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Anomeric 2-Amino-2-deoxy-D-glucofuranosyl Nucleosides of Adenine and 2-Amino-2-deoxy-β-D-glucopyranosyl Nucleosides of Thymine and 5-Methylcytosine

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Fusion of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride (1) with bis(trimethylsilyl)-thymine gave a relatively low yield of 1-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)thymine (2) which on controlled acidic hydrolysis gave either 1-(2-acetamido-2-deoxy-β-D-glucopyranosyl)thymine or the previously reported 1-(2-amino-2-deoxy-D-glucopyranosyl)thymine hydrochloride, herein established as the β-D anomer. Treatment of 2 with phosphorus pentasulfide and subsequent heating with methanolic ammonia at 100° gave 1-(2-amino-2-deoxy-β-D-glucopyranosyl)-5-methylcytosine dihydrochloride (6). In selected cases, therefore, the *N*-acetyl group can serve as an amino-protective group in these reactions. The previously reported ethyl tri-*O*-acetyl-2-acetamido-2-deoxy-1-thio-α-D-glucofuranoside (7) was completely deacetylated by successive treatment with phosphorus pentasulfide and methanolic ammonia. After introduction of the *N*-(2,4-dinitrophenyl) group and acetylation, ethylthio replacement by chlorine yielded a glycosyl chloride derivative 12 which was brought into reaction with *N*-acetylchloromercuriadenine to yield, after removal of the acetyl and 2,4-dinitrophenyl groups, a crystalline anomeric mixture of 9-(2-amino-2-deoxy-D-glucofuranosyl)adenine nucleosides which, by separation on a column of ion-exchange resin, yielded the pure, crystalline components in a ratio of three parts of the β-D to two parts of the α-D form. Anomeric assignments were made on the basis of nmr and polarimetric data.

In continuation of our program in establishing methods for the synthesis of nucleosides of 2-amino-2-deoxyglycoses, we report herein work done in a pyranose structure with the *N*-acetyl group as the amino-protective agent and the glycosyl chloride as the reagent. The condensation yield, by the trimethylsilylpyrimidine fusion method, was low. With an aldose in which the 2-acetamido group is in a trans position to a hydroxyl group, the acetamido group has been removed by base only with great difficulty. However, the de-*N*-acetylation procedure of Fox, *et al.*,[1] obviates this difficulty.

Fusion of 3,4,6-tri-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranosyl chloride[2] (1) and bis(trimethylsilyl)-thymine[3,4] gave a blocked nucleoside (2) in 14% yield (Figure 1). The nuclear magnetic resonance spectrum of 2, measured in deuteriochloroform, revealed a long doublet at δ 5.97 ppm with a first-order coupling constant, $J_{1',2'}$ = 9 cps, characteristic of an axial–axial relationship of the 1′ and 2′ protons. Since the *C1* D conformation for 2 is highly probable, these data establish the β-D configuration of 2. Hydrolysis of 2 with hydrochloric acid[5] yielded the nucleoside 1-(2-amino-2-deoxy-β-D-glucopyranosyl)thymine hydrochloride (5) whose synthesis had been reported by Wolfrom and Bhat[6] by another method and in much higher yield. Pyrimidine, but not purine, nucleosides are stable to such acid treatment. The β-D configuration is, therefore, established for the compound which Wolfrom and Bhat isolated. Treatment of 2 with methanolic hydrogen chloride[4] yielded 1-(2-acetamido-2-deoxy-β-D-glucopyranosyl)thymine, hitherto unreported.

Following the general de-*N*-acetylation procedure of Fox and associates,[1] 2 was brought into reaction with phosphorus pentasulfide in pyridine to give the syrupy intermediate 3. Compound 3 was purified by preparative thin layer chromatography and, without further characterization, was treated with methanolic ammonia[1] at 100° to give 1-(2-amino-2-deoxy-β-D-glucopyranosyl)-5-methylcytosine, isolated as the dihydrochloride (6).

Thus, although the *N*-acetyl is not the amino-protective group of choice in these reactions, this group can nevertheless be utilized, in certain cases, under properly selected conditions. Other workers[5,7,8] have utilized the *N*-acetyl blocking group with amino sugars containing the pyranose ring, although the *N*-acetyl was not always removed from the reaction product. When applied to the more reactive furanose structure, we have encountered oxazoline formation.[9]

The anomeric forms of 9-(2-amino-2-deoxy-D-glucopyranosyl)adenine have been synthesized[10] through the use of the *N*-(2,4-dinitrophenyl) group in the chloromercuri procedure of Davoll and Lowy.[11] We have described[9] the synthesis, in low yield, of a nucleoside derivative of 2-amino-2-deoxy-D-glucofuranose through

