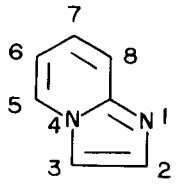
Aromaticity in Heterocyclic Systems III. The Structure and Proton Magnetic Resonance Spectra of Certain Imidazo[1,2-a]pyridines (1)

John P. Paolini and Roland K. Robins (2)

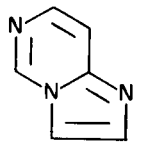
A number of improved laboratory procedures for the synthesis of derivatives of imidazo-[1,2-a]pyridines are reported. These methods have been employed for the preparation of 5-chloroimidazo[1,2-a]pyridine (IX), 5-aminoimidazo[1,2-a]pyridine (IV), 2-methyl and 2,3-dimethyl-5-aminoimidazo[1,2-a]pyridine. The proton magnetic resonance spectra of imidazo[1,2-a]pyridine (I) have been studied and the bands assigned by a comparison of spectral patterns of simple derivatives. The proton magnetic resonance spectra were then utilized to assign predominant tautomeric structures to imidazo[1,2-a]-2-pyridone (IIIb), imidazo[1,2-a]-(1H)-5-pyridone (VIIb) and 5-aminoimidazo-[1,2-a]pyridine (IV). The synthesis of imidazo[1,2-a]-(1H)-5-pyridone (VII) was accomplished from 5-chloro-imidazo[1,2-a]pyridine (IX) *via* 5-benzyloximidazo[1,2-a]pyridine (X) which was debenzylated catalytically to yield VII. Bromoacetaldehyde and 2-amino-4-chloropyridine gave 7-chloroimidazo[1,2-a]pyridine.

In accord with a continuing program designed to study the aromaticity of condensed nitrogen heterocyclic systems (3,4), certain derivatives of imidazo-[1,2-a]pyridine (I) were desired. Earlier proton magnetic resonance studies with imidazo[1,2-c]-pyrimidines (4) (II) have shown that a potentially



Imidazo[1,2-a]pyridine

I



Imidazo[1,2-c]pyrimidine

II

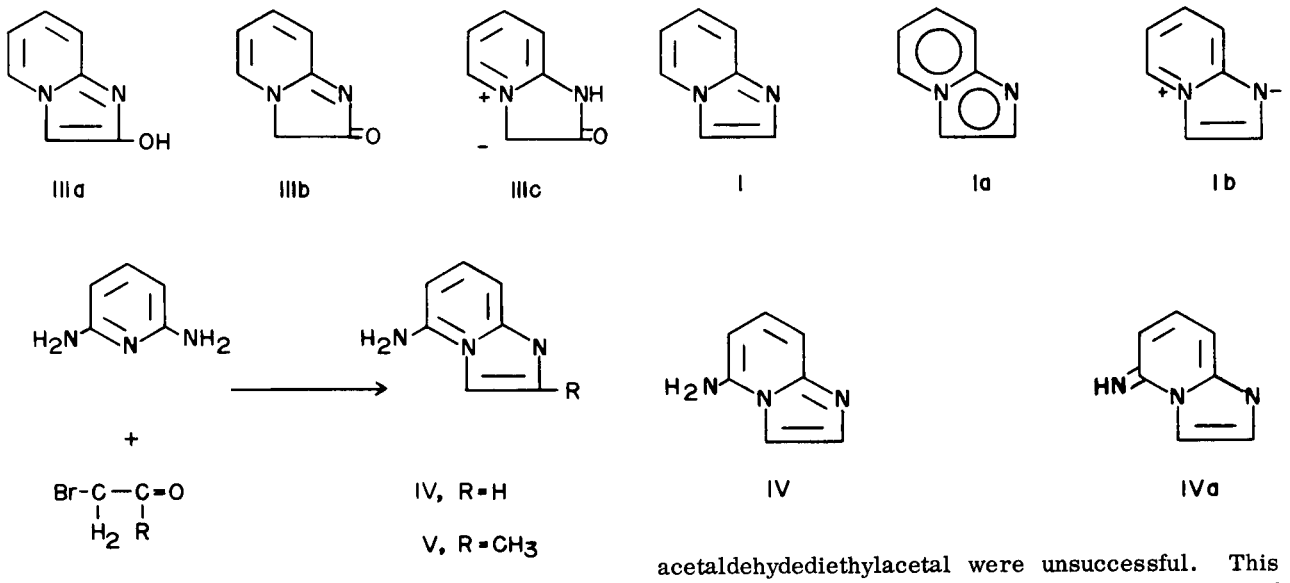
tautomeric hydroxyl group at position 2, in reality, exists in the keto form despite the fact that considerable aromaticity is lost in the 5-membered ring as a result. It seemed of interest to examine 2-hydroxyimidazo[1,2-a]pyridine (IIIa) to observe if this simpler system containing a similar bridgehead nitrogen with no substituents in the 6-membered ring, would exhibit similar structural features in the imidazole portion of the molecule. 2-Hydroxyimidazo-[1,2-a]pyridine (IIIa) could conceivably exist in three tautomeric forms, IIIa-c. The compound was prepared (5) and the proton magnetic resonance spectrum examined in deuterated dimethylsulfoxide (Fig. 1). The methylene group appears as a sharp singlet at 4.7 δ (2 protons) and readily established IIIb as the predominant structure. This sharp singlet ($-CH_2-$) appeared at 5.5 δ when III was observed in trifluoroacetic acid. The p.m.r. spectrum of the parent compound, imidazo[1,2-a]pyridine (I) is shown in Figure 2. It can clearly be observed that all the protons in this system are found in the aromatic region. In order to be able to assign each proton in I, the synthesis of a number of simple imidazo-[1,2-a]pyridines were required.

