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(27) The *C*-Ph substituent effect is very similar to those of the classical examples of [1,2] shifts cited in ref 23 and 24 and which are currently considered to occur with phenyl participation in the transition state. Moreover, an identical trend with that reported here has been taken as evidence for concerted thermolysis of triarylmethyl azides, in contrast to the photochemical reaction where substituents have little, if any, effect and which probably involves a discrete nitrene intermediate [W. H. Saunders, Jr., and E. A. Caress, *J. Am. Chem. Soc.*, **86**, 861 (1964)]. By contrast, in the thermal fragmentation of 2,5-diaryltetrazoles to 1,3-nitrile imines, a case of decomposition of a heterocyclic system without aryl migration, the *C*-Ph substituent effect is very small ($\rho = -0.23$) [S. Y. Hong and J. E. Baldwin, *Tetrahedron*, **24**, 3787 (1968)]. For a survey on this subject see O. P. Strausz, J. W. Lown, and H. E. Gunning, *Compr. Chem. Kinet.*, **5**, Chapter 5 (1972).
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(33) All temperatures are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 257 spectrometer which was also employed for measuring IR absorptions in kinetic experiments. NMR spectra were recorded with a JEOL 60-MHz instrument in CCl_4 or $CDCl_3$ with Me_4Si as an internal standard. Mass spectra were obtained on a Varian MAT 111 low-resolution mass spectrometer. TLC were done on silica gel plates (IB2-F from Backer Chemical Co.) using benzene or mixtures of benzene–ethyl ether as eluent. Microanalyses were performed by F. B. Strauss Microanalytical Laboratory, Oxford, England.
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Condensation of Aldehydes with Methylimidazo[1,2-*a*]pyridines

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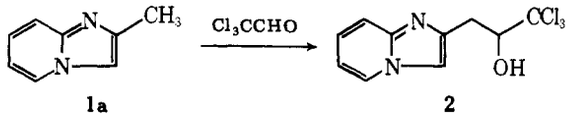
Received April 5, 1977

The reactions of various methylimidazo[1,2-*a*]pyridines (**1**) with acetaldehyde and chloral follow the usual course of electrophilic substitution at the 3 position, contrary to an earlier report of condensation at a methyl group. Initially formed adducts **6a–c** and **8** give secondary products, **5a–c**, **7a–c**, and **9**. Unusual IR, UV, and ^1H NMR spectral properties of the dichloro ketone **9** and the aldehyde **12**, which was formed by treating the chloral adduct **8** with strong base, are discussed.

The reported reaction[1] of the methyl group in 2-methylimidazo[1,2-*a*]pyridine (**1a**) with chloral to give the condensation product **2** must proceed via the anion **3**. Facile formation of such an anion, however, is incompatible with our finding that 7-methylimidazo[1,2-*a*]pyridine, which is expected to give a more stable anion (see **4**), does not readily give such an anion as shown by its failure to be oxidized to the aldehyde by selenium dioxide.[2] Further, reactions of imidazo[1,2-*a*]pyridine with other electrophilic reagents[3] generally occur at position 3. The reactivity of the methyl group in compound **1**, and concomitant correctness of structure **2**, therefore become questionable. The condensation of acetaldehyde with various methylimidazo[1,2-*a*]pyridines as



1a **2**

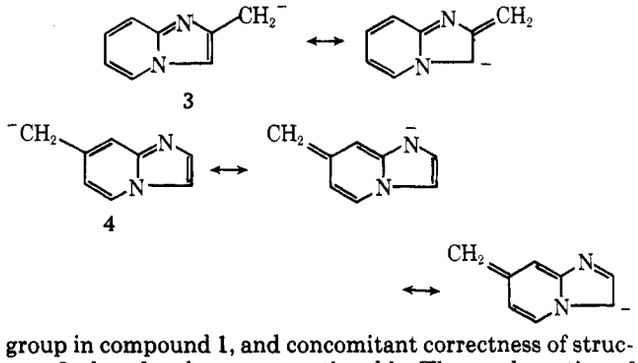
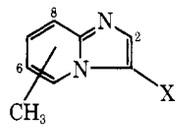
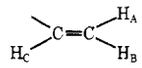
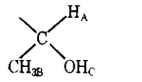
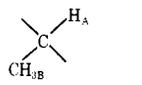


