collected until all the solvent has been used (see Table I to estimate the amount of solvent and fraction size). It is best not to let the column run dry since further elution is occasionally necessary. Purified components are identified as described in the text by TLC. If the foregoing instructions are followed *exactly*, there is little opportunity for the separation to fail.

Although we generally pack fresh columns for each separation, the expense of large-scale separations makes it advantageous to reuse large diameter columns. Column recycling is effected by first flushing (rate = 2 in./min) the column with approximately 5 in. of the more polar component in the eluant (generally ethyl acetate or acetone) and then with 5 in. of the desired eluant. If the eluant is relatively nonpolar (e.g., ≤10% EtOAc/petroleum ether), it may be more advisable to use a flushing solvent (e.g., 20–50% EtOAc/petroleum ether) which is somewhat less polar than the pure high polarity component.

Registry No.—**1**, 66417-28-5; **2**, 66417-27-4.

References and Notes

(1) Such units have been described and used extensively by J. M. McCall, R. E. TenBrinkt, and C. H. Lin at the Upjohn Company and A. I. Meyers at Colorado State University.
(2) B. J. Hunt and W. Rigby, *Chem. Ind. (London)*, 1868 (1967).
(3) This is not a limitation but is merely the scale range which we have used.
(4) This is the total time required for column packing, sample application, and complete elution.
(5) Standard conditions: 5 in. high bed of 40–63 μm silica gel 60 in a 20 mm diameter column packed as described in text, 2.0 in. of solvent flow/min, 200 mg of benzyl alcohol, 25% ethyl acetate/petroleum ether eluant.
(6) These gels are manufactured by E. Merck and are the following grades: <40 μm (silica gel H, No. 7736), 25–40 μm (LiChroPrep Si60, No. 9390), 40–63 μm (silica gel 60, No. 9385), 63–200 μm (silica gel 60, No. 10180).
(7) Slurry packing, incremental dry packing, or single portion dry packing gave identical results with the 40–63 μm gel. Since the last technique was the simplest, it was employed in all our studies.
(8) This is a particularly good general solvent system. For extremely polar compounds, acetone/petroleum ether or acetone/methylene chloride mixtures are often useful. Significantly higher viscosity solvents will require slower optimum resolution flow rates.
(9) If this R_f is given by a solvent having <2% of the polar component, a slightly less polar eluant is desirable. Thus if 1% ethyl acetate/petroleum ether gives a compound an R_f of 0.35 on TLC, the column is run with 0.5% ethyl acetate.
(10) 40–63 μm gel is also used for medium pressure chromatography[1] and is available from MCB in 1 kg ($45/kg) or 25 kg ($16/kg) lots.
(11) If the sample is only partially soluble in the eluant, just enough of the more polar component is added to give complete dissolution. Large quantities of very polar impurities are best removed prior to chromatography so that excessive quantities of solvent or large increases in solvent polarity will be unnecessary for sample application.

Homo-*C*-nucleosides. The Synthesis of Certain 6-Substituted 4-Pyrimidinones[1]

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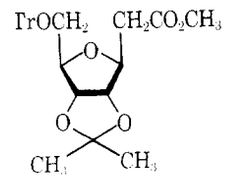
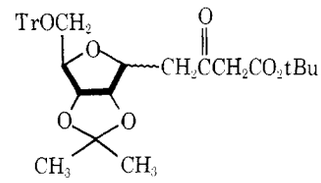
The chemistry of *C*-nucleosides has received considerable attention recently due to the biological activities of naturally occurring compounds such as showdomycin, formycin, and oxazinomycin.[2] Though synthetic methodology has evolved for the preparation of a number of *C*-nucleoside analogues,[2] only one investigation has dealt with the synthesis of homo-*C*-nucleosides,[3] compounds with a methylene unit between a carbon of the nitrogen base and the standard D-ribose moiety. This note describes the facile synthesis of a series of 6-substituted 4-pyrimidinone homo-*C*-nucleosides from the ester **1**, which is available in three steps from D-ribose.[4,5]