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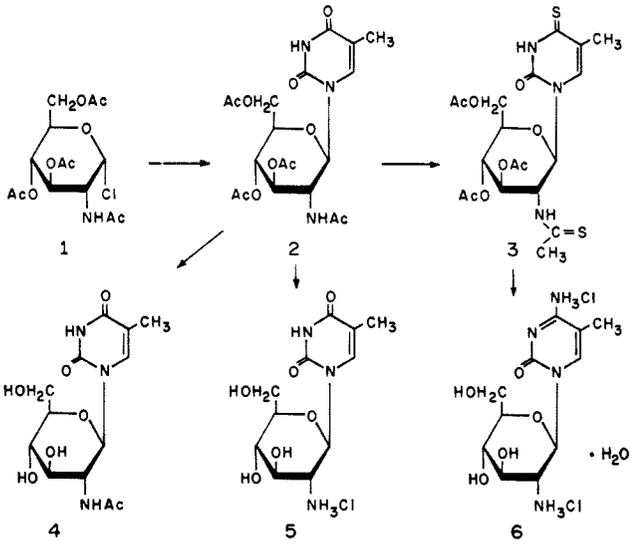

Figure 1.—3 was not obtained crystalline.

the use of an oxazoline formed when the ethylthio group of 2-acetamido-3,5,6-tri-*O*-acetyl-2-deoxy-1-thio-α-D-glucofuranoside[12,13] (**7**) was replaced by chlorine (Figure 2). We describe herein[14] the crystalline anomeric forms of 9-(2-amino-2-deoxy-D-glucofuranosyl)adenine prepared by utilization of the essentially nonparticipating *N*-(2,4-dinitrophenyl) group introduced in the sugar series by Lloyd and Stacey.[15]

In order to place the 2,4-dinitrophenyl group in the previously isolated[12,13] 1-thio-α-D-glucofuranosyl derivative of the amino sugar, the *N*-acetyl and *O*-acetyl groups were removed by the method of Fox and coworkers,[1] and the 2,4-dinitrophenyl group was directly introduced on the nitrogen atom of **9**. In this procedure, the fully acetylated ethyl 1-thio-α-D-glycoside (**7**) was converted into ethyl tri-*O*-acetyl-2-deoxy-2-(thioacetamido)-1-thio-α-D-glucofuranoside (**8**) by treatment with phosphorus pentasulfide in pyridine.[1] The syrupy product (**9**) which was obtained on treating **8** with methanolic ammonia[1] at 100° was characterized by the crystalline derivatives ethyl 2-(benzyloxycarbonylamino)-2-deoxy-1-thio-α-D-glucofuranoside (and its triacetate) and ethyl 2-deoxy-2-(2,4-dinitroanilino)-1-thio-α-D-glucofuranoside (**10**). Acetylation of **10** gave a syrupy triacetate (**11**) which in turn was converted by chlorine[16] into the syrupy glycosyl chloride **12**.

Use was then made of the chloromercuri procedure[11] to obtain a nucleoside of adenine. The reaction product from the condensation of the glycosyl chloride **12** with 6-*N*-acetyl-9-chloromercuriadenine was de-*N*-acetylated (on the purine) with picric acid[17] to yield a crystalline picrate (anomeric mixture) which was deblocked with a basic ion-exchange resin to give the crystalline anomeric mixture **13**. The nmr spectrum, in deuterium oxide, of **13** revealed a pair of isolated doublets at δ 6.00 ($J_{1',2'}$ = 2.5 cps) and 6.50 ppm ($J_{1',2'}$ = 5 cps). The protons at H-2 and H-8 of the purine ring appeared as two distinct singlets at δ 8.33 and 8.37 ppm and two overlapping singlets at δ 8.18 ppm as might be expected from a pair of anomers. The two singlets at lower magnetic field were somewhat diminished, by deuteration, on prolonged standing or on heating.[18]

An elegant separation of the two anomers was achieved by the method of Dekker.[19] Aqueous methanol elution from a column of basic ion-exchange resin separated the components very well. Assignment of anomeric form was made on the basis of nmr data[20] and was in agreement with the polarimetric values found. For the α-D anomer the presence of the doublet at δ 6.50 ($J_{1',2'}$ = 5 cps) and the absence of the one at 6.00 ppm ($J_{1',2'}$ = 2.5 cps) indicates a clear separation from the β-D anomer. The reverse held true for the β-D form. The X-ray powder diffraction data of the nucleoside anomeric mixture, in comparison with those of the separated components, clearly indicate a mechanical mixture of crystals and not a molecular compound. The latter was favored for an analogous but 1:1 anomeric mixture of adenine nucleosides of 2-amino-2-deoxy-D-ribofuranose.[21] The optical rotatory data of the isolated mixture would indicate a 63:37% (β-D:α-D) admixture, and indeed 63% β-D anomer was actually isolated in comparison with 31% α-D form.

