. II.[1] The Anomeric 1-*O*-Benzoyl-L-arabinopyranoses and 1-*O*-Benzoyl-L-arabinofuranoses and Their Tendencies to Undergo Acyl Migration

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The four 1-*O*-benzoyl-L-arabinoses have been prepared in pure form and their behavior in aqueous pyridine studied. Under the conditions chosen, both 1-*O*-benzoyl-α-L-arabinopyranose and 1-*O*-benzoyl-α-L-arabinofuranose are stable while the corresponding anomeric esters readily undergo acyl migration to yield 2-*O*-benzoyl-L-arabinopyranose. The rate of mutarotation of 1-*O*-benzoyl-β-L-arabinofuranose in aqueous pyridine is much faster than that of 1-*O*-benzoyl-β-L-arabinopyranose; since the rate of mutarotation of 2-*O*-benzoyl-β-L-arabinopyranose in aqueous pyridine is faster than either of the preceding mutarotations, it is concluded that the rates observed actually represent the acyl migration step in each of the two cases.

In 1956 Ness and Fletcher[3] observed that the 1-*O*-benzoyl group in 1,3,5-tri-*O*-benzoyl-α-D-ribofuranose readily migrates under mildly alkaline conditions to the C-2 position, giving 2,3,5-tri-*O*-benzoyl-D-ribofuranose. The ease with which this rearrangement takes place stands in marked contrast to the stability of 1-*O*-benzoyl-β-D-glucopyranose[4] under such conditions and suggested that 1-*O*-acyl aldoses may fall into two classes, *viz.*, those with a hydroxyl group at C-2 *cis* to the 1-*O*-acyl group and a second, more stable class having a *trans* arrangement. Recent researches by various workers have tended to support this view. Lemieux and Brice[5] predicted that 1,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose ought to rearrange to 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose and Bonner[6] later showed that such a rearrangement did indeed take place.

While a variety of 1-*O*-acyl-β-D-glucopyranoses have been discovered in nature, it is significant that no α-anomers having the acyl group *cis* to the hydroxyl at C-2 have been found. The first attempt to make a representative of this class, 1-*O*-mesitoyl-α-D-glucose,[7] clearly showed that the ester of even a sterically hindered acid readily undergoes migration from the C-1 to the C-2 position in α-D-glucopyranose.[8] It was only through the reaction of ethyl 1-thio-β-D-glucopyranoside with silver mesitoate that Pedersen and Fletcher[9] finally succeeded in synthesizing 1-*O*-mesitoyl-α-D-glucopyranose, the first 1-*O*-acyl-α-D-glucopyranose. When silver benzoate was used in this reaction only 2-*O*-benzoyl-D-glucose was obtained, indicating the

(1) The paper by R. Barker and H. G. Fletcher, Jr., entitled "2,3,5-Tri-*O*-benzyl-D-ribosyl- and -L-arabinosyl bromides" [*J. Org. Chem.*, **26**, 4605 (1961)] is regarded as I of this series.

(2) Visiting Associate of the Public Health Service, 1961–1962; Faculty of Pharmaceutical Sciences, School of Medicine, Hokkaido University, Sapporo, Japan.

(3) R. K. Ness and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **78**, 4710 (1956).

(4) L. Zervas, *Ber.*, **64**, 2289 (1931).

(5) R. U. Lemieux and C. Brice, *Can. J. Chem.*, **33**, 109 (1955).

(6) W. A. Bonner, *J. Org. Chem.*, **24**, 1388 (1959), found that the methylation of 1,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose with methyl iodide in the presence of silver oxide gives methyl β-D-glucopyranoside tetraacetate in 81.2% yield. It should be noted that the anomeric tetraacetate gave the same product under these conditions but in significantly lower yield (51%), demonstrating that migration between *trans* positions may indeed take place. However, the possibility of anomerization preceding acyl migration does not seem to be excluded here.

(7) H. B. Wood, Jr., and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **78**, 2849 (1956).

(8) As far as we are aware, this represents the only known case of an O → O migration of a mesitoyl group.

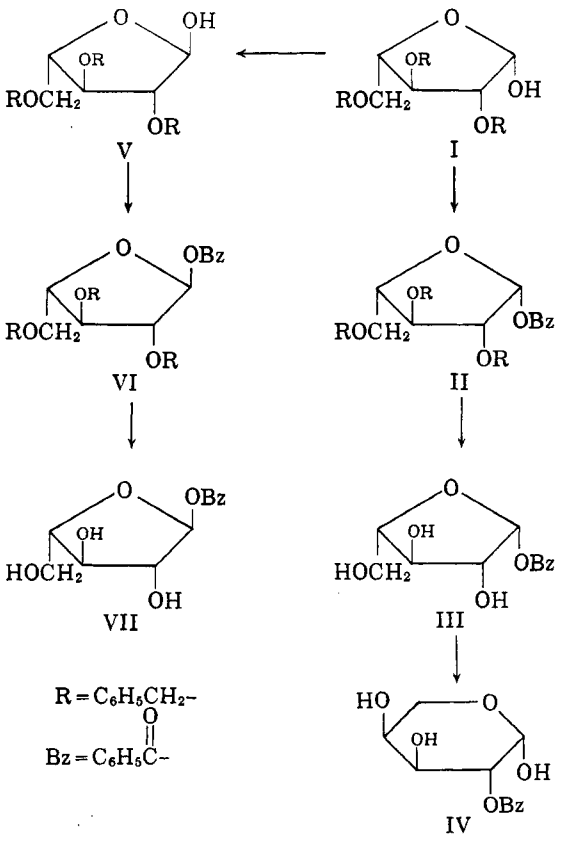
(9) C. Pedersen and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **82**, 3215 (1960).

very considerable lability to be expected with 1-*O*-benzoyl-α-D-glucopyranose.

