Imidazo[1,5-a]pyrazines. IV. Aromatic Substitution Reactions[1,2]

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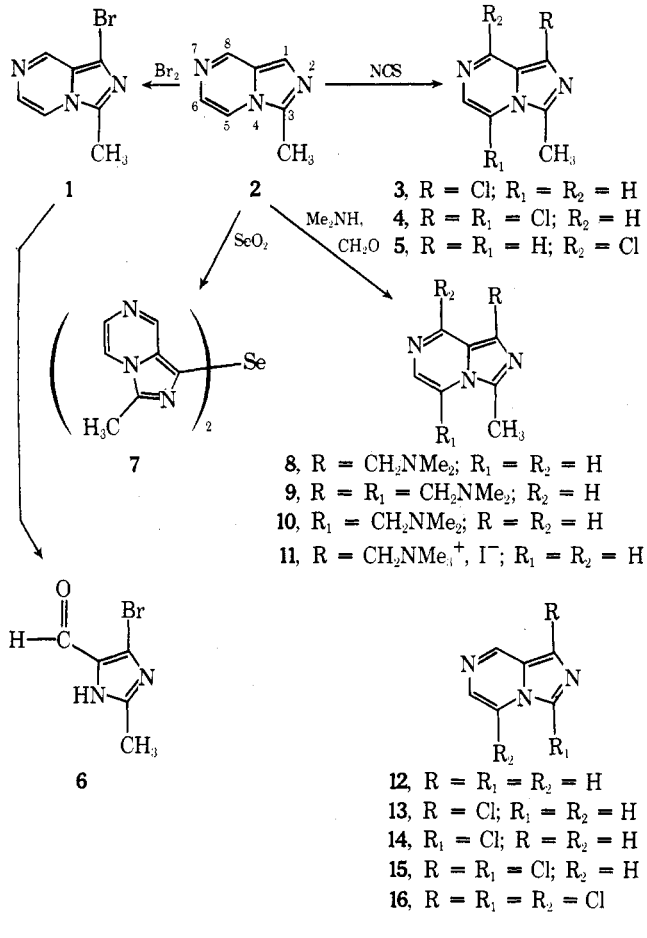
Aromatic substitution reactions on the imidazo[1,5-a]pyrazine nucleus were studied using a variety of electrophilic reagents. Three positions, namely, C-1, C-3 (when there is no substituent), and C-5, were found amenable to electrophilic attack. Chlorination of 3-methylimidazo[1,5-a]pyrazine (2) furnished the 1-chloro derivative (3) as well as the 1,5-dichloro derivative (4). Similarly chlorination of the parent nucleus 12 furnished four derivatives, 13–16, which involved substitution at the C-1, C-3, and (by analogy with 4) C-5. The positions of these substituents were confirmed by ^1H and ^{13}C NMR studies. Other reactions studied included bromination, reaction with selenium dioxide, and the Mannich reaction; in the latter case, the C-5 substitution position in 9 and 10 was assigned by analogy to the chlorination reaction.

Previous papers in this series have described approaches to synthesis of functionally substituted imidazo[1,5-a]pyrazines by way of cyclization of appropriate molecules. A more direct method of functionalization of the heterocyclic system would seem to be available via aromatic substitution reactions on the parent nucleus; this paper describes such studies.

Treatment of the 3-methyl derivative (2)[3] with a limited amount of *N*-chlorosuccinimide (NCS) in carbon tetrachloride with benzoyl peroxide present gave a mixture of two products which could be separated chromatographically. The major product was identified as the 1-chloro-3-methyl derivative (3) by the disappearance of the signal for the C-1 proton[3] from the ^1H NMR spectrum. The second product was the 1,5-dichloro-3-methyl derivative (4) as was shown by analysis of the ^{13}C NMR spectrum (vide infra). The reaction of 2 with iodosobenzene dichloride and with NCS in ethanol also yielded 3, suggesting that the substitution reaction was a normal, electrophilic substitution and that the benzoyl peroxide employed in the initial experiments did not influence the results.

