A Kinetic Method for Determining the Position of Alkylation of Polyaza Heterocycles. Substituted Pyrazines

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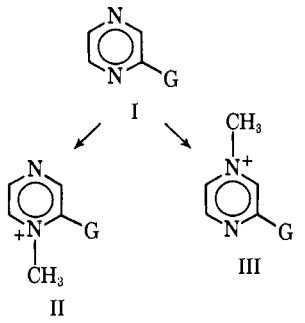
Abstract: The position of quaternization of 2-substituted pyrazines with methyl iodide in dimethyl sulfoxide at room temperature was determined by a kinetic, competition method. Reaction mixtures were analyzed by nmr. Assignment of the position of alkylation was made by comparisons with the relative rates of quaternization of 2- and 3-substituted pyridines. The major isomer in all cases is 1-methyl 3-substituted pyrazinium iodide. 2-Amino- and 2-methylpyrazine give, in addition, 1-methyl 2-substituted pyrazinium iodide, the isomer ratios being 2.9 and 3.9, respectively. Total rates of methylation relative to pyrazine are: NH_2, 8.8; CH_3, 2.0; CH_3O, 1.05; $CONH_2$, 0.53; F, 0.16; and Cl, 0.15. Relative rates corrected for isomer formation correlate on a logarithmic scale with relative rates for 3-substituted pyridines (slope = 1.06, correlation coefficient = 0.99). The second annular nitrogen atom has a constant effect on reactivity and substituent effects are larger in the pyrazine series. The competition method may be applied to a variety of heterocyclic systems capable of reacting at more than one center.

Polyaza heterocycles may undergo alkylation at the various annular nitrogen atoms. One of the outstanding problems in heterocyclic chemistry is the prediction and determination of the major site of alkylation of such molecules.[2]

Little work has been carried out on the quaternization of pyrazines. The literature to 1963 was reviewed[2] and since then no new work on simple substituted pyrazines has been reported. We have studied the methylation of 2-substituted pyrazines where reaction may take place ortho and meta to the substituent to give 1-methyl 2- or 3-substituted pyrazinium ions, eq 1. The major position of methylation was determined



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by a kinetic method which involves obtaining relative rates by product analysis using nmr. In cases where both II and III are formed, the isomer ratio was obtained. Our approach is characterized by its experimental simplicity and its potential for generalization.

Results and Discussion

Competition experiments involving a pyrazine, methyl iodide, and a second heterocycle capable of undergoing methylation were carried out using dimethyl sulfoxide (DMSO) as the solvent. A similar approach was employed using 2- and 3-substituted pyridines as model compounds where quaternization takes place at only one nitrogen atom. It was shown that the reaction between methyl iodide and DMSO[3] was negligible in comparison with the rate of heterocycle methylation.

A pyrazine or pyridine and a comparison heterocycle, 3-bromoquinoline or pyridazine, were allowed to compete for a deficiency of methyl iodide at room temperature. When the methyl iodide was consumed, the ratio of the methylated products was determined by nmr analysis of the methyl peaks.

The selection of a comparison substrate in the competition experiments required some care. In order to determine k_{rel} accurately, the nmr signals of the products had to be nonoverlapping. (Although we chose to examine the *N*-methyl product peak, in general, other product signals could be employed.) A few trials were initially required for the selection of comparison substrates. (We suggest that this be done by first finding a class of compounds giving a different nmr product peak from the compounds under investigation and then modifying the reactivity by introduction of a suitable substituent.)

Relative rates were determined for pyrazines and pyridines having amino, methyl, methoxy, carbamoyl, fluoro, and chloro substituents as well as for the parent compounds. Relative rates were calculated from the area ratio using eq 2[4] where CH_3I and Het are

$$k_{rel} = \frac{k_1}{k_2} = \frac{\log\left[1 - \frac{CH_3I}{Het_1}\frac{R}{1+R}\right]}{\log\left[1 - \frac{CH_3I}{Het_2}\frac{1}{1+R}\right]} \qquad (2)$$

the concentrations of methyl iodide and heterocycle, and $R = CH_3HET_1/CH_3HET_2$ = molar ratio of methylated products. Note that k is the total rate constant, reflecting the sum of the rate constants for reaction at each annular nitrogen in the polyaza heterocycle. The spread in reactivity in the pyrazine series is a factor of 59 and a factor of 39 for the pyridines, Table I. The relative rates are estimated to have a combined uncertainty of about 6%, based on an analsis of the uncertainties in the individual nmr area

(1) On leave from LaTrobe University, Melbourne, Australia.

