peaks, a small peak at 2.2 min (0.3%), corresponding to **5**, a peak at 3.2 min (60%), which had the same retention time as that of **4**, and a third peak at 4.9 min (39.5%), which was **3**. After 15 min the same sample was applied on HPLC, and the same three peaks, but with different percentages, were observed, the peak at 2.2 min (1.5%), the peak at 3.2 min (85.5%), and the peak at 4.9 min (13.2%): ^{1}H NMR (acetone-d_6) δ 1.57 (3 H, d, J = 7.5 Hz, 5′-CH_3), 2.13 (4 H, m, 2′-H, 3′-H), 3.25 (2 H, 7, 4′-H), 3.94 (3 H, s, 6-OCH_3), 4.1 (1 H, m, 1′-H), 7.63 (1 H, s, H-7), 7.81 (1 H, dd, J = 4.5 and 8.5 Hz, H-3), 8.72 (1 H, dd, J = 2.1 and 9.0 Hz, H-4), 8.95 (1 H, dd, J = 1.5 and 5.4 Hz, H-2); EIMS, m/e (relative intensity), 275 (6.18) [M], 258 (1.98, 257 (0.98), 243 (1.16), 231 (1.11), 218 (3.06), 203 (4.50), 202 (6.51), 191 (7.02), 190 (7.88), 189 (10.03), 175 (8.75), 147 (8.88), 103 (4.53), 99 (4.98), 89 (93.90), 80 (100), 79 (48.47). A sulfate salt was also quite hygroscopic. A chloroplatinate derivative precipitated from an alcoholic solution of chloroplatinic acid. Two precipitations with DMF and ethanol gave a dark red crystalline powder that sinters at 270 °C. TLC (solvent system B) showed the product at R_f ~0.60 plus traces of contaminants at R_f ~0.76 and at the origin. Anal. ($C_{15}H_{21}N_3O_2$·$PtCl_2$) C, H, N.

Incubations. Glucose-6-phosphate dehydrogenase (G6PD), glucose 6-phosphate (G6P), NADPH, and glutathione (GSH) were purchased from Sigma Chemical Co. Blood specimens (30–40 mL) were obtained from normal and G6PD-deficient volunteers with sodium edetate as the anticoagulant. Washed erythrocyte suspensions (50%) were prepared in buffered dextrose saline solution as described previously[2] and incubated at 37 °C with compounds 1 through 6 individually. At the end of the 2-h incubation period, the reaction was stopped by placing the flasks in an ice bath for 5 min. The erythrocytes were separated by centrifugation at 1500g for 10 min at 5 °C. They were washed twice by resuspension in ice-cold buffered saline dextrose, recentrifugation, and finally resuspended to produce a 50% mixture. Aliquots (0.1 mL) were used for measurements of MetHb and GSH levels as described previously.[2]

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Registry No. 1, 90-34-6; 2, 80038-07-9; 2·H_2SO_4, 88563-35-3; 2·2HI, 88563-36-4; 3, 57695-07-5; 3·3HBr, 57514-28-0; 3·XH_2SO_4, 88563-38-6; 3 (chloroplatinate), 88563-39-7; 4, 87321-06-0; 4·3HBr, 88563-37-5; 5, 17605-92-4; 5·2HBr, 7505-74-0; 6, 67472-57-5; 7, 7402-16-6; 8, 90-52-8; 8 [bis(trifluoroacetyl) derivative], 88563-33-1; 9, 57742-99-1; 9 (*N*-trifluoroacetyl derivative), 88563-34-2; 10, 47136-26-5; 10·$2H_3PO_4$, 5443-73-2; 6-methoxy-8-nitroquinoline, 85-81-4; glutathione, 70-18-8.

