Table V. Preparations and Some Data of Pyrazolopyridines

material no.	prod. no. (%)[a]	appearance	mp, °C	ν_{CO} (KBr)	ν_{CN} (KBr)
19	**25** (96)	yellow needles	102–103	1716	2240
20	**26** (93)	yellow needles	91–93	1675	
21	**29** (96)	yellow needles	190–192	1716	2240
22	**30** (92)[b]	yellow amorph		1685[c]	
23	**31** (96)	yellow needles	159–162	1713	2240
24	**32** (82)	yellow needles	102–104	1675	
36	(0)	no reaction			
37	(0)	decomposition			

[a] Satisfactory analyses were reported for compounds **25, 26, 29** and **31.** [b] Crystallization of **30** was unsuccessful. [c] Neat.

were prepared in quantitative yields by the reactions of pyridinium *N*-ylides **4–9**[5a,h,8] with methyl iodide in chloroform or without solvent at room temperature. These salts **10–16** were used for the next reactions without further purification because of the difficulty of their crystallization. The NMR data of salts **10–16** are listed in Table I.

Reactions of Pyridinium Salts 10–16 with Ethoxymethylene Compounds 17 and 18. General method: A solution of pyridinium salt (2.1 mmol) and ethyl ethoxymethylenecyanoacetate **17** (0.34 g, 2 mmol) or 3-ethoxymethylenepentane-2,4-dione **18** (0.31 g, 2 mmol) in chloroform (50 mL) was treated with potassium carbonate (5 g) at room temperature for 3–4 days. The reaction mixture was then filtered to remove insoluble inorganic substances and the filtrate was concentrated in vacuo. The residue was separated by column chromatography (alumina) using ether and then chloroform as eluents. Pyrazolopyridines **27, 28,** and **32–34** were isolated from the ether layer and allylidenedihydropyridines **19–24, 36,** and **37** from the chloroform layer. Recrystallizations of pyrazolopyridines **27, 28,** and **32–34** and allylidenedihydropyridines **19–23, 36,** and **37** were carried out from ether–hexane and chloroform–hexane, respectively. However, the preparation of the analytical sample of **24** was unsuccessful because **24** decomposed gradually even at room temperature to give pyrazolopyridine **32** and ethyl *N*-methylcarbamate **38.** Furthermore, ethyl isobutyrate **35** or ethyl *N*-methylcarbamate **38** was detected by GLC of the reaction solutions. These results and some physical data are shown in Tables II–IV.

Thermolyses of Allylidenedihydropyridines 19–24, 36, and 37. General method: A solution of 2-allylidenedihydropyridine (1 mmol) in xylene (50 mL) was heated at the reflux temperature until the disappearance of the starting material was observed by TLC (about 3–6 h). The reaction solution was concentrated in vacuo, and the residue was separated in the usual manner. Recrystallization from ether–hexane gave the corresponding 3-ethenylpyrazolopyridines **25, 26,** and **29–32.** The formation of ethyl *N*-methylcarbamate **38** was also confirmed by GLC of the reaction solutions. On the other hand, the thermolyses of allylidenedihydropyridines **36** and **37** did not give the expected pyrazolopyridinones but afforded only tarry substances. These results and some physical data are listed in Tables III and V.

Acknowledgment. The present work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education (No. 265251).

Registry No.—**4,** 60705-40-0; **5,** 60705-41-1; **6,** 60705-42-2; **7,** 60705-43-3; **8,** 66303-83-1; **9,** 22928-83-2; **17,** 94-05-3; **18,** 33884-41-2.

References and Notes

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(2) See the following recent review for the indolizine synthesis. T. Uchida and K. Matsumoto, *Synthesis*, 209 (1976).
(3) (a) A. Kakehi, S. Ito, T. Funahashi, and N. Ogasawara, *Chem. Lett.*, 919 (1975); (b) A. Kakehi, S. Ito, T. Funahashi, and N. Ogasawara, *Bull. Chem. Soc. Jpn.*, **49,** 2250 (1976).
(4) A. Kakehi, S. Ito, K. Uchiyama, and K. Kondo, *Chem. Lett.*, 545 (1977).
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(6) Compounds **23** and **24** were gradually converted to 3-ethenylpyrazolo[1,5-*a*]pyridines **31** and **32,** respectively.
(7) (a) T. Severin and H.-J. Böhme, *Chem. Ber.*, **101,** 2925 (1968); (b) R. M. Acheson and J. Woollard, *J. Chem. Soc., Perkin Trans. 1,* 744 (1975); (c) J. Kuthan, D. Ilavsky, J. Krechel, and P. Trska, *Tetrahedron Lett.*, 4763 (1976).
(8) *N*-Vinyliminopyridinium ylide **8,** red prisms, mp 131–134 °C, ν(KBr) 1535 cm^{-1} (CO) (Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.72; H, 7.70; N, 12.11) was prepared in 84% yield by the reaction of 1-aminopyridinium iodide with ethyl β-bromomethacrylate according to the Sasaki's procedure. See ref 5e.

Teleamination of the Imidazo[1,2-*a*]pyridine System

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The reaction of 3-bromoimidazo[1,2-*a*]pyridine (**2**) with strong bases leads to metal–halogen and alkyl–halogen (coupling) exchange at the 3 position of the imidazole ring with CH_3Li, but leads to debromination, coupling via the 5 position (to give the dehydrodimer **11**), and telesubstitution at *all* positions of the pyridinoid ring with metal amides. Which products are obtained depends on the amide used. The formation of the amination products is interpreted to proceed by attack at positions 5 and/or 7, followed by migration to adjacent positions via an aziridine intermediate. Only the first step of the established ANRORC (addition–nucleophilic–ring opening–ring closing) mechanism of other teleamination reactions can be retained for these reactions, subsequent steps including ring opening and ring closing, but in the reverse sequence. A bromination product, the formation of which implicates a positive bromine species, and a Chichibabin amination product are also formed. The coupling product **11** is obtained when the parent imidazo[1,2-*a*]pyridine (**1**) is treated with KNH_2.

