Tetrahedron Vol. 28, pp 1983 to 1993 Pergamon Press 1972. Printed in Great Britain

A METHOD OF PREDICTING THE SITE OF ALKYLATION OF HETEROCYCLIC POLYAZINES FROM KINETIC DATA ON MODEL COMPOUNDS

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(*Received in USA* 18 *October* 1971; *Received in UK for publication* 30 *December* 1971)

Abstract—A method is presented which enables calculation of isomer ratios resulting from the N-methylation of polyazines in dimethyl sulfoxide. The method assumes that substituent and annular nitrogen atom effects on reactivity are additive in the absence of steric factors. Kinetic studies on model azines provide rate factors which are employed in the calculations. Observed and calculated isomer ratios are compared for a number of polyazines. An extension to N-oxidation is suggested.

INTRODUCTION

PREDICTING THE SITE of alkylation of heterocyclic molecules containing multiple reactive nitrogen atoms is a classical problem in heterocyclic chemistry. The meager progress made to 1964 has been summarized.[2] Tradionally, conclusions regarding the site of alkylation have been based on methods which involve isolation of one or more isomers followed by chemical determination of their structures. More recently, major advances have been made using NMR to analyze reaction mixtures directly.[3,4] This approach often makes it possible to determine isomer ratios without the need for separations. However, the necessity of assigning structures still remains. In some cases, but not all, assignments may be made directly from a consideration of NMR spectra.

It has been long recognized that it is possible to assign structures to isomers in complex reaction mixtures from a consideration of kinetic data. This approach often is based on a knowledge of the reactivity of model compounds.

Quantitative results dealing with the rates of N-methylation of substituted pyridines[4-11] and other model compounds[4,11,12] are available. These are sufficient to allow predictions of the isomer distributions resulting from the N-methylation of polyazines. We here outline a method and provide rate factors to enable isomer ratios to be predicted for a large number of polyazines and consider a wide variety of examples to illustrate the validity and usefulness of this approach.

Briefly, our method of calculating isomer ratios may be summarized as follows: The reactivity of an annular nitrogen atom toward MeI in dimethylsulfoxide (DMSO) is to be estimated by algebraic addition of substituent and annular nitrogen rate factors derived from kinetic studies on model compounds. Comparison of the reactivities of the nitrogen atoms in a molecule gives an estimate of the product isomer ratio.

RESULTS AND DISCUSSION

We have measured earlier the rates of N-methylation of a large number of pyridine and other azine model compounds by MeI in DMSO at 23°.[4,10,11] Competition methods were employed to obtain these relative rates. The competition approach was adopted because it gives results quickly and easily and does not require special constant

temperature equipment. Hence this approach readily lends itself to those whose primary interests lie in the synthetic aspects of alkylation. At the same time, this method yields results good enough for those interested in structure-reactivity relationships. All reactions were carried out under conditions of kinetic control, *i.e.*, products are formed irreversibly.

Reaction mixtures were analyzed directly using NMR; the N-Me signals of the products often were examined. (Many substituents have little influence on the chemical shifts of N-alkyl groups.[4, 10, 13] In general it may be necessary to examine other proton signals or the signals of other nuclei[13] in order to determine isomer ratios.) Owing to the low sensitivity of PMR, it is possible that a minor isomer could go undetected when it is present to the extent of about 3%.[14]

DMSO was selected as solvent because it has good solvent properties, necessary for the relatively high concentrations required in the NMR method of analysis and because quaternization is rapid in this solvent at room temperature. For example, pyridine reacts with MeI seven times faster in DMSO ($2{\cdot}4 \times 10^{-3}\ M^{-1}\ sec^{-1}$, 25°) than in nitrobenzene ($3{\cdot}4 \times 10^{-4}\ M^{-1}\ sec^{-1}$, 25° [5]). Methiodides can readily be precipitated by the addition of 90% ether-acetone or EtOAc. A minor drawback of DMSO is its reaction with MeI to give oxotrimethylsulfonium iodide,[15] (I) m.p. ~220° dec., τ 6·0. But this side-reaction is significant only with the least reactive substrates studied.

