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Ring-Opening Reactions. The Reactivity of Pyrrolidinium and Piperidinium Ions in Solution

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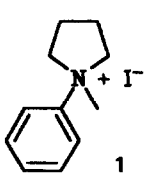
Abstract In this paper we report data on the reactivity of 1-phenyl-pyrrolidinium and -piperidinium iodides, and indolinium and tetrahydroquinolinium iodides, with MeO^- in methanol and compare them with the corresponding 1,1-dimethylazoniacycloalkane iodides

Many studies[1] have been published dealing with the reactivity of a series of 1,1-dimethyl cyclic ammonium ions The reaction of these compounds with nucleophiles consists of three parallel transformations, two substitution reactions and one elimination reaction The second-order overall rate constant and the product distribution depend on the ring strain energy of the substrate and on the ability to attain the configuration required in the transition state by the reaction mechanism

We have studied the reactivity of 1-methyl-1-phenylpyrrolidinium iodide (**1**) and 1-methyl-1-phenylpiperidinium iodide (**2**) with sodium methoxide in MeOH Whatever is the reaction involved, the product is an aniline derivative in which there is a mesomeric effect between the nitrogen lone pair and the aromatic ring This conjugation should influence the reaction rate and the product distribution

We have also studied the reactivity of 1,1-dimethylindolinium iodide (**3**) and 1,1-dimethyl-1,2,3,4-tetrahydroquinolinium iodide (**4**) In these compounds the benzocondensation causes an additional ring strain and a different steric hindrance on the electrophilic atom

In order to evaluate the effect of a phenyl group in an S_N2 reaction apart from ring strain and steric effects, we have chosen N,N,N-trimethylanilinium iodide (**5**) as a model compound



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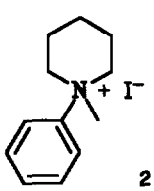

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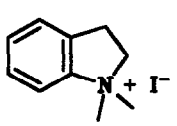

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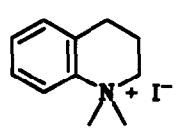

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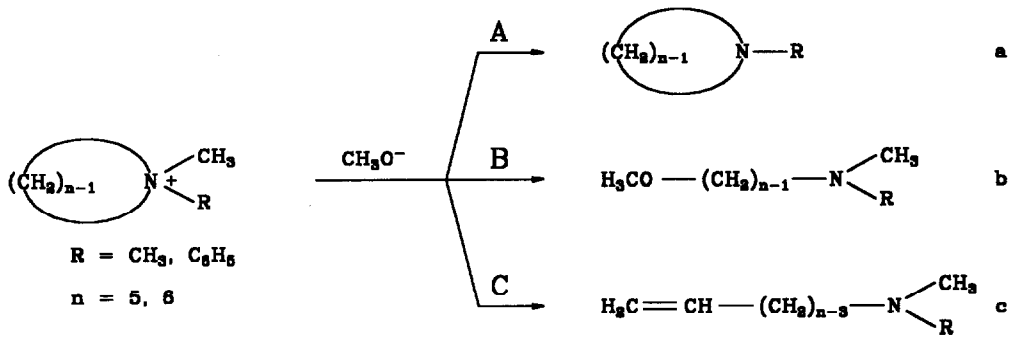
RESULTS AND DISCUSSION

When the substrates under investigation react with MeO^-, they follow a pathway that includes two substitution reactions (**A**, **B**) and one elimination reaction (**C**), according to the following Scheme.



The prevalence of a reaction with respect to another depended on the steric and electronic properties of the substrate, because we did not vary either the nucleophile or the solvent.

In Table 1 we report the product distribution for the reaction of **1** - **4** with MeO^- in MeOH and compare these data with that of 1,1-dimethylpyrrolidinium iodide (**6**) and 1,1-dimethylpiperidinium iodide (**7**), reported in literature.[1a] The substrates were investigated at 90° C; we also studied **1** and **2** at 130° C, since the data available on **6** and **7** were at 130° C. In this way we made it possible to investigate the influence of a phenyl group on these reactions.

TABLE 1. Product Analysis for the Reaction of Substrates 1 - 7 with Sodium Methoxide in Methanol at 90° and 130° C

	% reaction[i]					
	90° C			130° C		
Substrate	A	B	C	A	B	C
1	15	85	*	20	80	*
2	97	2	1	93	4	3
3	44	56	*			
4	100	*	*			
6[ii]				16	83	1
7[ii]				86	4	10

* Product not detected by GC analysis. [i]**A**, demethylation; **B**, ring-opening substitution; **C**, ring-opening elimination. [ii]Data from Ref. 1a.

