acidified with methanolic hydrogen chloride and the salt was crystallized from EtOH–EtOAc to give 1.12 g, mp 211–212° dec, and 0.344 g, mp 207.5–5–208.5° dec (23.9%), of **29** hydrochloride. An analytical sample was obtained: mp 209–210° dec; uv (EtOH) λ_{max} 219 mμ (ε 17,700), 276 (8550), 283 (8700), and 293 (inflection, 7650); ir (Nujol) 1640 cm^{-1} (C=N⁺); mass spectrum *m/e* (rel intensity) 228 (100), 213 (6.5), 200 (34), 199 (34), and 171 (16); nmr [$(CD_3)_2SO$–D_2O] δ 1.42 (t, 3, *J* = 7 Hz, CH_3CH_2N), 3.69 (s, 3, CH_3N), 3.87 (q, 2, *J* = 7 Hz, CH_3-CH_2N), and 7.39 (m, 4, C-6–9).

Anal. Calcd for $C_{15}H_{21}ClN_2$: C, 68.03; H, 7.99; Cl, 13.39; N, 10.58. Found: C, 67.73; H, 7.89; Cl, 13.46; N, 10.10.

The second compound eluted from the column was crystallized from EtOAc–Skellysolve B to give 1.42 g (25.4%) of **30**, mp 130–132.5°. The analytical sample was crystallized from EtOH–Skellysolve B: mp 125–125.5°; uv (EtOH) λ_{max} 226 mμ (ε 40,000), 285 (9290), 293 (8100), and 279 (inflection, 8560); ir (Nujol) 1670 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity) 242 (100), and 199 (77); nmr [$(CD_3)_2SO$] δ 1.81 [s, 3, CH_3-(C=O)N], 3.59 (s, 3, CH_3N), 4.56 (sextet, 1, *J* ≅ −13 and 3 Hz, C-2 equatorial), and 7.31 (m, 4, C-6–9).

Further elution of the column with EtOAc gave a mixture of two additional compounds which was rechromatographed on silica gel (150 g) with 2% Et_3N–23% cyclohexane–75% EtOAc.

The first compound eluted from this column was crystallized from EtOAc–Skellysolve B to give 0.408 g (6.87%) of **36**, mp 108.5–110°. An analytical sample was obtained: mp 105–108°; uv (EtOH) λ_{max} 217 mμ (ε 23,430), 277 (15,070), and 311 (2450); ir (Nujol) 1740 [CH_3(C=O)O] and 1675 cm^{-1} (C=N); mass spectrum (high resolution) *m/e* 258.1369; nmr ($CDCl_3$) δ 2.04 [s, 3, CH_3(C=O)O], 3.13 (s, 3, CH_3N), 3.72 (m, 2, C-2), and 6.91 (m, 4, C-6–9).

Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.85. Found: C, 69.61; H, 7.04; N, 10.36.

The second compound eluted from the column was crystallized from EtOAc–Skellysolve B (Darco) to give 0.169 g (2.81%) of **33**, mp 139–141°. An analytical sample was obtained: mp 141.5–142.5°; uv (EtOH) end absorption, λ_{max} 250 mμ (ε 12,950) and 306 (2625); ir (Nujol) 3280 (OH), and 1615 cm^{-1} (C=O); mass spectrum (high resolution) *m/e* 260.1514 (M^+) and 242.1429 ($M^+ - 18$); nmr ($CDCl_3$)[27] δ 2.18, 2.23 [s, 3, CH_3(C=O)N], 2.68, 2.72 (s, 3, CH_3N), 5.85, 5.20 (s, 1, C-10a), and 6.89 (m, 4, C-6–9).

Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 68.96; H, 7.86; N, 10.71.

1-Acetyl-1,2,3,4,5,10-hexahydro-10-methylazepino[2,3-*b*]indole (30).—A solution of **33** in benzene was treated with a few crystals of *p*-toluenesulfonic acid, stirred at ambient temperature under N_2 for 30 min, and poured into water. This mixture was extracted with ether; the extract was washed with water, dried (K_2CO_3), and concentrated. Crystallization of the residue from Et_2O–Skellysolve B gave **30**, mp 126.5–127.5°. This material was identical to the authentic sample by mixture melting point and ir and uv comparison.

