The Preparation and Characterization of Some *N*-Chloro-2- and *N*-Chloro-4-pyridones

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2-Pyridone and 5-chloro-2-pyridone with NaOCl yield 1-chloro-2-pyridone and 1,5-dichloro-2-pyridone, respectively, which rapidly rearrange into 5-chloro- and 3,5-dichloro-2-pyridone. 3,5-Dichloro-2-pyridone with NaOCl yields 1,3,5-trichloro-2-pyridone which shows considerable stability. 4-Pyridone is similarly converted by NaOCl into 3,5-dichloro-4-pyridone via an unstable *N*-chloro derivative. 1,3,5-Trichloro-4-pyridone was obtained from 3,5-dichloro-4-pyridone and NaOCl.

Monohalogenopyridones are normally prepared by indirect methods[1] because, although they are formed during the halogenation of 2- and 4-pyridone, further halogenation to the 3,5-disubstituted pyridone is so easy that it is difficult to stop the reaction at the monohalogeno stage.[2] However, *N*-chlorosuccinimide[3] and *tert*-butyl hypochlorite[4] have been shown to convert 2-pyridone into the 5-chloro derivative.

Studies of the chlorination of indoles,[5] pyrroles,[6] and anilines[7] show the initial formation of an *N*-chloro derivative with subsequent rearrangement. Many aliphatic nitrogen compounds such as amines, amides, imines, and imides also form *N*-halo derivatives:[8,9] of these, *N*-haloimides and *N*-alkyl-*N*-halosulfonamides can be isolated and used as potent halogenating agents (e.g., *N*-bromosuccinimide,[10] *N*-chlorosuccinimide,[11] and "Chloramine-T"[12]).

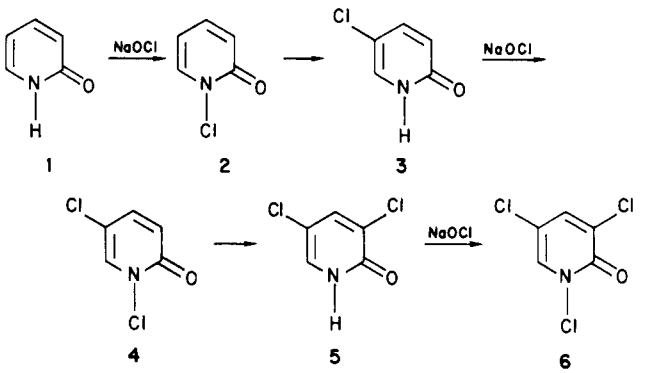
By analogy, chlorination of pyridones could occur via an *N*-chloro derivative and subsequent rearrangement. Indeed, a recent report[13] of the preparation of 1-fluoro-2-pyridone and its use as a fluorinating agent support this view. However, in studies, e.g., ref 14, of the bromination of 2-pyridones no such *N*-bromo derivative has been reported.

We have now studied the chlorination of 2- and 4-pyridones and report here on the stability and spectral properties of their *N*-chloro derivatives. Optimum conditions for the preparation of the *N*-chloro derivatives and their subsequent rearrangements have been developed.

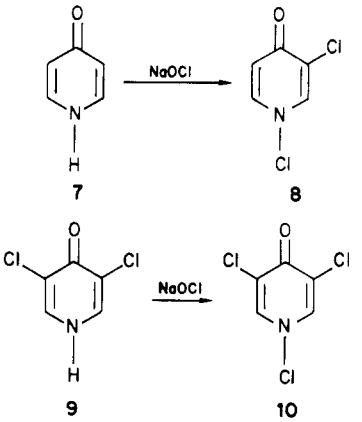
Results and Discussion

***N*-Chloro-2-pyridones.** The N-chlorination of 2-pyridone occurred quantitatively when a solution of 2-pyridone in CH_2Cl_2 was vigorously shaken with an aqueous solution of NaOCl for 30 s (Scheme I). The 1-chloro-2-pyridone (**2**) oxidized iodide ion and its concentration in $CHCl_3$ solution was determined iodometrically. Under the conditions used (see the Experimental Section) the formation of 1-chloro-2-pyridone was complete in 30 s.

