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Reversals in Regiospecificity. The Reactivity of Vinylogous Amides toward Bis Electrophiles

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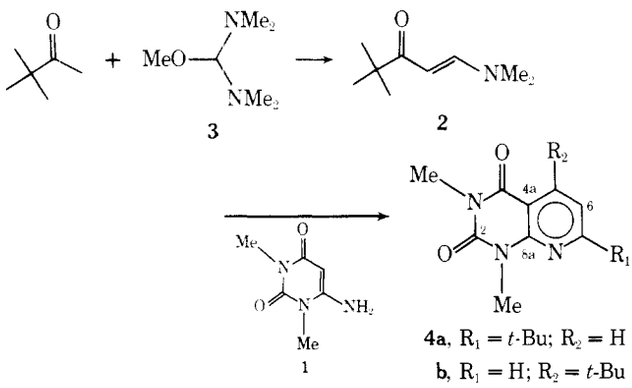
Several examples demonstrating the regiospecific reactivity of vinylogous amides toward bis electrophiles are presented. A reversal in this regiospecificity was accomplished by transformation of the vinylogous amide into the corresponding lithium imide prior to reaction with a bis electrophile.

The regioselective reactivity of primary enamino ketones such as 1,3-dimethyl-6-aminouracil (**1**) toward both mono and bis electrophiles has been established.[1-11] Furthermore, reversals of this regioselectivity have been accomplished by manipulation of catalyst and solvent.[2,4,10] Accompanying several of these examples were mechanistic proposals based on the difference in reactivity between the primary, exocyclic amino moiety and C-5 toward electrophiles.[1,2,10] The question of reactivity was reduced to one of C- vs. N-alkylation of the vinylogous amide bidentate system.[12]

No cases involving alkylation have been reported in which changes in nucleophilicity of the enamino ketone have resulted in reversal of regiospecificity. We wish to report an example of such a reversal and several others confirming the normal regioselective reactivity of enamino ketones.

Reaction of enamino ketone **1** with the tertiary enamino ketone **2**, prepared by the aminoformylation of pinacolone with Bredereck reagent **3**,[14] regiospecifically afforded only one of the two possible pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones **4a** and **4b**.

Scheme I



Compound **4a** would result from an orientation of reactants as depicted in Chart I, whereas **4b** would result from the orientation of Chart II.

The product obtained was assigned structure **4a** based upon a comparison of the product's ^{13}C NMR spectrum with the calculated resonances[15] for structures **4a** and **4b** (Table I), as well as the ^{13}C NMR off-resonance (sfor) carbon–hydrogen spin–spin splitting patterns for C-5 (d) and C-7 (s).

Chart I

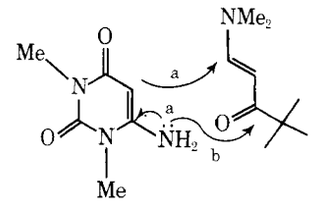
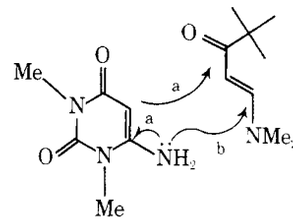


Chart II



Two reaction mechanisms, one involving initial C–C bond formation (pathway a) or one involving as its first step C–N bond formation (pathway b), can be postulated for the formation of **4a**.

There is adequate literature precedent[1,6] for postulating pathway a based on the reactivity of compound **1** toward mono electrophiles. It is to be expected that reaction at nitrogen would be less favorable for vinylogous amides than for enamines owing to the direct electron withdrawal by the carbonyl in the former. Nevertheless, N-acylation of various vinylogous amide systems has been observed.[16a]

It was anticipated that a reagent possessing a more significant difference in reactivity between its two electrophilic centers would be useful in providing further proof concerning the reaction mechanism. The reaction of such an electrophile, chlorosulfonyl isocyanate, with compound **1** also afforded a single product.