(27) This material was a mixture of two isomers; the more intense peaks are listed first.

Registry No.—**3**, 23240-49-5; **5**, 14384-39-5; **6**, 23240-51-9; **7**, 23240-52-0; **10**, 23240-53-1; **11**, 23240-54-2; **12**, 23240-55-3; **13** hydrochloride, 23240-56-4; **14**, 23240-57-5; **15**, 23240-58-6; **16**, 23240-59-7; **17**, 23240-60-0; **17** hydrochloride, 23240-61-1; **17** hydrobromide, 23240-62-2; **18**, 23240-63-3; **19** hydrochloride, 23240-64-4; **20** hydrochloride, 23240-65-5; **21**, 23240-66-6; **22**, 23240-67-7; **23**, 23231-29-0; **24** hydrochloride, 23231-00-7; **25**, 23231-01-8; **26**, 23231-02-9; **27**, 23231-03-0; **29** hydrochloride, 23231-04-1; **30**, 23231-05-2; **31**, 23263-76-5; **32**, 23231-06-3; **33**, 23231-07-4; **34**, 23240-68-8; **35**, 23231-08-5; **35** hydrochloride, 23231-09-6; **36**, 23231-10-9.

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The Mannich Reaction of Imidazoles

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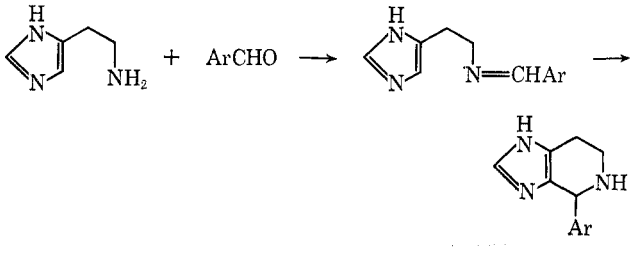
In the Mannich reaction of imidazoles, the ring is shown to be reactive at the four possible sites, the 1, 2, 4, and 5 positions. Only N-substituted imidazole Mannich bases are formed in acidic media. Both N-substituted and C-substituted products are formed in basic media. The process of N substitution is reversible in base, while C substitution is irreversible, resulting in the accumulation of C-substituted products over time in basic media. The 1 position is most reactive, with the 4 and 5 positions more reactive than the 2 position. Imidazoles having substituents at the 1 position do not react in the Mannich reaction. A mechanism is proposed which explains the behavior of the imidazole ring in the Mannich reaction.

The chemistry of imidazoles has considerable significance owing to the occurrence of this ring system in various biologically important compounds. Some 4-disubstituted aminomethyl imidazoles prepared by Turner, Huebner, and Scholz[2] in a multistep process were shown to have antihistaminic action, while others imitated histamine. It was of interest to study the Mannich reaction as a one-step method of introducing aminomethyl groups on to the imidazole ring.

Part of the rationale for studying the Mannich reaction of imidazoles grew out of our findings on the related facile base-catalyzed cyclization of histamine

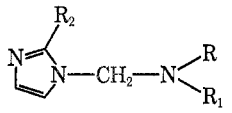


(1) (a) To whom all inquiries should be addressed. (b) This work was supported in part by the Public Health Service, National Institute of General Medical Sciences, Grant GM 10612-06.

(2) R. A. Turner, C. F. Huebner, and C. R. Scholz, *J. Amer. Chem. Soc.*, **71**, 2801 (1949).

