Ethyl α-selenophenylisobutyrate (8) from ethyl isobutyrate and benzeneselenenyl bromide (85%): bp 80–85° (0.025 mm); nmr (CCl_4) δ 7.1–7.6 (m, 5), 4.01 (q, 2, J = 7 Hz), 1.52 (s, 6), 1.17 (t, 3, J = 7 Hz).

Anal. Calcd for $C_{12}H_{16}O_2Se$: C, 53.13; H, 5.90. Found: C, 53.10; H, 5.99.

Methyl α-selenophenylhexanoate (9) from methyl hexanoate and benzeneselenenyl bromide (60%): bp 60–65° (0.05 mm); nmr (CCl_4) δ 7.1–7.7 (m, 5), 3.57 (s, 3), 1.0–2.0 (m, 7), 0.87 (t, 3, J = 6 Hz).

Anal. Calcd for $C_{13}H_{18}O_2Se$: C, 54.74; H, 6.36. Found: C, 55.10; H, 6.41.

Ethyl α-selenophenylacetate (10) from ethyl acetate and benzeneselenenyl bromide (80%): bp 77–80° (0.025 mm); nmr (CCl_4) δ 7.3 (m, 5), 4.10 (q, 2, J = 7 Hz), 3.50 (s, 2), 1.21 (t, 3, J = 7 Hz).

Anal. Calcd for $C_{10}H_{12}O_2Se$: C, 49.43; H, 4.97. Found: C, 49.73; H, 5.05.

Ethyl α-thiophenylisobutyrate (11) from ethyl isobutyrate and diphenyl disulfide (80%): bp 80° (0.025 mm); nmr (CCl_4) δ 7.3 (m, 5), 4.06 (q, 2, J = 7 Hz), 1.42 (s, 6), 1.20 (t, 3, J = 7 Hz).

Anal. Calcd for $C_{12}H_{16}O_2S$: C, 64.28; H, 7.14. Found: C, 64.40; H, 7.21.

Ethyl α-thiophenylacetate (12) from ethyl acetate and diphenyl disulfide (70%): bp 80° (0.05 mm) [lit.[26] bp 118° (2.7 mm)]; nmr (CCl_4) δ 7.1–7.6 (m, 5), 4.07 (q, 2, J = 7 Hz), 3.40 (s, 2), 1.18 (t, 3, J = 7 Hz).

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Registry No.—1, 1619-62-1; 3, 32864-38-3; 4, 40226-07-1; 5, 51364-90-0; 6, 51364-91-1; 7, 27784-76-5; 8, 51364-92-2; 9, 51364-93-3; 10, 51364-94-4; 11, 51364-95-5; 12, 7605-25-6; ethyl isobutyrate, 97-62-1; ethyl chloroformate, 541-41-3; *tert*-butyl acetate, 540-88-5; diethyl chlorophosphate, 814-49-3; dimethyl chlorophosphate, 813-77-4; methyl isobutyrate, 547-63-7; benzeneselenenyl bromide, 34837-55-3; methyl hexanoate, 106-70-7; ethyl acetate, 141-78-6; diphenyl disulfide, 882-33-7.

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Reaction of 1,3-Dimethyl-2-pyridone with *N*-Bromosuccinimide. A Reexamination

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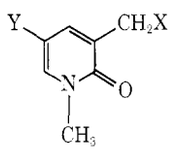
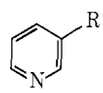
During our recent work on the total synthesis of camptothecin,[1] we had the opportunity to examine the reaction of 3-methyl-2-pyridone systems with *N*-bromosuccinimide (NBS). In a reported application of such a reaction,[2] 1,3-dimethyl-2-pyridone (1) was stated to react with NBS in the presence of dibenzoyl peroxide to yield 3-bromomethyl-1-methyl-2-pyridone (2). Since 1 had been chosen as a model compound, we sought to duplicate this experiment. On each of three attempts, following as closely as we could the experimental procedure described, the only product recovered was 5-bromo-1,3-dimethyl-2-pyridone (3). Comparison of this product with that previously reported proved difficult, since the characterization given[2] included only a melting point (98–99°) and an elemental analysis.





