Thermal Dealkylations of Quaternized Methoxyquinolinium and Methoxyisoquinolinium Iodides in the Mass Spectrometer

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Dealkylations of *N*-alkyl 6- and 7-methoxy quinolinium and isoquinolinium iodides in the mass spectrometer proceeded to give predominantly *O*-demethylation when resonance stabilized ions were produced. When *O*-demethylation did not provide a resonance stabilized ion, *N*-dealkylation predominated.

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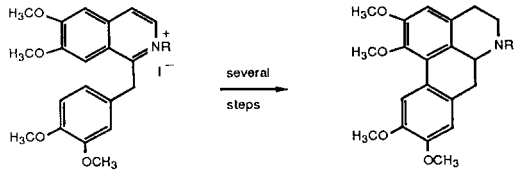
During the course of synthesizing isoquinoline alkaloid-like structures **2** for antitussive evaluation, we prepared 2-alkyl-1-benzylisoquinolinium iodides **1** and observed a facile loss of methyl iodide in addition to the loss of RI, when they were thermolyzed in the mass spectrometer. Although isoquinolinium salts are well-known in the literature, we found only two reports [1,2] dealing with thermolytic behavior and none describing competitive *O- versus*



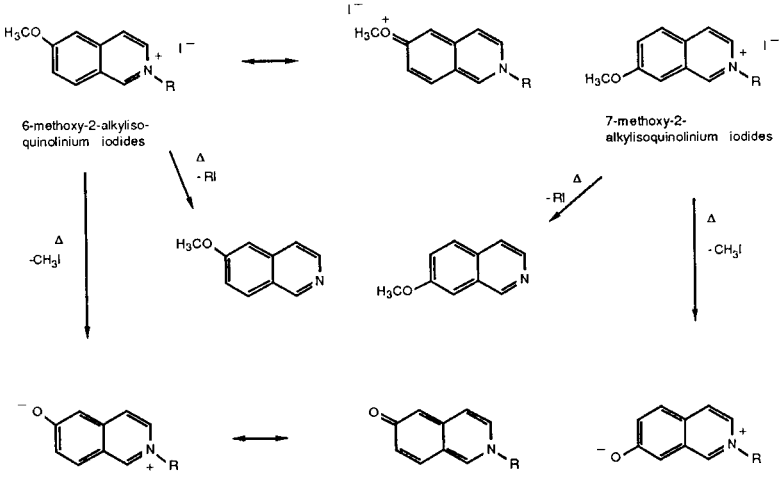
1 R = alkyl 2

N-dealkylations with alkoxy-substituted isoquinolinium salts. To study this interesting dealkylation in a simpler system, we prepared a group of 2-alkyl-6- and 7-methoxyisoquinolinium iodides and studied their thermolytic behavior in the mass spectrometer. Our goals were to determine the ease of *O*-dealkylation *versus* *N*-dealkylation with these compounds. We also extended this study to include 1-alkyl-6- and 7-methoxyquinolinium iodides.