O. T. Schmidt and his coworkers[10-12] recently have shown that both the *p*-hydroxybenzoyl and galloyl groups readily migrate from C-1 to C-2 in α-D-glucopyranose. They were able to synthesize 1-*O*-galloyl-α-D-glucopyranose through condensation of tri-*O*-benzylgalloyl chloride with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose[13] and subsequent hydrogenolysis of the benzyl groups.[14]

Inasmuch as the only anomeric pairs of 1-*O*-acylaldoses which have been studied were D-glucopyranose derivatives, it becomes of interest to examine the properties of a comparable pair of anomers in another sugar series and, particularly, of an aldofuranose. For this reason, we have undertaken the synthesis of the four possible 1-*O*-acyl-L-arabinoses.

Barker and Fletcher[1] described the synthesis of 2,3,5-tri-*O*-benzyl-β-L-arabinofuranose (I) *via* benzylation of crystalline methyl 2,3,5-tri-*O*-benzoyl-α-L-arabinofuranoside, followed by hydrolysis of the glycoside, the over-all yield from L-arabinose being approximately 27%. We have now found that I may be prepared directly from L-arabinose in 48% yield by a simple sequence of steps without the isolation of intermediates,



making this potentially valuable intermediate[15] readily available. Careful purification of I indicated that the sample originally described[1] had been most probably a mixture of anomers, the β-anomer predominating.

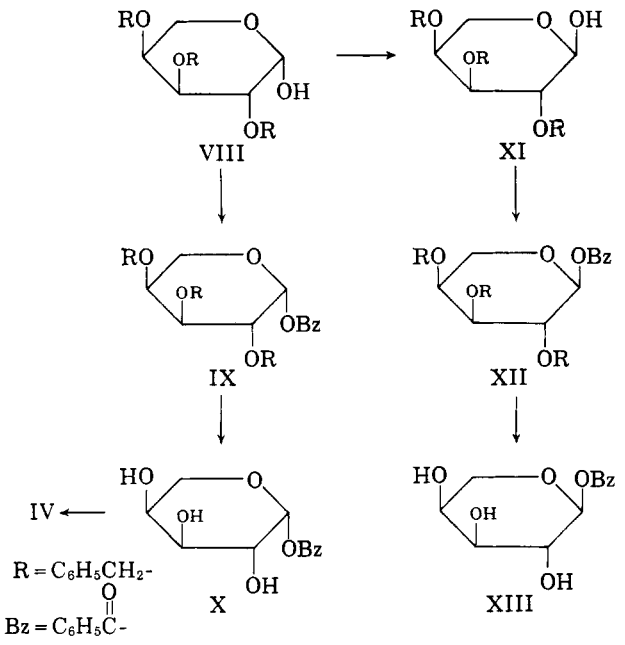
Under conditions chosen to minimize mutarotation, 2,3,5-tri-*O*-benzyl-β-L-arabinose (I) was benzoylated to give crystalline 1-*O*-benzoyl-2,3,5-tri-*O*-benzyl-β-L-arabinofuranose (II); catalytic hydrogenolysis of the benzyl groups of the latter afforded a mono-*O*-benzoylpentose which was stable in anhydrous pyridine and, on benzoylation in this solvent, was converted to the known β-L-arabinofuranose tetrabenzoate,[16] showing its structure to be 1-*O*-benzoyl-β-L-arabinofuranose (III). In 4:1 pyridine–water the *cis* ester III undergoes a rapid change which was followed polarimetrically; the rate was first order and the constant 0.026 (min., decimal logs), corresponding to a "half-life" of approximately 11.6 min. The product of the reaction was isolated in crystalline form and found to be identical with 2-*O*-benzoyl-β-L-arabinopyranose (IV), the enantiomorph of which was synthesized several years ago by Rammler and MacDonald.[17]

In anhydrous pyridine 2,3,5-tri-*O*-benzyl-β-L-arabinofuranose (I) undergoes mutarotation; subsequent removal of the pyridine, and crystallization of the residue from aqueous pyridine afforded 2,3,5-tri-*O*-benzyl-α-L-arabinose (V). Benzoylation of I after it had been allowed to mutarotate in pyridine solution gave the 1-*O*-benzoyl derivative (VI) which was hydrogenolyzed to 1-*O*-benzoyl-α-L-arabinofuranose (VII), the structure of which was confirmed by complete benzoylation to α-L-arabinofuranose tetrabenzoate.[16] As expected, the *trans* ester VII proved to be stable in both pyridine and 4:1 pyridine–water.

Successive benzylation and hydrolysis of methyl β-L-arabinopyranoside gave a crystalline tri-*O*-benzylpentose which showed a levomutarotation and is, therefore, 2,3,4-tri-*O*-benzyl-β-L-arabinopyranose (VIII). When benzoylated under conditions chosen to minimize prior anomerization, VIII afforded a crystalline benzoate IX which was debenzylated in the usual fashion to yield 1-*O*-benzoyl-β-L-arabinopyranose (X); complete benzoylation converted X to β-L-arabinopyranose tetrabenzoate.[18] In 4:1 pyridine–water 1-*O*-benzoyl-β-L-arabinopyranose (X) mutarotated very slowly, the first-order rate averaging 0.00016 (min., decimal logs), corresponding to a "half-life" of 1881 min. The product was isolated and identified as 2-*O*-benzoyl-β-L-arabinopyranose (IV).

Attempts to obtain 2,3,4-tri-*O*-benzyl-α-L-arabinopyranose (XI) in crystalline form were unsuccessful. However, benzoylation of an equilibrated 2,3,4-tri-*O*-benzyl-L-arabinopyranose (VIII + XI) readily gave 1-*O*-benzoyl-2,3,4-tri-*O*-benzyl-α-L-arabinopyranose (XII). Hydrogenolysis of the benzyl groups in XII afforded 1-*O*-benzoyl-α-L-arabinopyranose (XIII); the ester proved to be stable in 4:1 pyridine–water.