1, X = H; Y = H
2, X = Br; Y = H
3, X = H; Y = Br
4, X = OAc; Y = H
5, X = Cl; Y = H
6, X = OH; Y = H
7, X = OCH=CH_2; Y = H
10, X = $Ph_3P^+Br^-$; Y = H
11, X = OTs; Y = H
12, X = Py^+Br^-; Y = H
13, X = OMs; Y = H

8, R = CHO
9, R = CH_2OH

In characterizing the 5-bromo-1,3-dimethyl-2-pyridone (3) prepared in our study, the major additional datum was its nmr spectrum, which displayed singlets of three-proton intensity at δ 2.17 and 3.54 ppm. These correspond very closely with the methyl singlets at δ 2.14 and 3.52 in 1. The position of the bromine atom in 3 is established by disappearance of a one-proton triplet at δ 6.06 when the spectrum is compared with that of 1. The crude triplet at δ 7.2 corresponding to the remaining protons on the pyridone ring of 1 collapsed to a finely split doublet in the spectrum of 3. To verify that our interpretation of the nmr spectrum of 3 was correct, a series of compounds was prepared, substituted on the 3-methyl group but not at the 5 position of the ring. These included 3-acetoxymethyl-, 3-chloromethyl-, 3-hydroxymethyl-, and 3-vinyloxymethyl-1-methyl-2-pyridone (4, 5, 6, and 7, respectively). In each case, the corresponding nmr spectrum displayed a one-proton triplet near δ 6.0 for the proton on carbon 5 of the ring and a two-proton singlet in the δ 4.5–5.0 range for the methylene group bonded at carbon 3.

Finally, it was reported[2] that compound 2 gave a positive test with alcoholic silver nitrate. It is significant that our product also showed reactivity with alcoholic silver nitrate even after two recrystallizations from petroleum ether, the solvent reported as used for purifying 2. However, an analytically pure sample of 3 prepared by recrystallization and sublimation followed by preparative gc failed to react with silver nitrate and had mp 106–107°

compared with 100–102° after purification by recrystallization and sublimation alone.

In an attempt to determine the actual melting point of 3-bromomethyl-1-methyl-2-pyridone (2), and thus establish whether or not it might have indeed been prepared as reported, considerable effort was expended toward its unambiguous synthesis. The starting material chosen for this study was 3-hydroxymethyl-1-methyl-2-pyridone (6), which is easily obtained from pyridine-3-carboxaldehyde (8) *via* a modification of the reported route.[3] Rather than using the reported reduction of ethyl nicotinate in preparing the intermediate 3-hydroxymethylpyridine (9), we found it advantageous to reduce 8 with sodium borohydride.[4] Conversion of 9 to 6 followed the previously reported steps.

A variety of methods for displacement of a primary hydroxyl group with bromine have been reported. The two methods initially examined were reaction of 6 with phosphorus tribromide in the presence of pyridine[5] and treatment of 6 with carbon tetrabromide and triphenylphosphine.[6] In the former case, a very low yield of a mixture of products was recovered. As 6 is known to have a distribution between water and organic solvents strongly favoring the aqueous phase, it seems probable that 2 either failed to form or was hydrolyzed back to 6 during the isolation. Reaction of 6 with carbon tetrabromide and triphenylphosphine in acetonitrile also gave a mixture of products which apparently included unreacted 6, a small amount of 2, and the phosphonium salt 10, from reaction of 2 with triphenylphosphine. Attempts to separate the desired product from the mixture resulted in the reconversion to 6.

As 3-chloromethyl-1-methyl-2-pyridone (5) was formed in the course of attempted mesylate preparation from 6 and methanesulfonyl chloride, synthesis of 2 by reaction of 6 with *p*-toluenesulfonyl bromide or methanesulfonyl bromide also seemed reasonable. *p*-Toluenesulfonyl bromide[7] reacted with 6 in the presence of pyridine,[8] but mild aqueous work-up again gave no product readily extractable into an organic solvent. If tosylate 11 or the bromide 2 were forming, it also rapidly converted into a water-soluble product such as 6 or 12 during the course of the reaction or subsequent isolation. Methanesulfonyl bromide was prepared from mesyl chloride,[9] and reaction with 6 in the presence of 1,8-(dimethylamino)naphthalene again failed to give any product which could be identified as 2 or as the mesylate 13.

While the results of these attempted syntheses have not provided the desired unambiguous source of 2, they do indicate that the bromine in 2 would be extremely labile and subject to displacement under very mild conditions. It is doubtful that this extraordinary reactivity would go unnoticed if pure 2 were prepared. Our own characterization of 3 verifies that carbon 5 is the active site of 1,3-dimethyl-2-pyridone (1) when it is treated with NBS in the presence of dibenzoyl peroxide. This observation is entirely consistent with reports that upon treatment of 2-pyridones[10] and 1-methyl-2-pyridones[2] with NBS both the 3 and 5 positions are substituted with bromine. Thus the reported formation of 5-bromomethyl-1-methyl-2-pyridone in the reaction of 1,5-dimethyl-2-pyridone with NBS in the presence of dibenzoyl peroxide[2] is in doubt.

