# Perchloroimidazo[1,2-*a*]pyridine. Synthesis and Nucleophilic Substitutions

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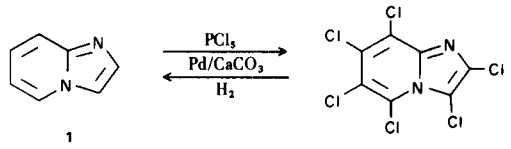
Perchloroimidazo[1,2-*a*]pyridine has been prepared and it has been shown that nucleophilic substitution occurs preferrentially at $C_5$ possibly followed by substition at $C_7$.

As part of a study aimed at the examination of perhalogenated polyazaindenes we have now prepared perchloroimidazo[1,2-*a*]pyridine (**2**) and have subjected it to nucleophilic displacement with several nucleophiles.

The perchloroimidazo[1,2-*a*]pyridine (**2**) was obtained

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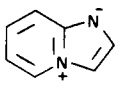
in high yield by treatment of imidazo[1,2-*a*]pyridine (**1**) with phosphorus pentachloride at 275° in a sealed tube.

The mass spectrum of this compound shows a parent peak at m/e 332 with a typical 6-chlorine isotope pattern. The molecular ion fragments with successive loss of the six chlorine atoms to give fragments at m/e 287, 252, 217, 182 and 147, respectively.

This information, along with the absence of any proton signals in the pmr spectrum, and the correct elemental analysis of this compound confirms its structure. Final proof that no skeletal rearrangement has taken place under the rather severe reaction conditions employed in the genesis of this compound is offered by the fact that hydrogenation with palladium on calcium carbonate regenerates imidazo[1,2-*a*]pyridine (**1**).

It now became of interest to examine the lability of the various chlorine atoms in perchloroimidazo[1,2-*a*]-pyridine towards different nucleophiles.

Neither 2-, nor 3-chloroimidazo[1,2-*a*]pyridine is subject to facile nucleophilic displacement of the halogen atom (1), an observation which is not surprising in view of the fact that the major resonance contributor to the ground-state of imidazo[1,2-*a*]pyridine is **3**.



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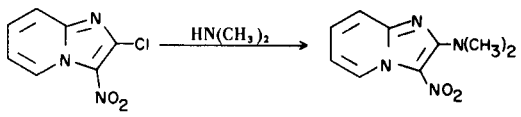
However, the chlorine atom in 2-chloro-3-nitromidazo-[1,2-*a*]pyridine (**4**) can be nucleophilically substituted by dimethylamine to afford compound **5** (2).

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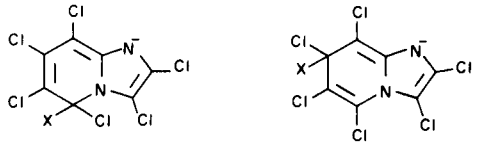
Paolini and Robins (1) have shown that 5-chloroimidazo-[1,2-*a*]pyridine is converted to the 5-methoxy derivative, when heated with sodium methoxide in methanol.

A consideration of the various Wheland intermediates involved in nucleophilic displacements of the different chlorine atoms in perchloroimidazo[1,2-*a*]pyridine suggests that the 5- and the 7-chlorine should be replaceable (cf. structures **6** and **7**). In all of the other feasible inter-



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mediates it is impossible to localize the extra negative charge on the highly preferred nitrogen atom $N_1$.

A comparison of structures **6** and **7** indicates that the more conjugated intermediate **6** should be preferred over the less stabilized one, **7**. Thus, the 5-chlorine atom should be the most susceptible of the six chlorine atoms in perchloroimidazo[1,2-*a*]pyridine towards nucleophilic displacement.

When perchloroimidazo[1,2-*a*]pyridine is treated with sodium methoxide in methanol at 0°, there is obtained a white crystalline product. The elemental analysis, mass spectrometric molecular weight, chlorine isotope cluster and the presence of a single proton signal at $\tau$ 5.94 is conclusive evidence that the compound is a monomethoxy-

pentachloroimidazo[1,2-*a*]pyridine (**8**).

In order to determine the site of substitution, the compound was treated with hydrogen in the presence of palladium on calcium carbonate to afford a compound which has a mass spectrometric molecular weight of 148 and whose elemental analysis confirms that it is a methoxyimidazo[1,2-*a*]pyridine.