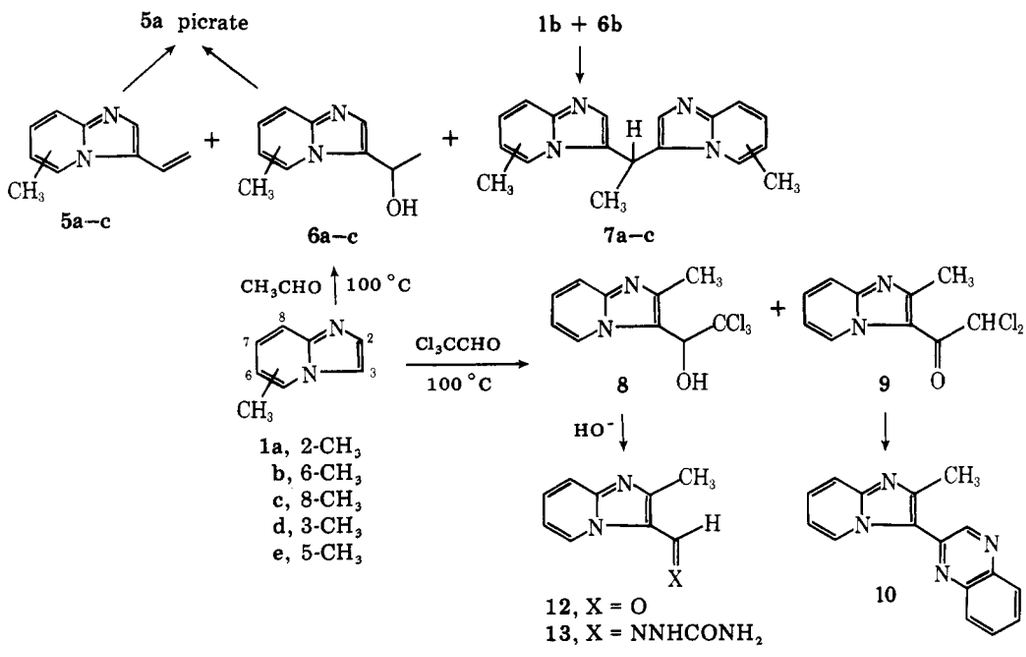
Table I. ^{1}H NMR Chemical Shifts (δ, ppm) of Some Imidazo[1,2-*a*]pyridines in $CDCl_3$[a]



			Registry no.	CH_3	H-2	H-3	H-5	H-6	H-7	H-8	H-A	H-B	H-C
X = H	2-CH_3	1a	934-37-2	2.42		7.27	7.97	6.64	7.04	7.48			
	6-CH_3	1b	874-38-4	2.27	7.54	7.45	7.85		6.95	7.49			
	8-CH_3	1c	874-10-2	2.63	7.62	7.56	7.98	6.66	6.94				
X = 	2-CH_3	5a	63076-78-8	2.56			8.17	6.84	7.16	7.56	5.60	5.45	6.87
	6-CH_3	5b	63076-66-4	2.32	7.71		7.89		6.99	7.49	5.68	5.29	6.76
	8-CH_3	5c	63076-67-5	2.62	7.77		8.03	~6.78	~7.00		5.75	5.34	~6.81
X = 	2-CH_3	6a	30489-51-1	2.08			8.49	6.71	7.08	7.40	5.23	1.63	4.42
	6-CH_3	6b	63076-68-6	2.32	7.10		8.16		6.99	7.35	5.09	1.70	4.23[c]
	8-CH_3	6c	63076-69-7	2.50	7.01		8.23	6.68	6.95		5.06	1.66	4.40
X = 	2-CH_3[b]	7a	63076-70-0	2.20			8.52	6.80	7.10	7.52	4.77	1.62	
	6-CH_3	7b	63076-71-1	2.26	7.46		7.64		7.03	7.47	4.70	1.92	
	8-CH_3	7c	63076-72-2	2.63	7.52		7.69	6.62	6.97		4.71	1.94	

[a] Relative to internal Me_4Si. Typical coupling constants: $J_{5,6} = 6$; $J_{6,7} = 6$; $J_{7,8} = 8$–10 Hz. For X = vinyl: $J_{A,B} \sim 1$; $J_{A,C} = 17$-18; $J_{B,C} = 12$ Hz. For X = $CH(OH)CH_3$: $J_{A,B} = 6$ Hz. For X = $CHCH_3$: $J_{A,B} = 7$ Hz. [b] Chemical shifts obtained from spectrum of a mixture containing compound **5a**. [c] Disappears upon addition of D_2O.

Scheme I



well as that of chloral with 2-methylimidazo[1,2-*a*]pyridine are the subject of this paper.

Results and Discussion

Condensation with Acetaldehyde. Prolonged heating of a mixture of 2-, 6-, or 8-methylimidazo[1,2-*a*]pyridine (**1a**, **b**, or **c**) with excess acetaldehyde at 100 °C gives in each case, besides starting material, three products. Their structures, established by mass spectral, ^{1}H NMR (see Table I), and elemental analyses, are **5a–c**, **6a–c**, and **7a–c** (see Scheme I). Compounds **5a–c**, low-melting, hygroscopic solids, were analyzed as picrates. ^{1}H NMR spectra show that reaction has not occurred at the CH_3 groups and that a vinyl substituent[4] has been introduced in the five-membered ring. Since the 2-CH_3 compound **1a** gives **5a**, substitution must have taken place at position 3.

Mass spectra of compounds **6a–c** indicate facile loss of water (base peak, $M^+ - 18$) and ^{1}H NMR spectra support these structures.[5] Further, compound **6a** gives the same picrate as the vinyl compound **5a**. Since loss of water from the α-ethanol compounds (**6a–c**) is relatively facile even under neutral conditions (cf. formation of the vinyl compounds **5a–c** during the aldehyde condensation), dehydration under acid conditions is expected.