Acetylenic Nucleosides. 3.[1] Synthesis and Biological Activities of Some 5-Ethynylpyrimidine Nucleosides

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Iodination of 1-(2,3,5-tri-*O*-acetyl-β-D-arabinofuranosyl)uracil furnished the 5-iodo derivative (Ib), which, on treatment with (trimethylsilyl)acetylene in the presence of catalytic amounts of $(Ph_3P)_2PdCl_2$/CuI and subsequent deblocking, afforded 1-β-D-arabinofuranosyl-5-ethynyluracil (Ie). Condensation of the trimethylsilyl derivative of 5-(dibromovinyl)uracil with 3-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-azido-D-arabinofuranosyl chloride, followed by treatment with phenyllithium, gave 1-(2-deoxy-2-azido-β-D-arabinofuranosyl)-5-ethynyluracil (IIb). Condensation of 3-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-D-arabinofuranosyl bromide with the trimethylsilyl derivative of 5-ethynylcytosine and subsequent removal of the protecting groups furnished 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-ethynylcytosine (IIIb). The structural assignment for IIb and IIIb was made by NMR and ORD spectra. Compounds Ie and IIIb inhibited the growth of leukemia L-1210 cells in culture by 50% at concentrations of 1.7×10^{-5} and 6×10^{-5} M, respectively. In addition, Ie and IIIb inhibited the replication of herpes simplex virus type I by 90% at concentrations of 2.8×10^{-5} and 5×10^{-5} M, respectively. Compound IIb did not show any antileukemic or antiherpes activity.

Previous studies[2] showed that the nature of the substituents at the C-5, as well as the C-2′, position of the pyrimidine nucleosides are important factors in the determination of biological activity. As part of our program of the design and synthesis of potential anticancer and antiviral nucleosides, we have been concerned with the synthesis of nucleosides substituted with the ethynyl function, which, in its size, is similar to the methyl group, but its electronegative effect on the pyrimidine ring closely approaches that of fluorine.[3] This report describes the synthesis and preliminary biological evaluation of 5-ethynyl derivatives of 1-β-D-arabinofuranosyluracil (Ie), 1-(2-deoxy-2-azido-β-D-arabinofuranosyl)uracil (IIb), and 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)cytosine (IIIb).

Chemistry. Acetylation of 1-β-D-arabinofuranosyluracil[4,5] with acetic anhydride in pyridine, followed by iodination[6] with iodine monochloride in methylene chlo-

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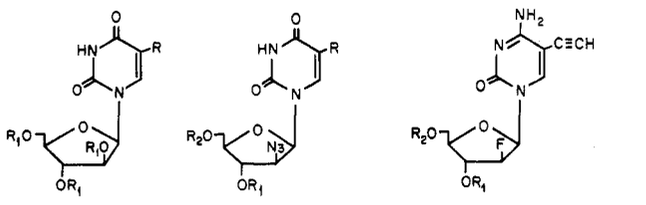

Ia, R = H; R_1 = $COCH_3$
b, R = I; R_1 = $COCH_3$
c, R = C≡CH; R_1 = $COCH_3$
d, R = C≡C-$Si(CH_3)_3$; R_1 = $COCH_3$
e, R = C≡CH; R_1 = H

IIa, R = CH=CBr_2; R_1 = $COCH_3$; R_2 = COC_6H_5
b, R = C≡CH; R_1 = R_2 = H

IIIa, R_1 = $COCH_3$; R_2 = COC_6H_5
b, R_1 = R_2 = H

ride, furnished 1-(2,3,5-tri-*O*-acetyl-β-D-arabinofuranosyl)-5-iodouracil (Ib), which was ethynylated by a slightly modified procedure of Robins et al.[7] A mixture of methylene chloride–triethylamine in place of triethylamine alone was used as the solvent for the reaction of Ib with (trimethylsilyl)acetylene in the presence of catalytic amounts of $(Ph_3P)_2PdCl_2$/CuI. This reaction gave a mixture of 1-(2,3,5-tri-*O*-acetyl-β-D-arabinofuranosyl)-5-ethynyluracil (Ic) and its trimethylsilyl derivative Id in an approximate 1:4 ratio. Attempts to separate Ic and Id on a silica gel column in methylene chloride/methanol led to desilylation of Id and isolation of Ic contaminated with a trace of Id. Treatment of Ic with potassium carbonate in methanol at room temperature gave 1-β-D-arabinofuranosyl-5-ethynyluracil (Ie).

