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On the Synthesis and Basicity of 1,3-Diaminoisoquinolines

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Summary. A series of 6- and 7-substituted derivatives of 1,3-diaminoisoquinoline were synthesized by the reaction of *N*,*N*-diethylarylacetamides with $POCl_3$ and then with *N*,*N*-dimethylcyanamide. The products were identified by means of spectroscopic methods and their pK_a dissociation constants were determined.

Keywords. 1,3-Diaminoisoquinolines; UV/Vis spectroscopy; pK_a values.

Introduction

Compounds containing a fused isoquinoline ring represent a broad class of compounds which has received considerable attention over the past years due to their wide range of biological activities [1]. One of the subgroups are aminoisoquinolines. They are interesting due to the central-nervous-system activity shown by some members of this group [2]. Methods for the construction of 1-amino- or 3-aminoisoquinolines are rather limited. The most popular one is the nucleophilic displacement of the appropriate chloro derivatives of isoquinoline with amines [3]. The others involve the reaction of amines with 2-cyanobenzyl cyanide precursors, which are rather hard to obtain [4]. Earlier studies on the reactions of 2-aryl-1-alkylvinyl compounds with different nitriles have proved a possibility to synthesize a wide range of isoquinoline compounds. Such a method is very useful because it starts from easily accessible alkyl-aryl ketones and organic cyanides which allow to introduce different substituents in position 1. A few 3-methylisoquinolines substituted with electron donating or withdrawing groups have been obtained in this way [5–7].

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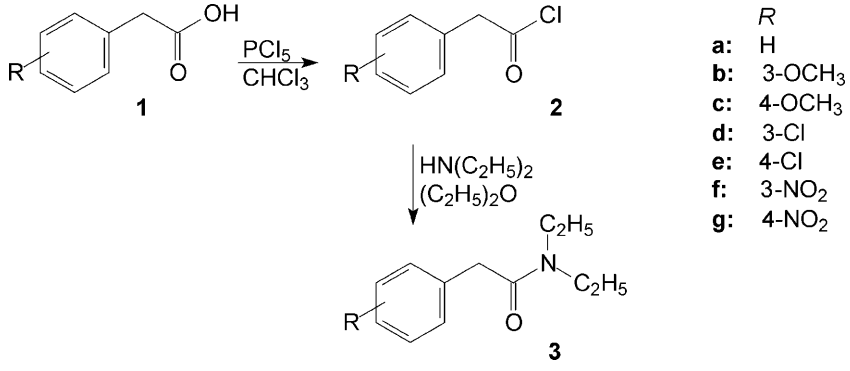
Results and Discussion

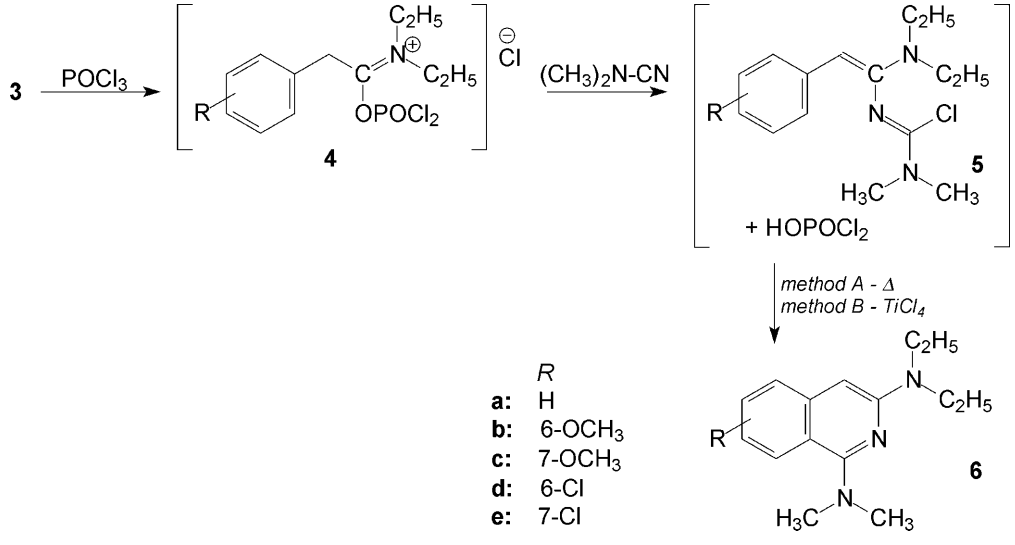
It was interesting to examine the use of *N*,*N*-diethylphenylacetamide derivatives instead of alkyl-aryl ketones as the intermediates in the synthesis of 1,3-diaminoisoquinolines. Tertiary amides had been applied earlier to the synthesis of 3-aminoisoquinolines [8], thus we thought that this method should be reasonable.