Experimental Section[22]

1-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-thymine (**2**).—A mixture of 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride[2] (**1**, 20 g) and bis(trimethylsilyl)thymine[3,4] (30 g) was fused at 125–135° under a slightly reduced pressure. After the vigorous effervescence had ceased, the mixture was cooled and 50% aqueous methanol was added, after which the mixture was boiled for a few minutes and evaporated to small volume. More aqueous methanol was added and again partially removed by evaporation to a small volume. This was followed by repeated evaporations to dryness with absolute ethanol. The residue was extracted with dichloromethane and the extract was washed with saturated, aqueous sodium hydrogen carbonate, and water. The dried (magnesium sulfate) solution was evaporated to a syrup which was crystallized from methanol–ether to yield 5.0 g of crude **2**, mp 177–185°. This product was extracted with chloroform, and the extract was evaporated to a syrup which was crystallized from methanol–ether to yield 3.55 g (14%): mp 208–209°; $[\alpha]^{22}D$ −20 ± 1° (*c* 2.13, methanol); λ_{max}^{KBr} 3.07 (NH), 5.72 (OAc), 5.90 (C=O of thymine), and 6.05, 6.48 (NHAc) μm; λ_{max}^{MeOH} 265 nm (ε 9800); nmr (deuteriochloro-

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(22) Melting points were determined with a Hershberg-type apparatus [A. Thompson and M. L. Wolfrom, *Methods Carbohyd. Chem.*, **1**, 517 (1962)]. Specific rotations were determined in a 2-dm polarimeter rube. Infrared spectra were measured with a Perkin–Elmer Infracord spectrometer. Ultraviolet spectra were measured with a Bausch and Lomb Spectronic 505 spectrometer. Nmr data were recorded by J. D. Wander and J. B. Hughes with a Varian A-60 nmr spectrometer and were taken in deuterium oxide (freshly prepared solutions) or deuteriochloroform with an internal standard of sodium 4,4-dimethyl-4-silapentane 1-sulfonate or tetramethylsilane, respectively. Microanalytical determinations were made by W. N. Rond. X-Ray powder diffraction data give interplanar spacings in angstroms, for Cu Kα radiation, λ 1.539 Å, nickel filter, camera diameter of 114.6 mm, and photographic recording. Relative intensities were estimated visually: s, strong; m, medium; w, weak; v, very. The strongest lines are numbered (1, strongest); multiple numbers indicate approximately equal intensities. Thin layer (0.25-mm thickness unless otherwise noted) chromatography was performed by the ascending method with Desaga equipment using silica gel G (E. Merck, Darmstadt, Germany) activated at 110° with detection by sulfuric acid for colorless materials. Indicated amounts of developer are by volume. Unless otherwise noted, evaporations were performed under diminished pressure.

form) δ 1.92 (3 H, singlet, methyl at C-5), 2.07, 2.10 (12 H, NHAc and OAc), 3.87–5.67 (6 H, sugar ring), 5.97 (1 H, doublet, $J_{1',2'}$ = 9 cps, H-1'), 7.13 (1 H, broad doublet, NH at C-2'), 7.37 (1 H, singlet, H-6), and 10.25 ppm (1 H, broad singlet, H-3); X-ray powder diffraction 9.82 s (1, 1), 8.42 vw, 5.75 s (1, 1), 4.98 m, 4.87 s (2), 4.62 m, 4.23 vw, 4.07 vw, 3.97 s (3), 3.81 m, 3.66 m, 3.47 m, 3.40 m, 3.23 vw, 3.13 vw, and 3.02 w.

Anal. Calcd for $C_{19}H_{25}N_3O_{10}$: C, 50.11; H, 5.53; N, 9.23. Found: C, 49.92; H, 5.46; N, 9.41.

This compound was homogeneous by thin layer chromatography with ethyl acetate–methanol (9:1) developer (R_f 0.74).

1-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)thymine (4).—The above-described compound (**2**, 0.83 g) was dissolved in anhydrous methanol (30 ml), and the solution was almost saturated at 0° with hydrogen chloride. After standing at room temperature for 24 hr, the solution was evaporated to dryness. A filterable solid was obtained on trituration of the residue with ether: yield 0.67 g; mp 170–180°. Pure material was obtained on crystallization from ethanol–1-propanol: yield 0.44 g (73%): mp 262–263° dec; $[\alpha]^{20}D$ +19 ± 1° (*c* 2.25, methanol); λ_{max}^{KBr} 2.90–3.10 (NH, OH), 5.8–6.1 (C=O of thymine, NHAc), and 6.50 (NHAc) μm; $\lambda_{max}^{H_2O}$ 265 nm (ε 9450); X-ray powder diffraction 10.16 m, 9.21 vw, 7.37 m, 6.51 s (2), 5.21 m, 4.79 w, 4.56 s (1), 4.29 w, 4.07 s (3), 3.96 w, 3.83 vw, 3.69 m, 3.57 w, 3.47 w, 3.31 m, 3.13 m, 2.94 w, 2.83 w, 2.73 m, and 2.61 w.

Anal. Calcd for $C_{13}H_{19}N_3O_7$: C, 47.41; H, 5.81; N, 12.76. Found: C, 47.13; H, 5.55; N, 12.74.

This compound was homogeneous by thin layer chromatography with ethyl acetate–methanol (7:3) developer (R_f 0.37).

1-(2-Amino-2-deoxy-β-D-glucopyranosyl)thymine Hydrochloride (5).—Compound **2** (0.28 g) in 6 *N* hydrochloric acid[5] (6 ml) was heated for 10 hr at 95° under reflux, after which the residue obtained on solvent removal was triturated with ether to obtain a filterable solid in a yield of 0.22 g. Pure material was obtained on recrystallization from water–ethanol–1-propanol in a yield of 141 mg (71%): mp 304–307° dec (with darkening at 294°); $[\alpha]^{25}D$ +27 ± 2° (*c* 1.00, water). The X-ray powder diffraction pattern was identical with that obtained by Wolfrom and Bhat[6] who also reported mp 301–304° and $[\alpha]^{22}D$ +35° (*c* 2.34, water).

