Tetrahedron Letters No. 24, pp 2185 - 2188.
0040-4039/79/0608-2185$02.00/0

THE ADDITION OF METHYLHYPOBROMITE TO 4-ACETAMIDO-3-BROMO-2-PYRIDONE

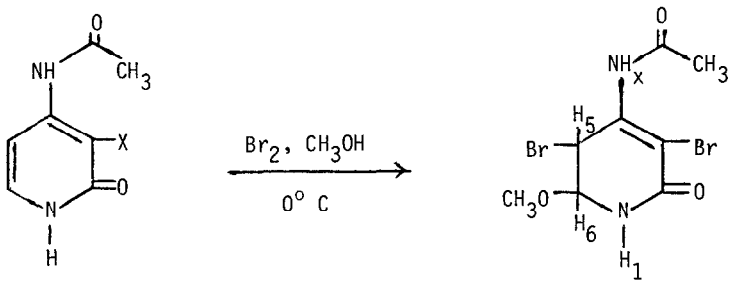
Robert L. Shone

Department of Chemical Research, Searle Laboratories,
P. O. Box 5110, Chicago, Illinois 60680

Summary. Bromination of 4-acetamido-3-bromo-2-pyridone in methanol results in the addition of methylhypobromite to the 5,6 double bond of the pyridone.

The addition of halogens in protic solvents (hypohalites) to the 5,6-double bond of the pyrimidine nucleic acid bases (uracil, thymine, and cytosine) and their nucleosides is a well known reaction that is synthetically useful.[1,2] Similar additions to the pyridine isosteres of these bases have not been observed. We wish to report one such example, the addition of the elements of methylhypobromite to 4-acetamido-3-bromo-2-pyridone.

When 4-acetamido-2-pyridone (N-4-acetyl-3-deazacytosine), 1, was treated with two equivalents of bromine in methanol, a stable[3] bromopyridone, 3, precipitates. The same product could also be obtained by treatment of 4-acetamido-3-bromo-2-pyridone, 2, with one equivalent of bromine in methanol. Microanalysis, mass spectroscopy (m/z 342), and pmr spectroscopy of the bromopyridone showed that it contained two bromines, an N-acetyl, and a methoxy group. In addition the pmr spectrum suggested the presence of a 5,6-disubstituted-5,6-dihydro-2-pyridone moiety since (a) the chemical shifts of the 5 and 6 hydrogens occur upfield 0.85 and 2.65 ppm respectively relative to those of 2, and (b) the multiplicities observed for H-5 and H-6 are not those expected for an aromatic bromo-2-pyridone. For example, H-6 (δ 4.73 ppm) of 3 appears as a doublet of doublets coupled to H-5 ($J_{5,6}$ 2.0 Hz) and H-1 ($J_{1,6}$ 4.7 Hz). The aromatic H-6 of a 4-substituted-2-pyridone normally occurs at δ 7-8 ppm as a doublet ($J_{5,6}$ 6-8 Hz). The pmr data observed for 3 is summarized in Table 1.



1 X = H

2 X = Br

3 83%

87%

Table 1: PMR Parameters of 3 in DMSO-d_6

	$CH_3\overset{O}{\overset{\|}{C}}-$	CH_3O	H_5	H_6	H_1	H_x
δ, ppm	2.13	3.30	6.13	4.73	9.17	9.40
multiplicity	s	s	d of d	d of d	d_{brd}	s_{brd}
J, Hz	-	-	2.0, 1.3*	4.7, 2.0*	5	-

* J's accurate to ±0.1 Hz. The assignment of $J_{1,6}$ and $J_{1,5}$ is based on literature[4] and experimental[5] data.

On the basis of the above the structure of the dibromo-2-pyridone was assigned as 3, d,l-4-acetamido-3,5-dibromo-5,6-dihydro-6-methoxy-2(1H)pyridone.[6] Corroborative evidence for structure 3 is provided by ^{13}C spectroscopy (Table 2). The difference in the chemical shifts of C-5 and C-6 of 3 (sp^3 hybridized carbons) from the other ring carbons (sp^2 hybridized) of 3 and those of C-5 and C-6 of the model 2-pyridones, 1, 2, and 5, is noteworthy.

Table 2: ^{13}C Chemical Shifts of 4-Acetamido-2-Pyridones (DMSO-d_6, $\delta^{13}C$ in ppm)

