Tetrahedron Vol. 34, pp. 2627–2631

0040-4020/78/0901-2627/$02.00/0

ENANTIOMERIC FORMS OF 9-(5,6-DIDEOXY-α-D-*ARABINO*-HEX-5-ENOFURANOSYL)ADENINE AND PREPARATION OF 9-(6-DEOXY-β-D-GALACTOFURANOSYL)ADENINE

FURTHER RESULTS WITH THE ACETOLYSIS OF HEXOFURANOSIDES

V. K. SRIVASTAVA and L. M. LERNER*
Department of Biochemistry, State University of New York, Downstate Medical Center, Brooklyn, NY 11203, U.S.A.

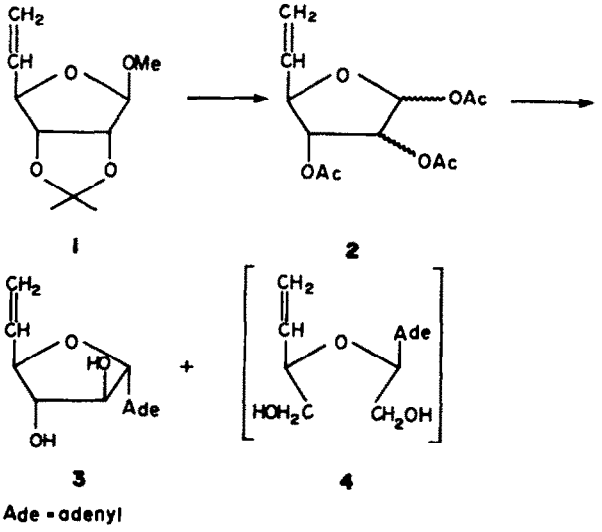
(*Received in USA 8 December 1977; received in UK for publication 23 March 1978*)

Abstract—Acetolysis of methyl 5,6-dideoxy-2,3-O-isopropylidene-β-D-*ribo*-hex-5-enofuranoside (1) and condensation of the product with 6-benzamidochloromercuripurine by the $TiCl_4$ method, gave 9-(5,6-dideoxy-α-D-*arabino*-hex-5-enofuranosyl) adenine (3) in low yield after removal of blocking groups. The main product was the D *ribo* nucleoside which was selectively destroyed by periodate oxidation to facilitate chromatographic purification of 3. The enantiomer 6 was prepared from methyl 5,6-dideoxy-2,3-O-isopropylidene-β-L-*ribo*-hex-5-enofuranoside (5) by the exact same route. The acetolysis reaction, in contrast to most previous experience, failed to epimerize C-2 of the sugar completely. An improved preparation of 6 is described which started from D-galactose. In addition, the latter pathway was used to prepare 9-(6-deoxy-β-D-galactofuranosyl)adenine (17).

Acetolysis of aldopentose and aldohexose derivatives frequently leads to epimerization at C-2.[1-3] The structural requirements are for a furanose ring and three contiguous OH groups, two of which at C-2 and C-3 should be in a *cis* relationship.[1-3] The protecting groups in this case must be exchangeable with acetate under the acetolysis conditions, which consist of 10:1 acetic acid–acetic anhydride and 3–5% conc. sulfuric acid.[1-4] Recent work has established the usefulness of this reaction in synthesis[5-12] and, in particular, the reaction has been a key step in the synthesis of various new hexofuranosyl nucleosides[7-11] and one pentofuranosyl nucleoside.[12]

We have recently been interested in the synthesis of 5′, 6′ unsaturated hexofuranosyl nucleosides because of recent findings of weak biological activity.[8,11] In previous work, the acetolysis reaction was used advantageously for the preparation of 5′, 6′ unsaturated nucleosides having the *xylo* configuration from unsaturated glycosides that originally had the *lyxo* configuration.[8] It was hoped that the same reaction sequence could be used to prepare the enantiomeric 5′, 6′ unsaturated nucleosides having the *arabino* configuration from glycosides that had the *ribo* configuration.