1-(2-Amino-2-deoxy-β-D-glucopyranosyl)-5-methylcytosine Dihydrochloride (6).—Following the general procedure of Fox and coworkers,[1] compound **2** (3.36 g) and phosphorus pentasulfide (13.1 g) in reagent grade pyridine (300 ml) was heated under reflux, with stirring, for 6 hr. The dark red solution was concentrated to small volume and extracted with chloroform. The extract was washed with water, 1 *N* hydrochloric acid, water, aqueous sodium hydrogen carbonate, and again with water. The dried (magnesium sulfate) solution was concentrated to a syrup which, on thin layer chromatography, exhibited a major yellow spot of R_f ~0.8. The product was then subjected to preparative thin layer chromatography on 200 × 200 × 1 mm plates (100 mg per plate). The principal yellow zone was excised and extracted with acetone. The residue obtained on acetone removal was extracted with dichloromethane to yield 1.57 g (44%) of a yellow syrup (**3**).

The syrup was dissolved in anhydrous methanol (20 ml), and to this was added a solution of methanol (80 ml) previously almost saturated at 0° with ammonia. The mixture was sealed in a steel cylinder and heated for 18 hr at 100°. The yellow solution so obtained was filtered; the residue obtained on solvent removal was treated with water; and a small quantity of Dowex 1X2 (OH^-, 50–100 mesh) was added to it. The mixture was filtered and washed with 60% aqueous methanol. The filtrate was evaporated to dryness, and the residue was subjected to an oil pump vacuum at 60°. The syrupy residue was dissolved in aqueous methanol, treated with decolorizing carbon, and filtered. The filtrate was evaporated to a syrup which was dissolved in aqueous ethanol and made acid to pH 3 by the dropwise addition of concentrated hydrochloric acid. 1-Propanol was added, and the solution was concentrated. Crystallization occurred to yield 0.79 g (73%), mp 209–211° dec. Recrystallization from concentrated hydrochloric acid by the addition of 1-propanol gave pure material: mp 219–221° dec (darkening at 210°); $[\alpha]^{24}D$ +43 ± 2° (*c* 1.34, water); λ_{max}^{KBr} 2.9–3.1 (NH, OH), 5.78, 5.90, 6.22, and 6.45 (NH_3R^+, pyrimidine) μm; $\lambda_{max}^{H_2O}$ 279 nm (ε 8320); X-ray powder diffraction 9.82 s (1, 1, 1), 8.19 vw, 7.49 w, 6.23 m, 5.18 m, 4.87 vw, 4.59 s (3, 3), 4.17 w, 4.05 s (3, 3), 3.75 s (2), 3.53 m, 3.35 s (1, 1, 1), 3.13 m, 2.99 s (1, 1, 1), 2.89 vw, 2.84 vw, 2.77 w, 2.65 w, 2.56 m, and 2.48 w.

Anal. Calcd for $C_{11}H_{20}N_4O_5Cl_2 \cdot H_2O$: C, 35.02; H, 5.88; N, 14.86; Cl, 18.79. Found: C, 35.00; H, 5.63; N, 15.09; Cl, 18.59.

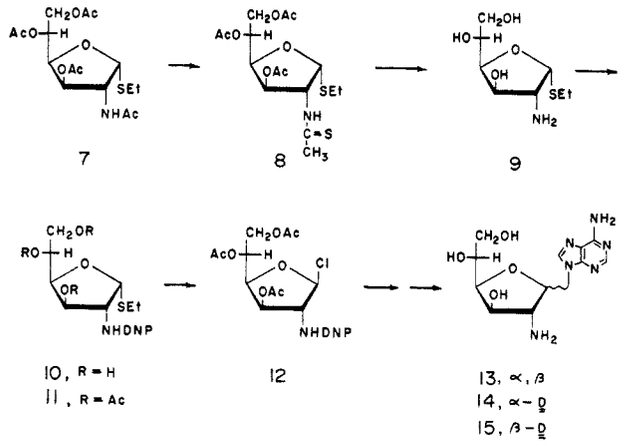

Figure 2.—**9**, **11**, and **12** were not obtained crystalline.

