These results suggest that the organoantimony catalysts may activate 1; the cyclic mechanism shown in Scheme II is suggested.

Experimental Section

General Methods. IR spectra were recorded on a Hitachi EPI-G2 spectrophotometer and ^1H NMR spectra on a JEOL Model PS-100 spectrometer with tetramethylsilane as an internal standard. Gas chromatographic analyses (GC) were performed on a Shimadzu GC-4BT gas chromatograph with a FID detector connected to an Apiezon L grease coated 30 m × 0.25 mm capillary column.

Materials. The organoantimony compounds used as catalysts, pentaphenylantimony (**4a**),[15] tetraphenylstibonium bromide (**4b**),[16] triphenylantimony dichloride and dibromide (**4c** and **4d**),[17] trimethylantimony dibromide (**4e**),[18] triphenylstibine oxide (**4f**),[19] triphenylstibine (**4g**),[20] and chlorodiphenylstibine (**4h**),[21] were prepared from commercial $SbCl_3$ as reported in the literature and confirmed by elemental analysis.

Epoxides **2a-d** were purrified and dried by the general procedure.

Reaction of 1 with 2. (a) General Reaction Procedure. Measured quantities of **2b** and the catalyst were placed in a 100-mL, stainless-steel autoclave, and **1** was then introduced under a pressure of ca. 50 kg/cm^2. After the pressure in the autoclave fell to a constant value, the reaction was discontinued by cooling and decompression of the autoclave. The crude reaction product was found to consist of **3b** and the catalyst from the results of ^1H NMR, GC, and IR. Catalysts **4b-e** could be recovered in good yields. Fractional distillation under reduced pressure was necessary for the runs of **2c** and **2d** because of their high boiling points, and in the case of **2d**, a poly(styrene oxide)[22a] was obtained from the distillation residue.

(b) Preheated Reactions. After a mixture of measured quantities of **2b** and the catalyst sealed in a glass ampule was heated at 120 °C for 2 h, the ampule was placed in the autoclave, and **1** was then introduced. The reaction was then carried out as described in part a.

Ring-Opening Polymerization of 2b and 2d. The homopolymerizations of **2b** and **2d** were carried out in the autoclave at 120 °C or in a glass ampule at 80 °C. The polymers obtained were purified by reprecipitation (benzene/ether) and identified as poly(propylene oxide) and poly(styrene oxide), respectively, by their IR spectra.[22]

Measurements of Lewis Acid Strength. (a) Measurement with Hammett Indicator.[11c,12b] To 1-5 wt % solution of organoantimony compounds in benzene was added 1 drop of a 0.1 wt % solution of indicators in benzene, and the color change of the indicators was observed.

(b) Measurement with IR Spectra.[12c] According to the method reported in the literature, an attempt was made to observe the lower wavenumber shift of $\nu_{C=O}$ of xanthone caused by complexation with organoantimony compounds, but no shift was detected.

Registry No. **1**, 124-38-9; **2a**, 75-21-8; **2b**, 75-56-9; poly-**2b**, 25322-69-4; **2c**, 106-89-8; **2d**, 96-09-3; poly-**2d**, 25189-69-9; **3a**, 96-49-1; **3b**, 108-32-7; **3c**, 2463-45-8; **3d**, 4427-92-3; **4a**, 2170-05-0; **4b**, 21450-52-2; **4c**, 594-31-0; **4d**, 1538-59-6; **4e**, 5835-64-3; **4f**, 4756-75-6; **4g**, 603-36-1; **4h**, 2629-47-2; $SbCl_3$, 10025-91-9.

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(17) (a) A. Michaelis and A. Reese, *Justus Liebigs Ann. Chem.*, **233**, 50 (1886); (b) P. Pfeiffer, *Ber. Dtsch. Chem. Ges.*, **37**, 4621 (1904).
(18) H. Hibert, *Ber. Dtsch. Chem. Ges.*, **39**, 160 (1906).
(19) D. L. Venezky, C. W. Sink, B. A. Nevett, and W. F. Fortescue, *J. Organomet. Chem.*, **35**, 131 (1972).
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(21) Netherlands Patent 6 505 216 (1965); *Chem. Abstr.*, **64**, 9766d (1966).
(22) (a) A. Kawasaki, J. Furukawa, T. Tsuruta, T. Saegusa, and G. Kakogawa, *Kogyo Kagaku Zasshi*, **63**, 871 (1960); (b) J. Furukawa, T. Tsuruta, R. Sakata, and T. Saegusa, *Makromol. Chem.*, **32**, 90 (1959).

Reaction of 3-Substituted Imidazo[1,2-*a*]pyridines with Br^+ and the Alleged 5-Bromo-Substituted Product

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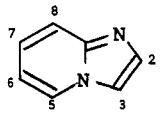
The reaction of 3-methylimidazo[1,2-*a*]pyridine with NBS was reinvestigated and is shown to give products formed by apparent *nucleophilic* substitution at the 2-position. NBS in $CHCl_3$ gave compounds **4** and **6**, while NBS in CCl_4 or Br_2 in $CHCl_3$ gave exclusively **4**. Mechanisms and differences in product formation are discussed; evidence that the previously reported NBS product was in fact 3-bromo-5-methylimidazo[1,2-*a*]pyridine, rather than the alleged 5-bromo-3-methyl derivative **3**, is presented. Compound **3** was prepared by diazotization of 5-amino-3-methylimidazo[1,2-*a*]pyridine in the presence of HBr and by condensation of 2-bromopropanal (or its acetal) with 2-amino-6-bromopyridine (**12**). This latter reaction of the weakly basic aminopyridine **12** is shown to follow the normal pattern in which the amino nitrogen condenses with the carbonyl carbon. Structures are established by infrared, mass, and ^1H NMR spectral analyses, mechanistic considerations, and diagnostic reactions. Experimental and computer-generated ^1H NMR spectra of compounds **3** and **13** are reproduced.

Electrophilic reagents react preferentially with the five-membered ring of imidazo[1,2-*a*]pyridines (**1**). Among



1

the numerous electrophilic reactions which usually lead to exclusive substitution at the 3-position are halogenation,[1,2] nitration,[1,2] nitrosation,[1] condensation with aldehydes,[3] H/D exchange,[1] and the Mannich reaction.[1]

In contrast, conflicting data are reported in the literature for the few known reactions of imidazo[1,2-*a*]pyridines in

