On addition of phenyl isocyanate to the ethereal solution of the semicarbazide, 1,2-bis(anilinoformyl)cyclohexylhydrazine was obtained, which was recrystallized from ethanol to give a pure sample: mp 200–202° (lit.[7] mp 202°); ν^{KBr} 1660 cm^{-1}.

Anal. Calcd for $C_{20}H_{24}N_4O_2$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.10; H, 6.90; N, 15.96.

Reaction of 8 with *p*-Phenetidine.—An equimolar mixture of **8** (224 mg, 0.67 mmol) and *p*-phenetidine (88 mg, 0.67 mmol) was heated at 100° for 2 hr, and the reaction mixture was treated with low boiling petroleum ether as in the preceding example. From the petroleum ether soluble part, 50 mg (31%) of pale yellow crystals of α-methylbenzylidene-*p*-phenetidine was obtained, mp 85–87° (lit.[9] mp 88°).

The product remaining on the filter (130 mg) was a mixture of 1-cyclohexyl-4-phenylsemicarbazide and **11**. Recrystallization of the mixture from ethanol gave 30 mg of **11**, mp 155°. However, a quantitative separation of **11** and the semicarbazide was impossible. Crystallization of crude **11** from ethanol gave a pure sample: mp 156–157°; ν^{KBr} 3200, 1700 cm^{-1}; δ^{CDCl_3} 0.7–2.2 (m, 13), 2.90 (br, 1, cyclohexyl α-CH), 6.30 (s, 1), 6.8–7.2 (m, 10).

Anal. Calcd for $C_{21}H_{25}N_3O$: C, 75.19; H, 7.51; N, 12.53. Found: C, 75.05; H, 7.51; N, 12.60.

Compound **11** was also obtained on heating of **8** (100 mg) at 100° for 1 hr. Treatment of the reaction product with low boiling petroleum ether gave 65 mg of **11** melting at 155°. The tlc of the reaction mixture showed the existence of remaining **8**.

Heating of **9** in the same way resulted in an extensive decomposition as judged from the tlc.

Acknowledgment.—We sincerely wish to thank Professor Yoshio Sasada, Tokyo Institute of Technology, for his kindest guidance in performing the X-ray crystal structure analysis.

Registry No.—**1a**, 538-51-2; **1b**, 2272-45-9; **2a**, 588-64-7; **2b**, 1858-99-7; **3**, 41316-28-3; **4**, 41316-29-4; **5h**, 41316-30-7; **5l**, 41316-31-8; **6h**, 41316-32-9; **6l**, 41316-33-0; **7**, 41316-34-1; **8**, 41316-35-2; **9**, 41316-36-3; **10**, 41316-37-4; **11**, 41316-38-5; α-methylbenzylidine cyclohexylamine, 1562-62-5; α-methylbenzylidenebenzylamine, 14428-98-9; benzylidenecyclohexylamine, 2211-66-7; benzylidenebenzylamine, 780-25-6; *p*-bromobenzylidinecyclohexylamine, 41316-43-2; hydroxylamine-*O*-sulfonic acid, 3400-11-1; 3-ethyl-3-methyloxaziridine, 41316-44-3; phenyl isocyanate, 103-71-9; *p*-phenetidine, 156-43-4; 1-cyclohexyl-4-phenylsemicarbazide, 41316-45-4; 1,2-bis(anilinoformyl)cyclohexylhydrazine, 41316-46-5.

Supplementary Material Available.—Atomic parameter and structure factor tables will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-3758.

Transmission of Substituent Effects in Heterocyclic Systems. Rates of Solvolysis of Substituted 1-(1-Methylimidazolyl)ethyl *p*-Nitrobenzoates[1]

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Reactivities of 1-(1-methyl-2-imidazolyl)ethyl *p*-nitrobenzoate (**2**), 1-(1-methyl-4-imidazolyl)ethyl *p*-nitrobenzoate (**4**), and 1-(1-methyl-5-imidazolyl)ethyl *p*-nitrobenzoate (**5**) are in the order 1:13:15. By comparison with other heteroarylethyl *p*-nitrobenzoates, effective replacement substituent constants, σ^+_{Ar}, are determined as $\sigma^+_{2\text{-Im}} = -0.82$, $\sigma^+_{4\text{-Im}} = -1.01$, and $\sigma^+_{5\text{-Im}} = -1.02$. Substituent effects on the rates of solvolysis of substituted 1-(1-methyl-2-imidazolyl)ethyl *p*-nitrobenzoates were examined, including the following substituents: 5-methyl, 5-chloro, 4-methyl, 4-phenyl, 4-chloro, 4-bromo, and 4,5-dimethyl. Though the rates for 5-substituents were satisfactorily represented by σ_p^+, σ_m^+ failed to account properly for the observed reactivities of 4-substituents. Various methods allowing greater proportions of resonance interaction were explored to seek an explanation for the latter fact and to provide a satisfactory basis for correlation of the observed relative reactivities.

Recent papers from these laboratories have examined the transmission of substituent effects in furan,[2-4] thiophene,[5,6] and thiazole[7] systems. These previous studies have shown that σ_p^+ gives a high quality representation of the influence of substituents when the substituent is located in a position capable of direct conjugation with the reacting side chain. Furthermore, the magnitude of ρ, which is found from the Hammett equation, is directly related to the changes in regional charges associated with the change $ArCH_3 \rightarrow ArCH_2^+$.[5,8] In the present study we examine the heterocyclic nucleus, imidazole.