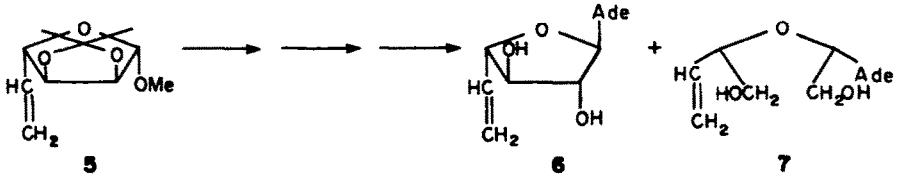
Acetolysis of methyl 5,6-dideoxy-2,3-O-isopropylidene-β-D-*ribo*-hex-5-enofuranoside (1)[11] gave a triacetate 2, which was condensed with 6-benzamidochloromercurpurine by the titanium tetrachloride method[13] (Scheme 1). Removal of the blocking groups with sodium methoxide and chromatography[14] on an ion-exchange resin gave two nucleosides from one peak, a fact that was deter-



Scheme 1.

mined by studying the rate of periodate consumption.[15] The acetolysis had not given complete epimerization at C-2 and as a result, a mixture of 9-(5,6-dideoxy-α-D-*arabino*-hex-5-enofuranosyl)adenine (3) and 9-(5,6-dideoxy-β-D-*ribo*-hex-5-enofuranosyl)adenine was obtained. In recent work from this laboratory, similar results were reported; 9-(6-deoxy-α-D-altrofuranosyl)-adenine was separated from 9-(6-deoxy-β-D-allofuranosyl)-adenine by selective destruction of the latter nucleoside with periodate.[10] The nucleoside mixture in the present case was treated with sodium periodate for a short time, and then treated with sodium borohydride. Rechromatography gave pure 3 and what appeared to be the dialcohol 4, although the NMR spectrum and optical rotation of the latter indicated that it was not a single isomer. The exact same approach was used to prepare the enantiomer 6 from methyl 5,6-dideoxy-2,3-O-isopropylidene-β-L-*ribo*-hex-5-enofuranoside (5),[11] along with the dialcohol 7 (Scheme 2). The yields of both 3 and 6 were low primarily because of the failure of the epimerization to go to completion. modifications of the published procedure,[16] and condensed it with 6-benzamidochloromercuripurine, again using the titanium tetrachloride method. The blocked nucleoside was partially purified by silica gel chromatography. Removal of the blocking groups and chromatography on an ion-exchange column afforded a 34% yield of 6. If 3 was found to possess biological activity, it would then be worthwhile to prepare it by this route starting from commercially available L-galactono-1,4-lactone.

The elemental analyses, UV, IR and NMR spectra supported the structures assigned to 3 and 6. The fact that 6 was also prepared directly from a D-galactose derivative was evidence that the acetolysis conditions did produce the *arabino* configuration. Additional evidence was obtained by recording the rate of periodate uptake[15] of 3 in comparison to 9-(5,6-dideoxy-β-D-*ribo*-hex-5-enofuranosyl)adenine, which revealed that the latter consumed the theoretical amount of periodate in a few minutes, whereas it took 5 days for 3 to consume an equivalent amount. During these studies it was noticed

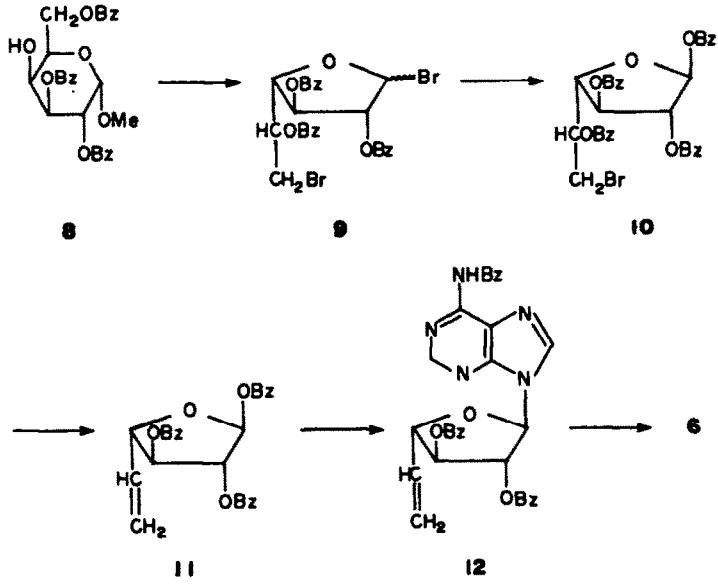


5 6 7

Scheme 2.