The reaction of 2 with bromine in carbon tetrachloride at ice temperature gave a reasonable yield of the 1-bromo derivative (1); more vigorous conditions led to a mixture of polybrominated products that could not be readily separated. In an effort to prepare a dibromo derivative of 2, the 1-bromo compound (1) was treated with bromine in water and the acid generated was neutralized with excess dilute sodium hydroxide solution. The only product isolated was the imidazole carboxaldehyde (6) presumably resulting from the addition of water across the 7,8 double bond followed by alkaline decomposition of the carbinolamine. Both the chlorine substituent in 3 and the bromine substituent in 1 were resistant to nucleophilic substitution by azide and thiocyanate ions, ammonia, thiourea, or hydrazine. At higher temperatures hydrazine appeared to give ring-opened compounds that could not be characterized. This contrasts with the reactivity of the 8-chloro substituent in 5 which reacted readily with thiourea to give the corresponding thione.[4]

The Mannich reaction[5] was investigated in another attempt to functionalize 2. Reaction with formaldehyde and dimethylamine gave a mixture of products that could be separated chromatographically. The major product was the 1-dimethylaminomethyl derivative (8), isolated as an oil and characterized as its crystalline methiodide, 11. A very small amount of another monosubstituted derivative was separated as well as a disubstituted product and these have



been assigned tentatively the 5 and 1,5 structures (10 and 9, respectively) by analogy with the substitution pattern noted in the dichloro derivative (4).

In an attempt to oxidize the 3-methyl substituent of 2 to a formyl group, the compound was treated with selenium dioxide but the product was that of a substitution reaction, namely the diselenide (7).

The parent compound, imidazo[1,5-a]pyrazine (12), was treated with *N*-chlorosuccinimide in a mixture of chloroform and carbon tetrachloride to give a complex mixture of products that was separated by chromatography. The major products could be identified, on the basis of ^1H NMR spectra, as the 1-chloro compound (13), the 3-chloro compound (14), and the 1,3-dichloro derivative (15). A small amount of a trichloro derivative was isolated and its

Table I
^{13}C NMR Data[a]

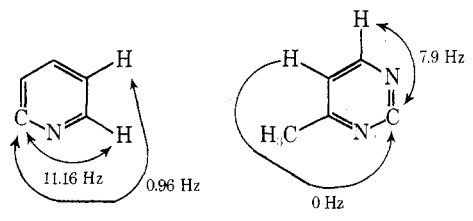
Compd	C_1	C_3	C_5	C_6	C_8	C_9	CH_3
2	123.4 (194, H-1)	136.8	113.5 (186.2, H-5; 11.1, H-6)	128.0 (185.1, H-6; 5.1, H-5; 12.7, H-8)	145.9 (185, H-8; 10.5, H-6)	126.4	12.0
3		135.6	113.6 (188, H-5; 13, H-6)	129.2 (186.8, H-6; 5, H-5; 13, H-8)	145.3 (188, H-8; second order H-6)	121.8	12.0
4		137.4 (8, CH_3)		128.3 (190, H-6; 14, H-8)	143.5 (198, H-8; 11, H-6)	124.2	17.0
5	124.6		112.7	126.6			12.5

[a] Chemical shifts are expressed in parts per million downfield from Me_4Si. Data in parentheses refer to coupling constants, in hertz, between the carbon and the indicated proton.

structure is written as the 1,3,5 derivative (**16**) by analogy with the results of the similar chlorination of **2**.