Experimental Section

Infrared absorption spectra were recorded on a Perkin-Elmer Infracord Model 137. The proton magnetic resonance spectra were recorded on a Varian T-60 nmr spectrometer, and chemical shifts are reported in δ units relative to internal tetramethylsilane. Mass spectra were obtained on a CEC-103 mass spectrometer. The glc analyses were performed on a Varian Aerograph gas–liquid chromatograph using helium as carrier gas. Elemental analyses were performed by the Analytical Laboratory, University of California, Berkeley, Calif.

1,3-Dimethyl-2-pyridone (1). This material was prepared from β-picoline:[11] gc on 5% QF-1 on Chromosorb W 80/100 AW-DMCS, 5 ft × 0.25 in., 123°, retention time 7.45 min; nmr ($CDCl_3$) δ 7.13 (d, J = 6.5 Hz, 2 H), 6.06 (t, J = 7 Hz, 1 H), 3.52 (s, 3 H), 2.14 (s, 3 H).

5-Bromo-1,3-dimethyl-2-pyridone (3). In a dry nitrogen filled flask was placed a solution of 0.83 g (6.7 mmol) of 1 in 12 ml of carbon tetrachloride which had been freshly distilled from P_2O_5. To the solution was added a mixture of 1.18 g (6.6 mmol) of NBS and 81 mg (0.34 mmol) of dibenzoyl peroxide. The mixture was then heated at 80° until reaction began, and the vigorous reaction was complete in about 5 min but reflux was continued for 0.5 hr. The hot mixture was filtered, the filtrate was evaporated, the residue was digested with petroleum ether–benzene and filtered hot, and the filtrate was evaporated. Recrystallization of the residue twice from petroleum ether (bp 40–60°) and sublimation gave material of mp 100–102°, raised to 106–107° after preparative gc: gc on 5% QF-1 on Chromosorb W 80/100, AW-DMCS 5 ft × 0.25 in., 175°, retention time 3.0 min; nmr ($CDCl_3$) δ 7.00–7.67 (m, 2 H), 3.54 (s, 3 H), 2.17 (s, 3 H); mass spectrum m/e 203, 201 (P), 174, 172, 122, 94.

Anal. Calcd for C_7H_8NOBr: C, 41.6; H, 4.0; N, 6.9. Found: C, 41.7; H, 4.0; N, 6.9.

3-Hydroxymethyl-1-methyl-2-pyridone (6). This compound was prepared from 3-hydroxymethylpyridine.[3] Distillation of the crude product obtained by continuous extraction of the reaction mixture with methylene chloride provided a fraction boiling at 121–123° (0.2 Torr): mp 79–82° on recrystallization from benzene (lit.[3] mp 80°); gc on 5% QF-1 on Chromosorb W, AW-DMCS, 10 ft × 0.25 in., 184°, retention time 7 min. Gas chromatography of the distilled but not recrystallized product revealed the presence of a small impurity of the isomeric **5-hydroxy-methyl-1-methyl-2-pyridone:** retention time 11.5 min; nmr ($CDCl_3$) δ 7.13–7.24 (m, 2 H), 6.20 (t, J = 6 Hz, 1 H), 4.06–4.76 (m, including s at 4.51, 3 H total), 3.54 (s, 3 H); nmr ($CDCl_3$–D_2O) δ 7.00–7.33 (m, 2 H), 6.06 (t, J = 6 Hz, 1 H), 4.46 (s, 2 H), 3.50 (s, 3 H); ir ($CHCl_3$) 3435, 3001, 1645, 1579, 1399, 1181, 1101 cm^{-1}; uv (EtOH) 298, 230 nm; mass spectrum m/e 139 (M^+).

3-Hydroxymethylpyridine (9). To a solution of 107 g (1.0 mol) of pyridine-3-carboxaldehyde (8) in 800 ml of absolute ethanol, cooled to 10° and flushed with nitrogen, was added 21 g (0.54 mol) of sodium borohydride at a rate to maintain the temperature below 25°. Most of the ethanol was evaporated at 40°, and the residue was poured into a solution of ice, salt, and ammonium chloride and stirred until hydrogen evolution ceased, 6 N HCl being added to maintain pH 5–6. The pH was adjusted to 7–8 with 4 N KOH and the 2 l. of aqueous solution was continuously extracted with methylene chloride for 24 hr. The dried extract was evaporated to give a quantitative yield of yellow oil pure by gc: bp 84–90° (0.1 Torr) [lit.[3] bp 110° (0.1 Torr)]; gc on 5% QF-1 on Chromosorb W, 10 ft × 0.25 in., 145°; nmr (CCl_4–$CDCl_3$) δ 8.33 and 8.22 (2 H), 7.62 (d, 1 H), 7.12 (d, 1 H), 6.06 (s, 1 H), 4.56 (s, 2 H).