Ethyl 3,5,6-Tri-*O*-acetyl-2-deoxy-2-(thioacetamido)-1-thio-α-D-glucofuranoside (8).—Ethyl 2-acetamido-3,5,6-tri-*O*-acetyl-2-deoxy-1-thio-α-D-glucofuranoside[12,13] (**7**, 19.54 g) was treated with phosphorus pentasulfide (11.26 g) in pyridine (500 ml) as described above for the synthesis of **3**, except that the washing of the chloroform extract with 1 *N* hydrochloric acid was omitted. The final, dried chloroform solution was evaporated to a slightly yellow syrup by several coevaporations with toluene. This syrup was crystallized from ethyl acetate–ether to yield 14.06 g (69%) of a slighly yellow solid, mp 111–112°. This solid was treated with decolorizing carbon in methanol solution. Carbon and solvent removal and crystallization from ethyl acetate–ether afforded a pure material as white crystals: mp 111–112°; $[\alpha]^{21}D$ +125 ± 1° (*c* 3.72, chloroform); λ_{max}^{KBr} 3.05 (NH), 5.71, 5.81 (OAc), and 6.50 μm (NH, amide); X-ray powder diffraction 10.91 s, 8.93 s, 7.56 s (2), 6.15 vw, 5.43 vw, 4.95 s (1), 4.69 w, 4.52 w, 4.35 w, 4.05 m, 3.60 s (3), 3.33 w, 3.14 m, 2.96 w, 2.90 vw, 2.71 w, and 2.54 w.

Anal. Calcd for $C_{16}H_{25}NO_7S_2$: C, 47.17; H, 6.18; N, 3.44; S, 15.74. Found: C, 47.20; H, 6.50; N, 3.80; S, 15.84.

This compound was homogeneous by thin layer chromatography with chloroform–ethyl acetate (1:1) developer.

Ethyl 2-Deoxy-2-(2,4-dinitroanilino)-1-thio-α-D-glucofuranoside (10).—The above-described compound **8** (5.0 g) was heated with ammoniacal methanol (100 ml) as described above for the synthesis of compound **6**. To the final, dried syrup (obtained just before the previously described conversion into the dihydrochloride **6**) was added sodium hydrogen carbonate (0.71 g) in water (50 ml) and 1-fluoro-2,4-dinitrobenzene (1.58 g) in ethanol (50 ml), and the mixture was shaken overnight. The resultant solution was concentrated to a small volume, whereupon a yellow solid separated. The mixture was diluted with water, and the solid was removed by filtration, washed with water, dried by suction, and washed with benzene to yield 3.06 g (63% from **8**), mp 135–136°. Recrystallization from ethyl acetate afforded pure **10**: mp 136–137°; $[\alpha]^{24}D$ −43 ± 2° (*c* 1.75, methanol); λ_{max}^{KBr} 2.8–3.1 (OH, NH), 6.13, 6.22, 6.64 (aryl C=C), 6.58 (NH, NO_2), 7.46 (NO_2), 12.18 and 13.40 μm (substituted phenyl); X-ray powder diffraction 8.75 s, 8.04 m, 7.13 vw, 5.47 s (1, 1), 5.09 w, 4.84 s (3), 4.71 s, 4.19 vw, 3.95 s (1, 1), 3.73 w, 3.50 s (2), 2.99 w, 2.94 w, 2.83 vw, 2.75 vw, 2.69 w, 2.65 m, and 2.58 w.

Anal. Calcd for $C_{14}H_{19}N_3O_8S$: C, 43.19; H, 4.92; N, 10.79; S, 8.23. Found: C, 43.00; H, 4.76; N, 10.00; S, 8.30.

This compound was homogeneous by thin layer chromatography with ethyl acetate developer.

Ethyl 2-(Benzyloxycarbonylamino)-2-deoxy-1-thio-α-D-glucofuranoside.—To crude **9** (6.10 g) prepared from **8** (6.45 g) in water (30 ml) was added sodium hydrogen carbonate (1.3 g) and benzyloxycarbonyl chloride (2.4 ml). The mixture was stirred vigorously for 15 min. Upon addition of a small piece of ice, precipitation occurred. The solid was removed by filtration and washed consecutively with an aqueous solution of potassium hydrogen carbonate and with water to yield 3.20 g (57% from **8**), mp 126–130°. Recrystallization from ethyl acetate afforded pure material in a yield of 2.02 g (35% from **8**):

mp 139–140°; $[\alpha]^{24}D$ +122 ± 2° (*c* 1.93, methanol); λ_{max}^{KBr} 2.80–3.10 (OH, NH), 5.93, 6.51 ($NHCO_2R$), 6.05 (aryl C=C), 13.70, and 4.40 μm (substituted benzene); X-ray powder diffraction 8.93 s (1), 7.76 s (3, 3), 5.86 s (3, 3), 5.18 m, 4.84 s (2), 4.62 m, 4.46 m, 4.31 w, and 3.95 w.

Anal. Calcd for $C_{16}H_{23}NO_8S$: C, 53.76; H, 6.48; N, 3.91; S, 8.97. Found: C, 53.34; H, 6.23; N, 3.88; S, 8.88.

This substance was homogeneous by thin layer chromatography using ethyl acetate–methanol (9:1) developer.