$$(CH_3)_3\overset{+}{S}O\ I^-$$

I

The method of calculating isomer ratios assumes additivity of effects. These include the effects of substituents bonded to annular carbon atoms as well as the effects of annular nitrogen atoms. For the present, it also is assumed that comparison compounds and the new substrates being examined have the same susceptibility to substituent effects, *i.e.*, they belong to reaction series having the same Hammett ρ value. This assumption is a limitation. However, results from *pKa* and alkylation studies suggest that it is not uncommon to find similar ρ values for different classes of molecules. For example, substituents have similar effects on the *pKa* values of pyridines, quinolines and isoquinolines.[16] Moreover, although monosubstituted pyrazines methylate more slowly than their pyridine counterparts, the ratio of the Hammett ρ values for the two series is only 1·06.[4]

Although our results and predictions apply directly to data obtained using DMSO as solvent at room temperature, they are expected to apply, at least semi-quantitatively, to other solvents over a range of temperatures. This is so because even though rates may be highly solvent and temperature dependent, rate constant ratios are much less dependent. Thus the ρ values for the quaternization of substituted pyridines by MeI differ by only 0·2 on changing from DMSO[11] to nitrobenzene solvent.[17] However, it should be remembered that some substituents show electronic effects which are noticeably solvent dependent.[18]

Non-additivity of effects may be expected to result when steric factors are present.[5, 19] This is the most severe limitation to our prediction; it is difficult to estimate the magnitudes of steric effects. Increasing the bulk of the alkylating agent is expected to decrease the reactivity of hindered nitrogen centers. For example, the ratio of the rate constants for the N-alkylation of 2-methylpyridine and of pyridine by methyl, ethyl

and isopropyl iodides in nitrobenzene at 25° decreases in the order 0·47:0·23:0·054, respectively.[5]

Rate factors for substituents bonded to carbon. Substituent rate factors are obtained from the rates of N-methylation of substituted pyridines relative to that for pyridine. Relative rate constants for reaction with MeI in DMSO at 23° which we have determined are listed in Table 1.* They are expressed logarithmically.

It has been shown that the rates of quaternization of 3- and 4-substituted pyridines in various solvents may be correlated by both the Hammett and Brønsted equations.[4, 6, 7, 11] We therefore have used our data to obtain parameters for such correlations so as to reflect N-methylation in DMSO. From equations 1 or 2 which employs σ_m and σ_p values or *pKa* values, new rate factors may be calculated to supplement those already given in

TABLE 1. SUBSTITUENT RATE FACTORS TO BE USED IN THE CALCULATION OF THE RELATIVE RATES OF N-METHYLATION OF PYRIDINE DERIVATIVES WITH METHYL IODIDE IN DMSO AT 23°.[a,b]

Substituent(s)	Position			
	ortho	*meta*	*para*	
NH_2	0·09	0·59	1·55[c]	
Me	−0·42	0·22	0·39[d]	
Et	−0·77	0·22[d]	0·34[d]	
CH_3CONH	−2·09	−0·48[d]	0·27[e]	
Bz	−1·09	—	0·17[e]	
Cl	−2·41	−0·86	−0·53[d]	
Br	−2·41	−0·90[d]	−0·53[d]	
COOMe	−2·08	−0·85[d]	−1·04[d]	
CN	−2·66	−1·28	−1·52[d]	
MeO	—	0·0	0·60[d]	
—N=[f]	−0·60	−1·36	−1·45	
2,6-$(Me)_2$				−1·64
2-NH_2-6-Me				−1·30
2,3-Benzo[g]				−0·98
3,4-Benzo[h]				0·0
2,3-Benzo-6-Me[i]				−2·21
1,10-Phenanthroline[j]				−1·32

[a] Pyridine is the reference compound.

[b] Logarithmic values. Unless noted otherwise, values are derived from our earlier studies; see refs. 4, 10 and 11.

[c] This work.

[d] Estimated from eq. 1.

[e] Estimated from eq. 2.

[f] Annular nitrogen.

[g] Quinoline.

[h] Isoquinoline.

[i] 2-Methylquinoline.

[j] Composite value statistically corrected for reaction of two equivalent nitrogen atoms. See text.

