Synthesis of 1-Substituted Derivatives of Anhydro(3-chloroacetyl-2-hydroxyimidazo[1,2-*a*]pyridinium Hydroxide)

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The reaction of chloroacetic anhydride and chloroacetic acid with *N*-substituted 2-aminopyridine derivatives **3** produced 1-substituted derivatives of anhydro(3-chloroacetyl-2-hydroxyimidazo[1,2-*a*]-pyridinium hydroxide) (**4**). The isomeric anhydro(1-benzyl-2-chloroacetyl-3-hydroxyimidazo[1,2-*a*]-pyridinium hydroxide) (**10***a*) was prepared by a reported procedure and the spectral data of the two isomeric series of compounds were compared. The significant differences in the n.m.r. spectra of the two series were attributable to the deshielding influence of the exocyclic acyl moiety.

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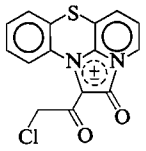
During an investigation of the reaction of 1-azaphenothiazine with chloroacetic anhydride and chloroacetic acid it was found that acylation of the secondary amine did not proceed as expected. 10-Chloroacetyl-1-azaphenothiazine was not obtained and the mesoionic compounds, **1** and **2**, have been proposed as possible structures for the compound produced from this reaction.[2]

The present investigation was undertaken as a model study to explore further the utility of this reaction in the synthesis of ring-fused mesoionic systems and to examine the structure of the compounds prepared.



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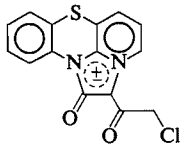

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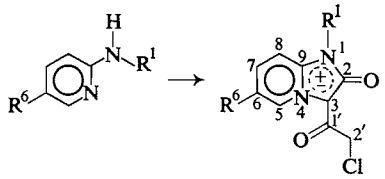
Reaction of chloroacetic anhydride (100 mmol) and chloroacetic acid (100 mmol) with 2-benzylaminopyridine (**3***a*; 50 mmol) for 1 h in refluxing dioxane gave anhydro(1-benzyl-3-chloroacetyl-2-hydroxyimidazo[1,2-*a*]pyridinium hydroxide) (1)[3] (**4***a*) in good yield. Similarly, reaction of **3***b*, *c*, *d*, and *e* with chloroacetic anhydride and chloroacetic acid yielded mesoionic compounds **4***b*, *c*, *d*, and *e* respectively. Melting points and microanalytical data for the compounds prepared are given in Table 1.

Scheme 1 outlines a possible mechanism for the formation of **4**. The first step involves chloroacetylation of **3** to give **5**. Acylation of the exocyclic nitrogen, in preference to the nuclear nitrogen, appears most probable based on the report by Jones and Katritzky (2*a*) that acylation of 2-amino- and 2-(methylamino)pyridine (with acetic anhydride–acetic acid) occurred exclusively on the exocyclic nitrogen.[4]



3 4

a $R^1 = -CH_2C_6H_5$; $R^6 = H$
b $R^1 = -C_6H_5$; $R^6 = H$
c $R^1 = -SO_2C_6H_5$; $R^6 = H$
d $R^1 = -CH_3$; $R^6 = H$
e $R^1 = -CH_3$; $R^6 = NO_2$

The situation for 2-benzenesulfonamidopyridine is less clear. It is known that 2-methanesulfonamido- and 2-benzenesulfonamido-pyridine exist in a tautomeric equilibria in which the imino forms predominate (2*b*). Thus acylation of **3***c* could have presumably occurred at the nuclear nitrogen, in which case compound **10***c* ($R^1 = SO_2C_6H_5$; R = Cl) would have been produced. The low field position of the C-5 proton in the n.m.r. spectra (see Table 2) is consistent with structure 4*c* and it was concluded that acylation

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[2]J. W. Steele *et al.* (8).
[3]Katritzky's nomenclature has been adopted in this paper.
[4]Several attempts were made to isolate the intermediate chloroacetate **5**. In each instance only cyclized, acylated mesoionic compounds **4** were isolated. Moreover, no intermediate was formed in sufficient concentration to be detected by t.l.c.

