ACID DEUTERIUM EXCHANGE IN METHOXYQUINOLINES AND THEIR N-OXIDES

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Kinetic studies of acid deuterium exchange have been carried out for a series of isomeric 6-, 7-, and 8-methoxyquinolines and their N-oxides, in comparison with the analogous carbocyclic compounds. It has been found that methoxyquinolines are deuterated in the N-protonated form, whereas the N-oxides are reactive in their neutral forms. In full agreement with data for the reactivity of these heterocycles in nitration, quantum chemical calculations show that in exchange in 6-methoxyquinoline and its N-oxide the preferred site for electrophilic attack is the 5-position, and in the 7-isomers the 8-position is preferred. The rate is lower in the 8-isomer, owing to the presence in the latter of intramolecular hydrogen bonding. The probable structure of the transition state in the reaction is discussed.

In studying the reactivity of bicyclic heteroaromatic compounds, it is useful to have available information on the rates of the simplest, least sterically hindered electrophilic substitution reactions, namely acid-catalyzed protium–deuterium exchange of hydrogen atoms directly bonded to the heteroaromatic ring (H–D exchange). In this connection, in order to establish those factors which determine reactivity it is important that all the kinetic data be obtained under comparable conditions, and can be considered in terms of a single reaction sequence. However, at the present time comparisons of the rates of H–D exchange in the types of compounds of interest to us (quinolines and their derivatives) with their carbocyclic analogs (naphthalene and its derivatives) are virtually impossible as a result of the lack of standardization in the determination of $\log K_D$ values (the logarithm of the H–D exchange rate). In fact, nitrogeneous heterocycles are capable of undergoing replacement of hydrogen by deuterium in the heteroaromatic ring only under severe conditions (150-180°C, reaction medium concentrated sulfuric acid [1-4]), whereas H–D exchange in most carbocyclic aromatic compounds (naphthalene and its derivatives [5, 6] and complex condensed structures [7]) takes place at a conveniently measurable rate in comparatively mild proton-donor media (anhydrous CF_3COOH, a moderately strong acid, or CF_3COOH with the addition of either CH_3COOH, aqueous H_2SO_4, or aqueous $HClO_4$), and at lower temperatures (0-70°C).

Consideration of currently accepted concepts of the mechanism of acid H–D exchange suggests that this reaction should take place in nitrogeneous bicycles in the absence of concentrated sulfuric acid, if an electron-donor substituent [CH_3, Cl, OCH_3, $N(CH_3)_2$] is introduced into the benzene ring of the molecule (positions 5-8). Such a substituent, in creating excess electron density at the ortho- and para-carbon atoms, should facilitate H–D exchange in comparison with the unsubstituted compounds. We found in preliminary experiments that when CF_3COOD with the addition of the strong acid $DClO_4$ was used as the reaction medium, the activating effects of CH_3 and Cl were insufficient to confer any appreciable activity on any of the positions in the heteroaromatic nucleus. For example, 6-methyl, 5-chloro-, and 6-chloroquinolines, dissolved in the system 92% CF_3COOD–25% $DClO_4$–5.5% D_2O, did not undergo H–D exchange even after keeping for 8-10 h at 200°C. In contrast, the introduction of such a powerful π-donor as the methoxy group into the 6-, 7-, or 8-position of the quinoline ring results in an adequate activating effect, since the reaction of the isomeric methoxyquinolines and their N-oxides takes place at a measurable rate in the temperature range 60-180°C.

The object of the present study was to obtain kinetic data for H–D exchange as a measure of the relative reactivities of the different positions of the heteroaromatic ring in isomeric methoxyquinolines and their N-oxides under conditions suitable for the measurement of differ-

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TABLE 1. Results of Experiments on Acid H–D Exchange in Methoxyquinolines