The *N*,*N*-diethylphenylacetamide derivatives **3a**–**3g** (Scheme 1) were prepared from the appropriate 3- or 4-substituted phenylacetic acids **1a**–**1g** in two steps. Phenylacetic acids **1** were reacted with PCl_5 in the first step forming arylacetic chlorides **2**. These products were then transformed into the corresponding *N*,*N*-diethylamides by the reaction with diethylamine under mild conditions. The new *N*,*N*-diethylphenylacetamides **3a**–**3g** were obtained in this way with good yields.

The *N*,*N*-diethylphenylacetamides **3** were heated with $POCl_3$ in anhydrous toluene to form diethylimmonium salts **4** (Scheme 2) [9]. These crude products were reacted with *N*,*N*-dimethylcyanamide in toluene producing formamidinium



Scheme 1

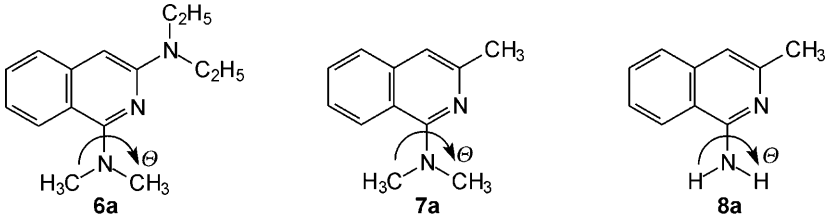


Scheme 2

salts [10] which after alkaline hydrolysis probably gave an acyclic product **5**, a derivative of 6-aryl-2-methyl-5-(*N*,*N*-diethylamino)-2,4-diaza-3,5-hexadiene [11]. This intermediate **5** underwent cyclization when heated for a few hours in toluene at elevated temperature. According to this, novel 6- and 7-substituted 1-(*N*,*N*-dimethylamino)-3-(*N*,*N*-diethylamino)-isoquinolines were synthesized (**6a**–**6e**, *method A*) with good yields (66–82%). Our investigation showed that an intramolecular cyclization of the 6-aryl-2-methyl-5-(*N*,*N*-diethylamino)-2,4-diaza-3,5-hexadiene derivative **5** took place only in the case of the activated compounds ($R = OCH_3$, H, Cl). The intermediates **5** with an electron-withdrawing group ($R = NO_2$) in position 3 or 4 did not react under these conditions. We also tried the activation of the formamidinium salts by the use of the *Lewis* acid catalyst $TiCl_4$ (*method B*) but the yields of **6a**–**6e** were only little higher (74–89%) in comparison to *method A*.

Considering the fact that a biological activity of compounds is also greatly dependent on their ability to acid–base interactions, the pK_a values of **6a**–**6e** were determined. The determination of the pK_a dissociation constants was performed according to the spectrophotometric method of *Albert* and *Serjeant* in 50% aqueous methanol solution (10^{-5} M, room temperature) [12]. The results show that electron-donating groups in positions 6 or 7 of the isoquinoline ring cause an increase compared with the pK_a of the parent compound **6a** ($R = H$); the opposite holds for electron-withdrawing groups.