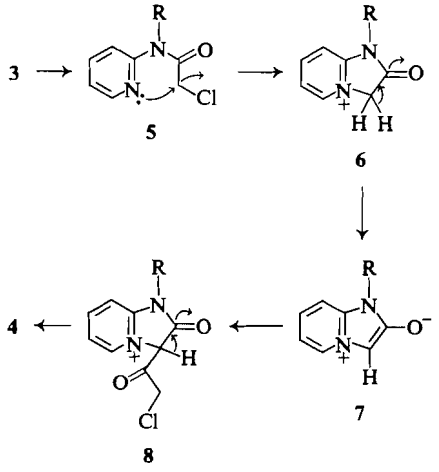
TABLE 1. Melting points and microanalytical data for 1-substituted derivatives of 3-chloroacetyl-2-hydroxy- and 2-chloroacetyl-2-hydroxyimidazo[1,2-*a*]pyridinium hydroxide

Compound*	Melting point (°C)†	Calculated (%)				Found (%)‡			
		C	H	Cl	N	C	H	Cl	N
4*a*	154–155‖	63.88	4.36	11.81	9.32	64.01	4.39	11.78	9.49
4*b*	194–195¶	62.81	3.87	12.39	9.77	63.22	3.65	12.50	9.72
4*c*§	214–215‖	51.35	3.16	10.13	7.99	51.56	3.12	10.35	7.95
4*d*	233.5–234**	53.44	4.04	15.81	12.47	53.61	4.14	15.90	12.40
4*e*	232–233††	44.53	2.99	13.18	15.58	44.53	3.03	13.21	15.54
10*a*	154–154.5‡‡	63.88	4.36	11.81	9.32	63.85	4.35	11.60	9.16

*Yields of pure products ranged from 10 to 60%; no attempts were made to optimize the yields.
†Melting points were determined in a capillary on a Melt Temp apparatus and are uncorrected.
‡Microanalyses were performed by Galbraith Laboratories.
§Anal. Calcd. for S: 9.12. Found: 9.29.
‖Recrystallized from $CHCl_3$–benzene–hexane.
¶Recrystallized from $CHCl_3$–benzene.
**Recrystallized from acetone–ethanol.
††Recrystallized from CH_2Cl_2–hexane.
‡‡Recrystallized from benzene–hexane; mixture m.p. with **4***a* showed significant depression.

of the exocyclic nitrogen was preferred in this reaction.

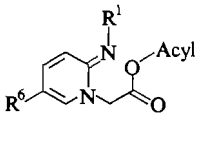
Intramolecular cyclization (3) of **5** with concomitant proton abstraction from **6** would afford the mesoionic intermediate **7**. Acylation (*4a–j*) of **7** with subsequent proton abstraction would give **4**.



SCHEME 1

An alternative explanation for the formation of **4** involving initial nucleophilic attack by the nuclear atom to form an imino intermediate **9**, was considered unlikely since chloroacetonitrile, chloroacetic acid, and α-bromopropionic acid failed to react with **3***a* in refluxing dioxane.

If the initial acylation of **3** occurred at the nuclear nitrogen, rather than the exocyclic nitrogen, the resultant product would be **10**. Although



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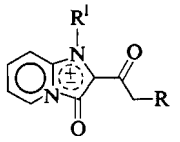

10

this seemed unlikely, the isomeric compound, **10***a*, was synthesized by an unambiguous route in order to effect a spectral comparison with **4***a*. Benzylation of *N*-2-pyridylaminoacetonitrile (prepared by treatment of 2-aminopyridine with formalin, sodium bisulfite, and sodium cyanide) followed by acid hydrolysis of the nitrile afforded *N*-benzyl-*N*-2-pyridylglycine, which was isolated as the sodium salt (*4i*, 5). Cyclization of sodium *N*-benzyl-*N*-2-pyridylglycine with chloroacetic anhydride and chloroacetic acid in refluxing dioxane gave anhydro(1-benzyl-2-chloroacetyl-3-hydroxyimidazo[1,2-*a*]pyridinium hydroxide (**10***a*: R^1 = —CH_2Ph; R = Cl). Cyclization with acetic anhydride afforded the known **10***b* (R^1 = —CH_2Ph; R = H) (*4i*).

The most significant differences between the n.m.r. spectra of the two isomeric series of compounds were the chemical shifts for the C-5 protons and the benzylic methylene protons of R^1 (see Table 2). The exocyclic acyl moiety strongly deshielded the C-5 aromatic proton in **4***a–e* while in the isomeric series (**10***a* and *b*) the benzylic methylene protons were shifted downfield by *ca.* τ 0.8.[5]

[5]*Cf.* the benzylic methylene protons of *N*-benzyl-2-aminopyridine acetamide which appeared as a 2-proton singlet at τ 4.87.