TABLE I

N-SUBSTITUTED MANNICH BASES[a]

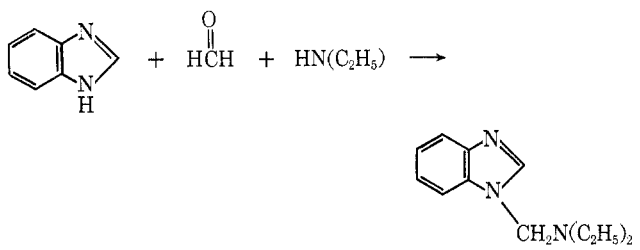


Registry no.	R	R_1	R_2	Nmr chemical shifts[b] 2 proton	4 proton	5 proton	CH_2 protons	Yield,[c] %	Bp (mm) or mp, °C
23230-39-9	CH_3	CH_3	H	7.60	7.15	7.04	4.68	82	95 (1.5)[d]
23230-40-2	CH_3	$C_6H_5CH_2$	H	7.45	7.04	6.94	4.71	94	73.5–75[e]
23230-41-3	$C_6H_5CH_2$	$C_6H_5CH_2$	H	7.40	7.12	6.94	4.78	90	67–68[e]
23230-42-4	N–RR_1 = piperidino		H	7.54	7.08	6.98	4.70	70	*f–h*
23230-43-5	N–RR_1 = morpholino		H	7.45	7.04	6.96	4.64	84	69–71[e,i]
23230-44-6	*j*		H	7.45	7.02	6.92	4.64	62	159–60[k]
23230-45-7	N–RR_1 = piperidino		CH_3	...	6.80	6.80	4.43	84	*f, l, m*
23230-46-8	*j*		CH_3	...	6.84	6.84	4.47	74	135.5–137[e]

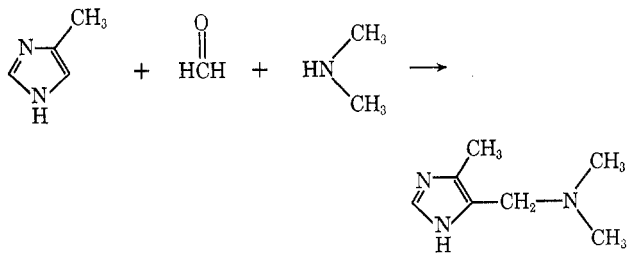
[a] Satisfactory analytical data (±0.3%) were obtained for these compounds (Ed.). [b] Shift values (δ 0) were determined in $CDCl_3$ with tetramethylsilane as an internal reference. [c] Crude yield. [d] $n^{23}D$ 1.4950. [e] Recrystallized from ligroin. [f] Separated by falling-film molecular distillation at 1.5 mm. [g] Pot temperature 97.2° (1-propanol). [h] $n^{23}D$ 1.5206. [i] Hygroscopic. [j] Piperazino-1,4-bis compound. [k] Recrystallized from benzene. [l] Pot temperature 80.1° (benzene). [m] $n^{23}D$ 1.5155.

Schiff bases.[3] The cyclization step is catalyzed by base.

Imidazole, 2-ethylimidazole, and 2-methyl-4,5-diphenylimidazole were initially reported as unreactive under normal Mannich reaction conditions by Bachman and Heisey[4] in 1946. Benzimidazole was reported to give Mannich bases substituted on the 1 position as shown.



Imidazole itself has four possible sites of reaction, the 1, 2, 4, and 5 positions. Heath, Lawson, and Rimington,[5] in 1951, reported substitution on the 5(4) position of the imidazole ring in the Mannich reaction on 2-mercapto-4(5)-methylimidazole. No proof of the site of the substitution was offered for the product. In 1952, Kato, Morkawa, and Suzuki[6] reported the reaction of imidazole and 4(5)-methylimidazole in the Mannich reaction with dimethylamine, giving a 4(5)-substituted product.



We now report that the Mannich reaction is successful at all four possible positions of the imidazole ring, and we describe factors affecting the orientation of substitution on the ring.