(10) O. T. Schmidt and H. Reuss, *Ann.*, **649**, 137 (1961).
(11) O. T. Schmidt and H. Schmadel, *ibid.*, **649**, 149 (1961).
(12) O. T. Schmidt and H. Schmadel, *ibid.*, **649**, 157 (1961).
(13) O. T. Schmidt, T. Auer, and H. Schmadel, *Ber.*, **93**, 556 (1960).
(14) In a recent paper [*Can. J. Chem.*, **40**, 2035 (1962)] J. J. Willard stated that "No reports have been found, in the literature, in which benzyl ether groups were removed by catalytic reduction from a carbohydrate also carrying ester groups. Since no other method is available for removal of benzyl ethers without loss of ester groups, the benzyl ether does not appear to be a useful blocking group in the synthesis of partial esters of the methyl glucosides." The work of Schmidt, Auer, and Schmadel (ref. 13) as well as that reported here clearly refutes this statement. Indeed, it is now obvious that *O*-benzyl groups may be cleaved in the presence of comparatively labile ester linkages.
(15) The utility of such compounds has been demonstrated by C. P. J. Glaudemans and H. G. Fletcher [*J. Org. Chem.*, **28**, 3004 (1963)] who employed the enantiomorph of I to synthesize 9-β-D-arabinofuranosyladenine, a type of substance which is difficultly accessible by other means.
(16) R. K. Ness and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **80**, 2007 (1958).
(17) D. H. Rammler and D. L. MacDonald, *Arch. Biochem. Biophys.*, **78**, 359 (1958).
(18) H. G. Fletcher, Jr., and C. S. Hudson, *J. Am. Chem. Soc.*, **69**, 1145 (1947).



In passing, it may be noted that each of the L-arabinofuranose derivatives described here is more levorotatory than the corresponding L-arabinopyranose derivative of the same anomeric configuration, in agreement with the generalization made recently by Bhattacharya, Ness, and Fletcher.[19]

Discussion

The conversions of 1-*O*-benzoyl-β-L-arabinopyranose (X) and of 1-*O*-benzoyl-β-L-arabinofuranose (III) to 2-*O*-benzoyl-L-arabinopyranose (IV) are obviously multi-step processes. In both cases the first step is acyl migration, C-1 to C-2. With the pyranose ester X, acyl migration is followed by anomerization of the form of 2-*O*-benzoyl-L-arabinose released (presumably β). With the furanose ester (III), the 2-*O*-benzoyl-L-arabinofuranose initially released (presumably β) may anomerize before ring expansion to 2-*O*-benzoyl-L-arabinopyranose (IV) which must then come to anomeric equilibrium. Since the over-all rate of mutarotation of the 1-*O*-benzoyl-β-L-arabinopyranose (X) is much slower than that of its furanose analog III, it seems reasonable to assume that the rate-controlling step is the acyl migration itself. However, with the faster reaction (III → IV) there is the possibility that the rate-controlling step is actually the anomerization of the 2-*O*-benzoyl-L-arabinopyranose (IV).[20] To settle this point, the rate of mutarotation of 2-*O*-benzoyl-L-arabinopyranose in aqueous pyridine was measured and found to be significantly faster (k = 0.064, $t_{1/2}$ = 4.7 min.) than the conversion of III to IV in the same solvent mixture.[21] It is, therefore, concluded that the acyl migration itself is most probably the rate-controlling step in the conversion of III to IV.

(19) A. K. Bhattacharya, R. K. Ness, and H. G. Fletcher, Jr., *J. Org. Chem.*, **28**, 428 (1963).

(20) It is assumed that the anomerization of 2-*O*-benzoyl-L-arabinofuranose and the ring expansion are comparatively rapid reactions.

(21) It may be appropriate to remind the reader that the rate of the conversion of A to A + B is the same as the rate of conversion of B into A + B in a system A ⇌ B, irrespective of the proportions of A and B at equilibrium. Thus the (as yet unknown) 2-*O*-benzoyl-α-L-arabinopyranose would mutarotate at the same rate as its β-anomer described here. The argument put forward above is therefore valid irrespective of which anomer of 2-*O*-benzoyl-L-arabinopyranose is an intermediate in the rearrangement of either III or IX.

It seems possible that a study of the relative rates of migration of various types of acyl groups in a given sugar as well as a study of the relative rates of migration of a given acyl group in a variety of aldoses might lead to interesting generalizations.

Experimental[22]

2,3,5-Tri-*O*-benzyl-β-L-arabinofuranose (I) from L-Arabinose.—Thirty grams of powdered L-arabinose was added to a mixture of 600 ml. of anhydrous methanol and 15 g. of Drierite and the suspension, after the addition of 4.5 ml. of concentrated sulfuric acid, was stirred at room temperature for 5 hr. The reaction mixture, then being devoid of reducing power, was filtered and the filtrate passed through a column containing 150 ml. of IR-45, the column being washed with 400 ml. of methanol. The combined solution and washings were concentrated *in vacuo* to a heavy sirup which was diluted with 50 ml. of freshly purified tetrahydrofuran and reconcentrated (35–40° bath). Freshly purified tetrahydrofuran (400 ml.) was added and the solution treated with 30 g. of Drierite, 156 g. of commercial powdered potassium hydroxide,[23] and 200 ml. of benzyl chloride. The mixture was stirred under gentle reflux overnight, cooled, filtered through a thin bed of Filter-Cel, and concentrated *in vacuo*, finally at *ca.* 1 mm. and 100° (bath). The crude sirupy methyl 2,3,5-tri-*O*-benzyl-L-arabinofuranoside mixture was dissolved in 400 ml. of glacial acetic acid and the solution diluted with 60 ml. of 6 *N* hydrochloric acid. It was heated at 65° for 1.25 hr., concentrated *in vacuo* to one-third its volume and poured into 1500 ml. of a mixture of ice and water. After seeding, the mixture was left at 5° overnight, the aqueous layer then being decanted from the partially crystalline mass which was dissolved in 200 ml. of dichloromethane. The solution was washed with cold aqueous sodium bicarbonate solution, dried with magnesium sulfate, filtered through a thin bed of decolorizing carbon, and concentrated *in vacuo* to a thin sirup. This residue, dissolved in 200 ml. of cyclohexane, seeded and left 1 hr. at room temperature and then at 5° overnight, afforded 40.1 g. (48%) of 2,3,5-tri-*O*-benzyl-β-L-arabinofuranose melting at 88–89°. In 9:1 (v./v.) dioxane–water (*c* 2.0) it gave $[\alpha]^{20}D$ +27.1° (2 min.) → −11.6° (20 hr., constant); in dichloromethane it showed $[\alpha]^{20}D$ +6.5° (*c* 4.25).