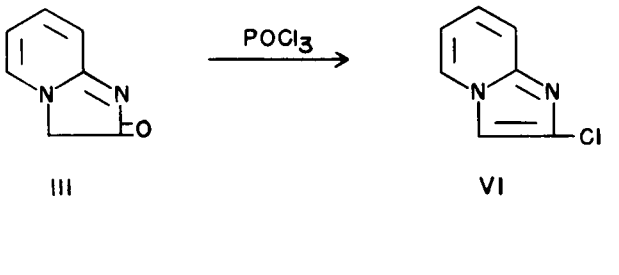
SYNTHESIS OF IMIDAZO[1,2-a]PYRIDINE DERIVATIVES

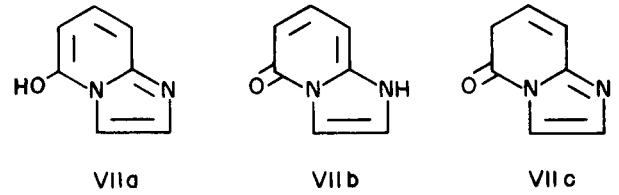
Imidazo[1,2-a]pyridine (I) was prepared by a modification of the method of Tschitschibabin (6) using bromoacetaldehyde, 2-aminopyridine and sodium bicarbonate in aqueous alcohol as suggested by Mosby (7).

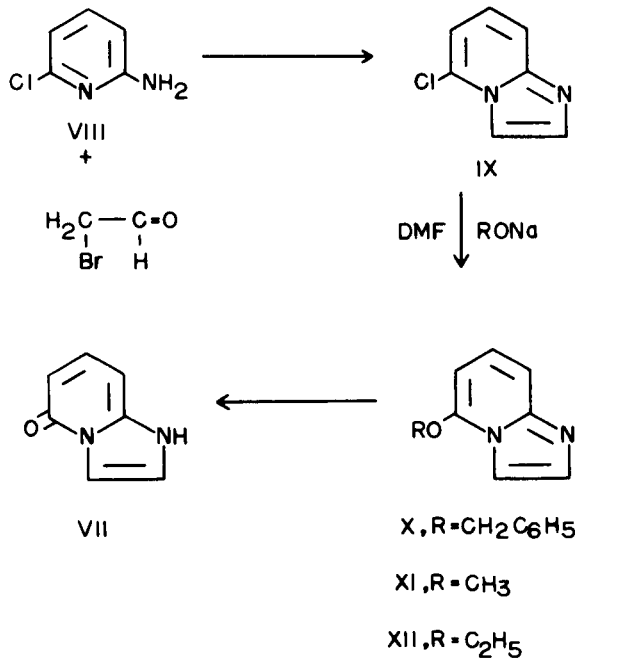
A very convenient synthesis of 3-methylimidazo-[1,2-a]pyridine has been accomplished from 2-bromopropionaldehyde and 2-aminopyridine. This procedure is simpler than that previously reported (8). The synthesis of 2,3-dimethylimidazo[1,2-a]pyridine from 3-bromobutanone and 2-aminopyridine is recorded for the first time. 2,6-Diaminopyridine has been reported (9) to fail in the ring closure to an imidazo[1,2-a]pyridine by reaction with α-haloketones. In our laboratory, however, 2,6-diaminopyridine and bromoacetaldehyde in the presence of sodium bicarbonate and 1,2-dimethoxyethane gave 80-90% yield of 5-aminoimidazo[1,2-a]pyridine (IV) isolated as the hydrobromide. This reaction was extended to the preparation of 5-amino-2-methylimidazo[1,2-a]pyridine (V). 3-Bromobutanone and 2,6-diaminopyridine under similar conditions gave 5-amino-2,3-dimethylimidazo[1,2-a]pyridine.

Treatment of imidazo[1,2-a]-2-pyridone (III) [as the sodium salt (10)] with phosphorus oxychloride readily gave 2-chloroimidazo[1,2-a]pyridine (VI). Attempts to replace the halogen in VI with alkoxide were unsuccessful. Another potentially tautomeric compound of interest was 5-hydroxyimidazo[1,2-a]-pyridine which could possess any of the three structures VIIIa-c. Attempts to prepare VII by ring closure of 2-amino-6-hydroxypyridine with bromo-









acetaldehydediethylacetal were unsuccessful. This synthesis was finally accomplished in a series of steps utilizing 2-amino-6-chloropyridine (11) (VIII) as starting material. Treatment of VII with bromoacetaldehyde in the presence of sodium bicarbonate gave 5-chloroimidazo[1,2-a]pyridine (IX) in 78% yield. Treatment of IX with sodium benzyloxide in N, N-dimethylformamide gave 5-benzyloximidazo[1, 2-a]-pyridine (X) in over 50% yield. Finally, catalytic reduction of X provided imidazo[1, 2-a]-5-pyridone (V) in quantitative yield. 5-Methoxyimidazo[1, 2-a]-pyridine (XI) was readily prepared from 5-chloroimidazo[1, 2-a]pyridine (IX) and sodium methoxide heated in N, N-dimethylsulfoxide on the steam bath. 5-Ethoxyimidazo[1, 2-a]pyridine (XII) was similarly prepared. 2-Amino-4-chloropyridine (11a) and bromoacetaldehyde gave a 78% yield of 7-chloroimidazo[1, 2-a]pyridine. Attempts to react 7-chloroimidazo[1, 2-a]pyridine with sodium alkoxides were unsuccessful.

PROTON MAGNETIC RESONANCE STUDY OF IMIDAZO[1, 2-a]PYRIDINE AND DERIVATIVES

The proton magnetic resonance spectrum of imidazo[1, 2-a]pyridine (I) (Fig. 3) in $CDCl_3$ shows the following bands: 6.73 δ (complex triplet); 7.13 δ (complex triplet); 7.6 δ *Ca.* (complex doublet); 8.1 δ (complex doublet) integrating for 1:1:3:1 protons. For convenience these bands have been designated as regions A, B, C and D, respectively. Region D is apparently the 5-proton. This band is absent in the spectrum of 5-chloroimidazo[1,2-a]pyridine (VII) (Fig. 4).