Results

Imidazoles unsubstituted at the 1 position readily undergo the Mannich reaction under conventional conditions. The classical, acidic conditions favor the formation of N-substituted imidazole Mannich bases (see Table I). These compounds were identified as N-substituted Mannich based primarily by nmr studies. The structural assignments were made on the basis of the singlet peak, owing to the methylene hydrogens of the substituted aminomethyl group, which appeared at *ca.* δ 4.7 in each nmr spectrum. The observed chemical shift is in good agreement with a theoretical value of δ 4.77 for the methylene hydrogens in a 1-substituted product, calculated by using shielding constants[7] and a spectrum of 1-benzylimidazole, and the observed shift is considerably different from the predicted value of δ 3.5[8] for C-substituted Mannich bases. The assignments are further supported by the absence of an imino hydrogen peak and by the 1:1 ratio of the methylene peak area to the peak area of the 4- and 5-position imidazole hydrogens.

Examination of nmr spectra of some crude 2-methylimidazole Mannich reaction mixtures produced in basic media indicated resonances expected of C substitution and peak area ratios consistent with a mixture composed of mono-, di-, and trisubstitution products.

By conducting reactions in basic conditions, using various alkyl-substituted imidazoles, the imidazole ring is shown to be reactive in the Mannich reaction at all four available positions. Some representative C-substituted Mannich bases have been isolated which illustrate substitution at each position. (See Table II.) The assignments of structures of the C-substituted prod-

(3) F. Stocker, M. Fordice, J. Larson, and J. Thorstenson, *J. Org. Chem.*, **31**, 2380 (1966).

(4) G. B. Bachman and L. V. Heisey, *J. Amer. Chem. Soc.*, **68**, 2496 (1946).

(5) H. Heath, A. Lawson, and C. Rimington, *J. Chem. Soc.*, 2217 (1951).

(6) T. Kato, T. Morkawa, and Y. Suzuki, *J. Pharm. Soc. Jap.*, **72**, 1177 (1952).

(7) R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1963, p 141.

(8) This value was indicated by shielding-constant calculations and was experimentally verified after synthesis of 4-(diethylaminomethyl)imidazole from 4(5)-hydroxymethylimidazole by the method of Turner, Huebner, and Scholz.[2]

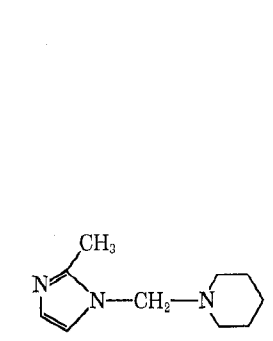
TABLE II
C-SUBSTITUTED IMIDAZOLE MANNICH BASES[a]

Imidazole	Registry no.	Substituent groups	Mp, °C	Methylene hydrogens[b]
2-Methyl-	23230-47-9	1,4,5-Tris(N-piperidinomethyl)	92–93	4.59, 3.53, 3.41
2-Methyl-	23230-48-0	4,5-Bis(N-piperidinomethyl)	149–150	3.43, 3.43
2-Methyl-	23230-49-1	4(5)-(N-Piperidinomethyl)	204–207[c]	3.52
4,5-Dimethyl-	23230-50-4	2-(N-Diethylaminomethyl)	112–113.5	3.54
2,4(5)-Dimethyl-	23230-51-5	5(4)-(N-Diethylaminomethyl)	75–77	3.48

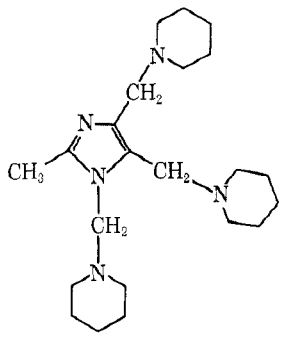
[a] Satisfactory analyses (±0.3%) were obtained for all compounds (Ed.). [b] Nmr shift values (δ 0) of aminomethylene hydrogens of substituent groups were determined in $CDCl_3$ using tetramethylsilane as an internal reference. [c] Melting point of dipicrate.

ucts were made by analysis of their nmr spectra and particularly the presence of methylene proton resonance in the δ 3.4–3.7 region. Table II shows the key aminomethylene shift values from the nmr spectra.