Generally, 1-(*N*,*N*-dimethylamino)-isoquinolines are weaker bases than the corresponding 1-aminoisoquinolines [7]. It is quite complicated to interpret an interaction of substituents in *ortho* position since the equilibrium depends on field, induction, resonance, and steric effects [13]. The derivatives with dimethylamino substituents behave quite unexpectedly because of a considerable secondary steric effect, which is related to the interaction of bulky substituents in position 1 of isoquinoline with hydrogen in position 8. This interaction leads to a twist of the dimethylamino group in 1-position from the ring plane (**6a**, **7a**, Scheme 3), and consequently to a limitation of electron coupling. It is not observed for small substituents (**8a**) which are left untwisted in the ring plane. As a result, 3-methyl-1-(*N*,*N*-dimethylamino)-isoquinoline (**7a**) and 3-(*N*,*N*-diethylamino)-1-(*N*,*N*-dimethylamino)-isoquinoline (**6a**) are weaker bases than 1-amino-3-methyisoquinoline (**8a**) in spite of the fact that the $N(CH_3)_2$ group is a better electron donor than NH_2.



pK_a = 6.70
Θ = 110°

pK_a = 6.29
Θ = 73°

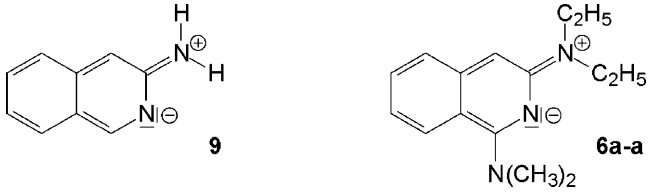
pK_a = 7.27
Θ = 11°

Scheme 3

Table 1. Dissociation constants pK_a of isoquinoline bases [14]

Entry	Isoquinoline	pK_a
1	isoquinoline[a]	5.42
2	1-aminoisoquinoline[a]	7.60
3	3-aminoisoquinoline[a]	5.23
4	3-methylisoquinoline[a]	5.64
5	3-amino-1-(*N*,*N*-dimethylamino)isoquinoline[b]	5.88 (6.29[c]–0.22[d]–0.19[e])

[a] The measurements were made in 50% methanol–water solution at room temperature; [b] the predicted value according to [16]; [c] dissociation constant pK_a for **7a**; [d] the introduction of CH_3 in 3-position {(4)–(1)}; [e] the introduction of NH_2 in 3-position {(3)–(1)}



Scheme 4

The replacement of the methyl group in position 3 of the isoquinoline with strongly electron-donating diethylamino group leads to unexpected changes in the basicity. It is known that two *ortho* isomers of aminoisoquinoline behave quite differently: 3-aminoisoquinoline is a considerably weaker base than 1-aminoisoquinoline (Table 1) [14]. This decrease in the base strength has been attributed to the lower contribution of the resonance structure **9** in the resonance hybride [15].

If such foundation holds the induction effect of the substituent in position 3 should be mainly responsible for the basicity. According to this **6a** should be less basic than **7a** because $N(C_2H_5)_2$ and CH_3 groups have opposite induction effects. *Brown* and *Kanner* have estimated the dissociation constants for 2,6-disubstituted pyridines on the basis of simple additivity [16]. The predicted and observed values are indeed similar for small substituents. If such a procedure is followed, the predicted pK_a value for 3-amino-1-(*N*,*N*-dimethylamino)-isoquinoline would be 5.88 (Table 1). The observed pK_a values for isoquinolines **6a**–**6e** (**6a**, $pK_a = 6.70$) indicate that the strongly electron-donating substituent in position 3 of isoquinoline behaves quite differently. The mesomeric effect ($+M$) of the dimethylamino group leads probably to a higher contribution of the structure **6a**–**a** in the resonance hybride and **6a** is a considerably stronger base than expected.

