1305, 1250 (shoulder), 1225, 1160 (SO_2), 1115, 1090, 1070, 1040, 1020, 988, 968, 937, 880, 827, 785, 777, 760, 720, and 691; λ_{max}^{MeOH}, in mμ (ε), 282 (18,400).

Anal. Calcd. for $C_{23}H_{12}NO_7S$: C, 60.65; H, 4.65; N, 3.08. Found: C, 60.42; H, 4.65; N, 3.05.

The dark brown filtrate, resulting from treatment of the crude oxidation product with methanol, and the residual methanolic liquor remaining after isolation of crude white products V and VI were combined and the solvent was evaporated under a current of air. The remaining brown glass (3.78 g.) was chromatographed on alumina. Benzenesulfonamide (0.9 g.) was obtained from the fractions eluted with ether and 5-benzenesulfonamidoacenaphthylene (VII), 0.58 g., was recovered using 10% methanol in ether. Crystallization of VII from benzene–petroleum ether (b.p. 85–100°) gave yellow needles: m.p. 154–155°; ν_{max}^{KBr}, in cm.$^{-1}$, 3290 (NH), 1485, 1430, 1350, 1325 (SO_2), 1295 (olefin CH), 1230, 1165 (SO_2), 1150, 957, 876, 836, 813, 768, 719, 700 (olefin CH), and 685.

Anal. Calcd. for $C_{18}H_{13}NO_2S$: C, 70.34; H, 4.26; N, 4.56. Found: C, 70.19; H, 4.24; N, 4.51.

Catalytic reduction of VII (0.2 g.) in the Parr hydrogenator (10% palladium on charcoal and absolute ethanol solvent) gave 0.2 g. of 5-benzenesulfonamidoacenaphthene as shown by identical spectra and no depression in a mixture melting point.

2-Acetoxy-5-benzenesulfonamidoacenaphthene (Va).—Two grams of V suspended in 100 ml. of absolute ethanol was placed in the Parr hydrogenator with 200 mg. of 10% palladium on charcoal, and the mixture was shaken for 18 hr. under a hydrogen pressure of 43 p.s.i. Removal of the catalyst by filtration gave a water-clear solution, and evaporation of the solvent *in vacuo* yielded 1.72 g. (99.5%) of the white product Va. In attempting to crystallize this material it was found to be very temperature sensitive and developed considerable yellow coloration at the boiling point of benzene. A satisfactory method of crystallization required the solution of the substance in a minimum of benzene at 40°, the addition of petroleum ether to incipient cloudiness, and cooling in the refrigerator. White microcrystals deposited: m.p. 147–148°; ν_{max}^{KBr}, in cm.$^{-1}$, 3220 (NH), 1735 (acetate C=O), 1590, 1500, 1450, 1415, 1390, 1370, 1355, 1320 (SO_2), 1235, 1165 (SO_2), 1090, 1048, 1019, 938, 890, 820, 798, 782, 770, 752, 732, 693 (shoulder), and 686.

Anal. Calcd. for $C_{20}H_{17}NO_4S$: C, 65.38; H, 4.67; N, 3.81. Found: C, 65.38; H, 4.88; N, 3.72.

When a solution of 0.65 g. of Va in 10 ml. of glacial acetic acid was refluxed for 5 hr., a yellow solution was formed which, when poured into cold water, gave 0.58 g. (100%) of 5-benzenesulfonamidoacenaphthylene (VII). The infrared spectrum of the purified material was identical with that of the yellow needles from the methanol-soluble fraction of the original oxidation mixture (*vide supra*) and of the compound prepared by an independent route (*vide infra*). Mixture melting point determinations showed no depression.

5-Benzenesulfonamidoacenaphthylene (VII).—One gram of 5-benzenesulfonamidoacenaphthene was suspended along with 0.8 g. of chloranil in 20 ml. of xylene. The mixture was refluxed for 24 hr. and gave a dark brown solution which contained a brown solid. Forty milliliters of benzene was added to dissolve all solids; the solution was filtered and then chromatographed on alumina. The fractions eluted with acetone yielded 0.26 g. of VII. Crystallization from benzene–petroleum ether gave yellow needles, m.p. 152–154°. The infrared spectrum was identical with that of the product VII obtained from the oxidation of 5-benzenesulfonamidoacenaphthene, and mixture melting points showed no depression.