Treatment of **1** with lithio-*tert*-butyl acetate[6] in toluene at 0 °C for several hours affords an anomeric mixture (ca. 3:1, β/α) of the β-keto ester **2** in 75% yield. The assignment of β to the major anomer was made on the basis of ^{13}C NMR data. In particular, the isopropylidene methyls of the major anomer

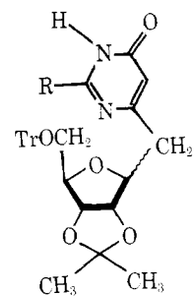


1

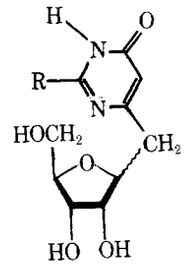


2

Tr = trityl



3



4

a, R = NH_2
b, R = CH_3
c, R = SH
d, R = phenyl
e, R = H

occur at δ 25.66 and 27.54, within the range strongly indicative of a β configuration (25.5 ± 0.2 and 27.5 ± 0.2).[7,8]

It has been shown that the α-anomer of **1** is more stable than the β,[4] and recently a rationalization for this seemingly unusual behavior has been presented.[9] On this basis it seems likely that the α anomer of **2** is also more stable than the β. The conditions involved in the preparation of **2** (low-temperature, aprotic solvent) probably do not allow equilibration, though there is some leakage to the α-anomer. Further support for these postulates is provided by the finding that β-**2** is isomerized readily under basic conditions to an α/β mixture which is predominantly α.

Condensation of **2** with guanidine, acetamidine, thiourea, and benzamidine under basic conditions afforded the protected nucleosides **3a–d** as anomeric mixtures (ca. 3:1, α/β) which were chromatographically inseparable. That the major anomers after condensation are all α is also indicated by the chemical shifts of the isopropylidene methyls. For example, the shifts of the methyls in **3a** are at δ 25.09 and 26.33, clearly in the α range (24.9 ± 0.3 and 26.3 ± 0.2).[7,8] In view of the ready isomerization of β-**2** to a mixture of anomers containing predominantly α-**2**, it seems likely that equilibration is occurring prior to cyclization, and that the anomeric composition of **2** after equilibration dictates the ratio of α- and β-homo-*C*-nucleosides. Desulfurization of **3c** with Raney Nickel in refluxing 95% ethanol provided the hydrogen-substituted compound **3e.** Interestingly, while both urea and formamidine reacted with **2,** neither led to the formation of cyclized material under a variety of conditions. The free nucleosides **4a–e** were obtained by treatment of **3a–e** with either methanolic hydrogen chloride or aqueous trifluoroacetic acid for several hours. These acidic conditions, even over longer periods of time (2 days), caused no change in the α/β ratio of the nucleosides. Chromatographic separation of the free nucleoside anomers was once again not possible. **4e** was also available by desulfurization of **4c.**

The ^{13}C NMR spectra of the free nucleosides contained characteristic signals for the five compounds, and all values are reported in the Experimental Section. Salient ^1H NMR values are the methyl singlet of **4b** at δ 2.28 and the pyrimidine C_2H singlet of **4e** at δ 8.92, as well as the pyrimidine C_5 signal of all five nucleosides in the neighborhood of δ 6.0.

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Thus, homo-*C*-nucleosides are available in only six (**4a–d**) or seven (**4e**) steps from D-ribose in reasonable yields.[10] The β-keto ester **2** is a stable and versatile intermediate which might also serve as a precursor to various other homo-*C*-nucleoside ring systems, as well.

Experimental Section[11]

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are corrected. ^{1}H NMR spectra were measured with Varian A60A or EM-360 instruments and ^{13}C NMR spectra with a Bruker WP80; chemical shifts are in parts per million downfield from internal tetramethylsilane or DSS (for D_2O). Mass spectra were recorded with an AEI-MS9 spectrometer at 70 eV. Microanalyses were done by Galbraith Laboratories, Inc. and Mr. William Rond, The Ohio State University.[12]

Methanol was dried by distillation from magnesium methoxide and toluene by distillation from calcium hydride.

