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Rearrangement of Anhydropyrimidine Nucleosides in Liquid Hydrogen Fluoride. Mechanism, Scope, and Synthetic Studies

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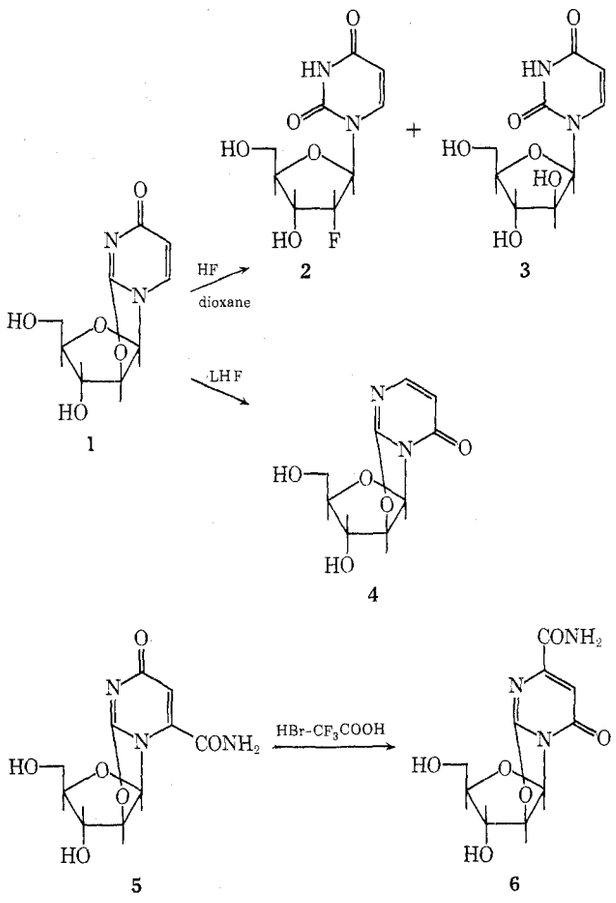
In contrast to the reaction of 2,2′-anhydro-1-β-D-arabinofuranosyluracil (1) with HF in dioxane which yields 2′-fluoro-2′-deoxyuridine (2), liquid hydrogen fluoride treatment of 1 resulted in rearrangement of the nucleosidic bond from N-1 to N-3. The mechanism proposed to account for the formation of 2,2′-anhydro-3-β-D-arabinofuranosyluracil (4) involves N-1–C-1′ bond cleavage of the protonated anhydro nucleoside with the formation of a resonance-stabilized carbonium ion in the carbohydrate portion of the molecule. Re-formation of the nucleosidic bond by electrophilic attack yields the thermodynamically more stable N-3 isomer. Other 2,2′-anhydropyrimidine nucleosides underwent similar rearrangement in liquid hydrogen fluoride, but 2,3′ and 2,5′-anhydro compounds were cleaved to the heterocyclic base. Cleavage of the anhydro bond of the rearranged nucleoside by aqueous base treatment yielded 3-β-D-arabinofuranosylpyrimidines. The di-*O*-benzoyl derivative of 4 (**20b**) served as a useful intermediate for the preparation of 3-β-D-ribofuranosyluracil (**21**) and 2′-deoxy-3-β-D-ribofuranosyluracil (**24**).

Aqueous acid or base hydrolysis of 2,2′-anhydropyrimidine nucleosides results in cleavage of the anhydro bond at C-2 of the pyrimidine nucleus with the formation of arabinosyl nucleosides.[1] In contrast, treatment of 2,2′-anhydro nucleosides under anhydrous conditions with hydrogen halides yields 2′-halogeno-2′-deoxyribofuranosylpyrimidine nucleosides. In this manner, 2′-chloro- and 2′-bromo-2′-deoxyuridine[2] have been obtained by reaction of 2,2′-anhydrouridine (1) with HCl in dioxane or HBr in trifluoroacetic acid, respectively. 2′-Chloro- and 2′-bromo-2′-deoxycytidine have been prepared from 2,2′-anhydrocytidine by reaction with hydrogen halides in DMF.[3] Treatment of 1 with hydrogen fluoride in dioxane solution gives 2′-fluoro-2′-deoxyuridine (2) in moderate yield.[2,4] Conflicting reports[3,5] exist as to the applicability of the HF–dioxane method for the preparation of the 2′-fluoro-2′-deoxy analog of cytidine from 2,2′-anhydrocytidine. The preparation of 2′-fluoro-2′-deoxycytidine from 2 by standard synthetic sequences has been reported.[4]

Fluorinated nucleoside 2 is desired in our laboratory as a precursor for the preparation of the corresponding 2′-fluorinated pyrimidine polynucleotides.[6,7] However, our large-scale preparations of 2, which are carried out essentially as reported,[2,4] contain a 3:2 ratio of 2 and 1-β-D-arabinofuranosyluracil (3). Nucleoside 3 is derived from 1 by hydrolytic cleavage, presumably from traces of moisture which are introduced into the mixture of 1 and dioxane during the addition of liquid hydrogen fluoride. Although 2 can readily be separated from 3 by acetylation[4] of the reaction products, our attempts to improve the yield of 2 were not successful. We therefore explored the reaction of 1 with neat liquid hydrogen fluoride (LHF) (Scheme I).

Treatment of 1 with LHF at elevated temperatures unexpectedly resulted in rearrangement of the nucleosidic linkage from N-1 of the uracil ring to N-3, with retention of the anhydro bond, to yield 2,2′-anhydro-3-β-D-arabinofuranosyluracil (4). We have previously reported the proof of