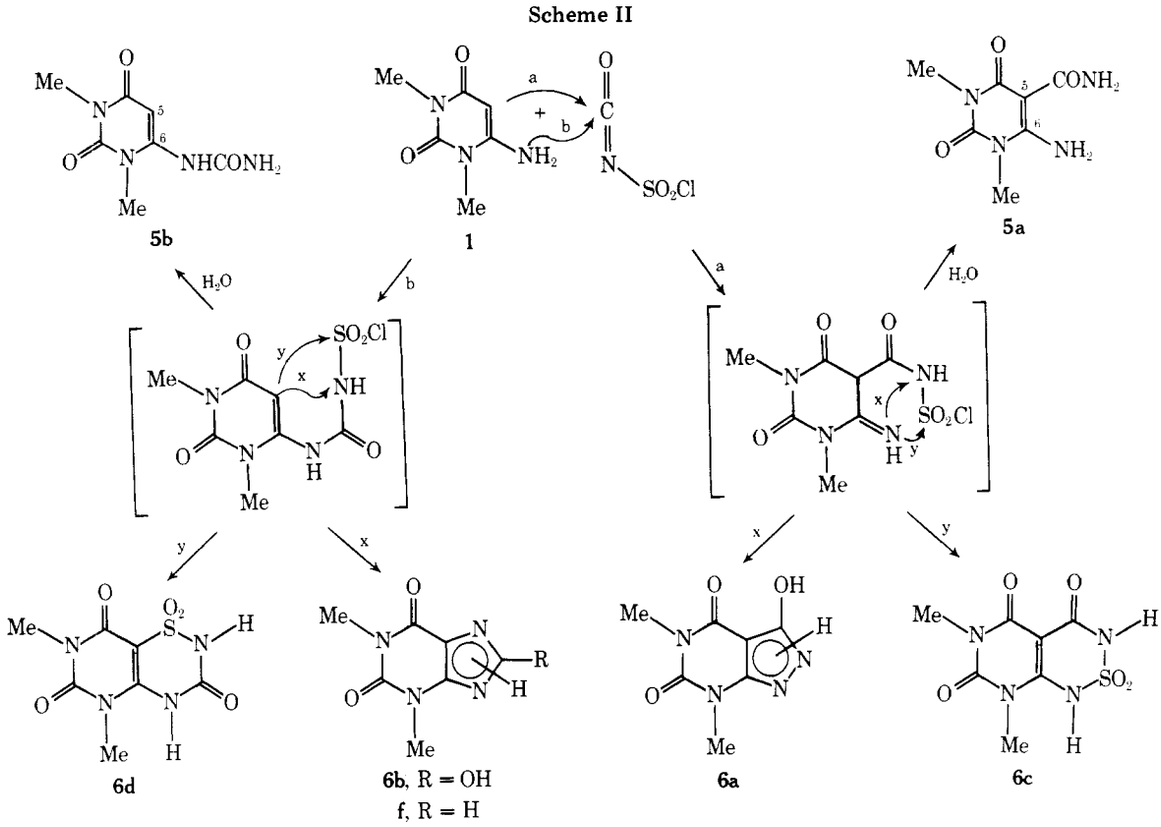
Scheme II depicts the various products that could arise from $ClSO_2NCO$ and **1** via reaction pathways a and b. From these products, **6c** and **6d** could be eliminated on the basis of an elemental analysis. The mass spectrum with a M^+ at *m/e* 198 helped eliminate structures **6a** and **6b** from consideration, but

Table I. Calculated and Observed ^{13}C Absorptions [a]