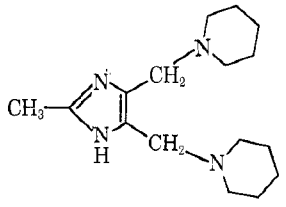
There are six possible products of a Mannich reaction between 2-methylimidazole, piperidine, and formaldehyde. Three of these products have been isolated and purified: 2-methyl-1-(N-piperidinomethyl)imidazole (I), 2-methyl-1,4,5-tris(N-piperidinomethyl)imidazole (II), and 2-methyl-4,5-bis(N-piperidinomethyl)-imidazole (III). A fourth compound, 2-methyl-4(5)-(N-piperidinomethyl)imidazole (IV), was isolated, but it failed to crystallize as the free base, thus making it necessary to form a derivative, the dipicrate, and crystallize it in the salt form.



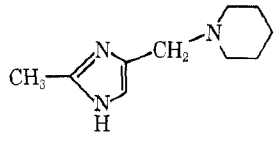
I



II



III



IV

The purification of C-substituted Mannich bases is difficult, chiefly because of the formation of multiple reaction products having similar physical and chemical properties. The simple N-substituted products are less associated and therefore more volatile than the other products and therefore they could sometimes be isolated by ordinary vacuum distillation or falling-film molecular distillation. Elution chromatography using an alumina column and a benzene–chloroform eluent effected the separation of some of the C-substituted products. Because of the difficulty of product separation, the Mannich reaction of imidazoles is most useful in the preparation of N-substituted Mannich bases, which can be isolated by distillation procedures, and for imidazoles that have a limited number of available sites, which restricts the number of reaction products.

A systematic study was made of the effect of pH on the position or substitution on the imidazole ring in the Mannich reaction. Diethylamine was used as the amine reagent and three imidazole compounds were used: imidazole, 2-methylimidazole, and 2,4-dimethylimidazole. Six reactions over a range of pH were run with each imidazole compound. No significant change in pH was observed during the reaction. Table III summarizes the results of this study in terms of per cent substitution on the carbon positions out of the total amount of substitution. The data were obtained from nmr spectra by comparing the areas of methylene hydrogen peaks owing to C substitution and N substitution.

TABLE III[a]
PER CENT C SUBSTITUTION *vs.* pH

pH (±0.07)	1.00	5.00	7.00	9.00	11.00	12.00
Imidazole	0	0	8	16	23	29
2-Methylimidazole	0	0	0	44	94	94
2,4-Dimethylimidazole	0	0	18	91	94	91

[a] 24 hr allowed for reaction.

It is evident from the pH study that only nitrogen-site substitution of the imidazole ring occurs in the acidic pH range. In basic reaction media, C substitution reaches significant proportions within the 24 hr allowed for reaction; nmr spectra of the products show the carbon positions to be the most substituted, except in the case of imidazole itself, in which 1 substitution still predominates. The statistical factor of the number of available sites apparently is not a significant factor; imidazole showed the least amount of C substitution, although it has a 3:1 ratio of available carbon to nitrogen sites. The 4 and 5 positions are more reactive than the 2 position, but experiments with 4,5-dimethylimidazole indicate that, when the 4 and 5 positions are blocked, the 2 position is reactive and follows the same general pattern of increased reactivity in basic media.

The formation, in basic conditions, of N-substituted imidazole Mannich products is a readily reversible process. A sample of 2-methyl-1-(N-piperidinomethyl)-imidazole in aqueous solution at pH 11.9 underwent reversal to reactants and reacted again until *ca.* 50% of the aminomethyl groups were substituted on the 4 and 5 positions within a 24-hr period. It could not be determined with certainty whether N-substituted products reverse in acid, although change in site of substitution or loss of substitution owing to such reversal was discovered to be less than 5% in 24 hr at pH 0.7. The formation of C-substituted imidazole Mannich bases is an irreversible process in basic conditions. A sample of 4-diethylaminomethylimidazole in aqueous solution at pH 11.8 for 24 hr showed no change of sub-