Region C is due to the 2-, 3- and 8- protons. This peak is an unsymmetrical doublet, integrating for 1-proton in the spectrum of 2, 3-dimethylimidazo-[1, 2-a]pyridine (Fig. 5). The spectrum of 8-methylimidazo[1, 2-a]pyridine (12) (Fig. 6), shows this band as a sharp singlet integrating for 2-protons. Thus, the 2- and 3-protons appear as a singlet which overlaps one of the peaks of the unsymmetrical doublet of the 8-proton in the parent compound I. The

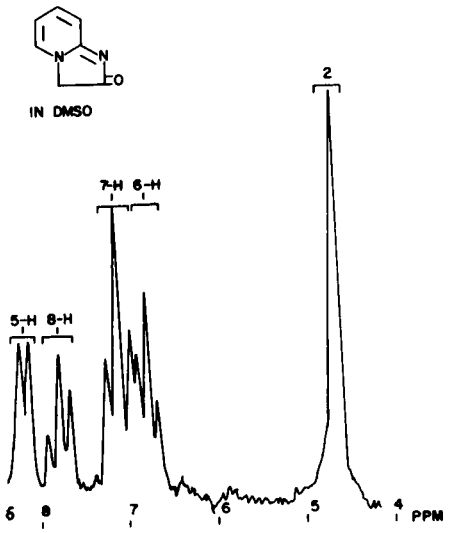


Figure 1

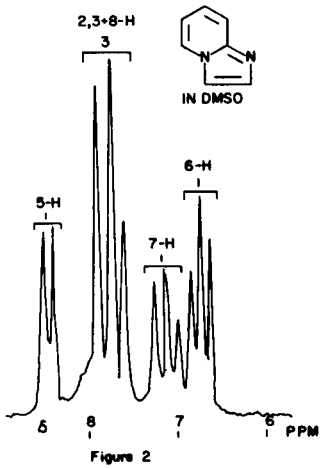


Figure 2

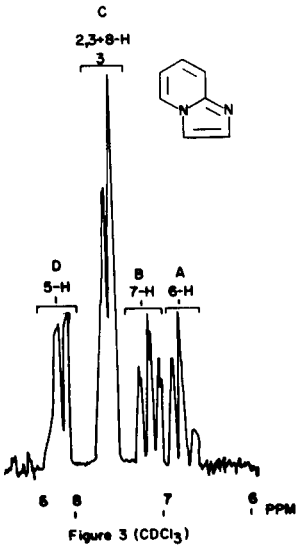


Figure 3 ($CDCl_3$)

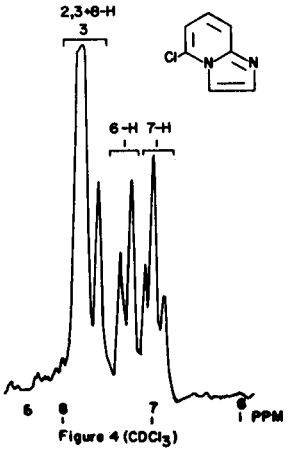


Figure 4 ($CDCl_3$)

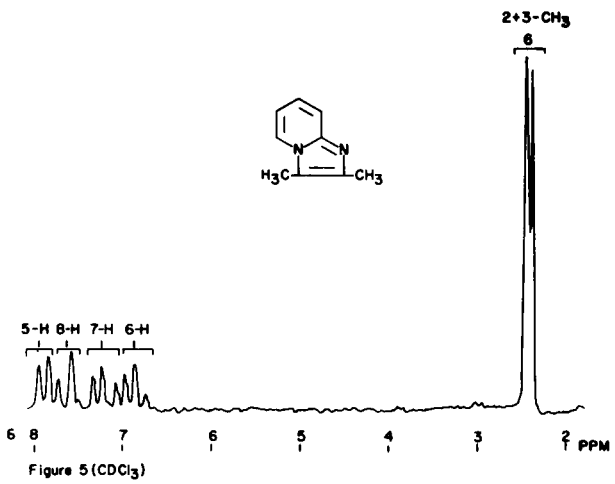


Figure 5 ($CDCl_3$)

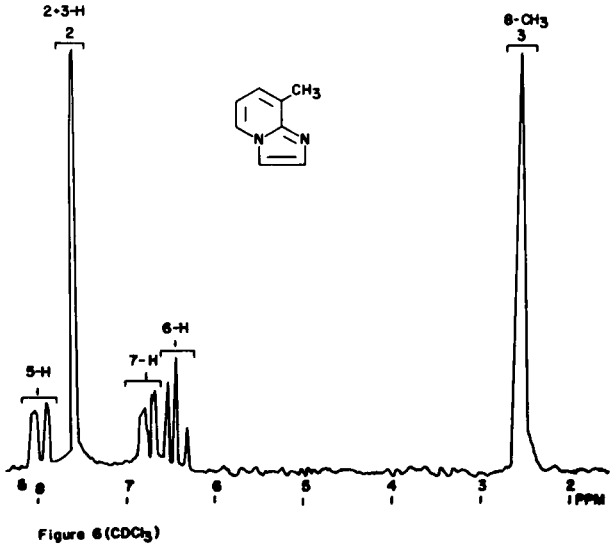


Figure 6 ($CDCl_3$)

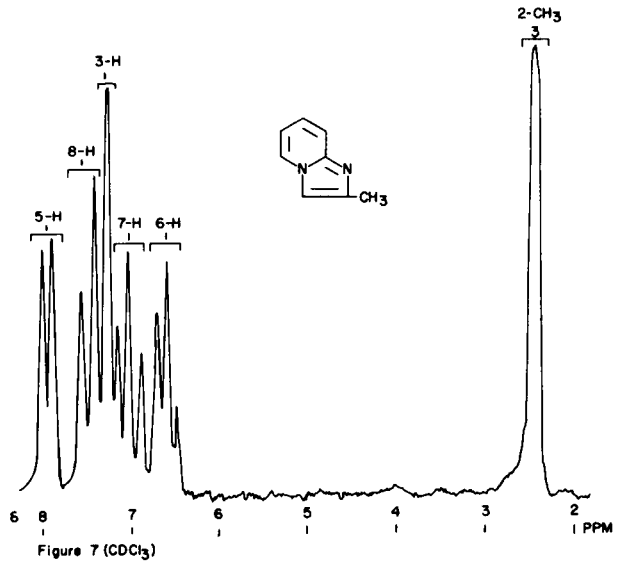


Figure 7 ($CDCl_3$)