	4a	4a calcd	4b calcd	5a	6f	12a	12a calcd	12b calcd	12c calcd	12d calcd
N_1CH_3 [b]	28.1	28	28	27.3	27.4					
C_2	150.4	152	152	158.5	151.4	170.9	170	169	160.4	159.4
N_3CH_3 [b]	29.1	36	36	29.4						
C_3						103.2	102	98	106.4	102.6
C_4	151.9	160	161	162.6	154.6	145.8	152	157	149.9	155.2
C_{4a}	108.3	107	107		106.5					
C_5	138.0	135	158	80.5		98.7	103	98	102.1	97.4
C_6	114.7	114	107	149.7	140.3	158.3	158	158	158.8	159.3
C_7	161.5	163	150							
C_{8a} (C_{7a})	175.6	161	161		(148.0)					
t-Bu**C**	38.6	38	38			51.0	51	51	50.9	50.8
									51.0	51.0
t-Bu**CH$_3$**	30.0	30	30			29.7	30	30	29.7	29.7
Ar**NHCH$_3$**						28.6	29	29		
-CONHR [c]				170.2		170.9	170	170		
CONHCH$_3$						21.0	21	21		
Ar**CH$_3$**						26.4	25	25	25.2	25.4
Ar**CO**CH$_3$									33.4	30.8
Ar**CO**CH$_3$									197.5	198.8

[a] Chemical shifts are reported in δ units using Me_4Si as the internal standard. [b] No distinction can be made between the absorption of N_1CH_3 and N_3CH_3. [c] R = H, CH_3.

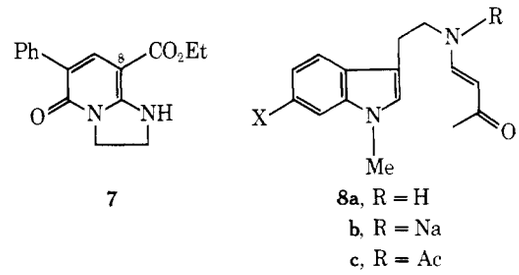
Scheme II



neither it, the high-resolution mass spectrum with a molecular ion at 198.0763 ($C_7H_{10}N_4O_3$), nor the ^1H NMR spectrum, which led us to favor **5a**, could eliminate **5b** as a possibility.

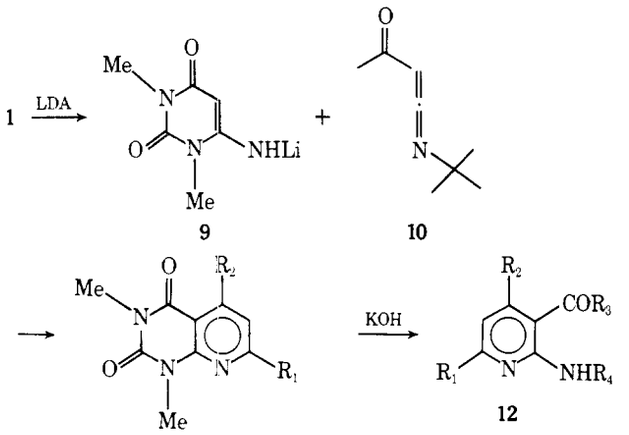
The ^{13}C NMR spectrum (Table I) provided the evidence necessary to assign structure **5a** to the product of the $ClSO_2NCO$ reaction. An unusually high field resonance at 80.5 ppm was assigned to C_5. By comparison, C_8 of compound **7**[17] displayed a resonance at 86.8 ppm. The ^{13}C NMR off-resonance (sfor) carbon–hydrogen spin–spin splitting pattern for C_5 (s) clearly demonstrated a quaternary carbon, thus eliminating **5b** as a possible structure.

The product's structure (**5a**) coupled with the known reactivity[18,19] of $ClSO_2NCO$ toward nucleophiles confirms the reaction mechanism as proposed in the literature,[1,2,10] i.e., initial electrophilic attack at C-5 of compound 1 (pathway a) is probably correct.