Scheme I

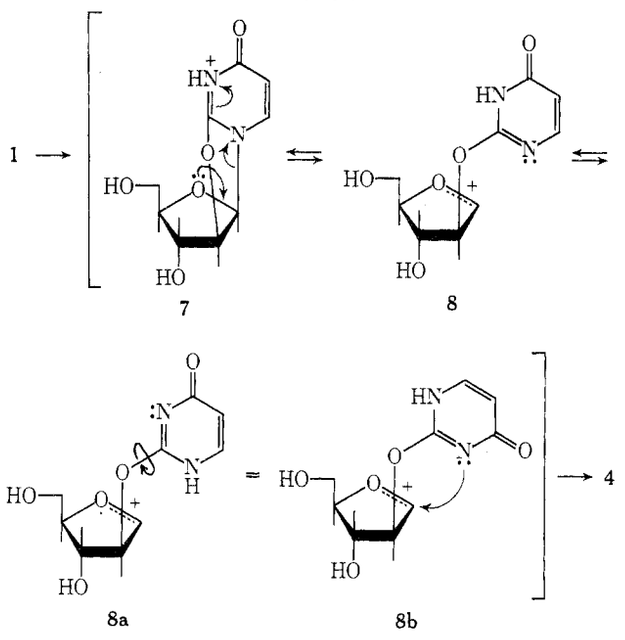


structure of this novel pyrimidine anhydro nucleoside.[8] The analogous rearrangement of 2,2′-anhydro-1-β-D-arabi-

nofuranosyluracil-6-carboxamide(**5**) to the N-3 isomer **6**, on treatment with trifluoroacetic acid saturated with HBr, has also been reported.[9] In view of the novelty of the 2,2′anhydro-N-3-pyrimidine nucleosides prepared by this rearrangement, we have further studied the mechanism and scope of the LHF-induced rearrangement as well as some synthetic transformations in this series of pyrimidine nucleosides. This report is concerned with the results of these studies.

Mechanism. The mechanism by which **1** rearranges to **4** in superacid media[10,11] is of interest in view of the reported facile cleavage of nucleosidic bonds in LHF.[12] Upon dissolution of **1** in LHF, protonation of the uracil nucleus occurs to give **7** (Scheme II). Pyrimidine anhydro nucleosides are known to be protonated, even by such weak acids as benzoic acid,[13] and cations of uracil and its alkylated derivatives have been observed in superacid solution.[14] Migration of the free electron pair in protonated anhydro nucleoside **7**, from N-1 into the heterocyclic ring, takes place with concurrent cleavage of the nucleosidic bond. Scission of the N-1–C-1′ bond gives rise to resonance-stabilized oxocarbonium ion **8**. A similar mechanism has been proposed for the aqueous acid catalyzed hydrolysis of the nucleosidic bond in pyrimidine nucleosides[15,16] and may also be the mechanism operative in the LHF-induced degradation of nucleosides and polynucleotides. Rotational equilibration about the LHF-stable O-2–C-2′ imino ester bond[17] then takes place. Re-formation of the nucleosidic bond from intermediates **8** occurs on cooling of the reaction mixture to give the thermodynamically more stable N-3 anhydro nucleoside **4**.

Scheme II



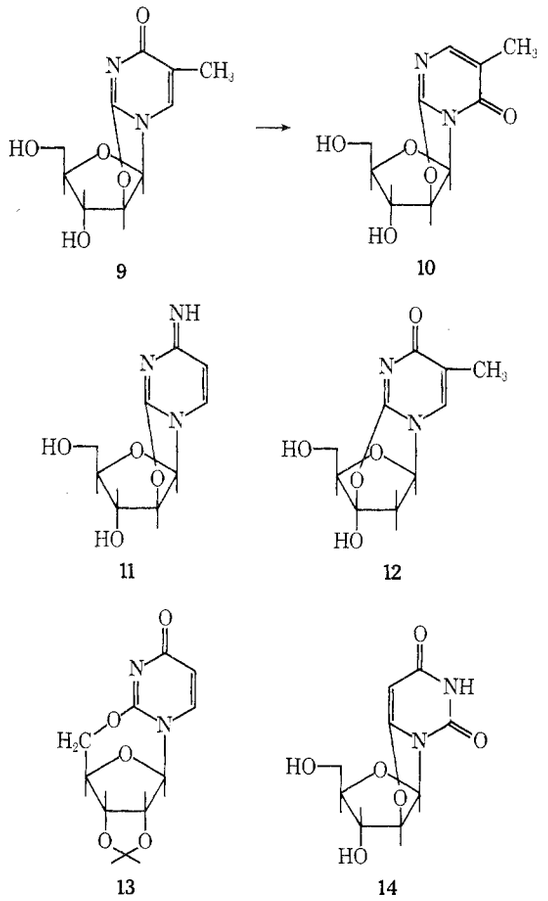
It should be noted that this mechanism differs from that proposed[18] by Tolman and coworkers for the rearrangement of **5** in HBr–CF_3COOH. In LHF, the poor nucleophilicity of fluoride ion makes displacement of the nucleosidic bond by F^- to form a glycosyl fluoride unlikely. Formation of a stabilized C-1′ carbonium ion followed by electrophilic attack of the neighboring heterocyclic ring is thus the more favored mechanism for the observed rearrangement in LHF. The uniqueness of HF–dioxane as a selective agent for the nucleophilic displacement of the anhydro bond in **1** to give **2**, in contrast to the rearrangement of **1** in LHF, is not readily apparent.

The preferential rearrangement of **1** to **4** cannot be explained on the basis of steric hindrance. An inspection of molecular models indicates that there is less steric hindrance in intermediate **8a** than in **8b** owing to the 4-oxo function. Reasons for re-formation of the nucleosidic bond from intermediate **8b** at the more hindered N-3 position, to give **4** as the major reaction product, are not evident. It has, however, been reported that diazomethane treatment of 2-methoxy-4-pyrimidone, a compound similar to cleaved intermediates **8**, results in preferential introduction of the second methyl group in the more hindered N-3 position.[19]

Thermodynamic control of the product distribution in the rearrangement of **1** to **4** has been shown by equilibration experiments (see Experimental Section for details). Treatment of either anhydro nucleoside **1** or **4**, with LHF at 80° for 18 hr, resulted in approximately the same N-1–N-3 product distribution with the N-3 isomer predominating by a ratio of approximately 7:2. It should be noted that only traces of uracil, resulting from cleavage of both the nucleosidic and anhydro bonds, were detected in these reactions. No other products could be demonstrated by tlc methods.

Scope. We have further investigated the rearrangement of some other pyrimidine anhydro nucleosides in LHF. Treatment of 2,2′-anhydro-1-β-D-arabinofuranosyl-5-methyluracil (**9**)[2] with LHF under standard conditions yielded the corresponding N-3 isomer **10** (Scheme III), in

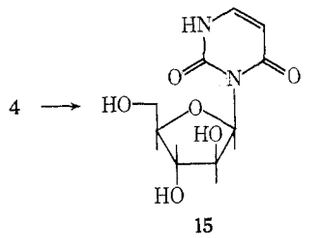
Scheme III



addition to traces of 5-methyluracil and unreacted starting material. The nmr spectrum of **10** clearly indicated H-1′ as a doublet with $J_{1'-2'}$ = 5.5 Hz, indicative of the cis relationship between H-1′–H-2′. Allylic coupling (J = 1.5 Hz) was observed between H-6 (δ 7.55) and the 5-methyl protons.

