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Synthesis of Sugar Moiety Substituted Nucleosides I: 9-[3-*O*-(*n*-Hexyl)-α,β-D-xylofuranosyl]adenine and 9-[3-*O*-(*n*-Hexyl)-5-deoxy-α,β-D-xylofuranosyl]adenine

DANIEL H. MURRAY and JOHN PROKOP

Abstract □ Isopropylidene-D-xylose was coverted *via* the 5-trityl compound to a 3-*O*-(*n*-hexyl) derivative. Following detritylation, benzoylation, and acetolysis, condensation with chloromercuri-6-benzamidopurine in the presence of titanium tetrachloride gave a crude nucleoside mixture. After deacylation, the mixture of anomeric nucleosides was resolved on ion-exchange resin (Bio-Rad AGl) to give 9-[3-*O*-(*n*-hexyl)-α-D-xylofuranosyl]adenine and 9-[3-*O*-(*n*-hexyl)-β-D-xylofuranosyl]adenine. Similarly, isopropylidene-5-deoxy-D-xylose was converted to a 3-*O*-(*n*-hexyl) derivative. Acetolysis and condensation with chloromercuri-6-benzamidopurine followed by deacylation and resolution on ion-exchange resin led to isolation of 9-[3-*O*-(*n*-hexyl)-5-deoxy-α-D-xylofuranosyl]adenine and 9-[3-*O*-(*n*-hexyl)-5-deoxy-β-D-xylofuranosyl]adenine.

Keyphrases □ Nucleosides, sugar moiety substituted—synthesis, isolation, separation □ 3-*O*-(*n*-Hexyl)adenine derivatives—synthesis, isolation □ Column chromatography—separation □ IR—identification □ UV spectrophotometry—identification □ Polarimetry—identification

In a continuing series of investigations, the authors have been exploring the structural features of the sugar moiety of adenine nucleosides required for interaction with the enzyme adenosine deaminase and/or inhibition of whole cells (1, 2). Other groups as well have devoted considerable attention to this area of study, particularly the laboratories of LePage (3), Schaeffer (4), and Bloch (5), among others. Compositely, the results of many studies such as those cited suggest that the 3′-hydroxyl group is usually not an important participant in an interaction with enzymes by which an adenine nucleoside may function as an *inhibitor* rather than as a *substrate*.

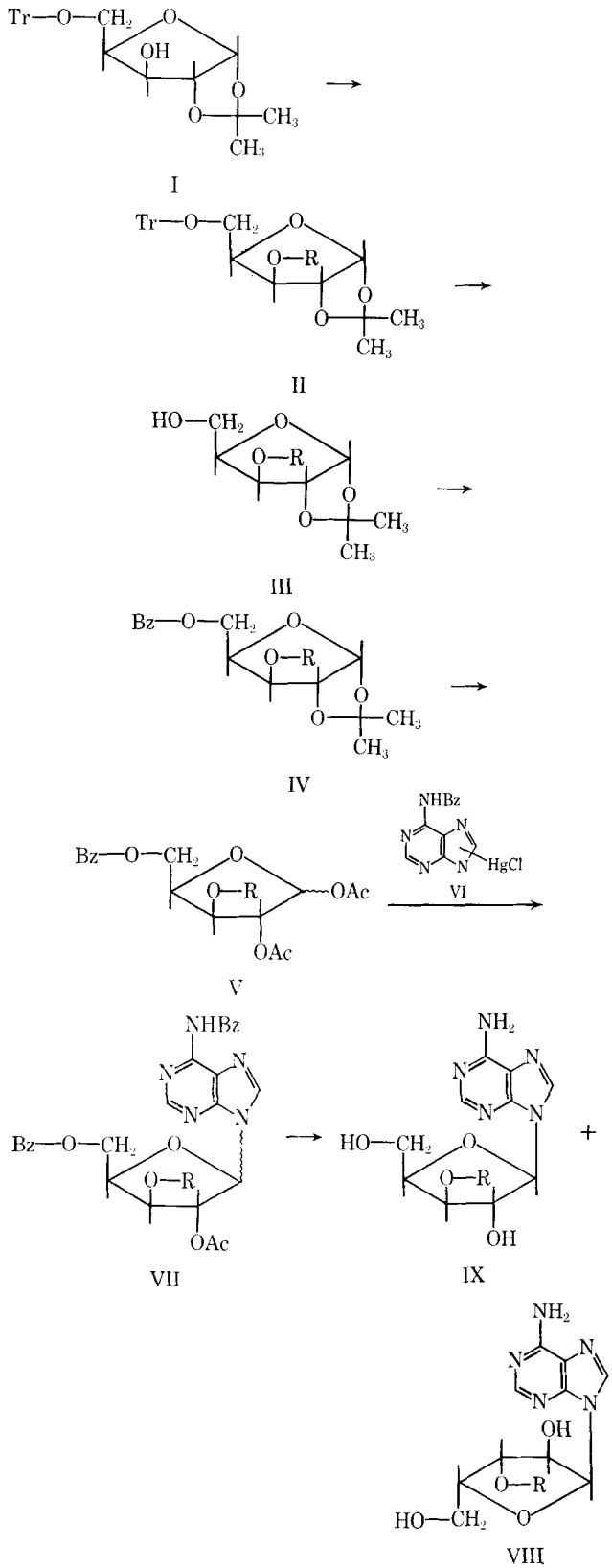
Recently, Baker (6) has collated many examples of the application of a principle he enunciated earlier (7): that a group which is found not to be important in interaction with an enzyme may be an ideal candidate for further modification with even quite bulky groups, including those which may react covalently with an enzyme to yield an active site directed, irreversible inhibitor. Both Baker (8) and Schaeffer (9) have now prepared a number of such irreversible inhibitors.