An excellent alternative preparation of 6 came about after the above work had been completed. Pedersen *et al.*[16] recently reported the preparation of tri-O-benzoyl-5,6-dideoxy-α-L-*arabino*-hex-5-enofuranose (11) by treatment of methyl 2,3,6-tri-O-benzoyl-α-D-galactopyranoside (8) with hydrogen bromide in acetic acid, which gave tri-O-benzoyl-6-bromo-6-deoxy-D-galactofuranosyl bromide (9) (Scheme 3). Treatment of 9 with silver benzoate gave 10 which was converted to 11 using zinc. We prepared 11 with only a few minor that some slow overoxidation tended to occur which became more apparent and troublesome in experiments designed to unequivocally prove the anomeric configuration.

The anomeric configuration of 3 (or 6) was not obtainable from the ^{1}H-NMR spectrum. In coupling reactions of the type described here, the nucleophilic base is expected to substitute trans to the OH group at C-2.[17] The optical rotations have values rather typical of hexofuranosyl nucleosides with the proposed configurations.



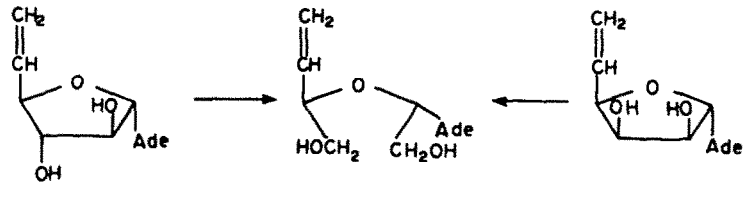
8 9 10 11 12 6

Scheme 3.

An attempt was made to unequivocally demonstrate the anomeric configuration of 3 by periodate oxidation and reduction to the dialcohol 13. As seen in Scheme 4, identical reactions performed on 9-(5,6-dideoxy-α-D-*lyxo*-hex-5-enofuranosyl)adenine [18] (14) should yield the same dialcohol 13. Since the anomeric configuration of 14 was already established, solutions having identical optical rotations in both cases would indicate identical configurations. Unfortunately, due to the length of exposure of 3 to periodate, overoxidation and release of iodine color occurred, and low values of rotation were obtained.

EXPERIMENTAL

M.ps were determined with a Kofler micro hot stage and correspond to corrected values. IR and UV spectra were recorded on Perkin–Elmer Model 21 and Beckman DK-2 spectrophometers, respectively. NMR spectra were obtained with a Varian T-60A spectrometer and TMS was the internal reference. Optical rotations were determined on a Rudolph polarimeter. Elemental analyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Michigan, U.S.A. Moist organic solutions were dried over $MgSO_4$. Evaporations were carried out under reduced pressure on a Büchi rotavapor with a bath temp. of 40–45°, unless stated otherwise.

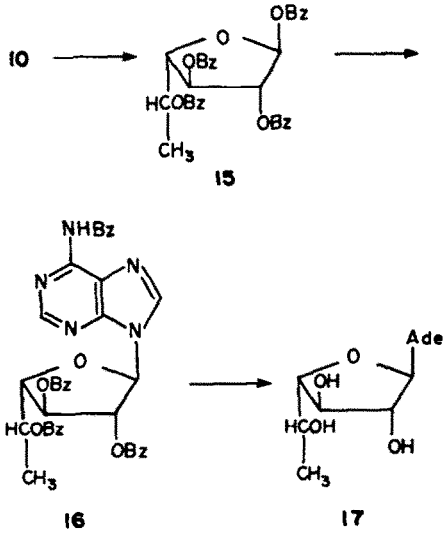


3 13 14

Scheme 4.