Structures **7a–c** were established as follows. While mass spectra of the starting materials **1a–c** do not show peaks attributable to loss of a CH_3 group, the very intense base peak ($M^+ - 15$) in the spectrum of compound **7b** indicates that one CH_3 group is readily lost. Formation of a dipicrate from compound **7b** demonstrates the presence of two noninteracting imidazopyridine ring systems. An integrated ^{1}H NMR spectrum of compound **7b** shows that two 6-methylimidazo[1,2-*a*]pyridine moieties are present for one $CHCH_3$ group, but the position of substitution cannot unambiguously be established from this spectrum, since the chemical shift of the peak assigned to H-5 appears at sufficiently high field to fall in the region where H-3 usually absorbs. That structure **7b** is indeed correct is shown by the ^{1}H NMR spectrum of the

Table II. ^{1}H NMR Chemical Shifts[a] (δ, ppm) of Picrates of Some Imidazo[1,2-*a*]pyridines in Me_2SO-d_6

	H-2,3	H-5	H-6	H-7,8	picrate-H
7b	8.08	8.72		7.95	8.61
1b	8.32, 8.20	8.77		7.91	8.63
5a		8.95	7.54	7.97	8.60

[a] Relative to internal Me_4Si. Chemical shifts of other protons: **7b**, 1.87 (d, J = 7, CH_3), 2.45 (s, CH_3), 5.19 (q, CH); **1b**, 2.45 (s, CH_3); **5a**, 2.61 (s, CH_3), 5.80 (d, J = 12), 5.92 (d, J = 18), 7.12 (q) for vinyl group.

protonated compound, i.e., the dipicrate (see Table II). The spectrum now shows a low-field singlet that can only be due to H-5 and has a chemical shift similar to those of H-5 in the picrates of the parent **1b** and the 2,3-disubstituted compound **5a**.

When the acetaldehyde condensation with 3- and 5-methylimidazo[1,2-*a*]pyridine (**1d** and **e**) was attempted, no reaction occurred. While this was expected for the 3-CH_3 compound **1d**, the lack of reactivity of the 5-CH_3 compound **1e** must be attributed to steric hindrance, the peri effect well-known in other multiple ring systems. It should be noted that compound **1e** does react with other electrophilic reagents, such as nitric acid[6] and bromine,[3a] to give 3-substituted products. These reactions, however, are in general very much more facile, require short reaction times, and take place at less than or at room temperatures.

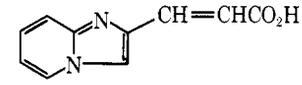
Thus, the reaction of acetaldehyde with imidazo[1,2-*a*]-pyridines proceeds by substitution at the 3 position to give adducts **6**, which can subsequently either form the vinyl compounds **5** by loss of water or condense with another molecule of starting materials (**1**) to give compounds **7**. When a mixture of compounds **6b** and **1b** is heated at 95 °C overnight, compound **7** is indeed formed. Alternate formation of compounds **7** from the vinyl compounds **5** and **1** cannot be excluded.

The Chloral Reaction. When 2-methylimidazo[1,2-*a*]-pyridine (**1a**) was treated with chloral as reported[1] (see, however, Experimental Section), two products were obtained. One of them forms a hydrochloride salt which shows the same melting behavior and analysis as reported[1] for compound **2**·HCl, and is stable toward refluxing ethanolic HCl. Its mass spectrum, however, does *not* contain peaks attributable to $M^+ - OH$ or $M^+ - H_2O$, which are mandatory[7] for structure **2**. This compound has in fact structure **8** (see Scheme I), and the other product has structure **9**.

The ^{1}H NMR spectrum (see Table III) of the adduct **8** clearly indicates that reaction has taken place at the 3 position. The considerably greater deshielding of H-5 in the adduct relative to the starting material **1a** is in accord with anisotropic effects of 3-substituents on H-5. The absence of deshielding of the CH_3 group implies restricted rotation of the $-CH(OH)CCl_3$ group.

Structure **9** is derived from the adduct **8** by loss of HCl followed by tautomerization. Formation of a quinoxaline derivative (**10**) establishes the presence of the $COCHCl_2$ group. Comparison of its ^{1}H NMR spectrum with that of imidazo-[1,2-*a*]pyridine-3-carboxaldehyde[8] shows that the $COCHCl_2$ group is indeed attached at the 3 position. All relevant protons are deshielded as compared to those of both the adduct **8** and the starting material **1a**, in accord with the presence of the strongly electron-withdrawing group. Other spectral properties of compound **9** are discussed below.