Experimental

UV spectra were recorded with a Shimadzu UV-2102 spectrophotometer; basic medium: 0.05 *M* NaOH in 50% aqueous methanol solution, acidic medium: 0.05 *M* HCl in 50% aqueous methanol solution. Absorption maxima of the isoquinoline ions (B band) were selected as analytical wave lengths. Elemental analyses were carried out using a Perkin Elmer 240c analyzer; they were in satisfactory agreement with the calculated values. ^{1}H-NMR spectra were recorded on a Varian Inova 300 spectrometer in $CDCl_3$ solution. MS were recorded on a Shimadzu QP-200 mass spectrometer.

Thin layer chromatography was carried out on silica gel 60 F_{254} (Merck) thin layer chromatography plates using a benzene–ethyl acetate–diethylamine mixture (6:2:1 $v/v/v$) as the mobile phase. Molecular geometries were optimized and twist angles Θ were calculated according to the MNDO method [17] by means of the WinMopac V2.0 program.

N,N-Diethylphenylacetamide Derivatives **3a–3g** *– General Procedure*

The substituted phenylacetic acid **1** (0.05 mol) was dissolved in 70 cm^3 anhydrous $CHCl_3$ and cooled down to 0°C. Then 10.5 g PCl_5 (0.05 mol) was gradually added followed by agitation. The mixture was refluxed for 10–16 h until the disappearance of the acid (TLC) was completed. $CHCl_3$ was removed using a rotary evaporator and the oily residue was distilled under vacuum. The arylacetic chloride **2** obtained in this way was dissolved in 50 cm^3 diethyl ether and this solution was added dropwise under agitation to a mixture of 10.4 cm^3 diethylamine (0.10 mol) and 50 cm^3 diethyl ether. After the dropping of arylacetic chloride was completed, agitation was continued for about 15 min. Then the precipitate was filtered off (diethylamine hydrochloride) and the solvent was evaporated. The crude yellowish oily **3** was distilled under vacuum.

N,N-Diethylphenylacetamide (**3a**, $C_{12}H_{17}NO$)

Yield 93.9%; bp 152–156°C/8 Torr; $R_f = 0.38$; ^{1}H NMR: $\delta = 1.06$ (t, $J = 7.2$ Hz, CH_2CH_3), 1.11 (t, $J = 7.2$ Hz, CH_2CH_3), 3.27 (q, $J = 7.2$ Hz, CH_2CH_3), 3.37 (q, $J = 7.2$ Hz, CH_2CH_3), 3.68 (s, CH_2-*Ph*), 7.20–7.26 (m, $5H_{ar}$) ppm; UV (*Me*OH): $\lambda_{max}\,(\varepsilon \cdot 10^{-3}) = 215\,(5.99)$ nm; MS: m/z (%) = 191 (M^+, 16).

3-Methoxy-N,N-diethylphenylacetamide (**3b**, $C_{13}H_{19}NO_2$)

Yield 82.7%; bp 206–208°C/23 Torr; $R_f = 0.32$; ^{1}H NMR: $\delta = 1.09$ (t, $J = 7.2$ Hz, CH_2CH_3), 1.12 (t, $J = 7.2$ Hz, CH_2CH_3), 3.29 (q, $J = 7.2$ Hz, CH_2CH_3), 3.39 (q, $J = 7.2$ Hz, CH_2CH_3), 3.67 (s, CH_2-*Ph*), 3.79 (s, OCH_3), 6.68–7.11 (m, $4H_{ar}$) ppm; MS: m/z (%) = 221 (M^+, 24).