Scheme I



Scheme II



1-Chloro-2-pyridone was characterized in solution by its spectral properties (^1H NMR, ^{13}C NMR, IR) which clearly show the presence of an N-substituent and the absence of C-substituents (Table I). At 25 °C, **2** spontaneously rearranges in solution into 5-chloro-2-pyridone (**3**) and the rearrangement is complete in 24 h, as was determined by following the reaction iodometrically. The product **3** was isolated in 60% yield: the crude material contained some 2-pyridone, but no 3-chloro-2-pyridone could be detected by TLC. Furthermore no peak was observed at ca 125 ppm in the ^{13}C spectrum as would be expected (cf. Table III) for 3-chloro-2-pyridone.

Analogous reaction of 5-chloro-2-pyridone (**3**) with excess NaOCl solution gives, as expected, 1,5-dichloro-2-pyridone

(1) Cava, M. P.; Bhattacharyya, N. K. *J. Org. Chem.* **1958**, *23*, 1614.
(2) Abramovitch, R. A.; Saha, J. G. *Adv. Heterocycl. Chem.* **1966**, *6*, 229.
(3) Paquette, L. A.; Farley, W. C. *J. Org. Chem.* **1967**, *32*, 2725.
(4) Ivashchenko, Y. N.; Yakovleva, O. N.; Moshchitskii, S. D.; Pavlenko, A. F. *Izobret., Prom. Obraztsy, Tovarnye Znaki* **1967**, *44(a)*, 44; *Chem. Abstr.* **1968**, *69*, 27253w.
(5) (a) De Rosa, M. *J. Chem. Soc., Chem. Commun.* **1975**, 482. (b) De Rosa, M.; Triana Alonso, J. L. *J. Org. Chem.* **1978**, *43*, 2639. (c) De Rosa, M.; Carbognani, L.; Febres, A. *Ibid.* **1981**, *46*, 2054.
(6) De Rosa, M. *J. Org. Chem.* **1982**, *47*, 1008.
(7) Paul, D. F.; Haberfield, P. *J. Org. Chem.* **1976**, *41*, 3170.
(8) March, J. "Advanced Organic Chemistry", 2nd. ed.; McGraw-Hill: New York, 1977; p 582.
(9) Kaminski, J. J.; Bodor, N. *Tetrahedron* **1976**, *32*, 1097.
(10) Ziegler, K.; Spath, A.; Schaaf, E.; Schumann, W.; Winkelmann, E. *Liebigs Ann. Chem.* **1942**, *551*, 80.
(11) Grob, C. A.; Schmid, H. J. *Helv. Chim. Acta* **1953**, *36*, 1763.
(12) Soper, F. G.; Smith, G. F. *J. Chem. Soc.* **1926**,m 1582.
(13) Purrington, S. T.; Jones, W. A. *J. Org. Chem.* **1983**, *48*, 761.
(14) Tee, O. S.; Paventi, M. *J. Am. Chem. Soc.* **1982**, *104*, 4142.

0022-3263/84/1949-4784$01.50/0

Table I. ^{1}H NMR Chemical Shifts (ppm),[a] Coupling Constants (Hz), and IR Spectra (cm^{-1}) for Mono-, Di-, and Trichloro-2-pyridones

		^{1}H NMR										IR spectra[b]	
no.	chloro	H-1	H-3	mult[e]	J	H-4	mult[e]	J	H-6	mult[e]	J	ν_{N-H}[c]	$\nu_{C=O}$[d]
1	*f,g*	13.85	6.23–6.80	m		7.40–7.75	m		7.40–7.75	m		3200–2500	1640
2	1[h]		6.75	dd	2, 10	7.45	dt	2.10	7.65	d	7		1678
3	5[i]	10.70	6.50	d	10	7.60–7.87	m		7.60–7.87	m		3200–2500	1655
4	1,5		6.67	d	10	7.50–7.80	m		7.50–7.80	m			1673
5	3,5	11.70				7.67	d	3	7.77	d	3	3200–2500	1660[j]
6	1,3,5					7.63	s		7.63	s			1715

[a] In $CDCl_3$ referenced to $(CH_3)_4Si$ except where stated. [b] In CH_2Cl_2, liquid cells. [c] NH stretching mode. [d] C=O/C=C stretch, amide I band. [e] Multiplicity: s = singlet, d = doublet, t = triplet, m = multiplet. [f] Reference 16. [g] H-5, δ 6.23–6.80, m. [h] H-5, δ 6.30, dt, J = 2, 1 Hz. [i] ^{1}H NMR in Me_2SO-d_6. [j] Reference 17.