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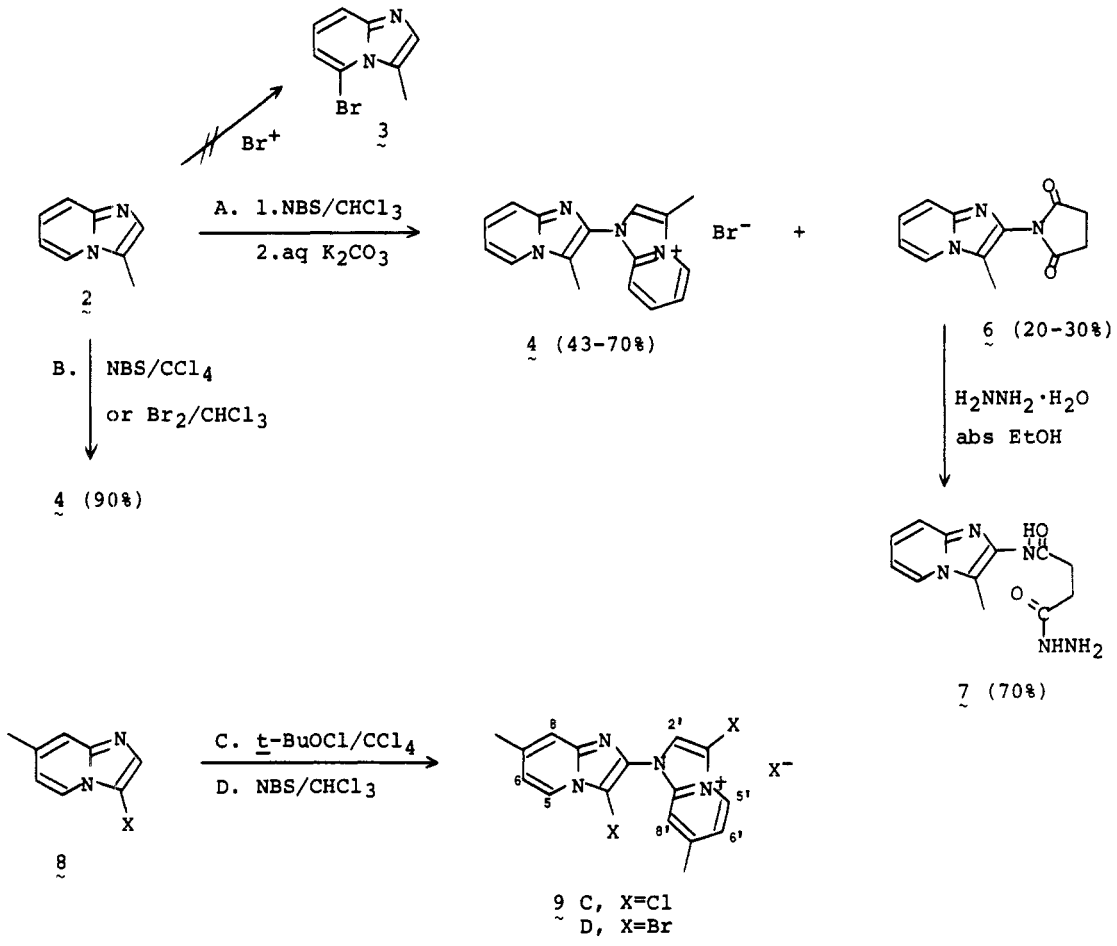
(2) Jacquier, R.; Lopez, H.; Maury, G. *J. Heterocycl. Chem.* **1973**, *10*, 755.
(3) Hand, E. S.; Paudler, W. W.; Zachow, S. *J. Org. Chem.* **1977**, *42*, 3377.

0022-3263/80/1945-3738$01.00/0

Scheme I



which the 3-position is blocked. On the one hand, bromination of 3-methylimidazo[1,2-a]pyridine (2) is reported[4] to occur in the π-deficient pyridine ring to give the 5-bromo derivative 3. Elemental analysis and the ^1H NMR spectrum appeared to support this structure. To the extent that frontier electron-density calculations can be used as indices of reactivity, this substitution was in accord with these calculations.[5] On the other hand, several reactions of electrophiles with 3-substituted imidazo[1,2-a]pyridines, which give products not involving the pyridine ring, are known: a 3-NO group has been replaced by bromine[6] and a 3-bromo substituent undergoes electrophilic substitution with introduction of selenium into the 3-position[7] whereas 3-halo compounds react with t-BuOCl or NBS to give 2-substituted products[8] (see Scheme I, 8 → 9). These products (9) are believed to arise via electrophilic reaction of Cl^+ or Br^+ at N-1 followed by nucleophilic attack at C-2. Thus, the generally high reactivity toward electrophiles of the π-excessive five-membered ring was observed here also.

The anomalous reaction of 3-methylimidazo[1,2-a]-pyridine with NBS was therefore reinvestigated.

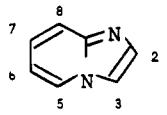
Results and Discussion

The reaction of compound 2 with NBS was carried out under the reported conditions.[4] Since it is known that the history of the NBS can affect the course of the reaction,[9] several different preparations of this reagent were used. In none of these reactions could any evidence for the formation of 5-bromo-3-methylimidazo[1,2-a]pyridine be obtained. Instead, reaction occurred at the 2-position with the formation of the succinimido and imidazopyridinium derivatives 6 and 4 (see Scheme I, A). [Trace amounts (<2%) of 3-bromoimidazo[1,2-a]pyridine (5) were also isolated and shown to arise from contamination of the 3-methyl compound 2 by the parent compound 1 (GC retention times and GC/MS). The source of the contaminant is not known.] Workup by chromatography on Florisil afforded only the succinimido compound 6 (and 5), and chromatography on alumina gave only the pyridinium compound 4 (and 5), although ^1H NMR spectra of the reaction products prior to chromatography showed the presence of both compounds 4 and 6. Since on percolating pure succinimido compound 6 through alumina only 25% was recovered, it is believed that alumina-catalyzed hydrolysis of compound 6 to the amido acid occurred.

The structure of compound 6 was established as follows. The presence of the succinimido group was confirmed by cleavage with hydrazine to give the derivative 7, $C_{12}H_{15}O_2N_5$. ^1H NMR spectra show the characteristic pattern of 2,3-disubstituted imidazo[1,2-a]pyridines (see Table I for compound 6 in $CDCl_3$ and the Experimental Section for 7 in Me_2SO). Mass spectra are readily interpreted in terms of these structures. Major m/e peaks correspond to fragmentation of the substituents. The molecular ion of 6 (m/e 229) is the base peak. Compound 7 gives the

(4) Paolini, J. P.; Robins, R. K. *J. Org. Chem.* **1965**, *30*, 4085.
(5) Paudler, W. W.; Blewitt, H. L. *J. Org. Chem.* **1965**, *30*, 4081.
(6) Matveev, V. K. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1936**, 1005; *Chem. Abstr.* **1937**, *31*, 5364.
(7) Hand, E. S.; Paudler, W. W. *J. Org. Chem.* **1975**, *40*, 2916.
(8) Hand, E. S.; Paudler, W. W. *J. Org. Chem.* **1976**, *41*, 3549.
(9) Horner, L.; Winkelmann, E. H. In "Newer Methods of Preparative Organic Chemistry"; W. Foerst, Ed.; Academic Press: New York, 1964; Vol 3, p 151.