Thin layer chromatographic evidence indicated that

Scheme IV



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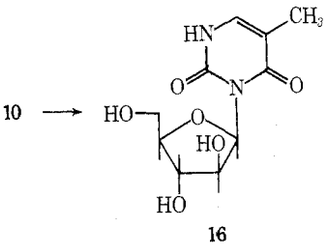


16

2,2′-anhydro-1-β-D-arabinofuranosylcytosine hydrochloride[5] (**11**) underwent reaction in LHF. However, attempts to isolate the rearranged N-3 product were unsuccessful owing to slow hydrolysis of the 4-amino group as indicated by a change in tlc migration of the reaction product. Complete hydrolysis of both the amino and anhydro functions was accomplished by ammonium hydroxide treatment. Acetylation of this crude mixture with acetic anhydride–pyridine yielded an approximately equimolar mixture of tetraacetyl-1-β-D-arabinofuranosylcytosine and triacetyl-3-β-D-arabinofuranosyluracil (**17a**) as the only nucleosidic products.

Treatment of 2,3′-anhydro-1-(2′-deoxy-β-D-lyxofuranosyl)thymine (**12**)[13a] or 2′,3′-*O*-isopropylidene-2,5′-anhydro-1-β-D-ribofuranosyluracil (**13**)[20] with LHF at 80° for 18 hr resulted in cleavage of both the anhydro and nucleosidic bonds. The free pyrimidine base was isolated from these reaction mixtures in nearly quantitative yield. Polymerization of the carbohydrate portion of the molecule was indicated by the formation of a dark, water-insoluble residue. Attempts were also made to rearrange **12** and **13** under milder temperatures and/or shorter periods of time. In cases where extensive degradation of the parent anhydro nucleoside to free base did not occur, conversion of **12** or **13** to products was minimal. The nucleosidic bond in anhydro nucleosides **12** (six-membered anhydro ring) and **13** (seven-membered anhydro ring) is apparently cleaved in LHF in an analogous manner to the nucleosidic bond in the 2,2′-anhydro nucleosides (five-membered anhydro ring). However, the distance from the C-1′ carbonium ion to the heterocyclic ring nitrogens is of sufficient length to prevent reformation of the nucleosidic bond at either N-1 or N-3. Further hydrolysis of the cleaved intermediates liberates the free base. 6,2′-Anhydro-1-β-D-ribofuranosyluracil (**14**)[21] was isolated unchanged upon treatment with LHF under the usual reaction conditions. This anhydro nucleoside is reported to be relatively stable in strong acid solution.[21]

Synthetic Transformations. The anhydro bond of the 2,2′-anhydro N-3 nucleosides, **4** and **10**, was rapidly cleaved by treatment with aqueous base to yield the N-3 nucleosides, **15** and **16** (Scheme IV). The large bathochromic shift observed for **15** and **16** in alkaline solution confirm the site of the nucleosidic bond at N-3 of the uracil chromophore.[22] The assignment of the arabino configuration for **15**, and thus of **4**, was made on the basis of nmr spectroscopy. The large coupling constant (8 Hz), together with the observed downfield shift (~0.4δ)[23] of the anomeric proton from that reported[24] for the corresponding ribo nucleoside (see also below), substantiate a cis arrangement of protons at H-1′–H-2′. It is noteworthy that the anomeric proton of **15** in DMSO-d_6–D_2O solution appears as an unsymmetrical doublet as a result of virtual coupling[25] between H-1′ and H-2′–H-3′. In D_2O solution, the anomeric proton appeared as the expected doublet.

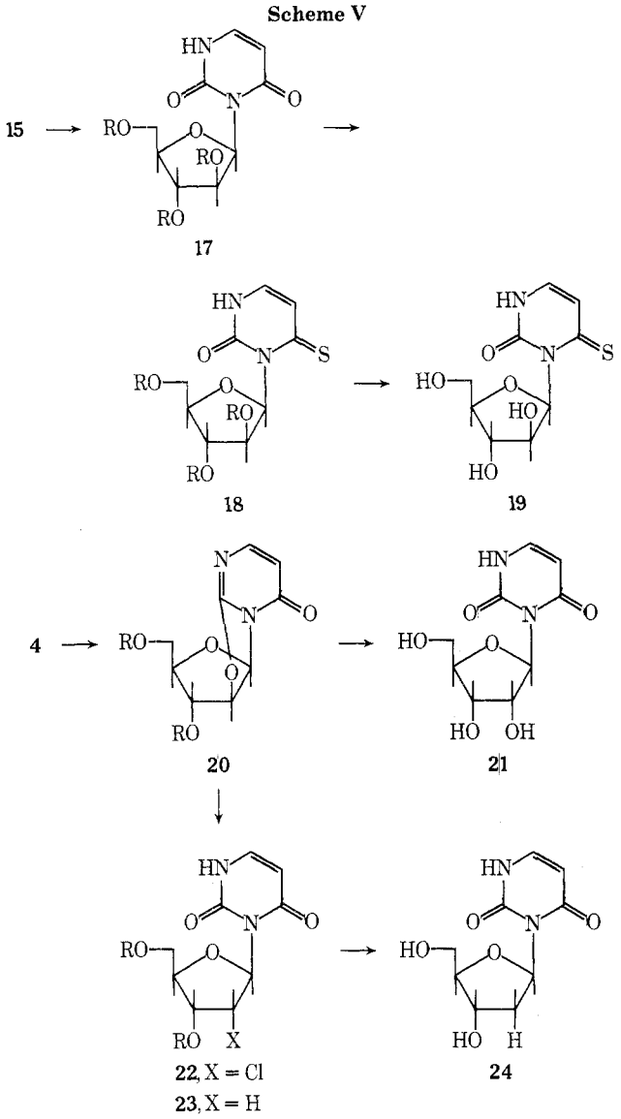
Although arabino nucleoside **15** could be isolated in crystalline form, it was more convenient to convert the syrupy hydrolysis product to crystalline acyl derivatives **17** for further synthetic transformations. Thiation of tribenzoate **17b** was smoothly effected by treatment with P_2S_5 in dioxane. Assignment of the thio group to the 4 position in **18** rests on analogy with the thiation of 3-methyluracil[26] and tri-*O*-benzoyl-3-β-D-ribofuranosyl-6-methyluracil.[27] Removal of the blocking groups by base-catalyzed methanolysis yielded the readily crystalline thioxo nucleoside **19**. The H-1′ proton signal for **19** (δ 7.51) was considerably shifted downfield from the H-1′ signal (δ 6.65) of the parent oxo nucleoside as a reflection of the magnetic anisotropy of the thione group.[28]