(2) Traditionally, the approach has been to isolate a pure isomer and to identify its structure by means of chemical interrelations and by ultraviolet absorption spectroscopy. For a review of the many contradictory and erroneous conclusions which have resulted, see G. F. Duffin, *Advan. Heterocycl. Chem.*, 3, 1 (1964).

(3) R. Kuhn, *Angew. Chem.*, 69, 570 (1957).

(4) This equation was derived in a slightly different form by C. K. Ingold and F. R. Shaw, *J. Chem. Soc.*, 2918 (1927).

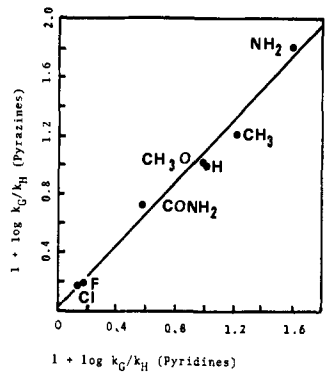

Figure 1. Log–log plot of the relative rates of quaternization of 2-substituted pyrazines and 3-substituted pyridines by methyl iodide in DMSO at room temperature. The unsubstituted compound is the standard. In the pyrazine series rates are corrected to reflect formation of the major isomer, 1-methyl 3-substituted pyrazinium iodide.

measurements. Using the experimental relative rates and eliminating the comparison heterocycle, rates relative to the parent compound, k_G/k_H, are obtained. For example, the k_G/k_H value for 3-aminopyridine is 3.9. Moreover, this value obtained *via* competition with pyridazine agrees with the value 4.1 obtained by direct competition with pyridine. This agreement provides strong support for the competition method.

Table I. Relative Rates of Reaction of 2-Substituted Pyrazines and 3-Substituted Pyridines with Methyl Iodide in DMSO

	k_{rel} — Substituent						
	NH_2	CH_3	H	CH_3O	$CONH_2$	F	Cl
Pyrazines[a]	8.8[b]	4.5[b]	2.2	2.3	1.2	0.35	0.34
	6.5[c]	3.6[c]					
Pyridines[d]	15.6	6.6	4.0	3.9	1.5	0.61	0.56
	4.1[e]						
	4.9[f]						

[a] Relative to methylation of 3-bromoquinoline except for NH_2 which is relative to pyrazine. The pyrazine value is statistically corrected. [b] Total relative rate. [c] Relative rate corrected to reflect formation of III only. [d] Relative to pyridazine and statistically corrected to reflect reaction at just one nitrogen atom. [e] By direct competition with pyridine. [f] 2-Aminopyridine is the substrate.

The nmr spectra of reaction mixtures of methoxy-, carbamoyl-, fluoro-, and chloropyrazine provided no indication of mixed methylated products, II and III. However, considering the sensitivity of the nmr method, about 3–6% of a minor isomer could have remained undetected.

Information regarding the formation of isomers in the pyrazine series may be obtained by a consideration of the reactivity of pyridine model compounds where there is only one annular nitrogen atom. For example, methyl iodide is reported[5] to react 15 times faster with 3-chloro- than with 2-chloropyridine. Assuming that the nitrogen atoms ortho and meta to chlorine in chloropyrazine have about the same relative nucleophilicity as do the chloropyridines, then about 6% of II may have formed along with III.

(5) G. Coppers, F. Declerck, C. Gillet, and J. Nasielski, *Bull. Soc. Chim. Belg.*, 72, 25 (1963).

Mixed methylation products definitely were found when methyl- and aminopyrazines were the substrates. The 60-MHz spectrum of the methylpyrazine reaction mixture gave a partially resolved doublet peak in the *N*-methyl region with the larger peak at lower field. This was completely resolved at 100 MHz and a ratio of 3.9:1 was obtained. The total rate of methylation of methylpyrazine relative to pyrazine is 2.06 (4.5/2.2), Table I. When this is corrected for isomer formation, the relative rate of formation of the major isomer is 1.65 (2.06 × 3.9/4.9). It has been reported[6] that the relative rate of quaternization of 3- to 2-methylpyridine is 4.4:1. This favorably compares with the methylpyrazine isomer ratio and suggests the major isomer is III.