The failure of the acetolysis reaction to produce complete inversion of configuration at C–2 was surprising considering the excellent results obtained previously.[6-9,11,12] However, as mentioned above, a similar problem arose simultaneously in the preparation of certain 6'-deoxyhexofuranosyl nucleosides.[10] It appears that the configuration of the two-carbon group at C–4 with respect to the configuration of OH groups at C–2 and C–3 may have a role in the outcome. The structural and thermodynamic reasons for the results of the acetolysis reaction are not obvious and will need further study. The two mechanisms[1,2] that have been proposed do not take into account these problems.

In their paper concerning the preparation of 11, Pedersen *et al.*[16] also prepared tetra-0-benzoyl-6-deoxy-β-D-galactofuranose (15) by catalytic hydrogenation of 10. We have used 15 to prepare 9-(6-deoxy-β-D-galactofuranosyl) adenine (17) (Scheme 5). The L form of this nucleoside has been reported.[10]



Scheme 5.

9-(5,6-Dideoxy-α-D-arabino-hex-5-enofuranosyl)adenine (3). Compound 1[11] (8.42g, 42 mmol) was dissolved in a mixture of Ac_2O (26 ml) and glacial HOAc (260 ml), chilled in an ice bath, and conc H_2SO_4 (13.5 ml) was added dropwise. The soln was kept at room temp. for 112 hr and poured into 600 ml of ice. After the ice melted, $CHCl_3$ was added and the mixture was stirred for 15 min. The $CHCl_3$ layer was separated and the aqueous layer was further extracted with $CHCl_3$ (4 × 75 ml). The $CHCl_3$ extracts were combined and washed with cold H_2O (2 × 300 ml), satd $NaHCO_3$ (300 ml), H_2O (300 ml), and dried. The solvent was evaporated and traces of HOAc were removed by coevaporation of benzene several times. A clear, colorless oil (2, 6.9 g, 60% yield) was obtained; NMR ($CDCl_3$) δ 2.10 (CH_3CO), no *gem*-dimethyl or OMe.

A mixture containing 2 (6.9 g, 25 mmol), 6-benzamidoçhloromercuripurine (14.9 g, 31.5 mmol), Celite-545 (14.9 g), and 1,2-dichloroethane was heated under reflux and 110 ml of solvent distilled through a take-off adapter to remove traces of moisture. To the hot, stirring mixture was added $TiCl_4$ (2.8 ml, 26 mmol) in 110 ml of dry 1,2-dichloroethane. The mixture was heated under reflux for 21 hr, cooled to room temp., and treated with sat $NaHCO_3$ (690 ml).[8,13] After 2 hr of stirring, the solids were removed by filtration through a Celite pad, and the filter cake was washed with hot 1,2-dichloroethane (300 ml). The organic layer was separated, the solvent was evaporated, and the syrupy residue was dissolved in $CHCl_3$ (150 ml), washed with 30% KI (2 × 150 ml), H_2O (150 ml), and dried. Evaporation afforded a thick, orange syrup (9.65 g), which was dissolved in warm MeOH (200 ml) and treated with 1N methanolic NaOMe (20 ml). The soln was boiled under reflux for 2 hr, cooled, and neutralized with Amberlite CG-120 (H^+) ion-exchange resin. The resin was removed by filtration and washed thoroughly with MeOH. The solvent was evaporated and methyl benzoate was removed as an azeotrope by several coevaporations with water. The residue was dissolved in hot MeOH (25 ml), hot water (50 ml) was slowly added, and the dark soln was applied to the top of a column (30 cm × 2 cm) of Bio-Rad AG1-X2 (200–400 mesh, OH^-) ion-exchange resin.[14] Fractions (20 ml) were collected using 35% aq. MeOH as the elution solvent. Fractions 6–12 contained a nonnucleosidic UV absorbing substance. Fractions 38–183 had the main peak and these fractions were combined, the solvents evaporated, and the residue dried by coevaporation three times with EtOH to yield a white solid (3.25 g), containing a mixture of *arabino* and *ribo* nucelosides. The solid was dissolved in hot water (140 ml), chilled to 15° and $NaIO_4$ (2.7 g) was added. After 15 min at room temp., ethylene glycol (1.1 g) in water (10 ml) was added, and 10 min later the solution was concentrated by