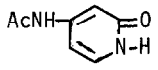
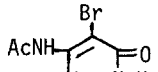
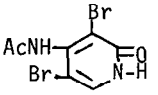
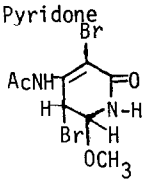
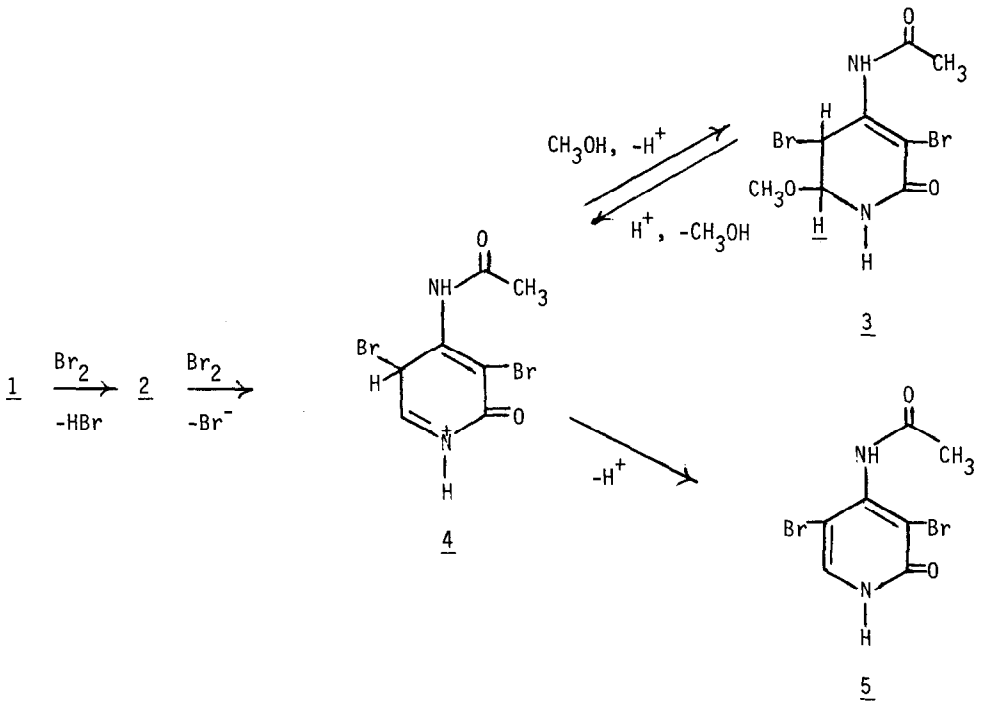
Pyridone		CH_3O	CH_3	$\rangle C{=}O$ endo	$\rangle C{=}O$ exo	C_3	C_4	C_5	C_6
	1	--	24.2	163.7	169.7	103.8*	149.3	99.4	135.4
	2	--	24.2	159.5	169.8	102.8*	147.8	101.4	133.7
	5	--	22.5	158.8	167.6	115.4*	147.0	99.6	135.6

Table 2 (continued)

Pyridone	CH_3O	CH_3	$\rangle C{=}O$ endo	$\rangle C{=}O$ exo	C_3	C_4	C_5	C_6
 3	54.9	23.9	159.7	169.9	105.9	144.6	44.1	84.1
Multiplicity for 3	q of d	q	d	q	t	t	d of d	d_{brd}
J, Hz	143,3	129	7	6	7	7	166,3	165

* Assignments of C_3 and C_5 may be reversed.

It is likely that the formation of 3 results from initial bromination at the reactive enolic 3 position of 1 to give the monobromopyridone 2 as an intermediate. A second attack of bromine at C-5 of 2 produces ion 4. The latter may then undergo covalent solvation to 3 or slow, irreversible proton loss to 5. The formation of 3 in a preparative sense may be aided by its low solubility in methanol.[7] Precedence for the conversion of 2 to 3 via 4 exists in the bromination of various pyrimidones. The detection and isolation of covalent solvates as bromination products of 2-pyrimidones, 4,6-dihydroxypyrimidine, 6-methyluracil, and uracils has been convincingly demonstrated by Tee[8] and Wang.[9]



References

1. J. L. Fourrey and P. Jouin, Tetrahedron Letters, 3393 (1977); R. Teoule, B. Fouque, and J. Cadet, Nucl. Acid. Res., 2, 487 (1975); M. J. Robins, G. Ramani, and M. MacCoss, J. Can. Chem., 53, 1302 (1975); L. Szabo, T. I. Kalman, and T. J. Bardos, J. Org. Chem., 35, 1434 (1970) and R. Duchinsky, T. Gabriel, W. Tantz, A. Nussbaum, M. Hoffer, E. Grunberg, J. Burchenal, and J. J. Fox, J. Med. Chem., 10, 47 (1967).
2. For reviews see T. K. Bradshaw and D. W. Hutchison, Chem. Soc. Revs., 6, 43, (1977) and N. K. Kochetkov and E. I. Budovskii, Ed., "Organic Chemistry of Nucleic Acids", pp. 269-307, Plenum Press, New York, 1972.
3. 3 is a stable solid at room temperature for long periods (>5 years) but will aromatize by loss of methanol to 5 when heated in solution in the presence of traces of acids or bases.
4. T. C. Thurber and L. B. Townsend, J. Het. Chem., 9, 629 (1972), report $J_{1,6}$ 3.7 Hz for 5-diazo-6-methoxy-1,6-dihydroxypyrimidine-2,4-(1H,3H,6H)dione.
5. The pmr spectrum of the N-1-methyl derivative of 3 exhibits H-5 and H-6 at δ 5.03 and 6.18 ppm as doublets with $J_{5,6}$ 2 Hz.
6. In the pyrimidine nucleoside 5-fluoro-2'-deoxyuridine, the presence of asymmetry in the sugar permits crystallization of the diastereoisomers resulting from addition of methylhypobromite to the 5,6 double bond. See the last citation of reference 1.
7. The appearance of 3 as a precipitate occurs after 1 has dissolved and approximately one-half of the two equivalents of bromine has been added.
8. S. Banerjee, O. S. Tee, and K. O. Wood, J. Org. Chem., 42, 3670 (1977); S. Banerjee and O. S. Tee, J. Org. Chem., 39, 3120 (1974); O. S. Tee and S. Banerjee, Can. J. Chem., 52, 451 (1974) and O. S. Tee, J. Org. Chem., 41, 4004 (1976).
9. S. Y. Wang, J. Amer. Chem. Soc., 81, 3786 (1959) and S. Y. Wang, J. Org. Chem., 24, 11 (1959).

10. Gratitude is expressed to Mr. E. Zelinski and associates for microanalyses, Dr. J. Hribar and associates for mass spectroscopy, and Mr. A. Damascus and associates, Dr. R. Bible, and Ms. L. Swenton for assistance with NMR data.

(Received in USA 15 February 1979)