The methyl ester, **11b**, was obtained quantitatively upon treatment of **10b** with methanol containing a trace of sulfuric acid (reflux during 16 h): mp 76–78 °C (pentane); ir (KBr) 3370 (s), 1725 (s), 1605, 1580 cm^{-1}; NMR ($CDCl_3$) δ 1.50 (3 H singlet), 2.35 (3 H singlet), 3.40 [2 H, AB quartet (J = 13 Hz)], 3.70 (3 H singlet), 4.60 (1 H, broad, disappears upon D_2O exchange), 6.20 (1 H doublet, J = 8 Hz), 6.45 (1 H doublet, J = 7 Hz), 6.90–7.45 (6 H multiplet).

Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.76; H, 6.99; N, 9.78.

Ring Opening of 6 in Chloroform. A solution of **6** (200 mg) in 20 ml of chloroform was heated under reflux for 5 days. The solvent was then evaporated and the crude residue extracted with three 25-ml portions of boiling petroleum ether (bp 30–60 °C). The combined extracts were concentrated to a volume of 15 ml and stored at −20 °C for 24 h, whereupon **7** precipitated as colorless crystals.

Reaction of α-Methyl-*trans*-cinnamoyl Chloride (8) with 2-Amino-4-methylpyridine (3c). To a solution of 2-amino-4-methylpyridine (0.432 g, 4 mmol) in 18 ml of benzene containing triethylamine (0.8 ml, 5.6 mmol) there was added a solution of α-methyl-*trans*-cinnamoyl chloride (0.724 g, 4 mmol) in 10 ml of benzene. After 1 h at room temperature, the precipitated triethylammonium chloride (0.53 g) was separated by filtration. Evaporation of the filtrate gave an oil (1.05 g), which by NMR analysis was a 1:1 mixture of **3c** and **9**. This crude material was dissolved in methylene chloride (100 ml), and extracted with two 50-ml portions of 0.25 N HCl, followed by two 60-ml portions of water. The organic layer was dried over $MgSO_4$, and concentrated to a volume of 15 ml, whereupon addition of pentane (50 ml) resulted in precipitation of **9** as a white solid (0.60 g, 75%): mp 123–123.5 °C; ir (KBr) 1705, 1650 (s), 1610 cm^{-1}; NMR ($CDCl_3$) δ 2.10 [6 H doublet (J = 1.5 Hz)], 2.40 (3 H singlet), 6.90–7.40 (14 H multiplet), 8.35 [1 H doublet (J = 5 Hz)].

Anal. Calcd for $C_{26}H_{24}N_2O_2$: C, 78.76; H, 6.10; N, 7.07. Found: C, 78.92; H, 6.27; N, 7.09.

Methanolysis of 9. A solution of **9** (0.140 g, 0.35 mmol) in 30 ml of methanol was heated under reflux for 16 h. After this time, evaporation of the solvent gave an oil, which by NMR analysis was a 1:1 mixture of **7c** and methyl α-methyl-*trans*-cinnamate. The crude product was taken up in 20 ml of boiling petroleum ether and stored at −20 °C for 24 h. The colorless crystals which precipitated (0.085 g, 97%, mp 85–87 °C) furnished an ir spectrum identical with that of **7c**. The soluble fraction afforded 0.060 g (100%) of the sweet-smelling methyl ester, identical with an authentic sample.

Acknowledgment. The authors acknowledge the financial assistance of FINEP (Financiadora de Estudos e Projetos).

Registry No.—**2**, 26307-30-2; **3a**, 504-29-0; **3b**, 1603-40-3; **3c**, 695-34-1; **3d**, 1603-41-4; **3e**, 1824-81-3; **6a**, 59938-68-0; **6b**, 59938-69-1; **6c**, 59938-70-4; **6d**, 59938-71-5; **7a**, 59938-72-6; **7b**, 59938-73-7; **7c**, 59938-74-8; **7d**, 59938-75-9; **8**, 38449-13-7; **9**, 59938-76-0; **10a**, 59938-77-1; **10b**, 59938-78-2; **11a**, 59938-79-3; **11b**, 59938-80-6.

References and Notes

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(4) T. L. Gilchrist, C. J. Harris, C. J. Moody, and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 1969 (1975).
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(6) A. Kascheres and J. A. R. Rodrigues, *J. Org. Chem.*, **40**, 1440 (1975).
(7) This product was also observed in the NMR spectra of the ether-soluble material from the reactions, but was not isolated from this source in the present study.
(8) The α-methyl-*trans*-cinnamic acid is, in fact, the stable form available commercially.
(9) A. Signor, L. Biondi, and E. Bordignon, *J. Org. Chem.*, **31**, 1403 (1966).
(10) All melting points were obtained on a Mettler FP 52 melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer 337 spectrophotometer. NMR spectra were recorded with a Varian T-60 spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a Finnigan 1015 S/L quadrupole instrument. The elemental analyses were performed by Alfred Bernhardt Laboratories, West Germany.

Imidazo[1,2-a]pyridines—Novel Substitution Reactions

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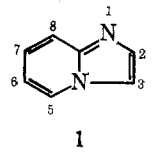
Treatment of imidazo[1,2-a]pyridines (1) with electrophilic reagents leads to substitution at either C_2 or C_3. While superficially both substitutions could occur via electrophilic attack, substitution at C_2 is interpreted to proceed via nucleophilic attack on an imidazo[1,2-a]pyridinium ion. Oxidation of 2-methyl-3-bromoimidazo[1,2-a]pyridine to its 2-carboxaldehyde is also described.

We have been interested in the chemistry of imidazo[1,2-a]pyridine[1-4] (1) for some time and wish to report here some results obtained when these compounds are subjected to electrophilic reagents. It is known that electrophilic substitution, such as bromination, nitrosation, and nitration,[3-5] takes place at position 3, in accord with frontier π-electron density calculations.[4] Such calculations show the highest π-electron density of the HOMO to be at position 1, followed



1

by position 3 and 5, and a node at the 2 position. One would predict, therefore, that electrophilic attack should occur preferentially at these positions in the order 1 > 3 > 5, and not at position 2. Indeed, no examples of electrophilic reaction at position 2 have been reported. One example of electrophilic substitution at position 5 is known: when the 3 position is blocked by a methyl group, bromination leads to the formation of 5-bromo-3-methylimidazo[1,2-a]pyridine.[5]

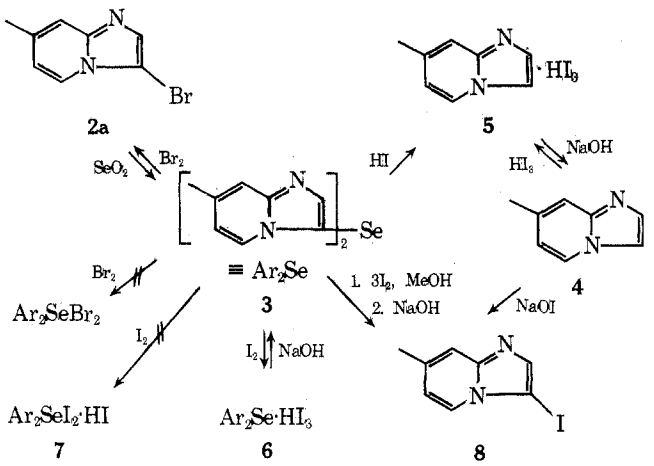
However, when the 3-substituted compound, 3-bromo-7-methylimidazo[1,2-a]pyridine (**2a**), was treated with selenium dioxide, neither the expected oxidation of the methyl group to the aldehyde, nor electrophilic substitution at position 5, occurred. Rather, displacement of bromine took place and the diarylselenide **3** was formed.[2] Furthermore, this reaction is reversible, as shown by the formation of **2a** when the diarylselenide **3** was treated with bromine.[2] Again, the expected reaction, formation of diaryldibromoselenide,[6,7] was not observed (see Scheme I).

These unexpected transformations implied a very high susceptibility of the 3 position in this ring system toward electrophilic attack. Some transformations which confirm this

implication and extend it are the subject of this paper.

Synthetic Considerations. Reaction of Diarylselenide (3) with Hydriodic Acid. Diarylselenides have been reported to give aryl iodides when treated with hydriodic acid.[8,9] However, when the diarylselenide **3** was treated with hydriodic acid, glistening black needles of a compound, $C_8H_9N_2I_3$ (**5**), were obtained. Since the ^1H NMR spectrum of this material in trifluoroacetic acid (TFAA) is identical with that of 7-methylimidazo[1,2-*a*]pyridine (**4**) in the same solvent, it was not surprising that treatment with base afforded the latter (**4**). The black compound (**5**), also readily prepared by treating **4** with aqueous hydrogen periodide, therefore has structure **5**, and, contrary to expectations, iodine was not introduced into the molecule to form compound **8**, but selenium was displaced by a proton instead (see Scheme I).