Imidazo[1,2-*a*]pyridine (**1**) contains both the π-excessive imidazole and the π-deficient pyridine rings. As such it is expected to undergo reactions of both types of molecules. The anticipated higher electron density in the five-membered ring is confirmed by frontier[1] and CNDO/2[2] calculations and is amply demonstrated by experimental evidence of electrophilic substitution at the 3 position.[3] When this position is blocked, electrophilic substitutions generally fail.[4] Much less is known about the reactivity of imidazo[1,2-*a*]pyridines toward nucleophiles. The parent compound **1** undergoes hydrogen–

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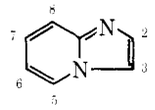
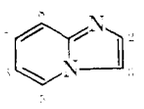
Table I. ^{1}H NMR Chemical Shifts (δ, ppm) of Some Imidazo[1,2-*a*]pyridines[a]



Substituent	Compd no.	Registry no.	H_2	H_3	H_5	H_6	H_7	H_8	$COCH_3$	CH_2	CH_3
None	1[b]	274-76-0	7.58	7.63	8.05	6.78	7.16	7.62			
3-Br	2	4926-47-0	7.67		8.19	6.95	7.25	7.67			
3-CH_3	3	5857-45-4	7.43		7.89	6.79	7.12	7.64			2.46
2-CH_3		934-37-2		7.29	7.99	6.63	7.03	7.48			2.40
6-Br, 7-NHEt	5	66358-04-1	7.41	7.28	8.19			6.57		3.16	1.37
6-Br	33	6188-23-4	7.68	7.60	8.32		7.20	7.59			
8-NEt_2	7	66358-05-2	7.58	7.51	7.70	6.66	6.28			3.76	1.17
7-NEt_2	8	66358-06-3	7.37	7.26	7.83	6.38		6.51		3.33	1.15
5-NEt_2	9	66358-07-4	7.66	7.66		6.35	7.18	7.44		3.20	1.10
5,7-diNEt_2	10	66358-08-5	7.40	7.33		5.98		6.44		3.40	1.22
										3.19	1.13
None	1[c]		7.98	7.64	8.59	6.88	7.22	7.62			
2-$NHCOCH_3$	19	38922-76-8		8.40	8.80	7.12	7.48	7.70	2.40		
3-$NHCOCH_3$	20	66358-09-6	7.85		8.46	7.26	7.56	7.91	2.50		
5-$NHCOCH_3$	17	66358-10-9	7.96	7.65		7.09	7.28	7.47	2.22		
6-$NHCOCH_3$	14	66358-11-0	8.00	7.54	9.22		7.15	7.55	2.09		
8-$NHCOCH_3$	18	66358-12-1	7.95	7.56	8.24	6.84	7.99		2.22		
5-CH_3		933-69-7	7.89	7.78		6.78	7.23	7.60			2.67
5-R[d,e]	11	66358-13-2	7.67	7.21		7.35	7.47	7.89			
3-NO_2		4926-45-8	8.84		9.45	7.53	7.83	8.05			
3-NO_2, 5-CH_3	31	34165-08-7	8.79			7.35	7.85[f]	7.85[f]			2.70
3-NO_2, 5(3′-NO_2)R[d,e]	25	66358-14-3	8.94			7.89	8.07	8.24			
3-NO_2, 5(3′-NO_2, 7′-$NHCOCH_3$)R[d]	27	66358-15-4	8.83 8.73			7.81 7.74	7.98	8.16 8.32	2.16		
3-NO_2,8-$NHCOCH_3$	32	66358-16-5	8.71		9.00	7.40	8.40		2.23		

[a] Assignments of chemical shifts are based not only on similarity to those of analogous compounds but primarily on the splitting patterns. Typical values of coupling constants are: $J_{2,3}$ ~1.2, $J_{3,8}$ ~0.5, $J_{5,6}$ = 6–7.5, $J_{5,7}$ = 0–2, $J_{5,8}$ = 0–1, $J_{6,7}$ = 6.5–7.5, $J_{6,8}$ = 1.5–2.5, $J_{7,8}$ = 8.5–9.5 Hz. Although the H_3 signal tends to be broader than that due to H_2, assignments to H_2 and H_3 may be inverted in some cases. [b] Data in the upper part of table are of dilute $CDCl_3$ solutions. [c] Data in the lower part of the table are of dilute Me_2SO-d_6 solutions. [d] R = 5′-imidazo[1,2-*a*]pyridyl. [e] Chemical shifts obtained from simulated spectra. [f] Center of overlapping multiplets.

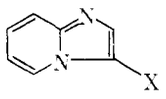
deuterium exchange in the presence of NaOD at positions 3 and 5 via the corresponding anions generated by proton ab-



1

straction.[5] Phenyllithium also abstracts hydrogen at the 3 position.[6] While attempts to displace bromine at the 3 position with various nucleophiles (CH_3O^-, morpholine, and piperidine) have failed, electrophilic displacement with SeO_2 has been achieved.[7] Reaction of alkoxide with either the 2- or the 7-chloro derivative is reported to be unsuccessful. However, a 5-chloro substituent can be displaced.[8] In a rare example of nucleophilic substitution at the 2 position,[9] substitution is facilitated by the presence of the highly activating NO_2 group in the 3 position. We have recently shown that nucleophilic attack can occur at C_2 or C_3 when N_1 carries an appropriate leaving group (Cl, Br,[10] $OPOCl_2$,[11] and OCH_3[12]). We report now the results of some further reactions with strong nucleophiles[13] (CH_3Li, KNH_2, EtNHLi, and Et_2NLi).

When a mixture of 3-bromoimidazo[1,2-*a*]pyridine (**2**) and

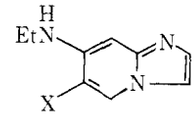


2, X = Br
3, X = CH_3
4, X = NO_2

methyllithium in ether is stirred for 45 min at 0 °C, debromination with concomitant formation of approximately equal amounts of the parent compound 1 and its 3-methyl derivative (**3**) occurs. These compounds were identified by comparison of properties of solid derivatives, the nitration product **4** of the parent compound 1 and the picrate of compound **3**, with those of authentic samples (see Table I for ^{1}H NMR spectral data). The reaction mixture consisted of at least 90% of these materials, since its ^{1}H NMR spectrum was almost the same[14] as that of a 1:1 mixture prepared from pure authentic compounds. Even small amounts of the possible 2-methyl derivative, if formed, would have been detectable by ^{1}H NMR spectroscopy since its H_3 signal appears as a sharp singlet in a region relatively free of other absorption.

Use of the aprotic solvent, ether, and strong anion base thus leads only to bromine–lithium exchange[15] and coupling.[16] Mechanisms for these types of reactions have been discussed.[17]

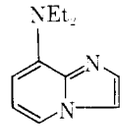
The reactions of 3-bromoimidazo[1,2-*a*]pyridine (**2**) with the amine anions lead to complex mixtures containing considerable amounts of tar. The major product (35%) from lithium ethylamide in 20% ethylamine/ether is the parent compound **1**. This reductive dehalogenation[18] evidently occurs by abstraction of Br^+ since a minor product (2.5%) is 6-bromo-7-ethylaminoimidazo[1,2-*a*]pyridine (**5**). The formation of this compound is readily explicable only by postulating



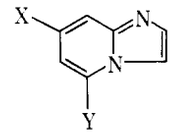
5, X = Br
6, X = H

electrophilic substitution at position 6 of 7-ethylaminoimidazo[1,2-*a*]pyridine (**6**), which in turn is formed by telesubstitution of bromine in compound **2** (vide infra). The structures of the bromo compound **5** and of most of the other new compounds were established by analysis of mass and ^{1}H NMR (see Table I) spectra and elemental composition.[19]

From the complex mixture of products of the reaction with lithium diethylamide in 30% Et_2NH/12% hexane/Et_2O, the parent compound **1** (10%) as well as the four substitution products, **7–10**, could be isolated.[20] It should be noted that the



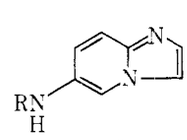
7 (9%)



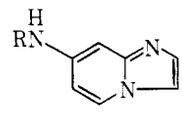
8, X = Et_2N; Y = H (13%)
9, X = H; Y = Et_2N (4%)
10, X = Y = Et_2N (1%)

7-diethylamino derivative **8** is formed in highest yield. The formation of the disubstituted product **10** can be attributed to a Chichibabin reaction of compound **8**.