Reduction of 2,3-Diacetoxy-2a-methoxy-5-benzenesulfonimido-2a,5-dihydroacenaphthene (VI).—Catalytic reduction of VI at 41 p.s.i. of hydrogen in the Parr apparatus gave a product which resisted crystallization and exhibited a broad melting point range.

Using platinum oxide (100 mg.) as the catalyst, 1 g. of VI was suspended in 50 ml. of absolute methanol plus 5 ml. of glacial acid, and the mixture was placed under 41 p.s.i. of hydrogen in the Parr hydrogenator. After shaking for 24 hr. the mixture was filtered and the solvent was evaporated (*in vacuo*), leaving 1 g. of a cream-colored glass. Crystallization from benzene–petroleum ether gave white needles: m.p. 150–152°; ν_{max}^{KBr}, in cm.$^{-1}$, 3300 (NH), 3070, 2900, 2680, 1735 (acetate C=O), 1490, 1450, 1408, 1370, 1320 (SO_2), 1260, 1238, 1165 (SO_2), 1137, 1110, 1095, 1070, 1028, 963, 942, 931, 915, 897, 798, 762, 751, 718 and 684; λ_{max}^{MeOH}, no peaks between 290 and 380 mμ. Analysis indicated the product was not a chemical entity as a reasonable empirical formula could not be calculated from the analytical data.

Anal. Found: C, 62.40; H, 5.42; N, 2.70.

All n.m.r. data were obtained on a Varian A-60 spectrometer. The spectra of V and VI were obtained using methylene chloride and deuterioacetone solutions. 1-Acetoxyacenaphthene was used as the neat liquid.

Ten π-Electron Nitrogen Heterocyclic Compounds. II. Bromination of Imidazo[1,2-*a*]pyridines

WILLIAM W. PAUDLER AND H. L. BLEWITT

Department of Chemistry, Ohio University, Athens, Ohio

Received June 14, 1965

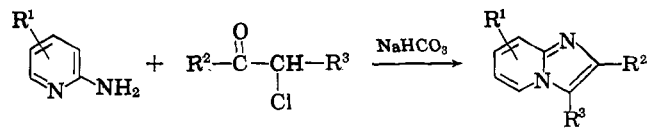
Bromination of several imidazo[1,2-*a*]pyridines has been shown to occur at position 3, in agreement with predictions based on frontier-electron calculations.

In the first paper of this series,[1] we reported the analysis of the n.m.r. spectra of some imidazo[1,2-*a*]-pyridines and some results of HMO calculations on this system.

We have now calculated the total π-electron, as well as the frontier-electron densities of several imidazo[1,2-*a*]pyridines (Table I). Both of the indices suggest that electrophilic substitution (on carbon) should occur at position 3. While the total π-electron densities predict almost equally probable substitution at several other positions (see Table I), the frontier-electron distribution suggests quite strongly that the most preferred position of substitution is position 3.

It is of interest to investigate a typical electrophilic substitution reaction in order to compare the experimental results with the prediction of the two different reactivity indices.

The compounds were prepared by the reaction sequence shown below.



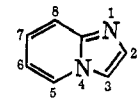
We decided to study the bromination[2] of some selected imidazo[1,2-*a*]pyridines, since it is well established that the substitution of a bromine for hydrogen does not significantly alter the chemical shift positions

(1) W. W. Paudler and H. L. Blewitt, *Tetrahedron*, **21**, 353 (1965).

(2) 2-Phenylimidazo[1,2-*a*]pyridine has previously been brominated: V. K. Matveen, *Bull. Acad. Sci. USSR, Classe sci. math. nat., Ser. Chem.*, 1005 (1936).