Conversion of thione **19** to a 4-amino derivative was attempted by reaction with methanolic or liquid ammonia under a variety of temperature conditions, or by oxidation of the thione to the sulfonate followed by reaction with aqueous ammonia.[29] Under conditions where reaction of **19** occurred (loss of starting material by tlc and uv), further work-up of these reactions resulted in regeneration of the 2,4-dioxo-N-3-substituted uracil chromophore. The inability to isolate a 4-amino compound is probably due to participation at C-4 by the 2′-*arabino*-hydroxyl group.[30] These results mirror those obtained upon rearrangement of **11** in LHF.

Reaction of **4** with acetic anhydride or benzoyl chloride in pyridine solution yielded the di-O-acylated derivatives **20** (Scheme V). Anhydro ring opening, with benzoyl participation, was effected by treatment of **20b** with boron trifluoride etherate[31] in refluxing methanol. The mixture of 2′(3′)-*ribo*-hydroxy benzoates thus obtained was further hydrolyzed to give 3-β-D-ribofuranosyluracil (**21**)[24] in moderate overall yield. It should be noted that whereas both the arabino nucleoside **15** and the ribo nucleoside **21** had the same tlc migration in chloroform–methanol solvents, these compounds were readily distinguishable by nmr and chemical means. The H-1′ proton of **21** (δ 6.26) exhibited a small H-1′–H-2′ coupling (3.5 Hz) which was further diminished upon the formation of an isopropylidene derivative.

Anhydro nucleoside **4** was converted to 2′-deoxy-3-β-D-ribofuranosyluracil (**24**) by the series of reactions described by Holý.[32] Anhydrous hydrogen chloride treatment of dibenzoate **20b** in DMF solution resulted in cleavage of the anhydro bond by nucleophilic displacement to give the 2′-chloro-2′-deoxyribo derivative **22b** as an analytically pure foam. The nmr spectrum of **22b**, in $CDCl_3$ solution, showed H-1′ (δ 6.82) as a doublet with $J_{1',2'}$ = 3.5 Hz, in contrast to the larger coupling constant ($J_{1',2'}$ = 6.0 Hz) observed for the H-1′ proton (δ 6.65) of **20b**, indicating inversion at C-2′ to the ribo configuration. In addition, the C-2′ proton (δ 5.42) was observed as an unsymmetrical quartet with $J_{2',3'}$ = 7.0 Hz. Hydrogenolysis of the 2′-chloro function in **22b** was smoothly effected by use of tri-*n*-butyltin hydride in refluxing benzene solution in the presence of a free-radical initiator to give the 2′-deoxy benzoylated nucleoside **23b** in pure crystalline form after chromatography. The H-1′ proton of **23b** was observed in $CDCl_3$ as an unsymmetrical quartet (δ 6.93, $J_{1',2',2''}$ = 4 and 8 Hz, $W_{1/2}$ = 13.5 Hz) in contrast to the expected pseudo-triplet.[33] Similar excep-

Scheme V



a series, R = $COCH_3$
b series, R = COC_6H_5

tions to the general rule for the assignment of anomeric configuration in 2′-deoxynucleosides have been observed.[34]

Debenzoylation of crude **23b** was smoothly accomplished by treatment with methanolic sodium methoxide. After purification by column chromatography, 2′-deoxy-3-β-D-ribofuranosyluracil (**24**) was obtained as a crystalline solid which could not be obtained in a solvent-free state with melting point comparable to that previously reported for this compound.[35] Several recrystallizations from 2-propanol, the reported crystallization solvent, did not give analytically pure material, although our product migrated as a single spot on tlc and had the reported spectroscopic characteristics.

It should be noted that attempts to apply the LHF-induced migration of nucleosidic bonds to the more acid-labile purine series were unsuccessful. Treatment of 8,2′-anhydro-8-oxo-9-β-D-arabinofuranosyladenosine with LHF resulted in a nearly quantitative recovery of 8-oxoadenine.

Experimental Section

General Procedures. Melting points were determined with a Thomas-Hoover apparatus (capillary method) and are uncorrected. Ultraviolet spectra were recorded on a Cary Model 15 spectrometer using previously reported procedures[6a] and nuclear magnetic resonance spectra were measured with a Varian A-60D (Sadtler Laboratories, Philadelphia, Pa.) or a Varian T-60A spectrometer in the solvents indicated with TMS or DSS as an internal standard. Values given for coupling constants (hertz) and chemical shifts (δ) are first order. Thin layer chromatographic separations were carried out on microscope slides (1 × 3 or 2 × 3 in.) coated with thin layers (0.25 mm) of silica gel GF-254 (EM reagents). Materials were detected with uv light and/or charring after spraying with 20% sulfuric acid in ethanol. Preparative column chromatographic separations were carried out over silica gel G (EM reagents) by a described method.[36] Evaporations were carried out under reduced pressure with bath temperatures below 45°. Microanalyses were performed by Research Division Analytical Services, Miles Laboratories, and by Galbraith Laboratories, Inc., Knoxville, Tenn.

General Procedures for Reactions with Liquid Hydrogen Fluoride. The hydrogen fluoride utilized in these experiments was obtained from Matheson Gas Products and was 99.9% minimum liquid phase purity. The desired amount of LHF was poured out of an inverted tank as directed[37] into plastic cylinders and then poured into a precooled (5°) Monel (40 ml) or stainless steel (200 ml) autoclave. The sealed autoclave was heated in a thermostated oil bath for the indicated time period. After cooling in ice, the autoclave was opened and the dark contents were poured into a plastic beaker. With magnetic stirring, the LHF was evaporated with the aid of a stream of warm air from a blower. The dark residue was dissolved in water and the solution was neutralized by the addition of solid calcium carbonate. Ethanol was added at intervals to control the foaming. The resulting neutral suspension was treated with charcoal, warmed on the steam bath, and filtered through Celite. The filtrate was further processed as described below.

