Synthesis and Unusual Stability of Pyridine and *N*-Methyl Pyridinium 1,3-Dioxolanes

Stephen T. Hobson*,†, Joseph D. Boecker, James H. Gifford, Tara L. Nohe, and Carl H. Wierks

Drug Assessment Division, United States Army Medical Research Institute of Chemical Defense, AberdeenProving Ground, MD 21010-5400
stephen.t.hobson@us.army.mil
Received October 9, 2002

Differentially substituted bridged pyridinium oximes are necessary in research on antidotes for organophosphate poisoning. A solid-phase synthesis would improve the yield and ease of purification of these compounds. To predict the lability of the linker in the final step of our proposed synthesis, we synthesized a series of pyridine and *N*-methyl pyridinium acetals. These compounds proved to be resistant to acid catalyzed hydrolysis. This stability may be useful for synthetic manipulation of pyridine aldehydes.

J. Heterocyclic Chem., **40**, 277(2003).

Introduction

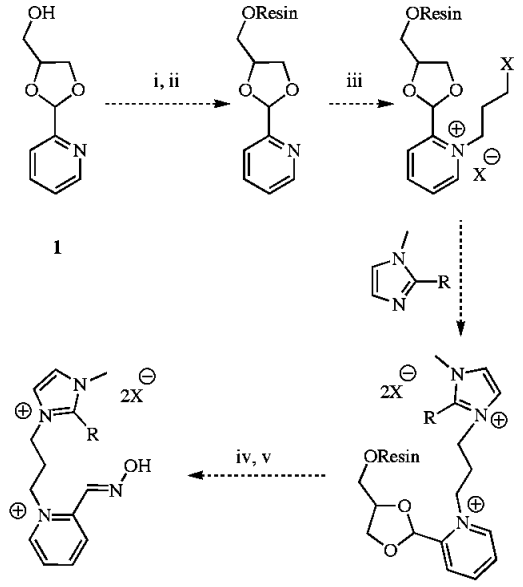
Organophosphorus chemical warfare agents were first discovered in the 1930's, by the German chemist Schrader, who synthesized the compound known today as tabun [1]. The high lethality and quick action of these compounds require effective medical countermeasures [2]. Oximes and pyridinium oximes have been proven to effectively reverse intoxication symptoms of nerve agent poisoning [3-6]. In 1962, U. S. Army scientists disclosed the use of bridged pyridinium oximes as effective antidotes to nerve agent poisoning [7]. Oldiges and Schoene followed this work in 1970 reporting that unsymmetrical bis-(substituted pyridinium) dimethyl ether derivatives showed a promising effect on soman (GD, pinacolyl methyl phosphonofluoridate) intoxication [8]. Further developments in the field included Hagedorn's synthesis of differentially substituted bridged pyridinium oximes [9] and a United States Army research effort from 1980-1991 that resulted in series of papers [10-13]. Our objective was to synthesize a number of novel bridged pyridinium and imidazolium oximes using solid phase parallel synthesis [14,15]. We envisioned using a hydroxymethyl acetal of 2-pyridine aldehyde with glycerol as a 'pre-loaded linker' to the resin [16]. This would be followed by alkylation of the pyridine with a bis-halogenated bridging group and nucleophilic substitution of the remaining halogen with an additional heterocycle (Scheme 1).

Since the final cleavage of the product from the solid support is vital to the proposed synthesis, acid catalyzed hydrolysis of the protected pyridinium aldehyde was fundamental to its success. Herein we report the synthesis and solution stability of 2- and 4- substituted pyridine and *N*-methyl pyridinium 1,3-dioxolanes.

Chemistry

Given that 1,3-dioxolane is the favored product in the condensation of glycerol with aromatic aldehydes under thermodynamic conditions [17], we expected similar

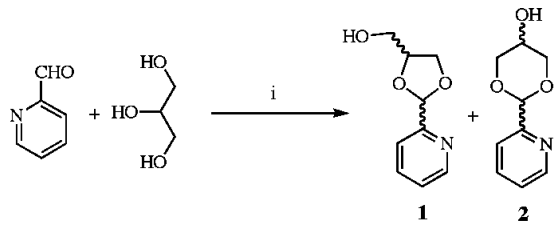
Scheme 1



i) NaH, DMF. ii) Merrifield Resin. iii) X-$(CH_2)_3$-X. iv) H^+, DMF. v) NH_2OH, EtOH $NaHCO_3$.

