2,4-Diamino-7-styrylpteridine (15, R = C_6H_5): 89% yield, mp (from DMF) 303 °C dec.

Anal. Calcd for $C_{14}H_{12}N_6$: C, 63.62; H, 4.58; N, 31.80. Found: C, 63.43; H, 4.77; N, 31.86.

2,4-Diamino-7-(2-methoxypropyl)pteridine (18): 60% yield, mp (from methanol) 223–224 °C dec.

Anal. Calcd for $C_{10}H_{14}N_6O$: C, 51.27; H, 6.02; N, 35.88. Found: C, 51.26; H, 6.05; N, 35.73.

2,4-Diamino-7-(3,4-dichlorostyryl)pteridine (15, R = 3,4-$Cl_2C_6H_3$): 79.5% yield, mp (from trituration with hot DMF) 338–339 °C dec.

Anal. Calcd for $C_{14}H_{10}N_6Cl_2$: C, 50.45; H, 3.00; N, 25.22; Cl, 21.32. Found: C, 50.36; H, 3.25; N, 25.24; Cl, 21.47.

2,4-Diamino-7-(3,4-methylenedioxystyryl)pteridine [15, R = 3,4-$(OCH_2O)C_6H_3$]: 91% yield, mp (from trituration with hot methanol) 334–335 °C dec.

Anal. Calcd for $C_{15}H_{12}N_6O_2$: C, 58.44; H, 3.92, N, 27.26. Found: C, 58.47; H, 3.94; N, 27.51.

Registry No.—**1**, 58091-59-1; **2**, 58091-60-4; **3**, 58091-61-5; **4**, 58091-62-6; **5**, 58091-63-7; **6**, 58091-64-8; **7**, 58091-65-9; **8**, 58091-66-0; **9**, 58091-67-1; **10**, 58091-68-2; **11**, 58091-69-3; **12**, 4215-07-0; **13**, 58091-70-6; **14** (R = Me), 58091-71-7; **14** (R = Ph), 58091-72-8; **14** (R = 3,4-diClC_6H_3), 58091-73-9; **14** [R = 3,4-$(OCH_2O)C_6H_3$], 58091-74-0; **15** (R = Ph), 58091-75-1; **15** (R = 3,4-diClC_6H_3), 58091-76-2; **15** [R = 3,4-$(OCH_2O)C_6H_3$], 58091-77-3; **16** (R = Me), 58091-78-4; **16** (R = Ph), 58091-79-5; **16** (R = CH_2OH), 58091-80-8; **16** (R = 2-thienyl), 58091-81-9; *cis*-**16** (R = CO_2H), 58091-82-0; **16** (R = CO_2H), 58091-83-1; **16** (R = 3-pyridyl), 58091-84-2; **17** (R = Ph), 58091-85-3; **18**, 58091-86-4; aminomalonitrile tosylate, 5098-14-6; α-oximino-β-chloropropionaldehyde, 4815-01-4; α-oximino-β-chlorobutyraldehyde, 4749-21-7; α-oximino-β-chlorocapraldehyde, 58091-87-5; 2-nitroso-3-chlorocyclohexanone dimer, 58091-89-7; 2-oximino-3-chlorocyclohexanone, 58091-90-0; triphenylphosphine, 603-35-0; benzaldehyde, 100-52-7; acetaldehyde, 75-07-0; glycolaldehyde, 141-46-8; thiophene-2-carboxaldehyde, 98-03-3; glyoxylic acid, 298-12-4; nicotinaldehyde, 500-22-1; 3,4-dichlorobenzaldehyde, 6287-38-3; piperonal, 120-57-0; guanidine HCl, 15827-40-4.

References and Notes

(1) For the previous paper in this series, see E. C. Taylor, R. C. Portnoy, D. C. Hochstetler, and T. Kobayashi, *J. Org. Chem.*, **40**, 2347 (1975).
(2) This work was supported by a grant (CA-12876) to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service.
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Covalent Amination. Substituent Effects on the Site of Addition of Ammonia to Quaternized Pyridines and Pyrazines

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1,3-Disubstituted pyridinium ions react completely at about −40 °C with ammonia to give covalent amination products. Addition occurs at C-6 when the C-3 group is $CONH_2$, CO_2CH_3, CF_3, or $COCH_3$. Addition at C-2 results when the 3 substituent is Cl or I, and a mixture is found for the 3-CN compound. Parent 1-methyl- and 1-benzylpyridinium ions do not yield 2 adducts unless powdered KOH is added to neutralize ammonium ion. 1-Methoxypyridinium ions at −50 °C give adducts which open to 5-amino-2(*cis*),4(*trans*)-pentadienal oxime *O*-methyl ether. 1-Methyl-3-substituted pyrazinium ions react at the 2 position when the substituent is Cl or CH_3O and at the 6 position in the $CONH_2$ case. 1-Methylpyrazinium ion first forms a 2 adduct and then a 2,3 diadduct.