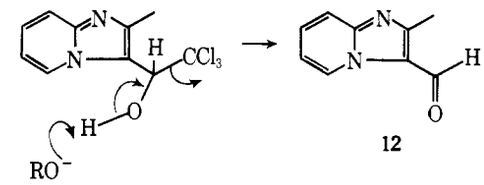
Lombardino[1] reported that treatment of the chloral adduct (**2**) with base, followed by acid, affords the acrylic acid **11**. In



11

our hands, the chloral adduct (with established structure **8**), when subjected to the described severe conditions, gives a compound which has the same melting point and ultraviolet absorption maxima[9] as reported for compound **11**. Its analysis, however, differs from that reported by the elements of CO, and its structure is **12**·HCl. The free base **12** gives a positive Tollens' test, forms a semicarbazone **13**, and displays a ^{1}H NMR spectrum (see Table III) that now approximates that of imidazo[1,2-*a*]pyridine-3-carboxaldehyde except for replacement of the H-2 singlet by a three-proton CH_3 singlet.

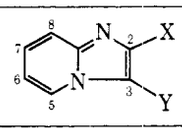
The reaction of the adduct **8** with strong base is envisioned to proceed by abstraction of a proton from the OH group and cleavage as shown. Formation of this product appears to de-

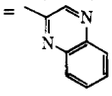


12

pend on the conditions used. Thus, trichloromethylphenylcarbinol, when boiled with water gives phenylhydroxyacetic acid, but when boiled with saturated potassium hydroxide solution, chloroform, benzaldehyde, and mandelic acid are formed.[11] Hydrolysis with dilute base of other trichloromethylcarbinols leads to hydroxyacetic acids,[12] which can only be converted to aldehydes by oxidation.[13] In our hands appreciably more aldehyde (75 vs. 43%) was obtained in very concentrated solution than in more dilute solution. For the latter conditions, concurrent formation of 3-imidazo-[1,2-*a*]pyridylhydroxyacetic acid, which could not be isolated

Table III. ^{1}H NMR Chemical Shifts[a] (δ, ppm) of Some Imidazo[1,2-*a*]pyridines in $CDCl_3$



		Registry no.	H-5	H-6	H-7	H-8	X	Y
1a,	X = CH_3; Y = H		7.97	6.64	7.04	7.48	2.42	7.27
8,	X = CH_3; Y = $CH(OH)CCl_3$	63076-73-3	9.07	6.78	7.16	7.35	2.32	5.66
9,	X = CH_3; Y = $C(=O)CHCl_2$	63076-74-4	9.79	7.18	7.66[b]	7.66[b]	2.92	6.85
	X = H; Y = $C(=O)H$[c]		9.60	7.11	7.55	7.81	8.33	9.95
12,	X = CH_3; Y = $C(=O)H$	30384-93-1	9.59	7.11	7.55	7.71	2.75	10.08
10,	X = CH_3; Y = 		9.84	7.00	7.40	7.71	2.90	9.28 (s)[d] 8.15, 7.91[e]

[a] X and Y substituents give sharp singlets, except as noted; H-5 and H-8 are doublets showing further fine splitting; H-6 is a triplet; H-7 is an unsymmetrical quartet. [b] Overlapping multiplets. [c] Taken from ref 8. [d] In quinoxaline itself, δ H-2 and H-3 = 8.73, δ H-5 and H-8 = 8.06, δ H-6 and H-7 = 7.67 ppm.[10] [e] Centers of A_2B_2 multiplets.

Table IV. Ultraviolet Data for Imidazo[1,2-a]pyridines[a] in 95% Ethanol and Ethanolic Hydrochloric Acid[b]

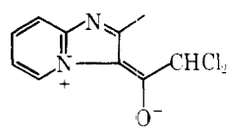
12 or 12·HCl[c,d,f]	12·HCl + HCl	9	9 + HCl[f]	8·HCl[f]	8·HCl + HCl
323 (9.7) ↓↓		338 (11.7) ↓↓	278 (7.0)	283 (5.8)	280 (7.4)
~300[e] (7.0) ~same	283 (7.5)	297 (5.7) → 281			
255 (25.5) ↓		261 (16.0) ↓	253 (7.8)		
248 (21.1) ↓	247 (12.0)	255 (15.2) ↓	247[e] (6.9)		
~242[e] (15.9) ~same	242[e] (11.1)	248[e] (12.6) ↓240[e]	240[e] (5.7)	231 (24.9)	
217 (20.0) ↓	220[e] (16.5)	219 (16.7) ↑	219 (18.6)	224 (21.7)	222 (27.2)
214 (18.4) ~same	213 (19.3)	216 (16.8) ↑	214 (21.9)	220[e]	219 (27.2)

[a] λ_{max}, nm ($\epsilon \times 10^{-3}$). [b] Ca. 2×10^{-2} N HCl. [c] Arrows indicate changes in extinction coefficient when 1 drop 0.1 N HCl is added to the solutions in the cells to give ca. 7.5×10^{-4} N HCl. [d] Reported for 11·HCl, λ_{max}, nm ($\epsilon \times 10^{-3}$): 324 (8.1); 300 (6.7); 256 (20.8); 248 (17.2). [e] Shoulder. [f] Registry no.: 12·HCl, 63076-75-5; 9·HCl, 63076-76-6; 8·HCl, 63076-77-7.