Compound*	T, °C	Time, h	Distribution of deuterium, %		$\sum_i d_i$, %	$K_D \cdot 10^5$,† sec^{-1}
			d_0	$d_1(d_2)$		
I	140	8	63,8	36,2	36,2	2,1
	140	20	40,1	59,9	59,9	1,9
	160	2	67,6	32,4	32,4	7,2
	160	6	41,6	58,4	58,4	6,2
	180	1	61,8	38,2	38,2	18
	180	2	40,0	60,0	60,0	19
	180	3	32,5	67,5	67,5	17
III	140	4	78,9	21,1	21,1	2,1
	140	6	73,3	26,7	26,7	1,9
	160	2	72,6	27,4	27,4	5,8
	160	3	61,1	38,9	38,9	6,2
	180	1	60,5	39,5	39,5	19
	180	2	39,9	60,1	60,1	19
	180	3	37,4	62,6	62,6	14
V	160	6	88,5	11,5	5,85	0,42
	160	9	81,2	18,8	10,2	0,38
	160	12	79,2	20,8	9,45	0,32
	180	9	80,0	19,0 (1,0)	10,4	0,48
	180	12	74,8	25,2	12,6	0,44
	200	4	21,4	62,8 (15,8)	47,2	7,1
	200	6	21,5	62,1 (16,3)	47,7	4,9

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*For compounds (I) and (III), the $\sum_i d_i$ and K_D values refer to a single exchangeable atom in the molecule, and for (V) the value K_D refers to two exchangeable atoms (see text).

†In calculating K_D from the first-order equation, the equilibrium concentration of deuterium (~80 at.%) was taken into account.

TABLE 2. Results of Experiments on Acid H–D Exchange in Methoxyquinoline

Compound	T, °C	Time, h	Deuterium distribution, %		$K_D \cdot 10^5$*, sec^{-1}
			d_0	d_1	
II	90	8	78,9	21,1	1,1
	90	12	72,8	27,2	1,1
	105	4	63,3	36,7	4,3
	105	6	51,8	48,2	4,3
	120	1	59,2	40,8	20
	120	2	42,1	57,9	18
	120	3	32,9	67,1	17
IV	90	6	83,1	16,9	1,1
	95	4	70,6	29,4	3,2
	95	6	66,2	33,8	2,5
	110	2	61,2	38,8	9,2
	110	6	37,6	62,4	7,0
	120	1	48,2	51,8	29
	120	2	34,8	65,2	23
VI	180	12	75,2	24,8	0,85
	180	18	62,1	37,9	0,90
	200	4	74,5	25,5	2,7
	200	6	64,0	36,0	2,8

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*Values of K_D refer to a single exchangeable atom.

ences in reactivity in comparison with the analogous carbocyclic compounds. A wider range of quinolines and their N-oxides was used here than in the only previously-published study [3]. In addition to the previously-studied [3] 6-methoxyquinoline (I), there were included 6-methoxyquinoline N-oxide (II), 7-methoxyquinoline (III) and its N-oxide (IV), 8-methoxyquinoline (V), and 4-methoxyquinoline N-oxide (VI).

The experimental conditions and results are shown in Tables 1 and 2. The rate constant calculated from the first order equation (K_D) was taken as a measure of reactivity.

TABLE 3. Results of Calculations of Reactivity Indices for H–D Exchange in Methoxyquinolines (PPDP/2 method)

Compound	Atom No.	Localization energy, eV		π-electron charges on atoms, e		(at $-\lg K_{180°}$)
		neutral molecule	N-protonated form	neutral molecule	N-protonated form	
I	3		7,1563	+0,0027	−0,0362	
	5	**14,1315**	**8,6962**	**−0,0558**	−0,0195	3,74
	7	13,2500	7,7163	−0,0253	+0,0690	
	8	13,7143	8,1503	−0,0039	**−0,0483**	
III	3		7,5603	−0,0278	−0,0683	
	5		7,7246	+0,0255	+0,0742	
	6	13,0360	8,3686	−0,0469	−0,0259	
	8	**13,7688**	**8,7197**	**−0,0854**	**−0,1262**	3,77
V	3		7,3282		**−0,0536**	
	5		8,5719		+0,0145	5,28
	6		8,0638		+0,0379	
	7		8,1323		+0,0405	

In order to explain the differences in reactivity in H–D exchange in (I-VI), in parallel with the experimental work model quantum chemical calculations were carried out for the neutral molecules and for the nitrogen-protonated heterocyclic bases, and for all the possible C-protonated forms (calculations for the N-protonated heterocycles (I), (III), and (IV) were necessary since the reaction in question is carried out in a proton-donor solvent). The results of the PPDP/2 calculations are shown in Tables 3 and 4.