Proposed solid phase synthesis of differential substituted bridged oximes.

Scheme 2



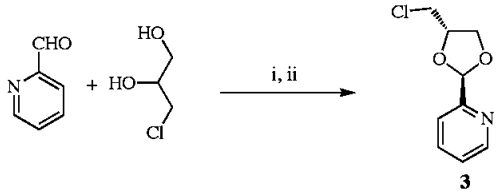
i) 2 eq TsOH, C_6H_6 80° C, 12 h

Reaction of glycerol with pyridine-2-aldehyde.

results with pyridine aldehydes. Our first attempts using glycerol and pyridine-2-carbaldehyde under standard conditions (PhH, 80°, cat *p*-TsOH) [18,19] resulted in recovered starting material. However, by increasing the amount of acid we obtained a mixture of 1,3-dioxolane **1** and 1,3-dioxane **2** in good yield (Scheme 2) [20,21].

This mixture having proved inseparable, we next prepared the chloromethyl substituted 1,3-dioxolane **3** (Scheme 3).

Scheme 3



i) 2 eq TsOH, C_6H_6 80° C, 12 h. (ii) 10% $NaHCO_{3(aq)}$ 12 h.

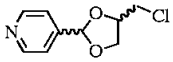
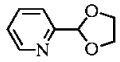
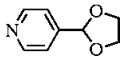
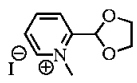
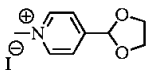
Synthesis of 2-chloromethyl substituted pyridine acetal.

We anticipated that **3** would be easily converted to necessary hydroxyl compound **1** by hydrolysis of the chloromethyl group. However, standard hydrolysis conditions (10% Na_2CO_3, 23° C) [22] did not result in **1** but rather resulted in the purification of **3** as a single diastereomer. Even Lewis Acid conditions reported to provide the alcohol from the alkyl chloride ($AgNO_3$, 2 *M* KOH) did not result in any hydrolysis product [23].

These anomalous results prompted us to investigate the hydrolysis of acetal **3** and other analogous compounds. These derivatives were prepared using conditions outlined above in good to moderate yields (Table 1) [24].

Table 1

Yields of 1,3-Dioxolanes from Pyridine and Pyridinium Aldehydes

Compound	Structure	Yield[a]
4		100
5		94
6		49
7[b]		40
8[b]		42

[a] Overall, isolated yields from starting aldehyde; [b] prepared by the methylation of **5** and **6** with CH_3I in THF [25]

Pyridine and pyridinium acetals were characterized by NMR (^1H, ^{13}C, COSY, HMQC) and mass spectroscopy. Residual water in **4** – **8** was seen in ^1H NMR and the combustion analysis. The relative stereochemistry of **3** is consistent with the 1D NOE enhancement (Figure 1).

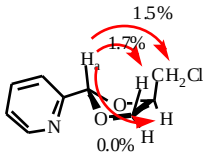


Figure 1. NOE enhancements upon irradiation at H_a (6.08 ppm) for **3**.

Having fully characterized **3** - **8**, the stability of the acetal linkage in the pyridine and pyridinium scaffold was tested in increasingly harsh conditions. Although deprotection reactions of **5** compounds have been recently reported, both conditions were not suitable for our proposed cleavage of the pyridinium acetal from the polymer resin (clay supported NH_4NO_3, microwave irradiation [26] or LiCl, H_2O, DMSO [27]). To determine the stability of the acetal linkage in compounds **3** – **8** to solution-phase hydrolytic conditions, we subjected all compounds to a series of standard acid catalyzed hydrolyses with increasing harshness [18]. Under all conditions, the compounds remained in their native state as ascertained by taking the ratio of the ^1H NMR signal from the acetal hydrogen (δ 5.3 – 6.3 ppm) to the NMR signal from the aldehyde proton (δ 9 ppm) in the starting material (Table 2).

Table 2.

Stability of pyridine and pyridinium acetals under acidic conditions.

Each entry is the percentage of acetal in the recovered products.