The experiments showed that the temperature did not greatly affect the product distribution. **1** undergoes

only substitution reactions, with the ring opening (**B**) predominant over demethylation (**A**) **1** does not follow reaction **C** probably because it cannot reach the conformation required by an E2 mechanism The presence of the phenyl group changes the product distribution only slightly relative to **6** for the complete disappearance of reaction **C**

The main product from **2** is 1-phenylpiperidine (**2a**) in which the azocycloalkane ring is preserved A six-membered ring is strainless and **2** is not lead toward a ring-opening reaction In spite of that, a small percentage of N-5-methoxypentyl-N-methylaniline (**2b**) and N-methyl-N-4-pentenylaniline (**2c**) are present If we compare the product distribution from **2** with that from **7**, we note that the percentage of elimination decreases with a consequent reduction of demethylation A similar effect was also observed in the Hofmann degradation of ammonium hydroxide [2] It appears that the replacement of a N-methyl with a N-phenyl group causes an inhibitory effect on β-elimination relative to substitution The product distribution from **1** and **2** is quite different because the main product from **1** is N-4-methoxybutyl-N-methylaniline (**1b**), a ring-opening product, and from **2** is **2a** This effect was already observed with **6** and **7** [1] The different strain energy between **1** and **2** can be, at least partially, responsible for this behaviour Unfortunately, data on strain energy of cyclic ammonium ions are not available but they should not largely differ from the corresponding cycloalkane because both are entirely formed from tetrahedral atoms The strain energy of cyclopentane and cyclohexane are 7 3 and 1 4 kcal mol^{-1}, respectively [3] Another aspect to take into account is the steric requirement of the approaching nucleophile In reaction **B** of five-membered rings, MeO^- can follow a pathway that is not hindered while in six-membered rings it is partially hampered by the C-H equatorial bond of the carbon atom in position 2

TABLE 2. Second-Order Overall Rate Constant k ($M^{-1}\cdot s^{-1}$) for the Reaction of 1 - 7 with Sodium Methoxide in Methanol at 90° and 130° C

	$10^4\cdot k$	
Substrate	**90° C**	**130° C**
1	21 0	4710
2	2 56	740
3	8 29	
4	5 06	
5	5 40	
6[1]		3 80
7[1]		0 702

[1]Data from Ref 1a

3 gives two products, 1-methylindoline (**3a**) and N,N-dimethyl-2-(2-methoxyethyl)aniline (**3b**) The absence of reaction **C** in spite of the fact that the product would be a conjugated alkene underlines again the importance of conformational requirements of an E2 **4** produces only 1-methyl-1,2,3,4-tetrahydroquinoline (**4a**) The complete disappearance of reaction **C** should not be ascribed to conformational effect because **4** is in

a half-chair conformation in which β-hydrogen atoms are in a suitable position [2] Evidently, the additional strain induced by the benzocondensation is not enough to carry toward an open chain product In fact, even if strain energy data of these compounds and of the corresponding hydrocarbons are not available, we can compare **3** and **4** with cycloalkenes Strain energies of cycloalkenes relative to force-field calculation show that the energy of cyclopentene is -0 60 kcal mol^{-1} with respect to cyclopentane and that of cyclohexene 0 86 kcal mol^{-1} with respect to cyclohexane [4] These differences are not large and the effect on the reactivity is almost negligible

In Table 2 we report the second-order overall rate constants and in Table 3 the partial rate coefficients for the reaction of substrates **1** - **7** with MeO^- in MeOH Taking into consideration the partial rate coefficients it is possible to make a comparison that overcomes statistical factors The partial rate coefficients of the demethylation reaction (k_A) at 90° C are nearly independent of the substrate, the largest change in rate involving a factor of 1 8 An analogous effect was observed in the series of cyclic N,N-dimethylammonium ions in which the demethylation rate did not depend on ring size These data are not surprising because the factors that influence an S_N2 reaction are the steric hindrance on the site of substitution and on the leaving group ability, under the same nucleophile and solvent These effects are very similar in the substrates under investigation and, consequently, k_A does not greatly vary