Many heteroaromatic molecules are known to undergo "covalent hydration" reactions in aqueous solution.[1] In the presence of acid or base, solvent adds to an annular carbon atom to form a covalently bonded hydrate. Quaternization of an annular nitrogen atom greatly promotes such a reaction with water; the product, a "pseudobase", may be in equilibrium with its ring-opened carbonyl tautomer.[2,3] The influence of structure on the position of hydration as well as on rates and equilibria involving aromatic material, its hydroxy adduct, and ring-opened isomer has long intrigued chemists.[4] Recognition of the existence of covalent hydrates in solution has allowed otherwise puzzling chemistry to become understandable.

Covalent amination involving ammonia as solvent has been a largely overlooked counterpart to hydration. No doubt this primarily is a consequence of the greater difficulty in handling ammonia with its low boiling point, −33 °C. However, NMR now makes examination of ammonia reaction mixtures at a variety of temperatures easy, if not routine, and provides access to an area of investigation which is likely to be as rewarding as that involving aqueous solutions.

Already, recognition of the covalent amination process is providing new insight into reactions of heteroaromatic molecules in ammonia. Many simple heteroaromatic molecules such as quinoline,[5] isoquinoline,[5] the three diazines,[6] and their halogenated derivatives[7] react rapidly and completely with ammonia containing amide ion to give anionic σ complexes in which an amino group is bonded to an annular carbon atom. This discovery makes understandable the surprising rearrangement reactions involving amide ion in ammonia and the halogenated derivatives of the heteroaromatic compounds.[8–10]

We now report the results of reactions involving quaternized heteroaromatic molecules and ammonia free of amide ion. Adducts having an amino group bonded to an annular carbon atom are produced in a reaction which is the amination counterpart to pseudobase formation in aqueous solution. Two ring systems, quaternized pyridines and pyrazines, are extensively studied. The site of amination is found to depend on substituents bonded to carbon. In some cases a single adduct is observed, in others, mixtures of adducts. Even diadducts are formed. Ring-opened isomers may be observed as well. The present study supplements our preliminary communication which revealed that many kinds of heterocyclic rings containing a quaternized nitrogen atom undergo covalent amination in ammonia.[11] The accompanying article shows that sulfur and carbon nucleo-

Table I. Chemical Shifts (τ) and Coupling Constants (Hz) for 1,5-Disubstituted 2-Amino-1,2-dihydropyridines (I)

Compd	1-Subst	5-Subst	H-2	H-3	H-4	H-6	Other	$J_{2,3}$	$J_{3,4}$	$J_{4,6}$	J_{CH_2}
Ia	CH_3	$CONH_2$	5.19	4.80	3.34	2.58	CH_3, 6.78	4.5	10	2	
b	CH_3	CO_2CH_3	5.10	4.79	3.51	2.48	NCH_3, 6.72; OCH_3, 6.33	4.5	10	1.5	
c	CH_3	CF_3	5.19	4.69	3.84	3.01	CH_3, 6.80	5	9.5	2	
d	$CH_2C_6H_5$	$CONH_2$	5.46	4.92	3.36	2.36	CH_2, 4.97, 5.48; C_6H_5, 2.58	4.5	10	1.5	15
e	$CH_2C_6H_4$-NO_2-*p*	$CONH_2$	5.31	4.74	3.31	2.36	CH_2, 4.72, 5.27; C_6H_4, 1.70, 2.28	4.5	9.5	1.5	16.5
f	$CH_2C_6H_5$	$COCH_3$	5.22	4.74	3.35	2.18	CH_2, 4.92, 5.32; C_6H_5, 2.59; CH_3, 7.87	4	10	2	15
g	CH_3	CN	5.13	4.72	3.81	2.52	CH_3, 6.76	4.5	9.5	1.5	
h	$CH_2C_6H_5$	CN	~5.2	~4.8	3.83	2.32	CH_2, 4.9, 5.4; C_6H_5, 2.55	4.5	9.5	1.5	15
i	$CH_2C_6H_4$-NO_2-*p*	CN	5.36	4.71	3.84	2.23	CH_2, 4.8, 5.2; C_6H_4, 1.8, 2.3	4.5	10	1.5	~16

Table II. Chemical Shifts (τ) and Coupling Constants (Hz) for 1,3-Disubstituted 2-Amino-1,2-dihydropyridines (II)[a] and for 1-Substituted 2-Amino-1,2-dihydropyridines (III)[a]