* The use of *ortho*, *meta* and *para* nomenclature to indicate the relative positions of an annular nitrogen atom and a substituent bonded to a six-membered heteroaromatic ring is uncommon but valid. Note that when an annular nitrogen atom is sterically hindered, an amino group bonded to an annular carbon atom may undergo alkylation.[10]

Table 1. (Compilations of σ[18–21] and pKa[22,23] values are available). It must be noted that equations 1 and 2 only apply to substituents *meta* or *para* to the reactive nitrogen center. They do not apply to *ortho* substituents which are also subject to the influence of steric effects. The list in Table 1 is not intended to be exhaustive. Rather, factors for some of the more common substituents are given.

$$\text{Rate Factor} = -2{\cdot}30\sigma \quad (1)$$

$$\text{Rate Factor} = 0{\cdot}36\,pKa\,(H_2O) - 1{\cdot}85 \quad (2)$$

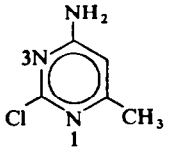
Equations 1 and 2 do not always give similar rate factors; often dissimilarities only reflect the normal scatter found in linear free energy plots.[21] As illustrations of the largest differences found, consider the rate factors for *para* $CONH_2$ (−0·83 and −0·55) and CN (−1·52 and −1·17) groups obtained from equations 1 and 2, respectively. The other groups in Table 1 show much smaller differences in their rate factors calculated by these equations.

Qualitatively, it can be seen from the rate factors in Table 1 that strongly electron donating substituents *para* to a quaternizing center have a powerful activating effect. With few exceptions *para* substitutent effects, whether activating or deactivating, are greater than *meta* effects. *Ortho* substituents which show both steric and electronic effects almost always are deactivating and deactivate more than *meta* and *para* groups.

The values for *ortho* substituents given in Table 1 were determined from the rates of N-methylation of 2-substituted pyridines.[10] They are not expected to correctly reflect the reactivities of more hindered nitrogen centers; nor are they applicable to larger alkylating agents. Note too that steric effects are not additive. Thus the effect of two *ortho* Me groups (−1·64) is not given by twice the factor for a single Me group (2X −0·42). Also, a 3,4-benzo group (as in isoquinoline) has a negligible effect on the reactivity of pyridine and so no special rate factor is needed, but a 2,3-benzo group (as in quinoline) is strongly deactiviating due to the steric effect of the peri position.

In the absence of rate factors for sterically hindered positions determined directly from studies using MeI in DMSO, some rough estimates from studies using other solvents may be employed. These include values for *ortho* iso-propyl[5] (−1·1), tert-butyl[5] (−3·7) and 2′-pyridyl[10] (−2·5) substituents. The pyridyl group roughly approximates the effect of a phenyl group. The hindered nitrogen atom in 8-methylquinoline has a rate factor of −3·8;[12] this value includes the effects of the fused ring and the Me group.

Steric factors may be similar in certain molecules and so may be neglected in an approximation of isomer ratios. In a molecule such as 2-chloro-4-amino-6-methylpyrimidine (II) the steric and electronic effects of the chloro group are expected to



II

be essentially the same on each adjacent nitrogen atom and the steric effects of the NH_2 and Me groups are likely to be similar as well.[10] Hence, the isomer ratio resulting from N-methylation can be estimated from NH_2 and Me rate factors alone. Beware of

oversimplifications regarding steric effects, particularly in molecules where one annular nitrogen atom is flanked by two *ortho* groups while another is *ortho* to only one substituent.

The behavior of a *para* amino substituent illustrates an interesting property of DMSO. From *pKa* studies employing water solvent a sigma value of −0·65 was found for this group[23] but from quaternization rates in nitrobenzene the value is −0·39.[7] The value we obtained by competition studies using DMSO is −0·67. It appears that DMSO is much like water in its effect on an amino group. The better electron-donating property of an amino group in water has been attributed to the better ability of the polar solvent to stablize separated charges.[7]

No attempt was made to examine systems where tautomerism is important. The distribution of tautomeric structures may be markedly solvent and temperature dependent[24] and this is expected to influence reactivity and product ratios.

The methylation of 2-methoxy-pyridine was not studied due to rapid disappearance of product, no doubt resulting from demethylation of the methoxy group.[2]

Rate factors for annular nitrogen atoms. Comparison of the reactivities toward MeI in DMSO of the three diazines relative to that for pyridine[11] provides rate factors for annular nitrogen atoms, Table 1. Rate constants for the diazines were statistically corrected for reaction of two equivalent centers. Hence the factors in Table 1 apply to a single nitrogen atom. Electron-withdrawing nitrogen atoms decrease the nucleophilicity of another annular nitrogen center in the same ring in the order *ortho* << *meta* < *para*. The deactiviating effects of the *meta* and *para* nitrogen atoms are among the largest of all the substituents.