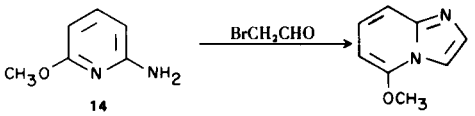
The pmr spectrum of this compound (**12**) shows an AB pattern at $\tau$ 2.39 and 2.80 (J = 1.0 cps). Clearly, this pattern is due to $H_2$ and $H_3$, respectively. If the methoxy group were located at either $C_6$ or $C_7$, we would expect to observe a singlet in the pmr spectrum corresponding to $H_5$ or $H_8$, respectively. The absence of such a singlet thus excludes the possibility that substitution has occured at either $C_6$ or $C_7$.

Consequently, the methoxy group must be situated either at $C_5$ or $C_8$.

We have shown earlier (3) that $H_5$ is the most deshielded proton in imidazo[1,2-*a*]pyridine and that $H_3$ is coupled to $H_8$. Since $H_3$, upon scale expansion, shows coupling ($J_{38}$ = 0.7 cps), in addition to that due to $H_2 - H_3$, one can suggest that the methoxy compound still has $H_8$ and thus the methoxy group is situated at $H_5$.

This analysis is further confirmed by the presence of $H_7$ at $\tau$ 2.88 ($J_{67}$ = 7.0; $J_{78}$ = 6.0 cps), of $H_6$ at $\tau$ 4.02 ($J_{67}$ = 7.0 cps) and of $H_8$ at $\tau$ 2.42 ($J_{78}$ = 6.0 cps, $J_{38}$ = 0.7 cps).

Final proof, that the methoxy compound is indeed the 5-methoxy imidazo[1,2-*a*]pyridine (**12**) is offered by its unequivocal synthesis from 2-amino-6-methoxypyridine (**14**), and the fact that the physical properties of this

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compound (m.p. of the B·HCl, pmr spectrum in trifluoroacetic acid) are the same as those reported for the methoxyimidazo[1,2-*a*]pyridine prepared by Paolini and Robins (1) by nucleophilic displacement of the chloro group of 5-chloroimidazo[1,2-*a*]pyridine with a methoxy group. Consequently, the suggestion that the Wheland intermediate **6** is the more stable is confirmed by experiment.

Treatment of the perchloro compound **2** with potassium *t*-butoxide also yielded a mono-substitution product (**9**) presumably the 5-*t*-butoxy-2,3,6,7,8-pentachloroimidazo[1,2-*a*]pyridine. An increase in the severity of the reaction conditions caused decomposition of the starting material.

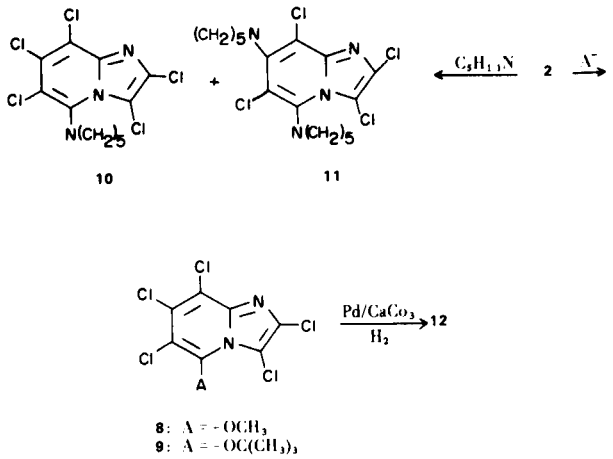
When, however, the nucleophile is piperidine, one can isolate in addition to a monosubstituted compound (**10**), a dipiperidyl derivative (**11**).

Unfortunately, all attempts at substituting the halogen atoms by hydrogens failed, and a definite structure proof of this compound has not yet been possible.

Nevertheless, one can suggest with some confidence that it is the 5,7-dipiperidyl-2,3,6,8-tetrachloroimidazo-[1,2-*a*]pyridine that is formed.

The various transformations described above are delineated in Scheme I.