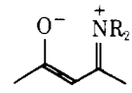
under the work-up conditions used, would explain the much lower yield.

Spectral Properties

Infrared. The carbonyl group of the dichloro ketone **9** absorbs at 1625 cm^{-1}, considerably beyond the lower limit observed for aromatic ketones (1700–1680 cm^{-1}).[14] Since an α-chloro group increases the frequency, the expected range is nearer 1720–1700 cm^{-1}. The low-frequency absorption indicates a weaker carbonyl double bond due to significant contribution of the resonance form **9a** to the ground state of the molecule. Equally unusual absorption of the aldehyde **12** at 1625 cm^{-1} is interpreted in the same manner. An analogy is found in β-amino-α,β-unsaturated ketones which absorb 20–80 cm^{-1} lower than expected and for which resonance structure **14** has been evoked.[15]



9a



14

Ultraviolet. The identity of the spectra of the aldehyde **12** and its salt (see Table IV) indicates complete, or nearly complete, dissociation of the pyridinium salt, which in turn corroborates the notion of charge separation in the neutral molecule that would lead to a lowering of the pK_a.

The spectra of the aldehyde **12** and the dichloro ketone **9** are similar. Complex changes observed in the spectra of both compounds when acid is added are interpretable in terms of the equilibria shown below. An immediate drop in the extinction coefficients of several bands (indicated by arrows in Table IV) caused by the addition of acid indicates protonation (equilibrium 1, Scheme II). The observation that the spectrum of compound **9** continues to change with time, while that of **12** remains the same, is attributed to more facile hemiacetal formation[16] (equilibria 2 and 4) of the dichloro ketone. The concentration of neutral hemiacetal must be very low, since its pK_a is expected to be near that (ca. 6)[3a] of alkyl-substituted imidazo[1,2-a]pyridines. Further addition of acid causes an immediate pronounced change in the spectra (only protonated species present). Both spectra now continue to change with time, so that the rate of acid-catalyzed hemiacetal formation of the aldehyde (**12**) has become sufficiently enhanced to be observable. Since no further changes occur when more acid is added, the spectra then are of the species involved in equilibrium 2. Three of the absorption bands are at wavelengths similar to bands found in the protonated chloral adduct **8** and can therefore be assigned to the protonated hemiacetals.[17] The remaining bands can then be attributed to protonated aldehyde and ketone.

Scheme II

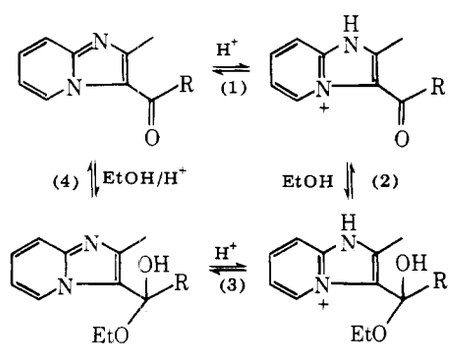


Table V. ^1H NMR Chemical Shifts (δ, ppm) of Imidazo[1,2-a]pyridines In Various Solvents[a]

	CH_3	H-5	C–H[b]	
		Me_2SO-d_6		
1a·HCl	2.91	9.39		
8·HCl	3.08	9.74	6.44	
9·HCl	3.37	10.11	7.90	
12·HCl	3.20	9.98	10.57	
		TFAA		
1a	2.66	8.60		
8·HCl	2.74	9.42	5.88	
9	3.18	10.06	6.85	
12	3.06	9.92	10.28	
		D_2O		
1a·HCl	2.95	8.97		
8·HCl	3.15	9.65		
9·HCl	3.18	9.66	6.78	low
	3.50	10.25	7.68	high
12·HCl	3.35	10.09	10.58	
		EtOH		
9	2.92	9.72	7.18	
12	2.72	9.51	10.06	
		EtOH/HCl		
8	2.76	9.44		
9	3.10	9.93	7.34	low
	2.79	9.41	6.38	high
12	2.97	9.78	10.30	low
	2.70	8.91		high

[a] Relative to external Me_4Si in Me_2SO-d_6 and D_2O, internal Me_4Si in TFAA and EtOH. [b] These are the chemical shifts of the substituent protons, i.e., $-CH(OH)CCl_3$, $-COCHCl_2$, and $-CHO$ of compounds **8**, **9**, and **12**, respectively.