Compound IIb was prepared by condensation of the trimethylsilyl derivative of 5-(2,2-dibromoethenyl)-2,4-(1*H*,3*H*)-pyrimidinedione[8] with 3-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-azido-D-arabinofuranosyl chloride[9] in 1,2-dichloroethane and in the presence of mercuric bromide, followed by treatment of the intermediate 5-dibromovinyl derivative IIa with phenyllithium in tetrahydrofuran. Compound IIb and its α-anomer were quite unstable, giving rise to more polar unidentified products.

Similarly, condensation of the trimethylsilyl derivative of 5-ethynylcytosine with 3-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-D-arabinofuranosyl bromide[10] provided IIIa as the major product, along with a partially deacetylated derivative of IIIa. Treatment of this mixture with potassium carbonate in methanol, followed by neutralization with Dowex (H^+) resin and purification by column chromatography, gave a mixture of free nucleoside IIIb and its α-anomer in almost equal ratio, as indicated by ^{13}C and ^1H NMR spectra. The isomers were separated in approximately 95% anomeric purity by reverse-phase high-pressure liquid chromatography and were further purified by crystallization to homogeneity.

The anomeric configuration of IIb and IIIb and their α-anomers was assigned on the basis of NMR and CD spectra. In the NMR spectra of the β-anomers IIb and IIIb, the signals arising due to H-1′ appeared at lower fields than those of the corresponding α anomers, which is in agreement with an empirical rule.[11] The larger coupling constants for the H-1′ protons of IIb and IIIb as compared to those of the corresponding α-anomers provided additional support to the β-configuration of IIb and IIIb. This assignment was further substantiated by a positive *Cotton effect* for the β-anomers and a negative one for the α-anomers.[12] In the NMR spectra, the signals arising from the protons of the exocyclic amino group of IIIb and its α-anomer appeared as two singlets, indicating the interaction between the protons of the amino group and the ethynyl function. A similar observation has been made previously in case of other 5-ethynylcytidine nucleosides.[1,13]

Biological Activity. Compounds Ie, IIb, and IIIb were evaluated for antitumor activity against L-1210 and B16 melanoma cell lines in culture. Whereas IIb was inactive at 10^{-4} M concentration, compound Ie was moderately inhibitory (1.7×10^{-5} M) to L-1210 cells, and IIIb showed moderate activity ($\sim 6 \times 10^{-5}$ M) against both cell lines.

The compounds were also evaluated for antiherpes activity in monkey kidney cells infected with herpes simplex virus type I strain KOS. Whereas IIb showed no antiherpes activity, compounds Ie and IIIb inhibited the replication of the virus with an ID_{90} of 2.8×10^{-5} and 5×10^{-5} M, respectively. These agents were also assessed for cytotoxicity to uninfected cells. After exposure of confluent, nondividing cells for 24 h to these compounds at concentrations as high as 10^{-4} M, a concentration that inhibited virus synthesis completely, no appreciable cytotoxicity was observed as determined by Neutral Red uptake.

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. UV spectra were measured on a Cary Model 118 spectrophotometer, and NMR spectra were measured on Varian XL-100 and Bruker 200 spectrometers using Me_4Si as the internal standard. TLC was performed on silica gel 60F-254 precoated plastic sheets (E. Merck), and column chromatography was carried out on silica gel (60–250 mesh; J. T. Baker no. 3405). Elemental analyses were performed by Robertson Laboratory, Florham Park, NJ, and were within ±0.4% of the calculated values.

1-(2,3,5-Tri-*O*-acetyl-β-D-arabinofuranosyl)-5-iodouracil (Ib). 2,2′-Anhydrouridine[4] (2.56 g, 11 mmol) was sequentially converted to 1-β-D-arabinofuranosyluracil[5] and the fully protected compound Ia by using acetic anhydride in pyridine, in 3.7 g (95%) yield. To a solution of Ia (3.7 g, 10 mmol) in 125 mL of methylene chloride was added 2.6 g (16 mmol) of iodine monochloride, and the reaction mixture was refluxed for 3 h. The mixture was cooled, diluted with 100 mL of methylene chloride, sequentially washed with 2% aqueous sodium bisulfite (2 × 100 mL) and water, and dried over anhydrous sodium sulfate. Evaporation of methylene chloride and trituration of the residue with ether gave light yellow solid in 4.5 g (91%) yield. This intermediate product for the synthesis of Ic was found by TLC in ethyl acetate to be sufficiently pure. The mass spectrum of the product showed molecular ion at 496.