To date there seems not to have been any attempt to apply the implications of the Baker principle to "unimportant" groups on the sugar moiety of nucleosides. As noted, the 3′-hydroxyl would appear to be such a group. The present and following reports describe the syntheses of a number of 3′-*O*-substituted nucleosides whose availability will allow a beginning to be made in assessing the practicality of designing an active site directed, irreversible inhibitor of a sugar moiety substituted type.

Initially, the *n*-hexyl substituent was selected since not only could it serve as the carrier of an alkylating function, but of itself might enhance binding of the nucleoside through interaction with potentially accessible hydrophobic regions on susceptible enzymes. That such a hydrophobic region exists on adenosine deaminase has been demonstrated by Schaeffer and Vogel with a series of 9-alkyl substituted adenines (10). Xylofuranosyladenine (3*c*) and 5′-deoxyxylofuranosyladenine (11), both of which show affinity toward adenosine deaminase, were slected as candidates for 3′-*O*-substitution. The present paper, therefore, reports the syntheses of the 3′-*O*-(*n*-hexyl) derivatives of these two nucleosides.

PROCEDURES

Etherification of 1,2-*O*-isopropylidene-5-*O*-triphenylmethyl-D-xylofuranose (12) (I, Scheme I) with 1-chlorohexane in the presence of potassium hydroxide gave the 3-*O*-(*n*-hexyl) derivative (II) as a noncrystallizing syrup in quantitative yield. Attempts to remove the trityl group by hydrogenolysis over palladium black or palladium-on-charcoal were unsuccessful. This group, however, was readily removed in good yield when II was refluxed in an aqueous ethanolic solution of acetic acid. The resulting distillable syrup (III) was contaminated with 8% of triphenylcarbinol which could be removed by