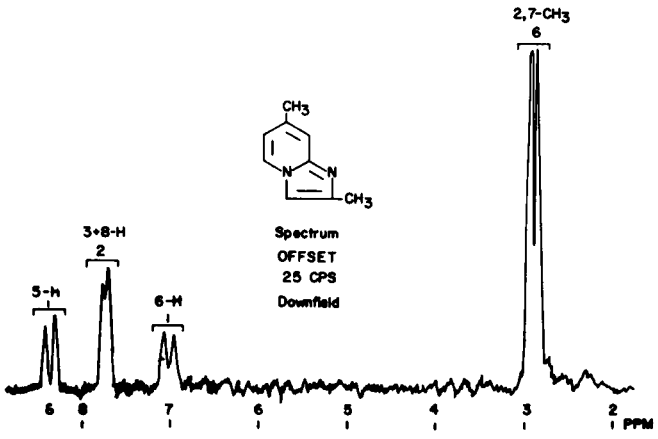


Figure 8 ($CDCl_3$)

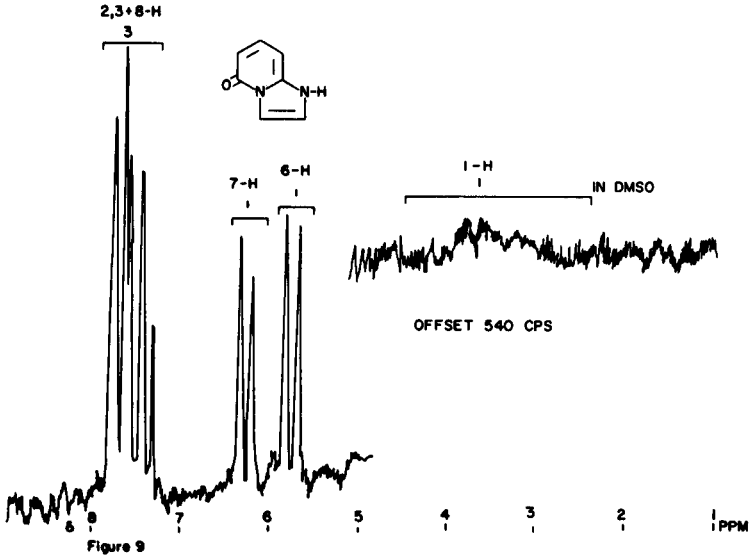


Figure 9

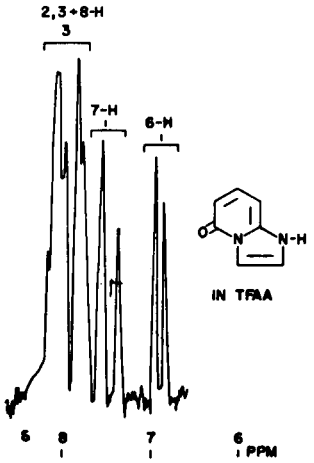


Figure 10

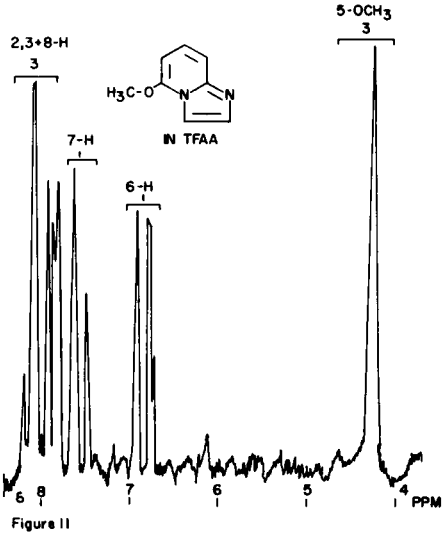


Figure 11

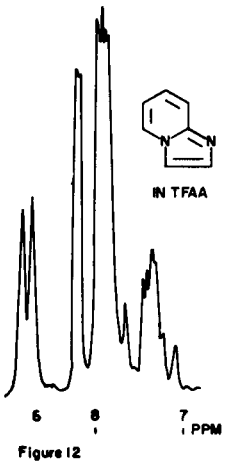


Figure 12

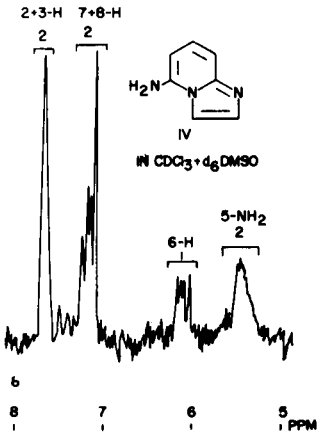


Figure 13

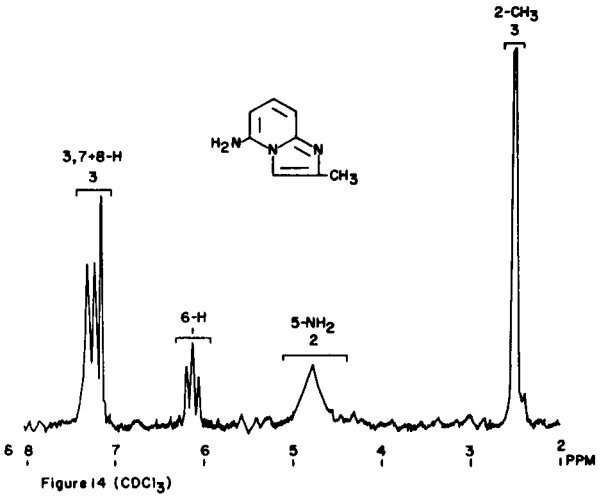


Figure 14 ($CDCl_3$)