The following comments relating to the results obtained here are necessary:

1. If the temperature dependence of the H–D exchange rate constant is shown in the form of the Arrhenius equation, it is easy to calculate the activation energy ΔE_a and the activation energy $\Delta S^{\neq}$ for compounds (I)-(IV). The values of ΔE_a and $\Delta S^{\neq}$ calculated in this way are equal to: $\Delta E_a(\mathrm{I}) = 21.4$, $\Delta E_a(\mathrm{II}) = 26.4$, $\Delta E_a(\mathrm{III}) = 19.9$, $\Delta E_a(\mathrm{IV}) = 34.3$ kcal/mole $\Delta S^{\neq}(\mathrm{I}) = -30{,}8$ $\Delta S^{\neq}(\mathrm{II}) = -10{,}9$, $\Delta S^{\neq}(\mathrm{III}) = -33{,}8$, $\Delta S^{\neq}(\mathrm{IV}) = 9{,}9$ e.u.

In principle, entropy of activation may be used to determine the chemical form of the reacting species if the criteria given in [8] are employed, according to which the value of $\Delta S^{\neq}$ in the case of reactions of protonated molecules should be less than −20 eu, i.e., the theoretical value of $\Delta S^{\neq}$ for a chemical reaction involving two charged substrates. It will be seen that the entropy of activation for H–D exchange in the N-oxides (II) and (IV) correspond to the case of reaction of neutral molecules. The validity of this argument is to some extent confirmed by the results reported in [3, 4], obtained from a study of the changes in the rate constant of H–D exchange in (I) as a function H_0 of the acidity of the medium (medium aqueous sulfuric acid, function H_0 varied from 0.3 to 0.8).

It is interesting to compare the above conclusions as to the nature of the reacting species with literature information for a typical electrophilic substitution reaction, namely the nitration of quinoline and its N-oxide [9]. It follows from Tables 1 and 2 that H–D exchange in the N-oxides (II) and (IV) takes place 40-50 times faster than the same reaction in the similarly substituted quinolinium salts (I) and (III). In contrast to this, the rate constant for the nitration of quinoline N-oxide is less than in the case of the quinolinium cation ($0.78 \cdot 10^4$ and $1.67 \cdot 10^4$ liter•mole•sec^{-1}, respectively [9]. It is evident that nitration differs from H–D exchange in that quinoline N-oxide takes part in the first reaction in its protonated form, the NOH^+ group here functioning as a stronger deactivating electron-acceptor than the NH^+ group in the quinolinium cation.

2. As noted above, the H–D exchange reaction was carried out between a "light" substrate and a mixture of deuterated acids, D_2SO_4 and 70% $DClO_4$ ("direct" H–D exchange). Since neither ^{1}H NMR nor IR spectroscopy gave unambiguous information on the sites of entry of deuterium into the condensed benzene ring, the directivity of isotope exchange was deduced indirectly. Firstly, it was found that the value of the H–D exchange rate constant (K_D) in compounds (I-IV) did not change even when the extent of exchange was greatly increased (Tables 1 and 2). This indicated that the reactivities of the different positions in the heteroaromatic ring were markedly different.

TABLE 4. Results of Calculations of Reactivity Indices for H—D Exchange in Methoxyquinoline N-Oxides (PPDP/2 method)

Compound	Atom No.	Localization energy, eV	π-Electron charges on atoms, e	$-\lg K_D$ (at 120°)
II	2	**14,0800**	**−0,1348**	
	4	**14,1200**	−0,0772	
	5	13,5827	−0,0877	3,92
	7	12,9140	−0,0480	
	8	12,6262	+0,0341	
IV	2	**14,6093**	**−0,1164**	
	4	13,1417	+0,0260	
	5	13,7500	−0,0026	
	6	13,1349	−0,0124	
	8	**14,0251**	−0,0458	3,66
VI	2	13,8610	**−0,0973**	
	3	12,7943	−0,0241	
	5	13,0875	−0,0104	6,5*
	8	12,8519	+0,0071	

*Approximate value, calculated from kinetic data at 180° and 200°C.

The selective nature of isotope exchange was supported by the appearance in the low-voltage mass spectra of strong peaks for the molecular ions, with m/z 160 (Tables 1 and 2).* Bearing in mind that these peaks are 1 amu greater than the low-intensity peaks for the non-deuterated ions, it may be concluded that the hydrogen atoms in all the positions in molecules (I)-(IV) save one are virtually non-enriched with deuterium, under conditions in which H—D exchange at one position has proceeded sufficiently far.