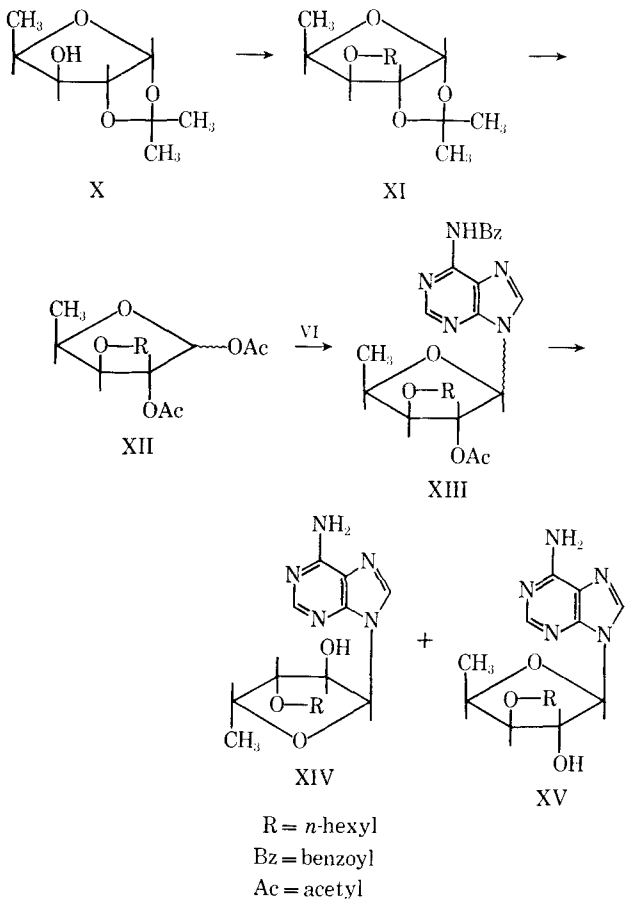


Tr = triphenylmethyl
R = *n*-hexyl
Bz = benzoyl
Ac = acetyl

Scheme I

chromatography on silica gel. Benzoylation of III in the usual manner gave a quantatiative yield of IV as a syrup. Acetolysis of IV gave the 1,2-diacetate (V) again as a syrup in quantitative yield. Condensation of V with chloromercuri-6-benzamidopurine (VI) in the presence of titanium tetrachloride resulted in a crude anomeric mixture of blocked nucleosides (VII) obtained as a glass. Without further purification, VII was deacylated with methanolic sodium methoxide, and the crude reaction products were chromatographed on ion-exchange resin[1] using 60% aqueous methanol. Rechromatographing the partially separated nucleosides gave the pure α and β anomers (VIII and IX, respectively) as crystalline solids in yields of 5.0% and 63%, respectively (from V).

In a similar manner, 5-deoxy-1,2-*O*-isopropylidene-D-xylofuranose (II) (X, Scheme II) was hexylated to give XI in 83% yield as a distillable liquid. Acetolysis of XI gave the 1,2-diacetate (XII) as a liquid which was coupled with VI in the presence of titanium tetrachloride. The resulting crude blocked nucleosides (XIII), obtained as a syrup, were deacylated and chromatographed as before. The pure crystalline α and β nucleosides (XIV and XV, respectively) were isolated, after rechromatographing the partially overlapping peaks, in yields of 5.8% and 36%, respectively (from XII).



R = *n*-hexyl
Bz = benzoyl
Ac = acetyl

Scheme II

The anomeric assignments of these nucleosides were made by application of Hudson's rules of isorotation as shown in Table I. So far as is known, no exceptions to these rules have been found for 9-glycofuranosyladenines. In addition, condensation reactions with 2-acyloxy intermediates (such as V and XII), even under titanium tetrachloride conditions, are known to obey the *trans* rule of Baker for nucleosides (1, 13); that is, the preponderant anomer will have a C1′, C2′ *trans* configuration of substituents. The yields shown in Table I confirm these assignments.

[1] Bio-Rad AGl × 8 (OH) is a more purified form of Dowex 1 supplied by Bioradlabs, New York, N. Y.

Table I—Specific Rotations and Yields of Nucleosides

Nucleoside	$[\alpha]_D^{25}$ (MeOH)	% Yield	Anomeric Assignment
VIII	$-0.6 \pm 0.2°$	5.0	α
IX	$-49.8°$	63	β
XIV	$+0.5 \pm 0.2°$	5.8	α
XV	$-61.7°$	36	β

The biological activity of the nucleosides reported in this paper is currently under investigation. The results will be the subject of a future report.