2,2′-Anhydro-3-β-D-arabinofuranosyluracil (4). A mixture of 1[38] (10.0 g, 44.6 mmol) and LHF (100 ml) was heated at 80° for 18 hr. The aqueous filtrate, obtained after neutralization of the reaction mixture, was evaporated to a thick syrup which was not allowed to crystallize, but was dissolved in chloroform–methanol and chromatographed on silica gel (1 kg) using 5:1 chloroform–methanol as the eluent. Fractions containing the desired product were combined, evaporated, and azeotroped with ethanol to give a foam. Crystallization of the foam was effected from a small amount of methanol with the addition of chloroform. After cooling overnight, the crystals were collected, washed with methanol–chloroform followed by chloroform, and dried at 60° to give 3.76 g of **4**, mp 144–146°. A second crop of material (1.57 g) with mp 144–146° was obtained by further processing of the mother liquor. The overall yield of **4** was 5.33 g (53%).

Material prepared in another reaction was recrystallized from methanol–chloroform to give an analytical sample of 2,2′-anhydro-3-β-D-arabinofuranosyluracil (**4**): mp 144–146°; λ_{max} (pH 2, 7) 271 nm (ε 6900), λ_{min} (pH 2, 7) 233 (900), λ_{max} (pH 12) 272 (6800), λ_{min} (pH 12) 235 (1100); nmr (DMSO-d_6) δ 7.73 (1 H, d, H-6), 6.48 (1 H, d, H-1′), 6.02 (1 H, d, H-5, J_{6-5} = 7 Hz), 5.82 (1 H, d, 3′-OH, $J_{3'-3'OH}$ = 4.5 Hz, exchanges with D_2O), 5.21 (1 H, d, H-2′, $J_{1'-2'}$ = 5.5 Hz), 4.86 (1 H, t, 5′-OH, $J_{5'A-5'B-5'-OH}$ = 5.5 Hz, exchanges with D_2O), 4.47 (1 H, m, H-3′), 4.12 (1, m, H-4′), 3.35 (2 H, m, H-5′A, -5′B, changes to d with J = 4.5 Hz on D_2O addition).

Anal. Calcd for $C_9H_{10}N_2O_5$: C, 47.79; H, 4.46; N, 12.38. Found: C, 47.72; H, 4.36; N, 12.25.

Equilibration Experiments. The appropriate anhydro nucleoside, **1** or **4** (0.10 g), was treated with LHF (10 ml) at 80° for 18 hr. After work-up in the usual manner, the resulting aqueous solution was evaporated to a syrup which dissolved in methanol. A portion of this methanolic solution was applied to 2 × 3 in. thin layer slides and the slides were developed with 6:1 chloroform–methanol. In this system, the products were cleanly separated and have the following R_f values: uracil (0.6), **4** (0.5), **1** (0.3). The uv-absorbing bands were scraped from the plates and eluted from the gel with water. The absorbance was determined *vs.* an appropriate blank portion of the plate. The percentage distribution of the products, averaged from two plates, was determined by ultraviolet spectroscopy using the reported extinction coefficients.

	Product distribution, %		
Starting Material	1	4	Uracil
1	20	74	6
4	22	73	5

2,2′-Anhydro-3-β-D-arabinofuranosyl-5-methyluracil (10). A mixture of **9** (1.80 g, 7.5 mmol) and LHF (25 ml) was heated in a Monel autoclave for 18 hr at 85°. The mixture was worked up as

described above to give a syrup which was chromatographed on silica gel (200 g) using 5:1 chloroform–methanol as the developing solvent. The fractions containing the desired product were combined and evaporated to give crystalline **10** (0.80 g, 44%). Recrystallization from ethanol gave an analytical sample of **10:** mp 180–181°; λ_{max} (pH 2, 7) 274 nm (ϵ 6900), λ_{min} (pH 2, 7) 238 (1300), λ_{max} (pH 12) 275 (6900), λ_{min} (pH 12) 239 (1500); nmr (DMSO-d_6) δ 7.55 (1 H, d, H-6, J = 1.5 Hz, coupled to CH_3), 6.39 (1 H, d, H-1′), 5.69 (1 H, d, OH-3′, $J_{3'\text{-OH-}3'\text{-H}}$ = 4.5 Hz, exchanges on addition of D_2O), 5.15 (1 H, d, H-2′, $J_{1'-2'}$ = 5.5 Hz), 4.85 (1 H, t, OH-5′, $J_{5'\text{-OH-}5'\text{A-}5'\text{B}}$ = 5.5 Hz, exchanges on addition of D_2O), 4.37 (1 H, m, H-3′), 4.04 (1 H, m, H-4′), 3.28 (2 H, m, H-5′A, -5′B, changes to d with J = 5 Hz on addition of D_2O), 1.87 (3 H, s with shoulder, methyl protons).

Anal. Calcd for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.04; N, 11.66. Found: C, 50.18; H, 4.93; N, 11.64.

3-β-D-Arabinofuranosyluracil (15). A solution of **4** (2.00 g, 8.8 mmol) in 1 *N* sodium hydroxide (40 ml) was stirred at room temperature for 30 min and then deionized by the addition of Dowex-50 H^+. After removal of the resin by filtration, the filtrate was evaporated and the residue was azeotroped with ethanol until a foam was obtained. The foam was taken up in boiling ethyl acetate (250 ml) with the addition of ethanol (25 ml). Storage of this solution in the cold overnight gave crystalline **15** (1.32 g, mp 172–174°). An additional crop (0.61 g, mp 172–174°) was obtained on evaporation of the mother liquor to give **15** in 90% overall yield. Recrystallization from ethyl acetate–ethanol gave analytically pure **15:** mp 172.5–174°; λ_{max} (pH 2) 263 nm (ϵ 7600), λ_{min} (pH 2) 231 (1700), λ_{max} (pH 12) 292 (10,400), λ_{min} (pH 12) 247 (700); nmr (D_2O) δ 7.47 (1 H, d, H-6), 6.65 (1 H, unsymmetrical d, H-1′, $J_{1'-2'}$ = 8.0 Hz), 5.80 (1 H, d, H-5, J_{5-6} = 8.0 Hz), 4.70 (4 H, s, exchangable protons), 4.70–4.40 (2 H, m, H-2′, H-3′), 4.04–3.74 (3 H, m, H-4′, H-5′A, -5′B).