***tert*-Butyl 4-*C*-(2,3-*O*-Isopropylidene-5-*O*-trityl-α- and -β-D-ribofuranosyl)-3-oxobutanoate (2).** A solution of 1.86 g (3.82 mmol) of **1** in 10 mL of toluene under nitrogen was cooled to 0–5 °C and 0.93 g (7.64 mmol) of lithio-*tert*-butyl acetate was added in one portion. The solution was stirred several hours and processed by washing several times with water, drying (Na_2SO_4), and evaporation to a light yellow syrup. Column chromatography (silica gel, 2.4 × 40 cm, elution with 4:1 petroleum ether (30–60 °C)–ether) afforded the colorless β-keto ester **2**, 1.46 g (68%), as a thick syrup. Comparable yields (60–75%) have been obtained on runs of up to 20 mmol: IR (neat) 1717, 1735 cm^{-1}; NMR ($CDCl_3$) δ 1.30 and 1.51 (2s, 6, $C(CH_3)_2$), 1.42 and 1.45 (2s, 9, $C(CH_3)_3$, β and α), 2.59–2.94 (m, 2, $CH_2C(O)C$), 3.13–3.72 (m, 4, CH_2OTr and $-C(O)CH_2C(O)-$), 4.02–4.80 (m, 4, C_1H, C_2H, C_3H, C_4H), 7.10–7.60 (m, 15, ArH); ^{13}C NMR ($CDCl_3$) δ 25.66, 27.54, 27.96, 46.62, 51.06, 64.22, 80.42, 80.90, 82.23, 83.57, 84.53, 86.73, 114.37, 127.04, 127.84, 128.75, 143.83, 166.18, 200.72; mass spectrum calcd *m/e* 572.2773; found 572.2781. Anal. Calcd for $C_{35}H_{40}O_7$: C, 73.40; H, 7.04. Found: C, 73.65; H, 7.25.

6-*C*-(2,3-*O*-Isopropylidene-5-*O*-trityl-α- and -β-D-ribofuranosyl)methyl-4-hydroxy-2-aminopyrimidine (3a). To a solution of 650 mg (1.14 mmol) of **2** in 12 mL of absolute ethanol was added 120 mg (1.25 mmol) of guanidine hydrochloride and 132 mg (1.25 mmol) of Na_2CO_3, and the mixture was heated at reflux (drying tube) for 12 h. Removal of solvent under reduced pressure followed by dissolution in $CHCl_3$, washing with H_2O, drying, and evaporation afforded an off-white foam, which was purified by column chromatography (silica gel, 2.5 × 20 cm, elution with 97.5–2.5 $CHCl_3$–CH_3OH) to afford 450 mg (73%) of a colorless foam. On standing in a small amount of CH_3OH, the α-anomer (as judged by ^{13}C NMR) crystallized out: mp 236–241 °C dec (begins turning brown at 228 °C); NMR ($CDCl_3$) δ 1.30 and 1.46 (2s, 6, $C(CH_3)_2$), 2.76 (m, 2, CH_2 pyrimidine), 3.21 (m, 2, CH_2OTr), 4.03–4.80 (m, 4, C_1H, C_2H, C_3H, C_4H of carbohydrate), 5.68, 5.73 (2s, 1, C=CH, α and β), 7.08–7.58 (m, 15, ArH); ^{13}C NMR ($CDCl_3$) δ 25.09, 26.33, 36.31, 64.69, 80.28, 82.17, 83.47, 87.30, 102.40, 112.49, 127.22, 127.92, 128.68, 143.62, 156.03, 168.55. Anal. Calcd for $C_{32}H_{33}N_3O_5$: C, 71.22; H, 6.16; N, 7.79. Found: C, 71.03; H. 6.16; N, 7.75.