EXPERIMENTAL[2]

3-*O*-(*n*-Hexyl)-1,2-*O*-isopropylidene-5-*O*-triphenylmethyl-D-xylofuranose (II)—A mixture of 4.32 g. of 1,2-*O*-isopropylidene-5-*O*-triphenylmethyl-D-xylofuranose (I) (12), m.p. 116–118°, 7.0 ml. of 1-chlorohexane, 3.0 g. of powdered potassium hydroxide,[3] and 5 ml. of benzene were stirred and heated under reflux overnight while protected from moisture. The cooled mixture was partitioned between 70 ml. of ether and 30 ml. of water. The organic phase was separated and washed further with water (2 × 30 ml.), then dried ($MgSO_4$), filtered, and evaporated at 0.05 mm. pressure and 55° for 3 hr. to give a stiff, yellow syrup which failed to crystallize; yield, 5.17 g. (100%). IR analysis showed a substantial increase in aliphatic C—H absorption at 3000–2860 cm.$^{-1}$ (addition of hexyl) and complete loss of hydroxyl absorption at 3450 cm.$^{-1}$; $[\alpha]_D^{25}$ $-25.4°$ (c 3.25, MeOH), $[\alpha]_{546}^{25}$ $-41.7°$.

Anal.[4]—Calcd. for $C_{33}H_{40}O_5$: C, 76.71; H, 7.80. Found: C, 76.33; H, 7.39.

3-*O*-(*n*-Hexyl)-1,2-*O*-isopropylidene-D-xylofuranose (III)—A mixture of 25.8 g. of II, 400 ml. of ethanol, 280 ml. of water, and 120 ml. of glacial acetic acid was heated under reflux for 2 hr. (complete solution occurred in 30 min.). After evaporation of the solvents, the residue was dissolved in 300 ml. of chloroform and washed with 100 ml. of 1 *N* sodium hydroxide solution and two 100-ml. portions of water. The chloroform solution was evaporated to dryness and the residue diluted with 75 ml. of methanol and stored overnight at 5°. Triphenylcarbinol, 9.99 g. (77% of theory), was removed by filtration. The filtrate was evaporated to dryness and the residue distilled, giving the crude product (contaminated with triphenylcarbinol as shown by TLC) as a colorless, viscous liquid in a yield of 12.6 g. (92%), b.p. 135–145°/0.04 mm. A 3.0-g. sample of this material was chromatographed on 70 g. of silica gel using benzene and gave 0.25 g. (8%) of triphenylcarbinol. Further elution with absolute ethanol gave the desired product (2.68 g.), which was distilled to give 2.53 g. (78% overall) of III as a colorless liquid, b.p. 128–134°/0.03 mm.; $\tilde{\nu}_{max.}^{film}$ (cm.$^{-1}$) 3500 (OH), strong bands in the 3000–2850 region (aliphatic C—H of hexyl) and 1375 (doublet, isopropylidene); $[\alpha]_D^{25}$ $-33.2°$ (c 3.31, MeOH), $[\alpha]_{546}^{25}$ $-39.6°$.

Anal.—Calcd. for $C_{14}H_{26}O_5$: C, 61.29; H, 9.55. Found: C, 61.23; H, 9.70.

5-*O*-Benzoyl-3-*O*-(*n*-hexyl)-1,2-*O*-isopropylidene-D-xylofuranose (IV)—To a stirred solution of 1.74 g. (6.4 mmoles) of pure III in 10 ml. of pyridine was added dropwise 1.0 ml. (8.7 mmoles) of benzoyl chloride below room temperature. The mixture was stored overnight at 5° in a stoppered flask and then quenched by the addition of 10 drops of water. After 30 min., the reaction was diluted with 50 ml. of chloroform and washed with 50 ml. of water, 50 ml. of aqueous-saturated sodium bicarbonate, and 50 ml. of water; it was then dried ($MgSO_4$), filtered, and evaporated to dryness. Traces of pyridine were removed from the residue by codistillation *in vacuo* with two 10-ml. portions of toluene. The resulting light-amber syrup was held for several hours at <1 mm. pressure; yield, 2.39 g. (100%); $\tilde{\nu}_{max.}^{film}$ (cm.$^{-1}$) loss of 3500 absorption (OH), 1725 (benzoate C=O), 1375 doublet (isopropylidene), 1280 (benzoate C—O—C), 710 (phenyl).