When the reaction was carried out with potassium amide in 55% NH_3/ether, the parent compound **1** (ca. 10%), a dehydrodimer (**11**) of compound **1**, an amino derivative (**12**) of the dehydrodimer (vide infra), and 6-aminoimidazo[1,2-*a*]pyridine (**13**, 50%) could be isolated. The 7-amino derivative **15** (<1%) is believed to be formed also. These materials were separated and identified as acetamido derivatives.

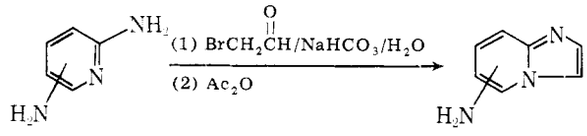


13, R = H
14, R = $COCH_3$



15, R = H
16, R = $COCH_3$

The structure of the acetamido compound (**14**) was confirmed by an unequivocal synthesis from 2,5-diaminopyridine and bromoacetaldehyde, followed by acetylation. Attempts to prepare compound **15** by similar condensation of 2,4-diaminopyridine failed, although both the 5- and the 8-acetamidoimidazo[1,2-*a*]pyridines (**17** and **18**) were readily ob-

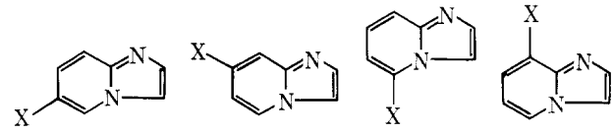


14, 6-$NHCOCH_3$
17, 5-$NHCOCH_3$
18, 8-$NHCOCH_3$

tained from the corresponding diaminopyridines. The remaining 2- and 3-acetamido isomers **19**[21] and **20**[9] were prepared by known procedures. TLC comparisons of the acetylated amination mixtures and the five authentic acetamido compounds showed unequivocally that *none* of either the 8- or the 3-acetamido compound was present. A component with the same R_f value as 2-acetamidoimidazo[1,2-*a*]pyridine (**19**) was formed in minute amount (<0.1%). Structure **16** is tentatively assigned to the acetyl derivative of compound **15** since it showed a mass spectral fragmentation pattern very similar to those of the other acetamido derivatives, but its melting point and IR spectrum differed from those of the other five isomers (**14**, **17–20**).

While no definitive statement can be made regarding the mechanism of the teleamination reactions, the substitution patterns in the isolated products (see Table II) nevertheless establish a trend which is consistent with the following mechanism (see Scheme I).

Table II. Isomer Distribution (%) in the Amination Reactions

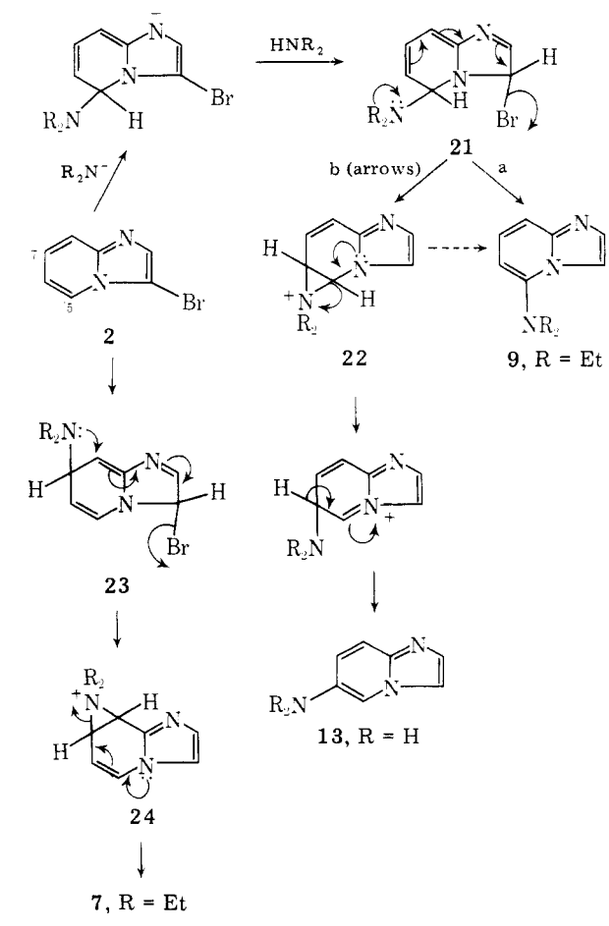


X	A	B	C	D
NH_2	50	Trace	?	
NHEt	?	2.5[a]	?	?
NEt_2	?	13	4	9

[a] Isolated as the 6-bromo derivative.

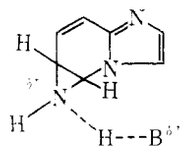
Attack by amide ion preferentially occurs at C_5 (and/or C_7) since in the resulting intermediate the negative charge can be accommodated by nitrogen. A factor contributing to the driving force may well be complexation of the metal ion, K^+ or Li^+, with N_1 in the neutral molecule (**2**). Subsequent or concomitant reaction with the protic amines gives the intermediate **21** from which elimination could occur by two different paths. While path a leads to direct rearomatization of the ring system, it is not necessarily involved in the formation of compound **9**. The high effective concentration of the attacking nucleophile (the NR_2 group in **21**), loss of Br^-, and aromatization of the five-membered ring can all contribute to the driving force for the formation of intermediate **22**. The 5-substituted product (**9**) can then be obtained by loss of H_5 and cleavage of the aziridine ring. However, preferential for-

Scheme I



mation of the 6-substituted product (**13**) is expected if cleavage of the three-membered ring is facilitated by neighboring group participation of N_4. Similar reaction sequences with initial attack at C_7 account for the formation of the 7- and 8-substituted products (**8** and **7**, respectively) with $LiNEt_2$. Since in this case both "non"- and "rearranged" products were isolated and since the 8-substituted compound, which should be formed to a *greater* extent from intermediate **24**, is actually obtained in *smaller* amount, the postulate that the two products are formed by two different reaction paths (a and b) receives some support.[34]

The formation of a very high percentage of "rearranged" 6-substituted product in the KNH_2 relative to the $LiNEt_2$ reaction can be attributed to two factors. Proper orientation for bond formation of the electrons on nitrogen should be easier in the intermediate containing the NH_2 group (**21**, R = H) compared to the bulky NEt_2 group. Furthermore, the newly formed intermediate **22** (R = H) almost certainly does not carry a full positive charge as it must where R = NEt_2, since H bonding to the solvents (Et_2O and NH_3, cf. **22a**) or



22a

proton transfer (to NH_2^-) are both possible. Hence the activation energy of intermediate formation should be considerably lower and the reaction proceeds preferentially via path b. Initial attack by NH_2^- at C_5 in preference to C_7 parallels the behavior of other N heterocycles in the Chichibabin reaction.[22] Preferred attack by NEt_2^- at C_7 rather than C_5 is attributed to greater bulkiness of this moiety.