Scheme I



Reactions of Diarylselenide (3) with Iodine. The reaction of the diarylselenide **3** with iodine was more complex. When a 10% excess of iodine was used, the instantaneously formed dark gray precipitate had the ^1H NMR spectrum (TFAA) of the starting material **3** (TFAA), but also displayed an extra "impurity" singlet in the aromatic region. Since it appeared probable that the "impurity" was formed from the dark solid, the reaction was carried out with excess selenide and also with excess iodine.

When, on the one hand, less than 1 equiv of iodine was used, the "impurity" ^1H NMR signal was not observed and elemental analysis indicated the addition of HI_3 to starting material ($C_{16}H_{15}N_4SeI_3$). Treatment of the product with cold dilute sodium hydroxide regenerated the diarylselenide **3**. While a priori two structures, **6** and **7** (see Scheme I), can be envisioned, structure **6** is thus preferred. Conclusive proof for structure **6** was obtained by comparison of its uv spectrum with that of the periodide **5**: both spectra display strong absorption maxima at 287 and 356 nm, attributable[10] to I_3^-.

When, on the other hand, the diarylselenide **3** was allowed to react overnight with 3 mol of iodine and the reaction mixture was then treated with base, a compound $C_8H_7N_2I$ (**8**) was obtained.[11] The same compound could be prepared by treating 7-methylimidazo[1,2-*a*]pyridine (**4**) with sodium hypoiodite, a reaction expected to give a 3-substituted imidazo[1,2-*a*]pyridine, compound **8**. The structure assignment was confirmed by the presence of a sharp singlet in the ^1H NMR spectrum of this compound: the H_2 signal of 3-substituted imidazo[1,2-*a*]pyridines is invariably sharp, while H_3 signals in 2-substituted compounds are broadened owing to coupling with H_8 (J = 0.5–0.8 Hz).

Reactions of 3-Haloimidazo[1,2-a]pyridines with Hypochlorite and NBS. In order to test whether the lability of the 3 substituents in these displacement reactions is due primarily to facile cleavage of the selenium–carbon bond, 3-bromo-7-methylimidazo[1,2-*a*]pyridine (**2a**) was treated with *tert*-butyl hypochlorite (see Scheme II). That halogen exchange had indeed occurred was shown by the isolation of a mixture of starting material and 3-chloro-7-methylimidazo[1,2-*a*]pyridine (**2b**) along with a dimeric material that contained three halogen atoms—both chlorine and bromine, the relative proportions of which varied from one preparation to another (see Experimental Section).

Reduction of the dimer with zinc and sulfuric acid afforded a quantitative yield of 7-methylimidazo[1,2-*a*]pyridine (**4**).[12] The formation of monomer implied the presence of a carbon–nitrogen linkage, perhaps in a pyridinium-type salt. Precedents for cleavage of certain N-substituted pyridinium compounds to pyridines by zinc and acid are available in the literature.[13] Under the same conditions, however, the *N*-alkyl substituted compound, 3-bromo-*N*-methylimidazo[1,2-*a*]-pyridinium iodide (**9**), gave only displacement of bromine by hydrogen, the *N*-methyl bond remaining intact.

Scheme II

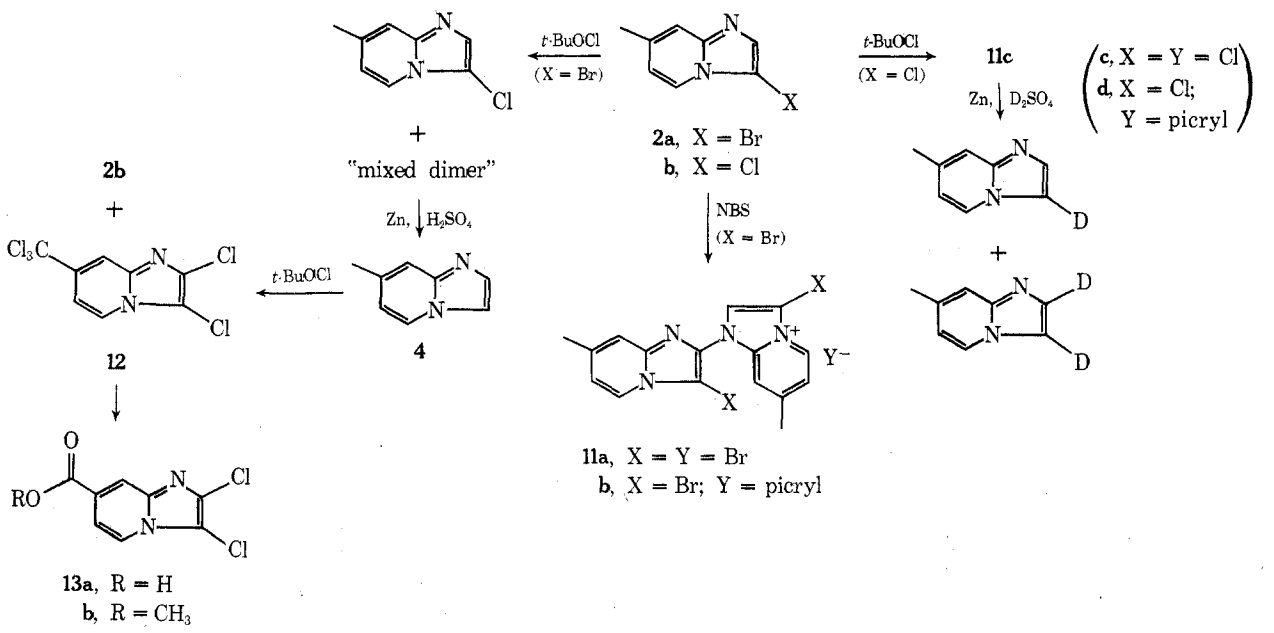
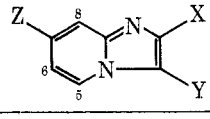


Table I. ^{1}H NMR Data of Dimeric and Other Pertinent Imidazo[1,2-*a*]pyridines (τ)

Registry no.		H_2	H_3	H_5	H_6	H_7	H_8
	$CDCl_3$						
59938-26-0	Br dimer **11a**	1.42		0.80, 1.66	1.96, 2.86		1.83, 2.47
59938-27-1	Cl dimer **11c**	1.11		0.67, 1.70[a]	1.86,[a] 2.86		1.65,[a] 2.45
	D_2O						
274-76-0	**1**	2.24	2.24	1.77	3.20	2.78	2.35
	HCl salt of 1[b]	1.93	1.78	1.25	2.45		~1.97
59938-43-1	CH_3I salt of 1[b]	1.87	1.70	1.18	2.40		~1.92
	TFAA						
56051-32-2	**2a**	2.11		1.45	2.45		2.18
	"Mixed" dimer	1.72		1.29,[a] 1.39[a]	2.23,[a] 2.31[a]		1.92, 2.13

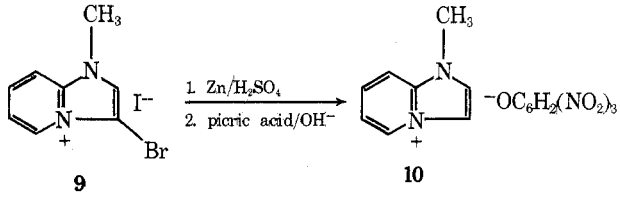
[a] These signals overlap. [b] Taken from ref 3; signals due to H_7 and H_8 overlap.

Table II. ^{1}H NMR Data of Some Haloimidazo[1,2-*a*]pyridines in $CDCl_3$ (τ)[a]



Registry no.	X	Y	Z	H_2	H_5	H_6	H_8	CH_3
	H	Br	CH_3 (**2a**)	2.43	2.00	3.25	2.62	7.56
59938-28-2	H	Cl	CH_3 (**2b**)	2.45	2.01	3.24	2.61	7.55
59938-29-3	Cl	Cl	CCl_3 (**12**)		1.87	2.52	1.84	
59938-30-6	Cl	Cl	CO_2CH_3 (**13b**)		1.97	2.36	1.66	5.97

[a] Approximate coupling constants are $J_{5,6} = 7.2$; $J_{6,8} = 1.6$–1.9; $J_{5,8} \leq 0.9$ Hz.