The partial rate factors for the individual positions in the heteroaromatic nucleus are comparable with each other in their π-electron charges on the carbon atoms q_π (C_i) ("static" factor) and electron delocalization energies L_e (C_i) ("dynamic" factor).

In the majority of calculations for (I) and (III), both theoretical measures of reactivity lead to the same predictions as to the sites of electrophilic attack (Table 3). An exception is the cation of (I), in which, notwithstanding the values of L_e the atom in the 5-position of the heteroaromatic nucleus, $C_{(5)}$ possesses greater π-electron density than $C_{(3)}$. Since, in assessing relative reactivities in aromatic substitution it is more correct to use localization energies, it may be said that in (I), H—D exchange involves the atom in the 5-position, whereas in (III) by far the greater part of the deuterium entering the molecule should be found in the 8-position. This conclusion is in full agreement with the orientations found for "elementary" electrophilic substitution reactions, since irrespective of its actual nature the electron-donor substituent in the condensed benzene ring in quinoline (positions 6 or 7) invariably directs electrophilic reagents to positions 5 or 8 adjacent ot the existing substituents [10]. The fact that the reactivity of the 5-position in (I) is much greater than those of positions 7 and 8 is supported by studies of the kinetics of the "inverse" exchange (protodedeuterization) of (I) in sulfuric acid solution [3].

An unexpected finding is that in H—D exchange in the N-oxides (II) and (IV), according to calculations of their L_e and q_π values the most reactive positions should be 2- and 4- in the heteroaromatic ring (Table 4). This finding can be scarcely be regarded as in accordance with fact, since in unsubstituted quinoline N-oxide and in some of its methoxy-derivatives qualitative studies of the relative reactivities of different positions in these compounds towards electrophilic substitution have shown that the methoxy-group has more powerful orienting effect than the N-oxide grouping, and reaction therefore takes place in the ortho-position to the methoxy-group [10].

In all probability, these inadequacies in the quantum-chemical approach are due to deficiencies in the PPDP/2 method of calculation, in which the interelectron repulsion integrals with p-functions are replaced by integrals with spherically symmetrical s-functions. If this artefact of the method is ignored, then it is found to give a completely realistic assessment

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*In the N-oxides of the heterocycles studied here, electron impact results in cleavage of oxygen from the heteroaromatic NO grouping with the formation of a molecular fragment with m/z 159, the peak for which is greatest in the spectra of nondeuterated samples.

of the relative reactivities of the different positions in the carbocyclic moiety of the N-oxide ring. As in the case of the corresponding unoxidized heterocycles (I) and (III), when a methoxy-group is present in the 6-position (compound II), according to calculations of the values of L_e and q_π H–D exchange takes place preferentially in the 5-position $[q_\pi(C_{(5)}) > q_\pi(C_{(7)}) > q_\pi(C_{(8)}); L_e(C_{(5)}) > L_e(C_{(7)}) > L_e(C_{(8)})]$, and when this group is in the 7-position (compound (IV), replacement in the 8-position predominantes $[q_\pi(C_{(8)}) > q_\pi(C_{(6)}) > q_\pi(C_{(5)}); L_e(C_{(8)}) > L_e(C_{(6)}) > L_e(C_{(5)})]$.

3. The relatively high positional selectivity shown by the H–D exchange reaction in (I-IV) is not seen in this reaction in (V). Indeed, in contrast to the mass spectra of (I-IV), in which the greatest peak is for the ion with m/z 160 corresponding to the monodeuterated form, the spectrum of (V) following extensive H–D exchange (200°C) shows not only an ion with m/z 160, but also an ion with m/z 161, the relative intensities of these peaks corresponding to randomization of the deuterium atoms between two positions in the heteroaromatic nucleus (Table 1).