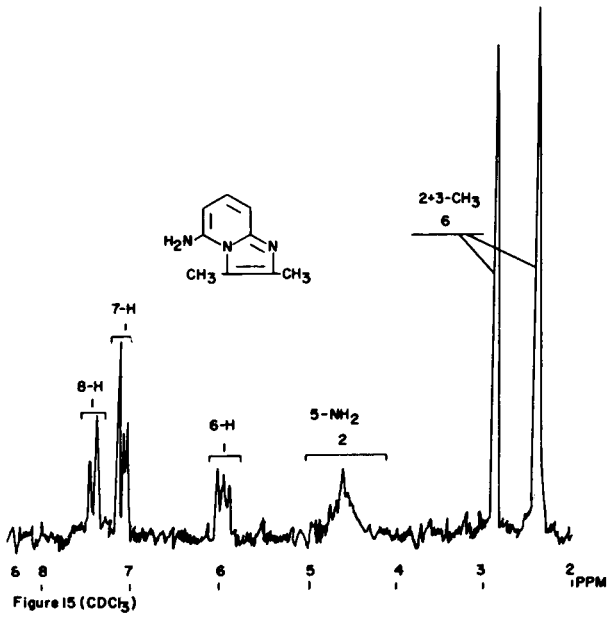


Figure 15 ($CDCl_3$)

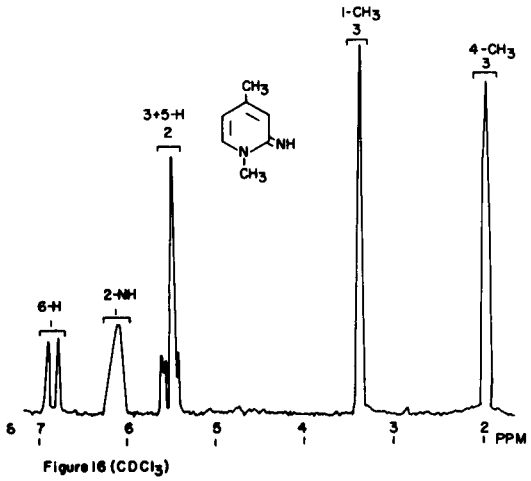


Figure 16 ($CDCl_3$)

spectrum of 2-methylimidazo[1,2-a]pyridine (6) (Fig. 7) shows region C as an unsymmetrical triplet, with peaks at 7.28 δ (the 3-proton peak shifted slightly upfield by the methyl group) as well as 7.53 δ and 7.57 δ, a doublet due to the 8-proton.

Region B represents the 7-proton, which is absent in the p.m.r. spectrum of 2,7-dimethylimidazo-[1,2-a]pyridine (13) (Fig. 8). This leaves region A due to the 6-proton which occurs as a doublet in Figure 8. Differentiation of the positions of the 6 and 7 protons can readily be made by inspection of the p.m.r. spectrum of 8-methylimidazo[1,2-a]-pyridine (Fig. 6) which shows H_6 as a triplet and H_7 as a doublet.

As it has been shown that ring currents in one ring of a fused aromatic system affect the line positions of protons in the other ring (14,15), it might be predicted, qualitatively, that in a condensed aromatic system the ring current of the electron-rich imidazole ring should shift the line positions of the pyridine protons upfield and the ring current of the more electron deficient pyridine ring should shift the line positions of the imidazole protons downfield. When compared with the spectra of imidazole and pyridine in deuterochloroform (16), it can be seen that the imidazole protons are shifted downfield from their positions in unsubstituted imidazole (from 7.14 δ to 7.6 δ) and that the α-proton of pyridine (now the 5-proton of imidazo[1,2-a]pyridine) is shifted upfield (from 8.6 δ to 8.16 δ). These observations indicate that imidazo[1,2-a]pyridine is indeed an aromatic compound, *i.e.*, "...a compound which will sustain an induced ring current" (17).

In order to sustain such an induced ring current it is quite probable that imidazo[1,2-a]pyridine is planar despite the bridgehead nitrogen atom and should best be represented by a formula such as Ia rather than a single fixed bond structure, I, or the zwitterionic form Ib.

In support of Ia is the fact that hydrogens 2 and 3 are found in very close to the same environment. Indeed, in 8-methylimidazo[1,2-a]pyridine (Fig. 6) where the overlapping 8 proton appear as a very sharp singlet. In other words, nitrogen 1 and 4 are essentially equivalent as far as the 2 and 3 proton are concerned. This excludes structure Ib. Indeed, the increased reactivity of 5-chloroimidazo-[1,2-a]pyridine which would be predicted by formula Ib due to a quaternized pyridine nitrogen is not borne out in experimental fact. One of the most striking observations of the present study is the fact the proton 7 is found so far upfield. Formula Ib predicts a downfield shift for the 7 proton over that of the corresponding proton in pyridine instead of the upfield shift actually observed. The upfield position of proton 7 correlates well with the inertness of 7-chloroimidazo[1,2-a]pyridine toward nucleophilic substitution. Apparently the bridgehead nitrogen and the fused imidazole ring have a significant deshielding effect on the 7-proton.