TABLE I

TOTAL π-ELECTRON DENSITIES AND FRONTIER-ELECTRON DENSITIES OF SOME IMIDAZO[1,2-a]PYRIDINES[a]



	Total π-electron densities — Position									Frontier-electron densities — Position								
Compound	1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8	9
Parent	1.462	1.036	1.112	1.482	0.947	1.022	0.976	1.017	0.954	0.592	0.052	0.508	0.003	0.315	0.074	0.186	0.228	0.042
2-Methyl	1.476	0.989	1.142	1.482	0.950	1.023	0.972	1.017	0.956	0.526	0.068	0.572	0.001	0.312	0.061	0.196	0.207	0.053
5-Methyl	1.467	1.039	1.113	1.491	0.898	1.050	0.967	1.035	0.954	0.575	0.052	0.482	0.000	0.301	0.125	0.156	0.277	0.027
5,7-Dimethyl	1.474	1.474	1.041	1.116	1.496	0.896	1.063	0.923	1.061	0.581	0.061	0.490	0.000	0.272	0.087	0.159	0.317	0.027
3-Methyl	1.471	1.100	1.010	1.494	0.951	1.025	0.977	1.016	0.964	0.553	0.120	0.516	0.006	0.298	0.063	0.191	0.185	0.068

[a] The calculations are based on the "heteroatom" model (*cf.* ref. 1).

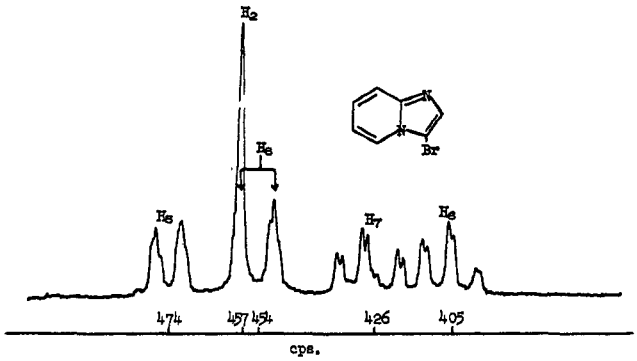


Figure 1.

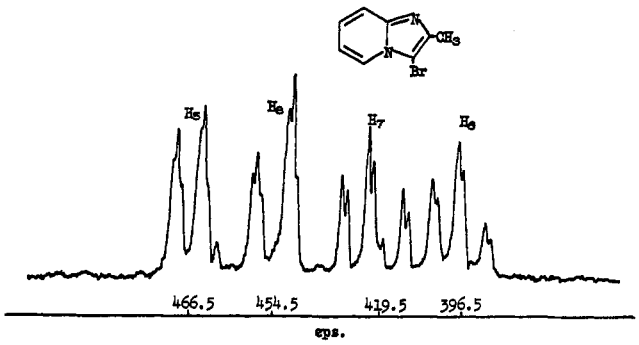
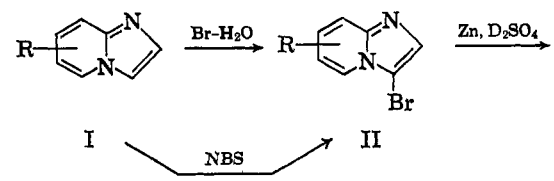
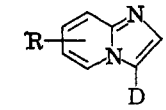


Figure 2.

of other protons in the n.m.r. spectra of aromatic compounds.[3] Thus, a comparison of the n.m.r. spectra of the unsubstituted with the brominated materials should facilitate confirmation of the position of the bromine atom. Furthermore, the halogen atom can readily be displaced by deuterium *via* reduction with zinc in deuteriosulfuric acid. Consequently, the position of substitution can be ascertained without question.

Treatment of imidazo[1,2-a]pyridine (I, R = H) with 1 mole of aqueous bromine in the presence or absence of daylight or with N-bromosuccinimide (NBS) in carbon tetrachloride yields a mixture of materials which, by thin layer chromatography, was shown to consist of mainly one basic component in addition to some starting material. Alumina chromatography permitted a facile separation of the starting material from a material which analyzed for a monobromination product of I (R = H). The n.m.r. spectrum of this compound (Figure 1) is void of one of the hydrogens previously assigned to the five-membered ring hydrogens. Unfortunately, the position of the remaining five-membered ring hydrogen is shifted to a value intermediate between the five-membered ring protons of the parent, such that it does not permit an assignment of the position of bromination strictly on the basis of chemical shift position.[4]





III

Reduction of the monobromo compound with zinc in deuteriosulfuric acid yielded a monodeuterio compound (III, R = H) whose n.m.r. spectrum is superimposable upon that of imidazo[1,2-a]pyridine except for the absence of the peak due to the 3-H. Bromination of the parent compound consequently yields 3-bromoimidazo[1,2-a]pyridine (II, R = H).