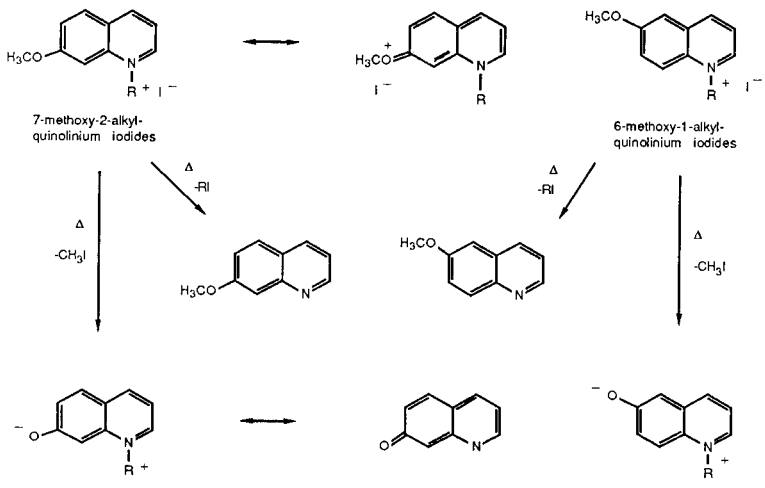
Scheme I shows generalized structures for 2-alkyl-6-methoxy- and 7-methoxyisoquinolinium iodides and their possible modes of dealkylation. For the 6-methoxy compounds, we postulated that *O*-dealkylation would be a preferred process, since a resonance-stabilized structure would result as shown [3]. With the 7-methoxy compounds, however, a corresponding resonance-stabilized structure for the *O*-dealkylated product cannot be drawn. Hence, we predicted that the ratio of *O*- to *N*-dealkylation would be *greater* for the 6-methoxy compounds than for the 7-methoxy compounds. In contrast to the corresponding isoquinolinium salts, the 6-methoxyquinolinium iodides (Scheme II) do not give rise to resonance-stabilized *O*-dealkylated structures. However, the 7-methoxy compounds do give resonance-stabilized structures upon *O*-dealkylation. Thus, we postulated that in the quinolinium group of compounds, the ratio of *O*- to *N*-dealkylation would be *greater* for the 7-methoxy compounds than for the 6-methoxy compounds.

We also investigated the mass spectra of 2-alkyl-6,7-methylenedioxyisoquinolinium iodides (Scheme III). With

Scheme I



Scheme II



these compounds, simple *N*-dealkylation would give the structure shown, but iodide-initiated *O*-dealkylation could give one of the *O*-dealkylated structures shown in which iodide was "trapped" in the thermolysis product.

The quinolines and isoquinolines needed for this mass spectral study were assembled using literature methods. In Scheme IV is shown the modified Pomeranz-Fritsch synthesis [5] which was employed for the synthesis of 7-methoxyisoquinoline (**7a**) and 6,7-methylenedioxyisoquinoline (**7c**). We found that 6-methoxyisoquinoline (**7b**) could not be prepared using this method. Dimethoxyacetal **6b** gave 4-methyl-*N*-[(4-methoxyphenyl)methyl]benzenesulfonamide (**8**) on treatment with hydrochloric acid in dioxane, rather than isoquinoline **7b**. Compound **8** has previously been isolated [5] on attempted conversion of **6b** to **7b**. Likewise, Schiff base **4b**, which is the classical Pomeranz-

Scheme III

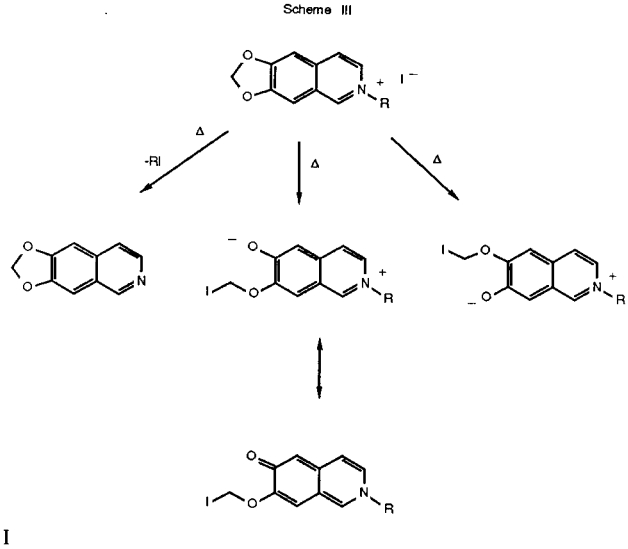
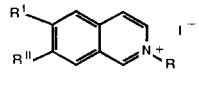