The reactivity of imidazole in electrophilic substitution has received substantial attention[9] with substitution at the 4(5) position being most facile. 1-Methylimidazole gives substantial amounts of both 1-methyl-4-nitroimidazole and 1-methyl-5-nitroimidazole on nitration. The solvolysis reaction is a useful probe for the susceptibility of an aromatic moiety to electrophilic substitution[2,6,10] and is particularly useful in the present case because of the marked basicity of imidazoles.

The rates of solvolysis of the three isomeric 1-(1-methylimidazolyl)ethyl *p*-nitrobenzoates, **2**, **4**, and **5**, are given in Table I.

The isomeric imidazoles bracket the reactivity of 1-(2-furyl)ethyl *p*-nitrobenzoate; all are somewhat more reactive than the related thiophene. It is of interest that the spread in reactivity of **2**, **4**, and **5** is substantially less than for the analogous set of isomers of

(1) Supported in part by a grant from the National Science Foundation, GP-6133X.

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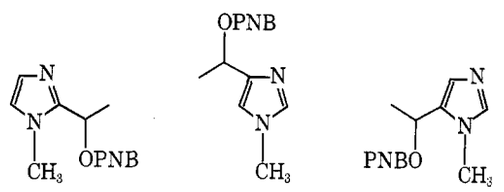
TABLE I

RATE CONSTANTS FOR THE SOLVOLYSIS OF IMIDAZOLYLETHYL *p*-NITROBENZOATES IN 80% ETHANOL

Compound solvolyzed	Temp., °C	10^5k, sec^{-1}	Method[a]	Rel rate	σ^+_{Ar}
2	25	0.313[b]		1	−0.82
	45	3.40 ± 0.04	A		
	45	3.34 ± 0.06	B		
	60	17.2 ± 0.1	A		
	60	16.5 ± 0.3	B		
	75	72.2 ± 1	A		
4	25	4.10[b]		13.1	−1.01
	45	43.0 ± 0.4	A		
	60	209 ± 2	A		
5	25	4.67 ± 0.08	A	15	−1.02
	45	53.0 ± 0.5	A		
	60	242 ± 4.0	A		
1-(2-Furyl)ethyl *p*-nitrobenzoate[c]	25	1.17			−0.93
	45	13.0			
1-(2-Thienyl)ethyl *p*-nitrobenzoate[d]	25	0.227			−0.80[d]
	45	2.61			

[a] A is at constant pH (8.0); B is by titrimetric methods on aliquots. [b] Extrapolated from data at higher temperatures. [c] From ref 2. [d] From ref 6.



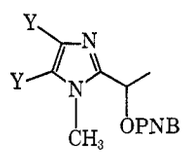
2 **4** **5**

the 1-(thiazolyl)ethyl system studied by Noyce and Fike.[7]

The replacement substituent constants[11] for the aromatic moiety replacing the entire phenyl group in 1-phenylethyl chloride may be easily calculated from the rate data in Table I. The values given in column 6 of Table I were obtained using ρ for the benzene series of −5.8, and starting from the value of $\sigma^+_{2\text{-thienyl}}$ of −0.80 as reported by Noyce, *et al.*[6] If Hill's[10] values are used for thienyl and furyl systems, then the σ^+_{Ar} values for the imidazole moieties are very slightly more negative. The very close similarity of the values derived from **4** and **5** is in gratifying correspondence with the nitration results mentioned above.

Substituent Effects.—We next examined the influence of substituents on the rate of solvolysis of 1-(1-methyl-2-imidazolyl)ethyl *p*-nitrobenzoate. The rates for compounds **8, 10, 12, 14, 17, 20,** and **22** are given in Table II, extrapolated where necessary to 45°. For the three compounds **2**, **8**, and **10**, the correlation of the observed rates with σ_p^+[12] is excellent and ρ is −5.6, very similar to that in the benzene series.

However, when the 4-substituted compounds **12**, **14**, **17**, and **20** are included and using σ_m^+, the quality of the correlation is destroyed. In every instance the 4-substituted compounds solvolyze more rapidly than predicted by the correlation established with the 5-substituted compounds.



8, X = H; Y = CH_3
10, X = H; Y = Cl
12, X = CH_3; Y = H
14, X = C_6H_5; Y = H
17, X = Cl; Y = H
20, X = Br; Y = H
22, X = CH_3; Y = CH_3

TABLE II

RATE CONSTANTS FOR THE SOLVOLYSES OF SUBSTITUTED 1-(1-METHYL-2-IMIDAZOLYL)ETHYL *p*-NITROBENZOATES AT 45.0° IN 80% ETHANOL

Compound solvolyzed	k_1, sec^{-1}	Log k/k_H	σ^+[a]	σ_{calcd}[b]
2	3.38×10^{-5}	(0.00)	(0.00)	
8 (5-Me)	1.67×10^{-3}	1.69	−0.311	
10 (5-Cl)	6.58×10^{-6}	−0.71	0.114	
12 (4-Me)	5.98×10^{-4}	1.25	−0.066	−0.146
14 (4-C_6H_5)	2.13×10^{-4}	0.80	0.109	−0.053
17 (4-Cl)	4.36×10^{-6}	−0.89	0.399	0.200
20 (4-Br)	3.54×10^{-6}	−0.98	0.405	0.214
22 (4,5-Me)$_2$	2.82×10^{-2}	2.92	−0.377[c]	−0.457[d]

[a] σ_p^+ for 5-substituents; σ_m^+ for 4-substituents. [b] See text, eq 2; $\sigma_{calcd} = \sigma_{m\alpha N}^+$. [c] Additivity assumed. [d] $\sigma_p^+ + \sigma_{calcd}$.