Inspection of the p.m.r. spectrum of imidazo-[1,2-a]-(1H)-5-pyridone (VII) (Fig. 9) in dimethylsulfoxide strongly suggests VIIb as the predominant tautomeric form. The presence of the typical imidazole -NH- absorption is noted by the broad band at 12.7 δ. The proton H_6 is strongly coupled to H_7 which in turn is only very slightly split by H_8. The doublets for H_6 and H_7 have moved upfield approximately 1 ppm. by the keto group at position 5. Structure VIIc is eliminated by the absence of a methylene group. In trifluoroacetic acid (TFAA) VII is protonated on the oxygen as well as N_1 to give a fully aromatic structure. The absorption due to H_6 and H_7 has moved downfield approximately 1 ppm. Comparison of the p.m.r. spectrum of 5-methoxyimidazo[1,2-a]pyridine (XI) in trifluoroacetic acid (Fig. 11) with VII (Fig. 10) in the same solvent reveals the aromatic region to be almost identical. In the case of XI the positions of H_6 and H_7 are very nearly the same in either dimethylsulfoxide or trifluoroacetic acid. Support for structure VIIb is found by examination of the ultra-violet absorption spectra of 5-methoxyimidazo[1,2-a]pyridine (XI) and imidazo[1,2-a]-(1H)-5-pyridone (VIIb). At *p*H of 7, VIIb exhibits λ max 262 mμ (ε, 9,150) and 318 mμ (ε, 13,400) while XI exhibits a single maximum at λ max 291 mμ (ε, 10,300). The ultra-violet spectra at *p*H 11 for VIIb and XI are also decidedly different (Table I). However, at *p*H of 1 both compounds show remarkably similar spectra (Table I). Thus, one may conclude that at *p*H 1 both N_1 and the oxygen at position 5 are protonated in compound VII. The difference in ultra-violet spectra at *p*H 7 would suggest that at neutral *p*H VII is not protonated on the oxygen.

It has been demonstrated that indole and pyrrocoline are protonated in acid at the 3-position (18,19). The p.m.r. spectrum of imidazo[1,2-a]pyridine (I) in trifluoroacetic acid (Fig. 12) shows no peak in the region of 5-6 δ which would be the expected location of a methylene group. It would thus appear that protonation takes place on position 1 rather than at carbon 2 or 3. Protonation of the bridgehead nitrogen would seem to be excluded from a study of pyrrocoline (19).

5-Aminoimidazo[1,2-a]pyridine (IV) could conceivably exist as the amino form (IV) or as the imino form IVa. Examination of the p.m.r. spectra of three derivatives of 5-aminoimidazo[1,2-a]pyridine (Fig. 13, 14 and 15) show conclusively that the amino form is perferred. The two "N-H" protons are in the same environment in all three cases. From an observation of the p.m.r. spectrum of 1,4-dimethyl-2-pyridoneimine (20), (Fig. 16) and related imino derivatives, one would expect the imine proton to be rather sharp and in the region 6-7.5 δ and the imidazole "NH" to be rather broad and in the 11-13 δ region.

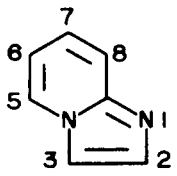
The ultraviolet absorption spectral data are presented in Table I for the imidazo[1,2-a]pyridine derivatives described in the present study.

ADDENDUM

After this paper was submitted for publication the p.m.r. spectrum of imidazo[1,2-a]pyridine was pub-

TABLE I

Ultraviolet Absorption Spectral Data for Certain Imidazo[1,2-a]pyridines



	*p*H 1				*p*H 11			
Substituent	λ max	ε max	λ min.	ε min.	λ max	ε max	λ min.	ε min.
5-Chloro	273s	7100	230	1400	273	5400	243	2500
IX	283	8600			281	6000		
	292s	6900			296s	5700		
5-Methoxy	237	8600	228	8000	290	11100	234	2500
XI	292	12000	259	3700	300s	8400		
None	250s	3600	225	1400	268s	4700	236	2200
I	274	6300			277	5000	285	4300
					292	4400		
2-Chloro	269s	9200	230	1600	272s	5200	240	2100
VI	275	9800			278	5800		
	281s	8400			292s	5000		
2,3-Dimethyl	283	9200	236	2500	273s	5500	255	3500
					283	6100	291	5000
					308	6000		
5-Benzyloxy	250	4300	230	2600	283s	10000	250	3300
X	295	13300	258	4100	296	10800		
					302	7700		
5-Oxy	237	7500	229	7000	280s	6500	241	2100
VII	296	12000	266	3300	313	12400		
	320s	1700						
3-Methyl	232	7900	227	7500	228s	17800	275	5300
	287	4900	254	2400	280	4200	284	4000
					310	5100		
2-Methyl	275	9300	231	800	272	4500	244	1100
					280	5200		
					294	4500		
5-Amino	264	6500	234	4300	300	10900	254	3100
IV	269s	6300	280	3400				
	312	13200						
5-Amino-	264	4200	240	1700	301	9200	249	2400
2-methyl	269s	4100	281	2300				
V	312	11200						
5-Amino-	231	38200	255	3200	235	33400	261	2100
2,3-dimethyl	271	3700	287	3100	313	9100		
	323	11600						
7-Chloro	280	8800	230	1900	274s	4300	247	2300
					281	4800	287	3600
					303	4000		

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lished, determined at 100 megacycles. [P. J. Black, M. L. Hefferman, L. M. Jackman, Q. N. Porter and G. R. Underwood, *Australian J. Chem.*, 17, 1128 (1964)]. The p.m.r. spectra of imidazo[1,2-a]-pyridine and several methyl derivatives have just been published with assignment of chemical shifts which are in agreement with the present work. [W. W. Paudler and H. L. Blewitt, *Tetrahedron*, 21, 353 (1965)].

EXPERIMENTAL (21)

All spectra were run in the indicated solvents with tetramethylsilane as an internal standard. Spectra were determined on a Varian model A-60 spectrometer.

2-Chloroimidazo[1,2-a]pyridine (VI).