Ethyl Tri-*O*-acetyl-2-(benzyloxycarbonylamino)-2-deoxy-1-thio-α-D-glucofuranoside.—Ethyl 2-(benzyloxycarbonylamino)-2-deoxy-1-thio-α-D-glucofuranoside (1.78 g) was acetylated overnight at room temperature with acetic anhydride (20 ml) and pyridine (20 ml). The precipitate that formed on pouring the mixture into ice and water was removed by filtration to yield 2.59 g. The solid was dissolved in dichloromethane, and the solution was washed consecutively with water, saturated aqueous, sodium hydrogen carbonate, and water. The syrup obtained on solvent removal from the dried (magnesium sulfate) dichloromethane solution was crystallized from dichloromethane–hexane to yield 2.29 g (95%): mp 121–122°; $[\alpha]^{25}D$ +125 ± 2° (*c* 2.48, methanol); λ_{max}^{KBr} 3.01 (NH), 5.75 (OAc), 5.90, 6.47 ($NHCO_2R$), 5.95 (aryl C=C), 13.17, and 14.23 μm (substituted benzene); X-ray powder diffraction 13.39 w, 10.65 s (3, 3), 8.42 s (2), 7.19 vw, 6.65 vw, 5.24 w, 4.90 s (1), 4.71 m, 4.37 w, 4.21 m, 4.00 m, 3.72 s (3, 3), 3.56 w, 3.40 m, 3.18 m, and 2.94 w.

Anal. Calcd for $C_{22}H_{29}NO_9S$: C, 54.66; H, 6.04; N, 2.89; S, 6.63. Found: C, 54.20; H, 6.00; N, 2.92; S, 6.93.

9-[3,5,6-Tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α,β-D-glucofuranosyl]adenine Picrate.—Acetic anhydride (50 ml) was added to a solution of **10** (4.87 g) in pyridine (50 ml), and the mixture was kept overnight at room temperature. The solution was poured into ice and water, and the precipitated syrup was separated by decantation and washed with water in the same manner. The washed syrup was dissolved in dichloromethane, and the solution was washed consecutively with cold, aqueous sodium hydrogen carbonate and with water. The dried (magnesium sulfate) solution was evaporated to dryness. Repeated evaporation with toluene removed the last traces of pyridine. The syrup was then dried in an oil pump vacuum overnight to yield 6.36 g (99%) of **11**. This syrup was homogeneous by thin layer chromatography with chloroform–ethyl acetate (9:1) developer.

Dry chlorine was passed for 10 min into an ice-cold solution of **11** (6.36 g) in dried (Drierite) dichloromethane (50 ml). The solution was evaporated to dryness, and the resultant syrup was transferred with 50 ml of dichloromethane to a stirred, azeotropically dried suspension of 6-*N*-acetyl-9-chloromercuriadenine[23] (12 g), cadmium carbonate (6 g), and Celite (6 g) in hot toluene (300 ml). The dichloromethane was removed by distillation, and the mixture was heated for 6.5 hr under reflux with vigorous stirring and under protection from moisture. The cooled mixture was filtered, and the filter cake was washed with a large volume of dichloromethane. The filtrate was evaporated to dryness, and the residue was extracted with dichloromethane. The extract was washed consecutively with 30% aqueous potassium iodide, cold, saturated, aqueous sodium hydrogen carbonate, and water. The dried (magnesium sulfate) extract was evaporated to dryness to yield 7.43 g. The residue was applied to 200 × 200 × 1 mm plates of silica gel (~100 mg per plate), and the plates were developed with ethyl acetate. The main yellow zone, R_f 0.25, was excised and eluted with acetone. The residue obtained on acetone removal was extracted with dichloromethane, and the solvent was removed by evaporation to yield 3.90 g (50% from **11**) of crude syrup.

To the above syrup (3.90 g) in ethyl acetate (40 ml) and methanol (160 ml) was added picric acid (4.5 g), and the mixture was heated for 30 min under reflux. The yellow, crystalline product which separated on cooling was removed by filtration and washed with methanol to yield 4.92 g (97%): mp 187–192° dec; $[\alpha]^{26}D$ +37 ± 2° (*c* 0.96, acetone); λ_{max}^{KBr} 5.70 (OAc), 5.88, 6.19, 6.37, 6.65 (picrate, aryl C=C, purine), 6.58, 7.58 (NO_2), and 13.43 μm. This crystalline picrate anomeric mixture exhibited a distinct X-ray powder diffraction diagram.

Anal. Calcd for $C_{29}H_{27}N_{11}O_{18}$: C, 42.61; H, 3.33; N, 18.85. Found: C, 42.97; H, 3.93; N, 18.93.