Sodium enolates of vinylogous amides are known to undergo both C- and N-methylation.[20] Buchi and co-workers,[21] as part of their elegant syntheses of vindorosine and vindoline, had observed that exposure of **8a** to acetic anhydride led to C-acylation, whereas treatment of the sodium salt **8b** with acetyl chloride provided the *N*-acyl derivative **8c.** It was, therefore, expected that such a manipulation of compound **1** might alter its regioselective reactivity in that initial electrophilic attack of **1** would be on nitrogen and not at C-5. Exposure of vinylogous lithium imide **9,** formed by the treatment of **1** with lithium diisopropylamide (LDA), to *N-tert*-butylacetylketenimine (**10**)[22] provided only one of the two possible regioisomers **11a** or **11b** (Scheme III). Compound **11a** would

Scheme III



	R_1	R_2	R_3	R_4
12a	NH-*t*-Bu	Me	NHMe	Me
b	Me	NH-*t*-Bu	NHMe	Me
c	NH-*t*-Bu	Me	Me	*t*-Bu
d	Me	NH-*t*-Bu	Me	*t*-Bu

result from an orientation of reactants as depicted in Chart III whereas **11b** would result from the Chart IV orientation.

Chart III

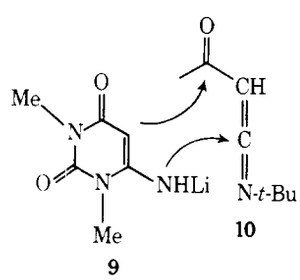
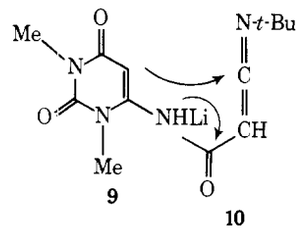


Chart IV



Because of solubility problems, this substance was converted by alkaline hydrolysis into the corresponding diaminonicotinamide **12.** After a comparison of the measured and calculated ^{13}C NMR spectra (Table I), structure **12a** was tentatively assigned to this product.

The calculated ^{13}C NMR resonances of **12a** and **12b** were derived from the ^{13}C NMR spectra of compounds **12c,** whose structure had been determined by x-ray analysis,[23] and **12d.** The syntheses and structure determinations of compounds **12c** and **12d** will be discussed in greater detail later in this publication.

There is adequate literature precedent involving the reactivity of ketenimines[24] as electrophiles to postulate a mechanism involving initial electrophilic attack of the ketenimine on the amide N followed by electrophilic ring closure at C-5 and dehydration.

Such a mechanism would represent a total reversal in the regioselectivity previously demonstrated by compound **1,** wherein initial electrophilic attack was at C-5, and represents the first such reported reversal resulting from a change in the nucleophilicity of the bis nucleophile.

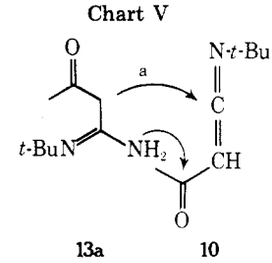
Exposure of aminouracil **1** to kentenimine **10** under neutral conditions, a reaction which should have provided **12b,** led only to products resulting from the decomposition of **10.**

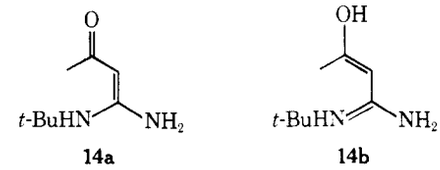
The reaction of lithium amide **9** with bis electrophile **2** was equally disappointing. Less than a 3% yield[25] of the anticipated product **4b** was realized. In addition to starting materials (>80%), a 13% yield of **4a** was also isolated from the product mixture.