The perturbation in the nucleophilicity of one annular nitrogen atom by a second widely separated nitrogen atom such as that in a naphthyridine is only moderately large. Studies on 1,5-naphthridine[25] (III) give a rate factor which, after statistical correction for the two equivalent centers in III, is −0·7, Table 2, for such a nitrogen atom. Although

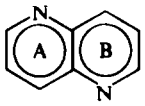
TABLE 2. RATE FACTORS FOR A NITROGEN ATOM IN RING B OF A FUSED BICYCLIC POLYAZINE REACTING AT RING A.

Ring/Position		Rate Factor[a]
A	B	
1 or 2	5, 6 or 7	−0·7
1	8	+0·6

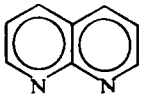
[a] Logarithmic values reflecting only the effect of the nitrogen atom not being quaternized. A rate factor for the fused ring, Table 1, must be used with these values.

MeCN was the solvent in these studies, it is expected that new work using DMSO would give similar rate factors. This expectation is based on a comparison of N-methylation results which show that the rate constant ratio for quinoline to isoquinoline using MeCN[25] (8·2) and DMSO[10, 11] (11) solvents are similar. It is assumed that the interactions of nitrogen atoms in rings A and B generally are independent of position,

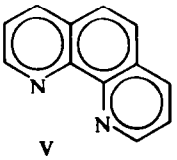
the 1,8 orientation being an exception. This is supported by naphthyridine kinetic results[25] and the known minor variations in the basicity of isomeric naphthyridines.[22] 1,8-Naphthyridine (IV) presents an interesting case because the nitrogen centers are less sterically hindered than that in quinoline and because there is a possibility of important electronic effects.[11,25] The value for a nitrogen atom in the 1,8 geometry is +0·6. (Note that rate factors for the nitrogen atoms in III and IV are derived by comparisons with quinoline reacting in MeCN.)



III



IV



V

A large negative value (−1·32) results for 1,10-phenanthroline (V) where in addition to electronic effects there is a large deactivating steric effect. This value is a composite one; it includes the effects of one nitrogen atom and the fused rings. (Pyridine is the comparison substrate.)

Isomer Distributions. The reactivity of a single annular nitrogen atom in a polyazine is given by equation 3 where R(MeN—X) represents the reactivity (relative to

$$\text{R(MeN—X)} = \text{Sum of Rate Factors} \tag{3}$$

pyridine) of N—X toward MeI as influenced by the additive effects of substituents and annular nitrogen atoms. An isomer ratio is given by the antilogarithm of the difference in reactivity of two centers, equation 4. It should be noted that the second order rate

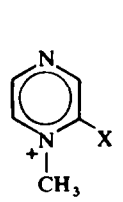
$$\text{antilog [R(MeN—Y) − R(MeN—X)]} = \%\ \text{MeN—Y/}\ \%\ \text{MeN—X} \tag{4}$$

constant for reaction at N—X is approximated by k_2 antilog [R(MeN—X)], where k_2 is the second order rate constant for the methylation of pyridine. However, product ratios generally are expected to be more accurately estimated than are rate constants. This is so because steric effects may cancel entirely or in part when dealing with isomer ratios. Also, rate constants apply only to N-methylation reactions but isomer ratios are likely to apply to N-alkylation generally when steric factors are unimportant.

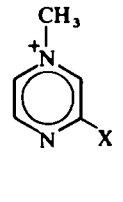
A comparison of observed and predicted isomer ratios is considered next. These comparisons employ literature as well as several new results for a wide variety of compounds. Only by such comparisons can the value of our method be judged.

Monocyclic azines. Pyrazines. Monosubstituted pyrazines bearing a Me or NH_2 substituent give two N-methylated products; these are 1-methyl-2-(VI) and 1-methyl-3-substituted pyrazinium (VII) salts. The 1,2 to 1,3 isomer distributions found (Me, 20 : 80%; NH_2, 26 : 74%) agree well with those predicted Me, 19 : 81%; NH_2, 24 : 76%). Many other substituents bring about the formation of essentially one isomer, the 1,3 structure.[4]

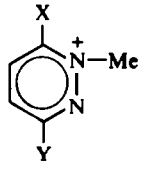
Pyridazines. 3,6-Disubstituted pyridazines having different substituents at the 3 and 6 positions can methylate to give isomers VIII and IX. Predicted and observed[3] isomer distributions are given in Table 3. In six out of seven reactions the major N-methylated isomer is correctly predicted. In the case of the lone failure, nearly equal amounts of both products are predicted and are found to be formed. Differences between predicted and



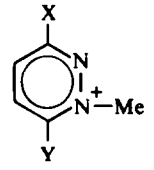
VI



VII



VIII



IX

observed percentages range from a low of −1% to a high of +23%. Note that both centers are subject to steric effects. Results pertain to reactions in MeCN at 50°.