6-*C*-(2,3-*O*-Isopropylidene-5-*O*-trityl-α- and -β-D-ribofuranosyl)methyl-4-hydroxy-2-methylpyrimidine (3b). A solution containing 1.098 g (1.92 mmol) of **2**, 363 mg (3.84 mmol) of acetamidine hydrochloride, and sodium methoxide (5.76 mmol) in 10 mL of methanol was heated at reflux (drying tube) for 10 h. After evaporation of the solvent under reduced pressure the residue was taken up in $CHCl_3$, washed with H_2O, dried, and evaporated to dryness. Purification was accomplished by column chromatography (silica gel, 2.5 × 18 cm, elution with 97.5–2.5 $CHCl_3$–CH_3OH), yielding 795 mg (77%) of a foam: NMR ($CDCl_3$) δ 1.32 and 1.52 (2s, 6, $C(CH_3)_2$), 2.33 and 2.41 (2s, 3, CH_3C=C, α- and β-anomers), 2.90 (m, 2, CH_2 pyrimidine), 3.23 (m, 2, CH_2OTr), 4.05–4.88 (m, 4, C_1H, C_2H, C_3H, C_4H of carbohydrate), 6.29 and 6.37 (2s, 1, C=CH, α- and β-anomers), 7.08–7.58 (m, 15, ArH); ^{13}C NMR ($CDCl_3$) δ 25.20, 26.38, 38.04, 64.69, 80.01, 82.17, 83.36, 83.52, 87.24, 110.71, 112.44, 127.11, 127.87, 128.68, 143.68, 158.52, 165.85, 167.20. Anal. Calcd for $C_{33}H_{34}N_2O_5$: C, 73.58; H, 6.36; N, 5.20. Found: C, 73.70; H, 6.50; N, 5.02.

6-*C*-(2,3-*O*-Isopropylidene-5-*O*-trityl-α- and β-D-ribofuranosyl)methyl-4-hydroxy-2-thiopyrimidine (3c). A solution containing 1.215 g (2.12 mmol) of **2**, 404 mg of thiourea (5.3 mmol), and sodium methoxide (4.25 mmol) in 15 mL of CH_3OH was heated at reflux (drying tube) for 5 h. After evaporation of the solvent under reduced pressure the residue was taken up in $CHCl_3$, washed with H_2O, dried, and evaporated to dryness. Purification was accomplished by column chromatography (silica gel, 2.5 × 40 cm, elution with 98.5–1.5 $CHCl_3$–CH_3OH) affording 692 mg (59%) of a colorless foam: NMR ($CDCl_3$) δ 1.35 and 1.52 (2s, 6, $C(CH_3)_2$), 2.74 (m, 2, CH_2 pyrimidine), 3.29 (m, 2, CH_2OTr), 4.13–4.83 (m, 4, C_1H, C_2H, C_3H, C_4H of carbohydrate), 5.78 (s, 1, C=CH), 7.05–7.58 (m, 15, ArH), 10.56 and 11.07 (2 br s, 2, 2 NH); ^{13}C NMR($CDCl_3$) δ 24.76, 26.17, 33.29, 64.74, 79.96, 81.85, 83.20, 84.06, 87.46, 104.56, 112.98, 127.33, 128.03, 128.57, 143.36, 153.71, 161.54, 175.57; mass spectrum calcd *m/e* 556.2032; found 556.2041. Anal. Calcd for $C_{32}H_{32}N_2O_5S$·CH_3OH: C, 67.33; H, 6.16; N, 4.76. Found: C, 67.17; H, 6.32; N, 4.68.

