Equilibration data on 2-chloro-4-methyltetrahydropyran show that an axial chlorine is *stabilized* by 2.2 kcal/mol when compared with a similarly placed equatorial chlorine.[11] Chlorocyclohexane, on the other hand, is more stable with the chlorine equatorial, and has $\Delta G^\circ = 0.5$ kcal/mol.[12] From these data, the anomeric effect can be estimated to be 2.2 + 0.5 = 2.7 kcal/mol. CNDO calculations[2d] on chloromethyl methyl ether indicate that the gauche form is more stable than the anti form by ~2 kcal/mol and that the barrier to internal rotation about the oxygen–methylene bond is slightly larger than 2 kcal/mol.[13] Thus, both experimental and theoretical data show that the magnitude of the anomeric effect in α-chloro ethers has a value of 2–3 kcal/mol.

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(7) The short C–O bond length and the small C–O–C bond angle should increase substantially the methyl–chlorine repulsions in the eclipsed form as compared to the situation in 1-chloropropane. The methyl–chlorine repulsion in eclipsed 1-chloropropane should be a little larger than the methyl–methyl repulsion in eclipsed butane (J. E. Anderson and H. Pearson, *J. Am. Chem. Soc.*, **97**, 764–769 (1975), footnote 5); eclipsed butane is estimated to be 6 kcal/mol higher in energy than gauche butane (E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis", Interscience Publishers, New York, N.Y., 1965, p 9).

(8) The steric barrier might be expected to be similar to the barrier to rotation of the methyl group in I.

(9) Two ab initio calculations[2a,b] on fluoromethanol give quite different gauche–anti energy differences (5.6 and 12.6 kcal/mol) as well as gauche–eclipsed energy differences (1.3 and 8.3 kcal/mol). CNDO/2 calculations[2c] give differences of the same signs as the ab initio calculations, but with much smaller magnitudes. Fluoromethanol is unfortunately not a known compound and thus no experimental data on this compound are presently available. Trifluoromethanol, (K. Seppelt, *Angew. Chem.*, **89**, 325 (1977)) has been prepared, but is not suitable for studying the anomeric effect.

(10) 1,3-Dioxacycloheptane (1,3-dioxopane) can have an arrangement similar to gauche dimethoxymethane in a ring system which is basically very flexible. However, neither the ^{1}H nor the ^{13}C spectrum of this compound showed any dynamic NMR effect down to −180 °C.

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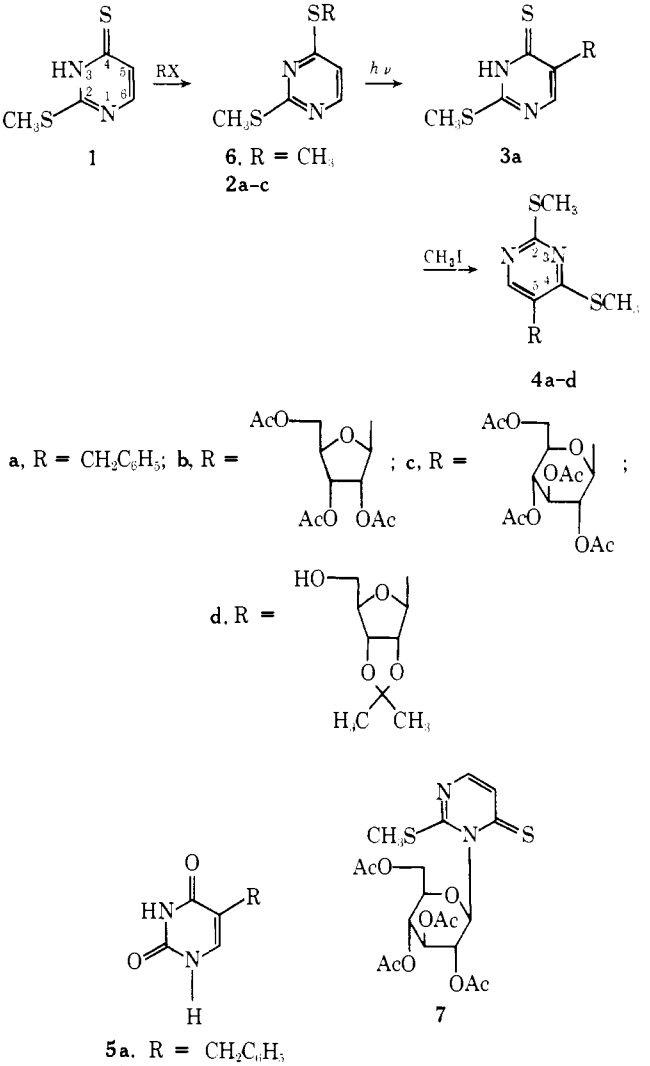
Pyrimidine *S*-Nucleoside Photorearrangement. New Access to Pseudonucleosides