4-Methoxy-N,N-diethylphenylacetamide (**3c**, $C_{13}H_{19}NO_2$)

Yield 76.5%; bp 194–196°C/9 Torr; $R_f = 0.16$; ^{1}H NMR: $\delta = 1.09$ (t, $J = 7.2$ Hz, CH_2CH_3), 1.11 (t, $J = 7.2$ Hz, CH_2CH_3), 3.29 (q, $J = 7.2$ Hz, CH_2CH_3), 3.37 (q, $J = 7.2$ Hz, CH_2CH_3), 3.56 (s, CH_2-*Ph*), 3.73 (s, OCH_3), 6.86–7.10 (m, $4H_{ar}$) ppm; MS: m/z (%) = 221 (M^+, 26).

3-Chloro-N,N-diethylphenylacetamide (**3d**, $C_{12}H_{16}NOCl$)

Yield 86.1%; bp 196–198°C/20 Torr; $R_f = 0.34$; ^{1}H NMR: $\delta = 1.06$ (t, $J = 7.2$ Hz, CH_2CH_3), 1.12 (t, $J = 7.2$ Hz, CH_2CH_3), 3.35 (q, $J = 7.2$ Hz, $2CH_2CH_3$), 3.62 (s, CH_2-*Ph*), 7.10–7.22 (m, $4H_{ar}$) ppm; MS: m/z (%) = 225 (M^+, 17).

4-Chloro-N,N-diethylphenylacetamide (**3e**, $C_{12}H_{16}NOCl$)

Yield 78.4%; bp 202–204°C/15 Torr; $R_f = 0.27$; ^{1}H NMR: $\delta = 1.05$ (t, $J = 7.2$ Hz, CH_2CH_3), 1.13 (t, $J = 7.2$ Hz, CH_2CH_3), 3.28 (q, $J = 7.2$ Hz, CH_2CH_3), 3.39 (q, $J = 7.2$ Hz, CH_2CH_3), 3.46 (s, CH_2-*Ph*), 7.19–7.29 (m, $4H_{ar}$) ppm; MS: m/z (%) = 225 (M^+, 15).

3-Nitro-N,N-diethylphenylacetamide (**3f**, $C_{12}H_{16}N_2O_3$)

Yield 74.5%; bp 194–198°C/27 Torr; $R_f = 0.27$; ^{1}H NMR: $\delta = 1.15$ (t, $J = 7.2$ Hz, CH_2CH_3), 1.20 (t, $J = 7.2$ Hz, CH_2CH_3), 3.36 (q, $J = 7.2$ Hz, CH_2CH_3), 3.44 (q, $J = 7.2$ Hz, CH_2CH_3), 3.75 (s, CH_2-*Ph*), 7.38–8.14 (m, $4H_{ar}$) ppm; MS: m/z (%) = 236 (M^+, 28).

4-Nitro-N,N-diethylphenylacetamide (**3g**, $C_{12}H_{16}N_2O_3$)

Yield 72.8%; bp 204–206°C/27 Torr; $R_f = 0.30$; ^{1}H NMR: $\delta = 1.14$ (t, $J = 7.2$ Hz, CH_2CH_3), 1.18 (t, $J = 7.2$ Hz, CH_2CH_3), 3.35 (q, $J = 7.2$ Hz, CH_2CH_3), 3.41 (q, $J = 7.2$ Hz, CH_2CH_3), 3.70 (s, CH_2-*Ph*), 7.32–8.18 (m, $4H_{ar}$) ppm; MS: m/z (%) = 236 (M^+, 20).

3-Aryl-2-dichlorophosphoryl-1,1-diethyl-1-azapropenylium Chlorides
4a–**4e** – *General Procedure*

The appropriate *N,N*-diethylarylacetamide **3** (0.05 mol), 70 cm^3 anhydrous toluene and 10 cm^3 $POCl_3$ (0.11 mol) were gently heated at about 50°C until the disappearance of amide (TLC) was completed (15–30 min.). Then toluene and $POCl_3$ were removed using a rotary evaporator. The crude product **4** was washed with 50 cm^3 anhydrous diethyl ether. The oily products **4** were chromatographically pure.