TABLE 3. EXPERIMENTAL[a] AND PREDICTED N-1/N-2 METHYLATION PRODUCT RATIOS FOR THE REACTION OF 3-X-6-Y-PYRIDAZINES WITH METHYL IODIDE IN ACETONITRILE

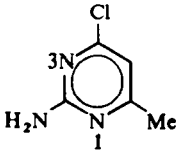
X	Y	%N-1/%N-2	
		Exptl.[b]	Calc.
Me	H	72/28	81/19
COOMe	H	>98/<2	94/6
Me	Cl	21/79	11/89
Me	Br	23/77	12/88
Me	NH_2	45/55	58/42
Me	CH_3CONH	11/89	10/90
Cl	NH_2	69/31	92/8

[a] Taken from reference 3.
[b] By NMR analyses of reaction mixtures.

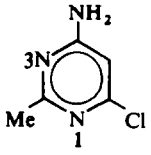
Pyrimidines. Some statements made about substituent effects on quaternization rates, based on results from preparative experiments, are likely to be incorrect. Thus rate factors, Table 1, indicate that the NH_2 group is always more activating than a Me or a Cl group in the same position and that the reactivity of amino pyrimidines should be 4 > 5 > 2, in contrast with earlier conclusions.[2]

As an illustration of the difficulty in predicting substituent effects from results of preparative experiments consider the following three examples.[26] The major product isolated in two cases is the one predicted by the rate factors but in a third case there is disagreement. Methylation in 2-ethoxyethanol of trisubstituted pyrimidines II and X is observed to take place largely at N-1; we predict 82 and 92% reaction at N-1,

respectively. But XI gives mostly the N-1 isomer whereas we predict 72% reaction at N-3. However, only about a 20% yield of products was reported in the case of XI; yields were constantly greater in the case of II and X. The effects of substituents at C-2 were neglected in making the calculations.

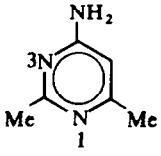


X



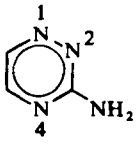
XI

We have found that methylation of 4-amino-2,6-dimethylpyrimidine (XII) results in an NMR product spectrum containing a small shoulder on the main N–Me peak. However, the aromatic region showed two broad singlets for H-5 in an area ratio of 7:1, corresponding to 88% of the major isomer. It is predicted that 86% of the reaction should occur at N-1.



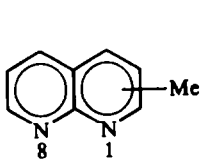
XII

1,2,4-*Triazine*. An attempt was made to determine the isomer ratio resulting from the N-methylation of 3-amino-1,2,4-triazine (XIII) in DMSO. The NMR spectrum of the product mixture contained two peaks in the N-Me region at τ 5·70 and 6·01 in a 1·6:1 ratio, the larger peak being at lower field. But a small shoulder on the minor peak may be indicative of a third isomer. Moreover, the main peak slowly diminished in area with time. The product ratio is predicted to be 18(N-1):7(N-2):1(N-4). The chemical shift of the low field peak is consistent with methylation at N-1; results (61%) are in reasonable agreement with the prediction (69%).

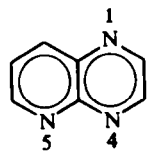


XIII

Benzazines. A comparison of calculated and experimental results for the methylation at N-1 of 2-, 3- or 4-methyl-1,8-naphthyridine[25] (XIV) in MeCN is given in Table 4. The calculations assume that the Me group only influences the reactivity of the nitrogen center in the ring to which it is bonded, *i.e.*, N-1. The agreement is satisfactory.



XIV



XV

TABLE 4. EXPERIMENTAL[a] AND PREDICTED N—1/N—8 METHYLATION PRODUCT RATIOS FOR THE REACTION OF METHYL-1,8-NAPHTHYRIDINES WITH METHYL IODIDE IN ACETONITRILE.

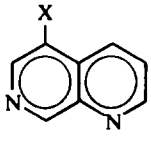
	%N—1/%N—8	
Position	Exptl.[b]	Calc.
2	>80/<20	73/27
3	50/50	63/37
4	63/34	71/29

[a] Reference 25.