6-*C*-(2,3-*O*-Isopropylidene-5-*O*-trityl-α and -β-D-ribofuranosyl)methyl-4-hydroxy-2-phenylpyrimidine (3d). A solution of **2** (762 mg, 1.36 mmol), benzamidine hydrochloride (277 mg, 1.77 mmol), and sodium ethoxide (3.13 mmol) in 12 mL of absolute ethanol was heated at reflux (drying tube) for 12 h. The reaction mixture was evaporated to dryness, taken up in $CHCl_3$, washed with H_2O, dried, and evaporated to an off-white foam. Purification was accomplished by column chromatography (silica gel, 2.5 × 15 cm, elution with 98–2 $CHCl_3$–CH_3OH), affording 541 mg (68%) of a colorless foam: NMR ($CDCl_3$) δ 1.33 and 1.53 (2s, 6, $C(CH_3)_2$), 2.78–3.50 (m, 4, $2CH_2$), 4.02–5.08 (m, 4, C_1H, C_2H, C_3H, C_4H of carbohydrate), 6.38, 6.46 (2s, 1, C=CH, β- and α-anomers), 6.98–7.65 (m, 18, ArH), 7.95–8.38 (m, 2, ortho protons of the 2-phenyl moiety); ^{13}C NMR ($CDCl_3$) δ 25.20, 26.44, 37.99, 65.01, 80.23, 82.28, 83.47, 87.24, 112.38, 127.06, 127.87, 128.63, 131.97, 143.62, 156.47, 165.46, 166.61; mass spectrum calcd *m/e* 600.2624; found 600.2636. Anal. Calcd for $C_{38}H_{36}N_2O_5$·CH_3OH: C, 74.02; H. 6.37; N, 4.43. Found: C, 73.74; H, 6.16; N, 4.20.

6-*C*-(2,3-*O*-Isopropylidene-5-*O*-trityl-α- and -β-D-ribofuranosyl)methyl-4-hydroxypyrimidine (3e). To a solution of 289 mg (0.52 mmol) of **3c** in 5 mL of 95% ethanol was added 580 mg of Raney Nickel, and the mixture heated at reflux 4 h. Processing and purification was accomplished by filtration through Celite (wash with 95% ethanol), evaporation, and thick layer chromatography (silica gel, two elutions with $CHCl_3$), to afford 196 mg (72%) of a colorless foam. On a 1–2 mmol scale column chromatography (elution with 95–5 $CHCl_3$–CH_3OH) was employed: NMR ($CDCl_3$) δ 1.32 and 1.52 (2s, 6, $C(CH_3)_2$), 2.73–3.46 (m, 4, $2CH_2$), 4.03–4.85 (m, 4, C_1H, C_2H, C_3H, C_4H of carbohydrate), 6.41, 6.50 (2s, 1, C_5H of pyrimidine, β- and α-anomers); 7.07–7.60 (m, 15, ArH), 8.09 (s, 1, C_2H of pyrimidine), 13.18 (br s, 1, NH); ^{13}C NMR ($CDCl_3$) δ 25.09, 26.33, 37.93, 64.53, 79.90. 82.06, 82.33, 83.30, 87.19, 112.39, 127.11, 127.87. 128.63, 143.62, 148.05, 164.56, 167.20. Anal. Calcd for $C_{32}H_{32}N_2O_5$·CH_3OH: C, 71.20, H. 6.52, N, 5.03. Found: C, 71.01; H, 6.26; N, 4.99.

General Procedure for the Preparation of 4a–e by Deprotection of 3a–e. A solution of **3a–e** (1 mmol) in 10 mL of 10% methanolic hydrogen chloride was allowed to stand at room temperature for 3 h. Solvent was evaporated and the residue was triturated with ether to remove trityl methyl ether. The residue was taken up in methanol and washed through an Amberlite IR-45 (OH^-) column (1 × 15 cm) with 200 mL of 50% aqueous methanol. Solvent was evaporated and the residue was purified by thick layer chromatography (elution with 1:1 $CHCl_3$–CH_3OH) to afford the free nucleoside as a colorless foam. Deprotection with 9:1 trifluoroacetic acid–H_2O gave comparable results.