evaporation (< 40°) to a volume of ~ 70 ml. The soln was poured into vigorously stirred EtOH (600 ml) and stirring continued for 30 min. The mixture was filtered and the pad washed with EtOH (100 ml). The solvents were evaporated (30°), the residue was suspended in water (225 ml), and treated dropwise with a soln of $NaBH_4$ (3.9 g) in water (60 ml). Dissolution of all solid material occurred within a few min. After 2 hr, the excess borohydride was destroyed and the pH adjusted to neutral with Bio-Rad AG50W-X8 (H^+) ion-exchange resin. The resin was removed by filtration and washed with water (100 ml). The water was evaporated and the residue was coevaporated with MeOH (3 × 100 ml) to remove boric acid as methyl borate. The remaining residue was dissolved in water, placed on a column (52 cm × 1.8 cm) of Bio-Rad AGI-X2 (200–400 mesh, OH^-) and the column was eluted with water. Fractions containing 18 ml each were collected. Fractions 14–43 afforded 925 mg of dialcohol **4** in three crops from acetone, m.p. 128–130°. (Found: C, 49.56; H, 5.64; N, 26.76. $C_{11}H_{15}N_5O_3$ requires: C, 49.80; H, 5.70 N, 26.40%). The NMR spectrum and the value of the optical rotation ($[\alpha]_D^{29}$ -9.9°) indicate that the sample is a mixture of diastereomers. The dialcohol derived from pure 9-(5,6-dideoxy-β-D-*ribo*-hex-5-enofuranosyl)adenine[11] has the value $[\alpha]_D^{28}$ + 37°.

The column was eluted with 65% aq. MeOH starting at tube 150 and fractions 166–196 were combined and the solvents evaporated. The residue was dried by several coevaporations with EtOH and crystallized from EtOAc, to afford 628 mg of **3**. The mother liquor afforded another 98 mg (726 mg total, 11% yield from **2**), m.p. 192–195°, $[\alpha]_D^{29}$ + 64.3° (*c* 0.885, 1 *N* HCl), UV max: pH 1, 256.5 (ε 14,240); H_2O, 259 (ε 14, 820); pH 13, 231.5 (ε 3760). (Found: C, 49.98; H, 7.76; N, 26.72, $C_{11}H_{13}N_5O_3$ requires: C, 50.18; H, 4.98; N, 26.60%).

Tetra-O-benzoyl-6-bromo-6-deoxy-β-D-galactofuranose (**10**). The procedure of Fogh *et al.*[16] was used to prepare **10**. The product required separation from a major contaminant and this was accomplished by silica gel chromatography (95:5 v/v $CHCl_3$–MeOH). The faster moving product **10** was crystallized from EtOH. From 5 g of **8**[19], 3.0 g (47%) of **10** was obtained, m.p. 164–166°. One recrystallization raised the m.p. to 166–168°; $[\alpha]_D^{27}$ -38.2° (*c* 2.5, $CHCl_3$); lit.[16] m.p. 163–165° (from Et_2O), $[\alpha]_D^{26}$ -37.0° (*c* 5.1. $CHCl_3$).

Tri-O-benzoyl-5,6-dideoxy-α-L-arabino-hex-5-enofuranose (**11**). The preparation of **11** from **10** was as described by Fogh *et al.*[16] The syrupy product was purified on a silica gel column using 1:1 v/v EtOAc-*n*-hexane as the eluant. The product was crystallized from MeOH (65% yield), m.p. 104–106°, $[\alpha]_D^{26}$ -24.6° (*c* 1.2, $CHCl_3$); lit.[16] m.p. 104–106°, $[\alpha]_D^{23}$ -23.1° (*c* 2.2, $CHCl_3$).