TABLE 3. Second-Order Rate Constants for the Individual Reactions (Partial Rate Coefficients) k ($M^{-1}\cdot s^{-1}$) of Substrates 1 - 7 with Sodium Methoxide in Methanol at 90° and 130° C

	$10^4 \cdot k$					
	90° C			130° C		
Substrate	[i]A	[i]B	[i]C	[i]A	[i]B	[i]C
1	3 2	8 9		940	1900	
2	2 5	0 03	0 01	690	15	11
3	1 8	4 6				
4	2 5					
5	1 8					
6[ii]				0 3	1 6	0 021
7[ii]				0 3	0 014	0 030

[i]A, demethylation, [i]B, ring-opening substitution, [i]C, ring-opening elimination [ii]Data from Ref 1a

In spite of the different product distribution, **1** and **3** show a similar reactivity, with a ratio $k_{B\,(1)} / k_{A\,(1)} = 2\,8$ and $k_{B\,(3)} / k_{A\,(3)} = 2\,6$, so the different product distribution only derives from a statistical effect because **1** and **3** differ in equivalent reaction sites, in fact in **1** there are one $N\text{-}CH_3$ and two $N\text{-}CH_2$ groups, while in **3** there are one $N\text{-}CH_2$ and two $N\text{-}CH_3$ groups This effect can also justify the disappearance of reaction **B** and **C** in **4**

The effect of the phenyl group on the reactivity of cyclic ammonium ions can be examined by comparing k_A, and k_B, in **2** and **7** The acceleration for **A** is larger than that for **B**, being $k_{A\,(2)} / k_{A\,(7)} = 2\,300$ and $k_{B\,(2)} / k_{B\,(7)} = 1\,070$ This could not be ascribed to a transition state in which the C-N bond breaking in **A** is

more advanced than in **B**, in order to undergo a larger conjugation effect, because the degree of C-N bond breaking should be more advanced in **B** than in **A** In fact, in the transition state, the C-N bond breaking does not depend on the leaving group ability, but on the nucleophile and on the substitution on the carbon atom [5] In the reactions under investigation, being the nucleophile the same, the substitution on the carbon atom would favour the C-N bond breaking in **B** relative to **A**, because the transition state of **B** is more crowded than **A** On the other hand, the delocalization is effective only if the angle between the incipient lone pair and the aromatic Π orbitals is small The conformation of **2** is unknown but it is reasonable to suppose that the azoniacycloalkane and the aromatic system lie on the same plane as much as possible, in order to minimise the steric hindrance between the aromatic ring and the axial hydrogen atoms of the azoniacycloalkanic ring In this conformation the incipient lone pair in reaction **A** will be in a more suitable position for the conjugation than in **B** and consequently the phenyl group will speed the demethylation more than the ring-opening substitution

EXPERIMENTAL

N M R spectra were recorded on a Brucker WP-80 spectrometer UV spectra were recorded on a Varian 210 spectrophotometer GC analyses were performed with a Carlo Erba HRGC 5300 Mega Series Instrument, using a SPB-35, 30 m × 0 25 mm capillary glass column GC/MS analyses were performed with a VG q mass spectrometer, using the same column

Amines

1-Phenylpiperidine (**2a**) was prepared as reported in literature [6] 1-Phenylpyrrolidine (**1a**) was prepared as described for **2a**, and compared with literature data [7] 1,2,3,4-Tetrahydroquinoline and indoline were commercial (Aldrich)

Ammonium salts

1-Methyl-1-phenylpyrrolidinium iodide (**1**), 1-methyl-1-phenylpiperidinium iodide (**2**), 1,1-dimethyl-indolinium iodide (**3**), and 1,1-dimethyl-1,2,3,4-tetrahydroquinolinium iodide (**4**) were prepared by alkylation of the corresponding amine with methyl iodide (Carlo Erba) in benzene Yields were up to 85% Structure assignments were made on the basis of ^{1}H N M R spectroscopy and, where available, on comparing with literature data **1** δ ($CDCl_3$) 7 82 - 7 57 (5H, m, C_6H_5), 4 32 - 4 19 (2H, m, CH_2), 4 12 - 3 96 (2H, m, CH_2), 3 45 (3H, s, CH_3), 2 50 - 2 45 (4H, m, CH_2) **2** [6] δ ($CDCl_3$) 7 83 - 7 62 (5H, m, C_6H_5), 4 40 (2H, d, CH_2), 3 79 (2H, t, CH_2), 3 43 (3H, s, CH_3), 2 06 - 1 90 (2H, m, CH_2), 1 88 - 1 65 (4H, m, CH_2) **3** [8] δ ($CDCl_3$) 7 95 - 7 45 (4H, m, C_6H_4), 4 58 (2H, t, CH_2), 3 92 (6H, s, CH_3), 3 47 (2H, t, CH_2) **4**.[9] δ ($CDCl_3$) 7 89 - 7 52 (4H, m, C_6H_4), 4 01 (2H, t, CH_2), 3 70 (6H, s, CH_3), 3 15 (2H, t, CH_2), 2 42 (2H, m, CH_2) N,N,N-Trimethyl-anilinium iodide (**5**) was commercial (Aldrich)