Table II. ^{1}H NMR Chemical Shifts (ppm),[a] Coupling Constants (Hz), and IR Spectra (cm^{-1}) for Mono-, Di-, and Trichloro-4-pyridones

		^{1}H NMR												IR spectra[b]	
no.	chloro	H-1	H-2	mult[e]	J	H-3	mult[e]	J	H-5	mult[e]	J	H-6	mult[e]	J	ν_{N-H}[c]	$\nu_{C=O}$[d]
7	*f,g*		7.92	d	10	6.63	d	10	6.63	d	10	7.92	d	10	3200–2500	1635
9	3,5[h]		7.90	s								7.90	s		3200–2500	1565
10	1,3,5[i]		8.10	s								8.10	s			

[a] In $CDCl_3$ referenced to $(CH_3)_4Si$ except where stated. [b] In CH_2Cl_2, liquid cells. [c] Stretching mode. [d] Amide I band. [e] Multiplicity: s = singlet, d = doublet, t = triplet, m = multiplet. [f] Reference 16. [g] D_2O. [h] Me_2SO-d_6. [i] Me_2SO-d_6 + $CDCl_3$.

Table III. ^{13}C NMR Spectra[a] for Mono-, Di-, and Trichloropyridones

	pyridone		chemical shifts for C atoms in ppm				
no.	type	chloro	2	3	4	5	6
1	2[b,c]		165.3	120.1	134.8	106.7	141.6
2	2[c]	1	163.5	120.6	132.7	106.7	142.2
3	2	5	161.4	119.6	135.4	112.3	141.1
4	2[c]	1,5	159.7	120.8	131.2	113.0	140.2
5	2	3,5	157.3	124.8	133.2	110.3	139.1
6	2[c]	1,3,5	*d*	126.1	136.5	112.5	138.6
7	4[e]		140.0	116.2	176.6	116.2	140.0
9	4	3,5	145.9	122.0	164.5	122.0	145.9

[a] In Me_2SO-d_6 except where stated. [b] Johnson, L. F.; Jankowski, W. C. "Carbon-13 NMR Spectra"; Wiley: New York, 1972; No. 107. [c] In $CDCl_3$. [d] Weak signal, not observed. [e] Reference 16.

(4), which is formed in solution in CH_2Cl_2 in quantitative yield. As before, 4 was determined iodometrically and spectral data of the *N*-chloro derivative 4 clearly indicated the 1,5-substitution pattern (Tables I–III). Iodometric titration showed that under the experimental conditions used the N-chlorination 3 → 4 was complete in 60 s and that 4 in CH_2Cl_2 solution rearranged to 3,5-dichloro-2-pyridone (5) (isolated in 40% yield) completely in 24 h.

Reaction of 5 with excess NaOCl solution gave the 1,3,5-trichloro-2-pyridone (6). Formation of 6 was slightly slower (120 s) compared to above; 6 also liberated iodine from KI. Rearrangement onto the ring is now blocked and 6 is more stable than 2 or 4. Solutions of 6 in $CHCl_3$ can be kept for at least a week at 0 °C.

In the 4-pyridone series, the transformation 7 → 8 occurs. The higher water solubility of 8 hinders its extraction and for this reason solid $Ca(OCl)_2$ was employed; although 8 could be detected by oxidation of KI to I_2, it mainly undergoes rearrangement into 3,5-dichloro-4-pyridone (9). However, 3,5-dichloro-4-pyridone (9) was converted into 1,3,5-trichloro-4-pyridone (10) as expected, extracted into $CHCl_3$, and determined iodometrically.

Treatment of 4-pyridone with SO_2Cl_2 has been reported to yield 1,2,2,3,3,5,6-heptachloro-2,3-dihydro-4-pyridone (9%).[15]

Spectral Properties of *N*-Chloropyridones. Substitution of chlorine in pyridones involves significant spectral changes[16] in the IR and ^{1}H NMR spectra (Tables I and II).

The ^{13}C NMR spectra of the 2-pyridones (Table III) show clearly the influence of chlorine substitution on the carbon chemical shifts to which the chlorine atoms are attached.

N-Chloro derivatives in the 4-pyridone series could not be fully characterized by spectroscopic methods due to their instability.

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded on Varian EM 360 L and JEOL FX 100 instruments, respectively; IR spectra were recorded on a Perkin-Elmer 283 B spectrophotometer. Melting points were determined on a Thomas-Hoover capillary apparatus. CHN analyses were carried out by Dr. R. W. King in this department.