While the position of substitution in the above compounds could be ascertained from their ^1H NMR spectra, this was not the case for the dehydrodimers, **11** and **26**, that were obtained in the potassium amide reaction. The complex second-order spectrum of compound **11** implied unsymmetrical linkage of the two imidazo[1,2-*a*]pyridine units, yet suggested the absence of C_5 protons (normally the most deshielded in this ring system[23]).

Nitration, which always takes place at C_3 in imidazo[1,2-*a*]pyridines, afforded a dinitro compound which however displays a much simpler ^1H NMR spectrum interpretable in terms of the symmetrical structure **25**. Typically, the spectra of nitration products show not only a *general* downfield shift of all of the ^1H NMR signals but also a *profound* downfield shift of the H_2 and H_5 resonance lines.[24] Signals attributable to H_5 are absent in the spectrum of compound **25**; the lowest field signal is a singlet which must be assigned to H_2; and the areas and splitting pattern of the remaining signals can only be due to three protons located at positions 6, 7, and 8. The dehydrodimer must therefore also have the 5,5′ linkage. Strong support for structures **11** and **25** was obtained from computer simulation of these spectra. The values of the chemical shifts and coupling constants used for the simulated spectrum of the dehydrodimer (**11**) are shown in Figure 1 together with the experimentally obtained spectrum.

The ^1H NMR spectrum of the acetamidodehydrodimer (**26**) could only be obtained in TFAA, a solvent in which the chemical shifts of the protons in this ring system are usually very similar, and could not be interpreted. However, nitration of this compound affords a dinitro derivative that is soluble in dimethyl sulfoxide. The ^1H NMR spectrum is in accord with structure **27**. In addition to the pattern observed for the dinitrodehydrodimer **25**, there are a 3-proton singlet (C(O)-CH_3), a one-proton singlet (H-2′), as well as an AB system.

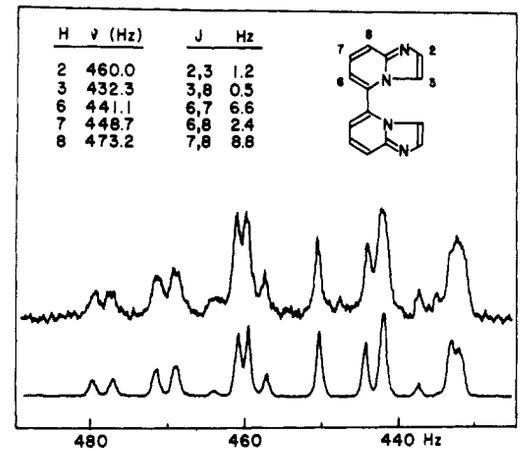
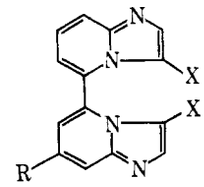


Figure 1. Top line: experimentally observed 60 MHz ^1H NMR spectrum of compound **11** (9mg/0.4 mL Me_2SO-d_6). Bottom line: theoretical spectrum obtained with a Varian Spin Simulation Routine and SS-100 computer system using the frequencies and coupling constants shown (line width = 2, scale factor = 5).

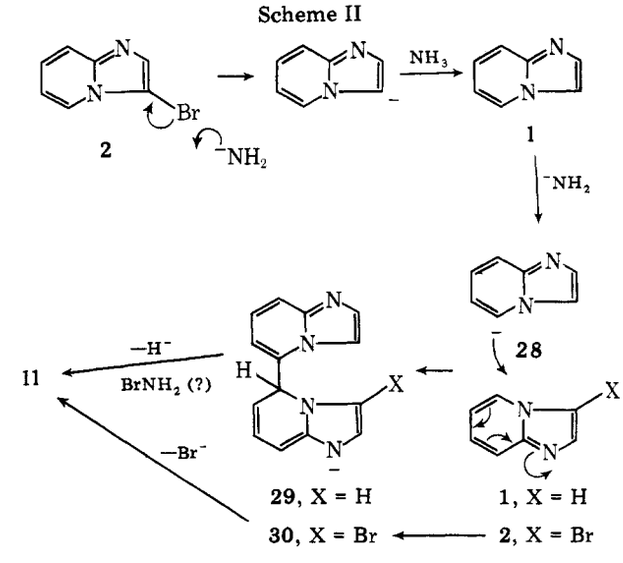


11, R = X = H
12, R = NH_2; X = H
25, R = H; X = NO_2
26, R = CH_3CONH; X = H
27, R = CH_3CONH; X = NO_2

The coupling constant of this pattern (2 Hz) precludes that the two protons are ortho to each other. Therefore, the acetamido group is at C_7′.

The dehydrodimer **11** is most likely formed by the sequence shown in Scheme II. That debromination occurs is shown by the fact that compound **1** was isolated. That proton abstraction at C_5 is reasonable is shown by H/D exchange in aqueous NaOD.[5] Attack of the anion **28** at C_5 of a neutral molecule (**1**) follows the same pattern postulated in the amination reactions. Oxidation of the anion **29**, or its protonation product, should be facile since an aromatic system is formed. Alternatively, reaction of the anion **28** with compound **2** leads to intermediate **30** from which the dehydrodimer **11** can be

Scheme II



formed by prototopic shift and loss of bromide ion. A Chichibabin-type amination of the dehydrodimer **11**, which should occur at C_7 on mechanistic grounds, then gives structure **12**.

Two further experimental findings indicate that the reaction sequence proceeding via intermediate **29** and subsequent amination is feasible. When the parent compound **1** is subjected to the amination conditions, the dehydrodimer **11** (15%) is formed. When this pure material (**11**) is resubjected to the amination conditions, followed by acetylation, compound **26** is present in the mixture.