9-(5,7deoxy-α-L-*arabino-hex*-5-*enofuranosyl*)-*adenine* (**6**)

Method A. 6-Benzamidochloromercuripurine (2 g, 4.2 mmol), compound **11** (1.6 g, 3.5 mmol), Celite-545 (2g), $TiCl_4$ (0.8 ml), and 1,2-dichloroethane (200 ml) were heated under reflux and worked up very nearly as described above for the preparation of **3**. The crude product was chromatographed on a column of silicic acid (80 g, Mallinckrodt 100 mesh, packed in benzene). Elution of the column with 5:1 v/v benzene EtOAc washed off unreacted sugar derivatives. Elution with 2:1 v/v benzene–EtOAc yielded 1.6 g of a foam **12**, UV max: MeOH, 279 nm. The foam was dissolved in MeOH (25 ml) and conc NH_4OH (25 ml) was slowly added. After 25 hr at room temp. the solvents were evaporated, the syrup was dissolved in a minimal amount of water, and chromatographed on a column of Bio-rad AG1-X2 resin as described above. The first UV absorbing peak was crystallized and identified as benzamide. The second peak afforded 0.37 g of **6**, which was recrystallized from EtOH to give 0.32 g (34% yield from **11**), m.p. 197–199°, $[\alpha]_D^{27}$ -66.9 (*c* 0.75, 1 *N* HCl); NMR (Me_2SO-d_6) 8.32, 8.20 (both s, 1 proton each, H-8, H-2), 7.26 (broad s, 2, NH_2), 5.98 (m, 1, H-5'), 5.95 (d, 1, $J_{1',2'}$ = 4.4 Hz, H-1'), 5.63–5.33 (m, 2, 2' and 3' OH), 5.46–5.16 (m, 2, H-6'$_a$ and H-6'$_b$), 4.73 (t, 1, H-2'), 4.50–4.18 (m, 2, H-3' and H-4'). The physical data and spectra of this preparation were identical to **6** prepared by Method B and identical to enantiomer **3**.

Method B. Compound **5**[11] (4.21 g, 21 mmol) was acetolyzed as described for the D form to give 3.8 g (66% yield) of the triacetate. This was condensed with 8.23 g of 6-benzamidochloromercuripurine by the identical procedure used before to give 4.52 g of blocked nucleoside and unreacted sugar derivatives. Removal of the blocking groups with NaOMe and chromatography on the ion-exchange column yielded 1.593 g of solid material. Treatment of this with $NaIO_4$ followed by $NaBH_4$ reduction and rechromatography gave **7** as the first major peak, 356 mg in three crops from acetone, m.p. 129–130°. (Found: C, 49.74; H, 5.53; N, 26.10. $C_{11}H_{15}N_5O_3$ requires: C, 49.80; H, 5.70; N, 26.40%).

Further elution of the column with 65% aq. MeOH yielded 266 mg of **6**, crystallized from EtOAc m.p. 194–197°. The properties of this compound were identical to enantiomer **3** and to the preparation from compound **11**. (Found: C, 50.17; H, 4.92; N, 26.42. $C_{11}H_{13}N_5O_3$ requires: C, 50.18; H, 4.98; N, 26.60%).

9-(6-*Deoxy-β-D-galactofuranosyl*)*adenine* (**17**). Compound **15** was prepared by catalytic reduction of **16**.[16] The preparation of the blocked nucleoside **16** was similar to the above preparations. From 0.7 g of **15**, 0.68g of **16** was obtained after silicic acid chromatography. Debenzoylation and chromatography on the ion-exchange resin afforded 0.21 g of crystals. Recrystallization from EtOH–H_2O gave 0.15 g (48% from **15**) of **17**, m.p. 247–248°, $[\alpha]_D^{25}$ -75.8° (*c* 0.57, H_2O); UV: H_2O, 259 nm (ε 14,700); NMR (Me_2SO-d_6) δ 8.23, 8.02 (both s, 1 proton each, H-8, H-2), 7.20 (broad s, 2, NH_2), 5.76 (d, 1, $J_{1'2'}$ = 5.0 Hz, H-1'), 5.36, 5.20 (both s, 1 proton each, 2' and 3' OH), 4.96 (m, 1, 5' OH), 4.50 (t, 1, H-2'), 4.0 (m, 1, H-5'), 3.70 (m, 2, H-3', H-4'), 1.03 (d, 3, 6'CH_3). (Found. C, 47.16; H, 5.38; N, 24.82. $C_{11}H_{15}N_5O_4$ requires: C, 46.97, H, 5.38; N, 24.90%).