NMR Spectra.[6] The small difference in chemical shift between H-5 and H-6 and the multiplicities of the signal in **2** did not permit an unambiguous assignment, based on ^1H NMR data, of the dichloro product from **2** to the 1,5-dichloro-3-methyl or to the 1,6-dichloro-3-methyl structure, although the 1,8-dichloro-3-methyl structure could be eliminated with confidence. Fortunately, the use of ^{13}C NMR data permitted the compound to be assigned as 1,5-dichloro-3-methylimidazo[1,5-*a*]pyrazine (**4**). The ^{13}C NMR data of compounds **2–5** are summarized in Table I. Chemical shift assignments in compound **2** were based on chemical transformations as well as analogies with similar compounds. Differences in peak intensities clearly identify quaternary carbons C-9 and C-3 at 126.4 and 136.8 ppm, respectively. Distinction between these two absorptions came from the spectrum of compound **4**, where careful decoupling studies were made and which showed a quaternary carbon as a quartet at 137.4 ppm, identifiable as C-3. Absorptions at 123.4 and 145.9 ppm were assigned to C-1 and C-8. These signals were absent in the spectra of compounds **3** and **5**, respectively. These two carbons are quaternary in **3** and **5**, respectively, and do not experience the full nuclear Overhauser enhancement which exists in the parent compound **2**.

The signals at 113.5 and 128.0 ppm were assigned to C-5 and C-6, respectively, based upon the magnitude of the coupling constants between these two absorptions and H-8 (Table I). The higher field absorption showed no detectable coupling while the lower field signal had a coupling constant ($^3J_{C,H}$) of 12.7 Hz. These data find analogy in both the pyridine and pyrimidine systems (**17** and **18**)



17 **18**

where $^3J_{C,H}$ and $^4J_{C,H}$ in pyridine were 11 and 1 Hz, respectively,[7] and the same splittings in 4-methylpyrimidine were of similar magnitudes.[8]

The complete assignment of ^{13}C chemical shifts allowed unambiguous determination of the structure of the dichloro compound as **4**. The noise decoupled spectrum of this compound lacked the 113.5-ppm signal. In addition a downfield shift (+5.0 ppm) of the C-3 methyl group was observed. This can be attributed to steric interactions between the C-3 and C-5 substituents in a manner similar to that reported for the 4-methyl group (+3.3 ppm) in 1,4,8-trimethyl-5-fluorophenanthrene.[9] A similar shift (+5.9 ppm) was observed for the methyl group in 1-methylnaphthalene[10] when another methyl group was introduced at C-8.[11]

Experimental Section

Melting points (uncorrected) were determined with a Thomas-Hoover capillary apparatus. ^1H NMR spectra were determined on a Varian A-60 apparatus or on a JEOLCO C-60-HL instrument using $CDCl_3$ and Me_4Si unless otherwise noted. ^{13}C NMR spectra were obtained on a Varian CFT-20 NMR spectrometer. Mass spectral molecular weights were obtained from either a Perkin-Elmer RMV-6E or a CEC 24-104 spectrometer. Microanalyses were performed by Microanalysis, Inc., Marshallton, Del. All evaporations were carried out in vacuo using a water aspirator or a water pump and solutions were dried over anhydrous sodium sulfate unless otherwise noted.

1-Bromo-3-methylimidazo[1,5-*a*]pyrazine (1). To a stirred solution of 0.27 g (2 mmol) of 3-methylimidazo[1,5-*a*]pyrazine (**2**)[3] in 50 ml of carbon tetrachloride at 0° was added, over a period of 5 min, a solution of 0.48 g (3 mmol) of bromine in 50 ml of carbon tetrachloride. After the mixture had been stirred for 10 min the solvent was evaporated and the residue dissolved in 5 ml of water. The aqueous solution was neutralized with 20% aqueous sodium hydroxide and the solution was extracted with three 50-ml portions of chloroform. Evaporation of the dried extracts left a residue that was crystallized from hexane–acetone to give 0.30 g (62%) of **1**: mp 119–120°; ^1H NMR δ 2.7 (CH_3, 3 H, s), 7.6 (H-5 and H-6, 2 H, m), 8.8 (H-8, 1 H, broad s).