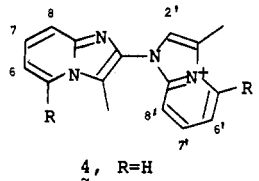
Table I. ^{1}H NMR Shifts (ppm)[a] of Imidazo[1,2-*a*]pyridines in $CDCl_3$



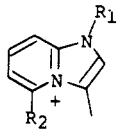
	H-2	H-3	H-5	H-6	H-7	H-8	CH_3
parent (1)	7.60	7.67	8.16	6.75	7.15	7.70	
3-CH_3 (2)	7.40		7.84	6.80	7.11	7.58	2.50
3-CH_3, 5-Br[b] (3)	7.32			6.89	6.86	7.48	2.85
2-CH_3		7.27	7.97	6.64	7.04	7.48	2.42
2-CH_3, 5-Br[b] (13)		7.535		6.948	7.01	7.49	2.49
3-Br, 5-CH_3 (15)	7.49			6.48	7.01	7.43	3.03
Br, CH_3[c]	7.50			6.45	7.00	7.43	?
3-CH_3, 2-S[d] (6)			7.83	6.84	7.16	7.55	2.34
3-CH_3, 5-NH_2[e] (11)	7.14			5.80	6.93[f]		2.85

[a] Relative to internal Me_4Si. Assignments, often possible on the basis of multiplicities alone since $J_{7,8} > J_{6,7} \approx J_{5,6} >> J_{6,8}$, are in accord with peak areas, coupling constants, and chemical shifts of related compounds. [b] The shifts of the aromatic protons are those used in spectra simulated for 0.31 M solutions. Coupling constants (hertz) for **3**, $J_{7,8} = 8.5$, $J_{6,7} = 7$, $J_{6,8} = 1.5$, $J_{2,8} = J_{2,7} = J_{2,6} = 0$, and $J_{2,CH_3} = 0.8$; for **13**, $J_{7,8} = 8.5$, $J_{6,7} = 7.2$, $J_{6,8} = 1.3$, $J_{3,8} = 0.9$, $J_{3,7} = J_{3,6} = 0$, and $J_{3,CH_3} = 0.8$. [c] lit.[4] mp 84–85 °C. [d] S = succinimido; $\delta_{CH_2CH_2}$ 2.93. [e] δ_{NH_2} 4.5 (br). [f] Approximate center of multiplet.

Table II. ^{1}H NMR Shifts (ppm) of Imidazo[1,2-*a*]pyridinium Salts



4, R=H
14, R=Br



10, R_1=CH_3, R_2=H
3·HBr, R_1=H, R_2=Br

	atom									
compd	2	5	6	7	8	2′	5′	6′	7′	8′
					D_2O[a]					
4		8.20	7.13	7.35–7.92		8.07	8.74	7.35–7.92		8.10
9C[b]		8.25	7.14		7.37	8.50	8.75	7.73		7.97
10						7.72	8.53	7.74	7.98	
					Me_2SO-d_6[c]					
14B-D			7.2–7.4		7.65	8.46		7.8–8.0[d]		
3	7.78		7.35–7.55		7.70					
3·HBr						8.10		7.65–8.0		

[a] Relative to the sodium salt of 4,4-dimethyl-4-silapentanesulfonic acid. [b] For structure and numbering see Scheme I. [c] Relative to internal Me_4Si. [d] Most of the absorption appears as a singlet at δ 7.90.

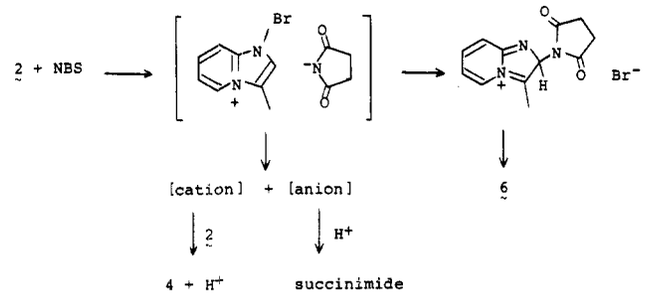
same *m/e* peak (46%, loss of H_2NNH_2) as well as *m/e* 230 (34%) and 261 (21%, molecular ion). The base peaks of **7**, *m/e* 147 and 146, correspond to the radical cation of 2-amino-3-methylimidazo[1,2-*a*]pyridine and the ion formed from this by loss of a hydrogen atom. Major peaks at *m/e* 78 ($C_5H_4N^+$), characteristically observed for imidazopyridines unsubstituted in the six-membered ring, are present in the spectra of both compounds.

Compound **4** was isolated in 43–70% yield, depending on the workup conditions, and is the only product formed (90%) under somewhat different conditions (see Scheme I, B). Elemental analysis ($C_{16}H_{15}N_4Br$) indicates the presence of two methylimidazopyridine moieties per bromine atom. The "dimeric" cation (*m/e* 263) is observable in the mass spectrum, and the major fragments (*m/e* 132 and 131) are those expected from C_2–N_1' bond cleavage. Facile displacement of bromide by picrate ion with formation of a dipicrate, $(C_{16}H_{16}N_4)^{2+}(C_6H_2N_3O_7^-)_2$, supports the structural assignment. The ^{1}H NMR spectrum (see Table II) of compound **4**, too complex for complete analysis, is in accord with this structure. Those signals which do not overlap have chemical shifts and splitting patterns similar to the signals of the corresponding protons in the model compounds **10** and **9C** (D_2O). The structure of **9C**, established in part by chemical degradation, is known to contain the C_2–N_1' linkage.[8] Chemical shifts of each of the seven different aromatic protons of **9C** are readily established since the signals are well-separated. In compound **4**, however, the absence of the 7-CH_3 substituents not only introduces two more aromatic protons but also causes downfield shifts of H-8 and H-8′ and consequent overlap of the signals attributable to protons 6′, 7, 7′, and 8. The usual upfield shift of H-2 when a 3-halo substituent is replaced by a CH_3 group is observed: H-2′ resonates at higher field in compound **4** than in **9C**.

The course of the reaction with NBS is best explained in terms of an ionic mechanism. The succinimido compound **6** is most likely formed by reaction of an initially formed ion pair (see below) since the product ratio (**6**/**4**) is unaffected by the presence of succinimide (3 equiv); i.e., this neutral species is not involved in the reaction. When separation of the ion pair occurs, the anion reacts with a proton (pK_a = 9.6 for succinimide → anion, in water),[10] and the cation reacts with compound **2** to give the "dimeric" product **4** (Scheme II).

(10) Walton, H. F.; Schilt, A. A. *J. Am. Chem. Soc.* **1952**, *74*, 4995.

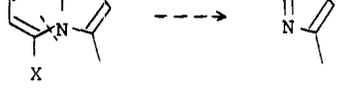
Scheme II



In the nonpolar solvent CCl_4, compound **4** is formed exclusively. The difference in product formation can be attributed to the low solubility of NBS in CCl_4. N-Bromination thus may well occur on the crystal surface of NBS. In this event, the succinimide anion is expected to be less mobile and of lower energy than in the ion pair. Also, more extensive aggregate formation of compound **2** in CCl_4 than in $CHCl_3$ increases the probability of encounter of the nucleophile **2** with the *N*-bromo cation.

Failure to obtain 5-bromo-3-methylimidazo[1,2-*a*]pyridine from compound **2** with our preparations of NBS placed some doubt on the correctness of the alleged structure **3**. In order to compare the reported properties[4] with those of an authentic sample, we carried out the synthesis of compound **3** by two alternate approaches: introduction of bromine by diazotization in the presence of HBr of the amino group in 3-methyl-5-aminoimidazo[1,2-*a*]pyridine (**11**) (prepared by condensing 2,6-diaminopyridine with 2-bromopropanal) and formation of the substituted imidazo ring from the pyridine moiety already bearing the bromine atom (see Scheme III). Both types of reaction afforded a compound, $C_8H_7N_2Br$, which has structure **3** (vide infra) and differs from the reported compound. The reactions and their ambiguities as well as the definitive proof of structure **3** and the probable structure of the reported compound are discussed in turn.