1-(2,3,5-Tri-*O*-acetyl-β-D-arabinofuranosyl)-5-ethynyluracil (Ic). A mixture containing 1.24 g (2.5 mmol) of Ib, 0.13 g of $(Ph_3P)_2PdCl_2$, 0.13 g of CuI, 0.5 g (5.1 mmol) of (trimethylsilyl)acetylene, and 100 mL each of dry CH_2Cl_2 and Et_3N was stirred at room temperature for 20 h, in a tightly sealed flask, under nitrogen. The mixture was then evaporated to dryness and coevaporated with 100 mL of toluene. The residue was dissolved in 200 mL of CH_2Cl_2 and filtered through Celite. The filtrate was successively washed with 2% aqueous ethylenediaminetetraacetic acid (EDTA) and water and then dried (Na_2SO_4). TLC of the mixture in MeOH/CH_2Cl_2 (1:24) showed two products, possibly Ic and Id, in an approximate ratio of 1:4. Purification of this mixture on a silica gel column, using MeOH/CH_2Cl_2 (1:24) and subsequently CH_2Cl_2/Me_2CO (85:15), and evaporation of the appropriate fractions led to the isolation of Ic as the major product

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in 0.9 g (90%) yield: mp 142–144 °C; NMR ($CDCl_3$) δ 7.8 (s, 1, H-6), 6.27 (d, 1, H-1′), 3.17 (s, 1, C≡CH), 8.7 (br s, 1, NH), 2.03, 2.10, and 2.13 (3 s, 9, OAc).

1-β-D-Arabinofuranosyl-5-ethynyluracil (Ie). A solution of Ic (0.9 g, 2.3 mmol) in 100 mL of methanol was stirred at room temperature with 0.2 g of K_2CO_3 for 20 h. The mixture was neutralized with Dowex 50 (H^+) resin and filtered, and the filtrate was evaporated. Trituration of the residue with ether gave compound Ie in 0.3 g (82%) yield. Ie was further purified by silica gel chromatography, eluting with CH_2Cl_2/MeOH (6:1), and finally by recrystallization from CH_2Cl_2/Me_2CO: mp 188–194 °C dec; UV λ_{max} (MeOH) 285 nm (ε 10 304), 224 (8362); λ_{min} 249 nm (ε 2497); NMR (Me_2SO-d_6) δ 11.73 (br s, 1, N^3H), 8:02 (s, 1, H-6), 6.0 (d, 1, $J_{1',2'}$ = 4 Hz, H-1′), 5.64, 5.50, and 5.16 (m, 3 H, OH protons), 4.10 (s, 1, C≡CH), 3.60–4.06 (m, 5, H-2′, H-3′, H-4′, H-5′), 3.34 (s, ~2, H_2O). Anal. ($C_{11}H_{12}N_2O_6 \cdot 1.25H_2O$) C, H, N.