Periodate uptake. Periodate was measured at 300 nm by the procedure of Rammler and Rabinowitz.[15] Nucleoside **3** consumed 0.96 molar equiv in 95 hr, whereas 9-(5,6-dideoxy-β-D-*ribo*-hex-5-enofuranosyl)adenine[11] consumed 0.89 molar equiv in less than 5 min.

Polarimetric studies. The procedure used to prepare the dialcohols of nucleosides for polarimetry has appeared previously.[9] The dialcohol from 9-(5,6-dideoxy-β-D-*lyxo*-hex-5-enofuranosyl)adenine[18] gave $[\alpha]_D^{28}$ -60° and the dialcohol from 9-(5,6-dideoxy-β-D-*ribo*-hex-5-enofuranosyl)adenine[11] gave $[\alpha]_D^{28}$ + 37°. The optical rotation of the dialcohols from **3** and 9-(5,6-dideoxy-β-D-*xylo*-hex-5-enofuranosyl)-adenine[8] were low absolute values and inconsistent. Because of the lengthy oxidation time required, the solutions developed the orange-brown color of I_2 typically found during periodate oxidation of hexofuranosides.[20]

Acknowledgement—The work reported here was supported by Grant No. CA 13802 from the National Institutes of Health, U.S. Public Health Service.

REFERENCES

[1]P. Jerkeman, *Acta Chem. Scand.* **17**, 2769 (1963).
[2]W. Sowa, *Can. J. Chem.* **49**, 3292 (1971); **50**, 1092 (1972).
[3]G. J. F. Chittenden, *Carbohydr. Res.* **22**, 491 (1972); P. J. Boon, A. W. Schwartz and G. J. F. Chittenden, *Ibid.* **30**, 179 (1973).
[4]L. M. Lerner, *J. Org. Chem.* **38**, 3704 (1973).
[5]L. M. Lerner, *Ibid.* **37**, 4386 (1972).
[6]L. M. Lerner, *Carbohydr. Res.* **36**, 392 (1974).
[7]L. M. Lerner, *J. Org. Chem.* **40**, 2400 (1975).
[8]L. M. Lerner, *Carbohydr. Res.* **44**, 13 (1975).
[9]L. M. Lerner, *J. Org. Chem.* **41**, 306 (1976).
[10]L. M. Lerner, *Ibid.* **43**, 962 (1978).
[11]L. M. Lerner, *Ibid.* **43**, to be published.
[12]L. M. Lerner, *Ibid*, **43**, 161 (1978).
[13]B. R. Baker, R. E. Schaub, J. P. Joseph and J. H. Williams, *J. Am. Chem. Soc.* **77**, 12 (1955). J. Prokop and D. H. Murray, *J. Pharm. Sci.* **54**, 359 (1965).
[14]C. A. Dekker, *J. Am. Chem. Soc.* **87**, 4027 (1965).
[15]D. H. Rammler and J. C. Rabinowitz, *Anal. Biochem.* **4**, 116 (1962).
[16]A. Fogh, I. Lundt and C. Pedersen, *Acta Chem. Scand.* B. **30**, 624 (1976).

[17]B. R. Baker, in Ciba Foundation Symposium, *Chemistry and Biology of Purines* (Edited by G. E. W. Wolstenholme and C. M. O'Connor) p. 120. Little, Brown, Boston, Mass (1957). L. Goodman, *Basic Principles in Nucleic Acid Chemistry*, Vol. 1, p. 93. P.O.P. Ts'O, Ed., Academic Press, New York (1974).

[18]L. M. Lerner, *J. Org. Chem.* 37, 470 (1972).

[19]J. M. Willimas and A. C. Richardson, *Tetrahedron* 23, 1369 (1967).

[20]J. M. Bobbitt, *Advan. Carbohydr. Chem.* 11, 1 (1956).