Although the amino group of 2-aminopyridine can be replaced with bromine only when concentrated $NaNO_2$/HBr solutions are employed,[11] 5-amino-3-methylimidazo[1,2-*a*]pyridine (**11**) yields ca. 10% of 5-bromo-3-methylimidazo[1,2-*a*]pyridine (**3**) in either concentrated or dilute solution. The ambiguity of the structure of the product in this reaction arises because of a possible Dimroth rearrangement, hitherto observed in imidazo[1,2-*a*]pyridines only when the pyridine ring bears the strongly electron-withdrawing nitro substituent and under alkaline conditions.[2] For other polyazaindenes, however, examples of rearrangement under acidic conditions are known.[12] Such a rearrangement, in which the N_4–C_5 bond is cleaved and a new bond is formed between C_5 and N_1, would lead to the isomeric 2-methyl-5-bromoimidazo[1,2-*a*]pyridine.



Condensation of 2-aminopyridines with α-halo aldehydes or ketones in the presence of $NaHCO_3$ is the most widely used, generally excellent method of forming imidazo[1,2-*a*]pyridines.[1] The reaction can be viewed as an initial displacement of halide by the pyridine N atom, followed by cyclization and dehydration. Condensation of 6-bromo-2-aminopyridine (**12**) with 2-bromopropanal is thus expected to, and does in fact, give the desired 3-methyl-5-bromo compound **3** (see Scheme IV, path a). Experimentally, this particular reaction is complicated by side reaction(s) of 2-bromopropanal[13] but can be forced to go to completion by repeated addition of bromopropanal. Complete reaction was desirable since simple purification methods (chromatography, sublimation, crystallization) failed to give pure product. Heterogeneous reactions in water at room temperature gave much better yields than a homogeneous reaction in refluxing 70% ethanol.

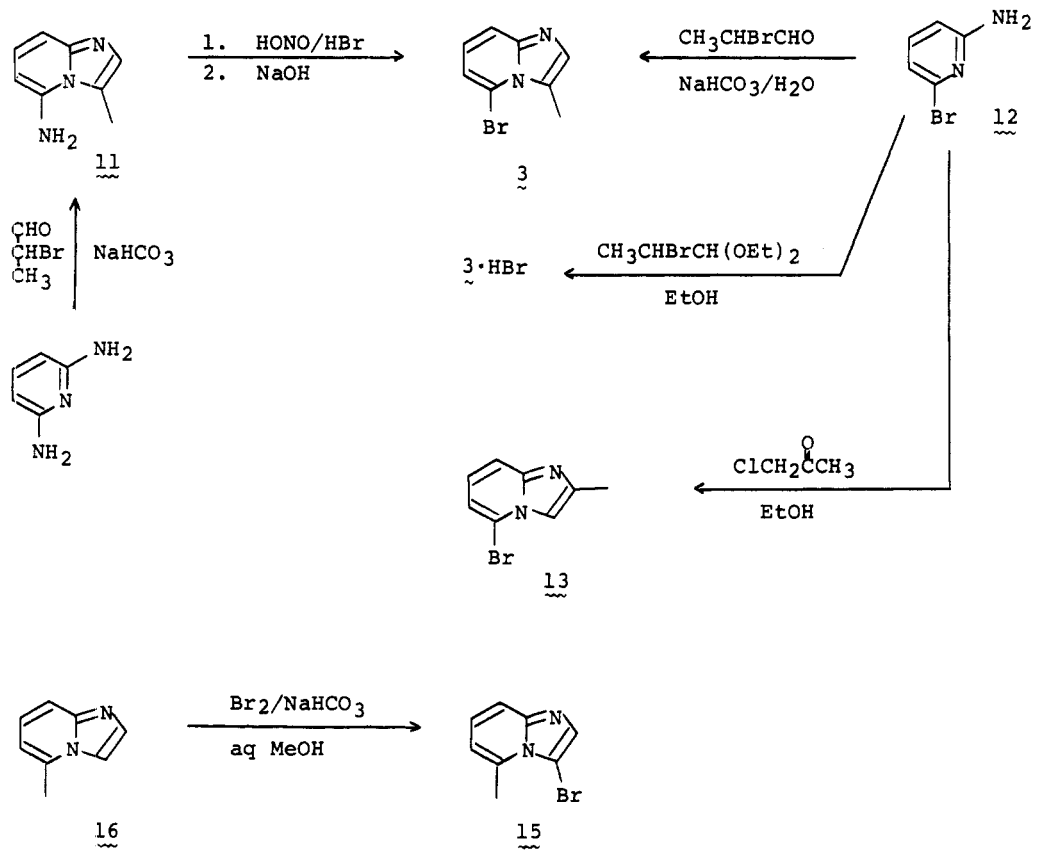
Quantitative formation of compound **3** can be achieved by treating 6-bromo-2-aminopyridine with the ethyl acetal of 2-bromopropanal in refluxing ethanol. The product, $C_8H_8N_2Br$ (**3**·HBr), crystallizes from the solution. Neutralization with NaOH yields the free base **3**. [Partial neutralization gives the insoluble double salt, $C_{16}H_{17}N_4Br_3O$, $(\mathbf{3})_2$·HBr·H_2O.]

As in the diazotization, the position of the methyl group in the product is again not definitively established. Although those reported reactions for which the structure of the product was carefully determined[15] are best explained by the sequence shown as path a in Scheme IV (or by initial condensation of the amine with the aldehyde group), the possibility of reaction via the undocumented path b exists. Considerations of steric requirements and pK_a relationships seem to support this possibility. For example, 2-aminopyridine (protonated form) has a pK_a = 6.86[16] whereas 6-bromo-2-aminopyridine (**12**) has a pK_a = 2.6.[17] The base strength of the pyridine N atom (at which protonation occurs) is thus considerably weakened by the presence of the bromine atom. Displacement of the hindered halide of 2-bromopropanal by the weakly basic, hindered pyridine N atom of compound **12** might well be less favorable than displacement by the amino N atom. In this event, the 2-substituted product **13** would be formed. This compound, 2-methyl-5-bromoimidazo[1,2-*a*]pyridine (vide infra), was obtained when 2-amino-6-bromopyridine was treated with chloroacetone. Thus, here also, the pyridine N atom displaces the halide. Compound **13** discolored on being allowed to stand briefly and was analyzed as its picrate, $C_{14}H_{10}N_5BrO_7$.

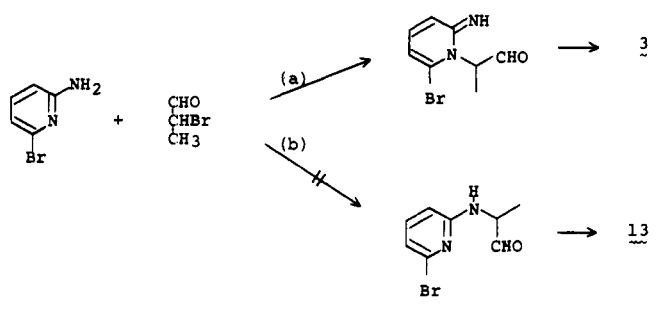
The orientations of the methyl groups in compounds **3** and **13** were established by the type of product(s) formed when compound **3** is treated with bromine in $CHCl_3$. As with other 3-substituted imidazo[1,2-*a*]pyridines, "dimer" formation is observed. Depending on whether and/or how the initially formed product was purified, four different compounds were isolated. As shown by infrared and ^1H NMR spectra, facile interconversion (see Scheme V), and elemental analyses,[22] the same "dimeric" cation **14** is present in each, and the differences are due to variations in the gegenion and/or protonation of the uncharged ring. The initially formed product is compound **14A** which on drying in vacuo loses HBr_3 to give **14B**. On attempted crystallization from ethanol, A loses 2 mol of bromine to give **14C**. **14C** is also formed from **14B** by heating with ethanolic HBr. Crystallization of **14C** from water or percolation through alumina causes loss of HBr to give