Still lacking an example of reversal in regioselectivity in which each of the two possible products from a bis nucleophile and bis electrophile was prepared in turn and in good yield, we next turned to the reactions of ketenimine **10** and amidine **13.**[26] Under neutral conditions (**13a** + **10**), a single product, **12c** or **12d,** was formed in 70% yield. Exposure of **10** to lithium salt **13b** led to a single but different product, again either **12c** or **12d** in 67% yield. Addition of LiBr to the former reaction had no effect on either product composition or yield. Based on ^1H and ^{13}C NMR, IR, UV, and MS data, structures **12c** or **12d** could be assigned to these products but one could not with confidence assign structure **12c** to one and **12d** to the other. An x-ray analysis[23] allowed the assignment of structure **12c** to the product resulting from exposure of ketenimine **10** to lithium amide **13b.** Structure **12d** could, then, by analogy, be assigned to the product resulting from the reaction of **10** with amidine **13a** under neutral conditions.[27] The actual tautomeric forms of **12c** and **12d** in solution cannot be assigned based on the analytical data.

Again, based on the fact that acylketenimines undergo initial nucleophilic attack (a) at the sp carbon, compound **12d** would result from an orientation of reactants as depicted in Chart V. This would require the tautomerization of **13a** into

Chart V

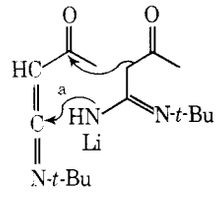




a form such that the methylene carbon might become more nucleophilic, e.g., **14a** or **14b**.

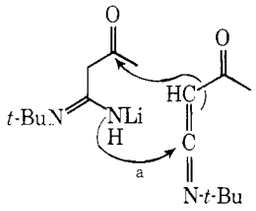
Either the orientation in Chart VI or that in Chart VII would lead to compound **12c**. With both, initial nucleophilic

Chart VI



10 **13b**

Chart VII



13b **10**

attack on the ketenimine (**10**) must be made by the amide nitrogen. These reactions thus represent a clear reversal in regioselectivity of a bis nucleophile toward a bis electrophile due to changes in the former's nucleophilic character.

With the exception of starting materials and their degradation products, no compounds other than those described above could be isolated from the reaction mixtures.

Experimental Section

The IR spectra were recorded on a Perkin-Elmer Model 257 or 457 grating spectrophotometer and NMR spectra were recorded using either a Varian T-60 or EM-360 spectrometer. ^{13}C NMR spectra were recorded using a Varian XLFT-100 spectrometer. Chemical shifts (δ) are recorded relative to Me_4Si; coupling constants (J) are given in hertz. Mass spectra were recorded using either an LKB 9000 or an AEI MS-30-D5-50 spectrometer. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. In all workup procedures, the drying process involved swirling over $MgSO_4$ and filtering prior to evaporation.

1-Dimethylaminomethylene-3,3-dimethyl-2-butanone (2). A solution of pinacolone (40.0 g, 0.40 mol) and bis(dimethylamino)-methoxymethane[14c] (80 ml) was heated under N_2 at 110 °C for 18 h. Concentration in vacuo followed by distillation (68–73 °C, 0.1 mm) provided 39.0 g (63%) of a yellow oil which solidified on standing at room temperature and which was used without further purification: NMR ($CDCl_3$) δ 1.15 (s, 9 H), 2.94 (s, 6 H), 5.23 (d, 1 H, J = 12 Hz), and 7.58 (d, 1 H, J = 12 Hz); IR ($CHCl_3$) 1650 cm^{-1}.

Anal. Calcd for $C_9H_{17}NO$: C, 69.6; H, 11.0; N, 9.0. Found: C, 69.1; H, 10.6; N, 8.5.

1,3-Dimethyl-7-(dimethylethyl)pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (4a). To a solution of 6-amino-1,3-dimethyluracil (15.5 g, 0.10 mol) in 10% aqueous HOAc (3 l.) at room temperature was added dropwise a solution of **2** (15.5 g, 0.10 mol) in absolute EtOH (50 ml). The mixture was heated under N_2 at reflux for 18 h, then cooled and the resulting precipitate removed by filtration and washed several times with H_2O. The crude solid was dissolved in Et_2O, and the solution dried and evaporated to give an off-white solid. Recrystallization from a minimum of Et_2O provided 15.0 g (61%) of white crystals: mp 83–85 °C; NMR ($CDCl_3$) δ 1.45 (s, 9 H), 3.44 (s, 3 H), 3.70 (s, 3 H), 7.19 (d, 1 H, J = 9 Hz), and 8.31 (d, 1 H, J = 9 Hz); IR ($CHCl_3$) 1710, 1600, 1605, and 1590 cm^{-1}.