3-Acetoxymethyl-1-methyl-2-pyridone (4). To a mixture of 2 ml of acetic anhydride and 4 ml of pyridine was added 140 mg (1.0 mmol) of 6, and the stoppered flask was allowed to stand for 24 hr. The excess reagents were removed *in vacuo*, leaving a solid residue which was sublimed to give 162 mg (92%) of 4: mp 79–82°; gc on 5% QF-1 on Chromosorb W, AW-DMCS, 10 ft × 0.25 in., 177°, retention time 9.5 min; nmr ($CDCl_3$) δ 7.42 (m, 2 H), 6.22 (t, J = 7 Hz, 1 H), 5.05 (s, 2 H), 3.57 (s, 3 H), 2.12 (s, 3 H).

Anal. Calcd for $C_9H_{11}NO_3$: C, 59.7; H, 6.1; N, 7.7. Found: C, 59.6; H, 6.1; N, 7.8.

3-Chloromethyl-1-methyl-2-pyridone (5). To a solution of 279 mg (2.0 mmol) of 6 in 10 ml of methylene chloride was added 304 mg (3.0 mmol) of triethylamine. To the cooled solution (0°) was added 300 mg (2.62 mmol) of mesyl chloride dissolved in 0.5 ml of methylene chloride, and after 10 min at 0°, the mixture was allowed to warm to room temperature. It was then again cooled and extracted successively with ice water, cold 2 N HCl, cold sodium bicarbonate solution, and saturated salt solution. The organic phase was dried over $MgSO_4$ and filtered and the solvent was removed to give 125 mg (40%) of 5: mp 79–80°; gc on 5% QF-1 on Chromosorb W 80/100, AW-DMCS, 5 ft × 0.25 in., 170°, retention time 3.6 min; nmr ($CDCl_3$) δ 7.45 (t, J = 7 Hz, of d, J = 2 Hz, 2 H), 6.18 (t, J = 7 Hz, 1 H), 4.55 (s, 2 H), 3.57 (s, 3 H); mass spectrum m/e 159, 157 (P), 122, 94, 93, 78, 67, 65, 51; high-resolution mass spectrum, m/e 157.0292 (calcd for C_7H_8ONCl, 157.0294).

3-Vinyloxymethyl-1-methyl-2-pyridone (7) was prepared from 6 and ethyl vinyl ether using mercuric acetate as catalyst,[12] yield 34% as a yellow oil: gc on 5% QF-1 on Chromosorb W 80/100, 10 ft × 0.25 in., 168°, retention time 6.4 min; nmr (CCl_4) δ 7.00–7.43 (crude t, 2 H), 6.43 (d, J_{cis} = 7 Hz, of d, J_{trans} = 14 Hz, 1 H), 6.02 (t, J = 7 Hz, 1 H), 4.59 (s, 2 H), 4.25 (d, J_{gem} = 2 Hz, of d, J_{trans} = 14 Hz, 1 H), 4.00 (d, J_{gem} = 2 Hz, of d, J_{cis} = 7 Hz, 1 H), 3.47 (s, 3 H); ir (film) 1651, 1600, 1561, 1407, 1198, 766 cm^{-1}; mass spectrum m/e 165 (P), 137, 122, 94.

Anal. Calcd for $C_9H_{11}NO_2$: C, 65.4; H, 6.7; N, 8.5. Found: C, 65.1; H, 6.4; N, 8.4.

Registry No.—**1**, 6456-92-4; **3**, 51417-13-1; **4**, 51417-14-2; **5**, 51417-15-3; **6**, 36721-61-6; **7**, 51417-16-4; **8**, 500-22-1; **9**, 100-55-0; NBS, 128-08-5.