9 **10**

The structure of the dimer was ascertained by using the same halogen for an electrophile as was present in the haloimidazo[1,2-*a*]pyridine as follows. Reaction of compound **2a** with NBS gave a similar dimer (**11a**), which formed a picrate containing only two bromine atoms, $C_{16}H_{13}N_4Br_2 \cdot C_6H_2N_3O_7$ (**11b**). Displacement of one bromine by picrate ion indicates the presence of one ionic bromine atom[14] and the positive counterion must then be an imidazopyridinium moiety. Since the ^{1}H NMR spectrum (see Table I) of the bromo dimer contains, besides two methyl groups (six protons), only seven aromatic hydrogens of which only one is a sharp singlet (H_2), the imidazopyridinium group (which retains H_2) must be bonded to C_2 of the other imidazopyridine. Structures **11a** and **11b** are now proposed for this compound and its picrate, respectively (see Scheme II). The signals in the complex ^{1}H NMR spectrum ($CDCl_3$) of this bromo dimer do not overlap, as is the case for the mixed bromo–chloro dimer, and can be assigned as shown in Table I. From the data shown for imidazo[1,2-*a*]pyridine[15] and its hydrochloride salt in D_2O, it is clear that the protons of a positively charged imidazopyridine are considerably more deshielded than the corresponding protons of the neutral species. The lower field chemical shifts of the sets shown for H_5, H_6, and H_8, as well as for H_2, of the bromo dimer **11a** (and of **11c**) are therefore readily assigned to the imidazopyridinium ring system. In TFAA the other ring system is also positively charged (protonated) as evidenced by the similarity of the chemical shifts within each set of protons ("mixed" dimer). Coupling constants are similar to those shown in Table II.

In a final set of experiments the chloro dimer **11c** ($C_{16}H_{13}N_4Cl_3$) was prepared by treating 3-chloro-7-methylimidazo[1,2-*a*]pyridine with *tert*-butyl hypochlorite. The dimer formed a picrate **11d** ($C_{22}H_{15}N_7Cl_2O_7$). Treatment of the dimer **11c** with zinc and *deuterio*sulfuric acid afforded a 1:1 mixture of 3-deuterio- and 2,3-dideuterioimidazo[1,2-*a*]pyridine as shown by its ^{1}H NMR spectrum: no signal due to H-3 was observed and the intensity of the H-2 absorption was exactly one-half that of the parent compound **4**. Thus, the sites of attachment of the two imidazo[1,2-*a*]pyridine moieties are conclusively demonstrated.

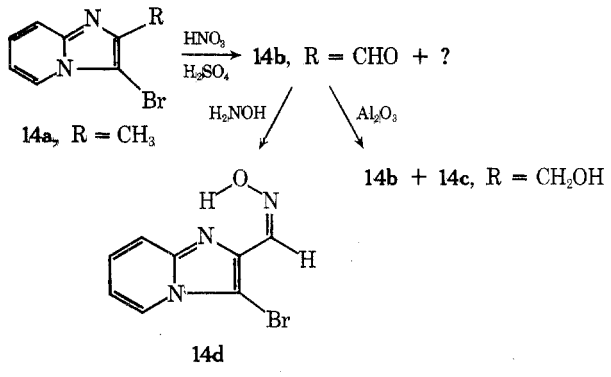
Reaction of 7-Methylimidazo[1,2-*a*]pyridine with Hypochlorite. The reaction of the parent compound **4** with *tert*-butyl hypochlorite yielded, besides 3-chloro-7-methylimidazo[1,2-*a*]pyridine (**2b**) and other products, a compound, $C_8H_3N_2Cl_5$ (**12**). The ^{1}H NMR spectrum of this substance (see Table II) lacked methyl proton absorption and showed a set of two quartets and a "broad" singlet in the aromatic region as expected for structure **12** (see Scheme II). Treatment of compound **12** with base achieved hydrolysis of the trichloromethyl group to give the acid **13a** which was converted with diazomethane to the ester **13b**, $C_9H_6N_2Cl_2O_2$.

Reactions of 3-Bromoimidazo[1,2-*a*]pyridines with Nitronium Ion. Attempts to displace the bromine in compound **2a** with nitronium ion led to the formation of an explosive material whose ^{1}H NMR spectrum displayed an upfield signal attributable to the methyl group and only two doublets and a "broad" singlet in the aromatic region (area ratio 1:1:1). Thus, a more complex reaction involving substitution at the 2 position has occurred.

When 2-methyl-3-bromoimidazo[1,2-*a*]pyridine (**14a**), in which the 2 position is blocked, is treated with nitric acid in the presence of sulfuric acid, two major products are formed. Neither retained the methyl group and one could not be purified to permit characterization. The other product, formed in ca. 50% yield, is the aldehyde **14b** (see Scheme III) as shown by its elemental analysis, $C_8H_5N_2OBr$, and its ^{1}H NMR spectrum ($CDCl_3$) which displays only aromatic protons and a sharp singlet at τ −0.28 (area ratio 4:1). None of the protons could be exchanged with D_2O. The presence of weak bands at 2770 and 2800 cm^{-1} and a very strong band at 1690 cm^{-1} in its ir spectrum (Nujol) confirms the structural assignment.

On attempted purification by chromatography only a small amount of aldehyde was recovered. A new substance, which contains two more hydrogen atoms than the aldehyde

Scheme III

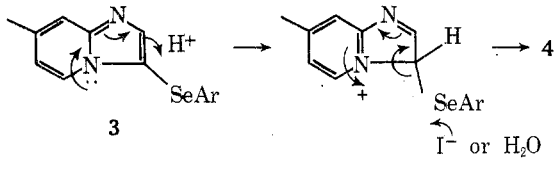


14a, R = CH_3 **14b**, R = CHO + ? **14b** + **14c**, R = CH_2OH **14d**

($C_8H_7N_2OBr$, **14c**), was eluted with 6% ethanol/chloroform. Its ^1H NMR spectrum ($CDCl_3$) showed, besides the typical complex pattern in the aromatic region of 2,3-disubstituted imidazo[1,2-*a*]pyridines, a sharp singlet at τ 5.12 (area ratio 4:2) and its ir spectrum (Nujol) had a medium-strong band at 3200 cm^{-1}. Since the high-field ^1H NMR signal and the ir absorption are readily interpretable in terms of an $ArCH_2OH$ group, structure **14c** is assigned to this material.

Treatment of the aldehyde **14b** with hydroxylamine afforded the expected oxime **14d**, $C_8H_6N_3OBr$, which contained in its ^1H NMR spectrum (Me_2SO-d_6) two sharp singlets at τ 1.72 and −1.72 and complex absorption in the aromatic region (area ratio 1:1:4). The lowest field signal disappeared on the addition of deuterium oxide and is therefore due to the OH group. The observation that the OH absorption of acetophenone oxime (Me_2SO-d_6) occurs at higher field (τ −1.32) indicates greater acidity for compound **14d** and this in turn implies intramolecular hydrogen bonding. The preferred stereochemistry of compound **14d** is thus as shown in Scheme III.

Mechanistic Considerations. While the formation of the parent compound 4 in the reaction of diarylselenide **3** with hydriodic acid could occur by electrophilic attack by proton followed by nucleophilic attack on selenium with concomitant cleavage of the carbon–selenium bond, such a reaction sequence should not require the specific use of hydriodic acid.

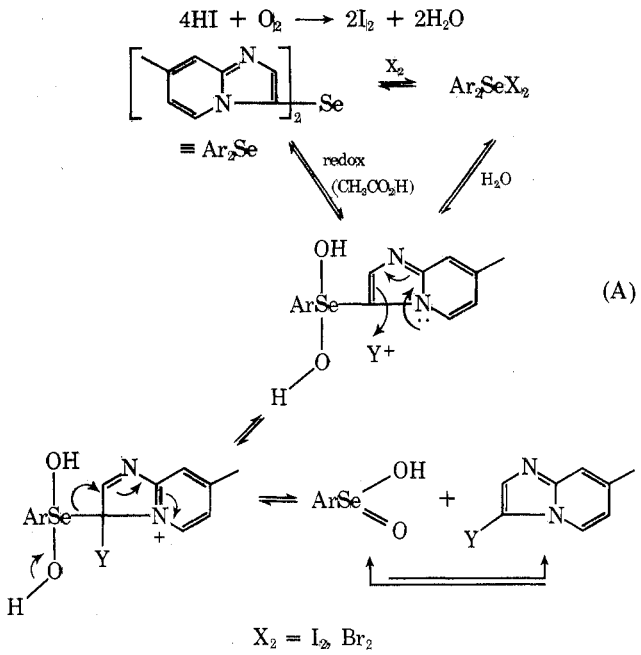


3

Because of the following—(1) hydrochloric acid does not affect this transformation,[16] (2) hydriodic acid is known to form iodine in the presence of air,[17] (3) selenides readily form dihaloselenides when treated with halogen,[6,7] and (4) the latter can be converted to dihydroxyselenides[7]—we propose the all-encompassing mechanism A.

The observation that black selenium is formed in the hydriodic acid reaction, but not in the reaction with bromine or iodine, lends support to this scheme since selenium dioxide should be formed in the final step and this with hydriodic acid is indeed reduced to black selenium.