(11) Markwald, W. *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 1317.
(12) Maury, G. *Chem. Heterocycl. Compd.* **1977**, *30*, 179.
(13) The aldehyde was prepared by acid hydrolysis of the acetal in hot water. Neutralization with $NaHCO_3$ always required more base than that which was equivalent to the amount of acid catalyst. Since the acetal is converted to 2-hydroxypropanal by boiling H_2O,[14] solvolytic side reactions are expected.
(14) Dworzak, R.; Pfifferling, P. *Monatsh. Chem.* **1927**, *48*, 251; *Chem. Abstr.* **1927**, *21*, 3608.
(15) See, for example: Adams, R.; Dix, J. S. *J. Am. Chem. Soc.* **1958**, *80*, 4618 and references therein.
(16) Albert, A.; Goldacre, R.; Phillips, J. *J. Chem. Soc.* **1948**, 2240.
(17) Barlin, G. B. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1459.

Scheme III

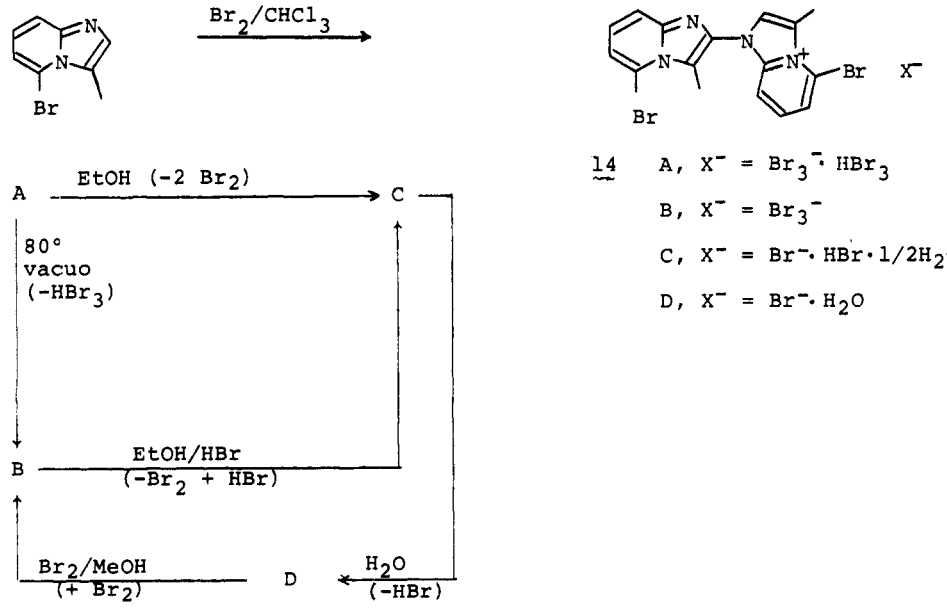


Scheme IV



14D, which is converted to 14B on treatment with bromine. 14C and 14D are colorless compounds. The yellow and orange-yellow color of 14B and 14A is in accord with the presence of perbromide ion(s). ^{1}H NMR spectra (Table II) of 14B–D in Me_2SO-d_6 are the same except for a singlet of variable intensity and chemical shifts due to water (14A is insoluble in Me_2SO). This singlet is at lower field (δ 5.2, sharp) in the spectrum of 14C than in the spectra of 14B and 14D (δ ~3.85, broad), as required if water reacts with 14C to give the cation 14 and H_3O^+. Further support for the structures stems from the infrared spectra; those of the protonated compounds A and C are

Scheme V



14 A, $X^- = Br_3^- \cdot HBr_3$

B, $X^- = Br_3^-$

C, $X^- = Br^- \cdot HBr \cdot 1/2H_2O$

D, $X^- = Br^- \cdot H_2O$

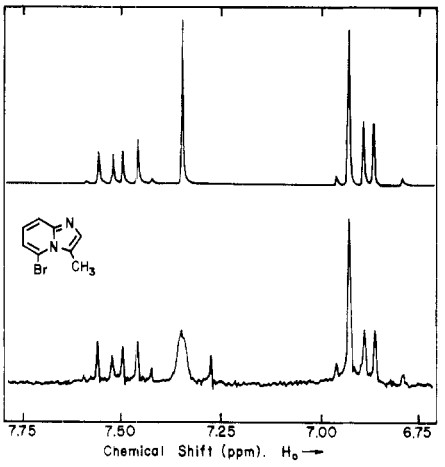


Figure 1. Aromatic region of computer-generated (top) and experimental (bottom) 100-MHz ^1H NMR spectra of 5-bromo-3-methylimidazo[1,2-*a*]pyridine ($CDCl_3$, 0.31 M). The signal at 7.28 ppm is due to $CHCl_3$. Parameters used for the simulation are shown in Table I.

similar (expect for variations in intensity and position of a band near 3300 cm^{-1}), and those of the nonprotonated **14B** and **14D** are almost the same (**14D** has an extra band near 3400 cm^{-1}).

Since the methyl group is at position 3 in compound **3**, it must be located at the 2-position in the isomeric compound **13**. Confirmation of this assignment was obtained by treating compound **13** with D_2O in the presence of acid. H/D exchange, known[18] to occur only at position 3, takes place as shown by the collapse of the ^1H NMR doublet of the CH_3 signal ($J_{H\text{-}3,CH_3}$ = 0.8 Hz) to a singlet and a change in the area ratio of the multiplets near 7.50 and 7.00 ppm from 2:2 to ca. 1:2 (see Figure 2, lower two spectra). The multiplet near 7.50 ppm is due to H-3, which shows long-range coupling with H-8 and the methyl protons, and H-8 coupled with H-3, -6, and -7 (vide infra).

The alleged compound **3** has nearly the same melting point (84–85 °C)[4] as the authentic compound **3** (82.5–83.5 °C), but their ^1H NMR spectra differ significantly (Table I). The published spectrum of the product (mp 84–85 °C) is almost superimposable on that of 3-bromo-5-methylimidazo[1,2-*a*]pyridine (**15**) (lit.[5] mp 85.2–86.5 °C) and shows the doublet of doublets for H-7, the doublet for H-6, and the doublet for H-8 (overlapping with the signal due to H-2) that are typically observed when the chemical shifts of these protons differ considerably.[19] It is believed that the product (mp 84–85 °C) was, in fact, compound **15**, which is readily obtained by bromination of another compound, 5-methylimidazo[1,2-*a*]pyridine (**16**).

The ^1H NMR spectrum of compound **3** could be analyzed only by comparison with simulated spectra since the difference in chemical shifts of H-6 and H-7 is less than their coupling constant. The parameters shown in Table I are those used to generate the aromatic portion of the spectrum shown in Figure 1. It was not possible to include the coupling of H-2 and the methyl protons ($J \approx 0.8$ Hz) since compound **3** contains seven protons and the simulation program was limited to a six-spin system. The H-2 signal therefore appears as a sharp singlet (7.32 ppm) in the simulated spectrum.