In conclusion, the reaction of 3-bromoimidazo[1,2-*a*]-pyridine (**2**) with strong nucleophiles leads to debromination, coupling, and various telesubstitution and Chichibabin amination products. No single mechanism can account for the formation of all of these. Displacement of bromine by direct substitution or by a benzyne-type mechanism does not occur, at least in the potassium amide reaction. It appears to be generally true that π-excessive heteroaromatic halides do not form benzyne-type intermediates. A number of precedents for telesubstitution spanning *one* six-membered ring are known.[25] More recently, after completion of this work, telesubstitution spanning both rings in polyazanaphthalenes has been described.[26] In all of the compounds undergoing teleamination, the halogen is relatively inert and the negative charge of the attacking amide ion can be placed on a ring nitrogen in the intermediate. In the case of compound **2** the amine group in the intermediate (**21**) must migrate before the observed product **13** can be formed, and this seems to be a novel combination of known reactions.

Further studies, to examine the validity of this telesubstitution mechanism, are in progress.

Experimental Section

Unless otherwise stated, Woelm neutral alumina, Brockmann grade 3, was used for chromatography and solutions were dried over anhydrous Na_2SO_4. Melting points are uncorrected. ^1H NMR spectra were obtained with either a Varian HA-100 or a Hitachi Perkin-Elmer R-20B NMR spectrometer. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6M, IR spectra with a Beckman Acculab 1 instrument. Elemental analyses[27] were determined by the Analytical Services Laboratory of The University of Alabama Chemistry Department or by Atlantic Microlab, Inc., Atlanta, Ga.

Imidazo[1,2-*a*]pyridine (1). While a number of synthetic routes are available,[28] the following simplified procedure leads to high yields (up to 100%). Prolonged heating of the acetal with acid must be avoided, and in order to achieve efficient salting out with NaCl, the product mixture must be acidified (to liberate CO_2) prior to basification. After a mixture of ethyl 2-bromoacetal (10 g, 0.05 mol), H_2O (40 mL), and concentrated HCl (1 mL, 0.012 mol) was stirrred vigorously for 2.5 h it was heated in an 80 °C oil bath for 0.5 h to give a clear solution. The cooled solution was treated with portions of $NaHCO_3$ (5.5 g, 0.065 mol) and 2-aminopyridine (3.8 g, 0.04 mol). The mixture was stirred overnight, acidified with concentrated HCl, treated with aqueous 10% NaOH to pH 9–10, saturated with NaCl, and extracted with $CHCl_3$ (4 × 20 mL). The extracts were dried over anhydrous Na_2CO_3, stripped of solvent, and distilled through a Vigreux column to give colorless compound **1** (bp 97–102 °C (0.25 Torr) (lit.[1b] bp 112–117 °C (3 Torr)) which turned dark overnight.

3-Bromoimidazo[1,2-*a*]pyridine (2), prepared by the NBS procedure[1b] (76%), was crystallized from hexane. Chromatography (C_6H_6) of the materials in the mother liquor also gave pure compound **2**, mp 90.5–91.5 °C (lit.[1b] mp 92.9–93.4 °C, lit.[9] mp 92–94 °C), which can be sublimed (90 °C (0.05 Torr)). The NaOBr procedure[9] gave lower yields (45–55%).

Reaction of Compound 2 with Methyllithium. A solution of compound **2** (3.0 g, 0.015 mol) in anhydrous Et_2O (100 mL) in a dry three-neck flask, equipped with stirrer, condenser (protected with Drierite), and septum, was stirred and cooled in ice. When ethereal CH_3Li (1.9 M, 12.0 mL) was added with a syringe during 3 min, an immediate white solid separated. The mixture was stirred for 45 min and then treated dropwise with H_2O (30 mL). The H_2O layer was saturated with NaCl and extracted with $CHCl_3$ (4 × 10 mL). The combined Et_2O and $CHCl_3$ layers were dried and stripped of solvents to give a mixture (ca. 1:1) of compounds **1** and **3** (^1H NMR). To an ice-cold swirled solution of the mixture (0.37 g) in concentrated H_2SO_4 (1.5 mL) was added dropwise concentrated HNO_3 (0.5 mL). After 5 min, the solution was poured onto ice and treated with aqueous 20% NaOH until no further solid separated. The yellow solid had the same melting point (mp 202–203 °C (lit.[9] mp 203–204 °C)) and IR spectrum as an authentic sample of **3-nitroimidazo[1,2-*a*]pyridine (4).**

The mixture of compounds **1** and **3** was subjected to chromatography (C_6H_6); the process was repeated on fractions enriched in compound **3.** The material in the fraction showing greatest enrichment in compound **3** (^1H NMR) was treated with picric acid in absolute EtOH. The picrate, after three recrystallizations from large volumes of absolute EtOH, had mp 231–232.5 °C, undepressed on admixture with picrate of authentic compound **3.**

3-Methylimidazo[1,2-*a*]pyridine Picrate (3·picrate). A hot ethanolic solution (1 mL) of compound **3**[1b] (0.13 g, 1 mmol) was treated with picric acid (0.23 g, 1 mmol) in hot EtOH (2 mL). The picrate (92%) after three crystallizations from absolute EtOH (100 mL) had mp 231–233 °C.

Reaction of Compound 2 with Lithium Ethylamide. A dry three-neck flask, equipped with stirrer, a dry ice/acetone condenser filled with ice and NaCl and protected with Drierite, and a gas inlet tube, was flushed with N_2 and charged with anhydrous Et_2O (50 mL) which was then cooled in an ice–NaCl bath (−13 °C). $EtNH_2$ was passed into the Et_2O until the volume had increased by ca. 10 mL. The gas inlet tube was replaced by a septum through which ethereal MeLi (96 mL, 1.9 M) was injected with a syringe while the mixture was stirred and cooled (colorless solid separated). A solution of compound **2** (3.75 g, 19 mmol) in anhydrous Et_2O (75 mL) was added during 20 min (black solids separated) and stirring was continued for 40 min. Volatile materials were removed at room temperature in a stream of N_2, Et_2O (40 mL) was added, and the process was repeated. Et_2O (50 mL) was added, the mixture was cooled in ice, Ac_2O (25 mL) was added dropwise during 10 min, and the mixture was warmed to drive off the Et_2O and then heated on a steam bath overnight. The mixture was treated with H_2O (25 mL), heated 10 min, and stripped of solvents under reduced pressure. The residue was treated with H_2O, ice, and aqueous 20% NaOH to pH 8 to give a black solid from which the aqueous solution was decanted. $CHCl_3$ extraction (6 × 30 mL) of the solution gave a mixture containing large amounts of Ac_2NEt and AcNHEt (^1H NMR), which were removed by treating the mixture with 1 N HCl to pH 2 and continuously extracting with $CHCl_3$. The $CHCl_3$ extracts contained no aromatic materials (^1H NMR). The acidic solution was treated with aqueous 20% NaOH (ice) and extracted with $CHCl_3$ (5 × 25 mL). The black solid A was extracted with boiling $CHCl_3$ (2 × 25 mL) and these extracts were combined, dried, and subjected to chromatography ($CHCl_3$) which gave the parent compound **1** (0.8 g, 35%) and compound **5** contaminated with **1** (0.17 g). Fractional sublimation gave compound **5,** mass spectrum mol wt 239 and 241, which was converted into its picrate for analysis. After three recrystallizations from absolute EtOH, compound **5**·picrate had mp 209–210 °C dec.