The formation of $Ar_2Se{\cdot}HI_3$ (in the reaction of Ar_2Se with <1 equiv of iodine) also implies the intermediacy of the dihydroxyselenide since the latter's postulated formation from dihaloselenide can be the source of the required iodide ion. In the presence of excess iodine a larger concentration of $Y^+(I^+)$, as well as longer reaction time, is available and the reaction then proceeds with the formation of 3-iodoimidazo[1,2-*a*]-pyridine. When HI is used, the concentration of iodine is very low so that Y^+ is H^+ and the parent imidazo[1,2-*a*]pyridine is formed.

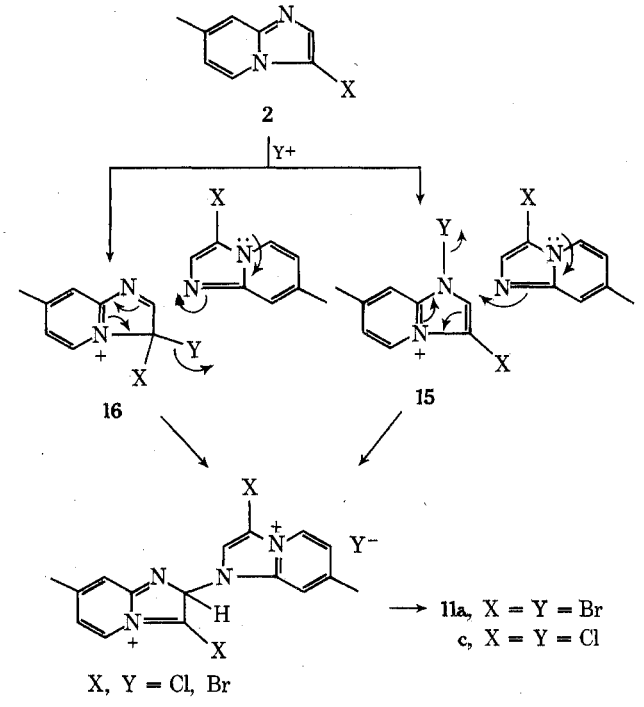


(A)

X_2 = I_2, Br_2
Y = H, Br, I

If the principle of microscopic reversibility is applied, the formation of selenide from bromoimidazo[1,2-*a*]pyridine is readily accounted for by the reverse reaction sequence with the exception of the final step, the conversion of diaryldihydroxyselenide to diarylselenide. This last step cannot proceed via the dihaloselenide since only Br^+ (Y^+) should be formed in the preceding step, but Br^- is required in this scheme for the dihaloselenide formation from dihydroxyselenide. Further, Br^+ (or, for that matter, bromine in any other oxidation state) is not essential for the conversion of the bromoimidazo[1,2-*a*]pyridine **2a** to the selenide **3** since the selenide is also readily prepared from the parent[2] imidazo[1,2-*a*]pyridine **4**. It appears likely, then, that the solvent, acetic acid, is involved in the redox reaction. The finding that no reaction occurs in refluxing ethanol[2] lends some support to this conclusion.[18]

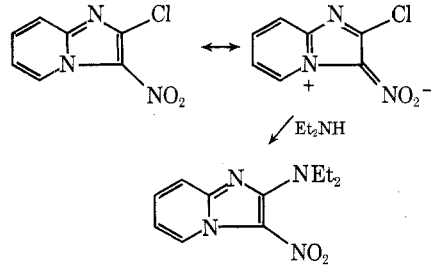
A scheme for the formation of the bromo, chloro, and "mixed" dimers is depicted below. Initial electrophilic attack by halogen gives an imidazopyridinium ion (**15** or **16** or both)



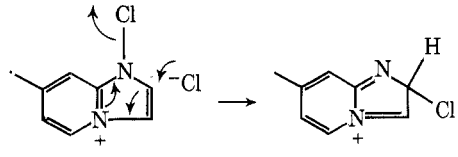
X, Y = Cl, Br

that now is susceptible to nucleophilic attack by a second molecule of **2** and also contains a good leaving group, chloride or bromide. Nucleophilic allylic displacement of Y, followed by loss of proton, affords the dimer. Although scrambling of halogen can, in principle, occur in the dimer (at least scrambling of the halogen attached to the uncharged ring), it is believed to occur principally via **16** since scrambling was observed in the starting material and because the "mixed" dimer obtained in one preparation contained more than one covalently bound chlorine atom (1.25).

The nucleophilic substitution on this ring system (dimerization step) is quite unusual. The presence of a good leaving group is not sufficient for reaction as shown by the failure of 2- or 3-haloimidazo[1,2-*a*]pyridines to react with amines.[19] One example, however, is available in the literature in which at least a partial positive charge is present in the imidazo ring and chloride can be displaced by amine,[5] viz.

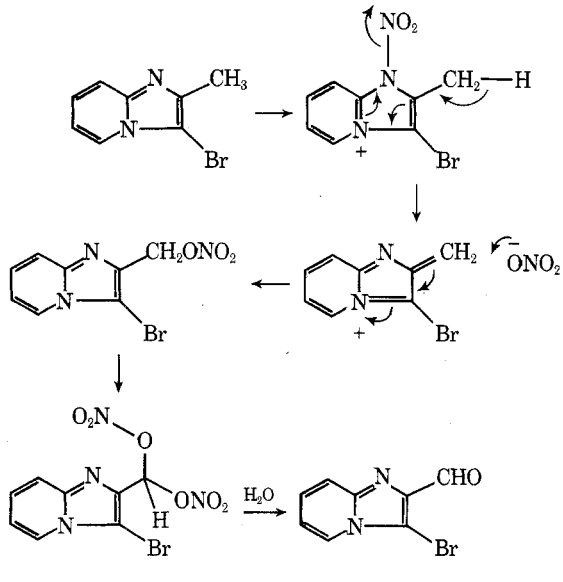


While on cursory inspection the formation of 2,3-dichloro-7-trichloromethylimidazo[1,2-*a*]pyridine (**12**) could be attributed to electrophilic substitution at the 2 position, the reaction is more readily understood in terms of a mechanism analogous to that of the dimerization. Chlorination on nitrogen gives the reactive species **17** which is subject to nucleophilic attack by chloride. Chlorination of position 3 and of the methyl group can occur prior, or subsequent, to this reaction.



17

The facile oxidation of the methyl group in 2-methyl-3-bromo[1,2-*a*]pyridine by nitric acid is also most easily rationalized by a similar reaction sequence, viz.



The isolation of this unstable aldehyde under oxidative conditions can be explained as follows: the large bromine atom should force the two geminal substituents on the methyl group (nitrate, as shown, or sulfate) directly into the path necessary for electrophilic attack on nitrogen. Formation of the postulated necessary nitramine intermediate (>N–NO_2) at this stage is thus prevented.

The alcohol **14c** is believed to be formed by a Cannizzaro disproportionation of the aldehyde **14b,** catalyzed by alumina, since no evidence was obtained for its presence prior to chromatography.

Conclusion

In summary, then, the reaction of imidazo[1,2-*a*]pyridines with electrophilic reagents leads to products in which displacement has occurred at either the 3 position or the 2 position. The formation of the latter is interpreted to arise by *nucleophilic* attack on an imidazopyridinium ion that contains a good leaving group on the 1 nitrogen and was formed by *electrophilic* attack. No evidence for electrophilic substitution at either the 2 or the 5 position was obtained. The several unexpected reactions of diarylselenide with halogen and hydriodic acid, its formation from parent or 3-bromoimidazo[1,2-*a*]pyridine with selenium dioxide, as well as the halogen scrambling observed when 3-bromo-7-methylimidazo[1,2-*a*]pyridine is treated with *tert*-butyl hypochlorite, confirm the high susceptibility of the π-excessive imidazole ring of imidazo[1,2-*a*]pyridine toward electrophilic attack.

Experimental Section

Woelm neutral alumina, Brockmann grade 3, was used for chromatography. Solutions were dried over anhydrous Na_2SO_4. Melting points were uncorrected. ^1H NMR spectra were obtained with a Hitachi Perkin-Elmer R-20B NMR spectrometer. Mass spectra were obtained with a CEC 21-104 instrument at 70 eV. Elemental analyses were determined by Atlantic Microlab, Inc., Atlanta, Ga.

Reaction of Diarylselenide 3 with Hydriodic Acid. A mixture of **3**[2] (0.20 g, 0.59 mmol) and aqueous 50% HI (2 ml) was placed in an oil bath at 130 °C for 0.5 h. The mixture was cooled, treated with H_2O (10 ml), and filtered, and the solids (A) were rinsed with H_2O (10 ml). The combined filtrate and washings deposited glistening black needles of compound **5** that were triturated with H_2O and had mp 120–122 °C (0.15 g). Anal. Calcd for $C_8H_9N_2I_3$: C, 18.69; H, 1.76; N, 5.45. Found: C, 18.54; H, 1.79; N, 5.39.