9-(2-Amino-2-deoxy-α,β-D-glucofuranosyl)adenine (13).—To a stirred solution of the above anomeric mixture of picrates (4.92 g) in acetone (320 ml) and water (80 ml) at 45–50° was added, portionwise, an excess of Dowex 1-X2 (OH^- resin, 50–100 mesh), and the mixture was stirred until it became colorless. The resin was removed by filtration and washed with a large volume of hot methanol. The filtrate and washings were evaporated to dryness, and the residue was triturated with methanol–dichloromethane until a filterable solid (1.46 g) was obtained. This material was decolorized by treating its aqueous methanol solution with activated carbon. The residue obtained on solvent removal was crystallized from aqueous ethanol to yield 0.88 g (49%): mp 214–222°; $[\alpha]^{25}D$ −41° (*c* 1.12, water); λ_{max}^{KBr} 2.90–3.10 (OH, NH), 6.01, 6.23, 6.40, and 6.82 μm (NH, purine); $\lambda_{max}^{H_2O}$ 262 nm (ε 14,400); nmr (deuterium oxide) δ 3.8–5.1 (solvent and sugar ring protons), 6.00 (0.6 H, isolated doublet, $J_{1',2'}$ = 2.5 cps, H-1'), 6.50 (0.4 H, isolated doublet, $J_{1',2'}$ = 5 cps, H-1'), 8.18 (2 overlapping singlets), and 8.33 and 8.37 ppm (distinct singlets, all 3 ascribed to H-2 and H-8); X-ray powder diffraction 8.58 m, 7.37 m, 5.68 s (2), 5.34 w, 4.92 s (3, 3), 4.71 w, 4.48 w, 4.31 s (3, 3), 4.02 s (1, 1), 3.78 vw, 3.63 vw, 3.40 s (1, 1), 3.09 wv, 3.01 vw, and 2.85 m.

Anal. Calcd for $C_{11}H_{16}N_6O_4$: C, 44.59; H, 5.44; N, 28.37. Found: C, 44.85; H, 5.85; N, 28.78.

Thin layer chromatography on silica gel with ethyl acetate–methanol (1:1) developer revealed two ninhydrin-positive components with R_f values 0.27 and 0.35. Paper chromatography with 1-butanol–ethanol–water (40:11:19) developer revealed two uv-absorbing and ninhydrin-positive components with $R_{adenine}$ 0.40 and 0.48.

Separation of the Anomeric 2-Amino-2-deoxy-D-glucofuranosyl Nucleosides 14 and 15.—Following the general procedure of Dekker,[19] the anomeric mixture of nucleosides (**13**, 500 mg) in methanol–water (3:7) (20 ml) was siphoned onto a column (31 × 3.1 cm) of Bio Rad AG1-X2 (OH^-, 200–400 mesh) resin, previously saturated with the same solvent mixture. Elution was effected with the same solvent mixture. The effluent was monitored by a uv analyzer, and 10-ml fractions were collected. At tube 79 a uv-absorbing component appeared and was completely removed at tube 118. At tube 137 the eluent was changed to 50% methanol, and a second uv-absorbing component appeared between tubes 165 and 206. The contents of tubes 79–118 (fraction 1) and tubes 165–206 (fraction 2) were separately pooled and evaporated to dryness. The residue from fraction 1 was crystallized from aqueous ethanol to yield 314 mg (63%) of **9-(2-amino-2-deoxy-β-D-glucofuranosyl)adenine (15)**: mp 225–226° dec; $[\alpha]^{22}D$ −57 ± 2° (*c* 1.23, water); λ_{max}^{KBr} 3.00–3.10 (NH, OH), 5.95, 6.23, 6.35, and 6.77 μm (NH, purine); $\lambda_{max}^{H_2O}$ 262 nm (ε 14,400); nmr (deuterium oxide) δ 3.8–5.1 (solvent and sugar ring), 6.00 (1 H, isolated doublet, $J_{1',2'}$ = 2.5 cps, H-1') and 8.18 and 8.37 ppm (2 H, singlets, H-2, H-8); X-ray powder diffraction 7.31 s (3), 5.68 w, 5.30 s (2, 2), 5.09 w, 4.74 w, 4.46 s (1, 1), 4.17 s (1, 1), 3.96 w, 3.76 w, 3.63 w, 3.40 s (2, 2), 3.11 w, 2.94 w, 2.80 s, 2.68 w, and 2.54 vw.

Anal. Calcd for $C_{11}H_{16}N_6O_4$: C, 44.59; H, 5.44; N, 28.37. Found: C, 44.66; H, 5.73; N, 28.37.

The residue from fraction 2 was crystallized from aqueous ethanol to give 153 mg (31%) of **9-(2-amino-2-deoxy-α-D-glucofuranosyl)adenine (14)**: mp 223–224° dec; $[\alpha]^{22}D$ −3 ± 1° (*c* 1.00, water); λ_{max}^{KBr} 2.90–3.10 (NH, OH), 5.95, 6.20, 6.38, and 6.80 μm (NH, purine); $\lambda_{max}^{H_2O}$ 262 nm (ε 14,500); nmr (deuterium oxide) δ 3.8–5.1 (solvent and sugar ring), 6.50 (1 H, isolated doublet, $J_{1',2'}$ = 5 cps, H-1'), and 8.18 and 8.33 ppm (2 H, singlets, H-2 and H-8); X-ray powder diffraction 11.48 m, 7.25 s (3), 6.60 w, 6.23 m, 5.86 vw, 5.40 w, 5.01 m, 4.82 w, 4.64 w, 4.41 s (2), 4.19 vw, 3.98 s, 3.72 vw, 3.56 s (1), 3.35 w, 3.27 w, 3.04 vw, and 2.95 vw.

Anal. Calcd for $C_{11}H_{16}N_6O_4$: C, 44.59; H, 5.44; N, 28.37. Found: C, 44.68; H, 5.58; N, 28.37.