This characteristic behavior has been noted previously with 1-(4-substituted 2-furyl)ethanol derivatives[3] and with 1-(4-substituted 2-thiazolyl)ethanol derivatives.[7]

It was shown, in the consideration of the thiazole results, that a larger proportion of a resonance component in the total influence of the substituent would serve to bring the results into a more satisfactory correlational alignment. For this purpose the observed reactivities of 2-(6-substituted 2-pyridyl)-2-chloropropanes[13] were used as a basis of comparison, with marked improvement in the quality of the correlation (correlation coefficient *vs.* σ_m^+ = 0.76, *vs.* 6-substituted pyridine reactivities = 0.99).

The number of 6-substituted pyridines studied was somewhat limited, and it is therefore desirable to seek means for predicting the expected behavior of additional substituents. Two procedures offer promise in this respect. A new substituent constant may be defined in terms of an inductive parameter and a resonance parameter. The Swain and Lupton approach[14] is excellent in this regard, with the inductive ($\mathcal{F}$) and reso-

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(12) H. C. Brown and Y. Okamoto, *ibid.*, **80**, 4979 (1958).
(13) D. S. Noyce and J. A. Virgilio, *J. Org. Chem.*, **38**, 2660 (1973).
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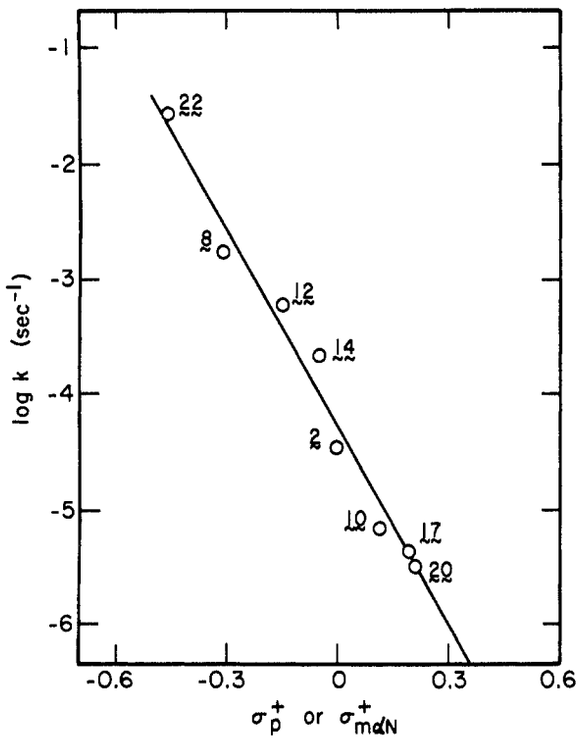

Figure 1.—Correlation of rates of solvolysis of substituted 1-(2-imidazolyl)ethyl *p*-nitrobenzoates with σ_p^+ and $\sigma_{m\alpha N}^+$.

nance parameters ($\mathcal{R}$) being blended to fit the observed reactivities. Alternatively, one may use Taft's σ_I,[15] which Swain and Lupton[14] have shown to be a pure field ($\mathcal{F}$) term within the limits of analysis, and Yukawa's $\Delta\sigma_R^+$ ($\Delta\sigma_R^+ = \sigma_p^+ - \sigma_p$),[16] which can be shown to be ~90% resonance ($\mathcal{R}$) in the Swain and Lupton approach.

Thus, an electrophilic substituent constant applicable to situations where the substituent is located adjacent to a pyridine-type nitrogen and in a "meta" relationship to the reacting side chain may be defined by eq 1 (Swain and Lupton) or eq 2 (using Charton's symbolism).[17]

$$\sigma_{m\alpha N}^+ = f\mathcal{F} + r\mathcal{R} \quad (1)$$

$$\sigma_{m\alpha N}^+ = \lambda\sigma_I + \delta\Delta\sigma_R^+ \quad (2)$$

The measured rates for pyridines[13] give, for eq 2, $\lambda = 0.614$ and $\delta = 0.762$. Using these values of λ and δ and the appropriate values of σ_I and $\Delta\sigma_R^+$, it is then possible to calculate a $\sigma_{m\alpha N}^+$ value for any substituent. Thus, the $\sigma_{m\alpha N}^+$ for bromine was calculated to be 0.214 and that for methylthio to be −0.235. Additivity was assumed in the case of the 4,5-dimethyl substituent. In Table II these values are given in the last column.

Applying $\sigma_{m\alpha N}^+$ to the observed substituent effects for 4-substituted 1-methyl-2-imidazolyl esters greatly improves the situation. The logarithms of the rates for the 4-substituted compounds correlate very nicely with $\sigma_{m\alpha N}^+$ ($\rho = -5.90$, cc = 0.994). In addition, if the rates of the 5-substituents are correlated against σ_p^+ and those of the 4-substituents against $\sigma_{m\alpha N}^+$, the entire set of results gives a satisfactory single correlation line with ρ equal to −5.77 and correlation coefficient (cc) equal to 0.99. This correlation is shown in Figure 1.