2,3,5-Tri-*O*-benzyl-α-L-arabinofuranose (V).—2,3,5-Tri-*O*-benzyl-β-L-arabinofuranose (2.9939 g.) in a 1.5-dm. polarimeter tube was treated with 25 ml. of dry pyridine. Solution was almost instantaneous, the observed rotation going from $[\alpha]^{20}D$ +8.29° to −2.12° (constant) in 328 min. After 8 hr. the solvent was removed *in vacuo* (40° bath); on standing, the sirupy residue crystallized completely after 6 hr. It was redissolved in 3 ml. of pyridine, the solution diluted with 3 ml. of water and the mixture (two layers) kept at −5° for 1 week to give a microcrystalline powder, m.p. 78–80° and $[\alpha]^{20}D$ −4.52° in dichloromethane (*c* 3.49).

Anal. Calcd. for $C_{26}H_{28}O_5$ (420.48): C, 74.26; H, 6.71. Found: C, 74.53; H, 6.77.

The infrared spectrum of the compound appeared to be indistinguishable from that of its β-anomer.

1-*O*-Benzoyl-2,3,5-tri-*O*-benzyl-β-L-arabinofuranose (II).—To a mixture of 45 ml. of dry pyridine and 2.5 ml. of benzoyl chloride which had been cooled to −15° was added (in small portions, with stirring) 5.6 g. of 2,3,5-tri-*O*-benzyl-β-L-arabinofuranose. After the addition was complete, the mixture was stirred for 1 hr. at room temperature and left at room temperature overnight. The excess benzoyl chloride was destroyed by the dropwise addition of 5 ml. of water and, 30 min. later, the reaction mixture was diluted with dichloromethane. After washing successively with cold water, 3 *N* sulfuric acid and cold half-saturated aqueous sodium bicarbonate the solution was dried with sodium sulfate and concentrated *in vacuo*. The residue, dissolved in 30 ml. of warm isopropyl ether and seeded,[24] gave long, colorless needles (5.4 g., 77%). Recrystallized three times from methanol (10 parts) the pure product was obtained; m.p. 48°, $[\alpha]^{20}D$ +54.6° (*c* 2.98, CH_2Cl_2).

Anal. Calcd. for $C_{33}H_{32}O_6$ (524.59): C, 75.55; H, 6.15. Found: C, 75.75; H, 6.30.

(22) Melting points are corrected.

(23) Hooker Chemical Corp., Niagara Falls, N. Y.

(24) Seeds were obtained by adding pentane to a portion of the solution.

1-*O*-Benzoyl-2,3,5-tri-*O*-benzyl-α-L-arabinofuranose (VI).—2,3,5-Tri-*O*-benzyl-β-L-arabinofuranose (40 g.) was dissolved in 350 ml. of dry pyridine and the solution kept at 20° until mutarotation had ceased. It was then cooled to −15° and, while stirred, treated dropwise with 15 ml. of benzoyl chloride. Stirring was continued at −15° for 1.25 hr. and the solution left at room temperature for 18 hr. Water (10 ml.) was added dropwise to the chilled solution to decompose the excess benzoyl chloride; the mixture was then diluted with dichloromethane and washed successively with cold 3 *N* sulfuric acid and aqueous sodium bicarbonate. Moisture was removed with sodium sulfate and the solution concentrated *in vacuo* (40° bath) to leave a residue (49 g., 98%) which crystallized completely. Recrystallized from 250 ml. of warm isopropyl ether the product (28 g., 56%) melted at 61–63° and showed $[\alpha]^{20}D$ −51.1° in dichloromethane (*c* 2.94).

Anal. Calcd. for $C_{33}H_{32}O_6$ (524.59): C, 75.55; H, 6.15. Found: C, 75.33; H, 6.38.

The same product was obtained in another experiment through the benzoylation of 2,3,5-tri-*O*-benzyl-α-L-arabinofuranose at a low temperature.

1-*O*-Benzoyl-α-L-arabinofuranose (VII).—A solution of 3.41 g. of 1-*O*-benzoyl-2,3,5-tri-*O*-benzyl-α-L-arabinofuranose in 200 ml. of ethyl acetate was treated with 0.4 g. of 10% palladium on charcoal[25] and the suspension was shaken with hydrogen at room temperature (25°) and pressure. The theoretical amount of hydrogen (476 ml.) was absorbed in 35 min. After removal of the catalyst, the solution was concentrated *in vacuo* to give a sirup which, dissolved in 20 ml. of dichloromethane, gave 1.5 g. (91%) of crystalline product. Recrystallized from 10 parts of boiling ethyl acetate, the ester melted at 130–131° and showed $[\alpha]^{20}D$ −93.2° in dry pyridine (*c* 2.31).

Anal. Calcd. for $C_{12}H_{14}O_6$ (254.23): C, 56.69; H, 5.55. Found: C, 56.70; H, 5.55.

1-*O*-Benzoyl-α-L-arabinofuranose failed to mutarotate in anhydrous pyridine solution over the course of 4.5 hr.; when the pyridine solution was diluted with a quarter of its volume of water no mutarotation could be observed over the course of 24 hr. and, thereafter, unchanged 1-*O*-benzoyl-α-L-arabinofuranose was recovered.