Two well-separated (Δ = 28 Hz) *N*-methyl peaks were obtained when aminopyrazine was methylated. The peak positions and chemical-shift difference corresponded closely to those from the methylation of 2- and 3-aminopyridines, suggesting that both II and III were formed. The peak area ratio was 2.9:1 and the larger peak at lower field had a chemical shift corresponding to that of methylated 3-aminopyridine, *i.e.*, III is the major product. Cheeseman concluded[7] from spectroscopic evidence that the product isolated by recrystallization of the crude aminopyrazine methylation mixture was III. When our crude product was treated with alkali a small amount of 1-methyl-2-pyrazinone was isolated, indicating the presence of II in the mixture.

Additional support for the assignment of II and III was provided by k_{rel} for 3-amino- *vs.* 2-aminopyridine. The value of 3.2, Table I, is in good agreement with the product ratio in the aminopyrazine mixture.

Methylation of 2-aminopyridine has been reported[8] to give a small amount of side-chain quaternization as well as the main ring-methylated product. Under the conditions of our experiments, no evidence for products other than those discussed was obtained for either 2-aminopyridine or aminopyrazine (run in DMSO-d_6).

When the k_G/k_H values for the pyrazines, corrected to reflect formation of the major isomer, are plotted on a logarithmic scale against similar values for 3-substituted pyridines, a good correlation (correlation coefficient = 0.99) results, Figure 1. This result and the results obtained by a consideration of the reactivity of 2- and 3-substituted pyridines provide strong evidence that III is the major isomer formed when substituted pyrazines react with methyl iodide. The major site of alkylation is the annular nitrogen atom meta to the substituents.

It has been demonstrated previously[9] that rates of quaternization of 3-substituted pyridines can be correlated with the σ_m parameter. The agreement between k_G/k_H values for pyrazines and pyridines, Figure 1, indicates that a σ_m correlation obtains for the pyrazines as well. Moreover, the slope of 1.06 indicates that substituent effects are slightly larger in the pyrazine series. This is reasonable in that the pyrazines

(6) H. C. Brown and A. Cahn, *J. Amer. Chem. Soc.*, 77, 1715 (1955).
(7) G. W. H. Cheeseman, *J. Chem. Soc.*, 242 (1960).
(8) A. E. Tschitschibabin, R. A. Konowalowa, and A. A. Konowalowa, *Ber.*, 54, 814 (1921).
(9) A. Fischer, W. J. Galloway, and J. Vaughan, *J. Chem. Soc.*, 3596 (1964).

are less reactive[10] and therefore more selective. Thus, with 2-substituted pyrazines the annular nitrogen atom ortho to the substituent acts as an independent but constant electron-withdrawing substituent. Deviations such as those observed[11] in the hydrolysis of methyl 2-substituted isonicotinate esters are not found in the alkyation reactions of pyrazines. In the ester series rate retardation was observed for those substrates having strongly electron-donating substituents. The ortho nitrogen effect observed previously[11] appears not to be general and may be limited to side-chain reactions.

This competition kinetic method is able to identify isomers from quaternization of a polyazaheterocycle without the need for difficult isomer separations. It is worth noting that the analytical sample of dimethylpyrazinium iodide, after three recrystallizations, had a sharp melting point, but nmr analysis showed that no significant change in the original isomer ratio had been achieved. Attempts to separate these by tlc were unsuccessful.

The kinetic method outlined here is potentially applicable to quaternization of a variety of systems. The approach assumes that substituent effects due to side-chain groups and to heteroatoms are additive so that extrapolations from simple to more complex systems are possible, *i.e.*, that linear free-energy relationships are found. The kinetic method can obviously be extended to other diazines and benzodiazines. However, further studies will be necessary to deal with substituent effects on the reactivity of five-membered rings and fused ring systems where nitrogen centers in different rings may quaternize. Little quantitative information is available. Kinetic studies such as the type outlined here can provide the necessary quantitative information about reactivity.

Experimental Section

Compounds. 3-Fluoro-[12] and 3-methoxypyridine[13] and fluoro-[14] and methoxypyrazine[15] were prepared by literature methods and the other compounds were commercially available (Aldrich Chemical Co.). DMSO was dried over molecular sieves.