6-*C*-(α- and β-D-Ribofuranosyl)methyl-4-hydroxy-2-aminopyrimidine (4a): 86%; NMR (Me_2SO-d_6) δ 2.63 (m, 2, CH_2 pyrimidine), 3.17–4.37 (m, 6, C_1H, C_2H, C_3H, C_4H, C***H***$_2$OH), 5.53 (s, 1, C=CH), 6.77 (br s, 2, NH_2); ^{13}C NMR (Me_2SO-d_6) δ 37.67 (CH_2 pyrimidine), 61.66 (CH_2OH), 71.76, 72.05, 78.55, 81.81 (C_1, C_2, C_3, C_4 of carbohydrate), 101.03 (pyrimidine C_5), 155.41 (pyrimidine C_6), 163.27 (pyrimidine C_4), 166.57 (pyrimidine C_2). Anal. Calcd for $C_{10}H_{15}N_3O_5$·0.5CH_3OH: C, 46.15; H. 6.27; N, 15.38. Found: C, 46.33; H, 6.06, N, 15.67.

6-*C*-(α- and β-D-Ribofuranosyl)methyl-4-hydroxy-2-methylpyrimidine (4b): 56%; NMR (Me_2SO-d_6) δ 2.28 (s, 3, CH_3), 2.73 (m, 2, CH_2 pyrimidine), 3.35–4.42 (m, 6, C_1H, C_2H, C_3H, C_4H, C***H***$_2$OH), 6.06 (s, 1, C=CH); ^{13}C NMR (Me_2SO-d_6) δ 21.02 (CH_3), 37.58 (CH_2 pyrimidine), 61.65 (CH_2OH), 71.76, 72.05, 78.26, 81.90 (C_1, C_2, C_3, C_4 of carbohydrate), 110.30 (pyrimidine C_5), 158.42, 162.54, 164.92 (pyrimidine C_2, C_4, C_6). Anal. Calcd for $C_{11}H_{16}N_2O_5$·0.5CH_3OH: C, 50.73; H, 6.66; N, 10.29. Found: C, 50.57; H. 6.34; N, 10.49.

6-*C*-(α- and β-D-Ribofuranosyl)methyl-4-hydroxy-2-thiopyrimidine (4c): 77%; NMR (Me_2SO-d_6) δ 2.65 (m, 2, CH_2 pyrimidine), 3.35–4.35 (m, 6, C_1H, C_2H, C_3H, C_4H, C***H***$_2$OH), 5.75 (s, 1, C=CH); ^{13}C NMR (Me_2SO-d_6) 32.92 (CH_2 pyrimidine), 61.41 (CH_2OH), 71.71, 77.73, 82.05 (C_1, C_2, C_3, C_4 of carbohydrate), 103.94 (pyrimidine C_5), 154.97 (pyrimidine C_6, 161.09 (pyrimidine C_4), 175.89 (pyrimidine C_2). Anal. Calcd for $C_{10}H_{14}N_2O_5S$·CH_3OH: C, 43.13; H, 5.92. Found: C, 43.27; H, 5.93.

6-*C*-(α- and β-D-Ribofuranosyl)methyl-4-hydroxy-2-

phenylpyrimidine (4d): 86%; (Me_2SO-d_6) δ 2.87 (m, 2, CH_2 pyrimidine), 3.30–4.57 (m, 6, C_1H, C_2H, C_3H, C_4H, CH_2OH), 5.85 (br s, OH), 6.29 (s, 1, C=CH), 7.58 (m, 3, *m*- and *p*-ArH), 8.17 (m, 2, *o*-ArH); ^{13}C NMR (Me_2SO-d_6) δ 37.77 (CH_2 pyrimidine), 61.66 (CH_2OH), 71.80, 72.05, 78.50, 81.95 (C_1, C_2, C_3, C_4 of carbohydrate), 110.40 (pyrimidine C_5), 127.68, 128.51, 131.32, 133.17 (aromatic), 157.30 (pyrimidine C_6), 164.29, 165.36 (pyrimidine C_2, C_4). Anal. Calcd for $C_{16}H_{18}N_2O_5 \cdot CH_3OH$: C, 58.28; H, 6.33; N, 8.00. Found: C, 58.70; H. 6.25; N, 7.93.