Compd	1-Subst	3-Subst	H-2	H-4	H-5	H-6	Other	$J_{4,5}$	$J_{5,6}$	Other
IIa	CH_3	Cl	5.25	3.75	5.21	3.67	CH_3, 6.95	6.5	6.5	
b	CH_3	I	5.39	3.59	5.29	3.42	CH_3, 6.97	7	6.5	
c	$CH_2C_6H_5$	I	5.26	3.39	5.18	3.35	CH_2, 5.19, 5.59; C_6H_5, 2.55	6.5	6.5	J_{CH_2} = 15
d	CH_3	CN	~5	3.09	~5	2.97	CH_3, 6.76	7	6	
e	$CH_2C_6H_5$	CN	5.33	3.01	~4.9	2.90	CH_2, 4.9, 5.4; C_6H_5, 2.55	~6	~6	J_{CH_2} ~ 15
f	$CH_2C_6H_4$-NO_2-*p*	CN	5.23	2.99	4.87	2.86	CH_2, 4.8, 5.2; C_6H_4, 1.8, 2.3	7	6.5	J_{CH_2} ~ 16
g	OCH_3	$CONH_2$	4.56	3.02	4.89	3.02	CH_3, 6.25	6.5	6.5	
IIIa	CH_3[b]	H	~5.4	3.80	5.19	3.72	CH_3, 6.95	5.5	7	$J_{2,3}$ = 5.0; $J_{3,4}$ = 9.5; $J_{3,5}$ = 1.5; $J_{3,6}$ = 1
b	$CH_2C_6H_5$[c]	H	5.34	3.90	4.96	3.61	CH_2, 5.19, 5.64; C_6H_5, 2.59	5.5	7	$J_{2,3}$ = 5.0; $J_{3,4}$ = 9.5; J_{CH_2} = 15.5
c	OCH_3[d]	H	5.12	3.97	5.03	3.45	CH_3, 6.30	5.2	7.5	$J_{2,3}$ = 5.0; $J_{3,4}$ = 9.8; $J_{3,5}$ = 1.8; $J_{3,6}$ = 0.8

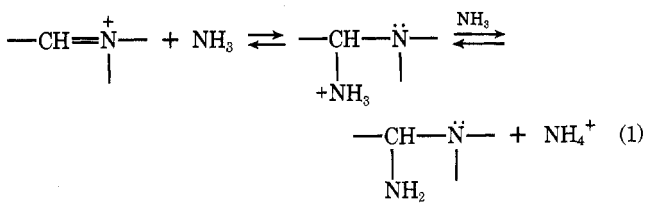
[a] $J_{2,4} \leq 1$ Hz. [b] H-3, τ 4.79; $J_{2,4}$ = 1.5 Hz. [c] H-3, τ 4.81. [d] H-3, τ 4.35; $J_{2,4}$ = 1.3 Hz.

philes can successfully compete with ammonia to produce new adducts.[12] Another investigation involves kinetic studies.[13]

Results and Discussion

Addition of a nucleophile to an aromatic ring to form a covalent, nonaromatic adduct can easily be detected by NMR. The adduct spectrum is characterized by upfield shifts; shieldings as large as 3–4 ppm are observed for the newly formed tetrahedral center. In many instances spectra were recorded over a range of temperatures; generally, good quality spectra were obtained over the interval −40 to 0 °C.

The nucleophile in the addition reactions must be ammonia and not the anion of quaternized compound, since halide and perchlorate salts give rise to the same spectrum. Spin coupling between the amino group of adduct and an adjacent proton usually was not observed. Ammonium ion is liberated in the addition reaction, eq 1; this acid catalyzes signal averaging between the protons of the amino group and solvent.[14]



(1)

When a prochiral benzyl or *p*-nitrobenzyl group was bonded to the annular nitrogen atom in place of a methyl group, the methylene protons became diastereotopic on adduct formation. Addition of ammonia to the ring produces a chiral carbon atom which maintains its chirality long enough to make the methylene protons diastereotopic. That is, a reaction leading to the loss of chirality, for example, by the reverse of addition, must be slow. The pseudo-first-order rate constant for such a dissociation must be less than about 10^2 s^{-1}.[15] Such amino group turnover has been shown in the case of adducts formed by the addition of ammonia to 2-benzylisoquinolinium ions to be accelerated by temperature and by ammonium ion.[13]

The main features of NMR spectra of adducts are given in tables; analyses of these spectra and those of by-products will be found in the supplement (see paragraph at end of paper regarding supplementary material).

Pyridinium Ions. Ammonia can add to positions 2, 4, or 6 of a 1,3-disubstituted pyridinium ion to form a carbon–nitrogen σ bond and give adducts which are amino dihydro compounds.[16] Addition to either the 2 or 6 position of the ion was observed, the site of addition being dependent upon the identity of the substituent at the 3 position of the ion. Heretofore, only addition of ammonia to the 6 position

Table III. Chemical Shifts (τ) and Coupling Constants (Hz) for 5-Amino-2,4-pentadienal Oxime *O*-Methyl Ether (IV) and Derivatives (V)

Compd	Subst	H-1	H-2	H-3	H-4	H-5	$NOCH_3$	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
IV	H	1.74	4.66	3.56	4.29	3.22	6.20	11	10.5	12	12.5
Va	2-$CONH_2$	1.64		2.29	4.04	2.67	6.15			13	12
b	2-CO_2^-	1.63		2.62	3.50	2.94	6.17			12	12.5
c	3-CO_2CH_3[c]	1.79	3.91	(CH_3O) (6.13)[a,b]	4.43	2.91	6.19[b]	10.5			12.5

[a] Ester group. [b] Assignments may be interchanged. [c] $J_{1,3}$ = 1.5 Hz.