	1:1 THF/ 5% $HCl_{(aq)}$ [a]	1M $HCl_{(aq)}$/ THF [b]	Conc $HCl_{(aq)}$	CH_3COOH 118°C [c]
3	99.5	100	100	100
4	100	100	100	100
5	77	97	100	[d]
6	100	100	100	100
7	100	100	100	100
8	100	100	100	100

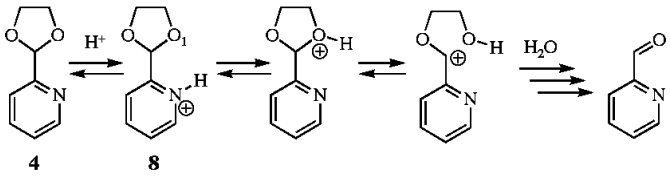
[a] P. A. Grieco, M. Nishizama, T. Oguri, S. D. Burke, N. Marinovic, *J. Am. Chem Soc.*, **99**, 5773 (1977); [b] P. A. Grieco, Y. Yokoyama, G. P. Withers, F. J. Okuniewicz and C. -L. Wang, *J. Org. Chem.*, **43**, 4178 (1978); [c] J. H. Babler, N. C. Malek and M. J. Coghlan *J. Org. Chem.*, **43**, 1821 (1978). [d] decomposition.

All compounds were universally stable even under strong acid conditions. Increasing the temperature resulted either in decomposition of the starting material or in recovery of the acetal (see Table 2). Our results confirm the earlier reports of anomalous reactivity of the di-n-butyl acetal of 2-pyridine aldehyde to solid phase [28] and Lewis Acid promoted

hydrolysis [29] and the stability in a compound derived from pyridine 3-aldehyde (3-[1,3]Dioxolan-2-yl-2-tributyl-stannyl-pyridine) to standard acidic hydrolysis [30]. They are further echoed by the acid stability of the isonicotinyl (iNoc) protecting group that has been used in solution phase peptide syntheses [31]. Furthermore, in other publications that used compounds **7** and **8**, the acetal protecting group was removed only after reduction of the pyridinium ring [32-34]. In contrast, the acetal formed from benzaldehyde and ethylene glycol (2-phenyl-[1,3]-dioxolane) smoothly reacts in 1:1 THF/5% HCl at ambient temperature over 12 h to give benzaldhyde in a 96% purity and >90% yield.

The stability of **3** – **8** in acid conditions may be due to the increased charge density of the protonated pyridine ring (**3** – **6**) or the *N*-methyl pyridinium ring (**7, 8**). Initially we proposed that after protonation of the pyridine nitrogen for **1** and **4** [35], the pyridine ring would intramolecularly transfer the proton to one of the oxygens in the acetal linkage followed by hydrolysis (Scheme 4).
of pyridine acetals.

Scheme 4



Proposed intramolecular proton transfer in acid catalyzed hydrolysis.

However, calculations using semi-empirical energy minimization [36] of **8** showed that the neither the bond angle (N_4-H_{26}-O_9 21.5°) nor the bond length (H_{26}-O_9 2.4 Å) is sufficient for an intramolecular hydrogen bond that presumably would be formed before the transfer of the proton (Figure 2) [37].

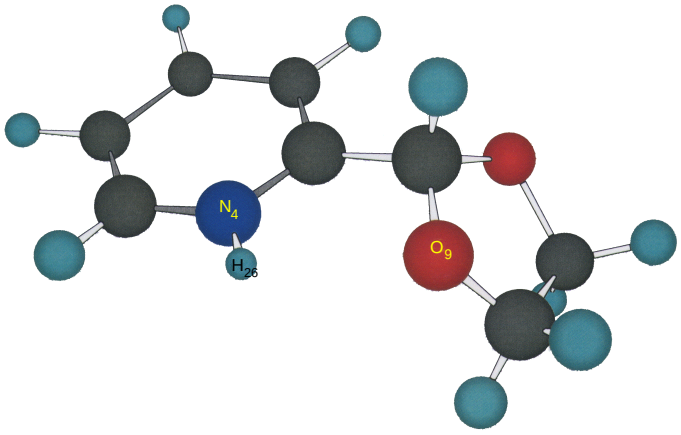


Figure 2. Lowest energy conformation [xxxvi] for protonated pyridine acetal **8** (gray = carbon, blue = nitrogen, teal = hydrogen, red = oxygen).

For the other compounds (**4, 6 - 8**), it seems likely that the increased charge density due to protonation or methylation prevents either an intermolecular proton transfer (**4, 6**) or the initial protonation of the acetal oxygen (**7, 8**). This hypothesis is supported by the reported hydrolysis of 6-bromo-2-(1',3'-dioxolan-2-yl)pyridine under relatively mild conditions (2 *M* $HCl_{(aq)}$, 60° C, 3 hr) [38]. Presumably, the substitution of the bromine at the *meta* position sufficiently reduces the basicity of the pyridine nitrogen to preclude protonation and allow hydrolysis of the acetal [39].