The solids A were extracted with EtOH until the extracts were colorless to give Se (0.045 g, 98%) as a fine black powder. Evaporation of the extracts to dryness gave **5** (0.14 g, 48%). Ir (Nujol) and ^1H NMR (Me_2SO-d_6) spectra were identical with those of authentic **5** (vide infra).

Formation of Compound 4 from Compound 5. A reddish-brown solution of **5** (0.14 g) in EtOH (1 ml) was treated with aqueous 10% NaOH until it was colorless (pH ca. 10), followed by H_2O (5 ml), when a very small amount of CHI_3 precipitated. The solid, presumably formed by reaction of liberated I_2 with EtOH, was filtered and the filtrate extracted with 3 × 5 ml of $CHCl_3$; the latter was dried and stripped of solvent. The residue, after distillation onto a coldfinger (80 °C, 0.05 Torr), had an ir spectrum superimposable on that of 7-methylimidazo[1,2-*a*]pyridine (**4**).

Treatment of Compound 4 with Hydrogen Periodide. When a solution of I_2 (0.50 g, 2 mmol) in aqueous 50% HI (1 ml) was added to a solution of **4**[3,20] (0.26 g, 2 mmol) in aqueous 50% HI (0.5 ml) a dark precipitate formed instantaneously. After addition of H_2O (5 ml), the mixture was filtered and the solid rinsed with H_2O. Compound **5** then had mp 122–124 °C; uv (EtOH) λ_{max} ($\epsilon \times 10^{-4}$) 215 (2.9), 224 sh (1.8), 287 (3.2), 356 nm (1.7).

Reaction of Diarylselenide 3 with Iodine. 1. A solution of **3** (0.10 g, 0.3 mmol) in warm MeOH (5 ml) was treated with a solution of I_2 (0.060 g, 0.24 mmol) in MeOH (5 ml). The instantaneously formed, dark gray precipitate, compound **6,** was filtered, rinsed with MeOH, and then had mp 210 °C. Anal. Calcd for $C_{16}H_{15}N_4SeI_3$: C, 26.58; H, 2.09; N, 7.75. Found: C, 26.25; H, 1.98; N, 7.64. Uv (EtOH) λ_{max} (approx. $\epsilon \times 10^{-4}$) 220 (4.2), 227 (4.1), 234 (3.9), 287 (3.6), 356 nm (1.3). The material is very insoluble in EtOH.

2. Solutions of diarylselenide **3** (0.34 g, 1 mmol) in warm MeOH (20 ml) and I_2 (0.80 g, 3.1 mmol) in warm MeOH (15 ml) were mixed and

left to stand overnight. The yellow solution obtained after addition of aqueous 10% NaOH (4 ml) was concentrated in vacuo until an oil separated. H_2O (25 ml) was added and the mixture extracted with 3 × 15 ml of $CHCl_3$. The extracts were dried, filtered, and stripped of solvent to give a mixture of starting material (**3**) and **8** according to TLC (alumina, 50% $C_6H_6/CHCl_3$). Partial separation was achieved by extraction with C_6H_6, in which **8** is more soluble. Sublimation (80 °C, 0.05 Torr) gave **8** (0.16 g, 90% based on recovered **3**, ir and ^1H NMR spectra identical with those of **8** prepared from **4**).

Formation of Compound 8 from Compound 4. To a solution of **4** (0.30 g, 2.3 mmol) in MeOH (5 ml) were added alternately solutions of aqueous 10% NaOH (3 ml total) and methanolic I_2 (0.90 g, 3.4 mmol). After standing overnight, the mixture was filtered and the filtrate concentrated in vacuo to ½ its volume and diluted to 30 ml with ice and H_2O. A solid (mixture of **8** and **4**) was filtered (filtrate A), crystallized from C_6H_6 (0.5 ml) (mother liquor B), and sublimed (80 °C, 0.01 Torr) to give fine, colorless needles of **8** (0.040 g), mp 114–115.5 °C (softens ca. 100 °C), mass spectrum mol wt 258. Anal. Calcd for $C_8H_7N_2I$: C, 37.23; H, 2.73; N, 10.86. Found: C, 37.21; H, 2.79; N, 10.82.

The filtrate A was extracted with 3 × 10 ml of $CHCl_3$; the extracts were combined with mother liquor B, dried, and stripped of solvent to give a residue that yielded via chromatography (40 g, alumina) with C_6H_6, compound **8** (0.13 g, 85% based on recovered starting material) and with 50% $C_6H_6/CHCl_3$ compound **4** (0.20 g).

Reaction of Compound 2a with *tert*-Butyl Hypochlorite. 1. To a swirled solution of **2a**[3,4] (0.42 g, 2 mmol) in $CHCl_3$ (5 ml) was added dropwise a solution of *t*-BuOCl (0.27 g, 2.5 mmol) in $CHCl_3$ (5 ml) with cooling in a water bath. After 80 min the solvent was removed in vacuo. The residue was treated with ice and aqueous 10% NaOH to pH 9 and then extracted with 3 × 15 ml of $CHCl_3$. The extracts were dried, concentrated to 2 ml, and treated with 8 ml of C_6H_6 to give a solid A and a black solution B. The solid A was subjected to chromatography (alumina, 10% absolute $EtOH/CHCl_3$), then treated with charcoal in MeOH, then twice crystallized by dissolution in hot MeOH and addition of EtOAc to the point of cloudiness to give the "mixed" dimer, mp 234 °C dec (darkens >225°). Anal. Calcd for $C_{16}H_{13}N_4Br_2Cl$: C, 42.05; H, 2.85; N, 12.28. Found: C, 42.18; H, 3.01; N, 12.32.

While elution of a salt ("mixed" dimer and bromo and chloro dimers) from alumina may appear surprising, the salt, 3-bromoimidazo[1,2-*a*]pyridine methiodide, also moves on alumina (TLC, 20% absolute $EtOH/CHCl_3$).

The material in the black solution B was percolated through alumina with $CHCl_3$. An early fraction (0.010 g) was a mixture of **2a** and **2b:** mass spectrum mol wt 210 and 212 (**2a**) and 166 and 168 (**2b**). Compound **2a** does not give mass spectral fragments at *m/e* 166 and 168.

2. About 1 min after solutions of **2a** (0.50 g, 2.4 mmol) in C_6H_6 (15 ml) and of *t*-BuOCl (0.50 g, 4.6 mmol) in C_6H_6 (5 ml) were mixed, a solid began to separate. The solid was filtered after 20 min (longer standing causes the solid to become gummy), rinsed with C_6H_6 and Et_2O, then percolated through alumina with 10% absolute $EtOH/CHCl_3$, and crystallized as above. A "mixed" dimer had mp 243 °C dec (darkens >220 °C). Anal. Calcd for $C_{16}H_{13}N_4Br_{1.5}Cl_{1.5}$: C, 44.21; H, 2.99; N, 12.90. Found: C, 44.52; H, 3.23; N, 12.98; total halogen as Br, 55.74; total halogen as Cl, 24.73.

3. The precipitate obtained after 2 h from **2a** (0.40 g, 1.9 mmol) and *t*-BuOCl (0.27 g, 2.4 mmol) in C_6H_6 was purified as above, and was then treated with picric acid in EtOH. After two recrystallizations from EtOH it had mp 191–192 °C. Anal. Calcd for $C_{22}H_{15}N_7Br_{0.75}Cl_{1.25}O_7$: C, 44.49; H, 2.53; N, 16.51. Found: C, 44.58; H, 2.38; N, 16.65.

Treatment of the "Mixed" Dimer with Zinc and Sulfuric Acid. A mixture of "mixed" dimer (0.31 g), 1.1 M H_2SO_4 (25 ml), and Zn dust (2.0 g) was stirred and heated in a 100 °C oil bath overnight, cooled, and the excess Zn was filtered. The filtrate was treated with ice and aqueous 20% NaOH to pH 10; a gelatinous precipitate was filtered. The filtrate was saturated with NaCl and extracted with 4 × 15 ml of $CHCl_3$ to give solution A. The (wet) precipitate was extracted with absolute EtOH (50 ml), the extract was evaporated to dryness in vacuo, and the residue extracted with $CHCl_3$ to give solution B. The combined solutions A and B were dried and stripped of solvents to give a thick oil (0.18 g, 100%) identified to be **4** by its ^1H NMR spectrum ($CDCl_3$).