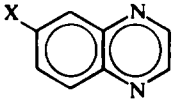
[b] By NMR analyses of reaction mixtures.

The methylation of 1,4,5-triazanaphthalene (XV) is predicted from rate factors to give the following product distribution, 100(N-5):20(N-4):1(N-1) or 83% methylation at N-5. We found the NMR spectrum to be consistent with the formation of a single product. That this product results from methylation at N-5 is suggested by the observation that the H-6,7,8 signals are shifted downfield considerably more than those for H-2,3.

Future developments. In general, quantitative predictions concerning the electronic effects of substituents on the reactivity of nitrogen centers in compounds such as XVI and XVII cannot yet be made. However, it seems likely that this deficiency could be remedied by studies of the effects of benzosubstituents on quaternization rates of quinoline and isoquinoline model compounds.



XVI



XVII

Very little is known about the quantitative aspects of the N-alkylation of 5-membered heteroaromatic compounds.[2] Studies such as those outlined here for azines are highly desirable for azole model compounds.

Our rate factors appear to be useful in making qualitative predictions concerning the isomer ratios resulting from the N-oxidation of heterocyclic compounds by peroxy

acids. Examination of a recent compilation of results[27] (information concerning isomer ratios is rare) indicates that the position of N-oxidation generally is that predicted by the use of the rate factors in Tables 1 and 2. There are some exceptions.[27, 28] But it seems likely that the rate factor approach outlined here for N-alkylation could be extended to N-oxidation as well. Some kinetic results are available.[29, 30] The suggestion that N-oxidation is less sensitive to steric effects than N-methylation should be noted.[30]

Clearly the additivity approach outlined here is a powerful and useful one. It provides reasonable predictions of isomer ratios of quaternization products in the systems discussed and provides a way to rectify many of the contradictory statements in the literature. Our method represents only a beginning but it can easily be refined and extended.

EXPERIMENTAL

NMR spectra were recorded using a Varian Associates A-60A instrument. Chemical shifts are relative to a DMSO ^{13}CH satellite peak at τ6·23. Heterocyclic compounds were obtained from Aldrich Chemical Co.

Methylation experiments were carried at 23° in NMR tubes using reported methods.[4, 10] MeI was employed in all cases.

The rate factor for a *para* amino group was obtained from the results of a competition experiment using 4-amino-2-methylquinoline[31] and 3-chloropyridine. NMR analysis of the N-Me product peaks allows a rate constant ratio of 1·59 to be obtained; the quinoline is more reactive than the pyridine. Use of the known 3-chloropyridine to pyridine rate constant ratio[4] results in a comparison of the quinoline to pyridine; log $k_{rel} = -0.66$. Assuming the additivity of substituent effects and the known log k_{rel} (pyridine as standard) of -2.21 for 2-methylquinoline allows a value of 1·55 for the *para* amino group to be calculated.

Methylation of 4-*amino*-2,6-*dimethylpyrimidine.* A spectrum of the product mixture in DMSO-d_6 showed that the N-Me signal at τ6·2 had a shoulder. The H—5 ring proton consisted of broad singlets at τ 3·33 and 3·13 in a 7:1 ratio. It was necessary to add trifluoroacetic acid (TFA) to the mixture to remove overlapping signals of unreacted starting material prior to analysis of the H-5 signals.

Methylation of 1,4,5-*triazanaphthalene.* The product spectrum (DMSO) was consistent with methylation entirely at N-5: τ 5·23 (NMe), 1·40 (q, H-7), 0·5 (m, H-2,3,8) and −0·02 (d, broad, H-6). The product was isolated by precipitation with ether and had m.p., 190° dec. after recrystallization from EtOH. Calcd for $C_8H_8N_3I$: C, 35·2; H, 2·9; N, 15·4. Found: C, 35·0; H, 3·0; N, 15·2%.

Rates of reaction of pyridine with methyl iodide. The reaction in DMSO at 25° was followed by NMR analyses. Samples of a solution of 0·534M pyridine and 0·274M MeI were quenched at suitable times by the addition of TFA. The NMe product peak was integrated, a ^{13}CH DMSO satellite peak serving as an internal standard. An infinity value allowed peak ratios to be converted into product concentrations and $k_2 = 2.4 \times 10^{-3}$ M^{-1} sec^{-1} was calculated from the standard second order rate expression.[32]

Acknowledgement—This work was kindly supported in part by the National Science Foundation (GP-25500).

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