1-(3-O-Acetyl-5-O-benzoyl-2-deoxy-2-azido-β-D-arabinofuranosyl)-5-dibromovinyluracil (IIa). 5-Dibromovinyluracil (4.69 g, 15.8 mmol) was silylated by refluxing with hexamethyldisilazane.[8] The trimethylsilyl derivative was stirred at 50–55 °C for 3 days, with 3-O-acetyl-5-O-benzoyl-2-deoxy-2-azido-D-arabinofuranosyl chloride[9] [prepared from 14.0 g (38.6 mmol) of the corresponding 1-O-acetate], in 300 mL of 1,2-dichloroethane containing 12 g of dry mercuric bromide. The mixture was filtered with the aid of Celite, and the solids were washed with 200 mL of 1,2-dichloroethane. The combined solution was successively washed with 20% aqueous potassium iodide (2 × 200 mL), aqueous sodium bicarbonate, and water and dried (Na_2SO_4). The mixture was chromatographed twice on silica gel, eluting first with 500 mL of toluene/ethyl acetate (8:1) and then with toluene/ethyl acetate (8:2), to afford 3.04 g of low R_f material, 1.96 g of high R_f material, and 3.0 g of a mixture of high and low R_f material. The total yield was 8.0 g (84%). Proton NMR spectra indicated the high R_f material to be the α-anomer of IIa and the low R_f material (IIa): NMR ($CDCl_3$) of IIa δ 8.9 (br s, 1, NH), 8.3 (s, 1, H-6), 7.16–8.1 (m, protons of the benzoyl and vinyl groups), 6.13 (d, 1, $J_{1',2'}$ = 4.5 Hz, H-1′), 5.23, 4.6, and 4.43 (m, 5, H-2′, H-3′, H-4′, H-5′), 2.16 (s, 3, OAc); NMR of the α-anomer δ 9.4 (br s, 1, NH), 8.3 (s, 1, H-6), 7.16–8.1 (m, protons of the benzoyl and vinyl groups), 5.96 (d, 1, $J_{1',2'}$ = 2 Hz, H-1′), 5.2 and 4.46–4.7 (m, 5, H-2′, H-3′, H-4′, H-5′), 2.06 (s, 3, OAc).

1-(2-Azido-2-deoxy-β-D-arabinofuranosyl)-5-ethynyluracil (IIb). A solution of IIa (3.0 g, 5 mmol) in 200 mL of dry tetrahydrofuran was cooled in a dry ice–acetone bath, and to this solution was added phenyllithium (22 mL, 41.7 mmol; 1.9 M solution in benzene/ether). The mixture was stirred for 2 h in a dry ice/acetone bath and then for 2 h in ice/water, diluted with 100 mL of methanol, neutralized with Dowex 50 (H^+) resin, and filtered. The resin was washed with methanol, and the combined solution was evaporated to dryness. The residue was triturated with ether and the ether-insoluble material, dissolved in a small amount of methanol, was poured on a dry silica gel column. The column was washed first with 300 mL of methylene chloride and then with 9:1 methylene chloride/2-propanol. The fractions containing compound IIb were combined and evaporated. The residue was dissolved in ethanol, treated with charcoal, and filtered, and the filtrate was evaporated to a small volume. Methylene chloride was added to this solution and cooled for crystallization. The crystals were filtered and washed with ether; the product that precipitated from the filtrate was filtered and combined with the first crop. Compound IIb was obtained in 0.565 g (39%) yield: mp (decomposition at broad range) 260–280 °C; UV λ_{max} (MeOH) 287, 225 nm; NMR (Me_2SO-d_6/H_2O) δ 8.34 (s, 1, H-6), 6.14 (d, 1, $J_{1,2'}$ = 4.5 Hz, H-1′) 4.45 (t, 1, $J_{2',3'}$ = 4.5 Hz, H-2′), 4.06 (q, 1, $J_{3',4'}$ = 5 Hz, H-3′) 3.64–3.76 (m, other sugar protons), 3.19 (s, 1, C≡CH). Anal. Calcd for ($C_{11}H_{11}N_5O_5$): C, 45.05; H, 3.75; N, 23.89. Found: C, 43.69; H, 3.94; N, 19.42.

The α-anomer of IIb was prepared by the procedure described above for IIb: UV λ_{max} (MeOH) 286 nm, 224; NMR (acetone-d_6) δ 8.07 (s, 1, H-6), 5.90 (d, 1, $J_{1',2'}$ = 4.4 Hz, H-1′). Although both compound IIb and its α-anomer were obtained in the crystalline forms and were chromatographically homogenous (CH_2Cl_2/2-propanol, 9:1), they did not give satisfactory elemental analyses. They decomposed when kept in solutions, and to a lower degree in the solid form even at 4 °C, as indicated by a change in color and by the appearance on TLC, in the above solvent system, of more polar unidentified products. These compounds start decomposing soon after purification to homogeneity.