Table IV. Chemical Shifts (τ) and Coupling Constants (Hz) for 1-Methyl-2-amino 3-Substituted 1,2-Dihydropyrazines (VI) and 1-Methyl-2-amino-1,2-dihydropyrazine (VIII)

Compd	3-Subst	H-2	H-5	H-6	NCH_3	Other	$J_{2,6}$	$J_{5,6}$	Other
VIa	CH_3	5.58	4.20	*a*	7.00	CH_3, 7.95, 8.10			
b	Cl	5.21	4.16	3.55	6.93		1	4.5	
c	CH_3O	5.53	4.28	4.00	7.06	CH_3O, 6.28	1.5	4.5	
VIII[b]	H	5.46	4.04	3.70	6.93	H-3, 3.08	1	5	$J_{2,3}$ = 4 $J_{3,6}$ < 1

[a] A methyl group is bonded to position 6.

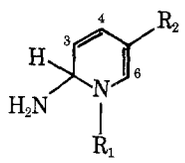
Table V. Chemical Shifts (τ) and Coupling Constants (Hz) for 1-Methyl-2-amino-5-carbamoyl-1,2-dihydropyrazine (VII) and 1-Methyl-2,3-diamino 5-Substituted 1,2,3,4-Tetrahydropyrazines (IX)

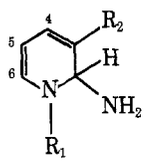
Compd	5-Subst	H-2	H-3	H-6	NCH_3	$J_{2,3}$	$J_{2,6}$	Other
VII	$CONH_2$	5.32	3.10	2.76	6.77	3.5	1.5	$J_{3,6}$ = 1
IXa[a]	H[b]	6.44	6.19	5.16	7.39	3	1.5	$J_{5,6}$ = 6; $J_{3,5}$ = 1
b[c]	$CONH_2$	6.21	6.05	3.45	7.03	~3	~1.5	

[a] Assignments for positions 2 and 3 may be interchanged as well as those for 5 and 6. [b] H-5, τ 4.67. [c] Low intensity prevents accurate analysis.

of such ions was observed; 3 substituents employed in the earlier study included SO_2CH_3, NO_2, or $COCH_3$.[11]

Numbering of annular positions of adduct I is different from that of the corresponding starting material. Positions





	R_1	R_2
Ia	CH_3	$CONH_2$
b	CH_3	CO_2CH_3
c	CH_3	CF_3
d	$CH_2C_6H_5$	$CONH_2$
e	$CH_2C_6H_4NO_2$-*p*	$CONH_2$
f	$CH_2C_6H_5$	$COCH_3$
g	CH_3	CN
h	$CH_2C_6H_5$	CN
i	$CH_2C_6H_4NO_2$-*p*	CN

	R_1	R_2
IIa	CH_3	Cl
b	CH_3	I
c	$CH_2C_6H_5$	I
d	CH_3	CN
e	$CH_2C_6H_5$	CN
f	$CH_2C_6H_4NO_2$-*p*	CN
g	OCH_3	$CONH_2$

	R_1	R_2
IIIa	CH_3	H
b	$CH_2C_6H_5$	H
c	OCH_3	H

in starting material and product are numbered in opposite sequences so that the substituent at position 3 in starting material corresponds to position 5 in adduct. Thus, when ammonia adds to the 6 position of aromatic ion, the amino group is located at position 2 of product. This confusing numbering arises in the case of pyridine adducts I and also pyrazine adduct VII.

When the substituent at position 3 of the ion was a strongly electron-attracting group such as $CONH_2$, CO_2CH_3, CF_3, or $COCH_3$, ammonia added to the 6 position of the ion to give a single adduct which is a 1,5-disubstituted 2-amino-1,2-dihydropyridine (Ia–f), Table I. Two observations support the structural assignment for I. (a) The ring proton at highest field, likely to be that associated with the newly formed tetrahedral site, shows an approximately 4.5 Hz coupling constant. A constant of this magnitude must be associated with coupling to an adjacent proton. Addition to the 2 position of the ion would give a proton bonded to a tetrahedral center with a much smaller coupling constant, since there is no adjacent proton. (b) The large 9.5–10 Hz coupling constant eliminates the possibility that the nucleophile added to position 4 of the ion. Known 4 adducts do not show coupling constants this large.[16,17]

Ammonia added to the 2 position of 1-substituted 3-chloro- or 3-iodopyridinium ion to give a new group of adducts, IIa–c, Table II. Characterizing such adducts are two moderately large coupling constants, each about 6.5 Hz. The ring proton at highest field shows only a small coupling, <1 Hz, indicating addition to position 2. A minor byproduct observed in the 1-benzyl-3-iodopyridinium ion reaction may be the 6 adduct.