Anal. Calcd for $C_{13}H_{17}N_3O_2$: C, 63.1; H, 6.9; N, 17.0. Found: C, 63.2; H, 7.3; N, 16.9.

6-Amino-1,3-dimethyl-2,4-dioxo-5-pyrimidinecarboxamide (5a). To a suspension of amino uracil **1** (9.30 g, 0.06 mol) and anhydrous $NaHCO_3$ (5.0 g, 0.06 mol) in CH_2Cl_2 (150 ml) under N_2 was added dropwise a solution of $ClSO_2NCO$ (8.46 g, 0.06 mol) in CH_2Cl_2 (50 ml) and the mixture was stirred at room temperature for 18 h. Water (15 ml) was added and the resulting solids collected and washed with additional H_2O and CH_2Cl_2. Recrystallization from DMF gave 7.94 g (68%) of **5** as a white solid: mp 257.5–259 °C; NMR (Me_2SO) δ 3.15 (s, 3 H), 3.24 (s, 3 H); IR (KBr) 3510, 3310, 1690, and 1640 cm^{-1}; mass spectrum m/e 198.0763 (calcd for $C_7H_{10}N_4O_3$; 198.0753).

Anal. Calcd for $C_7H_{10}N_4O_3$: C, 42.4; H, 5.1; N, 28.3. Found: C, 42.8; H, 4.9; N, 28.7.

1,3,5-Trimethyl-7-[(dimethylethyl)amino]pyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (11a). A solution of n-BuLi in hexane (25.0 ml of 1.6 M, 0.04 mol) was added dropwise to a cooled (20 °C) solution of diisopropylamine (4.04 g, 0.04 mol) in dry HMPA (50 ml). To this red solution under N_2 was added portionwise amino uracil **1** (6.2 g, 0.04 mol) and, after 0.5 h at room temperature, neat *N-tert*-butylacetylketenimine (**10**,[22] 6.20 g, 0.05 mol) was added. After stirring overnight at room temperature, the reaction mixture was stirred into an excess of cold aqueous NH_4Cl. The precipitated solids were collected and dried to give 6.0 g (55%) of the crude product **11a**. Recrystallization from MeOH–$CHCl_3$ gave a white solid: mp 354–356 °C; NMR (CF_3COOD) δ 1.63 (s, 9 H), 2.93 (s, 3 H), 3.38 (s, 3 H), 3.80 (s, 3 H), and 6.92 (s, 1 H).

Anal. Calcd for $C_{14}H_{20}N_4O_2$: C, 60.9; H, 7.3; N, 20.3. Found: C, 60.7; H, 6.9; N, 20.0.

***N*-Methyl-2-(methylamino)-4-methyl-6-[(dimethylethyl)amino]nicotinamide (12a).** A mixture of dione **11a** (1.00 g, 3.62 mmol) and 40% aqueous KOH (20 ml, 180 mmol) in Me_2SO (50 ml) was heated under N_2 at 130 °C for 4 days. Filtration followed by evaporation of the filtrate gave a residue which was dissolved in H_2O and thoroughly extracted with CH_2Cl_2. The combined organic extracts were dried and evaporated, and the residue chromatographed over silica gel (30:1) affording on $CHCl_3$ elution nicotinamide **12a**. Recrystallization from EtOAc–heptane gave 0.27 g (33%) of needles: mp 172–174 °C; NMR ($CDCl_3$) δ 1.47 (s, 9 H), 2.20 (s, 3 H), 2.87 (s, 3 H), 2.95 (s, 3 H), 5.45 (emergent s, 1 H), 5.40 (broad s, 1 H), and 6.60 (broad s, 1 H); IR ($CHCl_3$), 3440 and 1636 cm^{-1}.

