Imidazo[1,5-a]pyrazines. V. Electrophilic Addition, a Novel Reissert-Like Reaction[1-3]

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The reaction of imidazo[1,5-a]pyrazine (**1a**) and its 3-methyl derivative (**1b**) with acid chlorides and acid anhydrides resulted in addition rather than substitution reactions. Addition was shown to take place at the N-7, C-8 imine bond and in a manner analogous to the Reissert reaction. By varying the acylating reagents and quenching agents a variety of adducts (**3**) were prepared. Structure proof of the adducts was derived by converting **3a** and **3b** to the corresponding 8-chloro derivatives (**9**), which were shown to be susceptible to nucleophilic displacement with thiourea. In one instance the imidazo[1,5-a]pyrazine system was also found to be susceptible to hydrolytic cleavage to form imidazole carboxaldehydes. A possible mechanism for the addition and cleavage reactions is presented.

Electrophilic substitutions of the imidazo[1,5-a]pyrazine system were visualized as a convenient route for the functionalization of the nucleus. Previous studies[2] on this system have shown it, like other related systems,[4] to be susceptible to such reactions. This work describes the extension of these reactions to acid chlorides and anhydrides where a novel Reissert-like addition, rather than substitution, reaction has taken place.

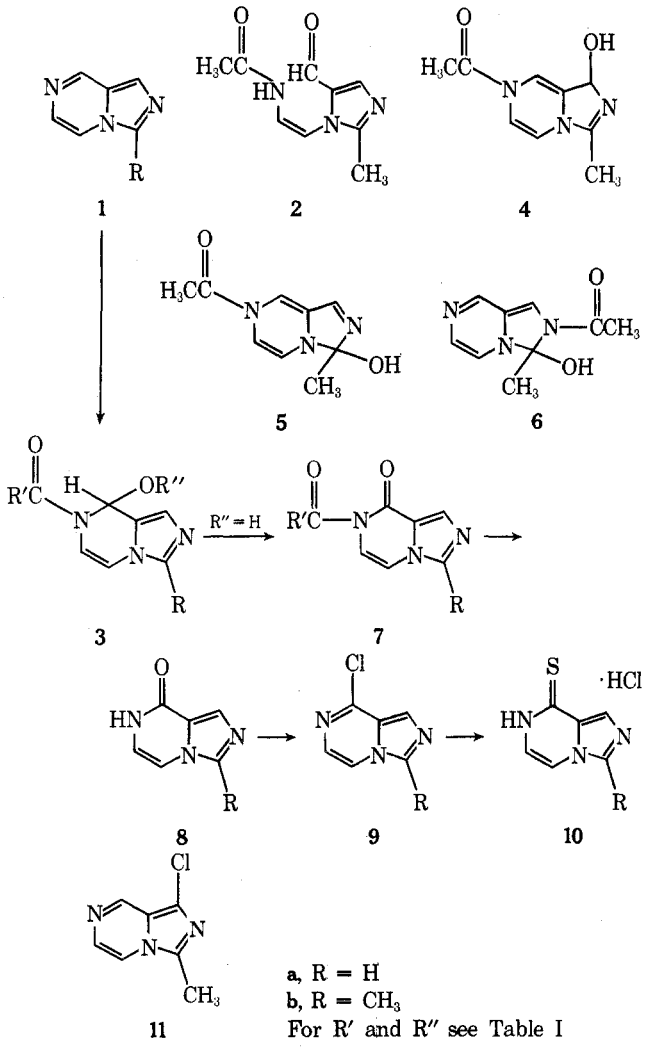
When compound **1b** was treated with acetyl chloride, or acetic anhydride, followed by aqueous work-up, the product isolated, in moderate yields, did not exhibit the spectral properties expected of an acetyl-substituted imidazo[1,5-a]pyrazine. The product had two methyl groups and a carbonyl band in the ^1H NMR and ir spectra, respectively. Its mass spectrum as well as elemental analysis indicated that the product obtained was an adduct of acetic acid to the starting material.