Reaction of Compound 2 with Lithium Diethylamide. Dry Et_2NH in a three-neck flask equipped with a condenser (protected with Drierite) and stirrer was cooled in ice, stirred, and treated with a hexane solution of *n*-BuLi (15 mL, 2.4 M) followed by the addition during 10 min of a solution of compound **2** (2.96 g, 0.015 mol) in anhydrous Et_2O (75 mL). After 1 h the dark mixture was treated with HCl (15 mL, 2.4 M), heated on a steam bath, and stripped of solvents under reduced pressure. The $CHCl_3$ soluble portion of the residue was separated by chromatography ($CHCl_3$) into fractions I (compounds **7** and **2**), II (compounds **9, 1, 10,** and **8**), and III (compounds **8** and **10**). Fraction I was subjected to molecular distillation (80 °C (0.05 Torr)) followed by chromatography (C_6H_6) to give the liquid compound **7** which was converted into its picrate for analysis. After four recrystallizations from absolute EtOH, it had mp 117.5–118.5 °C.

Fraction II was further separated by chromatography (20% CH_3CN/C_6H_6) into fractions IV (compounds **9, 1,** and **10**), V (compounds **1** and **8**), and VI (compound **8**). Fraction VI was subjected to molecular distillation (110 °C (0.05 Torr)) and then became a waxy solid. Fraction V was fractionated by chromatography (5% CH_3CN/C_6H_6) into compounds **1** and **8.** The latter was converted into its picrate which after two recrystallizations from 90% EtOH had mp 217–218 °C.

Fraction IV was separated by chromatography (2.5% CH_3CN/C_6H_6) into mixtures and pure compounds **9** and **10.** Compound **9,** mass spectrum mol wt 189, was converted into its picrate, which after crystallization from EtOH had mp 176–177 °C. Compound **10,** mass spectrum mol wt 260, failed to give a crystalline picrate derivative.

The percent yields shown in Table II, derived from ^1H NMR

spectra and weight of the various fractions, are estimated to be within 10% of their actual values.

When the lithium diethylamide reaction was carried out at a lower temperature (−35 °C), TLC indicated that an equally complex mixture was formed.

Reaction of 3-Bromoimidazo[1,2-*a*]pyridine (2) with Potassium Amide. A. To liquid NH_3 (250 mL), stirred in a three-neck flask, equipped with a dry ice/acetone condenser protected with solid KOH pellets in a drying tube, was added K metal (ca. 0.2 g) and a small crystal of ferric nitrate hydrate. Further 0.50 g portions of K (total of 3.5 g, 0.09 mol) were added whenever the blue color faded. A solution of compound **2** (3.5 g, 0.018 mol) in anhydrous Et_2O (100 mL) was added dropwise during 30 min. The dark mixture was stirred for an additional 2 h. NH_4Cl (4.6 g, 0.087 mol) was added and the mixture was stirred overnight to evaporate NH_3. The Et_2O was evaporated on a steam bath in a stream of N_2. The residue was heated with Ac_2O (40 mL) for 2.5 h on a steam bath, cooled, treated with H_2O (40 mL), heated on the steam bath for 10 min, and stripped of solvents under reduced pressure. After the residue was dissolved in H_2O (50 mL), cooled in ice, and treated with aqueous 20% NaOH to pH 9, the precipitated black and colorless solids (A) (3.13 g) were filtered and rinsed with H_2O. The filtrate was saturated with NaCl and continuously extracted with $CHCl_3$ for 2 days to give a brown oil (1.0 g) which on sublimation (room temperature, 0.05 Torr) yielded acetamide (0.55 g). The residue (0.43 g) consisted of starting material (**2**), acetamide, and compound **14** (mass spectrum and TLC).

Extraction of the solids (A) with boiling $CHCl_3$ (6 × 35 mL) left an insoluble black powder (0.83 g), mp >310 °C, which could not be purified, showed amide absorption in the IR, and is believed to be polymeric. The residue of the $CHCl_3$ extracts was dissolved in EtOH, concentrated (15 mL), treated with H_2O (25 mL), cooled, and scratched to give a solid that was recrystallized (charcoal) from $EtOH/H_2O$ to give compound **14** (1.49 g) as fine colorless needles, mp 167.5–168 °C. The residue from the mother liquor gave a black $CHCl_3$-insoluble material (0.18 g). Chromatography on Silica of the $CHCl_3$-soluble portion gave diacetamide and compound **14** (0.05 g, 50% total) as the only identifiable solids.

B. A similar amination mixture was stirred for 5 h and worked up as above to give compound **14** as major product. Noncrystallizable, $CHCl_3$-soluble materials, on chromatography ($CHCl_3$), gave trace amounts that contained a substance with the same R_f as compound **19**. Elution with 2% absolute $EtOH/CHCl_3$ gave a mixture which, after treatment with charcoal in EtOH, crystallized from aqueous 30% EtOH as dense kernels (35 mg) and a powdery solid (90 mg) which were sorted by hand. The dense kernels, compound **26**, crystallized by dissolving in $EtOH/H_2O$ and evaporating the EtOH, had mp 289 °C, amide absorption in the IR, and mass spectrum mol wt 291 (later scans showed a contaminant, presumably a diacetamidodehydrodimer, with *m/e* ca. 348). Compound **26** had the same R_f (alumina, 2% $MeOH/CHCl_3$) as compound **14** but gave a brown color with I_2 whereas the latter gives a purple color. The powdery solid, on preparative TLC (silica gel, 15% $MeOH/CHCl_3$), contained three major components (11 lines), compounds **14** and **26**, and a compound with mass spectrum mol wt 175, mp 222 °C (softens 193 °C), whose IR spectrum showed amide absorption but differed from the spectra of the isomeric compounds **14** and **17–20**. No evidence was obtained for the presence of either compound **20** or **18**.

C. A similar reaction mixture (3.5 g K, no ferric nitrate, and 3.5 g of compound **2**) was stirred for 2.75 h prior to the NH_4Cl addition. The solvents were evaporated and the oily residue was extracted with $CHCl_3$. The insoluble portion was further extracted with $CHCl_3$ (Soxhlet) to give a semisolid (2.37 g total). Chromatography (2% absolute $EtOH/C_6H_6$) afforded compounds **1** (0.3 g, 10%) and **11** (0.25 g, 8%). Elution with 10% absolute $EtOH/C_6H_6$ gave a fraction of predominantly one material (0.35 g) which was treated with Ac_2O (1 mL) on a steam bath for 1 h, heated 10 min with H_2O (1 mL), and stripped of solvents. Addition of ice/water to the black residue, followed by aqueous 10% NaOH, gave compound **26** (0.27 g, 7%), mp >300 °C, which was purified by dissolution in MeOH, charcoal treatment, and boiling down to the beginning of crystal formation. Three crystallizations afforded an analytical sample.