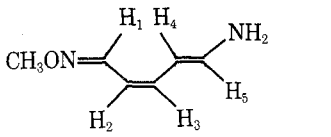
The 3-cyanopyridinium ion is especially interesting because it is converted to at least two adducts at about −40 °C. The major product (Ig, Ih, or Ii) results from the addition of ammonia to position 6 of the ion; some nucleophile also adds to position 2 (IId, IIe, or IIf). Careful analysis at 100 MHz of the mixture produced from the 1-*p*-nitrobenzyl substrate revealed the presence of a third component, perhaps the 4 adduct, but signal overlap precludes firm identification.

Neither 1-methyl- nor 1-benzylpyridinium ion underwent detectable covalent amination in neutral ammonia. However, when powdered KOH was added, adducts IIIa and IIIb, Table II, resulting from reaction of the heteroaromatic cation at the 2 position were observed. The presence of five nonequivalent protons indicates that addition to a 2 and not to a 4 position took place. The added strong base[18]

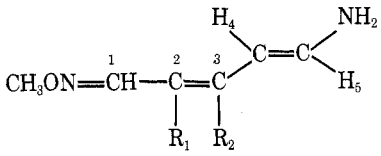
neutralized the ammonium ion acid formed by the addition reaction, eq 1, driving addition to apparent completion.

1-Methoxypyridinium ion is completely converted to adduct IIIc on addition to ammonia at −50 °C. Addition of KOH to promote adduct formation is unnecessary. Evidently, the *N*-methoxy group exerts an electron-withdrawing effect[19] which destabilizes the cation and thereby facilitates addition to the ring.

Allowing the adduct of 1-methoxypyridinium ion to stand at −50 °C or to warm resulted in the formation of a new product. Ring opening gives 5-amino-2(*cis*),4(*trans*)-pentadienal oxime *O*-methyl ether (IV), Table III. At −50 °C the half-life for this conversion is roughly 2 h. Strong evidence for a ring-opened structure is found in the presence of an aldoxime signal at τ 1.74 and in the large coupling constants. Although signals for an NH_2 group are observed, they are broad and their shifts are highly temperature dependent. Since the signals of the amino group are broad we are unable to determine coupling constants for this ABX system[20] and so we are unable to decide whether amino group rotation is "free" or restricted.[21] The cis–trans stereochemistry is suggested by the 10.5 and 12.5 Hz coupling constants, respectively. The other large coupling constants suggest s-trans conformations.[22] The stereochemistry is likely to be that given by IV.



IV



Va, $R_1 = CONH_2$; $R_2 = H$
b, $R_1 = CO_2^-$; $R_2 = H$
c, $R_1 = H$; $R_2 = CO_2CH_3$

Results for a 1-methoxy 3-substituted pyridinium ion are especially interesting. Ammonia could add to either a 2 or 6 position of the ion and either adduct could ring open by undergoing cleavage of the bond between the annular nitrogen and the tetrahedral carbon atoms. The results for 1-methoxy-3-carbamoylpyridinium ion are intriguing. At −60 °C adduct and ring-cleaved materials clearly are present; at −45 °C essentially only cleaved compound is found. However, the observed adduct is not the precursor of ring-opened material. Observed adduct must rearrange to a second isomer which is not present in detectable quantity; the second adduct must ring cleave faster than the first.

The observable adduct from 1-methoxy-3-carbamoylpyridinium ion is produced by the addition of ammonia to the 2 position of the ion to give IIg. The coupling constants of IIg, Table II, are similar to those of other adducts having structure II and different from those of I. This similarity is the basis for the structural assignment. Addition to the 2 position stands in marked contrast to addition to 6 which is observed for all the other 3-carbamoyl compounds considered here.

The ring-cleaved product from 1-methoxy-3-carbamoylpyridinium ion is likely to have structure Va, Table III, which results from an adduct formed by addition of ammonia to the 6 position of the ion. The proposed structure is based on the belief that the aldoxime proton is more deshielded than any olefinic proton[22,23] and that the magnitude of spin coupling to this proton allows isomeric structures to be distinguished. The most deshielded proton in the ring cleaved material is a sharp singlet; its chemical shift is very similar to that for IV and similar oximes.[22,24,25] The singlet results because a carbamoyl group rather than a proton is bonded to the adjacent carbon atom. If observed adduct IIg were the precursor to cleaved material, then the oxime proton of the isomeric structure would be a doublet having a large coupling constant due to the presence of a proton on the adjacent carbon; the substituent would be bonded to position 4 of V. That end of Va bearing the amino group has a trans double bond; the coupling constant is 12 Hz. Stereochemistry about the other carbon–carbon double bond cannot be assigned, spin coupling is not possible due to the presence of the carbamoyl group. Although some small signals of another component were present in the spectrum they were so low in intensity that they could not be identified as being due to the adduct giving rise to Va. From these results it appears that ring opening, like nucleophilic addition, is strongly substituent dependent.