1-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)-5-ethynylcytosine (IIIb). 5-Ethynylcytosine (0.85 g, 6.3 mmol) was converted to the trimethylsilyl derivative[1] and stirred at room temperature with 3-O-acetyl-5-O-benzoyl-2-deoxy-2-fluoro-D-arabinofuranosyl bromide[9] (prepared from 1.9 g, 5.6 mmol of the corresponding 1-O-acetate) in 200 mL of 1,2-dichloroethane containing 2.5 g of mercuric bromide (dried by distillation with toluene). The stirring was continued for 5 days at room temperature, and then the mixture was heated at 50–60 °C for 2 h. The mixture was filtered with the aid of Celite, and the solids were washed with 150 mL of 1,2-dichloroethane. The combined solution was successively washed twice with 20% aqueous potassium iodide, aqueous sodium bicarbonate, and water and dried (Na_2SO_4). TLC of this solution in ethyl acetate/methanol (9:1) showed one major spot, together with a minor spot having a lower R_f, which presumably was the partially deacylated product. Evaporation of the solution afforded 2 g (77%) of the crude mixture, which was dissolved in 150 mL of methanol and stirred with 0.2 g of potassium carbonate at room temperature for 15 h. The solution was neutralized with Dowex 50 (H^+) resin and filtered. The resin was washed with 100 mL of methanol, and the combined solution, evaporated to a small volume, was chromatographed twice on silica gel, eluting successively with 500 mL of CH_2Cl_2, 500 mL of CH_2Cl_2/MeOH (8:1) and CH_2Cl_2/MeOH (4:1). The appropriate fractions were combined and evaporated to yield 0.738 g (57%) of the product which showed a single spot by TLC in CH_2Cl_2/MeOH (4:1). However, the ^{13}C NMR spectrum and HPLC using reverse phase (Bondpack C_{18}, Waters) showed it to be a mixture of IIIb and its α-anomer in an almost equal ratio. The anomers were separated by reverse-phase high-pressure liquid chromatography in water/methanol (25:1) and obtained in approximately 95% purity. Further purification was achieved by recrystallization from ethanol. α-Anomer: mp 220–228 °C dec; NMR (Me_2SO-d_6) δ 7.96 (s, 1, H-6), 7.86 and 6.96 (2 br s, 2, exocyclic NH_2), 5.94 (q, 1, $J_{1',2'}$ = 1.5 Hz, $J_{1',F}$ = 16.2 Hz, H-1′), 4.40 (s, 1, C≡CH). The remaining protons were also accounted for. β-Anomer: mp 184–188 °C dec; UV λ_{max} (MeOH) 292 nm (ε 9916), 233 (19 150); NMR (Me_2SO-d_6) δ 8.10 (d, 1, $J_{6,F}$ = 0.9 Hz, H-6), 7.90 and 7.0 (2 br s, 2, exocyclic NH_2), 6.12 (q, 1, $J_{1',2'}$ = 3.9 Hz, $J_{1',F}$ = 17.2 Hz, H-1′), 5.90 and 5.20 (m, 2, OH groups), 5.04 (m, 1, H-2′), 4.44 (s, 1, C≡CH), 4.22 (m, 1, H-3′), 3.86 (m, 1, H-4′), 3.66 (m, 2, H-5′). Anal. ($C_{11}H_{12}FN_3O_4$) C, H, N, F.

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Registry No. Ia, 14057-18-2; Ib, 84500-33-4; Ic, 88425-49-4; Id, 88425-50-7; Ie, 84558-90-7; IIa, 88425-51-8; IIa (α isomer), 88425-55-2; IIb, 88425-52-9; IIb (α isomer), 88425-53-0; IIIa, 88425-56-3; IIIa (α isomer), 88425-57-4; IIIb, 85714-55-2; IIIb (α isomer), 88425-54-1; (trimethylsilyl)acetylene, 1066-54-2; 5-(dibromovinyl)uracil, 61135-31-7; 3-o-acetyl-5-o-benzoyl-2-deoxy-2-azido-D-arabinofuranosyl chloride, 67014-24-8; 1,3-o-diacetyl-5-O-benzoyl-2-deoxy-2-azido-D-arabinofuranose, 73952-84-8; 5-ethynylcytosine, 65223-79-2; 3-o-acetyl-5-o-benzoyl-2-deoxy-2-fluoro-D-arabinofuranosyl bromide, 56632-81-6.