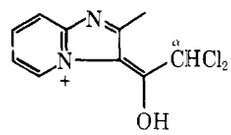
^1H NMR. The dichloro ketone **9** is also subject to hydration. A spectrum of its salt, 9·HCl, in D_2O (see Table V) exhibits two sets of peaks, while that of the aldehyde 12·HCl is normal. Of the several possible interpretations, i.e., presence of impurity, tautomerism (N, O, or C protonation), and partial hydration, the last is shown to be correct. The presence of an isomeric

Table VI. Analytical Data for Some Imidazo[1,2-*a*]pyridines

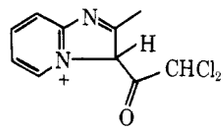
Compd			Calcd %				Found %			
Formula	No.[c]	Mp, °C	C	H	N	Cl	C	H	N	Cl
$C_{10}H_{10}N_2 \cdot C_6H_3N_3O_7$	**5a**·pic[a]	198.5–199.5					49.47	3.40	17.97	
	5b·pic	225–226	49.61	3.36	18.09		49.79	3.46	18.01	
	5c·pic	171–173					49.83	3.61	17.66	
$C_{10}H_{12}N_2O$	**6b**	149–151	68.18	6.82	15.91		68.20	6.84	15.92	
	6c	124–125					67.98	6.86	15.86	
$C_{18}H_{18}N_4 \cdot 2C_6H_3N_3O_7$	**7b**·pic	260–261.5 dec	48.13	3.21	18.72		48.18	3.35	18.73	
$C_{18}H_{18}N_4$	**7c**	180–181	74.48	6.21	19.31		74.38	6.22	19.26	
$C_{10}H_9N_2OCl_3 \cdot {}^1/_4H_2O$	**8**	102[b]	42.25	3.35	9.86		42.30	3.10	9.57	
$C_{10}H_9N_2OCl_3 \cdot HCl$	**8**·HCl	246 dec[b]	37.97	3.16	8.86		37.99	3.35	8.56	
$C_{10}H_8N_2OCl_2$	**9**	102–104	49.38	3.29	11.52	29.22	49.40	3.32	11.51	29.03
$C_{10}H_8N_2OCl_2 \cdot HCl$	**9**·HCl	204 dec[b]	42.93	3.22	10.02		42.97	3.22	10.03	
$C_{16}H_{12}N_4$	**10**	178–179[b]	73.85	4.62	21.54		73.96	4.66	21.30	
$C_9H_8N_2O$	**12**	107–109.5	67.50	5.00	17.50		67.58	5.17	17.20	
$C_9H_8N_2O \cdot HCl$	**12**·HCl	252 dec[b]	54.96	4.58	14.25	18.07	55.17	4.77	14.25	17.92
$C_{10}H_{11}N_5O$	**13**	251–265 dec[b]	55.30	5.07	32.26		55.19	5.12	32.10	

[a] Picrate. [b] These compounds either darkened prior to melting or showed peculiar melting characteristics; see Experimental Section. [c] Registry no.: **5a**·pic, 63076-79-9; **5b**·pic, 63076-80-2; **5c**·pic, 63076-81-3; **7b**·pic, 63076-82-4; **10**, 63076-83-5; **13**, 63104-20-1.

impurity is ruled out by the finding that compound **9**·HCl shows only one set of peaks in either Me_2SO-d_6 or trifluoroacetic acid (TFAA). Tautomerism between N vs. O protonated species is a priori unlikely, since such proton transfer is usually so rapid that only an average spectrum of the two forms is observable in the NMR;[18] further, in the O-protonated species **9b** the α proton should exchange in D_2O and this



9b



9c

is not observed. If protonation on C, a much slower process, were occurring (see **9c**), an extra peak should appear in the TFAA solution spectrum (total of nine protons), and this is not the case. The great similarity of the chemical shifts of the less intense set to those of H-5 and CH_3 in the chloral adduct **8**·HCl supports the supposition of partial hydration. The more intense set absorbs at relatively lower field, in accord with the anticipated greater deshielding by the carbonyl group, and as observed in the $CDCl_3$ solution spectra of the free bases **8** and **9**.

The chemical shifts of the aldehyde **12**·HCl in Me_2SO-d_6 and TFAA differ from those in D_2O by no more than expected for solvent effects (cf. data for **8**·HCl). The spectra of the protonated dichloro ketone **9**·HCl in these solvents are also best interpreted in terms of the ketone rather than the hydrated structure.

The spectra of both free bases **9** and **12** in absolute ethanol are normal; addition of acid causes not only downfield shifts expected for protonation, but also the appearance of a second set of peaks at higher field which increases in intensity with time at the expense of the other set. The conclusion drawn from the ultraviolet spectra that hemiacetals[19] are formed is thus directly confirmed. The ratios of hemiacetals to unreacted compounds **9** and **12** are ~3, that of hydrate to unreacted compound **9** is ~0.3.

In conclusion, since only the ketone forms a hydrate, although aldehydes in general hydrate more readily than ketones, the neighboring dichloromethyl group appreciably enhances the susceptibility of the ketone toward nucleophilic attack. The lack of hydration, the relatively slow semicarbazone formation of the aldehyde **12**, as well as IR and ^1H NMR data of the free bases **9** and **12**, indicate significant contribution of the charge-separated resonance forms to the ground state of the molecules. Indeed, for these compounds the zwitterionic structure appears to be a better pictoralization.