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Steric and Electrostatic Interactions in Reactions of Carbohydrates. II.[1] Stereochemistry of Addition Reactions to the Carbonyl Group of Glycopyranosiduloses. Synthesis of Methyl 4,6-*O*-Benzylidene-3-*O*-methyl-β-D-mannopyranoside[2]

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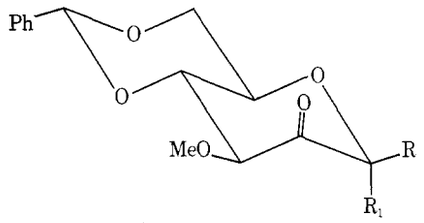
Received January 21, 1974

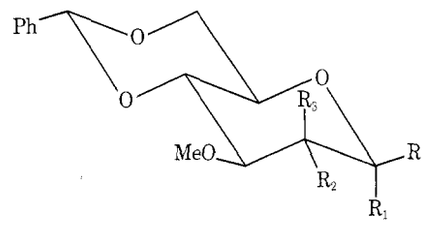
It has been reported that the reduction of benzyl 3-*O*-benzoyl-4,6-*O*-benzylidene-β-D-*lyxo*-hexopyranosid-2-ulose with lithium aluminum hydride gave benzyl 4,6-*O*-benzylidene-β-D-talopyranoside[3] (73%) whereas the reduction of methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-ethyl-α-D-*arabino*-hexopyranosid-2-ulose with lithium aluminum hydride gave methyl 4,6-*O*-benzylidene-3-deoxy-3-*C*-ethyl-α-D-glucopyranoside as the only product.[4] These observations, and our earlier observation on the dependence upon the anomeric configuration of the stereochemistry of the methyllithium and Grignard reagent additions to the C-4 carbonyl carbon atom of glycopyranosid-4-uloses,[1] prompted us to investigate the influence of the anomeric configuration on the stereochemical course of metal-hydride reduction of the C-2 carbonyl group of methyl 4,6-*O*-benzylidene-3-*O*-methyl-α- and -β-*arabino*-hexopyranosid-2-ulose (**1** and **2**).[10] The following were the reasons for undertaking this investigation.

Presently, a view has been adopted that the transition-state geometry for reactions of metal hydrides (and organometalic reagents) with carbonyl groups resembles the geometry of the starting ketone, and that nonbonded steric interactions, torsional strain, and electrostatic interactions (dipole–dipole repulsions) are decisive factors in determining the direction from which a nucleophile will approach a carbonyl group.[5] In the case of D-glycopyranosid-2-uloses of the β series, *e.g.*, **2**, the axial approach of the metal hydride anion to the C-2 carbonyl carbon atom, resulting in the formation of the transition state **3**, requires that the negatively charged metal hydride ion approaches the C-2 carbonyl carbon atom from a direction bisecting the C_1–O_1 and C_1–O_5 torsional angle. Since the C_1–O_1 and C_1–O_5 bonds are polarized and act as two equally oriented dipoles, an approach which will apposition a negatively charged ion between them should be energetically unfavorable owing to electrostatic interactions. An "equatorial" approach of the negatively charged metal hydride ion to the C-2 carbonyl carbon atom of **2**, resulting in the formation of the transition state **4**, will be, however, not only free from the electrostatic interactions, but the torsional strain and nonbonding steric interactions will be at a minimum as well.

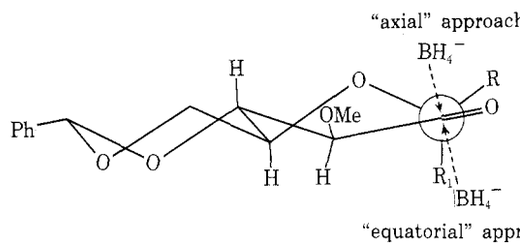
In the transition state **5**, which results from an "axial" approach of the negatively charged metal hydride ion to the C-2 carbonyl carbon atom of D-glycopyranosid-2-uloses of the α series, *e.g.*, **1**, the electrostatic interactions of the type described for the transition state **3** are not present. Furthermore, there will be no torsional strain. The only interaction present in **5** is one 1,3-nonbonding steric interaction between the axially oriented C-4 hydrogen atom and the incoming metal hydride anion. An "equatorial" approach of the negatively charged metal hydride ion to the C-2 carbonyl carbon atom of **1** resulting in the formation of the transition state **6** should give rise to generation of considerable torsional strain and dipolar interaction between the axially oriented C-1 methoxy group and the approaching metal hydride anion. Furthermore, in the transition state **6**, there will be two nonbonding steric interac-



1, R = H; R_1 = OCH_3
2, R = OCH_3; R_1 = H



7, R = R_3 = H; R_1 = OCH_3; R_2 = OH
8, R = OCH_3 R_1 = R_2 = H; R_3 = OH
9, R = OCH_3; R_1 = R_3 = H; R_2 = OH



3, R = OCH_3; R_1 = H ("axial" approach)
4, R = OCH_3; R_1 = H ("equatorial" approach)
5, R = H; R_1 = OCH_3 ("axial" approach)
6, R = H; R_1 = OCH_3 ("equatorial" approach)