The ^1H NMR spectrum of the 2-methyl-5-bromo compound **13** also could be analyzed only by simulation (Figure 2). As above, since coupling of H-3 and the methyl protons could not be included in the simulation, the generated H-3 signal (7.54 ppm) is less complex than that obtained experimentally. $J_{3,8}$ is included. The spectrum of this 2-methyl derivative (**13**) bears a curious resemblance to that of the 3-methyl isomer **3** in that the AB portions of the spectra due to H-6 and H-7 appear as mirror images of each other. This is a consequence of the inversion of chemical shifts (and similarity of coupling constants): H-6 is at higher field than H-7 in compound **13**, and the opposite is true for compound **3**. The inversion of chemical shifts of H-6 and H-7 is *not* observed in the absence of the 5-bromo substituent; and the pattern of 5-bromoimidazo[1,2-*a*]pyridine resembles that of compound **13** so that here again H-6 is at higher field than H-7. The "abnormal" chemical shifts in compound **3** may be attributed to interaction of the peri substituents and will be the subject of a forthcoming publication.

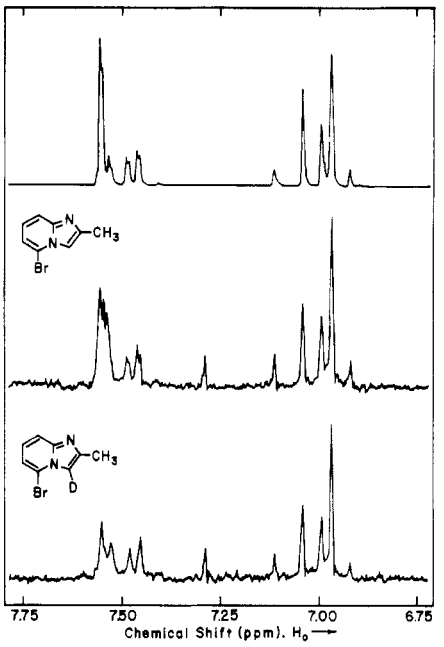


Figure 2. Aromatic region of computer-generated (top) and experimental (center) ^1H NMR spectra of 5-bromo-2-methylimidazo[1,2-*a*]pyridine ($CDCl_3$, 0.31 M). Parameters used for the calculated spectrum are shown in Table I. The spectrum of the 3-deuterio compound is shown at the bottom. The signal at 7.28 ppm in the experimental spectra is due to $CHCl_3$.

In conclusion, the π-deficient pyridine ring of imidazo[1,2-*a*]pyridine is not susceptible to electrophilic substitution. A compound, reported to form when 3-methylimidazo[1,2-*a*]pyridine is treated with NBS and assigned the structure of the 5-bromo derivative, has the properties of the 3-bromo-5-methyl derivative. The structure of the 5-bromo-3-methyl compound was established by alternate syntheses, reaction with bromine, spectral analysis, and comparison with the isomeric 3-bromo-5-methyl and 5-bromo-2-methyl compounds. No abnormal behavior in either the syntheses or the subsequent bromination was observed.

Experimental Section

^1H NMR spectra were recorded on either a Varian HA-100 or a Perkin-Elmer R-20B spectrometer. The simulated spectra were generated with a Varian simulation routine and an SS-100 computer system. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6M instrument with an ionizing voltage of 70 eV. A Beckman AccuLab 1 instrument was used for the determination of infrared spectra (Nujol mulls). Elemental analyses were carried out by either the Analytical Service Laboratories

(18) Paudler, W. W.; Helmick, L. S. *J. Org. Chem.* **1968**, *33*, 1087; *Chem. Commun.* **1967**, 377.

(19) For a list of references to such ^1H NMR spectra see ref 1 in: Hand, E. S.; Paudler, W. W. *Org. Magn. Reson.*, in press.

of the University of Alabama Chemistry Department or Atlantic Microlabs, Inc. Melting points, taken in capillaries on a Thomas-Hoover Unimelt or, if >280 °C, on a Mel-Temp apparatus, are uncorrected. Solutions were dried over anhydrous Na_2SO_4. The alumina (Woelm) used was neutral, Brockmann grade 3.

NBS. Different batches of commercial *N*-bromosuccinimide (Eastman) were used either crude or were crystallized from H_2O or from HOAc and dried in vacuo for several days.

Reaction of 3-Methylimidazo[1,2-*a*]pyridine (2) with NBS. Method A. For most runs the neutral compound **2**, prepared according to Paudler and Blewitt[5] and purified by chromatography on alumina, was used. The same results as those described below were obtained. In one experiment a $CHCl_3$ solution of compound **2** was prepared according to the reported procedure[4] by neutralization of an aqueous solution of its HBr salt (0.23 g, 1.7 mmol), extraction with $CHCl_3$, and percolation through a column of Florisil. When the $CHCl_3$ eluent (17 mL) was stirred and treated with NBS (0.29 g, 1.78 mmol), it turned yellow and then orange. After 20 min, aqueous 20% K_2CO_3 (5 mL) was added. During the requisite 10-min period of stirring, a colorless solid precipitated and then redissolved. The $CHCl_3$ layer, dried and stripped of solvent, gave a brown gum which then was only partially soluble in $CDCl_3$ and contained **4**, **6**, succinimide (^1H NMR), and **5** (TLC). This mixture was dissolved in MeOH (2 mL), filtered and treated with Et_2O (40 mL). The soluble material (0.18 g) was subjected to chromatography on Florisil (100–200 mesh). Succinimide and **5** were eluted with C_6H_6/Et_2O; $CHCl_3$ eluents contained no material; 2–5% absolute EtOH/$CHCl_3$ eluted **6** (80 mg, 20%), which crystallized from EtOAc as opaque, colorless needles, mp 160–161.5 °C.

Anal. Calcd for $C_{12}H_{11}N_3O_2 \cdot {}^1/_5EtOAc$: C, 62.29; H, 5.11; N, 17.03. Found: C, 62.30; H, 4.97; N, 17.10.

The aqueous (K_2CO_3) layer, on being allowed to stand for several days, deposited **4** as clear, long, sturdy needles which became opaque on being allowed to stand in air (95 mg). Another crop (19 mg, 43% total) was obtained by evaporation of H_2O, extraction of the residue with absolute EtOH, and evaporation of solvent followed by extraction with $CHCl_3$. Compound **4**, crystallized from $CHCl_3$ [mp 282–285 °C dec (darkens at ≳220 °C)], tenaciously retained $CHCl_3$.

Anal. Calcd for $C_{16}H_{15}N_4Br$: C, 55.98; H, 4.37; N, 16.33. Found: C, 45.31, 55.31, 55.57; H, 3.55, 4.27, 4.33; N, 12.65, 16.09, 16.14 (for a sample repeatedly dried in vacuo at 60 °C, 85 °C and 105 °C, respectively).

Treatment of **4** (17.2 mg, ca. 0.5 mmol) with picric acid (10 mg, 0.46 mmol) in absolute EtOH gave the dipicrate: 15.8 mg (85%), mp 177–178.5 °C dec.

Anal. Calcd for $C_{28}H_{20}N_{10}O_{14}$: C, 46.67; H, 2.78; N, 19.44. Found: C, 46.79; H, 2.42; N, 19.08.