In summary, we have presented the synthesis and unusual stability of pyridine and *N*-methyl pyridinium acetals. The 1,3-dioxolane (acetal) protecting group is not removed from these compounds even under strongly acidic conditions. Fast protonation of the pyridine ring nitrogen prevents both intra and intermolecular proton transfer to the acetal oxygen thus inhibiting the hydrolysis. Work on the solution and solid phase synthesis of bridged pyridinium oximes continues both in our laboratory and other laboratories at USAMRICD.

EXPERIMENTAL

^{1}H, and ^{13}C NMR spectra were recorded on a 600 MHz Varian Unity INOVA instrument. ^{1}H spectra were obtained at 599.8 MHz and ^{13}C at 150.8 MHz at 22 ºC. Chemical shifts are reported in ppm and referenced to residual proteated solvent peak as listed. Carbon and proton assignments were based on the following experiments: Carbon, Proton, g-COSY and g-HMQC. J values are reported in Hz. For the 1D NOE experiment, the following conditions were used: sfrq = 599.727, d_6-benzene, nt = 128, d1 = 10ms, dpwr = 5 doff = 616.65 (on resonance), 3381.86 (off resonance). TLC analyses were preformed on Merck silica 60F-254 on glass, 250μm layer, 20 x 20cm with fluorescent indicator and visualized using UV and iodine vapor. Mass spectra were obtained using the following conditions: samples were introduced into an Agilent G1946A quadrupole mass spectrometer directly using flow injection analysis with acetonitrile/water (50/50, v/v) at a flow rate of 0.1 ml min^{-1}. The mass spectrometer was fitted with an atmospheric pressure electrospray ionization interface. The following MS conditions were used: positive ion, mass scan range from 80 – 400 Da, fragmentor at 80 V, and capillary voltage at 4000 V. The drying gas was nitrogen introduced at a flow rate of 10 L min^{-1} and kept at 350 °C. Nitrogen was also used as the nebulization gas and maintained at a pressure of 40 psi. Elemental analysis was performed at Schwarzkopf Microanalytical Laboratory, Woodside, NY. Pyridine 2-aldehyde and pyridine 4-aldehyde and organic solvents were obtained from Sigma Aldrich. All other starting materials were obtained from Acros Organics. All solvents were HPLC grade. Chemicals were not purified or dried and used as obtained unless otherwise specified.

Acetals.

2-(4-Chloromethyl-[1,3]dioxolan-2-yl)-pyridine (**3**).

Pyridine-2-aldehyde (4.4 mL, 0.047 mol, 1eq), 3-chloro-1,2-propanediol (7.8 mL, 0.093 mol, 2.0 eq), *p*-toluenesulfonic acid

(16.10 g, 0.093 mol, 2.0 eq) and benzene (45 mL) were heated to reflux. The reaction was stopped when 0.85 mL (~100%) of H_2O was collected in a Dean-Stark apparatus. The orange liquid was neutralized with $NaHCO_{3(sat, aq)}$ (25 mL) and the aqueous layer was washed with C_6H_6 (4 x 50 mL). Organic layers were combined, dried over anhydrous $CaCl_2$ and excess solvent was removed via rotary evaporation to produce a green oil (9.60 g). To the green oil was added 10% Na_2CO_3 (30 mL). After stirring at 100 °C for 3 hours, the dark brown liquid was washed with ether (4 x 100 mL). Organic layers were combined, dried over anhydrous $MgSO_4$, and filtered. Removal of solvent *in vacuo* resulted in a clear brown oil as the *trans* diastereomer (3.8 g, 41%). ^{1}H NMR (perdeuteriobenzene): δ 2.95 (dd, 1H, J= 11.1, 7.0 Hz), 3.10 (dd, 1H, J = 11.1, 5.3 Hz), 3.45 (dd, 1H, J = 8.8, 5.9 Hz), 3.92 (dd, 1H, J = 8.8, 6.5 Hz), 4.13 (m, 1H), 6.08 (s, 1H), 6.60 (m, 1H), 7.05 (m, 1H), 7.28 (m, 1H), 8.40 (m, 1H). ^{13}C NMR (perdeuteriobenzene): δ 44.1, 68.9, 75.9, 105.0, 120.8 123.9, 136.2, 149.4, 157.6. ESI MS (M=199.63) (CH_3CN/H_2O 1/1 v/v) m/z 200.1 [(M^++H^+)].