On close inspection of the correlation line obtained when the data from the substituted 1-(1-methyl-2-imidazolyl)ethyl esters are plotted against $\sigma_{m\alpha N}^+$ and σ_p^+ (Figure 1), it can be seen that the 4-substituents still tend to fall somewhat above the correlation line. Inasmuch as all the 4-substituents examined were of the π electron donating type, this suggests that there is an even greater degree of resonance stabilization by the substituent for these systems than in the corresponding pyridine cases.

It is of course possible to derive, independently from these results with imidazole, applicable values for δ and λ. When this calculation is carried out, a larger value of δ is obtained, as would be anticipated by the observations noted above. Finally, it is instructive to express the ratio of resonance effects to inductive effects as δ/λ.[17] Some relevant comparisons are given in Table III for various substituent constants and reactivity series.

TABLE III
CORRELATIONS OF VARIOUS SUBSTITUENT CONSTANTS AND REACTIVITY SERIES

Substituent constant	λ	δ	δ/λ	%ℛ[b]
σ_m			0.3–0.5[a]	22
σ_m^+			0.42	33
σ_p			1.00[a]	53
σ_p^+	0.762	1.908	2.50	66
$\sigma_{m\alpha N}^+$	0.614	0.762	1.24	44
$\Delta\sigma_R^+$	0	1.00	∞	~90
Reactivity Series				
6-X-2-Pyridyl[c]			(1.24)	
2-X-4-Thiazolyl[d]			1.26	
4-X-2-Imidazolyl[e]	0.622	1.22	1.96	53

[a] Reference 17. [b] Reference 14. [c] Reference 13; defining series for $\sigma_{m\alpha N}^+$. [d] Reference 7. [e] Present study.

In summary, an enhanced resonance component in the substituent effect is observed when the substituent is α to a pyridine-type nitrogen and is "meta" to the reaction site.

Experimental Section[18]

1-(1-Methyl-2-imidazolyl)ethanol (1).—A solution of 20 g (0.24 mol) of 1-methylimidazole (Aldrich) in 500 ml of anhydrous diethyl ether, under nitrogen, was cooled to Dry Ice–acetone temperature. To this was added dropwise, over a period of 30 min 190 ml of 1.6 *M* *n*-butyllithium in *n*-hexane (Foote Mineral Co.). After the mixture was stirred for 1 hr, 25 ml of acetaldehyde was added in one portion. After 5 hr the reaction mixture was allowed to warm to room temperature and was quenched with water (250 ml). The aqueous phase was separated and continuously extracted with ethyl acetate. Evaporation of the ethyl acetate and distillation of the residue under vacuum yielded 10.6 g (35%) of 1-(1-methyl-2-imidazolyl)ethanol as a yellow oil which crystallized on standing. Crystallization from benzene–hexane yielded colorless prisms: mp 82–83.5°; bp 118–120° (2 mm); nmr ($CDCl_3$) δ 6.70 (s, 2, ring protons), 4.82 (q, 1, J = 7 Hz, $CH(OH)CH_3$), 3.66 (s, 3, NCH_3), and 1.50 (d, 3, J = 7 Hz, $CH(OH)CH_3$).

(15) R. W. Taft, Jr., and I. C. Lewis, *J. Amer. Chem. Soc.*, **80**, 2436 (1958).
(16) Y. Yukawa and Y. Tsuno, *Bull. Chem. Soc. Jap.*, **39**, 2274 (1966).
(17) M. Charton, *J. Amer. Chem. Soc.*, **86**, 2033 (1964).
(18) All melting and boiling points are uncorrected. Routine nmr spectra were determined on a Varian A-60 or a Varian T-60 instrument using tetramethylsilane as an internal standard. The elemental analyses were determined by the Microanalytical Services Laboratory, College of Chemistry, University of California, Berkeley, Calif.

Anal. Calcd for $C_6H_{10}N_2O$: C, 57.12; H, 7.99; N, 22.20. Found: C, 57.22; H, 8.19; N, 21.94.

1-(1-Methyl-2-imidazolyl)ethyl *p*-Nitrobenzoate (2).—To a solution of 5 g of 1-(1-methyl-2-imidazolyl)ethanol and 4.15 g of triethylamine in 50 ml of 1,2-dichloroethane was added dropwise 7.45 g (4.0×10^{-2} mol) of *p*-nitrobenzoyl chloride dissolved in 25 ml of 1,2-dichloroethane. Toward the end of the addition, triethylamine hydrochloride began to precipitate. After 1 hr the precipitated triethylamine hydrochloride was filtered off and the filtrate was washed with water and dried ($MgSO_4$), and the solvent was removed under vacuum. Crystallization from benzene–hexane gave 8.7 g (79%) of 1-(1-methyl-2-imidazolyl)-ethyl *p*-nitrobenzoate as colorless crystals: mp 101–102°; nmr ($CDCl_3$) δ 8.20 (s, 4, $O_2NC_6H_4$–), 7.00 (br s, 1, 4- or 5-H), 6.87 (d, 1, J = 1.1 Hz, 4- or 5-H), 6.28 (q, 1, J = 6.6 Hz, CH(OH)-CH_3), 3.74 (s, 3, NCH_3), and 1.87 (d, 3, J = 6.6 Hz, CH(OH)-CH_3).