Table VII. Conditions and Product Distribution of Acetaldehyde Condensation with Methylimidazo[1,2-*a*]pyridines (1)

Compd	(g)	Time, h	Yield, % 5	6	7
1a	(0.65)	18	40	47	13
1b	(1.0)	65	10	50	38
1c	(1.75)	40	8	21	27
1d	(1.96)	19			
1e	(2.77)	80		Traces	

Experimental Section

Woelm neutral alumina, Brockmann grade 3, was used for chromatography. Solutions were dried over anhydrous Na_2SO_4. Melting points are uncorrected. ^1H NMR spectra were recorded with a Varian HA-100 spectrometer. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6M instrument equipped with a solid sample injector; ionizing voltage was 73 eV. IR spectra were recorded of Nujol mulls with a Beckman AccuLab 1 instrument. UV spectra were taken with a Varian Techtron UV–vis spectrophotometer, Model 635. Elemental analyses were determined by either the Analytical Services Laboratory of the University of Alabama Chemistry Department or Atlantic Microlab, Inc., Atlanta, Ga. Analytical data are collected in Table VI.

Acetaldehyde Condensation with Methylimidazo[1,2-*a*]pyridines (1). Compounds **1** were purified by column chromatography on alumina with 50% $C_6H_6/CHCl_3$. Acetaldehyde was distilled just prior to use. A mixture of compound **1** and acetaldehyde (~15 equiv) was heated in a steam bath in a sealed tube and the reaction was monitored by TLC. In all cases except with compound **1a** starting material was still present when the reaction was stopped. Evaporation under reduced pressure left a brown liquid which was subjected to column chromatography. The **3-vinylimidazo[1,2-*a*]pyridines 5** and compounds **7** were eluted with 50% $C_6H_6/CHCl_3$, the **3-(1-hydroxyethyl)imidazo[1,2-*a*]pyridines 6** were eluted with $CHCl_3$. Conditions and product distribution are shown in Table VII. The yields are not of isolated pure compounds, since some overlap occurred in the chromatographic separations, but rather are meant to show approximate product distribution.

The hygroscopic vinyl compounds **5**, although pure according to TLC and ^1H NMR spectra, had wide melting ranges even after sublimation and were therefore converted into picrates. Typically, when a hot solution of picric acid (43 mg, 0.18 mmol) in EtOH (3 mL) was added to a hot solution of compound **5** (30 mg, 0.16 mmol), a quantitative yield of picrate was obtained. Analytical samples were prepared by two or three crystallizations from EtOH.

The hydroxy compounds **6b** and **6c** were further purified by sublimation [80–100 °C (0.025 Torr)] followed by two crystallizations from C_6H_6. When the hydroxy compound **6a** was treated with picric acid as above, a yellow solid, mp 193–194.5 °C, was obtained. Its ^1H NMR spectrum was identical with that of the picrate of compound **5a**, and a mixture melting point with pure compound **5a**·picrate (mp 198.5–199.5 °C) was 195–196 °C.

Compound **7b** was hygroscopic and was converted into its picrate. After crystallization from EtOH or DMF failed, crystallization was achieved by dissolving the compound (50 mg) in hot ethylene glycol (5 mL), filtering, and adding EtOH (4 mL). Compound **7c** was purified by two crystallizations from benzene. Compound **7a** was not obtained pure, but its formation was demonstrated by ^1H NMR spectral comparisons.

Alternate Formation of 1,1-Bis(6-methylimidazo[1,2-*a*]-pyrid-3-yl)ethane (7b). A mixture of the hydroxy compound **6b** (0.11 g, 0.6 mmol) and parent **1b** (0.10 g, 0.7 mmol) was maintained at 95 °C overnight. When fractionated by chromatography, compound **7b** (60 mg, ~30%) was obtained as shown by TLC and ^1H NMR spectral comparisons.

Reaction of 2-Methylimidazo[1,2-*a*]pyridine (1a) with Chloral. When Cl_3CCHO (Eastman, 12 mL) was added to compound **1a** (2.0 g, 15 mmol), a colorless solid separated and a light red solution was obtained. The deep red clear solution obtained on brief warming was heated the requisite 24 h on the steam bath,[1] although TLC indicated the absence of starting material after 1 h. Cooling gave a viscous gum that could not be induced to crystallize. Treatment with ice/water gave a mixture (pH 6) that was extracted with three 20-mL portions of $CHCl_3$ (pH then 5). The combined extracts were dried, stripped of solvent, and dried in vacuo (0.025 Torr) when a small amount of $Cl_3CCH(OH)_2$ sublimed. The residual thick oil was fractionated on 150 g of alumina with $CHCl_3$ to give needles of compounds **9**, mp 98–99.5 °C (0.62 g, 17%), trace amounts of other materials, and finally compound 8 as a glass (1.55 g, 37.5%). A second crop of compound 8 was obtained from the aqueous layer after treatment with $NaHCO_3$ and extracting with $CHCl_3$ (1.95 g, ~83% total). **Sublimation of 2-methyl-3-(2,2,2-trichloro-1-hydroxyethyl)imidazo-[1,2-*a*]pyridine** (8) led to extensive decomposition, but gave a small amount of fine, fluffy material (IR same as nonsublimed sample): mp softens and darkens ~92 °C, forms a glass ~102 °C, used for analysis.