The bromination of 2-methylimidazo[1,2-a]pyridine (I, R = 2-methyl) with aqueous bromine yielded a monobromination product (II, R = 2-methyl), the n.m.r. spectrum of which (Figure 2) is devoid of the broad singlet hydrogen ascribed to 3-H of the starting material. Consequently, bromination has again occurred at position 3.

The monobromination product (II, R = 5,7-dimethyl) obtained from the 5,7-dimethyl compound (I, R = 5,7-dimethyl) shows increased shielding of the ring protons and decreased shielding of the methyl group in the 5-position (Figure 3). Consequently, no assignment based on the chemical shift positions alone can be made. Reduction of this monobromo compound with zinc in deuteriosulfuric acid, yielded a monodeuterio product (III, R = 5,7-dimethyl), the n.m.r. spectrum of which is essentially superimposable upon that of the starting 5,7-dimethyl compound (I,

(3) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 260.

(4) Since submission of our first paper in this series, a publication [P. J. Black, M. L. Heffernan, L. M. Jackman, Q. N. Porter, and G. R. Underwood, *Australian J. Chem.*, **17**, 118 (1964)] describing the analysis of n.m.r. spectra of various diazaindenes has appeared. These authors showed the presence of $J_{3,8}$ while not observing $J_{2,5}$ as we had described. The resolution of our Varian A-60 instrument has now been improved by the installation of a "High C" circuit, and we have also been able to show the presence of $J_{3,8}$ in addition, as shown by the splitting pattern of 3-H and 5-H on the 8-methyl compound, to the previously reported $J_{3,5}$. J. P. Paolini and R. K. Robins [*J. Heterocyclic Chem.*, **2**, 53 (1965)] have also reported some n.m.r. spectra of imidazo[1,2-a]pyridines.

TABLE II

PREPARATION OF IMIDAZO[1,2-a]PYRIDINES

Reactants		Product		
Substituted 2-aminopyridine	α-Halocarbonyl compound	Substituted imidazo[1,2-a]pyridine	B.p. (mm.) or m.p., °C.	% yield
2-Aminopyridine	α-Chloroacetaldehyde	Imidazo[1,2-a]pyridine (I, R = H)[a]	112–117 (3)	52
6-Methyl-2-aminopyridine	α-Chloroacetaldehyde	5-Methylimidazo[1,2-a]pyridine (I, R = 5-methyl)	104–105 (0.05)	78
4,6-Dimethyl-2-aminopyridine	α-Chloroacetaldehyde	5,7-Dimethylimidazo[1,2-a]pyridine (I, R = 5,7-dimethyl)	140–142 (1.0–1.2)	82
2-Aminopyridine	Bromoacetone	2-Methylimidazo[1,2-a]pyridine (I, R = 2-methyl)	105 (0.4), 45–46	66
2-Aminopyridine	α-Bromopropionaldehyde	3-Methylimidazo[1,2-a]pyridine (I, R = 3-methyl)[a]	84–89 (1.3), 64–65.6	48

[a] Previously prepared: A. M. Roe, *J. Chem. Soc.*, 2195 (1963); A. E. Tschitschibabin, *Ber.*, 58, 1704 (1925).

R = 5,7-dimethyl) with the peak assigned to 3-H absent, demonstrating that bromination has occurred at 3-H.

The monobromination product obtained from the bromination of the 5-methyl compound (I, R = 5-methyl) is void of one of the five-membered ring hydrogens, with the remaining five-membered ring hydrogen not assignable with total assurance (see Figure 4) on the basis of the chemical shift position only, to either 2-H or 3-H. Furthermore, all of the ring protons are at a more shielded position than in the parent 5-methyl compound.[5] The methyl protons, on the other hand, are at a more shielded position in the bromo compound.