Anal. Calcd for $C_{13}H_{22}N_4O$: C, 62.4; H, 8.9; N, 22.4. Found: C, 62.2; H, 9.2; N, 22.6.

***N'-tert*-Butylacetoacetamidine (13a).** To a solution of freshly distilled NH_3 (90 ml) in CH_2Cl_2 (90 ml) at −50 to −60 °C was added a solution of *N-tert*-butyl-5-methylisoxazolinium perchlorate[22] (90 g, 0.375 mol) in CH_2Cl_2 (180 ml). The reaction mixture was allowed to warm to ambient temperature over 12 h, concentrated to 75 ml, and filtered.

The filtrate was washed with saturated K_2CO_3 solution and evaporated to dryness. Recrystallization of the residue from EtOAc gave 49 g (84%) of **13a**: mp 127–129 °C; NMR ($CDCl_3$) δ 1.40 (s, 9 H), 1.92 (s, 3 H), 4.58 (broad s, 1.6 H), 5.2 (broad s, 1 H), 7.9 (broad s, 1 H), and 11.03 (broad s, 0.4 H); IR ($CHCl_3$) 3510, 3440, and 1610–1560 cm^{-1}.

Anal. Calcd for $C_8H_{16}N_2O$: C, 61.5; H, 10.3; N, 17.9. Found: C, 61.6; H, 10.7; N, 18.3.

2,4-Di-*tert*-butylamino-3-acetyl-6-methylpyridine (12d). A mixture of amidine **13a** (31.2 g, 0.2 mol) and ketenimine **10**[22] (27.8 g, 0.2 mol) was heated in refluxing THF (200 ml) for 5 h. Evaporation to dryness and crystallization of the residue from MeOH–H_2O provided 38.7 g (70%) of diaminopyridine **12d**, mp 111–114 °C. Recrystallization from heptane gave an analytical sample: mp 115–116 °C; NMR ($CDCl_3$) δ 1.40 (s, 9 H), 1.48 (s, 9 H), 2.25 (s, 3 H), 2.48 (s, 3 H), 5.30 (broad s, 1 H), 6.00 (s, 1 H), and 8.06 (braod s, 1 H); IR ($CHCl_3$) 3460, 3260, and 1585 cm^{-1}; UV (MeOH) 2.19 nm (ϵ 22 800), 239 (14 800), and 334 (7450).

Anal. Calcd for $C_{16}H_{27}N_3O$: C, 69.3; H, 9.8; N, 15.2. Found: C, 69.6; H, 10.0; N, 15.2.

2,6-Di-*tert*-butylamino-3-acetyl-4-methylpyridine (12c). To a solution of amidine **13a** (46.8 g, 0.3 mol) in dry THF (600 ml) at 20–40 °C was added a 1.6 M solution of n-BuLi in hexane (192 ml, 0.3 mol) and after stirring at ambient temperature for 1 h a solution of ketenimine **10**[22] (41.7 g, 0.3 mol) in dry THF (200 ml) was added and the stirring was continued for 12 h. The reaction was quenched with saturated aqueous NH_4Cl solution (100 ml), and MeOH (500 ml) and Na_2SO_4 (250 g) were added. After the mixture was filtered (Celite) and the filtrate evaporated to dryness, the residue was dissolved in $CHCl_3$ (1 l.), washed with brine, and filtered through silica gel. The product, **12c**, was provided (55.3 g, 67%) by the addition of pentane (200 ml) to the concentrated filtrate: mp 129–131 °C; NMR ($CDCl_3$) δ 1.43 (s, 9 H), 1.47 (s, 9 H), 2.32 (s, 3 H), 2.43 (s, 3 H), 4.60 (broad s, 1 H), 5.47 (s, 1 H), and 9.94 (broad s, 1 H); IR ($CHCl_3$) 3440 and 1605–1580 cm^{-1}; UV (MeOH) 222 nm (ϵ 13 650), 267 (15 000), 286 (10 670), and 368 (20 500).