Anal. Calc'd. for $C_9H_{10}ClNO_2$: C, 54.15; H, 5.05; Cl, 17.76; N, 7.02. Found: C, 53.87; H, 5.30; Cl, 15.68; N, 7.11.

4-(4-Chloromethyl-[1,3]dioxolan-2-yl)-pyridine (**4**).

In a similar fashion to **3**, pyridine-4-aldehyde (4.60 mL, 0.048 mol, 1 eq), 3-chloro-1, 2-propanediol (8.00 mL, 0.096 mol, 2.00 eq), *p*-toluenesulfonic acid (16.12 g, 0.11 mol, 2.30 eq) and benzene (95 mL) were combined and heated until the reaction was complete. Workup and removal of solvent *in vacuo* gave a clear, yellow oil as a mixture of two diastereomers (10.60g, ~100%). ^{1}H NMR (perdeuteriobenzene): δ 2.89 (dd, 1H, J= 11.1, 7.6 Hz), 2.99 (m, 1H), 3.40 (m, 1H), 3.52 (m, 1H), 3.80 (m, 1H), 5.32 (s, 1H), 7.05 (m, 2H), 5.58, 8.55 (m, 2H) ppm. ^{13}C NMR (perdeuteriobenzene): δ 44.0, 44.2, 68.1, 68.3, 75.5, 76.1, 102.6, 103.0, 120.9, 121.1, 127.9, 128.5, 145.7, 146.3, 150.4, 150.5. ESI MS (M=199.63) (CH_3CN/H_2O 1/1 v/v) m/z 200.0 [(M^++H^+)].

Anal. Calc'd. for $C_9H_{10}ClNO_2$•$0.5H_20$: C, 51.81; H, 5.31; Cl, 16.99; N, 6.71. Found: C, 52.04; H, 5.04; Cl, 16.65; N, 6.77

2-[1,3]Dioxolan-2-yl-pyridine (**5**).

Pyridine-2-aldehyde (2.3 mL, 0.024 mol, 1 eq), ethylene glycol (2.7 mL, 0.048 mol, 2 eq), *p*-toluenesulfonic acid (1.2 g, 0.007 mol, 0.29 eq) and benzene (30 mL) were heated to reflux. The reaction was stopped when 0.43 mL of H_2O (100% theoretical) was collected in a Dean-Stark apparatus. The liquid was neutralized with saturated Na_2CO_3 (100 mL). The aqueous layer was washed with benzene (4 x 65 mL) and the organic layers were combined and dried over anhydrous $MgSO_4$. Filtration and removal of excess solvent *in vacuo* gave a clear yellow liquid (3.40 g, 94%). ^{1}H NMR (perdeuteriobenzene): δ 3.49 (m, 2H), 3.68 (m, 2H), 6.04 (s, 1H) , 6.64 (m, 1H), 7.10 (m, 1H), 7.42 (m 1H), 8.43 (m, 1H); ^{13}C NMR (perdeuteriobenzene): δ 65.4, 104.8, 120.8, 123.8, 136.2, 149.3, 158.4. ESI MS (CH_3CN/H_2O 1/1 v/v) (M=151.16) m/z 152.0 [(M^++H^+)].

Anal. Calc'd. for $C_8H_9NO_2$•$0.33H_20$: C, 61.14; H, 6.20; N, 8.91. Found: C, 61.36; H, 6.05; N, 8.98.

4-[1,3]Dioxolan-2-yl-pyridine (**6**).

In a similar fashion to **5**, pyridine-4-aldehyde (4.40 mL, 0.046 mol, 1 eq), ethylene glycol (5.30 mL, 0.095 mol, 2.00 eq), and *p*-toluenesulfonic acid (2.34 g, 0.014 mol, 0.30 eq) were combined with benzene (50 mL). After the reaction was complete, work-up and removal of solvent *in vacuo* gave a yellow oil (3.40g, 49%). ^{1}H NMR (perdeuteriobenzene): δ 3.37 (m, 2H), 3.51 (m, 2H), 5.50 (s, 1H), 7.12 (A_2X_2, 2H, J = 4.1, 1.8 Hz), 8.51 (A_2X_2, 2H, J = 4.1, 1.8 Hz). ^{13}C NMR (perdeuteriobenzene): δ 65.0, 102.1, 121.1, 146.9, 150.4. ESI MS (M=151.16) (CH_3CN/H_2O 1/1 v/v) 152.1 [(M^++H^+)].