Product distribution

The reactions were carried out with MeONa in MeOH in sealed vials for 24 h at 90° C and, for **1** and **2** only, at 130° C The product analysis was carried out by the GC method on the vial content The identification of the compounds was carried out by comparison with authentic samples, where available, either purchased (**5a**, Aldrich) or synthesised (**1a**, **1b**, **2a** , **2b**, **2c**, **3a**,[10] **4a**,[9]), or by GC/MS spectroscopy (**3b**)

N-4-Methoxybutyl-N-methylaniline (**1b**) **1b** was prepared by following a three-step procedure 1-Bromo-4-chlorobutane (Aldrich) was converted to 4-chlorobutyl methyl ether by treatment with sodium

methoxide in MeOH and then to 4-iodobutyl methyl ether with sodium iodide in acetone **1b** was obtained by reacting 4-iodobutyl methyl ether and N-methylaniline (Aldrich) in EtOH at refluxing temperature for 48 h ^{1}H N M R δ ($CDCl_3$) 7 78 - 6 60 (5H, m, C_6H_5), 3 35 (2H, t, OCH_2), 3 28 (3H, s, OCH_3), 3 27 (2H, t, NCH_2), 2 91 (3H, s, NCH_3), 2 10 - 1 14 (4H, m, CH_2) N-5-Methoxypentyl-N-methylaniline (**2b**) **2b** was prepared by as described for **1b**, using 1-bromo-5-chloropentane (Aldrich) ^{1}H N M R δ ($CDCl_3$) 7 25 - 6 40 (5H, m, C_6H_5), 3 30 (2H, t, OCH_2), 3 23 (2H, t, NCH_2), 2 83 (3H, s, NCH_3), 1 55 - 1 10 (6H, m, CH_2) N-Methyl-N-4-pentenylaniline (**2c**) **2c** was obtained by reacting 5-bromo-1-pentene (Fluka) in EtOH at refluxing temperature for 48 h ^{1}H N M R δ ($CDCl_3$) 7 40 - 6 44 (5H, m, C_6H_5), 6 15 - 5 51 (1H, m, CH), 5 22 - 4 77 (2H, m, CH_2), 3 48 - 3 11 (2H, t, NCH_2), 2 88 (3H, s, NCH_3), 2 33 - 1 48 (4H, m, CH_2) **3b** M/z (%) 179 (37), 164 (57), 148 (45), 134 (100), 120 (14), 119 (16), 118 (54), 117 (40), 77 (25), 65 (27), 45 (95)

Kinetic measurements

The reactions were carried out in MeOH in N_2 atmosphere at 90° C and, for **1** and **2** only, at 130° C For every reaction 10-15 sealed vials were prepared 5 10^{-5} M ammonium salt and 5 10^{-3} M MeONa in order to be in pseudo first order conditions The vials were placed in a thermostat and taken periodically A UV spectrum of the content of every vial was recorded Pseudo first-order constants (k_1) were calculated by using the kinetic equation (1)

$$\ln [(A_\infty - A_0) / (A_\infty - A_t)] = k_1 t \qquad (1)$$

where A_t was absorbance at λ maximum (255 nm) To calculate the overall second-order rate constant (k_2), k_1 was divided by [MeO^-] Partial rate coefficients (k_x, x = a, b, or c) were calculated by equation (2)

$$k_n = k_2 X / (100 n_x) \qquad (2)$$

where X was the percentage of product x and n_x the statistical factor that depends on the equivalent reaction sites

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