6-*C*-(α and β-D-Ribofuranosyl)methyl-4-hydroxypyrimidine (4e): 82%; NMR (D_2O) δ 2.87 (m, 2, CH_2 pyrimidine), 3.30–4.57 (m, 6, C_1H, C_2H, C_3H, C_4H, CH_2OH of carbohydrate), 6.51 (s, 1, pyrimidine C_5H), 8.92 (s, 1, pyrimidine C_2H); ^{13}C NMR (Me_2SO-d_6) δ 61.66 (CH_2OH), 71.73, 72.05, 78.24, 81.95 (C_1, C_2, C_3, C_4 of carbohydrate), 113.22 (pyrimidine C_5), 149.46 (pyrimidine C_2), 161.89, 164.95 (pyrimidine C_4, C_6), CH_2 pyrimidine obscured by Me_2SO peaks. Anal. Calcd for $C_{10}H_{14}N_2O_5 \cdot 0.8CH_3OH$: C, 48.43; H. 6.47; N, 10.46. Found: C, 48.08; H. 6.19; N, 10.62.

Acknowledgment. Support for this research was provided by the Research Corp. Quantities of 1 were prepared by T. J. Cousineau and M. A. Francisco.

Registry No.—**1**, 56752-57-9; α-**2**, 66358-76-7; β-**2**, 66358-77-8; α-**3a**, 66358-78-9; β-**3a**, 66358-79-0; α-**3b**, 66358-80-3; β-**3b**, 66358-81-4; α-**3c**, 66358-82-5; β-**3c**, 66358-83-6; α-**3d**, 66358-84-7; β-**3d**, 66358-85-8; α-**3e**, 66358-86-9; β-**3e**, 66358-87-0; α-**4a**, 66358-88-1; β-**4a**, 66358-89-2; α-**4b**, 66416-41-9; β-**4b**, 66358-90-5; α-**4c**, 66358-91-6; β-**4c**, 66358-92-7; α-**4d**, 66358-93-8; β-**4d**, 66358-94-9; α-**4e**, 66358-95-0; β-**4e**, 66358-96-1; guanidine hydrochloride, 50-01-1; acetamidine hydrochloride, 124-42-5; thiourea, 62-56-6; benzamidine hydrochloride, 1670-14-0.

References and Notes

(1) Dedicated to Professor Melvin S. Newman on the occasion of his 70th birthday.
(2) S. Hanessian and A. G. Pernet, *Adv. Carbohydr. Chem. Biochem.*, **33**, 111–188 (1976).
(3) W. J. Gensler, S. Chan, and D. B. Ball, *J. Am. Chem. Soc.*, **97**, 436–437 (1975).
(4) H. Ohrui, G. H. Jones, J. G. Moffatt, M. L. Maddox, A. T. Christensen, and S. K. Byram, *J. Am. Chem. Soc.*, **97**, 4602–4613 (1975).
(5) T. J. Cousineau and J. A. Secrist III, *J. Carbohydrates, Nucleosides, Nucleotides*, **3**, 185–189 (1976).
(6) M. W. Rathke and D. F. Sullivan, *J. Am. Chem. Soc.*, **95**, 3050–3051 (1973).
(7) See ref 4 for the first use of the shift positions in the ^{13}C NMR to assign anomeric configuration in *C*-nucleoside precursors.
(8) We have found that in the vast majority of cases $\Delta\delta$ for the β anomer is 1.89 ± 0.1 and for the α anomer 1.24 ± 0.1. Compound **3c** is slightly outisde this limit.
(9) H. Ohrui and S. Emoto, *J. Org. Chem.*, **42**, 1951–1957 (1977).
(10) Preliminary antibacterial screening on several of these compounds at the Lilly Research Laboratories has shown no significant activity.
(11) Spectral data are for the major anomer unless otherwise indicated for specific resonances.
(12) In all cases where analyses include methanol, the methyl protons were observed in the ^1H NMR spectrum.