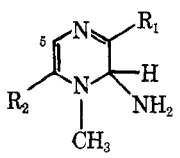
Ring-opened materials arising from two other substituted 1-methoxypyridinium ions were observed. In one, the substituted ion contained a carboxylate ion group at position 3, the other a 4-carbomethoxy substituent. In neither case was the intensity and quality of the spectrum of the precursor adduct sufficient for conclusive identification. Again, the 3-substituted ion gave rise to a ring-cleaved product (Vb) which resulted from the adduct produced by the addition of ammonia to position 6 of the ion. Only one ring-cleavage product is possible from the 4-substituted ion since the 2 and 6 positions are equivalent. The double bond about carbon atoms 4 and 5 of both Vb and Vc must be trans as in the case of IV. The propensity of 1-alkoxypyridinium ion adducts to ring open[24–27] is said to be due to the stability of the oxime functional group.[24]

Adducts having structure I after standing at room temperature were converted to the corresponding 3-substituted pyridine. Although dealkylation by nucleophilic attack on the side chain is a possible route to such products, it seems likely that a less direct pathway is followed. This involves ring opening of an adduct followed by ring closure so as to incorporate the nitrogen atom of the primary amino group into the ring; this is followed by expulsion of an alkylamine. Such a sequence has been demonstrated for other covalent adducts using isotopically labeled nitrogen.[28]

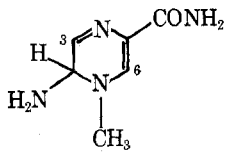
Pyrazinium Ions. Ammonia was observed to add either to the 2 position of a 3-substituted 1-methylpyrazinium ion to give a 1-methyl-2-amino 3-substituted 1,2-dihydropyrazine (VI) or to the 6 position of the ion to yield a 1-methyl-2-amino 5-substituted 1,2-dihydropyrazine (VII). Structural assignments are more difficult with pyrazine than with pyridine adducts, owing to smaller and fewer coupling constants associated with the presence of a second annular nitrogen atom. Model compounds were employed to aid assignments; one had a methyl group bonded to position 6, another a deuterium atom at position 2. A detailed analysis is found in the supplement.

Ammonia added to the 2 position of those ions having at the 3 position a CH_3, Cl, or CH_3O substituent to give VIa, VIb, or VIc. However, addition to the 6 position of the ion took place when the 3 substituent was $CONH_2$ (VII). Adducts VI having two adjacent sp^2-hybridized protons have a larger coupling constant (4.5 Hz) than VII (3.5 Hz) where the adjacent protons are sp^2 and sp^3. Moreover, the high-field proton which is associated with the tetrahedral ring site is highly spin coupled in VII but not in VI.

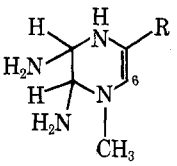
Interestingly, 1-methylpyrazinium ion is completely con-



VIa, $R_1 = R_2 = CH_3$
b, $R_1 = Cl$; $R_2 = H$
c, $R_1 = CH_3O$; $R_2 = H$



VII



VIII, $R_1 = R_2 = H$

IXa, R = H
b, R = $CONH_2$

verted to adduct VIII at −50 °C. Comparison of this result with that for 1-methylpyridinium ion which does not give an adduct[11] emphasizes the conclusion that electron-withdrawing groups or atoms facilitate adduct formation. The assignment placing the signal of H-3 at lower field than H-6 is based on coupling constants, Table IV. The minor component in this sample becomes the major product at higher temperatures; it has diadduct structure IXa.

At −28 °C a diadduct spectrum was found for 1-methylpyrazinium ion; none of the monoadduct VIII appeared to be present. Relative to VIII, all signals for IXa are shifted upfield; two, instead of the usual one, annular proton signals undergo large shieldings, Table V. No change in the spectrum was observed on warming the sample to −10 °C. Since IXa has two chiral carbon atoms, diastereomers are possible. However, we are unable to decide whether the sample consists of a single pair of enantiomers or whether rapidly equilibrating diastereomers are present. Therefore, no stereochemistry is to be implied by structure IXa.

A diadduct of 1-methyl-3-carbamoylpyrazinium ion probably is present at about 20 °C. However, this diadduct, IXb, is a minor component and the quality of the signal at τ 6.21 was not good enough to yield coupling constants and so the assignment in Table V is tentative.

Diaddition to a pyrazine ring is not unprecedented.[29,30] Under similar conditions the benzolog of diadduct IXa is produced.[11] Moreover, diaddition to a series of pteridines in ammonia has been reported.[31]

General. Significantly, repetition of reactions which gave rise to mixed products produced essentially the same product distributions. Reversibility of the amination reactions for several pyridines and pyrazines was demonstrated by regeneration of starting materials in high yields. Details are given in the Experimental Section. Preliminary experiments reveal that isolation of amino adducts in high yields will not be easy.

Our situation dealing with amino adduct formation is reminiscent of that a few years ago regarding the generation of anionic ("Meisenheimer") σ complexes just prior to the application of fast reaction techniques.[32] It is not unlikely that others who employ faster mixing–measuring methods will see other adducts before they rearrange to those observed by us. Interpretation of our results in terms of kinetic and thermodynamic control of addition is premature.

Covalent amination studies have considerable potential. Many more adducts will be found. The wide array of adduct structures and the ease with which their formation may be studied offer a new dimension to investigations involving the addition of nucleophiles to aromatic rings.