Anal. Calcd for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.26. Found: C, 56.65; H, 4.77; N, 15.09.

1-Methyl-4-imidazolecarboxaldehyde (3) was prepared by the method of Rapoport, *et al.*,[19] from α-amino-β-methylaminopropionic acid *via* **ethyl 1-methyl-2-imidazoline-4-carboxylate** (not purified) and **ethyl 1-methyl-4-imidazolecarboxylate**, mp 56–57°.

Anal. Calcd for $C_7H_{10}N_2O_2$: C, 54.54; H, 6.54; N, 18.17. Found: C, 54.62; H, 6.30; N, 18.04.

Reduction of this ester gave the reported **1-methyl-4-hydroxymethylimidazole**, mp 60–62° (lit.[19] 61–62°), which was oxidized with activated manganese dioxide to **1-methyl-4-imidazolecarboxaldehyde (3)**, mp 65–66° (lit.[19] 65–66.5°).

1-(1-Methyl-4-imidazolyl)ethanol was prepared by the addition of methylmagnesium bromide to **3** in tetrahydrofuran. Isolation in the usual manner, including final exhaustive extraction with chloroform, gave the alcohol, which was not exhaustively purified but was used directly in the preparation of the *p*-nitrobenzoate by the procedure described above for **2**.

Compound **4** was crystallized from benzene–hexane: mp 114–116°; nmr ($CDCl_3$) δ 8.22 (s, 4, $O_2NC_6H_4$–), 7.43 (br s, 1, 2-H), 6.97 (br s, 1, 5-H), 6.19 (q, 1, J = 6.8 Hz, CH(OH)CH_3), 3.67 (s, 3, NCH_3), and 1.75 (d, 3, J = 6.8 Hz, CH(OH)CH_3).

Anal. Calcd for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.26. Found: C, 56.95; H, 4.59; N, 15.02.

1-Methyl-5-imidazolecarboxaldehyde.—The procedures of Jones and McLaughlin[20,21] were followed for the preparation of **1-methyl-5-hydroxymethylimidazole**. Oxidation with activated manganese dioxide[19] gave the aldehyde, mp 53–55° (lit.[21] 53–54°).

1-(1-Methyl-5-imidazolyl)ethanol.—To a solution of 5.0 g of 1-methyl-5-imidazolecarboxaldehyde in 250 ml of anhydrous diethyl ether was added dropwise 45 ml of methyllithium (1.5 *M* in *n*-hexane, Foote Mineral Co.). During the addition the reaction mixture was maintained under a nitrogen atmosphere and the temperature was maintained below 5°. After stirring for 1 hr at 0°, the mixture was allowed to warm to room temperature, stirred for an additional 0.5 hr, and then quenched with 150 ml of water. The phases were separated and the aqueous phase was continuously extracted with methylene chloride for 16 hr. No product was detected in the ethereal phase. The methylene chloride extracts were concentrated under vacuum and the solid residue was crystallized from benzene to yield 4.5 g (78%) of 1-(1-methyl-5-imidazolyl)ethanol as colorless crystals: mp 126.5–127.5° (lit.[22] mp 128–130°); nmr ($CDCl_3$) δ 7.25 (d, 1, J = 1 Hz, ring proton), 6.75 (br s, 1, ring proton), 4.81 (q, 1, J = 1 Hz, ring proton), 6.75 (br s, 1, ring proton), 4.81 (q, 1, J = 6 Hz, CH(OH)CH_3), 3.66 (s, 3, NCH_3), and 1.57 (d, 3, J = 6 Hz, CH(OH)CH_3).

1-(1-Methyl-5-imidazolyl)ethyl *p*-nitrobenzoate (5) was prepared in the same fashion as **2**. The crude ester **5** was purified by column chromatography on silica gel eluting with chloroform to yield 3.3 g (50%) of 1-(1-methyl-5-imidazolyl)ethyl *p*-nitrobenzoate (**5**) as a pale yellow solid: mp 99–101°; nmr ($CDCl_3$) δ 8.27 (s, 4, $O_2NC_6H_4$–), 7.50 (s, 1, ring proton), 7.23 (s, 1, ring proton), 6.31 (q, 1, J = 6.8 Hz, CH(OH)CH_3), 3.70 (s, 3, NCH_3), and 1.82 (d, 3, J = 6.8 Hz, CH(OH)CH_3).

Anal. Calcd for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.26. Found: C, 56.52; H, 4.83; N, 15.28.

1,5-Dimethylimidazole (6).—2-Methylaminopropionaldehyde diethyl acetal[23] was converted to 1,5-dimethyl-2-mercaptoimidazole by treatment with potassium thiocyanate.[24] Oxidative removal of the mercapto group[20,25] gave **6** in 73% yield: bp 110–112° (30 mm); mp 21.5–22.0°; nmr ($CDCl_3$) δ 7.25 (br s, 1, 2-H), 6.63 (m, 1, 4-H), 3.37 (s, 3, NCH_3), and 2.06 (d, 3, J = 1.2 Hz, CH_3).

Anal. Calcd for $C_5H_8N_2$: C, 62.47; H, 8.39; N, 29.25. Found: C, 62.66; H, 8.47; N, 28.92.