Five possible structures (**2–6**) can be written for this adduct (Scheme I). One of these (**2**) can be ruled out from the NMR data since no aldehydic proton was observed. Differentiation between the four remaining structures (**3–6**) came from further chemical transformations outlined in Scheme I. Jones oxidation of the adducts (**3a** or **3b**) afforded products (**7a** and **7b**) whose mass spectrum showed a molecular ion two units less than that of the parent compounds.[5] This, along with other physical data, clearly showed that formulas **5** and **6** could not represent the correct structure of the adducts.

Final confirmation of the structure as **3** rather than **4** came from converting the oxidation product to the chloro compounds (**9a** and **9b**). Alcoholysis of the imides (**7**) furnished the lactams (**8**) which were identical with those obtained from the rearrangement of the 7-oxides.[6] Treatment with phosphoryl chloride gave chloro derivatives (**9**) whose spectral and chemical properties were different from those of the known 1-chloro compounds (**11**).[2]

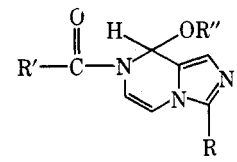
This novel addition finds analogy in the Reissert reaction.[7] Initial formation of an amide results in the generation of a carbonium ion (**12**) which is quenched by water to form the product. Cyanide ion failed to generate the corresponding cyano derivative. Preferential reactivity at N-7 rather than at C-1 as was previously observed[2] can best be explained by assuming that generation of **12** is kinetically favored over **13** as in electrophilic substitution at C-1. However, in the case of other electrophiles [(Cl_2, *N*-chlorosuccinimide (NCS), Br_2, $CH_2{=}N^+(CH_3)_2$)], the initial formation of a carbonium ion at C-8 (**14**) is in equilibrium

Scheme I



with the starting material, thus allowing the thermodynamic products to be formed. In an attempt to trap **14** (X = Cl), compound **1** was treated with 1 equiv of NCS in methanol. An unstable product was formed as evidenced by thin layer chromatography. However, upon the addition of 2 equiv of NCS a product was isolated in very poor yield whose NMR and mass spectral data strongly support the assigned diad-

Table I



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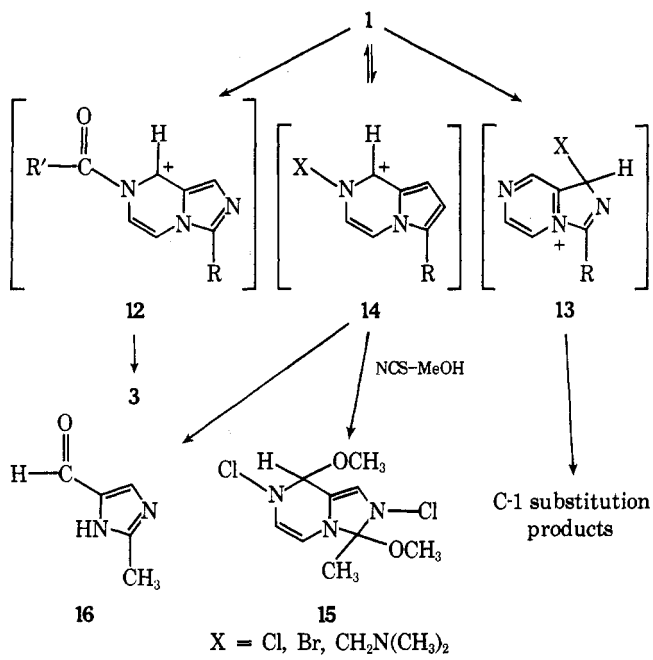
Compd (% yield)[a]	R	R′	R″	Mp, °C (solvent)	Elemental analysis found (calcd) C	H	N
3a (91)	H	OC_2H_5	H	163–165 (Me_2SO–H_2O)	51.56 (51.67)	5.46 (5.26)	19.97 (20.10)
3b (41)	CH_3	CH_3	H	168–169 (MeOH–ether)	56.27 (55.96)	5.85 (5.70)	21.50 (21.76)
3c (58)	CH_3	CH_3	CH_3	129–131 ($CHCl_3$–hexane)	57.89 (57.97)	6.35 (6.28)	20.02 (20.29)
3d (42)	CH_3	CH_3	C_2H_5	96–97 (ether–hexane)	59.51 (59.73)	6.75 (6.79)	18.46 (19.00)
3e (51)	CH_3	OC_2H_5	H	208 dec (Me_2SO)	53.80 (53.81)	5.82 (5.83)	18.54 (18.83)
3f (30)	CH_3	OC_2H_5	CH_3	103–105 (hexane–$CHCl_3$)	55.52) (55.70)	6.46) (6.33)	17.66 (17.72)
3g (15)	CH_3	OC_2H_5	C_2H_5	97–98 (ether–hexane)	57.59 (57.37)	6.59 (6.77)	16.53 (16.73)
3h (65)	CH_3	p-$NO_2C_6H_4$	H	166–167 (MeOH–$CHCl_3$)	56.24 (56.00)	4.04 (4.00)	18.35 (18.63)
3i (50)	CH_3	p-$NO_2C_6H_4$	C_2H_5	145–147[b]	58.27 (58.54)	4.71 (4.88)	17.08 (17.07)
3j (50)	CH_3	p-$NO_2C_6H_4$	p-$NO_2C_6H_4CO$	153–155 (MeOH)[c]	55.89 (56.12)	3.62 (3.34)	15.64 (15.59)