Sir:

Because of their biological importance, considerable effort has been directed toward the synthesis of pseudonucleosides (*C*-nucleosides)[1] during the past several years.[2] In the conventional preparation of these substances the crucial step is the introduction, with appropriate stereochemical control, of a functionalized carbon unit at the anomeric center of a suitably derivatized pentose. This newly introduced substituent serves to elaborate the nitrogenous heterocyclic portion of the molecule.[2] However, direct coupling of the aglycone with the carbohydrate moiety is possible in a few cases.[3] Since such single-step synthesis—even with moderate yield—might be preferred, we have devised in the *S*-nucleoside series a new rearrangement prone to generalization, which ends up in the formation of a pseudonucleoside.

From our recent observation that 4-benzylthiopyrimidin-2-ones undergo a photoreaction leading to 5-benzylpyrimidin-2-ones,[4] we were prompted to investigate the photochemistry of some 4-glycosylthiopyrimidines. We expected to obtain by photorearrangement their 5-glycosyl isomer.

Interest in a pyrimidine amenable to further chemical transformations which may provide a variety of useful pyrimidine derivatives led us to select 4-mercapto-2-methylthiopyrimidine (**1**) as a substrate. Its *S*-benzyl derivative **2a** (oil)[5] was prepared and exposed to light[6] resulting in the formation of **1** and **3a** (mp 170–172 °C) in 30 and 60% yield, re-



1 — 6, R = CH_3 (2a–c) — 3a — 4a–d

5a, R = $CH_2C_6H_5$
b, R = β-ribosyl

7

spectively. Compound **3a** whose structure was evident from the analytical and spectral data was methylated (CH_3I, acetone, K_2CO_3) to give 5-benzyl-2,4-dimethylthiopyrimidine (**4a**, oil).[5] Oxidation of the latter by H_2O_2 in acetic acid followed by acid hydrolysis of the resulting 2,4-dimethylsulfonylpyrimidine gave 5-benzyluracil (**5a**).[7]

The thioglycoside **2b** (mp 81–82 °C)[8] was prepared by treating **1** with either 1,2,3,5-tetra-*O*-acetyl-D-ribofuranose (BF_3·Et_2O, dichloroethane, 0 °C) or 2,3,5-tri-*O*-acetyl-D-ribofuranosyl bromide (acetone, K_2CO_3). The β configuration of this *S*-nucleoside was anticipated because of its method of synthesis.[9] Compound **2a** and **2b** displayed a closely related photochemical behavior. Irradiation[6] of **2b** gave a mixture which, after methylation, was separated by silica gel column chromatography affording 2,4-dimethylthiopyrimidine (**6**) and **4b** (oil, 15% yield).[8] Compound **4b** is a pseudonucleoside as shown by comparison of the NMR spectra of **2b** and **4b.** In the spectrum of **4b** the H-6 signal appears as a singlet at 8.31 ppm, whereas the H-1′[10] signal is observed at higher field as expected for a *C*-nucleoside. Comparison of the signals exhibited by the ribose carbons in the ^{13}C NMR spectra of **2b** and **4b** shows only minor differences for C-2′, C-3′, C-4′, and C-5′. However, the signal due to C-1′ is found at 78.01 ppm in **4b** instead of 84.10 ppm in **2b.** This upfield shift is compatible with the replacement of a C–S bond by a C–C bond at C-1′.

NMR spectroscopy and TLC indicated that compound **4b** was anomerically pure; the configuration at C-1′ was assigned on the basis of the observed difference of the chemical shift values between the methyl resonances in the isopropylidene derivative **4d.**[11] Deacetylation ($NaOCH_3/CH_3OH$) of **4b** afforded a *C*-nucleoside which was treated with 2,2-dimethoxypropane to yield **4d** (oil).[8] For this compound $\Delta\delta_{CH_3}$ was 0.264 ppm suggesting the β configuration. Hence, there is retention of chirality at C-1′ during the photorearrangement; as previously demonstrated in the case of 4-benzylthiopyrimidin-2-ones,[4] it might be inferred that this rearrangement was also *intra*molecular.