Experimental Section

Most compounds (perchlorate and/or iodide salts) were available from other studies.[33] A Varian A-60A spectrometer equipped with a V-6040 variable temperature controller or an XL-100 was employed. The spectra of IIIc and IV were simulated using a computer program (LAMP 2) kindly supplied by Dr. R. W. King. Spin decoupling of H-1 and H-2 of IV was carried out on the XL-100 to check signal assignments. Deuterated derivatives of IIIc and IV were prepared from 1-methoxypyridinium-2,6-d_2 ion. The general method of preparing samples for NMR analysis has been described.[11]

Preparation of 1-*p*-Nitrobenzyl-3-cyanopyridinium Bromide. A mixture of 2.6 g (25 mmol) of 3-cyanopyridine and 5.4 g (25 mmol) of *p*-nitrobenzyl bromide dissolved in 20 ml of acetonitrile was heated at reflux for 1 h. Crystalline product was removed from the cooled mixture and recrystallized from 95% ethanol to give 3.6 g (11.3 mmol, 45%) of product: mp 227–228 °C; NMR (D_2O) τ 0.32 (H-2), 0.62 (H-6), 0.85 (H-4), 1.52 (H-5), 1.9 (phenylene), 3.80 (CH_2), $J_{2,4} \sim 1.5$, $J_{2,6} \sim 1.5$, $J_{4,5} = 8$, $J_{4,6} \sim 1.5$, $J_{5,6} = 6$ Hz.

Anal. Calcd for $C_{13}H_{10}N_3O_2Br$: C, 48.77; H, 3.15; N, 13.13. Found: C, 48.73; H, 3.21; N, 13.20.

Preparation of 1-Methyl-3-chloropyrazinium-2-*d* Iodide. To 1.5 g (5.8 mmol) of 1-methyl-3-chloropyrazinium iodide dissolved in 4 ml of D_2O was added 0.20 ml of 1.0 M CH_3COOD and 0.20 ml of 1.0 M sodium acetate in D_2O. The solution was heated at 75 °C for 160 min; during this time five additional 1-ml aliquots of the acetate solution were added to keep the acidity of the solution approximately constant. The cooled sample then was acidified with concentrated HI, filtered, and freeze dried. The resultant solid was recrystallized from 95% ethanol to afford 1.05 g (4.1 mmol, 70%) of product containing 80% D (NMR) at the 2 position.

Recovery of Starting Materials from Amination Reaction Mixtures. A. Pyridinium Salts. To 0.20 g of either 1-methyl-3-carbamoyl- or 1-methyl-3-carbomethoxypyridinium iodide cooled in an acetone–dry ice bath was added 2 ml of ammonia. The sample was allowed to warm to −33 °C and held at this temperature for 5 min and then recooled with the dry ice mixture. After adding 5 ml of ether to the cold mixture, the sample was allowed to warm to room temperature. Crystalline amide (99%) was removed by filtration and compared with authentic starting material. Recovery in the case of ester amounted to approximately 86%; NMR analysis of the sample in D_2O showed the sample to consist of 30% starting material and 70% of amide solvolysis product, H-2 (τ 0.57, ester, and τ 0.71, amide) and OCH_3 (τ 5.92) serving to indicate composition.

B. Pyrazinium Salts. To 0.060 g of 1-methyl-, 1-methyl-3-chloro-, or 1-methyl-3-carbamoylpyrazinium iodide cooled in an acetone–dry ice bath was added about 0.5 ml of ammonia; the mixture was allowed to warm to −33 °C. After recooling to −78 °C, solvent was removed under vacuum. To the first two samples 0.5 ml of 4 M CF_3CO_2H in methanol and 0.10 ml of 1.0 M CH_3CO_2H in methanol (internal standard) were added to the residue at −78 °C; D_2O was the solvent in the case of the amide. Room-temperature NMR spectra indicated that at least 70% of the starting material had been regenerated. Comparison of the NMR spectra of the chloro sample with that of 1-methyl-3-aminopyrazinium ion indicated that no significant aminodechlorination had taken place.