Reaction of Compound 2a with NBS. A mixture of **2a** (0.20 g, 0.95 mmol) and NBS (0.20 g, 1.1 mmol) in $CHCl_3$ (25 ml) was refluxed for 21 h. After a small amount of solid was removed by filtration, the solution was percolated through 20 g of alumina. $CHCl_3$ eluted starting material (0.03 g); 10% absolute $EtOH/CHCl_3$ eluted the bromo dimer **11a** (0.090 g) contaminated with ca. 10% succinimide according to its ^1H NMR spectrum. Since succinimide does not form a picrate, the mixture was treated with picric acid in hot EtOH. The resulting picrate (**11b**) was twice crystallized from EtOH (5 ml) and then had mp 214–215 °C. Anal. Calcd for $C_{22}H_{15}N_7Br_2O_7$: C, 40.68; H, 2.31; N, 15.10. Found: C, 40.87; N, 2.39; N, 15.08.

3-Chloro-7-methylimidazo[1,2-*a*]pyridine (2b). To a solution of **4** (1.38 g, 10 mmol) in absolute EtOH (20 ml) was added dropwise 20 ml of Clorox. After 30 min EtOH was removed in vacuo, the resulting mixture was extracted with 4 × 10 ml of $CHCl_3$, and the extracts were dried and stripped of solvent. The residue was percolated through 125 g of alumina with 50% $C_6H_6/CHCl_3$. Early fractions gave **2b** (1.33 g, 90%); later fractions were mixtures of **2b** and **4** (0.20 g). After sublimation (60 °C, 0.05 Torr) **2b** had mp 53–55.5 °C. Anal. Calcd for $C_8H_7N_2Cl$: C, 57.66; H, 4.20; N, 16.82. Found: C, 57.56; H, 4.27; N, 16.86.

Reaction of Compound 2b with *tert*-Butyl Hypochlorite. To a solution of **2b** (0.50 g, 3 mmol) in C_6H_6 (15 ml) was added a solution of *t*-BuOCl (0.25 g, 3.3 mmol) in C_6H_6 (5 ml). The solution became yellow, a colorless solid separated, suddenly all turned dark, the solid became gummy, and some heat was liberated. On cooling the purple gum solidified. The solid was filtered after 10 min, rinsed with C_6H_6 and Et_2O, and percolated through 70 g of alumina with 20% absolute $EtOH/CHCl_3$ to give **11c** (0.30 g, ca. 50%) contaminated with *t*-BuOH according to its ^1H NMR spectrum. *t*-BuOH was not removed by crystallization from EtOH/EtOAc, but was at 100 °C (0.05 Torr). Compound **11c** then had mp 257.5–258 °C dec (darkens >250 °C). Anal. Calcd for $C_{16}H_{13}N_4Cl_3$: C, 52.24; H, 3.54; N, 15.24. Found: C, 52.28; H, 3.56; N, 15.27. The picrate **11d,** prepared in absolute EtOH, crystallized as fine, long, yellow needles, mp 196–197 °C. Anal. Calcd for $C_{22}H_{15}N_7Cl_2O_7$: C, 47.14; H, 2.68; N, 17.50. Found: C, 47.15; H, 2.72; N, 17.51.

Treatment of Compound 11c with Zinc and Deuteriosulfuric Acid. D_2SO_4, prepared by adding 0.70 ml of concentrated H_2SO_4 to 12 ml of D_2O, was added to **11c** (0.16 g) and Zn dust (1.0 g). The reaction was carried out as for the "mixed" dimer with H_2SO_4 (vide supra).

Reaction of Compound 4 with *tert*-Butyl Hypochlorite. When a solution of *t*-BuOCl (3.75 g, 34 mmol) in C_6H_6 (15 ml) was gradually added to **4** (1.5 g, 11 mmol) in C_6H_6 (20 ml), heat was evolved, the solution turned dark, and a purple gum separated. The mixture was cooled in a water bath to maintain <35 °C, and after ca. 20 min was stripped of solvent to give a gummy residue that was treated with ice–H_2O (30 ml) and aqueous 10% NaOH to pH 8–9. The resultant mixture was extracted with 4 × 25 ml of $CHCl_3$; the extracts were dried, concentrated in vacuo, and percolated through 125 g of alumina with $CHCl_3$. First eluted was **12** (0.16 g, 5.5%) which was purified by sublimation (90 °C, 0.025 Torr) followed by crystallization from hexane to give sturdy, colorless crystals: mp 80–81.5 °C; mass spectrum mol wt 302, 304, 306, 308, 310 with proper intensity distribution for 5 Cl atoms; base peaks 266, 268, 270, 272 (parent − HCl). Anal. Calcd for $C_8H_3N_2Cl_5$: C, 31.53; H, 0.99; N, 9.20. Found: C, 31.57; H, 1.02; N, 9.31.

The second component eluted was **2b** (ca. 0.05 g, 3%), and the third was compound **4** (0.25 g); mixtures of these and small amounts of other materials were also obtained. Elution with 20% absolute $EtOH/CHCl_3$ gave presumed dimeric compounds that could not be crystallized and most likely were formed from various polychloroimidazo[1,2-*a*]pyridines.

Hydrolysis of Compound 12 and Formation of Compound 13b. The material in the mother liquor from the hexane crystallization of **12** (0.10 g) was dissolved in EtOH, 7 drops of aqueous 20% NaOH were added, and the mixture was gently heated for 45 min; the EtOH was evaporated, H_2O (1 ml) added, and the solution was filtered through charcoal. When the charcoal was rinsed with H_2O, the filtrate became turbid. Addition of 3 drops of aqueous 2.4 N HCl to the filtrate gave an oil which solidified on scratching (0.20 g) and displayed typical carboxylic acid absorption in the ir [Nujol, 3400 (broad), 3200–2300, 1725, 1710 cm^{-1}].The solid was covered with Et_2O and treated with ethereal CH_2N_2. When evolution of N_2 ceased, the Et_2O was evaporated on the steam bath. The residue was percolated through 15 g of alumina with C_6H_6. The first eluents contained a small amount of material that was discarded. Later fractions contained **13b** (0.016 g) which was purified by sublimation (100 °C, 0.025 Torr), followed by crystallization from hexane and then had mp 141–146 °C (softens 139 °C); ir (Nujol) 1720 cm^{-1}. Anal. Calcd for $C_9H_6N_2Cl_2O_2$: C, 44.08; H, 2.45; N, 11.43. Found: C, 44.36; H, 2.60; N, 11.24.

3-Bromoimidazo[1,2-*a*]pyridine Methiodide (9). A solution of 3-bromoimidazo[1,2-*a*]pyridine[3] (3.0 g, 15 mmol) and CH_3I (5.4 g, 38 mmol) in absolute EtOH (10 ml) was kept at room temperature for 5 days. The solid was filtered, rinsed with EtOH, and recrystallized

from EtOH to give **9** (3.3 g, 64%): mp 257.5 °C dec (darken >230 °C); ^{1}H NMR (TFAA) τ H_2 1.98 (s), H_5 1.29 (set of triplets), $H_{6,7,8}$ 1.6–2.4 (complex multiplets). Anal. Calcd for $C_8H_8N_2BrI$: C, 28.33; H, 2.36; N, 8.26. Found: C, 28.38; H, 2.38; N, 8.23. Treatment of the mother liquors with more CH_3I afforded a second crop of compound **9** (98%).

Treatment of Compound 9 with Zinc and Sulfuric Acid. A mixture of concentrated H_2SO_4 (0.70 ml), H_2O (12 ml), **9** (0.50 g), and Zn dust (1.0 g) was stirred in a 100 °C oil bath overnight. It was cooled, excess Zn was filtered, and the filtrate was treated with ice and aqueous 20% NaOH to pH 10. A copious colorless precipitate was filtered and triturated with absolute EtOH. The combined filtrate and washings were stripped of solvents in vacuo and the residue was extracted with 4 × 40 ml of boiling absolute EtOH to give a solid that had the same ^{1}H NMR spectrum as imidazo[1,2-*a*]pyridine methiodide (D_2O). Since the solid was contaminated with inorganic salts, it was converted to its picrate (**10**) which was crystallized three times (absolute EtOH) to give long, yellow needles, mp 223–224 °C (depends on rate of heating), undepressed on admixture with authentic **10** (vide infra); ir spectrum identical with that of an authentic sample. Anal. Calcd for $C_{14}H_{11}N_5O_7$: C, 46.54; H, 3.05; N, 19.39. Found: C, 40.28; H, 2.48; N, 16.84; inorg. residue, 1.98. Compensating for residue:[21] C, 46.53; H, 2.87; N, 19.46.