[a] Yield of purified product. [b] Purified by silica gel chromatography. [c] Assumed to be formed from 3h with excess acylating reagent.

Scheme II



duct structure (**15**). The compound was not stable enough for elemental analysis. The trapping experiment was repeated using aqueous sodium hypochlorite. In this case cleavage of the pyrazine ring took place to form the known aldehyde **16**.[8] This cleavage offers a new and useful approach to the synthesis of substituted imidazole carboxaldehydes (Scheme II).[9]

Further support for the proposed rationalization can be derived from both ^1H and ^{13}C NMR data, which showed H-8[6] as well as C-8[2] as the most deshielded nuclei in the imidazo[1,5-a]pyrazine nucleus. This strongly suggests that N-7 is more electronegative than either N-2 or N-4. Similar observations in related systems have been reported recently.[10]

The generality of this reaction is shown by the variety of compounds prepared using various acylating agents and quenching compounds and tabulated in Table I.

Unlike previously prepared chloroimidazo[1,5-a]pyrazines,[2] the 8-chloro derivatives are amenable to nucleophilic attack. Mild treatment of **9a** and **9b** with thiourea furnished the corresponding 8-thiones (**10a** and **10b**) in good yields. This displacement clearly demonstrates the utility of this method for the preparation of other C-8 derivatives.

Experimental Section

Melting points (uncorrected) were determined with a Thomas-Hoover capillary apparatus. ^1H NMR spectra were determined on a Varian A-60 or on a JEOLCO C-60-HL spectrometer using $CDCl_3$ and Me_4Si unless otherwise indicated. Mass spectral fragmentations were obtained from either a Perkin-Elmer RMV-6E or CEC 24-104 mass spectrometer. Microanalyses were performed by MicroAnalysis, Inc., Marshallton, Del. All evaporations were carried out in vacuo using a water aspirator and solutions were dried over anhydrous magnesium sulfate unless otherwise noted. In the NMR spectra resonances were assigned whenever possible.

7-Acetyl-8-hydroxy-3-methyl-7,8-dihydroimidazo[1,5-a]pyrazine (3b). *The preparation of this compound serves as a general procedure for all adducts (3).* To 3-methylimidazo[1,5-a]pyrazine (**1b**, 1.33 g, 10 mmol) in dichloromethane (25 ml) was added acetic anhydride (2 ml) (or acetyl chloride) dropwise and with stirring. After a few minutes water (25 ml) was added and stirring was continued for 0.5 hr. Evaporation of the organic solvent was followed by the addition of water (50 ml) and neutralization with sodium bicarbonate. Extraction with an 8% methanol–chloroform mixture (100 ml × 3) and subsequent work-up gave the product: ^1H NMR δ 2.40 (CH_3, 6 H, s), 3.21–3.31 (CH_3, 3 H, broad, s),

6.31–7.11 (H-1, H-5, H-6, and H-8, 4 H, m); ir (KBr) 1670 cm^{-1}; mass spectrum *m/e* (rel intensity) 193 (M^+, 32), 176 (10), 151 (25), 134 (100).