To 50 ml. of phosphoryl chloride was added slowly, 16 g. of the sodium salt of imidazo[1,2-a]pyridin-2-(3H)-one (5) (III). A rather vigorous reaction occurred when the solid came in contact with the phosphoryl chloride. After addition was complete, the mixture was heated under reflux for 1.5 hrs. Then most of the excess phosphoryl chloride was removed by distillation, *in vacuo*, on a steam bath, until a thick syrupy residue of about 20 ml. remained. The syrup was poured onto ice and the flask was washed with ice and water. The cold, aqueous solution was extracted with chloroform (2 x 75 ml.). The chloroform extracts were discarded. The aqueous solution was made basic by the addition of sodium hydroxide solution and cooled with ice. The cold solution was extracted with chloroform (3 x 100 ml.). The chloroform extracts were dried over sodium carbonate and evaporated to an oily residue which solidified on standing. The product weighed 13.0 g. (83.3%). This residue was partially soluble in ether, and chloroform was added to effect solution. This solution was placed onto a column of alumina (50 g. Merck Acid washed alumina) and eluted with ether until the effluent liquid contained no more product. The ethereal solution was evaporated to dryness to yield 9.3 g. (59.5%) of product. This material was dissolved in benzene and percolated through a column of Florisil (100 g.). The effluent liquid was evaporated to dryness giving a white solid. This solid crystallized from Skelly-solve B to give white needles melting at 74.5-75.5°.

Anal. Calcd. for $C_7H_5N_2Cl$: C, 55.1; H, 3.30; N, 18.4; Cl, 23.2. Found: C, 55.0; H, 3.34; N, 18.4; Cl, 22.9.

5-Chloroimidazo[1,2-a]pyridine (IX).

A mixture of bromoacetaldehydediethylacetal (22) (40 ml.), water (40 ml.) and conc. hydrobromic acid (10 ml.) was heated under reflux for 1 1/4 hrs. The reaction mixture was poured into 600 ml. of water, stirred for 15 min. and filtered, by gravity. To the filtrate was added, gradually, 100 g. of sodium bicarbonate. Then 23 g. of 2-amino-6-chloropyridine (11) was added and the mixture stirred for 3 hrs. The mixture was extracted with chloroform (3 x 100 ml.), the chloroform extracts were combined, and percolated through a column of Florisil (2 x 12 cm.). The column was then washed with an additional 100 ml. of chloroform. The extracts were combined and evaporated to an oil weighing 21.3 g. (78.1%). Methanolic hydrogen chloride was added and the solution evaporated to dryness. The solid was crystallized from a mixture of methanol and 1,2-dimethoxyethane to yield the hydrochloride which decomposed above 200°.

Anal. Calcd. for $C_7H_6N_2Cl_2$: C, 44.5; H, 3.20; N, 14.8; Cl, 37.5. Found: C, 44.7; H, 3.31; N, 14.5; Cl, 37.5.

2,3-Dimethylimidazo[1,2-a]pyridine.

To 50 ml. of 1,2-dimethoxyethane was added 2-aminopyridine (23) (5 g.) and 3-bromobutanone (24) (8.8 g.). This mixture was stirred at room temperature, and after a few minutes a precipitate began to form; stirring was continued for 16 hrs. The mixture was filtered and the filter cake washed with acetone, giving 5.2 g. (41.4%) of product as the hydrobromide salt. This material was chloroform soluble and crystallized from a chloroform-acetone mixture, giving white needles melting at 222-224°.

Anal. Calcd. for $C_9H_{11}N_2Br$: C, 47.6; H, 4.88; N, 12.3; Br, 35.2. Found: C, 47.6; H, 5.25; N, 12.2; Br, 35.5.

5-Benzyloxyimidazo[1,2-a]pyridine (X).

To sodium (1.8 g.) in 250 ml. of dry toluene, was added benzyl alcohol (8.3 g.). This mixture was heated under reflux, with vigorous stirring, for 3 hrs., then the toluene was removed by evaporation *in vacuo*. To the dry sodium benzyloxide was added 5-chloroimidazo-[1,2-a]pyridine hydrochloride (IX) (10 g.) and 100 ml. of N,N-dimethylformamide. This mixture was heated on a steam bath for 15 min. and allowed to cool to room temperature for 30 min. The excess solvent was then removed by evaporation *in vacuo*. (A vacuum pump was attached to a rotary evaporator and the flask heated in a water bath at 70°). To the residue was added 100 ml. of 10% acetic acid and the mixture extracted with benzene. The aqueous phase was then made basic with 100 ml. of 10% sodium hydroxide solution, and extracted with chloroform (3 x 100 ml.). The chloroform extracts were combined and percolated through a column of Florisil and the column washed with chloroform. The effluent liquid was evaporated to an oil which solidified on cooling and crystallized from Skelly-solve B, giving 6 g. (51%) of white needles melting at 102-103°.

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 75.0; H, 5.36; N, 12.5. Found: C, 74.7; H, 5.14; N, 12.5.

5-Methoxyimidazo[1,2-a]pyridine (XI).

N,N-Dimethylformamide (100 ml.) was added to 6.5 g. of sodium methoxide. To this mixture was added 5-chloroimidazo[1,2-a]pyridine (IX) (7 g.) and the mixture heated on a steam bath for 20 min. and then allowed to stand at room temperature for 1 hr. The solvent was removed by evaporation *in vacuo*. The residue was dissolved in 100 ml. of 10% acetic acid and extracted with chloroform (3 x 50 ml.). The aqueous solution was made basic with potassium carbonate and extracted with chloroform (3 x 50 ml.). The chloroform extracts were combined and percolated through a column of Florisil (2 x 10 cm.). The column was washed with 75 ml. of chloroform. The chloroform was removed from the effluent liquid by evaporation and 3.7 g. (54.4%) was obtained. The oil was dissolved in methanol and treated with hydrogen chloride. The mixture was evaporated to dryness yielding a white solid which crystallized from ethanol, 1,2-dimethoxyethane mixture to yield needles melting at 161-162°.

Anal. Calcd. for $C_8H_9N_2ClO$: C, 52.0; H, 4.91; N, 15.2. Found: C, 52.2; H, 4.82; N, 14.9.

Imidazo[1,2-a]pyridin-5-(1H)-one (VII).

To 75 ml. of absolute ethanol was added 5-benzyloxiimidazo[1,2-a]-pyridine (X) (1 g.) and 150 mg. of 5% palladium-on-charcoal. This mixture was hydrogenated, with shaking, at a pressure of 45 p.s.i. for 20 hrs. The mixture was then filtered through a celite pad and the filtrate evaporated to dryness *in vacuo*, at room temperature giving 0.6 g. of solid. The solid crystallized from a mixture of 1-butanol and benzene. The product began to decompose above 200° and finally melted at 256-258°.