Anal. Calcd for $C_7H_6BrN_3$: C, 39.62; H, 2.83; N, 19.81; Br, 37.73. Found: C, 39.84; H, 2.90; N, 19.66; Br, 37.80.

1-Chloro-3-methylimidazo[1,5-*a*]pyrazine (3). A mixture of 0.67 g (5.0 mmol) of **2**, 0.80 g (6.0 mmol) of *N*-chlorosuccinimide, 0.015 g of benzoyl peroxide, and 100 ml of carbon tetrachloride was heated, with stirring, at reflux for 45 min, then cooled to 0° and filtered to separate the succinimide. The filtrate was evaporated and the residue was transferred to a dry alumina (75 g) column, eluting with dichloromethane. The first fraction yielded 0.015 g (1.5%) of 1,5-dichloro-3-methylimidazo[1,5-*a*]pyrazine (**4**) and was followed by 0.48 g (56%) of 1-chloro-3-methylimidazo[1,5-*a*]pyrazine (**3**), which was recrystallized from hexane: mp 102°; ^1H NMR δ 2.6 (CH_3, 3 H, s), 7.5 (H-5 and H-6, 2 H, m), 8.8 (H-8, 1 H, broad s).

Anal. Calcd for $C_7H_6ClN_3$: C, 50.15; H, 3.58; N, 25.07; Cl, 21.19. Found: C, 50.19; H, 3.87; N, 24.95; Cl, 21.13.

1,5-Dichloro-3-methylimidazo[1,5-*a*]pyrazine (4). The above procedure was repeated using 0.5 mmol of **2**, 1.1 mmol of NCS, 5 mg of benzoyl peroxide, and 20 ml of carbon tetrachloride. The chromatographic separation yielded 15% of **3** and 20% of **4**, which was recrystallized from hexane: mp 90–91°; ^1H NMR δ 3.0 (CH_3, 3 H, s), 7.5 (H-6, 1 H, s), 8.8 (H-8, 1 H, s).

Anal. Calcd for $C_7H_5Cl_2N_3$: C, 41.58; H, 2.47; N, 20.8; Cl, 35.15. Found: C, 41.57; H, 2.61; N, 20.91; Cl, 35.10.

4(5)-Bromo-5(4)-formyl-2-methylimidazole (6). To 0.21 g (1.0 mmol) of 1-bromo-3-methylimidazo[1,5-*a*]pyrazine (**1**) dissolved in 1 ml of water was added a solution of 0.32 g (2.0 mmol) of

bromine in 20 ml of water. The reaction mixture was then brought to pH 11 by the dropwise addition of 10% aqueous sodium hydroxide solution. The solution was extracted with four 75-ml portions of chloroform–methanol (9:1), and the extracts were dried over potassium carbonate and then evaporated to give a residue which was recrystallized twice from acetone–hexane (1:4) to furnish 0.058 g (31%) of the aldehyde **5**: mp 222–223° dec; ^{1}H NMR δ 2.4 (CH_3, 3 H, s), 9.6 (O=CH, 1 H, s), 13.3 (–NH, 1 H, broad, D_2O exchangeable).

Anal. Calcd for $C_5H_5BrN_2O$: C, 31.77; H, 2.67; N, 14.82; Br, 42.28. Found: C, 32.10; H, 2.75; N, 14.70; Br, 42.86.

1,1′-Selenobis(3-methylimidazo[1,5-a]pyrazine) (7). Freshly sublimed selenium oxide (1.11 g, 10.0 mmol) was added to a stirred solution of 1.33 g (10 mmol) of **2** in glacial acetic acid and the reaction mixture was heated under reflux for 2.5 hr. The mixture was cooled and evaporated, giving a residue that was extracted with five 20-ml portions of hot chloroform. The extracts were evaporated and the residue applied to a dry alumina (80 g) column, eluting with chloroform–methanol (99:1). The first fraction yielded 0.20 g of starting material **2** and was followed by 0.60 g (40%) of **7** which was recrystallized from 50% aqueous ethanol: mp 239–240°; ^{1}H NMR δ 2.63 (CH_3, 3 H, s), 7.57 (H-5 and H-6, 2 H, m), 9.13 (H-8, 1 H, broad s).