SCHEME I

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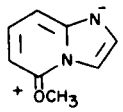
8: A = -OCH3
9: A = -OC(CH3)3

At this point, it is instructive to compare the pmr spectra of the methoxyimidazo[1,2-*a*]pyridine (**12**) and 5-methylimidazo[1,2-*a*[pyridine (**13**). As would be expected for a 5-methoxy derivative, H-6 in this derivative is more shielded than the same proton in the 5-methyl compound (**13**). The chemical shifts of the remaining protons are essentially unaltered when the 5-methyl group is replaced by the 5-methoxy function.

The one interesting feature is the decrease in $J_{78}$ when going from the 5-methyl to the 5-methoxy compound. This difference, 3.0 cps, reflects the contribution, to the ground state of the 5-methoxy compound, of structure **12a** where, clearly, the $C_7$–$C_8$ bond is longer than in the 5-methyl compound.




12a

TABLE I

NMR Data of 5-Methoxy- and 5-Methylimidazo[1,2-*a*]pyridine

| Compound | Chemical Shifts ($\tau$) | | | | | Coupling Constants (cps) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $H_2$ | $H_3$ | $H_6$ | $H_7$ | $H_8$ | $J_{23}$ | $J_{38}$ | $J_{67}$ | $J_{78}$ | $J_{68}$ |
| 5-Methylimidazo[1,2-*a*]pyridine (**13**) | 2.37 | 2.68 | 3.65 | 3.05 | 2.52 | 1.2 | 0.8 | 7.0 | 9.0 | 1.2 |
| 5-Methoxyimidazo[1,2-*a*]pyridine (**12**) | 2.39 | 2.80 | 4.02 | 2.88 | 2.42 | 1.0 | 0.7 | 7.0 | 6.0 | 1.4 |

## EXPERIMENTAL (5)

Perchloroimidazo[1,2-*a*]pyridine (**2**).

Imidazo[1,2-*a*]pyridine (2,4) (1 g., 8.1 mmoles), and 17.6 g. (81 mmoles) of phosphorus pentachloride was placed into a steel bomb and the sealed reaction vessel was heated at 275° for 4 hours. To the cooled bomb was then added 500 g. of ice and 250 ml. of chloroform. After the phosphorus pentachloride had been decomposed (about 1/2 hour of shaking), the mixture was collected and boiled on a steam-bath for 10 minutes, the chloroform layer was collected, boiled with Norite for 10 minutes and the mixture was filtered. The chloroform was removed *in vacuo* and the remaining solid was recrystallized from methanol to afford 1.8 g. (65% of theory) of perchloroimidazo[1,2-*a*]pyridine, m.p. 146.9-147.6°.

*Anal.* Calcd. for $C_7Cl_6N_2$: C, 25.88; N, 8.62; Cl, 65.49. Found: C, 26.03; N, 8.65; Cl (diff.), 65.32.

5-Methoxy-2,3,6,7,8-pentachloroimidazo[1,2-*a*]pyridine (**8**).

To 30 ml. of absolute methanol was slowly added 0.710 g. (32 mmoles) of sodium. When the sodium had completely reacted, the solution was cooled to 0° and 1 g. of perchloroimidazo[1,2-*a*]pyridine dissolved in 50 ml. of dry dioxane was added dropwise over a 3 hour period. During the course of the reaction the solution turned from light yellow to deep purple. After addition of all of the perchloro compound, the mixture was stirred for an additional 30 minutes. Water was then added to the solution until a precipitate began to separate. This solid was then collected, dried under vacuum and recrystallized from methanol to yield 0.37 g. (38% of theory) of 5-methoxy-2,3,6,7,8-pentachloroimidazo[1,2-*a*]pyridine (m.p. 178-179°).

*Anal.* Calcd. for $C_8H_3Cl_5N_2O$: C, 29.99; H, 0.94; N, 8.81. Found: C, 30.45; H, 0.91; N, 8.53.

5-*t*-Butoxy-2,3,6,7,8-pentachloroimidazo[1,2-*a*]pyridine (**9**).

A procedure similar to that described for the preparation of compound **8** was employed, except that the water solution was continuously extracted with chloroform to yield 0.02 g. (20% of theory) of 5-*t*-butoxy-2,3,6,7,8-pentachloroimidazo[1,2-*a*]pyridine (**9**) (m.p. 115-116°, after vacuum sublimation at 85°/0.5 mm).

*Anal.* Calcd. for $C_{11}H_9Cl_5N_2O$: C, 36.45; H, 2.50; N, 7.77. Found: C, 36.64; H, 2.52; N, 7.90.