These considerations are supported by literature reports of the regiospecificity of electrophilic substitution reactions in 8-hydroxy- and 8-methoxyquinolines. Previous studies [10] of the orientation of the incoming reagent in electrophilic attack were carried out using as an example the nitration of 8-hydroxyquinoline in strongly acidic media (mixture with concentrated sulfuric acid). No mono-nitro-compounds could be isolated from the products, only 5,7-dinitro-8-hydroxyquinoline being formed. Other electrophilic substitution reactions which have been described include halogenation, sulfonation, and nitrosation, which take place primarily in the 5-position of the quinoline nucleus, more severe conditions leading to the formation of the 5,7-disubstituted derivatives [10]. These findings suggest that in (V) also in H–D exchange under acidic conditions two positions will potentially be the most reactive, namely 5 and 7. This assumption is in qualitative agreement with the predictive calculations of the localization energy L_e indicating preferential isotope exchange in the 5-position (as will be seen from Table 3, the values of L_e in the formation of the σ-complex of the cation of (V) with a proton increase in the sequence $6 \leq 7 < 5$). Furtherfore, in this case there is no correspondence between the "dynamic" and "static" reactivity indices. According to MO calculations, the greatest π-electron density will be found at the atoms in positions 3 and 5.

If one adheres to the view that the course of electrophilic attack is determined by the reversible and limiting step of formation of a σ-complex, then from what has been said it may be concluded that the π-electron charges on the carbon atoms in (V) do not determine their relative reactivities, redistribution of electron density and the consequent resonance stabilization of the σ-complex in all likelihood having the greatest influence on changes in free energy of activation in the H–D exchange reaction in (V).

4. Evaluations of comparative reactivity in this series of isomeric methoxyquinolines from the localization energies at the most reactive carbon atom [$C_{(5)}$ in (I) and (V), and $C_{(8)}$ in (III)] show that the rate of H–D exchange in the 6- and 7-isomers should be similar in magnitude, but the relative reactivity of both heterocycles should be greater than that of the 8-isomer. Experiment has shown that the rate of H–D exchange in (I) differs little from that in (III) (at 160°C, $K_D = (6\text{-}7)\cdot 10^{5}$ sec^{-1}), whereas the rate of this reaction with the isomer (V) is 15 times slower (at 160°C, $K_D = 0.35\cdot 10^{-5}$ sec^{-1}).

The decrease in the H–D exchange rate constant in the (V) cation may be explained by steric interactions. The heteroatomic NH^+ grouping in the peri-position to the methoxy-substituent creates a barrier to pπ-conjugation of the latter with delocalized ring π-electrons in consequence of the formation of a strong intramolecular hydrogen bond between the oxygen and cyclic nitrogen atoms. The occurrence of such interaction has been shown in spectral studies of pK_{NH^+} values in a series of isomeric methoxyquinolines [11].

5. Although it is not possible from the results presented here to determine precisely the ratios of the rates of H–D exchange at each ortho-position to the methoxy-group in single molecules of (II-V;, we estimate it to be quite high, amounting to several $\log K_D$ units (see section 2). This confirms the hypothesis that the fixation of the double bonds in the quinoline ring is responsible for its chemical behavior [12]. The great differences in the reactivities of the α- and β-positions of the ring in (I-IV) is in general agreement with literature information on the orienting effect of the methoxy-substituent in acid T–H exchange (protodetritiation) in a carbocyclic analog of the heterocycles studied here, namely 2-methoxynaphthalene-α-T_1 and -β-T_1 (VII). It was found that the rates of T–H exchange in (VII) at the α- and β-positions were in the ratio $4\cdot 10^5:1$ (70°C, in anhydrous CF_3COOH [5]).

TABLE 5. Changes in the Rate Constant for the Acid H–D Exchange in Naphthalene and 2-Bromonapthalene with Respect to the Composition of the Reaction Medium

Compound	Temperature, °C	Reaction medium*	$K_D \cdot 10^5$, sec^{-1}	$-\lg K_D$ at 70°
VIII	70†	A	2,6	4,6
	40	B	2,2	
	50‡	B	7,2	3,1
IX	70	A	0,29	5,5
	70	B	9,2	4,1
X**	70	A	0,32	5,5
	40	B	0,62	
	50	B	2,3	(3,3)

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*A is anhydrous CF_3COOH, and B is 92% CF_3COOH + 2.5% $HClO_4$ + 5.5% H_2O.

†According to [5], in protodetritiation $K_T = 1.1 \cdot 10^{-5}$ sec^{-1}.

‡Approximate values for activation parameters, E_a = 25.3 kcal/mole, log A 13.0.