Table I

Physical Constants for Alkoxy 2-Alkylisoquinolinium Iodides

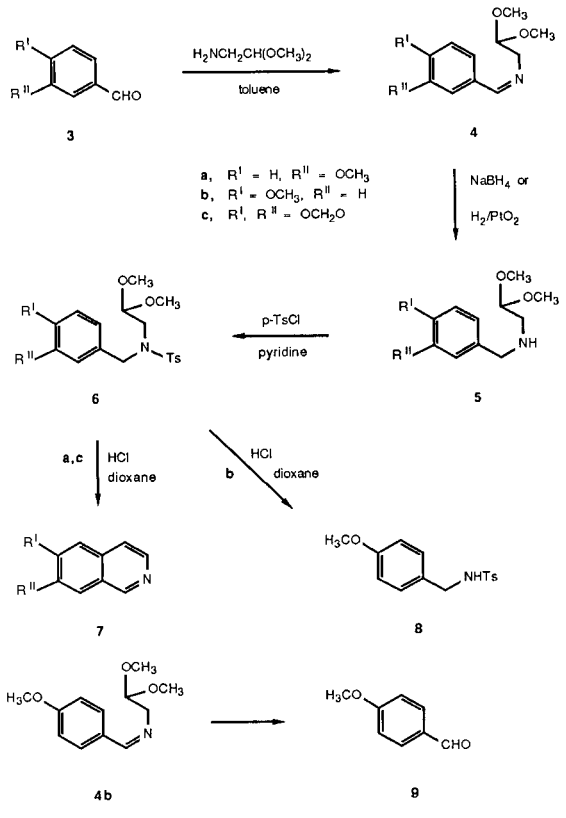


Compound	R	R′	R″	mp (°C)	Yield (%) [a]	Formula	Calcd. (%) C	H	N	Found (%) C	H	N
15	Et	MeO	H	160-161.5	72	$C_{12}H_{14}INO$	45.73	4.48	4.44	45.85	4.51	4.52
16	*n*-Pr	MeO	H	125-127	79	$C_{13}H_{16}INO$	47.43	4.90	4.26	47.39	4.91	4.07
17	Et	H	MeO	178.5-179.5	74	$C_{12}H_{14}INO$	45.73	4.48	4.44	45.47	4.36	4.29
18	*n*-Pr	H	MeO	114-117	72	$C_{13}H_{16}INO$	47.43	4.90	4.26	47.25	4.91	4.04
19	Et	-OCH_2O-		230-232	25	$C_{12}H_{12}INO_2$	43.79	3.68	4.26	43.76	3.73	4.33
20	*n*-Pr	-OCH_2O-		138-141	34	$C_{13}H_{14}INO_2$	45.50	4.11	4.08	45.35	4.10	4.04

[a] Yields reflect analytically pure material. All compounds were recrystallized from ethanol-ether.

Fritsch intermediate, gave only 4-methoxybenzaldehyde (**9**) on treatment with polyphosphoric acid (PPA). This result is also not surprising, in view of other attempted cyclizations of **4b** to **7b** which have failed [6].

Scheme IV



Another established method for preparing isoquinolines, which we considered for **7b**, was the Bischler-Napieralski reaction [7]. Although the 3,4-dihydroisoquinolines produced by this reaction are, in general, easily dehydrogenated to isoquinolines [8], no yields were reported for the preparation of 3,4-dihydro-**7b** using this method [9]. The Pictet-Spengler [10] reaction has been used to prepare 1,2,3,4-tetrahydro-**7b**, reportedly in 80% yield [11]. However, oxidation of tetrahydroisoquinolines to quinolines is apparently not general.

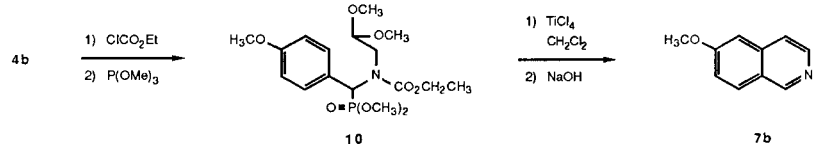
Although many additional methods are available for the synthesis of isoquinolines [12], we were intrigued with a recent report by Hendrickson and Rodriguez [13] in which they prepared carbamate phosphonate **10** (Scheme V) from **4b** by successive treatment with ethyl chloroformate and titanium tetrachloride. The phosphonate functionality in **10** apparently activates the benzene ring for cyclization, perhaps *via* the enol of the phosphonate. This proved to be an efficient method for preparing **7b**, although our yields were not as high as reported.