Confirmation of structure **4b** was achieved by transformation of this substance into β-pseudouridine (**5b**). Thus, overnight oxidation of **4b** with *m*-chloroperbenzoic acid in CH_2Cl_2 gave the corresponding 2,4-dimethylsulfonyl derivative which upon treatment in water at 90 °C followed by deacetylation ($NaOCH_3/CH_3OH$) afforded β-pseudouridine.[12]

The 4-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyl)-thio-2-methylthiopyrimidine (**2c,** mp 147–149 °C)[13] was quantitatively prepared by treating **1** with 2,3,4,6-tetra-*O*-acetylglucopyranosyl bromide (acetone, K_2CO_3). The coupling constant $J_{H\text{-}1',H\text{-}2'}$ = 10 Hz indicates that this new glycosylthiopyrimidine has the β configuration. It was irradiated[6] to give a mixture of photoproducts which after methylation (CH_3I, acetone, K_2CO_3) afforded the three pyrimidine derivatives **6, 4c,** (oil, yield 8%),[13] and **7** (mp 162–164 °C, yield 7%).[13]

Structures **4c** and **7** are based on spectral evidences. The presence of a thiocarbonyl in **7** is confirmed by UV. Its NMR spectrum displays an AB pattern (J = 6 Hz) attributed to H-5 and H-6; the lowest field signal at 7.95 ppm is due to the anomeric H-1′. The deshielding of this signal results from the anisotropy of the thiocarbonyl;[14] consequently the glycosyl moiety in **7** is at N-3. The value of the coupling constant $J_{H\text{-}1',H\text{-}2'}$ = 9.7 Hz suggests that this nucleoside has retained the β configuration of the starting material.

Compound **4c** is a 2,4-dimethylthiopyrimidine with a glycosyl residue at C-5. In its NMR spectrum the H-6 signal appears as a singlet at 8.46 ppm and the H-1′ signal is part of the multiplet due to H-2′, H-3′, and H-4′.

We have firmly established that thionueoside **2a** and **2c** undergo a photorearrangement to provide stereospecifically the corresponding C-5 pseudonucleosides. These results demonstrate the potential utility of this reaction with pentose derivatives. In the case of **2c** migration of the hexopyranosyl residue occurred unselectively toward C-5 as well as N-3 in poor yield. The extension of this rearrangement to other systems through modification of the heterocyclic and carbohydrate moieties is underway in this laboratory.

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(8) **2b:** M^+· 416; UV (EtOH) λ_{max} 253 and 303 nm; NMR ($CDCl_3$) δ 8.17 (1 H, d, J = 5 Hz, H-6), 6.83 (1 H, d, J = 5 Hz, H-5), 6.25 (1 H, d, J = 3 Hz, H-1′), and 2.52 (3 H, s, SCH_3). **4b:** M^+· 430; UV (EtOH) λ_{max} 257 and 303 nm; NMR ($CDCl_3$) δ 8.31 (1 H, s, H-6), 5.07 (1 H, d, J = 5 Hz, H-1′), and 2.58 (6 H, s, SCH_3). **4d:** M^+· 344; UV (EtOH) λ_{max} 256 and 304 nm; NMR ($CDCl_3$) δ 8.24 (1 H, s, H-6), 4.78 (1 H, d, J = 3 Hz, H-1′) and 2.58 (6 H, s, SCH_3).
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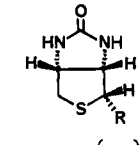
A Stereospecific Total Synthesis of (±)-Biotin[1]

Sir:

Biotin, a member of the B vitamin complex, plays an essential nutritional role in various CO_2 fixation reactions.[2] Recognition of biotin's important function as a growth factor in poultry, coupled with its relative unavailability from natural sources, spurred interest in synthetic approaches, and a stereoselective commercial synthesis has been developed.[3] We now wish to disclose a stereospecific total synthesis of (±)-biotin which differs fundamentally from previous approaches.[4]



Biotin, R = $(CH_2)_4COOH$
3, R = H