The position of the bromine can be ascertained by comparison with the spectrum (Figure 3) of the 3-bromo-5,7-dimethylimidazo[1,2-a]pyridine (II, R = 5,7-dimethyl). The peak ascribed to 2-H in this compound (442 c.p.s.) is also present in the bromination product of the 5-methyl compound (446 c.p.s.). Thus, compound IV is 3-bromo-5-methylimidazo[1,2-a]pyridine (II, R = 5-methyl).

In all of these cases bromination occurs at the position predicted by the frontier-electron density calculations. The total π-electron density calculations suggest that a mixture of isomeric monobromination products should be formed. Since the yields of the various monobromo compounds are usually quite high, any isomeric monobromination products can be present in very small amounts only, thus showing the inadequacy of the predictions based on the total π-electron density calculations.

A study of the bromination of these compounds can certainly not be concluded without attempting the bromination of an imidazo[1,2-a]pyridine with a substituent blocking the 3-position. Attempted brominations of 3-methylimidazo[1,2-a]pyridine (I, R = 3-methyl) with bromine in water afforded only starting material (see Figure 5 for the n.m.r. spectrum). This does, of course, not exclude the possibility of bromination at the predicted 5-position (see frontier-electron density calculations) under more vigorous conditions.

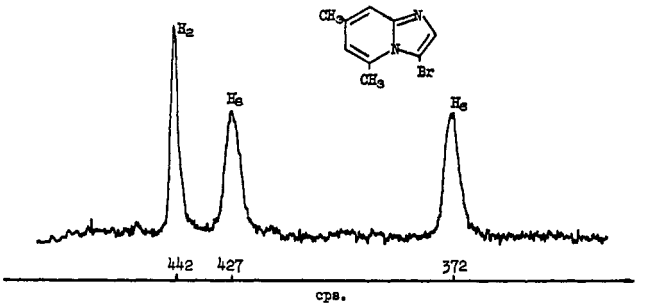


Figure 3.

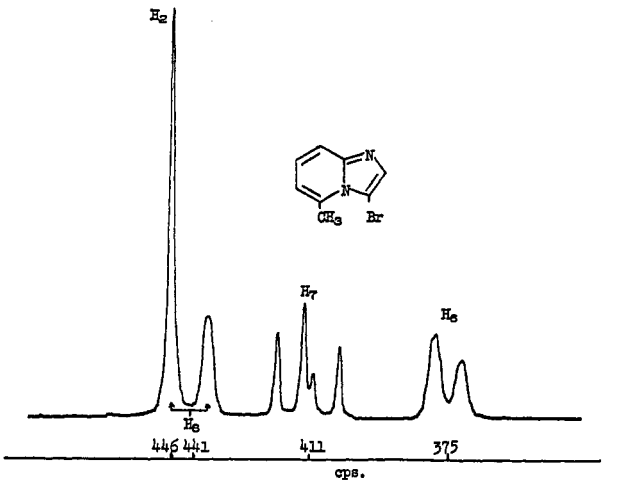


Figure 4.

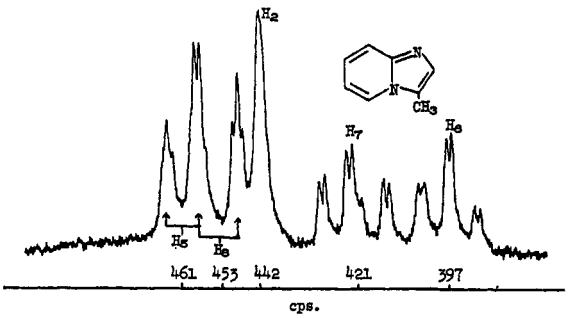


Figure 5.

Experimental Section[6]

Imidazo[1,2-a]pyridines. General Procedure.—To a solution of the appropriately substituted 2-aminopyridine (0.08 mole) in 95% ethanol or dioxane (30–50 ml.), was added an equimolar amount of the required α-halo ketone or α-haloaldehyde (see Table II). After the addition of 2 mole equiv. of $NaHCO_3$, the stirred mixture was refluxed for 14–22 hr. The dark brown

(5) The deshielding of the ring protons observed in the 3,5-disubstituted imidazo[1,2-a]pyridines and in related compounds will be subject of a forthcoming publication dealing with steric effects in these systems.