Registry No.—Ia, 58219-05-9; Ib, 58219-06-0; Ic, 58219-07-1; Id, 58219-08-2; Ie, 58219-09-3; If, 58219-10-6; Ig, 58219-11-7; Ih, 58219-12-8; Ii, 58219-13-9; IIa, 58219-14-0; IIb, 58219-15-1; IIc, 58219-16-2; IId, 58219-17-3; IIe, 58219-18-4; IIf, 58219-19-5; IIg, 58219-20-8; IIIa, 58219-21-9; IIIb, 58219-22-0; IIIc, 58219-23-1; IV, 58219-24-2; Va, 58219-25-3; Vb, 58219-26-4; Vc, 58219-27-5; VIa, 58219-28-6; VIb, 58219-29-7; VIc, 58219-30-0; VII, 58219-31-1; VIII, 58219-32-2; IXa, 58219-33-3; IXb, 58219-34-4; 1-*p*-nitrobenzyl-3-cyanopyridinium bromide, 58219-35-5; 3-cyanopyridine, 100-54-9; *p*-nitrobenzyl bromide, 100-11-8; 1-methyl-3-carbamoylpyridinium iodide, 6456-44-6; 1-methyl-3-carbomethoxypyridinium iodide, 58219-36-6; ammonia, 7664-41-7; 1-methylpyrazinium iodide, 6277-35-6; 1-methyl-3-chloropyrazinium iodide, 34260-02-1; 1-methyl-3-carbamoylpyrazinium iodide, 58219-37-7; 1-methyl-3-carbamoylpyridinium ion, 3106-60-3; 1-methyl-3-carbomethoxypyridinium ion, 18899-18-8; 1-methyl-3-trifluoromethylpyridinium ion, 58091-56-8; 1-benzyl-3-carbamoylpyridinium ion, 16183-83-8; 1-*p*-nitrobenzyl-3-carbamoylpyridinium ion, 58219-38-8; 1-benzyl-3-acetylpyridinium ion, 16183-85-0; 1-methyl-3-cyanopyridinium ion, 15923-33-8; 1-benzyl-3-cyanopyridinium ion, 16183-87-2; 1-*p*-nitrobenzyl-3-cyanopyridinium ion, 58219-39-9; 1-methyl-3-chlo-

ropyridinium ion, 54560-55-3; 1-methyl-3-iodopyridinium ion, 54560-56-4; 1-benzyl-3-iodopyridinium ion, 58219-40-2; 1-methoxy-3-carbamoylpyridinium ion, 54212-29-2; 1-methylpyridinium ion, 694-56-4; 1-benzylpyridinium ion, 15519-25-2; 1-methoxypyridinium ion, 30718-14-0; 1,2,5-trimethylpyrazinium ion, 58091-57-9; 1-methyl-3-chloropyrazinium ion, 58219-41-3; 1-methyl-3-methoxypyrazinium ion, 58219-42-4; 1-methyl-3-carbamoylpyrazinium ion, 58091-58-0; 1-methylpyrazinium ion, 17066-96-5.

Supplementary Material Available. Additional information on side reactions and NMR interpretation (2 pages). Ordering information is given on any current masthead page.

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Competitive Addition of Carbon, Sulfur, and Nitrogen Nucleophiles to Quaternized Heteroaromatic Compounds in Liquid Ammonia

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Nitromethide and ethanethiolate ions when present as ammonium salts in liquid ammonia add to the 4 position of 1-methylpyridinium ion. Each anion adds to the 4 positions of 3-iodo- and 3-cyano-1-methylpyridinium ions, to the 6 position of 1,2,5-trimethylpyrazinium ion, and to the 1 positions of 2-benzylisoquinolinium and 2-benzylphthalazinium ions. Carbanion addition to the 4 position of 3-substituted 1-methylpyridinium ions having CH_3, $CONH_2$, $COCH_3$, CO_2CH_3, and CF_3 substituents and to the 2 position of 3-methoxy-1-methylpyridinium ion also was observed. Carbanion addition is complete except with the 1-methyl-, 1,3-dimethyl-, and 1-methyl-3-methoxypyridinium and 2-benzylphthalazinium ions; aromatic starting material is present in the case of the pyridinium ions while 1-amino adduct is present in the phthalazinium ion case. Amino and not carbon adducts are detected for 3-chloro- and 3-carbamoyl-1-methylpyrazinium ions. Thiolate ion adds to the 4 and 6 positions of 3-acetyl- and 3-carbomethoxy-1-methylpyridinium ions to give mixtures. 3-Carbamoyl-1-methylpyridinium ion adds thiolate ion at the 4 and 6 positions; interconversion is fast enough to make the mixture appear by NMR as a single adduct. Thiolate ion addition is complete except in the cases of 1-methyl- and 1-methyl-3-methoxypyridinium ions.

Many quaternized heteroaromatic molecules on addition to liquid ammonia rapidly and quantitatively add solvent at an annular carbon atom to yield amino dihydro derivatives.[1-4] We now report that nitromethide and ethanethiolate ions dissolved in ammonia successfully compete with solvent to give carbon and sulfur addition products. In these competition reactions aromatic substrates often are completely transformed to a carbon or sulfur addition product. However, the site of addition of the carbon and sulfur nucleophiles may be different from that of ammonia. Nitromethide ion was selected for study because it is readily formed from nitromethane in ammonia[5] and it seemed likely that successful competition with ammonia might result. Many quaternized heteroaromatic molecules are known to add nitromethide ion in hydroxylic solvent.[6-8] The high carbon affinity of sulfur nucleophiles[9] prompted the selection of ethanethiolate ion, which is known to add to aromatic compounds to form anionic σ complexes.[10]

Results and Discussion

Addition of Nitromethide Ion. Deprotonation of nitroalkanes by liquid ammonia is unusual. The extent of proton transfer from the carbon acid to ammonia increases with decreasing temperatures,[5] in contrast to deprotona-