Formation of 5,5′-Biimidazo[1,2-*a*]pyridyl (11) from Imidazo[1,2-*a*]pyridine (1). To KNH_2 (1.8 g K, 45 mmol; a crystal of ferric nitrate hydrate) in liquid NH_3 (100 mL) was added dropwise with stirring a solution of compound **1** (2.0 g, 17 mmol) in anhydrous Et_2O (30 mL) during 0.5 h. After 5 h, NH_4Cl (2.5 g, 49 mmol) was added and the solvents were evaporated. The residue was heated on a steam bath for 2.5 h with Ac_2O (25 mL) and was then treated with H_2O (25 mL) and stripped of solvents. The residue was treated with H_2O (20 mL) and aqueous 10% NaOH to pH 9–10. The solution was decanted from a dark gum and both were extracted with $CHCl_3$. The $CHCl_3$-insoluble portion of the gum (0.87 g) could not be purified. The $CHCl_3$ extracts were stripped of solvent and the residue was extracted with C_6H_6. Chromatography ($CHCl_3/C_6H_6$ mixtures) of the extract gave compounds **1** (0.20 g) and **11** (0.22 g, 12%). Compound **11** was triturated with C_6H_6, dissolved in EtOH, and treated with charcoal. Water (2.5 mL) was added and the solution was boiled down to crystal formation. After another $EtOH/H_2O$ treatment followed by sublimation (150 °C (0.25 Torr)), compound **11** had mp 247.5–249 °C, mass spectrum mol wt 234. The C_6H_6 insoluble portion on chromatography ($CHCl_3$) gave compound **11** (0.05 g, 15% total) and a small amount of material, mp >310 °C, mass spectrum mol wt 466, and IR spectrum similar to that of compound **11**.

Reaction of the Dehydrodimer (11) with Potassium Amide. A mixture of KNH_2 (0.32 g K, 8 mmol), liquid NH_3 (30 mL), Et_2O (10 mL), and compound **11** (0.12 g, 0.5 mmol) was stirred for 4 h. The reaction was quenched with NH_4Cl (0.47 g, 8.8 mmol) and solvents were evaporated to give an orange residue that was extracted with hot $CHCl_3$ (5 × 8 mL). TLC (alumina, 10% absolute $EtOH/CHCl_3$) indicated the presence of much starting material and three other components, R_f 0.55, 0.75, and 0.85. The major components of the chromatogram fraction from which the acetamidodehydrodimer (**26**) had been obtained in the reaction of KNH_2 with compound **2** (see part C, above) had R_f 0.55. Evaporation of $CHCl_3$ gave a residue (0.11 g) which was treated with Ac_2O (0.5 mL) on a steam bath for 1 h. Addition of H_2O (1 mL) and evaporation under reduced pressure gave a thick oil that was treated with H_2O (5 mL) and aqueous 10% NaOH to pH 10, followed by extraction with $CHCl_3$ (3 × 5 mL). TLC (alumina, $CHCl_3$) indicated the presence of compound **11** and three components, R_f 0.10, 0.25, and 0.40. The acetamidodehydrodimer (**26**) obtained from compound **2** had R_f 0.25.

3,3′-Dinitro-5,5′-biimidazo[1,2-*a*]pyridyl (25). Compound **11** was dissolved in ice-cold concentrated H_2SO_4 (0.80 mL) and concentrated HNO_3 (0.3 mL) was added dropwise with stirring. The pale yellow solution was left to stand at room temperature for 30 min and then poured onto ice (10 g) and partially neutralized with aqueous 20% NaOH (pH ca. 2). The yellow solid was filtered, rinsed with H_2O, and dried at 60 °C (0.25 Torr) to give compound **25** (0.12 g, 96%): mp darkens >150 °C and explodes at 205 °C with formation of a purple solid; calcd mol wt 324; mass spectrum mol wt 279 (324 + H − NO_2). An analytical sample was obtained as fine yellow needles from 1,2-dimethoxyethane.

3,3′-Dinitro-7-acetamido-5,5′-biimidazo[1,2-*a*]pyridyl (27). After compound **26**, (70 mg, 0.24 mmol) was dissolved in chilled concentrated H_2SO_4 (0.7 mL), concentrated HNO_3 (0.3 mL) was added dropwise with stirring. The solution was left to stand at room temperature for 40 min and ice and aqueous 20% NaOH were added until precipitation was complete (pH 1–2). Filtration and rinsing with H_2O gave a yellow powder (90 mg, 98%), mp 85 °C dec. On attempted crystallization from EtOH, the material partially decomposed.

3-Nitro-8-acetamidoimidazo[1,2-*a*]pyridine (32), prepared as above from compound **18**, was recrystallized three times from absolute EtOH to give an analytical sample as fine yellow needles, mp 222.5–223.5 °C (no dec, changes to kernels >210 °C).

3-Nitro-5-methylimidazo[1,2-*a*]pyridine (31). To a chilled solution of 5-methylimidazo[1,2-*a*]pyridine[29] (0.50 g, 3.8 mmol) in concentrated H_2SO_4 (4.0 mL) was added dropwise concentrated HNO_3 (1.0 mL) with stirring. The solution was stirred for 25 min at room temperature, poured onto ice, and partially neutralized with solid NaOH, to give a brown powder (0.20 g), which was dissolved in 1,2-dimethoxyethane (15 mL), treated with charcoal, filtered, and concentrated (2 mL) to yield sturdy yellow needles, mp 115–116 °C, soluble in most solvents, including H_2O from which it can be crystallized. An analytical sample, twice crystallized from hexane, and then sublimed rapidly (100 °C/0.25 Torr), was obtained as fine yellow needles,[30] mp 115.9–117.2 °C.

2,5-Diaminopyridine. A mixture of 5-nitro-2-aminopyridine[31] (2.8 g, 20 mmol), EtOH (25 mL), and 10% Pd/C was hydrogenated in a Paar shaker (initial pressure 49 psi) for 2 days, filtered through Celite, concentrated to dryness under reduced pressure, and dried (room temperature, 0.25 Torr) to give 2,5-diaminopyridine as a purple solid, mp 95–98 °C (lit.[32] mp 108–110 °C).

