

Strained heterocyclic systems. Part 21.¹ The Menshutkin reaction[†]

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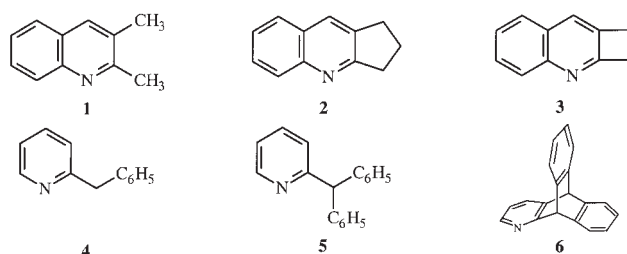
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Rate constants are determined for methyl iodide quaternisations of a series of 2-substituted quinolines and pyridines. Relative rates are interpreted in terms of steric effects, electronic effects and calculated geometries.

The rates of quaternisation of nitrogen heterocycles with a methyl halide were first reported a century ago and, from the outset, it was evident that relative rates reflected both steric and electronic influences.² Since that time, this particular variation of the Menshutkin reaction has received vast attention. Over the past few decades all aspects of this process have been reviewed,³ and structural variations were interpreted in terms of steric, inductive, and resonance components. The impact of steric effects, although not without some subtleties, is rather straightforward; the correlation of electronic effects, however, is more problematic. Although linear relationships between quaternisation rates and pK_a data are sometimes observed,⁴ that is not always the case.^{5,6} Moreover, the general utility of such correlations has been questioned.⁷

The present report focuses on compounds **1–3** and **4–6**, which constitute orderly gradations of steric effects while maintaining constant inductive and/or resonance components. Thus, these systems are well-suited for assessing steric effects while controlling electronic effects. Since the basicities of **1–6** are known,⁸ the opportunity also exists to relate quaternisation rates and pK_a data. (Scheme 1).



Scheme 1

Results

Quaternisations of **1–6** were carried out with excess methyl iodide in acetonitrile at 50°C. Rates were measured by NMR. Second-order rate coefficients and pK_a data are summarized in Table 1. Ideally, the comparative series of quinoline derivatives would be 1,2,3,4-tetrahydroacridine (**7**), **2**, and **3**. Unfortunately, under the reaction conditions, the rate of aromatization of the methiodide of **7** to acridine (**8**) methiodide was of a quite comparable rate to the quaternisation complicating the reaction. We therefore used 2,3-dimethylquinoline (**1**) as a surrogate for **7**. This choice posed a potential problem – *viz.*, that the rotation of the alpha methyl group at C(2) in **1** would not necessarily provide a conformation comparable to **2** and **3**

Table 1 Kinetic data for reaction of methyl iodide with substituted quinolines and pyridines; pK_a data

Compd/	$10^4 \cdot k_2^a$ l mol ⁻¹ s ⁻¹	k_{rel}	pK_a
1	0.0467	1.00	5.99
2	1.77	37.9	5.45
3	1.78	38.1	4.55
4	1.79	38.3	5.13
5	1.67	35.8	4.51
6	1.98	42.4	3.66

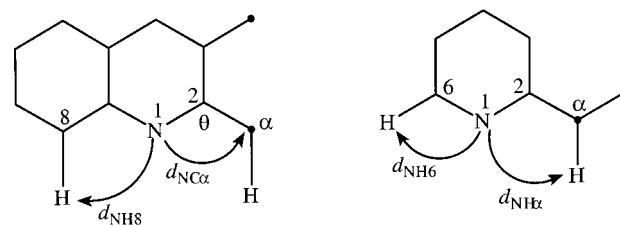
^aRate coefficients were reproducible to $\pm 1.5\%$.

in which the H atoms straddle the plane formed by N(1)–C(2)–C(α). In the case of 2,3-lutidine (**9**), four possible rotamers have been assessed by MINDO/3 calculations, and the lowest energy conformation possessed a H atom coplanar with the ring and parallel to the N atom lone-pair orbital.⁹ However, since the total energy range for the four rotamers was only 1 kcal/mol and since others have concluded from relevant kinetic data that steric effects of spherical methyl groups require no reference to their polyhedral shape,¹⁰ the inclusion of **1** in the present study is warranted.