Method B. A stirred $CHCl_3$ solution (20 mL) of **2** (0.23 g, 1.7 mmol) and succinimide (0.5 g, 5 mmol) was treated during 5 min with a warm $CHCl_3$ solution (10 mL) of NBS (0.29 g, 1.8 mmol). After ca. 30 min, the solvent was removed under reduced pressure and the residue treated with H_2O (20 mL). A solid (40 mg) was collected by filtration. [Since the IR spectrum of this material resembled that of **4** except that a broad band near 3300 cm^{-1} was missing and an extra sharp band at 3100 cm^{-1} was present and since its mass spectrum had the same intensity ratios of *m/e* 263, 264, 131, 132, and 78 but also showed fragments of *m/e* 80 and 82 ($HBr^{+\cdot}$) and *m/e* 81 and 83 (H_2Br^+), structure **4**·HBr is indicated.] The filtrate was treated with NaOH to pH 9 and extracted with $CHCl_3$ (3 × 10 mL). The extracted material (0.14 g) was a 2:1 mixture of succinimide and **6** (^1H NMR). Both layers were evaporated to dryness. The combined residues were subjected to chromatography on alumina. Elution with 50% $C_6H_6/CHCl_3$ gave **5** (0.8%) and starting material (8.7 mg), $CHCl_3$ gave traces of **6**, 2–5% absolute EtOH/$CHCl_3$ gave succinimide, and 10% absolute EtOH/$CHCl_3$ gave **4** (0.2 g, 70%).

Compound **6** (47 mg) was deposited on alumina (ca. 0.5 g). After 1 h this mixture was placed on an alumina column (10 × 1 cm) and eluted with $CHCl_3$; 24% of **6** was recovered.

Method C. A mixture of **2** (0.23 g, 1.7 mmol), NBS (0.29 g, 1.8 mmol), and CCl_4 (10 mL) was stirred for 10.5 h. Evaporation of the solvent gave a residue that was dissolved in H_2O (10 mL) and treated with NaOH to pH 10. Extraction with $CHCl_3$ (3 × 10 mL) gave starting material (0.05 g). The material in the aqueous layer was subjected to chromatography on alumina: 10% absolute EtOH/$CHCl_3$ eluted **4** (0.21 g, 90%).

Method D. A $CHCl_3$ solution (8 mL) of Br_2 (0.27 g, 1.7 mmol) was added during 2 min to a stirred $CHCl_3$ solution (5 mL) of **2** (0.44 g, 3.3 mmol). After 30 min, the $CHCl_3$ was evaporated, and H_2O was added to the residue, followed by addition of NaOH to pH 9 and extraction with $CHCl_3$ (3 × 10 mL). The extract contained starting material (0.14 g) and trace amounts of **5**. The aqueous layer was saturated with NaBr. Overnight a mixture of **4** and NaBr separated. From this mixture and the residue of the aqueous solution could be isolated compound **4** (90%) by repeated extraction with absolute EtOH, evaporation of EtOH, and extraction with $CHCl_3$.

1-Amino-2-(3-methylimidazo[1,2-*a*]pyridyl)-4-hydrazinobutan-1,4-dione (7). Compound **6** (48.6 mg, 0.21 mmol) in absolute EtOH (3 mL) was treated with $H_2NNH_2 \cdot H_2O$ (12 mg, 0.21 mmol) in absolute EtOH (1 mL). After 16 h, evaporation of the mixture in a stream of N_2 to ca. 1 mL gave off-white needles (38.6 mg, 70%) which were crystallized from absolute EtOH: mp 181–182.5 °C; ^1H NMR (Me_2SO-d_6, relative to external Me_4Si) δ ~4.5 (br, NH_2), 9.3 and 10.22 (NH), ~2.9 (CH_2CH_2 and Me_2SO), 2.65 (CH_3), 8.53 (H-5), 7.24 (H-6), 7.51 (H-7), 7.77 (H-8).

Anal. Calcd for $C_{12}H_{15}O_2N_5$: C, 55.17; H, 5.75; N, 26.82. Found: C, 55.15; H, 5.93; N, 26.54.

3-Methyl-5-aminoimidazo[1,2-*a*]pyridine (11). A mixture of the ethyl acetal of 2-bromopropanal[20] (4.5 g, 21 mmol) and aqueous HBr (10 mL, 0.9 M) was vigorously stirred while being refluxed for 2 h. The solution was cooled, treated with $NaHCO_3$ (5.0 g, 60 mmol) followed by 2,6-diaminopyridine (1.5 g, 13.7 mmol), stirred for several hours, treated with concentrated HCl to pH 4, and left to stand overnight. A solid was removed by filtration. When the filtrate was extracted with $CHCl_3$ (3 × 25 mL), more solid separated. The aqueous layer was filtered and treated with 2.5 N NaOH to pH 10, which caused a gum to separate. The supernatant was extracted with $CHCl_3$ (4 × 20 mL). The extracts were dried and stripped of solvent to give a tan solid (**11**; 1.17 g, 57%) which was crystallized from C_6H_6. (Charcoal was not used for decolorization since it caused the light brown C_6H_6 solution to turn violet and gave compound **11** as a lavender solid, mp 147.5–149 °C dec.) An analytical sample had a melting point of 149–151.5 °C dec and a molecular weight (mass spectrum) of 147. The compound sublimes at 100 °C (0.2 torr) to give colorless needles which darken on standing.

Anal. Calcd for $C_8H_9N_3$: C, 65.29; H, 6.16; N, 28.55. Found: C, 65.02; H, 6.28; N, 28.33.

3-Methyl-5-bromoimidazo[1,2-*a*]pyridine (3). Method A. To a stirred solution of **11** (0.30 g, 2 mmol) and NaBr (15 g) in aqueous HBr (30 mL, 0.21 N) at −5 °C was added dropwise a cold solution of $NaNO_2$ (0.15 g, 2.2 mmol) in H_2O (5 mL). The solution turned deep red, a gas was given off, and a dark solid separated. After 30 min, the mixture was filtered. The filtrate was treated with 2.5 N NaOH to pH 9 and extracted with $CHCl_3$ (2 × 20 mL). The extracts were dried, treated with charcoal, filtered through Celite, and evaporated to give **3** as a thick brown oil that had the same R_f (TLC) value and ^1H NMR spectrum as pure **3** obtained by methods B and C. Similar results were obtained when 48% HBr and no NaBr were used.

Method B. 2-Bromopropanal acetal (6.0 g, 30 mmol) was hydrolyzed as above and the mixture cooled and treated with $NaHCO_3$ (5.0 g, 60 mmol) followed by 2-amino-6-bromopyridine[21] (**12**, 2.8 g, 16 mmol). The mixture was stirred vigorously, refluxed for 3 h, cooled, and extracted with $CHCl_3$ (2 × 20 mL) to give a mixture (^1H NMR) of **3** (ca. 40%) and starting material that could not be separated adequately by TLC, steam distillation, sublimation, or acetylation followed by TLC or sublimation. The reaction was repeated with the mixture but with stirring at 22 °C for 18 h. Nonbasic materials were removed by extracting the acidified reaction mixture with $CHCl_3$ (3 × 15 mL). The aqueous layer was treated with charcoal, filtered through Celite, made alkaline, and extracted with $CHCl_3$ (4 × 10 mL). The $CHCl_3$ layer, after treatment with charcoal and Na_2SO_4, gave **3** (3 g, ca. 90%)

(20) Burtles, R.; Pyman, F. L.; Roylance, J. *J. Chem. Soc.* **1925**, 127, 581.