Anal. Calcd for $C_9H_{12}N_2O_6$: C, 44.27; H, 4.95; N, 11.47. Found: C, 44.31; H, 4.88; N, 11.26.

3-β-D-Arabinofuranosyl-5-methyluracil (16). A solution of **10** (413 mg, 1.7 mmol) in 1 *N* sodium hydroxide (10 ml) was stirred at room temperature for 75 min and then deionized by the addition of Dowex-50 H^+. After filtration from the resin, the filtrate was evaporated to a syrup and azeotroped with ethanol to give a foam (426 mg). The foam was dissolved in hot ethyl acetate and the solution was decanted from some insoluble material. The ethyl acetate solution, on cooling overnight, gave crystals of **16** (261 mg, 59%), sinters at 105°, melts at 216–218°. Recrystallization from ethyl acetate gave pure **16:** mp 215–216.5°; λ_{max} (pH 2) 269 nm (ϵ 7100), λ_{min} (pH 2) 241 (1600), λ_{max} (pH 7) 269 (7100), λ_{min} (pH 7) 236 (1600), λ_{max} (pH 12) 299 (9400), λ_{min} (pH 12) 251 (700); nmr (D_2O) δ 7.30 (1 H, d, H-6, J_{6-CH_3} = 1.5 Hz), 6.66 (1 H, unsymmetrical d, H-1′, $J_{1'-2'}$ = 8 Hz), 4.94–4.26 (6 H, m, H-2′, H-3′ and exchangeable protons), 3.87 (3 H, m, H-4′, 5′A, -5′B), 1.81 (3 H, narrow d, methyl protons).

Anal. Calcd for $C_{10}H_{14}N_2O_6$: C, 46.51; H, 5.46; N, 10.85. Found: C, 46.56; H, 5.55; N, 10.59.

2′,3′,5′-Tri-*O*-acetyl-3-β-D-arabinofuranosyluracil (17a). From 15. A Mixture of **15** (489 mg, 2 mmol) and acetic anhydride (0.7 ml, 7 mmol) in dry pyridine (10 ml) was stirred overnight at room temperature. The mixture was evaporated and azeotroped with aqueous ethanol followed by ethanol until crystals formed. The crystals were collected to give **17a** (574 mg, 78%), mp 165–166.5°.

From 4. Anhydro nucleoside **4** (1.00 g, 4.4 mmol) was hydrolyzed in 1 *N* sodium hydroxide (20 ml) for 30 min. The solution was deionized by the addition of Dowex-50 H^+ and, after filtration from the resin, evaporated to a foam. The foam was azeotroped several times with dry pyridine and finally dissolved in dry pyridine (20 ml) and treated with acetic anhydride (1.8 ml, 19 mmol) overnight at room temperature. Work-up as above gave **17a** as a crystalline solid (1.34 g, 82%), mp 164–166°. Recrystallization from ethanol gave analytically pure **17a:** mp 166–167°; λ_{max} (pH 2) 263 nm (ϵ 7300), λ_{min} (pH 2) 231 (1300), λ_{max} (pH 12) 294 (10,100), λ_{min} (pH 12) 247 (500); nmr (DMSO-d_6) δ 10.75 (1 H, broad s, NH, exchanges on addition of D_2O), 7.48 (1 H, m, H-6, on addition of D_2O becomes a doublet, J_{6-5} = 7.5 Hz), 6.78 (1 H, d, H-1′, $J_{1'-2'}$ = 7.5 Hz), 6.03–5.40 (3 H, complex m, H-2′, H-3′, H-5; after D_2O addition, H-5 is a doublet at 5.65), 4.40–4.00 (3 H, complex m, H-4′, -5′A, -5′B), 2.12–1.86 (9 H, three sharp singlets for acetate protons).

Anal. Calcd for $C_{15}H_{18}N_2O_9$: C, 48.65; H, 4.90; N, 7.56. Found: C, 48.83; H, 4.98; N, 7.36.

2′,3′,5′-Tri-*O*-benzoyl-3-β-D-arabinofuranosyluracil (17b). The foam resulting from the hydrolysis of **15** (5.00 g, 22 mmol) was azeotroped with portions of dry pyridine and finally dissolved in pyridine (75 ml), cooled, and treated dropwise with benzoyl chloride (12.4 g, 88 mmol). Stirring was continued overnight at room temperature. Addition of ice was followed by evaporation of the pyridine and dilution of the residue with methylene chloride. The methylene chloride solution was washed successively with water, sodium bicarbonate solution, water, 2 *N* HCl, and water. After drying ($MgSO_4$), the organic solution was evaporated to a foam which crystallized on trituration with benzene. The crystals were collected to give **17b** (11.55 g, 82%), mp 108–111°. The benzene solvate of **17b,** mp 112–114°, was obtained on recrystallization from benzene: nmr (DMSO-d_6) δ 8.12–7.21 (22 H, complex, benzoyl H's, benzene, H-6), 7.08 (1 H, d, H-1′, $J_{1'-2'}$ = 8 Hz), 6.64–6.02 (2 H, complex, H-2′, H-3′), 5.61 (1 H, d, H-5, J_{5-6} = 7.5 Hz), 4.85–4.53 (3 H, m, H-4′, 5′A, -5′B).

Anal. Calcd for $C_{30}H_{24}N_2O_9 \cdot C_6H_6$: C, 68.13; H, 4.76; N, 4.41. Found: C, 67.80; H, 4.73; N, 4.42.

2′,3′,5′-Tri-*O*-benzoyl-3-β-D-arabinofuranosyl-4-thiouracil (18b). To a solution of **17b** (11.00 g, 17 mmol) in warm dioxane (200 ml) was added phosphorus pentasulfide (8.9 g, 40 mmol) and the mixture was refluxed for 3.5 hr. The hot solution was filtered through glass wool and the filtrate was evaporated to a syrup. The residual syrup was triturated with water and finally dissolved in chloroform. After washing of the organic solution three times with brine, the dried ($MgSO_4$) chloroform solution was evaporated to a syrup and dissolved in methanol. The crystals which formed were collected to give a quantitive yield of **18b,** mp 180–186°, which migrated as a single spot on tlc. Several recrystallizations of a portion of this material gave the hemimethanolate (presence of methanol confirmed by nmr) of **18b** as yellow plates: mp 195–197°; nmr (DMSO-d_6) δ 11.66 (1 H, broad s, NH, exchanges on addition of D_2O), 8.20–7.16 (17 H, benzoyl H's, H-6, H-1′), 6.54–6.13 (3 H, H-5, H-2′, H-3′), 4.94–4.50 (3 H, m, H-4′, -5′A, -5′B), 4.02 (CH_3OH).