Imidazo[1,2-*a*]pyridine Methopicrate (10). 1. When imidazo[1,2-*a*]pyridine methiodide[3] (0.2 g, 0.77 mmol) in hot absolute EtOH (5 ml) was treated with picric acid (0.20 g, 0.87 mmol) in hot absolute EtOH, and the solution concentrated to 5 ml and allowed to cool, yellow-brown needles, mp 150–154 °C (shrivel 140 °C), separated. Addition of Et_2O to the filtrate gave another solid, mp 202–205 °C, undepressed on admixture with starting material. On crystallization of the yellow-brown needles from EtOH, two kinds of crystals separated. The methopicrate therefore has solubility properties similar to those of the methiodide.

2. When the picrate was prepared as above, but in the presence of a few drops of aqueous 10% NaOH, it had mp 220–222 °C (depends on rate of heating), and was twice crystallized from absolute EtOH. Anal. Calcd for $C_{14}H_{11}N_5O_7$: C, 46.54; H, 3.05; N, 19.39. Found: C, 40.45; H, 2.36; N, 17.03; inorganic residue, 3.98. Compensating[21] for residue: C, 46.52; H, 2.71; N, 19.58.

Reaction of 3-Bromo-7-methylimidazo[1,2-*a*]pyridine (2a) with Nitric Acid. Compound **2a** (0.20 g) was dissolved in ice-cold concentrated H_2SO_4 (0.75 ml), cooled in ice, stirred, treated dropwise with concentrated HNO_3 (0.3 ml), left to stand for 5 min, and then treated with ice and aqueous 10% NaOH to pH ca. 5. The precipitated, almost colorless solid was filtered and rinsed with ice–water, EtOH, and Et_2O to give 0.11 g, mp explodes ca. 130 °C. A solution of this material in reagent grade acetone (30 ml) was filtered and then evaporated in a stream of N_2 to 1 ml to give a colorless solid which on drying at room temperature in vacuo turned yellow: ^{1}H NMR (Me_2SO-d_6) τ 1.04 (d, $J \sim 8$ Hz), 2.24 (broad), 2.95 (q, $J \sim 8$ and 2 Hz) (area ratio 1:1:1), and 7.50 (overlaps with Me_2SO peak).

Reaction of 3-Bromo-2-methylimidazo[1,2-*a*]pyridine (14a) with Nitric Acid. Crude **14a**[3] was twice subjected to chromatography, once eluted with $CHCl_3$, the second time with C_6H_6. TLC (alumina, 50% $CHCl_3$/C_6H_6) developed with I_2 showed only one component. Later scrutiny (TLC, uv detection, and NMR) indicated the presence of 10–15% 2-methylimidazo[1,2-*a*]pyridine.

1. This material (0.20 g, 0.85 mmol **14a**) was treated with concentrated H_2SO_4 (0.75 ml) and concentrated HNO_3 (0.50 ml) as above; the solution was left to stand for 3 min, poured on ice, and treated with aqueous 20% NaOH to pH ca. 2. A pale yellowish solid was filtered (0.080 g, mp 180 °C dec). Attempts to purify it failed. The filtrate was extracted with 4 × 10 ml of $CHCl_3$; the extracts were dried and stripped of solvent to give a 3:1 mixture (0.11 g) of **14b** (ca. 50%) and 2-methyl-3-nitroimidazo[1,2-*a*]pyridine according to its ^{1}H NMR spectrum. The mixture was percolated through 15 g of alumina with C_6H_6 which eluted 2-methyl-3-nitroimidazo[1,2-*a*]pyridine (0.02 g), identical with an authentic sample (vide infra). The column was left overnight when the top ⅔ had turned pale yellow. Elution with $CHCl_3$ gave only small amounts of **14b.** Elution with 6% absolute EtOH/$CHCl_3$ gave the alcohol **14c** (0.020 g), which was crystallized from C_6H_6 (0.3 ml, charcoal) and sublimed (100 °C, 0.025 Torr), and then had mp 131–134 °C; ^{1}H NMR ($CDCl_3$) τ H_5 1.89 (d, showing further fine splitting), H_8 2.36 (m), H_7 2.73 (m), H_6 3.08 (m), CH_2O 5.12 (s). Anal. Calcd for $C_8H_7N_2OBr$: C, 42.29; H, 3.08; N, 12.33; Br, 35.24. Found: C, 42.10; H, 3.15; N, 12.26; Br, 35.06.

2. A similar experiment (0.5 g of **14a**) afforded after chromatography 0.035 g of the aldehyde **14b,** which was sublimed (100 °C, 0.02 Torr) and then was colorless and had mp 123–125 °C (darken >110 °C); ^{1}H NMR ($CDCl_3$) τ CH=O −0.28 (s), H_5 1.74 (d, showing further fine splitting), H_6, H_7, H_8 ca. 2.55 (center of overlapping m). The aldehyde is air and heat sensitive. Anal. Calcd for $C_8H_5N_2OBr$: C, 42.67; H, 2.22; N, 12.44; Br, 35.56. Found: C, 42.93; H, 2.28; N, 12.52; Br, 35.32.

3. The $CHCl_3$ extracted mixture from another experiment (0.20 g of **14a**) was dissolved in EtOH (2 ml), a solution of H_2NOH·HCl (0.25 g, 3.6 mmol) in H_2O (1.5 ml) and aqueous 10% NaOH (1 ml) was added, and the solution was heated for 10 min on the steam bath (pH ca. 6). After the addition of 2 drops of aqueous 10% NaOH (pH 7), the solution was cooled in ice. The precipitate (0.070 g) was filtered, rinsed with H_2O, and recrystallized three times from absolute EtOH (0.5 ml) to give pale yellow oxime **14d:** mp 193 °C dec; ^{1}H NMR (Me_2SO-d_6) τ OH −1.72 (s), H_5 1.55 (d, showing further fine splitting), ch=N 1.72 (s), H_7, H_8 2.40 (center of overlapping m), H_6 2.80 (m). Anal. Calcd for $C_8H_6N_3OBr$: C, 40.00; H, 2.50; N, 17.50; Br, 33.33. Found: C, 39.93; H, 2.58; N, 17.60; Br, 33.10.

2-Methyl-3-nitroimidazo[1,2-*a*]pyridine. When crude 2-methylimidazo[1,2-*a*]pyridine (0.50 g) was treated with concentrated H_2SO_4 (2.5 ml) and concentrated HNO_3 (2.0 ml) as above, poured on ice, and treated with aqueous 20% NaOH to pH 3, a brown precipitate (0.33 g) was obtained. This was extracted with hot C_6H_6 (20 ml, charcoal). The solvent was evaporated and the residue recrystallized from 50% aqueous EtOH, followed by sublimation (100 °C, 0.02 Torr) to give the pale yellow product: mp 136–137 °C; ^{1}H NMR ($CDCl_3$) τ H_5 0.55 (d, showing further fine splitting), H_6 2.76 (m), H_7, H_8 2.36 (center of overlapping m), CH_3 7.12. Anal. Calcd for $C_8H_7N_3O_2$: C, 54.24; H, 3.95; N, 23.73. Found: C, 54.22; H, 3.99; N, 23.83.

Registry No.—**3,** 56051-29-7; **4,** 874-39-5; **5,** 59938-31-7; **6,** 59938-32-8; **8,** 59938-33-9; **9,** 59938-34-0; **10,** 59938-35-1; **11b,** 59938-37-3; **11d,** 59938-39-5; **14a,** 4805-70-3; **14b,** 59938-40-8; **14c,** 59938-41-9; **14d,** 59938-42-0; 3-bromoimidazo[1,2-*a*]pyridine, 4926-47-0; 3-nitro-7-methylimidazo[1,2-*a*]pyridine, 34165-07-6; 2-methyl-3-nitroimidazo[1,2-*a*]pyridine, 34165-09-8; 2-methylimidazo[1,2-*a*]pyridine, 934-37-2.

References and Notes

(1) W. W. Paudler and J. N. Chasman, *J. Heterocycl. Chem.*, **10,** 449 (1973); W. W. Paudler, C. I. Chao, and L. S. Helmick, *ibid.*, **9,** 995, 1157 (1972); W. W. Paudler, D. J. Pokorny, and J. J. Good, *ibid.*, **8,** 37 (1971); W. W. Paudler and H. G. Shin, *J. Org. Chem.*, **33,** 1638 (1968); W. W. Paudler and L. S. Helmick, *ibid.*, **33,** 1087 (1968); W. W. Paudler, J. E. Kuder, and L. S. Helmick, *ibid.*, **33,** 1379 (1968); W. W. Paudler and L. S. Helmick, *Chem. Commun.*, 377 (1967); W. W. Paudler and J. E. Kuder *J. Heterocycl. Chem.*, **3,** 33 (1966); W. W. Paudler and D. E. Dunham, *ibid.*, **2,** 410 (1965); W. W. Paudler and H. L. Blewitt, *J. Org. Chem.*, **31,** 1295 (1966); *Tetrahedron,* **21,** 353 (1965); *J. Heterocycl. Chem.*, **2,** 410 (1965).