Standard sodium thiosulfate solution (0.1 N) was prepared by dilution of the appropriate commercial Acculute solution with glass-distilled water. $Ca(OCl_2)$ was as supplied by Alfa Product. Its active chlorine content (97.8%) was determined by titration[17] prior to use. NaOCl solution was prepared by dissolving $Ca(OCl)_2$ (75 g, 0.52 mol) in glass-distilled water (1 L) followed by addition of anhydrous Na_2CO_3 (55 g, 0.52 mol). After 5 min, the $CaCO_3$ precipitate was removed by filtration. The molarity of the NaOCl solution so obtained (1.01 M) was determined by iodometric

(15) Den Hertog, H. J.; Maas, J.; Kolder, C. R.; Combe, W. P. *Recl. Trav. Chim. Pays-Bas* **1955**, *74*, 59.

(16) ^{1}H, ^{13}C NMR, and IR spectra of 2- and 4-pyridones were taken from "Sadtler Standard Spectra", Sadtler Research Laboratories Inc., 1977; reference numbers ^{1}H NMR (9891, 16076), ^{13}C NMR (2633, 2420), IR (21407, 24808), respectively.

(17) Fritz, J. S. "Standard Methods of Chemical Analysis" 6th ed.; Welcher, F. J., Ed.; D. Van Nostrand: Princeton, 1965; Vol. 2, p 278.

titration. Aliquots (50 mL) of this solution were diluted with glass-distilled water (75 mL) to give stock solutions of NaOCl (0.4 M, 125 mL) which were saturated with NaCl (ca. 60 g) and filtered before use as described below.

2-Pyridone was purified by distillation (bp 130 °C (2.5 mmHg)) as was 4-pyridone (bp 130 °C (0.25 mmHg)).

Optimization of *N*-Chloropyridone Formation. The pyridone (2.5 mmol) in CH_2Cl_2 (25 mL) was shaken with the stock NaOCl solution (30 mL, 0.4 M) for a known time after which the organic layer was separated and dried by passing through a 10-cm column of anhydrous K_2CO_3. An aliquot (5 mL) was added to a solution of KI (2 g) in EtOH/AcOH (50:50, v/v, 20 mL) and the resultant mixture was titrated with standard sodium thiosulfate solution (0.01 N).

Time of *N*-Chloro to *C*-Chloro Rearrangement. The pyridone (10 mmol) in CH_2Cl_2 (100 mL) was shaken with a NaOCl solution (120 mL, 0.4 M) for the time previously determined as optimum for *N*-chloro formation. Then as above, the organic layer was separated and dried, and the *N*-chloropyridone content of aliquots (5 mL) was iodometrically determined at known time intervals until maximum conversion had occurred.

5-Chloro-2-pyridone. 2-Pyridone (4 g, 0.042 mol) in CH_2Cl_2 (400 mL) was shaken for 30 s with NaOCl solution (0.4 M, 520 mL, 0.21 mol) and saturated with NaCl. The organic layer was separated, dried with anhydrous K_2CO_3, and left standing for 24 h. The solvent was evaporated in vacuo and the resulting 5-chloro-2-pyridone (**3**) was recrystallized from C_6H_6 as needles (3.2 g, 59%), mp 163 °C (lit.[1] mp 163–165 °C).

3,5-Dichloro-2-pyridone. 5-Chloro-2-pyridone (0.5 g, 3.9 mmol) in CH_2Cl_2 (50 mL) was shaken for 1 min with a stock NaOCl solution (0.4 M, 60 mL, 24 mmol). The organic layer was separated, dried with anhydrous K_2CO_3, and left standing for 24 h. Evaporation of the solvent in vacuo gave the crude (0.39 g) product, which yielded 3,5-dichloro-2-pyridone (**5**) (0.25 g, 39%), mp 172 °C (lit.[1] mp 170–173 °C), as needles from C_6H_6.

1,3,5-Trichloro-2-pyridone. 3,5-Dichloro-2-pyridone (0.16 g, 1 mmol) in CH_2Cl_2 (16 mL) was shaken for 2 min with stock NaOCl solution (0.4 M, 20 mL, 8 mmol). The organic layer was separated and dried by passing though a 10-cm column of anhydrous K_2CO_3. The solvent was evaporated in vacuo at room temperature and the residue was immediately taken up into $CDCl_3$ (ca. 2 mL) for spectral analysis (Tables I–III). An aliquot (5 mL) of the organic layer before evaporation liberated I_2 from KI solution as described in the optimization procedure. The samples in $CDCl_3$ or $CHCl_3$, kept at 0 °C, remained stable (by ^1H NMR and iodometric titration) for at least a week.