When methanol or ethanol were used to quench the reaction, the corresponding 8-methoxy (**3c**) and 8-ethoxy (**3d**) derivatives were obtained.

7-Acetyl-3-methylimidazo[1,5-*a*]pyrazin-8(7*H*)-one (7b, R′ = CH_3). To 7-acetyl-8-hydroxy-3-methyl-7,8-dihydroimidazo[1,5-*a*]pyrazine (**3b**, 0.19 g, 1 mmol) suspended in cold (10°) acetone (20 ml) was added Jones reagent[11] (0.4 ml) dropwise with vigorous stirring. After 5 min the reaction mixture was concentrated under reduced pressure to small volume and mixed with ice (5 g). The water solution was extracted with chloroform (50 ml × 5). The residue obtained on evaporation of chloroform was filtered through a short silica gel column with chloroform as eluent to give the product as a white, crystalline solid (0.08 g, 42% yield): mp 174–176°; ^1H NMR δ 2.47 (CH_3, 3 H, s), 2.53 (CH_3, 3 H, s), 6.68 and 7.40 (H-5 and H-6, 2 H, doublets, J = 6 Hz), and 7.83 (H-1, 1 H, s); ir (KBr) 1740, 1720, and 1690 cm^{-1} (C=O); mass spectrum m/e (rel intensity) 191 (M^+, 20), 150 (12), 149 ($M^+ - CH_2{=}C{=}O$, 100), 148 (12), 122 (8), and 109 (8).

Anal. Calcd for $C_9H_9N_3O_2$: C, 56.54; H, 4.71; N, 21.98. Found: C, 56.79; H, 4.94; N, 21.79.

7-Carboethoxyimidazo[1,5-*a*]pyrazin-8(7*H*)-one (7a, R′ = OEt). The procedure followed was essentially that for preparation of **7b**. Thus, 7-carboethoxy-8-hydroxy-7,8-dihydroimidazo[1,5-*a*]pyrazine (**3a**, 0.93 g, 4.4 mmol) was mixed with Jones reagent (1.6 ml). Upon work-up a white, crystalline solid (0.37 g, 40% yield) was obtained: mp 171–172°; ^1H NMR δ 1.47 (CH_3, 3 H, t), 4.50 (CH_2, 2 H, q), 7.17 and 7.29 (H-5 and H-6, 2 H, doublets, J = 6 Hz), 7.93 and 8.05 (H-1 and H-3, 2 H, s); ir (KBr) 3100, 1750, and 1680 cm^{-1} (C=O).

Anal. Calcd for $C_9H_9N_3O_3$: C, 52.17; H, 4.35; N, 20.29. Found: C, 52.34; H, 4.28; N, 20.28.

Imidazo[1,5-*a*]pyrazin-8(7*H*)-one (8a). The imide (**7a**, R′ = OEt) (0.3 g, 1.45 mmol) was dissolved in ethanol (10 ml), refluxed for 1 hr, and the solution evaporated to dryness. The residue, washed once with dichloromethane–ethyl ether (1:3) (50 ml), was filtered through a short silica gel column with chloroform–methanol (92:8) as eluent to give the product as a white, crystalline solid (0.18 g, 91% yield): mp 270° dec; ^1H NMR (Me_2SO-d_6) δ 6.75 (1 H, m), 7.5 (1 H, d), 7.87 and 8.35 (H-1 and H-3, 2 H, s), and 10.67 (broad, 1 H, deuterium oxide exchangeable).