stitution site and no loss of substitution. This combination of irreversible C substitution and reversible N substitution in basic conditions results in an accumulation of C-substituted products and a decrease in N substitution over a period of time. A time study following the progress of the Mannich reaction of diethylamine with formaldehyde and 2-methylimidazole, at pH 12.3 using nmr analysis, indicated that the nitrogen position is the most reactive position in basic as well as acidic media, but C substitution reaches substantial proportions owing to the steady accumulation at the carbon positions as the reversal of N substitution provides reactants. The formation of C-substituted products is not due to an internal-shift mechanism, because complete loss of aminomethyl groups is seen during N-substitution reversal when a volatile amine is used.

The percentages of carbon- *vs.* nitrogen-site substitution can easily be determined from the nmr spectra of reaction mixtures, but the information obtainable from the spectra is neither sufficient nor accurate enough in most cases to determine the percentages of the actual compounds contained in the mixtures. Several combinations of variously substituted Mannich bases and unreacted imidazole could account for the observed peaks and integration ratios. The exact percentages reported in the pH study using diethylamine cannot be extended to reactions involving other amines, although the trend of high pH favoring C-substituted products is generally applicable.

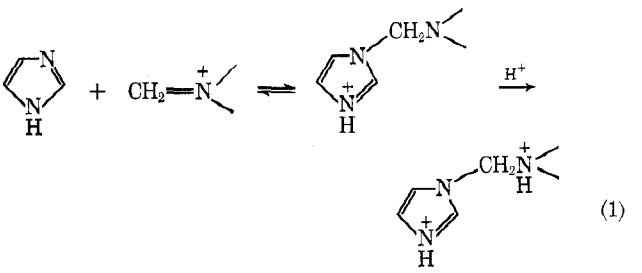
Experiments carried out on 1-alkyl-substituted imidazoles indicate that the 1 position of the imidazole ring must be unsubstituted for the Mannich reaction to be successful. Mannich reactions were attempted in both acidic and basic media on 1-methylimidazole, 1-benzylimidazole, 1-benzyl-2-methylimidazole, and 1,2-dimethylimidazole. In all cases, the imidazole compound was recovered unreacted.

Kato's[6] procedure in the Mannich reaction of imidazole with dimethylamine in acidic media was repeated and a 1-substituted product was obtained instead of the 4(5)-substituted product he reported. The nmr spectrum of the crude reaction mixture indicated N substitution, with no peaks that could be attributed to the resonance of methylene protons of a C-substituted product. Moreover, we were unable to prepare the picrate he reported, thereby casting some doubt on the formation of a 4(5)-substituted Mannich base in his procedure. However, we suggest that a C-substituted product may have been obtained if the reaction products were to remain long enough in conditions favoring reversal of N-substituted products and formation of C-substituted products.

Discussion

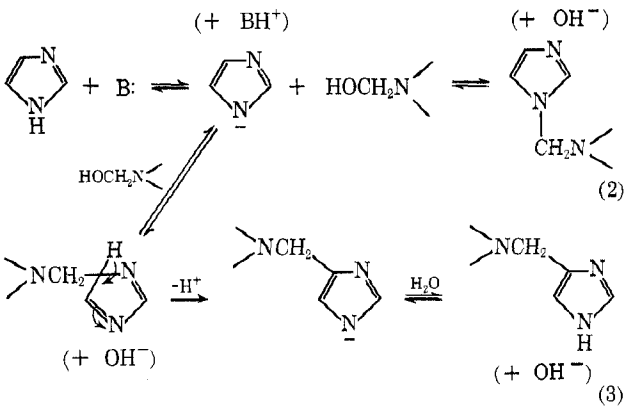
Cummings and Shelton[9] postulated from their kinetic study of cyclohexanone in the Mannich reaction that the reaction in basic media involves the condensation of a carbanion, derived from the active hydrogen compound, with an aminomethylol, R_2NCH_2OH, formed from the amine and formaldehyde. In acidic media, they suggested that the reaction involves the reaction of a carbonium ion, $R_2NCH_2^+ \leftrightarrow R_2\overset{+}{N}CH_2$, derived from the aminomethylol or methylene bisamine formed in reaction between the amine and formaldehyde, with the active hydrogen compound. Assuming the mechanistic steps of Cummings and Shelton in forming the aminomethyl intermediates, we propose the following processes for the final step in the mechanisms of the Mannich reaction of imidazoles, in explanation of the behavior of the imidazole ring in the reaction.[10]

In acid, eq 1 is proposed.