(21) denHertog, H. J.; Wibaut, J. P. *Recl. Trav. Chim. Pays-Bas* **1936**, *55*, 122.

which crystallized from hexane as needles, mp 78–83 °C. Compound **3** was best purified by crystallization of its HBr salt from absolute EtOH. Neutralization of an aqueous solution of pure **3**·HBr and extraction with $CHCl_3$ gave colorless needles of **3**, mp 82.5–83.5 °C. An analytical sample was prepared by sublimation at 70 °C (0.2 torr).

Anal. Calcd for $C_8H_7N_2Br$: C, 45.53; H, 3.34; N, 13.27. Found: C, 45.55; H, 3.36; N, 13.36.

Carrying out a similar but homogeneous reaction in 70% EtOH at reflux for 22 h gave only 2–3% of **3**.

Method C. When a solution of **12** (1.0 g, 5.8 mmol) and the ethyl acetal of 2-bromopropanal (2.0 g, 9.5 mmol) in EtOH (10 mL) had been refluxed for 18 h, a solid had precipitated. Filtration of the cooled mixture gave compound **3**·HBr (1.4 g) as nearly colorless needles. A second crop (0.15 g, 92% total) was obtained by addition of Et_2O to the filtrate. The compound was dissolved in hot EtOH and reprecipitated (1.50 g) with Et_2O. An analytical sample [mp 288 °C (darkens at ≳250 °C)] was crystallized from absolute EtOH.

Anal. Calcd for $C_8H_7N_2Br$·HBr: C, 32.91; H, 2.76; N, 9.59; Br, 54.74. Found: C, 32.91; H, 2.76; N, 9.58; Br, 54.68.

Partial neutralization (pH 6.20) of an aqueous solution of pure **3**·HBr with 2.5 N NaOH gave a solid which was filtered, rinsed with H_2O, and dried in vacuo. It does not melt below 295 °C but darkens.

Anal. Calcd for $(C_8H_7N_2Br)_2$·HBr·H_2O: C, 36.88; H, 3.29; N, 10.75. Found: C, 37.13; H, 2.98; N, 10.76.

Reaction of 3-Methyl-5-bromoimidazo[1,2-*a*]pyridine (3) with Bromine. When a stirred solution of **3** (0.45 g, 2.1 mmol) in $CHCl_3$ (20 mL) was treated dropwise with a solution of Br_2 (0.64 g, 4 mmol) in $CHCl_3$ (8 mL), an oil separated. The oil gradually changed to an orange-yellow solid (**14A**) which was filtered after 1 h (0.65 g, 68%) and had a melting point of 187–189 °C (depends on rate of heating). Since the material changes on drying or recrystallization, it was analyzed directly.

Anal. Calcd for $(C_{16}H_{13}N_4Br_2)^+Br_3^-$·$HBr_3$: C, 21.32; H, 1.57; N, 6.21. Found: C, 21.99; H, 1.64; N, 6.28.

On drying at 80 °C (0.25 torr) for 17 h, compound **14A** changed to the yellow compound **14B**, mp 205 °C dec (browns at ca. 180 °C).

Anal.[22] Calcd for $(C_{16}H_{13}N_4Br_2)^+Br_3^-$: C, 29.08; H, 1.98; N, 8.48; Br, 60.46. Found: C, 30.07; H, 2.14; N, 8.68; Br, 58.86.

(22) Deviations from theoretical values of the analytical data for **14B** (1% high in C, 1.5% low in Br) are attributed to the presence of ca. 3% of **14D**, formed by the loss of bromine. The found values of H and N are compatible with this interpretation.

Compound **14B** was also formed by treating a methanolic solution of **14D** with Br_2 dissolved in $CHCl_3$.

When compound **14A** (0.35 g, 0.39 mmol) was heated in EtOH (30 mL), it gradually dissolved to give a strongly acidic solution which, on concentration to 8 mL, deposited a colorless powder (**14C**): 0.15 g (66%); mp 278 °C dec (darkens at ≳240 °C). It was twice crystallized from EtOH, to which a few drops of concentrated HBr were added, and dried at 120 °C (0.25 torr) for 15 h.

Anal. Calcd for $(C_{16}H_{13}N_4Br_2)^+Br^-$·HBr·$^1/_2H_2O$: C, 32.52; H, 2.56; N, 9.48; Br, 54.09. Found: C, 32.47; H, 2.61; N, 9.47; Br, 54.02.

Compound **14B** is similarly converted into **14C**. Crystallization of **14C** from H_2O gave a strongly acidic solution, and the colorless neutral compound **14D**, which darkens at ≳240 °C, is black by 280 °C but does not melt at <300 °C. Two additional crystallizations from H_2O gave a neutral supernatant and long, fine needles, which were dried at 120 °C (0.25 torr) for 4 h.

Anal. Calcd for $(C_{16}H_{13}N_4Br_2)^+Br^-$·$H_2O$: C, 37.03; H, 2.91; N, 10.79; Br, 46.18. Found: C, 37.04; H, 2.92; N, 10.77; Br, 46.22.

2-Methyl-5-bromoimidazo[1,2-*a*]pyridine (15). A solution of 2-amino-6-bromopyridine (**12**; 1.0 g, 5.8 mmol) and chloroacetone (1.0 g, 10.8 mmol) in EtOH (10 mL) was refluxed for 4 days, concentrated, treated with H_2O, and extracted with $CHCl_3$ (3 × 15 mL). The extract (0.75 g) contained primarily starting materials (^1H NMR). The aqueous layer was made alkaline and extracted with $CHCl_3$ (3 × 15 mL) to give a mixture of compounds **12** and **15**. The mixture was further enriched in product (**15**) by extracting a $CHCl_3$ solution (A) with H_2O containing sufficient HCl to give an extract of pH 3, treating the aqueous layer with NaOH to pH 9–10, and extracting it with $CHCl_3$ to give solution B. Chromatography of B on alumina gave **15** (0.17 g) with 5% $CHCl_3/C_6H_6$. From extract A, only the earliest eluent fractions gave **15**: 0.10 g (22% total); mp 55–56.5 °C. Later fractions were mixtures. Compound **15** is waxy and discolors on standing. With picric acid in absolute EtOH, it quantitatively gave a picrate, mp 225–226 °C.

Anal. Calcd for $C_8H_7N_2Br$·$C_6H_3N_3O_7$: C, 38.20; H, 2.29; N, 15.91; Br, 18.15. Found: C, 38.36; H, 2.34; N, 15.87; Br, 18.18.

Registry No. **1**, 274-76-0; **2**, 5857-45-4; **3**, 4926-54-9; **3**·HBr, 74420-43-2; **4**, 74420-44-3; **4**·dipicrate, 74420-47-6; **5**, 4926-47-0; **6**, 74420-48-7; **7**, 74420-49-8; **9c**, 59938-27-1; **10**, 74432-10-3; **11**, 74420-50-1; **12**, 19798-81-3; **13**, 74420-51-2; **14A**, 74432-11-4; **14B**, 74420-53-4; **14C**, 74420-54-5; **14D**, 74420-55-6; **15**, 5857-47-6; **15**·picrate, 74420-56-7; *N*-bromosuccinimide, 128-08-5; succinimide, 123-56-8; 2-bromopropanal ethyl acetal, 3400-55-3; 2,6-diaminopyridine, 141-86-6; 2-bromopropanal, 19967-57-8; chloroacetone, 78-95-5.