We employed the Skraup synthesis [14,15,16] for the preparation of 7-methoxyquinoline (**12**), as shown in Scheme VI. The resulting 4:1 mixture of **12** and **13**, respectively, was efficiently separated using silica gel flash chromatography (1:1::hexane:ethyl acetate). 7-Methoxyquinoline (**12**) is also accessible from the flash vacuum pyrolysis of the *O*-methyl oxime of *p*-methoxycinnamaldehyde [17]. 6-Methoxyquinoline (**14**), the other quinoline needed for our study, was commercially available.

The alkoxyisoquinolines and alkoxyquinolines were quaternized with ethyl and propyl iodides. Physical constants for these quaternary compounds are displayed in Tables I and II.

In Table III are shown the results of our mass spectral study. The iodide salts of our quinolines and isoquinolines were volatilized from a direct exposure probe (DEP) wire in the mass spectrometer operating in the electron impact mode and the major fragments of the decomposition pro-

SCHEME V



Scheme VI

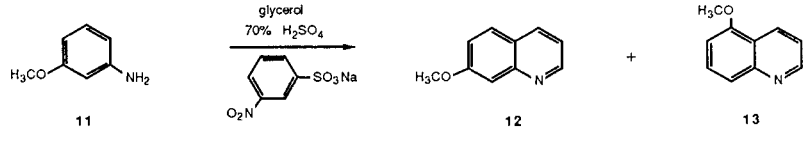
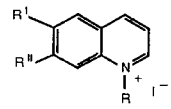


Table II

Physical Constants for Alkoxy 1-Alkylquinolinium Iodides



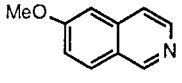
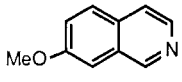
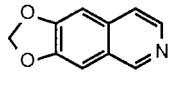
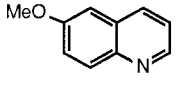
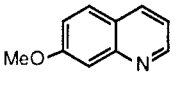
Compound	R	R′	R″	mp (°C)	Yield (%) [a]	Formula	Calcd. (%) C	H	N	Found (%) C	H	N
21	Et	MeO	H	182-183	31 [b]	$C_{12}H_{14}INO$	45.73	4.48	4.44	45.62	4.57	4.34
22	*n*-Pr	MeO	H	115-116	21 [b]	$C_{13}H_{16}INO$	47.43	4.90	4.26	47.20	4.98	4.17
23	Et	H	MeO	161-163	51 [c]	$C_{12}H_{14}INO$	45.73	4.48	4.44	45.81	4.51	4.56
24	*n*-Pr	H	MeO	194.5-196.5	40 [c]	$C_{13}H_{16}INO$	47.43	4.90	4.26	47.52	4.93	4.10

[a] Yields reflect analytically pure material. [b] Recrystallized from 2-propanol-ether. [c] Recrystallized from ethanol-ether.

ducts are listed as percentages of the base peak, including fragments derived from *O*- and *N*-dealkylation. Also listed is the ratio of *O*-dealkylation to *N*-dealkylation (M^+-Me over M^+-R). Our prediction, for the isoquinolinium iodides, was that the ratio of *O*- to *N*-dealkylation would be *greater* for the 6-methoxy compounds than for the 7-methoxy compounds. This prediction was borne out with compounds **15-18**. The ratio of 2.3 for **15** is greater than that of 0.54 for **17**, and the ratio of 0.75 for **16** is greater than that of 0.21 for **18**.

Table III.