2-Dichlorophosphoryl-1,1-diethyl-3-phenyl 1-azapropenylium Chloride (**4a**, $C_{12}H_{17}NO_2PCl_3$)

Yield 96.0%; $R_f = 0.05$; ^{1}H NMR: $\delta = 0.77$ (t, $J = 7.2$ Hz, CH_2CH_3), 0.98 (t, $J = 7.2$ Hz, CH_2CH_3), 1.14 (s, CH_2-*Ph*), 3.19 (q, $J = 7.2$ Hz, CH_2CH_3), 3.47 (q, $J = 7.2$ Hz, CH_2CH_3), 7.28–7.58 (m, $5H_{ar}$) ppm; UV (*Me*OH): λ_{max} ($\varepsilon \cdot 10^{-3}$) = 206 (17.50), 298 (12.22) nm.

3-(N,N-Diethylamino)-1-(N,N-dimethylamino)-(6,7)-R-substituted Isoquinolines
6a–**6e** – *General Procedure*

The appropriate compound **4** was dissolved in 70 cm^3 anhydrous toluene and 3.5 g *N,N*-dimethylcyanamide (0.05 mol) in 5 cm^3 anhydrous diethyl ether was added and left for 1–2 h.

Method A: The crude formamidinium salt **5** prepared from the diethylimmonium salt **4** and *N,N*-dimethylcyanamide was heated under reflux in 70 cm^3 toluene for about 4–5 h. The formation of **6** can be monitored by TLC. After cooling it was alkalyzed with 20% aqueous NaOH and extracted with $CHCl_3$. The combined extracts were concentrated and chromatographed on silica (benzene:ethyl acetate = 3:1).

Method B: A solution of 5 cm^3 $TiCl_4$ (0.05 mol) in 10 cm^3 anhydrous toluene was gradually added to the crude formamidinium salt **5**. The agitation was continued at 50°C for about 3 h. Toluene was decanted from the resulting gluey solid (salts of 1,3-diaminoisoquinolines) and alkalyzed with 20% aqueous NaOH. After a rapid decomposition the mixture was extracted with $CHCl_3$. The combined extracts were concentrated and the crude products **6** were chromatographed as in the *method A*.

3-(N,N-Diethylamino)-1-(N,N-dimethylamino)-isoquinoline (**6a**, $C_{15}H_{21}N_3$)

Yield 66.0 (*A*), 76.5 (*B*) %; $R_f = 0.64$; ^{1}H NMR: $\delta = 1.21$ (t, $J = 7.2$ Hz, $2CH_2CH_3$), 3.01 (s, $2CH_3$), 3.57 (q, $J = 7.2$ Hz, $2CH_2CH_3$), 6.11 (s, H-4), 7.01 (dd, $J = 7.2$, 7.8 Hz, H-7), 7.31 (dd, $J = 7.2$, 7.8 Hz, H-6), 7.42 (d, $J = 7.8$ Hz, H-5), 7.85 (d, $J = 7.8$ Hz, H-8) ppm; UV (*Me*OH-H_2O): λ_{max} ($\varepsilon \cdot 10^{-3}$) = 201.2 (27.57), 248.2 (13.40), 312.6 (6.23) nm (acidic), 215.2 (16.85), 243.4 (10.93), 301.4 (6.58) nm (basic); MS: m/z (%) = 243 (M^+, 100); $pK_a = 6.70 \pm 0.21$.