Anal.—Calcd. for $C_{21}H_{30}O_6$: C, 66.64; H, 7.99. Found: C, 66.51; H, 7.80.

1,2-Di-*O*-acetyl-5-*O*-benzoyl-3-*O*-(*n*-hexyl)-D-xylofuranose (V)—To a stirred solution of 5.46 g. of IV in 58 ml. of glacial acetic acid and 6.4 ml. of acetic anhydride was added dropwise, at 15–20°, 2.8 ml. of concentrated sulfuric acid. The reaction was allowed to stand overnight in a stoppered flask and was then poured, with stirring, into 200 ml. of cold 10% aqueous sodium acetate. After 1 hr., the mixture was extracted with four 50-ml. portions of chloroform. These extracts were combined and washed with 200 ml. of water, 200 ml. of aqueous-saturated sodium bicarbonate, and 200 ml. of water; they were then dried ($MgSO_4$), filtered, and evaporated to dryness at 0.05 mm. pressure and 50° to give an almost colorless syrup; yield, 6.00 g. (99%); $\tilde{\nu}_{max.}^{film}$ (cm.$^{-1}$) 1750 (acetate C=O), 1725 (benzoate C=O), 1375 singlet (C-methyl), 1280 (benzoate C—O—C), 1220 (acetate C—O—C), 710 (phenyl).

Anal.—Calcd. for $C_{22}H_{30}O_8$: C, 62.54; H, 7.16. Found: C, 63.34; H, 7.19.

9-[3-*O*-(*n*-Hexyl)-α- and β-D-xylofuranosyl]adenine (VIII and IX, respectively)—A mixture of 2.28 g. (5.4 mmoles) of V, 2.56 g. (5.4 mmoles) of chloromercuri-6-benzamidopurine (1) (VI), 2.6 g. of diatomaceous earth,[5] and 100 ml. of ethylene dichloride was distilled until 25 ml. of distillate had been collected. After cooling to room temperature, a solution of 0.60 ml. (5.4 mmoles) of titanium tetrachloride in 6 ml. of ethylene dichloride was added dropwise and the mixture was heated under reflux overnight while protected from moisture. To the cooled reaction was added 10 ml. of aqueous-saturated sodium bicarbonate with vigorous stirring, followed by additional solid sodium bicarbonate in small portions until a neutral reaction was obtained. After filtration through a diatomaceous earth pad, the filtrate was evaporated to dryness. A solution of the residue in 50 ml. of chloroform was washed with 50 ml. of 30% aqueous potassium iodide and 50 ml. of water, then dried ($MgSO_4$), filtered, and evaporated to dryness at 0.05 mm. pressure and 50° to give the crude, blocked nucleosides (VII) as an amber glass; yield, 2.90 g. (89); $\tilde{\nu}_{max.}^{film}$ (cm.$^{-1}$) 1750 (acetate C=O), 1725 (benzoate C=O), 1700 shoulder (amide C=O), 1610, 1580 (C=C and C=N), 1280 (benzoate C—O—C), 1225 (acetate C—O—C), 710 (phenyl).

A solution of 2.57 g. of VII in 50 ml. of 0.1 *N* methanolic sodium methoxide was heated under reflux for 3 hr. The cooled reaction was neutralized with acetic acid and evaporated to dryness. Methyl benzoate was removed by codistillation *in vacuo* with three 10-ml. portions of water. The residue was dissolved in 75 ml. of 50% aqueous ethanol and chromatographed on a column (38 mm. × 50 cm.) of ion-exchange resin using 60% aqueous methanol.[6] The partially separated peaks[7] corresponding to the anomeric nucleosides were each rechromatographed under the same conditions to give the pure isomers. The α-anomer (VIII) eluted first, and evaporation of the solvents gave 84 mg. (5.6%) of a crystalline solid, m.p. 174–177°. Recrystallization from 50% aqueous methanol gave the pure compound, m.p. 180–181°; $[\alpha]_D^{25}$ $-0.6° \pm 0.2°$ (c 1.07, MeOH), $[\alpha]_{546}^{25}$ $+0.5° \pm 0.2°$; $[\alpha]_{365}^{25}$ $+34.1°$; $\lambda_{max.\ (m\mu)}^{95\%\ ETOH}$ 260 (ϵ 15,000).