1-(1,5-Dimethyl-2-imidazolyl)ethanol (7).—Transmetalation of **6** (20 g) with *n*-butyllithium at −80° was followed by the addition of acetaldehyde (20 ml) at 0°. Work-up in the usual manner gave a crude product which was shown by nmr to be a mixture of **6** and **7**. The mixture was separated by chromatography on silica gel to afford 11.6 g (58%) of recovered **6** and 9.0 g (30%) of 1-(1,5-dimethyl-2-imidazolyl)ethanol (**7**). **7** was purified by crystallization from benzene–hexane: mp 99–100°; nmr ($CDCl_3$) δ 6.48 (br s, 1, 4-H), 4.79 (q, 1, J = 6.7 Hz, CH-(OH)CH_3), 3.53 (s, 3, NCH_3), 2.10 (d, 3, J = 0.9 Hz, CH_3), and 1.51 (d, 3, J = 6.7 Hz, CH(OH)CH_3).

Anal. Calcd for $C_7H_{12}N_2O$: C, 59.98; H, 8.63; N, 19.98. Found: C, 60.12; H, 8.53; N, 19.78.

1-(1,5-Dimethyl-2-imidazolyl)ethyl *p*-nitrobenzoate (8) was prepared as above for **2**. Crude **8** was crystallized from benzene–hexane to give 1-(1,5-dimethyl-2-imidazolyl)ethyl *p*-nitrobenzoate (**8**) as white crystals: mp 116.5–118°; nmr ($CDCl_3$) δ 8.22 (s, 4, $O_2NC_6H_4$–), 6.78 (br s, 1, 4-H), 6.27 (q, 1, J = 6.6 Hz, CH(OH)CH_3), 3.57 (s, 3, NCH_3), 2.20 (d, 3, J = 0.9 Hz, CH_3), and 1.85 (d, 3, J = 6.6 Hz, CH(OH)CH_3).

Anal. Calcd for $C_{14}H_{15}N_3O_4$: C, 58.13; H, 5.23; N, 14.52. Found: C, 57.93; H, 5.11; N, 14.55.

1-(1-Methyl-5-chloro-2-imidazolyl)ethanol (9).—A solution of 10 g of 1-methyl-5-chloroimidazole[26] in 250 ml of ether was transmetalated with 1 equiv of *n*-butyllithium in hexane at −80°, and a threefold excess of acetaldehyde was added at room temperature. Work-up in the usual manner afforded crude **9**, which was crystallized from ether to give 8.2 g (64%) of **9** as colorless needles: mp 110–111°; nmr ($CDCl_3$) δ 6.70 (s, 1, 4-H), 4.81 (q, 1, J = 7 Hz, CH(OH)CH_3), 3.60 (s, 3, NCH_3), and 1.54 (d, 3, J = 7 Hz, CH(OH)CH_3).

1-(1-Methyl-5-chloro-2-imidazolyl)ethyl *p*-Nitrobenzoate (10).—Compound **9** was converted to the *p*-nitrobenzoate (**10**) as above, yielding pale yellow prisms from benzene–hexane: mp 127–128.5°; nmr ($CDCl_3$) δ 8.16 (s, 4, $O_2NC_6H_4$–), 6.90 (s, 1, 4-H), 6.22 (q, 1, J = 7 Hz, CH(OH)CH_3), 3.63 (s, 3, NCH_3), and 1.84 (d, 3, J = 7 Hz, CH(OH)CH_3).

Anal. Calcd for $C_{13}H_{12}ClN_3O_4$: C, 50.42; H, 3.91; Cl, 11.45; N, 13.57. Found: C, 50.58; H, 3.81; Cl, 11.27; N, 13.32.

1-(1,4-Dimethyl-2-imidazolyl)ethanol (11) was prepared from 1,4-dimethylimidazole[23,25] by transmetalation and treatment with acetaldehyde. A sample purified by chromatography was characterized by nmr: δ ($CDCl_3$) 6.38 (br s, 1, 5-H), 4.78 (q, 1, J = 6.5 Hz, CH(OH)CH_3), 3.58 (s, 3, NCH_3), 2.05 (s, 3, CH_3), and 1.47 (d, 3, J = 6.5 Hz, CH(OH)CH_3).

1-(1,4-Dimethyl-2-imidazolyl)ethyl *p*-Nitrobenzoate (12).—Conversion of **11** to the ester was accomplished in the usual manner. 1-(1,4-Dimethyl-2-imidazolyl)ethyl *p*-nitrobenzoate **12** crystallized from benzene–hexane as pale yellow crystals: mp 124–125°; nmr ($CDCl_3$) δ 8.20 (s, 4, $O_2NC_6H_4$–), 6.60 (br s, 1, 5-H), 6.25 (q, 1, J = 6.6 Hz, CH(OH)CH_3), 3.67 (s, 3, NCH_3), 2.22 (s, 3, CH_3), and 1.86 (d, 3, J = 6.6 Hz, CH(OH)CH_3).

Anal. Calcd for $C_{14}H_{15}N_3O_4$: C, 58.13; H, 5.23; N, 14.52. Found: C, 58.31; H, 5.21; N, 14.37.