(6) Melting points are corrected. The ultraviolet spectra were recorded with a Cary 14 recording spectrophotometer. N.m.r. spectra were obtained with a Varian A-60 spectrometer. The microanalyses were performed by Mrs. C. Warner of this department. All t.l.c. was done on silica gel G plates using 25:75 methanol–ethyl acetate. The alumina used for column chromatography was neutral Woelm alumina (Brockman grade III).

TABLE III

PREPARATION OF 3-BROMOIMIDAZO[1,2-*a*]PYRIDINES

Reactant	Product	% yield	M.p., °C.	Method of purification	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
Imidazo[1,2-a]-pyridine	3-Bromoimidazo-[1,2-*a*]pyridine	79[a] 91[b] 80[c]	92.9–93.4	From cyclo-hexane or sublimation	$C_7H_5BrN_2$	42.67	2.56	14.22	42.16	2.54	14.00
2-Methylimidazo-[1,2-*a*]pyridine	3-Bromo-2-methyl-imidazo[1,2-*a*]-pyridine	75	71.8–73.2	Sublimation	$C_8H_7BrN_2$	45.52	3.34	13.27	45.96	3.22	12.93
5-Methylimidazo-[1,2-*a*]pyridine	3-Bromo-5-methyl-imidazo[1,2-*a*]-pyridine	92[a]	85.2–86.5	Sublimation	$C_8H_9BrN_2$	45.52	3.34	13.27	45.79	3.31	13.65
5,7-Dimethyl-imidazo[1,2-*a*]-pyridine	3-Bromo-5,7-di-methylimidazo-[1,2-*a*]pyridine	58[a]	80.0–80.8	From cyclo-hexane or sublimation	$C_8H_9BrN_2$	48.02	4.03	12.45	47.73	4.03	12.17

[a] Refers to yield obtained when no precautions are taken to eliminate light. [b] Refers to yield obtained when reaction was run in the absence of light. [c] Refers to yield obtained when NBS is used as the brominating agent.

TABLE IV

PROTON CHEMICAL SHIFT POSITIONS OF SOME IMIDAZO[1,2-*a*]PYRIDINES

	Chemical shift (δ), p.p.m. — Position						
Imidazo[1,2-*a*]pyridine	2-H	3-H	5-H	6-H	7-H	8-H	Substituent
Parent	7.67	7.60	8.05	6.55	6.97	7.69	...
2-Methyl	...	7.18	7.88	6.47	6.92	7.42	2.40
3-Methyl	7.37	...	7.68	6.62	7.02	7.55	2.27
5-Methyl	7.63	7.32	...	6.35	6.95	7.48	2.23
5,7-Dimethyl	7.72	7.40	...	6.35	...	7.37	2.22 (7-methyl) 2.32 (5-methyl)
3-Bromo-2-methyl	...	...	7.76	6.60	6.99	7.58	2.40
3-Bromo-5-methyl	7.43	...	...	6.25	6.85	7.35	2.80
3-Bromo-5,7-dimethyl	7.37	...	...	6.20	...	7.12	2.83 (5-methyl) 2.22 (7-methyl)
3-Bromo	7.62	...	7.90	6.75	7.10	7.57	...

reaction mixture was then filtered and the filtrate was made basic (pH 10) with 5% aqueous NaOH. The aqueous solution was extracted with three 100-ml. portions of $CHCl_3$ and the combined extracts were dried (anhydrous Na_2CO_3) and filtered. The $CHCl_3$ was then removed *in vacuo* and the residual oil was vacuum distilled to yield the substituted imidazo[1,2-*a*]pyridine.

5-Methylimidazo[1,2-*a*]pyridine hydrochloride was purified by vacuum sublimation, m.p. 216–217.2.

Anal. Calcd. for $C_8H_9ClN_2$: C, 56.99; H, 5.39; N, 16.61. Found: C, 56.75; H, 5.23; N, 17.13.

5,7-Dimethylimidazo[1,2-*a*]pyridine hydrochloride was purified by vacuum sublimination, m.p. 284–286 dec.