(1)

In base, eq 2 and 3 are proposed.



(2)

(3)

In acidic media, the experimental evidence indicates that substitution occurs only at the 1 position. In the proposed mechanism (eq 1), the cationic imine reacts at the electron-rich basic nitrogen site of the neutral imidazole molecule, which is in equilibrium with the protonated imidazole in acid. As shown experimentally, the final step of nitrogen-site substitution in acid may be slightly reversible, with reversal requiring a free amino group and a protonated imidazole ring.

Experimental observations showing that the 1 position of the imidazole ring must be unsubstituted for the Mannich reaction to be successful imply that the imidazole anion, resulting from the loss of the imino proton, is the reactive species in the Mannich reaction mechanism which results in carbon-site substitution. No reaction occurs when formation of the anion is prohibited by substitution on the 1 position. If the imidazole anion is required for the mechanism of C substitution, C substitution would be expected to occur only in basic media, as is reported in this paper. In base, the reaction (eq 2) between the aminomethylol intermediate and the imidazole anion, which results in N substitution, is a reversible step, whereas C substitution (eq 3) is irreversible. As observed experimentally, in base the nitrogen position is substituted first, then C substitution occurs slowly as the N-substitution reversal supplies the imidazole anion. In the mechanistic scheme we propose, the equilibrium of eq 2 would be forced to the

(9) T. F. Cummings and J. R. Shelton, *J. Org. Chem.*, **25**, 419 (1960).

(10) A referee has suggested that, instead of the methylolamine itself, the imonium cation available from the reversible dissociation of the methylolamine might be the intermediate functioning in basic media.

left with increasing base strength, thereby increasing the proportion of C substitution. Thus, in base, N substitution is favored kinetically while C substitution is favored thermodynamically.

Experimental Section

General.—All nmr spectra were determined on a Jeolco C-60HL or a Varian A-60A spectrometer using $CDCl_3$ as a solvent with tetramethylsilane as an internal reference. Melting points are corrected. Microanalyses were by Galbraith Laboratories, Inc., Knoxville, Tenn. The crude products of imidazole Mannich reactions are typically pale yellow syrups. The 1-substituted Mannich bases were purified by vacuum distillation, falling-film distillation, or recrystallization (see Table I), depending on the specific properties of the product. Thermal decomposition is a serious factor during distillation of the liquid products if the temperature and pressure are allowed to exceed 100° and 1.5 mm. After separation from other products, C-substituted Mannich bases were purified by recrystallization from ligroin or benzene–ligroin. (The ligroin used in this work has a boiling range of 66–75°.) Given below are descriptions of representative reactions of the formation of a 1-substituted and a C-substituted Mannich base. The separate procedures for isolation of the C-substituted products from the crude mixtures are given.

2-(N-Diethylaminomethyl)-4,5-dimethylimidazole.—To a solution of 0.99 g (0.0135 mol) of $(C_2H_5)_2NH$ and 1.64 g (0.020 mol) of 37% formalin in 10 ml of H_2O, 1.30 g (0.0135 mol) of 4,5-dimethylimidazole in 10 ml of H_2O was added dropwise with stirring over 0.5 hr. Reaction was allowed to continue for 48 hr at room temperature without further stirring. The mixture was made distinctly alkaline with a 20% KOH solution, and the organic material was salted out with K_2CO_3 and extracted with three 10-ml portions of $CHCl_3$. The $CHCl_3$ extracts were combined, dried (K_2CO_3), and concentrated to give 1.20 g of a yellow, semicrystalline syrup. The syrup was taken up in 10 ml of absolute EtOH and combined with 1.10 g of HCl in dry EtOH, and the dihydrochloride was crystallized by addition of ether. The dihydrochloride (mp 214–217°, uncorrected) was recrystallized twice from EtOH–ether, and then the base was freed by addition of NaOH solution and extracted with $CHCl_3$. The free Mannich base was recrystallized from ligroin, then sublimed under vacuum at 100° to give white needles, mp 112–113.5°, yield 0.98 g (40%).