Anal.—Calcd. for $C_{16}H_{25}N_5O_4$: C, 54.68; H, 7.17; N, 19.93. Found: C, 54.65; H, 7.13; N, 19.87.

The β-anomer (IX) eluted next and amounted to 1.06 g. (71%) after removal of the solvents, m.p. 159–160°. Two recrystallizations from aqueous methanol gave the analytical sample, m.p. 160–160.5°; $[\alpha]_D^{25}$ $-49.8°$ (c 1.21, MeOH), $[\alpha]_{546}^{25}$ $-60.1°$; $\lambda_{max.\ (m\mu)}^{95\%\ ETOH}$ 260 (ϵ 15,100).

Anal.—Calcd. for $C_{16}H_{25}N_5O_4$: C, 54.68; H, 7.17; N, 19.93. Found: C, 54.87; H, 6.94; N, 19.48

5-Deoxy-3-*O*-(*n*-hexyl)-1,2-*O*-isopropylidene-D-xylofuranose (XI)—A stirred mixture of 10.4 g. of 5-deoxy-1,2-*O*-isopropylidene-D-xylofuranose (11) (X), m.p. 68–70°, 42 ml. of 1-chlorohexane, 30 ml. of benzene, and 18 g. of powdered potassium hydroxide were heated under reflux overnight while protected from moisture. The cooled mixture was partitioned between 300 ml. of ether and 100 ml.

[2] All evaporations were conducted *in vacuo* in a Buchler-type evaporator at 40–45° unless specified otherwise. Melting points were determined on a Mel-Temp apparatus and are uncorrected. The IR, UV, and polarimetric determinations were made using Perkin-Elmer models 337, 202, and 141, respectively.

[3] Obtained from the Riverside Chemical Co., Inc., North Tonawanda, N. Y.

[4] Galbraith Laboratories, Knoxville, Tenn., performed the elemental analyses.

[5] Celite, Johns Manville, New York, N. Y.

[6] Practical grade methanol was entirely satisfactory.

[7] Since these chromatograms generally required 2–3 days of continuous operation, the eluate was conveniently monitored by the use of an ISCO model UA analyzer equipped with a recorder operating at 1.27 cm. (0.5 in.)/hr.

of water. The ether layer was further washed with water (2 × 100 ml.), dried ($MgSO_4$), filtered, and evaporated to dryness. The resulting liquid was vacuum distilled, giving 12.9 g. (83%) of XI as a colorless distillate, b.p. 75–80°/0.02 mm.; $\bar{\nu}_{max.}^{film}$ (cm.$^{-1}$) loss of 3500 band (OH), several strong bands at 3000–2850 (aliphatic C—H of hexyl), 1375 doublet (isopropylidene); $[\alpha]_D^{25}$ −28.3° (c 1.22, MeOH), $[\alpha]_{546}^{25}$ −33.1°.

Anal.—Calcd. for $C_{14}H_{26}O_4$: C, 65.08; H, 10.14. Found: C, 64.81; H, 10.18.

1,2-Di-*O*-acetyl-5-deoxy-3-*O*-(*n*-hexyl)-D-xylofuranose (XII)—To a stirred solution of 11.5 g. of XI in 180 ml. of glacial acetic acid and 21.3 ml. of acetic anhydride was added dropwise, at 15–20°, 8.5 ml. of concentrated sulfuric acid. The reaction was stored overnight at room temperature in a stoppered flask, then poured into 650 ml. of cold 10% aqueous sodium acetate with stirring. After 40 min., the mixture was extracted with four 125-ml. portions of chloroform. The combined extracts were washed with 300 ml. of water, 300 ml. of aqueous-saturated sodium bicarbonate, and 300 ml. of water; dried ($MgSO_4$); filtered; and evaporated to dryness at 0.1 mm. pressure and 50° to give XII as a pale-yellow liquid; yield, 13.7 g. (101%); $\bar{\nu}_{max.}^{film}$ (cm.$^{-1}$) 1750 (acetate C=O), 1375 singlet (C-methyl), 1220 (acetate C—O—C).