Anal. Calc'd. for $C_8H_9NO_2$•$0.75H_20$: C, 58.35; H, 6.43; N, 8.51. Found: C, 58.02; H, 5.77; N, 8.61.

2-[1,3]Dioxolan-2-yl-1-methyl-pyridinium Iodide (**7**).

In a round bottom flask was added 2-[1,3]dioxolan-2-yl-pyridine **5** (1.51 g, 0.010 mol, 1 eq), 3 mL THF, and methyl iodide (0.62 mL, 0.010 mol, 1 eq). The reaction was stirred under $N_{2(g)}$ overnight resulting in a yellow solid. Filtration and removal of residual solvent *in vacuo* gave a yellow powder (1.25 g, 43%). ^{1}H NMR (deuterium oxide): δ 4.10 (m, 4H), 4.20 (s, 3H), 6.47 (s, 1H), 8.15 (m, 1H), 8.20 (m, 1H), 8.64 (m, 1H), 9.08 (m, 1H). ^{13}C NMR (deuterium oxide): δ 45.8, 65.7, 97.5, 125.2, 128.0, 146.5, 148.2, 152.0. ESI MS (M=309.14) (CH_3CN/H_2O 1/1 v/v) 166.1 (M^+-I^-).

Anal. Calc'd. for $C_{10}H_{16}INO_2$•$0.5H_20$: C, 35.78; H, 4.34; I, 42.01; N, 4.64. Found: C, 36.19; H, 4.23; I, 41.04, N, 4.70.

4-[1,3]Dioxolan-2-yl-1-methyl-pyridinium Iodide (**8**).

In a similar fashion to **7**, 4-[1,3]dioxolan-2-yl-pyridine (2.74 g, 0.018 mol, 1 eq), 10 mL THF, and methyl iodide (1.13 mL, 0.018 mol, 1 eq) were combined. Analogous workup gave a brown solid (4.49 g, 85%). ^{1}H (deuterium oxide): δ 3.96 (m, 4H), 4.23 (s, 3H), 6.00 (s, 1H) , 7.96 (d, 2H, J = 6.4 Hz), 8.66 (d, 2H, J = 6.4 Hz). ^{13}C NMR (deuterium oxide): δ 48.5, 65.0, 100.0, 125.9, 145.9, 156.0ppm. ESI MS (M=309.14) (CH_3CN/H_2O 1/1 v/v) 166.1 (M^+).

Anal. Calc'd. for $C_{10}H_{16}INO_2$: C, 36.88; H, 4.13; I, 43.30; N, 4.78. Found: C, 37.27; H, 4.45; I, 43.00; N, 4.85.

Representative Procedures for Attempted Hydrolysis of Acetals.

4-(4-Chloromethyl-[1,3]dioxolan-2-yl)-pyridine (**4**).

1:1THF/5 % HCl.

In a 25 mL round bottom flask, equipped with stir bar, were added **4** (1.07 g, 0.005 mol) and 30 mL of a 1:1 THF/5 % HCl solution. After 5 days stirring at room temperature the yellow solution was neutralized with saturated Na_2HCO_3. It was then extracted 4 x 50 mL CH_2Cl_2. Organic layers were combined and dried over anhydrous $CaCl_2$, filtered, and excess solvent was removed *via* rotary evaporator to produce a yellow oil with a mass of (0.98 g). According to NMR data the product contains 0% aldehyde and 100% 4-(4-chloromethyl-[1,3]dioxolan-2-yl)-pyridine.

1 *M* HCl/THF.

In a 100 mL round bottom flask, equipped with stir bar, were added **4** (0.82 g, 0.004 mol) and 63 mL THF. This was cooled using an ice bath after which 10 mL of 1 M HCl was added and warmed to room temperature. After 5 days stirring at room temperature the yellow solution was neutralized with 2 N NaOH. The solution was then extracted with 4 x 50 mL ethyl acetate. Organic layers were combined, dried over anhydrous $MgSO_4$, filtered and the solvent was removed *in vacuo* to produce a yellow oil (0.79g). According to NMR data the product appears to contain 0% aldehyde and 100% 4-(4-Chloromethyl- [1,3] dioxolan-2-yl)-pyridine.

Concentrated HCl.