A sample (0.5 g.) of 1-*O*-benzoyl-α-L-arabinofuranose was benzoylated in conventional fashion with benzoyl chloride in pyridine solution to give from ethanol 0.9 g. (81%) of **α-L-arabinofuranose tetrabenzoate** melting at 117–121° and showing $[\alpha]^{20}D$ −25.1° in chloroform (*c* 2.33). Ness and Fletcher[16] reported m.p. 117–121° and $[\alpha]^{20}D$ +27.9° (chloroform) for the enantiomorph of this compound.

1-*O*-Benzoyl-β-L-arabinofuranose (III).—A solution of 5.27 g. of 1-*O*-benzoyl-2,3,5-tri-*O*-benzyl-β-L-arabinofuranose in 300 ml. of ethyl acetate was reduced catalytically in the presence of 0.673 g. of 10% palladium-on-charcoal at room temperature (27°) and atmospheric pressure. The theoretical amount of hydrogen (735 ml.) was absorbed during 1.75 hr. The catalyst was removed by filtration and the solution concentrated *in vacuo* (40° bath) to 30 ml.; colorless needles formed spontaneously and, after storage at −5° overnight, were removed, 2 g. (78%). Recrystallized from boiling ethyl acetate, the 1-*O*-benzoyl-β-L-arabinofuranose melted at 140–143° and showed $[\alpha]^{20}D$ +59.8° in dry pyridine (*c* 1.98).

Anal. Calcd. for $C_{12}H_{14}O_6$ (254.23): C, 56.69; H, 5.55. Found: C, 56.58; H, 5.99.

A sample (0.5 g.) of this ester was benzoylated in conventional fashion with benzoyl chloride in pyridine solution at −10° to give, from ethanol, 0.9 g. (81%) of **β-L-arabinofuranose tetrabenzoate** melting at 121–122° and showing $[\alpha]^{20}D$ +94.1° in chloroform (*c* 2.23). Ness and Fletcher[16] reported m.p. 120–122° and $[\alpha]^{20}D$ −94.0° (chloroform) for the D-form.

2-*O*-Benzoyl-β-L-arabinopyranose (IV) from 1-*O*-Benzoyl-β-L-arabinofuranose (III).—To 0.1065 g. of pure 1-*O*-benzoyl-β-L-arabinofuranose in a 1.5-dm. all glass polarimeter tube was added 10 ml. of anhydrous pyridine. As soon as solution was complete, the solution was diluted with 2.50 ml. of water and the resulting mutarotation observed. The changing specific rotation and first-order reaction constants calculated therefrom are given in Table I. Based on an average reaction rate of 0.026 the "half-life" of the reaction was approximately 11.6 min.

(25) In subsequent work the palladium black, made by the reduction (with hydrogen) of palladium chloride in methanol solution according to the method of O. T. Schmidt and W. Staab [*Ber.*, **87**, 393 (1954)], was found markedly superior to all other palladium catalysts for such debenzylations.

TABLE I

MUTAROTATION OF 1-*O*-BENZOYL-β-L-ARABINOFURANOSE IN AQUEOUS PYRIDINE

t, min.	$[\alpha]^{20}D$[a]	*k*, min., decimal logs
0	73 (extrapolated)	...
4	82	0.023
5	84	.023
5.5	85	.023
7	89	.026
9	93	.027
14	101	.028
15	103	.029
24	111	.030
44	117	.027
79	120	...
100	120	...

[a] Uncorrected for the small increase in volume caused by the solute.

In an experiment, essentially identical with the preceding rate measurement, using 0.393 g. of 1-*O*-benzoyl-β-L-arabinofuranose, the solution was concentrated *in vacuo* (40° bath) when mutarotation had ceased. The residual sirup was dissolved in a mixture of 5 ml. of ethyl acetate and 3 ml. of pentane and the solution kept at −5° overnight to give short needles. Recrystallized from 5 ml. of warm ethyl acetate, the product (0.3 g., 76%) melted at 133–135° and showed $[\alpha]^{20}D$ +145.4 → +102.5° in methanol (*c* 1.29). Rammler and MacDonald[17] reported m.p. 132–133° and $[\alpha]^{23}D$ −152 → −100° (methanol) for 2-*O*-benzoyl-β-D-arabinopyranose.

Anal. Calcd. for $C_{12}H_{14}O_6$ (254.23): C, 56.69; H, 5.55. Found: C, 56.82; H, 5.77.

An authentic specimen of 2-*O*-benzoyl-β-L-arabinopyranose, prepared through the hydrogenolysis of benzyl 2-*O*-benzoyl-β-L-arabinopyranoside,[17] failed to depress the melting point of the product obtained through the rearrangement of 1-*O*-benzoyl-β-L-arabinofuranose.

The mutarotation of 2-*O*-benzoyl-β-L-arabinopyranose was measured as follows. A sample (33.6 mg.) of the crystalline ester in a 1-dm. polarimeter tube was dissolved in 3.00 ml. of anhydrous pyridine. Over the course of 4 min. the rotation (2.24°) was constant. Water (0.75 ml.) was then added and the mutarotation observed at 20°. The specific rotations and first-order rate constants are given in Table II.

TABLE II

MUTAROTATION OF 2-*O*-BENZOYL-β-L-ARABINOPYRANOSE IN AQUEOUS PYRIDINE

t, min.	$[\alpha]^{20}D$[a]	*k*, min., decimal logs
0	157 (extrapolated)	...
0.5	155	0.051
3	146	.059
5	142	.052
6	137	.068
7	134	.075
9	132	.068
11	129	.072
13	128	.070
31	124	...

[a] Uncorrected for the small increase in volume caused by the solute and assuming that the final volume was 3.75 ml. Based on an average rate of 0.064, $t_{1/2}$ was 4.7 min.