Anal.—Calcd. for $C_{15}H_{26}O_6$: C, 59.58; H, 8.67. Found: C, 60.11; H, 8.87.

9-[5-Deoxy-3-*O*-(*n*-hexyl)-α- and β-D-xylofuranosyl]adenine (XIV and XV, respectively)—A mixture of 4.82 g. (16 mmoles) of XII, 7.57 g. (16 mmoles) of chloromercuri-6-benzamidopurine, 8 g. of diatomaceous earth, and 290 ml. of ethylene dichloride was distilled until 55 ml. of distillate had been collected. The mixture was cooled to room temperature and a solution of 1.8 ml. (16 mmoles) of titanium tetrachloride in 9 ml. of ethylene dichloride was added dropwise. The reaction was heated under reflux 20 hr. while protected from moisture. After cooling, 20 ml. of aqueous-saturated sodium bicarbonate was added with vigorous stirring, followed by additional solid sodium bicarbonate in small portions until a neutral reaction was obtained on pH paper. The mixture was filtered through a diatomaceous earth pad, the cake washed with two 50-ml. portions of ethylene dichloride, and the combined filtrate and washings were evaporated to dryness. A solution of the residue in 100 ml. of chloroform was washed with 100 ml. of 30% aqueous potassium iodide, 100 ml. of aqueous-saturated sodium bicarbonate, and 100 ml. of water; it was then dried ($MgSO_4$), filtered, and evaporated to dryness at 0.1 mm. pressure and 55° to give the crude, blocked nucleosides (XIII) as a pale-brown syrup; yield, 6.82 g. (89%); $\bar{\nu}_{max.}^{film}$ (cm.$^{-1}$) 1750 (acetate C=O), 1700 (amide C=O), 1225 (acetate C—O—C), 710 (phenyl).

A solution of 6.81 g. of XIII in 100 ml. of 0.1 *N* methanolic sodium methoxide was heated under reflux for 2.5 hr. while protected from moisture. The cooled reaction was neutralized with acetic acid and the solvent evaporated. Methyl benzoate was removed by co-distillation of the residue with three 20-ml. portions of water *in vacuo*. A solution of the residue in 70 ml. of 80% aqueous methanol was divided into two equal portions, each of which was chromatographed on a column (58 mm. × 50 cm.) of ion-exchange resin (200–400 mesh) using 60% aqueous methanol. The resulting chromatogram showed a minor UV absorbing peak followed by a major peak with some overlapping of the two materials. These overlap regions were combined from the two runs and rechromatographed to give the cleanly separated isomers. The first peak to elute, the α-anomer (XIV), gave white needles after evaporation; yield, 0.31 g. (6.5%). Recrystallization from 30 ml. of 50% aqueous methanol gave fine white needles, m.p. 139–140°; $[\alpha]_D^{25}$ +0.5° ± 0.2° (c 1.11, MeOH), $[\alpha]_{546}^{25}$ +1.2° ± 0.2°, $[\alpha]_{365}^{25}$ +39.1°; $\lambda_{max.\ (m\mu)}^{95\%\ ETOH}$ 260 (ε 15,400).

Anal.—Calcd. for $C_{16}H_{25}N_5O_3$: C, 57.29; H, 7.51; N, 20.88. Found: C, 57.01; H, 7.53; N, 20.58.

The major peak, the β-anomer (XV), gave 1.91 g. (40%) of white crystals on evaporation, m.p. 149–151°. Recrystallization from 45 ml. of 65% aqueous methanol gave white needles, m.p. 150–151°; $[\alpha]_D^{25}$ −61.7° (c 1.29, MeOH), $[\alpha]_{546}^{25}$ −75.2°; $\lambda_{max.\ (m\mu)}^{95\%\ ETOH}$ 260 (ε 15,600).

Anal.—Calcd. for $C_{16}H_{25}N_5O_3$: C, 57.29; H, 7.51; N, 20.88. Found: C, 57.46; H, 7.67; N, 20.93.

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