Anal. Calcd for $C_{14}H_{12}SeN_6$: C, 48.98; H, 3.50; N, 24.65. Found: C, 48.73, H, 3.50; N, 24.48.

Mannich Reaction with 2. A solution of the Mannich reagent was prepared by mixing with mild agitation 45 ml (0.12 mol) of 35% aqueous dimethylamine (precooled to 5°), 15.5 g (0.26 mol) of glacial acetic acid (precooled to 5°), and 20 ml (0.10 mol) of 40% aqueous formaldehyde (precooled to 5°). This solution was added to 9.3 g (0.07 mol) of 3-methylimidazo[1,5-a]pyrazine (**2**) contained in the pressure vessel of a low-pressure Parr hydrogenator. The reaction mixture was heated on a steam bath for 2 hr, cooled, and treated with more of the Mannich reagent, prepared as above, from 15 ml of 35% aqueous dimethylamine, 5.2 g of acetic acid, and 6 ml of 40% aqueous formaldehyde. The solution was again heated on the steam bath for 1.5 hr, then cooled and brought to neutrality with 20% aqueous sodium hydroxide. The solution was extracted with five 200-ml portions of chloroform and the extract was dried and evaporated to give 12 g of residue which was applied to a dry alumina (800 g) column using ethyl acetate as the eluent. The first fraction contained 0.090 g (0.07% yield) of an oil, identified by ^{1}H NMR spectrum as 5-dimethylaminomethyl-3-methylimidazo[1,5-a]pyrazine (**10**): ^{1}H NMR δ 2.3 (CH_3, 6 H, s), 3.1 (heterocyclic CH_3, 3 H, s), 3.6 (CH_2, 2 H, s), 7.3 (H-6, 1 H, s), 7.8 (H-1, 1 H, s), 8.8 (H-8, 1 H, s); *m/e* 190 (parent), 145 (base). The second fraction afforded 1.3 g (7.5%) of an oil, considered, on the basis of its ^{1}H NMR spectrum, to be 1,5-bis(dimethylaminomethyl)-3-methylimidazo[1,5-a]pyrazine (**9**): ^{1}H NMR δ 2.28 (CH_3, 6 H, s), 2.3 (CH_3, 6 H, s), 3.0 (heterocyclic CH_3, 3 H, s), 3.6 (CH_2, 2 H, s), 3.8 (CH_2, 2 H, s), 7.3 (H-6, 1 H, broad s), 9.0 (H-8, 1 H, broad s); *m/e* 247 (parent), 58 (base). The third fraction furnished 5.02 g (38%) of 1-dimethylaminomethyl-3-methylimidazo[1,5-a]pyrazine (**8**), again as an oil: ^{1}H NMR δ 2.3 (CH_3, 6 H, s), 2.7 (heterocyclic CH_3, 3 H, s), 3.8 (CH_2, 2 H, s), 7.6 (H-6, 1 H, d, $J_{5,6}$ = 5 Hz), 7.7 (H-5, 1 H, q, $J_{5,6}$ = 5, $J_{5,8}$ = 1.5 Hz), 9.1 (H-8, 1 H, d, $J_{5,8}$ = 1.5 Hz); *m/e* 190 (parent), 147 (base).