2,3,4-Tri-*O*-benzyl-β-L-arabinopyranose (VIII).—Pure methyl β-L-arabinopyranoside[26] (44.5 g.), powdered potassium hydroxide[23] (212 g.), and pure tetrahydrofuran (543 ml.) were combined and treated with 271 ml. of benzyl chloride. The mixture was stirred under reflux for 5.5 hr., cooled, and filtered through Filter-Cel which was thereafter washed with dichloromethane. The combined filtrate and washings were concentrated *in vacuo*, finally being held at 140° (bath) and 0.01-mm. pressure. The

(26) C. S. Hudson, *J. Am. Chem. Soc.*, **45**, 265 (1925).

crude, pale yellow methyl 2,3,4-tri-*O*-benzyl-β-L-arabinopyranoside (110 g., 94%) was dissolved in 2.2 l. of glacial acetic acid and the solution diluted with 880 ml. of 2 *N* hydrochloric acid. After being heated at 80° for 16 hr. the reaction mixture was cooled and poured into 18 l. of ice–water, seeded[27], and left at +5° until crystallization appeared to be complete (2 weeks). The 50.0 g. of tan solid was dissolved in 300 ml. of hot isopropyl ether, the solution filtered through a thin layer of Darco X, and left at room temperature, 54.2 g. (48%), m.p. 71–79°, $[\alpha]^{20}D$ +93.2° (*c* 0.84 in 9:1 dioxane–water, 3 min.). Recrystallized from 6.8 parts of warm cyclohexane, the 2,3,4-tri-*O*-benzyl-β-L-arabinopyranose was obtained in pure form as long, fine needles, m.p. 83–86°. In 9:1 dioxane–water (v./v.), containing a trace of ammonia the substance showed $[\alpha]^{20}D$ +92.2° (3.5 min.) → +87.6° (3 hr.) (*c* 0.97); in dichloromethane (*c* 1.76) the substance showed $[\alpha]^{20}D$ +66.5° → +51.1° (2 days).

Anal. Calcd. for $C_{26}H_{28}O_5$ (420.48): C, 74.26; H, 6.71. Found: C, 74.45; H, 6.95.

1-*O*-Benzoyl-2,3,4-tri-*O*-benzyl-β-L-arabinopyranose (IX).—To a mixture of 3.5 ml. of benzoyl chloride and 30 ml. of dry pyridine which was kept at 0° was added 10.0 g. of 2,3,4-tri-*O*-benzyl-β-L-arabinopyranose. The mixture was allowed to warm to room temperature and, after 1 hr., was worked up in the usual way. When the purified sirupy product was dissolved in 50 ml. of warm methanol crystallization was spontaneous, 10.4 g. (83%), m.p. 81–83°, $[\alpha]^{20}D$ +129° (CH_2Cl_2, *c* 0.40). A second crop (1.67 g.) proved to be crude 1-*O*-benzoyl-2,3,4-tri-*O*-benzyl-α-L-arabinopyranose. Recrystallization of the first crop from isopropyl ether, cyclohexane, isopropyl ether and, finally from methanol yielded pure 1-*O*-benzoyl-2,3,4-tri-*O*-benzyl-β-L-arabinopyranose as clear, stubby prisms, m.p. 82–83°, $[\alpha]^{20}D$ +127.2° (CH_2Cl_2, *c* 0.91).

Anal. Calcd. for $C_{33}H_{32}O_6$ (524.59): C, 75.55; H, 6.15. Found: C, 75.85; H, 6.33.

1-*O*-Benzoyl-2,3,4-tri-*O*-benzyl-α-L-arabinopyranose (XII).—2,3,4-Tri-*O*-benzyl-β-L-arabinopyranose (15.5 g.) was dissolved in 80 ml. of dioxane, the solution treated with a little dilute aqueous ammonia and then diluted to 100 ml. with water. After 2 days at 20° the solution had ceased to mutarotate; it was then freeze-dried to give a sirup which was diluted with 15 ml. of pyridine. The solvent was removed *in vacuo* at less than room temperature and the amorphous residue diluted with 50 ml. of pyridine. The solution was cooled to below 0° and treated with 10 ml. of benzoyl chloride. After being allowed to warm slowly to room temperature the reaction mixture was worked up in the customary manner to give a stiff sirup which was dissolved in 300 ml. of boiling methanol. On standing at room temperature the solution deposited 7.2 g. of nearly pure 1-*O*-benzoyl-2,3,4-tri-*O*-benzyl-α-L-arabinopyranose; a second crop (4.0 g.), obtained by evaporation of the mother liquor was less pure, while a third crop (6.9 g.) proved to be largely the β-anomer. In separating the two anomers advantage was taken of the fact that the α-anomer is comparatively insoluble in methanol while the β-anomer is comparatively insoluble in isopropyl ether. In this fashion 9.1 g. (47%) of nearly pure α-anomer was obtained. One further recrystallization from methanol afforded the pure product, m.p. 105°, $[\alpha]^{20}D$ −31.5° (CH_2Cl_2, *c* 0.82).

Anal. Calcd. for $C_{33}H_{32}O_6$ (524.59): C, 75.55; H, 6.15. Found: C, 75.49; H, 6.29.