Substitution Reactions of 17α-Vinyl-17β-trifluoroacetoxy Steroids

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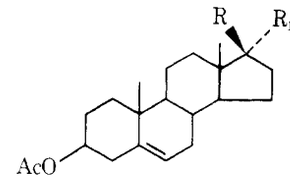
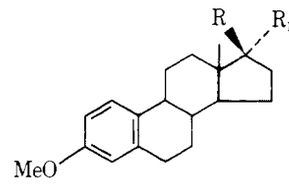
In continuation of our studies[1] on the trifluoroacetoxy group as a useful intermediate in the nucleophilic substitution of those steroid alcohols whose tosylates are difficult to obtain or isolate we became interested in the behavior of the 17α-vinyl-17β-trifluoroacetoxy derivatives 1 and **2**, prepared from the corresponding alcohols **1a**[2] and **2a**[3] with trifluoroacetic anhydride–pyridine at 0 °C.

Methanolysis of 1 in the presence of sodium acetate afforded 17α-methoxypregna-5,20-dien-3β-yl acetate (**1b**), (*E*)-21-methoxypregna-5,17(20)-dien-3β-yl acetate (**1c**), starting alcohol **1a**, and (*E*)-pregna-5,17(20)-dien-3β,21-diol 3-acetate (**1d**).[4]



1, R = $OCOCF_3$; R_1 = CH=CH_2
1a, R = OH; R_1 = CH=CH_2
b, R = CH=CH_2; R_1 = OMe
c, R = R_1 = =$CHCH_2OMe$[a]
d, R = R_1 = =$CHCH_2OH$[a]
e, R = R_1 = =$CHCH_2N_3$[a]
f, R = R_1 = =$CHCH_2OCOCF_3$[a]
g, R = R_1 = =$CHCH_2Cl$[a]
h, R = R_1 = =$CHCH_2OAc$[a]



2, R = $OCOCF_3$; R_1 = CH=CH_2
2a, R = OH; R_1 = CH=CH_2
b, R = R_1 = =$CHCH_2N_3$[a]
c, R = R_1 = =$CHCH_2Cl$[a]

[a] *E* isomers.

The structures **1b**, **1c**, and **1d** were inferred from their analytical and spectral (IR and ^1H-NMR) data.

The methoxy group in **1b** was assigned the 17α configuration on the basis of the upfield position of the 13-Me group compared with that of the 17β derivatives **1**, **1a**, and **2**.[1a]

Evidence for the trans stereochemistry at the 17(20) double bond in **1c** and **1d** was likewise obtained by comparison of their 13-Me shifts with those of compounds of known stereochemistry.[5]

1d was furthermore acetylated to give the known diacetate **1h**.[3]

The product pattern was nearly what one would expect from competing S_N1 and $B_{Ac}2$ mechanisms,[1a] the absence of a 17β-methoxy derivative being expected because of steric reasons.[1a]

The presence in high yield of the rearranged alcohol **1d** required nevertheless further investigation.

Isomerization of the initially formed alcohol **1a** appeared untenable since conversions of this type are acid catalyzed.[3]

1d could have instead resulted, via an acyl–oxygen cleavage, from the corresponding trifluoroacetate **1f**, in turn obtained by partial isomerization of 1 in the reaction medium.

That **1f** is probably the precursor of **1d** was supported by the fact that buffered methanolysis of **1f** in the same conditions as used for 1 afforded very quickly **1d** exclusively.

This fast consumption of **1f** joined to its probable slow formation (also see later) should account for our inability to detect it in the course of the methanolysis of **1**.

Bimolecular substitutions of **1** and **2** by azide ion in hexamethylphosphotriamide (HMPT) to give the 21-azido derivatives **1e** and **2b** proceeded in high yield (>70%).

1e and **2b** were assigned the trans stereochemistry on the same basis as discussed before.

As to the mechanism, these azidolyses cannot be regarded as pure S_N2' processes, since 1 has been found to rearrange partially into **1f** in HMPT and this latter was shown to afford quantitatively **1e** in the presence of NaN_3.

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