In a 10 mL round bottom flask, were added **4** and 5 mL HCl. After 4 days stirring at room temperature the yellow solution was neutralized with saturated NaOH. The solution was then extracted with 3 x 50 mL ether. Organic layers were combined, dried over anhydrous $CaCl_2$, filtered and solvent was removed *in vacuo* to produce a yellow oil (0.35 g). According to NMR data the product appears to contain 0% aldehyde and 100% 4-(4-Chloromethyl-[1,3]dioxolan-2-yl)-pyridine.

Acetic Acid.

In a 100 mL round bottom flask, were added **4** and 50 mL acetic acid. After refluxing for 3 days the brown solution was neutralized with saturated $NaHCO_3$. The solution was then extracted with 3 x 100 mL ether. Organic layers were combined, dried over anhydrous $MgSO_4$, filtered and solvent was removed *in vacuo* to produce a yellow oil with a mass of 0.80 g. According to NMR data the product appears to contain 0% aldehyde and 100% 4-(4-Chloromethyl-[1,3]dioxolan-2-yl)-pyridine.

Acknowledgment.

This research is supported by the Department of Defense under a Defense Technology Objective. J. H. G. thanks the United Stated Military Academy and USAMRICD for support under an IAD. T. L. N., J. D. B., and C. H. W. acknowledge that this research was supported in part by an appointment to the Research Participation Program at the U.S. Army Medical Research Institute of Chemical Defense administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the U.S. Department of Energy and USAMRICD.

REFERENCES AND NOTES

[*] The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Army or the Department of Defense.

[†] Current Address: 24901 Camino Villa, Lake Forest, CA 92630.

[1] F. R. Sidell, in Textbook of Military Medicine, Medical Aspects of Chemical and Biological Warfare,1997, edited by F. R.Sidell, E. T. Takafuji and D. R. Franz eds, Office of the Surgeon General at TMM Publications, Washington, D. C. 1997, p 30.

[2] LD50 for soman (GD) = 350 mg/70 kg man. See F. R. Sidell, in Textbook of Military Medicine, Medical Aspects of Chemical and Biological Warfare,1997, edited by F. R. Sidell, E. T.Takafuji and D. R. Franz eds, Office of the Surgeon General at TMM Publications, Washington, D. C. 1997, p 141.

[3] I. B. Wilson, *J Biol Chem.*, **190**, 111, (1951).

[4] I. B. Wilson and S. Ginsburg, *Biochim Biophys Acta* ., **18**, 168, (1955).

[5] I. B. Wilson, D. Nachmansohn and S. Ginsburg, U. S. Patent 2,816,113 (1957); *Chem. Abstr*., **52**, 10212h, (1957).

[6] A. J. Funckes, *Arch Environ Health.* **1**, 404, (1960).

[7] B. E. Hackley Jr., E. J. Poziomek and G. M. Steinberg G. M. U. S. Patent 3,045,025 (1962); *Chem. Abstr*., **58**, 4525h, (1962).

[8] H. Oldiges and K. Schoene, *Arch. Toxicol*., **26**, 293, (1970).

[9] I. Hagedorn, I. Stark, K. Schoene and H. Schenkel, *Arzneim.-Forsch.*, **28**, 2055, (1978).

[10] C. A. Broomfield, B. A. Hackley Jr.,. B. E. Hahn, D. E. Lenz and D. M. Maxwell, Evaluation of H-Series Oximes, USABML-SP-81-001; US Army Medical Research and Material Command, Biomedical Laboratory, Aberdeen Proving Ground, MD, 1981.

[11] C. D. Bedford, R. N. Harris III, R. A. Howd, A. Miller, H. W. Nolen III and R. A. Kenley, *J. Med. Chem.*, **27**, 1431, (1984)

[12] C. D. Bedford, R. N. Harris III, R. A. Howd, D. A. Goff, G. A. Koolpe, M. Petesch, A. Miller, H. W. Nolen III, H. A., Musallam, R. O., Pick, D. E. Jones, I. Koplozitz and W. E. Sultan, *J. Med. Chem.*, **32**, 493, (1989).

[13] D. A. Goff, G. A. Koolpe, A. B. Kelson, H. M., Vu, D. L., Taylor, C. D., Bedford, H. A., Musallam, I. Koplovitz and R. N. Harris III. *J. Med. Chem.*, **34**, 1363 (1991).

[14] S. Wendenborn, A. de MesMaeker, W. K.-D Brill and S.Berteina, *Acc. Chem. Res.*, **33**, 215, (2000).

[15] F. Guillier, D. Orain and M. Bradley, *Chem. Rev*., **100**, 2091 (2000).