Anal. Calcd for $C_6H_5N_3O$: C, 53.33; H, 3.70; N, 31.11. Found: C, 53.08; H, 3.87; N, 30.95.

3-Methylimidazo[1,5-*a*]pyrazin-8(7*H*)-one (8b). This was prepared as indicated for **8a** from **7b** (R′ = CH_3) (0.48 g, 2.5 mmol) in quantitative yield: mass spectrum *m/e* (rel intensity) 149 (M^+, 100), 122 (8), 109 (10), 81 (15), 80 (20), and 153 (45); mp 280° dec.

Anal. Calcd for $C_7H_7N_3O$: C, 56.38; H, 4.70; N, 28.19. Found: C, 56.48; H, 4.89; N, 28.06.

8-Chloroimidazo[1,5-*a*]pyrazine (9a). The lactam **8a** (0.4 g, 2.9 mmol) was added to phosphoryl chloride (25 ml) and heated on an oil bath (135°) for 1 hr. The residue after evaporation was dissolved in ice water (10 ml). The water solution was neutralized with 5% sodium bicarbonate and extracted with dichloromethane (50 ml × 5). Evaporation of the dried dichloromethane extract gave the product as a slightly orange solid (0.21 g, 47% yield), mp 100–103°. The analytical sample was obtained by recrystallization from ether–hexane as needles: mp 105–106°; ^1H NMR δ 7.48 and 7.91 (H-5 and H-6, 2 H, doublets, J = 6 Hz), 7.97 (H-1, 1 H, broad), 8.38 (H-3, 1 H, broad); uv (EtOH) λ_{max} 268 nm (ε 2000), 278 (2500), 289 (2200), and 350 (1700); ir ($CHCl_3$) 2950, 1600, 1500, 1450, 1430, and 1340 cm^{-1}; mass spectrum *m/e* (rel intensity) 155 (33), 153 (100), 156 (3), 154 (9), 128 (3), 126 (7), 118 (14), 117 (32), 101 (9), and 99 (18).

Anal. Calcd for $C_6H_4ClN_3$: C, 46.91; H, 2.61; N, 27.36; Cl, 23.13. Found: C, 46.98; H, 2.79; N, 27.27; Cl, 23.33.

8-Chloro-3-methylimidazo[1,5-*a*]pyrazine (9b). This was prepared from **8b** (0.3 g, 2.1 mmol) in a manner similar to that for **9a** in 74% yield, mp 126–127°.

Anal. Calcd for $C_7H_6ClN_3$: C, 50.15; H, 3.58; N, 25.07; Cl, 21.19. Found: C, 50.40; H, 3.81; N, 24.89; Cl, 21.15.

3-Methylimidazo[1,5-*a*]pyrazine-8(7*H*)-thione Hydrochloride (10b). An ethanol solution (10 ml) of 8-chloro-3-methylimidazo[1,5-*a*]pyrazine (**9b**, 85 mg, 0.5 mmol) and thiourea (40 mg, 0.5 mmol) was refluxed for 10 min. Upon cooling the product crystallized and was filtered (74 mg, 75% yield): mp 305°; ^1H NMR (CF_3COOH) δ 2.98 (CH_3, 3 H, s), 7.07 (1 H, d, J = 6 Hz), 7.45 (1 H, m, J = 6 Hz), and 8.26 (H-1, 1 H, s).

Anal. Calcd for $C_7H_8ClN_3S$: C, 41.69; H, 3.97; N, 20.84. Found: C, 42.24; H, 4.06; N, 20.61.

Imidazo[1,5-*a*]pyrazine-8(7*H*)-thione Hydrochloride (10a). This was prepared from **9a** as in the preparation of **10b** to give a 94% yield of yellow needles, mp >310°.

Anal. Calcd for $C_6H_6ClN_3S$: C, 38.40; H, 3.20; N, 22.40. Found: C, 38.49; H, 3.17; N, 22.59.