Anal. Calcd. for $C_7H_6N_2O$: C, 62.7; H, 4.51; N, 20.9. Found: C, 62.8; H, 4.08; N, 20.8.

5-Aminoimidazo[1,2-a]pyridine (IV).

A mixture of bromoacetaldehydediethylacetal (20 g.), concentrated hydrobromic acid (5 ml.) and water (5 ml.) were heated under reflux for 2 hrs. and then poured into 200 ml. of 1,2-dimethoxyethane. To this solution was added 50 g. of dry sodium bicarbonate and this mixture was stirred until the evolution of gas stopped. The mixture was filtered and 2,6-diaminopyridine (23) (7 g.) added to the filtrate. After a few minutes a solid separated. The mixture was stirred for 3 hrs., then filtered and washed with 1,2-dimethoxyethane giving 13.4 g. (88.4%). This product crystallized from a mixture of 1,2-dimethoxyethane and ethanol to yield a solid melting at 100°.

Anal. Calcd. for $C_7H_7N_3 \cdot HBr \cdot 1/4H_2O$: C, 38.5; H, 3.97; N, 19.2; Br, 36.6. Found: C, 38.5; H, 4.27; N, 19.4; Br, 37.2.

5-Amino-2-methylimidazo[1,2-a]pyridine (V).

A mixture of 2,6-diaminopyridine (23) (2 g.) and chloroacetone (24) (1.7 g.) in 25 ml. of ethanol, were heated under reflux for 4 hrs. Most of the solvent was then removed by evaporation *in vacuo* and the slurry was added to a mixture of ethanol-chloroform (1:30). This mixture was filtered and washed with a mixture of chloroform and ethanol (30:1), yielding 0.8 g. of the hydrochloride salt. This material crystallized from ethanol and slowly decomposed above 240° without melting.

Anal. Calcd. for $C_8H_{10}N_3Cl$: C, 52.3; H, 5.45; N, 22.9. Found: C, 52.3; H, 5.55; N, 23.2.

5-Amino-2,3-dimethylimidazo[1,2-a]pyridine.

A solution of 2,6-diaminopyridine (23) (10 g.) in ethanol (70 ml.) was added dropwise to a refluxing solution of 3-bromobutanone (10 ml.) in ethanol (20 ml.), over a period of 1 hr. Refluxing was continued for 1 hr. after addition was complete. Most of the solvent was removed by evaporation *in vacuo*, leaving a syrup. Chloroform was added to the hot syrup. The mixture was cooled and filtered to yield 10.8 g. (48.3%) of product. This material crystallized from a mixture of ethanol and methanol, to give needles which decomposed, without melting, above 300°.

Anal. Calcd. for $C_9H_{11}N_3 \cdot HBr$: C, 44.7; H, 4.99; N, 17.4; Br, 33.0. Found: C, 44.9; H, 5.18; N, 17.3; Br, 33.8.

3-Methylimidazo[1,2-a]pyridine.

A mixture of 2-aminopyridine (23) (10 g.), 2-bromopropionaldehyde (25) (15 g.), and 1,2-dimethoxyethane was stirred for 16 hrs. at room temperature. The mixture was then filtered and the filter cake washed with 1,2-dimethoxyethane. The dry solid weighed 5.3 g. (21.5%) and was treated with charcoal in a mixture of ethanol and 1,2-dimethoxyethane. This mixture was filtered through a celite pad. The filtrate was cooled to yield the hydrobromide, melting at 127-129°.

Anal. Calcd. for $C_8H_9N_2Br \cdot H_2O$: C, 41.6; H, 4.79; N, 12.1; Br, 34.6. Found: C, 41.9; H, 4.84; N, 12.1; Br, 35.0.

5-Ethoxyimidazo[1,2-a]pyridine (XII).

To sodium ethoxide (1.5 g.) in N,N-dimethylformamide was added

5-chloroimidazo[1,2-a]pyridine (IX) (2 g.). After standing at room temperature for 30 min., the solvent was removed by evaporation *in vacuo* (the flask was heated in a water bath at 70°). The residue was triturated with hot Skelly-solve B (3 x 50 ml.). The Skelly-solve B fractions were combined and filtered through a celite pad. The filtrate was cooled and crystals formed which weighed 1.3 g. and melted at 71-73°.

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.6; H, 6.21; N, 17.3. Found: C, 66.3; H, 6.1; N, 17.2.

7-Chloroimidazo[1,2-a]pyridine.

A mixture of bromoacetaldehydediethylacetal (35 ml.), water (50 ml.) and concentrated hydrobromic acid (5 ml.) was heated under reflux for 1 hr. The mixture was then poured into 250 ml. of water and neutralized with potassium carbonate. Then 25 g. of sodium bicarbonate was added. To the stirred solution was added 2-amino-4-chloropyridine (11a) (15 g.), and the mixture was heated to 55°. When gas evolution ceased (after about 1 hr.), ice was added and the mixture was extracted with chloroform (4 x 100 ml.). The chloroform extracts were combined and percolated through a column of Florisil (2.5 x 11 cm.). The column was washed with 125 ml. of chloroform. The effluent liquid was evaporated to dryness to yield 13.9 g. (78.2%) of yellow oil. This oil was dissolved in petroleum ether (60-110°). The cooled solution gave needles, m.p. 49-51°. An analytical sample was prepared by crystallization of the product first from water, then from petroleum ether.

Anal. Calcd. for $C_7H_5N_2Cl \cdot 1/2H_2O$: C, 52.0; H, 3.71; N, 17.3; Cl, 22.0. Found: C, 51.6; H, 3.82; N, 17.1; Cl, 22.3.

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(2) Present address: Department of Chemistry, University of Utah, Salt Lake City, Utah.

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