2-Methyl-1-(N-piperidinomethyl)imidazole.—To a solution of 4.10 g (0.05 mol) of 2-methylimidazole and 4.25 g (0.05 mol) of piperidine in 15 ml of H_2O was added, with cooling, 8.4 ml (0.10 mol) of 12 *N* HCl. The 37% formalin (4.86 g, 0.06 mol) was poured into the solution and the mixture was stirred for 1 hr. Reaction was allowed to continue for 24 hr at room temperature without further stirring. The mixture was made distinctly alkaline with a 20% KOH solution, and the organic material was salted out with K_2CO_3 and extracted with three 25-ml portions of $CHCl_3$. The $CHCl_3$ extracts were combined, dried (K_2CO_3), and concentrated to give 8.22 g (92%) of a pale yellow liquid which was purified by repeated treatment on a falling-film molecular still at 80.1° (benzene) and 1.5 mm.

2-Methyl-1,4,5-tris(N-piperidinomethyl)imidazole.—This compound was isolated from the crude product obtained by the nonacidic reaction process followed by extraction procedures by elution chromatography with an alumina column. A 60% $CHCl_3$–benzene solvent was used for elution, which on concentration yielded a yellow semisolid. Recrystallization from ligroin gave a white solid, mp 92–93°.

2-Methyl-4,5-bis(N-piperidinomethyl)imidazole.—This compound was eluted from the same column as the above trisubstituted product in later fractions of the 60% $CHCl_3$–benzene solvent. Thin layer chromatography was used to follow the progress of the elution chromatography. The product was isolated as a yellow semisolid which was recrystallized from benzene–ligroin to give light yellow crystals, mp 149–150°.

2-Methyl-4(5)-(N-piperidinomethyl)imidazole.—For this compound the general procedure was altered to use 2 equiv of 2-methylimidazole. After $CHCl_3$ extraction, the $CHCl_3$ solution was washed with H_2O to remove excess 2-methylimidazole. The yellow syrup was concentrated, taken up in benzene, and absorbed on an alumina column, and the products were eluted by a 60% $CHCl_3$–benzene solvent. This compound was eluted after the above tri- and disubstituted products. When it failed to crystallize as the free base, it was converted into the dipicrate, which was recrystallized from 95% EtOH, mp 204–207°.

5(4)-(N-Diethylaminomethyl)-2,4(5)-dimethylimidazole.—Following the general reaction and extraction procedures, the dipicrate was formed and recrystallized from 95% EtOH several times, mp 195–197°. The product was freed from the picrate and sublimed under vacuum at 100° to give white crystals, mp 75–77°.

General Reaction Procedure of pH Experiment.—Precooled 6 *N* HCl was added to a solution of 0.010 mol of the imidazole compound and 0.73 g (0.010 mol) of diethylamine in 3 ml of H_2O until the desired pH was reached. The 37% formalin (1.22 g, 0.015 mol) was poured into the solution with stirring, and reaction was allowed to continue for 24 hr at room temperature without further stirring. The mixture was made distinctly alkaline with 20% KOH solution and was extracted with four 4-ml portions of $CHCl_3$. The $CHCl_3$ extracts were combined and dried (K_2CO_3), and a nmr spectrum was run immediately on the $CHCl_3$ solution.

Registry No.—2-(N-Diethylaminomethyl)-4,5-dimethylimidazole dihydrochloride, 23263-75-4.

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