The following new pyrazine methiodides were isolated: 3-chloro-1-methylpyrazinium iodide, mp 175–176° (EtOH) (*Anal.* Calcd for $C_5H_6N_2ClI$: C, 23.4; H, 2.3; N, 10.9. Found: C, 23.7; H, 2.5; N, 10.8); 3-fluoro-1-methylpyrazinium iodide, mp 142–143° (EtOH–ether) (*Anal.* Calcd for $C_5H_6N_2FI$: C, 25.0; H, 2.5; N, 11.7. Found: C, 25.25; H, 2.7; N, 11.9); 3-methoxy-1-methylpyrazinium iodide, mp 129–130° (EtOH) (*Anal.* Calcd for $C_6H_9N_2OI$: C, 28.6; H, 3.6; N, 11.1. Found: C, 28.9; H, 3.8; N, 11.1); 1,2- and 1,3-dimethylpyrazinium iodides, mp 126–128° (EtOH) (*Anal.* Calcd for $C_6H_9N_2I$: C, 30.5; H, 3.8; N, 11.9. Found: C, 30.3; H, 3.65; N, 11.7).

Relative Rate Determination. Relative concentrations of heterocyclic reactants were chosen so that a not disproportionate product ratio was obtained.

In a typical experiment 0.058 g of pyridine (0.735 mol) and 0.087 g of pyridazine (1.09 mol) were weighed into a 1-ml volumetric flask and dissolved in just under 1 ml of DMSO. The volume was made up to 1 ml with 0.038 g of methyl iodide (0.268 mol), the flask was shaken thoroughly, and a sample was transferred to an nmr tube. After standing for 6 hr at room temperature (up to 24 hr for slower reactions) the spectrum was recorded and the *N*-methyl peaks were integrated on a Varian A-60A or an XL-100 spectrometer.

The *N*-methyl peaks generally occurred at *ca.* 100 Hz downfield from the solvent peak. However, methylation of aminopyrazine was carried out in DMSO-d_6 as an *N*-methyl peak partially overlapped the ^{13}CH solvent peak in undeuterated DMSO. Chemical shifts of the methyl groups examined are given in Table II.

Table II. Chemical Shifts of the 1-Methyl Group of 1-Methyl 2- or 3-Substituted Pyridinium and Pyrazinium Iodides in DMSO[a,b]

Pyridinium iodide	τ	Pyrazinium iodide	τ
H	5.53	H	5.40
2-CH_3	5.65	2-CH_3	5.58
3-CH_3	5.56	3-CH_3	5.50
2-NH_2	6.15	2-NH_2	6.18
3-NH_2	5.73	3-NH_2	5.66
3-CH_3O	5.53	3-CH_3O	5.53
3-Cl	5.53	3-Cl	5.46
3-F	5.48	3-F	5.42
3-$CONH_2$	5.45	3-$CONH_2$	5.36

[a] The DMSO satellite peak at τ 6.23 served as a reference standard. [b] 1-Methyl-3-bromoquinolinium iodide, τ 5.26, and 1-methylpyridazinium iodide, τ 5.30.

Hydrolysis of the Aminopyrazine Methiodide Reaction Mixture. Aminopyrazine and excess methyl iodide in methanol were allowed to react at room temperature for 2 days. Solid separated during this time and the mixture was evaporated to dryness. A sample of the crude methiodide was warmed with a little 5% sodium hydroxide solution for 0.5 hr. Ammonia was evolved. The cooled solution was extracted (three times) with chloroform. The dried extract was evaporated and the residue was recrystallized from hexane. This material was then sublimed at 65–70° (1 mm) to give a small amount of 1-methyl-2-pyrazinone: mp 77–79° after shrinking (lit.[7] mp 84°); nmr $\delta_{TMS}^{CDCl_3}$ 3.53 (s, 3 H), 7.12 (d, 1 H), 7.33 (d, 1 H, J = 4 Hz), 8.15 (s, 1 H).

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(10) From unpublished observations, $k_{pyridine}/k_{pyrazine}$ = 28.
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(12) A. Roe and G. F. Hawkins, *J. Amer. Chem. Soc.*, **69**, 2443 (1947).
(13) D. A. Prins, *Recl. Trav. Chim. Pays-Bas*, **76**, 58 (1957).
(14) H. Rutner and P. E. Spoerri, *J. Heterocycl. Chem.*, **3**, 435 (1966).
(15) A. Albert and J. N. Phillips, *J. Chem. Soc.*, 1294 (1956).