1-(1-Methyl-4-phenyl-2-imidazolyl)ethanol (13).—Transmetalation of 1-methyl-4-phenylimidazole[27] at −80° with *n*-butyllithium was followed by addition of a threefold excess of acetaldehyde at 0°. Isolation in the usual fashion afforded crude **13**. Crystallization from benzene–hexane gave 62% of 1-(1-methyl-4-phenyl-2-imidazolyl)ethanol as colorless crystals: mp 121–122°; nmr ($CDCl_3$) δ 7.38 (m, 5, phenyl), 6.72 (s, 1, 5-H), 4.90 (q, 1,

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J = 6.4 Hz, CH(OH)CH_3), 3.26 (s, 3, NCH_3), and 1.56 (d, 3, J = 6.4 Hz, CH(OH)CH_3).

Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.03; H, 6.91; N, 14.03.

1-(1-Methyl-4-phenyl-2-imidazolyl)ethyl *p*-nitrobenzoate (14) was prepared in the usual fashion: mp 112–113°; nmr ($CDCl_3$) δ 8.19 (s, 4, $O_2NC_6H_4$–), 7.75 (m, 2, phenyl), 7.32 (m, 3, phenyl), 7.12 (s, 1, 5-H), 6.31 (q, 1, J = 6.6 Hz, CH(OH)CH_3), 3.73 (s, 3, NCH_3), and 1.93 (d, 3, J = 6.6 Hz, CH(OH)CH_3).

Anal. Calcd for $C_{19}H_{17}N_3O_4$: C, 64.95; H, 4.88; N, 11.96. Found: C, 65.06; H, 4.73; N, 11.82.

1-Methyl-4-chloroimidazole (15).—A solution of 17.8 g (0.153 mol) of 1-methyl-5-chloroimidazole,[28] 57 g (0.4 mol) of methyl iodide, and 150 ml of benzene was refluxed for 1 hr. On cooling, the precipitated 1,3-dimethyl-4(5)-chloroimidazolium iodide was collected by filtration. This was transferred to a round-bottomed flask and heated to 220°. Methyl iodide was evolved. After the majority of the methyl iodide had been removed, the residue was distilled to give 11.1 g (62%) of 1-methyl-4-chloroimidazole and a small amount of the 1,5 isomer, bp 124–125° (20 mm).

1-(1-Methyl-4-chloro-2-imidazolyl)ethyl *p*-Nitrobenzoate (17).—Metalation of **15** was accomplished with *n*-butyllithium, and the resulting 2-lithio derivative was treated with acetaldehyde. The resulting mixture was poured into water, the phases were separated, and the aqueous phase was extracted with chloroform. The combined extracts were dried (Na_2SO_4) and concentrated. The resulting red oil was chromatographed on silica gel, eluting with chloroform to yield 4.6 g (48%) of 1-(1-methyl-4-chloro-2-imidazolyl)ethanol (**16**) contaminated with traces of **9**.

The crude **16** was directly converted to 1-(1-methyl-4-chloro-2-imidazolyl)ethyl *p*-nitrobenzoate (**17**): mp 162–163° (needles from benzene–hexane); nmr ($CDCl_3$) δ 8.27 (s, 4 H, $O_2NC_6H_4$–), 6.82 (s, 1, 5-H), 6.22 (q, 1 H, J = 7 Hz, CH(OH)CH_3), 3.75 (s, 3, NCH_3), and 1.84 (d, 3, J = 7 Hz, CH(OH)CH_3). There was no indication of the 1,5 isomer by nmr.

Anal. Calcd for $C_{13}H_{12}ClN_3O_4$: C, 50.42; H, 3.91; Cl, 11.45; N, 13.57. Found: C, 50.25; H, 3.81; Cl, 11.42; N, 13.42.

1-(1-Methyl-4-bromo-2-imidazolyl)ethanol (19).—A solution of 8.0 g of 1-methyl-4-bromoimidazole[29] in ether was treated with *n*-butyllithium in hexane at −80°. The resulting 2-lithio derivative was treated with a twofold excess of acetaldehyde at −80°. Isolation in the usual manner and chromatography on silica gel ($CHCl_3$ eluent) afforded 4.7 g of **19** as a viscous pale yellow oil,[30] characterized by nmr and used directly for the preparation of the *p*-nitrobenzoate: nmr ($CDCl_3$) δ 6.73 (s, 1, 5-H), 4.89 (q, 1, J = 6.8 Hz, CH(OH)CH_3), 3.68 (s, 3, NCH_3), and 1.52 (d, 3, J = 6.8 Hz, CH(OH)CH_3).

1-(1-Methyl-4-bromo-2-imidazolyl)ethyl *p*-Nitrobenzoate (20).—Conversion of **19** to **20** was accomplished in the usual fashion: mp 156–157°; nmr ($CDCl_3$) δ 8.27 (s, 4, $O_2NC_6H_4$–), 6.90 (s, 1, 5-H), 6.22 (q, 1, J = 6.8 Hz, CH(OH)CH_3), 3.77 (s, 3, NCH_3), and 1.85 (d, 3, J = 6.8 Hz, CH(OH)CH_3).

Anal. Calcd for $C_{13}H_{12}BrN_3O_4$: C, 44.09; H, 3.42; Br, 22.56; N, 11.86. Found: C, 44.30; H, 3.52; Br, 22.74; N, 11.62.