**"Direct" H–D exchange.

With respect to the construction of a general scale of electrophilic reactivities based on the values of the H–D exchange rate constants in heteroaromatic bicycles and π-isoelectronic systems without a heteroatom, it is necessary to bear in mind the difficulty due to the immeasurably fast introduction of deuterium into the 1-position of the napthalene ring in (VII) even when extremely small amounts of the strong acid $HClO_4$ (~0.001%) are added to the CF_3COOH (after 10 min at –20°C, one atom of hydrogen has been completely replaced by deuterium). In order to obtain kinetic data for the heterocycles (I-IV) and for (VII) (together with other substituted naphthalenes) in a single system, we had recourse to a factor describing the increase in the rate of H–D exchange when anhydrous CF_3COOH is replaced by CF_3COOH with added $CHlO_4$ and H_2O for related compounds of comparatively low reactivity, namely naphthalene-1-D_1 (VIII), naphthalene-2-D_1 (IX), and 2-bromonaphthalene (X). It was assumed that the conversion factor for the rates to conditions chosen for the reaction retained its numerical value, and was applicable to compound (VII).

It will be seen from Table 5, which gives a summary of the kinetic measurements in both reaction media, that acid H–D exchange in $CF_3COOD + DClO_4 + D_2O$ solution takes place 25-40 times more rapidly than in anhydrous CF_3COOD. Bearing in mind that the rate constant for "reverse" T–H exchange in (VII) is $K_T = 2 \cdot 10^1$ sec^{-1} at 70°C [5], we obtain the value $K_T \approx 6 \cdot 10^2$ sec^{-1} for a medium which differs from that employed in [5] by the presence of added aqueous $DClO_4$.

Table 6 presents kinetic data on H–D exchange in (I), (II) and (VII) in the form of comparable rate constants (70°C, medium $CF_3COOD + DClO_4 + D_2O$); also shown are the rate constants for the nitration of unsubstituted analogs of the compound under examination, namely naphthalene, quinoline, and quinoline N-oxide. It will be seen from Table 6 that the deactivating effects of the NH^+ and NOH^+ groups, shown by their "standard" nitration rate constants, although very high (Δ log K_D ~ 8.2-8.4) are nevertheless lower than in the H–D exchange reaction, in which it is $\Delta \log K_D$ ~ 9-6- This difference in the ranges of $\log K_D$ values may be explained as follows. The reactivity of the unsubstituted compounds is determined by the relative stability of the intermediate σ-complex, whereas that of (I) and (II) towards H–D exchange (reaction with more 'reactive' substrates) may be largely determined by electron density transfer in the transition state from the carbon atoms of the aromatic (heteroaromatic) ring to the lowest unoccupied orbital of the electrophile. This unusual mechanism for H–D exchange, involving as it does partial transfer of electron density, may be responsible for the lack of agreement between the increases in the rate constants for H–D exchange in the sequence $NH^+ < NO < CH$, and the predictions of MO calculations using the localization energy L_e as a measure of reactivity (Table 6).

6. In addition to the N-oxides (II) and (IV), which contain a methoxy group in the benzene moiety of the molecule, H–D exchange has been studied in the N-oxide (VI), in which direct conjugation between the methoxy group and the N-oxide group has a substantial effect on electrophilic reactivity. We regard support for this view as being provided by the fact that

TABLE 6. Logarithms of the Rate Constants for the Acid H–D Exchange and Nitration for Some Heteroaromatic Bicycles, and Calculated C-Protonation Energies

Compound	$\lg K_D$ (T 70°)	L_e*, eV	Compound	$\lg K_2$†
	H–D exchange		Nitration	
2-Methoxynaphthalene	2,8	13,8022	Naphthalene	1,85
6-Methoxyquinoline	−6,8	8,6962 (14,1315)	Quinoline	−6,36
6-Methoxyquinoline N-oxide	−6,5	13,5827	Quinoline N-oxide	−6,6

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*For 6-methoxyquinoline, L_e values for the cationic form of the heterocycle are given, with (in brackets) the unprotonated molecule.