Anal. Calcd. for $C_9H_{11}ClN_2$: C, 59.18; H, 6.07; N, 15.33. Found: C, 59.26; H, 6.07; N, 15.08.

Bromoimidazo[1,2-*a*]pyridines. General Procedure.—To a stirred solution of an imidazo[1,2-*a*]pyridine (0.008 mole) in 20 ml. of 95% ethanol was added (dropwise) a slight molar excess of Br_2 dissolved in the minimum amount of water. After addition was complete, the solution was stirred for 8 hr., made basic (pH 10) with 10% aqueous NaOH, and then extracted with three 75-ml. portions of $CHCl_3$. The combined $CHCl_3$ extracts were dried (anhydrous Na_2CO_3) and filtered. The $CHCl_3$ was removed *in vacuo* and the oily solid (usually a mixture of monobromo compound and starting material as determined by t.l.c.) was then purified by chromatography on neutral alumina (grade III). This mixture was separated by eluting with benzene to obtain the monobromo compound, followed by elution with ether to recover unreacted starting material. Usually more than 70% of the starting material was accounted for in these reactions (see Table III).

Reaction of Imidazo[1,2-*a*]pyridine with N-Bromosuccinimide.—A stirred solution of 0.50 g. (4 mmoles) of imidazo[1,2-*a*]pyridine and 0.75 g. (4.7 mmoles) of NBS in 25 ml. of CCl_4 was heated at reflux for 2 hr., and stirring was continued for an additional 12 hr. at room temperature. The insoluble succinimide was removed by filtration and the resulting yellow solution was evaporated (*in vacuo*) to dryness to yield 0.73 g. of a tan oily solid. This solid was chromatographed on 80 g. of grade III neutral alumina. Elution with benzene yielded 0.65 g. of 3-bromoimidazo[1,2-*a*]-pyridine (II, R = H). The unreacted starting material (0.04 g.) was finally recovered by elution with ether.

3-Deuterioimidazo[1,2-*a*]pyridine.—To a stirred solution of 3-bromoimidazo[1,2-*a*]pyridine (0.51 g., 2.5 mmoles) in 25 ml. of 0.13 *N* D_2SO_4 in D_2O was added 2.5 g. (0.04 mg.-atom) of zinc dust, and the resulting mixture was refluxed for 18 hr. The solution was then stirred at room temperature overnight. The work-up of the reaction mixture was the same as that described for the preparation of 5,7-dimethyl-3-deuterioimidazo[1,2-*a*]pyridine. 3-Deuterioimidazo[1,2-*a*]pyridine was obtained in 97% yield (0.29 g.).

5,7-Dimethyl-3-deuterioimidazo[1,2-*a*]pyridine.—To a stirred solution of 0.5 g. of 5,7-dimethyl-3-bromoimidazopyridine in 40 ml. of 1.0 *N* D_2SO_4 was added 2.18 g. (0.034 mg.-atom) of zinc dust; the resulting mixture was refluxed for 9 hr. The solution was then stirred at room temperature overnight. The nearly colorless reaction mixture was filtered and the filtrate was made strongly basic (pH 10) with 10% aqueous NaOH. The solution was repeatedly extracted with $CHCl_3$ and the combined extracts were dried (anhydrous Na_2CO_3) and filtered. The $CHCl_3$ was then removed *in vacuo* yielding 0.33 g. of 5,7-dimethyl-3-deuteroimidazo[1,2-*a*]pyridine (100% yield).

Proton Coupling Constants of Imidazo[1,2-*a*]pyridines.—The average proton–proton spin coupling constants (±0.2 c.p.s.) of the different imidazo[1,2-*a*]pyridines (see Table I for numbering) previously reported[1] and those listed above are as follows: $J_{2,3} = 1.2$, $J_{3,5} = 0.6$, $J_{3,8} = 0.8$, $J_{5,6} = 1.0$, $J_{5,7} = 1.3$, $J_{5,8} = 1.3$, $J_{6,7} = 6.7$, $J_{6,8} = 1.3$, and $J_{7,8} = 9.1$ c.p.s. The chemical shift portions are summarized in Table IV.