5-Piperidyl- and 5,7-Dipiperidylperchloroimidazo[1,2-*a*]pyridine (**10** and **11**).

To a solution of 1.68 g. of potassium hydroxide in 50 ml. of piperidine was added 1 g. of perchloroimidazo[1,2-*a*]pyridine. The mixture was heated at reflux with stirring for 60 hours. The reaction was monitored by means of TLC (silica-gel, chloroform) until no more starting material was present. The excess piperidine was removed *in vacuo*, 50 ml. of water was added to the residue and the aqueous solution was continuously extracted (24 hours) with chloroform. The chloroform extract was dried (anhydrous sodium carbonate), filtered and evaporated to dryness. The residue was then chromatographed on Grade II neutral alumina. A dipiperidyl compound was eluted with hexane and the monopiperidyl derivative with 20% ether in hexane.

The monopiperidyl derivative **10** was obtained in 4% yield (0.045 g., m.p. 274-275°) and the dipiperidyl derivative **11** was isolated in 22% yield (0.277 g., m.p. 177-178°). Both compounds were purified by recrystallization from methanol.

*Anal.* Calcd. for $C_{12}H_{10}Cl_5N_3$ (compound **10**): C, 38.59; H, 2.70; N, 11.32. Found: C, 38.75; H, 2.77; N, 11.13.

*Anal.* Calcd. for $C_{17}H_{20}Cl_4N_4$ (compound **11**): C, 48.36; H, 4.76; N, 13.33. Found: C, 48.67; H, 4.89; N, 13.27.

5-Methoxyimidazo[1,2-*a*]pyridine (**12**).

(A) From Reduction of 5-Methoxy-2,3,6,7,8-pentachloroimidazo-[1,2-*a*]pyridine (**8**).

A solution of 164 mg. (0.5 mm) of compound **8** in 10 ml. of dioxane was added to a prereduced suspension of 300 mg. of palladium on calcium carbonate in 30 ml. of methanol containing 0.7 g. of potassium hydroxide. This mixture was then stirred in a hydrogen atmosphere at room temperature and atmospheric pressure for 24 hours. The suspended catalyst was removed by titration and the filtrate was evaporated to dryness. The solid residue was then dissolved in 10 ml. of water and the solution was continuously extracted with chloroform for 10 hours. Removal of the dried (anhydrous sodium sulfate) chloroform left a yellow oil which was collected (50 mg., 69% yield), on a cold finger, by distillation at 70°/1 mm.

(B) From 2-Amino-6-methoxypyridine.

The 2-amino-6-methoxypyridine (**14**) was obtained from 2,6-dibromopyridine by the method of den Hertog and Wibaut (4). To a mixture of 1 g. of sodium bicarbonate, 145 mg. (1.17 mm) of the aminopyridine **14** in 3 ml. of water was added a solution of bromoacetaldehyde prepared by heating 0.4 ml. of bromoacetaldehyde diethyl acetal in 0.4 ml. of water and 0.1 ml. of concentrated hydrobromic acid for one hour. This reaction mixture was then stirred for 2 hours and after the addition of 5 ml. of water, the solution was extracted exhaustively (5 x 10 ml.) with chloroform. The combined chloroform extracts were passed through a short alumina column (20 g., Brockman Grade III, neutral alumina) and the product was eluted with a total of 150 ml. of chloroform.

Evaporation of the chloroform eluate afforded 122 mg. (70% yield) of 5-methoxyimidazo[1,2-*a*]pyridine. The pmr spectrum, behavior on TLC, mass spectrum and the m.p. of the base hydrochloride (m.p. 161-162°) are identical with the compound obtained by procedure A, above, and the material described by Paolini and Robins (1).

## REFERENCES

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

(3) W. W. Paudler and H. L. Blewitt, *Tetrahedron*, **21**, 356 (1965).

(4) H. J. dec Hertog and J. P. Wibaut, *Rec. Trav. Chim.*, **55**, 122 (1936).

(5) NMR Spectra were obtained with a Varian HA-100 instrument as dilute solutions in chloroform. The mass spectra were obtained with a Hitachi-Perkin Elmer RMU-6E instrument. Elemental analyses were done by Mrs. P. Jones of this department.