3,5-Dichloro-4-pyridone. 4-Pyridone (0.6 g, 6.3 mmol) in $CHCl_3$ (100 mL) was shaken for 30 s with stock NaOCl solution (0.4 M, 120 mL, 48 mmol). The aqueous layer was separated and left standing overnight. A white precipitate of **9** formed which was filtered off, dried, and recrystallized from water as needles (1.0 g, 97%): mp >340 °C (lit.[18] mp >322–325 °C); *m/e* 167 (M + 4, 10.2%), 165 (M + 2, 62.0%), 163 (M, 100%), 162 (M − 1), 128 (M − 35) (loss of Cl atom), M − 70 (loss of 2Cl atoms).

1,3-Dichloro-4-pyridone. 4-Pyridone (0.476 g, 5 mmol), $CHCl_3$ (200 mL), $Ca(ClO)_2$ (1.9 g, 13 mmol), and H_2O (1 mL) were stirred at 20 °C for 4 h. The organic layer was separated and dried (K_2CO_3), and its 1,3-dichloro-4-pyridone content (8.2%) was determined iodometrically.

1,3,5-Trichloro-4-pyridone. 3,5-Dichloro-4-pyridone (0.330 g, 2.0 mmol) in $CHCl_3$ (200 mL) was shaken for 20 min with aqueous NaOCl (0.4 M, 25 mL, 10.0 mmol). The organic layer was separated and the aqueous layer repeatedly extracted with chloroform (100 mL, 50 mL, 40 mL). The chloroform extracts were mixed and dried (anhydrous K_2CO_3). 1,3,5-Trichloro-4-pyridone content was determined iodometrically (71%).

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(18) Katritzky, A. R.; Rowe, R. D.; Roy, S. K. *J. Chem. Soc. B* **1966**, 758.

The Preparation of 2(1*H*)-Pyridinones and 2,3-Dihydro-5(1*H*)-indolizinones via Transition Metal Mediated Cocyclization of Alkynes and Isocyanates. A Novel Construction of the Antitumor Agent Camptothecin

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The intermolecular cocyclization of two alkynes with an isocyanate was examined utilizing (η^5-cyclopentadienyl)cobalt dicarbonyl [$CpCo(CO)_2$] and bis(η^4-1,5-cyclooctadiene)nickel [$(COD)_2Ni$] as catalysts. It was found that these compounds produced different amounts of 2-pyridone regioisomers. $CpCo(CO)_2$ also effectively catalyzes the cocyclization of 5-isocyanatoalkynes with monoalkynes to give 2,3-dihydro-5(1*H*)-indolizinones. The use of trimethylsilyl substituents ensures regioselectivity and allows the further elaboration of the 6-position to bear halo, alkenyl, and alkynyl substituents. This strategy is applied to synthetic approaches to the antitumor alkaloid camptothecin.

Structures containing the 2(1*H*)-pyridinone (2-pyridone) skeleton are rapidly gaining importance in synthetic and natural products chemistry. Compounds incorporating this nucleus are quite versatile as synthetic intermediates.[1] For example, treatment of 2-pyridones with phosphorus pentachloride generates 2-chloropyridines. The pyridone nucleus can be partially reduced via catalytic hydrogenation to piperidinones or further reduced to fully saturated piperidines.[1] Electrophilic substitution reactions with halogens occur often under mild conditions, furnishing products substituted in the 3- and 5-positions.[2] Nitration is also possible, yielding 3- or 5-nitro- and 3,5-dinitro-2-pyridones. The diene portion of the molecule can undergo Diels–Alder cycloaddition reactions with dienophiles,[3] or one double bond may act as a dienophile to an added

(1) Tieckelmann, H. In "Pyridine and its Derivatives"; Abramovitch, R. A., Ed.; Interscience: New York, 1974; Vol. 14 Supplement, Part 3, Chapter 12, p 597 and references cited therein. Smith, D. M. In "Rodd's Chemistry of Carbon Compounds", 2nd ed.; Coffey, S., Ed.; Elsevier: Amsterdam, 1976; Vol. 4F, Chapter 24.

(2) (a) Abramovitch, R. A.; Saha, J. G. *Adv. Heterocycl. Chem.* **1966**, *6*, 229. (b) Tee, O. S.; Paventi, M. *J. Am. Chem. Soc.* **1982**, *104*, 4142.

(3) Gisby, G. P.; Royall, S. E.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1* **1982**, 169.

0022-3263/84/1949-4786$01.50/0