Discussion

The relative rates for **1–3** clearly establish that steric effects are the major factor in these reactions. The fact that strain-induced orbital rehybridisation causes **2** and **3** to be weaker bases than **1** is a minor factor. The nearly identical rate coefficients for **2** and **3** were unexpected. This result implies that once the α -carbon is sufficiently distant from the reaction site, secondary electronic effects are noticeable. With **4–6** the same trend is observed, although the relative rates are less dramatic.

To explore the geometries of these systems, we carried out molecular mechanics calculations on **1–6**;¹¹ the results are presented in Table 2. The key parameters are defined in Scheme 2. Similar analyses aided the interpretation of relative rates for methyl iodide quaternisations of 2,3-disubstituted



The numbering of **1** is used for **1–3**, since each compound has a different pattern of carbon designations; similarly, the numbering of **4** and **5** is used for **6**.

Scheme 2

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[†] This is a Short Paper, there is therefore no corresponding material in *J. Chem. Research (M)*.

Table 2 Calculated geometries^a

Compd.	Θ/deg	$d_{\text{NC}\alpha}/\text{\AA}$	$d_{\text{NH}\alpha}/\text{\AA}$	$d_{\text{NH8}}/\text{\AA}$	$d_{\text{NH6}}/\text{\AA}$	Ref.
1	114.1	2.341	2.646	2.639		<i>b</i>
2	125.1	2.460	2.767	2.627		<i>b</i>
3	142.0 (137.6) ^c	2.625 (2.631) ^c	3.095	2.622		<i>b</i> 12
4	116.4	2.371	2.502		2.044	<i>b</i>
5	116.2 (117.9) ^c	2.372 (2.465) ^c	2.850		2.044	<i>b</i> 13
6	120.3	2.423	2.635		2.050	<i>b</i>

^aSee text for definition of parameters. ^bPresent work.

^cDetermined by X-ray crystallography.

pyridines.⁶ In those prior discussions, the angle Θ formed by N(1)–C(2)–C(α) and the distance between the reaction site and the H atom on the alpha C atom ($d_{\text{NH}\alpha}$) provided the basis for rationalizing the relative rates of **9**, 2,3-cyclohexenopyridine (**10**) and 2,3-cyclopentenopyridine (**11**)⁶.

With quinolines the *peri* hydrogen (H-8) exerts a major retardation effect. Rate reductions of 6–60 fold have been reported for quinolines compared to the corresponding pyridines.^{2,5,14} Retardation factors of similar magnitude are observed for **1** vs **9** and **2** vs **11**. The principal difference between quinolines **1–3** and pyridines **9–11** lies in the relative rates of **11:9** (4.5:1)⁶ vs **2:1** (38:1). The much faster rate of **2** compared to **1** can be attributed to the combined influences of *peri* H-8 and $d_{\text{NH}\alpha}$. The quaternisation step is impacted by the following steric effects. With quinolines, H-8 skews the axis of approach for methyl iodide toward C-2. Any substituent at C-2 exerts an opposite effect. Since d_{NH8} remains virtually constant for **1–3**, the dimensions represented by Θ and $d_{\text{NH}\alpha}$ are determinative. Thus, **1** reacts more slowly than **2** because **1** has less space between N and the α -methyl group at C-2. The fact that **3**, despite a much larger value of Θ , is no more reactive than **2** correlates with the reduced basicity of such systems.^{8,15} The same considerations apply to **4–6**, although the similarity of their rate constants to **2** and **3** was unexpected. In pyridines **4** and **5** the increased steric factor of the benzyl substituents¹⁶ compensates for the absence of a *peri* H-8 steric effect. The slightly faster rate of **6** vs **5** reflects the competing effects of Θ and $\text{p}K_{\text{a}}$, while comparable rates of **4** and **5** reflect their similar geometries and the known conformation of **5**.¹³ In summary, relative rates of the Menshutkin reaction of some strained heterocyclic systems have been correlated with steric and electronic effects and with calculated geometries.