6-Acetamidoimidazo[1,2-*a*]pyridine (14). A mixture of H_2O (20 mL), concentrated HCl (1.0 mL) and ethyl 2-bromoacetal (5.5 g, 28 mmol) was refluxed for 1.5 h, cooled, and treated with $NaHCO_3$ (5.5 g, 65 mmol) followed by all of the 2,5-diaminopyridine (prepared above) dissolved in H_2O (15 mL). At once a dark solid separated and CO_2 was evolved. After the mixture was refluxed for 20 h, then cooled, a black solid was filtered and discarded. The filtrate was saturated with NaCl and extracted with $CHCl_3$ (5×). After drying, the extract

was stripped of solvent to give a light brown solid (1.1 g, 41%) which rapidly turned green and could be sublimed (140 °C (0.25 Torr)) to give colorless needles that turned green on exposure to air and had mp ~110–117 °C dec. To all of the material was added Ac_2O (5 mL). Before all had dissolved, another colorless material separated. The mixture was briefly heated on a steam bath to effect solution and was then chilled over ice. The precipitate was filtered, rinsed with Ac_2O and acetone, and identified to be the acetic acid salt of compound **14** (1.27 g, 65%) by its IR spectrum. The solid was dissolved in H_2O (5 mL) and treated with aqueous 10% NaOH to pH 10. The precipitated nearly colorless compound **14** was purified by dissolution in EtOH (10 mL), treatment with charcoal, addition of H_2O (6 mL), and boiling down (8 mL). Sublimation (160–180 °C (0.25 Torr)) afforded an analytical sample, mp 168–170 °C dec.

5-Acetamidoimidazo[1,2-*a*]pyridine (17). 5-Aminoimidazo[1,2-*a*]pyridine, was sublimed (150 °C (0.1 Torr)) to give off-white crystals. On standing it turned dark and was black after several weeks. Freshly sublimed compound (0.29 g) was heated with Ac_2O (1.25 mL) on a steam bath for 0.5 h then treated with H_2O (1.5 mL), heated for 5 min, and stripped of solvents under reduced pressure. Addition of H_2O (1 mL) and aqueous 10% NaOH to pH 9–10 gave a solid (0.35 g, 92%) which was dissolved in EtOH (10 mL), treated with charcoal, and filtered. Addition of H_2O (5 mL) and concentrating the solution (5 mL) gave long colorless needles, which were sublimed (140 °C (0.1 Torr)) to give an analytical sample, mp 146.5–147 °C.

8-Acetamidoimidazo[1,2-*a*]pyridine (18) was prepared by Paudler and Blewitt's[1b] general method of refluxing a solution of ethyl 2-bromoacetal (5.5 g, 28 mmol) in pure dioxane (15 mL), H_2O (4 mL), and concentrated HCl (0.4 mL) for 0.5 h, cooling, adding $NaHCO_3$ (5.5 g, 65 mmol), followed by 2,3-diaminopyridine (2.2 g, 20 mmol), refluxing for 12 h, cooling, making basic with aqueous 10% NaOH (pH 10), and extracting with $CHCl_3$ (4 × 25 mL). The extract was decanted from a dark oil, dried, filtered through Celite, and stripped of solvent to give a viscous dark oil (2.7 g). An Ac_2O solution (10 mL) of the crude product was refluxed for 45 min, cooled, treated with H_2O (10 mL), boiled for 10 min, stripped of solvents, and treated with H_2O and aqueous 10% NaOH (to pH 9) to give nearly colorless compound **18** (2.6 g, 74%). It was purified by dissolution in EtOH (30 mL), treatment with charcoal, addition of H_2O (20 mL), and boiling down (25 mL). Sublimation gave an analytical sample as sturdy crystals, mp 144–145 °C.

2-Acetamidoimidazo[1,2-*a*]pyridine (19), prepared according to Bristow[21] and recrystallized from absolute EtOH, had mp 228–229 °C (lit.[21] mp 229 °C).

3-Acetamidoimidazo[1,2-*a*]pyridine (20), mp 196–197 °C (lit.[9] mp 197 °C), was prepared according to Paolini and Robins,[9] except that 3-nitroimidazo[1,2-*a*]pyridine was reduced to 3-aminoimidazo[1,2-*a*]pyridine in the presence of Pd/C in lieu of Raney Ni.

2-Methylimidazo[1,2-*a*]pyridine was prepared according to Paudler and Blewitt.[1]

6-Bromoimidazo[1,2-*a*]pyridine, 33, prepared in 65% yield by the general method[1] of refluxing an aqueous EtOH solution of 5-bromo-2-aminopyridine[33] with bromoacetaldehyde, was purified by chromatography (50% $C_6H_6/CHCl_3$). Sublimation (80 °C (0.05 Torr)) gave an anlytical sample, mp 78.5–80 °C (lit.[28b] mp 53–55 °C).

Registry No.—**3** picrate, 66358-17-6; **5** picrate, 66358-18-7; **7** picrate, 66358-19-8; **8** picrate, 66358-20-1; **9** picrate, 66358-21-2; **26,** 66358-22-3; ethyl 2-bromoacetal, 2032-35-1; 2-aminopyridine, 504-29-0; lithium ethylamide, 50835-31-9; lithium diethylamide, 816-43-3; 2,5-diaminopyridine, 4318-76-7; 5-nitro-2-aminopyridine, 4214-76-0; 5-aminoimidazo[1,2-*a*]pyridine, 66358-23-4; 2,3-diaminopyridine, 452-58-4; 5-bromo-2-aminopyridine, 1072-97-5.

References and Notes

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(12) Unpublished results.
(13) The major aspects of this work were presented at the ACS Meeting in Miniature, Tuscaloosa, Ala., 1974.
(14) A slight preponderance of compound **3** was present in the mixture obtained with CH_3Li.
(15) This type of reaction is frequently employed in the preparation of organolithium compounds. See, for example, "Organic Reactions", Vol. VI, R. Adams, Ed., Wiley, New York, N.Y., 1951, p 339.
(16) Coupling is frequently observed especially with long reaction times, during halogen–lithium exchange reactions. See ref 15 and W. Langham, R. Q. Brewster, and H. Gilman, *J. Am. Chem. Soc.*, **63**, 545 (1941).
(17) See, for example, C. G. Screttas and J. F. Eastham, *J. Am. Chem., Soc.*, **88**, 5668 (1966), and references therein.
(18) T. Kauffmann and R. Wirthwein, *Angew. Chem., Int. Ed. Engl.*, **10**, 20, (1971), state that such dehalogenation tends to occur as a side reaction when hetaryl bromides (or iodides) are treated with relatively bulky aminolithium compounds. Debromination can, however, also occur with KNH_2; see A. P. Kroon and H. C. van der Plas, *Recl. Trav. Chim. Pays-Bas*, **93**, 227 (1974).
(19) Compound **10** was not analyzed.
(20) Analogous products may well have been formed in the preceding reaction where identification of other products could not be achieved since these were either gums or glasses and/or discolored or rearranged on standing.
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(34) Of a number of other mechanisms we had considered, the one (also suggested by a reviewer) involving attack by a second $^-NH_2$ on **21** was rejected in view of the formation of the 8-NEt_2 compound (**7**). If a self-consistent mechanism is to obtain for these $^-NR_2$ reactions, the σ complex initially formed by addition to C-7 then yields **23** in which attack by another bulky NEt_2 moiety at C-8 is severely hindered by the C-7 NEt_2 group and the peri lone pair of electrons on N-1. Such constraints are absent in the postulated intramolecular aziridine formation.