The HCl salt of compound 8 had mp 248 °C dec (darkens ≳200 °C), lit.[1] mp 249.5–252.5 °C. An analytical sample, obtained by two crystallizations from EtOH/EtOAc, had mp 229 °C dec (darkens ≳220 °C), lit.[1] mp 240.5–241.5 °C, and after drying [4 h, 95 °C (0.025 Torr)] mp 246 °C dec (darkens ≳220 °C).

According to TLC, IR, and mp, compound 8·HCl remained unchanged when treated with refluxing absolute EtOH/HCl for 24 h.

3-(2,2-Dichloroacetyl)-2-methylimidazo[1,2-*a*]pyridine (9) crystallized as colorless needles from hexane. Sublimation [95 °C (0.025 Torr)] afforded an analytical sample. Treatment of compound 9 with absolute EtOH/HCl and evaporating to dryness gave compound **9**·HCl. An analytical sample, obtained by two crystallizations from absolute EtOH/EtOAc, had mp 204 °C dec (darkens ~180 °C) and could be sublimed [90 °C (0.025 Torr)].

The salt, after heating with absolute EtOH/HCl for 5 days, had the same mp, IR, ^1H NMR, and mass spectra as the above sample.

2-Methyl-3-(2-quinoxalyl)imidazo[1,2-*a*]pyridine (10). Since after heating a mixture of compound **?** (50 mg, 0.2 mmol), *o*-phenylenediamine (23 mg, 0.21 mmol), and H_2O (3 mL) for 1 h on the steam bath much insoluble starting material remained, solution was affected by the addition of EtOH and heating was continued overnight. Treatment with aqueous NaOH (to pH 8) gave a yellow solid, **10**, which was filtered. TLC of the filtrate showed the presence of starting materials. The solid was extracted with hot hexane (30 mL) and the extract concentrated (2 mL) to give sturdy yellow needles, which after sublimation [100 °C (0.025 Torr)] had mp 178–179 °C (darkens ≳160 °C) (~8 mg, 15%).

Base Treatment of Compound 8: Formation of 3-Formyl-2-methylimidazo[1,2-*a*]pyridine (12). (1) When a solution of the crude second crop of compound 8 (1.95 g) in absolute EtOH (10 mL) was treated dropwise with aqueous NaOH (1.1 g in 2 mL), it turned dark red and heat was liberated. Brief warming on a steam bath induced a vigorous exothermic reaction and separation of NaCl. The mixture was then gently refluxed for 20 min, cooled, and filtered. The solid was washed with absolute EtOH, and the filtrate stripped of solvent to give a sticky solid that was extracted with three 10-mL portions of hot $CHCl_3$. The extracted material was subjected to chromatography on 120 g of alumina with 50% $C_6H_6/CHCl_3$. Early fractions yielded compound **12** (0.48 g, ~43%), mp 110–111 °C. An analytical sample, obtained by sublimation [80 °C (0.025 Torr)], gave a positive Tollens' test.

The HCl salt of compound **12**, twice crystallized from EtOH/EtOAc, had mp 252 °C dec (darkens ≳200 °C, lit.[1] for compound 11·HCl, 252.5–254.5 °C) and could be sublimed [120 °C (0.025 Torr)].

(2) Base treatment, followed by acidification, under the reported conditions,[1] also afforded the HCl salt of compound **12** (55%) as established by TLC, mp, and IR spectral comparisons. A further crop, isolated as the free base, was obtained by chromatography of the material in the basified mother liquor (75% total).

3-Formyl-2-methylimidazo[1,2-*a*]pyridine Semicarbazone (13). The reaction of compound **12** (50 mg, 0.31 mmol) with semicarbazide hydrochloride (50 mg, 0.45 mmol) and NaOAc (75 mg, 0.91 mmol) in H_2O (5 mL) on the steam bath was followed by TLC. Reaction was complete after 1.5 h. Concentration to 2 mL caused the separation of pale yellow crystals, which were filtered and rinsed with H_2O to give 70 mg (100%). The product, after dissolution in EtOH (5 mL), addition of H_2O (2 mL), concentration to 2 mL, cooling, and filtering the precipitate, had mp 254–268 °C dec (softens 232 °C). The wide melting-point range implied that perhaps some HOAc salt contaminated the product. However, when it was treated with $NaHCO_3$ in EtOH/H_2O, no gas evolved and it then had mp 251–265 °C dec (softens 232 °C).

Acknowledgment. We wish to thank Diamond Shamrock Corporation for partial financial support.

Registry No.—**1a** HCl, 2549-26-0; **1d**, 5857-45-4; **1e**, 933-69-7; **6a** picrate, 63076-84-6; 11 HCl, 2717-93-3; acetaldehyde, 75-07-0; chloral, 75-87-6.

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(17) Acetal formation is unlikely, since the spectra were obtained in 95% ethanol.
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(19) Since absolute ethanol was used in the ^1H NMR experiments, formation of acetals cannot rigorously be excluded.