1-(1,4,5-Trimethyl-2-imidazolyl)ethanol (21).—A solution of 11 g of 1,4,5-trimethylimidazole[31] in dry ether was metalated at −80° with *n*-butyllithium. The resulting 2-lithio derivative was treated with a threefold excess of acetaldehyde at 0°. Work-up in the usual manner afforded a modest yield of **21**, which was recrystallized from benzene–hexane to give 3.6 g (24%) of 1-(1,4,5-trimethyl-2-imidazolyl)ethanol (**21**) as colorless needles: mp 126.5–128°; nmr ($CDCl_3$) δ 4.78 (q, 1, J = 7.0 Hz, CH(OH)CH_3), 3.58 (s, 3, NCH_3), 2.07 (s, 6, 4-CH_3 + 5-CH_3), and 1.5 (d, 3, J = 7.0 Hz, CH(OH)CH_3).

Anal. Calcd for $C_8H_{14}N_2O$: C, 62.31; H, 9.15; N, 18.17. Found: C, 62.10; H, 8.95; N, 17.95.

1-(1,4,5-Trimethyl-2-imidazolyl)ethyl *p*-Nitrobenzoate (22).—Alcohol **21** was converted to the *p*-nitrobenzoate in the usual manner: mp 127.5–128.5° (yellow needles from benzene–hexane); nmr ($CDCl_3$) δ 8.28 (s, 4, phenyl), 6.31 (q, 1, J = 6.8 Hz, CH(OPNB)CH_3), 3.57 (s, 3, NCH_3), 2.12 (s, 3, CH_3), 2.11 (s, 3, CH_3), and 1.86 (d, 3, J = 6.8 Hz, CH(OPNB)CH_3).

Anal. Calcd for $C_{15}H_{17}N_3O_4$: C, 59.40; H, 5.65; N, 13.85. Found: C, 59.30; H, 5.43; N, 13.62.

Kinetic methods have been described previously.[13] Directly measured rate constants are given in Table IV.

TABLE IV

EXPERIMENTAL RATE CONSTANTS FOR THE SOLVOLYSIS OF SUBSTITUTED IMIDAZOLYLETHYL *p*-NITROBENZOATES IN 80% ETHANOL

Compound solvolyzed	Temp, °C	Method[a]	$10^5 k$, sec^{-1}
2	45.00	A	3.38 ± 0.05
	60.00	B	16.5 ± 0.3
	60.00	A	17.2 ± 0.2
	75.00	A	72.2 ± 0.8
4	45.00	A	43.0 ± 0.4
	60.00	A	208.0 ± 2.0
5	25.00	A	4.67 ± 0.08
	45.00	A	53.0 ± 0.3
	60.00	A	243.0 ± 4.0
8	25.00	A	18.7 ± 0.3
	45.00	A	167.0 ± 2.0
	60.00	A	712.0 ± 8.0
10	45.00	B	0.658 ± 0.01
	60.00	B	3.85 ± 0.1
	75.00	B	19.4 ± 0.6
12	25.00	A	6.36 ± 0.2
	45.00	A	59.80 ± 0.6
	60.00	A	257.0 ± 5.0
14	25.00	A	1.91 ± 0.04
	45.00	A	21.3 ± 0.3
	45.00	B	22.7 ± 0.4
	60.00	A	106.0 ± 2.0
17	45.00	B	0.436 ± 0.02
	60.00	B	2.82 ± 0.08
	75.00	B	13.2 ± 0.2
20	60.00	B	2.25 ± 0.05
	75.00	B	12.2 ± 0.2
	75.00	A	12.1 ± 0.2
22	0.00	A	13.1 ± 0.2
	8.25	A	41.8 ± 0.8
	25.00	A	317.0 ± 5.0

[a] A is at constant pH (8.0); B is by aliquot.

Registry No.—**1**, 41507-36-2; **2**, 41507-37-3; **3**, 17289-26-8; **4**, 41507-39-5; **5**, 41507-40-8; **6**, 10447-93-5; **7**, 41507-42-0; **8**, 41507-43-1; **9**, 41507-44-2; **10**, 41507-45-3; **11**, 41507-46-4; **12**, 41507-47-5; **13**, 41507-48-6; **14**, 41507-49-7; **15**, 4897-21-6; **17**, 41507-51-1; **19**, 41507-52-2; **20**, 41507-53-3; **21**, 41507-54-4; **22**, 41507-55-5; 1-methylimidazole, 616-47-7; acetaldehyde, 75-07-0; *p*-nitrobenzoyl chloride, 122-04-3; ethyl 1-methyl-4-imidazolecarboxylate, 41507-56-6; methyl bromide, 74-83-9; 1-(1-methyl-5-imidazolyl)ethanol, 23428-92-4; 1-methyl-5-imidazolecarboxaldehyde, 39021-62-0; 2-methylaminopropionaldehyde diethyl acetal, 41507-59-9; 1-methyl-5-chloroimidazole, 872-49-1; 1,4-dimethylimidazole, 6338-45-0; 1-methyl-4-phenylimidazole, 2411-77-0; methyl iodide, 74-88-4; 1-methyl-4-bromoimidazole, 25676-75-9; 1,4,5-trimethylimidazole, 20185-22-2.

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(29) Prepared by methylating 4(5)-bromoimidazole (**18**) with methyl iodide in the presence of excess 10 *N* sodium hydroxide and fractionating the product. Roughly equal quantities of **18** and of 1-methyl-5-bromoimidazole resulted.

(30) Reversing the order of addition or substituting methyllithium for *n*-butyllithium does not change the product obtained. However, when 1-methyl-5-bromoimidazole is subjected to the same sequence, halogen–metal interchange ensues, and the product obtained is 1-(1-methyl-5-imidazolyl)-ethanol.

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