6-Methoxy-3-(N,N-diethylamino)-1-(N,N-dimethylamino)-isoquinoline (**6b**, $C_{16}H_{23}N_3O$)

Yield 82.0 (*A*), 89.0 (*B*) %; mp 180–183°C; $R_f = 0.63$; ^{1}H NMR: $\delta = 1.20$ (t, $J = 7.2$ Hz, $2CH_2CH_3$), 3.02 (s, $2CH_3$), 3.55 (q, $J = 7.2$ Hz, $2CH_2CH_3$), 3.85 (s, OCH_3), 6.05 (s, H-4), 6.65 (d, $J = 7.2$ Hz, H-7), 6.73 (s, H-5), 7.77 (d, $J = 7.2$ Hz, H-8) ppm; UV (*Me*OH-H_2O): λ_{max} ($\varepsilon \cdot 10^{-3}$) = 200.2 (17.26), 289.6 (9.14), 319.0 (7.14) nm (acidic), 216.0 (16.57), 264.0 (17.90), 315.8 (5.44) nm (basic); MS: m/z (%) = 273 (M^+, 34); $pK_a = 7.15 \pm 0.12$.

7-Methoxy-3-(N,N-diethylamino)-1-(N,N-dimethylamino)-isoquinoline (**6c**, $C_{16}H_{23}N_3O$)

Yield 69.0 (*A*), 74.0 (*B*) %; mp 168–170°C; $R_f = 0.65$; ^{1}H NMR: $\delta = 1.19$ (t, $J = 7.2$ Hz, $2CH_2CH_3$), 3.01 (s, $2CH_3$), 3.55 (q, $J = 7.2$ Hz, $2CH_2CH_3$), 3.87 (s, OCH_3), 6.15 (s, H-4), 7.07 (d, $J = 7.8$ Hz, H-6), 7.22 (d, $J = 7.8$ Hz, H-5), 7.38 (s, H-8) ppm; UV (*Me*OH-H_2O): λ_{max} ($\varepsilon \cdot 10^{-3}$) = 227.4 (23.07), 301.6 (6.24), 348.2 (3.32) nm (acidic), 216.0 (25.48), 303.0 (6.30), 397.0 (2.00) nm (basic); MS: m/z (%) = 273 (M^+, 32); $pK_a = 6.61 \pm 0.14$.

6-Chloro-3-(N,N-diethylamino)-1-(N,N-dimethylamino)-isoquinoline (**6d**, $C_{15}H_{20}N_3Cl$)

Yield 68.0 (*A*), 76.0 (*B*) %; $R_f = 0.48$; ^{1}H NMR: $\delta = 1.23$ (t, $J = 7.2$ Hz, $2CH_2CH_3$), 3.04 (s, $2CH_3$), 3.54 (q, $J = 7.2$ Hz, $2CH_2CH_3$), 6.01 (s, H-4), 6.91 (d, $J = 7.8$ Hz, H-7), 7.38 (s, H-5), 7.88 (d, $J = 7.8$ Hz, H-6) ppm; UV (*Me*OH-H_2O): λ_{max} ($\varepsilon \cdot 10^{-3}$) = 200.4 (23.59), 292.8 (3.97) nm (acidic), 214.6 (10.96), 250.0 (5.15), 301.2 (2.10) nm (basic); MS: m/z (%) = 277 (M^+, 98); $pK_a = 6.45 \pm 0.04$.

7-Chloro-3-(N,N-diethylamino)-1-(N,N-dimethylamino)-isoquinoline (**6e**, $C_{15}H_{20}N_3Cl$)

Yield 72.0 (*A*), 80.0 (*B*) %; mp 170–172°C; $R_f = 0.51$; ^{1}H NMR: $\delta = 1.20$ (t, $J = 7.2$ Hz, $2CH_2CH_3$), 3.04 (s, $2CH_3$), 3.56 (q, $J = 7.2$ Hz, $2CH_2CH_3$), 6.08 (s, H-4), 7.09–7.18 (m, H-5,6), 7.85 (s, H-8) ppm; UV (*Me*OH-H_2O): λ_{max} ($\varepsilon \cdot 10^{-3}$) = 221.8 (16.30), 322.1 (2.20) nm (acidic), 214.0 (10.41), 260.6 (5.60), 335.8 (3.52) nm (basic); MS: m/z (%) = 277 (M^+, 100); $pK_a = 6.14 \pm 0.08$.

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