2,7-Dichloro-3,8-dimethoxy-3-methyl-2,3,7,8-tetrahydroimidazo[1,5-*a*]pyrazine (15). A solution of 3-methylimidazo[1,5-*a*]pyrazine (**3b**, 0.55 g, 5 mmol) and *N*-chlorosuccinimide (1.34 g, 10 mmol) in methanol (50 ml) was allowed to stand at room temperature for 3 days. Evaporation of the methanol followed by dry column chromatography (silica gel, 5% methanol in chloroform as eluent) gave a yellow gum which was mainly a mixture of two compounds as indicated by thin layer chromatography (silica gel, using 4% methanol in chloroform). A small quantity (19 mg) of the compound (R_f 0.63] was obtained from several TLC plates and appeared as a yellow gum, which could not be further purified owing to decomposition: ^1H NMR δ 2.71 (CH_3, 3 H, s), 3.53 (CH_3, 3 H, s), 4.02 (CH_3, 3 H, s), 4.65 (1 H, s), 5.34 (1 H, d, J = 1 Hz), 6.07 (1 H, d, J = 1 Hz), and 7.43 (1 H, s); ir ($CHCl_3$) 2950, 1630, and 1330 cm^{-1}; mass spectrum *m/e* (rel intensity) 267 (2), 265 (2.5), 236 (10), 234 (17), 231 (30), 229 (82), 216 (33), 214 (100), 194 (50.

The second spot (R_f 0.58) was insufficient for characterization.

2-Methylimidazole-4(5)-carboxaldehyde (16). To an ice-cooled solution of 3-methylimidazo[1,5-*a*]pyrazine (**3b**, 0.53 g, 4 mmol) in water (10 ml) was added 5% sodium hypochlorite solution (30 ml) with stirring. After 5 min the ice bath was removed and the reaction mixture was stirred for another 5 min. The water solution was washed with ether (30 ml) and evaporated to dryness. The residue was heated with methanol (20 ml) and the insoluble material was discarded. Evaporation of the methanol solution followed by filtration through a short silica gel column with chloroform–methanol (92:8) as eluent gave a white, crystalline solid (156 mg, 40% yield): mp 159° dec; ir (KBr) 3130 (–NH), 3040, 2900, 2750 (CH), and 1670 cm^{-1} (C=O); ^1H NMR (Me_2SO-d_6) δ 1.35 (CH_3, 3 H, s), 7.83 (2 H, broad, s, one is D_2O exchangeable), and 9.65 (1 H, s). This material agrees in spectral characteristic and physical properties with the product from irradiation of 2-methylpyrimidine *N*-oxide (lit.[8] mp 160–162°).

Registry No.—**1b**, 39204-53-0; **3a**, 56468-09-8; **3b**, 56468-10-1; **3c**, 56468-11-2; **3d**, 56468-12-3; **3e**, 56468-13-4; **3f**, 56468-14-5; **3g**, 56468-15-6; **3h**, 56468-16-7; **3i**, 56468-17-8; **3j**, 56468-18-9; **7a** (R′ = OEt), 56468-19-0; **7b** (R′ = CH_3), 56468-20-3; **8a**, 56468-21-4; **8b**, 56468-22-5; **9a**, 56468-23-6; **9b**, 56468-24-7; **10a**, 56468-25-8; **10b**, 56468-26-9; **15**, 56468-27-0; **16**, 35034-22-1; phosphoryl chloride, 10025-87-3; *N*-bromosuccinimide, 128-08-5.

References and Notes

(1) This work was supported by Contract NIH-71-2312 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education and Welfare.

(2) Part IV: E. Abushanab, A. P. Bindra, D.-Y. Lee, and L. Goodman, *J. Org. Chem.*, preceding paper in this issue.

(3) Taken in part from the Ph.D. Thesis of D.-Y. Lee, University of Rhode Island, 1975.

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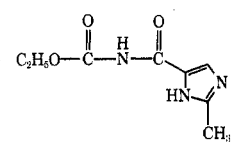
(5) When chromic acid oxidation was carried out on **3a** in acetic acid, an additional product was isolated whose NMR and mass spectral data suggest structure **i**.



i

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(9) For other examples of this cleavage reaction see ref 2.

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