Summary of Major Mass Spectral Fragments of Methoxyisoquinolinium and Methoxyquinolinium Iodides

Structure	No.	R	MeI $^+$ (%)	RI $^+$ (%)	Mass Spectral Fragments [a] M^+ (%) [b]	M^+ - - Me (%)	M^+ - - R(%)	Ratio $\frac{M^+ - \cdot Me}{M^+ - \cdot R}$
	**15**	Et	100 ±0	5 ±2	1 ±0	14 ±7	6 ±1	2.3
	16	*n*-Pr	100 ±0	4 ±3	1 ±0	9 ±3	12 ±2	0.75
	**17**	Et	92 ±11	69 ±7	11 ±1	35 ±3	65 ±8	0.54
	18	*n*-Pr	100 ±0	22 ±3	16 ±2	18 ±1	84 ±12	0.21
	**19**	Et	-	88 ±9	2 ±1	-	100 ±0	-
	20	*n*-Pr	-	46 ±11	2 ±1	-	100 ±0	-
	**21**	Et	95 ±5	88 ±5	30 ±3	22 ±4	78 ±3	0.28
	22	*n*-Pr	100 ±0	32 ±3	29 ±5	7 ±1	75 ±18	0.09
	**23**	Et	100 ±0	8 ±2	4 ±1	27 ±6	7 ±1	3.9
	24	*n*-Pr	100 ±0	4 ±1	1 ±0	40 ±9	9 ±1	4.4

[a] All values are listed in percent of the base peak ± standard deviation. Values listed are the means of five separate determinations. [b] The M^+ ions in this table are the alkyl isoquinolinium and quinolinium ions without associated iodide.

O-Dealkylations of **19** and **20** would have given ions corresponding to $M^+ + I$, which were not seen. Thus, we were not able to trap iodide in the thermolyses of the methylenedioxy compounds; only *N*-dealkylation was observed.

In the case of methoxyquinolinium iodides **21-24**, our prediction was that the ratio of *O*- to *N*-dealkylation would be *greater* for the 7-methoxy compounds than for the 6-methoxy compounds. This prediction was realized as well, since the ratios for compound pairs **21** and **23** were 0.28 and 3.9, respectively, and 0.09 and 4.4 for **22** and **24**, respectively.

Thus, we have shown that in both the methoxyisoquinolinium and methoxyquinolinium iodides, the ratio of thermal *O*- to *N*-dealkylation depends on the potential for resonance-stabilization of the *O*-dealkylated species. This suggests that the transition states for the observed displacement reactions have product character, and when the product is resonance-stabilized, the transition state energies are correspondingly lowered. Consequently, the activation energies for the dealkylations leading to resonance-stabilized products are probably lower than for those which do not.

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded with Perkin-Elmer Model 727B and Model 1310 spectrophotometers, nmr spectra with Perkin-Elmer R-32 (90 MHz), Varian EM-360A and Varian XL-300 (multinuclear probe) spectrometers, and mass spectra with a Finnigan Model 4500 (electron impact and chemical ionization) mass spectrometer. The mass spectra of the iodide salts in Table III were recorded in the electron impact mode at 70 eV with an ion source temperature of 150°. Samples were introduced by deposition (*ca.* 600 ng) on a DEP wire, and volatilized by heating the substrate wire at a rate of 50 milliamps per second.

Materials.

7-Methoxyisoquinoline (**7a**) and 1,3-dioxolo[4,5-*g*]isoquinoline (**7c**) were prepared from *m*-anisidine (**3a**) and piperonal (**3c**), respectively, by the modified Pomeranz-Fritsch procedure of Birch, Jackson and Shannon [5]. 6-Methoxyisoquinoline (**7b**) was prepared from *p*-anisaldehyde (**3b**) by the procedure of Hendrickson and Rodriguez [13]. 7-Methoxyquinoline (**12**) was prepared from *m*-anisidine (**11**) by the Skraup synthesis [14,15,16]. 6-Methoxyquinoline (**14**) was purchased from Aldrich Chemical Company, Inc.

General Procedure for the Preparation of Alkyl Isoquinolinium and Quinolinium Iodides.