Experimental

GC–MS analyses were performed on a Hewlett Packard 5890 Series II gas chromatograph with a capillary SPB-5 polydiphenyl (5%)–dimethyl (95%) silicone column (30 m x 200 μm with 0.2 μm film) and Hewlett Packard 5971A mass spectrometer (EI, 70 eV). Proton NMR spectra were recorded at 300 MHz in acetonitrile- d_3 on a Bruker DPX 300 spectrometer; chemical shifts are reported in parts

Table 3 Physical characteristics of methiodides of **1–8**

Compd	Time ^a /h	M.p./°C	δ^b
1	22	218–221 lit. ²⁰ 218	4.49
2	23	215–216 lit. ²¹ 207 (ethanol)	4.44
3	22	226–227 <i>c</i>	4.28
4	69	159–160 lit. ²² 159	4.27
5	69	222–224 lit. ²³ 222–224	4.21
6	20	304–305 <i>c</i>	4.56
7	22	208–210 lit. ¹⁹ 202–204	4.34
8	72	220–222 lit. ²⁴ 220–222	4.81

^aReaction time at room temperature. ^b¹H NMR signal (s, 3H) for N–CH₃ in CD₃CN. ^cSatisfactory combustion analyses for %C, H and N.

per million (δ) relative to tetramethylsilane. Melting points (uncorrected) were determined on a modified Hersberg apparatus with matched Anschutz thermometers. Microanalyses were performed by Galbraith Laboratories Inc., Knoxville, TX, USA.

Methyl iodide, *t*-butylbenzene, acetonitrile- d_3 (99.6 atom % D), **4**, **5**, and **8** were obtained commercially; **4** was distilled *in vacuo* and stored under argon. Compounds **1**,¹⁷ **2**,¹⁸ **3**,¹⁷ **6**⁸ and **7**¹⁹ were prepared according to literature procedures and purified to the reported physical and spectral properties. The purities of **1–8** were >99.5% by GC–MS analyses.

Methiodides: In a typical procedure a solution of the heterocyclic base (0.50 mmol) and methyl iodide (0.142 g, 1.00 mmol) in dry acetone (1 ml) was stirred under argon. The crystalline product was collected by suction filtration, washed with cold diethyl ether, and dried *in vacuo* to give the products listed in Table 3.

Rate measurements: Reaction rates were determined on a Bruker DPX 300 spectrometer fitted with a BDTC/EURO THERM 847 temperature controller; temperature stability was 50.0 \pm 0.1 °C. To a 1-ml volumetric flask were added *t*-butylbenzene (0.00060 g, 0.0040 mmol) as an internal standard (0.20 ml of a solution of 0.012 g, 0.090 mmol *t*-butylbenzene in 4.0 ml CD₃CN), the quinoline or pyridine (0.040 mmol; 0.20 ml of a solution of 0.20 mmol **1–6** in 1.0 ml CD₃CN), methyl iodide (0.058 g, 0.40 mmol), and CD₃CN to the mark. A portion of this solution was transferred to the NMR tube and the rate of appearance of the *N*-methyl singlet (Table 3) was measured against the internal standard, using shims optimized during a preliminary kinetic run.

Separate control experiments established that no other peaks interfered with the chemical shift of the *N*-methyl singlet and that no reaction occurred between the solvent, methyl iodide, and the internal standard. All reactions were followed for a minimum of three half-lives; infinity points were measured after ten half-lives. Rate coefficients ($\pm 1.5\%$) were derived from graphical plots of duplicate runs, which were linear (average R for all runs 0.9972) and showed no evidence of reversibility.

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