Thin layer chromatography with ethyl acetate–methanol (1:1) developer showed that each of the components was homogeneous with the faster moving being the α-D anomer. The ir spectra of the two anomers were very similar except in the 10.3–12.4-μm spectral region.

Registry No.—**2**, 17478-49-8; **4**, 17478-50-1; **5**, 17478-51-2; **6**, 17478-52-3; **8**, 13190-62-0; **10**, 13190-63-1; **13**, 17519-22-1; **14**, 13190-59-5; **15**, 14402-55-2; ethyl 2-(benzyloxycarboxylamino)-2-deoxy-1-thio-α-D-glucofuranoside, 17478-57-8; ethyl tri-*O*-acetyl-2-(benzyloxycarbonylamino)-2-deoxy-1-thio-α-D-glucofu-

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ranoside, 17478-58-9; 9-[3,5,6-tri-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α,β-D-glucofuranosyl]adenine picrate, 17519-23-2.

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The Baeyer–Villiger Reaction of Alkyl Aryl Ketones[1]

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The Baeyer–Villiger reaction of nitroacetophenones with trifluoroperoxyacetic acid was studied. The normal preferential aryl migration was observed with the *meta* and *para* isomers, whereas a reversal of migration aptitudes of the nitrophenyl and methyl groups was observed with the *ortho* isomer (Ar/Me ratio, 0.06–0.10). A unique participation of the protonated "Criegee intermediate" has been suggested to account for the unusually active methyl migration. The study was extended to other nuclear substituted aromatic ketones. The electronic effects and possible participation of the substituents are discussed. The relative migration aptitudes of the substituents investigated were determined by product distributions.

In the course of degradation studies of tryptophan, it was necessary to study the oxidation of 2′-aminoacetophenone. The oxidizing agent, trifluoroperoxyacetic acid, which is effective for the oxidation of anilines to the corresponding nitro compounds, was employed.[3] It was found that the amino ketone was oxidized initially to the nitro ketone, 2′-nitroacetophenone (**1**), which then underwent the Baeyer–Villiger reaction to yield a mixture of methyl *o*-nitrobenzoate and *o*-nitrophenyl acetate. Pure 2′-nitroacetophenone was treated with excess peroxy acid under similar conditions, and the products were isolated and hydrolyzed to *o*-nitrobenzoic acid and *o*-nitrophenol. The ratio of phenol to the benzoic acid was found to be 0.06 by isolation procedure and 0.10 by a titration method (Table I). These values may be taken as a reflection of the ratio of methyl and aryl migration and unambiguously indicate that, in 2′-nitroacetophenone, the methyl group migration is about ten times the nitrophenyl migration.

For comparison the *meta* and *para* isomers, 3′- and 4′-nitroacetophenone (**2** and **3**), were treated in the same manner, and the products were analyzed by titration (Table I). The phenol/benzoic acid ratios with these two isomers were greater than unity, indicating that the normal preferential aryl migration had occurred even in the presence of the electron-withdrawing effect of the nitro group.

The unusual reversed order of preference for migration observed with the *ortho*-nitro compound **1** was considered to be of significance. The change in migration aptitude observed with this compound indicates that the nitro group in the *ortho* position participates in such a manner as to create a net effect which either retards the aryl migration, facilitates the methyl migration, or is involved in both of these effects.

Of the three nitroacetophenones, only the *meta* and *para* isomers (**2** and **3**) have been studied previously.[4–7] Conducting rate studies by following the consumption of peroxybenzoic acid in the oxidation of **2** and **3**, Friess and Soloway[7] were unable to isolate the expected ester products. Hawthorne and Emmons[5] gave only the rate constants for the reaction of 3′-nitroacetophenone (**2**) and other substituted acetophenones including 4′-bromo- and 4′-methylacetophenones. The 4′-chloroacetophenone was found to give 2.9% of methyl migration.[6] The product distribution in the reaction of **3** with trifluoroperoxyacetic acid is given in Table I.

When oxidized by peroxybenzoic acid in chloroform, all acetophenones which were studied gave no detectable amount of the corresponding methyl benzoate.[7] In other words, in no case was there evidence for methyl migration. Similarly, only phenols were obtained from peroxyacetic acid oxidation of 4′-nitro- and 4′-methoxyacetophenone.[4,8]

The order of preference for migration among alkyl groups in this rearrangement has been reported to be tertiary > secondary > primary > methyl.[4,6,9] Phenyl approximates isopropyl, cyclopentyl, and benzyl in migratory aptitude.[6] Thus, it can be generalized that methyl ketones will give mostly, if not entirely, acetate esters.[10] Furthermore, electron-releasing substituents enhance, whereas electron-attracting substituents decrease, the migratory aptitude of aryl groups.[6,11]

One could postulate the participation of the nitro group in the decomposition of the protonated Criegee intermediate **4**. The nucleophilic attack of the oxygen atom of the nitro group at one of the oxygen atoms of the peroxy ester linkage aids the leaving of the trifluoroacetic acid molecule, leading to the formation of a six-membered cyclic intermediate **5**.

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(2) Taken in part from the Ph.D. Dissertation presented by J. P. Li, to the Graduate School of the University of Kansas, Jan 1966.

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