(2) E. S. Hand and W. W. Paudler, *J. Org. Chem.*, **40,** 2916 (1975).

(3) H. L. Blewitt, Ph.D. Thesis, Ohio University, 1966.

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(5) J. P. Paolini and R. K. Robins, *J. Org. Chem.*, **30,** 4085 (1965).

(6) H. Rheinboldt in Houben-Weyl, "Methoden der Organischen Chemie", Vol. 9, E. Müller, Ed., Georg Thieme Verlag, Stuttgart, 1955, p 917.

(7) D. L. Klayman and W. H. H. Günther, Ed., "Organic Selenium Compounds: Their Chemistry and Biology", Wiley-Interscience, New York, N.Y., 1973.

(8) G. T. Morgan and F. H. Burstall, *J. Chem. Soc.*, 3260 (1928).

(9) In fact, this reaction has been suggested to be of diagnostic value in establishing the position of substitution by selenium.[6]

(10) A. D. Awtrey and R. E. Conwick, *J. Am. Chem. Soc.*, **73,** 1842 (1951), give λ_{max} ($\epsilon \times 10^{-4}$) 287 (4) and 353 nm (2.64) for I_3^- in H_2O.

(11) It should be noted that the formation of 3-haloimidazo[1,2-*a*]pyridine from the diarylselenide does not proceed nearly as readily with iodine as with bromine. In the latter case, the instantaneously formed precipitate no longer contains selenium and is, in fact, 3-bromoimidazo[1,2-*a*]pyridinium perbromide.[2]

(12) Loss of halogen was expected since we have already shown that 3-bromoimidazo[1,2-*a*]pyridine is converted to the parent compound **4** under these conditions.[3,4]

(13) C. A. Henrick, E. Ritchie, and W. C. Tayler, *Aust. J. Chem.*, **20,** 2441, 2445 (1967); J. W. Cornforth, R. Gigg, and M. S. Tute, *ibid.*, **20,** 2479 (1967); E. C. Taylor, W. W. Paudler, and C. K. Cain, *J. Org. Chem.*, **20,** 264 (1955).

(14) The usual silver nitrate test for ionic halogen could not be applied since imidazopyridines give insoluble silver complexes.

(15) Compounds **2** (3-halo-7-methylimidazo[1,2-*a*]pyridines), **4** (7-methylimidazo[1,2-*a*]pyridine), and the dimers **11** are not sufficiently soluble in D_2O to permit detection of chemical shift changes in the neutral vs. protonated species. Similarly, direct spectral comparison ($CDCl_3$) of the dimers and model compounds **2** and their hydrochloride or methiodide salts is not possible since the latter are insoluble in $CDCl_3$.

(16) The only reaction is the formation of small amounts of diselenide and parent compound which are also formed in refluxing acetic acid (ref 2).

(17) See, e.g., H. H. Willard and N. H. Furman, "Elementary Quantitative Analysis", 3d ed, Van Nostrand, Princeton, N.J., 1940, p 264.

(18) G. V. Boyd, M. Doughty, and J. Kenyon, *J. Chem. Soc.*, 2196 (1949), converted (p-$CH_3OC_6H_4)_2Se(OH)_2$ to (p-$CH_3OC_6H_4)_2Se$ by refluxing in 50%

acetic acid in the presence of Se and speculate that Se is the reducing agent. While Se *is* formed in the reaction of the bromoimidazo-[1,2-*a*]pyridine **2a** with SeO_2 in refluxing acetic acid and thus could, in principle, cause the reduction, it is *not* formed in the reaction of parent **4** with SeO_2 in refluxing acetic acid. These observations also implicate acetic acid.

(19) Unpublished results, our laboratory; ref 5.

(20) A. M. Roe, *J. Chem. Soc.*, 2195 (1963).

(21) The found percentages of C, H, and N were multiplied by the same factor to obtain the compensated percentages. The factor is arbitrary since the structures of inorganic material and its combustion product are not known and therefore the percent inorganic material prior to combustion cannot be calculated. In any event, the found C, H, and N percentages are in the ratio of 14:11:5, as required.

An Example of the Amine Catalyzed Retro-Aldol Reaction. Dehydration and Cleavage of 1-(3-Chlorophenyl)-1-methyl-2-phenyl-2-(2-pyridine)ethanol. A Case of Kinetic and Thermodynamic Competition

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The behavior of the two racemic pairs of 1-(3-chlorophenyl)-1-methyl-2-phenyl-2-(2-pyridine)ethanol (1) on treatment with heat and acid is reported. Initially, in 85% phosphoric acid dehydration to the terminal olefin 2-(3-chlorophenyl)-3-phenyl-3-(2-pyridine)propene (**2**) occurs followed by isomerization to the conjugated, thermodynamically preferred material, 2-(3-chlorophenyl)-1-phenyl-1-(2-pyridine)propene (**3**). The dehydration pathway is in direct competition with fragmentation of **1** to 3-chloroacetophenone (**4**) and 2-benzylpyridine (**5**). Exclusive thermal rearrangement of **1** to **4** and **5** is the first example of an amine catalyzed retro-aldol reaction where the intermediate Schiff's base is contained within a heterocyclic ring. On the basis of greater thermal stability of isomer **1a** as compared to **1b**, structures are proposed for the two racemic pairs of compound **1**.

1-(3-Chlorophenyl)-1-methyl-2-phenyl-2-(2-pyridine)-ethanol (**1**), on oral administration to the rat, possesses excellent hypocholesteremic activity and extremely low toxicity.[1] Unfortunately, in monkeys and man it is not hypocholesteremic.[1] Currently this dichotomy of activity is being investigated by examining the metabolic products obtained from dosages of radiolabeled **1** to both rats and monkeys and exploring its physical and chemical properties.[2,3] Knowledge gained by these studies hopefully will lead to the design and synthesis of compounds effective in man.

It should be noted that compound **1** contains two chiral centers and it is obtained from synthesis as a mixture of two racemic pairs.[1,2] These pairs, which can be separated by fractional crystallization, are distinguished by characteristic NMR and melting points. Only the higher melting racemate (**1a**) possesses significant ability to lower blood cholesterol levels in the rat. One of a number of likely candidates for a metabolite of **1** is the conjugated alkene, 2-(3-chlorophenyl)-1-phenyl-1-(2-pyridine)propene (**3**), derived from **1** by the loss of water. An earlier report[1] describes dehydration of a number of 2-(2-pyridyl)-1,2-diarylalkanols by treatment with 85% phosphoric acid at 100 °C for 3 h. Conjugated alkenes analogous to **3** were the only reported products.[1] The present study involves investigation of the behavior of alcohol **1** to treatment with phosphoric acid both as a pathway to the synthesis of possible metabolite **3** and to gain knowledge of its acid sensitivity with respect to decomposition.

Compound **1**, as a mixture of the two racemic pairs, was dissolved in 85% phosphoric acid and was stirred at 110 °C for 3 h. A white, crystalline solid was isolated from the reaction mixture in 33.4% yield after numerous purifications. It proved to be the terminal olefin **2** and not the expected conjugated alkene **3**. The reaction mixture also contained approximately equal amounts of 3-chloroacetophenone (**4**) and 2-benzylpyridine (**5**), small amounts of unreacted **1**, and a trace of a material which was later identified as the conjugated alkene **3** (Scheme I).

These results led to an investigation of the behavior of the higher and lower melting racemates of **1** separately but under identical conditions. When the higher melting racemate (**1a**) was treated under these conditions, **2** was again isolated but with a yield which had increased to 70%. Though all other side products were also present, combined they represented a much smaller percentage of the total product yield than that of the previous experiment (Table I). The lower melting racemate (**1b**), when treated in the same fashion, also produced the same five compounds. In this case, the high yield of decomposition products 3-chloroacetophenone and 2-benzylpyridine made separation of **2** or **3** from the reaction mixture difficult. These results coupled with earlier experimental findings[4] suggest that **1a** is more stable to conditions of heat and acid than its lower melting counterpart (**1b**). Yet these data do not explain the predominance of the dehydrated product **2** in preference to the expected conjugated alkene **3**.

When a mixture of both racemic pairs of **1** was submitted to identical reaction conditions for 5 h instead of the usual 3 h, the product distribution was essentially the same. But when the reaction time was extended to 24 h, a definite change took place. Conjugated alkene **3** was now present in substantial quantity along with **2** and decomposition products **4** and **5**. After treatment of **1** under these conditions for 72 h, only a trace of **2** remained, and **3**, now a major product, was isolated as a white, crystalline solid. These data strongly suggest that **2** is the initially formed kinetic product which is then isomerized to the thermodynamically more stable conjugated al-