TABLE 2. Spectral data for 1-substituted derivatives of 3-chloroacetyl-2-hydroxy- and 2-acyl-3-hydroxyimidazo[1,2-*a*]pyridinium hydroxide

			60 MHz n.m.r. data (τ, $CDCl_3$–TMS)‡			
Compound	Infrared (KBr) μ*	λ_{max} (MeOH) nm (log ε)†	C-5	C-2′	R^1§	C-6, -7, -8, and aromatic protons of R^1
4*a*	5.95; 6.20	230 (4.225), 264 (4.363), 316 sh (4.003), and 344 (4.147).	−0.07 d	5.07	4.77 (2H)	2.62 m (8H)
4*b*	5.95; 6.12	232 (4.267), 265 (4.371), 320 sh (3.989), and 344 (4.129).	−0.12 d	5.12	—	2.42 s (7H) 2.75 m (1H)
4*c*‖	5.84; 6.20	220 (4.245), 257 (4.421), and 340 (4.168).	−0.05 d	5.33	—	1.80 d (3H) 2.25 m (5H)
4*d*	5.98; 6.31	230 (4.208), 264 (4.335), 318 sh (4.143), and 343 (4.193).	−0.13	5.13	6.45 (3H)	2.48 m (1H) 2.80 m (2H)
4*e*‖	5.91; 6.22	259 (4.382) and 300 (4.258)	−0.73 d (2.5)	5.18	6.45 (3H)	1.32 q (1H: 9.5; 2.5) 2.10 d (1H: 9.5)
10*a*	5.94; 6.22	261 (4.017) and 400 (4.041)	1.53 d	5.07	4.07 (2H)	2.68 s (8H)
10*b*¶	5.97; 6.27	262 (4.170)	1.53 d	7.31	4.06 (2H)	2.72 s (8H)

*The i.r. spectra were obtained on a Perkin–Elmer model 237 spectrophotometer.
†The u.v. data were obtained on a Beckman DB-G spectrophotometer.
‡The n.m.r. spectra were obtained on a Varian A60 spectrometer; coupling constants, in Hz, are given in parentheses.
§Excluding aromatic protons of R^1.
‖The n.m.r. solvent was d^6-DMSO–TMS.
¶The u.v. solvent was 95% ethanol.

The first reported example of this mesoionic 4-oxoimidazole system was the dye "Besthorn's red" (6). The only other fused ring system of this type has been prepared by Ohta and Sato (7). The monocyclic mesoionic ring system has been synthesized by Lawson and Mills (4*i*) and more recently by Roche and Stansloski (4*j*). The advantage of the method reported in this communication lies in the relatively simple synthesis for these ring systems. Furthermore, the reaction may have potential application in the synthesis of other mesoionic ring systems (*e.g.* thiaza and oxaza systems).

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Measurement of Depolarization Ratios in the Raman Spectra of Powdered Crystalline Solids

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The change in apparent depolarization ratio as a function of the refractive index of the surrounding liquid medium has been measured for the Raman active vibrational modes of powdered crystalline barium nitrate and sodium sulfate. This method provides an accurate measurement of the refractive index and depolarization ratios for barium nitrate, but fails to do so for sodium sulfate due to birefringent effects. The general applications of this technique for determining depolarization ratios of powdered crystalline solids are discussed.

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Introduction

The recent advances in instrumentation brought about by the introduction of continuous-wave laser excitation have made the recording of excellent Raman spectra from powdered crystalline samples almost a routine matter. Nowhere has this advantage been recognized more than in the study of solid inorganic compounds, for which the alternative and more usual technique of making measurements on solutions is frequently hindered by lack of an appropriate solvent or because of problems associated with complexing or dissociation. Where measurements on solutions are practicable, the additional information from depolarization measurements considerably aids assignment by enabling bands which arise from totally symmetric modes to be distinguished. Similar information may be obtained from the study of oriented single crystals. However, experience shows that the Raman emission from powdered crystalline solids is almost invariably depolarized as a result of the multiple reflections and refractions which both the polarized incident radiation and the Raman emitted light suffer at crystal surfaces within the sample. Two authors (1, 2) have recently de-