1-*O*-Benzoyl-α-L-arabinopyranose (XIII).—Palladium chloride (0.6 g.) was suspended in ethyl acetate and reduced with hydrogen at room temperature. When the reduction was complete the catalyst was washed with ethyl acetate by decantation and a solution of 1-*O*-benzoyl-2,3,4-tri-*O*-benzyl-α-L-arabinopyranose (2.97 g.) in a mixture of 90 ml. of ethyl acetate and 10 ml. of methanol added. Stirred vigorously at room temperature, the mixture absorbed the theoretical amount of hydrogen in 4 hr. After removal of the catalyst, the solution was concentrated *in vacuo* at room temperature to a sirup. The sirup was diluted with 20 ml. of ethyl acetate and the solution reconcentrated in the same fashion. From 3 ml. of ethyl acetate the product slowly crystallized as very fine needles, 0.72 g. (48%), m.p. 122–125°. A second crop (0.3 g., m.p. 113–125°) raised the total yield to 68%. Recrystallization of the first crop from ethyl acetate afforded pure 1-*O*-benzoyl-α-L-arabinopyranose, m.p. 123–125°, $[\alpha]^{20}D$ +4.1° (methanol, *c* 0.86). In anhydrous pyridine (*c* 1.62) the pure ester showed $[\alpha]^{20}D$ −6.2°. When the solution was diluted with a quarter of its volume of water the rotation became $[\alpha]^{20}D$ +6.2°,[28] no mutarotation being observed over the course of 48 min.

Anal. Calcd. for $C_{12}H_{14}O_6$ (254.23): C, 56.69; H, 5.55. Found: C, 56.79; H, 5.81.

A sample of the 1-*O*-benzoyl-α-L-arabinopyranose was benzoylated in conventional fashion to give α-L-arabinopyranose tetrabenzoate in 34% yield, m.p. 159°, $[\alpha]^{20}D$ +114.0° (chloroform, *c* 1.08). Fletcher and Hudson[18] reported m.p. 160–161° and $[\alpha]^{20}D$ +114.1° (chloroform) for this substance.

1-*O*-Benzoyl-β-L-arabinopyranose (X).—1-*O*-Benzoyl-2,3,4-tri-*O*-benzyl-β-L-arabinopyranose (4.04 g.), dissolved in a mixture of 44 ml. of methanol and 44 ml. of ethyl acetate, was added to palladium which had been freshly made by the reduction of 0.43 g. of palladium chloride in the same solvent mixture. Stirred vigorously at room temperature, the mixture absorbed the theoretical amount of hydrogen in 3 hr. The catalyst was removed by filtration and the solution concentrated *in vacuo* at room temperature to a dry crystalline residue. Recrystallized at room temperature from a mixture of methanol and ethyl acetate, the product was obtained as elongated rectangular plates, 1.75 g. (89%), m.p. 136–143°, $[\alpha]^{20}D$ +173° (methanol, *c* 0.55). Recrystallized from warm acetone, the 1-*O*-benzoyl-β-L-arabinopyranose melted at 134–150° and showed $[\alpha]^{20}D$ +175° (methanol, *c* 0.82). Further recrystallization failed either to narrow the melting point range or alter the specific rotation.

Anal. Calcd. for $C_{12}H_{14}O_6$ (254.43): C, 56.69; H, 5.55. Found: C, 56.82; H, 5.57.

Benzoylation of a sample of the 1-*O*-benzoyl-β-L-arabinopyranose in the usual fashion afforded β-L-arabinopyranose tetrabenzoate in 67% yield, m.p. 176°, $[\alpha]^{20}D$ +321.9° (chloroform, *c* 1.38). Wolfrom and Christman[29] reported m.p. 173–174° and $[\alpha]^{20}D$ +325° (chloroform) for β-L-arabinopyranose tetrabenzoate.

2-*O*-Benzoyl-β-L-arabinopyranose (IV) from 1-*O*-Benzoyl-β-L-arabinopyranose (X).—1-*O*-Benzoyl-β-L-arabinopyranose (0.3308 g.), dissolved in pyridine to a total volume of 10.0 ml., showed $[\alpha]^{20}D$ +164°, unchanged over the course of 11 min. Water (2.5

TABLE III

MUTAROTATION OF 1-*O*-BENZOYL-β-L-ARABINOPYRANOSE IN AQUEOUS PYRIDINE

t, min.	$[\alpha]^{20}D$[a]	*k*, min., decimal logs
0	158	.....
75	157	0.00017
120	156	.00013
183	155	.00018
285	154	.00018
475	152	.00017
640	150	.00018
1220	145	.00017
1611	142	.00017
2045	140	.00016
2697	137	.00015
4305	131	.00015
6000	128	.00014
7500	127	.00013
9985	125	.00014
11455	124	.....

[a] Assuming the volumes were additive.

(27) Seeds were initially obtained by chromatographing a sample of the sirupy material on neutralized Alcoa alumina, eluting with benzene–ether (1:1), and evaporating the eluate *in vacuo*. A sample of the crude hydrolysate was freed of acid at this point and found to give a negligible quantity of 2,3,4-tri-*O*-benzyl-β-L-arabinopyranose. Since it showed ester carbonyl (as well as hydroxyl) absorption in the infrared region, the sample was treated briefly with sodium methoxide in methanol; a substantial quantity of 2,3,4-tri-*O*-benzyl-β-L-arabinopyranose was then isolated. On the basis of this evidence, it seems likely that some 1-*O*-acetyl-2,3,4-tri-*O*-benzyl-L-arabinopyranose is formed during the hydrolysis and that this ester is subsequently hydrolyzed during the extended period after the reaction mixture is diluted with the very large proportion of water.

(28) It is assumed that the volumes were additive. No satisfactory explanation of this reversal of the sign of rotation can be made at this juncture. Concentration of the aqueous pyridine solution led to the isolation of unchanged 1-*O*-benzoyl-α-L-arabinopyranose.

(29) M. L. Wolfrom and C. C. Christman, *J. Am. Chem. Soc.*, **58**, 39 (1936).

ml.) was then added and the mutarotation observed at 20°. The specific rotations and first-order rate constants are given in Table III. Based on an average rate of 0.00016, the "half-life" of the reaction was 1881 min.

When mutarotation had ceased, the solvent was removed *in vacuo* to give a sirup which was crystallized from ethyl acetate–pentane. The short, colorless needles thus obtained were recrystallized from the same solvent mixture 0.2 g. (66%), m.p. 133–135°, $[\alpha]^{20}D$ +145.4° → +102.5° (methanol, *c* 1.27). These values agree with those reported earlier in this paper for 2-*O*-benzoyl-β-L-arabinopyranose.