†The logarithms of the "standard" nitration rate constants are given ($\log K_2$ at 25°C, and H 6.6 in aqueous sulfuric acid [13]).

the rate of H–D exchange in (VI) is at least 1000 times less than that in the most "reactive" sites in (II) and (IV) (Table 2). It will be seen from Table 2 that the height of the peak with m/z 160 corresponds to the presence of nearly 40% of the monodeuterated form in the mixture of isotopic modifications, more highly-deuterated forms being absent. This indicates that H–D exchange in (VI) is a selective reaction (at 200°C). We have at our disposal no data for the unambiguous location of the site of entry of the deuterium into the heteroaromatic ring in (VI). A definite argument for the assumption that the 3-position is more reactive than the 2- and remaining positions in the N-oxide ring in (VI) is provided by studies of the nitration of 4-hydroxyquinoline N-oxide, which have shown that the electrophile is preferentially oriented in the 3-position [10]. This finding is not in accordance with the preferential formation of 2- and 5-deuterated forms predicted from the L_e values.

More precise location of the site of entry of deuterium in the ring of (VI) will require further investigation.

EXPERIMENTAL

The mass spectra of the compounds were obtained on an MI-1309 instrument with direct introduction of the sample into the ion source, ionizing electron energy 12-18 eV, sample heated to 20-40°C (I, III-V) or 50-100°C (II, VI), emission current 0.4-0.5 mA.

Compounds (I), (III), and (V) were obtained by the methods reviewed in [14] (see also [15]), and (II), (IV), and (VI) as described in [16]. The H–D exchange reaction was carried out in sealed glass ampuls with metal sheathing. The thermostat accuracy was ±0.5°C. The ratio of number of moles of the acid CF_3COOD to the compound was 100-150. When the reaction was complete, the mixture was poured into a 5% solution of sodium bicarbonate, the product extracted with chloroform, the chloroform solution dried ($CaCO_3$), and the chloroform removed under reduced pressure. The energy of activation $\Delta S^{\neq}$, (eu) was calculated from the equation

$$\Delta S^{\neq} = 4{,}576 \lg (A/T) - 49.21.$$

In calculations for the neutral molecules and the cations by the PPDP/2 method, standard geometry was assumed [17]. The model chosen for the σ-complex was a molecular system in which the ring geometry remained unchanged, and the geminal angle (the site of proton addition) had the following geometric parameters: $r_{CH} = 1.08$ Å, $\angle HCH = 109°$, projection of the CH bonds on the plane of the ring coincident with the direction of the CH bonds in the original heterocycle. Calculations were carried out on a BÉSM-6 computer.

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α-PHENYLISOCINCHOMERONIC AND 4-AZAFLUORENONE 3-CARBOXYLIC ACIDS

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3,6-Dimethyl-6-phenylpyridine, obtained on phenylation of 2,5-lutidine, has been used in the synthesis of α-phenylisocinchomeronic acid, derivatives of it, and also for the preparation of 4-azafluorenone 3-carboxylic acid. It was established that 4-hydroxy-3,6-dimethyl-2-phenylpyridine was formed on phenylation of 2,5-lutidine.

Pyridine bases containing methyl and phenyl substituents in the ring seemed of interest for the preparation of phenyl substituted pyridine carboxylic acids and also of condensed heterocycles. Compounds of such type are the subject of numerous investigations carried out mainly with the aim of obtaining effective physiologically active compounds.

The initial subject of the present work was 3,6-dimethyl-2-phenylpyridine (I). Its preparation from the oxime 5-hydroxy-2-methyl-1-phenylhexa-1,3-diene has been described in [1], and also from 2,5-lutidine by a multistage synthesis in [2]. Various melting points were cited in these studies for the picrate of (I) base, viz., 179-180°C in [1] and 134-135°C in [2]. The data obtained by us corresponded to the second value.

Considering that the most convenient means of synthesizing 3-methyl-2-phenylpyridine (30% yield) is the phenylation of β-picoline from [3] we examined the possibility of obtaining pyridine (I) by this method. The reaction of 2,5-lutidine with phenyllithium was carried out on gentle boiling in ether. 3,6-Dimethyl-2-phenylpyridine (I), formed in 21% yield, was characterized as the picrate and iodomethylate. A special feature of its mass spectral fragmentation was the formation of a $[M - H]^+$ ion peak of maximum intensity which confirmed the presence of the phenyl substituent in the ortho position relative to the nitrogen atom. The presence in the mass spectrum of peaks with m/z 167 $[M - H - CH_3]^+$ and 152 $[M - H - CH_3 - CH_3]^+$ confirmed the presence of two methyl groups. The high intensity of the ion peak with m/z 167 indicated that a methyl group was found in the ortho position relative to the nitrogen atom.

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