A solution of 30 mmoles of the isoquinoline or quinoline and 60 mmoles of the alkyl iodide in 50 ml of toluene was heated at reflux for a period of time ranging from 45 minutes to 22 hours. The mixture was cooled and the solid was collected and recrystallized. Melting points, recrystallization solvents, percent yields and combustion analytical data for alkyl isoquinolinium iodides **15-20** are listed in Table I. In Table II is listed corresponding data for alkyl quinolinium iodides **21-24**. The ^1H nmr spectra were recorded for all of the iodide salts and were in complete agreement with structure.

4-Methyl-*N*-[(4-methoxyphenyl)methyl]benzenesulfonamide (**8**).

To a solution of 11.0 g (29.0 mmoles) of **6b** in 100 ml of dioxane was added 30 ml of 5*N* hydrochloric acid and the dark solution was heated at reflux for 6 hours under a nitrogen atmosphere in the absence of light. The solution was concentrated, diluted with water and basified with 35 ml of 5*N* sodium hydroxide. The mixture was extracted with methylene chloride, and the extracts were dried (sodium sulfate) and concentrated to leave 7.75 g of dark oil. An ether extraction of this oil removed, after concentration, 4.84 g of purified oil, which was triturated with toluene to give 1.18 g (14%) of pure **8** as a white solid, mp 121-123° (lit [5] mp 115-116°); nmr (dimethylsulfoxide-d_6): δ 7.91 (t, J = 6.5 Hz, 1H, NH, deuterium oxide-exchangeable), 7.50 (dd, 4H, aromatic), 6.98 (dd, 4H, aromatic), 3.88 (d, J = 6.5 Hz, 2H, CH_2, collapses to a singlet upon addition of deuterium oxide), 3.68 (s, 3H, OCH_3), 2.38 (s, 3H, $ArCH_3$); ms: (70 eV, electron impact) m/e 291 (molecular ion).

REFERENCES AND NOTES

[1] R. Salsmans and G. van Binst, *Org. Mass Spectrom.*, **8**, 357 (1974).

[2] O. P. Sheichenko and O. N. Tolkachev, *Khim. Prir. Soedin.*, 676 (1979); *Chem. Abstr.*, **94**, 157124g (1981).

[3] Resonance-stabilized anionic and cationic structures for 6-hydroxyisoquinoline, analogous to those shown for our *O*-dealkylated species in Scheme I, have been postulated to explain the differences in its ultraviolet spectra as compared to other hydroxyisoquinolines [4].

[4] K. Nakanishi, M. Ohashi, S. Kumasaki and H. Koike, *Bull. Chem. Soc. Japan*, **34**, 533 (1961).

[5] A. J. Birch, A. H. Jackson and P. V. R. Shannon, *J. Chem. Soc., Perkin Trans. 1*, 2185 (1974).

[6] W. J. Gensler, *Org. React.*, **6**, 191 (1951).

[7] W. M. Whaley and T. R. Govindachari, *Org. React.*, **6**, 74 (1951).

[8] F. W. Fowler in "Comprehensive Heterocyclic Chemistry", **2**, A. J. Boulton and A. McKillop, eds, Pergamon Press, New York, NY, 1984, p 411.

[9] Reference 5, p 105.

[10] W. M. Whaley and T. R. Govindachari, *Org. React.*, **6**, 151 (1951).

[11] Reference 8, p 175.

[12] T. Kametani and K. Fukumoto in "Heterocyclic Compounds", **38**, Part 1, G. Grethe, ed, John Wiley and Sons, New York, NY, 1981, pp 139-274.

[13] J. B. Hendrickson and C. Rodriguez, *J. Org. Chem.*, **48**, 3344 (1983).

[14] T. J. Elliot and F. M. Rowe, *J. Chem. Soc.*, 437 (1935).

[15] M. H. Palmer, *J. Chem. Soc.*, 3645 (1962).

[16] D. M. Clugston and D. B. MacLean, *Can. J. Chem.*, **44**, 781 (1966).

[17] C. L. Hickson and H. McNab, *J. Chem. Soc., Perkin Trans. 1*, 1569 (1984).