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Syntheses with Partially Benzylated Sugars. III.[1] A Simple Pathway to a "*cis*-Nucleoside," 9-β-D-Arabinofuranosyladenine (Spongoadenosine)

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Condensation of 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride with methanol leads predominantly to methyl 2,3,5-tri-*O*-benzyl-β-D-arabinofuranoside. Condensation of the same halide with N-benzoyladenine and subsequent removal of the protecting groups readily gives 9-β-D-arabinofuranosyladenine, a type of glycoside which is difficultly accessible by other means.

The most generally applicable method for the synthesis of glycosides is that which Koenigs and Knorr[3] devised over sixty years ago. However, the condensation of a fully acylated glycosyl halide with a potential aglycon is normally a limited process in the sense that it leads to a product in which the aglycon is *trans* to the acyloxy group at C-2. With an acylated glycosyl halide bearing a halogen at C-1 *cis* to an acyloxy group at C-2, simple inversion predominates; with a *trans*-halide, participation of the acyloxy group at C-2 in the displacement of the halogen results either in no net inversion or formation of an ortho ester derivative.

A wide variety of special methods have been devised for the synthesis of 1,2-*cis*-glycosides. Two of these methods deserve particular attention. In the first, the configuration of C-2 in a *trans*-glycoside is inverted by one means or other. The ingenious synthesis of 9-β-D-arabinofuranosyladenine (V) from 9-β-D-xylofuranosyladenine, described by Reist, Benitez, Goodman, Baker, and Lee,[4] illustrates this approach. A second method involves the use of a glycosyl halide in which the hydroxyl group at C-2 is masked with a group which does not participate in the displacement of the halogen at C-1. The synthesis of the *cis*-linked disaccharide isomaltose (6-*O*-α-D-glucopyranosyl-D-glucose) through 3,4,6-tri-*O*-acetyl-2-*O*-nitro-β-D-glucopyranosyl chloride by Wolfrom, Pittet, and Gillam[5] is of this type.

While the two aforementioned methods are eminently successful in some sugar series, their success depends, ultimately, on selective substitutions at C-2 of aldose derivatives; such selective substitution always involves a number of steps and is not practicable with some aldoses. The concept of using a glycosyl halide, *fully* substituted with the nonparticipating benzyl group has many attractive features inasmuch as hydroxyl groups are readily masked as benzyl ethers and the benzyl groups readily cleaved by catalytic hydrogenation. Exploratory work by Barker and Fletcher[6] recently showed that 2,3,5-tri-*O*-benzyl-D-ribofuranosyl and 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl bromides could be prepared, albeit only as highly reactive sirups. We wish now to describe the preparation of the more stable 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride (III) and the studies of this substance which have led to the practicable synthesis of a 1,2-*cis*-nucleoside.

2,3,5-Tri-*O*-benzyl-β-D-arabinofuranose (I), readily preparable from D-arabinose by the improved procedure which Tejima and Fletcher[1] described for its enanthiomorph, was converted into 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride (III) either directly with hydrogen chloride in the presence of a desiccant or indirectly through the action of hydrogen chloride on a mixture of anomers of 2,3,5-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-D-arabinofuranose (II).[7] The chloride III proved to be a nearly colorless sirup, markedly more stable than the corresponding bromide.[6] On condensation with methanol in the presence of sodium methoxide, it afforded a sirupy mixture of the anomeric methyl 2,3,5-tri-*O*-benzyl-D-arabinofuranosides; vapor phase chromatography showed that the β-anomer (a 1,2-*cis*-glycoside) predominated.

In order to ascertain whether other β-D-arabinofuranosides could be made by this process, a purine[8] was used as an aglycon since there is considerable current interest in the biochemical properties of nucleosides containing the β-D-arabinofuranosyl moiety,[9] and adequate special

(1) Paper II of this series: S. Tejima and H. G. Fletcher, Jr., *J. Org. Chem.*, 2999 (1963).

(2) Visiting Associate of the Public Health Service, 1962–1963.

(3) W. Koenigs and E. Knorr, *Sitzber. Math. Naturw. Kl. Bayer. Akad. Wiss. Muenchen*, **30**, 108 (1900); *Ber.*, **34**, 957 (1901).

(4) E. J. Reist, A. Benitez, L. Goodman, B. R. Baker, and W. W. Lee, *J. Org. Chem.*, **25**, 3274 (1962).

(5) M. L. Wolfrom, A. O. Pittet, and I. C. Gillam, *Proc. Natl. Acad. Sci. U. S.*, **45**, 700 (1961).

(6) R. Barker and H. G. Fletcher, Jr., *J. Org. Chem.*, **26**, 4605 (1961).

(7) It should be noted, however, that the 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride (III) differed in certain properties depending upon whether it was prepared from I or II. The available evidence appears to indicate that this difference arises from differing proportions of anomers in the two preparations of III; see the Experimental.

(8) The suggestion that adenine be used as first made to us by Professor B. R. Baker.

(9) M. Hubert-Habart and S. S. Cohen, *Biochim. Biophys. Acta*, **59**, 468 (1962); H. Tono, *J. Biol. Chem.*, **237**, 1271 (1962); M. G. Chu and G. A. Fischer, *Biochem. Pharmacol.*, **11**, 423 (1962); G. E. Underwood, *Proc. Soc. Exp. Biol. Med.*, **111**, 660 (1962); R. W. Talley and V. K. Vaitkevicius, *Blood*, **21**, 352 (1963); J. J. Brink and G. A. LePage, *Federation Proc.*, **22**, 184 (1963); G. A. LePage and I. G. Junga, *Cancer Res.*, **23**, 739 (1963); S. S. Cohen, *Perspectives Biol. Med.*, **6**, 215 (1963).