Anal. Calcd for $C_{30}H_{24}N_2O_8S \cdot 0.5CH_3OH$: C, 62.26; H, 4.45; N, 4.76. Found: C, 62.27; H, 4.15; N, 4.66.

3-β-D-Arabinofuranosyl-4-thiouracil (19). A suspension of **18b** (1.20 g, 2.0 mmol) in methanol (20 ml) was adjusted to pH ~ 12 (moist pH paper) by the addition of 1 *M* sodium methoxide in methanol. The clear yellow solution which resulted was stirred for 1 hr, after which the reaction mixture was deionized by the addition of Dowex-50 H^+. Removal of the resin followed by evaporation of the filtrate gave a syrup which was azeotroped extensively with ethanol until a crystalline residue formed. The crystals were dissolved in hot ethanol and filtered and the solution was evaporated to a small volume. The crystals which formed on cooling were collected to give analytically pure **19** (0.29 g, 55%): mp 166–167°; λ_{max} (pH 2) 334 nm (ϵ 11,700), λ_{min} (pH 2) 286 (3000), λ_{max} (pH 12) 348 (13,600), λ_{min} (pH 12) 282 (2200); nmr (DMSO-d_6 with D_2O) δ 7.51 (1 H, d, H-1′, $J_{1'-2'}$ = 8 Hz), 7.23 (1 H, d, H-6), 6.48 (1 H, d, H-5, J_{5-6} = 7.5 Hz), 4.60–3.40 (9 H).

Anal. Calcd for $C_9H_{12}N_2O_5S$: C, 41.54; H, 4.65; N, 10.77. Found: C, 41.52; H, 4.74; N, 10.75.

3′,5′-Di-*O*-acetyl-2,2′-anhydro-3-β-D-arabinofuranosyluracil (20a). A solution of **4** (500 mg, 2.2 mmol) in dry pyridine (10 ml) was treated with acetic anhydride (0.56 ml, 5.6 mmol) for 18 hr at room temperature. After the addition of ethanol, the solvents were removed and the residue was azeotroped with aqueous ethanol, followed by ethanol, until crystals formed. The crystals were collected and recrystallized from ethanol to give **20a** (528 mg, 77%): mp 112–115°; λ_{max} (pH 7) 270 nm (ϵ 6700), λ_{min} (pH 7) 233 (950); nmr (DMSO-d_6) δ 7.80 (1 H, d, H-6), 6.52 (1 H, d, H-1′), 6.08 (1 H, d, H-5, J_{5-6} = 7.0 Hz), 5.50 (1 H, d, H-2′, $J_{1'-2'}$ = 5.5 Hz), 5.34 (1 H, d, H-3′), 4.56 (1 H, m, H-4′), 4.08 (2 H, m, H-5′A, -5′B), 2.13 (3 H, s, acetate CH_3), 1.92 (3 H, s, acetate CH_3).

Anal. Calcd for $C_{13}H_{14}N_2O_7$: C, 50.33; H, 4.55; N, 9.06. Found: C, 50.44; H, 4.49; N, 9.05.

3′,5′-Di-*O*-benzoyl-2,2′-anhydro-3-β-D-arabinofuranosyluracil (20b). A. By Use of Benzoyl Chloride. A solution of **4** (500 mg) in dry pyridine (25 ml) was treated with benzoyl chloride (0.75 ml, 6.4 mmol) at room temperature for 5 hr. After the addition of water (10 ml), the reaction mixture was evaporated to a thick syrup. The syrup was dissolved in chloroform and the chloroform solution was washed with water, saturated sodium bicarbonate solution, water, 2 *N* HCl, and water. The organic layer was dried ($MgSO_4$), filtered from salts, and evaporated to a crystalline residue. The crystals were collected and washed with ethanol to give 1.04 g of **20b** with mp 136–140°, homogeneous by tlc. Recrystallization from ethanol gave 740 mg (77%) of analytically pure **20b,** mp 156.5–157.5°.

B. By Use of Benzoyl Cyanide.[39] To a mixture of **4** (4.5 g, 20 mmol) and benzoyl cyanide (5.8 g, 44 mmol) in dimethylformamide (25 ml) was added tri-*n*-butylamine (0.2 ml). After stirring for 30 min, methanol (10 ml) was added and the reaction mixture was concentrated to a thick syrup under high vacuum. Crystallization of the syrup from ethanol followed by recrystallization of the crude product gave **20b** (6.8 g, 79%): mp 156.5–157.5°; nmr (DMSO-d_6) δ 8.27–7.30 (11 H, complex, benzoyl H's, H-6), 6.65 (1 H, d, H-1′, $J_{1'-2'}$ = 6.0 Hz), 6.09 (1 H, d, H-5, J_{5-6} = 7.5 Hz), 5.83–5.66 (2 H, m, H-2′, H-3′), 5.04–4.72 (1 H, m, H-4′), 4.60–4.33 (2 H, m, H-5′A, -5′B).

Anal. Calcd for $C_{23}H_{18}N_2O_7$: C, 63.59; H, 4.18; N, 6.45. Found: C, 63.53; H, 4.10; N, 6.31.

3-β-D-Ribofuranosyluracil (21). A mixture of **20b** (2.10 g, 4.8 mmol) and freshly distilled boron trifluoride etherate (1.1 ml, 8.7 mmol) in dry methanol (50 ml) was refluxed with the exclusion of atmospheric moisture for 2 hr. The cooled reaction mixture was evaporated to a syrup and dissolved in chloroform. After washing of the chloroform solution with saturated sodium bicarbonate followed by water, the organic layer was dried ($MgSO_4$), filtered, and evaporated to a syrup. The syrup was azeotroped several times with ethanol, dissolved in methanol (25 ml), and stirred with 1 *M* sodium methoxide in methanol (7 ml) at room temperature for 5 hr. After deionization with Dowex-50 H^+, the solution was evaporated to a semicrystalline residue. The residue was triturated with ether and the crystalline material was collected to give **21** (570 mg, 48%), homogeneous by thin layer chromatography. Recrystallization from ethanol–ether gave pure **21** (412 mg): mp 197–198° (lit.[24] mp 200–202°); nmr (D_2O) δ 7.48 (1 H, d, H-6), 6.26 (1 H, d, H-1′, $J_{1'-2'}$ = 3.5 Hz), 5.83 (1 H, d, H-5, J_{5-6} = 8.0 Hz), 4.90–4.60 (1 H, m, H-2′), 4.55–4.29 (1 H, t, $W_{1/2}$ = 12.0 Hz, H-3′, $J_{3'-2'}$ = 6.0 Hz), 4.06–3.52 (3 H, complex, H-4′, H-5′A, -5′B).