Anal. Calcd for $C_{16}H_{27}N_3O$: C, 69.3; H, 9.8; N, 15.2. Found: C, 69.3; H, 10.2; N, 15.4.

Acknowledgment. The services of the Analytical Section of the Chemistry Department are gratefully acknowledged.

In particular the ^{13}C NMR measurements of Ms. A. D. Kahle, the mass spectral determination of Dr. R. A. Coombs, and the x-ray work of Dr. H. P. Weber, Sandoz, Basle, are appreciated.

Registry No.—**1**, 6642-31-5; **2**, 6135-14-4; **3**, 1186-70-5; **4a**, 60581-88-6; **5a**, 60581-89-7; **6f**, 58-55-9; **10**, 10513-47-0; **11a**, 60581-90-0; **12a**, 60581-91-1; **12c**, 58253-99-9; **12d**, 60581-92-2; **13a**, 60581-93-3; pinacolone, 75-97-8; 6-amino-1,3-dimethyluracil, 6642-31-5; $ClSO_2NCO$, 1189-71-5; *N-tert*-butyl-5-methylisooxazolinium perchlorale, 60581-94-4.

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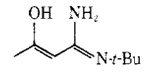
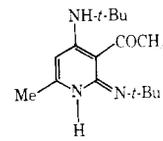
(25) This yield was based on a study of the crude product's ^1H NMR spectrum.
(26) Amidine **13a** exists in solution as a 60:40 equilibrium mixture of **13a** and tautomer i.



i

(27) An isomeric structure, such as ii, cannot be ruled out on the basis of our analytical data.



ii

Determination of Ionization Constants of Alkaloids by Paper Electrophoresis

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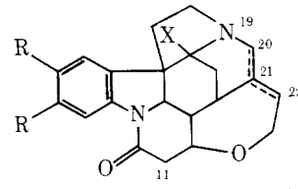
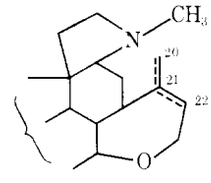
The ionization constants in water of strychnine, brucine, and seven related compounds have been determined by paper electrophoresis using microgram quantities of the bases. Results are in fair agreement with values obtained by potentiometric titration or by changes in solubility as a function of pH.

Arguments based on pK values are often useful in establishing the structures of alkaloids and other natural products.[1] A very simple method for determining pK by paper electrophoresis has been described,[2] but was tested only with fairly simple compounds, all reasonably soluble in water. In this paper we examine the usefulness of this method for strychnine (**1**), brucine (**2**), and several related compounds of very limited solubility in water. For such compounds the temptation to determine pK values in mixed aqueous organic solvents is very great but, according to Albert and Serjeant, "should be resisted",[3] because otherwise one loses the advantages accruing from the immense amount of data in the literature for purely aqueous solutions. To check the values obtained by paper electrophoresis, we have also determined the pK values of the bases **1**–**5** and **7**–**9** by a solubility method[3] which takes advantage of the limited water solubility of these compounds. The *N*-oxide **6** was sufficiently soluble in water for the conventional potentiometric titration procedure to be used.





1, strychnine: R = X = H; Δ^{21}
2, brucine: R = OMe; X = H; Δ^{21}
3, neostrychnine: R = X = H; Δ^{20}
4, neobrucine: R = OMe; X = H; Δ^{20}
5, pseudostrychnine: R = H; X = OH; Δ^{21}
6, strychnine *N*-oxide: $\rangle\overset{+}{N}^{19}\!\!-\!\!\!-\!\!\overline{O}$ in place of $\rangle N^{19}$
7, benzylidene strychnine: $\rangle C^{11}{=}CHPh$ in place of $\rangle C^{11}H_2$
8, base C, Δ^{20}, R = H
9, base D, Δ^{21}, R = H