[16] S. Chamoin, S. Houldsworth, C. G. Kruse, W. Iwema Bakker and V. Snieckus, *Tetrahedron Lett.*, **39**, 4179, (1998).

[17] A. J. Showler and P. A. Darley, *Chem. Rev*., **67**, 427. (1967).

[18] T. W. Green and P. G. M. Wuts, Protective Groups in Organic Chemistry, 2nd Ed., John Wiley & Sons, New York, 1991, p189.

[19] R. A. Daignault and E. L. Eliel, *Org. Synth. Collect. Vol. V.*, 303, (1973).

[20] C. K. Bradsher and J. C. Parham, *J. Org. Chem.*, **28**, 83, (1963).

[21] U. G. Ibatullin, T. F. Pertushina, L. Y. Leitis, I. N. Plesanova, R. A. Skolmeistere, V. V. Shimanskaya and M. G. Safarove, *Chem. Hetero. Comp., Eng. Ed. (Khim. Geter. Soed.)*., **25**, 663, (1989).

[22] P. J. Ashworth, G. H. Mansfield and M. C. Whiting, *Org. Synth., Collect. Vol. IV*, 128, (1973).

[23] G. S. Alieva, L. G. Truzhenikova and I. N. Belova, *Zh. Obshch. Khim.*, **32**, 3565, (1962).

[24] A reviewer suggested that the low yields observed for **6** – **8** was due to a similar instability of the carbocation in the formation of the acetals from the aldehydes. However, microscopic reversibility only applies when the conditions of the synthesis and the hydrolysis are identical.

[25] Y. Benito, L. Canoira, N. Marinez-Lopez, J. G. Rodriguez and F. Temprano. *J. Heterocyclic. Chem.*, **24**, 623 (1987).

[26] H. M. Meshram, G. Sumithra, G. S. Reddy, Y. S. S. Ganesh and J. S. Yadav, *Synth. Comun.*, **29**, 2807, (1999).

[27] P. K. Mandal, P. Dutta and S. C. Roy, *Tetrahedron. Lett.*, **38**, 7271, (1997). We gratefully acknowledge a reviewer for bringing this work to our attention.

[28] S. Raja, N. Xavier and S. J. Arulraj, *Indian J. Chem.*, **27B**, 916, (1988).

[29] S. Raja, N. Xavier and S. J. Arulraj, *Indian J. Chem.*, **28B**, 687, (1989).

[30] P. Björk, A.-B. Hörnfeldt and S. Gronowitz, *J. Heterocyclic Chem.*, **31**, 1161, (1994).

[31] R. Camble, R. Garner and G. T. Young, *Nature*, **217**, 227, (1968).

[32] A. T. Nielsen and E. N. Platt, *J. Heterocyclic Chem.*, **6**, 891, (1969).

[33] Y. Benito, L. Canoira, N. Martinez-Lopez, J. G. Rodriguez and F. Temprano, *J. Heterocyclic Chem*., **24**, 623, (1987).

[34] A reviewer suggested that the hydrolysis of these protecting groups had been demonstrated in other publications. However, the compounds in these publications were ketals (Henegar, K. E.; Ashford, S. W.; Baughman, T. A.; Sih, J. C.; Gu, R.-L.; *J. Org. Chem.* **62,** 6588 (1997) and J. L. LaMattina, *J. Heterocyclic Chem.* **20**, 533 (1983)) or was a more complex heterocycle (1,3-dioxolane of 5-formyl-6-azaindole compound) (Robert H. Dodd, Catherine Ouannes, Malka Robert-Gero, Pierre Potier; *J. Med. Chem*., **32,** 1272 (1989)

[35] pK_a pydidium ~ 5.4; pK_a CH2O+(H)CH2 ~ -2.1. see F. G. Bordwell, *Acc. Chem. Res.* **21**, 456, (1988).

[36] PM3, closed shell, minimum RMS gradient = 0.100, *CS MOPAC Pro*, version 6.0, CambridgeSoft.Com: Cambridge MA, 2000.

[37] G. A. Jeffrey, An Introduction to Hydrogen Bonding, Oxford University Press, New York, 1997, Ch. 2.

[38] F. R. Hiertzler, M. Neuburger, M. Zehnder and E. C. Constable, *Liebigs Ann./Recueil* 297 (1997). This reference was included at the suggestion of a referee.

[39] Br σ_m = +0.39 see C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.*, **91**, 165 (1991).