(3-Methylimidazo[1,5-a]pyrazinyl-1-methyl)trimethylammonium Iodide (11). To a solution of 2.01 g (10.6 mmol) of **8** in 100 ml of acetone was added 4.3 g (30 mmol) of iodomethane. A precipitate formed rapidly and, after 5 min, was separated by filtration and recrystallized from ethanol to give 1.52 g (43%) of **11**: mp 214–215° dec; ^{1}H NMR (Me_2SO-d_6) δ 2.7 (heterocyclic CH_3, 3 H, s), 3.2 (CH_3, 9 H, s), 5.0 (CH_2, 2 H, s), 7.7 (H-6, 1 H, d, $J_{5,6}$ = 5 Hz), 8.3 (H-5, 1 H, q, $J_{5,6}$ = 5, $J_{5,8}$ = 2 Hz), 9.5 (H-8, 1 H, d, $J_{5,8}$ = 2 Hz).

Anal. Calcd for $C_{12}H_{17}IN_4$: C, 39.75; H, 5.10; N, 16.86. Found: C, 39.89; H, 5.10; N, 16.60.

Chlorination of Imidazo[1,5-a]pyrazine (12). A mixture of 5.95 g (0.05 mol) of imidazo[1,5-a]pyrazine (**12**), 7.5 g (0.055 mol) of NCS, 100 mg of benzoyl peroxide, 100 ml of chloroform, and 100 ml of carbon tetrachloride was heated at reflux, with stirring, for 10 min, then processed as in the chlorination of **2**. The residue was separated by chromatography on dry alumina (400 g) using dichloromethane as eluent. The first fraction consisted of 1.9 g (23%) of 1,3-dichloroimidazo[1,5-a]pyrazine (**15**) which melted at 109° after recrystallization from hexane: ^{1}H NMR δ 7.8 (H-5 and H-6, 2 H, s), 9.0 (H-8, 1 H, broad s).

Anal. Calcd for $C_6H_3Cl_2N_3$: C, 38.30; H, 1.60; N, 22.34; Cl, 37.77. Found: C, 38.56; H, 1.87; N, 22.31; Cl, 38.10.

The second fraction (2.3 g) was a mixture of 1-chloroimidazo[1,5-a]pyrazine (**13**) and 3-chloroimidazo[1,5-a]pyrazine (**14**) which was separated by preparative thin layer chromatogaphy on alumina using hexane–chloroform (3:2) as eluent. There was obtained 1.2 g (18%) of **14** which was recrystallized from hexane to give mp 136–137° and 0.6 g (9%) of **13** which was recrystallized from acetone–hexane to give mp 128–129°; ^{1}H NMR (for **13**) δ 7.8 (H-6, 1 H, d, $J_{5,6}$ = 5 Hz), 8.0 (H-5, 1 H, q, $J_{5,6}$ = 5, $J_{5,8}$ = 2 Hz), 8.3 (H-3, 1 H, s), 9.0 (H-8, 1 H, broad s); for **14** 7.8 (H-1, H-5, H-6, 3 H, m), 9.0 (H-8, 1 H, broad s).

Anal. Calcd for $C_6H_4ClN_3$: C, 46.91; H, 2.61; N, 27.36; Cl, 23.13. Found (for **13**): C, 47.15; H, 2.90; N, 27.24; Cl, 23.23. Found (for **14**): C, 47.15; H, 2.66; N, 27.31; Cl, 23.07.

The final fraction, eluted with chloroform, consisted of 0.8 g of recovered **12**.

When the chlorination was repeated as above but with 2 molar equiv of NCS, there was obtained, from the first chromatography fraction, a 14% yield of 1,3,5-trichloroimidazo[1,5-a]pyrazine (**16**) which was recrystallized from hexane to give mp 89°; ^{1}H NMR δ 7.6 (H-6, 1 H, s), 8.8 (H-8, 1 H, s).

Anal. Calcd for $C_6H_2Cl_3N_3$: C, 32.36; H, 0.90; N, 18.88; Cl, 47.86. Found: C, 32.51; H, 1.18; N, 19.14; Cl, 47.66.

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References and Notes

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