Anal. Calcd for $C_9H_{12}N_2O_6$: C, 44.27; H, 4.95; N, 11.47. Found: C, 44.19; H, 4.98; N, 11.47

3′,5′-Di-*O*-benzoyl-2′-chloro-2′-deoxy-3β-D-ribofuranosyluracil (22b). A solution of **20b** (1.00 g, 2.3 mmol) in dimethylformamide (20 ml) containing HCl (1 g) was heated at 100° for 30 min. The reaction mixture was poured into water (500 ml), and the solid precipitate which formed was collected and washed well with water. The collected insoluble material was chromatographed on silica gel (100 g) using 15:1 chloroform–methanol as the eluent. Fractions containing the desired product were evaporated to give **22b** (750 mg, 69%) as a foam, homogeneous by tlc, which could not be induced to crystallize: nmr ($CDCl_3$) δ 10.03 (1 H, broad d, NH, J_{NH-6} = 6.5 Hz, exchanges on addition of D_2O), 8.20–7.12 (11 H, complex, benzoyl H's, H-6), 6.82 (1 H, d, H-1′), 5.97 (1 H, complex, H-3′), 5.76 (1 H, unsymmetrical d, H-5, J_{6-5} = 8.0 Hz), 5.42 (1 H, unsymmetrical, H-2′, $J_{1'-2'}$ = 3.5, $J_{2'-3'}$ = 7.0 Hz), 4.74–4.50 (3 H, m, H-4′, -5′A, -5′B).

Anal. Calcd for $C_{23}H_{19}ClN_2O_7$: C, 58.67; N, 4.07; N, 5.95. Found: 58.53; H, 3.85; N, 5.85.

3′,5′-Di-*O*-benzoyl-2′-deoxy-3-β-D-ribofuranosyluracil (23b). A solution of **22b** (2.00 g, 4.25 mmol), tri-*n*-butyltin hydride (4 ml), and 2,2′-azobis(2-methylproprionitrile) (40 mg) in dry benzene (50 ml) was refluxed under a nitrogen atmosphere for 3.5 hr. The reaction mixture was evaporated to dryness and the residue was triturated several times with light petroleum ether. Crystallization of the residue from benzene–hexane gave 1.64 g (88%) of crystalline material, mp 110–115°. Chromatography of a portion (1.00 g) of this material over silica gel yielded 680 mg of pure crystalline **23b:** mp 115–120°; nmr ($CDCl_3$) δ 10.13 (1 H, broad s, NH, exchanges with D_2O), 8.20–7.16 (11 H, complex, benzoyl H's and H-6), 6.93 (1 H, d of doublets, H-1′, $J_{1'-2'A}$ = 4, $J_{1'-2'B}$ = 8 Hz, $W_{1/2}$ = 13.5 Hz), 6.08–5.63 (1 H, complex, H-3′), 5.73 (1 H, d, H-5, J_{6-5} = 8 Hz), 4.82–4.42 (3 H, m, H-4′, -5′A, -5′B), 3.58–2.92 (1 H, complex, H-2′A), 2.77–2.17 (complex, H-2′B).

Anal. Calcd for $C_{23}H_{20}N_2O_7$: C, 63.30; H, 4.62; N, 6.42. Found: C, 63.62; H, 4.65; N, 6.08.

2′-Deoxy-3-β-D-ribofuranosyluracil (24). A solution of **23b** (2.00 g, 4.6 mmol) in methanol (25 ml) was made basic by the addition of 1 *M* sodium methoxide in methanol. The solution was stirred at room temperature for 6 hr, then deionized by the addition of methanol-washed Dowex-50 H^+ and filtered from the resin. The filtrate was evaporated to dryness, dissolved with water, and extracted several times with chloroform. Evaporation of the aqueous solution was followed by azeotropic distillation with ethanol to give crystalline **24** (778 mg, 74%), contaminated with traces of impurities as determined by tlc. This material was column chromatographed to give 495 mg of chromatographically pure **24,** mp 97–105°. Recrystallization from hot 2-propanol gave the hemi-2-propanolate of **24:** mp 82–90° (lit.[35] mp 169–170°); λ_{max} (pH 2) 262 nm (ϵ 7000), λ_{min} (pH 2) 231 (1600), λ_{max} (pH 7) 263 (6800), λ_{min} (pH 7) 232 (1500), λ_{max} (pH 12) 292 (9900), λ_{min} (pH 12) 248 (600). The presence of 2-propanol in this sample was confirmed by nmr spectroscopy (D_2O): δ 7.43 (1 H, d, H-5), 6.68 (1 H, unsymmetrical q, H-1′, $J_{1'-2'A}$ = 3.0, $J_{1'-2'B}$ = 8.5 Hz, $W_{1/2}$ = 16.0 Hz), 5.77 (1 H, d, H-6, J_{6-5} = 7.5 Hz), 3.13–2.65 and 2.47–1.94 (2 H, complex m, H-2′A, 2′B). All attempts to remove the 2-propanol by gradual heating under reduced pressure yielded a foam which did not give a satisfactory analysis.

Anal. Calcd for $C_9H_{12}N_2O_5 \cdot 0.5C_3H_8O$: C, 48.68; H, 6.15; N, 11.00. Found: C, 48.70; H, 6.27; N, 11.22.

Registry No.—**1,** 3736-77-4; **4,** 50664-09-0; **9,** 22423-26-3; **10,** 52259-53-7; **15,** 52305-37-0; **16,** 52259-54-8; **17a,** 50664-11-4; **17b,** 52259-55-9; **18b,** 52259-56-0; **19,** 52259-57-1; **20a,** 50664-10-3; **20b,** 52259-58-2; **21,** 6745-33-1; **22b,** 52259-59-3; **23b,** 52259-60-6; **24,** 29031-49-0.

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